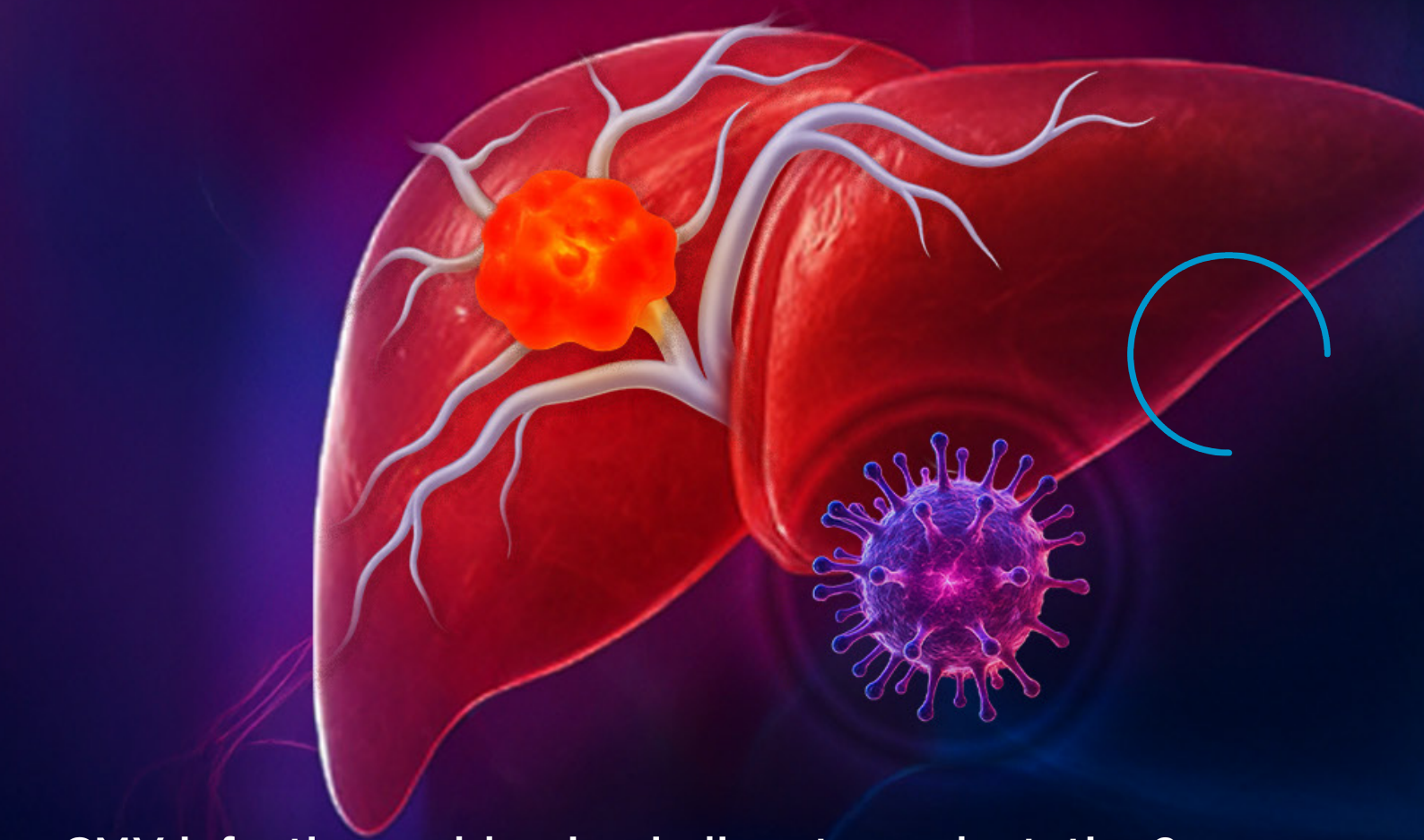
ESOT

Volume 38 | Issue 06
June 2025

# Transplant International



## CMV infection : a blessing in liver transplantation?

Transplant International

frontiers | Publishing Partnerships

Transplant International



ESOT

Transplant International

# CMV infection: a blessing in Liver transplantation?



ISSN 1432-2277
ISBN 978-2-8325-6664-0
DOI 10.3389/978-2-8325-6664-0

**Generative AI statement**
Any alternative text (Alt text) provided alongside figures in the articles in this ebook has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Transplant International

# Table of contents

## Cover Article



## Guidelines



## Original Research

## Letters to the Editor

ESOT®
Leading the way
in transplantation




# **2025** CALENDAR OF EVENTS




Join us for a dynamic lineup of educational **webinars**, **hands-on workshops**, and **in-person events**, dedicated to advancing transplantation through shared knowledge and collaboration.

For the full scope of events, visit:

**www.esot.org/events**

# Grants

#PoweredByESOT

## 6 October

Application deadline

**ESOT Transplant Fellowship** 55.000

**ESOT Sevda Hassan Mobility Grant (Europe)** 4.000

**ESOT Mobility Grant (International)** 6.000

**ESOT Learning Grant (Europe)** 1.000

**ESOT Learning Grant (International)** 2.000


ESOT®
Leading the way
in transplantation

# Are You a Member?

**Join us to help shape and nurture the future of ESOT!**

Learn more about membership benefits, access, discounts, including reduced publishing fees in Transplant International

**ESOT Membership**

ESOT TRANSPLANT LIVE ONLINE EDUCATION

# TRANSPLANT LIVE

## ONLINE EDUCATION

**Management of CMV in Solid Organ Transplantation**

**Quality of Care in Post-transplant Infectious Disease**

Discover **Transplant Live**
Your Gateway to Excellence in Transplant Education

**Transplant Live**, the official online education platform of **ESOT**, delivers high-quality, accessible learning for the global transplant community. Explore EACCME-accredited courses, case studies, and highlights from ESOT Congress and more.

Scan the QR code and unlock a wealth of resources tailored for transplant professionals.

ESOT | Transplant International

ORIGINAL RESEARCH
published: 10 June 2025
doi: 10.3389/ti.2025.14553

# Cytomegalovirus Reactivation Is Associated With Lower Rates of Hepatocellular Carcinoma Recurrence After Liver Transplantation

*Victoria Aguilera[1*†‡], Sarai Romero Moreno[2†], Isabel Conde[3], Angel Rubín[3], Angela Carvalho-Gomes[4], Mario Romero[5], Javier Zamora-Olaya[6], Miguel Angel Gómez-Bravo[7], Esteban Fuentes-Valenzuela[8], Cristina Dopazo[9], Nikita Bilbao[9], Antonio González[10], Ana Sánchez-Martínez[11], Sonia Pascual[12], Jesús Rivera-Esteban[13], José Ignacio Herrero[14], Sara Lorente[15], Antonio Cuadrado-Lavín[16], Flor Nogueras[17], Laura Martínez-Arenas[18], Rocío González-Grande[19], Marina Berenguer[1‡] and Manuel Rodriguez-Perálvarez[20‡]*

[1]Hepatology and Liver Transplant Unit, La Fe Universitary and Politécnic Hospital, Instituto de Investigación Sanitaria (IIS) La Fe, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Faculty of Medicine, Valencia University, Valencia, Spain, [2]Hepatology and Liver Transplant Unit, La Fe Universitary and Politécnic Hospital, Valencia, Spain, [3]Hepatology and Liver Transplant Unit Trasplante Hepático, La Fe Universitary and Politécnic Hospital, Instituto de Investigación Sanitaria (IIS) La Fe, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Valencia, Spain, [4]Laboratorio de Hepatología, Cirugía HBP y Trasplantes, Instituto de Investigación Sanitaria (IIS) La Fe, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Valencia, Spain, [5]Department of Hepatology and Liver Transplantation, HUGregorio Marañón, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain, [6]Department of Hepatology and Liver Transplantation, Hospital Universitario Reina Sofía, Instituto Maimonides de Investigación Biomédica de Córdoba (IMIBIC) and University of Córdoba, Córdoba, Spain, [7]Hospital Virgen del Rocio, Unidad de Cirugía Hepatobilipancreática, Sevilla, Spain, [8]Unidad de Hepatología y Trasplante Hepático, HURio Hortega, Valladolid, Spain, [9]Department of HPB Surgery and Transplants, Vall d'Hebron Hospital Universitari, Vall d'Hebron Institut de Recerca (VHIR), Vall d'Hebron Barcelona Hospital Campus, Universitat Autónoma de Barcelona, Barcelona, Spain, [10]Department of Hepatology, Hospital Universitario Ntra. Sra. de la Candelaria, Tenerife, Spain, [11]Liver Transplantation Unit, Hospital Universitario Virgen de la Arrixaca and IMIB, Murcia, Spain, [12]Unidad de Hepatología y Trasplante Hepático, Instituto de Investigación Sanitaria y Biomédica de Alicate (ISABIAL), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), HGU Dr Balmes, Alicante, Spain, [13]Department of Gastroenterology and Hepatology, Hospital Universitario Puerta de Hierro, Instituto de Investigación Sanitaria Puerta de Hierro - Segovia de Arada (IDIPHISA), Majadahonda, Spain, [14]Liver Unit, Clínica Universidad de Navarra and IdiSNA, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Pamplona, Spain, [15]Department of Hepatology and Liver Transplantation, Hospital Clínico Lozano Blesa, University of Zaragoza and ISS Aragón, Zaragoza, Spain, [16]Gastroenterology and Hepatology Department, Clinical and Translational Research in Digestive Diseases, Valdecilla Research Institute (IDIVAL), Marqués de Valdecilla University Hospital, Cantabria University, Santander, Spain, [17]Department of Hepatology and Liver Transplantation, Hospital Virgen de las Nieves, Granada, Spain, [18]Hepatology, Hepatobiliopancreatic Surgery and Transplant Laboratory, Instituto de Investigación Sanitaria (IIS) La Fe Health Research Institute, Universitat Politècnica de València, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), ISCIII, Valencia, Spain, [19]Department of Hepatology and Liver Transplantation, Hospital Regional Universitario de Málaga, Málaga, Spain, [20]Department of Hepatology and Liver Transplantation, Hospital Universitario Reina Sofía, University of Córdoba, Instituto Maimonides de Investigación Biomédica de Córdoba (IMIBIC), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Córdoba, Spain

OPEN ACCESS

***Correspondence**
Victoria Aguilera,
toyagui@hotmail.com

†These authors have contributed equally to this work

‡These authors share senior authorship

**Received:** 27 February 2025
**Accepted:** 23 May 2025
**Published:** 10 June 2025

**Citation:**
Aguilera V, Romero Moreno S, Conde I, Rubín A, Carvalho-Gomes A, Romero M, Zamora-Olaya J, Gómez-Bravo MA, Fuentes-Valenzuela E, Dopazo C, Bilbao N, González A, Sánchez-Martínez A, Pascual S, Rivera-Esteban J, Herrero JI, Lorente S, Cuadrado-Lavín A, Nogueras F, Martínez-Arenas L, González-Grande R, Berenguer M and Rodriguez-Perálvarez M (2025) Cytomegalovirus Reactivation Is Associated With Lower Rates of Hepatocellular Carcinoma Recurrence After Liver Transplantation. Transpl. Int. 38:14553. doi: 10.3389/ti.2025.14553

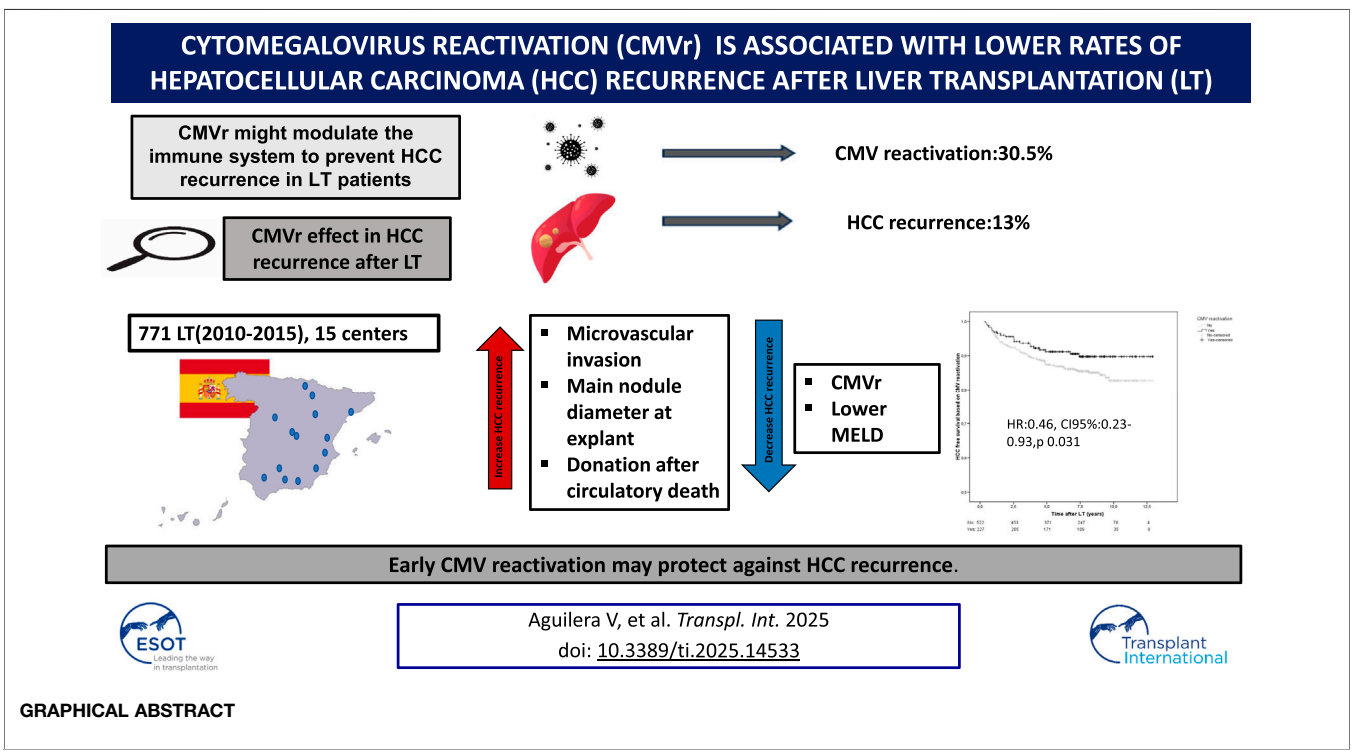
**Abbreviations:** AFP, alpha fetoprotein; BMI, Body Mass Index; CMV, cytomegalovirus; CMVr, Cytomegalovirus reactivation after Liver transplantation; CI, confidence Interval; CNI, calcineurin inhibitors; CVE, Cardiovascular events; D, Donor; DCD, Donation after Circulatory Death; eGFR, estimated Glomerular Filtration Rate; HBV, Hepatitis B Virus; HCC, Hepatocellular carcinoma; HCV, Hepatitis C Virus; LT, liver transplantation; MASH, Metabolic dysfunction-associated steatohepatitis; MELD, Model for End-stage Liver Disease; mTORi, mammalian target of rapamycin inhibitors; R, Recipient; SD, Standard Deviation; VL, Viral load.

In patients with hepatocellular carcinoma (HCC), undergoing liver transplantation (LT), cytomegalovirus reactivation (CMVr) may modulate the immune system to prevent tumor recurrence. In this multicenter retrospective study (2010–2015) involving 15 institutions, we assessed the effect of early CMVr in tumor recurrence rates among 771-LT HCC patients with tacrolimus-based immunosuppression (88% men, mean age 58 years). CMV prophylaxis was implemented for 19.7% of patients, while the rest were managed with preemptive therapy. The Milan criteria were met by 88% of patients. Microvascular invasion was present in 12.7% of explanted livers. The serum AFP level before transplantation was 5.1 (3–15) ng/mL. After a median follow-up of 7.4 years, 101 patients (13%) experienced HCC recurrence. CMVr occurred in 235 patients (30.5%) at a median of 41.5 days post-LT and 42 patients (5.6%) had CMV disease. Cumulative exposure to tacrolimus within the first 3 months after LT was similar among patients with and without CMVr. In a multivariate Cox regression analysis, factors associated with an increased rate of HCC recurrence included microvascular invasion [HR:2.82, CI95%:1.55–5.14; p 0.0001], donation after circulatory determination of death [HR:4.43,CI95%:1.52–12.9; p 0.006) and diameter of the main nodule at explant [HR:1.04, CI95%:1.02–1.06; p < 0.001]. Meanwhile CMVr [HR: 0.46, CI95%:0.23–0.93, p 0.031] and MELD [HR:0.93, CI95%:0.87–0.99; p0.017] exhibited protective effects. In conclusion, early CMVr may protect against HCC recurrence. The underlying immune mechanisms warrant further investigation.

**Keywords: liver transplantation, cytomegalovirus, survival, hepatocellular carcinoma, donation after circulatory determination of death, Immunosupression**

## INTRODUCTION

Recurrence of hepatocellular carcinoma (HCC) following liver transplantation (LT) occurs in approximately 8%–20% of Well-selected patients is an accepted terminology in HCC and LT in literature [1–4]. Clinical, pathological, and biological factors influence the risk of HCC recurrence [3] with several imperfect models proposed to assess this risk both pre- and post-LT [1, 2, 5, 6]. In addition, there are no established surveillance guidelines for HCC recurrence and there is a significant heterogeneity across different




**GRAPHICAL ABSTRACT**

institutions [6, 7]. Transplanting within the MILAN criteria mitigates the risk; however, the majority of centers are now expanding the criteria. Because exposure to immunosuppressive drugs, particularly calcineurin inhibitors (CNIs) early after LT, is also associated with oncogenesis in a dose-dependent manner via impairment of the immune surveillance [8–10], tacrolimus minimization and addition of mammalian target of rapamycin inhibitors (mTORi) is a strategy used by some centers albeit with limited benefit [8, 9, 11].

Established factors favoring HCC recurrence include microvascular invasion and high alpha-fetoprotein (AFP) levels, along with tumor numbers and size. Although cytomegalovirus (CMV) infection is the most common opportunistic infection in LT recipients and remains a cause of life-threatening disease and allograft rejection [12, 13], recent studies have suggested a potential beneficial effect of CMV reactivation (CMVr) in some tumors [14, 15]. Immune modulation and modification of the tumor microenvironment following CMVr could be responsible for tumor control in this scenario [16–20].

In the present retrospective multicenter cohort study, we aimed to evaluate whether the occurrence of CMVr after LT in patients with HCC has a potential effect against tumor recurrence.

# MATERIALS AND METHODS

## Study Subjects and Analyzed Variables

This is a retrospective multicenter study that involved 15 institutions representing 62% of Spanish LT activity. Patients undergoing LT due to HCC between January 2010 and December 2015 under tacrolimus-based immunosuppression, were consecutively included. The MILAN criteria were used by the majority of centers during the study period [21]. Exclusion criteria were age <18, re-transplantation, combined organ transplantation, death within the first 6 months after LT, and relevant missing data concerning CMVr or HCC recurrence. Patients were followed until death or November 2022, whichever occurred first.

HCC was confirmed by the pathological examination of the explanted liver in all cases with the exception of patients showing complete tumor necrosis related to pre-LT locoregional bridging therapies, with previous radiological HCC diagnosis according to international guidelines.

The study protocol was approved by the Ethics Committee of Clinical Research of La Fe Universitari and Politécnic Hospital (ref number: 2022-601-1) and was conducted in accordance with the 1975 Helsinki Declaration. Given the retrospective nature of the data, the ethics committee waived the need for informed consent at the other participating hospitals.

Collected variables included donor and recipient serology, donor and recipient mismatch, pre-emptive therapy, CMVr after LT, primary infection, CMV disease and the need for antiviral therapy.

The main risk variable was CMVr, which was defined as a detectable viral DNA above the local quantification threshold after LT. We also recorded CMV primary infection for descriptive purposes, which was defined as a positive post-LT viral CMV DNA in a patient with a negative CMV serology test before LT. To study the relationship between CMV and HCC recurrence, we considered CMVr a more appropriate risk factor because it is an accepted surrogate for lower immune system awareness; in contrast, CMV primary infection, which is primarily related to Donor-Recipient mismatch, was controlled as a potential confounder in the multivariable analysis.

The main study outcome was HCC recurrence as a time-dependent event accounting for the interval between LT and imaging or pathological diagnosis of tumor recurrence, whichever occurred first. The secondary outcomes were disease-free survival and overall survival rates.

Other collected variables associated with HCC recurrence and death included:

(i) Related to the donor: demographics and type of donor.
(ii) Related to the recipient: sex, age, indication for LT, functional MELD score, presence of renal failure (estimated glomerular filtration rate [eGFR] < 60 mL/min), cardiovascular risk factors (arterial hypertension, diabetes mellitus), and human immunodeficiency virus (HIV) infection.
(iii) Related to HCC: bridging and/or downstaging to the Milan criteria, type of locoregional therapy (radiofrequency ablation, chemoembolization, radioembolization, combination therapy), pathological features at explant including microvascular invasion and grade of differentiation, AFP levels at listing and at LT, number of nodules, and diameter of the largest nodule in both the radiological assessment and the explanted liver.
(iv) Immunosuppression: in a subgroup of patients who participated in a previous study [8, 10], cumulative exposure to tacrolimus, defined as the area under curve of trough concentrations within the first 3 and 12 months after LT was obtained.
(v) Patient and graft survival and cause of death.

## Variable Definitions

CMVr or primary infection were defined as detectable viral DNA above the local quantification threshold after LT. We defined primary infection as occurring in those patients witha negative CMV serology test before LT.

CMV disease was defined using internationally agreed-upon criteria, including the presence of appropriate clinical symptoms and documentation of CMV in tissue using different techniques (histopathology, virus isolation, immunohistochemistry, or nucleic acid hybridization) [22].

We collected the first positive CMV viral load (VL) and the peak VL (defined as the highest detectable DNAemia per each patient) in both CMVr and primary infection. We also collected the median CMV VL in those patients who were treated with antivirals.

## Management of CMVr and HCC Surveillance

Prophylaxis with valganciclovir (900 mg once daily) was administered within the first 3–6 months after LT to CMV-negative patients who had received a CMV-positive donor liver.

All remaining patients underwent only CMV DNA surveillance. Serial blood samples were obtained weekly during the first month, every 2 weeks from months 1–3, and at the time of clinical visits thereafter. CMV surveillance lasted for the first 6–12 months. Preemptive therapy with valganciclovir (900 mg bd) was implemented immediately after patients showed detectable and/or an increasing CMV viremia without a prespecified threshold or when an upward trend was observed for both primary infection or reactivation and maintained up to the confirmation of two consecutive negative samples, at least 4 weeks apart [12].

Surveillance of HCC recurrence after LT was performed according to each center's practice by combining serum AFP and imaging techniques. The majority of centers used abdominal ultrasounds and/or whole-body computed tomography scans performed at least every 6 months for the first 2–5 years after LT depending on risk factors.

All patients received tacrolimus-based immunosuppression and tapering corticosteroids, which were withdrawn between the third and sixth months after liver transplantation, except in cases of autoimmune disease, where the lowest tolerated dose was maintained. The majority of centers did not implement specific protocols for patients with HCC. Seven centers used everolimus as part of the immunosuppression protocol, which was introduced in week 4 post-LT [11] in patients with poor prognostic factors.

## Statistical Analysis

Continuous variables were summarized as mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. Categorical variables were presented as absolute numbers and frequencies. Normal distribution of variables was assessed using the Kolmogorov-Smirnov test. A Student's t-test was used for quantitative variables, and a Chi-square and Fisher's exact test were used for categorical variables.

Patient survival analysis was performed with Kaplan-Meier survival curves.

The initial multivariable model included the variables with p-values <0.10 in the univariate analysis. Variables with a p-value above this threshold could be included if they were considered clinically relevant by the investigators or if found to be related to HCC recurrence in previous studies. Regarding HCC morphological variables, we included those available at baseline after the analysis of the explanted liver (number of nodules, diameter of the main nodule) excluding models that combined some of these morphological variables.

Patients with AFP >1000 ng/mL (n = 6) were excluded from the regression analysis to avoid distortion and inconsistencies due to edged values.

The significance level was set at 5% ($p < 0.05$) for all analyses.

Data analysis was performed using SPSS version 22.0 (IBM, Chicago, USA).

# RESULTS

The eligible cohort comprised a total of 771 LT patients with HCC on explant out of an initial cohort of 816 patients, from 15 Spanish institutions. Forty-five patients with missing data relevant to the analysis [CMVr (n = 19) or HCC recurrence (n = 26)] were excluded from the analysis. The median follow-up was 7.4 years (IQR 4.9–9.1) after LT. The flowchart showing the study population is represented in **Figure 1**.

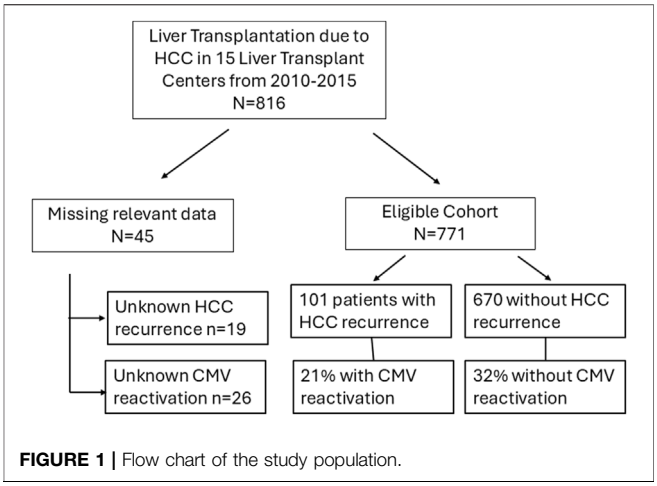



**FIGURE 1 |** Flow chart of the study population.

**TABLE 1 |** Pre-transplant features.

| **Baseline features (n = 771)** | |
|---|---|
| Age (years), median (IQR) | 58.7 (53.8–63.6) |
| Sex (% men) | 681 (88%) |
| Donor age (years), median (IQR) | 62 (49–73) |
| Type of donor, n (% of Brain death) | 745 (97.5%) |
| Etiology of cirrhosis, n (%) | |
| HCV | 390 (50.5%) |
| Alcohol | 399 (52%) |
| HBV | 65 (8.4%) |
| MASH | 19 (2.5%) |
| MELD score at LT (median, IQR) | 12 (9–16) |
| Diabetes mellitus (with oral antidiabetics or insulin), n (%) | 274 (36%) |
| eGFR ml/min, median (IQR) | 91 (80–100) |
| Duration of follow up (years), median (IQR) | 7.4 (4.9–9.1) |

*HCV, Hepatitis C virus; HBV, Hepatitis B virus; eGFR: estimated-glomerular filtrate rate; LT, liver transplantation; MASH, metabolic dysfunction-associated steatohepatitis.*

Baseline features of the included cohort are shown in **Table 1**. The majority of patients were men (n = 681, 88%), with a median age of 58.7 years (IQR 53.8–63.6) at LT. The median donor age was 62 (IQR 49–73) years. The majority of patients received a brain-dead donor liver (n = 745, 97.5%). The most frequent etiologies of liver disease that led to LT were alcohol and hepatitis C virus (HCV) (n = 399, 52% and n = 390, 50.5%, respectively). The median MELD score at LT was 12 (IQR 9–16). More than a third of patients were diabetic at the time of LT and the median eGFR was 91.2 mL/min (IQR 80–100).

Regarding HCC features before LT and at the time of explant (**Table 2**), the majority of patients met the Milan criteria (88%) or the Up-to-Seven criteria (98%). The median AFP at inclusion was 6 ng/mL (IQR 3.4–17). A high proportion of patients were treated with locoregional therapy, with transarterial chemoembolization and radiofrequency ablation being the most common (36.2% and

**TABLE 2 |** Hepatocellular (HCC) features in the overall cohort (n = 771).

| | |
|---|---|
| Bridging, n (%) | |
| Transarterial chemoembolization | 279 (36.2%) |
| Radiofrequency ablation | 139 (18%) |
| Radioembolization | 7 (1%) |
| Combination therapy | 8 (8%) |
| None | 252 (33%) |
| Downstaging, n (%) | 103 (13.4%) |
| AFP at WL inclusion (ng/mL)(median, IQR) | 6 (3.4–17) |
| AFP at LT (ng/mL) (median, IQR) | 5.1 (3–15) |
| Milan "in" Criteria (n = 753), % | 664 (88%) |
| Up to Seven Criteria (n = 755), % | 737 (98%) |
| Retreat Score (n = 549) | |
| 0-3 points | 443 (81%) |
| 4-8 points | 106 (19%) |
| Number of nodules at imaging (median, IQR) | 1 (1–2) |
| Size of larger nodule at imaging(mm), (median,IQR) | 22 (15–30) |
| Number of viable nodules at pathology (mm), (median, IQR) | 1 (1–2) |
| Size of the largest nodule at pathology (mm) | 20 (12–18) |
| Microscopic intravascular invasion at pathology, n (%) | 98 (12.7%) |
| Differentiation grade, n (%) | |
| Well differentiated | 218 (30%) |
| Moderate differentiation | 343 (48%) |
| Poor differentiated | 49 (7%) |
| Complete necrosis | 108 (15%) |

*AFP, alpha-fetoprotein; WL, waiting list.*

**TABLE 3 |** Cytomegalovirus related features (n = 771).

| | |
|---|---|
| Mismatch CMV, n (%) | |
| D/R +/+ | 421 (67.5%) |
| D/R +/– | 72 (11.5%) |
| D/R–/+ | 116 (18.6%) |
| D/R–/– | 15 (2.4%) |
| CMV Prophylaxis n (%) | 148 (19.7%) |
| CMV primary infection, n (%) | 47 (6.1%) |
| CMV reactivation (CMVr), n (%) | 235 (30.5%) |
| First positive CMV VL (median, IQR) (UI/mL) | |
| In patients with CMVr | 758 (405–2,340) |
| In patients with primary infection | 4,849 (1,590–25800) |
| Peak CMV VL (UI/mL) (median, IQR) | |
| In patients with CMVr | 1915 (604–6,941) |
| In patients with primary infection) | 7,084 (3,265–34214) |
| First positive CMV VL (median, IQR) (UI/mL) if followed by antiviral therapy | 906 (408–3,310) |
| In patients with CMVr | 4,035 |
| In patients with primary infection | (1,362–34214) |
| Peak CMV VL (median, IQR) (UI/mL) if followed by antiviral therapy | 2,978 |
| In patients with CMVr | (1,026–11000) |
| In patients with primary infection | 8,938 (2,810–49600) |
| Time to CMV reactivation (days, median, IQR) | 41.5 (26–56) |
| CMV disease, n (%) | 42 (5.6%) |
| Need of antiviral treatment, n (%) | |
| In those with primary infection or reactivation | 187 (66.3%) |

*CMV: cytomegalovirus, CMVr: CMV, reactivation; D: donor, R: recipient, VL: viral load.*

18%, respectively). A minority of patients (13.4%) was waitlisted after downstaging. Microvascular invasion was present in 12.7% of the explants and more than half of the HCCs were moderately or poorly differentiated (48% and 7%, respectively).

**TABLE 4 |** Cox Regression model for variables associated with HCC recurrence.

| Variable | HR | 95% IC | p-value |
|---|---|---|---|
| Sex | | | |
| Men | 1 | | |
| Women | 1.26 | 0.44–3.57 | 0.671 |
| Recipient age (years) | 0.97 | 0.93–1.01 | 0.088 |
| Donor type | | | |
| Circulatory death | 4.43 | 1.52–12.9 | 0.006** |
| HBV etiology | 0.84 | 0.34–2.11 | 0.717 |
| MELD score | 0.93 | 0.87–0.99 | 0.017* |
| AFP at WL | 1 | 1–1 | 0.961 |
| AFP at LT | 1 | 1–1 | 0.721 |
| Nodule size at last imaging before LT | 1.03 | 0.77–1.37 | 0.843 |
| Number of nodules at last imaging before LT | 0.99 | 0.97–1.01 | 0.264 |
| Nodule size at explant | 1.04 | 1.02–1.06 | <0.001*** |
| Number of nodules at explant | 1.03 | 0.97–1.10 | 0.259 |
| CMV reactivation | 0.46 | 0.23–0.93 | 0.031* |
| Micro-vascular invasion at explant | 2.82 | 1.55–5.14 | 0.001** |
| Differentiation grade | | | |
| Moderate or poor | 1.41 | 0.79–2.52 | 0.248 |

**p < 0.05; **p < 0.01; ***p < 0.001, The multivariate final model was made with 465 LT patients.*
*CMV, cytomegalovirus; HBV, Hepatitis B virus; LT; liver transplantation; WL, waiting list.*

CMV-related features are shown in **Table 3**. Both CMV serologies of donors and recipients were positive in 67.5% of patients. A donor-recipient mismatch (D+/R–) was found in 11.5% of patients, negative donor with positive recipient in 18.6% of patients and negative donor with negative recipient in 2.4% of patients. Approximately one-third of patients (30.9%) had CMVr at a median of 41.5 days (IQR 26–56) but only 5.6% of these patients developed CMV disease. Antiviral therapy against CMV was administered to 66% of those with reactivation or primary infection and the remaining patients were managed with reduction of immunosuppression only or exhibited spontaneous clearance. The first detectable and the peak VL were higher in those with primary infection as opposed to patients with CMVr, regardless of subsequent antiviral therapy (see **Table 3**).

HCC recurrence occurred in 13.1% (n = 101) of patients after a mean of 2.78 (SD +/−2.3) years. HCC recurrence-free survival at 1, 3, 5, and 7 years after LT was 96%, 91.6%, 88.2% and 86.8%, respectively (**Supplementary Figure S2**). The overall survival rate for patients without HCC recurrence was 99.5%, 92.1%, 86.7% and 81.5% at 1, 3, 5, and 7 years, respectively, which was significantly higher than that for patients with HCC recurrence (96,9%,62.9%,38.1% and 21.6% at 1, 3, 5, and 7 years, respectively) (Log Rank $p < 0.05$) (**Supplementary Figure S3**).

Data on immunosuppression, cumulative exposure to tacrolimus and rejection were available for 324 patients (42% of the entire cohort). We decided not to perform a sensitivity analysis in this sub-cohort because it showed different HCC features, and the number of HCC recurrence events was insufficient to allow meaningful comparisons. Of note, patients with and without CMV reactivation showed comparable cumulative exposure to tacrolimus within the first 3 months after LT, with 41% and 43% of patients, respectively, stratified as receiving high tacrolimus exposure ($p = 0.497$). In contrast, a high cumulative exposure to tacrolimus was associated with increased HCC recurrence rates. Basiliximab was used

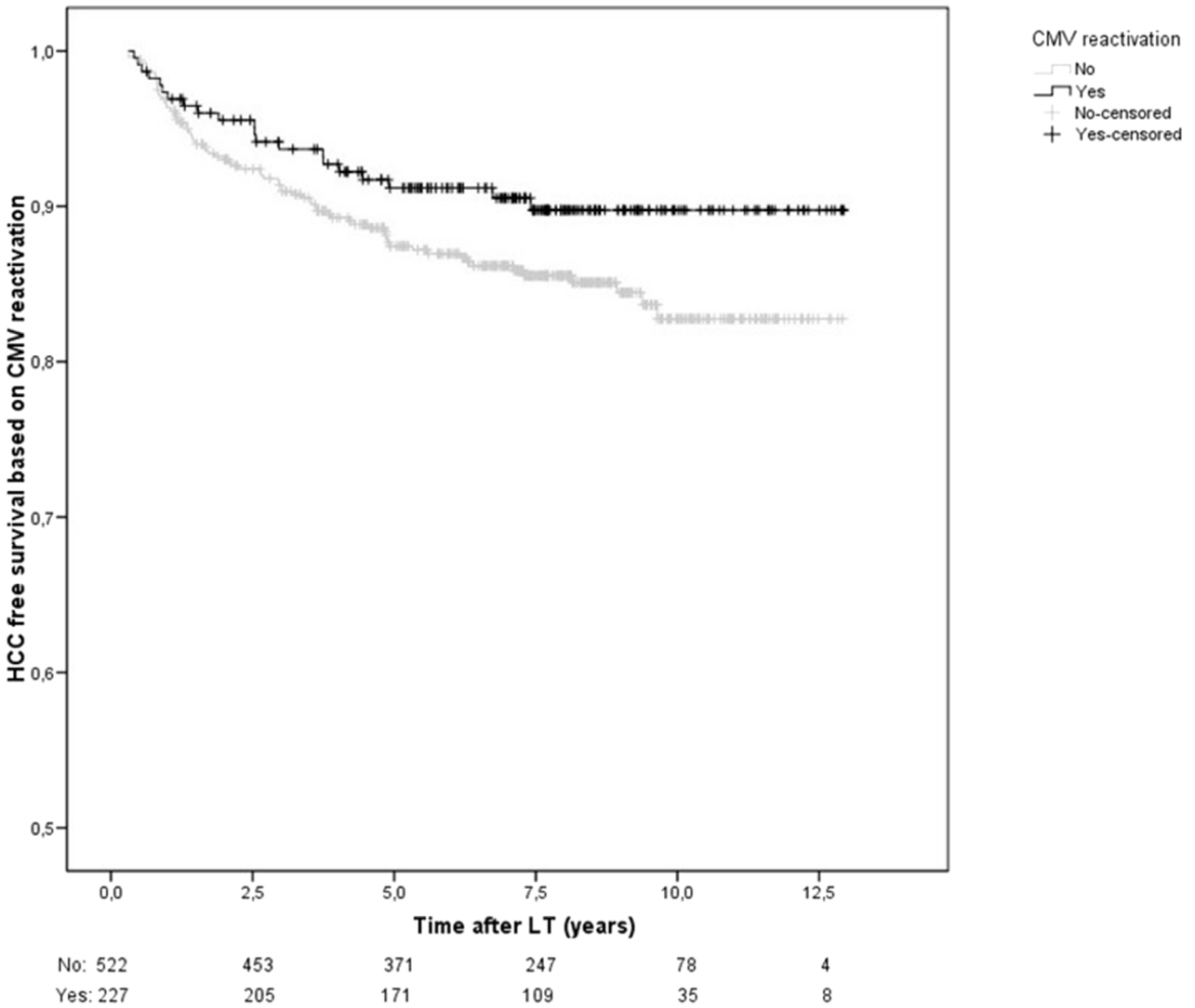



**FIGURE 2 |** HCC-recurrence free survival based on CMV reactivation. HCC recurrence free survival was significantly higher in those with CMVr (HR 0.46, 95%CI 0.23–0.93, p = 0.031).

by 13.6% of subjects in the studied cohort and overall, 11% of patients were treated with mTORi. In total 16% of patients developed a biopsy-proven acute cellular rejectionduring study period.

The predictors of post-LT HCC recurrence in the univariate and multivariable Cox-regression analyses (performed on 465 patients with available data on all the variables included) are shown in **Supplementary Table S1** and in **Table 4**, respectively. Of note, we reproduce the multivariable analysis after excluding variables with missing values in more than 10% of patients, namely (AFP at WL, AFP at LT, Number of nodules at explant, and cumulative exposure to tacrolimus at months 3 and 12). The new analysis included 615 patients (79.8% of the entire study population) and produced consistent results regarding the protective effect of CMVr against HCC recurrence (HR = 0.57; p = 0.037) and recurrence-free survival (HR = 0.77; p = 0.112) (data not shown).

Factors independently associated with an increased risk of HCC recurrence were donation after circulatory determination of death (HR 4.43, 95%CI 1.52–12.9, p = 0.006), diameter of the main nodule at explant (HR 1.04, 95%CI 1.02–1.06, p < 0.001) and microvascular invasion (HR 2.82, 95%CI1.55-5.14, p = 0.001) while lower MELD scores at transplant (HR 0.93; 95%CI 0.87–0.99, p = 0.017), and CMVr (HR 0.46, 95%CI 0.23–0.93, p = 0.031) having a protective effect. Patients with CMVr had better HCC free-survival than those without CMVr after LT (**Figure 2**). However, CMV primary infection was not associated with lower HCC recurrence.

In addition, we also explored whether CMV mismatch or the need for antiviral treatment after CMVr (antiviral treatment vs. spontaneous clearance) could have affected HCC recurrence. For CMV mismatch, an additional exploratory analysis was conducted in which no association was found (HR: 1.69, 95%CI 0.8–3.57, p = 0.169). An alternative multivariable model was built to test the interaction between CMVr and antiviral treatment, which did not obtain statistical significance (p = 0.534), meaning that the decision to treat or not CMVr may not have an influence on HCC recurrence

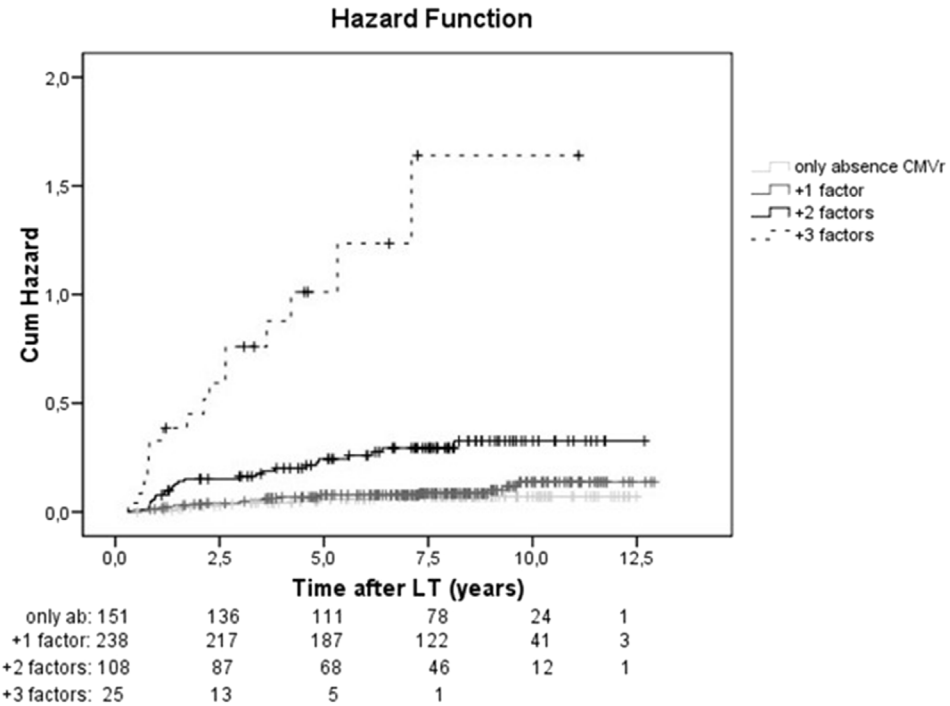



**FIGURE 3 |** Cumulative risk of HCC recurrence stratified according to risk factors. Kaplan-Meier curve showing the cumulative risk of hepatocellular carcinoma recurrence after liver transplantation. For the analysis, the study population was stratified according to the number of risk factors, which included: absence of reactivation of cytomegalovirus (CMVr), size of the main nodule at explant, MELD score and microvascular invasion. (light grey solid line: only absence of CMVr, dark grey solid line: absence of CMVr and 1 added factor, black solid line: absence of CMVr and 2 added factors, absence of CMVr and 3 added factors: black dashed line).

**TABLE 5 |** Outcomes after LT.

| | |
|---|---|
| HCC recurrence (%, IC95%) | 101 (13.1%, 10–15.5) |
| Time to recurrence (years, SD) | 2.78, 2.3 |
| Death (%) | 237 (30.7%) |
| Causes of Death (%) | |
| Disease recurrence (n,%) | 84 (40.8%) |
| De *novo* tumors (n,%) | 50 (23.8%) |
| CVE (n,%) | 10 (4.9%) |
| Others (n,%) | 64 (30.8%) |

*HCC, hepatocelullar carcinoma; CVE, cardiovascular events.*

**TABLE 6 |** Cox regression model of factors associated with survival.

| Variable | HR | 95% CI | p-value |
|---|---|---|---|
| Donor age (years) | 1.00 | 0.99–1.02 | 0.429 |
| Recipient age (years) | 1.01 | 0.98–1.03 | 0.676 |
| Sex (men) | 1.11 | 0.58–2.13 | 0.758 |
| HCV etiology | 0.83 | 0.55–1.25 | 0.378 |
| Alcohol etiology | 1.12 | 0.75–1.68 | 0.571 |
| AFP at WL | 0.998 | 0.995–1.002 | 0.295 |
| AFP at LT | 1.002 | 1.001–1.004 | 0.009** |
| Number of nodules (preLT imaging) | 1.03 | 0.86–1.24 | 0.755 |
| Nodule size at explant | 1.018 | 1.01–1.03 | 0.001** |
| Number of nodules at explant | 0.98 | 0.91–1.05 | 0.577 |
| Micro-vascular invasion | 1.42 | 0.91–2.12 | 0.120 |
| Differentiation grade | | | |
| Moderate or poor | 1.26 | 0.89–1.79 | 0.188 |
| CMV reactivation | 0.67 | 0.45–0.99 | 0.049* |

**p < 0.05; **p < 0.01; ***p < 0.001, The multivariate final model was based on 481 LT, patients.*
*CMV, cytomegalovirus; HCV, Hepatitis C virus; HBV, Hepatitis B virus; LT, liver transplantation; WL, waiting list.*

rates. In addition, we stratified our study population according to the occurrence of CMVr and antiviral therapy usage into three groups: patients without reactivation, patients with untreated reactivation, and patients with treated reactivation. The multivariable Cox model showed no statistically significant difference in the risk of HCC recurrence between patients with treated (HR = 0.28, p = 0.22) or untreated CMVr (HR = 0.49, p = 0.07), and the reference group (non-reactivated) (**Supplementary Table S3**).

A Kaplan-Meier curve with the cumulative risk of hepatocellular carcinoma recurrence after liver transplantation is shown in **Figure 3**. The study population was stratified by the number of risk factors, which included absence of CMV reactivation, size of the main nodule at explant, higher MELD score and microvascular invasion. The sum of the predictive clinical factors had an incremental effect on the risk of HCC recurrence (HR = 3.07, p < 0.001) (**Figure 3**). Adding one factor to the absence of CMVr had a modest effect on HCC recurrence rate (HR = 1.4, p = 0.361), but the addition of 2 or 3 factors resulted in a significant increase in the risk of HCC recurrence (HR 4.51, p < 0.001 and HR 21.5, p < 0.001, respectively).

A total of 237 patients (30.7%) died, and the main cause of death was HCC recurrence (n = 84), 41%) followed by *de novo* tumors (n =

50, 24%) (**Table 5**). Variables associated with survival in the univariate analysis were donor age, recipient age, sex, alcohol etiology, Milan criteria, Retreat score, AFP levels at listing and at LT, tumor burden, microvascular invasion, tumor differentiation grade and CMVr (**Supplementary Table S2**). In the multivariable analysis, increased AFP at LT, and diameter of the main nodule at explant were associated with reduced survival, while CMVr reduced the risk of death by 33%, (HR 0.67, P = 0.049) (**Table 6**).

## DISCUSSION

Although HCC recurrence accounts for a small percentage of patients, it significantly impacts survival. Identification of specific factors before and/or after LT that can be modified to enhance prognosis is an active area of research [9–11]. This multicenter retrospective observational Spanish study, involving a large number of patients, reveals that CMV reactivation is associated with a lower rate of HCC recurrence after LT. Other well-described factors such as microvascular invasion and nodule size at explant, were also significantly associated with recurrence in our study [23, 24]. Of note, treatment of CMVr did not influence HCC recurrence. In addition, CMVr was also associated with improved overall survival further strengthening the association.

Pathophysiological explanations for the role of CMV in modulating the tumor microenvironment have been hypothesized. A potential oncolytic effect of CMV inducing remission, ablation, or tumor death has been postulated through different mechanisms such as stimulating cytokine inhibition, interfering with tumor extravasation, or tumor vascularization taking a multimodal approach. In mouse models of melanoma and HCC, CMV infection showed clearance of the established tumor [18, 25, 26]. Specifically, in a murine model of HCC cells (HepG2), Kumar et al. demonstrated that CMV infection of the HCC cells resulted in the absence of tumor or limited tumor growth by promoting cancer cell apoptosis through the activation of caspases [26]. Other studies have shown that CMV reactivation induces tumor cell apoptosis directly or by stimulating cytokines and antitumor immune responses [19]. Cross-reactivity between CMV-stimulated innate and adaptive immune responses and cancer cells has also been reported. Natural killer cells and Vδ2 $^{neg}$ϒδ T cells have been reported to expand when stimulated by CMV reactivation, with the subsequent ability to kill both CMV-infected cells and carcinoma cells *in vitro* due to the shared reactivity of the Vδ2 $^{neg}$ϒδ T cells against CMV-infected cells and tumor intestinal epithelial cells [16, 27]. Additionally, the role of CMV-specific CD8 T cell responses in targeting tumors with CMV epitope-conjugated viral antigens presented by HLA-I has been described [28].

In oncological clinical scenarios, the protective effect of CMV reactivation has also been described. Takenaka et al. showed a beneficial effect in allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia. CMV reactivation decreased the risk of relapse (20% vs. 26.4%, p: 0.027). This anti-leukemic effect was attributed to the CMV-driven expansion of donor-derived memory-like NKG2C + NK and Vδ2 negϒδT cells, which demonstrated an ability to kill both infected CMV cells and leukemic cells due to shared reactivity [29]. This effect was also observed in patients with acute lymphoblastic leukemia (HR 0.81; 95%CI 0.66–0.92, p: 0.045) [30]. Rahbar A et al. also described an inverse association between multiforme glioblastoma and CMV infection [31], and Couzi et al. described a reduction in cancer risk in kidney transplants linked to an increase in Vδ2negϒδT[17]. More recently, a potential protective effect of CMV reactivation on HCC and LT was described by Hsu et al. In that retrospective study, CMV reactivation, as measured by pp65 antigenemia, was associated with lower HCC recurrence after LT [14]. A significantly superior 5-year recurrence-free survival rate was observed in CMV antigenemia-positive patients compared to those who were negative (89% vs. 79%, p < 0.005). Our study shows that CMV reactivation is independently associated with reduced HCC recurrence, even after adjusting for other clinical and statistically significant factors. In addition, CMV reactivation also showed a trending protective effect on survival in association with other known factors such as AFP at LT and nodule size at explant. Hypothetically, CMVr could trigger a cross-reactive immunological response that might simultaneously reduce HCC recurrence. Patients who died due to HCC recurrence as opposed to those who died due to other causes, had lower rates of CMV reactivation (23% vs. 31.2%). Of note, cumulative exposure to tacrolimus was comparable in patients with and without CMVr thus eliminating the potential confounding effect of immunosuppression on the relationship between CMVr and HCC recurrence.

In our study, more than a third of the entire cohort suffered CMV reactivation or primary infection after a median of 41.5 days after LT, with need of antiviral treatment in 66% of the patients, and only 5.6% of the patients developed CMV disease. In fact, CMV DNA levels at first CMV reactivation were relatively low (median: 758(IQR: 405–2,340). Some studies have reported that low CMV levels without need for immediate treatment is protective by increasing the number and the activity of CMV-antigen-specific T cells [32], thereby hypothesizing a potential oncological protective effect by the above-described mechanisms without a deleterious effect on CMV control. In line with these results, in a recent *post hoc* analysis of a randomized controlled trial in D+/R-recipients that compared preemptive prophylaxis versus antiviral therapy, CMV DNAemia at six- and 12-months post-transplant were significantly higher in the group treated with universal prophylaxis as opposed to the preemptive approach and the higher DNAemia was also associated with increased mortality, suggesting a possible protective role for pre-emptive therapy secondary to an improved CMV-specific immunity while on preemptive versus prophylaxis [33]. Low-level CMV replication early after liver transplantation may enhance CMV-specific immunity, contribute to DNAemia control, and reduce inflammatory alloimmune responses and immunosenescence, which could ultimately impact survival, findings that are consistent with those observed in our study. Despite the fact that pre-emptive therapy is logistically more complex, practical real-world implementations have been recently advised [34]. Some studies have even postulated that universal prophylaxis could be harmful by delaying immune reconstitution against CMV [35]. However, facilitating CMV reactivation to diminish HCC recurrence may not be advisable until the underlying mechanisms are fully understood.

The use of immunotherapy in the LT arena when HCC recurs is still limited due to an enhanced risk of rejection [36, 37]. If the

association between CMV reactivation and HCC recurrence is confirmed in larger, prospective multicenter studies, a potential use of oncolytic CMV therapies such as vaccine vectors, or a controlled preemptive approach could become a real strategy, at least for patients with a high risk of recurrence [37, 38].

As with other studies, additional known risk factors predicted HCC recurrence [1, 2, 5, 23, 39–41], including microvascular invasion and tumor size at explant. We also found that the use of DCD donors or the MELD score impacted HCC recurrence There is controversy regarding DCD and HCC recurrence [42–45]. A double ischemia impact, that could exacerbate liver tumor growth and favor metastasis through marked activation of cell adhesion, invasion, and angiogenesis pathways [42], could explain this association. However, we acknowledge caution is necessary when assessing this association given the small number of DCDs and a temporal bias (learning curve) [42–44]. Regarding the association between low MELD and lower HCC recurrence, it is possibly related to longer waiting time in this setting which provides an opportunity to better select patients with less aggressive tumor biology [46, 47].

Our study has some limitations. First, the retrospective approach and the multicenter participation have introduced heterogeneity related to CMV monitoring, diagnosis, including varying CMV detection methods and management. We made however a significant effort to ensure that the centers participating in this study followed a similar approach regarding CMV management, in accordance with international consensus [12]. Second, although HCC surveillance was done by each center practice, it is likely that it was not misdiagnosed due to the clinical relevance of HCC recurrence and close follow-up of the LT patients. In addition, information regarding immunosuppression including tacrolimus cumulative exposure was only available in a subgroup of patients and could not be controlled in the multivariable analysis.

In conclusion, CMVr reduces the risk of tumor recurrence in patients with HCC undergoing LT, particularly among patients showing other well-known risk factors such as increased tumor burden, microvascular invasion, or increased AFP at transplant. The most plausible mechanism involves immune-regulation pathways triggered by CMV although future studies are required to fully unravel the pathogenesis.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The study protocol was approved by the Ethics Committee of Clinical Research of La Fe Universitari and Politécnic Hospital (ref number: 2022-601-1) and was conducted in accordance with the Helsinki Declaration of 1975 at La Fe Hospital. Given the retrospective nature of the data, the ethical committee waived the need of informed 114 consent in the other participant hospitals.

## AUTHOR CONTRIBUTIONS

VA, SRM, IC, MR, JZ-O, MG-B, EF-V, CD, NB, AG, AS-M, SP, JR-E, JH, SL, AC-L, FN, RG-G collected data. VA, SRM, MB and MR-P wrote the manuscript. IC, AC-G, LM-A, CD, JH, JR-E and AC-L reviewed the manuscript.

## FUNDING

The author(s) declare that financial support was received for the research and/or publication of this article. This study was supported by competitive grants from the Instituto de Salud Carlos III (grant numbers: PI13/01770 and PI18/01759), and co-financed by the European Regional Development Fund "A way to achieve Europe." AC-G and MB were also supported by the Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd) (https://www.ciberehd.org/), which is funded by the Instituto de Salud Carlos III (co-financed by the European Regional Development Fund). VA has received a grant from the AEEH (Asociación Española para el Estudio del Hígado, Spain): Beca de Intensificación. AC-G received a postdoctoral Fellowship from CiberEHD and MB was supported by competitive grants from the Instituto de Salud Carlos III (grant numbers PI23/00088 and INT24/00021) and by Generalitat Valenciana (grant numbers AICO/2021/035 and CIPROM/2023/16). Victoria Aguilera received a grant from the AEEH "Beca de intensificación para investigadores" in 2021. LM-A was supported by the Instituto de Salud Carlos III (grant numbers FI20/00033 and MV22/00053).

## CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## GENERATIVE AI STATEMENT

The authors declare that no Generative AI was used in the creation of this manuscript.

## ACKNOWLEDGMENTS

We thank JLG for the work done in the statistical analysis.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.14553/full#supplementary-material

**SUPPLEMENTARY FIGURE S1 |** Hepatocellular Carcinoma Free Survival.

**SUPPLEMENTARY FIGURE S2 |** Survival according to hepatocellular carcinoma recurrence.

## REFERENCES


1. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver Transplantation for the Treatment of Small Hepatocellular Carcinomas in Patients with Cirrhosis. *N Engl J Med* (1996) 334(11):693–9. doi:10.1056/NEJM199603143341104
2. Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting Survival after Liver Transplantation in Patients with Hepatocellular Carcinoma beyond the Milan Criteria: A Retrospective, Exploratory Analysis. *Lancet Oncol* (2009) 10(1):35–43. doi:10.1016/S1470-2045(08)70284-5
3. Filgueira NA. Hepatocellular Carcinoma Recurrence after Liver Transplantation: Risk Factors, Screening and Clinical Presentation. *World J Hepatol* (2019) 11(3):261–72. doi:10.4254/wjh.v11.i3.261
4. Silva M, Moya A, Berenguer M, Sanjuan F, López-Andujar R, Pareja E, et al. Expanded Criteria for Liver Transplantation in Patients with Cirrhosis and Hepatocellular Carcinoma. *Liver Transpl* (2008) 14(10):1449–60. doi:10.1002/lt.21576
5. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver Transplantation for Hepatocellular Carcinoma: Expansion of the Tumor Size Limits Does Not Adversely Impact Survival. *Hepatology* (2001) 33(6):1394–403. doi:10.1053/jhep.2001.24563
6. Mehta N, Heimbach J, Harnois DM, Sapisochin G, Dodge JL, Lee D, et al. Validation of a Risk Estimation of Tumor Recurrence after Transplant (RETREAT) Score for Hepatocellular Carcinoma Recurrence after Liver Transplant. *JAMA Oncol* (2017) 3(4):493–500. doi:10.1001/jamaoncol.2016.5116
7. Aggarwal A, Te HS, Verna EC, Desai AP. A National Survey of Hepatocellular Carcinoma Surveillance Practices Following Liver Transplantation. *Transpl Direct* (2020) 7(1):E638. doi:10.1097/TXD.0000000000001086
8. Rodríguez-Perálvarez M, Tsochatzis E, Naveas MC, Pieri G, García-Caparrós C, O'Beirne J, et al. Reduced Exposure to Calcineurin Inhibitors Early after Liver Transplantation Prevents Recurrence of Hepatocellular Carcinoma. *J Hepatol* (2013) 59(6):1193–9. doi:10.1016/j.jhep.2013.07.012
9. Abrahamsson J, Sternby Eilard M, Rizell M, Bennett W, Åberg F. Reduced Calcineurin Inhibitor Exposure with Antibody Induction and Recurrent Hepatocellular Carcinoma after Liver Transplantation. *Scand J Gastroenterol* (2022) 57(3):325–32. doi:10.1080/00365521.2021.2010799
10. Rodríguez-Perálvarez M, De La Mata M, Burroughs AK. Liver Transplantation: Immunosuppression and Oncology. *Curr Opin Organ Transpl* (2014) 19(3):253–60. doi:10.1097/MOT.0000000000000069
11. Toso C, Merani S, Bigam DL, Shapiro AMJ, Kneteman NM. Sirolimus-based Immunosuppression Is Associated with Increased Survival after Liver Transplantation for Hepatocellular Carcinoma. *Hepatology* (2010) 51(4):1237–43. doi:10.1002/hep.23437
12. Kotton CN, Kumar D, Caliendo AM, Huprikar S, Chou S, Danziger-Isakov L, et al. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-Organ Transplantation. *Transplantation* (2018) 102:900–31. doi:10.1097/TP.0000000000002191
13. Razonable RR, Humar A. Cytomegalovirus in Solid Organ Transplant Recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transpl* (2019) 33(9):e13512. doi:10.1111/ctr.13512
14. Hsu PJ, Hung HC, Lee JC, Wang YC, Cheng CH, Wu TH, et al. Human Cytomegalovirus Is Associated with Lower Hcc Recurrence in Liver Transplant Patients. *Curr Oncol* (2021) 28(6):4281–90. doi:10.3390/curroncol28060364
15. Michaelis M, Doerr HW, Cinatl J. The Story of Human Cytomegalovirus and Cancer: Increasing Evidence and Open Questions. *Neoplasia* (2009) 11(1):1–9. doi:10.1593/neo.81178
16. Litjens NHR, van der Wagen L, Kuball J, Kwekkeboom J. Potential Beneficial Effects of Cytomegalovirus Infection after Transplantation. *Front Immunol* (2018) 9(MAR):389. doi:10.3389/fimmu.2018.00389
17. Couzi L, Levaillant Y, Jamai A, Pitard V, Lassalle R, Martin K, et al. Cytomegalovirus-induced γδ T Cells Associate with Reduced Cancer Risk after Kidney Transplantation. *J Am Soc Nephrol* (2010) 21(1):181–8. doi:10.1681/ASN.2008101072
18. Erkes DA, Wilski NA, Snyder CM. Intratumoral Infection by CMV May Change the Tumor Environment by Directly Interacting with Tumor-Associated Macrophages to Promote Cancer Immunity. *Hum Vaccin Immunother.* (2017) 13(8):1778–85. doi:10.1080/21645515.2017.1331795
19. El Baba R, Herbein G. Immune Landscape of CMV Infection in Cancer Patients: From "Canonical" Diseases toward Virus-Elicited Oncomodulation. *Front Immunol* (2021) 12(September):730765–17. doi:10.3389/fimmu.2021.730765
20. Quentin L, Aziz Khan K, Di Martino V, Herbein G. Cytomegalovirus and Tumors: Two Players for One Goal-Immune Escape. *Open Virol J* (2011) 5(1):60–9. doi:10.2174/1874357901105010060
21. Rodríguez-Perálvarez M, Gómez-Bravo MÁ, Sánchez-Antolín G, De La Rosa G, Bilbao I, Colmenero J, et al. Expanding Indications of Liver Transplantation in Spain: Consensus Statement and Recommendations by the Spanish Society of Liver Transplantation. *Transplantation* (2021) 105(3):602–7. doi:10.1097/TP.0000000000003281
22. Ljungman P, Chemaly R, Khawaya F, Alain S, Avery R, Badshah C, et al. Consensus Definitions of Cytomegalovirus (CMV) Infection and Disease in Transplant Patients Including Resistant and Refractory CMV for Use in Clinical Trials: 2024 Update from the Transplant Associated Virus Infections Forum. *Clin Infect Dis* (2024) 79(3):787–94. doi:10.1093/cid/ciae321
23. Mazzaferro V, Sposito C, Zhou J, Pinna AD, De Carlis L, Fan J, et al. Metroticket 2.0 Model for Analysis of Competing Risks of Death after Liver Transplantation for Hepatocellular Carcinoma. *Gastroenterology* (2018) 154(1):128–39. doi:10.1053/j.gastro.2017.09.025
24. Jonas S, Bechstein WO, Steinmüller T, Herrmann M, Radke C, Berg T, et al. Vascular Invasion and Histopathologic Grading Determine Outcome after Liver Transplantation for Hepatocellular Carcinoma in Cirrhosis. *Hepatology* (2001) 33(5):1080–6. doi:10.1053/jhep.2001.23561
25. Erkes DA, Xu G, Daskalakis C, Zurbach KA, Wilski NA, Moghbeli T, et al. Intratumoral Infection with Murine Cytomegalovirus Synergizes with PD-L1 Blockade to Clear Melanoma Lesions and Induce Long-Term Immunity. *Mol Ther* (2016) 24(8):1444–55. doi:10.1038/mt.2016.121
26. Kumar A, Coquard L, Pasquereau S, Russo L, Valmary-Degano S, Borg C, et al. Tumor Control by Human Cytomegalovirus in a Murine Model of Hepatocellular Carcinoma. *Mol Ther - Oncolytics* (2016) 3(January):16012–0. doi:10.1038/mto.2016.12
27. Halary F, Pitard V, Dlubek D, Krysiek R, de la Salle H, Merville P, et al. Shared Reactivity of Vδ2neg γδ T Cells against Cytomegalovirus-Infected Cells and Tumor Intestinal Epithelial Cells. *J Exp Med* (2005) 201(10):1567–78. doi:10.1084/jem.20041851
28. Millar DG, Ramjiawan RR, Kawaguchi K, Gupta N, Chen J, Zhang S, et al. Antibody-mediated Delivery of Viral Epitopes to Tumors Harnesses CMV-specific T Cells for Cancer Therapy. *Nat Biotechnol* (2020) 38(4):420–5. doi:10.1038/s41587-019-0404-8
29. Takenaka K, Nishida T, Asano-Mori Y, Oshima K, Ohashi K, Mori T, et al. Cytomegalovirus Reactivation after Allogeneic Hematopoietic Stem Cell Transplantation Is Associated with a Reduced Risk of Relapse in Patients with Acute Myeloid Leukemia Who Survived to Day 100 after Transplantation: The Japan Society for Hematopoietic C. *Biol Blood Marrow Transpl* (2015) 21(11):2008–16. doi:10.1016/j.bbmt.2015.07.019
30. Akahoshi Y, Nakasone H, Takenaka K, Yamasaki S, Nakamura M, Doki N, et al. CMV Reactivation after Allogeneic HCT Is Associated with a Reduced Risk of Relapse in Acute Lymphoblastic Leukemia. *Blood Adv* (2023) 7(12):2699–708. doi:10.1182/bloodadvances.2022009376
31. Rahbar A, Stragliotto G, Orrego A, Peredo I, Taher C, Willems J, et al. Low Levels of Human Cytomegalovirus Infection in Glioblastoma Multiforme Associates with Patient Survival; -a Case-Control Study. *Herpesviridae* (2012) 3(1):3–7. doi:10.1186/2042-4280-3-3
32. Chen GL, Wallace PK, Zhang Y, Tario JD, Przespolewski AC, Becker J, et al. Low-Level Cytomegalovirus Antigenemia Promotes Protective Cytomegalovirus Antigen-specific T Cells after Allogeneic Hematopoietic Cell Transplantation. *Biol Blood Marrow Transpl* (2020) 26(11):2147–54. doi:10.1016/j.bbmt.2020.07.024
33. Kumar L, Dasgupta S, Murray-Krezan C, Singh N, Rakita RM, Fisher CE, et al. Association of Cytomegalovirus (CMV) DNAemia with Long-Term Mortality in a Randomized Trial of Preemptive Therapy and Antiviral Prophylaxis for

Prevention of CMV Disease in High-Risk Donor Seropositive, Recipient Seronegative Liver Transplant Recipients. *Clin Infect Dis* (2024) 78(3): 719–22. doi:10.1093/cid/ciad643

34. Heldman MR, Dunn B, Clemens E, Henderson M, Fisher CE, Rakita RM, et al. A Practical Guide to Real-World Implementation of Pre-emptive Therapy for Cytomegalovirus Disease Prevention in High-Risk Seronegative Liver Transplant Recipients with Seropositive Donors. *Transpl Infect Dis* (2024) 26(3):e14229. doi:10.1111/tid.14229
35. Suessmuth Y, Mukherjee R, Watkins B, Koura DT, Finstermeier K, Desmarais C, et al. CMV Reactivation Drives Posttransplant T-Cell Reconstitution and Results in Defects in the Underlying TCRβ Repertoire. *Blood* (2015) 125(25): 3835–50. doi:10.1182/blood-2015-03-631853
36. Rimassa L, Finn RS, Sangro B. Combination Immunotherapy for Hepatocellular Carcinoma. *J Hepatol* (2023) 79(2):506–15. doi:10.1016/j.jhep.2023.03.003
37. Grainne O'K, Parissa T, Laia A, Kulik LSG. Integrating Immune Check Inhibitors in Liver Transplantation for Hepatocellular Carcinoma: The Right Time and the Right Patient. *Am J Transpl* (2024) 18(24):00379–4. doi:10.1016/j.ajt.2024.06.006
38. Šustić M, Brdovčak MC, Krmpotić A, Jonjić S. CD8 T Cell Vaccines and a Cytomegalovirus-Based Vector Approach. *Life* (2021) 11(10):1097. doi:10.3390/life11101097
39. Iwatsuki S, Starzl TE, Sheahan DG, Yokoyama I, Demetris AJ, Todo S, et al. Hepatic Resection versus Transplantation for Hepatocellular Carcinoma. *Ann Surg* (1991) 214(3):221–8. doi:10.1097/00000658-199109000-00005
40. Zimmerman MA, Ghobrial RM, Tong MJ, Hiatt JR, Cameron AM, Hong J, et al. Recurrence of Hepatocellular Carcinoma Following Liver Transplantation: A Review of Preoperative and Postoperative Prognostic Indicators. *Arch Surg* (2008) 143(2):182–8. doi:10.1001/archsurg.2007.39
41. Löhe F, Angele MK, Gerbes AL, Löhrs U, Jauch KW, Schauer RJ. Tumour Size Is an Important Predictor for the Outcome after Liver Transplantation for Hepatocellular Carcinoma. *Eur J Surg Oncol* (2005) 31(9):994–9. doi:10.1016/j.ejso.2005.06.003
42. Croome KP, Wall W, Chandok N, Beck G, Marotta P, Hernandez-Alejandro R. Inferior Survival in Liver Transplant Recipients with Hepatocellular Carcinoma Receiving Donation after Cardiac Death Liver Allografts. *Liver Transpl* (2013) 19(11):1214–23. doi:10.1002/lt.23715
43. Croome KP, Lee DD, Burns JM, Musto K, Paz D, Nguyen JH, et al. The Use of Donation after Cardiac Death Allografts Does Not Increase Recurrence of Hepatocellular Carcinoma. *Am J Transpl* (2015) 15(10):2704–11. doi:10.1111/ajt.13306
44. Vagefi PA, Dodge JL, Yao FY, Roberts JP. Potential Role of the Donor in Hepatocellular Carcinoma Recurrence after Liver Transplantation. *Liver Transpl* (2015) 21(2):187–94. doi:10.1002/lt.24042
45. Silverstein J, Roll G, Dodge JL, Grab JD, Yao FY, Mehta N. Donation after Circulatory Death Is Associated with Similar Posttransplant Survival in All but the Highest-Risk Hepatocellular Carcinoma Patients. *Liver Transpl* (2020) 26(9):1100–11. doi:10.1002/lt.25819
46. Guerrini GP, Pinelli D, Marini E, Corno V, Guizzetti M, Zambelli M, et al. Value of HCC-MELD Score in Patients with Hepatocellular Carcinoma Undergoing Liver Transplantation. *Prog Transpl* (2018) 28(1):63–9. doi:10.1177/1526924817746686
47. Mehta N, Dodge JL, Hirose R, Roberts JP, Yao FY. Predictors of Low Risk for Dropout from the Liver Transplant Waiting List for Hepatocellular Carcinoma in Long Wait Time Regions: Implications for Organ Allocation. *Am J Transpl* (2019) 19(8):2210–8. doi:10.1111/ajt.15353

ESOT | Transplant International

GUIDELINES
published: 26 June 2025
doi: 10.3389/ti.2025.14596

# Optimizing the Use of Deceased Donor Kidneys at Risk of Discard: A Clinical Practice Guideline

*Joanna C. Dionne[1,2,3], Patricia Campbell[4], Héloïse Cardinal[5,6], Tatiana Giannidis[1], Aviva Goldberg[7], S. Joseph Kim[8,9], Greg Knoll[10], Michel Pâquet[6], Christina Parsons[11], Yuhong Yuan[3] and Rahul Mainra[12]**

[1]Department of Medicine, McMaster University, Hamilton, ON, Canada, [2]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada, [3]Division of Gastroenterology, McMaster University, Hamilton, ON, Canada, [4]Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, AB, Canada, [5]Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada, [6]Division of Nephrology, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada, [7]Department of Pediatrics and Child Health, University of Manitoba Max Rady College of Medicine, Winnipeg, MB, Canada, [8]Division of Nephrology, Department of Medicine, University of Toronto, Toronto, ON, Canada, [9]Ajmera Transplant Centre, University Health Network, Toronto, ON, Canada, [10]Division of Nephrology, Department of Medicine, University of Ottawa and the Ottawa Hospital Research Institute, Ottawa, ON, Canada, [11]Canadian Blood Services, Ottawa, ON, Canada, [12]Division of Nephrology, Department of Medicine, University of Saskatchewan, Saskatoon, SK, Canada

Underutilization of deceased donor organs has worsened the gap in the number of kidneys available for transplantation. The purpose of this clinical practice guideline is to provide recommendations on the utilization of donor kidneys at risk of discard. Six conditional recommendations were made all with very low certainty of evidence: 1) We suggest utilizing extended criteria donor (ECD) kidneys for transplantation rather than remaining on the wait list and continuing with dialysis; 2) We suggest utilizing kidneys from ECD versus non-ECD in selected transplant candidates; 3) We suggest that organs from older kidney donors can be used in selected transplant candidates who may derive benefit from them; 4) We suggest that kidneys from deceased donors with acute kidney injury can be used for transplantation based on clinician assessment and donor factors; 5) We suggest that donor kidneys with acute kidney injury from either ECD or non-ECD be used for kidney transplantation; 6) We suggest using kidneys from donors after death determination by circulatory criteria for transplantation. This clinical practice guideline provides evidence for the use of deceased donor kidneys that are at risk of discard and may improve the shared decision-making between transplant physicians and wait-listed patients.

**Keywords: kidney transplant, decision making, utilization, organ discard, clinical practice guideline**

OPEN ACCESS

***Correspondence**
Rahul Mainra,
rahul.mainra@usask.ca

***Received:*** *09 March 2025*
***Accepted:*** *11 June 2025*
***Published:*** *26 June 2025*

***Citation:***
*Dionne JC, Campbell P, Cardinal H, Giannidis T, Goldberg A, Kim SJ, Knoll G, Pâquet M, Parsons C, Yuan Y and Mainra R (2025) Optimizing the Use of Deceased Donor Kidneys at Risk of Discard: A Clinical Practice Guideline. Transpl. Int. 38:14596. doi: 10.3389/ti.2025.14596*

**Abbreviations:** AKI, acute kidney injury; AKIN, acute kidney injury network; CI, confidence interval; DCC, death determination by circulatory criteria; DCD, donation following circulatory death; DGF, delayed graft function; DNC, death determination by neurological criteria; ECD, extended criteria donor; eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; EtD, evidence to decision; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; HMP, hypothermic machine perfusion; KDPI, kidney donor profile index; KDQS, kidney donor quality score; KDRI, kidney donor risk index; NDD, neurological death determination; ODO, organ donation organizations; OR, odds ratio; MD, mean difference; PICO, Population, Intervention, Comparison and Outcome; RCTs, randomized controlled trials; RR, relative risk; SC, steering committee.

# INTRODUCTION

Kidney transplantation remains the preferred treatment for patients with end stage kidney disease (ESKD), leading to improved life expectancy and quality of life when compared to remaining on dialysis [1, 2]. Unfortunately, there is a gap in the supply and demand for transplantable organs. Exacerbating this gap is the underutilization of deceased donor kidneys, reported to be as high as 20% of donated kidneys [3]. Meanwhile, patients die while awaiting this lifesaving gift. Despite the availability of compatible deceased donor kidneys, physicians may decline offers on behalf of their patients with the main concern being around kidney quality. These decisions lead to longer wait times, waitlist removal and sometimes death for patients awaiting transplantation [4].

In 2019, Canadian Blood Services convened a Steering Committee of transplant nephrologists, surgeons, and representatives from organ donation organizations (ODOs) to discuss the concern of potential organ (kidney) underutilization in Canada. One main priority identified by this group was to examine the current literature and perform a systematic review to guide evidence-based decision-making at the time of a deceased organ donor offer.

Kidneys at risk of underutilization are generally those with acute kidney injury (AKI), from older donor age, extended criteria donor (ECD) or with high Kidney Donor Risk Index (KDRI). Extended criteria donors are deceased donors aged 60 and above or 50–59 with at least 2 of the following characteristics: history of hypertension, stroke as cause of death or terminal serum creatinine above 132 μmol/L. In a seminal 2002 publication, transplantations of kidneys from ECD were associated with a risk (hazard ratio) of graft loss defined as death, return to dialysis or re-transplantation above 1.7 [5]. The KDRI is a score including donor variables which has been derived from a large retrospective cohort study including all first kidney transplant recipients in the US between 1995 and 2005 [6]. This score is associated with the risk of graft loss and can be expressed as the kidney donor profile index (KDPI), which is the percentile of a donor's KDRI in the distribution of all donor KDRIs of a reference year. KDPI values are hence comprised between 0% and 100%, with higher values indicating a higher risk of graft loss.

Therefore, we present recommendations on common clinical questions that physicians face when making decisions to accept or decline kidneys that are at risk of discard.

# MATERIALS AND METHODS

## The Steering Committee

A steering committee (SC) was formed to address optimizing the use of extended criteria deceased organ donors in kidney transplantation. The SC included experts in paediatric and adult transplant nephrology, surgery, ethics and guideline methodology.

## Sponsorship

This guideline was supported and endorsed by Canadian Blood Services.

## Question Development

Priority questions were developed in PICO (Population, Intervention, Comparison and Outcome) format to address evidence for use of extended criteria donor kidneys including, age, presence of acute kidney injury, and donation after death determination by circulatory criteria (DCC, also known as DCD or donation following circulatory death) compared to donation after death determination by neurologic criteria (DNC, also known as NDD or neurological death determination). Questions were developed with the steering committee via teleconferences. Outcomes were then identified and voted upon using an anonymous online voting website. Outcomes were rated as critical [7–9], important [4–6], or limited important [1–3] [7]. Each committee member voted on the outcomes using a modified Delphi approach. Critical outcomes included: mortality, graft survival, graft failure (patient death and graft failure requiring re-transplant or return to dialysis), and quality of life. Important outcomes included: rejection, readmission to hospital, DGF, estimated glomerular filtration rate (eGFR) at 1 year and 3 years, hospital length of stay, infection risk, and malignancy risk.

## Search Strategy and Screening

A search strategy was developed by a medical librarian. We searched MEDLINE, EMBASE, and Cochrane from inception until April 2024. The search strategy also underwent peer review from a second medical librarian. Search terms included: kidney transplant, renal transplant, extended criteria, ECD, acute kidney failure, acute kidney injury, kidney donor, age, infection, neurologic determination of death and donation after cardiac death. The results from the search were uploaded into COVIDENCE [8]. Four reviewers (JCD, YY, CP, TG) screened results for clinical trials, observational studies, and systematic reviews for relevant citations. Title, abstract and full text screening were done in duplicate (JCD, YY, TG). Any disagreement about inclusion at the full text stage was resolved through consensus.

## Data Extraction and Risk of Bias Assessment

Systematic reviews were conducted for each of the PICO questions. Using a standardised pilot data extraction form, the methodology team (JCD, YY, TG) performed data extraction and risk of bias assessment, which in turn were verified by a second reviewer. For clinical trials, the Cochrane Risk of Bias tool 2.0 [9] was used. For observational studies, the Newcastle-Ottawa Risk of Bias [10] assessment tool was employed.

## Data Analysis

For PICO questions that had sufficient data for analysis, a meta-analysis was performed using RevMan version 5.4 [11]. For all outcomes, we calculated fixed and random effects estimates. For PICO questions with less than five studies, we utilised a fixed effects model. For most PICO questions, a random effects model was used. For dichotomous outcomes, we reported a relative risk (RR) or odds ratios (OR). For continuous variables, a mean

difference (MD) was used. All effect size measures are reported with 95% confidence intervals (CI). For PICO questions where there was insufficient data to allow for meta-analysis, the evidence was synthesised narratively.

The certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) process [12]. In accordance with GRADE, we rated the certainty of evidence for each outcome as high, moderate, low or very low [13]. We rated the certainty of evidence for each outcome as high if data were from randomized controlled trials (RCTs) and low if data were from observational studies. The data were rated down 1 or 2 levels if the results were at serious, or very serious risk of bias, if there were serious inconsistencies across studies, if the evidence was indirect, or if there were concerns regarding publication bias. Data were rated up in observational studies if there were large effect sizes or dose-response gradients.

## Evidence Summary and Recommendation Formulation

Evidence summaries for each of the PICO questions (**Supplementary Material S1**) were developed by the methodologists (JCD, YY) including information on the methodology of each study, population, interventions, pooled estimates for each outcome, and overall rating of the certainty of evidence. Evidence to decision (EtD) frameworks (**Supplementary Material S2**) were completed by the SC to draft recommendations considering certainty of the evidence, balance of desirable and undesirable effects, resources required, feasibility, acceptability, and equity. Recommendations were considered approved if at least 80% of the committee agreed with the statement.

# GUIDELINES

## Part 1: The Evidence for the Use of Extended Criteria Donor Kidneys

### Recommendation 1: We Suggest Utilizing ECD Kidneys for Transplantation Rather than Remaining on the Wait List and Continuing with Dialysis (Conditional Recommendation, Very Low Certainty of Evidence)

*Evidence Summary*

Transplantation with kidneys from ECD are associated with a lower risk of mortality (pooled RR 0.88, 95% CI 0.84, 0.92) [14, 15] when compared with remaining on dialysis.

*Justification*

Although kidneys from ECD are associated with a moderately higher risk of graft loss than those from non-ECD, the decision to accept or decline such kidneys must be made by comparing the benefits and risks of transplantation versus remaining on dialysis waiting for a better offer. Our systematic review of the literature and meta-analysis show that transplantation with kidneys from ECD is associated with lower mortality than remaining on dialysis (pooled RR 0.88, 95% CI 0.84, 0.92) [14, 15]. In the largest study supporting this result, the survival benefit was seen in recipients aged more than 40, especially in areas with long wait times [14].

Due to heterogeneity in KDPI categories and outcomes in relevant studies, we could not perform a meta-analysis of the data expressing transplant outcomes according to donor KDPI. Nevertheless, we identified one large retrospective cohort study which provided results similar to those presented in our systematic review for ECD. This study showed that accepting a kidney from a donor with high KDPI was associated with a survival benefit compared with remaining on dialysis [16].

The quality of evidence is very low as a result of the high risk of bias given the retrospective nature of the studies and the inconsistencies in results between studies.

*Implementation*

Kidneys from ECD are already utilized in clinical practice. Implementation considerations include identifying ways to operationalize wider utilization, promote transplant physician and candidate education as to the survival benefit of transplantation with kidneys from ECD to improve shared decision-making when kidneys from ECD are offered.

*Research Priorities*

Impact of transplantation with kidneys from ECD on cost effectiveness of the procedure and quality of life of kidney transplant candidates and recipients are needed. A provider preferences survey including conjoint analysis with transplant recipients could help determine the elements driving decision-making for accepting or declining kidneys from ECD. Better data are needed to determine which patients are the best candidates to receive ECD kidneys and efforts should be made to implement more consistent practices across the country.

### Recommendation 2: We Suggest Utilizing Kidneys from ECD Versus Non-ECD in Selected Transplant Candidates (Conditional Recommendation, Very Low Certainty of Evidence)

*Evidence Summary*

Transplantation with kidneys from ECD versus non-ECD is associated with a moderately increased risk of mortality [14, 17–28], graft loss, DGF, and a small decrease in death-censored graft survival. There were no differences in the incidence of acute rejection, and hospital readmissions in transplantations performed with kidneys from ECD versus non-ECD.

*Justification*

Our systematic review of the literature and meta-analysis indicate that the risk of mortality (pooled RR 1.5, 95% CI 1.25, 1.80) [17–19, 21–26, 28–36], graft loss (pooled RR 1.63, 95% CI 1.32, 2.02) [18, 27, 28, 35, 37–39] and DGF (pooled RR 1.23, 95% CI 1.04, 1.46 [17–19, 21–26, 31, 35, 37–70] were moderately increased when transplantation was performed with kidneys from ECD versus non-ECD, while death-censored graft survival was only mildly improved when non-ECD were transplanted as compared with ECD (pooled RR 0.95, 95% CI 0.90, 0.99) [14, 26, 36, 42, 64–66, 71]. The risk of acute rejection (pooled RR 1.10, 95% CI 0.89, 1.37) [17–19, 21–24, 26, 31, 32, 35,

37–41, 45, 46, 48, 50, 52, 53, 55–57, 61, 63, 65, 66, 72–77] and hospital readmission (pooled RR 1.17, 95% CI 0.71, 1.92) [32, 37, 38, 62, 66, 67, 76] were not different when transplantation with kidneys from ECD was compared with transplantation with kidneys from non-ECD.

We performed a literature search to identify transplant outcomes by donor quality when the latter was expressed as the KDPI. Due to heterogeneity in KDPI cut-offs that define risk donor categories across studies, we were unable to perform a meta-analysis on the data. Nevertheless, the results of studies comparing transplantations with kidneys from donors with high versus low KDPI were similar to those comparing outcomes of transplantation in patients receiving ECD versus non-ECD. Transplantation with kidneys from donors with high KDPI reported a higher risk of graft loss and DGF compared with kidneys from donors with lower KDPI values.

The quality of the evidence was very low due to limitations in study design (observational studies only), the risk of selection and confounding biases due to differences in recipient characteristics among those who get offered kidneys from ECD, and double counting across studies using similar databases.

### *Implementation*

Kidneys from ECD are already utilized in clinical practice. Implementation considerations are similar to Recommendation 1, Part 1. Ultimately identifying patients that will benefit from accepting an ECD kidney transplant compared to remaining on dialysis is imperative in wider utilization.

### *Research Priorities*

Studies that address the barriers and facilitators that promote wider utilization should be performed, as well as studies that evaluate the impacts of using more ECD on cost-effectiveness and quality of life of transplant candidates and recipients. Research is also required to better understand which potential transplant candidates will benefit the most from these kidneys vs. remaining on dialysis.

## Recommendation 3: We Suggest that Organs from Older Kidney Donors Can be Used in Selected Transplant Candidates Who May Derive Benefit from them (Conditional Recommendation, Very Low Certainty of Evidence).

### *Evidence Summary*

The data supporting the recommendations were derived from non-randomised (i.e., observational) studies. The studies span the spectrum in scope, ranging from single centre reports to large national registry analyses. In addition, follow-up varied across studies from 1, 3, 5, to 10 years. Most studies dichotomized "younger" vs. "older" deceased donors as < 65 years vs. >/ = 65 years. It was acknowledged by the panel that age cut-offs used in these analyses are somewhat arbitrary, but 65 years of age seemed to be a widely adopted threshold for categorising the deceased donor population.

The pooled data showed that kidneys from younger (vs. older) deceased donors were generally associated with a higher relative likelihood of patient survival (RR 0.95, 95% CI: 0.93, 0.98) [21, 56, 78–97] and graft survival (RR 0.88, 95% CI: 0.86, 0.91) [21, 56, 78–80, 82–85, 87–89, 92, 98–113]. Furthermore, recipients of kidneys from older donors were more likely to experience DGF (RR 1.29, 95% CI: 1.12, 1.48) [78, 80–84, 86, 87, 89–92, 97, 98, 111, 113–124] and acute rejection (RR 1.18, 95% CI: 1.02, 1.37) [78, 82, 83, 90, 92, 96, 98, 99, 107, 115, 119, 122, 123, 125] when compared to recipients of kidneys from younger donors. Despite these differences, it was noted by the panel members that these differences were relatively small and other outcomes such as death-censored graft survival were comparable across the two groups (RR 0.97, 95% CI: 0.94, 1.00) [21, 78, 82, 84, 86, 87, 90–92, 94, 97, 117, 122].

The overall certainty of the evidence was very low given that the estimates were derived from comparisons in donor age groups with varying degrees of control for confounding and selection biases. Variation in the application of age cut-offs and the decision to dichotomize a continuous variable such as donor age to facilitate presentation of the results may have led to measurement bias.

### *Justification*

Although the comparison of recipient outcomes between kidney transplanted from younger vs. older donors favoured younger donors in various domains (including graft survival), it was highlighted by the panel members that the net benefit of using kidneys from older donors in appropriate recipient candidates may provide substantial benefit at a system level in light of their broad availability, the continued mismatch between supply and demand for organs, and the relatively small differences in recipient outcomes between kidney transplants from younger vs. older donors. It is notable that the certainty of the evidence is very low given the risk for bias in the outcome estimates from observational studies.

The included studies provided no information on the cost-effectiveness of different strategies for using younger vs. older donor kidneys nor did they explicitly address issues of equity. Given that kidneys from a wide spectrum of donor ages are already being used in clinical practice, the panel felt that developing strategies to optimise the use of older donor kidneys would be both acceptable and feasible.

### *Implementation*

The panel highlighted that donor age is a continuum and thus implementation of policies around the use of these kidneys should consider the impact of extremes of age on recipient outcomes. Other implementation considerations include defining the best approach to operationalizing the use of kidneys from a wider age spectrum, including the integration of shared decision-making frameworks that account of patient and provider preferences.

### *Research Priorities*

One main research priority is being able to identify which recipients will benefit from transplantation with older donor kidneys. Future studies should establish the quality of life of recipients receiving older vs. younger donor kidneys. Furthermore, it would be important to establish the cost-

effectiveness of strategy that expands the use of kidneys from older donors. Research on ways to modify and improve the function as well as long-term outcomes of older donor kidneys should be a priority. These studies may include interventions on donors and/or recipients as well as the rational application of biomarkers in supporting the management of the organ and patient.

## Part 2: The Evidence for the Use of Kidneys With Acute Kidney Injury

### Recommendation 1: We Suggest that Kidneys from Deceased Donors with AKI Can be Used for Transplantation Based on Clinician Assessment and Donor Factors (Conditional Recommendation, Very Low Certainty of Evidence).

*Evidence Summary*

For the comparison of outcomes of renal transplantation using kidneys from deceased donors who had an acute kidney injury vs. deceased donors who did not (non-AKI), only observational studies were included in the analysis. Thereby, the risk of bias is high. Outcomes that were analysed included mortality and graft survival at different time points, and acute rejection up to a year. Graft survival at 1 year in 12 observational studies including over 16,000 patients was lower in donors with AKI: (RR 1.14, 95% CI: 1.02, 1.27) [22, 26, 35, 126–134]. No difference was found in graft loss at 3 years (RR 1.03, 95% CI: 0.84, 1.26) [56, 127, 128]. Mortality was similar at varying time points from 1 to 6 years (RR 0.80, 95% CI: 0.56, 1.14) [26, 35, 56, 127, 131–137]. No significant difference was found in the rate of DGF when the deceased donor had AKI (RR 1.53, 95% CI: 0.88, 2.68) [26, 35, 50, 53, 127–129, 131–154], and little to no difference was found in the rate of acute rejection up to 1 year after transplant as a function of deceased donor AKI status (RR 1.02, 95% CI: 0.94, 1.11) [26, 53, 127, 131–134, 138–142, 144, 149, 150, 152, 155].

*Justification*

No worrisome signal was seen in outcomes from kidneys whose donor had AKI. In particular, there was no difference in graft survival up to 10 years post-transplant, no difference in mortality up to 5 years and no difference in acute rejection at 1 year. Therefore, we suggest that kidneys from donors with AKI can be used for transplantation. However, this is based on very low certainty of evidence. Of note, severity of AKI (stage 1, 2 or 3) or the need for renal replacement therapy in deceased donors was not considered in these observational studies. Moreover, the studies could only ascertain the outcomes of AKI kidneys that were transplanted. The factors distinguishing AKI kidneys that were declined vs. used (and the outcomes of the former if they did get used for transplantation) are not clear. Having said this, using kidneys from deceased donors with AKI is both feasible and acceptable under the appropriate settings.

*Implementation*

The relative effect of using kidneys from deceased donors with AKI on graft loss is trivial. These kidneys are already being used by some transplant programs, but more widespread use should be encouraged. Implementation of the widespread use of donors with AKI will require improved education of accepting physicians on the positive outcomes of these specific kidneys. Furthermore, awareness of critical care and donor physicians that such kidneys may be donated is needed. Although not universal, some physicians do request a reassuring biopsy prior to accepting these organs. Resources to increase access of timely renal biopsy results may also be required, however this was not studied by our group.

*Research Priorities*

The very low certainty of evidence points to a research priority assessing the efficacy and the safety of using kidneys from deceased donors with AKI for kidney transplantation. Such future multicentre studies should use a standardised definition of AKI, stage of AKI, cause of AKI, and whether donor kidney replacement therapy was needed. Outcomes in different transplant candidate subgroups might identify specific transplant candidates who would benefit most from these kidneys.

### Recommendation 2: We Suggest that Donor Kidneys with AKI from Either ECD or Non-ECD be Used for Kidney Transplantation (Weak Recommendation, Very Low Certainty of Evidence)

*Evidence Summary*

A total of six observational studies were found in the literature [22, 26, 50, 53, 126, 137]. The definition of AKI was not standardized and varied from between studies. Overall, there was no statistically significant differences in any of the outcomes of interest between donor kidneys with AKI labelled as ECD or non-ECD. There was a small difference in overall graft survival with a RR 1.1 (95% CI 1.0–1.2) favouring non-ECD kidneys with AKI [26, 53, 55]. However, there was no difference in mortality [22, 26, 134], DGF [22, 26, 50, 53, 134, 137], acute rejection [26, 50, 53, 135, 137] or eGFR [22, 26, 50, 53] at 1 year.

*Justification*

The available studies suggest that donors with AKI have similar outcomes regardless of ECD or non-ECD status. Given the lack of standardization of AKI definition and the uncertainty around the use of renal biopsy prior to transplantation, this is a weak recommendation. The outcome measures do not suggest any significant harm from transplanting kidneys from ECD with AKI. It is therefore feasible that this category of donor kidneys can be transplanted safely in selected recipients. None of the studies discussed cost utilization given the potential for DGF, although the data did not suggest a higher risk in ECD with AKI.

*Implementation*

It is possible that ECD with AKI make up a large proportion of underutilized organs. Appropriate use of these organs can lead to increased access to transplantation for selected patients with ESKD. Improving knowledge and education along with shared decision making between clinicians and patients is important to consider in the implementation of this strategy. Other

implementation concerns are highlighted in Recommendation 1, Part 2.

*Research Priorities*

The evidence guiding this recommendation is of very low certainty and there is opportunity to inform the transplant community with well-designed studies using a standardized definition of AKI. Biopsy practices vary and additional research could focus on biopsy results and transplant outcomes. Other research questions are mentioned in Recommendation 1, Part 2.

## Part 3: The Evidence for the Use of Kidneys From Donors After Circulatory and Neurologic Determination of Death

### Recommendation 1: We suggest Using Kidneys from Donors After Death Determination by Circulatory Criteria for Transplantation (Conditional Recommendation, Very Low Certainty of Evidence)

*Evidence Summary*

The literature comparing recipient outcomes of kidneys transplanted from donors after DNC vs. DCC are based on observational studies from single-centre, multicentre, and national data sources. There are no randomised controlled trials that have established the comparative effectiveness of these two approaches. DCC kidney transplants have seen a resurgence over the last 20 years due to advances in surgical recovery techniques, organ preservation, and the continued gap between the supply and demand for transplantable organs.

The evidence synthesis showed that recipients of DCC kidneys experienced a higher risk of all-cause mortality (RR 1.33, 95% CI: 1.15, 1.54) [156–164] and graft loss (RR 1.08, 95% CI: 1.00, 1.17) [158–161, 163–165] when compared to recipients of DNC kidneys. The relative likelihood of death-censored graft loss was comparable between the two groups (RR 1.04, 95% CI: 0.92, 1.17) [159, 162]. Recipients of DCC kidney transplants had an 89% increase in the risk of DGF when compared to those who received a DNC kidney transplant (RR 1.89, 95% CI: 1.80, 1.99) [19, 156, 158, 160, 162, 163, 166–169]. Although the point estimate for acute rejection suggested a 62% increased risk among DCC (vs. DNC) kidney recipients, the level of precision did not allow for definitive conclusions (RR 1.62, 95% CI: 0.77, 3.42) [19, 157, 160, 163, 167, 169, 170].

Similar to other analyses that compare recipient outcomes across specific donor characteristics, the overall certainty of the evidence was very low due to the estimates being derived from comparisons that vary in terms of bias control for confounding and selection. The inclusion of studies derived from the same data sources (e.g., national registry) may lead to double counting of subjects and events, leading to measurement bias.

*Justification*

There was a moderately desirable effect of DNC over DCC kidney transplants, particularly in the domains of mortality and delayed graft function. DCC kidney transplants clearly had a notably higher relative likelihood of DGF, which is consistent with the mechanism of donation (i.e., longer warm ischemia time in DCC than DNC). Of note, differences in graft loss and acute rejection were null or trivial. This supports the recommendation to explore ways to increase the use DCC kidneys, when available, in patient groups that may benefit from them.

*Implementation*

DCC kidney transplants are being used in many organ donation and transplantation systems across the world but there may be opportunities to expand their deployment in certain countries, regions, and jurisdictions. One must also consider the resources/costs associated with properly undertaking life-support discontinuation, donor monitoring, and rapid preservation/recovery of organs after cessation of circulation in the donor. DCC kidney recipients are almost two-fold more likely to experience DGF, which has implications of inpatient dialysis services and length of stay.

*Research Priorities*

Reliable methods to predict death following discontinuation of life-support will support the rational allocation of resources to optimise the availability of DCC organs for transplantation. Moreover, research on ways to safely extend the time from withdrawal of life-sustaining therapies until death and techniques to improve organ viability (with reductions in DGF rates) should be prioritised.

## DISCUSSION

Organ utilization is a primary concern for a wide spectrum of healthcare users, providers, and payers. Kidney transplantation provides patients with an improved quality of life and overall life expectancy compared to remaining on dialysis and is the preferred treatment for ESKD. Not only is there clinical benefit for patients, but transplantation leads to considerable cost savings [171, 172]. Kidney underutilization exacerbates the organ shortage problem facing patients with ESKD, increasing wait times, and reducing access to transplantation. Furthermore, the public may lose trust in the organ donation and transplant systems if utilization of this precious gift is not optimized.

Clinicians are faced with the difficult decision of accepting or declining a kidney that is non-standard criteria. This clinical practice guideline summarizes the available evidence on the outcomes of non-standard criteria donor kidneys, labelled as either ECD, older age, DCC or those with AKI. We present the recommendations of six PICOs that may assist in clinical decision making. There was ample evidence in the literature, however given the limitations of the data, only conditional recommendations could be provided for all PICOs. The nature of retrospective, registry data with the potential for double-counting leads to the potential for bias, which limits the strength of these recommendations.

It is important to appreciate that the results of all these studies includes kidneys that were ultimately transplanted. There are likely many kidneys that are not transplanted which outcomes are unknown. One could assume that if all kidneys were transplanted,

outcomes may be worse with non-standard criteria donor kidneys. However, we are not advocating that all kidneys are transplanted but appropriate clinical decision making to identify those that will provide patients with improved outcomes. We feel confident that our data are inclusive of all relevant literature up to April of 2024. We undertook rigorous methodological assessments following well established GRADE criteria to determine the strength of the data. Lastly, our steering committee did not have a patient partner that was guiding our PICO question development and determination of outcomes that are important to patients. However, we do believe that these are important questions that carry importance to our patients.

Overall, the majority of studies show small or trivial differences in outcomes of importance when transplanting a kidney from an older donor, ECD, DCC or those donors suffering AKI. Although some studies revealed the potential for poorer outcomes, we believe the limitations of the data call to question these results. Ultimately this decision must balance the risk of potential negative outcomes to the benefit of improved life expectancy and quality of life with a transplant compared to remaining on dialysis.

A recent study published after our search was complete present a systematic review of the literature on the outcomes of kidney transplantation from donors with AKI. Overall, their results were in concordance with ours when investigating specifically donors with AKI and graft outcomes. They do present a few studies that highlighted the impact of AKIN stages on graft outcomes. Only stage 3 AKI portended a poorer prognosis with higher rates of DGF, but this did not lead to worse long term graft outcomes. They also highlighted the differences in the aetiology of AKI and its impact on graft outcomes comparing hemodynamic, intrinsic and mixed causes. Only intrinsic AKI resulted in higher rates of DGF and a lower 1-year eGFR [173].

This guideline is only one component in our attempts to improved kidney utilization. The importance of patient knowledge and education cannot be understated. Patients awaiting transplantation must have easy to understand education provided in a time of low stress, in other words not at the time of an organ offer. Prior work from our group has confirmed this and suggested that most elderly patients are willing to accept a kidney transplant with reduced long-term outcomes to provide them freedom from dialysis for 3–5 years [174]. Identifying the right recipient for the right kidney can lead to improved patient outcomes and improved organ utilization. Ultimately as we transplant more kidneys that are at risk of underutilization, we must accept as a community the potential for reduced long-term outcomes. Individual programs that are focused on performance indicators such as long-term graft survival may have to shift their priority to other markers of success. Furthermore, the utilization of non-standard kidneys into an ever-increasing complex patient population may also lead to higher healthcare needs and the financial costs associated with it. To address this adequately, high quality prospective research is required.

There are other clinical factors which have an impact on organ underutilization. There is robust evidence that hypothermic machine perfusion (HMP) reduces the risk of DGF in deceased donor kidney transplantation [175]. Graft survival was also improved with the use of HMP in some but not all studies. An interesting pharmacoeconomic analysis proposed that the use of HMP for ECD kidneys led to an improvement in utilization with a higher number of transplants. Overall costs were higher but in their proposed scenario of HMP for ECD kidneys and static cold storage for SCD kidneys, there were cost savings realized on the fifth year [176]. Other reports also document the potential for a lower discard rate with the use of HMP [177, 178]. Despite the limited evidence that histological findings on recovered deceased donor kidneys is associated with graft outcomes, procurement biopsy for ECD kidneys is a common practice [179]. There is a strong association between biopsy findings and organ discard rate with the degree of glomerulosclerosis (>20%) and macroscopic arteriosclerosis being important histological findings affecting decision making [180, 181]. If procurement biopsies are a common practice for ECD kidneys to assist with decision making, utilizing standardized clinical pathological scores may improve utilization. Zhang and colleagues developed a kidney donor quality score (KDQS) based on deep learning assessment of procurement biopsies [182]. The KDQS in addition to clinical covariates predicted one- and five-year graft loss with an area under the curve of 0.70 and 0.64, respectively, and thus has the potential to reduce kidney discards. Lastly, dual kidney transplantation may improve utilization of ECD kidneys that would otherwise be discarded. Donor kidneys that are at risk of discard based on histological or clinical criteria can be successfully transplanted using an algorithm decision tree [183]. High risk donors based on clinical and histological criteria underwent dual kidney transplantation resulting in similar graft survival as single kidney transplantation from similar donors but lower biopsy lesions.

We highlight several research priorities and unmet needs in this topic. Further research is required to determine cost effectiveness of this strategy, patient quality of life, and more accurate ways of identifying characteristics of recipients and donor kidneys to improve overall outcomes. This clinical guideline has the potential to increase kidney utilization reducing the gap of organ shortage for patients with ESKD.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants'

legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

JD: Participated in research design, data analysis, performance of the research, writing of the paper. PC: Participated in research design, performance of the research, writing of the paper. HC: Participated in research design, performance of the research, writing of the paper. TG: Participated in research design, data analysis, performance of the research. AG: Participated in research design, performance of the research, writing of the paper. SK: Participated in research design, performance of the research, writing of the paper. GK: Participated in research design, performance of the research, writing of the paper. MP: Participated in research design, performance of the research, writing of the paper. CP: Participated in research design, performance of the research. YY: Participated in research design, data analysis, performance of the research. RM: Participated in research design, performance of the research, writing of the paper. All authors contributed to the article and approved the submitted version.

## FUNDING

The author(s) declare that financial support was received for the research and/or publication of this article. The authors declare that this study received funding from Canadian Blood Services. The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

## CONFLICT OF INTEREST

PC is retired and no longer works at University of Alberta. CP no longer works with Canadian Blood Services. This work was presented as an abstract at the Canadian Society of Transplant Annual Scientific Meeting, October 2024.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## GENERATIVE AI STATEMENT

The author(s) declare that no Generative AI was used in the creation of this manuscript.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.14596/full#supplementary-material

## REFERENCES

1. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of Mortality in All Patients on Dialysis, Patients on Dialysis Awaiting Transplantation, and Recipients of a First Cadaveric Transplant. *N Engl J Med* (1999) 341(23):1725–30. doi:10.1056/NEJM199912023412303
2. Laupacis A, Keown P, Pus N, Krueger H, Ferguson B, Wong C, et al. A Study of the Quality of Life and Cost-Utility of Renal Transplantation. *Kidney Int* (1996) 50(1):235–42. doi:10.1038/ki.1996.307
3. Hart A, Smith JM, Skeans MA, Gustafson SK, Wilk AR, Castro S, et al. OPTN/SRTR 2018 Annual Data Report: Kidney. *Am J Transpl* (2020) 20(Suppl. s1):20–130. doi:10.1111/ajt.15672
4. Husain SA, King KL, Pastan S, Patzer RE, Cohen DJ, Radhakrishnan J, et al. Association between Declined Offers of Deceased Donor Kidney Allograft and Outcomes in Kidney Transplant Candidates. *JAMA Netw Open* (2019) 2(8):e1910312. doi:10.1001/jamanetworkopen.2019.10312
5. Port FK, Bragg-Gresham JL, Metzger RA, Dykstra DM, Gillespie BW, Young EW, et al. Donor Characteristics Associated with Reduced Graft Survival: An Approach to Expanding the Pool of Kidney Donors. *Transplantation* (2002) 74(9):1281–6. doi:10.1097/00007890-200211150-00014
6. Rao PS, Schaubel DE, Guidinger MK, Andreoni KA, Wolfe RA, Merion RM, et al. A Comprehensive Risk Quantification Score for Deceased Donor Kidneys: The Kidney Donor Risk Index. *Transplantation* (2009) 88(2):231–6. doi:10.1097/TP.0b013e3181ac620b
7. Schünemann HBJ. GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations (2013).
8. Veritas Health Innovation. *Covidence Systematic Review Software*. Melbourne, Australia (2019). (Covidence systematic review software).
9. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: A Revised Tool for Assessing Risk of Bias in Randomised Trials. *BMJ* (2019) 366:l4898. doi:10.1136/bmj.l4898
10. Peterson J. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses (2011).
11. The Cochrane Collaboration. *Review Manager. Version 5.4. Copenhagen: The Nordic Cochrane Centre* (2014).
12. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: An Emerging Consensus on Rating Quality of Evidence and Strength of Recommendations. *BMJ* (2008) 336(7650):924–6. doi:10.1136/bmj.39489.470347.AD
13. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE Guidelines: 4. Rating the Quality of Evidence--Study Limitations (Risk of Bias). *J Clin Epidemiol* (2011) 64(4):407–15. doi:10.1016/j.jclinepi.2010.07.017
14. Merion RM, Ashby VB, Wolfe RA, Distant DA, Hulbert-Shearon TE, Metzger RA, et al. Deceased-Donor Characteristics and the Survival Benefit of Kidney Transplantation. *JAMA* (2005) 294(21):2726–33. doi:10.1001/jama.294.21.2726
15. Martin Navarro J, Ortega M, Gutierrez MJ, Garcia Martin F, Alcazar JM, Morales JM, et al. Survival of Patients Older Than 60 Years with Kidneys Transplanted from Spanish Expanded Criteria Donors versus Patients Continued on Hemodialysis. *Transplant Proc* (2009) 41(6):2376–8. doi:10.1016/j.transproceed.2009.06.176
16. Massie AB, Luo X, Chow EKH, Alejo JL, Desai NM, Segev DL. Survival Benefit of Primary Deceased Donor Transplantation with High-KDPI Kidneys. *Am J Transpl* (2014) 14(10):2310–6. doi:10.1111/ajt.12830
17. Aubert O, Vernerey D, Empana JP, Kamar N, Rostaing L, Viglietti D, et al. Long Term Outcomes of Transplantation Using Kidneys from Expanded Criteria Donors: Prospective, Population Based Cohort Study. *BMJ (Online)* (2015) 351:h3557. doi:10.1136/bmj.h3557

18. Barba J, Zudaire JJ, Robles JE, Rosell D, Berian JM, Pascual I. Complications of Kidney Transplantation with Grafts from Expanded Criteria Donors. *World J Urol* (2013) 31(4):893–900. doi:10.1007/s00345-012-0831-3
19. Bell R, Farid S, Upasani V, Ahmad N, Pandanaboyana S, Baker R. The Evolution of Donation after Circulatory Death Renal Transplantation: A Decade of Experience. *Nephrol Dial Transplant* (2019) 34(10):1788–98. doi:10.1093/ndt/gfy160
20. Domagala P, Kwiatkowski A, Wszola M, Cybula K, Chmura A, Trzebicki J, et al. Complications of Transplantation of Kidneys from Expanded-Criteria Donors. *Transplant Proc* (2009) 41(8):2970–1. doi:10.1016/j.transproceed.2009.07.085
21. Ferreira E, Costa J, Romaozinho C, Santos L, Macario F, Alves R, et al. Long-Term Outcomes of Kidney Transplantation from Expanded-Criteria Deceased Donors: A Single-Center Experience. *Transplant Proc* (2017) 49(4):770–6. doi:10.1016/j.transproceed.2017.01.051
22. Jung D, Park S, Kim SH, Eom M, Kim JS, Yang JW, et al. Decision Making by Young Transplant Surgeons Regarding Expanded-Criteria Donors with Acute Kidney Injury or Allocation Failure. *Transplant Proc* (2016) 48(3): 695–700. doi:10.1016/j.transproceed.2015.11.025
23. Keitel E, Michelon T, dos Santos AF, Bittar AE, Goldani JC, D'Almeida Bianco P, et al. Renal Transplants Using Expanded Cadaver Donor Criteria. *Ann Transplant : Q Polish Transplant Soc* (2004) 9(2):23–4.
24. Khan SM, Moritz MJ, Saeed MI, Kumar A, Jaglan S, Heifets M, et al. Successful Transplantation of Kidneys from Deceased Donors with Acute Renal Failure: Three-Year Results. *Transplantation* (2006) 82(12):1640–5. doi:10.1097/01.tp.0000250908.62948.8f
25. Kim BS, Joo SH, Ahn HJ, Choi JH, Park HC, Lee SH. Outcomes of Expanded-Criteria Deceased Donor Kidney Transplantation in a Single Center. *Transplant Proc* (2014) 46(4):1067–70. doi:10.1016/j.transproceed.2013.12.014
26. Klein R, Galante NZ, de Sandes-Freitas TV, de Franco MF, Tedesco-Silva H, Medina-Pestana JO. Transplantation with Kidneys Retrieved from Deceased Donors with Acute Renal Failure. *Transplantation* (2013) 95(4):611–6. doi:10.1097/TP.0b013e318279153c
27. Lee KW, Park JB, Cha SR, Lee SH, Chung YJ, Yoo H, et al. Dual Kidney Transplantation Offers a Safe and Effective Way to Use Kidneys from Deceased Donors Older Than 70 Years. *BMC Nephrol* (2020) 21(1):3. doi:10.1186/s12882-019-1664-8
28. Singh RP, Farney AC, Rogers J, Zuckerman J, Reeves-Daniel A, Hartmann E, et al. Kidney Transplantation from Donation after Cardiac Death Donors: Lack of Impact of Delayed Graft Function on Post-Transplant Outcomes. *Clin Transplant* (2011) 25(2):255–64. doi:10.1111/j.1399-0012.2010.01241.x
29. Al-Shraideh Y, Stratta R, Farney A, Orlando G, Palanisamy A, Reeves-Daniel A, et al. Primary Non Function after Deceased Donor Kidney Transplantation: Risks and Consequences. *Abstract# D2484 Transplant* (2014) 98:631. doi:10.1097/00007890-201407151-02136
30. Domagala P, Kwiatkowski A, Wszola M, Panufnik L, Chmura A, Perkowska-Ptasinska A, et al. Assessment of Kidneys Procured from Expanded Criteria Donors before Transplantation. *Transplant Proc* (2009) 41(8):2966–9. doi:10.1016/j.transproceed.2009.08.004
31. Lee CM, Carter JT, Randall HB, Hiose R, Stock PG, Melzer JS, et al. The Effect of Age and Prolonged Cold Ischemia Times on the National Allocation of Cadaveric Renal Allografts. *J Surg Res* (2000) 91(1):83–8. doi:10.1006/jsre.2000.5921
32. Moore PS, Farney AC, Rogers J, Gautreaux MD, Hairston G, Stratta RJ, et al. Experience with Deceased Donor Kidney Transplantation in 114 Patients Over Age 60. *Surgery* (2007) 142(4):514–23.e5232. doi:10.1016/j.surg.2007.08.005
33. Ojo AO, Hanson JA, Meier-Kriesche HU, Okechukwu CN, Wolfe RA, Leichtman AB, et al. Survival in Recipients of Marginal Cadaveric Donor Kidneys Compared with Other Recipients and Wait-Listed Transplant Candidates. *J Am Soc Nephrol* (2001) 12(3):589–97. doi:10.1681/ASN.V123589
34. Alexander JW, Whiting JF, Golconda M, First MR, Smith R, O'Brien S. Economic Costs of Expanded Criteria Donors in Renal Transplantation. *Transplantation* (1998) 65(2):204–7. doi:10.1097/00007890-199801270-00010
35. Wiwattanathum P, Ingsathit A, Kantachuvesiri S, Arpornsujaritkun N, Tirapanich W, Sumethkul V. Stabilization of Estimated Glomerular Filtration Rate in Kidney Transplantation from Deceased Donors with Acute Kidney Injuries. *World J Transplant* (2016) 6(4):712–8. doi:10.5500/wjt.v6.i4.712
36. Rigotti P, Capovilla G, Di Bella C, Silvestre C, Donato P, Baldan N, et al. A Single-Center Experience with 200 Dual Kidney Transplantations. *Clin Transpl* (2014) 28(12):1433–40. doi:10.1111/ctr.12475
37. Bonsignore P, Pagano D, Piazza S, Ricotta C, di Francesco F, Cintorino D, et al. Crucial Role of Extended Criteria Donors in Deceased Donor Single Kidney Transplantation to Face Chronic Shortage in the Heart of the Mediterranean Basin: A Single-Center Experience. *Transplant Proc* (2019) 51(9):2868–72. doi:10.1016/j.transproceed.2019.02.075
38. Farney AC, Singh RP, Rogers J, Gautreaux MD, Stratta RJ, Hines MH, et al. Experience in Renal and Extrarenal Transplantation with Donation after Cardiac Death Donors with Selective Use of Extracorporeal Support. *J Am Coll Surgeons* (2008) 206(5):1028–37. doi:10.1016/j.jamcollsurg.2007.12.029
39. Nakamura Y, Kihara Y, Yokoyama T, Konno O, Iwamoto H. Similar Outcomes of Kidney Transplantations Using Organs from Donors after Cardiac Death and Donors after Brain Death. *Transplant Proc* (2018) 50(8):2404–11. doi:10.1016/j.transproceed.2018.03.088
40. Serwanska-Swietek M, Wszola M, Domagala P, Berman A, Bieniasz M, Kieszek R, et al. Analysis of Distribution of Expanded- and Standard-Criteria Donors and Complications Among Polish Recipients by Kidney Donor Risk Index Value. *Transplant Proc* (2018) 50(6):1686–90. doi:10.1016/j.transproceed.2018.02.132
41. Zadori G, Kovacs DA, Fedor R, Kanyari Z, Zsom L, Asztalos L, et al. Results of Expanded-Criteria Donor Kidneys: A Single-Center Experience in Hungary. *Transplant Proc* (2015) 47(7):2189–91. doi:10.1016/j.transproceed.2015.07.023
42. Al-Shraideh Y, Farooq U, Farney AC, Palanisamy A, Rogers J, Orlando G, et al. Influence of Recipient Age on Deceased Donor Kidney Transplant Outcomes in the Expanded Criteria Donor Era. *Clin Transpl* (2014) 28(12): 1372–82. doi:10.1111/ctr.12463
43. Balaz P, Rokosny S, Wohlfahrtova M, Viklicky O, Wohlfahrt P, Bartonova A, et al. Identification of Expanded-Criteria Donor Kidney Grafts at Lower Risk of Delayed Graft Function. *Transplantation* (2013) 96(7):633–8. doi:10.1097/TP.0b013e31829d9225
44. Cardinal H, Lamarche F, Grondin S, Marsolais P, Lagace AM, Duca A, et al. Organ Donor Management and Delayed Graft Function in Kidney Transplant Recipients: A Multicenter Retrospective Cohort Study. *Am J Transplant* (2019) 19(1):277–84. doi:10.1111/ajt.15127
45. Farney AC, Al-Geizawi S, Rogers J, Stratta RJ, Hines MH. Lessons Learned from a Single Center's Experience with 134 Donation after Cardiac Death Donor Kidney Transplants. *J Am Coll Surgeons* (2011) 212(4):440–51. doi:10.1016/j.jamcollsurg.2010.12.033
46. Ferrer F, Mota A, Alves R, Bastos C, Macario F, Figueiredo A, et al. Renal Transplantation with Expanded Criteria Donors: The Experience of One Portuguese Center. *Transplant Proc* (2009) 41(3):791–3. doi:10.1016/j.transproceed.2009.02.044
47. Frutos MA, Mansilla JJ, Ruiz P, Seller G, Sola E, Martin-Gomez A. Expanded Criteria Donors for Kidney Transplantation: Quality Control and Results. *Transplant Proc* (2006) 38(8):2371–3. doi:10.1016/j.transproceed.2006.08.035
48. Goplani KR, Kute VB, Vanikar AV, Shah PR, Gumber MR, Patel HV, et al. Expanded Criteria Donor Kidneys for Younger Recipients: Acceptable Outcomes. *Transplant Proc* (2010) 42(10):3931–4. doi:10.1016/j.transproceed.2010.09.040
49. Han M, Jeon HJ, Ryu HJ, Jeong JC, Koo TY, Kwon HY, et al. Kidney Donor Risk Index Is a Good Prognostic Tool for Graft Outcomes in Deceased Donor Kidney Transplantation with Short, Cold Ischemic Time. *Clin Transplant* (2014) 28(3):337–44. doi:10.1111/ctr.12318
50. Heilman RL, Huskey J, Chakkera HA, Khamash H, Smith ML, Kurian SM, et al. Transplanting Kidneys from Deceased Donors with Severe Acute Kidney Injury. *Am J Transplant* (2015) 15(8):2143–51. doi:10.1111/ajt.13260
51. Helantera I, Ibrahim HN, Lempinen M, Finne P. Donor Age, Cold Ischemia Time, and Delayed Graft Function. *Clin J Am Soc Nephrol : CJASN* (2020) 15(6):813–21. doi:10.2215/CJN.13711119

52. Hwang JK, Park SC, Kim JI, Kwon KH, Moon IS, Choi BS, et al. Long-Term Outcomes of Kidney Transplantation from Expanded Criteria Deceased Donors at a Single Center: Comparison with Standard Criteria Deceased Donors. *Transplant Proc* (2014) 46(2):431–6. doi:10.1016/j.transproceed.2013.11.061
53. Jacobi J, Rebhan D, Heller K, Velden J, Hilgers KF, Wullich B, et al. Donor Acute Kidney Injury and Short-Term Graft Outcome in Renal Transplantation. *Clin Transplant* (2014) 28(10):1131–41. doi:10.1111/ctr.12425
54. Kim SM, Ahn S, Min SI, Park D, Park T, Min SK, et al. Cold Ischemic Time Is Critical in Outcomes of Expanded Criteria Donor Renal Transplantation. *Clin Transplant* (2013) 27(1):132–9. doi:10.1111/ctr.12034
55. Ko KJ, Kim YH, Kwon KH, Kim MH, Park SC, Yun SS, et al. Kidney Transplantation Using Expanded-Criteria Deceased Donors: A Comparison with Ideal Deceased Donors and Non-Expanded-Criteria Deceased Donors. *Transplant Proc* (2018) 50(10):3222–7. doi:10.1016/j.transproceed.2018.05.028
56. Kumar MS, Panigrahi D, Dezii CM, Abouna GM, Chvala R, Brezin J, et al. Long-Term Function and Survival of Elderly Donor Kidneys Transplanted into Young Adults. *Transplantation* (1998) 65(2):282–5. doi:10.1097/00007890-199801270-00027
57. Lionaki S, Kapsia H, Makropoulos I, Metsini A, Skalioti C, Zavos G, et al. Kidney Transplantation Outcomes from Expanded Criteria Donors, Standard Criteria Donors or Living Donors Older Than 60 Years. *Ren Fail* (2014) 36(4):526–33. doi:10.3109/0886022X.2013.876348
58. Locke JE, Segev DL, Warren DS, Simpkins CE, Montgomery RA, Dominici F. Outcomes of Kidneys from Donors after Cardiac Death: Implications for Allocation and Preservation. *Am J Transplant* (2007) 7(7):1797–807. doi:10.1111/j.1600-6143.2007.01852.x
59. Mohan S, Tanriover B, Ali N, Crew RJ, Dube GK, Radhakrishnan J, et al. Availability, Utilization and Outcomes of Deceased Diabetic Donor Kidneys; Analysis Based on the UNOS Registry. *Am J Transplant* (2012) 12(8):2098–105. doi:10.1111/j.1600-6143.2012.04167.x
60. Moore PS, Farney AC, Rohr MS, Gautreaux MD, Rogers J, Anderson TK, et al. Dual Kidney Transplantation: A Case-Control Comparison with Single Kidney Transplantation from Standard and Expanded Criteria Donors. *Transplantation* (2007) 83(12):1551–6. doi:10.1097/01.tp.0000266579.11595.95
61. Papachristou E, Provatopoulou S, Savvidaki E, Kaplanis N, Kalliakmani P, Papasotiriou M, et al. Outcome of Transplantation in Renal Allograft Recipients from Cadaveric Donors with Standard and Expanded Criteria: A Single-Center Experience. *Transplant Proc* (2014) 46(9):3172–4. doi:10.1016/j.transproceed.2014.10.030
62. Saidi RF, Elias N, Kawai T, Hertl M, Farrell ML, Delmonico FL, et al. Outcome of Kidney Transplantation Using Expanded Criteria Donors and Donation after Cardiac Death Kidneys: Realities and Costs. *Am J Transplant* (2007) 7(12):2769–74. doi:10.1111/j.1600-6143.2007.01993.x
63. Serur D, Kapur S, Saal S, Leeser D, Gerber LM, Wang J, et al. Excellent Outcomes with Expanded Criteria Donor Kidneys: The Role of the Recipient's Age. *Clin transplants* (2013) 85–91.
64. Smail N, Baran D, Mucsi I, Cantarovich M, Tchervenkov J, Paraskevas S, et al. Impact of Early Graft Function on 10-Year Graft Survival in Recipients of Kidneys from Standard- or Expanded-Criteria Donors. *Transplantation* (2013) 96(2):176–81. doi:10.1097/TP.0b013e318297443b
65. Song SH, Lim SH, Lee J, Lee JG, Huh KH, Kim SI, et al. Impact of Korea Network for Organ Sharing Expanded Donor Criteria on Delayed Graft Fuction in Kidney Transplantation: A Single-Center Experience. *Transplant Proc* (2018) 50(8):2363–7. doi:10.1016/j.transproceed.2018.04.046
66. Stratta RJ, Farney AC, Orlando G, Farooq U, Al-Shraideh Y, Gautreaux MD, et al. Dual Kidney Transplants from Adult Marginal Donors Successfully Expand the Limited Deceased Donor Organ Pool. *Clin Transplant* (2016) 30(4):380–92. doi:10.1111/ctr.12697
67. Sundberg AK, Armstrong G, Hairston G, Hartmann E, Farney AC, Roskopf J, et al. Increased Kidney Transplantation Utilizing Expanded Criteria Deceased Organ Donors with Results Comparable to Standard Criteria Donor Transplant. *Ann Surg* (2004) 239(5):688–97. doi:10.1097/01.sla.0000124296.46712.67
68. Swami YK, Singh DV, Gupta SK, Pradhan AA, Rana YPS, Harkar S, et al. Deceased Donor Renal Transplantation at Army Hospital Research and Referral: Our Experience. *Indian J Urol* (2013) 29(2):105–9. doi:10.4103/0970-1591.114029
69. Tomita Y, Iwadoh K, Nakajima I, Fuchinoue S, Tojimbara T. Long-Term Outcomes in Kidney Transplantation from Expanded-Criteria Donors after Circulatory Death. *Transplant Proc* (2017) 49(1):45–8. doi:10.1016/j.transproceed.2016.10.009
70. Yap YT, Ho QY, Kee T, Ng CY, Chionh CY. Impact of Pre-Transplant Biopsy on 5-Year Outcomes of Expanded Criteria Donor Kidney Transplantation. *Nephrology (Carlton, Vic)* (2021) 26(1):70–7. doi:10.1111/nep.13788
71. Antonieta Azancot M, Moreso F, Cantarell C, Perello M, Torres IB, Sellares J, et al. The Reproducibility and Predictive Value on Outcome of Renal Biopsies from Expanded Criteria Donors. *Kidney Int* (2014) 85(5):1161–8. doi:10.1038/ki.2013.461
72. Nardo B, Bertelli R, Cavallari G, Capocasale E, Cappelli G, Mazzoni MP, et al. Analysis of 80 Dual-Kidney Transplantations: A Multicenter Experience. *Transplant Proc* (2011) 43(5):1559–65. doi:10.1016/j.transproceed.2010.11.030
73. Dedinska I, Palkoci B, Vojtko M, Osinova D, Lajiakova M. Experiences with Expanded Criteria Donors: 10-Year Analysis of the Martin, Slovakia Transplant Center. *Exp Clin Transplant* (2019) 17(1):6–10. doi:10.6002/ect.2017.0188
74. Gambino G, Gioviale MC, Maione C, Di Bona A, Buffa D, Virzi C, et al. Use of Marginal Donors in Kidney Transplantation: Our Experience. *Transplant Proc* (2006) 38(4):999–1000. doi:10.1016/j.transproceed.2006.02.148
75. Hamed MO, Watson CJ, Bradley JA, Pettigrew G, Saeb-Parsy K, Chen Y, et al. Early Graft Loss after Kidney Transplantation: Risk Factors and Consequences. *Am J Transplant* (2015) 15(6):1632–43.
76. Mezrich JD, Pirsch JD, Fernandez LA, Foley DP, Bellingham JM, Odorico JS, et al. Differential Outcomes of Expanded-Criteria Donor Renal Allografts According to Recipient Age. *Clin J Am Soc Nephrol* (2012) 7(7):1163–71. doi:10.2215/CJN.00150112
77. Palkoci B, Vojtko M, Fialova J, Osinova D, Lajciakova M. Results of Kidney Transplantation from Expanded Criteria Donors: A Single-Center Experience. *Int J Organ Transplant Med* (2018) 9(1):1–9.
78. Saudan P, Berney T, Goumaz C, Morel P, Martin PY. Renal Transplantation with Donors Aged Over 50: A Long-Term, Single Centre Experience. *Swiss Med weekly* (2001) 131(9–10):117–21. doi:10.4414/smw.2001.06145
79. Olaverri JG, Christian JM, Elorrieta P, Esnaola K, Rodriguez P, Marron I, et al. Utilization of Advanced-Age Donors in Renal Transplantation. *Transplant Proc* (2011) 43(9):3340–3. doi:10.1016/j.transproceed.2011.09.089
80. Basar H, Scantlebury VP, McCauley J, Irish W, Fung JJ, Soran A, et al. Renal Transplantation in Recipients over the Age of 60: The Impact of Donor Age. *Transplantation* (1999) 67(8):1191–3. doi:10.1097/00007890-199904270-00019
81. Carmellini M, Vistoli F, Boggi U, Bellini R, Mosca F. Delayed Graft Function Incidence as Predictive Variable of Survival of Kidney Grafts Retrieved from Elderly Donors. *Transplant Proc* (2000) 32(1):128–30. doi:10.1016/s0041-1345(99)00909-4
82. Collins MG, Chang SH, Russ GR, McDonald SP. Outcomes of Transplantation Using Kidneys from Donors Meeting Expanded Criteria in Australia and New Zealand, 1991 to 2005. *Transplantation* (2009) 87(8):1201–9. doi:10.1097/TP.0b013e31819ec3a6
83. Di Cocco P, Orlando G, D'Angelo M, Rizza V, De Luca L, Famulari A, et al. Kidney Transplantation from Older Donors. *Transplant Proc* (2011) 43(4):1033–5. doi:10.1016/j.transproceed.2011.01.149
84. Favi E, Puliatti C, Iesari S, Monaco A, Ferraresso M, Cacciola R. Impact of Donor Age on Clinical Outcomes of Primary Single Kidney Transplantation from Maastricht Category-III Donors after Circulatory Death. *Transplant direct* (2018) 4(10):e396. doi:10.1097/TXD.0000000000000835
85. Galeano C, Marcen R, Jimenez S, Fernandez Rodriguez A, Sosa H, Villafruela JJ, et al. Utilization of Elderly Kidney Donors (>70 Years) Does Not Affect Graft Survival in the Medium Term. *Transplant Proc* (2010) 42(10):3935–7. doi:10.1016/j.transproceed.2010.08.069
86. Han SY, Kong JM, Kwon OJ, Kim MG, Jung CW, Kim SH, et al. Outcomes of Kidney Transplantation from Elderly Deceased Donors of a Korean Registry. *PloS one* (2020) 15(6 June):e0232177. doi:10.1371/journal.pone.0232177

87. Peters-Sengers H, Arashi D, Van Der Heide JJH, Ten Berge IJM, Bemelman FJ, Idu MM, et al. Stretching the Limits of Renal Transplantation in Elderly Recipients of Grafts from Elderly Deceased Donors. *J Am Soc Nephrol* (2017) 28(2):621–31.
88. Rao KV, Kasiske BL, Odlund MD, Ney AL, Andersen RC. Influence of Cadaver Donor Age on Posttransplant Renal Function and Graft Outcome. *Transplantation* (1990) 49(1):91–5. doi:10.1097/00007890-199001000-00020
89. Sekta S, Ziaja J, Klimunt J, Krol R, Cierpka L, Kolonko A, et al. Donation and Transplantation of Kidneys Harvested from Deceased Donors over the Age of 60 Years in the Upper Silesia Region. *Transplant Proc* (2016) 48(5):1466–71. doi:10.1016/j.transproceed.2015.11.038
90. Snoeijs MGJ, Schaefer S, Buurman WA, Van Heurn LWE, Christiaans MH, Van Hooff JP, et al. Kidney Transplantation Using Elderly Non-Heart-Beating Donors: A Single-Center Experience. *Am J Transplant* (2006) 6(5 I):1066–71. doi:10.1111/j.1600-6143.2006.01312.x
91. Tekin S, Yavuz HA, Yuksel Y, Demirbas A, Yucetin L, Ates I, et al. Kidney Transplantation from Elderly Donor. *Transplant Proc* (2015) 47(5):1309–11. doi:10.1016/j.transproceed.2015.04.015
92. Gohh R, Yango A, Gautam A, Monaco AP, Morrissey PE, Colacchio TA. Renal Transplant Survival from Older Donors: A Single Center Experience. *Arch Surg* (2004) 139(4):384–9. doi:10.1001/archsurg.139.4.384
93. Bilgin N, Karakayali H, Moray G, Demirag A, Arslan G, Akkoc H, et al. Outcome of Renal Transplantation from Elderly Donors. *Transplant Proc* (1998) 30(3):744–6. doi:10.1016/s0041-1345(98)00031-1
94. Gerbase-DeLima M, de Marco R, Mine KL, Monteiro F, Tedesco-Silva H, Medina-Pestana JO. Impact of Combinations of Donor and Recipient Ages and Other Factors on Kidney Graft Outcomes. *Front Immunol* (2020) 11:954. doi:10.3389/fimmu.2020.00954
95. Hermanowicz M, Przygoda J, Podobinska I, Lewandowska D, Czerwinski J, Danielewicz R. Organ Donation from Elderly Deceased Donors and Transplantation to Elderly Recipients in Poland: Numbers and Outcomes. *Transplant Proc* (2016) 48(5):1390–3. doi:10.1016/j.transproceed.2016.01.048
96. Messa P, Brezzi B, Cresseri D, Berardinelli L, Poli F, Scalamogna M, et al. Immediate Graft Function Positively Affects Long-Term Outcome of Renal Allografts from Older but Not from Younger Donors. *Transplant Proc* (2006) 38(10):3377–81. doi:10.1016/j.transproceed.2006.10.073
97. Messina M, Diena D, Dellepiane S, Guzzo G, Lo Sardo L, Fop F, et al. Long-Term Outcomes and Discard Rate of Kidneys by Decade of Extended Criteria Donor Age. *Clin J Am Soc Nephrol : CJASN* (2017) 12(2):323–31. doi:10.2215/CJN.06550616
98. Navarro MD, Lopez-Andreu M, Rodriguez-Benot A, Morales MLA, Garcia PA, Ortega-Salas R, et al. Significance of Preimplantation Analysis of Kidney Biopsies from Expanded Criteria Donors in Long-Term Outcome. *Transplantation* (2011) 91(4):432–9. doi:10.1097/TP.0b013e318204bdd7
99. Akoh JA, Rana TA. Impact of Donor Age on Outcome of Kidney Transplantation from Controlled Donation after Cardiac Death. *Saudi J kidney Dis Transplant* (2013) 24(4):673–81. doi:10.4103/1319-2442.113846
100. Cohen EP, Hariharan S, McBride MA, Bennett LE. Risk Factors for Renal Allograft Survival from Older Cadaver Donors. *Transplantation* (1997) 64(12):1748–54. doi:10.1097/00007890-199712270-00022
101. Donnelly PK, Simpson AR, Milner AD, Nicholson ML, Horsburgh T, Veitch PS, et al. Age-Matching Improves the Results of Renal Transplantation with Older Donors. *Nephrol Dial Transplant* (1990) 5(9):808–11. doi:10.1093/ndt/5.9.808
102. Foster MC, Wenham PW, Rowe PA, Blamey RW, Bishop MC, Burden RP, et al. Use of Older Patients as Cadaveric Kidney Donors. *Br J Surg* (1988) 75(8):767–9. doi:10.1002/bjs.1800750815
103. Kwon OJ, Lee HG, Kwak JY. The Impact of Donor and Recipient Age on the Outcome of Kidney Transplantation. *Transplant Proc* (2004) 36(7):2043–5. doi:10.1016/j.transproceed.2004.07.047
104. Lloveras J, Arcos E, Comas J, Crespo M, Pascual J. A Paired Survival Analysis Comparing Hemodialysis and Kidney Transplantation from Deceased Elderly Donors Older Than 65 Years. *Transplantation* (2015) 99(5):991–6. doi:10.1097/TP.0000000000000474
105. Mizutani K, Yamada S, Katoh N, Ono Y, Ohshima S, Kinukawa T, et al. Cadaveric Kidneys from Older Donors and Their Effective Use in Transplantation: A Risk Factor for Long-Term Graft Survival. *Transplant Proc* (1997) 29(1–2):113–5. doi:10.1016/s0041-1345(96)00028-0
106. Morling N, Ladefoged J, Lange P, Nerstrom B, Nielsen B, Nielsen LS, et al. Kidney Transplantation and Donor Age. *Tissue Antigens* (1975) 6(3):163–6. doi:10.1111/j.1399-0039.1975.tb00630.x
107. Nakatani T, Kim T, Uchida J, Kumada N, Tsuchida K, Takemoto Y, et al. Clinical Study on 53 Cases of Cadaveric Kidney Transplantation at Osaka City University Hospital. *Osaka city Med J* (2001) 47(2):95–103.
108. Pessione F, Cohen S, Durand D, Hourmant M, Kessler M, Legendre C, et al. Multivariate Analysis of Donor Risk Factors for Graft Survival in Kidney Transplantation. *Transplantation* (2003) 75(3):361–7. doi:10.1097/01.TP.0000044171.97375.61
109. Pirsch JD, D'Alessandro AM, Sollinger HW, Hoffmann RM, Roecker E, Voss BJ, et al. The Effect of Donor Age, Recipient Age, and HLA Match on Immunologic Graft Survival in Cadaver Renal Transplant Recipients. *Transplantation* (1992) 53(1):55–9. doi:10.1097/00007890-199201000-00010
110. Shaheen MF, Al Sayyari A, Shaheen FAM, Attar B, Elamin K, Al Hayyan H. Impact of Recipient and Donor Nonimmunologic Factors on the Outcome of Deceased Donor Kidney Transplantation. *Transplant Proc* (2010) 42(1):273–6. doi:10.1016/j.transproceed.2009.12.052
111. Snoeijs MGJ, Buurman WA, Christiaans MHL, van Hooff JP, Goldschmeding R, van Suylen RJ, et al. Histological Assessment of Preimplantation Biopsies May Improve Selection of Kidneys from Old Donors after Cardiac Death. *Am J Transplant* (2008) 8(9):1844–51. doi:10.1111/j.1600-6143.2008.02318.x
112. Vivas CA, O'Donovan RM, Jordan ML, Hickey DP, Hrebinko R, Shapiro R, et al. Cadaveric Renal Transplantation Using Kidneys from Donors Greater Than 60 Years Old. *Clin Transplant* (1992) 6(2):77–80. doi:10.1111/j.1399-0012.1992.tb00595.x
113. Wahlberg J, Tufveson G, Larsson A, Backman U, Frodin L. Influence of the Age of Cadaveric Kidney Donors on Transplantation Outcome and Rate of Surgical Complications. *Scand J Urol Nephrol Supplementum* (1990) 131:39–42.
114. Ballesteros MA, Suberviola B, Belmar Vega L, Ruiz San Millan JC, Fernandez-Santiago R, Campos Fernandez S, et al. Impact of the Elderly Donor on an Abdominal Organ Transplantation Program. *Eur Surg - Acta Chirurgica Austriaca* (2020) 52(5):223–8. doi:10.1007/s10353-020-00637-0
115. Burrows L, Knight RJ. The Combined Impact of Donor Age and Acute Rejection on Long-Term Cadaver Renal Allograft Survival. *Surgery* (1999) 125(3):0318–24. doi:10.1067/msy.1999.95681
116. Buxeda A, Velis G, Arias-Cabrales C, Zapatero A, Burballa C, Redondo-Pachon D, et al. Kidney Transplantation Outcomes from Elderly Donors after Circulatory Death: A Comparison with Elderly Brain-Dead Donors. *Clin kidney J* (2021) 14(4):1181–9. doi:10.1093/ckj/sfaa114
117. Lim WH, Chang S, Chadban S, Campbell S, Dent H, Russ GR, et al. Donor-Recipient Age Matching Improves Years of Graft Function in Deceased-Donor Kidney Transplantation. *Nephrol Dial Transplant* (2010) 25(9):3082–9. doi:10.1093/ndt/gfq127
118. Magott-Procelewska M, Madziarska K, Boratynska M, Chudoba P, Lepiesza A, Mazanowska O, et al. Kidney Transplantation from Old Deceased Donors: Impact of Uric Acid Level-A Quarter-Century of Experience in One Transplant Center. *Transplant Proc* (2018) 50(6):1701–4. doi:10.1016/j.transproceed.2018.02.127
119. Martins J, Barreto S, Bravo P, Santos JP, Ferreira MJ, Oliveira C, et al. Kidney Transplant from Elderly Donors: A Center Experience. *Transplant Proc* (2020) 52(5):1265–8. doi:10.1016/j.transproceed.2019.12.051
120. Oppenheimer F, Aljama P, Asensio Peinado C, Bustamante Bustamante J, Crespo Albiach JF, Guirado Perich L. The Impact of Donor Age on the Results of Renal Transplantation. *Nephrol Dial Transplant* (2004) 19:iii11–5. doi:10.1093/ndt/gfh1008
121. Perez-Saez MJ, Lafuente Covarrubias O, Hernandez D, Moreso F, Melilli E, Juega J, et al. Early Outcomes of Kidney Transplantation from Elderly Donors after Circulatory Death (GEODAS Study). *BMC Nephrol* (2019) 20(1):233. doi:10.1186/s12882-019-1412-0
122. Resende L, Guerra J, Santana A, Mil-Homens C, Abreu F, da Costa AG. Impact of Donor Age on Renal Allograft Function and Survival. *Transplant Proc* (2009) 41(3):794–6. doi:10.1016/j.transproceed.2009.01.064
123. Roselli E, Rossetti O, Soldano S, Aseni P, Colombo V, De Gasperi A, et al. Renal Grafts from Elderly Donors: Histological Studies and Long-Term

Results. *Transplant Proc* (2007) 39(6):1820–2. doi:10.1016/j.transproceed.2007.05.034
124. Thornton SR, Hamilton N, Evans D, Fleming T, Clarke E, Morgan J, et al. Outcome of Kidney Transplantation from Elderly Donors after Cardiac Death. *Transplant Proc* (2011) 43(10):3686–9. doi:10.1016/j.transproceed.2011.09.078
125. Hricik DE, Poggio ED, Woodside KJ, Sarabu N, Sanchez EQ, Schulak JA, et al. Effects of Cellular Sensitization and Donor Age on Acute Rejection and Graft Function after Deceased-Donor Kidney Transplantation. *Transplantation* (2013) 95(10):1254–8. doi:10.1097/TP.0b013e31828ad866
126. Park WY, Choi MS, Kim YS, Choi BS, Park CW, Yang CW, et al. Impact of Acute Kidney Injury in Expanded Criteria Deceased Donors on Post-Transplant Clinical Outcomes: Multicenter Cohort Study. *BMC Nephrol* (2019) 20(1):39. doi:10.1186/s12882-019-1225-1
127. Yu CC, Ho HC, Ou YC, Cheng CL, Su CK, Chen WM, et al. Kidneys from Standard-Criteria Donors with Different Severities of Terminal Acute Kidney Injury. *Transplant Proc* (2014) 46(10):3335–8. doi:10.1016/j.transproceed.2014.11.002
128. Hall IE, Schroppel B, Doshi MD, Ficek J, Weng FL, Hasz RD, et al. Associations of Deceased Donor Kidney Injury with Kidney Discard and Function after Transplantation. *Am J Transplant* (2015) 15(6):1623–31. doi:10.1111/ajt.13144
129. Boffa C, van de Leemkolk F, Curnow E, Homan van der Heide J, Gilbert J, Sharples E, et al. Transplantation of Kidneys from Donors with Acute Kidney Injury: Friend or Foe? *Am J Transpl* (2017) 17(2):411–9. doi:10.1111/ajt.13966
130. Yu Myeon, Kim YC, Yu BC, Min SI, Ha J, Yang J, et al. Trend, Not Severity, of Acute Kidney Injury Affects Graft Outcome in Deceased Donor Kidney Transplantation. *Clin Transplant* (2018) 32(12):e13431. doi:10.1111/ctr.13431
131. Torabi J, Graham JA, Choinski K, Suresh S, Chokechanachaisakul A, Ajaimy M, et al. Young Donors with Severe Acute Kidney Injury Offer an Opportunity to Expand the Donor Pool. *Am J Surg* (2019) 218(1):7–13. doi:10.1016/j.amjsurg.2019.04.005
132. Kwon JA, Park H, Park SJ, Cho HR, Noh M, Kwon EK, et al. Factors of Acute Kidney Injury Donors Affecting Outcomes of Kidney Transplantation from Deceased Donors. *Transplant Proc* (2019) 51(8):2575–81. doi:10.1016/j.transproceed.2019.03.068
133. van der Windt DJ, Jorgensen DR, Bou-Samra P, Molinari M, Wijkstrom M, Ganoza A, et al. Donor Acute Kidney Injury and its Effect on 1-Year Post-Transplant Kidney Allograft Fibrosis. *Clin Transplant* (2020) 34(2):e13770. doi:10.1111/ctr.13770
134. Park WY, Chang YK, Kim YS, Jin K, Yang CW, Han S, et al. Impact of Acute Kidney Injury in Deceased Donors with High Kidney Donor Profile Index on Posttransplant Clinical Outcomes: A Multicenter Cohort Study. *Kidney Res Clin Pract* (2021) 40(1):162–74. doi:10.23876/j.krcp.20.083
135. Jung CW, Park KT, Kim SY, Kim SJ, Kim MG, Jo SK, et al. Clinical Outcomes in Kidney Transplantation Patients from Deceased Donors with Acute Kidney Injury. *Transplant Proc* (2013) 45(8):2941–5. doi:10.1016/j.transproceed.2013.08.048
136. Farney AC, Rogers J, Orlando G, Al-Geizawi S, Buckley M, Farooq U, et al. Evolving Experience Using Kidneys from Deceased Donors with Terminal Acute Kidney Injury. *J Am Coll Surgeons* (2013) 216(4):645–55. doi:10.1016/j.jamcollsurg.2012.12.020
137. Ko KJ, Kim YH, Kim MH, Jun KW, Kwon KH, Kim HS, et al. Kidney Transplantation Using Expanded Criteria Deceased Donors with Terminal Acute Kidney Injury: A Single Center Experience in Korea. *Ann Surg Treat Res* (2018) 95(5):278–85. doi:10.4174/astr.2018.95.5.278
138. Ugarte R, Kraus E, Montgomery RA, Burdick JF, Ratner L, Haas M, et al. Excellent Outcomes after Transplantation of Deceased Donor Kidneys with High Terminal Creatinine and Mild Pathologic Lesions. *Transplantation* (2005) 80(6):794–800. doi:10.1097/01.tp.0000173801.33878.bf
139. Karachristos A, Herrera A, Darrah J, Baribault C, Lee I, Leech SH, et al. Outcomes of Renal Transplantation in Older High Risk Recipients: Is There an Age Effect? *J Surg Res* (2010) 161(2):173–8.
140. Sohrabi S, Navarro AP, Wilson C, Sanni A, Wyrley-Birch H, Anand DV, et al. Donation after Cardiac Death Kidneys with Low Severity Pre-Arrest Acute Renal Failure. *Am J Transplant* (2007) 7(3):571–5. doi:10.1111/j.1600-6143.2006.01639.x
141. Zuckerman JM, Singh RP, Farney AC, Rogers J, Stratta RJ. Single Center Experience Transplanting Kidneys from Deceased Donors with Terminal Acute Renal Failure. *Surgery* (2009) 146(4):686–94. doi:10.1016/j.surg.2009.06.036
142. Rodrigo E, Pinera C, Fernandez-Fresnedo G, Ruiz J, Ruiz J, Gago M, et al. Using RIFLE Criteria to Evaluate Acute Kidney Injury in Brain-Deceased Kidney Donors. *Nephrol Dial Transplant* (2010) 25(5):1531–7.
143. Kolonko A, Wiecek A, Chudek J, Pawlik A, Wilk J, Jalowiecki P. Acute Kidney Injury before Organ Procurement Is Associated with Worse Long-Term Kidney Graft Outcome. *Transplant Proc* (2011) 43(8):2871–4. doi:10.1016/j.transproceed.2011.07.017
144. Yuan XP, Han M, Wang XP, Zhou J, Jiao XY, Wang CX, et al. Kidney Transplantation from Cardiac Death Donors with Terminal Acute Renal Failure. *Transpl Proc* (2014) 46(4):1057–60. doi:10.1016/j.transproceed.2013.11.055
145. Lee MH, Jeong EG, Chang JY, Kim Y, Kim JI, Moon IS, et al. Clinical Outcome of Kidney Transplantation from Deceased Donors with Acute Kidney Injury by Acute Kidney Injury Network Criteria. *J Crit Care* (2014) 29(3):432–7. doi:10.1016/j.jcrc.2013.12.016
146. Molina M, Apaza J, Gonzalez Monte E, Gutierrez Martinez E, Sevillano AM, Polanco N, et al. Results of Kidney Transplantation from Deceased Donors with Acute Kidney Injury. *Transplant Proc* (2015) 47(1):42–4. doi:10.1016/j.transproceed.2014.11.007
147. Ali T, Dimassi W, Elgamal H, Alabassi A, Aleid H, Altalhi M, et al. Outcomes of Kidneys Utilized from Deceased Donors with Severe Acute Kidney Injury. *QJM* (2015) 108(10):803–11. doi:10.1093/qjmed/hcv033
148. Gwon JG, Jung CW, Kim MG, Park KT, Ko SY. Clinical Outcomes in Kidney Transplantation from Deceased Donors with Acute Kidney Injury Based on Acute Kidney Injury Network Criteria. *Transplant Proc* (2018) 50(8):2426–30. doi:10.1016/j.transproceed.2018.03.072
149. Bauer J, Grzella S, Bialobrzecka M, Berger L, Viebahn R, Schenker P, et al. Success of Kidney Transplantations from Deceased Donors with Acute Kidney Injury. *Ann Transplant* (2018) 23:836–44. doi:10.12659/AOT.912660
150. Jiang Y, Song T, Liu J, Wang Z, Wang X, Huang Z, et al. Single Kidney Transplantation from Donors with Acute Kidney Injury: A Single-Center Experience. *Pediatr Transplant* (2019) 23(3):e13326. doi:10.1111/petr.13326
151. Cima L, Ghimenton C, Valotto G, Brunelli M, Eccher A, Nacchia F, et al. Histopathology and Long-Term Outcome of Kidneys Transplanted from Donors with Severe Acute Kidney Injury. *Prog Transplant (Aliso Viejo, Calif)* (2019) 29(1):36–42. doi:10.1177/1526924818817054
152. Domagala P, Gorski L, Wszola M, Kieszek R, Diuwe P, Goralski P, et al. Successful Transplantation of Kidneys from Deceased Donors with Terminal Acute Kidney Injury. *Ren Fail* (2019) 41(1):167–74. doi:10.1080/0886022X.2019.1590209
153. Schutte-Nutgen K, Finke M, Ehlert S, Tholking G, Pavenstadt H, Suwelack B, et al. Expanding the Donor Pool in Kidney Transplantation: Should Organs with Acute Kidney Injury Be Accepted? A Retrospective Study. *PloS one* (2019) 14(3):e0213608. doi:10.1371/journal.pone.0213608
154. Liu C, Hall IE, Mansour S, Thiessen Philbrook HR, Jia Y, Parikh CR. Association of Deceased Donor Acute Kidney Injury with Recipient Graft Survival. *JAMA Netw open* (2020) 3(1):e1918634. doi:10.1001/jamanetworkopen.2019.18634
155. Ko K, Kim YH, Kim MH, Jun KW, Hwang JK, Kim SD, et al. Effect of Donor-Recipient Age Match in Expanded Criteria Deceased Donor Kidney Transplantation. *Transplant Proc* (2017) 49(5):982–6. doi:10.1016/j.transproceed.2017.03.058
156. Pérez-Sáez MJ, Juega J, Zapatero A, Comas J, Tort J, Lauzurica R, et al. Kidney Transplant Outcomes in Elderly Recipients with Controlled Donation after Circulatory Death or Donation after Brain Death Donors: A Registry Cohort Study. *Transpl Int* (2021) 34(12):2507–14.
157. Sánchez-Fructuoso AI, Pérez-Flores I, Del Río F, Blázquez J, Calvo N, et al. Moreno de la Higuera MÁ Uncontrolled Donation after Circulatory Death: A Cohort Study of Data from a Long-Standing Deceased-Donor Kidney Transplantation Program. *Am J Transpl* (2019) 19(6):1693–707. doi:10.1111/ajt.15243
158. Molina M, Guerrero-Ramos F, Fernández-Ruiz M, González E, Cabrera J, Morales E, et al. Kidney Transplant from Uncontrolled Donation after

Circulatory Death Donors Maintained by nECMO Has Long-Term Outcomes Comparable to Standard Criteria Donation after Brain Death. *Am J Transpl* (2019) 19(2):434–47. doi:10.1111/ajt.14991

159. Aida N, Ito T, Kurihara K, Naka Mieno M, Nakagawa Y, Kenmochi T. Analysis of Risk Factors for Donation after Circulatory Death Kidney Transplantation in Japan. *Clin Exp Nephrol* (2022) 26(1):86–94. doi:10.1007/s10157-021-02128-2
160. Chen G, Wang C, Ko DSC, Qiu J, Yuan X, Han M, et al. Comparison of Outcomes of Kidney Transplantation from Donation after Brain Death, Donation after Circulatory Death, and Donation after Brain Death Followed by Circulatory Death Donors. *Clin Transpl* (2017) 31(11). doi:10.1111/ctr.13110
161. Snoeijs MGJ, Winkens B, Heemskerk MBA, Hoitsma AJ, Christiaans MHL, Buurman WA, et al. Kidney Transplantation from Donors after Cardiac Death: A 25-Year Experience. *Transplantation* (2010) 90(10):1106–12. doi:10.1097/TP.0b013e3181f83b0b
162. Trotter PB, Jochmans I, Hulme W, Robb M, Watson C, Neuberger J, et al. Transplantation of Kidneys from DCD and DBD Donors Who Died after Ligature Asphyxiation: The UK Experience. *Am J Transpl* (2018) 18(11):2739–51. doi:10.1111/ajt.14989
163. Yuan Xpeng, Han M, Wang Xping, Zhou J, Chen Cbao, shun HX. One Center's Experiences of 101 Cases of Kidney Transplants from Cardiac Death Donors. *Exp Clin Transpl* (2014) 12(4):304–9.
164. Savoye E, Legeai C, Branchereau J, Gay S, Riou B, Gaudez F, et al. Optimal Donation of Kidney Transplants after Controlled Circulatory Death. *Am J Transpl* (2021) 21(7):2424–36. doi:10.1111/ajt.16425
165. Heylen L, Jochmans I, Samuel U, Tieken I, Naesens M, Pirenne J, et al. The Duration of Asystolic Ischemia Determines the Risk of Graft Failure after Circulatory-Dead Donor Kidney Transplantation: A Eurotransplant Cohort Study. *Am J Transpl* (2018) 18(4):881–9. doi:10.1111/ajt.14526
166. Kostakis ID, Kassimatis T, Flach C, Karydis N, Kessaris N, Loukopoulos I. Hypoperfusion Warm Ischaemia Time in Renal Transplants from Donors after Circulatory Death. *Nephrol Dial Transpl* (2020) 35(9):1628–34. doi:10.1093/ndt/gfaa160
167. Lafuente O, Sánchez-Sobrino B, Pérez M, López-Sánchez P, Janeiro D, Rubio E, et al. Midterm Results of Renal Transplantation from Controlled Cardiac Death Donors Are Similar to Those from Brain Death Donors. *Transpl Proc* (2016) 48(9):2862–6. doi:10.1016/j.transproceed.2016.08.039
168. Lia D, Singer P, Nair V, Yang J, Teperman L, Grodstein E. DCD Renal Transplantation from Donors with Acute Kidney Injury. *Transplantation* (2021) 105(4):886–90. doi:10.1097/TP.0000000000003317
169. Miñambres E, Rodrigo E, Suberviola B, Valero R, Quintana A, Campos F, et al. Strict Selection Criteria in Uncontrolled Donation after Circulatory Death Provide Excellent Long-Term Kidney Graft Survival. *Clin Transpl* (2020) 34(9):e14010. doi:10.1111/ctr.14010
170. Chopra B, Sureshkumar KK, Rajasundaram D, Rodrigo EC. Outcomes of Kidney Transplant Recipients (KTRs) Comparing Brain Dead Donors' vs Donation after Cardiac Death Stratified by KDPI, Focus on Marginal Kidneys: A UNOS Database Analysis. *Am J Transplant* 21(S4):356–7.
171. Axelrod DA, Schnitzler MA, Xiao H, Irish W, Tuttle-Newhall E, Chang SH, et al. An Economic Assessment of Contemporary Kidney Transplant Practice. *Am J Transplant* (2018) 18(5):1168–76. doi:10.1111/ajt.14702
172. Whiting JF, Woodward RS, Zavala EY, Cohen DS, Martin JE, Singer GG, et al. Economic Cost of Expanded Criteria Donors in Cadaveric Renal Transplantation: Analysis of Medicare Payments. *Transplantation* (2000) 70(5):755–60. doi:10.1097/00007890-200009150-00007
173. Yaffe HC, von Ahrens D, Urioste A, Mas VR, Akalin E. Impact of Deceased-Donor Acute Kidney Injury on Kidney Transplantation. *Transplantation* (2024) 108(6):1283–95. doi:10.1097/TP.0000000000004848
174. Rosaasen C, Rosaasen N, Mainra R, Trachtenberg A, Ho J, Parsons C, et al. Waitlisted and Transplant Patient Perspectives on Expanding Access to Deceased-Donor Kidney Transplant: A Qualitative Study. *Can J Kidney Health Dis* (2022) 9:20543581221100291. doi:10.1177/20543581221100291
175. Tingle SJ, Figueiredo RS, Moir JA, Goodfellow M, Talbot D, Wilson CH. Machine Perfusion Preservation versus Static Cold Storage for Deceased Donor Kidney Transplantation. *Cochrane Database Syst Rev* (2019) 2019(3):CD011671. doi:10.1002/14651858.CD011671.pub2
176. Tedesco Silva H, Ramos TRde M, de Carvalho DDBM, Ferreira GF, de Andrade JMM, de Andrade LGM, et al. Use of Machine Perfusion to Increase the Number of Expanded Criteria Deceased Donor Kidney Transplants: A Pharmacoeconomic Analysis. *Transpl Direct* (2024) 10(8):e1668. doi:10.1097/TXD.0000000000001668
177. Cho YW, Bunnapradist S, Cho ES, Stadtler M, Simmons V, Locke J, et al. Can Machine Perfusion Decrease the Likelihood of Discard Among Biopsied Kidneys? *Transpl Proc* (2008) 40(4):1029–31. doi:10.1016/j.transproceed.2008.03.062
178. Stewart DE, Garcia VC, Rosendale JD, Klassen DK, Carrico BJ. Diagnosing the Decades-Long Rise in the Deceased Donor Kidney Discard Rate in the United States. *Transplantation* (2017) 101(3):575–87. doi:10.1097/TP.0000000000001539
179. Lentine KL, Kasiske B, Axelrod DA. Procurement Biopsies in Kidney Transplantation: More Information May Not Lead to Better Decisions. *J Am Soc Nephrol* (2021) 32(8):1835–7. doi:10.1681/ASN.2021030403
180. Sung RS, Christensen LL, Leichtman AB, Greenstein SM, Distant DA, Wynn JJ, et al. Determinants of Discard of Expanded Criteria Donor Kidneys: Impact of Biopsy and Machine Perfusion. *Am J Transplant* (2008) 8(4):783–92. doi:10.1111/j.1600-6143.2008.02157.x
181. Keijbeck A, Veenstra R, Pol RA, Konijn C, Jansen N, Van Goor H, et al. The Association between Macroscopic Arteriosclerosis of the Renal Artery, Microscopic Arteriosclerosis, Organ Discard, and Kidney Transplant Outcome. *Transplantation* (2020) 104(12):2567–74. doi:10.1097/TP.0000000000003189
182. Yi Z, Xi C, Menon MC, Cravedi P, Tedla F, Soto A, et al. A Large-Scale Retrospective Study Enabled Deep-Learning Based Pathological Assessment of Frozen Procurement Kidney Biopsies to Predict Graft Loss and Guide Organ Utilization. *Kidney Int* (2024) 105(2):281–92. doi:10.1016/j.kint.2023.09.031
183. Pierobon ES, Sandrini S, De Fazio N, Rossini G, Fontana I, Boschiero L, et al. Optimizing Utilization of Kidneys from Deceased Donors over 60 Years: Five-Year Outcomes after Implementation of a Combined Clinical and Histological Allocation Algorithm. *Transpl Int* (2013) 26(8):833–41. doi:10.1111/tri.12135

ESOT | Transplant International

ORIGINAL RESEARCH
published: 27 June 2025
doi: 10.3389/ti.2025.14748

# Long-Term Prognostic Value of AFP and PIVKA-II in HCC After Living Donor Liver Transplantation: A Single-Center Retrospective Study

*Saran Ochir Gongor[1], YoungRok Choi[1,2]*, Gayoung Kim[2], Min Kyoung Kim[2], Sang Hyuk Park[2], Jiyoung Kim[2], Jae-Yoon Kim[1,2], Su young Hong[2], Jeong-Moo Lee[2], Suk Kyun Hong[1,2] and Kwang-Woong Lee[1,2]*

[1]Department of Surgery, Seoul National University College of Medicine, Seoul, Republic of Korea, [2]Department of Surgery, Seoul National University Hospital, Seoul, Republic of Korea

Despite the development of numerous prognostic models for hepatocellular carcinoma (HCC) recurrence and mortality after liver transplantation, tumor biomarkers such as alpha-fetoprotein (AFP) and protein induced by vitamin K absence-II (PIVKA-II) remain widely used in clinical practice. This study evaluated the performance of AFP and PIVKA-II compared with six prognostic models (RETREAT, SNAPP, MoRAL, R3-AFP, METROTICKET 2.0, and SALT) in a retrospective cohort of 707 adults who underwent living donor liver transplantation (LDLT) for HCC between 2003 and 2018. Patients were stratified into Milan and Beyond Milan groups. Time-dependent receiver operating characteristic curve analysis was conducted using integrated area under the curve (iAUC) and concordance index (C-index) to assess recurrence and mortality. AFP and PIVKA-II (continuous) achieved iAUCs of 0.68–0.75 for recurrence and C-indices of 0.66–0.77 for mortality. Their combination reached iAUCs up to 0.78 and C-indices up to 0.80. Threshold models (AFP ≥200, PIVKA-II ≥400) showed modest predictive performance. Among multivariable models, R3-AFP demonstrated the most consistent performance (iAUC 0.76–0.81; C-index 0.78–0.82). SNAPP, MoRAL, and SALT also performed well. AFP and PIVKA-II may offer practical utility in resource-limited settings. However, multivariable models remain the preferred approach where comprehensive diagnostics are available.

**Keywords: hepatocellular carcinoma (HCC), alpha-fetoprotein, living donor liver transplantation (LDLT), des-gamma carboxyprothrombin, tumor biomarker, PIVKA-II**

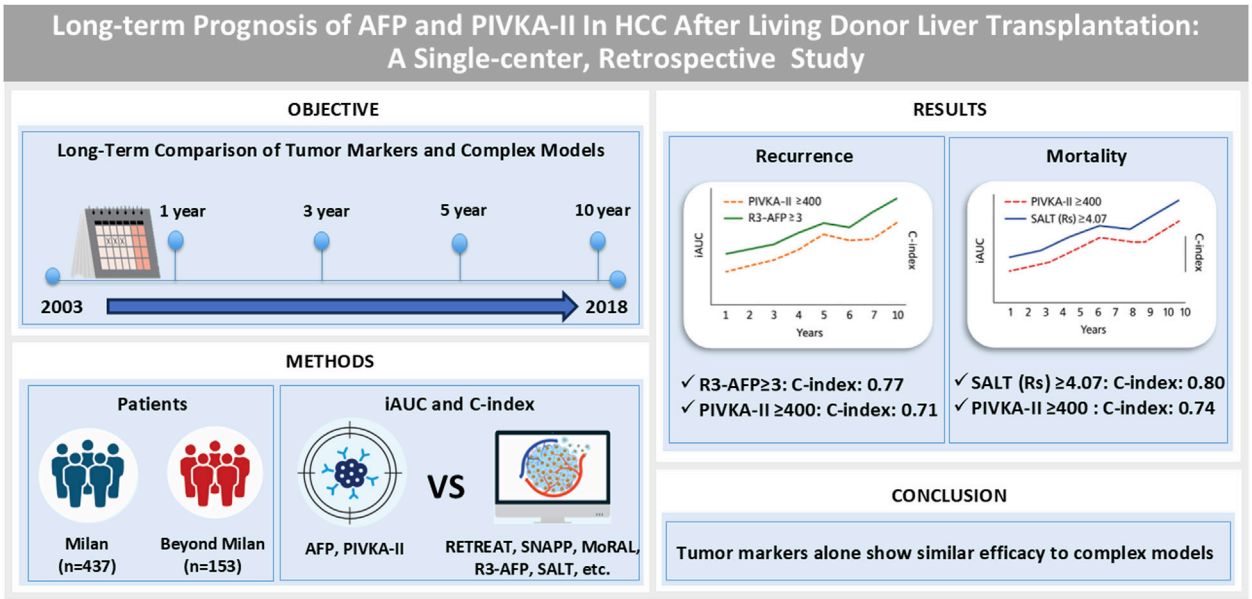
OPEN ACCESS

***Correspondence**
YoungRok Choi,
choiyoungrok@gmail.com,
play@snu.ac.kr

***Received:*** *10 April 2025*
***Accepted:*** *29 May 2025*
***Published:*** *27 June 2025*

***Citation:***
*Gongor SO, Choi Y, Kim G, Kim MK, Park SH, Kim J, Kim JY, Hong Sy, Lee JM, Hong SK and Lee KW (2025) Long-Term Prognostic Value of AFP and PIVKA-II in HCC After Living Donor Liver Transplantation: A Single-Center Retrospective Study. Transpl. Int. 38:14748. doi: 10.3389/ti.2025.14748*

**Abbreviations:** AFP, alpha-fetoprotein; DDLT, deceased-donor liver transplantation; EMR, electronic medical record; HCC, hepatocellular carcinoma; iAUC, integrated area under the curve; LDLT, living-donor liver transplantation; LT, liver transplantation; MoRAL, Model for Recurrence After Liver Transplantation; PIVKA-II, protein induced by vitamin K absence-II; R3-AFP, Recurrence-Risk Reassessment AFP; RETREAT, Risk Estimation of Tumor Recurrence After Transplant; SALT, Survival After Liver Transplantation; SNAPP, Size and Number, AFP, PIVKA-II, PET.




**GRAPHICAL ABSTRACT |**

## INTRODUCTION

Hepatocellular carcinoma (HCC) recurrence remains a concern in liver transplantation (LT), with rates ranging from 10% to 21% [1–6]. Post-LT recurrence also significantly contributes to patient mortality [2, 4, 6], despite advances in surgical and perioperative care. The Milan criteria have historically ensured excellent post-LT outcomes [2, 3, 5]. However, with an increasing number of recipients exceeding these strict morphological boundaries, the Milan criteria alone are no longer sufficient to accurately predict post-transplant outcomes.

Owing to these limitations, particularly their emphasis on tumor size and number, a paradigm shift has emerged toward incorporating tumor biology using surrogate tumor biological markers [2, 7]. This approach aims to better capture the intrinsic behavior of HCC and enhance the selection process for LT candidates [2, 7]. Moreover, the lack of standardized post-LT HCC surveillance guidelines [8, 9] has prompted the development of diverse prognostic scoring systems and refined selection protocols [3, 5, 10]. These models now integrate a broader range of factors, including radiological [2], molecular [2], serological [2, 11], and morphological [2, 5, 9] factors to promote recurrence detection and improve post-transplant survival.

The rising demand for living donor liver transplantation (LDLT) [12, 13], which frequently involves patients beyond the Milan criteria, further highlights the need for expanded selection criteria and LDLT-specific predictive models [10, 12, 13]. Consequently, several prognostic systems for LDLT have been developed, particularly in Asian centers [12, 13]. In 2016, our center introduced the Model for Recurrence After Liver Transplantation (MoRAL), a prognostic score based solely on surrogate tumor biological markers, which showed strong predictive performance, but still required complex calculations [14]. Similarly, another major Korean center proposed the SNAPP (Size and Number, alpha-fetoprotein (AFP), protein induced by vitamin K absence-II (PIVKA-II), and positron-emission tomography (PET) score, which incorporates morphological, biological (AFP and PIVKA-II), and radiological (PET) factors, demonstrating excellent prognostic utility, but requires PET results [15].

Moreover, in Western countries, the majority of LT is performed with deceased donor liver transplantation (DDLT) settings; therefore, most prognostic systems are developed based on DDLT. This could be another reason for the unlimited access to certain LDLT centers [14–17]. In particular, among deceased-donor LT (DDLT) cohorts, scoring systems such as the Risk Estimation of Tumor Recurrence After Transplant (RETREAT), which integrates additional microvascular invasion status [16], and the recurrence-risk reassessment AFP (R3-AFP) [17], have also been developed and have demonstrated strong predictive performance for HCC recurrence but still require additional factors such as histopathologic differentiation grade. For survival-specific outcomes, tools such as the Survival After Liver Transplantation (SALT) calculator [18] and METROTICKET 2.0 [19] have yielded concordance (C)-indices exceeding 70%. It is fair to say that most high-volume centers worldwide proposed their own selection criteria or

scoring systems for HCC in LT; however, unlike during the Milan era, these models are not uniformly reached to an consensus or consistently adopted in routine clinical practice [2, 7]. Since the target groups differ [14–17], their actual clinical applicability is limited. Moreover, despite the robust predictive performance of these models, their complexity and reliance on advanced diagnostics [8, 20] hamper their routine clinical implementation. Consequently, only a few of these scoring systems are consistently utilized in clinical practice, especially in LDLT [8, 20].

Advances in surgical techniques, immunosuppressive strategies, and systemic therapies, including immune checkpoint inhibitors [21], have significantly improved long-term post-transplant survival [22], with mean survival rates now exceeding 20 years [23, 24]. Despite this progress, long-term outcomes, such as HCC recurrence and mortality over extended periods, remain insufficiently understood [25]. Most prognostic models are designed to predict recurrence or post-LT mortality within 3 or 5 years [2, 7]. In particular, there is a lack of validated, simplified prognostic models for long-term (>5 years) outcomes after LDLT that rely solely on biochemical markers such as AFP and PIVKA-II [25].

In this context, AFP [1, 11, 26–30] and PIVKA-II [26, 31] levels remain pivotal as readily obtainable biomarkers, with decades-long validation as accurate and reliable indicators in clinical practice, and continue to provide crucial insights into tumor recurrence and survival outcomes through simple and singular measurements. More complex prognostic models, however, require additional measurements, and their use is generally limited to specific circumstances [17, 20], meaning they are typically only available in tertiary or quaternary medical facilities.

We hypothesized that AFP and PIVKA-II levels would show performance comparable to that of highly accurate complex prognostic models, particularly for predicting recurrence, mortality, and outcomes beyond 5-year post-LT, while being simpler to use. This study, therefore, compared the predictive accuracy of models for predicting recurrence and mortality with that of these two traditional biomarkers. Additionally, we evaluated the accuracy of the predictive ability of individual and combined values of AFP and PIVKA-II for predicting outcomes beyond 5-year post-LT and their utility in predicting location-specific HCC recurrence.

# MATERIALS AND METHODS

## Study Design and Patients

A single-center, retrospective analysis was performed on 707 patients with HCC who underwent adult LDLT at Seoul National University Hospital between 2003.01.01 and 2018.12.31. The last follow-up date was 2024.01.31 (**Figure 1**). The inclusion criteria were as follows: 1. age ≥19 years; 2. diagnosis of HCC following LDLT based on explant pathology reports; and 3. with available AFP and PIVKA-II measurements prior to transplantation. The exclusion criteria were as follows: 1. non-diagnosis of HCC following LDLT based on explant pathology; 2. re-transplantation; 3. missing AFP and PIVKA-II measurements; and 4. combined intra-hepatic carcinoma-hepatocellular carcinoma or intra-hepatic carcinoma. Diagnosis of HCC was based on postoperative histopathological examination. The study patients were subsequently categorized into the Milan cohort (MC) and Beyond Milan cohort (BMC) based on explant pathology.

## Data Collection

Preoperative data, including demographic and clinical information, such as age, sex, body mass index (BMI), arterial hypertension, diabetes mellitus, underlying disease (such as HCV and HBV infections), AFP level, PIVKA-II level, and Model for End-stage Liver Disease scores, were extracted from electronic medical records (EMRs). Records of pre-transplant interventions, such as hepatectomy, transarterial chemoembolization, radiofrequency ablation, and percutaneous ethanol injection therapy, were reviewed from the EMRs. Tumor characteristics, including vascular invasion status (microvascular or macrovascular), tumor size, number of tumors, tumor stage, and differentiation grade, were extracted from post-LT pathological reports. HCC diagnosis, total necrosis, and graft-to-recipient weight ratio were confirmed by explant pathology findings. Overall survival (OS) was defined as the period from the date of liver transplantation until death from any cause. Patients who were alive at the last follow-up were censored. Recurrence-free survival (RFS) was defined as the duration from the date of liver transplantation to the first radiological or pathological evidence of HCC recurrence or death from any cause, whichever occurred first. Patients without recurrence or death were censored at the last follow-up date.

## Assessment of Cox Prediction Models and Statistical Analysis

Preoperative AFP and PIVKA-II levels, as individual predictors, and four prognostic scores for HCC recurrence (SNAPP, RETREAT, MoRAL, and R3-AFP) were evaluated in both the MC and BMC [14–17]. AFP, PIVKA-II, SALT, and METROTICKET 2.0 scores were evaluated to predict post-LT mortality for both the MC and BMC [18, 19]. All prognostic scores were calculated retrospectively utilizing explant pathology reports, preoperative measurements, and radiological data. Time-dependent receiver operating characteristic (ROC) analysis was performed using Uno's integrated area under the curve (iAUC), with inverse probability of censoring weighting (IPCW), to evaluate the dynamic predictive performance of the Cox regression models applied to both composite scores and individual biological tumor markers for HCC recurrence and mortality [32]. Furthermore, to assess the overall predictive ability of each model, Harrell's C-index was calculated from the Cox regression models for both recurrence and mortality outcomes [33]. Confidence intervals for Uno's iAUC were derived from 1,000 bootstrap samples, and iAUC values were compared between models using 1,000 bootstrap iterations to ensure the robustness and statistical reliability of the estimate [34, 35].

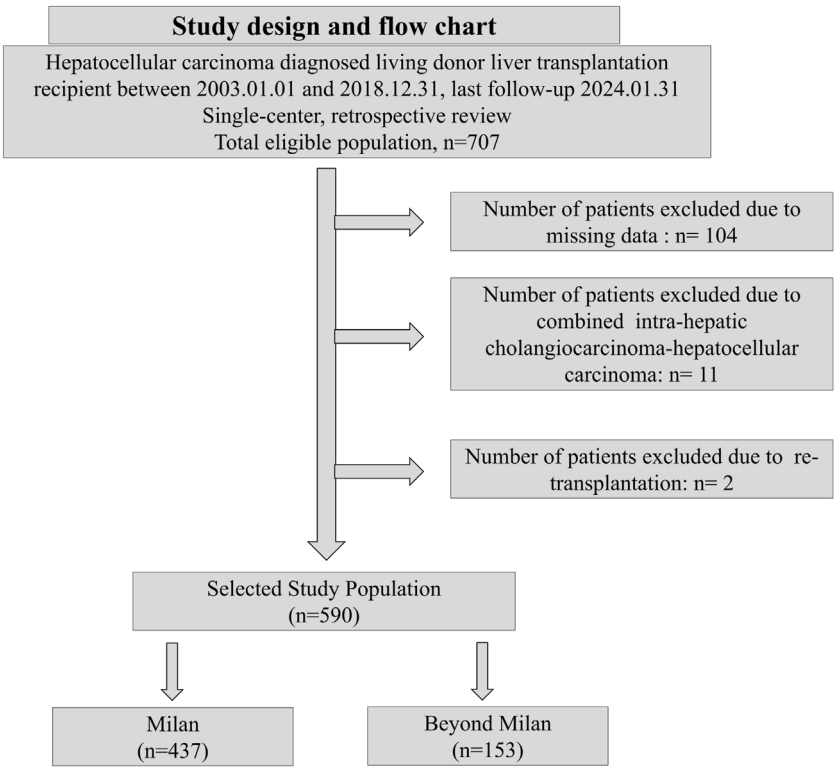



**FIGURE 1 |** Study design and flow chart.

Continuous variable Cox regression models utilized calculated scores from prognostic models or measurements of biological markers, such as AFP and PIVKA-II levels, to predict HCC recurrence or survival following LDLT. In contrast, the threshold value binary Cox regression models were constructed using previously reported or validated threshold values (**Supplementary Table S3**). The Cox model specifications were as follows: AFP ≥200 (ng/mL) and PIVKA-II ≥400 (mAU/mL) cutoff values for predicting HCC recurrence and mortality were employed, as previously described [36, 37]. The SNAPP score was calculated using AFP, PIVKA-II, tumor size, number, and PET metabolic status, with a SNAPP ≥5 score used as a cutoff to indicate a high risk of HCC recurrence, as previously described [15]. The RETREAT score was calculated using the explant microvascular invasion status, largest tumor size, and preoperative AFP level, with RETREAT ≥5 indicating the high-risk group and as a threshold, as previously described [16]. The MoRAL score was calculated using preoperative AFP and PIVKA-II levels with a cutoff of 314.8, as previously described [14]. The R3-AFP score was based on the number of nodules, size of the largest tumor nodule, AFP level, microvascular invasion status, and tumor differentiation grade (Edmonson and Steiner grade >2), with a cutoff R3-AFP ≥3 score for cox models, as previously described [17]. SALT was based on the risk score, with a risk score ≥4.07 used as a threshold for higher mortality, as previously described [18]. The METROTICKET transplantability score was based on three categories: 1. If AFP <200 ng/mL, the sum of the number and size ≤7; 2; if 200 ≤ AFP <400 ng/mL, the sum of the number and size ≤5; 3. if 400 ≤ AFP <1,000 ng/mL, the sum of the number and size ≤4, as described previously [19].

The Kaplan–Meier method was used to estimate overall survival and recurrence-free survival. Chi-square or Fisher's exact tests were used to compare categorical variables, and Student's t-test was used for continuous variables. Statistical analyses were performed using SPSS version 29 (IBM SPSS Inc., Armonk, NY, United States) and R version 4.4.1[1]. Uno's iAUC was calculated using "survAUC" package, and Harrell's C-index was computed using "survcomp" package in R. Cox models were fitted using "survival." All statistical tests were two-sided, with a significance threshold of 0·05, and were performed within an exploratory framework.

## Ethical Statements

This study adhered to the Declaration of Helsinki and Istanbul guidelines and was approved by the Institutional Review Board of Seoul National University Hospital (IRB-H-2502-060-1612). The need to obtain informed patient consent was waived owing to the retrospective nature of the study. This study adhered to the STROBE guideline for retrospective study and check lists are provided in the **Supplementary Material**.

[1]https://cran.r-project.org/bin/windows/base/old/4.4.1/

**TABLE 1 |** Baseline characteristics of study population.

| Variables | Milan Cohort (N = 437) | Beyond Milan Cohort (N = 153) | p-value |
|---|---|---|---|
| Age (years) | 55.5 ± 7.5 | 56.0 ± 9.4 | 0.52 |
| Sex, male | 359 (82.2%) | 137 (89.5%) | 0.03 |
| BMI | 24.2 ± 11.9 | 23.5 ± 3.3 | 0.49 |
| Hypertension | 44 (10.1%) | 16 (10.5%) | 0.89 |
| Diabetes mellitus | 70 (17.6%) | 24 (15.7%) | 0.59 |
| MELD score | 13.4 ± 7.1 | 13.1 ± 6.5 | 0.66 |
| Underlying disease | | | 0.15 |
| HBV | 354 (81.0%) | 116 (75.8%) | |
| HCV | 36 (8.2%) | 20 (13.1%) | |
| Alcoholic liver disease | 29 (6.6%) | 7 (4.6%) | |
| Others | 18 (4.1%) | 10 (6.5%) | |
| AFP (ng/mL) | 48.4 ± 149.9 | 15,125.0 ± 140,747.1 | 0.03 |
| AFP ≥200 (ng/mL) | 26 (5.9%) | 32 (20.9%) | <0.01 |
| PIVKA-II (mAU/mL) | 69.5 ± 155.4 | 3556.6 ± 11,703.0 | <0.01 |
| PIVKA-II ≥400 (mAU/mL) | 16 (3.7%) | 38 (24.8%) | <0.01 |
| MoRAL score | 81.54 ± 58.51 | 359.74 ± 687.84 | <0.01 |
| MoRAL ≥314.8 | 5 (1.1%) | 35 (22.9%) | <0.01 |
| RETREAT score | 1.4 ± 1.0 | 3.2 ± 2.0 | <0.01 |
| RETREAT ≥5 | 6 (1.4%) | 38 (24.8%) | <0.01 |
| SNAPP score | 0.9 ± 1.0 | 3.6 ± 1.7 | <0.01 |
| SNAPP ≥5 | 3 (0.7%) | 41 (26.8%) | <0.01 |
| Risk score (SALT) | 2.3 ± 0.6 | 3.4 ± 1.3 | <0.01 |
| Risk score (SALT) ≥4.07 | 4 (0.9%) | 41 (26.8%) | <0.01 |
| R3-AFP score | 0.8 ± 0.9 | 3.7 ± 2.4 | <0.01 |
| R3-AFP ≥3 | 18 (4.1%) | 88 (57.5%) | <0.01 |
| METROTICKET 2.0 transplantability | | | <0.01 |
| Eligible | 416 (95.2%) | 51 (33.3%) | |
| Ineligible | 21 (4.8%) | 102 (66.7%) | |

*Values are present with number (%) or mean ±SD or median (IQR).*

*BMI, body mass index; MELD, Model for End-Stage Liver Disease; HBV, hepatitis B virus; HCV, hepatitis C virus; LT, liver transplantation; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; PEIT, percutaneous ethanol injection therapy; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; MoRAL, Model for Recurrence After Liver Transplantation; RETREAT, Risk Estimation of Tumor Recurrence After Transplant; SNAPP, Size and Number, AFP, PIVKA-II, PET; SALT, Survival After Liver Transplantation; R3-AFP, Recurrence-Risk Reassessment AFP.*

# RESULTS

## Baseline Characteristics and Post-LT Outcomes

From 707 screened patients, 117 were excluded due to missing data, combined cholangiocarcinoma-hepatocellular carcinoma, or re-transplantation history. Finally, 590 patients who underwent LDLT were categorized into the MC (n = 437) and BMC (n = 153) groups (**Figure 1**). The baseline characteristics were similar between the groups (**Table 1**). Hepatitis B was more common in the MC (81.0% vs. 75.8%), whereas hepatitis C was more common in the BMC (13.1% vs. 8.2%, $p < 0.01$). BMC showed elevated tumor markers with higher AFP (15,125.0 vs. 48.4 ng/mL, $p = 0.03$) and PIVKA-II levels (3,556.6 vs. 69.4 mAU/mL, $p < 0.01$). More BMC patients had AFP ≥200 ng/mL and PIVKA-II ≥400 mAU/mL. Prognostic scores, tumor characteristics, and PET-CT hypermetabolic activity were worse in the BMC (44.4% vs. 11.7%, $p < 0.01$, **Table 1**; **Supplementary Table S1**). BMC patients had higher recurrence rates (50.3% vs. 10.3%), mortality (46.4% vs. 15.6%), and HCC-specific deaths (87.3% vs. 45.6%, **Table 2**). The median follow-up was longer in the MC group (113.05 vs. 70.54 months, **Table 2**), whereas recurrence-free survival was shorter in the BMC group (51.8 vs. 89.8 months, $p < 0.01$). The median follow-up duration for the entire population was 104.6 months (IQR: 68.0–145.9 months).

## Post-LT HCC Recurrence and Mortality Prediction

Individual tumor markers showed modest predictive performance (**Table 3**; **Figure 2**). In the Milan cohort, AFP (continuous, **Table 3**; **Figure 2A**) yielded an iAUC of 0.58 (95% CI: 0.47–0.68) and PIVKA-II 0.68 (95% CI: 0.60–0.75). In the Beyond Milan cohort, AFP and PIVKA-II achieved iAUCs of 0.69 (95% CI: 0.61–0.79) and 0.68 (95% CI: 0.58–0.78, **Table 3**; **Figure 2B**), respectively. Threshold models followed similar trends. AFP ≥200 had C-indices of 0.71 (95% CI: 0.53–0.90) in Milan and 0.76 (95% CI: 0.66–0.86) in Beyond Milan; PIVKA-II ≥400 reached 0.73 (95% CI: 0.52–0.93) and 0.71 (95% CI: 0.60–0.83). Combination marker models (AFP + PIVKA-II) showed improved performance. The continuous model yielded iAUCs of 0.64 (95% CI: 0.55–0.72) in Milan and 0.72 (95% CI: 0.62–0.80) in Beyond Milan. The threshold version yielded C-indices of 0.68 (95% CI: 0.50–0.86) and 0.73 (95% CI: 0.66–0.81). The MoRAL model, designed for Beyond Milan populations, achieved an iAUC of 0.65 (95% CI: 0.58–0.73, **Figure 2D**) and a C-index of 0.75 (95% CI: 0.65–0.86).

**TABLE 2 |** Post-LT outcomes.

| Variables | Milan Cohort (N = 437) | Beyond Milan Cohort (N = 153) | p-value |
|---|---|---|---|
| Recurrence | 45 (10.3%) | 77 (50.3%) | <0.01 |
| Intra-hepatic | 10 (2.3%) | 22 (14.4%) | <0.01 |
| Extra-hepatic | 35 (8.0%) | 55 (35.9%) | <0.01 |
| Number of intra-hepatic recurred tumor | | | 0.77 |
| 1 | 6 (50.0%) | 17 (47.2%) | |
| 2 | 1 (8.3%) | 6 (16.7%) | |
| Multiple | 5 (41.7%) | 13 (36.1%) | |
| Post-Recurrence Treatment | | | 0.24 |
| Untreated | 6 (13.3%) | 5 (6.5%) | |
| Transarterial chemoembolization | 10 (22.2%) | 28 (36.4%) | |
| Surgical resection | 18 (40.0%) | 21 (27.3%) | |
| Radiotherapy | 6 (13.3%) | 18 (18.2%) | |
| Chemotherapy | 3 (6.7%) | 8 (10.4%) | |
| Radiofrequency ablation | 2 (4.4%) | 1 (1.3%) | |
| Mortality | 68 (15.6%) | 71 (46.4%) | <0.01 |
| HCC specific mortality | 31 (45.6%) | 62 (87.3%) | <0.01 |
| Median follow-up, months (IQR) | 113.1 (77.7–149.0) | 70.5 (27.3–135.8) | <0.01 |
| Median recurrence free survival, months (IQR) | 89.8 ± 56.4 | 51.8 (11.8–128.2) | <0.01 |

*Values are present with number (%) or mean ±SD or median (IQR) HCC, hepatocellular carcinoma; IQR, interquartile range.*

**TABLE 3 |** Integrated AUC and C-index of HCC recurrence of both Milan and Beyond Milan cohorts.

| Prediction Cox Models | Milan Cohort (N = 437) | | Beyond Milan Cohort (N = 153) | |
|---|---|---|---|---|
| | Recurrence | | Recurrence | |
| | iAUC (95% CI) | C-index (95% CI) | iAUC (95% CI) | C-index (95% CI) |
| AFP (continuous) | 0.58 (0.47–0.68) | 0.64 (0.56–0.72) | 0.69 (0.61–0.79) | 0.63 (0.57–0.68) |
| AFP ≥200 (threshold) | 0.52 (0.48–0.57) | 0.71 (0.53–0.9) | 0.68 (0.61–0.75) | 0.76 (0.66–0.86) |
| PIVKA-II (continuous) | 0.68 (0.6–0.75) | 0.64 (0.57–0.72) | 0.68 (0.58–0.78) | 0.62 (0.55–0.69) |
| PIVKA-II ≥400 (threshold) | 0.5 (0.48–0.53) | 0.73 (0.52–0.93) | 0.63 (0.56–0.78) | 0.71 (0.6–0.83) |
| PIVKA-II + AFP (continuous) | 0.64 (0.55–0.72) | 0.66 (0.58–0.73) | 0.72 (0.62–0.8) | 0.64 (0.58–0.71) |
| PIVKA-II ≥400+AFP ≥200 (threshold) | 0.51 (0.46–0.57) | 0.68 (0.5–0.86) | 0.74 (0.65–0.82) | 0.73 (0.66–0.81) |
| SNAPP (continuous) | 0.54 (0.42–0.65) | 0.57 (0.45–0.7) | 0.72 (0.63–0.82) | 0.68 (0.61–0.76) |
| SNAPP ≥5 (threshold) | 0.52 (0.5–0.56) | 0.88 (0.72–1) | 0.73 (0.65–0.81) | 0.78 (0.69–0.87) |
| RETREAT (continuous) | 0.6 (0.48–0.72) | 0.69 (0.58–0.8) | | |
| RETREAT ≥5 (threshold) | 0.51 (0.49–0.55) | 0.75 (0.3–1) | | |
| MoRAL (continuous) | | | 0.65 (0.58–0.73) | 0.65 (0.59–0.72) |
| MoRAL ≥314.8 (threshold) | | | 0.65 (0.58–0.73) | 0.75 (0.65–0.86) |
| R3-AFP (continuous) | 0.64 (0.54–0.74) | 0.74 (0.64–0.83) | 0.79 (0.71–0.86) | 0.71 (0.64–0.77) |
| R3-AFP ≥3 (threshold) | 0.54 (0.48–0.6) | 0.76 (0.58–0.93) | 0.7 (0.63–0.76) | 0.77 (0.67–0.87) |

*iAUC, integrated area under curve; C-index, concordance index; 95%CI, 95% confidence interval; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; SNAPP, size and number, AFP, PIVKA-II, PET; RETREAT, risk estimation of tumor recurrence after transplant; MoRAL, model for recurrence after liver transplantation; R3-AFP, Recurrence-Risk Reassessment AFP.*

Models incorporating morphology and vascular invasion showed stronger performance. R3-AFP (continuous, **Table 3**; **Figure 2A**) yielded iAUCs of 0.64 (95% CI: 0.54–0.74, **Figure 2A**) in Milan and 0.79 (95% CI: 0.71–0.86, **Figure 2B**) in Beyond Milan. R3-AFP ≥3 showed C-indices of 0.76 (95% CI: 0.58–0.93) and 0.77 (95% CI: 0.67–0.87). RETREAT, evaluated specifically in the Milan cohort, showed an iAUC of 0.60 (95% CI: 0.48–0.72), and RETREAT ≥5 achieved a C-index of 0.75 (95% CI: 0.30–1.00). The SNAPP model, which incorporates tumor biology, morphology, vascular invasion, and PET metabolism, showed an iAUC of 0.54 (95% CI: 0.42–0.65) in Milan and 0.72 (95% CI: 0.63–0.82) in Beyond Milan. SNAPP ≥5 demonstrated (**Table 3**; **Figure 2**) the strongest threshold performance: 0.88 (95% CI: 0.72–1.00) in Milan and 0.78 (95% CI: 0.69–0.87) in Beyond Milan.

Individual tumor markers, including AFP and PIVKA-II, showed moderate predictive accuracy, with slightly better performance in the Beyond Milan cohort (**Table 3**). While combining these markers modestly improved discrimination, complex models such as R3-AFP and SNAPP ≥5 consistently showed higher iAUCs and C-indices across both cohorts. Recurrence-free survival for each threshold model and marker was evaluated, and results are shown in **Figure 3**.

In mortality prediction, PIVKA-II (iAUC 0.71, **Table 4**; **Figure 4**) outperformed AFP (0.53) in Milan, with

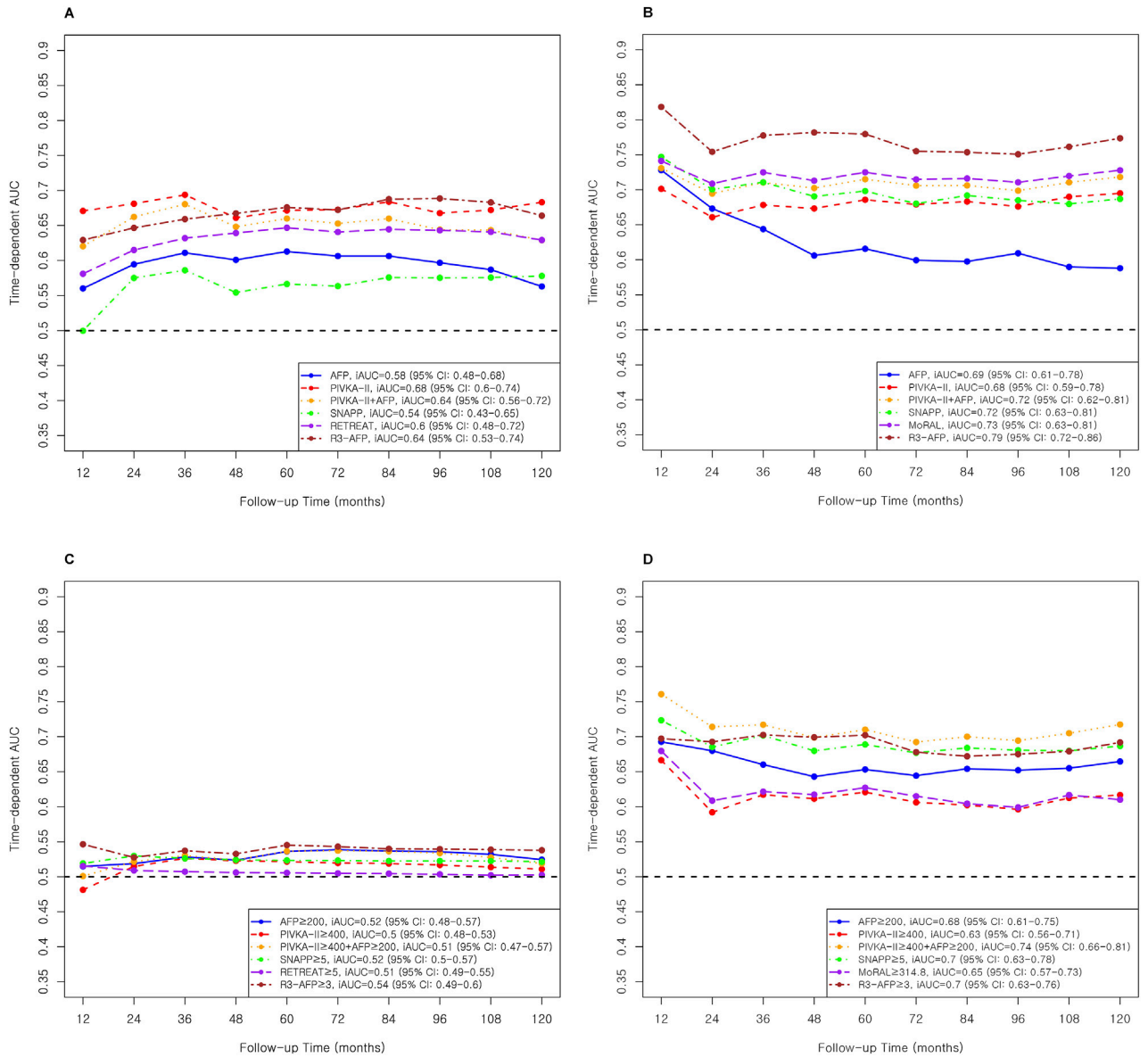



**FIGURE 2 |** AUC and iAUC for Recurrence Prediction in Milan and Beyond Milan cohort. **(A)** Continuous variable–based AUC and iAUC in the Milan cohort. **(B)** Continuous variable–based AUC and iAUC in the Beyond Milan cohort. **(C)** Threshold-based AUC and iAUC in the Milan cohort. **(D)** Threshold-based AUC and iAUC in the Beyond Milan cohort.

improvement when combined (0.66). SALT ≥4.07 had the highest C-index in Milan (0.86; 95% CI: 0.72–1.00). In Beyond Milan (**Table 4**; **Figure 4**), SALT and METROTICKET 2.0 showed C-indices of 0.80 (95% CI: 0.71–0.89) and 0.74 (95% CI: 0.62–0.86), respectively. Overall survival rates for each model are presented in **Figure 5**.

## Post-LT Location Specific HCC Recurrence Prediction

We further analyzed location-specific HCC recurrence by intrahepatic and extrahepatic patterns (**Supplementary Figures S1,S2**; **Supplementary Table S2**). In the Milan cohort, complex prognostic models incorporating tumor morphology, vascular invasion, and PET metabolic activity showed improved performance for intrahepatic recurrence. R3-AFP achieved an iAUC of 0.82 (95% CI 0.63–0.94), RETREAT ≥5 a C-index of 0.93 (95% CI 0.79–1.00), and SNAPP ≥5 a C-index of 0.96 (95% CI 0.85–1.00). In the Beyond Milan cohort, R3-AFP yielded an iAUC of 0.68 (95% CI 0.52–0.82), SNAPP ≥5 a C-index of 0.71 (95% CI 0.52–0.90), and MoRAL ≥314.8 a C-index of 0.78 (95% CI 0.61–0.94).

For extrahepatic recurrence in the Milan cohort (**Supplementary Figure S2**; **Supplementary Table S2**), AFP

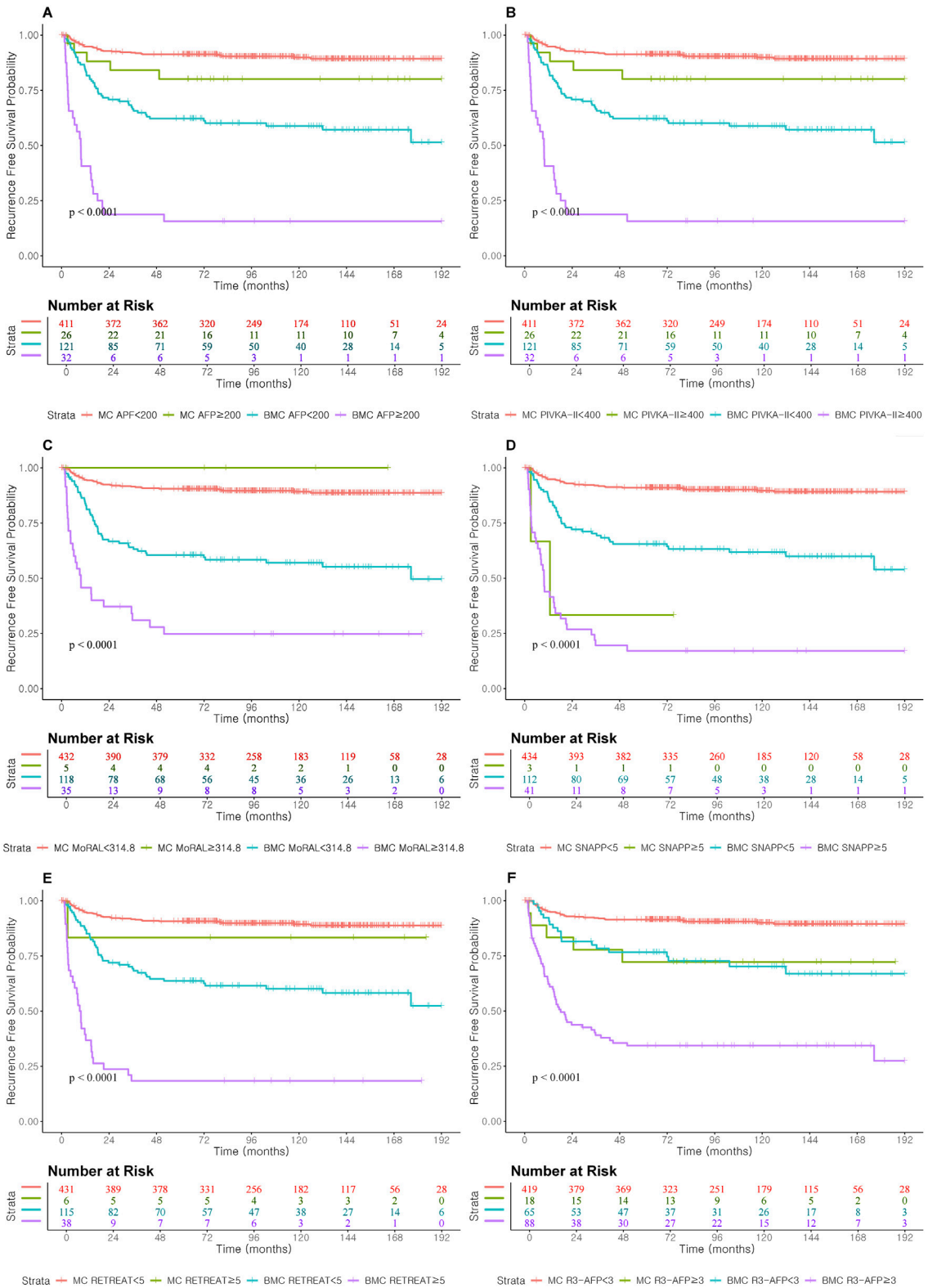



**FIGURE 3 |** Recurrence Free Survival according to prognostic score cut-off and AFP and PIVKA-II cut-off level in Milan and Beyond Milan cohort. **(A)** Recurrence Free Survival according to AFP ≥200. **(B)** Recurrence Free Survival according to PIVKA-II ≥400. **(C)** Recurrence Free Survival according to MORAL ≥314.8. **(D)** Recurrence Free Survival according to SNAPP ≥5. **(E)** Recurrence Free Survival according to RETREAT ≥5. **(F)** Recurrence Free Survival according to R3-AFP ≥3.

**TABLE 4 |** Integrated AUC and C-index of mortality prediction for both Milan and Beyond Milan cohorts.

| Prediction Cox Models | Milan Cohort (N = 437) | | Beyond Milan Cohort (N = 153) | |
|---|---|---|---|---|
| | Mortality | | Mortality | |
| | iAUC (95% CI) | C-index (95% CI) | iAUC (95% CI) | C-index (95% CI) |
| AFP (continuous) | 0.53 (0.44–0.64) | 0.6 (0.53–0.68) | 0.66 (0.57–0.76) | 0.61 (0.55–0.66) |
| AFP ≥200 (threshold) | 0.54 (0.49–0.61) | 0.72 (0.54–0.89) | 0.66 (0.58–0.74) | 0.73 (0.62–0.84) |
| PIVKA-II (continuous) | 0.71 (0.62–0.78) | 0.66 (0.59–0.73) | 0.69 (0.58–0.78) | 0.62 (0.55–0.69) |
| PIVKA-II ≥400 (threshold) | 0.53 (0.49–0.57) | 0.79 (0.65–0.93) | 0.65 (0.57–0.73) | 0.74 (0.63–0.85) |
| PIVKA-II + AFP (continuous) | 0.66 (0.57–0.75) | 0.67 (0.61–0.74) | 0.71 (0.61–0.8) | 0.64 (0.57–0.71) |
| PIVKA-II ≥400+AFP ≥200 (threshold) | 0.55 (0.49–0.62) | 0.72 (0.59–0.86) | 0.72 (0.64–0.81) | 0.73 (0.65–0.81) |
| SALT (continuous) | 0.65 (0.56–0.73) | 0.66 (0.59–0.73) | 0.72 (0.63–0.82) | 0.67 (0.61–0.74) |
| SALT ≥4.07 (threshold) | 0.53 (0.5–0.59) | 0.86 (0.72–1) | 0.69 (0.61–0.77) | 0.8 (0.71–0.89) |
| METROTICKET 2.0 (threshold) | 0.53 (0.49–0.58) | 0.74 (0.6–0.88) | 0.63 (0.56–0.69) | 0.74 (0.62–0.86) |

*iAUC, integrated area under curve; C-index, concordance index; 95%CI, 95% confidence interval; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; SALT, survival after liver transplantation.*

and PIVKA-II showed iAUCs of 0.56 (95% CI 0.45–0.67) and 0.66 (95% CI 0.57–0.75), respectively. The combined AFP + PIVKA-II model reached an iAUC of 0.61 (95% CI 0.51–0.70). Composite models outperformed individual markers: R3-AFP reached 0.60 (95% CI 0.49–0.72), and SNAPP ≥5 achieved the highest C-index at 0.81 (95% CI 0.56–1.00). In the Beyond Milan cohort, R3-AFP showed the highest iAUC at 0.83 (95% CI 0.75–0.89), followed by SNAPP at 0.77 (95% CI 0.67–0.96) and AFP + PIVKA-II at 0.73 (95% CI 0.62–0.92). Threshold models R3-AFP ≥3 and SNAPP ≥5 demonstrated C-indices of 0.86 (95% CI 0.76–0.95) and 0.80 (95% CI 0.71–0.90), respectively.

Overall, complex prognostic models provided higher predictive accuracy for both intrahepatic and extrahepatic recurrence than biomarker-only approaches (**Supplementary Table S2**). Performance was generally higher in the Beyond Milan cohort.

## DISCUSSION

The current study evaluated the predictive performance of AFP, PIVKA-II, and multiple prognostic models for HCC recurrence (RETREAT, MoRAL, SNAPP, and R3-AFP) and mortality (SALT and METROTICKET 2.0) in both MC and BMC over a 10-year period (**Table 3**). PIVKA-II exhibited consistently strong predictive performance across both cohorts. Among the complex models, R3-AFP, MoRAL, and SALT demonstrated high accuracy based on the iAUC and C-index values. The combined AFP and PIVKA-II model showed modest gains in the MC but performed comparably to the complex scores in the BMC. Continuous Cox models yielded higher iAUC values than threshold-based models by capturing the full biomarker variability, enabling precise risk estimation. Threshold models, such as AFP ≥200 or PIVKA-II ≥400, showed lower iAUCs but maintained moderate-to-high C-indices in the BMC.

### HCC Recurrence Prediction Performance of Cox Models

Single tumor markers, including PIVKA-II and AFP, showed comparable predictive accuracy to selected multivariable models in post-LT recurrence prediction. In the Milan cohort, PIVKA-II achieved higher iAUC than AFP (0.68 vs. 0.58, **Table 3**; **Figures 2A,C**), while both performed similarly in the Beyond Milan cohort (0.68 vs. 0.69). AFP showed better early discrimination but declined after 2 years, whereas SNAPP, MoRAL, and R3-AFP remained stable [3, 28, 29, 38–41]. AFP was limited in long-term prediction. Combining AFP and PIVKA-II improved prediction in Beyond Milan (iAUC: 0.72), comparable to SNAPP and MoRAL (0.72–0.73). In threshold models, PIVKA-II ≥400 had the highest C-index in Milan (0.73), whereas AFP ≥200 performed better in Beyond Milan (0.76). SNAPP ≥5 showed the highest C-index in Milan (0.88). While AFP remains widely used, dynamic assessment offers better early prediction but weaker long-term value [3, 28, 29, 38–41]. PIVKA-II shows independent accuracy, particularly for early recurrence [36, 40, 42, 43]. Continuous models offer time-sensitive monitoring advantages over fixed thresholds, and AFP and PIVKA-II integration improves risk stratification post-LT [1, 40].

The R3-AFP model, developed using data from 47 Euro-American centers, showed C-index values of 0.76–0.78 in external validation [17]. In this study, it showed the strongest long-term recurrence prediction among evaluated models (iAUC: 0.64 in Milan and 0.79 in Beyond Milan, **Table 3**; **Figures 2A,B**), and strong threshold performance (C-index: 0.76 in Milan and 0.77 in Beyond Milan). Although initially developed in DDLT populations, R3-AFP generalized well to LDLT settings. The incorporation of tumor burden and pathology appears to enhance its predictive power compared to single markers [17]. A recent study validated R3-AFP's prognostic value in LT recipients with mammalian target of rapamycin inhibitor (mTORi)-based immunosuppression, which could potentially decrease HCC recurrence and improve survival [44].

The SNAPP score showed limited performance as a continuous Cox model in the MC (iAUC: 0.58; C-index: 0.57, **Table 3**; **Figure 2**) and BMC. However, SNAPP ≥5 performed better, with C-indices of 0.88 in MC and 0.78 in BMC. For intrahepatic recurrence, continuous SNAPP had the second highest iAUC (0.73) after R3-AFP (0.82), whereas its threshold model

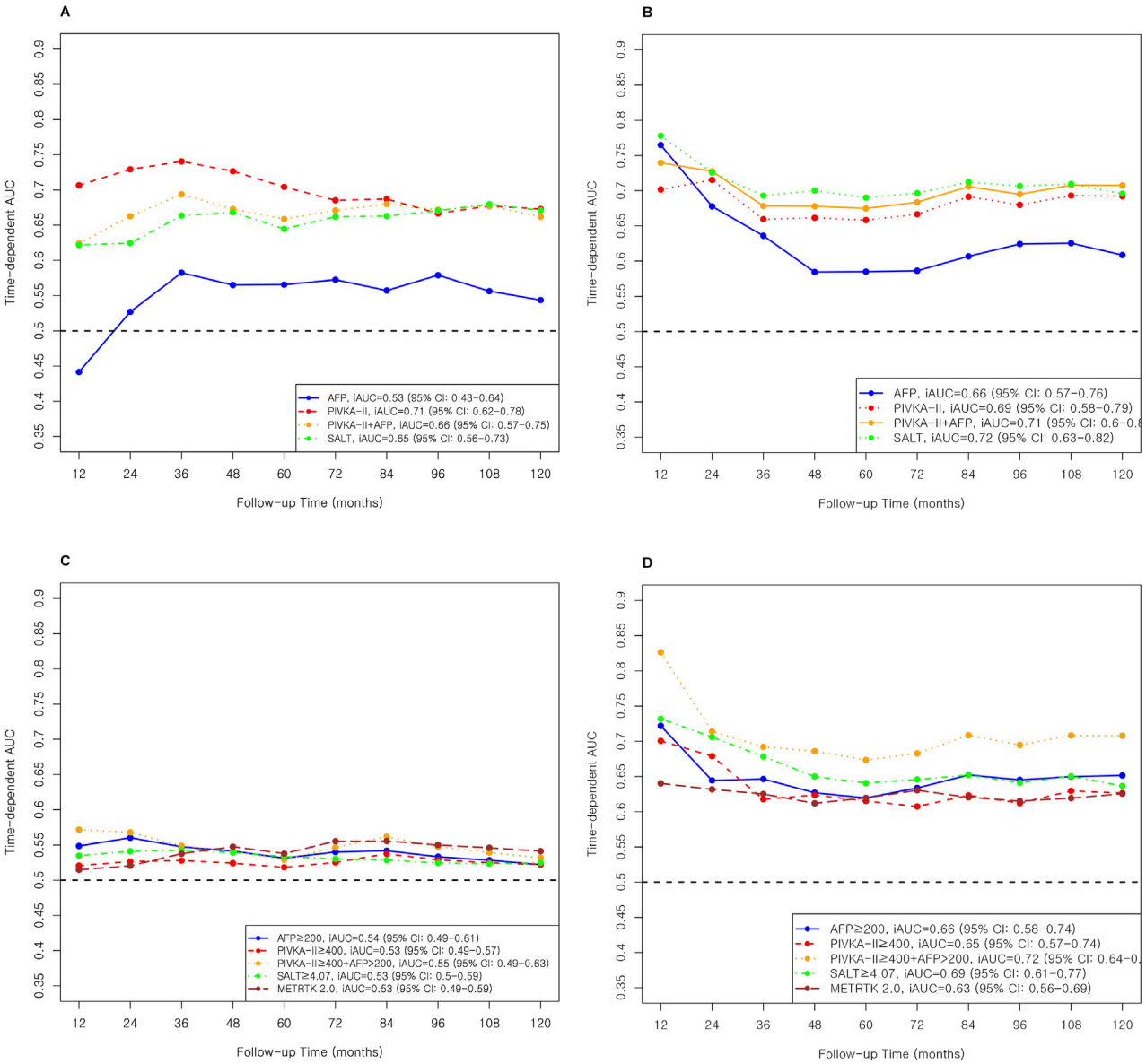



**FIGURE 4 |** AUC and iAUC for Mortality prediction in Miland and Beyond Milan cohort. **(A)** Continuous variable–based AUC and iAUC in the Milan cohort. **(B)** Continuous variable–based AUC and iAUC in the Beyond Milan cohort. **(C)** Threshold-based AUC and iAUC in the Milan cohort. **(D)** Threshold-based AUC and iAUC in the Beyond Milan cohort.

achieved the highest C-index (0.96) in the MC. For extrahepatic recurrence, SNAPP ≥5 maintained C-indices above 0.80 in both cohorts (**Supplementary Table S2**; **Supplementary Figure S2**). These results align with the model's design for LDLT populations in HBV-endemic Asian regions [15, 45]. Prior validation showed a C-index of 0.84 [15]; however, as SNAPP was developed for 5-year recurrence prediction, its fifth-year C-indices were below 80% in both cohorts (**Supplementary Tables S1, S2**).

The MoRAL score, developed in our center to assess recurrence risk beyond Milan criteria previously, was based on data collected between 2001 and 2013 [14]. Although a C-index above 80% was expected, the BMC showed a C-index of 0.75 (**Table 3**; **Figure 2**). The 10-year iAUC of MoRAL was 0.65 for BMC, similar to that of AFP and PIVKA-II. For intra-hepatic recurrence, MoRAL showed lower performance (iAUC 0.64), whereas MoRAL ≥314.8 achieved better discrimination (C-index 0.78). Lower early AUCs may reflect the model's focus on tumor markers. Studies have validated MoRAL in hepatectomy [46], and deep learning integration has improved accuracy [47]. However, partial data overlap with the original cohort requires further validation [14].

RETREAT, which was primarily validated in DDLT populations, was evaluated in the MC, aligning with its

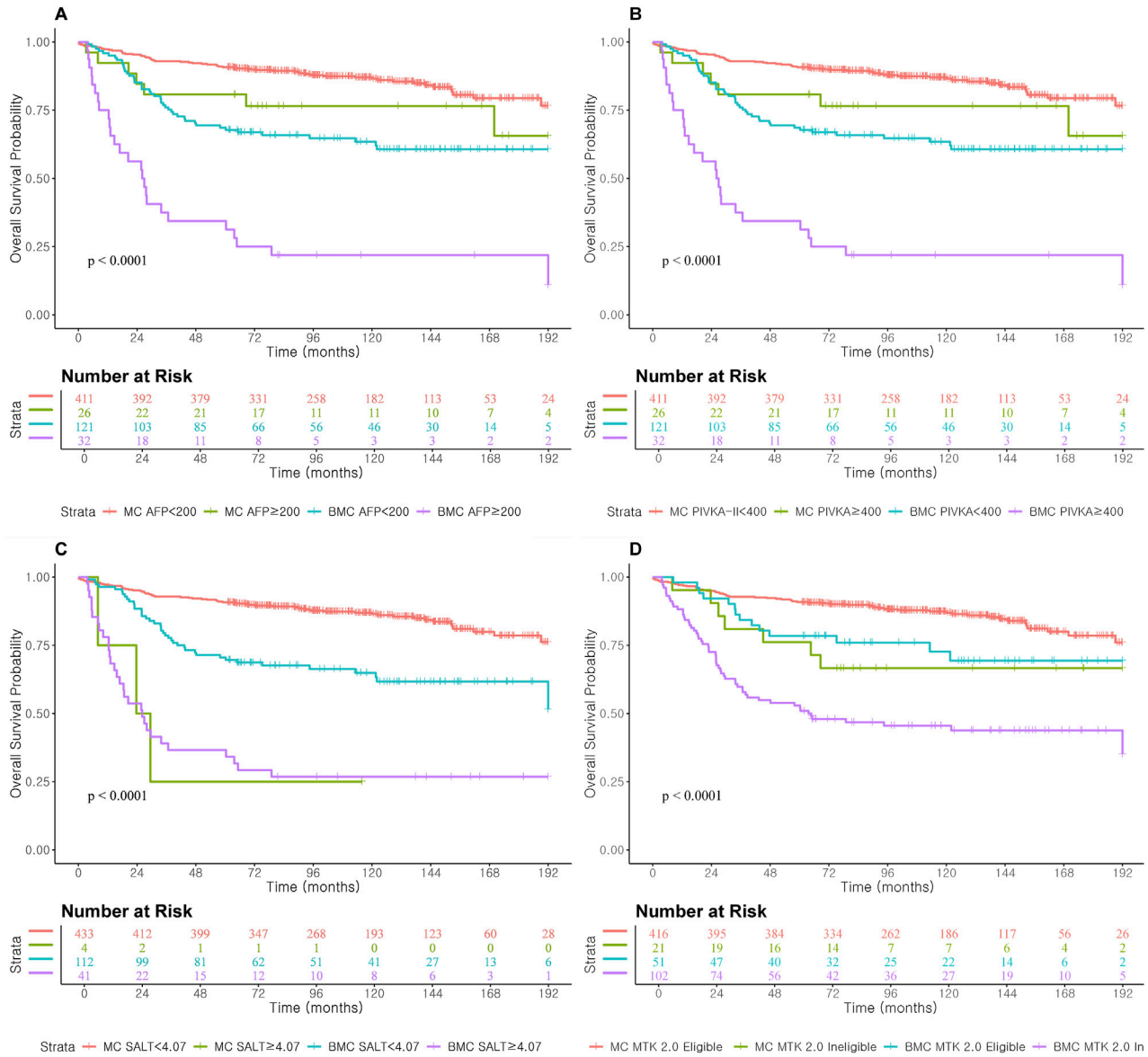



**FIGURE 5 |** Overall Survival according to prognostic score cut-off and AFP and PIVKA-II cut-off level in Milan and Beyond Milan cohort. **(A)** Overall Survival according to AFP ≥200. **(B)** Overall Survival according to PIVKA-II ≥400. **(C)** Overall Survival according to SALT ≥4.07. **(D)** Overall Survival according to METROTICKET 2.0.

original purpose [16]. The continuous RETREAT model showed an iAUC of 0.60, which was lower than that of PIVKA-II but similar to those of R3-AFP and AFP + PIVKA-II combination. Its threshold version (RETREAT ≥5) performed better, with a C-index of 0.75, ranking third after SNAPP ≥5 and R3-AFP ≥3 (**Table 3**; **Figure 2**). For intra-hepatic recurrence, the continuous model showed moderate accuracy (iAUC 0.70, **Supplementary Table S2**; **Supplementary Figure S1**), whereas the threshold model demonstrated excellent discrimination (C-index 0.93). RETREAT has been validated in North American cohorts with strong discrimination [48, 49]. UK data confirmed its utility (C-index 0.77) [50], and European data showed a 10-year prediction capability for low-risk HCC recurrence groups [51]. The recent addition of AFP-L3 and PIVKA-II has improved its prognostic performance [52].

## Mortality Prediction Performance of Cox Models

PIVKA-II, as an individual marker and in combination with AFP, showed strong and consistent predictive abilities for post-LT mortality in both MC and BMCs (**Table 4**; **Figure 4**). In the MC, PIVKA-II clearly outperformed AFP, highlighting the growing relevance of tumor biology markers in long-term risk

assessment [36, 40, 42, 43]. Together, AFP and PIVKA-II, particularly when combined, offer a practical and accessible option for risk stratification, although multivariable models, such as SALT, remained superior for long-term individualized prognostication.

This retrospective study has several limitations. Selection bias and variations in clinical management between the MC and BMC cohorts may have affected model performance. Differences in tumor biology and the predominance of viral hepatitis in this cohort may limit generalizability to Western populations, where non-viral etiologies such as metabolic associated liver diseases are more common. The higher recurrence and mortality rates observed in BMC may have led to an overestimation of risk. Furthermore, our study did not adjust for differences in recurrence treatments such as TACE or chemotherapy, which may have introduced bias. Additionally, immunosuppressive agents such as mammalian target of rapamycin inhibitors (mTORi) and steroids were not standardized and may have varied during model development, potentially impacting predictive performance. From a methodological standpoint, although Uno's iAUC and Harrell's C-index offer robust time-dependent and overall performance assessments, these statistical measures do not directly translate to clinical decision-making. The clinical relevance of modest differences in performance metrics remains uncertain. The prognostic models evaluated were developed under varying conditions. SNAPP and MoRAL were designed for LDLT populations, whereas RETREAT and R3-AFP were validated in DDLT settings. MoRAL and SALT were derived from single-center data, which may introduce institutional bias. Furthermore, the lack of an external validation cohort remains a major limitation. Future multicenter studies are necessary to confirm the generalizability and clinical utility of these findings.

However, this study provides long-term validation of prognostic models and tumor biomarkers for post-transplant outcomes in MC and BMCs, evaluating four recurrence and two mortality models over 5 years. In settings where LDLT recipients return to local care with limited diagnostic access, preoperative AFP and PIVKA-II levels could serve as accessible risk assessment markers. When applied as continuous variables, they showed moderate to strong predictive performance, with PIVKA-II outperforming AFP, particularly for long-term mortality. Their combination improved accuracy, matching complex models in high-risk populations. Their threshold-based models demonstrated performance comparable to that of complex models, particularly in BMC. R3-AFP showed the highest consistent predictive performance, whereas SNAPP, MoRAL, and SALT also performed well for BMC. Prognostic models and tumor biological scores generally performed better, particularly in the BMC cohort, where tumors were morphologically larger.

In conclusion, preoperative PIVKA-II, alone or in combination with AFP, may serve as an accessible long-term risk assessment marker for HCC recurrence and mortality following LDLT. However, AFP and PIVKA-II do not fully replace validated multivariable models, which remain the preferred approach in centers with advanced diagnostic capabilities.

## DATA AVAILABILITY STATEMENT

The datasets presented in this article are not publicly available due to institutional IRB policies requiring prior approval for use. Requests to access the data should be directed to the corresponding author.

## ETHICS STATEMENT

The studies involving humans were approved by Institutional Review Board of Seoul National University Hospital and Seoul National University College of Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because we retrospectively reviewed electron medical data and no harm was given to the participants.

## AUTHOR CONTRIBUTIONS

YC and SG conceptualized the study. Data curation was performed by YC, SG, K-WL, GK, MK, SP, SKH, J-ML, J-YK, SyH, and JK. YC and SG have performed investigations. Methodology development was conducted by YC, SG, K-WL, GK, MK, SP, SKH, J-ML, J-YK, SyH, and JK. All authors provided the resources. All authors contributed to drafting the original manuscript and reviewing and editing the final version.

## FUNDING

The author(s) declare that no financial support was received for the research and/or publication of this article.

## CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## GENERATIVE AI STATEMENT

The authors declare that no Generative AI was used in the creation of this manuscript.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.14748/full#supplementary-material

## REFERENCES


1. Duvoux C, Roudot-Thoraval F, Decaens T, Pessione F, Badran H, Piardi T, et al. Liver Transplantation for Hepatocellular Carcinoma: A Model Including Alpha-Fetoprotein Improves the Performance of Milan Criteria. *Gastroenterology* (2012) 143(4):986–e15. doi:10.1053/j.gastro.2012.05.052
2. Zhang X, Chen C, Wang Y, Xu J. Recurrence Risk Prediction Models for Hepatocellular Carcinoma after Liver Transplantation. *J Gastroenterol Hepatol* (2024) 39(11):2272–80. doi:10.1111/jgh.16693
3. Mehta N, Bhangui P, Yao FY, Mazzaferro V, Toso C, Akamatsu N, et al. Liver Transplantation for Hepatocellular Carcinoma. Working Group Report from the ILTS Transplant Oncology Consensus Conference. *Transplantation* (2020) 104(6):1136–42. doi:10.1097/TP.0000000000003174
4. Agarwal PD, Lucey MR. Management of Hepatocellular Carcinoma Recurrence after Liver Transplantation. *Ann Hepatol* (2022) 27(1):100654. doi:10.1016/j.aohep.2021.100654
5. Kim B, Kahn J, Terrault NA. Liver Transplantation as Therapy for Hepatocellular Carcinoma. *Liver Int* (2020) 40(Suppl. 1):116–21. doi:10.1111/liv.14346
6. Bzeizi KI, Abdullah M, Vidyasagar K, Alqahthani SA, Broering D. Hepatocellular Carcinoma Recurrence and Mortality Rate Post Liver Transplantation: Meta-Analysis and Systematic Review of Real-World Evidence. *Cancers (Basel)* (2022) 14(20):5114. doi:10.3390/cancers14205114
7. Shimamura T, Goto R, Watanabe M, Kawamura N, Takada Y. Liver Transplantation for Hepatocellular Carcinoma: How Should We Improve the Thresholds? *Cancers (Basel)* (2022) 14(2):419. doi:10.3390/cancers14020419
8. Lee DD, Sapisochin G, Mehta N, Gorgen A, Musto KR, Hajda H, et al. Surveillance for HCC after Liver Transplantation: Increased Monitoring May Yield Aggressive Treatment Options and Improved Postrecurrence Survival. *Transplantation* (2020) 104(10):2105–12. doi:10.1097/TP.0000000000003117
9. Clavien PA, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A, et al. Recommendations for Liver Transplantation for Hepatocellular Carcinoma: An International Consensus Conference Report. *Lancet Oncol* (2012) 13(1):e11–22. doi:10.1016/S1470-2045(11)70175-9
10. Halazun KJ, Tabrizian P, Najjar M, Florman S, Schwartz M, Michelassi F, et al. Is It Time to Abandon the Milan Criteria? Results of a Bicoastal US Collaboration to Redefine Hepatocellular Carcinoma Liver Transplantation Selection Policies. *Ann Surg* (2018) 268(4):690–9. doi:10.1097/SLA.0000000000002964
11. Hakeem AR, Young RS, Marangoni G, Lodge JP, Prasad KR. Systematic Review: The Prognostic Role of Alpha-Fetoprotein Following Liver Transplantation for Hepatocellular Carcinoma. *Aliment Pharmacol Ther* (2012) 35(9):987–99. doi:10.1111/j.1365-2036.2012.05060.x
12. Yoon YI, Lee SG. Living Donor Liver Transplantation for Hepatocellular Carcinoma: An Asian Perspective. *Dig Dis Sci* (2019) 64(4):993–1000. doi:10.1007/s10620-019-05551-4
13. Park GC, Song GW, Moon DB, Lee SG. A Review of Current Status of Living Donor Liver Transplantation. *Hepatobiliary Surg Nutr* (2016) 5(2):107–17. doi:10.3978/j.issn.2304-3881.2015.08.04
14. Lee JH, Cho Y, Kim HY, Cho EJ, Lee DH, Yu SJ, et al. Serum Tumor Markers Provide Refined Prognostication in Selecting Liver Transplantation Candidate for Hepatocellular Carcinoma Patients beyond the Milan Criteria. *Ann Surg* (2016) 263(5):842–50. doi:10.1097/SLA.0000000000001578
15. Kim S-H, Moon D-B, Park G-C, Lee S-G, Hwang S, Ahn C-S, et al. Preoperative Prediction Score of Hepatocellular Carcinoma Recurrence in Living Donor Liver Transplantation: Validation of SNAPP Score Developed at Asan Medical Center. *Am J Transplant* (2021) 21(2):604–13. doi:10.1111/ajt.16227
16. Mehta N, Heimbach J, Harnois DM, Sapisochin G, Dodge JL, Lee D, et al. Validation of a Risk Estimation of Tumor Recurrence after Transplant (RETREAT) Score for Hepatocellular Carcinoma Recurrence after Liver Transplant. *JAMA Oncol* (2017) 3(4):493–500. doi:10.1001/jamaoncol.2016.5116
17. Costentin C, Pinero F, Degroote H, Notarpaolo A, Boin IF, Boudjema K, et al. R3-AFP Score Is a New Composite Tool to Refine Prediction of Hepatocellular Carcinoma Recurrence after Liver Transplantation. *JHEP Rep* (2022) 4(5):100445. doi:10.1016/j.jhepr.2022.100445
18. Jamtani I, Lee KW, Choi Y, Choi Y, Lee JM, Han ES, et al. Tailored Prediction Model of Survival after Liver Transplantation for Hepatocellular Carcinoma. *J Clin Med* (2021) 10(13):2869. doi:10.3390/jcm10132869
19. Mazzaferro V, Sposito C, Zhou J, Pinna AD, De Carlis L, Fan J, et al. Metroticket 2.0 Model for Analysis of Competing Risks of Death after Liver Transplantation for Hepatocellular Carcinoma. *Gastroenterology* (2018) 154(1):128–39. doi:10.1053/j.gastro.2017.09.025
20. Challener DW, Prokop LJ, Abu-Saleh O. The Proliferation of Reports on Clinical Scoring Systems: Issues about Uptake and Clinical Utility. *JAMA* (2019) 321(24):2405–6. doi:10.1001/jama.2019.5284
21. Montano-Loza AJ, Rodriguez-Peralvarez ML, Pageaux GP, Sanchez-Fueyo A, Feng S. Liver Transplantation Immunology: Immunosuppression, Rejection, and Immunomodulation. *J Hepatol* (2023) 78(6):1199–215. doi:10.1016/j.jhep.2023.01.030
22. Kwong AJ, Ebel NH, Kim WR, Lake JR, Smith JM, Schladt DP, et al. OPTN/SRTR 2020 Annual Data Report: Liver. *Am J Transpl* (2022) 22(Suppl. 2):204–309. doi:10.1111/ajt.16978
23. Graham CN, Watson C, Barlev A, Stevenson M, Dharnidharka VR. Mean Lifetime Survival Estimates Following Solid Organ Transplantation in the US and UK. *J Med Econ* (2022) 25(1):230–7. doi:10.1080/13696998.2022.2033050
24. Lucey MR, Furuya KN, Foley DP. Liver Transplantation. *N Engl J Med* (2023) 389(20):1888–900. doi:10.1056/NEJMra2200923
25. Palaniyappan N, Peach E, Pearce F, Dhaliwal A, Campos-Varela I, Cant MR, et al. Long-term Outcomes (Beyond 5 Years) of Liver Transplant Recipients-A Transatlantic Multicenter Study. *Liver Transpl* (2024) 30(2):170–81. doi:10.1097/LVT.0000000000000244
26. Choi J, Kim GA, Han S, Lee W, Chun S, Lim YS. Longitudinal Assessment of Three Serum Biomarkers to Detect Very Early-Stage Hepatocellular Carcinoma. *Hepatology* (2019) 69(5):1983–94. doi:10.1002/hep.30233
27. Mazzaferro V, Droz dit Busset M, Bhoori S. Alpha-fetoprotein in Liver Transplantation for Hepatocellular Carcinoma: The Lower, the Better. *Hepatology* (2018) 68(2):775–7. doi:10.1002/hep.29835
28. Goldman ML, Zhou K, Dodge JL, Yao F, Mehta N. Lower Alpha-Fetoprotein Threshold of 500 ng/mL for Liver Transplantation May Improve Posttransplant Outcomes in Patients with Hepatocellular Carcinoma. *Liver Transpl* (2022) 28(5):763–73. doi:10.1002/lt.26392
29. Halazun KJ, Rosenblatt RE, Mehta N, Lai Q, Hajifathalian K, Gorgen A, et al. Dynamic Alpha-Fetoprotein Response and Outcomes after Liver Transplant for Hepatocellular Carcinoma. *JAMA Surg* (2021) 156(6):559–67. doi:10.1001/jamasurg.2021.0954
30. Galle PR, Foerster F, Kudo M, Chan SL, Llovet JM, Qin S, et al. Biology and Significance of Alpha-Fetoprotein in Hepatocellular Carcinoma. *Liver Int* (2019) 39(12):2214–29. doi:10.1111/liv.14223
31. Zhou Z, Liu Q, Liu J, Li W, Cao S, Xu J, et al. Research Progress of Protein Induced by Vitamin K Absence or Antagonist II in Liver Transplantation for Hepatocellular Carcinoma. *Heliyon* (2024) 10(9):e30622. doi:10.1016/j.heliyon.2024.e30622
32. Heagerty PJ, Zheng Y. Survival Model Predictive Accuracy and ROC Curves. *Biometrics* (2005) 61(1):92–105. doi:10.1111/j.0006-341X.2005.030814.x
33. Guinney J, Wang T, Laajala TD, Winner KK, Bare JC, Neto EC, et al. Prediction of Overall Survival for Patients with Metastatic Castration-Resistant Prostate Cancer: Development of a Prognostic Model through a Crowdsourced Challenge with Open Clinical Trial Data. *Lancet Oncol* (2017) 18(1):132–42. doi:10.1016/S1470-2045(16)30560-5
34. Kamarudin AN, Cox T, Kolamunnage-Dona R. Time-dependent ROC Curve Analysis in Medical Research: Current Methods and Applications. *BMC Med Res Methodol* (2017) 17(1):53. doi:10.1186/s12874-017-0332-6
35. Lambert J, Chevret S. Summary Measure of Discrimination in Survival Models Based on Cumulative/dynamic Time-dependent ROC Curves. *Stat Methods Med Res* (2016) 25(5):2088–102. doi:10.1177/0962280213515571
36. Lai Q, Ito T, Iesari S, Ikegami T, Nicolini D, Larghi Laureiro Z, et al. Role of Protein Induced by Vitamin-K Absence-II in Transplanted Patients with HCC Not Producing Alpha-Fetoprotein. *Liver Transpl* (2024) 30(5):472–83. doi:10.1097/LVT.0000000000000259
37. Lopes CA, Alves de Mattos Â, Diniz MA, Gonçalves FGE, Santana FBIF, Martins Alves da Silva RC, et al. P-112 Alpha-Fetoprotein as a Prognostic

Factor in Patients with Hepatocellular Carcinoma Submitted to Liver Transplantation – Brazilian Multicenter Study. *Ann Hepatol* (2021) 24: 100472. doi:10.1016/j.aohep.2021.100472

38. Toso C, Meeberg G, Hernandez-Alejandro R, Dufour JF, Marotta P, Majno P, et al. Total Tumor Volume and Alpha-Fetoprotein for Selection of Transplant Candidates with Hepatocellular Carcinoma: A Prospective Validation. *Hepatology* (2015) 62(1):158–65. doi:10.1002/hep.27787
39. Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular Carcinoma. *Lancet* (2022) 400(10360):1345–62. doi:10.1016/S0140-6736(22)01200-4
40. Kim DY, Toan BN, Tan CK, Hasan I, Setiawan L, Yu ML, et al. Utility of Combining PIVKA-II and AFP in the Surveillance and Monitoring of Hepatocellular Carcinoma in the Asia-Pacific Region. *Clin Mol Hepatol* (2023) 29(2):277–92. doi:10.3350/cmh.2022.0212
41. Koch C, Bette T, Waidmann O, Filmann N, Schrecker C, Trojan J, et al. AFP Ratio Predicts HCC Recurrence after Liver Transplantation. *PLoS One* (2020) 15(7):e0235576. doi:10.1371/journal.pone.0235576
42. Kim SH, Moon DB, Kim WJ, Kang WH, Kwon JH, Jwa EK, et al. Preoperative Prognostic Values of Alpha-Fetoprotein (AFP) and Protein Induced by Vitamin K Absence or Antagonist-II (PIVKA-II) in Patients with Hepatocellular Carcinoma for Living Donor Liver Transplantation. *Hepatobiliary Surg Nutr* (2016) 5(6):461–9. doi:10.21037/hbsn.2016.11.05
43. Devillers MJC, Pluimers JKF, van Hooff MC, Doukas M, Polak WG, de Man RA, et al. The Role of PIVKA-II as a Predictor of Early Hepatocellular Carcinoma Recurrence-free Survival after Liver Transplantation in a Low Alpha-Fetoprotein Population. *Cancers (Basel)* (2023) 16(1):4. doi:10.3390/cancers16010004
44. Pinero F, Lai Q, Costentin C, Degroote H, Schnitzbauer A, Geissler EK, et al. Validation of the R3-AFP Model for Risk Prediction of HCC Recurrence after Liver Transplantation in the SiLVER Randomized Clinical Trial. *Liver Transpl* (2025) 31(1):45–57. doi:10.1097/LVT.0000000000000487
45. Tan DJH, Wong C, Ng CH, Poh CW, Jain SR, Huang DQ, et al. A Meta-Analysis on the Rate of Hepatocellular Carcinoma Recurrence after Liver Transplant and Associations to Etiology, Alpha-Fetoprotein, Income and Ethnicity. *J Clin Med* (2021) 10(2):238. doi:10.3390/jcm10020238
46. Kim SJ, Kim JM, Yi NJ, Choi GS, Lee KW, Suh KS, et al. Validation for Models for Tumor Recurrence after Liver Transplantation in Hepatectomy Patients. *Ann Surg Treat Res* (2022) 102(3):131–8. doi:10.4174/astr.2022.102.3.131
47. Nam JY, Lee JH, Bae J, Chang Y, Cho Y, Sinn DH, et al. Novel Model to Predict HCC Recurrence after Liver Transplantation Obtained Using Deep Learning: A Multicenter Study. *Cancers (Basel)* (2020) 12(10):2791. doi:10.3390/cancers12102791
48. Mehta N, Dodge JL, Roberts JP, Yao FY. Validation of the Prognostic Power of the RETREAT Score for Hepatocellular Carcinoma Recurrence Using the UNOS Database. *Am J Transpl* (2018) 18(5):1206–13. doi:10.1111/ajt.14549
49. Hasan B, Colak Y, Khalid RA, Castillo M, Castaneda D, Tandon K, et al. Early Detection of Hepatocellular Carcinoma Recurrence in the Posttransplant Population: A Comparison of RETREAT and Cleveland Clinic Florida Scoring System. *Transpl Proc* (2021) 53(1):193–9. doi:10.1016/j.transproceed.2020.09.015
50. Reddy SHS, Mehta N, Dodge JL, Hakeem AR, Khorsandi SE, Jassem W, et al. Liver Transplantation for HCC: Validation of Prognostic Power of the RETREAT Score for Recurrence in a UK Cohort. *HPB (Oxford)* (2022) 24(5):596–605. doi:10.1016/j.hpb.2021.09.008
51. van Hooff MC, Sonneveld MJ, Ijzermans JN, Doukas M, Sprengers D, Metselaar HJ, et al. External Validation of the RETREAT Score for Prediction of Hepatocellular Carcinoma Recurrence after Liver Transplantation. *Cancers (Basel)* (2022) 14(3):630. doi:10.3390/cancers14030630
52. Norman JS, Li PJ, Kotwani P, Yao FY, Pham S, Gamez J, et al. Enhancing the Prognostic Accuracy of the RETREAT Score with AFP-L3 and DCP Tumor Markers. *Liver Transpl* (2024) 31:727–36. doi:10.1097/LVT.0000000000000551

ESOT | Transplant International

ORIGINAL RESEARCH
published: 24 June 2025
doi: 10.3389/ti.2025.14121

# Machine Learning for 1-Year Mortality Prediction in Lung Transplant Recipients: ISHLT Registry

*Hye Ju Yeo*[1,2†], *Dasom Noh*[3†], *Eunjeong Son*[1,2], *Sunyoung Kwon*[3,4,5*] *and Woo Hyun Cho*[1,2*]

[1]*Transplant Research Center, Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, Republic of Korea,* [2]*Department of Internal Medicine, School of Medicine, Pusan National University, Busan, Republic of Korea,* [3]*Department of Information Convergence Engineering, Pusan National University, Yangsan, Republic of Korea,* [4]*School of Biomedical Convergence Engineering, Pusan National University, Yangsan, Republic of Korea,* [5]*Center for Artificial Intelligence Research, Pusan National University, Busan, Republic of Korea*

Optimizing lung transplant candidate selection is crucial for maximizing resource efficiency and improving patient outcomes. Using data from the International Society for Heart and Lung Transplantation (ISHLT) registry (29,364 patients), we developed a deep learning model to predict 1-year survival after lung transplantation. Initially, 25 pretransplant factors were identified, and their importance was assessed using SHapley Additive exPlanations values. We refined the model by selecting the top 10 most influential factors and compared its performance with the original model. Additionally, we conducted external validation using an independent in-house dataset. Among the 29,364 patients, 4,729 (16.1%) died within 1 year, while 24,635 survived. The Gradient Boosting Machine (GBM) model achieved the highest performance (AUC: 0.958, accuracy: 0.949). Notably, the streamlined model using only the top 10 factors maintained identical performance (AUC: 0.958, accuracy: 0.949). The in-house dataset used for external validation showed significant compositional differences compared to the ISHLT dataset. Despite these differences, the GBM model performed well (AUC: 0.852, accuracy: 0.764). Notably, the Multilayer Perceptron model demonstrated superior generalization with an AUC of 0.911 and accuracy of 0.870. Our machine learning-based approach effectively predicts 1-year mortality in lung transplant recipients using a minimal set of pretransplant factors.

**Keywords: lung transplantation, mortality, machine learning, risk factors, prediction model**



***Correspondence**
*Sunyoung Kwon,*
*sy.kwon@pusan.ac.kr*
*Woo Hyun Cho,*
*popeyes0212@hanmail.net*

*†These authors have contributed equally to this work*

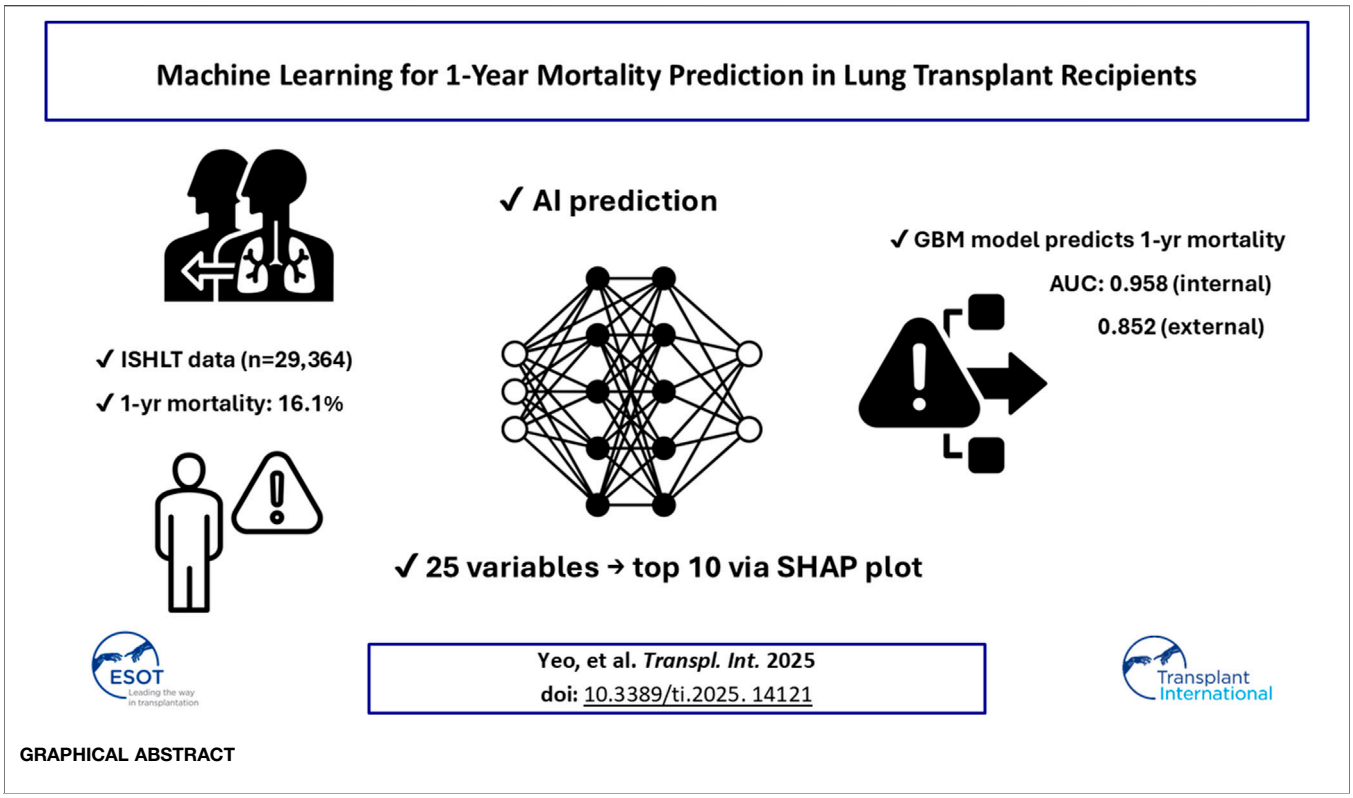
***Received:*** *26 November 2024*
***Accepted:*** *23 May 2025*
***Published:*** *24 June 2025*

***Citation:***
*Yeo HJ, Noh D, Son E, Kwon S and Cho WH (2025) Machine Learning for 1-Year Mortality Prediction in Lung Transplant Recipients: ISHLT Registry. Transpl. Int. 38:14121. doi: 10.3389/ti.2025.14121*

## INTRODUCTION

Lung transplantation is a critical intervention for patients with end-stage lung disease, providing significant survival benefits. As the population ages and medical technologies advance, the demand for lung transplants continues to rise [1]. However, the global supply of organ donors is insufficient to meet this growing demand [2]. Despite advancements in surgical techniques and immunosuppressive therapies, the post-transplant environment remains challenging, with various factors influencing outcomes [3]. Given the scarcity of medical resources, prioritizing patients with a low risk of mortality post-transplant is imperative. Predicting 1-year mortality

**Abbreviations:** AUC, area under the curve; GBM, Gradient Boosting Machine; ISHLT, International Society for Heart and Lung Transplantation; SHAP, Shapley Additive explanations.




**GRAPHICAL ABSTRACT**

following lung transplantation is, therefore, a critical goal to optimize patient care and enhance clinical decision-making.

Traditional methods for predicting mortality after lung transplantation have primarily relied on clinical judgment and risk-scoring systems [4–7]. While these scoring systems aid in prioritizing candidates, they often fail to account for the complexity of individual patient trajectories. This is due to the limited number of variables they include and their heavy reliance on clinical judgment. Additionally, several factors traditionally considered important, such as recipient age, body mass index (BMI), and the duration of preoperative mechanical ventilation, have not consistently shown the expected prognostic impact in previous studies [8]. A recent meta-analysis found that only one factor, postoperative extracorporeal membrane oxygenation (ECMO) use, was significantly associated with 1-year mortality, while other commonly accepted risk factors demonstrated minimal prognostic significance [8]. These limitations emphasize the need for more accurate, personalized risk prediction methods, as existing models may lack the granularity required for individualized treatment.

In this context, machine learning approaches offer the potential to develop predictive algorithms that can integrate diverse patient data and identify subtle patterns that traditional methods may overlook. Machine learning models can enhance pretransplant risk stratification, assist clinicians in selecting and counseling candidates, guide post-transplant surveillance strategies, and inform interventions to mitigate adverse outcomes. By providing timely insights into individual patient trajectories, these models can improve resource allocation and patient-centered care. Despite their potential, however, machine learning models predicting patient prognosis post-lung transplantation have not been extensively studied [9–11]. In this study, we developed and validated a machine learning-based model to predict 1-year mortality among lung transplant recipients using data from the International Society for Heart and Lung Transplantation (ISHLT). Additionally, we performed external validation using the in-house dataset from our hospital.

## MATERIALS AND METHODS

Patients who underwent lung transplantation and who were registered in the ISHLT registry from June 2009 to June 2018 were included (**Figure 1**). By early 2019, 45 centers worldwide had submitted data to the ISHLT International Thoracic Organ Transplant Registry using a secure, web-based data entry system. Detailed spreadsheets of the data elements collected in the Registry are available on the ISHLT International thoracic organ transplant website[1]. We excluded patients < 18 years, those who had undergone retransplantation or multiple organ transplants, and those with unavailable follow-up status or missing data. Consequently, 29,364 patients were available for analysis. The ethics committees and review board of

[1]https://ishlt.org/research-data/registries/ttx-registry

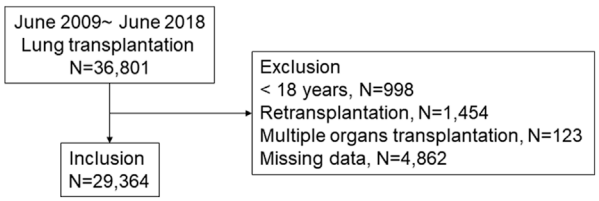



**FIGURE 1 |** Patient inclusion. A total of 29,364 lung transplant patients were included in this study.

Pusan National University Yangsan Hospital (PNUYH) (55-2024-128) approved the current study, and informed consent was waived due to the retrospective nature of the study. This study adhered to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) reporting guideline. Initially, key variables were selected through regression analysis to develop a predictive model for 1-year mortality following lung transplantation. This analysis identified 25 variables significantly associated with 1-year mortality. We then evaluated feature importance using SHapley Additive exPlanations (SHAP) values (**Figure 2A**) (**Supplementary Figure S1**) and developed a refined model incorporating the top 10 most important features. The performance of this refined model was compared with that of the original model, which included all 25 variables. Finally, external validation was conducted using our hospital's in-house dataset.

## Machine Learning-Based Model Development

We employed six machine learning models to predict 1-year mortality after lung transplantation: Logistic Regression (LR) [12], Support Vector Machine (SVM) [13], Random Forest (RF) [14], Gradient Boosting Machine (GBM) [15], Balanced Random Forest (BRF) [16], and a neural network model, Multilayer Perceptron (MLP) [17]. To evaluate model performance, we conducted five-fold cross-validation. The entire dataset was divided into five subsets, and during each iteration, one subset was used for validation while the remaining four were used for training. This process was repeated until each subset had been used for validation once, and the final results were reported as the average performance across all five iterations (**Supplementary Figure S2**). To interpret the predictions of our models, we employed SHAP [18], a widely used method for estimating the contribution of each feature to a prediction. SHAP provides explanations based on Shapley values derived from game theory. Specifically, we utilized the Python SHAP package [18] and applied the TreeExplainer for GBM. We used the scikit-learn package [19] for most models, except for BRF, which was implemented using the imbalanced-learn

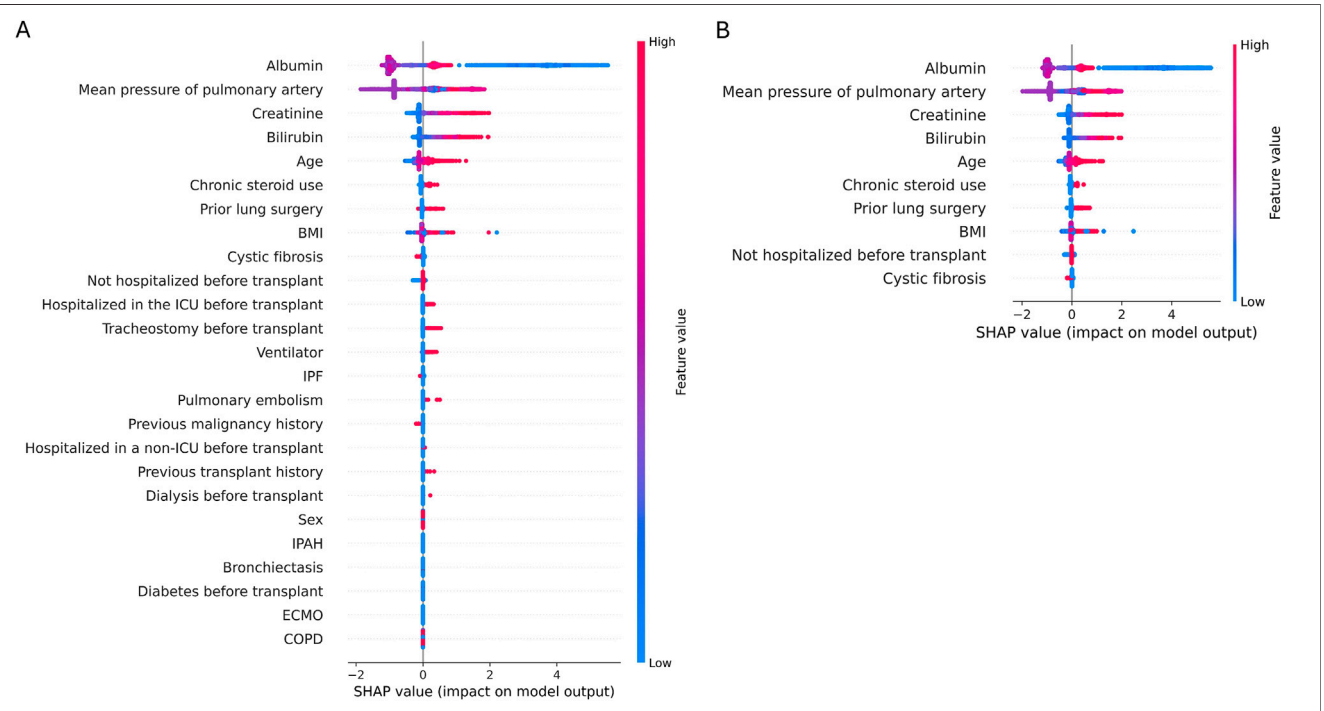



**FIGURE 2 |** Shapley Additive explanations (SHAP). A SHAP plot illustrates the influence of each feature's value on the prediction outcome, with red indicating an increase in prediction and blue indicating a decrease. It demonstrates notable impacts in the following sequence: albumin, mean pulmonary artery pressure, and functional status. Increasing albumin levels correlate with decreased mortality (blue), while higher mean pulmonary artery pressure correlates with increased mortality (red). **(A)** SHAP plot of 25 features, **(B)** SHAP plot of 10 features.

package [20]. Default model settings were applied without additional hyperparameter tuning. However, due to class imbalance in the ISHLT dataset, class weight adjustments were applied for LR, RF, SVM, and BRF to account for the imbalance. Additionally, survival analysis based on model predictions was performed using the lifelines Python package [21]. Finally, external validation of the developed models was conducted using our hospital's in-house dataset, further assessing their generalizability and robustness.

## Statistical Analyses

Variables with excessive missing values (defined as more than 20% missing data) were removed, and patient samples with any missing data were excluded. This approach ensures that the analysis is based on complete cases, minimizing potential biases from missing data. Continuous variables are reported as either the mean ± standard deviation or the median with interquartile range (IQR), depending on their distribution. Statistical comparisons of continuous variables were performed using the Student's t-test or the Mann-Whitney U test, as appropriate. Categorical variables are expressed as frequencies and percentages and analyzed using the chi-square or Fisher's exact test, as appropriate. To identify factors associated with 1-year mortality after lung transplantation, we conducted univariate regression analysis. Additionally, we validated the GBM model by comparing the actual survival curves of patients, grouped based on the model's predictions. Patients predicted by the model to die were classified into the high-risk group (death group), and those predicted to survive were classified into the low-risk group (survival group). Survival curves for these two groups were illustrated using Kaplan-Meier plots, and the log-rank test was performed to compare survival rates between the groups. All statistical analyses were performed using R software (version 4.2.0; R Foundation for Statistical Computing, Vienna, Austria[2]). Statistical significance was set at $P < 0.05$.

# RESULTS

## Patient Characteristics

Among the 29,364 patients included in the study, 4,729 (16.1%) died within 1 year, whereas 24,635 survived. The baseline pretransplant characteristics of the patients are summarized in **Table 1**. Their average age was 53.4 ± 13.4 years, with 17,032 (58%) males, and the average body mass index (BMI) was 24.9 ± 4.5. The primary diagnoses were as follows: chronic obstructive pulmonary disease (COPD) in 27.9%, idiopathic pulmonary fibrosis (IPF) in 26.8%, cystic fibrosis in 14.6%, nonidiopathic interstitial pneumonia (nonIIP) ILD in 7.3%, nonIPF idiopathic interstitial pneumonia (IIP) in 4.7%, alpha-1 antitrypsin deficiency in 3.4%, idiopathic pulmonary arterial hypertension (IPAH) in 2.8%, noncystic fibrosis (nonCF) bronchiectasis in 2.6%, sarcoidosis in 2.5%, nonIPAH pulmonary hypertension in 1.7%, connective tissue disease-associated ILD (CTDILD) in 1.3%, obliterative bronchiolitis in 0.9%, lymphangioleiomyomatosis in 0.8%, and other diagnoses in 2.6%. Pretransplant, 1,757 patients (6%) were admitted to the intensive care unit (ICU), 1,515 (5.2%) were hospitalized in general wards, and 26,092 (88.9%) were not hospitalized. Additionally, 1,021 patients (3.5%) were on ventilators, and 642 (2.2%) were on extracorporeal membrane oxygenation (ECMO). Pretransplant diabetes was present in 3,288 patients (11.2%), pretransplant dialysis was performed in 61 patients (0.2%), and 64 patients had a history of organ transplantation other than the lung. Additionally, 781 (2.7%) and 2,601 (8.9%) patients had previous heart and lung surgeries, respectively.

**TABLE 1 |** Baseline characteristics of patients before the transplant.

| Variable | Survivors (N = 24,635) | Death (N = 4,729) | P |
|---|---|---|---|
| Age, years | 53.2 ± 13.5 | 54.5 ± 13.1 | <0.001 |
| Male | 14,186 (57.6) | 2,846 (60.2) | 0.001 |
| BMI, kg/m$^2$ | 25.3 ± 4.3 | 23.1 ± 4.9 | <0.001 |
| Total bilirubin, mg/dL | 0.6 ± 0.9 | 2.0 ± 2.0 | <0.001 |
| Creatinine, mg/dL | 0.8 ± 0.3 | 1.7 ± 1.0 | <0.001 |
| Albumin, g/dL | 3.7 ± 0.4 | 3.1 ± 0.6 | <0.001 |
| Diagnosis | | | |
| COPD | 7036 (28.6) | 1,171 (24.8) | <0.001 |
| Alpha-1 antitrypsin deficiency | 847 (3.4) | 151 (3.2) | 0.394 |
| Cystic fibrosis | 3,782 (15.4) | 516 (10.9) | <0.001 |
| Non-cystic fibrosis bronchiectasis | 616 (2.5) | 147 (3.1) | 0.016 |
| IPF | 6,425 (26.1) | 1,438 (30.4) | <0.001 |
| IIP, non-IPF | 136 (4.6) | 254 (5.4) | 0.024 |
| ILD, non-IIP | 1803 (7.3) | 352 (7.4) | 0.763 |
| CTD ILD | 319 (1.3) | 52 (1.1) | 0.271 |
| Sarcoidosis | 612 (2.5) | 134 (2.8) | 0.162 |
| Lymphangioleiomyomatosis | 200 (0.8) | 35 (0.7) | 0.612 |
| Idiopathic pulmonary artery hypertension | 652 (2.6) | 184 (3.9) | <0.001 |
| Pulmonary hypertension- not idiopathic | 385 (1.6) | 102 (2.2) | 0.003 |
| Obliterative bronchiolitis | 236 (1.0) | 29 (0.6) | 0.022 |
| Other | 586 (2.4) | 164 (3.5) | <0.001 |
| Diabetes | 2,826 (11.5) | 462 (9.8) | 0.001 |
| Malignancy history | 1,205 (4.9) | 196 (4.1) | 0.027 |
| Ventilator use | 818 (3.3) | 203 (4.3) | 0.001 |
| ECMO use | 508 (2.1) | 134 (2.8) | 0.001 |
| Prior cardiac surgery | 637 (2.6) | 144 (3.0) | 0.072 |
| Dialysis | 45 (0.2) | 16 (0.3) | 0.031 |
| Prior lung surgery | 2,234 (9.1) | 367 (7.8) | 0.004 |
| Chronic steroid use | 6,185 (25.1) | 1,079 (22.8) | 0.001 |
| Tracheostomy before transplant | 484 (2) | 122 (2.6) | 0.006 |
| Previous transplant history except lung | 48 (0.2) | 16 (0.3) | 0.053 |
| Pulmonary embolism | 60 (0.2) | 24 (0.5) | 0.002 |
| FEV1 | 39.2 ± 20.9 | 40.7 ± 20.1 | 0.002 |
| Mean pulmonary artery pressure, mmHg | 27.9 ± 8.4 | 32.4 ± 9.1 | <0.001 |
| Medical condition before transplant | | | <0.001 |
| ICU admission | 1,401 (5.7) | 356 (7.5) | |
| General ward admission | 1,304 (5.3) | 211 (4.5) | |
| No admission | 21,930 (89) | 4,162 (88) | |

*Data are presented as means ± SD, or number (%).*

[2]https://www.R-project.org/

**TABLE 2 |** Univariate associations of pretransplant characteristics with 1-year survival.

| Variable | OR (95% CI) | P |
|---|---|---|
| Age | 1.01 (1.00–1.01) | <0.001 |
| Male | 1.10 (1.04–1.17) | 0.001 |
| Prior lung surgery | 1.17 (1.06–1.31) | 0.003 |
| any previous transplantation history | 1.67 (1.03–2.74) | 0.040 |
| Albumin | 0.22 (0.21–0.22) | <0.001 |
| Chronic steroid use | 0.88 (0.83–0.95) | <0.001 |
| Diabetes | 1.20 (1.09–1.32) | <0.001 |
| total bilirubin | 1.09 (1.09–1.10) | <0.001 |
| BMI | 0.90 (0.90–0.91) | <0.001 |
| creatinine | 1.32 (1.31–1.33) | <0.001 |
| Previous malignancy history | 1.18 (1.03–1.37) | 0.021 |
| mean pulmonary artery pressure | 1.04 (1.04–1.04) | <0.001 |
| non-hospitalized before transplant | 0.91 (0.82–1.00) | 0.043 |
| non-ICU hospitalized before transplantation | 0.84 (0.72–0.97) | 0.018 |
| ICU hospitalized before transplantation | 1.35 (1.20–1.52) | <0.001 |
| Ventilator | 1.27 (1.10–1.46) | 0.001 |
| ECMO | 1.36 (1.14–1.61) | <0.001 |
| COPD | 0.82 (0.77–0.88) | <0.001 |
| Cystic fibrosis | 0.68 (0.61–0.75) | <0.001 |
| IPF | 1.49 (1.26–1.76) | <0.001 |
| non-CF bronchiectasis | 1.25 (1.04–1.50) | 0.016 |
| IPAH | 1.43 (1.23–1.66) | <0.001 |
| Dialysis | 1.80 (1.10–2.94) | 0.019 |
| Pulmonary embolism before transplant | 1.93 (1.29–2.88) | 0.001 |
| Tracheostomy before transplantation | 1.29 (1.08–1.54) | 0.006 |

*OR; odds ratio, CI; confidence interval, BMI; body mass index, ICU; intensive care unit, ECMO; extracorporeal membrane oxygenation, COPD; chronic obstructive pulmonary disease, IPF; idiopathic pulmonary fibrosis, CF; cystic fibrosis, CTD-ILD; connective tissue disease associated interstitial lung disease, IPAH; idiopathic pulmonary artery hypertension.*

**TABLE 3 |** Performance of 1-year mortality prediction model after lung transplantation with 25 features.

| Model | AUC | Accuracy | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|
| LR | 0.884 ± 0.005 | 0.881 ± 0.006 | 0.792 ± 0.006 | 0.898 ± 0.007 | 0.600 ± 0.017 | 0.958 ± 0.001 |
| SVM | 0.870 ± 0.004 | 0.917 ± 0.002 | 0.790 ± 0.006 | 0.941 ± 0.003 | 0.719 ± 0.009 | 0.959 ± 0.001 |
| RF | 0.951 ± 0.004 | 0.948 ± 0.002 | 0.731 ± 0.011 | 0.989 ± 0.002 | 0.929 ± 0.012 | 0.950 ± 0.002 |
| GBM | 0.958 ± 0.002 | 0.949 ± 0.002 | 0.756 ± 0.003 | 0.986 ± 0.002 | 0.911 ± 0.011 | 0.955 ± 0.001 |
| BRF | 0.954 ± 0.003 | 0.939 ± 0.002 | 0.788 ± 0.006 | 0.968 ± 0.002 | 0.826 ± 0.010 | 0.960 ± 0.001 |
| MLP | 0.924 ± 0.005 | 0.930 ± 0.004 | 0.649 ± 0.020 | 0.984 ± 0.002 | 0.886 ± 0.015 | 0.936 ± 0.003 |

*This Table summarizes the performance indicators of various prediction models using 25 factors for 1-year mortality after lung transplantation.*
*AUC: area under the curve, PPV: positive predictive value, NPV: negative predictive value, LR: logistic regression, RF: random forest, SVM: support vector machine, GBM: gradient boosting machine, MLP: multilayer perceptron, BRF: balanced random forest.*

## Machine Learning-Based Model Performance and Model Interpretation

We performed univariate regression analysis of 1-year mortality. **Table 2** presents the odds ratio of the 25 factors used in the model. We evaluated the performance of six machine learning models with 25 pretransplant features for predicting 1-year mortality after lung transplantation. The results are presented in **Table 3**. We used area under the curve (AUC), accuracy, sensitivity, specificity, positive predictive value, and negative predictive value as evaluation metrics. Most models exhibited high performance, with AUC and accuracy either surpassing or closely approaching 0.9. The GBM model achieved the highest performance, with an AUC and accuracy of 0.958 and 0.949, respectively.

Feature importance was analyzed using SHAP, with **Figure 2** displaying the feature importance for the GBM model. The most important feature was albumin, with lower levels associated with higher mortality 1-year post-transplant. Other significant predictors included mean pulmonary artery pressure, creatinine levels, total bilirubin, and age.

Based on the SHAP results, we trained a new model using the top-10 most important features (**Table 4**). Despite reducing the number of features from 25 to 10, the performances of the six models remained largely unchanged. Some models, including LR, RF, SVM, and MLP, exhibited slight improvements in AUC, although accuracy was slightly decreased. The GBM model continued to demonstrate the highest performance with an AUC and accuracy of 0.958 and 0.949, respectively, even with only 10 features.

**TABLE 4 |** Performance of 1-year mortality prediction model after lung transplantation with 10 features.

| Model | AUC | Accuracy | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|
| LR | 0.882 ± 0.005 | 0.884 ± 0.005 | 0.786 ± 0.003 | 0.902 ± 0.006 | 0.607 ± 0.015 | 0.956 ± 0.001 |
| SVM | 0.869 ± 0.005 | 0.917 ± 0.002 | 0.786 ± 0.006 | 0.942 ± 0.003 | 0.722 ± 0.010 | 0.958 ± 0.001 |
| RF | 0.951 ± 0.003 | 0.948 ± 0.002 | 0.735 ± 0.008 | 0.989 ± 0.002 | 0.926 ± 0.013 | 0.951 ± 0.001 |
| GBM | 0.958 ± 0.002 | 0.949 ± 0.002 | 0.755 ± 0.003 | 0.986 ± 0.002 | 0.914 ± 0.009 | 0.955 ± 0.001 |
| BRF | 0.953 ± 0.002 | 0.938 ± 0.002 | 0.791 ± 0.005 | 0.967 ± 0.002 | 0.821 ± 0.009 | 0.960 ± 0.001 |
| MLP | 0.939 ± 0.005 | 0.935 ± 0.001 | 0.664 ± 0.008 | 0.987 ± 0.002 | 0.906 ± 0.011 | 0.939 ± 0.001 |

*This Table summarizes the performance indicators of various prediction models using 10 factors for 1-year mortality after lung transplantation.*
*AUC: area under the curve, PPV: positive predictive value, NPV: negative predictive value, LR: logistic regression, RF: random forest, SVM: support vector machine, GBM: gradient boosting machine, MLP: multilayer perceptron, BRF: balanced random forest.*

## Actual Survival Curves: Low-Risk vs. High-Risk Groups by the GBM Model

We further validated the GBM model by comparing the actual survival curves of patients who were classified into two groups based on the model's predictions. Patients predicted by the model to die were assigned to the high-risk group (death group), while those predicted to survive were placed in the low-risk group

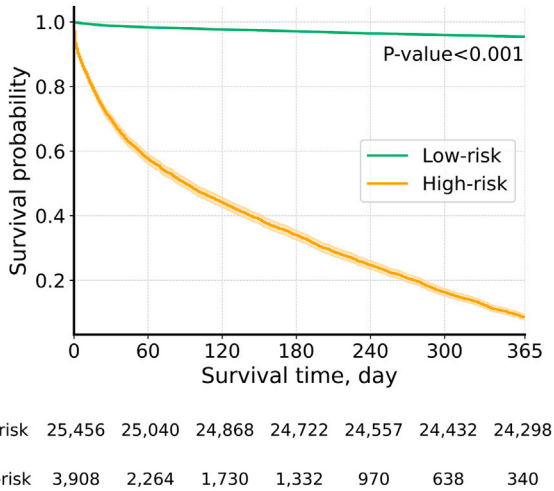



**FIGURE 3 |** Actual survival curves: low-risk vs. high-risk groups by the GBM model. Graph depicting actual survival curves of the group whose survival was predicted by the GBM model.

(survival group). As shown in **Figure 3**, the survival curves demonstrated a statistically significant difference between the two groups ($p < 0.001$). Among the predicted high-risk group, 91.4% experienced actual mortality, while 95.5% of the predicted low-risk group survived. These findings highlight the model's robust predictive performance for distinguishing between mortality and survival outcomes.

## External Validation on In-House Dataset of PNUYH

To evaluate the generalizability of our model, we conducted an external validation using data from Pusan National University Yangsan Hospital (PNUYH) (**Table 5**). The model was developed using all 29,364 samples included in this study and subsequently validated on the in-house dataset of PNUYH. Between January 2012 and March 2024, a total of 228 adult patients (aged ≥18 years) underwent lung transplantation at PNUYH. After excluding 12 patients who underwent retransplantation, 216 patients were included in the external validation cohort. Among them, 70 (32.4%) died within 1 year of transplantation. Key preoperative characteristics of these patients are summarized in **Supplementary Table S1**. Notably, the mortality group had a significantly higher BMI compared to the survival group (23.2 vs. 21.3, $p = 0.001$). Serum albumin levels were lower in the mortality group (2.5 vs. 3.7, $p < 0.001$), and steroid use was more frequent (47.1% vs. 24.0%, $p = 0.001$). Additionally, a history of lung surgery prior to transplantation was more common in the mortality group (5.7% vs. 0.7%, $p = 0.021$).

The PNUYH dataset used for external validation had a significantly different distribution compared to the ISHLT dataset used for training (**Supplementary Table S2**), with all 10 model variables showing statistically significant differences between the two cohorts. Despite these differences, the GBM, which had the highest

**TABLE 5 |** Results of External Validation for 1-Year Mortality Prediction Model After Lung Transplantation Using 10 Features on in-house dataset of PNUYH.

| Model | AUC | Accuracy | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|
| LR | 0.905 | 0.708 | 0.986 | 0.575 | 0.527 | 0.988 |
| SVM | 0.936 | 0.750 | 0.957 | 0.651 | 0.568 | 0.969 |
| RF | 0.870 | 0.769 | 0.443 | 0.925 | 0.738 | 0.776 |
| GBM | 0.852 | 0.764 | 0.529 | 0.877 | 0.673 | 0.795 |
| BRF | 0.888 | 0.815 | 0.857 | 0.795 | 0.667 | 0.921 |
| MLP | 0.911 | 0.870 | 0.886 | 0.863 | 0.756 | 0.940 |

*This table summarizes the results of external validation on in-house dataset of PNUYH, using various prediction models with 10 features for 1-year mortality after lung transplantation.*

*AUC: area under the curve, PPV: positive predictive value, NPV: negative predictive value, LR: logistic regression, RF: random forest, SVM: support vector machine, GBM: gradient boosting machine, MLP: multilayer perceptron, BRF: balanced random forest.*

performance in the ISHLT dataset, demonstrated excellent external validation results (AUC: 0.852, accuracy: 0.764). Among all tested models, the highest AUC was observed for the SVM model (0.936). However, when considering both AUC and accuracy, the best-performing model was the MLP, a deep learning-based approach. The MLP achieved an AUC of 0.911 and an accuracy of 0.870, consistently outperforming other models across all evaluation metrics. Given the substantial distributional differences between the ISHLT and PNUYH datasets, the MLP model's strong generalization performance underscores its robustness. These findings highlight the model's ability to maintain high predictive performance in an external population, supporting its potential clinical utility in lung transplant candidate selection.

# DISCUSSION

In this study, we developed and validated a deep learning-based model to predict 1-year survival following lung transplantation using a large, multicenter, international dataset. Our model demonstrated strong predictive performance, effectively identifying key determinants of post-transplant survival. By leveraging GBM techniques, we constructed a highly accurate and robust prediction model. Notably, a simplified version of our model, incorporating only the 10 most influential predictors, achieved performance comparable to that of more complex models utilizing 25 variables. Furthermore, the model's generalizability was confirmed through external validation using the in-house dataset from PNUYH. The GBM model achieved an AUC of 0.852 and an accuracy of 0.764, and the MLP model demonstrated superior performance, achieving an AUC of 0.911 and accuracy of 0.870. These findings underscore the potential clinical applicability of our model in improving risk stratification and decision-making for lung transplant recipients.

The 10 predictors identified in this study were critical in assessing the potential benefit of lung transplantation. Among these, age, BMI, creatinine levels, total bilirubin levels, and mean pulmonary artery pressure have been well-established as critical indicators for assessing patient urgency and potential benefit in previous Lung Allocation Scores (LAS) [22] and the current

Composite Allocation Score (CAS) [23]. Factors such as albumin levels, chronic steroid use, and prior lung surgery, newly highlighted in our study, further emphasize their potential to refine patient assessments and improve prediction accuracy. Albumin is traditionally a marker of nutritional status and inflammation, with lower levels associated with poorer post-transplant outcomes in previous studies [24]. This underscores the importance of evaluating nutritional and inflammatory status during pretransplant assessments. Chronic steroid use, identified in earlier studies, increases post-transplant morbidity and mortality [25], with some suggesting that long-term steroid use may be a contraindication for surgery [26]. Long-term steroid usage increases the risk of infection, poor wound healing, and other complications, all of which may be important predictors of transplant outcomes. Furthermore, prior major lung resection has been recognized as a significant risk factor for increased perioperative mortality and complications such as the need for dialysis [27]. This increased risk can be attributed to factors such as altered anatomy, potential for adhesions, and bleeding, all of which complicate the transplant procedure. These findings highlight the importance of thorough preoperative assessment in patients with a history of major lung resection.

Traditionally, prognosis following lung transplantation has been significantly influenced by the underlying primary disease necessitating the transplant. Different lung diseases impact post-transplant outcomes due to their distinct pathophysiology, patient demographics, and associated comorbidities. For example, patients with cystic fibrosis (CF) generally exhibit better post-transplant survival rates compared to those with idiopathic pulmonary fibrosis or chronic obstructive pulmonary disease [8]. In that regard, patient diagnosis plays an important role in both LAS and CAS, and several studies have incorporated diagnoses into prediction models. In our study, only cystic fibrosis was included as a predictor, but it had the lowest importance in the model (**Figure 2B**). Additionally, no patients with cystic fibrosis were included in the PNUYH in-house dataset used for external validation. Nevertheless, our model demonstrated excellent predictive performance, suggesting that preoperative conditions, such as organ function, nutritional status, and preoperative hospitalization, may be more critical prognostic indicators than the underlying disease itself. Thus, general aspects of patient health prior to transplantation could be more important than the specific underlying disease in pretransplant management.

While several studies have attempted to predict mortality in lung transplant patients, accurate predictions have not always been achieved due to limited performance (**Supplementary Table S3**) [28–30]. A recent study accurately predicted 1-year survival using 22 factors, including postoperative variables such as operation time, donor PaO2/FiO2 ratio, postoperative ECMO time, ventilator time, ICU stay, primary graft dysfunction grade, and cold ischemic time, achieving an AUC of 0.921 in patients from a single center [9]. Although these factors provide valuable insights into post-transplant outcomes, they are not available preoperatively, limiting their utility in pretransplant decision-making and patient prioritization. Our study addresses this limitation by focusing on preoperative variables that can be assessed before transplantation, thereby enhancing the ability to predict transplant outcomes and prioritize patients more effectively. Notably, achieving similar predictive accuracy with fewer variables has significant implications for clinical practice, as it simplifies the assessment process and makes it more feasible to implement in diverse healthcare settings without compromising predictive power. Furthermore, the external validation using in-house datasets further underscores the high generalizability of our model. Despite the fundamental differences between the training and validation datasets, the model demonstrated excellent performance, emphasizing its robustness and applicability across varied populations.

The use of machine learning approaches, particularly GBM, in this study highlights the transformative potential of these methods in healthcare. Machine learning models can handle complex interactions between variables and provide more accurate predictions compared to traditional statistical methods. This study demonstrates how machine learning models, such as GBM, can capture nonlinear relationships between variables, such as pulmonary artery pressure and BMI, which may not follow linear patterns. By incorporating these nonlinear interactions, the predictive performance of the model is significantly improved compared to traditional methods. SHAP values were used to visually explore the interactions between variables, providing insights into which characteristics contribute most to predictions. This ability to visualize complex interactions enhances the interpretability of the model, offering a deeper understanding of its decision-making process. Furthermore, comparing linear models (e.g., logistic regression, support vector machines) to nonlinear models (e.g., random forest, XGBoost) illustrates how traditional methods may miss out on capturing nonlinear patterns, which are crucial for accurate prediction of post-transplant outcomes. Our study advocates for the integration of machine learning technologies into clinical workflows. This integration can enhance clinical decision-making, providing more accurate predictions and improving patient outcomes. By leveraging machine learning models, clinicians can identify high-risk patients and tailor pretransplant management strategies to optimize post-transplant survival.

One significant limitation of our study was its reliance on registry data, meaning that the model's performance depends on the accuracy and completeness of the recorded information. We mitigated this issue by excluding instances with missing data to use the most precise data available. We developed and internally validated the model using the ISHLT registry, which offers a large and diverse sample, and externally validated it using our own cohort, demonstrating the model's generalizability. Future research should explore incorporating additional potential predictors and leveraging longitudinal data to further refine the model. These efforts would contribute to enhancing the model's robustness and applicability in clinical practice. Additionally, further validation and ethical considerations should be conducted

before applying the model to donor lung allocation, ensuring it addresses any ethical concerns.

In conclusion, our study confirmed that a machine learning-based approach can accurately predict 1-year mortality in lung transplant recipients using a minimal set of pretransplant factors. The development of a streamlined model with high predictive accuracy facilitates better patient selection, ensuring that lung transplantation resources are utilized efficiently and patient care is optimized. This model holds promise for enhancing clinical decision-making and improving post-transplant outcomes in lung transplant recipients. Investigating the underlying mechanisms by which specific pretransplant characteristics influence post-transplant outcomes could further enhance patient management strategies.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

## ETHICS STATEMENT

The studies involving humans were approved by Pusan National University Yangsan Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because Consent was waived as there was no harm to the patient.

## AUTHOR CONTRIBUTIONS

HY contributed to the conceptualization and methodology of the study, and reviewed and edited the manuscript. DN performed the formal analysis, and wrote the original draft of the manuscript. WC and ES reviewed and edited the manuscript. SK validated the data, created visualizations, and also reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

## FUNDING

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by institute of information and communications technology planning and evaluation (IITP) under the artificial intelligence convergence innovation human resources development (IITP-2025-RS-2023-00254177) grant funded by the Korea government (MSIT). This research was supported by a grant of Korean ARPA-H project through the Korea health industry development institute (KHIDI), funded by the Ministry of health and welfare, republic of Korea (grant number: RS-2024-00512375).

## CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## GENERATIVE AI STATEMENT

The authors declare that no Generative AI was used in the creation of this manuscript.

## ACKNOWLEDGMENTS

We thank the International Society for Heart and Lung Transplantation (ISHLT) registry for providing the data used in this study.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.14121/full#supplementary-material

## REFERENCES

1. Yeo HJ, Oh DK, Yu WS, Choi SM, Jeon K, Ha M, et al. Outcomes of Patients on the Lung Transplantation Waitlist in Korea: A Korean Network for Organ Sharing Data Analysis. *J Korean Med Sci.* (2022) 37:e294. doi:10.3346/jkms.2022.37.e294
2. Yeo HJ. Allocation of Donor Lungs in Korea. *J Chest Surg* (2022) 55:274–6. doi:10.5090/jcs.22.047
3. Yeo HJ, Kim DH, Kim YS, Jeon D, Cho WH. Performance Changes Following the Revision of Organ Allocation System of Lung Transplant: Analysis of Korean Network for Organ Sharing Data. *J Korean Med Sci.* (2021) 36:e79. doi:10.3346/jkms.2021.36.e79
4. Grimm JC, Valero V, 3rd, Magruder JT, Kilic A, Dungan SP, Silhan LL, et al. A Novel Risk Score that Incorporates Recipient and Donor Variables to Predict 1-year Mortality in the Current Era of Lung Transplantation. *J Heart Lung Transpl* (2015) 34(11):1449–54. doi:10.1016/j.healun.2015.07.001
5. Russo MJ, Davies RR, Hong KN, Iribarne A, Kawut S, Bacchetta M, et al. Who Is the High-Risk Recipient? Predicting Mortality after Lung Transplantation Using Pretransplant Risk Factors. *J Thorac Cardiovasc Surg* (2009) 138(5):1234–8. doi:10.1016/j.jtcvs.2009.07.036
6. Huppmann P, Neurohr C, Leuschner S, Leuchte H, Baumgartner R, Zimmermann G, et al. The Munich-LTX-Score: Predictor for Survival after Lung Transplantation. *Clin Transpl* (2012) 26(1):173–83. doi:10.1111/j.1399-0012.2011.01573.x
7. Belaroussi Y, Hustache-Castaing R, Maury JM, Lehot L, Rodriguez A, Demant X, et al. Prediction of Survival after a Lung Transplant at 1 Year (SALTO Cohort) Using Information Available at Different Key Time Points. *Eur J Cardiothorac Surg* (2023) 63(5):ezad167. doi:10.1093/ejcts/ezad167

8. Foroutan F, Malik A, Clark KE, Buchan TA, Yang H, Cheong GHL, et al. Predictors of 1-year Mortality after Adult Lung Transplantation: Systematic Review and Meta-Analyses. *J Heart Lung Transpl* (2022) 41(7):937–51. doi:10.1016/j.healun.2022.03.017
9. Tian D, Yan HJ, Huang H, Zuo YJ, Liu MZ, Zhao J, et al. Machine Learning-Based Prognostic Model for Patients after Lung Transplantation. *JAMA Netw Open* (2023) 6:e2312022. doi:10.1001/jamanetworkopen.2023.12022
10. Michelson AP, Oh I, Gupta A, Puri V, Kreisel D, Gelman AE, et al. Developing Machine Learning Models to Predict Primary Graft Dysfunction after Lung Transplantation. *Am J Transpl* (2024) 24:458–67. doi:10.1016/j.ajt.2023.07.008
11. Gholamzadeh M, Abtahi H, Safdari R. Machine Learning-Based Techniques to Improve Lung Transplantation Outcomes and Complications: A Systematic Review. *BMC Med Res Methodol* (2022) 22:331. doi:10.1186/s12874-022-01823-2
12. Hosmer DW, Lemeshow S, Sturdivant RX. *Applied Logistic Regression*. 3rd ed. John Wiley and Sons (2013).
13. Cortes C, Vapnik V. Support-vector Networks. *Machine Learn* (1995) 20:273–97. doi:10.1007/bf00994018
14. Breiman L. Random Forests. *Machine Learn* (2001) 45:5–32. doi:10.1023/a:1010933404324
15. Friedman JH. Greedy Function Approximation: A Gradient Boosting Machine. *Ann Stat* (2001) 29:1189–232. doi:10.1214/aos/1013203451
16. Chen C, Liaw A, Breiman L. *Using Random Forest to Learn Imbalanced Data*. Berkeley: University of California (2004).
17. Rumelhart DE, Hinton GE, Williams RJ. Learning Representations by Back-Propagating Errors. *Nature* (1986) 323:533–6. doi:10.1038/323533a0
18. Lundberg SM, Lee S-I. A Unified Approach to Interpreting Model Predictions. *Adv Neural Inf Process Syst* (2017) 30.
19. Pedregosa F, Varoquaux G, Gramfort A, Michel V, Thirion B, Grisel O. Duchesnay E. Scikit-Learn: Machine Learning in Python. *J Mach Learn Res* (2011) 12:2825–30.
20. Lemaitre G, Nogueira F, Aridas CK. Imbalanced-learn: A Python Toolbox to Tackle the Curse of Imbalanced Datasets in Machine Learning. *J Mach Learn Res* (2017) 18:1–5.
21. Davidson-Pilon C. Lifelines: Survival Analysis in Python. *J Open Source Softw.* (2019) 4:1317. doi:10.21105/joss.01317
22. Eurotransplant. *LAS Calculator*. (2024). Available online at: https://www.eurotransplant.org/las-calculator/ (Accessed: July, 2024).
23. Organ Procurement and Transplantation Network (OPTN). Lung CAS Calculator. (2024). Available online at: https://optn.transplant.hrsa.gov/data/allocation-calculators/lung-cas-calculator/ (Accessed: July, 2024).
24. Baldwin MR, Arcasoy SM, Shah A, Schulze PC, Sze J, Sonett JR, et al. Hypoalbuminemia and Early Mortality after Lung Transplantation: A Cohort Study. *Am J Transpl* (2012) 12:1256–67. doi:10.1111/j.1600-6143.2011.03965.x
25. Mosher CL, Weber JM, Frankel CW, Neely ML, Palmer SM. Risk Factors for Mortality in Lung Transplant Recipients Aged ≥65 Years: A Retrospective Cohort Study of 5,815 Patients in the Scientific Registry of Transplant Recipients. *J Heart Lung Transpl* (2021) 40:42–55. doi:10.1016/j.healun.2020.10.009
26. Schäfers HJ, Wagner TO, Demertzis S, Hamm M, Wahlers T, Cremer J, et al. Preoperative Corticosteroids. A Contraindication to Lung Transplantation? *Chest* (1992) 102:1522–5. doi:10.1378/chest.102.5.1522
27. Ganapathi AM, Speicher PJ, Castleberry AW, Englum BR, Osho AA, Davis RD, et al. The Effect of Prior Pneumonectomy or Lobectomy on Subsequent Lung Transplantation. *Ann Thorac Surg* (2014) 98:1922–8. doi:10.1016/j.athoracsur.2014.06.042
28. Chan EY, Nguyen DT, Kaleekal TS, Goodarzi A, Graviss EA, Gaber AO, et al. The Houston Methodist Lung Transplant Risk Model: A Validated Tool for Pretransplant Risk Assessment. *Ann Thorac Surg* (2019) 108:1094–100. doi:10.1016/j.athoracsur.2019.03.108
29. Gries CJ, Rue TC, Heagerty PJ, Edelman JD, Mulligan MS, Goss CH. Development of a Predictive Model for Long-Term Survival after Lung Transplantation and Implications for the Lung Allocation Score. *J Heart Lung Transpl* (2010) 29:731–8. doi:10.1016/j.healun.2010.02.007
30. Brahmbhatt JM, Hee WT, Goss CH, Lease ED, Merlo CA, Kapnadak SG, et al. The Lung Allocation Score and Other Available Models Lack Predictive Accuracy for Post-lung Transplant Survival. *J Heart Lung Transpl* (2022) 41:1063–74. doi:10.1016/j.healun.2022.05.008

ESOT | Transplant International

ORIGINAL RESEARCH
published: 02 June 2025
doi: 10.3389/ti.2025.14153

# Clinical and Histopathological Determinants for Kidney Allograft Survival in the Eurotransplant Senior Program (ESP) at the Time of Allocation

*Tom N. Langer[1,2], Thorsten Wiech[3,4], Mercedes Noriega[3], Sergey Biniaminov[5], Tobias B. Huber[1,4], Lutz Fischer[2,6], Florian Grahammer[1,2,4†] and Malte A. Kluger[1,2*†]*

[1]III. Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [2]University Transplant Center (UTC), University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [3]Institute of Pathology, Nephropathology Section, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [4]Hamburg Center for Kidney Health (HCKH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [5]HS Analysis GmbH, Karlsruhe, Germany, [6]Department of Visceral Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

To address the shortage of organs for kidney transplantation, the Eurotransplant Senior Program (ESP) was established to enhance kidney allocation from elderly donors. This study aimed to evaluate post-transplant outcomes of deceased donor grafts and identify prognostic factors within the ESP population. We therefore analyzed patient data from 64 ESP recipients and their donors transplanted at our center between 2017 and 2022. Time-zero biopsies were analyzed using AI image analysis software for glomerular density and glomerulosclerosis. One-year patient and allograft survival rates were 96.9% and 85.9%. 5-year survival rate was 74.6%, as opposed to about 41.0% historically reported for patients on dialysis. Delayed Graft Function occurred in 29.7% of cases, with recipient coronary heart disease, BMI-disparities, and prolonged cold ischemia time as major predictors ($P < 0.05$). Histopathological analysis revealed that the degree of glomerulosclerosis and interstitial fibrosis and tubular atrophy (IFTA) were associated with graft failure in multivariable analyses ($P < 0.05$). Arteriolosclerosis (arteriolar hyalinosis) correlated with a higher risk for primary non-function ($P < 0.05$). The number of HLA mismatches was not significantly associated with graft outcome. Including prognostic baseline characteristics as well as histopathological AI analysis into individual allocation decisions during organ-acceptance process might improve allograft survival within the ESP and should prospectively be studied.

**Keywords: kidney transplantation, elderly, ESP European Senior Program, AI histopathology, machine learning**

OPEN ACCESS

***Correspondence**
*Malte A. Kluger,*
*m.kluger@uke.de*

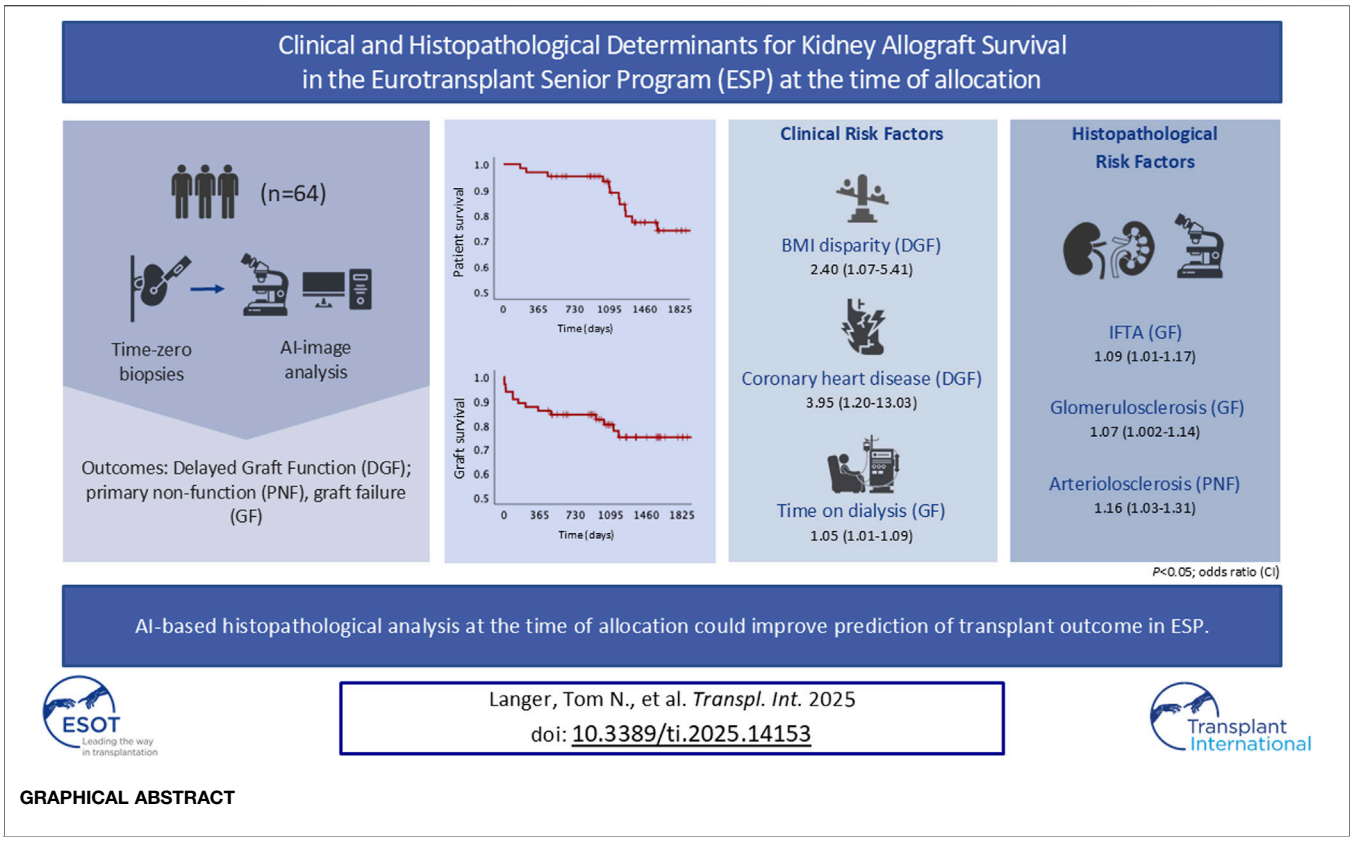
*†These authors have contributed equally to this work*

***Received:** 03 December 2024*
***Accepted:** 19 May 2025*
***Published:** 02 June 2025*

***Citation:***
*Langer TN, Wiech T, Noriega M, Biniaminov S, Huber TB, Fischer L, Grahammer F and Kluger MA (2025) Clinical and Histopathological Determinants for Kidney Allograft Survival in the Eurotransplant Senior Program (ESP) at the Time of Allocation. Transpl. Int. 38:14153. doi: 10.3389/ti.2025.14153*

## INTRODUCTION

At present, kidney transplantation represents the only treatment option for patients suffering from terminal kidney failure that offers perspectives for prolonged survival and benefits for the quality of life. In response to the demographic changes, including the rising numbers of elderly patients with end-stage kidney diseases on the waiting list but persisting shortage of donated organs, Eurotransplant established the European Senior Program (ESP) for this group in 1999. The ESP




**GRAPHICAL ABSTRACT**

allocates kidneys from deceased donors aged ≥65 years to elderly recipients ≥65 years of age who left the general kidney waiting list (ETKAS) for the benefit of significantly shorter waiting times. Its medical outcome is mainly based on minimizing cold ischemia time (CIT) by allocating organs locally, still based on blood group compatibility and waiting time. In contrast to the Eurotransplant Kidney Allocation System (ETKAS), the ESP does not include human leukocyte antigen (HLA) A-B-DR matching or specific immunological criteria. The latter have to be evaluated by the accepting centers, although inclusion of HLA-DR matching has recently been discussed [1]. Taken together, relevant reductions in waiting times for patients that otherwise might not even live up to their ETKAS-transplantation, as well as improved mortality rates among these elderly patients when compared to those continuing on dialysis, seem to be the major significant advantages of this program [2, 3].

Despite 25 years of experience with the ESP, selecting suitable organs from elderly donors remains a complex challenge due to the lack of extensive scientific studies identifying robust prognostic factors for satisfactory transplant outcomes. Frequently debated factors contain donor and recipient age, number of HLA mismatches, kidney re-transplantation, and body mass index (BMI) [1, 4–6]. Delayed graft function (DGF) is a significant prognostic indicator for graft survival and immunological response in ESP patients [4, 7–9]. Identifying modifiable risk factors for DGF could therefore contribute to improved outcomes in the future.

In this retrospective single-center study, we analyzed patient and graft survival in recipients of kidneys allocated via the ESP. Donor and recipient data were utilized to identify prognostic factors associated with kidney allograft survival and DGF. Furthermore, we evaluated whether the results of in-advance biopsies, that in our center are currently performed as time-zero analysis during transplantation, could potentially even further improve the prediction of the graft outcome when added to the aforementioned criteria, especially when their personnel- and time-sensitive processing could at least partially be automated. In addition, we aimed to review whether the ESP-recipients at our center in general still benefit from their transplantation.

## MATERIAL AND METHODS

### Study Design

From 1 September 2017 to 1 September 2022, 64 waitlisted recipients aged ≥65 years at the Hamburg University Transplant Center (UKE) received deceased donor kidneys via the ESP allocation algorithm. All renal allografts were obtained from donors after brain death, aged ≥65 years. Following the standard ESP criteria, HLA matching was not utilized during allocation. Induction immunosuppressive treatment consisted of basiliximab and steroids. Highly immunologically sensitized patients or patients with a high risk for DGF (e.g., longer CIT received thymoglobulin instead together with steroids. Maintenance

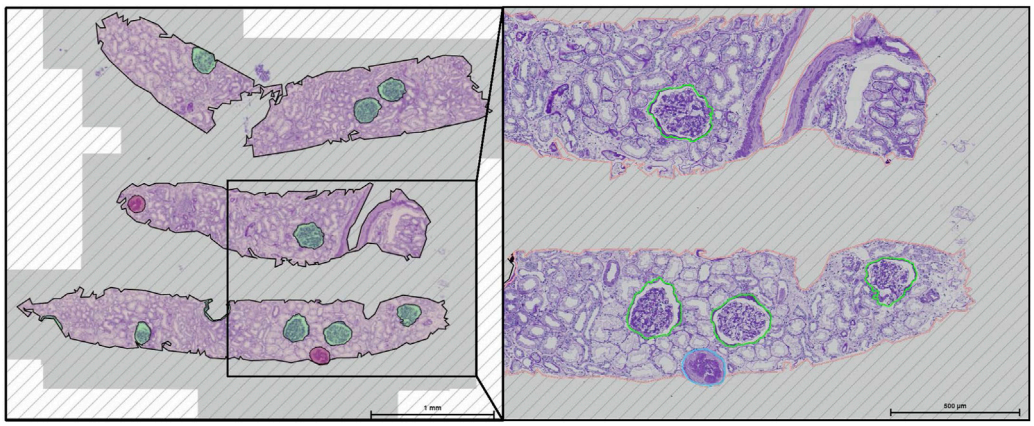


**FIGURE 1 |** Deep learning-based glomeruli detection in HAS KIT from periodic acid Schiff stained kidney.

immunosuppression included calcineurin inhibitors (mostly tacrolimus) and antimetabolites (mycophenolate mofetil or mTOR inhibitor) with or without steroids. From 2021 on, patients with low immunological risk were routinely placed on a steroid-free maintenance therapy from day eight after transplantation, following the HARMONY-study protocol [7].

## Data Collection

Donor data was extracted from Eurotransplant's donor kidney reports. Recipient data was collected in a retrospective manner, utilizing the patient files and hospital discharge reports, with a minimum follow-up of 16 months. 18G-time-zero biopsies were performed by the implanting transplant surgeon after reperfusion. Paraffin-embedded kidney biopsies were cut into 1–2 µm sections and stained according to a standard PAS staining protocol. Slides were digitized using Zeiss AxioScan.Z1 slide scanner (ZEISS Group, Oberkochen, Germany) with a ×20 objective and retrospectively analyzed using explainable deep-learning-based software HSA KIT (HS Analysis GmbH, Karlsruhe, Germany; **Supplementary Material S1**), which calculated in a reproducible and objective manner the surface area of the renal cortex and automatically quantified glomeruli. The evaluation enabled the calculation of glomerular density and the ratio of sclerosed glomeruli to the total number of glomeruli in a biopsy section (**Figure 1**). Histological findings of these biopsies were not available prior to transplantation and did therefore not influence decisions of the transplanting team in these patients. Data on interstitial fibrosis and tubular atrophy (IFTA), arteriolosclerosis, and arterial intimal fibrosis (AIF) were obtained from post-transplant pathology reports. Follow-up data were collected from patients undergoing routine check-up appointments at the outpatient clinic.

## Outcome Parameters

Recipient survival was defined as the time from transplantation until death, kidney graft failure by return to dialysis, excluding deaths with a functioning graft (DWFG). In the event of sepsis-induced multiple organ failure, documentation of dialysis therapy for at least 3 days prior to death was used for considering acute kidney injury as graft failure. DGF was defined as requiring more than one dialysis treatment within the first post-transplant week. Primary non-function (PNF) was defined for grafts never obtaining enough function to stop dialysis treatment after transplantation.

## Statistical Analysis

Descriptive statistics were determined for continuous (mean ± standard deviation, median, and minimum-maximum) and categorical variables (absolute values and percentages). Two-sided t-test was used to ascertain significant differences between two groups for continuous variables. Pearson's chi-square test was applied to calculate correlations between pairs of categorical variables. The Kaplan-Meier method was employed to examine graft and patient survival and log-rank test to analyze differences in graft survival. $P$-values $< 0.05$ were considered to be statistically significant. The $P$-values are of descriptive nature. There was no adjustment for multiplicity. The Intraclass Correlation Coefficient (ICC) was calculated using a two-way mixed effects model with an absolute agreement model. Univariable regression analysis was conducted to determine potential prognostic factors for graft loss, PNF and DGF. Variables yielding statistical significance in the univariable analysis were evaluated through a stepwise regression process within a multivariable analysis, utilizing a binary logistic regression model. Cox proportional hazard regressions were performed univariable and multivariable in order to analyze the effect of variables on graft survival. For the multivariable model, variables with a $P$-value $< 0.05$ in univariable analysis were included, and backward stepwise selection was applied using a removal criterion of $P > 0.10$. All data were analyzed using SPSS 29.0 (IBM Corp., Armonk, NY, United States).

# RESULTS

## Donor and Recipients Baseline Characteristics

A total of 64 patients who underwent kidney transplantation after ESP allocation were included in this study. All organs

**TABLE 1 |** Demographics and clinical characteristics.

| Variable | n = 64 |
|---|---|
| Recipient age (years) | 71.3 ± 4.3 (65–81) |
| Recipient sex m/f | 44/20 (68.8%/31.3%) |
| Recipient BMI (kg/m$^2$) | 26.8 ± 4.06 (17.7–37.5) |
| Recipient Comorbidities | |
| Hypertension | 56 (87.5%) |
| Coronary heart disease | 29 (45.3%) |
| Diabetes | 14 (21.9%) |
| Past history of tumor | 21 (32.8%) |
| Renal cell cancer | 6 (9.4%) |
| Prostate cancer | 4 (6.3%) |
| Colorectal cancer | 4 (6.3%) |
| Others | 7 (10.9%) |
| Donor age (years) | 72.9 ± 6.3 (65–86) |
| Donor sex m/f | 36/28 (56.3%/43.8%) |
| Donor BMI (kg/m$^2$) | 26.7 ± 4.8 (18.4–54.9) |
| Donor creatinine prior to organ procurement (mg/dL) | 1.02 ± 0.50 (0.43–2.81) |
| Donor Comorbidities | |
| Hypertension | 34 (53.1%) |
| Smoking | 14 (21.9%) |
| Diabetes | 10 (15.6%) |
| Time on dialysis (months) | 45.0 ± 24.52 (8.72–98.69) |
| Renal replacement therapy HD/PD | 52/12 (81.3%/18.8%) |
| 2nd kidney transplantation | 7 (10.9%) |
| Dual kidney transplant | 3 (4.7%) |
| Causes for kidney failure | |
| Nephrosclerosis or hypertensive nephropathy | 17 (26.6%) |
| ADPKD | 9 (14.1%) |
| IgA-nephropathy | 8 (12.5%) |
| Diabetic nephropathy | 7 (10.9%) |
| Nephropathy of unknown case | 4 (6.3%) |
| Interstitial nephritis | 2 (3.1%) |
| FSGS | 2 (3.1%) |
| Membranous glomerulonephritis | 2 (3.1%) |
| Membranoproliferative glomerulonephritis | 1 (1.6%) |
| Goodpasture-syndrome | 1 (1.6%) |
| Others | 11 (17.2%) |

*Data are presented as absolute values (percentages) for categorical variables; mean ± standard deviation (minimum–maximum) for continuous variables. BMI, body mass index; HD, hemodialysis; PD, peritoneal dialysis; ADPKD, autosomal dominant polycystic kidney disease; FSGS, focal segmental glomerulosclerosis.*

were obtained after brain death, as donations after circulatory death are currently not permitted in Germany. **Table 1** summarizes the baseline characteristics. The mean follow-up period was 49.2 ± 16.6 months. The proportion of males was higher among both recipients (68.8%) and donors (56.3%). The mean age of the recipients was 71.3 ± 4.3 years, while the donors had a mean age of 72.9 ± 6.3 years. According to the WHO definition, male recipients showed a considerable prevalence of increased bodyweight (79.5%), compared to the overall male population in Germany within the same age group (68.2%) [8]. Mean dialysis time before transplantation was 45 months. The leading cause of renal insufficiency was hypertensive nephropathy (26.6%). The mean CIT was 8.70 ± 3.0 h, and the mean warm ischemia time (WIT) was 37.5 ± 11.5 min. Due to the missing HLA matching in the ESP, 82.8% of patients had ≥4 HLA mismatches, while only 4.7% received a full-house match.

## Predictors for Delayed Graft Function

DGF occurred in 19 out of 64 cases (29.7%). A minimal BMI disparity of ≤2.5 kg/m$^2$ between donor and recipient was associated with significantly lower prevalence of DGF (11.1%), compared to >2.5 kg/m$^2$ (36.9%, $P < 0.05$). Univariable analyses indicated that an unfavorable BMI match (subdivided into ≤2.5, 2.51–5.0, >5.0 kg/m$^2$), higher recipient BMI, presence of CHD, and prolonged CIT significantly increased the odds of DGF. Each additional hour of CIT increased DGF-risk by 24% ($P < 0.05$). **Table 2** displays the results of the uni- and multivariable analyses. In a multivariable regression model, the combination of CHD and BMI disparity reached statistical significance for the event of DGF.

## Graft and Patient Outcome

Patients immunosuppressive therapy and outcome are described in **Table 3**. During the entire follow-up period, 12 patients (18.8%) died. The 1-year survival rate was 96.9%, with two patients dying within the first year and another 10 patients dying thereafter. Initially, patient survival remained nearly consistent, with a 3-year survival rate of 91.1%. After the first 3 years, the survival rate dropped, with the 5-year survival rate being only 74.0%. Seven recipients dies with a functional graft (DWFG). The primary cause of mortality was sepsis (58.3%).

Graft loss occurred in 14 patients (21.9%; DWFG excluded), with 1- and 5-year graft survival rates of 85.9% and 75.0%. Kaplan-Meier curves are shown in **Figures 2A,B**. PNF was observed in five patients. Excluding patients with PNF, the mean time to graft failure was 617.22 ± 446.83 days (89–1,177 days). Biopsy-proven rejection was observed in 14 recipients (21.9%). However, graft loss due to chronic rejection was rare, accounting for only one case. During follow-up, DSA were identified in 14 patients (21.9%), but their presence did not correlate with graft survival or rejection events. A total of 44 patients (68.8%) were hospitalized for at least 7 days due to infection-related complications. COVID-19 was diagnosed in 15 recipients (23.4%) during one of their inpatient stays. The presence of COVID-19, BK virus infection, or cytomegalovirus did not show any statistically significant correlation with mortality or graft failure.

## Predictors for Graft Failure

Follow-up data at 4 weeks ($P < 0.006$), as well as at three ($P = 0.039$), six ($P = 0.006$) and twelve ($P = 0.003$) months after transplantation, demonstrated a statistically significant correlation between elevated creatinine levels and graft loss in univariable logistic regression model. The mean creatinine level at 4 weeks post-transplant in patients who later experienced graft failure was 3.44 mg/dL ± 1.71, compared to 2.09 ± 0.95 mg/dL in those who did not experience graft failure. Additionally, the length of hospitalization post-transplant emerged as a predictor for graft failure probability: the relative risk for the loss of a graft increased by 8% for each additional day spent in the hospital after transplantation ($P = 0.029$). As our study aimed to define parameters already available at the time of allocation, these

**TABLE 2 |** Uni- and multivariable analysis of potential risk factors for Delayed Graft Function.

| Factors | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | OR (95% CI) | P-value | OR (95% CI) | P-value |
| BMI match (≤2,5; 2,51–5.0; >5.0 kg/m$^2$) | 2.38 (1.10; 5.17) | 0.028[a] | 2.40 (1.07; 5.41) | 0.035[a] |
| CHD | 3.93 (1.25; 12.33) | 0.019[a] | 3.95 (1.20; 13.03) | 0.024[a] |
| CIT (h) | 1.24 (1.02; 1.50) | 0.033[a] | -- | -- |
| Recipient BMI (kg/m$^2$) | 1.20 (1.03; 1.40) | 0.021[a] | -- | -- |

*BMI, body mass index; BMI match, disparity in BMI between recipient and donor; CHD, coronary heart disease; CIT, cold ischemia time; OR, odds ratio; CI, confidence interval.*
[a]*Significance 0.05. -- not included.*

**TABLE 3 |** Immunosuppressive therapy, patient- and graft survival.

| Variable | n = 64 |
|---|---|
| HLA mismatch | 4.4 ± 1.5 |
| PRA positive recipient | 12 (18.8%) |
| Induction therapy | 60 (93.8%) |
| Basiliximab/simulect | 4 (6.3%) |
| Antithymocyte globuline | |
| Use of tacrolimus as initial CNI on day eight | 59 (92.2%) |
| Use of cyclosporine A as initial CNI on day eight | 5 (7.8%) |
| Use of an antimetabolite (MMF/MPA) on day eight | 47 (73.4%) |
| Use of a mTOR inhibitor on day eight | 17 (26.6%) |
| Steroid-free immunosuppression on day eight | 14 (21.9%) |
| Delayed graft function | 19 (29,7%) |
| Mean hospital stay after transplantation (days) | 19.0 ± 8.5 (6–47) |
| Death | 12 (18.6%) |
| Cause of death | *n = 12* |
| Sepsis | 7 (58.3%) |
| Cardiovascular event | 1 (8.3%) |
| Aneurysm-related hemorrhage | 1 (8.3%) |
| Cancer | 1 (8.3%) |
| Unknown | 2 (16.7%) |
| Graft failure | 14 (21.9%) |
| Cause of graft failure | *n = 14* |
| Primary non-function | 5 (35.7%) |
| As a result of infection/sepsis | 2 (14.3%) |
| Rejection | 1 (7.1%) |
| BK virus infection | 1 (7.1%) |
| Cardiac decompensation | 1 (7.1%) |
| Unknown | 2 (14.3%) |
| Others | 2 (14.3%) |
| Duration between transplantation and graft loss (days) | 617.22 ± 446.83 (89–1,177) |
| NODAT | 11 (17.2%) |
| DSA | 14 (21.9%) |

*Data are presented as absolute values (percentages) for categorical variables; mean ± standard deviation (minimum–maximum) for continuous variables. HLA, human leukocyte antigen (Loci A, B, DR); PRA, panel reactive antibodies; CNI, calcineurin-inhibitor; NODAT, new onset diabetes after transplantation; DSA,* de novo *donor-specific antibodies.*

data are presented in the **Supplementary Material S2**, along with factors that remained non-significant in univariate analysis and therefore were not included.

Focusing on kidney donors, histopathological analysis was performed for all available 51 time-zero biopsies. There was a very good agreement on glomerulosclerosis grading between the pathologist and the retrospective semi-automated deep learning quantification (ICC = 0.913; 95% Confidence Interval = 0.85–0.95). Univariable analyses identified IFTA, the percentage of arteriolosclerosis (arteriolar hyalinosis), and glomerulosclerosis as significant risk factors for graft failure (**Table 4**). Glomerular density and AIF did not reach statistical significance. When focusing on the recipients, prolonged time on dialysis was associated with increased failure rates. Patients exceeding 3 years of dialysis treatment had a 35.3% risk of graft failure, compared to a 6.6% risk for those with less than 3 years of renal replacement therapy ($P$ = 0.006). The combination of IFTA, glomerulosclerosis, and time on dialysis reached statistical significance in a multivariable Cox proportional hazard model. The corresponding Kaplan-Meier analyses and log-rank tests are shown in **Figures 3A–C**. Additionally, arteriolosclerosis showed a significant correlation for the event of PNF ($P$ = 0.016; odds ratio = 1.16; 95% Confidence interval = 1.03–1.31). However, the number of HLA mismatches did not significantly influence graft survival in our ESP collective.

## DISCUSSION

This study aimed to identify potential prognostic factors for short- and long-term outcomes of ESP-kidney transplantations to improve organ allocation strategies within the participating transplant centers in the future. Therefore, we comparatively reevaluated those parameters proposed from previous studies [1, 4, 6] for our ESP recipients and investigated potentially predictive additional variables available at the time of the organ offer, such as the matching of baseline characteristics between donors and recipients. Finally, we used deep learning based image analysis software HSA KIT as human-machine interaction tool to retrospectively quantify histopathological data obtained from time-zero kidney biopsies and its potential as a future prospective tool prior to final organ acceptance when half-automatically integrated into the allocation process.

Our univariable analysis indicated that disparity in BMI, higher recipient BMI, CHD, and prolonged CIT significantly correlated with a higher prevalence of DGF. These factors, when modifiable, may be considered in future transplant evaluations, as existing literature has demonstrated that DGF is associated with poorer outcomes [4, 9–11]. However, due to the limited size of our patient cohort, not all variables could be included in the multivariable analysis. Previous studies have consistently shown that an increased BMI in either the recipient or the donor is associated with a higher risk of DGF and graft loss [4, 12–16].

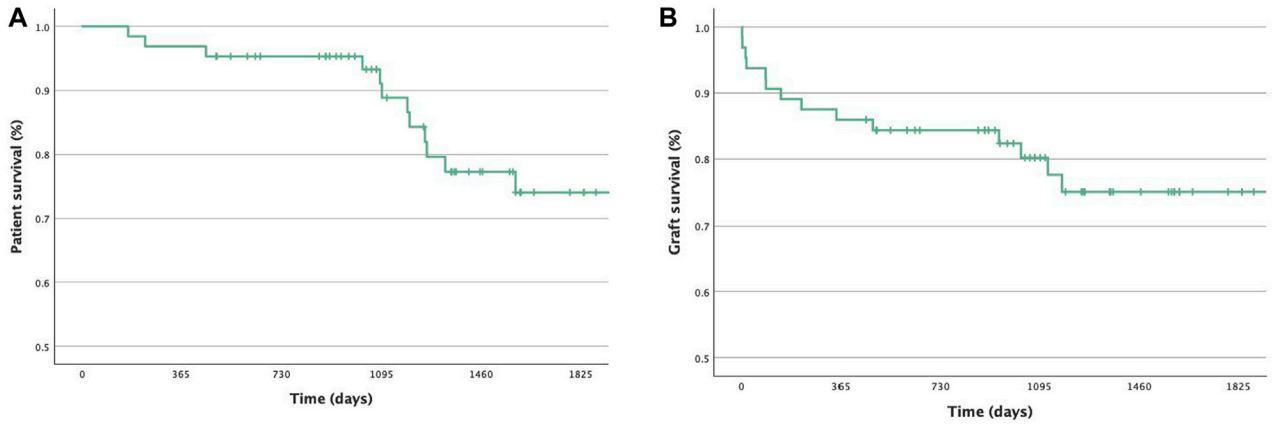



**FIGURE 2 |** Kaplan-Meier plots for **(A)** Patient survival during follow-up. **(B)** Graft survival during follow-up (censored due to end of observation period or death with functional graft).

But to our knowledge, this study is the first to report the impact of BMI disparities, rather than absolute values, between donor recipient pairs within the ESP as a measure that could indeed be part of an individualized allocation decision, favoring closer BMI matches to improve outcomes, as the match might indeed guide a decision for factors (absolute BMI of donor and recipient) are non-modifiable at the time of allocation.

Analyses of time-zero biopsies revealed that histopathological findings such as IFTA and the degree of glomerulosclerosis and arteriolosclerosis represented independent predictors of graft survival in ESP recipients. Our Cox proportional hazard model points to IFTA as one of the main histological factors associated with graft survival. Ouellet et al. used IFTA scoring to demonstrate that each unit increase in IFTA at 6 months is associated with a higher risk of graft loss [17]. In this respect, it is important to emphasize that validation of AI automated IFTA scoring is still in progress at our center. Our results regarding the influence of glomerulosclerosis on graft survival as the other major histopathological determinant align with findings from other studies [18–20]. In contrast to Keijbeck et al., our observations revealed a significant association between histological arteriolosclerosis and graft outcome [21]. Much to our surprise, glomerular density and AIF were not significantly associated with graft survival, while the importance of AIF in predicting kidney function after transplantation was recently demonstrated [20].

The retrospective findings of Jacobi et al. revealed that higher biopsy scores in pre-implantation biopsies from ESP kidneys were associated with an increased prevalence of PNF and higher creatinine levels 1-year post-transplant [5]. The value of preimplantation biopsies is still a matter of debate. Given that the logistics and economics (24/7 on-call nephropathologists and technical staff), as well as the resulting time delay, would only legitimate the effort if major improvements in outcome could still be expected, considering prolonged CIT already as one of the relevant determinants of DGF and prognosis. This is where semi-automated deep learning systems could help to reduce this delay. They could be operated by the cryosectioning team (technician and pathologist), typically available at transplant centers, which are usually situated at highly specialized university hospitals. In the future, this tool may not necessarily require a designated nephropathologist during routine analysis, as only the location of the analyzed area (glomerulus, blood vessel, tubulointerstitium) needs to be validated. The agreement between retrospective semi-automated quantification and pathologist grading of glomerulosclerosis was very good [22]. However, we have not yet been able to automate the analysis of time-zero biopsies for IFTA and arteriolosclerosis. This remains a promising area for future research. Nevertheless, combining automated glomerulosclerosis-scoring with IFTA assessment by a cryosectioning on duty team might be a feasible concept today already.

In addition, a biopsy only represents a limited section of the kidney, and there may be some variation in the distribution of healthy and sclerosed glomeruli. Still, final interpretation of biopsy results needs the context of clinical and laboratory findings, although we find the opportunity of utilizing quite reliable specific parameters via deep learning systems in the environment of sparse resources very intriguing as well as applicable during our routines. Taken together, such efforts must still be justified by a significant improvement of the transplant outcomes for individual patients, considering the potential benefits of knowing histopathological details compared to the effects of procedural extension of ischemia times.

Our retrospective study was not able to confirm the positive impact of HLA-DR matching on ESP-graft survival. Fijiter et al. lately reported that HLA-DR matching for ESP-recipients resulted in reduced waiting time on dialysis (2.6 vs. 4.1 years) and improved graft survival, despite an increase in CIT (12.0 vs. 10.6 h) [1]. Furthermore, Koch et al. assert that HLA matching is even beneficial for organs from donors aged 75 and older [6]. In

**TABLE 4 |** Uni- and multivariable analysis of potential risk factors for graft failure using Cox Regression.

| Factors | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| IFTA (%) | 1.04 (1.006; 1.07) | 0.021[a] | 1.08 (1.03; 1.41) | 0.002[a] |
| Glomerulosclerosis (%) | 1.05 (1.01; 1.09) | 0.025[a] | 1.07 (1.02; 1.12) | 0.011[a] |
| Time on dialysis (months) | 1.02 (1.002; 1.04) | 0.031[a] | 1.05 (1.02; 1.09) | 0.004[a] |
| Arteriolosclerosis (%) | 1.05 (1.01; 1.09) | 0.011[a] | -- | -- |
| Arterial intima fibrosis (%) | 1.01 (0.98; 1.05) | 0.483 | -- | -- |
| HLA-MM | 0.99 (0.66; 1.50) | 0.969 | -- | -- |

*IFTA, Interstitial fibrosis and tubular atrophy; Glomerulosclerosis - ratio of sclerosed glomeruli to total number of glomeruli; HLA-MM, number of human leucocyte antigen mismatches; HR, Hazard ratio; CI, confidence interval.*

[a]*Significance 0.05. – not included.*

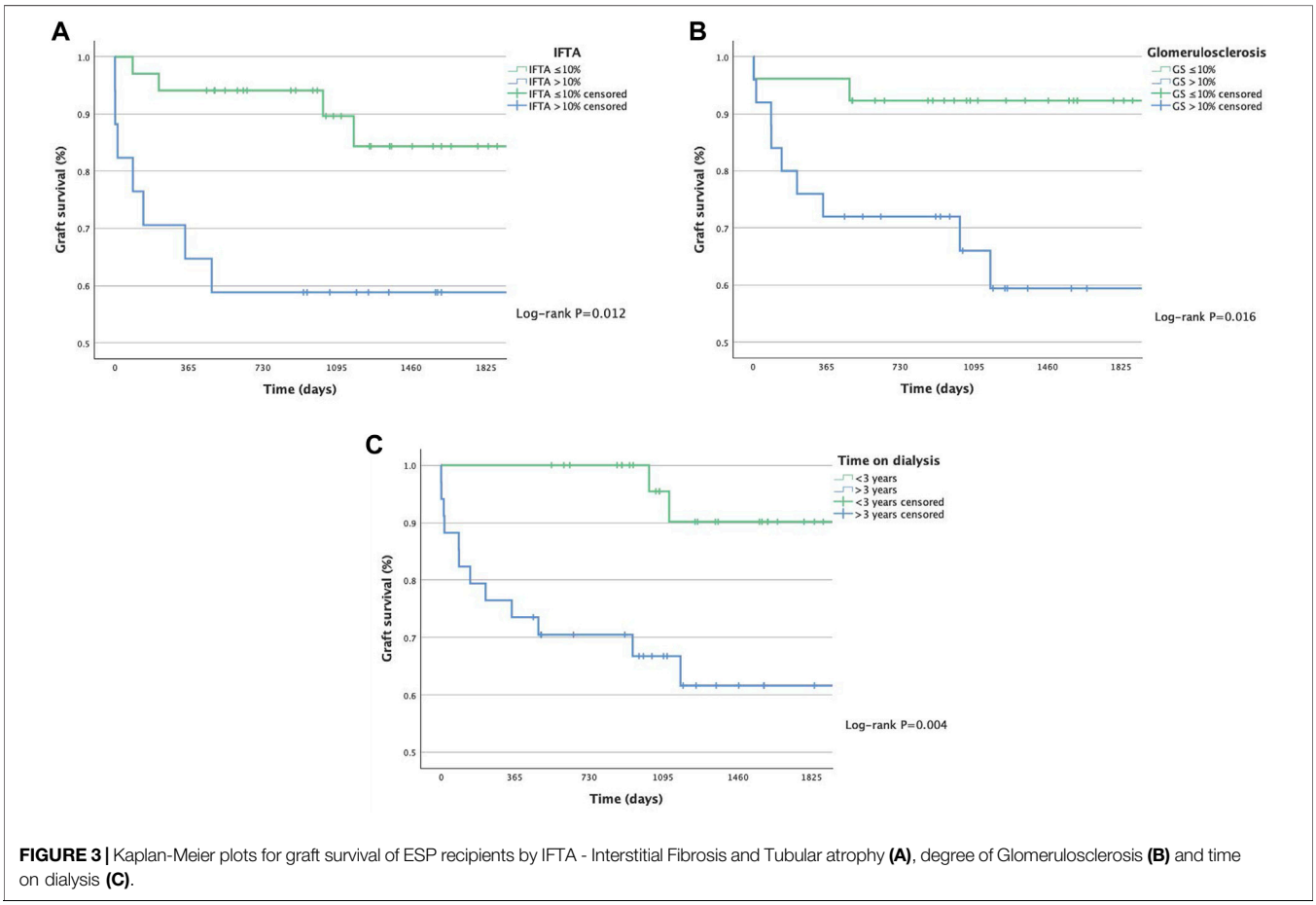



**FIGURE 3 |** Kaplan-Meier plots for graft survival of ESP recipients by IFTA - Interstitial Fibrosis and Tubular atrophy **(A)**, degree of Glomerulosclerosis **(B)** and time on dialysis **(C)**.

contrast, our findings indicate that prolonged CIT is associated with an increased risk of DGF, whereas better HLA match in our recipients did not correlate with improved outcomes. Several other studies also confirmed that extended CIT correlates with a higher incidence of DGF and graft loss [4, 11, 22, 23]. The increased susceptibility of older organs to damage from cold ischemia underscores the importance of minimizing CIT. The reduction in waiting time resulting from prospective HLA-DR matching may be the reason for better outcome, as our retrospective study again pronounces the negative impact of prolonged dialysis duration on later graft survival, as reported in the literature before [24].

DGF-rates, graft and patient survival in our study were comparable to those reported in similar studies evaluating the ESP. One- and 5-year graft survival rates ranged between 84%–87% and 63%–77%. Patient survival rates were 92%–94% and 65%–73% [4, 5, 25]. The incidence of DGF ranged between 19%–41.1% [4–6, 23, 25]. Excluding cases of PNF in our cohort, patient

and graft survival rates remained stable throughout the initial 3 years, with a notable increase in mortality thereafter. Death with a functional graft occurred in 58.3% of deceased patients, which is also in line with recent ESP observations [4, 5, 16, 23]. Compared to one- and 5-year survival rates of elderly dialysis patients with end-stage kidney disease, recipients still benefited from a transplantation within the ESP. In our cohort, the 5-year survival rate for recipients aged between 65–74 years was 74.6%, as opposed to 41.0% reported for patients on dialysis [3].

In our elderly cohort of transplant recipients, sepsis was identified as the primary cause of death. This once again highlights the unmet need for individually assessed and optimized levels of immunosuppression, considering initial renal disease and immunological burden by prior immunization, immunosenescence, and the patient's history of infections. Our results suggest that implementing less-potent immunosuppressive regimens might be advantageous, although no specific correlations of immunosuppressive therapy with patient or graft survival could be detected. In contrast to findings in previous ESP studies, in our cohort graft survival and DGF were not associated with rejection events [16]. However, the incidence of graft loss due to chronic rejection was low, and the limited number of chronic rejection cases precluded our statistical analysis from detecting potentially significant results. Taken together, follow-up care should especially evaluate the individual risk for infections and the adjustment of the immunosuppressive regimen as long as measures for individualized immunosuppressive guidance [26] cannot routinely be used.

The primary limitation of our study, next to its retrospective setup, is the relatively small sample size in terms of events for statistical testing. This constraint may have prevented identifying relationships between post-transplant outcomes and baseline characteristics such as age, diabetes mellitus, re-transplantation, and number of HLA mismatches. These factors were significant determinants of graft survival in prior ESP studies [4, 6, 16]. Our analysis of glomerular density did not yield statistically stable information regarding graft survival. An alternative approach might involve correlating glomerular density from biopsies and graft volume, which could facilitate the calculation of the total number of glomeruli in terms of "transplanted functional tissue" as a potential predictor of later transplant outcomes. These limitations could be addressed by multi-center studies with larger cohorts to prospectively validate the prognostic factors identified in this study for use during allocation. Moreover, we are quite aware that deep-learning-driven quantification would need to be validated and adapted for the use of fast-track HE-stained frozen sections, which, according to the manufacturer, would generally be technically realizable, but not yet included in our analysis.

## DATA AVAILABILITY STATEMENT

The data presented in this study are available on reasonable request by a qualified investigator for three years after the date of publication from the corresponding author.

## ETHICS STATEMENT

The requirement of ethical approval was waived by Ethikkommission der Aerztekammer Hamburg, Weidestrasse 122b, Hamburg, Germany for the studies on humans because retrospectively analyzed anonymous data obtained during standard medical care without any additional sampling usually receive a waiver from our board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements. The human samples used in this study were acquired from no additional sample analyses performed, anonymous evaluation of digital routine-care data that already existed.

## AUTHOR CONTRIBUTIONS

TL, FG, and MK established the study design. TL, FG, and MK performed literature research. TL collected the data and performed the statistical analyses. TW and MN performed nephropathological analysis, TW developed, validated and supervised the machine-learning processes, SB provided the software and technical support for automated histopathological analyses. TL, FG, and MK wrote the initial draft of the manuscript. All authors contributed to the article and approved the submitted version.

## FUNDING

The author(s) declare that financial support was received for the research and/or publication of this article. FG was supported by the DFG (German Research Foundation) (CRC 1140, CRC 1192, and GR3933/1-1), TBH was supported by the DFG (CRC1192, HU 1016/8-2, HU 1016/11-1, and HU 1016/12-1), by the German Federal Ministry of Education and Research (BMBF) (STOP-FSGS01GM1901C, ephrESA-031L0191E, and UPTAKE-01EK2105D), and by the H2020-IMI2 consortium BEAt-DKD (115974) this joint undertaking receives support from the European Union'sHorizon 2020 research and innovation program and EFPIA and JDRF.

## CONFLICT OF INTEREST

SB is the founder of HS Analysis.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## GENERATIVE AI STATEMENT

The authors declare that no Generative AI was used in the creation of this manuscript.

## ACKNOWLEDGMENTS

We would like to express our sincere gratitude to the Institute of Medical Biometry and Epidemiology (University Medical Center Hamburg-Eppendorf) for their valuable advice and support throughout the planning and execution of this project. We thank Sonia Wulf for excellent technical assistance.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.14153/full#supplementary-material

## REFERENCES

1. de Fijter J, Dreyer G, Mallat M, Budde K, Pratschke J, Klempnauer J, et al. A Paired-Kidney Allocation Study Found Superior Survival with HLA-DR Compatible Kidney Transplants in the Eurotransplant Senior Program. *Kidney Int* (2023) 104(3):552–61. doi:10.1016/j.kint.2023.05.025
2. Zecher D, Tieken I, Wadewitz J, Zeman F, Rahmel A, Banas B. Regional Differences in Waiting Times for Kidney Transplantation in Germany. *Dtsch Arztebl Int* (2023) 120(23):393–9. doi:10.3238/arztebl.m2023.0098
3. *European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry, ERA-EDTA Registry Annual Report 2019*. Amsterdam UMC (2023).
4. Bahde R, Vowinkel T, Unser J, Anthoni C, Hölzen JP, Suwelack B, et al. Prognostic Factors for Kidney Allograft Survival in the Eurotransplant Senior Program. *Ann Transpl* (2014) 19:201–9. doi:10.12659/AOT.890125
5. Jacobi J, Beckmann S, Heller K, Hilgers KF, Apel H, Spriewald B, et al. Deceased Donor Kidney Transplantation in the Eurotransplant Senior Program (ESP): A Single-Center Experience from 2008 to 2013. *Ann Transpl* (2016) 21:94–104. doi:10.12659/aot.895731
6. Koch M, Zecher D, Lopau K, Weinmann-Menke J, Schulze A, Nashan B, et al. Human Leucocyte Antigen-Matching Can Improve Long Term Outcome of Renal Allografts from Donors Older Than 75 Years. *Transpl Proc* (2023) 55(2): 309–16. doi:10.1016/j.transproceed.2022.12.014
7. Stumpf J, Thomusch O, Opgenoorth M, Wiesener M, Pascher A, Woitas RP, et al. Excellent Efficacy and Beneficial Safety during Observational 5-year Follow-Up of Rapid Steroid Withdrawal after Renal Transplantation (Harmony FU Study). *Nephrol Dial Transpl* (2023) 39(1):141–50. doi:10.1093/ndt/gfad130
8. Schienkiewitz A, Kuhnert R, Blume M, Mensink GBM. Overweight and Obesity Among Adults in Germany - Results from GEDA 2019/2020-EHIS. *J Health Monit* (2022) 7(3):21–8. doi:10.25646/10293
9. Ojo AO, Wolfe RA, Held PJ, Port FK, Schmouder RL. Delayed Graft Function: Risk Factors and Implications for Renal Allograft Survival. *Transplantation* (1997) 63(7):968–74. doi:10.1097/00007890-199704150-00011
10. Yarlagadda SG, Coca SG, Formica RN, Jr., Poggio ED, Parikh CR. Association between Delayed Graft Function and Allograft and Patient Survival: A Systematic Review and Meta-Analysis. *Nephrol Dial Transpl* (2009) 24(3): 1039–47. doi:10.1093/ndt/gfn667
11. Frei U, Noeldeke J, Machold-Fabrizii V, Arbogast H, Margreiter R, Fricke L, et al. Prospective Age-Matching in Elderly Kidney Transplant Recipients--a 5-year Analysis of the Eurotransplant Senior Program. *Am J Transpl* (2008) 8(1): 50–7. doi:10.1111/j.1600-6143.2007.02014.x
12. Prudhomme T, Bento L, Frontczak A, Timsit MO, Boissier R, Transplant Committee from the French Association of Urology CTAFU. Effect of Recipient Body Mass Index on Kidney Transplantation Outcomes: A Systematic Review and Meta-Analysis by the Transplant Committee from the French Association of Urology. *Eur Urol Focus* (2023) 10:551–63. doi:10.1016/j.euf.2023.11.003
13. Chang SH, Coates PT, McDonald SP. Effects of Body Mass Index at Transplant on Outcomes of Kidney Transplantation. *Transplantation* (2007) 84(8):981–7. doi:10.1097/01.tp.0000285290.77406.7b
14. Liese J, Bottner N, Büttner S, Reinisch A, Woeste G, Wortmann M, et al. Influence of the Recipient Body Mass Index on the Outcomes after Kidney Transplantation. *Langenbecks Arch Surg* (2018) 403(1):73–82. doi:10.1007/s00423-017-1584-7
15. Arshad A, Hodson J, Chappelow I, Inston NG, Ready AR, Nath J, et al. The Impact of Donor Body Mass Index on Outcomes after Deceased Kidney Transplantation - a National Population-Cohort Study. *Transpl Int* (2018) 31(10):1099–109. doi:10.1111/tri.13263
16. Zompolas I, Peters R, Liefeldt L, Lehner LJ, Budde K, Ralla B, et al. Outcomes of Deceased Donor Kidney Transplantation in the Eurotransplant Senior Program with A Focus on Recipients ≥75 Years. *J Clin Med* (2021) 10(23): 5633. doi:10.3390/jcm10235633
17. Ouellet G, Houde I, Riopel J, Latulippe E, Douville P, Lesage J, et al. The Progression of Interstitial Fibrosis and Tubular Atrophy at 6 Months Is an Independent Predictor of Poor Graft Outcomes in Kidney Transplant Recipients. *Transpl Direct* (2022) 8(12):e1375. doi:10.1097/TXD.0000000000001375
18. Cheungpasitporn W, Thongprayoon C, Vaitla PK, Chewcharat A, Hansrivijit P, Koller FL, et al. Degree of Glomerulosclerosis in Procurement Kidney Biopsies from Marginal Donor Kidneys and Their Implications in Predicting Graft Outcomes. *J Clin Med* (2020) 9(5):1469. doi:10.3390/jcm9051469
19. Wang CJ, Wetmore JB, Wey A, Miller J, Snyder JJ, Israni AK. Impact of Donor Kidney Biopsy on Kidney Yield and Posttransplant Outcomes. *Am J Transpl* (2023) 23(3):387–92. doi:10.1016/j.ajt.2022.11.020
20. Perez-Gutierrez A, Danz D, Chang A, Sekar P, Cummings R, Bachul PJ, et al. Arterial Intimal Fibrosis in Reperfusion Biopsy Correlates with Graft Function after Kidney Transplant. *Nephron* (2021) 145(2):150–6. doi:10.1159/000513120
21. Keijbeck A, Veenstra R, Pol RA, Konijn C, Jansen N, van Goor H, et al. The Association between Macroscopic Arteriosclerosis of the Renal Artery, Microscopic Arteriosclerosis, Organ Discard, and Kidney Transplant Outcome. *Transplantation* (2020) 104(12):2567–74. doi:10.1097/TP.0000000000003189
22. Peters-Sengers H, Houtzager JHE, Idu MM, Heemskerk MBA, van Heurn ELW, Homan van der Heide JJ, et al. Impact of Cold Ischemia Time on Outcomes of Deceased Donor Kidney Transplantation: An Analysis of a National Registry. *Transpl Direct* (2019) 5(5):e448. doi:10.1097/TXD.0000000000000888
23. Boesmueller C, Biebl M, Scheidl S, Oellinger R, Margreiter C, Pratschke J, et al. Long-term Outcome in Kidney Transplant Recipients over 70 Years in the Eurotransplant Senior Kidney Transplant Program: A Single Center Experience. *Transplantation* (2011) 92(2):210–6. doi:10.1097/TP.0b013e318222ca2f
24. Lim JH, Jeon Y, Kim DG, Kim YH, Kim JK, Yang J, et al. Effect of Pretransplant Dialysis Vintage on Clinical Outcomes in Deceased Donor Kidney Transplant. *Sci Rep* (2022) 12(1):17614. doi:10.1038/s41598-022-20003-2
25. Bentas W, Jones J, Karaoguz A, Tilp U, Probst M, Scheuermann E, et al. Renal Transplantation in the Elderly: Surgical Complications and Outcome with Special Emphasis on the Eurotransplant Senior Programme. *Nephrol Dial Transpl* (2008) 23(6):2043–51. doi:10.1093/ndt/gfm912
26. Aubert O, Ursule-Dufait C, Brousse R, Gueguen J, Racapé M, Raynaud M, et al. Cell-free DNA for the Detection of Kidney Allograft Rejection. *Nat Med* (2024) 30(8):2320–7. doi:10.1038/s41591-024-03087-3

ESOT | Transplant International

Best oral communication from the 8th congress of the Sociedad Española De Trasplante

SET SOCIEDAD ESPAÑOLA DE TRASPLANTE

ORIGINAL RESEARCH
published: 24 June 2025
doi: 10.3389/ti.2025.14098



OPEN ACCESS

***Correspondence**
María José Pérez-Sáez,
mperezsaez@hmar.cat

**†ORCID:**
María José Pérez-Sáez
orcid.org/0000-0002-8601-2699
Edoardo Melilli
orcid.org/0000-0001-6965-3745
Marta Arias
orcid.org/0000-0001-8023-2589
Antonio Franco
orcid.org/0000-0002-1349-1764
Asunción Sancho
orcid.org/0000-0002-4170-9003
María Molina
orcid.org/0000-0003-0033-4214
Carme Facundo
orcid.org/0000-0003-1254-5553
Verónica López
orcid.org/0000-0002-1793-7065
Auxiliadora Mazuecos
orcid.org/0000-0002-5860-2309
Sheila Cabello
orcid.org/0000-0001-9319-6935
María Elena González García
orcid.org/0000-0003-2003-4737
Ingrid Auyanet
orcid.org/0009-0001-4452-4370
Jordi Espi
orcid.org/0000-0003-2443-1035
Juan Carlos Ruiz
orcid.org/0000-0002-7904-8730
Cristina Galeano
orcid.org/0000-0003-2785-8886
José María Portolés
orcid.org/0000-0002-2114-1385
María Auxiliadora Santana
orcid.org/0009-0001-1198-2631
Paloma Martín-Moreno
orcid.org/0000-0001-5335-0555
Marta Calvo
orcid.org/0000-0002-5894-5360
Manuel Macía
orcid.org/0000-0002-0011-7706
María Lourdes Pérez-Tamajón
orcid.org/0000-0001-9812-5706
Javier de Teresa
orcid.org/0000-0002-3416-5490
Sagrario Soriano
orcid.org/0000-0002-0530-3022
Guadalupe Tabernero
orcid.org/0000-0002-1917-0769
Lourdes de la Vara
orcid.org/0009-0005-5835-0147
Ana María Ramos
orcid.org/0000-0001-8137-8483
Julio Pascual
orcid.org/0000-0002-4735-7838
Leocadio Rodríguez-Mañas
orcid.org/0000-0002-6551-1333

# Frailty Prevalence and Characterization Among Kidney Transplant Candidates in Spain: A Multicenter Study

*María José Pérez-Sáez[1,2*†], Edoardo Melilli[3†], Marta Arias[4†], Antonio Franco[5†], Rocío Martínez[6], Asunción Sancho[7†], María Molina[8†], Carme Facundo[9†], Natalia Polanco[10], Verónica López[11,12†], Auxiliadora Mazuecos[13†], Sheila Cabello[14†], María Elena González García[15†], María Luisa Suárez[16], Ingrid Auyanet[17†], Jordi Espi[18†], Teresa García Falcón[19], Juan Carlos Ruiz[20†], Cristina Galeano[21†], Marta Artamendi[22], María Luisa Rodríguez-Ferrero[23], José María Portolés[24†], María Auxiliadora Santana[25†], Paloma Leticia Martín-Moreno[26†], Nisrine Arhda[27], Marta Calvo[28†], Alicia Mendiluce[29], Manuel Macía[30†], María Lourdes Pérez-Tamajón[31†], Javier de Teresa[32†], Blanca Gascó[33], Sagrario Soriano[34†], Guadalupe Tabernero[35†], Lourdes de la Vara[36†], Ana María Ramos[37†], Rafael Martínez[38], Enrique Montero de Espinosa[38], José Luis Zalve[38], Julio Pascual[10†], Leocadio Rodríguez-Mañas[39†], Alex Gutiérrez-Dalmau[40†‡] and Francesc Moreso[41†‡]*

[1]Nephrology Department, Hospital del Mar, RICORS2040 RD21/0005/0022, Barcelona, Spain, [2]Hospital del Mar Research Institute, Barcelona, Spain, [3]Nephrology Department, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain, [4]Nephrology Department, Hospital Clínic, Barcelona, Spain, [5]Nephrology Department, Hospital General Universitario, Alicante, Spain, [6]Nephrology Department, Hospital Universitario Infanta Cristina, Badajoz, Spain, [7]Nephrology Department, Hospital Universitario Doctor Peset, Valencia, Spain, [8]Nephrology Department, Hospital Universitari Germans Trias i Pujol, RICORS2040, Barcelona, Spain, [9]Nephrology Department, Fundació Puigvert, Institut de Recerca Sant Pau (IR Sant Pau), RICORS2040, Barcelona, Spain, [10]Nephrology Department, Hospital 12 de Octubre, Madrid, Spain, [11]Nephrology Department, Hospital Regional Universitario de Málaga, Málaga, Spain, [12]National Network for Kidney Research RICORS2040 RD21/0005/0012, Instituto Biomédico de Investigación de Málaga (IBIMA), Universidad de Málaga, Málaga, Spain, [13]Nephrology Department, Hospital Universitario Puerta del Mar, Cádiz, Spain, [14]Nephrology Department, Hospital Universitari Son Espases, Palma de Mallorca, Spain, [15]Nephrology Department, Hospital Universitario La Paz, Madrid, Spain, [16]Nephrology Department, Hospital Universitario Central de Asturias, Oviedo, Spain, [17]Nephrology Department, Complejo Hospitalario Insular de Gran Canaria, Las Palmas de Gran Canaria, Spain, [18]Nephrology Department, Hospital Universitario y Politécnico La Fe, Valencia, Spain, [19]Nephrology Department, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain, [20]Nephrology Department, Hospital Universitario Marqués de Valdecilla, Instituto de Investigación Valdecilla (Idival), Santander, Spain, [21]Nephrology Department, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRyCIS), Madrid, Spain, [22]Nephrology Department, Hospital San Pedro, La Rioja, Spain, [23]Nephrology Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain, [24]Nephrology Department, Hospital Universitario Puerta de Hierro, Madrid, Spain, [25]Nephrology Department, Hospital Universitario de Cruces, Barakaldo, Bizkaia, Spain, [26]Nephrology Department, Clínica Universidad de Navarra, Navarra Institute for Health Research (IdiSNA), Pamplona, Spain, [27]Nephrology Department, Hospital Clínico Universitario de Santiago, Santiago de Compostela, Spain, [28]Nephrology Department, Hospital Clínico San Carlos, Madrid, Spain, [29]Nephrology Department, Hospital Clínico Universitario de Valladolid, Valladolid, Spain, [30]Nephrology Department, Hospital Virgen de la Candelaria, Santa Cruz de Tenerife, Spain, [31]Nephrology Department, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain, [32]Nephrology Department, Hospital Universitario Virgen de las Nieves, Granada, Spain, [33]Nephrology Department, Hospital Virgen del Rocío, Sevilla, Spain, [34]Nephrology Department, Hospital Universitario Reina Sofía, Córdoba, Spain, [35]Nephrology Department, Hospital Universitario de Salamanca, Instituto de Investigación Biomédica de Salamanca (IBSAL), Salamanca, Spain, [36]Nephrology Department, Complejo Hospitalario General Universitario de Albacete, Albacete, Spain, [37]Nephrology Department, Fundación Jiménez Díaz, Madrid, Spain, [38]Sandoz Farmacéutica SA, Head of Medical Department, Madrid, Spain, [39]Geriatrics Department, Hospital Universitario de Getafe, Madrid, Spain, [40]Nephrology Department, Hospital Universitario Miguel Servet, Zaragoza, Spain, [41]Nephrology Department, Hospital Universitario General Vall d' Hebron, Barcelona, Spain

Frailty is a frequent condition among kidney transplant candidates (KTc) that confers poor outcomes after transplantation. We aimed to establish frailty prevalence in a representative

*Alex Gutiérrez-Dalmau*
*orcid.org/0000-0002-2253-7779*
*Francesc Moreso*
*orcid.org/0000-0002-7267-3963*
*‡These authors share senior authorship*

***Received:*** *21 November 2024*
***Accepted:*** *30 May 2025*
***Published:*** *24 June 2025*

***Citation:***
*Pérez-Sáez MJ, Melilli E, Arias M, Franco A, Martínez R, Sancho A, Molina M, Facundo C, Polanco N, López V, Mazuecos A, Cabello S, González García ME, Suárez ML, Auyanet I, Espi J, García Falcón T, Ruiz JC, Galeano C, Artamendi M, Rodríguez-Ferrero ML, Portolés JM, Santana MA, Martín-Moreno PL, Arhda N, Calvo M, Mendiluce A, Macía M, Pérez-Tamajón ML, de Teresa J, Gascó B, Soriano S, Tabernero G, de la Vara L, Ramos AM, Martínez R, Montero de Espinosa E, Zalve JL, Pascual J, Rodríguez-Mañas L, Gutiérrez-Dalmau A and Moreso F (2025) Frailty Prevalence and Characterization Among Kidney Transplant Candidates in Spain: A Multicenter Study. Transpl. Int. 38:14098. doi: 10.3389/ti.2025.14098*

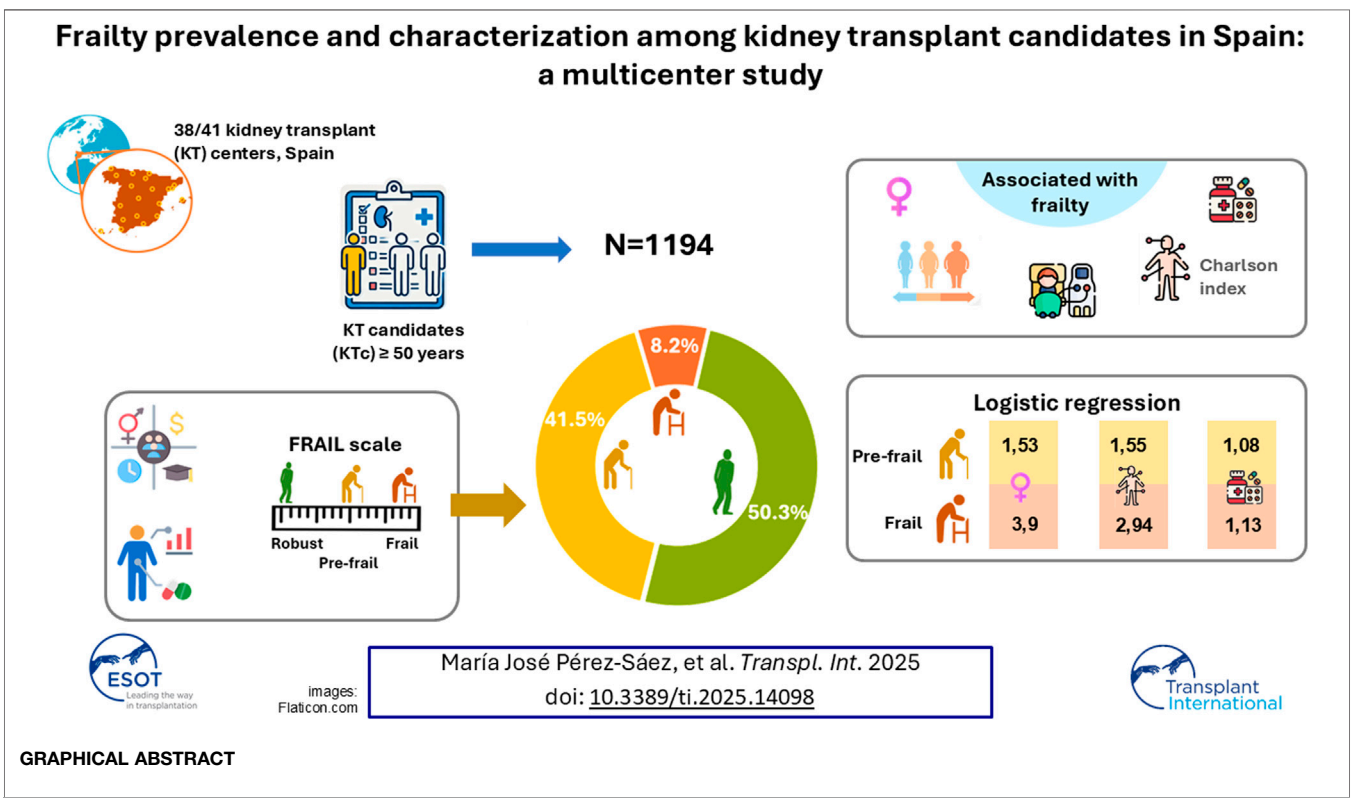
sample of KTc in Spain. We conducted a multicenter cross-sectional study including 1194 KTc ≥50 years. Frailty was assessed by the FRAIL scale. Mean age was 64.2 years; 38.4% were female. Median Charlson comorbidity index (CCI) was 6 [4–7] and the total number of medications was 9 [7–12]. We found that 8.2% of patients were frail and 41.5% were pre-frail. Frailty was more frequent among females (60.2% of frail vs. 32.8% of robust; $p < 0.001$), hemodialysis patients (74.5% of frail vs. 67.1% of robust; $p = 0.02$), and those with a high burden of disease (54.6% of frail patients with CCI >6 vs. 29.3% of robust; $p < 0.001$). The multivariable analysis confirmed that frailty was associated with the female sex (OR 3.9 [2.5–6.2]); higher CCI (>6 OR 2.9 [1.6–54]); and the number of medications (OR –per medication- 1.13 [1.07–1.2]). Almost 50% of KTc in Spain are pre-frail or frail. Frailty is more prevalent between women and patients with high comorbidity burden. Identifying those candidates at risk is essential to establish risks and implement strategies to minimize them.

**Keywords: FRAIL, frailty, kidney transplant, waiting list, candidate**

## INTRODUCTION

Frailty is characterized by a reduced physiological reserve to stressors and was initially studied within the aging population residing in communities [1]. Among individuals with advanced chronic kidney disease (CKD), frailty is a frequent condition and has been reported to affect up to 70% of patients receiving hemodialysis [2, 3]. These patients experience poorer outcomes while on dialysis, including higher mortality rates [4, 5].

Frail CKD patients have also restricted access to the kidney transplantation (KT) waiting list and their chances of receiving a transplant are notably reduced [6, 7]. Among subjects evaluated for KT, frailty prevalence ranges from 5% to more than 50%, depending on the series and the scale used




**GRAPHICAL ABSTRACT**

[6–9]. Eventually, pooled analysis of different studies shows that about 17% of KT recipients are identified as frail [10]. However, most of the studies included in the systematic reviews of frailty among KT recipients come from US cohorts, with a very small representation of European studies [11]. Sociodemographic differences between American and European populations prevent direct extrapolation of the results.

Frail KT recipients experience heightened rates of complications such as intolerance to immunosuppressants [12], prolonged length of stay and a higher rate of readmissions [13, 14], higher rate of delayed graft function and surgical complications [15, 16], and, more importantly, higher post-transplant mortality [14, 17–21].

In Spain, fewer than 20% of dialysis patients have access to KT [22]. Possibly, frailty hampers this access, especially among elderly recipients. Despite the recognized impact of frailty on KT outcomes, clinicians often encounter challenges in assessing frailty during outpatient visits, and questions arise regarding the best scale to use and the potential utility of the information obtained [23]. A survey across 133 KT programs in the US revealed that 69% of centers reported performing standardized frailty assessments during transplant evaluations, yet there was little consensus on the preferred tool for measuring frailty [24]. The scale proposed by Linda Fried more than 20 years ago, the Physical Frailty Phenotype (PFP), has emerged as the most used frailty scale in research involving KT candidates and recipients [1]. However, other less time-consuming metrics, like the FRAIL scale, have also found utility in this context [7, 25]. Centers conducting frailty evaluations through validated tools have demonstrated better waitlist and transplant outcomes, regardless of the tool used [26]. Although correlation among different frailty metrics is poor [27–29], identifying patients at risk for unfavorable results holds paramount importance in assessing prognosis, establishing preventive strategies, and implementing therapeutic interventions such as prehabilitation.

This is a multicenter cross-sectional study carried out with the participation of the vast majority of KT Units in Spain. We aimed to establish frailty prevalence and associated factors among KT candidates over 50 years in our setting, as well as to boost the universal implementation of the frailty measurement as part of the KT candidacy study work-up.

# PATIENTS AND METHODS

## Study Design and Participants

This is a multicenter, cross-sectional study carried out in 38 KT Units in Spain during 2022.

All KT Units in Spain were invited to participate and 38 out of 41 agreed. During the outpatient visits, subjects ≥50 years old included on the KT waiting list and able to consent were invited to participate in the study. Both patients already included on the waiting list and those who were new inclusions during the visit could be included in the study. Patients with a major psychiatric disorder, cognitive impairment, or an acute condition that to the judgment of the investigator could cause a physical impairment were excluded from the study.

The study started in March 2022 and the inclusion was competitive among centers until the end of the study (December 2022). The number of patients included was different across centers, depending on the number of patients included on their KT waiting list, the frequency of the visits, etc. Although there were differences, with a maximum of 169 and a minimum of 2 patients per center, 50% centers included more than 20 patients in the study.

Clinical and epidemiological variables and the FRAIL scale were collected at each center and introduced in a central database. Data extraction and analysis were further conducted.

## Ethics

The Institutional Review Board of Hospital del Mar approved the study (2020/9349), and all enrolled participants provided written informed consent at the time of frailty evaluation. The study followed the principles of the Declaration of Helsinki, only relying on the official database.

## Frailty Assessment

Frailty was assessed according to the FRAIL scale which includes 5 questions (all of them self-reported) assessing fatigue, resistance, ambulation, illness, and loss of weight. In both scales, each component or question scores 0/1 depending on its presence or absence. Robust patients were defined by a score of 0, pre-frail as those who ranked 1–2, and frail patients were defined by a score ≥3 [30].

The FRAIL scale has been proposed as a screening tool for frailty in general population [31]. It has been used in Spanish geriatric population [32] but also in Spanish KT candidates [7, 28].

## Study Variables

Besides the FRAIL scale, we included demographics (age, sex, ethnicity); social (education -defined by 4 categories: elementary, primary education, secondary education, and tertiary education-, family or social support –living by their own, in family, with friends, in a health/social facility-); and clinical data (body mass index (BMI), Charlson comorbidity index (CCI) [33], total number of medications, cause of renal disease, type of renal replacement therapy (RRT), date of dialysis initiation and date of waiting list inclusion, candidate to re-transplantation, albumin levels, C-reactive protein levels).

## Statistics

Continuous variables were expressed as mean ± standard deviation (SD), or median and interquartile range (IQR), according to normal distribution. Categorical data were expressed as absolute numbers and percentages. Comparisons of baseline characteristics between two groups were made using Chi-square or Fisher's exact tests to analyze categorical variables, Student's t-test for continuous variables with normal distribution, and Mann–Whitney test for non-parametric variables. When three categories were present, the Chi-square test was also used to compare categorical variables, the ANOVA test to compare quantitative variables with normal distribution, and the Kruskal-Wallis test for quantitative variables without normal distribution. Binomial and multinomial logistic regression

**TABLE 1 |** Baseline and clinical characteristics of the 1194 KT candidates included in the study.

| | KT candidates (n = 1,194) |
|---|---|
| Age (years, mean ± sd) *n = 0, 0%* | 64.2 ± 8.4 |
| Sex (female, n (%)) *n = 0, 0%* | 459 (38.4) |
| Ethnicity (Caucasian, n (%)) *n = 9, 0.8%* | 1,107 (92.7) |
| Education (elementary, n (%)) *n = 170, 14.2%* | 208 (17.4) |
| Family/social support (living alone, (%)) *n = 84, 7%* | 140 (11.7) |
| BMI (Kg/m$^2$, mean ± sd) *n = 79, 6.6%* | 26.7 ± 4.5 |
| Cause of renal disease *n = 5, 0.4%* | |
| Unknown | 285 (23.9) |
| Diabetic nephropathy | 183 (15.3) |
| Glomerular disease | 233 (19.5) |
| Others | 493 (41.3) |
| Previous KT (yes, n, (%)) *n = 14, 1.2%* | 329 (27.6) |
| Number of previous KT (median [max-min]) | 1 [1–5] |
| Renal replacement therapy modality (n, (%)) *n = 3, 0.3%* | |
| Hemodialysis | 775 (64.9) |
| Peritoneal dialysis | 215 (18) |
| Preemptive transplant | 201 (19.8) |
| Time from dialysis onset to WL entry (years, median [IQR]) *n= 291, 24.7%* | 1 [0.5–1.9] 2 [1–3.9] |
| Time from dialysis onset to frailty determination (years, median [IQR]) *n = 0, 0%* | |
| Charlson comorbidity index (median [IQR]) *n = 18, 1.5%* | 6 [4–7] |
| Low comorbidity = 3–4 | 337 (28.7) |
| Intermediate comorbidity = 5–6 | 420 (35.7) |
| High comorbidity >6 | 419 (35.6) |
| Total number of different medications (median [IQR]) *n = 0, 0%* | 9 [7–12] |
| Albumin (g/dL, mean ± sd) *n = 200, 16.7%* | 4 ± 0.6 |
| CRP (mg/dL, median [IQR]) *n = 370, 31%* | 0.6 [0.2–1.9] |

*KT, kidney transplant; sd, standard deviation; BMI, body mass index; IQR, interquartile range; WL, waiting list; CRP, C-reactive protein. *Frequencies and % of missing data of each variable.*

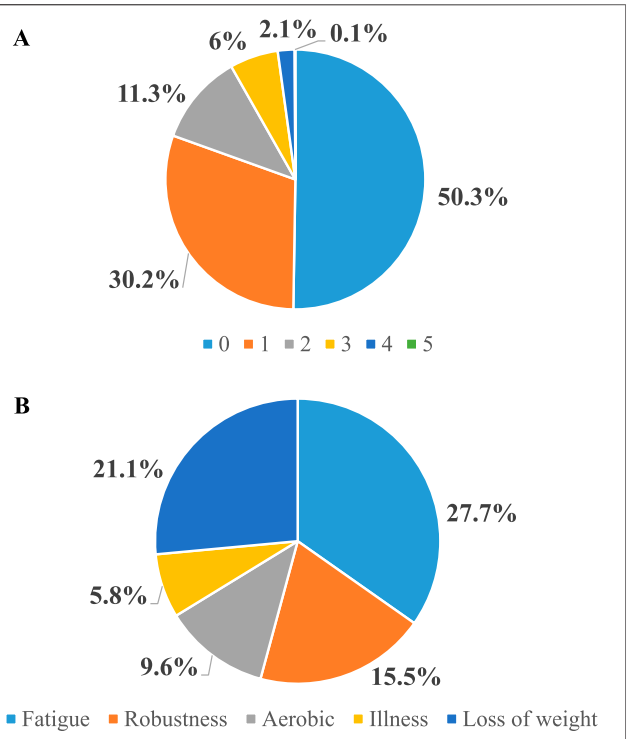



**FIGURE 1 | (A)** Frailty prevalence according to the FRAIL scale among 1194 KT candidates in Spain. **(B)** FRAIL items distribution.

models considering frailty as yes/no (merging pre-frailty and frailty status) or with the three categories (robust, pre-frail, and frail) were conducted. Variables were considered to be included in the multinomial model if a p-value ≤0.20 was found in the bivariate analysis. Two multinominal logistic regression models were conducted: one including the global CCI (ranking 0–24), and other including only cardiovascular disease as Charlson comorbidities (ranking 0 to 4: myocardial infarction, congestive heart disease, peripheral vascular disease and cerebrovascular disease). Statistical analysis was performed using SPSS version 29 software (IBM, Armonk, NY, USA). P-values <0.05 were considered statistically significant.

## RESULTS

A total number of 1194 KT candidates ≥50 years old were included in the study. **Table 1** displays the main characteristics of the cohort. The mean age was 64.2 years, 38.4% of them were female and 92.7% were Caucasian. In terms of education and social support, 17.4% declared themselves as having received elementary education and 11.7% lived on their own. The most frequent cause of CKD was unknown (23.9%) followed by glomerular disease (19.5%). Almost one-third of candidates had received at least one kidney transplant before (27.6%). In terms of RRT modality, 64.9% were on hemodialysis, 18% were on peritoneal dialysis and 19.8% were on a situation of advanced CKD pre-dialysis. The median time from dialysis onset to the waiting list entry was 12 months. KT candidates presented with a high comorbidity burden (CCI >6) in 35.6% of the cases. Subsequently, the total number of medications prescribed to each patient was high (9). In terms of laboratory parameters, mean albumin levels were 4 g/dL and mean levels of C-reactive protein were 0.6 mg/dL.

Frailty prevalence was determined by the FRAIL scale. Half of the patients were robust (50.3%), 41.5% were pre-frail, and 8.2% were frail. The most frequently reported item was fatigue (27.7%), followed by loss of weight (21.1%) and lack of robustness (15.5%). **Figure 1**.

**Table 2** compares KT candidates who were robust, pre-frail, and frail. We found a higher percentage of females as the frail score increases (32.8% of robust patients; 40.9% of pre-frail; and 60.2% of frail patients). Frail candidates were also slightly more overweighted (BMI 27.5 kg/m$^2$ in frail candidates vs. 26.1 kg/m$^2$ in robust ones), were more frequently receiving hemodialysis as RRT (74.5% -frail- vs. 67.1% -robust-), had higher comorbidity burden (CCI >6 54.6% -frail- vs. 29.3% -robust-), and were on more medications (11 –frail- vs. 8.5 –robust-). On the contrary, the mean age was similar among robust and frail candidates. No differences in terms of albumin or C-reactive protein levels were found between robust or frail patients either.

**TABLE 2 |** Baseline and clinical characteristics of KT candidates according to their FRAIL score.

| Baseline and clinical characteristics of KT candidates | Robust group | Pre-frail group | Frail group | p-value |
|---|---|---|---|---|
| | FRAIL = 0 (n = 600) | FRAIL = 1–2 (n = 496) | FRAIL ≥3 (n = 98) | |
| Age (years, mean ± sd) | 64.1 ± 8.2 | 64.5 ± 8.7 | 63.3 ± 8.1 | 0.475 |
| Sex (female, n (%)) | 197 (32.8) | 203 (40.9) | 59 (60.2) | <0.001 |
| Ethnicity (Caucasian, n (%)) | 553 (93.3) | 464 (93.9) | 90 (91.8) | 0.729 |
| Education (basic, n (%)) | 99 (19.4) | 87 (20.3) | 22 (26.2) | 0.093 |
| Family/social support (living alone, (%)) | 70 (12.6) | 53 (11.4) | 17 (18.5) | 0.230 |
| BMI (Kg/m$^2$, mean ± sd) | 26.1 ± 4.1 | 27.1 ± 4.6 | 27.5 ± 5.4 | 0.002 |
| Cause of renal disease | | | | |
| Unknown | 128 (21.5) | 129 (26.1) | 28 (28.6) | |
| Diabetic nephropathy | 88 (14.8) | 79 (16) | 16 (16.3) | 0.734 |
| Glomerular disease | 116 (19.5) | 98 (19.8) | 19 (19.4) | |
| Others | 268 (44.6) | 190 (19.8) | 35 (35.7) | |
| Previous KT (yes, n, (%)) | 167 (28.1) | 129 (26.4) | 33 (34.4) | 0.276 |
| Number of previous KT (median [max-min]) | 1 [1–3] | 1 [1–5] | 1 [1–3] | 0.993 |
| Renal replacement therapy modality (n, (%)) | | | | |
| Hemodialysis | 402 (67.1) | 300 (60.7) | 73 (74.5) | |
| Peritoneal dialysis | 106 (17.7) | 93 (18.8) | 16 (16.3) | 0.020 |
| Preemptive transplant | 91 (15.2) | 101 (20.4) | 9 (9.2) | |
| Time from dialysis onset to WL entry (years, median [IQR]) | 1.1 [0.6–2.3] | 1.2 [0.6–2.3] | 1.5 [0.7–4.1] | 0.105 |
| Time from dialysis onset to frailty determination (years, median [IQR]) | 2 [1–3.8] | 1.8 [1–3.8] | 3 [1.-4.9] | 0.471 |
| Charlson comorbidity index | | | | |
| Low comorbidity = 3–4 | 195 (33.2) | 124 (25.3) | 18 (18.6) | |
| Intermediate comorbidity = 5–6 | 221 (37.6) | 173 (35.2) | 26 (26.8) | <0.001 |
| High comorbidity >6 | 172 (29.3) | 194 (39.5) | 53 (54.6) | |
| Charlson comorbidity index (only considering CV risk factors (0–4) | | | | |
| Low comorbidity = 0 | 394 (55.9) | 282 (40) | 29 (4.1) | |
| Intermediate comorbidity = 1 | 138 (42.6) | 149 (46) | 37 (11.4) | <0.001 |
| High comorbidity =2–4 | 56 (9.52) | 60 (12.2) | 31 (31.9) | |
| Total number of different medications (median [IQR]) | 8.5 [7–11] | 10 [7–12] | 11 [8–13] | <0.001 |
| Albumin (g/dL, mean ± sd) | 4 ± 0.6 | 4 ± 0.5 | 3.9 ± 0.5 | 0.688 |
| CRP (mg/dl, median [IQR]) | 0.6 [0.2–1.8] | 0.5 [0.2–1.7] | 1 [0.2–2.6] | 0.205 |

*KT, kidney transplant; sd, standard deviation; BMI, body mass index; IQR, interquartile range; WL, waiting list; CV, cardiovascular; CRP, C-reactive protein.*

Two multinomial logistic regression analyses were conducted to analyze factors associated with pre-frailty and frailty in KT candidates (**Table 3**). In the first model, including global Charlson index as comorbidity index, female sex (odds ratio (OR) 1.53 [1.19–1.98]), high comorbidity burden (OR 1.55 [1.13–2.13]), and total number of medications (OR 1.08 per medication [1.04–1.12]) were associated with pre-frailty status. The same factors with higher intensity were also associated with frailty: female sex (OR 3.90 [2.46–6.19]), high comorbidity burden (OR 2.93 [1.61–5.41]), and total number of medications (OR 1.13 per medication [1.07–1.20]), **Table 3**. The second model included only cardiovascular disease (myocardial infarction, congestive heart disease, peripheral vascular disease and cerebrovascular disease) as comorbidity burden. Cardiovascular disease was highly associated with frailty in this cohort, starting at one cardiovascular problem (OR 3.46 [2.02–5.95], and increasing this association along with the number of cardiovascular problems (**Table 3**).

## DISCUSSION

Herein, we present a multicenter cross-sectional study involving thirty-eight out of the total forty-one Kidney Transplant Units in Spain and more than 1000 CKD patients who are KT candidates that establishes the prevalence of frailty according to the FRAIL scale and factors associated. This sample represents about 50% of all patients over 50 years included in the KT waiting list in Spain (data provided by Spanish National Transplant Organization). Although less than 10% of KT candidates ≥50 years old in Spain are frail, the prevalence of pre-frailty and frailty together was almost 50% of the cohort. Female sex, comorbidity, and medications were strongly associated with frailty status.

The prevalence of frailty among KT candidates already listed for transplantation may vary from less than 5% to more than 50%, depending on the population and the scale used [6–9]. A large multicenter study from the US identified 18% of individuals as frail at the time of initial evaluation, while only 12% of individuals were identified as being frail among those who were ultimately listed for KT [6]. Among KT recipients, frailty prevalence before transplantation was established at 17.1% when a pooled analysis was made [10]. However, eleven of the fourteen studies included in the analysis were from the US. In Europe, two single-center studies have explored the prevalence of frailty in KT candidates/recipients: 15% of KT recipients were frail according to the Groningen Frailty Indicator in a Dutch study [11], and 10.5% and 3.6% of KT candidates were frail according to the PFP and the FRAIL scale, respectively, in a Spanish study [7]. In this multicenter study, we describe a large cohort of Spanish KT candidates over 50 years listed for transplantation with a prevalence of frailty of 8.2% according to the FRAIL scale.

**TABLE 3 |** Multinomial logistic regression of factors associated with pre-frailty and frailty in KT candidates. A) Considering global Charslon index; B) Considering a cardiovascular Charlson index (0–4).

| Independent variables | OR | 95% CI | |
|---|---|---|---|
| A | | | |
| Pre-frailty (FRAIL = 1–2) | | | |
| Sex (ref: male) | 1.531 | 1.186 | 1.978 |
| Charlson index (ref: 3–4) | | | |
| 5–6 | 1.097 | 0.806 | 1.492 |
| >6 | 1.550 | 1.126 | 2.135 |
| Number of medications (per each one) | 1.081 | 1.045 | 1.118 |
| Frailty (FRAIL ≥3) | | | |
| Sex (ref: male) | 3.904 | 2.462 | 6.190 |
| Charlson index (ref: 3–4) | | | |
| 5–6 | 1.030 | 0.539 | 1.970 |
| >6 | 2.935 | 1.612 | 5.412 |
| Number of medications (per each one) | 1.132 | 1.067 | 1.200 |
| B | | | |
| Pre-frailty (FRAIL = 1–2) | | | |
| Sex (ref: male) | 1.504 | 1.166 | 1.941 |
| Charlson CV index (ref: 0) | | | |
| 1 | 1.387 | 1.043 | 1.844 |
| 2 | 1.369 | 0.876 | 2.139 |
| 3 | 1.369 | 0.541 | 3.462 |
| 4 | 1.416 | 0.196 | 10.247 |
| Number of medications (per each one) | 1.084 | 1.049 | 1.122 |
| Frailty (FRAIL ≥3) | | | |
| Sex (ref: male) | 4.117 | 2.572 | 6.591 |
| Charlson CV index (ref: 0) | | | |
| 1 | 3.466 | 2.019 | 5.948 |
| 2 | 8.204 | 4.278 | 15.731 |
| 3 | 7.897 | 2.337 | 26.682 |
| 4 | 7.897 | 2.337 | 26.682 |

*KT, kidney transplant; CI, confidence interval; OR, odds ratio.*
*We initially explored factors associated with pre-frailty and frailty through a binomial logistic regression. Factors with a p-value <0.2 were included in the final multinomial analysis: A) age, sex, body mass index, level of education, renal replacement therapy modality, C-reactive protein levels, Charlson comorbidity index, and number of medications; B) age, sex, body mass index, level of education, renal replacement therapy modality, C-reactive protein levels, Charlson cardiovascular comorbidity index, and number of medications.*

Pre-frailty was a very frequent finding, with 41.5% of candidates scoring 1 or 2 points by FRAIL. This has relevance as not only frailty but also pre-frailty has been associated with poorer outcomes in patients after transplantation [20]. In our cohort, the most frequently reported item was fatigue, followed by loss of weight. The lack of robustness was present in 15.5% of the patients. The latter is especially relevant given that pre-transplant grip strength has been found to be the most important frailty item related to post-transplant outcomes [34].

Differences in frailty prevalence may respond to different scales applied. Although there is an agreement regarding the underlying conceptual framework of frailty, there is a low level of consensus regarding the constituent elements to be included in operational definitions of frailty [35]. Consequently, various frailty metrics, encompassing different aspects like physical reserve, morbidity, cognition, or social factors, have been developed to date [3]. The PFP remains the most popular one for KT candidates and recipients and is characterized by the presence of three out of five indicators: slow walking speed, low physical activity, unintentional weight loss, weakness, and exhaustion. It has been suggested as the preferred choice for measuring physical reserve [36]. In contrast, the FRAIL scale also requires 3 out of 5 criteria—weight loss, resistance, fatigue, ambulation, and illness—but all items are self-reported [25], and, therefore, easier and faster to apply in the clinical practice setting. On the other hand, as the FRAIL scale did not account for objective measurements of physical reserve, it might underestimate the presence of frailty and classify as robust a patient who can be pre-frail or frail [28]. The decision regarding which scale to utilize during candidate evaluation will hinge on various factors, including the scale's feasibility concerning time and resource consumption. In any case, clinicians should opt for a validated frailty scale, as they have demonstrated better transplant outcomes [26]. In our study, the prevalence of frailty was lower than the reported in studies from the US (8.2% vs. 15%–20%). This may reflect population differences, but also scale-dependent differences, as FRAIL usually estimates a lower prevalence of frailty than others that include physical domains [28]. There is no clear consensus on what frailty tool should be used in this population, and no systematic determinations are held during KT candidates' evaluation [37]. Reasons to choose one frailty tool over the rest are broad, and KT candidates lack of a specific frailty tool (in contrast to liver transplant candidates) [38]. We chose the FRAIL scale because at that time 90% of KT centers in Spain were not systematically measuring frailty in their KT candidates. FRAIL scale has been acknowledged as a validated screening tool for frailty and is very easy to implement [39]. Our aim was to dimension and highlight the problem of frailty, and we needed to establish the frailty prevalence with a tool that most of the centers were willing and able to do.

Despite being a geriatric syndrome, age was not related to frailty in KT candidates, similar to what other studies in the CKD population have found [2, 40, 41]. Additionally, this fact could be related to a more restrictive selection of older candidates included in the waiting list [42]. We did find that female sex and comorbidity/treatment are associated with frailty in our cohort of patients. The second one is foreseeable as the FRAIL scale accounts for disease as part of its frailty phenotype. Importantly, cardiovascular disease seems to play the leading role in this association. On the contrary, time on dialysis was not associated with frailty, despite frail patients presented with a substantial longer time on dialysis. Although patient's functional status decline seem irreversible after starting dialysis, studies have reported improvement in frailty status in up to one third of patients after starting dialysis [43]. Regarding sex, studies in community-dwelling populations have revealed a higher prevalence of frailty in females compared to males [44]. Studies including liver and kidney transplant candidates have found similar results [40, 45]. However, although women present with more frailty than men do, health results in the general population are usually worse in the latter, known as the male-female health-survival paradox [44, 46]. In liver transplant candidates, however, women present with higher mortality rates on the waiting list [45], while female kidney transplant candidates have lower mortality rates than men [47, 48]. Moreover, not only the prevalence but also the components and characteristics of frailty differ between male and female frail patients [40]. Examining sex-based disparities in frailty holds the potential to enhance risk assessment before transplantation and tailor specific, personalized interventions. Regarding BMI and albumin levels, we did not find any association with frailty status in this cohort. This may reflect how

poorly BMI and albumin levels detect potential sarcopenia in these patients. Conversely, a higher BMI was found among frail patients. As sarcopenia is defined as reduced muscle mass and strength, a higher BMI does not necessarily reflect less risk of sarcopenia [49]. Moreover, it has been described that albumin levels may not differ among robust and frail KT candidates but sarcopenia does [28]. Novel biomarkers should guide the future investigation in this regard [50].

Our study has limitations, as it is a cross-sectional study that analyzes frailty prevalence and factors associated, lacking a follow-up of the patients. Regarding the study design, it has a potential selection bias, as there were centers with a high number of patients included while others only included a few patients. In addition, the FRAIL scale has been proposed as a screening frailty tool [23, 31], and its sensitivity detecting CKD frail patients may be lower [7, 28, 39]. However, this is to our knowledge the largest cohort of European KT candidates with frailty measurement reported so far. We aimed to establish the dimensions of the frailty problem in the KT waiting list in Spain, using a representative cohort. More than 1,000 patients over 50 years have been analyzed, from a total (considering all ages) of 4000 individuals included in the KT waiting list in Spain by the end of 2023 [22]. We provide important information about the prevalence and factors associated with frailty that may serve to implement adequate preventive and treatment interventions in this population. The photograph of the situation might be also useful for changing health policies.

In conclusion, less than 10% of the KT waiting list in Spain is frail according to the FRAIL scale, but pre-frailty and frailty together account for half of the patients. Female sex and comorbidity burden are factors associated with frailty. As frailty has a negative impact on outcomes after transplantation, measurements to improve/revert frailty should be part of the healthcare and preparation of candidates for KT.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving humans were approved by Institutional Review Board of Hospital del Mar approved the study (2020/9349). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

MP-S conducted the multicenter study, ran the analysis, and wrote the manuscript. AG-D and FM conceptualized the study and interpreted the results. RM, EME, and JZ supported and organized the study. The rest of the authors included patients in the study. All authors contributed to the article and approved the submitted version.

## FUNDING

The author(s) declare that financial support was received for the research and/or publication of this article. The authors declare that this study received funding from Sandoz Farmacéutica SA, Spain. The funder contributed to the study by providing financial support for data collection and statistical analysis, as well as participating in the preparation of the final English version of the manuscript. The funder had no involvement in the study design, data collection, analysis, interpretation, or the decision to submit the article for publication.

## CONFLICT OF INTEREST

Authors RM, EME, and JZ were employed by the company Sandoz Farmacéutica SA.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## GENERATIVE AI STATEMENT

The author(s) declare that no Generative AI was used in the creation of this manuscript.

## REFERENCES

1. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in Older Adults: Evidence for a Phenotype. *J Gerontol A Biol Sci Med Sci* (2001) 56(3):146–M156. doi:10.1093/gerona/56.3.m146
2. Bao Y, Dalrymple L, Chertow GM, Kaysen GA, Johansen KL. Frailty, Dialysis Initiation, and Mortality in End-Stage Renal Disease. *Arch Intern Med* (2012) 172(14):1071–7. doi:10.1001/archinternmed.2012.3020
3. Harhay MN, Rao MK, Woodside KJ, Johansen KL, Lentine KL, Tullius SG, et al. An Overview of Frailty in Kidney Transplantation: Measurement, Management and Future Considerations. *Nephrol Dial Transpl* (2020) 35(7):1099–112. doi:10.1093/ndt/gfaa016
4. Johansen KL, Chertow GM, Jin C, Kutner NG. Significance of Frailty Among Dialysis Patients. *J Am Soc Nephrol* (2007) 18(11):2960–7. doi:10.1681/ASN.2007020221
5. McAdams-Demarco MA, Law A, Salter ML, Boyarsky B, Gimenez L, Jaar BG, et al. Frailty as a Novel Predictor of Mortality and Hospitalization in Individuals of All Ages Undergoing Hemodialysis. *J Am Geriatr Soc* (2013) 61(6):896–901. doi:10.1111/jgs.12266
6. Haugen CE, Chu NM, Ying H, Warsame F, Holscher CM, Desai NM, et al. Frailty and Access to Kidney Transplantation. *Clin J Am Soc Nephrol* (2019) 14(4):576–82. doi:10.2215/CJN.12921118

7. Pérez-Sáez MJ, Redondo-Pachón D, Arias-Cabrales CE, Faura A, Bach A, Buxeda A, et al. Outcomes of Frail Patients while Waiting for Kidney Transplantation: Differences between Physical Frailty Phenotype and FRAIL Scale. *J Clin Med* (2022) 11(3):672. doi:10.3390/JCM11030672
8. Haugen CE, Agoons D, Chu NM, Liyanage L, Long J, Desai NM, et al. Physical Impairment and Access to Kidney Transplantation. *Transplantation* (2020) 104(2):367–73. doi:10.1097/TP.0000000000002778
9. Haugen CE, Thomas AG, Chu NM, Shaffer AA, Norman SP, Bingaman AW, et al. Prevalence of Frailty Among Kidney Transplant Candidates and Recipients in the United States: Estimates from a National Registry and Multicenter Cohort Study. *Am J Transpl* (2020) 20(4):1170–80. doi:10.1111/ajt.15709
10. Quint EE, Zogaj D, Banning LBD, Benjamens S, Annema C, Bakker SJL, et al. Frailty and Kidney Transplantation: A Systematic Review and Meta-Analysis. *Transpl Direct* (2021) 7(6):E701. doi:10.1097/TXD.0000000000001156
11. Schopmeyer L, El Moumni M, Nieuwenhuijs-Moeke GJ, Berger SP, Bakker SJL, Pol RA. Frailty Has a Significant Influence on Postoperative Complications after Kidney Transplantation—A Prospective Study on Short-Term Outcomes. *Transpl Int* (2019) 32(1):66–74. doi:10.1111/tri.13330
12. McAdams-Demarco MA, Law A, Tan J, Delp C, King EA, Orandi B, et al. Frailty, Mycophenolate Reduction, and Graft Loss in Kidney Transplant Recipients. *Transplantation* (2015) 99(4):805–10. doi:10.1097/TP.0000000000000444
13. Goldfarb DA. Re: Frailty and Early Hospital Readmission after Kidney Transplantation. *J Urol* (2014) 191(5):1366–7. doi:10.1016/j.juro.2014.02.016
14. McAdams-Demarco MA, King EA, Luo X, Haugen C, DiBrito S, Shaffer A, et al. Frailty, Length of Stay, and Mortality in Kidney Transplant Recipients: A National Registry and Prospective Cohort Study. *Ann Surg* (2017) 266(6):1084–90. doi:10.1097/SLA.0000000000002025
15. Garonzik-Wang JM, Govindan P, Grinnan JW, Liu M, Ali HM, Chakraborty A, et al. Frailty and Delayed Graft Function in Kidney Transplant Recipients. *Arch Surg* (2012) 147(2):190–3. doi:10.1001/archsurg.2011.1229
16. Makary MA, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P, et al. Frailty as a Predictor of Surgical Outcomes in Older Patients. *J Am Coll Surg* (2010) 210(6):901–8. doi:10.1016/j.jamcollsurg.2010.01.028
17. McAdams-DeMarco MA, Ying H, Olorundare I, King EA, Haugen C, Buta B, et al. Individual Frailty Components and Mortality in Kidney Transplant Recipients. *Transplantation* (2017) 101(9):2126–32. doi:10.1097/TP.0000000000001546
18. McAdams-DeMarco MA, Chu NM, Segev DL. Frailty and Long-Term Post-Kidney Transplant Outcomes. *Curr Transpl Rep* (2019) 6(1):45–51. doi:10.1007/s40472-019-0231-3
19. McAdams-Demarco MA, Law A, King E, Orandi B, Salter M, Gupta N, et al. Frailty and Mortality in Kidney Transplant Recipients. *Am J Transpl* (2015) 15(1):149–54. doi:10.1111/ajt.12992
20. Pérez-Sáez MJ, Arias-Cabrales CE, Redondo-Pachón D, Burballa C, Buxeda A, Bach A, et al. Increased Mortality after Kidney Transplantation in Mildly Frail Recipients. *Clin Kidney J* (2022) 15(11):2089–96. doi:10.1093/CKJ/SFAC159
21. Alfieri C, Malvica S, Cesari M, Vettoretti S, Benedetti M, Cicero E, et al. Frailty in Kidney Transplantation: A Review on its Evaluation, Variation and Long-Term Impact. *Clin Kidney J* (2022) 15(11):2020–6. doi:10.1093/ckj/sfac149
22. Actividad De Donación Y Trasplante Renal España. Organización Nacional de Trasplantes (2023).
23. McAdams-DeMarco MA, Thind AK, Nixon AC, Woywodt A. Frailty Assessment as Part of Transplant Listing: Yes, No or Maybe? *Clin Kidney J* (2022) 16(5):809–16. doi:10.1093/CKJ/SFAC277
24. McAdams-DeMarco MA, Van Pilsum Rasmussen SE, Chu NM, Agoons D, Parsons RF, Alhamad T, et al. Perceptions and Practices Regarding Frailty in Kidney Transplantation: Results of a National Survey. *Transplantation* (2020) 104(2):349–56. doi:10.1097/TP.0000000000002779
25. Morley JE, Malmstrom TK, Miller DK. A Simple Frailty Questionnaire (FRAIL) Predicts Outcomes in Middle Aged African Americans. *J Nutr Heal Aging* (2012) 16(7):601–8. doi:10.1007/s12603-012-0084-2
26. Chen X, Liu Y, Thompson V, Chu NM, King EA, Walston JD, et al. Transplant Centers that Assess Frailty as Part of Clinical Practice Have Better Outcomes. *BMC Geriatr* (2022) 22(1):82–12. doi:10.1186/S12877-022-02777-2
27. van Loon IN, Goto NA, Boereboom FTJ, Bots ML, Verhaar MC, Hamaker ME. Frailty Screening Tools for Elderly Patients Incident to Dialysis. *Clin J Am Soc Nephrol* (2017) 12(9):1480–8. doi:10.2215/CJN.11801116
28. Pérez-Sáez MJ, Dávalos-Yerovi V, Redondo-Pachón D. Frailty in Kidney Transplant Candidates: A Comparison between Physical Frailty Phenotype and FRAIL Scales. *J Nephrol*. doi:10.1007/s40620-021-01234-4
29. Malmstrom TK, Miller DK, Morley JE. A Comparison of Four Frailty Models. *J Am Geriatr Soc* (2014) 62(4):721–6. doi:10.1111/JGS.12735
30. Morley JE, Vellas B, Abellan van Kan G, Anker SD, Bauer JM, Bernabei R, et al. Frailty Consensus: A Call to Action. *J Am Med Dir Assoc* (2013) 14(6):392–7. doi:10.1016/J.JAMDA.2013.03.022
31. HOW TO CHOOSE. How to Choose a Frailty Tool. Available online at: https://efrailty.hsl.harvard.edu/HowtoChoose.html (Accessed March 10, 2025).
32. Oviedo-Briones M, Laso ÁR, Carnicero JA, Cesari M, Grodzicki T, Gryglewska B, et al. A Comparison of Frailty Assessment Instruments in Different Clinical and Social Care Settings: The Frailtools Project. *J Am Med Dir Assoc* (2020) 22:607.e7–607.e12. doi:10.1016/j.jamda.2020.09.024
33. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation. *J Chronic Dis* (1987) 40(5):373–83. doi:10.1016/0021-9681(87)90171-8
34. Parajuli S, Astor BC, Lorden HM, O'Toole KA, Wallschlaeger RE, Breyer IC, et al. Analysis of Individual Components of Frailty: Pre-Transplant Grip Strength Is the Strongest Predictor of Post Kidney Transplant Outcomes. *Clin Transpl* (2022) 36(12):e14827. doi:10.1111/CTR.14827
35. Rodríguez-Mañas L, Féart C, Mann G, Viña J, Chatterji S, Chodzko-Zajko W, et al. Searching for an Operational Definition of Frailty: A Delphi Method Based Consensus Statement. The Frailty Operative Definition-Consensus Conference Project. *Journals Gerontol Ser A Biol Sci Med Sci* (2013) 68(1):62–7. doi:10.1093/GERONA/GLS119
36. Bandeen-Roche K, Gross AL, Varadhan R, Buta B, Carlson MC, Huisingh-Scheetz M, et al. Principles and Issues for Physical Frailty Measurement and its Clinical Application. *Journals Gerontol Ser A Biol Sci Med Sci* (2020) 75(6):1107–12. doi:10.1093/GERONA/GLZ158
37. Levin A, Ahmed SB, Carrero JJ, Foster B, Francis A, Hall RK, et al. Executive Summary of the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease: Known Knowns and Known Unknowns. *Kidney Int* (2024) 105(4):684–701. doi:10.1016/j.kint.2023.10.016
38. Lai JC, Covinsky KE, Dodge JL, Boscardin WJ, Segev DL, Roberts JP, et al. Development of a Novel Frailty Index to Predict Mortality in Patients with End-Stage Liver Disease. *Hepatology* (2017) 66(2):564–74. doi:10.1002/HEP.29219
39. Pérez-Sáez MJ, Pascual J. Unmet Questions about Frailty in Kidney Transplant Candidates. *Transplantation* (2024). doi:10.1097/TP.0000000000005093
40. Pérez-Sáez MJ, Arias-Cabrales CE, Dávalos-Yerovi V, Redondo D, Faura A, Vera M, et al. Frailty Among Chronic Kidney Disease Patients on the Kidney Transplant Waiting List: The Sex-Frailty Paradox. *Clin Kidney J* (2021) 15(1):109–18. doi:10.1093/CKJ/SFAB133
41. Chowdhury R, Peel NM, Krosch M, Hubbard RE. Frailty and Chronic Kidney Disease: A Systematic Review. *Arch Gerontol Geriatr* (2017) 68:135–42. doi:10.1016/j.archger.2016.10.007
42. Buford J, Retzloff S, Wilk AS, McPherson L, Harding JL, Pastan SO, et al. Race, Age, and Kidney Transplant Waitlisting Among Patients Receiving Incident Dialysis in the United States. *Kidney Med* (2023) 5(10):100706. doi:10.1016/J.XKME.2023.100706
43. Johansen KL. *Frailty Among Patients Receiving Hemodialysis: Evolution of Components and Associations with Mortality* (2019). p. 1–31.
44. Gordon EH, Peel NM, Samanta M, Theou O, Howlett SE, Hubbard RE. Sex Differences in Frailty: A Systematic Review and Meta-Analysis. *Exp Gerontol* (2017) 89:30–40. doi:10.1016/j.exger.2016.12.021
45. Lai JC, Ganger DR, Volk ML, Dodge JL, Dunn MA, Duarte-Rojo A, et al. Association of Frailty and Sex with Wait List Mortality in Liver Transplant Candidates in the Multicenter Functional Assessment in Liver Transplantation (FrAILT) Study. JAMA Surg *Published Online* (2021) 156:256–62. doi:10.1001/jamasurg.2020.5674

46. Oksuzyan A, Juel K, Vaupel JW, Christensen K. Men: Good Health and High Mortality. Sex Differences in Health and Aging. *Aging Clin Exp Res* (2008) 20(2):91–102. doi:10.1007/BF03324754
47. Lynch RJ, Rebecca Z, Patzer RE, Larsen CP, Adams AB. Waitlist Hospital Admissions Predict Resource Utilization and Survival after Renal Transplantation. *Ann Surg* (2016) 264(6):1168–73. doi:10.1097/SLA.0000000000001574
48. Lynch RJ, Zhang R, Patzer RE, Larsen CP, Adams AB. First-Year Waitlist Hospitalization and Subsequent Waitlist and Transplant Outcome. *Am J Transpl* (2017) 17(4):1031–41. doi:10.1111/ajt.14061
49. Curtis M, Swan L, Fox R, Warters A, O'Sullivan M. Associations between Body Mass Index and Probable Sarcopenia in Community-Dwelling Older Adults. *Nutrients* (2023) 15(6):1505. doi:10.3390/NU15061505
50. Madrid-Gambin F, Pérez-Sáez MJ, Gómez-Gómez A, Haro N, Redondo-Pachón D, Dávalos-Yerovi V, et al. Frailty and Sarcopenia Metabolomic Signatures in Kidney Transplant Candidates: The FRAILMar Study. *Clin Kidney J* (2025) 18(1):366. doi:10.1093/CKJ/SFAE366

ESOT | Transplant International

ORIGINAL RESEARCH
published: 16 June 2025
doi: 10.3389/ti.2025.14487

# Renal Cell Carcinoma in Native Kidney After Kidney Transplantation: A Multicenter Case Control Study With a Focus on Screening Strategy

*Pierre Pommerolle*[1,2]*, *Maryam Assem*[1,2,3], *Marine Uhl*[4], *Philippe De Sousa*[4], *Dominique Guerrot*[5], *Marc Hazzan*[6], *Thierry Lobbedez*[7], *Ophélie Fourdinier*[1] and *Gabriel Choukroun*[1,2]

[1]Department of Nephrology, Dialysis, and Transplantation, Amiens University Hospital, Amiens, France, [2]MP3CV Research Unit, University of Picardie Jules Verne, Amiens, France, [3]Department of Nephrology, Tanger University Hospital, Tanger, Morocco, [4]Department of Urology and Transplantation, Amiens University Hospital, Amiens, France, [5]Department of Nephrology, Dialysis, and Transplantation, Rouen University Hospital, Rouen, France, [6]Department of Nephrology, Dialysis, and Transplantation, Lille University Hospital, Lille, France, [7]Department of Nephrology, Dialysis, and Transplantation, Caen University Hospital, Caen, France

Renal cell carcinoma (RCC) of native kidney is more prevalent after kidney transplantation than in the general population. Risk factors and the value of screening remain unclear. We conducted a multicenter case-control study in kidney transplant recipients transplanted between 1989 and 2017. All patients with RCC were included, and two controls were matched to each case. Two centers performed annual screening (AnS group) and the other two had other strategies (OS group). A total of 125 cancers were found in 113 patients. The majority of cancers were stage T1-T2 (92.0%), 1.6% had metastasis at diagnosis and ten (9.0%) had recurrence after nephrectomy. Men [OR 2.2; IC 95% (1.2–4.4); p = 0.02] and acquired cystic kidney disease [OR 3.2; IC 95% (1.8–5.9); p < 0.01] were associated with cancer in multivariate analysis. The 10-year survival was poorer in cases (65.6% vs. 79.1%, p < 0.001). The AnS group had fewer relapses (5.0% vs. 18.2%, p = 0.02) and a lower rate of cancer-related deaths (16.0% vs. 46.1%, p = 0.04). Survival of patients with RCC is lower than in control patients. Annual screening could improve cancer prognosis, its benefit needs to be evaluated in larger studies.

**Keywords: renal cell carcinoma, native kidney, kidney transplantation, screening, survival**

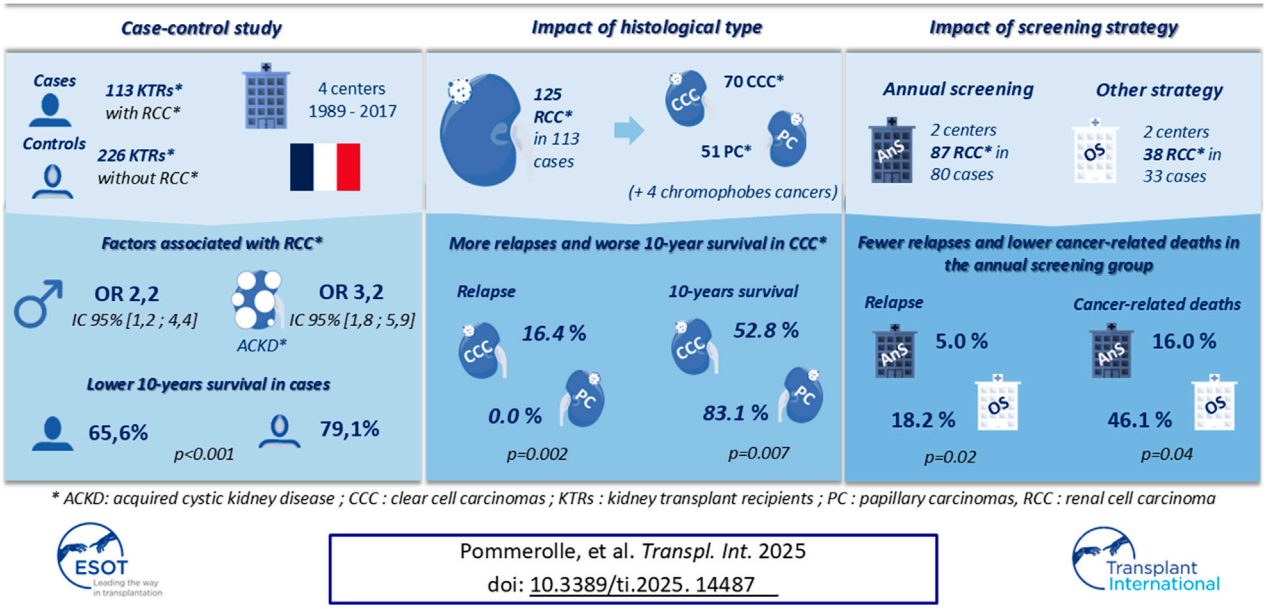
OPEN ACCESS

***Correspondence**
Pierre Pommerolle,
pommerolle.pierre@chu-amiens.fr

***Received:*** *12 February 2025*
***Accepted:*** *03 June 2025*
***Published:*** *16 June 2025*

***Citation:***
*Pommerolle P, Assem M, Uhl M, De Sousa P, Guerrot D, Hazzan M, Lobbedez T, Fourdinier O and Choukroun G (2025) Renal Cell Carcinoma in Native Kidney After Kidney Transplantation: A Multicenter Case Control Study With a Focus on Screening Strategy. Transpl. Int. 38:14487. doi: 10.3389/ti.2025.14487*

**Abbreviations:** ACKD, acquired cystic kidney disease; Ans, annual screening group; ADPKD, autosomal dominant polycystic kidney disease; CVD, cardiovascular disease; Ch, chromophobe; CCC, clear cell carcinoma; CKD, chronic kidney disease; DSA, donor specific antibody; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; KT, kidney transplantation; KTRs, kidney transplant recipients; Os, other strategy group; PC, papillary carcinoma; RCC, renal cell carcinoma.




**GRAPHICAL ABSTRACT |**

## INTRODUCTION

Kidney transplantation (KT) is the treatment of choice for chronic kidney disease (CKD), offering, in comparison to dialysis, a better quality of life and survival. However, the use of immunosuppressive treatments increases the risk of post-transplantation complications, mostly infections and cancers. Thus, the risk of cancer is 2 to 5-fold higher in kidney transplant recipients (KTRs) than in the general population [1, 2], and 20% of KTRs will develop cancer within 10 years after KT [3]. A higher risk is observed, compared to the general population, for skin cancer, Kaposi's sarcoma, post-transplantation lymphomas, and urological malignancies particularly the renal cell carcinoma (RCC) of native kidney [1, 2].

Every year, RCC affects 350,000 new patients worldwide and 30,000 patients die from their cancer [4]. The main risk factors for RCC are age older than 60 [5], male gender [5], smoking [6], high blood pressure [7–9], obesity [10, 11], and CKD [12]. Acquired cystic kidney disease (ACKD) is a multi-cystic differentiation of native kidneys, mainly affecting patients with end-stage of CKD. ACKD is suspected to be a risk factor for RCC, due to the strong association between ACKD and CKD-patients with RCC (70%–90%) [13]. Treatment for RCC is usually surgical but medical treatment (in particular the use of immunotherapies and tyrosine kinase inhibitors) has clearly improved prognosis of patients with metastatic disease [14, 15].

Several studies, generally retrospective, monocentric, and with small numbers of patients, have studied the risk of RCC in KTRs [16–27]. RCC is 15-fold higher in KT than in the general population [28, 29], and occurred in 0.7% of KTRs [30]. Interestingly, several studies have suggested that the frequency of RCC may be higher when systematic screening is performed (2.7%–4.6%) [18, 21, 23]. The explanations for this higher frequency in KT have not been optimally studied, due to a lack of studies comparing the characteristics of KTRs with RCC to those of KTRs without cancer. The impact of immunosuppressive regimen notably, remains unclear [31]. Finally, there is no consensus on systematic screening of RCC in KTRs. Indeed, the American Society of Transplantation and the Kidney Disease Improving Global Outcomes do not recommend systematic screening [2, 32], while the European Association of Urology recommends performing an annual ultrasound of the native kidneys [33]. The aim of this study is to determine the characteristics of KTRs with RCC in a large population of transplant patients. To evaluate the risk factors of RCC in KT, we compared characteristics of this population to a healthy and matched population of KTRs. Finally, we evaluated the outcome of KTRs with RCC according to the screening strategy of their center.

## PATIENTS AND METHODS

### Study Design

We conducted a multicentric, retrospective, case-control study in four University Hospitals in France (Amiens, Caen, Lille and Rouen). The study included KTRs transplanted between April 1989 and December 2017. The end of the follow-up was 31 January 2019.

## Selection of Cases and Controls

All patients with a diagnosis of RCC during graft follow-up were included, while patients with a diagnosis of benign tumor of native kidney, graft cancer, or urinary tract malignancy were not. Cases were selected in all centers by the search for "Cancer of native kidney" or "Kidney carcinoma" in the CRISTAL database (Agence de la Biomedecine, Paris, France) and supplemented by questioning the Pathology Department of each center. Finally, the analysis of medical records ensured the diagnosis of RCC. Controls were selected from KTRs transplanted over the same period. All patients underwent pre-transplant evaluation, including abdominal imaging, to rule out active malignancy and RCC. We assigned two controls per case, matching by center, year of transplantation (±2 years), and age at transplantation (±2 years). Cases had to be alive with a functioning graft at the time of the case's cancer onset and anephric controls were excluded. These criteria was verified in the patient's medical records.

## Patients' Medical Records

All data were collected retrospectively from the patients' medical records. The variables collected included sex, age at transplantation, age at cancer diagnosis (for cases), the number of transplants received, the type and duration of dialysis treatment before KT, cancer history, the presence of a single native kidney, smoking (current or former), obesity, diabetes mellitus, presence of ACKD, cause of end-stage renal disease (ESRD), estimated glomerular filtration rate (eGFR), immune complications (biopsy-proven graft rejection, rejection type and *de novo* donor-specific antibodies [DSA]), immunosuppression characteristics (regimen, drugs, blood calcineurin inhibitor level, and the dose of mycophenolate mofetil received), the histologic characteristics of cancers, cancer treatments (including initial treatment, treatment of recurrence and changes in immunosuppressive therapy). Single native kidney was defined as a single anatomical kidney (acquired or congenital) before KT; obesity was defined as a body mass index >30 kg/m$^2$; eGFR was calculated using the Modification of Diet in Renal Disease equation [34]; ACKD was defined as the presence of at least three single cysts in each native kidney on imaging tests (ultrasound, CT scan or magnetic resonance imaging), patients with autosomal dominant polycystic kidney disease (ADPKD) and those without available imaging examinations were excluded from this analysis. Tumors were classified by histological type according to current classifications the year of the discovery of the cancer, and according to the classifications of Fuhrman or International Society of Urological Pathology (based on date of diagnosis) for the tumor grade [35, 36]. The stage of the disease was evaluated according to the Union for International Cancer Control TNM 2017 classification [37, 38].

## RCC Screening

We defined two groups of patients according to the screening strategy of each center: the "annual screening group" (AnS, including patients from Amiens and Rouen) and the "other strategy group" (OS, including patients from Caen and Lille). The annual screening strategy involved alternating CT scans and ultrasounds in Amiens center (alternately) and only an ultrasound screening in Rouen center. The use of iodinated contrast agent for CT scans was permitted but left to the discretion of the nephrologist. In the OS group, Caen center carried out ultrasound at 1 year of KT then every 3 years, while Lille center did not perform systematic screening. Patients in both groups (Ans and OS) could undergo additional imaging, after screening or incidental diagnosis.

## Statistical Analysis

The normality tests used were the Shapiro-Wilk test and the Kolmogorov Smirnov test. In case of normal distribution, means and standard deviations were used to describe continuous variables. Otherwise, we described the results with the median and the interquartile range (IQR). For unpaired subjects, the means were compared by Student's t-test or the Mann-Whitney (depending on whether the variables were normally distributed or not), and frequencies by the chi-square test or the Fisher test. For matched subjects, frequencies were compared by the Cochran-Mantel-Haenszel test. Survival data (patient survival and graft survival) were evaluated at 10 years from baseline. Baseline corresponded to the date of cancer diagnosis in the cases, and the date of cancer of the matched case for the controls. For patients who had contralateral RCC, only the date of the first cancer was used in the analyses. Graft survival data were censored at the time of recipient death. Survival was analyzed by the Kaplan Meier method. Survival curves were compared by the Logrank test. The odds ratios, described with a 95% confidence interval, were calculated in a bivariate analysis, then included in a multivariate model if p was less than 0.1 using a logistic regression model. The results were considered significant for a p-value less than 0.05. Statistical analyses were performed using SPSS® software (version 21 SPSS Inc., Chicago, IL, United States) and Graphpad Prism (Graphpad Software San Diego, California, United States).

## Ethics

The study followed the 1964 Declaration of Helsinki and its later amendments. In line with the French legislation on retrospective, non-interventional studies, this study was reviewed and approved by an ethic committee (Comité de Protection des Personnes Nord Ouest II, n°2011/17), all patients were informed about the collection of their data and were free to decline participation in the study. The study was registered with the French National Data Protection Commission (Commission Nationale de l'Informatique et des Libertés, Paris, France; registration number: CNIL MR001: n°1449904).

# RESULTS

## Comparison of Cases and Controls

Seven thousand and eighty-four patients were transplanted in the four centers between April 1989 and December 2017 (1511 in Amiens, 1377 in Caen, 2887 in Lille, 1449 in Rouen). One hundred and thirteen patients had a RCC during the study

**TABLE 1** | Cases and controls characteristics.

| Variables | Patients | | |
|---|---|---|---|
| | Cases n = 113 | Controls n = 226 | p |
| Male | 87 (77.0) | 143 (63.3) | 0.03 |
| Age at transplantation | 51.3 (10.9) | 51.2 (10.9) | ns |
| Age at baseline | 56.1 (10.6) | 56.1 (10.7) | ns |
| Smoke | 39 (33.6) | 75 (33.2) | ns |
| Body mass index, kg/m$^2$ | 26.1 (23.4–28.9) | 25.9 (22.8–28.5) | ns |
| Obesity | 23 (20.4) | 43 (19.0) | ns |
| Diabetes mellitus | 21 (18.6) | 40 (17.7) | ns |
| Acquired cystic kidney disease[a] | 52 (50.0) | 39 (24.1) | 0.01 |
| Single native kidney | 12 (10.6) | 23 (10.2) | ns |
| Dialysis before transplantation | 106 (93.8) | 211 (93.4) | ns |
| Hemodialysis | 94 (88.7) | 185 (87.7) | ns |
| Time to dialysis, months | 27.2 (16.6–45.6) | 23.7 (14.8–38.5) | ns |
| Time to dialysis >3 years | 40 (35.4) | 58 (25.7) | ns |
| eGFR at baseline, mL/min/1.73 m$^2$ | 47.0 (36.5–60.0) | 46.0 (35.0–57.0) | ns |
| Prior cancer history | 11 (9.7) | 14 (6.2) | ns |
| History of pre-transplant RCC | 2 (1.8) | 0 (0.0) | ns |
| Prior transplantation | 16 (14.2) | 20 (8.8) | ns |
| Cause of ESRD | | | |
| Glomerulonephritis | 55 (48.7) | 84 (37.2) | 0.04 |
| Nephroangiosclerosis | 14 (12.4) | 10 (4.4) | 0.02 |
| Diabetes mellitus | 8 (7.1) | 10 (4.4) | ns |
| ADPKD | 7 (6.2) | 52 (23.0) | 0.01 |
| Chronic Interstitial Disease | 7 (6.2) | 14 (6.2) | ns |
| Urologic malformation | 4 (3.5) | 25 (11.1) | 0.04 |
| Other | 8 (7.1) | 8 (3.5) | ns |
| Unknown | 10 (8.8) | 23 (10.2) | ns |

*Data are expressed as mean (standard deviation) or median (interquartile range) for continuous variables (depending on the normal distribution or not) and number (percentage) for categorial variables. eGFR, estimated glomerular filtrate rate; RCC, renal cell carcinoma; ESRD, end stage renal disease; ADPKD, autosomal dominant polycystic kidney disease; ns, non-significant.*

[a]*Patients with autosomal dominant polycystic kidney disease and those for whom imaging examinations were not available were excluded from the analysis of this variable.*

period, i.e., a prevalence of 1.6% in the entire population. The characteristics of the patients are summarized in **Table 1**.

Cases and controls mostly received a graft from a deceased donor (98.2% in cases and 97.8% in controls). Cases were more likely to be men (77.0% vs. 63.3%; p = 0.03) and to have an ACKD (50.0% vs. 24.1%; p = 0.01). The cause of ESRD was more frequently a glomerulonephritis (48.7% vs. 37.2%; p = 0.04) or a nephroangiosclerosis (12.4% vs. 4.4%; p = 0.02) in the cases, while ADPKD (6.2% vs. 23.0%; p = 0.01) and uropathies (3.5% vs. 11.1%; p = 0.04) were more frequent in controls (**Table 1**). There was no difference in the immunosuppressive treatment and immunological complications before baseline (**Table 2**).

In the univariate analysis, male gender [OR 1.9; CI 95% (1.1–3.1); p = 0.01], ACKD [OR 3.4; CI 95% (2.0–5.7); p < 0.01], glomerulonephritis [OR 1.7; CI 95% (1.0–2.7); p = 0.01] and nephroangiosclerosis [OR 2.8; CI 95% (1.2–6.5); p = 0.02] as a cause of ESRD were associated with RCC, while ADPKD [OR 0.2; CI 95% (0.1–0.5); p < 0.01] and uropathies [OR 0.4; CI 95% (0.1–0.9); p = 0.04] were protective factors. Only male gender [OR 2.2; CI 95% (1.2–4.4); p = 0.02] and ACKD [OR 3.2; IC 95% (1.8–5.9); p < 0.001] remained associated with the risk of RCC in the multivariate analysis (see the **Supplementary Table** for comprehensive results).

With respective median follow-up times of 62.5 months (IQR 29.9–120.1) and 82.1 months (IQR 39.9–134.4), the mortality rate (33.6% vs. 18.6%, p = 0.02) and 10-year survival (65.6% vs. 79.1%, p < 0.001; **Figure 1**) were better in controls. Patients with metastatic disease at diagnosis had a median survival of 9.0 months (IQR 8.6–9.3). RCC was the second cause of death in cases (10/38, 26.3%) after cardiovascular disease (CVD; 12/38, 31.6%) while infections (13/42, 30.9%), malignancies (10/42, 23.8%) and CVD (9/42, 21.4%) were the most common causes of death in controls. There was no difference in the 10-year graft survival censored on patient death (82.7% in cases vs. 86.7% in controls, p = 0.38; **Figure 2**), and chronic allograft nephropathy was the most common cause of graft loss in the two groups (60.0% in cases and 65.2% in controls). Finally, the risks after baseline of allograft nephropathy (9.7% in cases vs 6.2% in controls), humoral rejection (7.1% in cases vs. 5.6% in controls), cellular rejection (4.4% in cases and 1.3% in controls) and appearance of DSA (14.2% in cases and 13.5% in controls) were similar between the two groups.

## RCC Characteristics

One hundred and twenty-five cancers were diagnosed in the 113 cases (**Figure 3**). Clear cell carcinoma (CCC) was the most common type of cancer (56.0%), followed by papillary (PC; 40.8%) and chromophobe subtypes (Ch; 3.2%). Due to the low number of Ch cancers, only CCC and PC were included in the following analysis. The median time between cancer diagnosis and transplantation was 38.4 months (17.3–84.3) for CCC and 42.1 months (15.2–102.2) for PC. There was no difference in the clinical characteristics according to the histological subtypes, except for ciclosporin use which was more frequent in patients with CCC (61.9% vs 36.6%; p = 0.01). Most cancers were low stage (stage T1-T2, 94.2%) and low grade (grade 1 or 2, 63.0%) at

**TABLE 2 |** Immunosuppressive treatments and immunological complications of cases and controls before baseline.

| Variables | Patients | |
|---|---|---|
| | **Cases n = 113** | **Controls n = 226** |
| Induction therapy | | |
| None | 2 (1.8) | 5 (2.2) |
| Thymoglobulin | 69 (61.1) | 134 (59.3) |
| Anti-IL2-R | 42 (37.2) | 87 (38.5) |
| Maintenance IS therapy | | |
| Tacrolimus | 50 (44.2) | 95 (42.0) |
| Ciclosporin | 58 (51.3) | 116 (51.3) |
| Corticoids | 86 (76.1) | 166 (73.5) |
| Mycophenolic acid | 85 (75.2) | 171 (75.7) |
| Azathioprine | 9 (8.0) | 14 (6.2) |
| mTOR inhibitors | 5 (4.4) | 18 (8.0) |
| Belatacept | 3 (2.7) | 0 (0.0) |
| Dose/weight mycophenolate mofetil, mg/kg | 17.3 (7.3) | 16.1 (7.3) |
| Dose/weight mycophenolate sodium, mg/kg | 10.6 (6.0) | 13.2 (6.3) |
| Exposure time to CNI, months | 40.8 (15.6–99.6) | 44.6 (16.3–91.8) |
| Exposure time to TIT, months | 18.0 (4.8–59.3) | 14.6 (4.0–62.3) |
| Immunological complications | | |
| Allograft nephropathy | 10 (8.8) | 22 (9.7) |
| Active-AMR | 2 (1.8) | 5 (2.2) |
| Chronic-AMR | 1 (0.9) | 1 (0.4) |
| Acute-TCMR | 2 (1.8) | 8 (3.6) |
| Acute rejection (type not specified) | 6 (5.3) | 9 (4.0) |
| *De novo* DSA | 2 (1.8) | 7 (3.1) |

*Data are expressed as mean (standard deviation) or median (interquartile range) for continuous variables (depending on the normal distribution or not) and number (percentage) for categorial variables. Baseline correspond to date of cancer diagnosis for cases and for controls on the date of cancer of the matched case; IL2R: interleukin-2, receptor; mTOR: mechanistic target of rapamycin; CNI: calcineurin inhibitor; TIT: triple immunosuppressive therapy; AMR: antibody-mediated rejection; TCMR: T cell-mediated rejection; DSA: donor specific antibody. There was no significant difference between cases and controls (p-value >0.05 for all variables).*

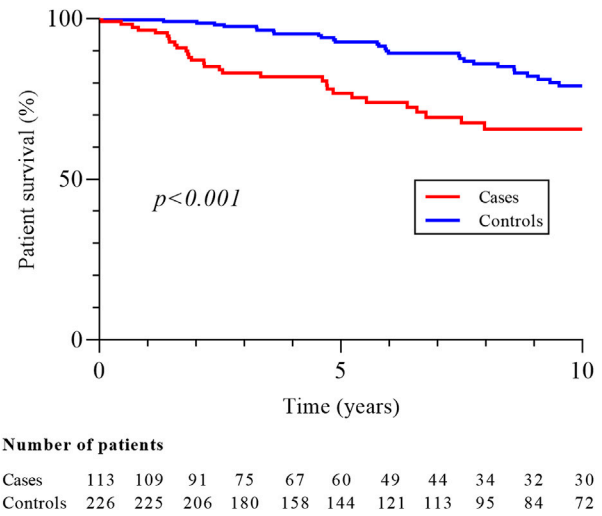



**FIGURE 1 |** Patient survival in cases and controls groups. Patient survival was measured from baseline, corresponding date of cancer diagnosis for cases and for controls on the date of cancer of the matched case.

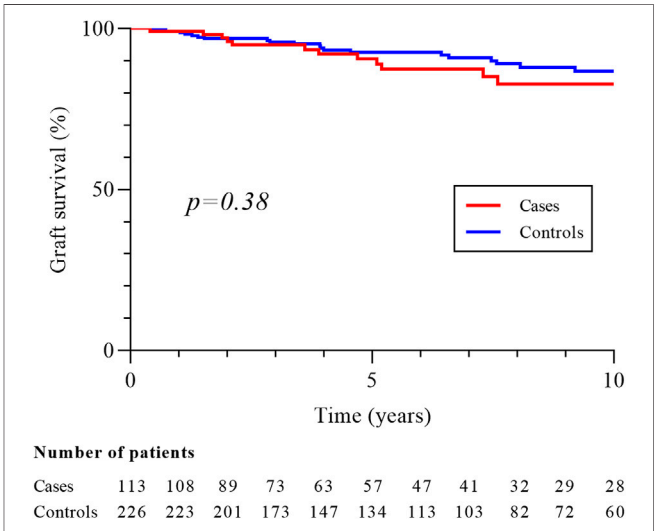



**FIGURE 2 |** Graft survival in cases and controls groups. Graft survival is censored on patient death and measured from baseline, corresponding date of cancer diagnosis for cases and for controls on the date of cancer of the matched case.

diagnosis in both types of cancer and there was no difference between CCC and PC for tumor size, stage, grade and focality (**Table 3**). Despite this, 10-year survival was worse in patients with CCC (52.8% vs 83.1%, p = 0.007; **Figure 4**), and the rate of cancer-related deaths had a clear tendency to be higher (33.3% vs. 0.0%, p = 0.07).

## Treatment and Relapse

All cancers were treated by nephrectomy. A contralateral preventive nephrectomy was performed in 19 patients resulting in the diagnosis of 6 cancers. The immunosuppressive treatment was mostly unmodified after the surgery (68.0%) and 24 patients (19.2%)

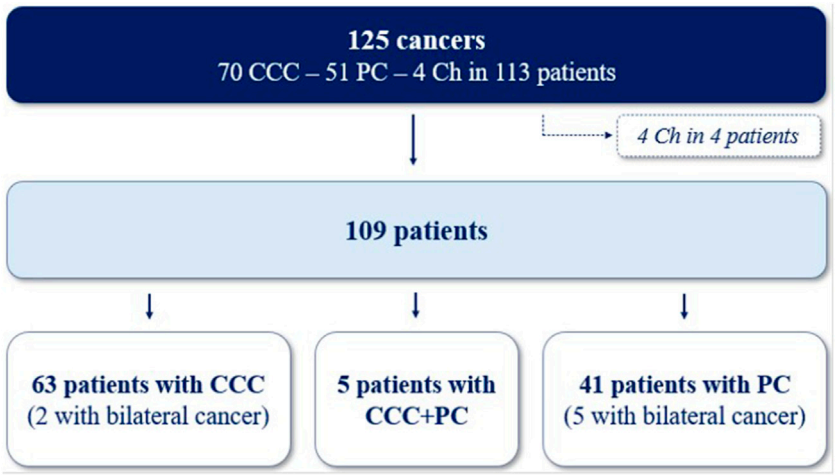



**FIGURE 3 |** Repartition of 125 cancers in 113 patients. CCC, clear-cell carcinomas; PC, papillary carcinomas; Ch, chromophobes cancers.

**TABLE 3 |** Histological characteristics of clear-cells and papillary carcinomas.

| Variables | Cancers | |
|---|---|---|
| | Clear cells n = 70 | Papillary n = 51 |
| Tumor size, mm | 23.5 (15.5–37.5) | 22.0 (15.0–33.0) |
| TNM stage | | |
| T1-T2 | 64 (91.4) | 50 (98.0) |
| T3-T4 | 6 (8.6) | 1 (2.0) |
| N+ | 1 (1.4) | 0 (0.0) |
| M+ | 2 (2.9) | 0 (0.0) |
| Grade[a] | | |
| G1-G2 | 38 (62.3) | 25 (64.1) |
| G3-G4 | 23 (37.7) | 14 (35.9) |
| Multifocal | 12 (17.1) | 16 (31.4) |

*Data are expressed as median (interquartile range) for continuous variables and number (percentage) for categorial variables. Ns: non-significant.*
*[a]21 patients with unknown histological grade (9 in Clear cells group and 12 in Papillary group) were excluded from the analysis. There was no significant difference between two groups (p-value >0.05 for all variables).*

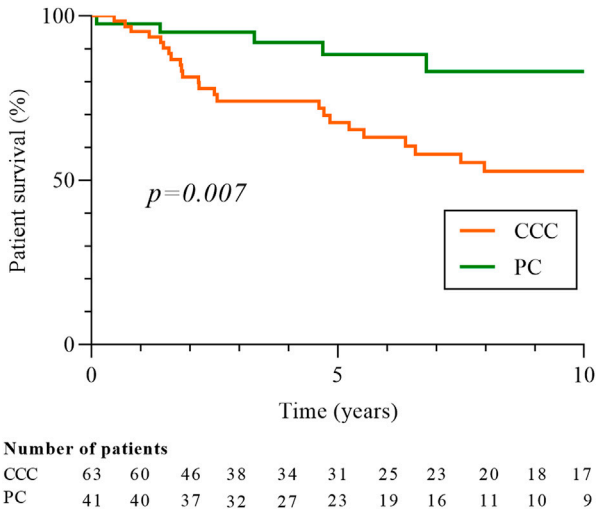



**FIGURE 4 |** Patients' survival according to histologic type of RCC, clear-cell or papillary carcinomas. Patient survival is measured from date of cancer diagnosis. Five patients with CCC and PC were excluded from the analysis. CCC: clear-cells carcinomas; PC: papillary carcinomas.

were switched to an mTOR inhibitor. Only one patient (with metastatic disease at diagnosis) received anti-angiogenic therapy. Ten patients (9.0%) relapsed after surgery, among whom 9 had metastases (**Table 4**). The median delay of relapse was 9.5 months (4.5–47.7). Patients were mostly men (90.0%), aged over 60 at diagnosis (80.0%) and all these patients had CCC (relapse rate: 16.4% for CCC and 0.0% for PC, p = 0.002). Changes in immunosuppressive treatments after relapse were not different from those across the cohort. This recurrence was treated by antiangiogenic therapy in 4 patients (2 with Sunitinib and 2 unspecified, 40.0%), and by an mTOR inhibitor in 3 (30.0%). Eight patients (80.0%) died after this relapse, mainly due to the progression of RCC (75.0%). The median delay between death and relapse was 24 months (19.7–44.9) and 21.6 months (17.0–27.0) for patients who died from RCC.

## Impact of Screening Strategy

Eighty-seven cancers were diagnosed in the 80 patients from the AnS-group and 38 in the 33 patients of the OS-group. The two patients with a history of pre-transplant RCC were in the AnS group, and their screening strategy did not differ from that of the rest of the group. The prevalence of RCC was 2.7% in the AnS-cohort and 0.8% in the OS-cohort (p < 0.0001). The median time between cancer diagnosis and transplantation was 40.5 months (15.3–90.8) in the AnS-group and 46.4 months (21.1–101.5) in the OS-group (p = 0.34). Patients in the AnS-group (compared to-OS group) were younger at baseline (54.7 ± 10.5 vs. 59.5 ± 10.4 years, p = 0.03), more frequently dialyzed before transplantation (97.5% vs. 84.8%, p = 0.01), had more ciclosporin (60.0% vs. 30.3%, p = 0.004), corticoids (81.2% vs. 63.6, p = 0.04), less tacrolimus (33.7% vs. 69.7%, p < 0.001), and a lower dose of mycophenolate mofetil [dose/weight ratio: 14.4

**TABLE 4 |** Characteristics of patients with relapse.

| No | Sex | Age[a] | IT[a] | Histology | Stage | Grade | Relapse (delay) | Treatment | Death (cause) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 63 | Cs, MMF, CT | CCC | T1bN0 | G2 | M+, lung, bones (47 months) | Addition of imTOR | Yes (INF) |
| 2 | M | 62 | Tac, MMF, CT | CCC | T1aN0 | G2 | M+, pancreas (85 months) | Palliative care | No |
| 3 | M | 61 | Cs, MMF | CCC | T1aN0 | G1 | M+, lung, liver, bones (6 months) | Stop of Cs for imTOR | Yes (RCC) |
| 4 | M | 68 | Tac, MMF | CCC | T1aN0 | G2 | M+, lung, bones, brain (12 months) | Stop of MMF | Yes (RCC) |
| 5 | M | 62 | Tac, MS, CT | CCC | T3N0 | G4 | M+, lung (5 months) | Addition of imTOR | Yes (RCC) |
| 6 | M | 65 | Cs, CT | CCC | T3N0 | G3 | Local (7 months) | Surgical | Yes (CVD) |
| 7 | F | 63 | Tac, CT | CCC | T1aN0 | G3 | M+, lung, bones (22 months) | Sunitinib | Yes (RCC) |
| 8 | M | 44 | Cs, MMF, CT | CCC | T3N0 | G3 | M+, bones (3 months) | Sunitinib | Yes (RCC) |
| 9 | M | 65 | Tac, MMF, CT | CCC | T3N0 | G3 | M+, pleura (2 months) | AAG | Yes (RCC) |
| 10 | M | 51 | Tac, MMF | CCC | unknown | unknown | M+, bones (50 months) | AAG | No |

*IT: immunosuppressive treatments; M: male; F: female; Cs: ciclosporin; MMF: mycophenolate mofétil; CT: corticoids; Tac: tacrolimus; CCC: clear-cell carcinoma; M+: metastasis; imTOR: inhibitor of mechanistic target of rapamycin; AAG: anti-angiogenic therapy; INF: infection; RCC: renal cell carcinoma; CVD: cardiovascular disease.*
[a]*Data at baseline.*

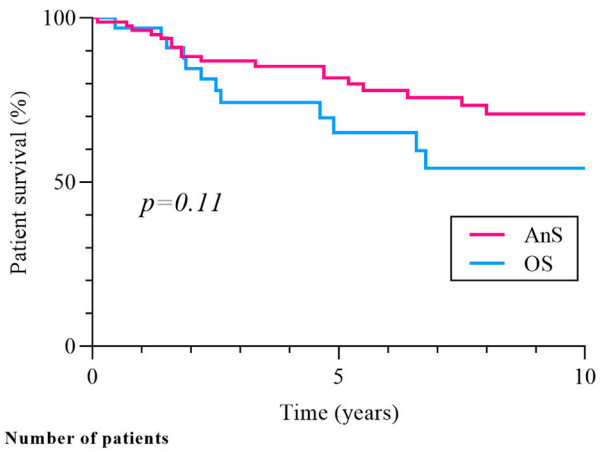



**FIGURE 5 |** Patients' survival according to screening strategy. Patient survival is measured from date of cancer diagnosis. Ans, annual screening, OS, other strategy.

(11.8–19.9) vs. 17.6 (14.3–25.3) mg/kg, p = 0.02]. Similar to the entire cohort, CCC remained the main histological subtype in each group (57.5% in AnS and 52.6% in OS, p = 0.61). Stage and grade were similar between the two cohorts, but cancers were significantly smaller in the AnS-group [median tumor size: 20.0 (15.5–32.5) vs. 30.0 (20.0–40.0) mm, p = 0.01]. Both patients with metastasis at diagnosis were in the AnS group, at the center alternating CT and ultrasound screening. Their last negative screening test was an ultrasound, performed respectively 3 and 12 months prior to the diagnosis of metastatic RCC. Relapses were less frequent in the AnS group (5.0% vs. 18.2%, p = 0.02) and the time between cancer diagnosis and relapse tended to be longer [29.5 (7.9–75.4) vs. 6.0 (2.7–29.0) months, p = 0.26). Finally, mortality rate (31.2% vs 39.4%, p = 0.40) and 10-year survival (70.3% vs 54.2%, p = 0.11, **Figure 5**] did not differ between the two groups, but the rate of cancer-related deaths was significantly lower in the AnS group (16.0% vs. 46.1%, p = 0.04).

## DISCUSSION

This retrospective study reports the characteristics and outcome of 113 patients who presented RCC out of a population of just over 7,000 KTRs in four University Hospitals. One hundred and twenty-five cancers were diagnosed in this population during a 27-year period, mostly clear cell carcinomas at low grade and early stage. We identified two risk factors for the occurrence of native kidney cancer in KTRs: male gender and ACKD. RCC was associated with a reduction in patient survival but did not influence graft survival or immunological complications. Mortality was particularly high in patients with disseminated disease, whether at diagnosis or at relapse. Clear cell carcinoma was associated with a poorer prognosis, reduced survival and increased risk of recurrence compared to papillary carcinoma. We focused on the impact of screening and showed that patients in centers with annual screening had smaller cancers, a lower relapse rate, and a lower rate of cancer-related deaths.

Several studies have analyzed the risk of occurrence of RCC during KT, but most of them included only a small number of patients [16–27]. Moreover, these studies did not compare the characteristics of these patients to a control population, making it impossible to study the risk factors of RCC in KT. This work is, to our knowledge, the first study comparing patients with RCC to a control population of KTRs without RCC and is also one of the cohorts with the largest number of patients.

The recognized risk factors for RCC in the general population are age over 60, male gender, smoking, high blood pressure, obesity, and certain genetic disorders [5–12]. In the present study, only male gender and the presence of ACKD remain associated with an increase-risk of RCC in the multivariate analysis. Several potential RCC risk factors, including smoking quantification and family history, could not be assessed due to missing data inherent to the study design. Several studies have suggested an association between ACKD and RCC, due to the high prevalence of this anomaly in ESRD patients with RCC (70%–90%) [13, 17, 32]. ACKD and its potential link to RCC are not fully understood. Nephron reduction associated with renal failure could lead to the expression of growth factors (such as *Epidermal Growth Factor* and *Hepatocyte Growth Factor*) and proto-oncogenes (such as

c-jun), which can promote the hypertrophy and hyperplasia of tubular cells (contributing to the appearance of cysts), but also the development of RCC [13]. No difference in immunosuppression or immunological complications before baseline was observed between cases and controls. However, our analysis was mainly qualitative, as accurately quantifying immunosuppression remains challenging. Use of emerging biomarkers of immunosuppression levels, like Torque Teno Virus viremia, may offer a better assessment of the link between immunosuppression and RCC development [39, 40].

In line with previous studies RCC were mostly at low stage and low grade, and had a lower rate of relapse than in the general population (30.0%–40.0%) [35]. Despite these good outcomes we also showed that KTRs with RCC had a lower survival rate than controls. However, the higher frequency of males in RCC patients could partly explain this difference. Clear cell carcinomas were particularly associated with a poor prognosis, reflected by more recurrence and a higher mortality than papillary cancers. This poorer outcomes were already reported in the general population and could be related with worse stage and histological grade at diagnosis [41, 42], however we did not highlight any difference on these criteria in our analysis.

All cancers were managed by nephrectomy and no patient received alternative treatment such as radiofrequency ablation, cryotherapy, or active surveillance. Biopsy followed by active surveillance remains a possible option in transplant recipients, especially in frail patients or those with high surgical risk [29]. The management of immunosuppressive therapy after the diagnosis of cancer is an important concern for Transplant-nephrologists. We showed that the overall immunosuppression was modified in one-third of the patients, mainly for the use of a mTOR inhibitor. mTOR inhibitors indeed have immunosuppressive and anti-cancer effects, making them interesting in the treatment of post-transplant cancers [2]. However, the use of mTOR inhibitors in this indication has only been validated in the context of non-melanoma skin cancers and Kaposi sarcoma, moreover these treatments have lower immunosuppressive effects than CNI and can lead to the increase in proteinuria. Furthermore, mTOR inhibitors are used in the general population in the treatment of metastatic RCC, but they are not used as adjuvant treatment of localized cancers. Based on these elements and results of the present study, our opinion is that the use of an mTOR inhibitor in KTRs has a strong rational in the context of metastatic RCC and can be discussed in localized clear cell carcinomas (which have in the present study an increased risk of recurrence and mortality). Conversely, the best prognosis of papillary subtype that we report does not tend to offer these therapies in patients with localized papillary cancer.

The benefit of CRN screening in KTRs remains subject to debate. Although our study was not designed to evaluate the benefit of a screening procedure, we studied the association between the annual screening with abdominal imaging and the outcomes of KTRs with RCC. Our data suggest that annual screening is associated with earlier cancer diagnosis, leading to fewer relapses and fewer cancer-related deaths. However, we were not able to demonstrate a statistical link between annual screening and a better survival. From our point of view, there was a clear trend towards better survival in the AnS-group, and this result could be explained by a lack of statistical power linked to the low numbers in the OS-group. Despite these elements, systematic screening for RCC appears to have several limitations. Indeed, in our study, two patients undergoing annual screening presented with metastasis at diagnosis, and none in the OS-groups. Interestingly, both patients had a negative ultrasound as their last screening test, raising concerns about the sensitivity of this modality for RCC screening in transplant recipients. In addition, 19 preventive nephrectomies (therefore without visible anomaly on imaging) were performed in our study and almost a third of these allowed the incidental diagnosis of another cancer, which may suggest a lack of sensitivity of imaging tests. More of that, Tillou *et al,* presented a series of 21 RCCs from 31 patients in whom an imaging examination (ultrasound or scanner) had detected a suspicious lesion [23]. Here, almost a third of the operated patients (10/31, 32.3%) ultimately did not have cancer, also suggesting a risk of low specificity of imaging tests. Thus, our encouraging results regarding annual screening need to be confirmed in future work and on a larger cohort. Given the existing doubt about the benefit of RCC screening in KTRs, it seems appropriate to target this screening in patients at risk (notably in males and patients with ACKD).

This study has limitations and biases. Due to the retrospective design of the work, there are probably missing or incomplete data, particularly for older ones. We analyzed RCCs occurring after transplantation; however, despite thorough screening before transplantation, some tumors—especially those diagnosed soon after transplantation—may have preexisted. In addition, the high prevalence of native kidney cancer in one of the four centers may cause a "center-effect." More, we had a long study period, which could have led to heterogeneity in the definitions, classifications and patient care. Finally, we presented the outcome of patients with RCC as well as the centers' screening policy but did not collect the type of follow-up after the cancer diagnosis. A difference in monitoring that could interfere with the outcome of patients.

## CONCLUSION

This work made it possible to better clarify the characteristics and outcome of kidney transplant recipients who developed native kidney cancer. Most cancers were localized at the time of diagnosis and recurrence after nephrectomy was rare. However, the prognosis of patients with disseminated disease was poor and survival of cases was lower than that of controls. Clear cell carcinomas had a particularly poor prognosis than papillary carcinomas and a modification of immunosuppressive treatment should be discussed. Finally, patients benefiting from annual screening tended to have cancers with better characteristics. The benefit of screening requires studies with larger numbers. As male sex and acquired cystic kidney disease are associated with native kidney cancer, these populations could constitute an interesting target for the screening.

## DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: All data are available on request from the corresponding author. Requests to access these datasets should be directed to pommerolle.pierre@chu-amiens.fr.

## ETHICS STATEMENT

The studies involving humans were approved by the French Comité de Protection des Personnes Nord Ouest II, n°2011/17. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because, in line with the French legislation on retrospective, non-interventional studies, written consent was not mandatory, all patients were informed about the collection of their data and were free to decline participation in the study.

## AUTHOR CONTRIBUTIONS

PP performed data collection. PP and MA performed statistical analysis. All authors contributed to the article and approved the submitted version.

## FUNDING

The author(s) declare that no financial support was received for the research and/or publication of this article.

## CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## GENERATIVE AI STATEMENT

The author(s) declare that no Generative AI was used in the creation of this manuscript.

## ACKNOWLEDGMENTS

We thank the four centers and the study patients for agreeing to participate.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.14487/full#supplementary-material

## REFERENCES

1. Piselli P, Serraino D, Segoloni GP, Sandrini S, Piredda GB, Scolari MP, et al. Risk of De Novo Cancers after Transplantation: Results from a Cohort of 7217 Kidney Transplant Recipients, Italy 1997-2009. *Eur J Cancer Oxf Engl* (2013) 49(2):336–44. doi:10.1016/j.ejca.2012.09.013
2. Małyszko J, Bamias A, Danesh FR, Dębska-Ślizień A, Gallieni M, Gertz MA, et al. KDIGO Controversies Conference on Onco-Nephrology: Kidney Disease in Hematological Malignancies and the Burden of Cancer after Kidney Transplantation. *Kidney Int* (2020) 98(6):1407–18. doi:10.1016/j.kint.2020.07.012
3. Vajdic CM, McDonald SP, McCredie MRE, van Leeuwen MT, Stewart JH, Law M, et al. Cancer Incidence before and after Kidney Transplantation. *JAMA* (2006) 296(23):2823–31. doi:10.1001/jama.296.23.2823
4. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer Incidence and Mortality Worldwide: Sources, Methods and Major Patterns in GLOBOCAN 2012. *Int J Cancer* (2015) 136(5):E359–386. doi:10.1002/ijc.29210
5. Levi F, Ferlay J, Galeone C, Lucchini F, Negri E, Boyle P, et al. The Changing Pattern of Kidney Cancer Incidence and Mortality in Europe. *BJU Int* (2008) 101(8):949–58. doi:10.1111/j.1464-410X.2008.07451.x
6. Theis RP, Dolwick Grieb SM, Burr D, Siddiqui T, Asal NR. Smoking, Environmental Tobacco Smoke, and Risk of Renal Cell Cancer: A Population-Based Case-Control Study. *BMC Cancer* (2008) 8:387. doi:10.1186/1471-2407-8-387
7. Zucchetto A, Dal Maso L, Tavani A, Montella M, Ramazzotti V, Talamini R, et al. History of Treated Hypertension and Diabetes Mellitus and Risk of Renal Cell Cancer. *Ann Oncol Off J Eur Soc Med Oncol* (2007) 18(3):596–600. doi:10.1093/annonc/mdl438
8. Deckers IA, van den Brandt PA, van Engeland M, van Schooten FJ, Godschalk RW, Keszei AP, et al. Polymorphisms in Genes of the Renin-Angiotensin-Aldosterone System and Renal Cell Cancer Risk: Interplay with Hypertension and Intakes of Sodium, Potassium and Fluid. *Int J Cancer* (2015) 136(5):1104–16. doi:10.1002/ijc.29060
9. Corrao G, Scotti L, Bagnardi V, Sega R. Hypertension, Antihypertensive Therapy and Renal-Cell Cancer: A Meta-Analysis. *Curr Drug Saf* (2007) 2(2):125–33. doi:10.2174/157488607780598296
10. Gati A, Kouidhi S, Marrakchi R, El Gaaied A, Kourda N, Derouiche A, et al. Obesity and Renal Cancer: Role of Adipokines in the Tumor-Immune System Conflict. *Oncoimmunology* (2014) 3(1):e27810. doi:10.4161/onci.27810
11. Bergström A, Hsieh CC, Lindblad P, Lu CM, Cook NR, Wolk A. Obesity and Renal Cell Cancer--a Quantitative Review. *Br J Cancer* (2001) 85(7):984–90. doi:10.1054/bjoc.2001.2040
12. Ljungberg B, Campbell SC, Choi HY, Jacqmin D, Lee JE, Weikert S, et al. The Epidemiology of Renal Cell Carcinoma. *Eur Urol* (2011) 60(4):615–21. doi:10.1016/j.eururo.2011.06.049
13. Rahbari-Oskoui F, O'Neill WC. Diagnosis and Management of Acquired Cystic Kidney Disease and Renal Tumors in ESRD Patients. *Semin Dial* (2017) 30(4):373–9. doi:10.1111/sdi.12605
14. Barata PC, Rini BI. Treatment of Renal Cell Carcinoma: Current Status and Future Directions. *CA Cancer J Clin* (2017) 67(6):507–24. doi:10.3322/caac.21411
15. Jonasch E, Gao J, Rathmell WK. Renal Cell Carcinoma. *BMJ* (2014) 349:g4797. doi:10.1136/bmj.g4797
16. Neuzillet Y, Lay F, Luccioni A, Daniel L, Berland Y, Coulange C, et al. De Novo Renal Cell Carcinoma of Native Kidney in Renal Transplant Recipients. *Cancer* (2005) 103(2):251–7. doi:10.1002/cncr.20745
17. Filocamo MT, Zanazzi M, Li MV, Guidoni L, Villari D, Dattolo E, et al. Renal Cell Carcinoma of Native Kidney after Renal Transplantation: Clinical

Relevance of Early Detection. *Transpl Proc* (2009) 41(10):4197–201. doi:10.1016/j.transproceed.2009.08.082
18. Moudouni SM, Lakmichi A, Tligui M, Rafii A, Tchala K, Haab F, et al. Renal Cell Carcinoma of Native Kidney in Renal Transplant Recipients. *BJU Int* (2006) 98(2):298–302. doi:10.1111/j.1464-410X.2006.06267.x
19. Leveridge M, Musquera M, Evans A, Cardella C, Pei Y, Jewett M, et al. Renal Cell Carcinoma in the Native and Allograft Kidneys of Renal Transplant Recipients. *J Urol* (2011) 186(1):219–23. doi:10.1016/j.juro.2011.03.032
20. Lee HH, Choi KH, Yang SC, Han WK. Renal Cell Carcinoma in Kidney Transplant Recipients and Dialysis Patients. *Korean J Urol* (2012) 53(4):229–33. doi:10.4111/kju.2012.53.4.229
21. Schwarz A, Vatandaslar S, Merkel S, Haller H. Renal Cell Carcinoma in Transplant Recipients with Acquired Cystic Kidney Disease. *Clin J Am Soc Nephrol CJASN* (2007) 2(4):750–6. doi:10.2215/CJN.03661106
22. Karczewski M, Rzymski P, Karczewski J. De Novo Renal Cell Carcinoma of Native Kidneys in Renal Transplant Recipients: A Single-Center Experience. *Exp Clin Transpl Off J Middle East Soc Organ Transpl* (2012) 10(4):310–3. doi:10.6002/ect.2011.0194
23. Tillou X, Demailly M, Hakami F, Westeel PF, Saint F, Petit J. De Novo Renal Carcinoma in Renal Transplant Recipients: Effect of Early Treatment. *Transpl Proc* (2009) 41(8):3314–6. doi:10.1016/j.transproceed.2009.08.036
24. Klatte T, Seitz C, Waldert M, de Martino M, Kikic Z, Böhmig GA, et al. Features and Outcomes of Renal Cell Carcinoma of Native Kidneys in Renal Transplant Recipients. *BJU Int* (2010) 105(9):1260–5. doi:10.1111/j.1464-410X.2009.08941.x
25. Moris D, Kakavia K, Argyrou C, Garmpis N, Bokos J, Vernadakis S, et al. De Novo Renal Cell Carcinoma of Native Kidneys in Renal Transplant Recipients: A Single-Center Experience. *Anticancer Res* (2017) 37(2):773–9. doi:10.21873/anticanres.11376
26. Gigante M, Neuzillet Y, Patard JJ, Tillou X, Thuret R, Branchereau J, et al. Renal Cell Carcinoma (RCC) Arising in Native Kidneys of Dialyzed and Transplant Patients: Are They Different Entities? *BJU Int* (2012) 110(11 Pt B):E570–573. doi:10.1111/j.1464-410X.2012.11273.x
27. Végsö G, Toronyi E, Hajdu M, Piros L, Görög D, Deák PA, et al. Renal Cell Carcinoma of the Native Kidney: A Frequent Tumor after Kidney Transplantation with Favorable Prognosis in Case of Early Diagnosis. *Transpl Proc* (2011) 43(4):1261–3. doi:10.1016/j.transproceed.2011.03.068
28. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after Kidney Transplantation in the United States. *Am J Transpl Off J Am Soc Transpl Am Soc Transpl Surg* (2004) 4(6):905–13. doi:10.1111/j.1600-6143.2004.00450.x
29. Goujon A, Verhoest G, Sallusto F, Branchereau J, Boutin JM, Bessede T, et al. Renal Cell Carcinoma in Candidates for Renal Transplantation and Recipients of a Kidney Transplant: The French Guidelines from CTAFU. *Progres En Urol J Assoc Francaise Urol Soc Francaise Urol* (2021) 31(1):18–23. doi:10.1016/j.purol.2020.04.030
30. Chewcharat A, Thongprayoon C, Bathini T, Aeddula NR, Boonpheng B, Kaewput W, et al. Incidence and Mortality of Renal Cell Carcinoma after Kidney Transplantation: A Meta-Analysis. *J Clin Med* (2019) 8(4):E530. doi:10.3390/jcm8040530
31. Yanik EL, Clarke CA, Snyder JJ, Pfeiffer RM, Engels EA. Variation in Cancer Incidence Among Patients with ESRD during Kidney Function and Nonfunction Intervals. *J Am Soc Nephrol JASN* (2016) 27(5):1495–504. doi:10.1681/ASN.2015040373
32. Frascà GM, Sandrini S, Cosmai L, Porta C, Asch W, Santoni M, et al. Renal Cancer in Kidney Transplanted Patients. *J Nephrol* (2015) 28(6):659–68. doi:10.1007/s40620-015-0219-8
33. Rodríguez Faba O, Boissier R, Budde K, Figueiredo A, Taylor CF, Hevia V, et al. European Association of Urology Guidelines on Renal Transplantation: Update 2018. *Eur Urol Focus* (2018) 4(2):208–15. doi:10.1016/j.euf.2018.07.014
34. Musso CG, Álvarez-Gregori J, Jauregui J, Macías-Núñez JF. Glomerular Filtration Rate Equations: A Comprehensive Review. *Int Urol Nephrol* (2016) 48(7):1105–10. doi:10.1007/s11255-016-1276-1
35. Bensalah K, Bigot P, Albiges L, Bernhard JC, Bodin T, Boissier R, et al. French ccAFU Guidelines - Update 2020-2022: Management of Kidney Cancer. *Progres En Urol J Assoc Francaise Urol Soc Francaise Urol* (2020) 30(12S):S2–S51. doi:10.1016/S1166-7087(20)30749-1
36. Delahunt B, Eble JN, Egevad L, Samaratunga H. Grading of Renal Cell Carcinoma. *Histopathology* (2019) 74(1):4–17. doi:10.1111/his.13735
37. Paner GP, Stadler WM, Hansel DE, Montironi R, Lin DW, Amin MB. Updates in the Eighth Edition of the Tumor-Node-Metastasis Staging Classification for Urologic Cancers. *Eur Urol* (2018) 73(4):560–9. doi:10.1016/j.eururo.2017.12.018
38. Gray RE, Harris GT. Renal Cell Carcinoma: Diagnosis and Management. *Am Fam Physician* (2019) 99(3):179–84.
39. van Rijn AL, Wunderink HF, Sidorov IA, de Brouwer CS, Kroes AC, Putter H, et al. Torque Teno Virus Loads after Kidney Transplantation Predict Allograft Rejection but Not Viral Infection. *J Clin Virol Off Publ Pan Am Soc Clin Virol* (2021) 140:104871. doi:10.1016/j.jcv.2021.104871
40. Chauvelot L, Barba T, Saison C, Siska E, Kulifaj D, Bakker SJL, et al. Longitudinal Monitoring of Torque Teno Virus DNAemia in Kidney Transplant Recipients Correlates with Long-Term Complications of Inadequate Immunosuppression. *J Med Virol* (2024) 96(7):e29806. doi:10.1002/jmv.29806
41. Bensalah K, Albiges L, Bernhard JC, Bigot P, Bodin T, Boissier R, et al. French ccAFU Guidelines - Update 2018-2020: Management of Kidney Cancer. *Progres En Urol J Assoc Francaise Urol Soc Francaise Urol* (2018) 28(Suppl. 1):R5–R33. doi:10.1016/j.purol.2019.01.004
42. Patard JJ, Verhoest G, Culine S. Prognostic Factors in Localized and in Metastatic Renal Cell Carcinomas. *Progres En Urol J Assoc Francaise Urol Soc Francaise Urol* (2007) 17(5):912–6. doi:10.1016/s1166-7087(07)92387-8

ESOT | Transplant International

Best oral communication from the 8th congress of the Sociedad Española De Trasplante

SET SOCIEDAD ESPAÑOLA DE TRASPLANTE

LETTER TO THE EDITOR
published: 27 June 2025
doi: 10.3389/ti.2025.14457

# High HLA Sensitization After Early Renal Allograft Vascular Thrombosis

*María José Pérez-Sáez[1,2]*, Jordi Comas[3], Edoardo Melilli[4], Francesc Moreso[5], Lluis Guirado[6], Anna Vila[7], Fritz Diekmann[8], Eduard Palou[9], Jaume Tort[3], Dolores Redondo-Pachón[1,2†] and Marta Crespo[1,2†]*

[1]Nephrology Department, Hospital del Mar, RICORS2040 RD21/0005/0022, Barcelona, Spain, [2]Hospital del Mar Research Institute, Barcelona, Spain, [3]Organització Catalana de Trasplantaments, Barcelona, Spain, [4]Nephrology Department, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain, [5]Nephrology Department, Hospital Universitario General Vall d' Hebron, Barcelona, Spain, [6]Nephrology Department, Fundació Puigvert, Institut de Recerca Sant Pau (IR Sant Pau), RICORS2040, Barcelona, Spain, [7]Nephrology Department, Hospital Universitari Germans Trias i Pujol, RICORS2040, Barcelona, Spain, [8]Nephrology Department, Hospital Clínic, Barcelona, Spain, [9]Laboratory of Histocompatibility of Catalunya, Barcelona, Spain

**Keywords: immunosuppression, sensitization, HLA, PRA, vascular thrombosis**

Dear Editors,

Renal allograft thrombosis represents the most frequent cause of early allograft loss in our media, only preceded by the death of the recipient with a functioning graft in recent years [1, 2]. For a long time, the immediate surgical loss of the graft has been accompanied by graft removal and immediate immunosuppression cessation. However, there is scarce information about the impact these early failed kidney transplants (KT) might have on mid- and long-term recipient human leukocyte antigen (HLA) sensitization, with small studies revealing a potential HLA sensitization phenomenon if patients wait a long time before the new transplant [3, 4]. Besides the graft itself and the time for HLA antigens allorecognition, it seems biologically plausible that the remaining donor vascular tissue after graft nephrectomy could serve as a font for recipient HLA sensitization. Although recent guidelines encourage clinicians to maintain immunosuppression if the patient is a candidate for another transplant, even when the graft duration inside the recipient may be only a few hours [5], other and also recent consensus documents still recommend withdrawing immunosuppression after renal allograft surgical failure [6]. Outcomes in recipients who experience early graft loss are usually worse, with only 50% being re-listed [7], and with lower graft survival probability in their following transplantation if they got highly sensitized [8]. In addition, there are no clear strategies or policies to prioritize these recipients once they are relisted for transplantation. In Catalonia, recipients maintain their original time on dialysis (not considering the failed transplantation as a new starting point), but without any other exceptional measures to speed up the new transplant.

Using data from the Renal Catalan Registry, we aimed to analyze the calculated panel reactive antibody (cPRA) class I and class II evolution after an early allograft vascular thrombosis in a cohort of KT recipients. For this purpose, we performed a retrospective analysis including data from recipients of their first KT performed in Catalonia between 2015 and 2023 who suffered from an allograft loss because of vascular thrombosis within the first 30 days after transplantation. To analyze cPRA evolution, we selected those patients re-included on the KT waiting list for a second transplantation after the thrombosis (and, therefore, with available cPRA data). We excluded multiorgan transplants and recipients with a pretransplant cPRAI+II >90%. Trying to isolate the thrombosis as the sole event of sensitization, we also excluded patients who received blood transfusions after the transplant, merging our database with the Catalan Blood and Tissue Bank transfusions data. We analyzed the trend in cPRA after graft loss during the first year after relisting in those who did not get a second transplant. The MFI threshold for defining unacceptable antigens was set as follows: 1) above 750, and 2) exceeding the bead-specific threshold for the lowest bead within

OPEN ACCESS

***Correspondence**
María José Pérez-Sáez,
mperezsaez@hmar.cat

[†]These authors share senior authorship

**Received:** 06 February 2025
**Accepted:** 06 June 2025
**Published:** 27 June 2025

**Citation:**
Pérez-Sáez MJ, Comas J, Melilli E, Moreso F, Guirado L, Vila A, Diekmann F, Palou E, Tort J, Redondo-Pachón D and Crespo M (2025) High HLA Sensitization After Early Renal Allograft Vascular Thrombosis. Transpl. Int. 38:14457. doi: 10.3389/ti.2025.14457

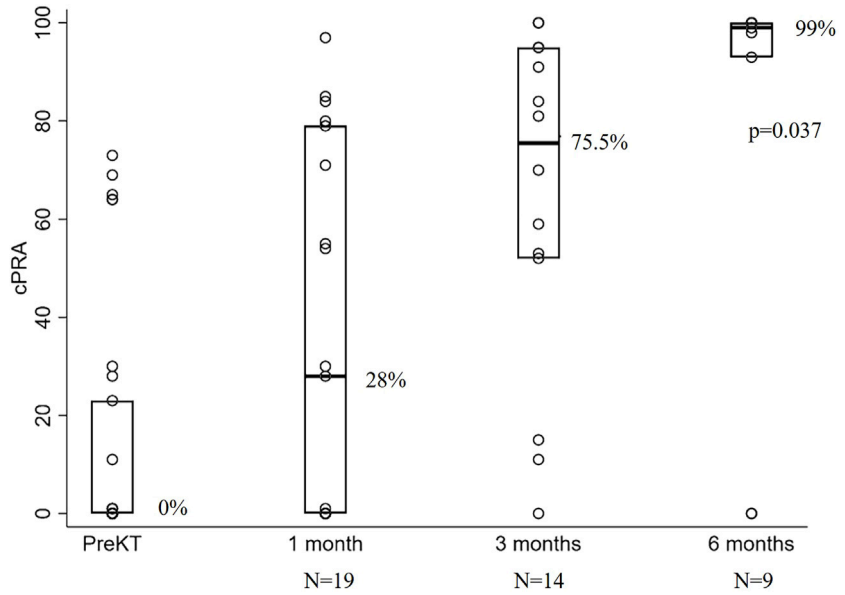



**FIGURE 1 |** Strip plot showing cPRA evolution after vascular kidney allograft thrombosis. N represents the number of patients with available cPRA data at each time point.

the same locus. The loci included in the cPRA calculation were HLA-A, B, C, DRB1, and DQB1. DRB3/4/5, DQA1, DPB1 and DPA1 loci were not included in the calculation.

During the study period, 5484 1st KT were performed in Catalonia. Of those, 249 failed within 1 month after transplantation (40 patients died and 209 lost their grafts). One hundred twenty-two patients experienced a vascular allograft thrombosis, representing 58.4% of early graft losses (<30 days), and 2.2% of the overall graft losses. Seventy-six cases of these thrombosis (62%) happened within the first 72h post-transplant–immediate thrombosis-; and 46 from day 4 to day 30 after transplantation–early thrombosis-. Recipients were 64.8% male and the mean age was 61.7 years old. Renal grafts came from donors after brain death in 53.3% of the cases; 33.6% from controlled cardiocirculatory death donors; 9% from living donors; and 4.1% from uncontrolled cardiocirculatory death donors. After the transplant, 52.5% of the recipients received blood transfusions. We analyzed cPRA data from 45 patients (32 with immediate thrombosis and 13 with early thrombosis) who had pre-KT cPRA 0% [interquartile range 0–23], who did not receive any blood transfusion after transplant, and who were re-included on the KT waiting list until December 2023. All subjects discontinued the antimetabolite immunosuppressive drug immediately following transplantectomy. Regarding tacrolimus, 33 subjects discontinued the drug early after transplantectomy (mean time: 1.6 days), while 12 patients continued tacrolimus for a longer period (at least 1 year). Steroids were discontinued shortly after graft loss in 34 patients (mean time: 2.5 days), whereas 11 subjects maintained a minimum dose of prednisone for a longer duration, alongside tacrolimus.

One month after transplant (median 28 days; interquartile range [17–39], n = 19), median cPRA increased from 0% to 28%, interquartile range [0–79]; after 3 months (88.5 days [72–100], n = 14) to 75.5% [52–95]; and after 6 months (196 days [174–198], n = 9) cPRA reached 99% [93–100] (p = 0.037), **Figure 1**. From the total 45 cases included in the study, last-follow-up cPRA was 87% [0–100]. In addition, 10.8% of these recipients needed to be included in a national prioritization program to find an HLA compatible donor for their following transplant because of a cPRA ≥98%.

Regarding relisting and retransplantation rate, as of September 2024, 75.4% of the 122 cases of thrombosis-related graft failure were relisted (81/122 (66.4%) cases during the first year after graft failure), and 60.7% underwent retransplantation (35/122 (28.7%) during the first year after relisting. The median time between listing and transplantation was 397 days (interquartile range [IQR]: 120–670). For all second deceased-donor kidney transplants performed in Catalonia between 2015 and 2023, the median wait time was 404.5 days (IQR: 116–1015).

After this analysis, the Catalan renal allocation program changed their policy and prioritized these patients for a second transplant. Currently, recipients with a history of graft thrombosis are prioritized for their second transplant using the first available deceased-donor kidney in Catalonia, provided it is not allocated to other prioritization programs such as simultaneous pancreas-kidney, pediatric, or highly sensitized recipients. With this policy, patients should be transplanted before they become highly sensitized.

In conclusion, despite the low number of patients, this study shows that solely renal allograft vascular thrombosis represents a strong HLA sensitization event for the recipient and potential candidate for a second transplant. These results should be considered for prioritization allocation policies and clinical practice to decide on immunosuppression reduction/cessation after graft loss.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

Ethical approval was not required for the studies involving humans because RMRC follows all the principles in the World Medical Association Declaration of Helsinki, only relying in the official center database. As a mandatory population-based registry, data were obtained retrospectively, and no informed consent or institutional ethics board review was required. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements because RMRC follows all the principles in the World Medical Association Declaration of Helsinki, only relying in the official center database. As a mandatory population-based registry, data were obtained retrospectively, and no informed consent or institutional ethics board review was required.

## AUTHOR CONTRIBUTIONS

MP-S, DR-P, and MC conceptualized the study, analyzed and interpreted the data and wrote the manuscript. JC run the analysis. EM, FM, LG, AV, FD, and JT interpreted the data. All authors contributed to the article and approved the submitted version.

## FUNDING

The author(s) declare that no financial support was received for the research and/or publication of this article.

## CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## GENERATIVE AI STATEMENT

The author(s) declare that no Generative AI was used in the creation of this manuscript.

## REFERENCES

1. Redondo-Pachón D, Calatayud E, Buxeda A, Pérez-Sáez MJ, Arias-Cabrales C, Gimeno J, et al. Evolution of Kidney Allograft Loss Causes over 40 Years (1979–2019). *Nefrologia* (2023) 43(3):316–27. doi:10.1016/j.nefroe.2023.07.003
2. Organització Catalana de Trasplantaments. Informe estadístic del Registre de malalts Renals de Catalunya Organització Catalana de Trasplantaments. Published online (2022).
3. Rodríguez-Espinosa D, Broseta JJ, Hermida E, Cuadrado E, Guillén-Olmos E, Montagud-Marrahi E, et al. Rapid Re-Transplantation Safety Following Early Kidney Graft Loss. *Nephrology* (2021) 26(9):742–7. doi:10.1111/nep.13907
4. Del Bello A, Congy-Jolivet N, Sallusto F, Guilbeau-Frugier C, Cardeau-Desangles I, Fort M, et al. Donor-Specific Antibodies after Ceasing Immunosuppressive Therapy, with or without an Allograft Nephrectomy. *Clin J Am Soc Nephrol* (2012) 7(8):1310–9. doi:10.2215/CJN.00260112
5. British Transplant Socieity. UK Guideline for the Management of the Patient with A Failing Kidney Transplant. In: *British Transplant Society Guidelines and Standardds* (2023) Available online at: https://bts.org.uk/uk-guideline-for-the-management-of-the-patient-with-a-failing-kidney-transplant/ (Accessed January 18, 2025).
6. Josephson MA, Becker Y, Budde K, Kasiske BL, Kiberd BA, Loupy A, et al. Challenges in the Management of the Kidney Allograft: From Decline to Failure: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* (2023) 104:1076–91. doi:10.1016/j.kint.2023.05.010
7. Hamed MO, Chen Y, Pasea L, Watson CJ, Torpey N, Bradley JA, et al. Early Graft Loss after Kidney Transplantation: Risk Factors and Consequences. *Am J Transpl* (2015) 15(6):1632–43. doi:10.1111/ajt.13162
8. Redfield RR, Scalea JR, Zens TJ, Mandelbrot DA, Leverson G, Kaufman DB, et al. The Mode of Sensitization and its Influence on Allograft Outcomes in Highly Sensitized Kidney Transplant Recipients. *Nephrol Dial Transpl* (2016) 31(10):1746–53. doi:10.1093/ndt/gfw099

ESOT | Transplant International

LETTER TO THE EDITOR
published: 23 June 2025
doi: 10.3389/ti.2025.14749

# Risk Factors for One-Year Post-Nephrectomy Decline in Renal Function of Living Kidney Donors: Quantile Regression Analysis Based on Estimated Glomerular Filtration Rate Reduction Percentiles

*Alfonso Hernandez Santos[1]*, Hisham Ibrahim[1], Kawther Alquadan[1], Amer Belal[1], Muhannad Leghrouz[1], Rohan Mehta[1], Xuerong Wen[2] and Georgios Vrakas[3]*

*[1]Department of Medicine, College of Medicine, University of Florida, Gainesville, FL, United States, [2]College of Pharmacy, University of Rhode Island, Kingston, RI, United States, [3]Department of Surgery, College of Medicine, University of Florida, Gainesville, FL, United States*

**Keywords: quantile regression, donor nephrectomy, renal function reduction, risk factors, living kidney donor**

Dear Editors,

The association of risk factors with renal outcomes of living kidney donors (LKDs) is typically analyzed with models using the average glomerular filtration rate (GFR) or its change over time [1]. Hence, risk factors associated with the decline of LKDs' renal function beyond the average or central measure are not typically characterized. Therefore, there is a need to identify risk factors for higher-than-average severity of renal function deterioration post-donor nephrectomy (post-DN) in LKDs, considering the increasing trend of accepting medically complex LKD candidates [2, 3].

This study aimed to identify pre-donation demographic, anthropometric, and systemic blood pressure (BP)-related risk factors associated with the mean and the 50th, 75th, 90th, and 95th percentiles of eGFR reduction 1-year post-DN in LKDs and show the applicability of quantile regression (QR) in analyzing quantitative transplant data. Compared with ordinary least squares regression (OLSR), which concentrates on the average outcomes, QR can find how risk factors influence varying degrees or severities of outcomes. Additionally, QR is more robust to outliers and non-normal data than OLSR [4].

After institutional review board approval of the study protocol, we used the transplant center data to study 37 LKDs between 7/2012 and 12/2023 with complete baseline pre-kidney donation demographics, anthropometric, serum creatinine, and 12th-month post-DN blood pressure and serum creatinine records. We calculated the LKDs' estimated GFR (eGFR) based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) [5] formula, pre-DN, and 1-year post-DN. The study outcome was the percentage change in the LKDs' CKD-Epi eGFR between pre- and 1-year post-DN. We analyzed associations between risk factors and the outcome using bivariate OLSR and bivariate quantile regressions (QRs) in the 50th, 75th, 90th, and 95th percentiles of eGFR reduction in percent at 1-year post-DN [4]. When applicable, we performed multivariate regression using the significant risk factors ($P < 0.05$) from the bivariate analysis as covariates. Results were presented as coefficients (β) and 95% confidence interval (CI).

Median LKD age was 45 years (range 23–71 years), 82% were Caucasians, and 84% were females. The median pre-donation body mass index (BMI) was 25.7 kg/m2 (range 20.4 kg/m$^2$–35.7 kg/m$^2$). The baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP) median (and range) values were 121.5 mm Hg (98.0–151.0 mm Hg) and 76.5 mm Hg (62.0–90.0 mm Hg), respectively. The baseline pre-donation

OPEN ACCESS

***Correspondence**
Alfonso Hernandez Santos,
alfonso.santos@medicine.ufl.edu

**Received:** 10 April 2025
**Accepted:** 09 June 2025
**Published:** 23 June 2025

**Citation:**
Santos AH, Ibrahim H, Alquadan K, Belal A, Leghrouz M, Mehta R, Wen X and Vrakas G (2025) Risk Factors for One-Year Post-Nephrectomy Decline in Renal Function of Living Kidney Donors: Quantile Regression Analysis Based on Estimated Glomerular Filtration Rate Reduction Percentiles. Transpl. Int. 38:14749. doi: 10.3389/ti.2025.14749

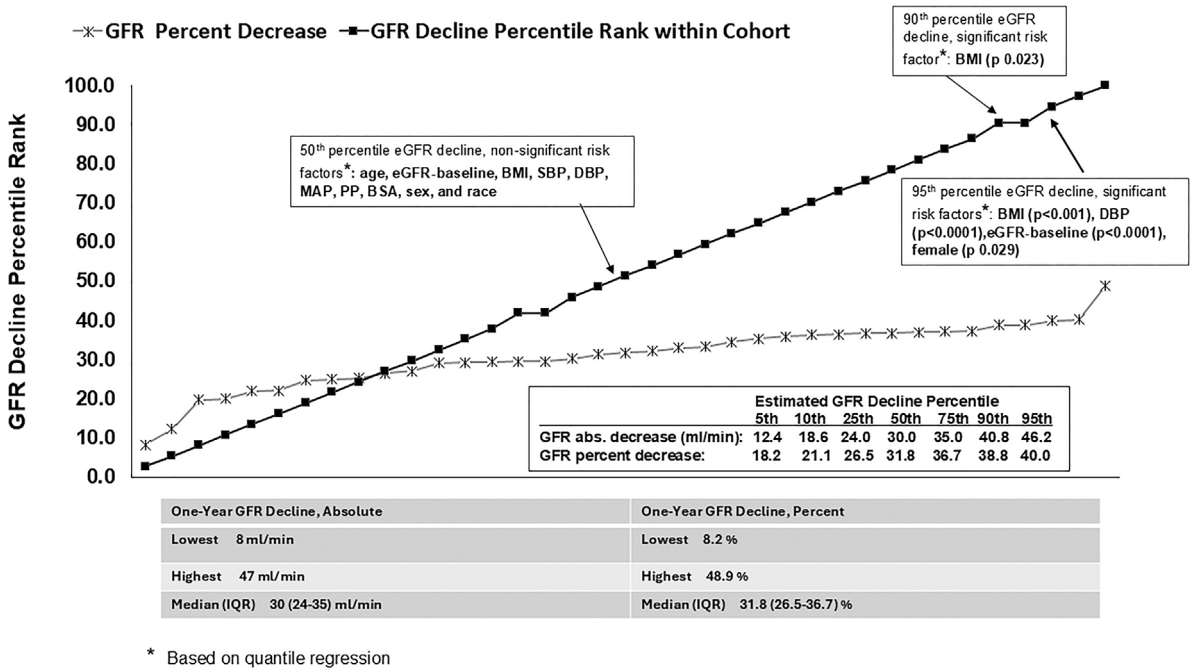



**FIGURE 1 |** Decline in estimated glomerular filtration rate (eGFR) one year post-nephrectomy in living kidney donors.

median eGFR was 95 mL/min. (range = 65–122 mL/min). The 1-year post-DN median eGFR was 63 mL/min. (range = 48–95 mL/min). The mean percentage (SD) and absolute (SD) 1-year post-DN eGFR reduction were 30.0% (SD = 8.1) and 29.9 mL/min (SD = 1.6), respectively. The 50th, 75th, 90th, and 95th eGFR reduction percentiles at 12 months post-DN corresponded to percentage (and absolute) eGFR decrements of 31.8% (30 mL/min), 36.7% (35.0 mL/min), 38.8% (40.8 mL/min), and 40.0% (46.2 mL/min), respectively (**Figure 1**). On OLSR and QR on the 50th percentile eGFR reduction (**Figure 1**; **Supplementary Table S1**), the following were non-significant risk factors for renal function reduction at year-one post-DN: age at donation, baseline eGFR, body mass index, systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), pulse pressure (PP), body surface area (BSA), sex, and race. Baseline eGFR was a risk factor for 75th percentile eGFR reduction (**Supplementary Table S1**). Based on unadjusted analysis, BMI and baseline DBP were positive and negative risk factors for 90th percentile eGFR reduction; however, baseline DBP was not significant on adjusted analysis (**Supplementary Table S1**). Baseline BMI, DBP, eGFR, and female sex were risk factors on unadjusted and adjusted analyses for 95th percentile eGFR reduction (**Figure 1**; **Supplementary Table S1**).

Aside from the known detrimental outcome of obesity-associated glomerulopathy, high BMI has been associated histologically with renal tubular vacuolization and vascular hyalinosis [6]. It is associated with an unfavorable renal prognosis post-DN due to the lack of reserve capacity for compensation in the remaining kidney [3, 7]. Our study showed that the detrimental impact of high pre-donation BMI is most evident with higher severity of renal function reduction. High pre-donation BMIs were associated with eGFR reductions in the 90th and 95th percentiles (corresponding to minus 41 mL/min and 48 mL/min absolute eGFR drop) at 1-year post-DN. High pre-donation BMI was not associated with eGFR reductions in the lower (50th and 75th) percentiles.

Using central tendency-based statistics, Tent et al. [8] showed that living kidney donors with hypertension had stable renal function post-donation. Our study also showed no association between BP parameters (SBP, DBP, MAP, and PP) and the 50th, 75th, and 90th percentiles of eGFR reduction 1-year post-DN. However, baseline DBP was a risk factor, while baseline SBP was a mitigating factor, for eGFR reduction in the 95th percentile. We acknowledge that the conflicting associations of pre-DN SBP and DBP with renal function changes of LKDs seen in this study have not been reported previously and will need confirmation. However, we are aware of the report that DBP tends to be more strongly associated with CKD and renal function deterioration than SBP in the non-LKD population [9].

In a longitudinal study, Berglund et al. [10] reported a higher first-visit GFR among LDs who later experienced a reduction in post-donation GFR. In this study, we saw a similar phenomenon in the association of pre-DN eGFR with the 75th and 95th percentile eGFR reduction 1-year post-DN.

In summary, our results indicate that at 1-year post-DN, risk factors were not associated with mean or median eGFR reduction; however, pre-DN BMI is a risk factor for eGFR reduction in the 90th

and 95th eGFR reduction percentiles, and pre-DN DBP, eGFR, and female sex were additional risk factors for eGFR reduction in the 95th percentile. Our study is limited by low LKD nephrectomy volume that could impact center experience and outcomes, and the small sample analyzed limited statistical power. Nevertheless, it shows that quantile regression could be used to uncover relationships between risk factors and outcome distributions beyond the mean or median in transplantation research. Our findings are hypothesis-generating and need to be confirmed by larger studies with longer follow-up, preferably using QR analysis.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

The studies involving humans were approved by University of Florida Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because not practical to be able to reach patients.

## AUTHOR CONTRIBUTIONS

AS: conceptualization, methodology; writing – original draft (lead); formal analysis (lead); writing – review and editing; visualization: AB: writing – review and editing: RM: writing – review and editing: KA: writing – review and editing; HI: data curation, writing – review and editing: ML: writing – review and editing. GV: writing – review and editing: XW: statistical analysis, review and editing.

## FUNDING

The author(s) declare that financial support was received for the research and/or publication of this article. The author(s) declare that financial support was received from the Michael Stabile Memorial Fund for Kidney Disease Research for the research and/or publication of this article.

## CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## GENERATIVE AI STATEMENT

The author(s) declare that no Generative AI was used in the creation of this manuscript.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.14749/full#supplementary-material

## REFERENCES

1. Lam NN, Lloyd A, Lentine KL, Quinn RR, Ravani P, Hemmelgarn BR, et al. Changes in Kidney Function Follow Living Donor Nephrectomy. *Kidney Int* (2020) 98(1):176–86. doi:10.1016/j.kint.2020.03.034
2. Steiner RW Heeding the Increased Exponential Accumulation of ESRD after Living Kidney Donation. *Transplantation* (2024) 108(4):836–8. doi:10.1097/TP.0000000000004705
3. Rook M, Bosma RJ, van Son WJ, Hofker HS, van der Heide JJ, ter Wee PM, et al. Nephrectomy Elicits Impact of Age and BMI on Renal Hemodynamics: Lower Postdonation Reserve Capacity in Older or Overweight Kidney Donors. *Am J Transpl* (2008) 8(10):2077–85. doi:10.1111/j.1600-6143.2008.02355.x
4. Austin PC, Schull MJ. Quantile Regression: A Statistical Tool for Out-Of-Hospital Research. *Acad Emerg Med* (2003) 10(7):789–97. doi:10.1111/j.1553-2712.2003.tb00075.x
5. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. *N Engl J Med* (2021) 385(19):1737–49. doi:10.1056/NEJMoa2102953
6. Rea DJ, Heimbach JK, Grande JP, Textor SC, Taler SJ, Prieto M, et al. Glomerular Volume and Renal Histology in Obese and Non-obese Living Kidney Donors. *Kidney Int* (2006) 70:1636–41. doi:10.1038/sj.ki.5001799
7. Shinoda K, Morita S, Akita H, Tamaki S, Takahashi R, Kono H, et al. Pre-donation BMI and Preserved Kidney Volume Can Predict the Cohort with Unfavorable Renal Functional Compensation at 1-year after Kidney Donation. *BMC Nephrol* (2019) 20(1):46. doi:10.1186/s12882-019-1242-0
8. Rook M, Hofker HS, Van Son WJ, Homan van der Heide JJ, Ploeg RJ, Navis GJ. Predictive Capacity of Pre-donation GFR and Renal Reserve Capacity for Donor Renal Function after Living Kidney Donation. *Am J Transplant* (2006) 6:1653–9. doi:10.1111/j.1600-6143.2006.01359.x
9. Suenaga T, Satoh M, Murakami T, Hirose T, Obara T, Nakayama S, et al. Cross-classification by Systolic and Diastolic Blood Pressure Levels and Chronic Kidney Disease, Proteinuria, or Kidney Function Decline. *Hypertens Res* (2023) 46:1860–9. doi:10.1038/s41440-023-01267-1
10. Berglund DM, Zhang L, Matas AJ, Ibrahim HN. Measured Glomerular Filtration Rate after Kidney Donation: No Evidence of Accelerated Decay. *Transplantation* (2018) 102(10):1756–61. doi:10.1097/TP.0000000000002215

ESOT | Transplant International

LETTER TO THE EDITOR
published: 12 June 2025
doi: 10.3389/ti.2025.14668

# The New Era of Organ Transplantation in Greece: Time to Converge With the Western World

*Dimitrios Moris*[1] *and Emmanouil Giorgakis*[2]*

[1]Department of Surgery, MedStar Georgetown Transplant Institute, Washington, DC, United States, [2]Division of Abdominal Transplantation, Department of Surgery, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, United States

**Keywords: organ allocation, policies, organ and tissue donation and transplantation, Greece, innovation**

Dear Editors,

Greece has a relatively long history in organ transplantation with the first successful kidney transplant being performed in 1968. Over the last decade, in the midst of the worst financial crisis in the history of the country [1], due to the brain drain and the lack of political and administrative vision, the organ donation and transplantation reached a historic low [2, 3]. Over the recent few years, a reversal of the trend is noticed. The current momentum, the rising donor rates, the establishment of an Academic Department for Liver Transplantation in Athens, the Pancreas Transplant Unit in the University Hospital of Patras and the Onassis National Transplant Center, structural reforms of the Hellenic Transplant Organization (HTO; including placement of local transplant coordinators in Intensive Care Units) and the brain regain, might facilitate the effort that Hellenic Transplant System is making to converge with the international transplant standards.

Compared to our analysis from almost 10 years ago [2], there are some changes in the number and structure of the transplant programs. Greece has 5 kidney transplant programs (with 1 program that has extensive experience of >4,000 deceased-donor and 1,000 living-donor kidney transplants) and another 1 new kidney transplant program expected to be fully operational in the next few years. Currently, Greece has 2 active liver transplant programs performing deceased-donor liver transplants, based in Thessaloniki and Athens. The latter recently successfully performed the first couple living-donor liver transplants, with the assistance of foreign collaborators. Two of the kidney programs are licensed to perform pediatric kidney transplants. Moreover, now there are 2 pancreas transplant programs established, and 1 cardiac and lung transplant program. Currently, there is no active small bowel or dedicated pediatric transplant program. As mentioned before [2], children older than 14 years are registered and get priority on the adult kidney list, whereas children younger than 14 years are still referred to centers abroad. All transplant programs are public, and no transplantation license has been issued in the private health sector.

In a closer look of the transplant frame in Greece, a "soft opt-out" consent system has been in effect since 2023 (an opt-in system was in place since 2017) and there has been clear transplant legislation that defines brain death. Ongoing convergence of our legislature to the international guidelines on the role of ancillary tests to confirm brain death, could mitigate the high levels of public distrust in the system. Pediatric live donation is prohibited. There are some provisions for donation after circulatory death since 2023 but unfortunately no DCD organs have been transplanted to date as well as no clear guidelines regarding donor warm ischemia time have been defined. Moreover, no provisions exist regarding directed or non-directed altruistic donation: all policies that, if implemented, will definitely increase the pool of available organs [4].

A recent workforce analysis that pioneered the use of conceptual frameworks as resources to guide the evaluation and the transformation of organ donation and transplantation in Greece [5], showed

OPEN ACCESS

***Correspondence**
Emmanouil Giorgakis,
emmanouil_giorgakis@med.unc.edu

**Received:** 25 March 2025
**Accepted:** 04 June 2025
**Published:** 12 June 2025

**Citation:**
Moris D and Giorgakis E (2025) The New Era of Organ Transplantation in Greece: Time to Converge With the Western World. Transpl. Int. 38:14668. doi: 10.3389/ti.2025.14668

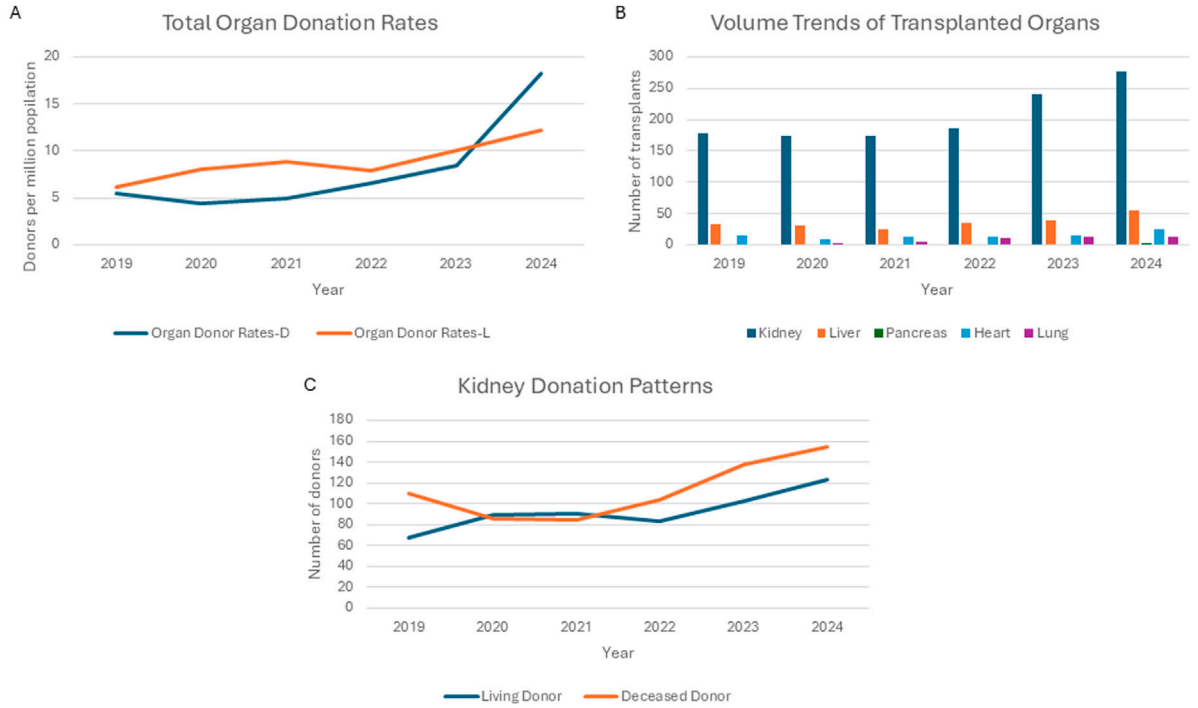



**FIGURE 1 | (A)** Trends of total organ donation rates during the period 2019–2024. **(B)** Volume trends of transplanted organs during the period 2019-2024. **(C)**. Increasing kidney donation numbers during the same period (orange line: deceased donors, blue line: living donors).

that medical staffing levels in Hellenic Transplant System were below the average of other European and Mediterranean countries across all specialties (including surgeons, physicians, anesthesiologists, and others) [6]. There is also an urgent need to expand operating room capacity for both donation (national donor center) [7] and transplantation procedures, and to improve access quality of ancillary services (radiology, transplant infectious diseases, endoscopy, interventional radiology, pathology and histocompatibility testing etc.) across all existing units.

Using data from IRODaT (International Registry on Organ Donation and Transplantation), since 2019 (time of financial recovery of Greek Economy after 10 years of financial regression), there was a gradual increase in actual donation from deceased donors per year, from 5.5 deceased donors/million population and 6.2 living donors/million population in 2019 to 18.2 and 12.1 in 2024 respectively (**Figure 1A**), which is higher than the previously reported period in our analysis 10 years ago (average 4 and 5, respectively) [2]. However, from the 188 deceased donors performed, organs from only 102 donors were utilized in 2024. The number of utilized donors during the same period showed similar trajectory with the actual donors (data are not shown), however the IRODAT data are not granular enough to provide more insights about the reasons for discarding organs, that is a known phenomenon observed in many countries [8]. Moreover, there was a gradual increase in the number of solid organ transplants during the same period (2019–2024), with 178 kidney, 33 liver and 15 heart, 0 lung and 0 pancreas transplants in 2019 to 277 kidney, 55 liver, 24 heart and 12 lung and 2 pancreas transplants in 2024. Three multiorgan transplants (2 kidney-pancreas and 1 liver-kidney) were performed. No intestinal transplants or transplants from DCD were performed during the same period (**Figure 1B**) [9].

It is clear from the data presented above that the performance of the Hellenic Transplant System has improved during the recent years, especially if we focus on the years after the financial regression. This improvement is multifactorial. First, Greece is undergoing a period of political, governmental and administrative stability, that allowed better mid- and long-term planning as well as sustainability of the transplant system. Of course, the Hellenic Transplant System requires better organization and deep structural reforms, such as establishment of national or regional transplant center(s); better staffing, including specialized coordinators; national donor and recipient registries; transparency at the level of individual programs as well as nationwide in outcome reporting, quality maintenance and improvement initiatives. The current political environment appears supportive to the changes needed. Moreover, the financial recovery that Greek economy had the last few years allowed for more incentives to be offered to all parties involved (facilities and staff), to be compensated for their work in organ donation and transplantation. Furthermore, the successful implementation of minimally invasive techniques for kidney donation (with the establishment of a high volume center that contributes to the rising living donor numbers found in our analysis, **Figure 1C**) [10] the successful performance of cases of adult living liver donation [11] as well as the simultaneous

transplantation of renal and pancreatic allografts in patients with end-stage renal disease and diabetes, really boosted public trust around transplantation personnel and their mission, and acted as a great national campaign strategy for organ donation.

Unfortunately, the Hellenic Transplant System made no progress in improving the leadership capacity and the workforce to support a modern transplant system according to international standards. It is obvious that living donation in kidney transplantation can be a sustainable solution to organ demand. However, in liver transplantation, living donation is more nuanced and requires significant expertise on patient selection, and transparency on the listing process (low vs. high MELD patients; exemption points for transplant oncology patients; streamlined process to list patients with high MELD; split or reduced grafts for adult and pediatric transplant recipients). Also, the adoption of DCD, and at later staged the inclusion of normothermic regional perfusion (NRP) as well as the use of machine perfusion as a primary organ storage modality will allow the utilization of extended criteria donors and augment the available organ pool [12, 13]. Especially, in a country like Greece, given its topography and the numerous islands, machine perfusion could allow utilization of organs with longer cold ischemia times without compromising outcomes.

Despite the brain regain that is currently taking place, the academic surgical and transplant community remain resistant to change. There is a plethora of Greek surgeon-scientists who had left the country during the years of financial crisis and currently possess the expertise and the zest to join the effort of Hellenic Transplant System modernization. Greek transplant physicians and surgeons currently practicing abroad could cover the obvious gaps in technical skills (in living liver donation, laparoscopic/robotic living donation/transplant, pancreas and bowel transplant, multiorgan transplant, extended criteria donor utilization, advanced organ procurement and machine perfusion modalities, surgical innovation), scientific extroversion and networking (through international collaborations and research initiatives), patient care optimization (e.g., through modernization of immunosuppressive protocols, personalized care, transplant oncology, donor and recipient evaluation, inpatient and outpatient care), transplant logistics, and training of the next-generation of transplant professionals.

Transplantation is considered the epitome of surgical technique. It is philosophically based on the pillars of altruism (organ donation), and utilitarianism (equitable distribution of life-saving organs, prioritizing those most in need). However, transplantation is a delicate system to thrive. Transplant networks remain healthcare's proverbial canary in the mine: it takes a robust healthcare system and an empathetic, altruistic society for transplantation to be operational and thrive; and *vice versa*, transplantation as an organism will suffer if a healthcare system is under strain or if a socioeconomical system is in decline, as it has been shown in our recent past.

Until recently, Greece lacked the vision to invest on comprehensive organ donation and transplantation services, the benefit of which is certainly indisputable. The current comparative socioeconomical and political stability has afforded an opportunity for transplantation to reach its long-awaited puberty in Greece; yet it is still fledgling, and the growth spurt should be steep if it is to catch up with the transplant revolution witnessed elsewhere. It must therefore be nurtured by the political and healthcare stakeholders, who, among other, should embrace a more meritocratic approach in attracting and retaining talent ostracized during the country's lean years, currently pushing transplant boundaries overseas.

The recent steps forward, in terms of social acceptance, innovation and outcomes should be the steppingstone to the foundation of a modern transplant system that Greek medical tradition and patient population deserve.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

## FUNDING

The author(s) declare that no financial support was received for the research and/or publication of this article.

## CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## GENERATIVE AI STATEMENT

The author(s) declare that no Generative AI was used in the creation of this manuscript.

## REFERENCES

1. Moris D, Zavos G, Menoudakou G, Karampinis A, Boletis J. Organ Organ donation during the financial crisis in Greeceonation during the Financial Crisis in Greece. *Lancet* (2016) 387(10027):1511–-2. doi:10.1016/S0140-6736(16)30130-1
2. Moris D, Menoudakou G, Zavos G. Organ Transplantation in Greece. *Transplantation* (2016) 100(8):1589–91. doi:10.1097/TP.0000000000001349
3. Giorgakis E, Singer AL, Khorsandi SE, Prachalias A. Transplantation Transplantation Crisis at the Time of Economic Recession in Greecerisis at the Time of Economic Recession in Greece. *Public Health* (2018) 160:125–-8. doi:10.1016/j.puhe.2018.03.031

4. Moris D, Tsilimigras DI, Bokos J, Vernadakis S. Organ Donation Organ Donation After Circulatory Death in Greece: Time to Considerfter Circulatory Death in Greece: Time to Consider. *Exp Clin Transpl* (2020) 18(4):539–40. doi:10.6002/ect.2019.0100
5. Johnston-Webber C, Mah J, Streit S, Prionas A, Wharton G, Mossialos E, et al. A Conceptual Framework for Evaluating National Organ Donation and Transplantation Programs. *Transpl Int* (2023) 36:11006. doi:10.3389/ti.2023.11006
6. Johnston-Webber C, Prionas A, Wharton G, Streit S, Mah J, Boletis I, et al. The National Organ Donation and Transplantation Program in Greece: Gap Analysis and Recommendations for Change. *Transpl Int* (2023) 36:11013. doi:10.3389/ti.2023.11013
7. Johnston-Webber C, Wharton G, Mossialos E, Papalois V. Maximising Potential in Organ Donation and Transplantation: Transferrable Paradigms. *Transpl Int* (2022) 35:11005. doi:10.3389/ti.2022.11005
8. Moris D, Schmitz R, Dimitrokallis N, Schmidt T, Vernadakis S. The Paradox of Increasing Waiting List Mortality and Declining Utilization of Deceased Donor Grafts in Kidney Transplant. *Exp Clin Transpl* (2021) 19(1):92–3. doi:10.6002/ect.2019.0427
9. DTL. Database (2023). Available online at: https://www.irodat.org/?p=database&c=GR&year=2023#data (Accessed May 21, 2025).
10. Vernadakis S, Marinaki S, Darema M, Soukouli I, Michelakis IE, Beletsioti C, et al. The Evolution of Living Donor Nephrectomy Program at A Hellenic Transplant Center. Laparoscopic vs. Open Donor Nephrectomy: Single-Center Experience. *J Clin Med* (2021) 10(6):1195. doi:10.3390/jcm10061195
11. Machairas NSGC. Living Donor Liver Transplantation Could Solve Shortage of Liver Grafts in Greece. *Hell J Surg* (2024) 94(3):165–7.
12. Tingle SJ, Dobbins JJ, Thompson ER, Figueiredo RS, Mahendran B, Pandanaboyana S, et al. Machine Machine Perfusion in Liver Transplantationerfusion in Liver Transplantation. *Cochrane Database Syst Rev* (2023) 9(9):CD014685. doi:10.1002/14651858.CD014685.pub2
13. Malinoski D, Saunders C, Swain S, Groat T, Wood PR, Reese J, et al. Hypothermia or Machine Perfusion in Kidney Donors. *N Engl J Med* (2023) 388(5):418–26. doi:10.1056/NEJMoa2118265

# Transplant International

Official journal of the European Society for Organ Transplantation


## Editorial Office

Avenue du Tribunal Fédéral 34
CH – 1005 Lausanne
Switzerland

Tel +41 (0)21 510 17 40
Fax +41 (0)21 510 17 01

tieditorialoffice@frontierspartnerships.org
frontierspartnerships.org/journals/transplant-international

frontiers | Publishing Partnerships