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Table of contents

Cover Articles

Original Research

Letters to the Editor

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REVIEW
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Past, Present, and Future: A Review of Uterus Transplant

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Since the first live birth in 2014 after uterus transplantation, the procedure has become a viable fertility treatment worldwide for the 1 in 500 women affected by absolute uterine factor infertility. In this review, we provide insight on Mayer-Rokitansky-Kuster-Hauser syndrome (MRKH) and the other conditions that lead to the development of AUFI. Additionally, we provide a comprehensive overview of the evolution of uterus transplantation from the first sporadic cases to the current clinical status of the procedure, and detail multiple aspects that go into a successful UTx. Furthermore, we review some of the more recent developments in this rapidly expanding field and evaluate the prospective direction of UTx.

Keywords: transplant, absolute uterine factor infertility, mayer-rokitansky-kuster-hauser syndrome (MRKH), female infertility, uterus transplant

INTRODUCTION

With the advancement of knowledge and technology in the fields of transplant, gynecology and reproductive endocrinology, Uterus transplant (UTx) has emerged as a new type of fertility treatment that provides the 1 in 500 women affected by absolute uterine factor infertility (AUFI) a viable path towards parenthood. Uterus Transplant is unique insofar as it is the only solution to AUFI that allows the experience of pregnancy and delivery. Since the first live birth following UTx in 2014, the field of UTx has rapidly developed as shown in **Figure 1** and has become an option for family planning in multiple countries [1]. While UTx has grown significantly, the field is still in its infancy, making it imperative to evaluate the many aspects that go into a successful transplant and, ultimately, the birth and development of a child born from a mother recipient of a uterus transplant. In this review, we discuss the path that led to the development of UTx, the most recent developments in the field, and its future directions.

ABSOLUTE UTERINE FACTOR INFERTILITY

Infertility due to uterine factor is either congenital or acquired. The acquired form can be caused by a previous hysterectomy or by conditions making the uterus incapable of embryo implantation or completion of pregnancy. Conditions affecting the uterus reproductive ability can be cavital, such as, Asherman syndrome which presents as significant scarring of the endometrial lining caused by severe postpartum hemorrhage or endometrial infection, or myometrial, such as, fibroids that can lead to distortion of the uterine cavity and affect implantation [2]. Uterine fibroids can be identified in 20–40 percent of reproductive aged women and present in up to 27 percent of patients seeking reproductive assistance [3, 4]. Additional conditions affecting uterus functionality include uterine septa which are present in roughly 2 to 3 percent of the general population and are associated with

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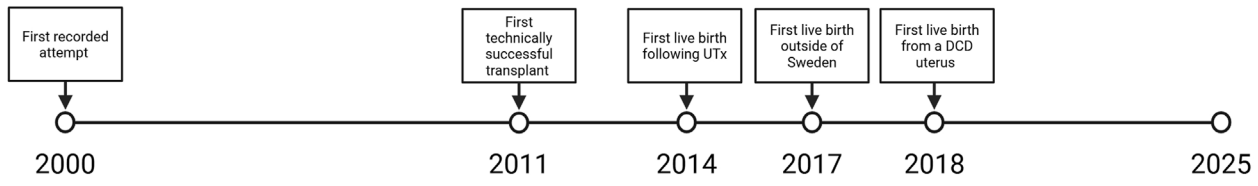

FIGURE 1 | Significant moments in uterus transplantation.

poor pregnancy outcomes [5]. Hysterectomy is one of the most common surgical procedures performed in women in the United States, totaling around 600,000 per year [6]. Most hysterectomies are performed for benign conditions such as myomas, abnormal uterine bleeding and endometriosis, with only ~10% performed as treatment for cancer [6].

MAYER-ROKITANSKY-KUSTER-HAUSER SYNDROME (MRKH)

Congenital uterine agenesis (MRKH) is to date the most common indications for UTx. The exact underlying genetic aspects are not yet fully understood. However, some have suggested that this condition is autosomal dominant with incomplete penetrance, although this hypothesis has been challenged [7–11].

Women with this diagnosis have a genetic karyotyping of 21 females with uterovaginal agenesis and typical secondary sexual characteristics and XX Chromosomes [12]. MRKH can be sorted into two different types [13–15]. Type II MRKH often presents with renal abnormalities such as renal agenesis or a pelvic kidney [16]. However, both types present with significant agenesis/aplasia of the uterus and upper portion of the vagina leading to AUFI. AUFI has significant implications for the psychological wellbeing of those affected. Women with MRKH scored significantly higher on questionnaires for anxiety, depression, eating disorders, and low self-esteem [17]. Additional studies have indicated significant impairment of mental-health-related quality of life and generally poorer mental health in MRKH patients when compared to controls [18, 19]. Furthermore, the interviewing process for UTx has revealed that AUFI and MRKH have significant impact on self-perception and the relationships of those affected [20].

EARLY UTERUS TRANSPLANTATION

The first published human UTx attempt occurred in Saudi Arabia in 2000 [21]. The living donor graft had to be removed 3 months post-transplant due to thrombosis and necrosis. This initial attempt generated interest worldwide and represented a major event in the field of UTx despite not resulting in a live birth. The next reported UTx was performed in Turkey in 2011 from a deceased donor [22]. For many years this case was considered a technical success with a viable graft but lacking a successful reproductive outcome. Nine years after the transplant, in 2020, the recipient had a live birth [23]. Both these two initial cases are representative of the challenges and coordination required in the time frame between transplant and the live birth of a child.

In 2014, the first live birth of a child following UTx was reported from Sweden [1]. This case was proof of concept for the procedure and would ultimately establish the definition of a successful UTx [1]. The patient was a 35-year-old woman with type 2 MRKH who received a UTx via directed living donation [1]. She had a single embryo transfer 1-year post-transplant that resulted in pregnancy [1]. A male baby was delivered prematurely at 31 weeks and 5 days via cesarean section. This first live birth was preceded and made possible by over a decade of extensive research in animal models and well-established protocols [24–27]. In the results of the rest of the Swedish clinical trial six women gave birth to nine children. The live birth weight per successful transplant was 67% [28]. Additionally, none of the children born were undersized for gestational age [28].

Expansion of UTx

The first live birth after UTx served as a catalyst for further growth in the field of UTx. Several transplant centers around the world began to establish clinical UTx trials. In 2016, two programs started in the United States (Cleveland Clinic in Cleveland, Ohio; Baylor University Medical Center, Dallas) [29]. The Dallas group [Dallas Uterus Transplant Study (DUETS)] became the first group in the world to replicate the success of a live birth after UTx of the Swedish transplant team in 2017 [30]. The first 20 cases were performed as an IRB study (2016–2019) and resulted in 17 live births [31]. The remarkable outcome of this study was that when the transplant was a technical success (viable graft 30 days post surgery), 100% of cases had at least one live birth. This study aided in proving the reproductive potential of the transplanted uterus [31]. The results of this study have helped considerably in adding to the existing knowledge in the field and in developing protocols in UTx. Currently, there are four active UTx programs in the United States (Cleveland Clinic in Cleveland, University of Pennsylvania, UAB, Baylor University Medical Center) and the added volume in cases and live births correspond to approximately 60% of the volume worldwide [29].

While DUETS was underway, researchers in other countries began assessing the feasibility of UTx in their transplant centers as well. In South America, Brazil is currently the only country with reported attempts and a reported live birth. The live birth in Brazil also represented another significant clinical first for UTx as it was the first live birth following the transplantation of a

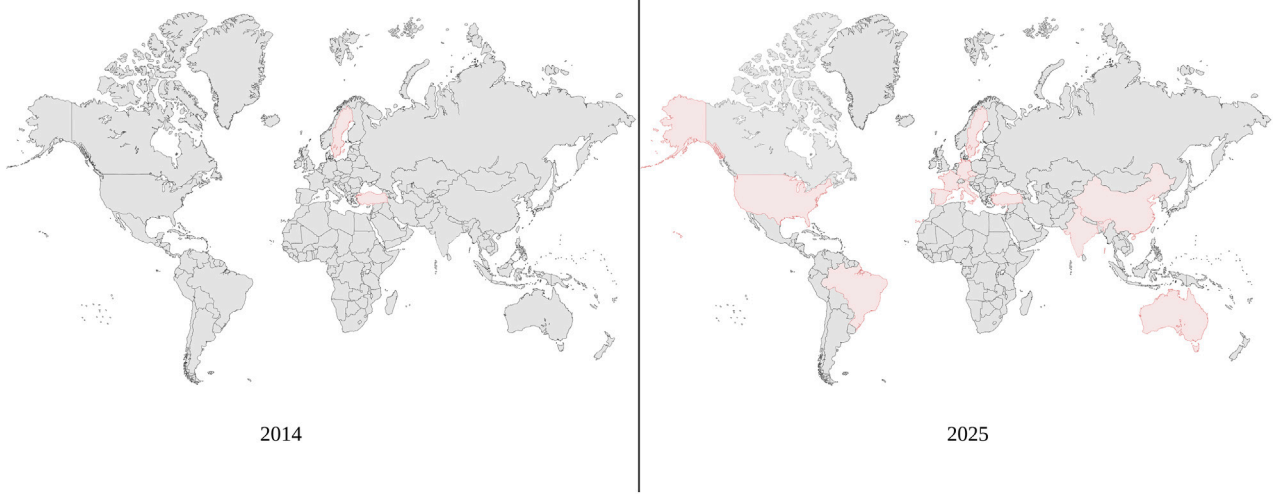

FIGURE 2 | Global expansion of uterus transplantation. Since 2014, uterus transplantation has expanded to more countries and become more prominent globally.

deceased donor's uterus [32]. In this case, immunosuppression was induced with prednisone and thymoglobulin [32]. Immunosuppression was maintained via tacrolimus and mycophenalate mofetil (MMF) until 5 months post-transplant in which azathioprine replaced MMF [32]. The recipient's first menstruation occurred 37 days post-transplant, and embryo transfer occurred 7 months post-transplant [32]. Following the embryo transfer, a baby girl was delivered at 36 weeks gestation. At birth, the baby weighed 2,550 g [32]. Remarkably, no episodes of rejection occurred post-transplant and graft hysterectomy was performed at delivery [32].

In Europe, the second country to begin a clinical trial for UTx was the Czech Republic [33]. In their initial experience, 7 of 10 attempts resulted in a successful transplant. The results saw three pregnancies which would ultimately lead to the live birth of two children [34]. Additionally, the initial Czech experience provided further evidence for the viability of deceased donors in UTx with one of the children being born in a recipient with a graft procured from a deceased donor [33]. Following the Czech clinical trial, clinical trials and initial attempts at UTx would take place in France, Germany, Italy, and the United Kingdom [35–38]. Currently, there no documented case reports or case series detailing the results seen in UTx recipients in France. In the German trial, 4 women received a uterus transplant from directed living donors with the fifth attempt being stopped due to the discovery of insufficient vasculature of the prospective graft during back table preparation Two of the women would go on to give birth at 35 weeks and 36 weeks with both of the children born being in the 15th percentile for birthweight [36]. In the Italian clinical trial, investigators performed two transplants using deceased donors with one of the transplants resulting in graft loss due to thrombosis and the other resulting in a live birth [37]. The live birth was delivered via cesarean section at 34 weeks and weighed 1725 g at birth [37]. In the United Kingdom, there is a published case report detailing a successful transplant attempt [38]. However, there is no indication of whether or not the transplant resulted in the live birth of a child.

In Asia, there have been reported attempts of UTx using living donors in both China and India [39, 40]. Notably, the case report in China documents the first use of robotic assistance in the procurement of a uterine graft [39]. In this attempt, the living donor was a 42-year-old woman who had two previous vaginal deliveries. Following the successful transplant, the recipient had their first menstrual cycle 40 days post-transplant [39]. The experience in India provided additional support of the viability of UTx. In the Indian attempts, both transplants were successful and the recipients had their first menstrual cycle at 34- and 48-day post-transplant [40]. In Australia, there are two established UTx programs with the first Australian live birth occurring in 2024 [41]. More recently, UTx has expanded into Singapore. In this instance, a living donor was used for the operation and the transplant was a technical success with the recipient having their first menstruation 38 days post-transplant [42]. As UTx has expanded on a more global scale, the International Society of Uterus Transplantation (ISUTx) was founded in 2016 [43]. **Figure 2** displays how UTx has expanded globally since the first live birth in 2014.

PRESENT DAY UTERUS TRANSPLANTATION

As UTx has become more prevalent, there has been a push to standardize the various aspects of the procedure shown in **Figure 3**, such as the evaluation process, operational procedures, post-op recovery, IVF, and delivery. Standardization of UTx allows for better outcomes for the donor and recipient, better graft viability, and ultimately more

FIGURE 3 | Stages of uterus transplant. Prospective patients must undergo evaluation for UTx per the transplant center's protocol to determine if candidate. Once a patient is cleared, transplant surgery will be scheduled in coordination with living donor or tentatively planned pending deceased donor. The recipient's surgery takes 5 or 6 h with an average hospital stay of 6 days to follow. Depending on patient's post-op recovery period, initial IVF embryo transfer occurs between 2–7 months post-op. Additional rounds of IVF may be necessary to achieve pregnancy. UTx recipient pregnancies have proven to result in third-trimester live births, at which point the baby will be delivered via cesarean section. Graft hysterectomy may occur at the time of delivery or at a later time depending on the UTx recipient preference. UTx recipients have been able to safely carry two pregnancies, so if cleared, the recipient may go through additional rounds of IVF.

live births. The collaboration between researchers has been pivotal for the continued development of the field and remains paramount as the field of UTx continues to evolve. As the field of UTx has evolved, so have many of the important aspects of the procedure.

Recipient Evaluation for Uterus Transplantation

The age range for potential recipients in centers performing UTx is typically set to childbearing age (18–40 years), with the upper limit being set to reduce the risk of potential pregnancy complications and to ensure oocyte quality [37]. For a majority of centers, the recipient inclusion and exclusion criteria were similar to the position statement on UTx released by the American Society for Reproductive Medicine, which in summary required no severe medical comorbidities and a body mass index less than 30 [44]. In addition to having no severe medical comorbidities, centers often completed extensive interviews and psychological evaluations before proceeding forward with the selection of a candidate for UTx. The intensive interviews and psychological screening allow for care providers to adequately assess current mental health, adequate social support, and adaptive coping skills necessary to deal with the numerous stressors that go along with the transplant surgery, the possible side effects of the immunosuppressive therapy, the uncertainty of successful embryo transfer and the potential complications of pregnancy and delivery [45–47]. Overwhelmingly, the results of these interviews and psychological assessments revealed unique insights into the motivation behind seeking UTx and how AUFI can mentally impact the women it afflicts. One of the most common motivations for seeking UTx amongst potential recipients was often the desire to experience gestation [48–50]. Other common reasons included wanting to defy the odds and the desire to have a biological child [48, 50].

Donor Selection and Care Post Uterus Transplantation

In UTx, utilization of deceased and living donor grafts has been proven to be equally successful [32]. Nonetheless, both options have their respective challenges. A deceased donor graft eliminates the risk of surgical and psychological complications that can arise with a living donor and gives an opportunity to access extended graft vascularity [51]. However, several logistical aspects require a substantial amount of planning. Utilization of a deceased donor is restricted by donor availability due to UTx currently requiring a brain-dead donor. As a result, uterus grafts from deceased donors have been reported to have limited availability in multiple countries [52–54]. Another logistical issue present with uterus procurement from deceased donors is the lack of standardized evaluation criteria, which reduces the ability to extensively screen the donor for abnormal pap smears, absence of major abdominal or pelvic surgery, history of donor infertility/subfertility, human papillomavirus, and other relevant systemic disease limiting the knowledge regarding the quality of the graft [52]. Furthermore, the recipient and her family may have to relocate to an area close to the hospital for an extended period of time, which may result in increased psychological stress [52, 55].

The utilization of a living donor graft involves a major elective surgery on a healthy woman, without direct benefits to herself, and with potential risks. While the use of robotic hysterectomy has made substantial strides in reducing risk, the overall risk is not zero [56]. The most commonly seen complication is ureteric injury, this has been seen in both robotic assisted approach and the open laparoscopic approach [21, 33, 57]. Nonetheless, similar to other types of living donation, there remains the risk of infection and even death. Thorough assessment of living donors prior to surgery and transparency of the potential risks involved is paramount when a living donor donates.

Surgical Aspects of Uterus Transplantation

The surgical aspects of UTx can be broken down into three separate components: donor hysterectomy, graft implantation, and graft hysterectomy. The first part, the donor hysterectomy was initially performed through open laparotomy. However, the introduction of robotic assisted techniques in several centers has been shown to be beneficial [56]. During the donor hysterectomy, the vascular pedicles of the uterus must be recovered to ensure graft inflow and outflow [58]. The uterine artery in conjunction with the whole trunk of internal iliac artery or only the anterior branch is utilized to provide inflow with the inferior and superior uterine veins being used to establish outflow [58–60]. In living donors, the use of robotic assisted approaches has been shown to result in lower estimated blood loss, decreased hospital stay, and decreased length of sick leave when compared to the open approach [61]. In addition, the use of robotic assisted techniques has demonstrated better graft viability [56].

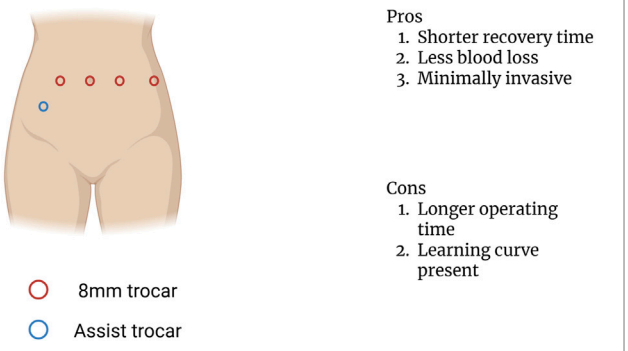

FIGURE 4 | Robotic assisted hysterectomy trocar insertion points.

Furthermore, the use of robotic assisted techniques allows for better operative visibility and greater intraoperative maneuverability while minimally invasive with the points of trocar insertion being illustrated in **Figure 4** [62].

The second part of the surgery, the back table procedure, follows the donor hysterectomy. The uterine graft is flushed with cold preservation fluid, and vascular reconstruction is performed when necessary [63]. The final and third part of the surgery is the recipient transplantation surgery that starts with the dissection of the external iliac vessels and the top of the vaginal vault. The uterine graft vasculature is thereafter anastomosed bilaterally to the external iliac vessels in the recipient. After graft reperfusion the vaginal rim of the uterine graft is anastomosed to the vaginal vault in the recipient [58, 64]. The connections made in the recipient surgery are illustrated in **Figure 5**. Since UTx is a temporary transplantation, only meant to stay with the recipient for pregnancy and childbirth, a graft hysterectomy is planned after delivery of 1–3 children. A second and potential third pregnancy is possible if the recipient so wishes, and there are no medical conditions related to complications of immunosuppression or gestational pathologies that would increase the risk for the mother.

Recipient Care Post Uterus Transplant

The immunosuppression regiment (IR) in UTx recipients is an aspect of care that requires careful consideration. The mainstay of immunosuppressive therapy is not dissimilar from any other solid organ transplant: induction with Thymoglobulin and maintenance with a calcineurin inhibitor, an antimetabolite, and steroids as an addition in some cases. None of these drugs have a profile free of side effects and the goal is to minimize the impact on the wellbeing of the mother and the child. Calcineurin inhibitors are known to be nephrotoxic due to their arteriolar vasoconstrictive effects [65]. In the initial experience with Utx, the antimetabolite of choice in many centers was mycophenolate mofetil (MMF) [32, 33, 36, 37, 66]. MMF was used immediately

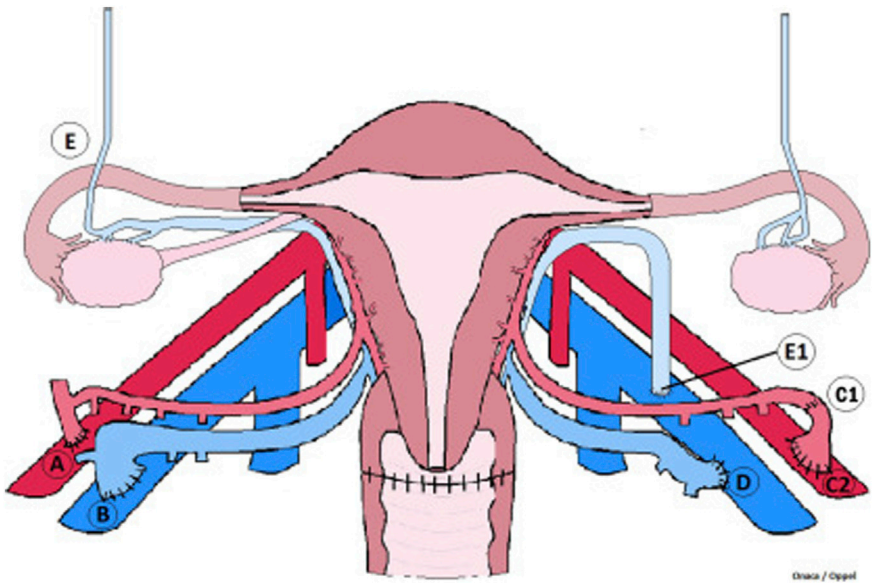

FIGURE 5 | Vascular connections of a uterus transplant procedure. Illustrated are the vascular connections made during graft placement. (A) illustrates anastomosis between internal iliac segment in continuity with uterine artery and external iliac artery. (B) illustrates anastomosis of the uterine vein and external iliac vein with venotomy performed as a simple slit at the superior aspect of iliac vein. (C1) represents a reconstructed uterine artery end-to-end with pudenal artery branch. (C2) shows the internal iliac artery patch end to side with the external iliac artery. (D) demonstrates modified vein anastomosis of the external iliac vein venotomy performed at the medial aspect of the vein as a large oval orifice. (E) shows ovaries fallopian tubes and utero-ovarian vessels. (E1) illustrates anastomosis of utero-ovarian vein and external iliac vein with venotomy performed as a simple slit at the superior aspect of iliac vein. This figure was initially published in the article "Living Donor Uterus Transplantation: A Single Center's Observations and Lessons Learned From Early Setbacks to Technical Success".

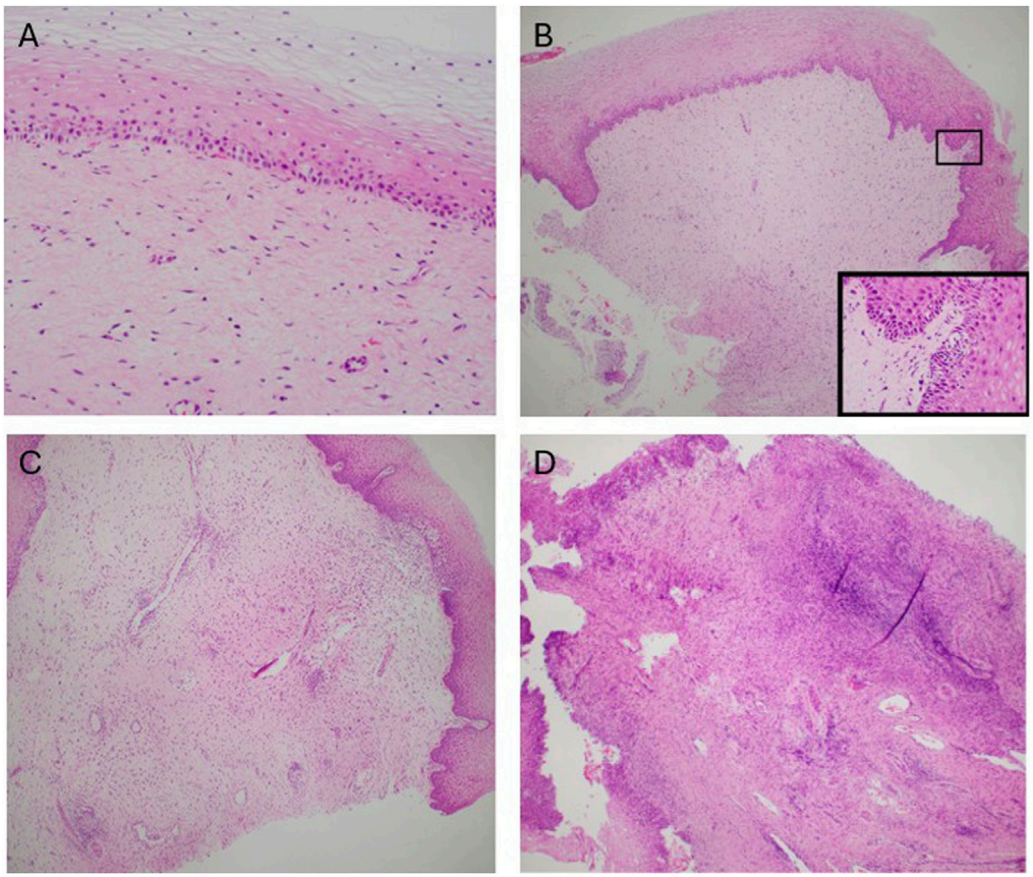

FIGURE 6 | Stages of graft rejection **(A)** No rejection **(B)** Mild rejection **(C)** Moderate rejection **(D)** Severe rejection. This figure was initially published in the article "Clinicopathological Analysis of Uterine Allografts Including Proposed Scoring of Ischemia Reperfusion Injury and T-cell–mediated Rejection—Dallas UtErus Transplant Study: A Pilot Study".

post-transplant but had to be stopped at least 3 months prior to embryo transfer due to its fetotoxic profile with increased risk of spontaneous abortion and congenital malformations [67–70]. The Dallas team started to completely eliminate MMF and substitute it with Azathioprine, another antimetabolite with a more benign profile, that is started immediately post-surgery [70]. This approach is now utilized by most teams worldwide. The medications used today are safe at therapeutic doses during pregnancy and solid organ transplant recipients have comparable maternal-fetal outcomes to nontransplant patients [71–73].

In UTX recipients, monitoring renal function post-operatively is imperative. Among UTx recipients, 30 percent developed pre-eclampsia which is a risk factor for subsequent kidney injury [74, 75]. Post-transplant, recipients typically see reductions in their glomerular filtration rate (GFR) [74, 76]. However, those who developed pre-eclampsia have sustained reductions in GFR while those that did not develop pre-eclampsia have a return to baseline GFR following withdrawal of immunosuppression [74]. The combination of renal comorbidities that can be congenitally present in MRKH recipients and the need for immunosuppression places UTx recipients at risk for renal dysfunction [77]. Nonetheless, the renal outcomes of UTx recipients should continue to be investigated to ensure safe outcomes, and to provide adequate information during the informed consent process.

Episodes of graft rejection in UTx are common and have no clinical manifestations and are diagnosed via cervical biopsy. In addition, there is no serum marker that can assist in the detection or diagnosis of acute cellular rejection. For this reason, frequent monitoring with cervical biopsies are performed [78, 79]. It is only when the acute cellular rejection is not detected and treated that there is progression to clinical signs and symptoms: discoloration of the uterus, increased uterine volume, watery discharge, abdominal pain, and changes in the normal urogenital flora to the presence of beta-hemolytic *streptococcus* Group B [80]. The stages of graft failure are shown in **Figure 6**. Further investigation into moderate to severe episodes of rejection have identified 13 genes with overlapping expression amongst moderate to severe cases with 5 genes (AGHDIB, BASP1, FCGR3A/B, KLF4, PTPN6) being associated with rejection in other types of organ transplant [81]. Additional

investigation in graft rejection has focused on determining non-histological biomarkers that can be used to determine rejection with Keratin 1 granzyme B, IL1β emerging as a potential indicator [82]. However, further investigation amongst larger patient populations is still needed to validate Keratin 1 granzyme B, IL1β′s effectiveness in determining rejection amongst UTx recipients. So far, there are currently no reported cases of graft loss due to treatment resistant acute rejection [83]. Episodes of graft rejection have been shown to be responsive to treatment with corticosteroids with live birth still being possible even after severe episodes of rejection [84, 85].

In vitro Fertilization in Uterus Transplantation

In vitro fertilization (IVF) is a necessity for fertilization following UTx since the Fallopian tubes are not included in the uterine graft. Embryos are generated prior to transplant [86]. Amongst centers, there is some variation in the required number of embryos generated with some centers requiring at least 2 and others requiring 6 with IVF treatment and cycle management being left to the discretion of the reproductive endocrinologist [87]. In the event of embryo exhaustion, additional oocyte retrievals can be performed post-transplant, although this will ultimately prolong the time the recipient is on immunosuppressive medication [87]. Currently, reported rates of embryo exhaustion are 20 percent amongst US centers [87]. However, this patient cohort remains too small to generalize across UTx recipients and requires further investigation as the number of UTx recipients grows to determine the standard rate of embryo exhaustion.

In the early days of UTx, embryo transfer was delayed to 1 year post-transplant [84]. The year long wait was based on recommendations for other types of organ transplant by the American Society of Transplantation in 2005 [88]. These recommendations were concerned with many of the same aspects that apply to UTx such as risk of acute rejection, risk of infection that could endanger the fetus, the fetotoxic profile of immunosuppressive medications, and adequate graft function. However, the recommendations made by the American Society of Transplantation were primarily concerned with long-term graft function. UTx is a temporary transplant where a main concern is minimizing a healthy person's long-term exposure to immunosuppressive medications that could potentially damage their renal function [65]. As a result, transplant centers have elected to shorten their timeframe from UTx to embryo transfer to 3–6 months [86, 89]. The shorter time frame is a patient-centered approach that accounts for graft viability and risk or infection while minimizing the exposure to immunosuppressive medications. The outcome data suggests that it is feasible, safe, and associated with a high implantation rate, to transfer an embryo as early as 3 months after the transplant [89].

Outcomes of the Children Born After Uterus Transplantation

The long-term outcomes of children born after UTx is limited due to the novelty of the procedure. The longest follow up in the world is 11 years and in the US 8 years [90]. All deliveries have so far been performed via cesarean section due to concerns for vaginal anastomosis dehiscence and the potential for damaging the neovagina and surrounding structures during vaginal labor [29]. Initial experiences in the US have reported a median gestational age at delivery is 36 weeks [29, 91]. No congenital malformations have been recorded [29, 92]. In addition, the median birth weight amongst live births in the US has been reported to be 2,860 g suggesting that low birth weight in UTx may not be as prevalent compared to other forms of organ transplant [93–95]. Long term follow-up of the children has indicated normal neurological and functional development [96]. Overall, the initial long-term outcomes of the children born because of UTx have been favorable. Nonetheless, this remains an ongoing area of research in UTx and additional longitudinal studies are still needed to verify the results seen so far.

FUTURE DIRECTIONS OF UTERUS TRANSPLANTATION

Currently, the cost of UTx remains a potential barrier to access. Estimates have placed the cost of a single live birth in the US to be $116,137.20, and the total cost per live birth from the Swedish clinical trial being €107,120 [97, 98]. Future efforts to mitigate the costs associated with UTx through insurance coverage can help alleviate this barrier. However, this remains a more complex challenge in healthcare systems like the United States. Nonetheless, future studies on the costs associated with UTx are needed to inform potential recipients and donors fully, and so that conversations regarding potential coverage can occur.

As the field of UTx continues to expand, various aspects still need to be addressed. One such aspect is that the general population's knowledge of UTx remains relatively low. In a cross-sectional survey, only 33 percent of respondents who were aware of overall organ transplant indicated they had heard of UTx [99]. These results represent how those who may benefit from UTx may not be aware of the procedure, indicating a potential visibility issue, making it difficult to assess overall demand. While provider support has been favorable, determining provider knowledge and awareness in countries and regions without UTx may help increase UTx's visibility to eligible patient groups as UTx continues to expand in the clinical setting [100]. The further expansion of UTx in a clinical setting also warrants reassessment of patient groups who may not have AUFI, but experience significant challenges in family planning, such as patients with endometriosis. Another similar example is UTx in transgender women. While this topic has been heavily discussed as an additional patient population, there have not been any documented attempted transplants in this patient population [101–103]. Nonetheless, in a study consisting of 186 transgender women, 94 percent agreed or strongly agreed that gestation and childbirth would enhance their self-perception of their femininity [103]. Additionally, nearly all felt that UTx would lead to a greater sense of happiness in male to female transgender women [103]. The

results of this study suggest that UTx has significant interest in this currently underserved population. As the field of UTx progresses forward, the inclusion of transgender women has significant potential to expand the pool of potential recipients. Further discussion regarding expanding UTx to this population should focus on the identification of the technical aspects that go into a successful transplant, and identification of barriers to access unique to male to female transgender women.

With the near-horizon expansion of the potential recipient pool, the supply of grafts may need to adjust accordingly. One potential possibility noted is the reuse of uterine grafts or "domino transplants" similar to what has been seen in heart, liver, and kidney transplant [104]. While this is a potential possibility, it will likely remain theoretical. To our knowledge, there have been no attempts, and an attempt would require a significant amount of coincidence and be a significant logistical undertaking, making it an unlikely option for significant meaningful expansion. Instead, a more fruitful option comes in the form of biologically engineered grafts. The current research needed to make this a potential reality is already underway in various different animal models [105, 106]. The significance of biologically engineered grafts is that it nullifies both the challenges associated with deceased donation and the risk of potential complications in living donors. However, before integration in human transplant, a significant amount of further testing is needed to ensure its safety and validity.

CONCLUSION

While there remain aspects of UTx that need further assessment and discussion, UTx is an established treatment for AUFI. Coordination and collaboration amongst providers is vital to further expansion of UTx in the clinical setting. As more transplants are performed and additional live births occur, ancillary studies are necessary to build upon the existing knowledge of the field and ensure favorable outcomes.

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

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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.

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REVIEW
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A Comprehensive Review of *Ex-Vivo* Machine Perfusion in Uterus Transplantation

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Uterine transplantation has revolutionized previously incurable causes of infertility. While most transplants are performed with live donors, the use of deceased donors could potentially expand the donor pool and increase the number of transplants performed. One limitation of deceased donor use is warm and cold ischemia time, which may be potentially mitigated by the implementation of *ex-vivo* machine perfusion (EVMP). This comprehensive review synthesizes the existing literature on uterine EVMP, highlighting both experimental and translational developments up to February 2025. A total of 31 relevant studies were identified from 244 screened articles, most involving human aor large-animal uteri. The majority of studies employed normothermic machine perfusion (NMP) as a model for physiologic conditions, focusing on endocrine or functional analysis, inflammatory reactions, or technical aspects of perfusion. Only in the past 6 years have articles looked at EVMP as a preservation technique for transplantation, or employed hypothermic machine perfusion (HMP). While EVMP has only recently increased in popularity for transplant preservation, uterine EVMP has historically been used in multiple studies as a model for physiologic conditions. While further research is needed to optimize preservation protocols, much can be gleaned from prior models of uterine perfusion.

Keywords: uterus transplantation, machine perfusion, machine preservation, *ex vivo* perfusion, vascularized composite allotransplantation

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INTRODUCTION

Absolute uterine factor infertility is a significant cause of infertility, and was considered incurable until the last decade. Uterine transplantation represents a revolutionary approach to addressing infertility in women with absent or nonfunctional uteri, which may result from congenital uterine agenesis or hysterectomy due to malignant disease, postpartum hemorrhage, uterine fibroids, and congenital abnormalities [1]. Distinct from other solid organ transplants, uterine transplant poses unique challenges; it must not only be technically and immunologically feasible but also enable the transplanted uterus to sustain pregnancy and facilitate a healthy live birth [2].

The first human uterine transplant attempt was conducted in 2000 [3], but the first live birth occurred in 2014 in Sweden [4]. Since then, over 80 uterine transplants have been performed globally,

resulting in more than 40 live births [5, 6]. Approximately 72% of the registered uterine transplants were from live donors, according to the United States Uterus Transplant Consortium (USUTC) and the International Society of Uterus Transplantation (ISUTx) [5, 6]. However, recent research has now focused on using deceased (brain-dead) donors as graft sources. While this would potentially increase the donor pool, it also requires more attention to organ preservation.

Despite advancements in uterus transplantation, significant knowledge gaps persist, necessitating further research in surgical techniques, immune modulation, and graft rejection studies [7]. Moreover, the effects of warm and cold ischemia in uterus transplantation are still not well understood. Uterine grafts have been shown to tolerate static cold ischemic storage (SCS) for at least 6 h while maintaining histologic integrity, ATP concentrations, and contractile ability [8].

One concern in the field of uterine transplantation is the tolerance of the uterus to ischemia, and the effects of warm and cold ischemia on graft viability and functionality. According to previous studies using animal models, the uterus exhibits a relative tolerance to both cold and warm ischemia [9, 10]. In the mouse model of uterus transplantation, it has been demonstrated that live births can be achieved following a cold ischemia duration of 24 h [11]. However, the optimal duration of cold ischemia for uterine grafts remains undetermined, necessitating further investigation. During the 24 h of cold storage of human uterine, Gauthier et al, demonstrated that no significant histomorphology changes had occurred in the tissue, and there was little evidence of apoptosis [12]. In the clinical setting, live births have resulted from both living and deceased donors, although living donors comprise the majority of live births [5, 6]. Deceased donors have a significantly longer cold ischemia time (CIT) as compared to living donors [5], but successful live births have resulted from CIT as long as 6.5 h [13] and 9 h [14]. Among uterus transplants in the United States, early graft loss was associated with longer warm ischemia time (WIT), but no association was found between CIT and clinical outcomes [5].

SCS has long been considered the gold standard for organ preservation [15]. However, advancements in *ex-vivo* machine perfusion (EVMP) technology, originally developed for solid organs, have opened new avenues for preserving a wider range of organs and delivering therapeutic agents [15]. Previous large-scale studies have indicated that EVMP may offer advantages over SCS in liver and kidney transplants, including improved patient survival rates, reduced adverse events, and enhanced short- and long-term functional outcomes [16, 17]. In addition, EVMP may offer several advantages, such as reducing cold ischemia and hypoxic injuries by ensuring a continuous supply of oxygen and nutrients, clearing toxic metabolites, and improving the quality and viability of the graft [18, 19].

In clinical settings, this technique is now frequently applied for lung, heart, liver, and kidney transplantation [20–22]. In particular, EVMP has shown potential for extremity vascularized composite allotransplantation (VCA), in which static cold storage typically requires reperfusion within 10–12 h to maintain viability, with optimal functional recovery anticipated between 3 and 6 h of cold ischemia [23]. The implementation of EVMP may be particularly important in uterus transplantation due to the non-vital nature of the uterus, which often leads to prolonged CIT during multi-organ procurement surgeries, as hysterectomies are performed as the last procedure in some protocols [24, 25].

Despite the growing fields of research in both uterus transplantation and EVMP, no comprehensive review papers exist on uterus machine perfusion. The purpose of this study is to conduct a extensive review of literature on uterus *ex-vivo* machine perfusion, including identification of relevant literature, characterization of these studies in terms of perfusion protocol and outcomes, and comparison of protocols.

Search Approach and Evidence Selection

A comprehensive literature search of manuscripts listed in PubMed, Scopus, EMBASE, Cochrane Library, and ClinicalTrials.gov databases was conducted in January 2025. The following search terms were used: [(uterus) OR (uteri) OR (uterine)] AND [(machine perfusion) OR (machine preservation) OR (*ex vivo* perfusion) OR (extracorporeal perfusion) OR (extracorporeal circulation)]. Selected studies met the following inclusion criteria: (1) preclinical articles studying machine perfusion; (2) perfusion of uterus grafts; (3) randomized control trials, prospective and retrospective case-control and cohort studies, cross-sectional cohort studies, case reports, and technique papers. Exclusion criteria were: (1) reviews without presentation of new data; (2) abstracts, conference papers, editorials, or comments; (3) articles about solid-organ or non-uterine VCA perfusion. Historically, however, perfusion systems have been extensively used for physiological and hormonal studies of the uterus, providing a valuable foundation for the future development of this approach in organ preservation. Despite the heterogeneity among existing studies, we included all such research in our review to capture the full scope of relevant evidence.

The literature search yielded 244 articles, of which 31 articles met criteria (see **Figure 1**; **Table 1**) [7, 26–33, 35–56]. Included studies were published between 1970 and 2025. Ten studies utilized human uteri, while the remaining 21 used animal models. Of these animal models, all but one were in large animals, with swine being the most common (15 studies). Other animals included sheep (2 studies), cows (2 studies), and horses (1 study). Only one study [28] used a small animal model (rabbits), and no studies used rodents.

Experimental Focus

The included studies comprise a variety of experimental aims. As machine perfusion has only recently increased in popularity for organ preservation, many of the total published works on uterus machine perfusion do not have an end goal of transplantation or organ preservation. The most common experimental aim was endocrine and/or functional analysis (16 studies), which involved contraction monitoring and biochemical analysis after the administration of various hormones, drugs, or prostaglandins. Another portion of studies focused on technical aspects of the

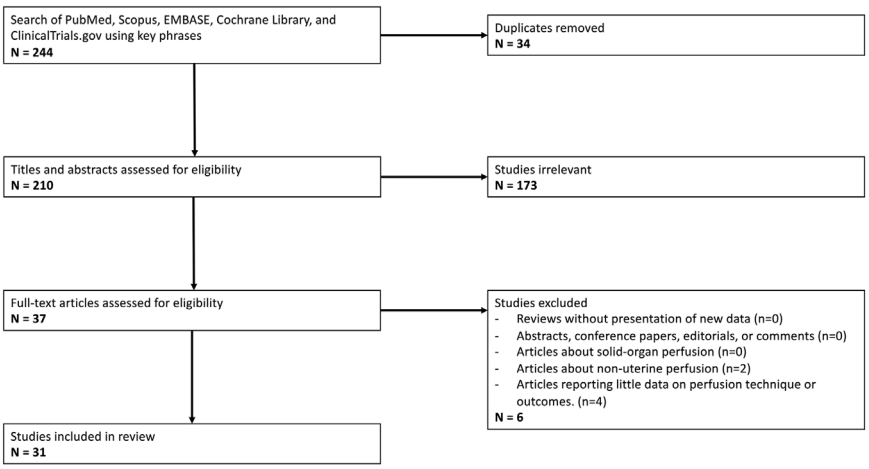

FIGURE 1 | PRISMA Flow Diagram outlining inclusion and exclusion criteria, number of abstracts screened, and full texts retrieved.

perfusion (5 studies), including perfusate composition, perfusion flow and pressure, and the influence of perfusate exchange. Four studies analyzed EVMP as a storage method, comparing machine-perfused uteri to uteri stored statically on ice. Of these four studies, two included subsequent transplantation. Other experimental aims included EVMP as a model for inflammatory reactions (2 studies), preservation of a pregnant sheep uterus (1 study), preservation of an intrauterine trophoblastic tumor (1 study), *in vitro* fertilization of a machine-perfused uterus (1 study), and analysis of fibroid blood supply via addition of methylene blue (1 study).

Surgical Technique and Anatomical Considerations

The uterus is relatively unique in its blood supply as compared to other transplants (see **Figure 2**). The majority of other solid organ transplants and VCAs have a single-artery and single-vein blood supply, allowing for simplified machine perfusion with a single roller pump. The body of the uterus (as well as the uterine horns in large animal anatomy) is perfused via bilateral uterine arteries, which arise from the bilateral internal iliac arteries. They drain via bilateral uterine veins (also referred to in humans as inferior uterine veins) [57], which drain into the bilateral internal iliac veins. The ovaries have a separate blood supply, bilateral ovarian arteries and veins, which originate directly from the aorta and drain directly into the inferior vena cava, respectively. In humans, the distal ovarian vein is referred to as the superior uterine vein, and accounts for a large portion of uterine venous drainage [57]. The majority of studies (27 studies) cannulated the bilateral uterine arteries. Of these studies, eight also cannulated the uterine veins bilaterally. One study cannulated both the uterine and ovarian arteries bilaterally, although the ovarian arteries do not provide a significant blood supply to the uterine body and are not utilized for anastomosis in uterine transplantation [57]. While the majority of studies kept the uterine body intact, one study divided the uterus along the midline to perfuse both sides simultaneously [46]. Another study, the only one to use a small animal model [28], isolated a single uterine horn and cannulated it through the abdominal aorta, ligating all other arterial branches. Three recent studies [53, 54, 56] use a technique of removing the uterus *en bloc* with the abdominal aorta and inferior vena cava, thereby allowing for a single cannulation site at the aorta for perfusion of both uterine arteries and both ovarian arteries. A number of studies (17 studies) removed the uterus after euthanasia, most commonly in the setting of sourcing research animals from slaughterhouses.

Perfusion Machine Design

The bilateral blood supply of the uterus poses a challenge for traditional machine perfusion devices, which typically have a single arterial inflow and single venous outflow. While some studies utilized a Y-connector after a single perfusion pump (6 studies), the majority of studies employed two separate pumps (21 studies), enabling adjustments to each artery individually and preventing unequal flow (see **Figure 3**). The studies cannulating the aorta all used a single pump for perfusion. All studies employed oxygenation of the perfusate, with the majority (28 studies) using carbogen gas. The perfusate medium was blood-based in 6 studies, but the majority of studies employed various organ preservation solutions, including Krebs-Ringer bicarbonate buffer, Krebs-Henseleit buffer, and UW solution. Multiple studies utilized perfusate additives, including heparin, antibiotics, and insulin. The duration of the perfusions varied, with 11 studies perfusing for 1–6 h, 11 studies perfusing for 6–12 h, and 10 studies perfusing for more than 12 h. The longest perfusion was 52 h, utilizing a non-blood-based perfusate [32].

As in solid organ machine perfusion, there is no consensus for the optimal temperature of uterus EVMP. As the majority of studies were not focused on storage or transplantation, most studies (28 studies) employed normothermic machine perfusion (NMP) (37 °C–39 °C) to mimic physiologic conditions. Three

TABLE 1 | Summary of reviewed papers, n = 31.

Author (Year)	Species (Details)	Surgical Details	Cannulation Details	Temp (°C)	Duration (Hr)	Flow (mL/min)	Pressure (mmHg)	Perfusion Pump Setup	Perfusate Details	Perfusion Monitoring	Study Design (# of uteri)	Outcomes
Peirce [26]	Sheep (38–62 kg, near-term)	Pregnant uterus removed and placed in "artificial abdomen"	Bilateral uterine arteries	37	0.5–5	300+	NR	2 roller pumps, artificial membrane lung for oxygenation	Heparinized maternal blood	Perfusate chemistry and gas	NMP [15]	Early fetal death early in all but 5 perfusions, survival up to 5 h in one experiment
Tojo [27]	Human	Hysterectomy for benign disease and trophoblastic tumor	Bilateral uterine arteries	37	5	25–40	NR	1 diaphragm pump with Y-connector, oxygenator with oxygen	Hank's solution, 20% autologous whole blood, 4% dextran	Perfusate chemistry and gas, EMG uterine muscle, biopsy tumor tissue, angiogram after perfusion	NMP [2]	Viability up to 5 h, preservation of trophoblastic tumor *in utero*
Bloch [28]	Rabbit (3–4 kg)	Single uterine horn included, contralateral blood supply ligated	Aorta	37	7–10	6–8	NR	1 pump, oxygenator with carbogen	Krebs-henseliet buffer, dextran	Perfusate prostaglandin levels	NMP with angiotensin II, oxytocin, epinephrine, and arachidonic acid [29]	Increased prostacyclin release with all substances, most effectively for arachidonic acid
Bulletti [30]	Human	Scheduled hysterectomies for benign and malignant diseases	Bilateral uterine arteries and veins, 16G	37	12	10–30	80–120	2 roller pumps, oxygenator with carbogen	KRBB, heparin	Perfusate chemistry and gas, uterine biopsy	NMP [9]	Viability up to 12 h
Bulletti [31]	Human	Scheduled hysterectomies for benign and malignant diseases	Bilateral uterine arteries and veins, 16G	37	48	12–35	80–120	2 roller pumps, oxygenator with carbogen	KRBB, heparin	Perfusate chemistry and gas, uterine biopsy	NMP [20]	Viability up to 48 h, tissue is responsive to estrogen and progesterone
Bulletti [32]	Human	Scheduled hysterectomies for benign and malignant diseases	Bilateral uterine arteries and veins, 16G	37	52	18–30	80–120	2 roller pumps, oxygenator with carbogen	KRBB, heparin	Uterine biopsy	NMP after injection of fertilized embryo [3]	Successful implantation and trophoblastic invasion after 52 h in one of three uteri
Bulletti [33]	Human	Scheduled hysterectomies for benign and malignant diseases	Bilateral uterine arteries and veins, 16G	37	1	30	120	2 roller pumps, oxygenator with carbogen	KRBB, heparin	Perfusate estrogen levels, uterine biopsy	NMP with radio-labeled compounds to assess estrogen uptake [34]	Differential permeability of uterine vascular beds during proliferative and secretive phases
Bulletti [35]	Human (36–42 years)	Scheduled hysterectomies for benign and malignant diseases	Bilateral uterine arteries and veins, 16G	37	1.5, 48	NR	NR	2 roller pumps, oxygenator with carbogen	KRBB, heparin	Perfusate chemistry and gas, IUP, EMG uterine muscle	NMP for 48 h [3] NMP for 1.5 h with estrogen [5], estrogen/ progesterone [5]	No spontaneous muscle activity in control uteri, increased muscle activity with estrogen, decreased with progesterone

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TABLE 1 | (*Continued*) Summary of reviewed papers, n = 31.

Author (Year)	Species (Details)	Surgical Details	Cannulation Details	Temp (°C)	Duration (Hr)	Flow (mL/min)	Pressure (mmHg)	Perfusion Pump Setup	Perfusate Details	Perfusion Monitoring	Study Design (# of uteri)	Outcomes
Richter [36]	Human (28–56 years)	Scheduled hysterectomies for benign diseases	Bilateral uterine arteries, 14G	37	24	15–35	70–130	2 roller pumps, oxygenator with carbogen	Modified KRBB[a], gentamicin	Perfusate chemistry and gas, uterine biopsy	NMP without exchange [5] NMP with exchange every 1 h [5], 2 h [5], 4 h [5], 6 h [5]	Increased damage with exchange every 6 h, viabillity in 1–4h groups
Baumer [37]	Cow (2+ years)	Post-mortem excision, 30–45 min WIT	Bilateral uterine arteries and veins	39	5	12–17	NR	1 peristaltic pump with Y-connector, oxygenator with carbogen	Autologous whole blood plus tyrode solution (4: 1 ratio), heparin	Perfusate chemistry and gas, uterine biopsy	NMP [4] NMP with addition of Lugol's solution [4], arachidonic acid [5]	Viability up to 5 h, adequate inflammatory response to irritants
Dittrich [38]	Swine (5–18 months)	Post-mortem excision	Bilateral uterine arteries and veins, 16–24G	37	7	15	100	2 roller pumps, oxygenator with carbogen, no recirculation	Modified KRBB[a], calcium carbonate	Perfusate chemistry and gas, IUP	NMP with oxytocin [15], PGE2 [15]	Viability up to 7 h, contractions induced by both oxytocin and PGE2
Richter [29]	Human (34–46 years)	Scheduled hysterectomies for benign diseases	Bilateral uterine arteries, 14G	37	27	15–35	70–130	2 roller pumps, oxygenator with carbogen	Modified KRBB[a]	Perfusate chemistry and gas, uterine biopsy	NMP with oxytocin [5], estradiol/ oxytocin [5]	Increased oxytocin receptor concentration in estradiol/oxytocin group compared to oxytocin alone
Richter [39]	Human (31–46 years)	Scheduled hysterectomies for benign diseases	Bilateral uterine arteries, 14G	37	27	15–35	70–130	2 roller pumps, oxygenator with carbogen	Modified KRBB[a]	Perfusate chemistry and gas, uterine biopsy	NMP [5] NMP with oxytocin [5], estradiol/ oxytocin [5]	Increased oxytocin receptor gene expression in estradiol/oxytocin group compared to oxytocin alone
Braun [40]	Cow (2+ years)	Post-mortem excision, 75 min WIT	Bilateral uterine arteries and veins	39	6	17	NR	1 peristaltic pump with Y-connector, oxygenator with carbogen	Autologous whole blood plus tyrode solution (4: 1 ratio), heparin	Perfusate chemistry and gas, uterine biopsy	NMP [6] NMP with addition of arachidonic acid [18]	Viability up to 6 h, increased inflammatory markers in arachidonic acid exposure group
Maltaris [41]	Swine (5–18 months)	Post-mortem excision	Bilateral uterine arteries, 16–24G	37	8	15	100	2 roller pumps, oxygenator with carbogen	Modified KRBB[a]	Perfusate chemistry and gas, IUP	NMP with acetylsalicylic acid [5], atosiban [5], ethanol [5], fenoterol [5], ritodrine [5], terbutaline [5], propofol [5], glyceryl trinitate [5], verapamil [5]	Increased contractility with all substances, most effectively with fenoterol

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TABLE 1 | (*Continued*) Summary of reviewed papers, n = 31.

Author (Year)	Species (Details)	Surgical Details	Cannulation Details	Temp (°C)	Duration (Hr)	Flow (mL/min)	Pressure (mmHg)	Perfusion Pump Setup	Perfusate Details	Perfusion Monitoring	Study Design (# of uteri)	Outcomes
Mueller [42]	Swine (5–18 months)	Post-mortem excision	Bilateral uterine arteries, 16–24G	37	8	15	100	2 roller pumps, oxygenator with carbogen	Modified KRBB[a], oxytocin added to induce contractions	Perfusate chemistry and gas, IUP	NMP with estrogen [34], progesterone [34], estrogen/ progesterone [34]	Estrogen increased contracility, progesterone antagonized effects of estrogen
Mueller [43]	Swine (5–18 months)	Post-mortem excision	Bilateral uterine arteries, 16–24G	37	8	15	100	2 roller pumps, oxygenator with carbogen	Modified KRBB[a]	Perfusate chemistry and gas, IUP in corpus and isthmus	NMP with PGF2a [15], PGE1 [15], PGE2 [15], oxytocin [15]	Increased IUP globally with oxytocin and PGF2a, IUP gradient (isthmus > corpus) with PGE1 and PGE2
Mueller [44]	Swine (5–18 months)	Post-mortem excision	Bilateral uterine arteries	37	8	15	100	2 roller pumps, oxygenator with carbogen	Modified KRBB[a], oxytocin added to induce contractions	Perfusate chemistry and gas, bilateral IUP	NMP with unilateral addition of estrogen [20], progesterone [20], estrogen/ progesterone [20]	Estrogen increased contractility in ispilateral horn but not contralateral, progesterone antagonized effects of estrogen
Kunzel [45]	Swine (5–18 months)	Post-mortem excision	Bilateral uterine arteries, 16G	37	8	15	100	2 roller pumps, oxygenator with carbogen	Modified KRBB[a], oxytocin added to induce contractions	Perfusate chemistry and gas, IUP	NMP with butylscopolamine [12], atropine [13], denaverine [15], morphine [7], metamizole [9], pethidine [10], celandine [14]	Decreased contractility with all substances, most effectively for denaverine
Dittrich [46]	Swine (5–18 months)	Post-mortem excision, division into two horns for simultaneous perfusion	Bilateral uterine arteries, 16–24G	37	3.5	NR	NR	2 roller pumps, oxygenator with carbogen	Modified KRBB[a], oxytocin added to induce contractions	Bilateral IUP	Simultaneous NMP of bilateral horns with unilateral addition of human seminal plasma [17]	Improved contractility on human seminal plasma side
Geisler [47]	Swine (5–18 months)	Post-mortem excision	Bilateral uterine arteries, 16G	37	24	15	NR	2 roller pumps, oxygenator with carbogen	KRBB or modified KRBB[a], oxytocin added to induce contractions	Perfusate chemistry and gas, IUP	NMP with KRBB [11], modified KRBB[a] [18], modified KRBB with exchange every 2 h [11]	Improved contractility with modified KRBB[a], viability up to 17 h with perfusate exchange

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TABLE 1 | (*Continued*) Summary of reviewed papers, n = 31.

Author (Year)	Species (Details)	Surgical Details	Cannulation Details	Temp (°C)	Duration (Hr)	Flow (mL/min)	Pressure (mmHg)	Perfusion Pump Setup	Perfusate Details	Perfusion Monitoring	Study Design (# of uteri)	Outcomes
Kunzel [48]	Swine (5–18 months)	Post-mortem excision	Bilateral uterine arteries, 16G	37	NR	15	80–100	2 roller pumps, oxygenator with carbogen	Modified KRBB[a]	Perfusate chemistry and gas, IUP	NMP with PGE1 [3], PGE2 [3], PGF2a [3], progesterone/ PGE1 [18], progesterone/ PGE2 [16], progesterone/ PGF2a [15]	Prostaglandin-induced contractions reduced by progesterone
Stirland [49]	Human	Scheduled hysterectomies for fibroids	Bilateral uterine arteries	38	8	NR	100	1 peristaltic pump with Y-connector, oxygenator with carbogen	Krebs-henseleit buffer, heparin, gentamicin, insulin, glutathione	Perfusate chemistry and gas, uterine biopsy	NMP with methylene blue [14]	Poor methylene blue staining in fibroids
Oppelt [50]	Swine (5–18 months)	Post-mortem excision	Bilateral uterine arteries, 24G	37	4	10–15	60–80	2 roller pumps, oxygenator with carbogen	Modified KRBB[a]	Perfusate chemistry and gas, IUP in corpus and isthmus	NMP control [18] NMP with progesterone [26], dienogest [38]	Progesterone decreased contractility globally, dienogest decreased contractility at ithmus only
Weinschenk [51]	Swine (7–18 months)	Post-mortem excision, 20min WIT	Bilateral uterine arteries, 16G	37	1	6	NR	2 roller pumps, oxygenator with carbogen	Modified KRBB[a]	IUP	NMP with procaine [31], lidocaine [31], ropivacaine [32]	Lidocaine and ropivacaine reduce contracitlity in higher concentrations
Padma [7]	Sheep (9–12 months)	Post-mortem excision	Bilateral uterine arteries, 26G	37	48	NR	45–55	1 peristaltic pump with Y-connector, oxygenator with carbogen	DMEM/F-12, GlutaMAX, fetal bovine serum, antibiotic-antimicotic solution	Perfusate chemistry and gas, uterine biopsy	SCS 4 h then NMP 48 h [6] SCS 48 h then NMP 48 h [7]	Reperfusion damage in 48 h storage but not 4 h storage
Kohne [52]	Horse (8–25 years)	Post-mortem exicsion after exsanguination, 60–100 min WIT	Bilateral uterine and ovarian arteries, 14–18G	39	8	30	NR	1 peristaltic pump with 3 Y-connectors, oxygenator with oxygen	Autologous whole blood plus autologous plasma (3: 2 ratio), heparin	Perfusate chemistry and gas, uterine biopsy, sonomicrometry	NMP [12]	Viability up to 6 h, decreased function after 4 h s
Dion [53]	Swine	Uterus removed *en bloc* with aorta and IVC	Aorta	4	18	NR	NR	VitaSmart machine perfusion system (1 peristaltic pump)	UW solution	Macroscopic assessment	HMP 18h then transplant (NR)	Viable transplant

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TABLE 1 | (*Continued*) Summary of reviewed papers, n = 31.

Author (Year)	Species (Details)	Surgical Details	Cannulation Details	Temp (°C)	Duration (Hr)	Flow (mL/min)	Pressure (mmHg)	Perfusion Pump Setup	Perfusate Details	Perfusion Monitoring	Study Design (# of uteri)	Outcomes
Loiseau [54]	Swine (150 kg)	Post-mortem excision, 60min WIT, uterus removed *en bloc* with aorta and IVC	Aorta	4 (HMP) or 37 (NMP)	12 (HMP) or 2 (NMP)	NR	15 (HMP) or 30–35 (NMP)	VitaSmart machine perfusion system (1 peristaltic pump) (HMP) or liverassist machine perfusion system (1 peristaltic pump) (NMP)	UW solution (HMP) or heparinized autologous whole blood (NMP)	Perfusate chemistry and gas, uterine biopsy	SCS 12h then NMP 2h [5] HMP 12h then NMP 2h [5]	Decreased resistance indices and higher tissue oxygenation during reperfusion in HMP group as compared to SCS
Cabanel [55]	Swine (30–40 kg)	Post-mortem excision, less than 60min WIT	Bilateral uterine arteries, 18G	20	4	2.5–10	25–35	2 roller pumps, oxygenator with carbogen	Steen+ solution	Perfusate chemistry and gas, serial weights, post-perfusion angiography	SNMP [4]	Viability for 4 h perfusion, stable weight throughout perfusion, well-identified microvasculature post-perfusion
Sousa [56]	Swine	Uterus removed *en bloc* with aorta and IVC	Aorta	4	18	NR	3	VitaSmart machine perfusion system (1 peristaltic pump)	UW solution	Macroscopic assessment, uterine biopsy, post-transplant blood samples	SCS in HTK 18h then transplant [5] SCS in UW 18h then transplant [5] HMP 18h then transplant [5]	Improved histology after transplant in HMP group initially but equivocal after 3 h, no biomarkers for uterus viability identified

NR, not recorded; WIT, warm ischemia time; NMP, normothermic machine perfusion; SNMP, sub-normothermic machine perfusion; HMP, hypothermic machine perfusion; SCS, static cold storage; IUP, intrauterine pressure; KRBB, Krebs-Ringer bicarbonate buffer.

[a]*Modified KRBB, Krebs-Ringer bicarbonate buffer with added saccharose, glutathione, dithiothreitol, 50 IU/L regular insulin.*

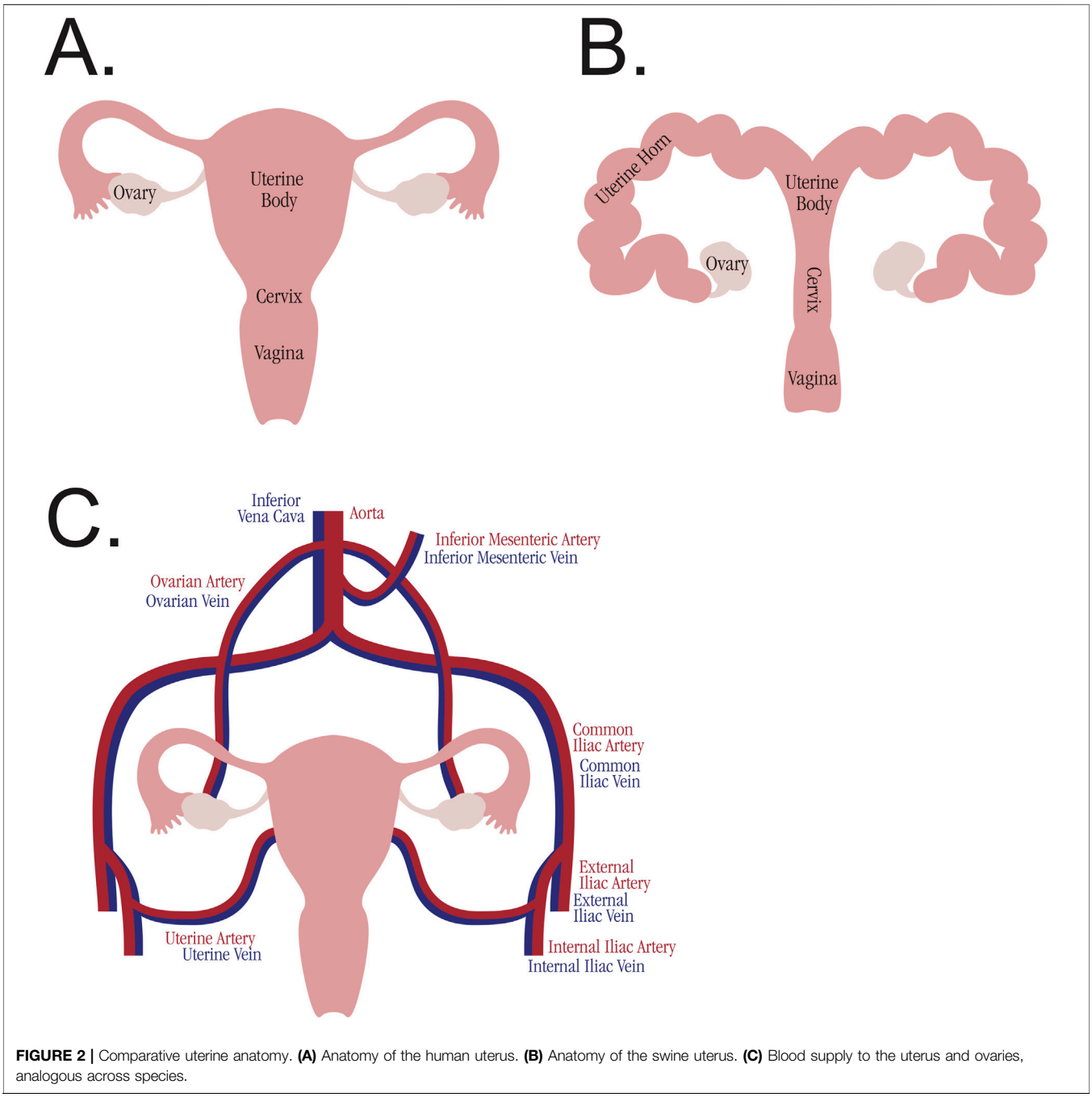

FIGURE 2 | Comparative uterine anatomy. **(A)** Anatomy of the human uterus. **(B)** Anatomy of the swine uterus. **(C)** Blood supply to the uterus and ovaries, analogous across species.

recent studies on uterine transplant preservation analyzed hypothermic machine perfusion (HMP) (4 ˚C) [53, 54, 56], and a fourth recent study on preservation analyzed sub-normothermic machine perfusion (SNMP) (20 ˚C) [55].

Flow and pressure varied greatly among studies that reported these values. These studies encompass perfusion of uteri from both humans and a variety of large animal models, thereby representing a wide range of uterine sizes. However, many studies (16 studies) employed normotensive or near-normotensive pressures (approximately 80–120 mmHg). Three recent studies [54–56], all in swine and all focused on transplant preservation, utilized much lower pressures (15–35 mmHg), aiming to mimic the low pressures employed in pancreas machine perfusion.

Graft Monitoring

In addition to flow, pressure, and temperature monitoring, there are multiple methods for assessing the uterine graft during and after machine perfusion. The majority of studies (24 studies) collected perfusate samples for chemistry and gas analysis,

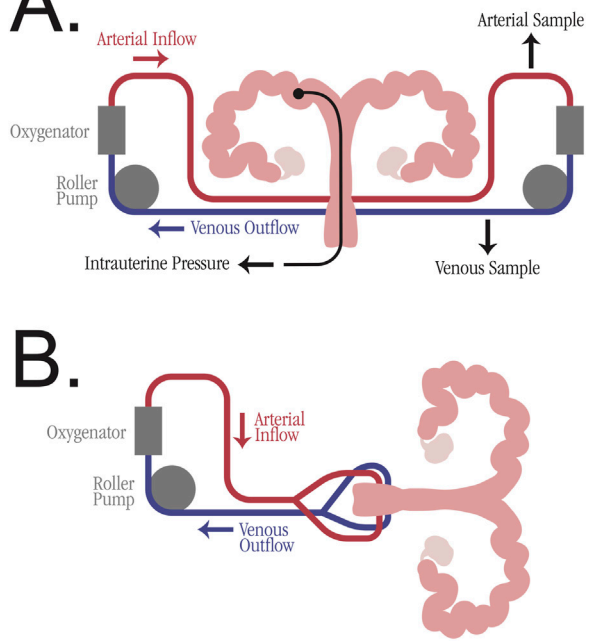

FIGURE 3 | Simplified perfusion machine diagrams for uterus machine perfusion. **(A)** Individual arteriovenous circulation model with two roller pumps and oxygenator. Potential sampling venues are marked, including arterial perfusate sample, venous perfusate sample, and intrauterine pressure sample. **(B)** Mixed arteriovenous circulation model with one roller pump and a Y-connector for division of perfusate into bilateral uterine arteries.

looking at changes in pH, pCO_2, pO_2, bicarbonate, potassium, and lactate over time. Many studies calculated change in uterine weight to assess edema during perfusion. The structural integrity of the uterus was assessed through various methods, including uterine biopsy, macroscopic appearance of the graft, and post-perfusion angiography. Multiple studies also utilized methods to assess the functional status of the organ, most commonly with the measurement of intrauterine pressure, but also through electromyography of the uterine muscle. Intrauterine pressure catheters allowed for the measurement and calculation of uterine contractions, many of which were induced artificially by the addition of oxytocin or prostaglandins.

DISCUSSION

Surgical Model

The uterus poses unique challenges in the implementation of successful EVMP, especially in preclinical animal models. While the swine uterus was the most common animal model utilized, the anatomy is not identical to humans (see **Figure 2**). Furthermore, animal size and age both influence the uterine graft size and therefore the caliber of the arteries cannulated. Studies utilizing larger animals such as cows, or animals which had previously given birth, reported cannulating the uterine arteries with 14G or 16G catheters. Other studies which used 6 to 18-month-old swine reported uterine artery cannulation with catheters as small as 24G. Swine do not typically start to sexually mature until at least 7–8 months of age [58], so the use of younger swine further limits the uterine size. The one study to utilize a small animal model cannulated the aorta of the rabbit, presumably due to the uterine arteries being too small to cannulate. Even if cannulated, small-caliber arteries may not be amenable to successful anastomosis during subsequent transplantation, especially with the multiple vessel anastomoses required for uterine transplant. Therefore, animal size and age should be taken into serious consideration when choosing a model species.

One method for circumventing the surgical challenge of small-caliber arteries and multiple transplant anastomoses is to remove the uterus *en bloc* and cannulate via the aorta, which is described in three recent studies [53, 54, 56]. This technique has been previously described in preclinical uterine transplant models [58, 59]. In addition to reducing the anastomosis and cannulation site to a single large-caliber artery, this technique also incorporates the bilateral ovarian arteries and veins, which are often excluded from uterine EVMP models. However, this technique is surgically challenging, requiring the skeletonization of the aorta and its bifurcation, the inferior vena cava (IVC) and bifurcation, and the bilateral iliac vessels. All non-utero-ovarian branches from the infrarenal aorta, infrarenal IVC, and bilateral internal iliac vessels must be identified and ligated. The rectum or sigmoid colon must be transected in order to remove the uterine blood supply *en bloc*. The studies utilizing this model flushed the uterus with cold preservation solution retrograde through an external iliac artery (while clamping the infrarenal aorta), prior to definitive dissection of the uterine vessels. The reason for this is twofold: to minimize warm ischemia time during a lengthy dissection, and to mimic human deceased donor uterine procurements, in which the uterus is removed after all other essential organs are procured. Overall, this method for uterine procurement can be beneficial, especially if working with a smaller or younger animal model, but it requires an experienced surgical team and complex anatomical knowledge. This method is also limited to being performed as a terminal procedure and allotransplant model, preventing the utilization of an autotransplant model.

Optimal Perfusion Protocol

Given the breadth of variables involved in EVMP, it is difficult to devise an optimal perfusion protocol. Among VCA EVMP, there is no consensus on temperature or perfusate composition, although multiple studies have shown its benefit when compared to SCS [34, 60]. However, synthesis of the reviewed studies can identify some best practices for implementing EVMP in a uterine graft. The use of two perfusion pumps with individual pressure and flow adjustments is preferable to a single pump with a Y-connector (see **Figure 3**). This dual-pump system prevents unequal flow in the bilateral arteries due to variable pressure gradients [55]. In addition to oxygenation with carbogen, a perfusion medium should be prepared containing an organ preservation solution. While some studies added autologous whole blood to the perfusion medium, this may be impractical

in clinical translation for a multi-organ deceased donor procurement.

The goal perfusion pressure varied between studies. The majority of large animal non-uterine VCA perfusions utilize normotensive pressures (60–80 mmHg) [34, 60], and many of the reviewed uterine studies reported similar goal pressures. However, three recent swine studies [54–56] utilized lower pressures (15–35 mmHg), citing the small caliber of the vessels and modeling the protocol after pancreas machine perfusion. Further research is needed to determine the optimal perfusion pressure, which likely will depend on animal size and vessel caliber.

As in solid organ EVMP, there is no consensus for optimal perfusion temperature in non-uterine VCA EVMP [15, 34, 60]. The articles reviewed in this paper predominantly utilize NMP, as many are using EVMP to model physiologic conditions rather than as a preservation method. Additional research into uterine HMP and SNMP is required to determine if lower temperatures are beneficial for uterine graft preservation.

Advantages and Limitations of *Ex-Vivo* Machine Perfusion in Uterus Transplantation

EVMP offers several potential advantages over static cold storage in the context of uterus transplantation. First, it may provide prolonged preservation times beyond those available through cold storage [61]. EVMP is able to continuously monitor perfusion parameters, such as flow, pressure, and metabolic activity, which may provide valuable insight into the viability of grafts prior to transplantation [61, 62]. Furthermore, it provides a therapeutic platform that helps to attenuate ischemia-reperfusion injury by providing oxygenated perfusate and targeted pharmacological or immunomodulatory interventions during preservation [62]. By enabling real-time evaluation of perfusion dynamics, EVMP may support viability testing and help identify uterine grafts with the greatest likelihood of successful transplantation.

Although EVMP has demonstrated promising results for solid organ preservation, the supporting evidence for its use in uterus transplantation remains preliminary because most studies have been conducted in animal models with limited human experience; therefore, its benefits for uterine preservation have not yet been conclusively determined. Perfusion systems, on the other hand, are expensive, technically complex, and require specialized knowledge [63]. In addition, perfusion itself may introduce risks, such as mechanical injury to delicate vascular endothelium or oxidative stress due to inadequate oxygenation [64].

Future Applications

As a whole, EVMP has the potential to not only prolong storage of uterine grafts, but also to optimize the graft itself. In solid organs, EVMP has been shown to recondition non-acceptable organs to be successfully transplanted [65, 66], thereby increasing organ availability and expanding the donor pool. The potential for extended storage times, organ optimization, and even immune engineering make EVMP a promising future technology for the practice of uterus transplantation.

Limitations and Suggestions for Future Research

This review is presented with the acknowledgement of several limitations. The literature search was conducted under the assumption that all relevant articles would be identifiable by the designated search terms and the databases utilized. Additionally, the review excluded abstracts, conference presentations, and unpublished data. There is a possibility that significant and noteworthy research on uterine EVMP was not included in the literature review, which might have allowed further insight into this topic.

Many of the articles discussed in this paper were published over 10 years ago. These studies did not have access to the most up-to-date protocols or designs of EVMP, especially as this is a rapidly-evolving technology. Therefore, the methods discussed in these articles may be outdated and not applicable to modern uterine transplantation practices. Only four articles, all published within the past 6 years, looked at EVMP as a method for transplant preservation. This small sample size makes it difficult to generalize and translate the studies into clinical practice. More studies on EVMP as a preservation method, especially HMP and SNMP, are needed to further research on this topic.

Despite its potential benefits, questions remain regarding the definitive effects of EVMP on uterus transplantation. In contrast to all other organs, uterine transplants are temporary, with hysterectomies performed after the birth of one or two children. Therefore, the improved long-term graft function associated with EVMP may be of lesser significance for the uterus. Additionally, no studies discussed in this paper are able to model or assess the true functionality of the uterus: embryo implantation and the ability to carry a pregnancy to term. Myometrial function is not analogous to endometrial function, and without adequate modeling of the functionality of the endometrium, no definitive conclusions can be made regarding the benefits of EVMP. Future preclinical studies involving embryo implantation and fetal development are necessary to determine the significance of EVMP for uterine transplant.

CONCLUSION

Ex-vivo machine perfusion is a versatile modality with the potential to preserve and optimize uterine grafts prior to transplantation. While many of the studies on uterine EVMP have been unrelated to preservation or transplantation, historical protocols can be used to inform future perfusions, in terms of surgical technique, perfusion machine design, perfusate composition, and graft monitoring. Further preclinical studies are needed to determine optimal perfusion protocols, to model endometrial function, and to definitively show a benefit to EVMP as compared to the current standard of SCS.

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ED study conceptualization, manuscript writing, literature review, data analysis. SK manuscript writing, literature review, manuscript review. AL literature review, manuscript review. NL literature review, manuscript review. LJ literature review, manuscript review. BO study conceptualization, literature review, manuscript review. GB study conceptualization, literature review, manuscript review. All authors contributed to the article and approved the submitted version.

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Trends in Liver Transplantation for Acute Liver Failure in a Spanish Multicenter Cohort

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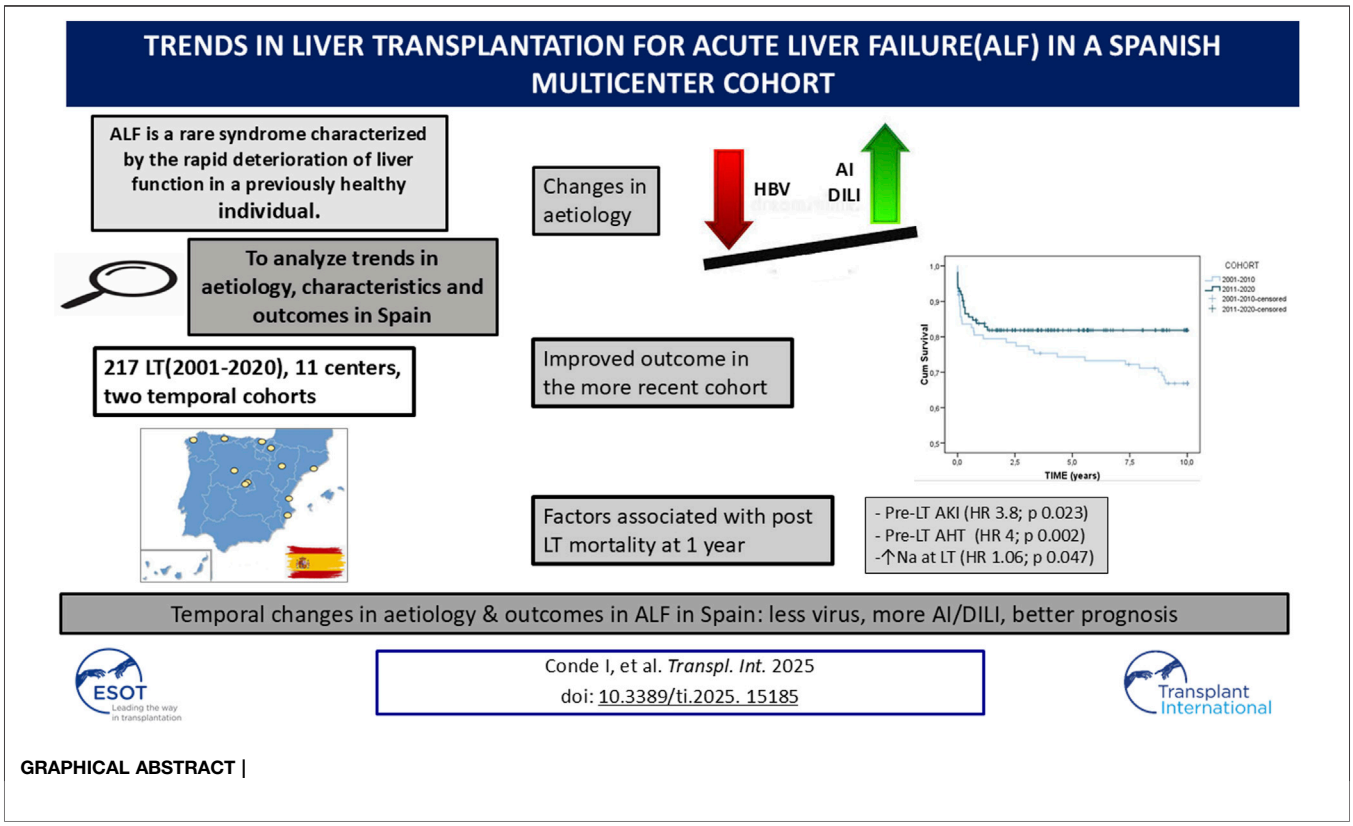
Background and Aims: Acute liver failure (ALF) is a rare and severe condition with high mortality. Liver transplantation (LT) has improved patient outcomes. This study analysed trends in aetiology, characteristics, and outcomes of ALF patients undergoing LT in Spain.

Methods: We retrospectively reviewed 217 adult ALF-LT cases from 11 Spanish centers (2001 -2020), divided into two 10-year periods. Clinical, biochemical, and outcome data were collected, and predictors of mortality were identified.

Results: 217 adult ALF-LT patients were included (61.8% women, mean age: 41 years). Common aetiologies were cryptogenic (26.7%), autoimmune (26.3%), and viral (18%), with sex differences. Over time, autoimmune and drug-induced liver injury increased (22.3% vs 29.8% and 13.6% vs 21.1%), with a low prevalence of acetaminophen toxicity, and hepatitis B virus declined (23.3% vs 11.4%). Despite higher infection rates (52.5% vs 66.2%) linked to stronger immunosuppression, respiratory failure (29.1% vs 16.1%), chronic kidney disease (27.1% vs 13.6%), cardiovascular events (10.6% vs 1%), and mortality (37.6% vs 17.9%) decreased. Pre-LT hypertension, pre-LT acute kidney injury, and hypernatremia at LT were independently associated with worse survival. This large multicenter study revealed temporal changes in aetiologies, immunosuppressive treatment, and post-LT complications, with an improvement in outcome.

Keywords: liver transplantation, outcomes, acute liver failure, aetiology, sex differences



GRAPHICAL ABSTRACT |

INTRODUCTION

Acute liver failure (ALF) is a rare syndrome characterized by the rapid deterioration of liver function in a previously healthy individual. Although its prevalence is low, the exact incidence remains poorly defined. A retrospective Spanish study estimated an incidence of 1.4 cases per million population [1], while an American study reported 5.5 cases per million population [2], both published in 2007. Despite its infrequency, ALF is associated with significant morbidity and mortality, accounting for 6% of deaths related to liver disease [3].

ALF is highly heterogeneous in terms of aetiology, clinical presentation, and progression. These variations underscore the knowledge gaps in the field and the lack of large, high-quality studies. The natural history of ALF is also variable. In 10%–20% of patients, the condition is reversible, and liver regeneration occurs, leading to full recovery. However, in the remaining patients, complications such as cerebral oedema, renal failure, sepsis, and multiorgan failure are common, resulting in high mortality. The introduction of liver transplantation (LT) has significantly improved prognosis, with one-year survival rates approaching 90% in recent studies [4]. According to data from the Spanish National Transplant Organization (ONT), between 1984 and 2022, ALF accounted for 4.9% of LT indications, rising to 22% among individuals aged 16–39 years [5].

The aetiology of ALF varies depending on geographical location and age at presentation. Causes include viral hepatitis, drug overdose, idiosyncratic drug reactions, toxic ingestion, autoimmune diseases, and metabolic disorders [6, 7]. Descriptive studies have shown that in the United Kingdom and the United States, acetaminophen overdose is the most common cause [8, 9], while in highly endemic regions like India, acute hepatitis E is the leading cause [10]. In Germany, hepatotoxicity unrelated to acetaminophen was the most frequent aetiology [11]. In Spain, the most common cause of ALF was acute hepatitis due to hepatitis B virus (HBV), followed by drug and toxic substance ingestion. In more than 30% of cases, the cause of ALF could not be determined [1, 12]. Additionally, the incidence of drug-induced liver injury (DILI) has risen globally, likely due to the introduction of new pharmaceuticals, increased life expectancy, polypharmacy, and the widespread use of herbal products. DILI has become the leading cause of fulminant hepatic failure in both the United States and Europe [8, 13].

Sex-based differences have been observed in the aetiology of liver disease leading to LT, with several studies documenting sex inequities in access to LT [14, 15]. Specifically, women are at higher risk of developing DILI, and they tend to experience more severe outcomes and increased susceptibility to hepatotoxicity-related ALF [16, 17]. A recent article showed sex disparities in waitlisting and LT for ALF [18].

There are few studies on ALF in Spain, and none have been conducted in the past decade. Previous studies include a multicentre retrospective analysis of cases from 1992 to 2000 and a unicentric prospective study covering 2000–2010 [1, 12]. Despite Spain having one of the highest

rates of LT *per capita*, the outcomes of LT in ALF patients have not been specifically analyzed.

This project aims to fill this gap by evaluating the recent indications, management, and outcomes of LT in ALF patients in Spain. Data were gathered from 11 large, renowned LT centers, that performed a total of over 400 LTs annually as of 2020, according to the Spanish Registry of Liver Transplantation (RETH). [5]. Our primary objectives were to describe: (i) the evolution of indications for LT in ALF, (ii) the changes over time in ALF-LT outcome, and (iii) the predictors of early post-LT mortality at 1 year. Our secondary objective was to highlight sex-based differences in ALF-LT.

MATERIALS AND METHODS

Study Design

We conducted a retrospective Spanish multicenter study involving 11 centers with extensive experience in LT. These centers accounted for 43% of the total number of LTs performed in Spain in 2020 [5].

Urgent LT performed in patients >18 years due to ALF between 2001–2020 were included. Criteria for ALF were a severe acute liver injury lasting less than 26 weeks, with jaundice, liver synthetic failure (INR ≥1.5 or prothrombin rate <40%), and hepatic encephalopathy (HE) in a patient without known chronic liver disease.

Exclusion criteria comprised patients under 18 years old and patients with pre-existing liver disease. The acute manifestation of certain chronic liver diseases (Wilson's disease, HBV reactivation in a non-cirrhotic liver, acute Budd-Chiari, and autoimmune hepatitis) was included as an exception. Patients with prior LT and acute liver injury due to primary graft nonfunction or other causes were excluded.

Data were acquired from each LT center through a review of medical records.

Indications of LT in ALF and Legal Situation in Spain

In Spain, when a patient experiences ALF, the criteria to indicate an urgent LT are based on either fulfilling King`s College Criteria (KCC) [19], Clichy criteria [20] or presence of HE. A national urgent code is activated, enabling the allocation of the first suitable organ available within the country to the ALF patient. The median time until a liver is offered is approximately 40 h, and around 50% of patients receive a LT within 24 h [21].

Ethical Statement

This study was approved by the Ethics Committee of Clinical Research of La Fe Universitari and Politécnic Hospital (ref number: 2021-096-1) and was conducted according to the standards of Good Clinical Practice, adhering to the ethical principles outlined in the 1975 Declaration of Helsinki.

An exemption from the requirement for informed consent was granted due to the retrospective nature of the study. Some patients had been relocated or were no longer reachable during the study period.

To ensure confidentiality, patient information included in the database was anonymized and identified by a numerical code, in compliance with data protection legislation.

Collected Variables

The recorded variables included donor and recipient demographic features, epidemiological information, clinical and biochemical data before and after LT, clinical post-LT outcomes, patient and graft survival and variables associated with mortality.

i. Recipient variables (demographics, co-morbidities and toxics abuse)
ii. Variables pre-LT associated with ALF: aetiology, type of presentation, clinical data, hepatic and extra-hepatic complications, KCC and Clichy criteria, management (antibiotic prophylaxis, N-Acetylcysteine (NAC) and Molecular Adsorbent Recirculating System (MARS)), days of admission until LT and on the waiting list (WL)
iii. Biochemical tests before LT (at admission, on days 3, 7, and the day of LT).
iv. Donor and surgical related-variables
v. Histology of the explanted liver (massive or sub-massive necrosis)
vi. Early post-LT follow-up (1st–3rd month): days in the ICU and total hospitalization days, hepatic and extra-hepatic complications.
vii. Late post-LT follow-up: long term hepatic and extra-hepatic complications.
viii. Immunosuppression
ix. Outcome: re-LT and/or death, and causes.

Operational Definitions

The diagnosis of cryptogenic ALF was reached after excluding any other aetiology through an exhaustive pre-LT differential diagnosis and the explant biopsy. Patients who received a LT in the context of an AI hepatitis fulfilled the criteria for ALF. No evidence of liver cirrhosis was found in the explants. The temporal classification of ALF (hyper acute, acute and sub-acute) was defined according to the interval between the onset of jaundice and the development of hepatic encephalopathy (published by O'Grady JG in 1993) [22].

Regarding pre- and post-LT complications, acute kidney injury (AKI) and chronic kidney disease (CKD) were established following KDIGO criteria [23, 24]. Renal replacement therapy (RRT) included both intermittent haemodialysis and continuous RRT. Infections were confirmed with positive culture or resolution after antibiotic treatment. Respiratory failure was defined as the necessity for mechanical ventilation, rather than in the context of HE. Early graft dysfunction was based on the definition proposed by Olthoff et al. [25], and acute liver allograft rejection was categorized following the Banff classification [26]. Finally, graft steatosis was assessed by biopsy.

TABLE 1 | Clinical characteristics pre-LT.

Variable	N	
Age (years)	217	41 (32–53)
Sex (women)	217	134 (61.8)
Race	217	
Caucasian		181 (83.4)
Other		36 (16.6)
BMI (kg/m^2)	152	25 (21.3–27)
AHT	216	25 (11.6)
Diabetes	216	8 (3.7)
Dyslipidaemia	216	18 (8.3)
Aetiology	217	
HBV		37 (17.1)
Other viruses		9 (5.1)
AI		57 (26.3)
DILI		38 (17.1)
Acetaminophen		9 (4.1)
Cryptogenic		58 (26.7)
Other		17 (7.9)
Clinical presentation	217	
Hyperacute		68 (31.3)
Acute		88 (40.6)
Subacute		59 (27.2)
Encephalopathy	212	
I-II		62 (29.2)
III-IV		150 (70.8)
Ascites	208	89 (42.8)
Respiratory failure (MV)	212	51 (24.1)
Infection	215	30 (14)
GI haemorrhage	216	12 (5.6)
AKI	213	83 (39)
RRT	213	47 (22.1)
Antibiotic prophylaxis	187	137 (73.3)
NAC	215	39 (18.1)
MARS	216	11 (5.1)
Time on waiting list (Days)	208	1 (1–2)
Meet KCC criteria	205	188 (91.7)
Meet clichy criteria	59	33 (55.9)
MELD - LT day	142	25 (19–29)

Data are given as median (IQR) or number (percentage).
Abbreviations: BMI, Body mass index; AHT, Arterial hypertension; HBV, Hepatitis B virus; AI, Autoimmune; DILI, Drug Induced Liver Injury; MV, Mechanical ventilation; GI, Gastrointestinal; AKI, Acute Kidney Injury; RRT, Renal Replacement Therapy; NAC, N-Acetylcysteine; MARS, Molecular Adsorbent Recirculating System; KCC, Kings College Criteria; MELD, Model for End-Stage Liver Disease; LT, Liver Transplant.

Statistical Analysis

A descriptive analysis was conducted for all the studied variables. Continuous variables are described as means or medians with standard deviation (SD) or quartiles 1 (Q1) and 3 (Q3) as appropriate, and qualitative variables as absolute and relative frequencies.

The normal distribution of outcome variables was confirmed using the Kolmogorov-Smirnov test. Chi-square and Fisher's exact test were used to assess the degree of association between categorical variables, Student's t and ANOVA model to compare quantitative variables, and non-parametric Mann-Whitney and Kruskal-Wallis tests to analyse the distribution of at least ordinal variables in 2 or more independent groups.

Graft and patient survival analyses were performed with Kaplan-Meier survival curves.

Variables associated with mortality and re-transplantation were determined using univariate and multivariate Cox regression tests and expressed by hazard ratio (HR) and 95% confidence interval (CI). The initial multivariate model included the variables with a p value < 0.10 in the univariate analysis. Variables with a p value above this threshold could be included if considered clinically relevant by the investigators.

A p-value of <0.05 was considered significant for all analyses.

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

RESULTS

Baseline Features and Management Before LT

A total of 217 adult patients received urgent LT due to ALF between January 2001 and December 2020. Among them, 134 were women (61.8%). The overall median age was 41 years old (IQR 32–53). Baseline clinical variables and pre-LT management are shown in **Table 1**, and analytical data on the LT Day in **Supplementary Table 1**.

A small number of patients had concomitant diseases or toxic habits. The prevalence of arterial hypertension (AHT), diabetes and dyslipidaemia were 11.6%, 3.7% and 8.3%, respectively. Regarding toxic substances, the smoking rate was 27.8%, 15% consumed alcohol regularly and 7.5% were drug users. A concomitant autoimmune non-liver disease was present in 14.4%, and 12.1% reported a psychiatric disease.

The predominant aetiologies of ALF were cryptogenic (26.7%) and autoimmune (26.3%). Viral aetiologies accounted for less than 25%, with hepatitis B (HBV) being the most common (17.1%). Drug-induced liver injury (DILI) represented 17% of LT indications. Only 4.1% of patients who underwent LT due to DILI-ALF did so in the context of acetaminophen intake.

In terms of temporality, most cases were acute (40.6%) and hyperacute (31.3%). The most frequent complications were ascites (42.8%) and AKI (39%), while infections and haemorrhagic complications were uncommon. RRT was used in 22.1%. The median MELD (Model for end-stage Liver Disease) score on the day of LT was 25.

Before LT, antibiotic prophylaxis was widely implemented (73.3%). The use of NAC and especially MARS had little relevance in our cohort of patients.

All the patients were transplanted with a national urgent priority, resulting in a median time on the WL of only 1 day (IQR: 1–2 days).

Compliance with the KCC and Clichy criteria was 91.7% and 55.9%, respectively. Of note, only a limited number of patients (n = 59) had Factor V determination performed, especially during the early years.

Evolution of Indications of LT in ALF

The cohort was subdivided into two 10-year periods (2001–2010 and 2011–2020). The number of ALF-LT remained stable overtime: 113 patients (3.6%) in 2001–2010 and 114 patients (3.1%) in 2011–2020.

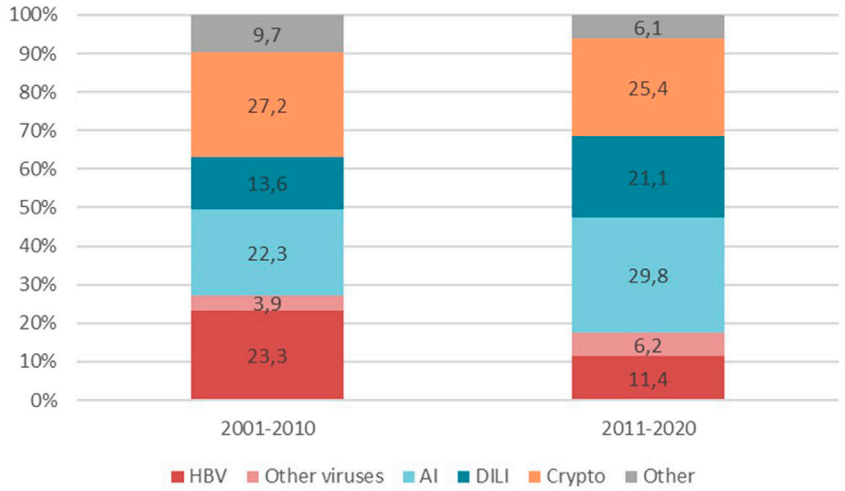


FIGURE 1 | Evolution of ALF aetiologies in LT candidates Differences in ALF aetiologies between the two time periods 2001–2010 and 2011–2020 (p-value 0.115). Abbreviations: HBV, Hepatitis B virus; AI, Autoimmune; DILI, Drug Induced Liver Injury.

Cryptogenic and autoimmune were the most common aetiologies of ALF-LT overall. Autoimmune (22.3% vs. 29.8%) and DILI (13.6% vs. 21.1%) aetiologies increased with time while HBV showed a decline (23.3% vs. 11.4%), although without reaching statistical significance (p 0.115). Despite the increase in DILI, Acetaminophen toxicity was not particularly prevalent and even decreased with time (8.7% and 3.5%). Cryptogenic ALF remained stable. Other viruses, such as HAV (1% and 1.8%) or HEV (1% and 0.9%) were extremely uncommon in both periods (**Figure 1**).

Changes Over Time in ALF-LT Characteristics and Outcomes

We first conducted an analysis of LT characteristics and post-LT evolution of the whole cohort (**Supplementary Table 2**). Most grafts were total (98.6%), with AB0 compatibility (isogroup 62.5% and compatible 37%), and showed minimal steatosis (<10% in 91.3% of grafts) and most donors were brain dead. In the early post-LT period, the main complications were infections (60.7%) and AKI (61%), while in the late post-LT period, AHT (30.3%), biliary complications (27.4%) and CKD (19.7%) predominated. The mortality rate was 27.2%, with infections (41.5%) and liver-related complications (20.8%) being the leading causes of death. The survival rates at 1, 5, and 10 years were 82%, 78% and 72%, respectively (**Supplementary Figure 1**).

Regarding differences over time in pre-LT characteristics and management (**Table 2**), there was a trend towards an increase of women (55.3% vs. 67.3%) approaching statistical significance (p 0.065) and a decline in the rate of Caucasian race (90.3% vs. 77.2%; p 0.001). Alcohol consumption was reported less frequently in recent years (21.6% vs. 8.9%; p 0.01). Antibiotic prophylaxis and, notably, the use of NAC significantly increased (65.4% vs. 78.9%; p 0.04% and 4% vs. 30.1%; $p < 0.001$).

We also examined the changes in post-transplant management and outcome between the first and second decade (**Table 2**). There was a higher use of triple immunosuppression (61.9%–79.1%; $p < 0.001$) and basiliximab (34.1%–67%; p 0.002) in the recent cohort. Some differences were found in post-LT complications. Infection rates increased overtime (52.5% vs. 66.2%; p 0.02) while respiratory insufficiency decreased (29.1% vs. 16.1%; p 0.022). In the long-term, there was a reduction in CKD (27.1% vs. 13.6%; p 0.022), cardiovascular events (10.6% vs. 1%; p 0.003) and mortality (37.6% vs. 17.9%; p 0.001) in recent years. One year mortality improved with time, not reaching statistical significance (19% in the first cohort vs. 16.1% in the latter, p 0.575). Evolution of patient survival rates between the two time periods is shown in **Figure 2**. (80.5%, 74% and 67% vs 84%, 82% and 82% at 1, 5, and 10 years, respectively).

Given the observed increase in AI/DILI aetiologies, we implemented an analysis to determine whether there were differences in management and outcome when comparing AI/DILI ALF group to the rest of aetiologies (**Supplementary Table 4**). A total of 95 patients were transplanted in the context of AI or DILI ALF, and 122 patients had other ALF aetiologies. Subacute presentations were more prevalent in AI/DILI aetiologies (34.7% vs. 21.7%; p 0.044), with a different trend for hyperacute presentations. AKI was significantly less common AI/DILI subgroup (30.1% vs. 45.8%; p 0.024). In terms of post-LT outcome, differences were observed in the IS management (higher use of triple IS, p 0.034) and in early complications (lower requirement for RRT, p 0.015; higher incidence of infections, with a lower rate of bacterial infections, p 0.017; and a decrease in bleeding and CV complications, p 0.020 and p 0.021). A significant finding in late post-LT outcome was the lower rate of *de novo* tumours in AI/DILI aetiologies (3.6% vs. 10.6%, p 0.034), as well as lower mortality at 1-year post-LT (12% vs. 21.7%, approaching statistical significance: p 0.065).

TABLE 2 | Differences over time in ALF-LT.

Variable	2001–2010		2011–2020		p-value
	n = 103		n = 114		
	n		n		
Clinical characteristics and management pre-LT					
Sex (women)	103	57 (55.3)	114	77 (67.5)	0.065
Race	103		114		**0.001**
Caucasian		93 (90.3)		68 (77.2)	
Other		10 (9.7)		26 (22.8)	
Alcohol	102	22 (21.6)	112	10 (8.9)	**0.010**
Aetiology	103		114		0.115
HBV		24 (23.3)		13 (11.4)	
Other viruses		4 (3.9)		8 (6.2)	
AI		23 (22.3)		34 (29.8)	
DILI		14 (13.6)		24 (21.1)	
Acetaminophen		5 (8.7)		4 (3.5)	
Cryptogenic		28 (27.2)		29 (25.4)	
Other		10 (9.7)		7 (6.1)	
Antibiotic prophylaxis	78	51 (65.4)	109	86 (78.9)	**0.040**
NAC	102	5 (4.0)	113	34 (30.1)	**<0.001**
MARS	102	8 (7.8)	114	3 (2.6)	0.082
Donor					
Steatosis	82		80		**0.037**
<10%		78 (95.1)		70 (87.5)	
10%–30%		2 (2.4)		9 (11.3)	
>30%		2 (2.4)		1 (1.3)	
Immunosuppression					
Induction IS	97		110		**<0.001**
Triple IS		60 (61.9)		87 (79.1)	
Double IS		33 (34)		12 (10.9)	
Other		4 (4.1)		11 (10)	
Basiliximab	82	28 (34.1)	107	61 (67)	**0.002**
Early post-LT complications					
Resuscitation unit (days)	99	6 (4–11)	113	5 (3–9)	0.077
Infection	101	53 (52.5)	110	75 (68.2)	**0.020**
Respiratory insufficiency	103	30 (29.1)	112	18 (16.1)	**0.022**
Late post-LT complications					
CKD	85	23 (27.1)	103	14 (13.6)	**0.021**
CV event	85	9 (10.6)	103	1 (1)	**0.003**
Death	101	38 (37.6)	112	20 (17.9)	**0.001**
Death 1yr		19 (19)		18 (16.1)	**0.575**

Data are given as median (IQR) or number (percentage). The bold values indicate variables that are statistically significant (p < 0.05).
Abbreviations: HBV, Hepatitis B virus; AI, Autoimmune; DILI, Drug Induced Liver Injury; NAC, N-Acetylcysteine; MARS, Molecular Adsorbent Recirculating System; IS, Immunosuppression; CKD, Chronic Kidney Disease; CV, Cardiovascular.

Factors Associated With Post-LT Mortality

Given that most deaths occurred early post-LT, we determined variables independently associated with mortality at 1-year post-LT (**Table 3**).

Significant variables related to patient's baseline characteristics, clinical presentation, pre-LT complications and laboratory data at LT predicted poor outcomes in the univariate logistic analysis. Obese patients were at a significantly higher risk of death than those with normal BMI (HR = 3.33; p = 0.037). AHT and dyslipidaemia significantly influenced survival time (HR = 2.75; p = 0.008 and HR = 2.75; p = 0.016). Acute presentation was related to lower mortality (HR = 0.37; p = 0.017). Among the complications detected prior to transplantation, AKI, respiratory insufficiency, infections and vasopressor use significantly worsened the prognosis (p < 0.05). Finally, an increase in creatinine, sodium, phosphorus, ammonium, and lactate levels and a decrease in Factor V were independently associated with death (p < 0.05). The remaining pre-LT variables were not statistically significant.

Multivariable logistic regression analysis was performed on selected baseline variables from the univariate analyses, including independent predictors with clinical relevance, that were previously identified as significant (p < 0.05) and that were available in a relevant number of patients. Obesity, AHT, AKI, infections and sodium level on LT-day were entered into the multivariable model, and AHT, AKI and sodium remained as independent risk factors (HR 4.002 p 0.022, HR 3.819 p 0.023 and HR 1.065 p 0.047, respectively).

Differences According to Sex in ALF-LT

There was a trend towards an increase of women over time (55.3% vs. 67.5%), although this difference was not statistically significant (p 0.065) (**Table 2**).

Autoimmune and cryptogenic aetiologies were more frequent in women (31% vs. 19% and 31% vs. 20%) while HBV was more common in men (29% vs. 10%) (p 0.007).

Before LT, men had a higher history of alcohol, tobacco and drug consumption (p < 0.05). AKI was more frequently observed in men (52% vs. 29%). Renal function, ALT levels, platelets count and MELD score pre-LT were worse in men (p < 0.05). No significant differences were found in other pre-LT characteristics.

Early post-LT complications such as AKI (73% vs. 53%) and haemorrhage (26% vs. 14%) were more frequent in men, while rejection was more common in women (11% vs. 22.5%) (p < 0.05). Later complications including AHT (36% vs. 27%), dyslipidaemia (25% vs. 11%), CKD (24% vs. 17%) and biliary complications (32% vs. 21%) were all more frequent in men but without reaching statistical significance. Causes of death, survival and re-LT were similar in both groups (**Supplementary Table 3**).

DISCUSSION

This study includes a large multicenter cohort of patients, allowing for an accurate overview of the evolution and outcomes of LT for ALF in Spain from 2001 to 2020. The only prior Spanish multicenter study, published in 2007, evaluated ALF patients between 1992 and 2000 [1]. Our analysis covers a more recent period (2001–2020), and provides an update on the evolution of this condition in patients who eventually required LT. Additionally, there are two older European studies: a German multicentre study that included ALF patients diagnosed in 2008–2009 [11], and a second study that assessed patients included in the European Liver Transplant Registry (ELTR) database between 1988 and 2009 [27]. Although there are discrepancies in ALF epidemiology and management across Europe, our study may serve as a current benchmark for the region.

Our study highlights differences in the aetiology of ALF compared to other regions. The most frequent aetiologies in our cohort were cryptogenic, autoimmune, and viral, with a notable shift towards autoimmune and DILI aetiologies and a

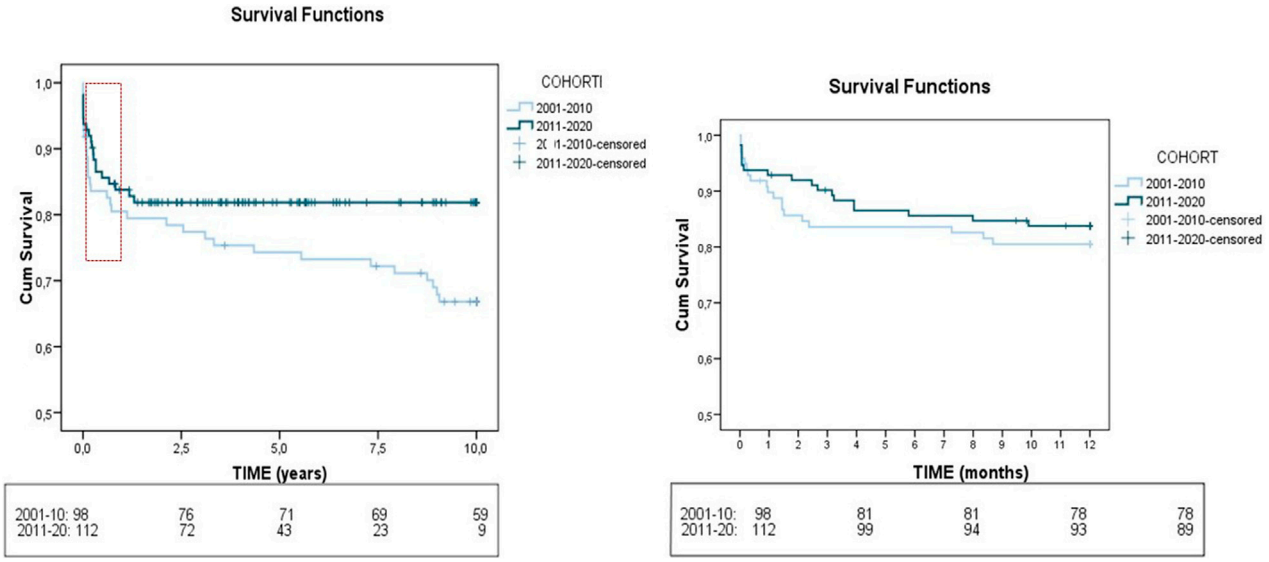


FIGURE 2 | Evolution of patient survival rates between the two time periods 2001–2010 and 2011–2020. The Kaplan-Meier plot illustrates the differences in post-LT survival rates between the 103 ALF patients who underwent LT in 2001–2010 versus 114 patients who underwent LT in 2011–2020.

TABLE 3 | Factors associated with post-LT mortality.

Variable	N	Univariate analysis				Multivariate analysis			
		HR	95% CI		p-value	HR	95% CI		p-value
Aetiology AI-DILI	217	0.52	0.26	1.06	0.072				
Obesity	152	3.33	1.07	10.3	**0.037**	2.693	0.972	7.456	0.057
AHT	216	2.75	1.30	5.84	**0.008**	4.002	1.222	13.106	**0.022**
Dyslipidaemia	216	2.75	1.21	6.26	**0.016**				
Acute presentation	217	0.37	0.17	0.84	**0.017**				
AKI pre-LT	213	2.83	1.46	5.5	**0.002**	3.819	1.199	12.159	**0.023**
Respiratory insuff.	212	1.97	1.01	3.82	**0.046**				
Infections	215	2.41	1.16	4.97	**0.018**	3.120	0.872	11.162	0.080
Vasopressors	150	2.14	1.02	4.5	**0.044**				
Na - LT day	189	1.087	1.027	1.149	**0.004**	1.065	1.001	1.133	**0.047**
Cr - LT day	193	1.253	1.013	1.550	**0.038**				
P - LT day	76	1.307	1.044	1.636	**0.019**				
Ammonium - LT day	70	1.007	1.001	1.013	**0.021**				
Lactate - LT day	69	1.119	1.008	1.242	**0.036**				
Factor V - LT day	37	0.893	0.803	0.993	**0.037**				

Univariate and multivariate analysis. Results of Cox multiple regression models, adjusted hazard ratio (HR), 95%CI and p-value. The bold values indicate variables that are statistically significant ($p < 0.05$).

Abbreviations: AI, Autoimmune; DILI, Drug Induced Liver Injury; AHT, Arterial Hypertension; LT, Liver Transplant; AKI, Acute Kidney Injury; Na, Sodium; Cr, Creatinine; P, Phosphorus.

decreased relevance of HBV in recent years. While DILI is the most common cause in Anglo-Saxon countries, viral hepatitis remains significant in developing countries. Notably, DILI was less common in our study compared to Western countries, similar to previous Spanish data published by Escorsell in 2007 [1], but its frequency has increased over time. Another significant distinction is that acetaminophen toxicity was uncommon in our cohort and has even decreased in recent years, probably due to the implementation of NAC protocols and the fact that it is less accessible to the general population than in other countries. International cohort studies, such as one from the US, have reported similar trends, with an increase in autoimmune cases and a decrease in HBV and DILI over time [24, 28].

Some changes in the outcome of ALF-LT in recent years have been documented in our cohort. We have observed a decrease in certain short- and long-term post-LT complications: respiratory insufficiency, CKD, cardiovascular events and even mortality. The higher use of monoclonal antibodies in the induction IS facilitates the reduction of the CNI dose from the moment of transplantation, and possibly justifies the downward trend in CKD. Survival rates were consistent with data from other series

reaching 82%, 78% and 72% at 1, 5 and 10 years after LT, respectively. Recent studies have reported lower mortality in recent years [1, 4, 25], with improved peri-transplant management in intensive care units being a key factor. In our study, we also detected a trend toward a decrease in 1-year post-LT mortality. However, mortality remains high in the early post-transplant period, especially during the first 3 months (13%). One notable finding is the increase in infections in the early post-LT period (although without impact on survival), which may be explained by the use of more potent immunosuppression regimes in recent years.

When compared to other aetiologies, distinct clinical characteristics were observed in the AI-DILI group. Notably, the subacute presentation was more frequent, likely associated with the early use of corticosteroids. Post-transplant, patients with AI-DILI were more frequently maintained on a triple IS regimen, and fungal and viral infections were more commonly observed. These findings may be related to pre-transplant immunosuppressive therapy, including corticosteroids, administered in an attempt to avoid LT. A significant finding was the lower rate of *de novo* tumours, despite the higher IS, and mortality in AI-DILI aetiologies. This may be related to the higher prevalence of women in this subgroup, the lower rate of toxic habits among them, and possibly the shorter follow up of this group of patients.

Several pre-transplant parameters were associated with 1-year mortality. The significant predictors of post-transplant survival in the univariate were baseline features such as obesity, AHT and dyslipidaemia, pre-transplant clinical complications (AKI, respiratory insufficiency, infections and vasopressors need), and laboratory variables (sodium, creatinine, phosphorus, ammonium, lactate and factor V). These variables are consistent with previously published prognostic factors linked to poor survival in ALF [29–31]. Serum sodium levels showed an inverse relationship with post-LT survival. Classically studies linked pretransplant hyponatremia with increased post-LT mortality, recent large-scale analyses have suggested that hypernatremia is associated with worse outcome in ALF [32]. Other variables reported in previous studies, such as recipient and donor age, ABO incompatibility and intracranial pressure (ICP) monitoring pre-LT [4, 27] did not reach statistical significance in our analysis. The use of high-quality donors (young, compatible, with minimal steatosis) may explain some of these results. We have no data on ICP; however, HE, and more specifically grade IV HE, was not statistically significant in the univariate analysis.

Regarding potential sex differences, we observed an increasing rate of women undergoing LT for ALF across years and a higher number of ALF due to autoimmune hepatitis and cryptogenic liver disease. The increasing prevalence of autoimmune diseases among women may explain this [33]. Men presented in worse clinical condition at the time of LT, leading to a higher rate of post-LT complications, except for rejection, which was more common in women. Long-term outcomes, however, were similar for both sexes, with no differences in mortality. This data is particularly noteworthy in contrast to previous series which showed sex differences in pre-LT disease course in favour of men [18, 34].

Some limitations of the study should be mentioned. The retrospective design of the study may have led to partial loss of information, especially in the early years. Inclusion of only 11 out of 26 national LT centers may potentially bias some of the results; yet we incorporated the larger centers with more expertise. Potential heterogeneity in ALF management and transplantation protocols across centers may result in biases in patient selection and therapeutic decisions. For example, antibiotics, NAC or MARS are not addressed in national protocols. In our centers, NAC was administered in all instances of acetaminophen-induced ALF. In recent years, it was also used in select cases of non-acetaminophen ALF during the early stages of HE, in accordance with published potential benefit in this clinical scenario [35]. Antibiotic prophylaxis was not universally implemented, but was consistently prescribed at the slightest suspicion of infection following clinical practice guidelines [36]. The use of MARS was minimal, probably due to the low availability of this technique in our country, the short waiting time, and the lack of evidence supporting its efficacy [37]. Finally, data from ALF patients who have not undergone LT are not available in the majority of centers. The lack of these patients may introduce a selection bias. We plan to perform a prospective study to assess this very relevant piece of information to understand the process of patient referral and LT selection.

In conclusion, with data based on 11 large reference LT centers, this study is a picture of LT for ALF in Spain and reflects the trends over time in the last 20 years. The study revealed temporal changes in aetiologies (with an increase in autoimmune and DILI aetiologies, with a marginal relevance of acetaminophen overdose, and a decreased relevance of HBV in recent years), pre-LT management, immunosuppressive treatment, and post-LT complications. Overall, outcomes in this critically ill patient group have improved with increased survival over time. Early post-LT mortality was associated with pre-transplant AHT, AKI and hypernatremia.

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 Comité de Ética de la Investigación con medicamentos del Hospital Universitario y Politécnico La Fe. 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 it is a retrospective study.

AUTHOR CONTRIBUTIONS

IC: Conceptualization, Data acquisition, Formal analysis, Writing – original draft, Writing – review and editing. SM, AB, MS, RM, CA, MG, SL, AO, MR-S, JH, LA, and AF: Data acquisition, Writing – review and editing. MB and VA: Conceptualization, Formal analysis, Writing – review and editing, Supervision. All authors contributed to the article and approved the submitted version.

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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.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.15185/full#supplementary-material

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GLOSSARY

AHT Arterial Hypertension
AI autoimmune
AKI Acute Kidney Injury
RRT Renal Replacement Therapy
ALF Acute Liver Failure
ALT Alanine Aminotransferase
AP Alkaline Phosphatase
AST Aspartate Aminotransferase
AZA Azathioprine
CKD Chronic Kidney Disease
CNI Calcineurin Inhibitor
CV Cardiovascular
DILI Drug Induced Liver Injury
GFR Glomerular Filtration Rate
HAV Hepatitis A Virus
HBV Hepatitis B Virus
HE Hepatic Encephalopathy
HEV Hepatitis E Virus
HR Hazard Ratio
ICU Intensive Care Unit
IQR Interquartile Range
INR International Normalized Ratio
IS Immunosuppression
KCC King's College Criteria
LT Liver Transplantation
MARS Molecular Adsorbent Recirculating System
WL Waiting list
MELD Model for End-Stage Liver Disease
MMF Mycophenolate Mofetil
NAC N-Acetylcysteine
PDN Prednisone
SD Standard Deviation

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LETTER TO THE EDITOR
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Transition From Open to Full Robotic Living Donor Left Liver Graft Procurement for Pediatric Recipients-Experience From a Western Center

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Keywords: living donor liver transplantation, robotic surgery, donor safety, partial liver graft, pediatric liver transplantation

Dear Editors,

Recent recommendations state that robotic living donor partial hepatectomy (R-LDH) does not negatively affect recipient outcomes and provides a higher precision for bile duct dissection [1]. Furthermore, data from a high-volume center for R-LDH show a reduction in donor morbi-mortality compared to the open and laparoscopic approaches [2, 3]. In addition, a worldwide survey from 2023 has shown that the majority of minimally invasive LDH are now performed by a robotic approach (64%) and 41% of the centers performing R-LDH transitioned directly from open to the robotic approach [4]. In light of these recent developments, there is an urgent need to assess the safety of the transition from open to R-LDH in the setting of a low-volume LDH center.

We report all consecutive LDH performed from September 2019 to March 2025 in a high volume tertiary hepatobiliary and liver transplant center from France (>100 liver resections and >100 liver transplantations per year). Of note, all LDH were left grafts allocated to pediatric recipients. The transition from open to R-LDH took place in October 2023 after a 15-year experience with laparoscopic oncological liver surgery and 30 major HPB robotic interventions. Our technique for R-LDH has been previously described [5]. In the open LDH group we performed a supraumbilical midline incision while in the R-LDH group, the graft was extracted by a suprapubic incision. Of note, the technique for parenchymal transection was the same for open and R-LDH and consisted in an irrigated bipolar coagulation without the use of energy devices or CUSA®. The same donor selection criteria were applied to open and robotic LDH. This IDEAL Stage 2a study aims to assess safety of R-LDH in comparison to open-LDH. The primary safety endpoint is the absence of major donor morbidity (CD > II) after 90 postoperative days, based on the Clavien-Dindo Classification (CD). Secondary safety endpoints include graft warm ischemia time defined as the duration from division of the left portal vein to cold flush of the partial graft on the back table, conversion rates, biliary complications and 90-day graft survival. The local ethical review board granted ethical approval of the study.

During the study period, 23 LDHs were performed, with 16 (70%) open LDHs and 7 (30%) robotic LDHs (**Table 1**). The majority of LDHs were G23 (n = 21, 91%) with one G1234MHV in the open-LDH and one G234 in the R-LDH group. The operative duration of robotic-LDH was significantly longer (356 min vs. 243 min, $p = 0.026$) but intraoperative blood loss was further reduced (50 mL vs. 125 mL $p < 0.001$) and no conversion was required. There was no need for

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TABLE 1 | Overall donor characteristics and outcomes between open and robotic approach.

	All LDH (n = 23)	Open LDH (n =16)	Robotic LDH (n = 7)	*p*
Preoperative donor characteristics				
Age, y (IQR)	33 (30.5; 38.5)	36.5 (32; 39)	32 (30.5; 32.5)	ns
BMI, kg/m^2 (IQR)	23 (20.5; 26)	24.5 (20.75; 26.25)	22 (20.5; 22.5)	ns
Operative characteristics				
Graft type:				ns
G23, n (%)	21 (91)	15 (94)	6 (85)	
G234, n (%)	1 (4)	0 (0)	1 (15)	
G1234MHV, n (%)	1 (4)	1 (6)	0 (0)	
Operative time, min (IQR)	272 (235; 322)	243 (223; 300)	356 (278; 372)	*p = 0.026*
Graft weight, g (IQR)	300 (245; 330)	300 (262; 342)	270 (245; 300)	ns
Intraoperative transfusion, mL	0	0	0	ns
Conversion, n	0	n.a.	0	ns
Blood loss, mL (IQR)	100 (50; 175)	125 (95; 212)	50 (0; 50)	*p < 0.001*
Post-operative donor outcomes				
Transfusion during hospital stay, mL	0	0	0	ns
ICU stay, d (IQR)	2 (1; 2)	1 (1; 2)	2 (2; 2.5)	ns
Length of hospital stay, d (IQR)	7 (6; 7.5)	7 (6.7; 7.2)	7 (5.5; 8)	ns
Peak AST, U/L (IQR)	370 (232; 566)	428.5 (284.5; 630.5)	264 (198; 376)	ns
Peak ALT, U/L (IQR)	546 (250; 765)	765 (507.5; 821)	348 (249; 447)	ns
Peak serum bilirubin, μmol/L (IQR)	19 (16; 25.5)	23.5 (17.5; 29.5)	17 (14; 18.5)	*p = 0.0523*
Peak INR, (IQR)	1.3 (1.24; 1.44)	1.34 (1.26; 1.45)	1.15 (1.14; 1.27)	*p = 0.0210*
Peak PLT, x109/L (IQR)	173 (155; 200)	167.5 (152.75; 196.5)	185 (175.5; 204)	ns
90 days post-operative complications				
<90 days Clavien Dindo > II, n (%)	0 (0)	0 (0)	0 (0)	ns
<90 days Clavien Dindo I – II, n (%)	5 (22)	4 (25)	1 (14)	ns
Infection (urinary, pulmonary, colitis etc.), n (CD)	4 (CD II)	4 (CD II)	0	ns
Urinary retention, n (CD)	1 (CD II)	0 (0)	1 (CD II)	ns
Opioid use for pain management n (%)	3 (13)	2 (12)	1 (14)	ns
Mortality, n (%)	0 (0)	0 (0)	0 (0)	ns

Abbreviations: BMI, body mass index; IQR, Interquartile, range; ICU, intensive care unit; LDH, living donor hepatectomy.

pedicular clamping during parenchymal transection and hilar plate division in both groups. Donor warm ischemia time was <5 min in both groups. At 90 days, there were no CD > II complications in the R-LDH and open group. The R-LDH group had a significantly lower peak INR (1.15 vs. 1.34 $p = 0.025$) without significant differences in postoperative hepatocyte injury (AST: 264 UI/L vs. 428.5 UI/L, $p = 0.222$; ALT: 348 UI/L vs. 765 UI/L, $p = 0.109$) and peak serum bilirubin (17 vs. 23.5 μmol/L, $p = 0.0523$). There was no significant difference in length of hospital stay between the two groups (7 days vs. 7 days, $p = 0.45$). After a median overall follow-up of 25 months, one donor in the open LDH group presented with a symptomatic incisional hernia with the need for a surgical repair (CD IIIb) and graft and recipient survival was 100% in both groups.

In this IDEAL 2a study in a small volume LDH center, direct transition from open to R-LDH maintains the open-LDH donor safety standards with the absence of major 90-day donor morbidity. While with R-LDH operative duration was increased by 113 min, there was a significant reduction of intraoperative blood loss, no need for pedicular clamping and no conversion to an open procedure.

In contrast to LT centers from Asia and the Middle East, the experience with LDH in Europe is limited due to availability of deceased donor grafts. Indeed, there are only 15–20 LDH performed every year in France. Furthermore, the team from Brussels, who have one of the largest experiences with LDH in Europe, achieved benchmark outcomes with open-LDH [6]. In their series of 438 open living donor left hepatectomies, the rate of CD Grade III complications was 6% without any Grade IV or postoperative death. In this context, setting-up a LDH program using a minimal-invasive surgical approach is challenging. Thus to launch our LDH program in 2019 we advocated the open approach, in close collaboration with the team from Brussels, with donor safety being the highest priority. After standardizing the open LDH procedure at our center and in the absence of major donor morbidity in the first 16 cases, we decided to directly transition to R-LDH in October 2023. In contrast to laparoscopic LDH, R-LDH allows for a straightforward transposition of operative techniques and steps from the open approach. For example, we applied the same parenchymal transection technique in R-LDH as in open LDH translating into minimal intraoperative blood loss and no need for pedicular clamping. Importantly, despite our small experience, we are convinced that R-LDH offers a real benefit in the dissection of the hilar plate as well as left bile duct division [1]. Although the current series is too small to identify a significant impact on recipient biliary complications, larger series point to a reduction of biliary complications in both donors and recipients with the robotic approach [2].

In conclusion, the transition from open to R-LDH in the setting of a low-volume LDH center can be achieved without compromising donor safety. An extensive experience in minimal-invasive HPB surgery contributes to a safe transition from open to R-LDH.

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 Comité Scientifique et Ethique des Hospices Civils De Lyon AGORA N°25-5243. 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.

AUTHOR CONTRIBUTIONS

Conceptualization: XM, KM, and J-YM. Investigation: LP, XM, GR, RD, TA, and MR. Methodology: XM, GR, KM, and J-YM. Writing – original draft: LP, XM, GR. Writing – review and editing: TA, MR, RD, KM, and J-YM. Final review and editing: LP, XM, and J-YM. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

GENERATIVE AI STATEMENT

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LETTER TO THE EDITOR
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Real-World Evaluation of Letermovir Use in Kidney Transplant Recipients: Drug Interactions, Safety, and Impact on Renal Function

Ilies Benotmane[1,2], Betoul Schvartz[3], Cyril Garrouste[4], Florence Runyo[5], Charlotte Boud'hors[5,6], Gauthier Flahaut[7], Clément Danthu[8], Dominique Bertrand[9] and Sophie Caillard[1,2]*

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Keywords: cytomegalovirus, letermovir, drug interactions, kidney transplant, kidney function

Dear Editors,

Letermovir is approved for primary prophylaxis of cytomegalovirus (CMV) infection in seropositive donor/seronegative kidney transplant recipients (KTRs) [1, 2]. Letermovir inhibits CYP3A4, raising the risk of interactions with calcineurin inhibitors (CNIs) and mTOR inhibitors (mTORi) [3]. Real-world data regarding these interactions are limited [4]. This retrospective multicenter study evaluated letermovir-immunosuppressant interactions and assessed letermovir safety and efficacy.

Twenty-six KTRs were included. Detailed methods are provided in the **Supplementary Material**, and patient characteristics in **Supplementary Table S1**. Letermovir was initiated at a median of 135 days [IQR: 109–139] post-transplantation for primary prophylaxis (patients with a history of or current valganciclovir resistance or intolerance, n = 5), 264 days [192–397] for curative treatment (n = 11), and 296 days [252–423] for secondary prophylaxis (n = 10). At data cutoff, five patients remained on letermovir; one died of CMV disease and another lost graft function. Among the rest, median treatment duration was 151 days [66–361].

In the 16 patients receiving tacrolimus, the median daily dose significantly decreased from 3.6 mg [2.6–7.1] before letermovir to 2.3 mg [1–4.8] during treatment ($p = 0.002$, **Figure 1A**; **Supplementary Table S2**), corresponding to a median 33% dose reduction (range: 0%–75%). Similar findings have been reported in transplant recipients, with most studies recommending a 30%–50% dose reduction [5–7]. Two patients also receiving CYP3A4 inhibitors (lansoprazole, amiodarone) had among the largest tacrolimus dose reductions—74% and 60%—suggesting a cumulative effect. No association was found between dose reduction and body mass index (Spearman $\rho = -0.04$, $p = 0.87$), or with tacrolimus formulation (immediate-release: 33% reduction; melt-dose: 38%; prolonged-release: 0%; $p = 0.41$). Tacrolimus trough levels significantly increased from a median of 6.2 ng/mL [5.1–9.3] to 8.3 ng/mL [7.3–13.3] during letermovir treatment ($p = 0.006$, **Figure 1B**).

Among 12 patients with post-letermovir treatment data, tacrolimus daily doses remained stable (3.5 mg [1.6–7.3] vs. 4.3 mg [1.6–7.4], $p = 0.88$), but trough levels significantly decreased after discontinuation (from 8.1 ng/mL [7.1–12.4] to 7 ng/mL [3.9–7.0], $p = 0.01$).

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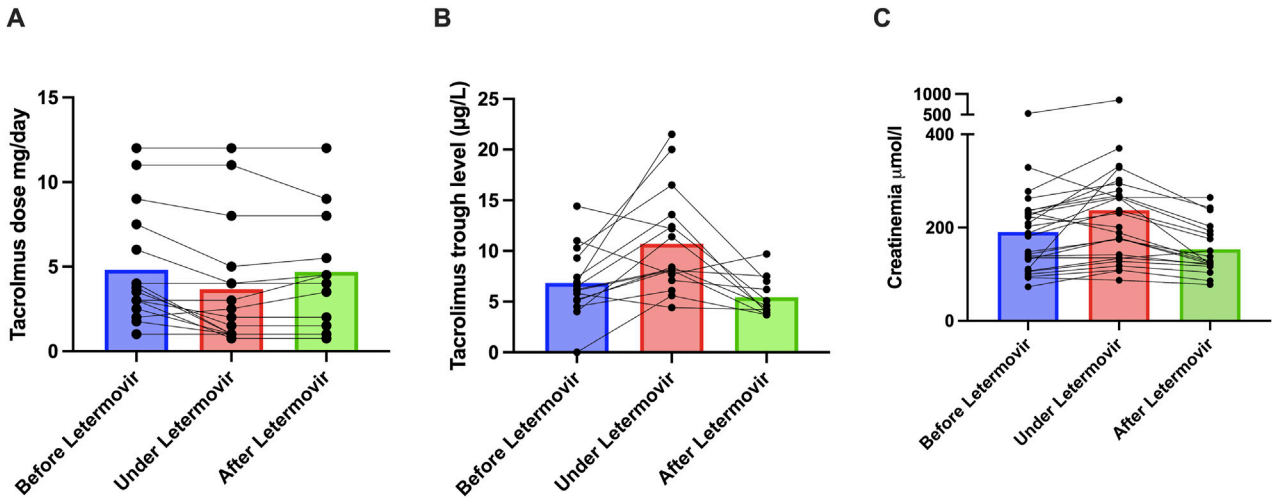

FIGURE 1 | Impact of Letermovir on Tacrolimus dosage, Tacrolimus residual levels and renal function. **(A)** Changes in tacrolimus dosage before (n = 16), during (n = 16), and after stopping letermovir (n = 12). **(B)** Changes in tacrolimus residual levels before (n = 15), during (n = 16), and after stopping letermovir (n = 11). The tacrolimus trough level was below the limit of detection for one patient therefore, a value of zero was assigned. **(C)** Creatinine in µmol/L before (n = 26), during (n = 26), and after (n = 19) treatment with letermovir. Each dots represents a patient. The plot represents the median (bar).

In the 5 patients receiving ciclosporin, the median dose decreased from 200 mg/day [125–200] to 100 mg/day [90–200], without reaching statistical significance ($p = 0.25$). In four patients with available through levels, concentrations increased from 71 ng/mL [55–126] to 169 ng/mL [152–406] ($p = 0.13$). In three patients with post-letermovir treatment data, doses remained unchanged in two and doubled in one. Notably, previous pharmacokinetic data showed a 1.7-fold increase in ciclosporin AUC with letermovir [3].

Among four patients on everolimus, one discontinued the drug shortly after starting letermovir. In the remaining three, trough levels increased (11.3, 10.8, and 9.1 ng/mL), prompting 50% dose reductions in two cases. In healthy volunteers, letermovir increased everolimus AUC by 3.4-fold [3].

An unanticipated observation was a transient 18% increase in serum creatinine following letermovir initiation from 185 µmol/L [110–235] to 216 µmol/L [135–284] ($p = 0.0006$), with 17 of 26 patients (65%) meeting KDIGO 1 criteria for acute kidney injury (AKI, defined as a ≥26 µmol/L increase). Seven of them also experienced gastrointestinal side effects that may have led to functional AKI. In 19 patients with post-letermovir treatment data, creatinine increased from 143 µmol/L [107–230] to 178 µmol/L [128–264] during treatment ($p = 0.03$), and then decreased to 126 µmol/L [120–193] after discontinuation ($p = 0.0002$), indicating reversibility (**Figure 1C**). No correlation was found between creatinine increase and tacrolimus peak levels (Spearman $\rho = -0.08$, $p = 0.72$), and creatinine elevation occurred also in all five patients not on CNIs (ranging from 28 µmol/L to 123 µmol/L). Possible mechanisms include inhibition of renal tubular OAT3 transporters by letermovir impairing creatinine elimination [8] or gastrointestinal symptoms leading to functional AKI. In the trial by Limaye et al. [9], AKI occurred in only 6.8% of patients receiving letermovir, similar to the valganciclovir group. As letermovir was initiated early post-transplant—when renal function is recovering—minor creatinine increases may have been difficult to detect.

Gastrointestinal adverse events, including diarrhea and vomiting, were reported in 9 patients (35%), consistent with earlier reports [9, 10]. These events were not associated with CNI exposure (7/9 vs. 14/17, $p > 0.99$) or tacrolimus trough levels (8.3 vs. 9.8 ng/mL, $p = 0.7$).

Letermovir was used for prophylaxis in 15 patients—10 due to valganciclovir-induced cytopenia and five for a prior history of valganciclovir resistance or poor virologic response. CMV replication occurred in three patients on secondary prophylaxis. Resistance was excluded in one case; two were not tested. These findings support cautious off-label use of letermovir for secondary prophylaxis in select cases [10].

Letermovir was used as curative therapy in 11 patients, mainly for CMV resistant to first-line antivirals (n = 10), and often in combination with other anti-CMV agents (n = 6). Treatment was initiated in a context of low viral load (median 3.49 $\log_{10}$ IU/mL [3.22–3.72]). Two patients experienced viral load increases (from 3.3 to 5.6 $\log_{10}$ IU/mL and from 3.2 to 4.3 $\log_{10}$ IU/mL, respectively), and both developed confirmed letermovir resistance. One of these patients died from CMV disease.

Because letermovir is unapproved for curative therapy and carries a low genetic barrier to resistance, it should only be considered in selected low viral load refractory cases, as a last-resort option in combination with other antiviral agents.

Despite limitations—including retrospective design, small sample size, and lack of standardized therapeutic drug protocols—this study suggests that letermovir use is associated with significant pharmacokinetic interactions with CNIs and mTORi, warranting close drug level monitoring during initiation and discontinuation. Clinicians

should also be alert to the potential for renal function decline hopefully reversible.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Patients had provided informed consent for participation in the ASTRE database, which collects clinical and biological data across these centers (DR-2012-518). 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.

AUTHOR CONTRIBUTIONS

IB, designed the study, collected and analyzed the data and wrote the article. SC designed the study and reviewed the article. BS, CG, FR, CB, GF, CD, and DB collected the data and reviewed the article. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

IB received speaker fees from AstraZeneca, MSD and Biotest, was on advisory boards for Chiesi, Takeda, and MSD and received travel grants from Chiesi, MSD, AstraZeneca and Biotest. BS was on advisory boards for Chiesi and Takeda. SC received speaker fees from Pfizer, was on advisory boards for Astellas, ALexion, Astra Zeneca, Pierre Fabre, GSK, Chiesi and received travel grants from Alexion, Sanofi and Pierre Fabre.

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

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.15371/full#supplementary-material

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LETTER TO THE EDITOR
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Estimated Number of Prevalent Kidney Transplant Recipients in Japan From 1964 to 2023

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Keywords: dialysis, kidney failure, kidney replacement therapy, kidney translant, kidney transplantation

Dear Editors,

Kidney transplantation is one of the primary modalities of kidney replacement therapy (KRT) for patients with kidney failure. Compared with dialysis, it offers multiple advantages, including improved survival, better quality of life, and reduced healthcare costs [1, 2]. Therefore, understanding the implementation of kidney transplantation is essential for appropriate healthcare resource allocation and policy planning in each region. In Western countries, kidney transplantation is highly prevalent, with approximately 30%–50% of patients receiving KRT being transplant recipients [3, 4]. In contrast, in Japan, kidney transplantation remains a relatively limited treatment modality, primarily due to donor shortages and potential cultural factors [5–7].

The Japan Society for Transplantation, in collaboration with the Japanese Society for Clinical Renal Transplantation, has long collected detailed data at the time of transplantation, providing accurate statistics on the number of transplants and donor types [5–7]. However, long-term post-transplant follow-up is not always complete, leaving the number of kidney transplant recipients with functioning grafts (i.e., prevalent recipients) uncertain. This lack of information represents a significant limitation for evaluating the proportion of transplant recipients relative to patients on dialysis and for conducting international comparisons.

To address this, we estimated temporal trends in the number of prevalent kidney transplant recipients in Japan using summary statistics published by the Japan Society for Transplantation [5–7]. Furthermore, using data from the Japan Society for Dialysis Therapy Renal Data Registry [8], we calculated the proportion of prevalent kidney transplant recipients among all patients receiving KRT.

The annual numbers of living- and deceased-donor kidney transplants performed from 1964 to 2023, obtained from the Japan Society for Transplantation records [5–7], are summarized in **Supplementary Figure S1** and **Supplementary Table S1**. The number of transplants was very low in the 1960s, gradually increased from the late 1970s, and has stabilized at approximately 1,500–2,000 per year since the 2010s. By 2023, a total of 47,466 transplants had been performed, comprising 39,543 living-donor and 7,923 deceased-donor transplants.

Temporal trends in the number of prevalent kidney transplant recipients, estimated based on graft survival for each era (**Supplementary Figure S2**), are shown in **Figure 1a** and **Supplementary Table S2**. The estimated number of prevalent recipients increased over time, reaching 27,935 living-donor recipients, 3,617 deceased-donor recipients, and a total of 31,552 recipients by 2023.

Temporal trends in the estimated number of prevalent kidney transplant recipients, compared with the number of patients on dialysis reported by the JSDT Renal Data Registry [8], are shown in **Figure 1b** and **Supplementary Table S3**. The proportion of these patients relative to the total population in Japan is shown in **Supplementary Figure S3**. The estimated proportion of prevalent

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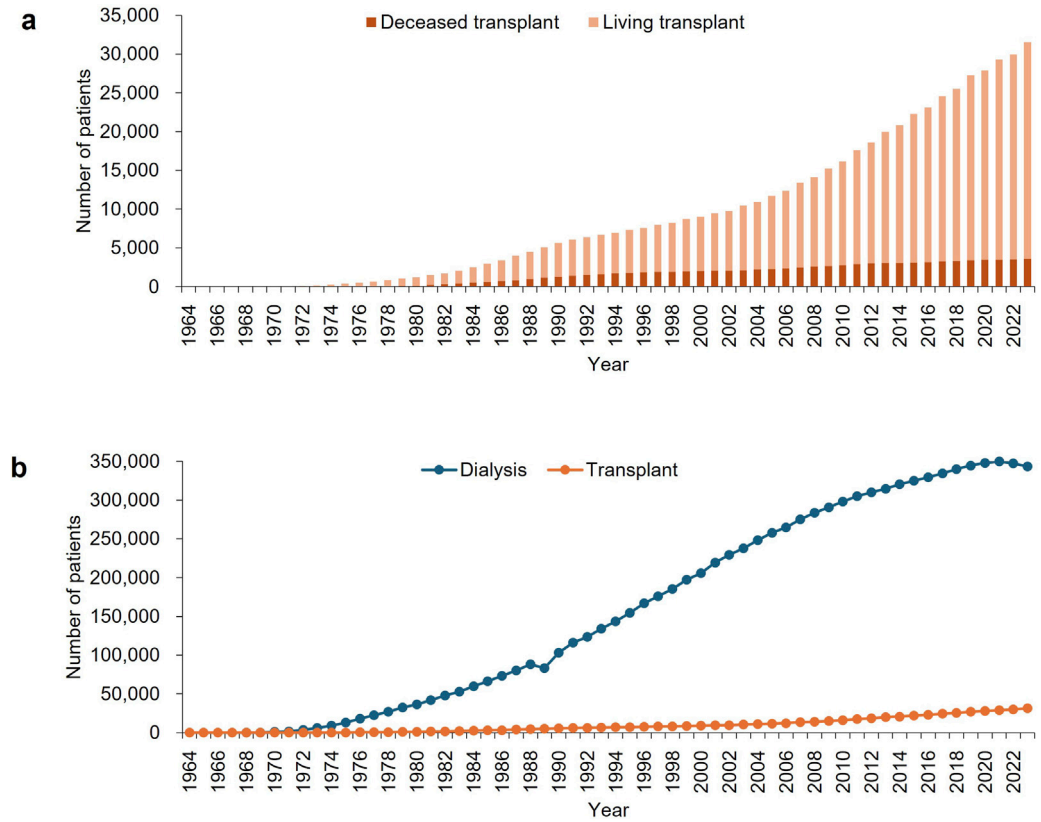

FIGURE 1 | Temporal trends from 1964 to 2023 in **(a)** the estimated numbers of living- and deceased-donor prevalent kidney transplant recipients, and **(b)** the estimated total number of prevalent kidney transplant recipients, compared with the number of patients undergoing dialysis. Data on patients undergoing dialysis were obtained from the Japan Society for Dialysis Therapy Renal Data Registry [8]. Detailed numerical data are provided in **Supplementary Tables S2, S3**.

kidney transplant recipients among all patients receiving KRT in Japan gradually increased over time, reaching 8.4% in 2023.

This study reports that the estimated number of prevalent kidney transplant recipients in Japan has steadily increased, surpassing 30,000 in 2023 and accounting for 8.4% of all patients receiving KRT. These data provide an important reference not only for understanding the current status of kidney transplantation in Japan, but also for enabling international comparisons and contributing to global discussions on transplantation practices.

A notable finding is that, compared with Western countries [3, 4], the proportion of prevalent kidney transplant recipients in Japan remains low, primarily due to the limited number of deceased-donor transplants. Contributing factors include delayed societal recognition of brain-dead organ donation, regulatory constraints, and challenges in obtaining family consent [9]. In addition, population aging and advances in chronic kidney disease management have led to an older demographic among patients requiring KRT [8], which may limit eligibility for kidney transplantation. Nonetheless, we observed a steady increase in prevalent recipients, likely reflecting both the gradual increase in the number of kidney transplants and the favorable long-term outcomes of kidney transplantation in Japan [5–7].

This study has several limitations. Most importantly, the estimates were derived from registry-reported transplant numbers and graft survival rates, rather than from a direct count of prevalent recipients. The graft survival rates were based on recipients with available follow-up, so outcomes of those lost to follow-up may differ. Furthermore, this secondary analysis relied entirely on summary data without access to individual-level information. Further investigation is needed to collect comprehensive patient-level data on prevalent kidney transplant recipients. The newly developed national transplant registry system, TRACER (TRAnsplant CEntral Registry), may help address these gaps.

In conclusion, kidney transplantation remains a relatively uncommon KRT modality in Japan, but the number of recipients with functioning grafts has steadily increased. Continued efforts are needed to refine these estimates and to establish a robust foundation for meaningful international comparisons.

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

HK conducted the analysis and drafted the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.15732/full#supplementary-material

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