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META-ANALYSIS

A meta-analysis of the cumulative incidence, risk factors, and clinical outcomes associated with chronic kidney disease after liver transplantation

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SUMMARY

Chronic kidney disease (CKD) remains a relatively common complication after liver transplantation (LT), and significantly impacts overall survival. We sought to assess the cumulative incidence, risk factors and mortality associated with post-LT CKD. CKD was defined as eGFR <60 ml/min/1.73 m^2 as estimated by the Modified Diet in Renal Disease (MDRD) formula. Single-arm meta-analysis was done to evaluate the cumulative incidence of CKD at 1-, 3-, and 5-year timepoints post-LT. Risk factors for CKD were evaluated using hazard ratios (HR). Twenty-one studies involving 44 383 patients were included. Cumulative incidence of stage 3–5 CKD was 31.44% (CI 0.182–0.447), 36.71% (CI 0.188–0.546), and 43.52% (CI 0.296–0.574) at 1, 3, and 5 years after LT, respectively. Stage 5 CKD cumulative incidence increased from 0.274% (CI 0.001–0.005) at 1 year to 2.06% (CI 0.009–0.045) at 5 years post-LT. Age, female sex, diabetes, and peri-operative acute kidney injury (AKI) were significant risk factors for CKD. Stage 4–5 CKD was associated with a decrease in overall survival (HR 3.23, 95% CI 1.74–5.98, $P < 0.01$). CKD after LT is relatively common, and is associated with significantly reduced overall survival. Identification of patients at high risk of developing CKD allows physicians to prophylactically use renal-sparing immunosuppression which may be crucial in achieving desirable clinical outcomes.

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Introduction

Advances in surgical techniques, post-liver transplant (LT) immunosuppressive regimens, and clinical management of complications have greatly improved survival outcomes for liver transplant recipients [1]. However, chronic kidney disease (CKD) remains a relatively common complication in these patients that affects their long-term survival [2], with an increasing proportion of post-transplant morbidity and mortality being attributed to CKD [3,4]. Progressive renal scarring and parenchymal damage in CKD after LT may lead to need for kidney replacement therapy (KRT) or kidney transplantation in post-LT patients. This results in increased healthcare costs [5,6], reduced quality of life [7], and further contributes to the global shortage of allografts for transplantation [8]. Comorbidities such as diabetes mellitus and hypertension can result in diabetic nephropathy and hypertensive vascular changes following transplant [9–11]. Additionally, post-transplant factors including calcineurin inhibitor (CNI) toxicity and acute kidney injury (AKI) peri-operatively, further predispose to CKD development [12].

In the existing literature, the reported rate of CKD after LT ranges from 20% to 50% [2,13,14]. These widely variable estimates may be attributed to a combination of inconsistent follow-up periods and definitions for CKD staging [13]. Additionally, methods used to assess renal function via estimated glomerular filtration rate (eGFR) produce differing results based on formula and also lack standardization across studies [15]. Creatinine-based methods often overestimate glomerular filtration rate (GFR) in liver transplantation (LT) patients, resulting in under-reporting of CKD occurrence and contributing to heterogeneity in results [16]. Thus, this meta-analysis and systematic review aims to assess the cumulative incidence, risk factors, and mortality outcomes associated with post-LT CKD with standardized definitions of CKD staging and methods for estimating GFR during follow-up.

Methods

Search strategy

This review was registered with PROSPERO (CRD42021225254). With reference to the PRISMA guidelines [17], a search was conducted on Medline and Embase databases for articles relating to post-transplant CKD after LT. The date of search was 8 March 2021, and no date filter was applied. Additionally, the references of included articles were screened for relevant articles. The search strategy used was "exp renal insufficiency, chronic/OR (CAPD or CCPD or APD).tw OR (endstage renal or endstage kidney or end-stage renal or end-stage kidney or ESRF or ESKF or ESKD or ESRD).tw OR (chronic kidney or chronic renal or CKF or CKD or CRF or CRD).tw" and "exp liver transplantation/OR ((liver* or hepatic*) adj3 (transplant* or graft*)).tw" in English language articles only. References were managed with Endnote X9 and duplicates were removed before the title and abstract screening.

Study selection and data extraction

Three authors (SYL, RW, DJHT) were involved in the screening of abstracts to check the eligibility for inclusion, with disputes being resolved through consensus from a fourth independent author (EXXT). Studies relating to the occurrence, risk factors, and outcomes of CKD after LT were included for analysis. Retrospective and prospective cohort studies, and cross-sectional studies were considered for inclusion. Systematic reviews, meta-analyses, and editorials were excluded. Additionally, only English language articles were considered for inclusion. To maintain homogeneity, only studies that estimated GFR via the Modified Diet in Renal Disease (MDRD) formula [18] were considered for inclusion. Furthermore, studies that included patients that had undergone simultaneous liver-kidney transplant were excluded from the analysis. CKD stages were defined per the Kidney Disease Improving Global Outcomes (KDIGO 2012)

guidelines [19]. CKD stages 3, 4, and 5 were defined as GFR of 30–59 ml/min/1.73 m^2, 15–29 ml/min/1.73 m^2, and <15 ml/min/1.73 m^2, respectively.

Relevant data from included articles were then extracted by a pair of independent authors into a structured proforma. The baseline demographics, including but not limited to, author, year of publication, country of study, sample size, gender, and eGFR prior to and at LT were extracted. The primary outcome of interest was the cumulative incidence of post-LT CKD at specific timepoint intervals of 1, 3 and 5 years after LT. Risk factors associated with CKD including age, female gender, body mass index (BMI), hypertension, diabetes, Model for End-Stage Liver Disease (MELD), pre-transplant CKD, perioperative AKI, and postoperative immunosuppressive regimen were also extracted. Additionally, long-term outcomes including mortality, the need for hemodialysis or peritoneal dialysis, kidney transplantation, acute graft rejection, and chronic graft rejection were included in our analysis. KRT was defined as long-term usage of hemodialysis or peritoneal dialysis due to declining renal function, or kidney transplantation. Patients only requiring supportive therapy due to AKI after LT were not counted as needing KRT. Acute and chronic graft rejections were diagnosed via a combination of abnormal liver function tests, and histologic findings on liver biopsy (Banff criteria) where available.

Statistical analysis and quality assessment

When possible, meta-analysis was conducted in RSTUDIO (Version 1.3.1073) or STATA (Statacorp 16.1) and a systematic reporting of results was undertaken where there are insufficient studies for any meaningful comparisons. A single arm analysis of binary outcomes was pooled in the form of proportions using the generalized linear mixed model (GLMM) with Clopper-Pearson intervals to stabilize the variance [20]. Simulation studies have found that the GLMM model provides the most accurate estimate in single-arm meta-analysis [20]. Next, a subgroup analysis was conducted on the cumulative incidence of CKD after LT based on the region (Asian vs. Western). Differences between regions were also computed in an odds ratio (OR) using a generalized linear model with a binomial family and logit link with inverse variance-weights [21,22]. A sensitivity analysis was also conducted for studies that excluded patients with eGFR <60 ml/min/1.73 m^2 prior to LT to evaluate the proportion of new-onset CKD. Publication bias was not assessed due to the lack of a suitable tool in single arm meta-analysis to assess publication bias and the relatively small quantity of included studies [23].

A comparative meta-analysis was done in hazard ratios (HR) using the DerSimonian and Laird random effects model to assess the risk factors associated with CKD after LT, as well as the effect of CKD on postoperative overall survival. Statistical heterogeneity was assessed via I^2 and Cochran Q test values, where an I^2 value of 25%, 50%, and 75% represented low, moderate and high degree of heterogeneity, respectively [24,25]. A Cochran Q test with P-value of ≤ 0.10 was considered significant for heterogeneity. Random effects model was used in all analysis regardless of heterogeneity as recent evidence suggests that it provides more robust outcome measures compared to the alternative fixed effects models [26]. Statistical significance was considered for outcomes with a P value ≤ 0.05. Quality assessment of included articles was done with the Joanna Briggs Institute (JBI) Critical Appraisal Tool. The JBI assessment rates the risk of bias of cohort studies on the premises of appropriateness of sample frame, sampling method, adequacy of sample size, data analysis, methods for identification, and measurement of relevant conditions, statistical analysis, and response rate adequacy.

Results

Summary of included articles

Three thousand twelve articles were included in the initial search after removal of duplicates, of which 166 were selected for full text review. Twenty-one articles met the final inclusion criteria (Fig. 1), with eight articles from the United States [2,13,27–32], three each from Italy [33–35] and the United Kingdom [36–38], two from South Korea [39,40], and one each from Australia [41], France [42], Japan [14], Poland [43], and Singapore [44]. Table S1 contains the summary of the key characteristics and quality assessment for included articles. A total of 44,383 patients were included in our analysis with a mean age of 45.04 ± 17.34 years. The large majority of included articles were retrospective studies (n = 17) with only four studies being prospective studies. All included articles eGFR using the MDRD formula and CKD stage was defined in accordance with KDIGO 2012 guidelines. Table S2 summarizes the quality assessment of included articles and most included articles were at low risk of bias.

Cumulative incidence of post-LT CKD

Cumulative incidence of post-LT CKD (stage 3–5) was analyzed at 1, 3, and 5 years post-LT (Fig. 2). From

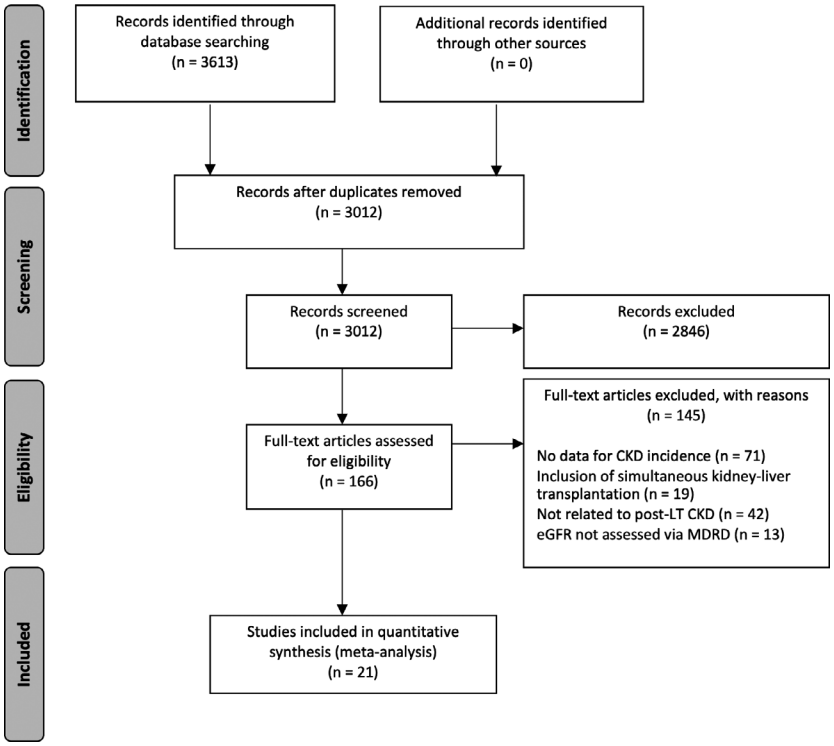

Figure 1 PRISMA flowchart of included articles.

pooled analysis of 32 830 patients, the cumulative incidence of post-LT CKD 1 year after LT was 31.44% (CI 0.182–0.447). The cumulative incidence of post-LT CKD increased to 36.71% (CI 0.188–0.546), and 43.52% (CI 0.296–0.574) 3 and 5 years after LT, respectively. A sensitivity analysis was conducted to further stratified according to the severity of kidney impairment (Table 1). Cumulative incidence of stage 4 CKD was found to be 3.37% (CI 0.024–0.047) at 1 year, 4.70% (CI 0.004–0.006) at 3 years and 4.78% (CI 0.031–0.072) at 5 years after LT. In addition, cumulative incidence of stage 5 CKD was 0.274% (CI 0.001–0.005), 0.557% (CI 0.001–0.012), and 2.06% (CI 0.009–0.045) at 1, 3, and 5 years post-LT, respectively.

Regional difference

A subgroup analysis of the cumulative incidence of post-LT CKD was conducted according to region of transplant center. At 1 year after transplantation, cumulative incidence of CKD in patients from Western centers was 25.00% (CI 0.143–0.399), compared to 33.39% (CI 0.209–0.487) in Asian centers. Cumulative incidence of CKD at 3 years after LT was 35.41% (CI 0.212–0.528) in Western centers, compared to 34.02% (CI 0.234–0.465) in the Asian center subgroup. At 5 years after LT, cumulative incidence was 45.09% (CI 0.347–0.559) and 35.42% (CI 0.246–0.479) for Western and Asian centers respectively. There was no significant difference in occurrence of CKD after LT between Western and Asian centers at 1 year (OR 0.708; 95% CI 0.296–1.689; $P = 0.44$), 3 years (OR 1.14; 95% CI 0.501–2.60; $P = 0.75$), and 5 years post-LT (OR 1.34; 95% CI 0.673–2.67; $P = 0.41$).

Sensitivity analysis for new-onset CKD post-LT only

From pooled analysis of studies that only included patients with pretransplant eGFR ≥60 ml/min/1.73 m^2, the cumulative incidence of new-onset CKD post-LT was 34.87% (CI 0.261–0.447) at 1 year after LT. This increased to 47.73% (CI 0.405–0.551) and 54.01% (CI 0.383–0.690) 3 and 5 years after LT, respectively.

Risk factors for post-LT CKD

Background demographics

Pooled analysis was conducted for the various risk factors associated with CKD after LT (Table 2). Older age (HR 1.08; 95% CI 1.04–1.12; $P < 0.01$), female gender (HR 1.41; 95% CI 1.14–1.74; $P < 0.01$), diabetes (HR 1.73; 95% CI 1.04–2.89; $P = 0.04$) and peri-operative AKI (HR 1.74; 95% CI 1.62–1.88; $P < 0.01$) were

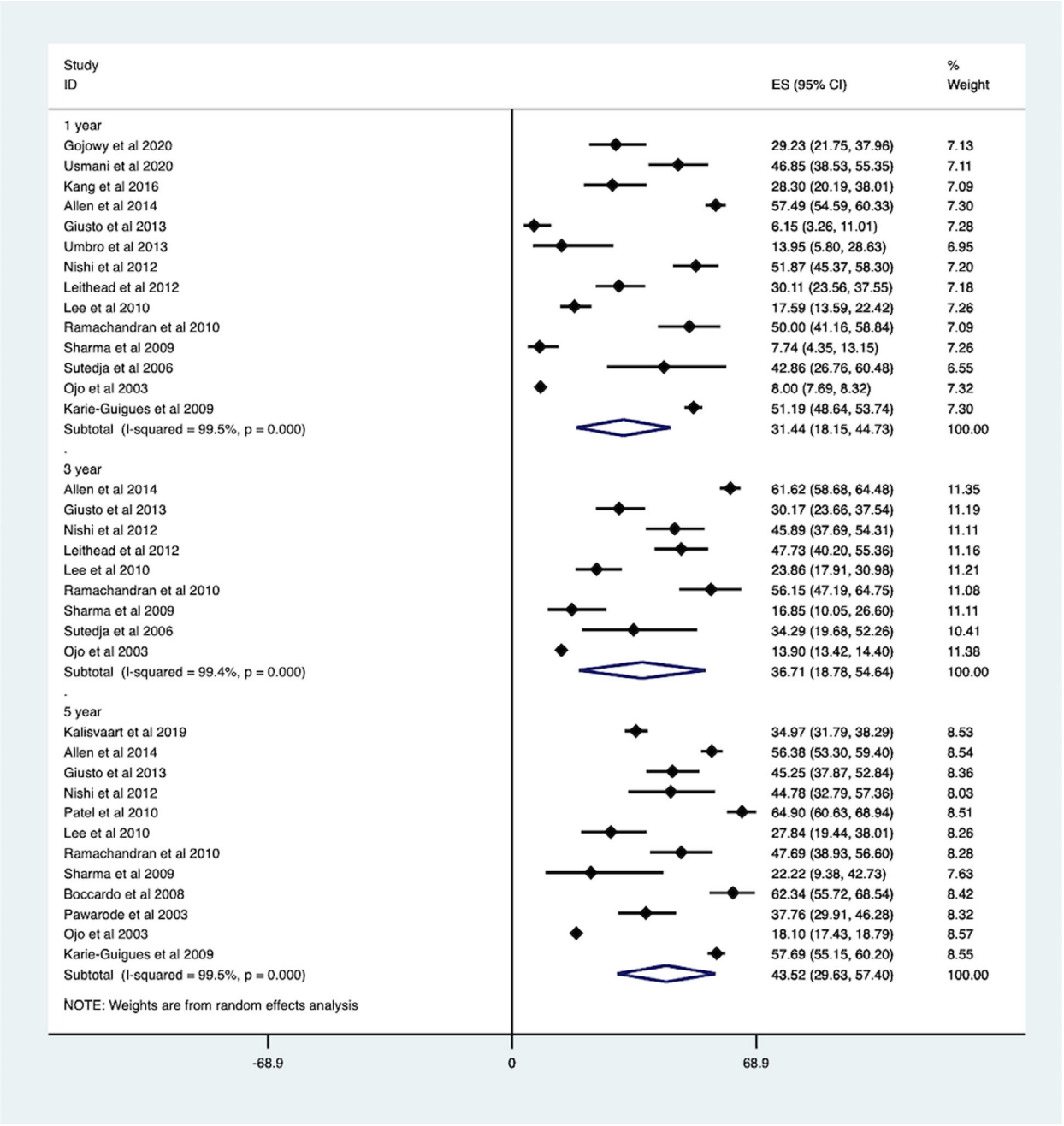

Figure 2 Cumulative incidence of chronic kidney disease after liver transplantation stratified by year.

significantly associated with CKD after LT. There was no significant association between diagnosis of hypertension prior to LT, BMI, MELD score, and pretransplant CKD and post-LT CKD.

Background immunosuppression

Six studies reported the effects of immunosuppressive regimen on the occurrence of post-LT CKD (Fig. 3) [14,34,36,40,42,43]. Three studies reported that increased dosage of tacrolimus significantly affected long-term renal function after transplantation. Of these, two studies found that increased blood tacrolimus trough levels were associated with reduced eGFR during follow-up [34,43]. One study reported significantly higher cyclosporine trough levels in patients that developed CKD [34], although another study reported nonsignificant effects [14]. For purine synthesis inhibitors including mycophenolate and azathioprine, one study found nonsignificant effects of both drugs on CKD after LT [40]. However,

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Table 1. Summary of cumulative incidence of chronic kidney disease after liver transplant.

	No. of studies	Events	Sample	Cumulative incidence
1 year				
Stage 3–5	14	4163	32 830	31.44 (0.182–0.447)
Stage 4	3	94	2918	3.37 (0.024–0.047)
Stage 5	3	8	2918	0.274 (0.001–0.005)
Predominantly Asian	4	224	689	33.39 (0.209–0.487)
Predominantly Western	10	3167	30 633	25.00 (0.143–0.399)
3 year				
Stage 3–5	9	3734	21 549	36.71 (0.188–0.546)
Stage 4	2	59	1256	4.70 (0.004–0.006)
Stage 5	2	7	1256	0.557 (0.001–0.012)
Predominantly Asian	3	121	357	34.02 (0.234–0.465)
Predominantly Western	6	3610	21 192	35.41 (0.212–0.528)
5 year				
Stage 3–5	12	4845	17 379	43.52 (0.296–0.574)
Stage 4	7	214	4369	4.78 (0.031–0.072)
Stage 5	7	83	4369	2.06 (0.009–0.045)
Predominantly Asian	2	57	164	35.42 (0.246–0.479)
Predominantly Western	10	3918	15 707	45.09 (0.347–0.559)

Table 2. Risk factors associated with chronic kidney disease after liver transplant.

Risk factors	No. of studies	Sample	HR (95% CI)	*P* value
Age	4	1666	1.08 (1.04–1.12)	<0.01*
Female sex	4	1520	1.41 (1.14–1.74)	<0.01*
BMI	2	1357	0.99 (0.97–1.01)	0.37
Hypertension	4	1666	1.51 (0.90–2.53)	0.12
Diabetes	5	1741	1.73 (1.04–2.89)	0.04*
MELD	4	1666	1.03 (0.99–1.06)	0.16
Pre-transplant CKD	5	1692	1.03 (0.96–1.11)	0.35
Perioperative AKI	3	1432	1.74 (1.62–1.88)	<0.01*

AKI, acute kidney injury; BMI, body mass index; CKD, chronic kidney disease; MELD, model for end-stage liver disease.
*Statistically significant at $P < 0.05$.

Karie-Guigues *et al.* reported that patients on mycophenolate in combination with CNI experienced a less severe decline in renal function after LT, compared to patients receiving only CNI (15.5% vs. 29.9% decrease in eGFR 1 year after LT, $P = 0.04$) [42]. Regarding the dosage of CNIs, Leithead *et al.* [37] found that a renal-sparing immunosuppressive regime, consisting of tacrolimus to maintain a serum trough level of 5–8 μg/l and decreasing dosage of steroids eventually discontinued by 3 months did not significantly affect the cumulative incidence of CKD (HR 1.63, 95% CI 0.54–4.93, $P = 0.383$) [37]. Additionally, Sharma *et al.* [31] reported that a delay in introducing CNI after LT was not an independent predictive variable of CKD post-LT (HR 1.86, 95% CI 0.87–3.97, $P = 0.10$) [31]. However, pooled estimates of the effects of varying immunosuppressive regimen on CKD were unavailable due to paucity of data.

Survival outcomes associated with post-LT CKD

Overall mortality rate was 10.71% (CI 0.059–0.187) from analysis of 4219 patients. Acute and chronic hepatic graft rejection were reported in 22.07% (CI 0.144–0.323) and 3.24% (CI 0.012–0.082) in 1935 and 2128 patients, respectively. From analysis of 2979 patients, KRT was required in 2.38% (CI 0.006–0.084) of patients. Specifically, long-term peritoneal dialysis or hemodialysis was indicated in 1.60% (CI 0.007–0.038) of patients, while kidney transplantation was performed in 0.437% (CI 0.001–0.047) of patients. When

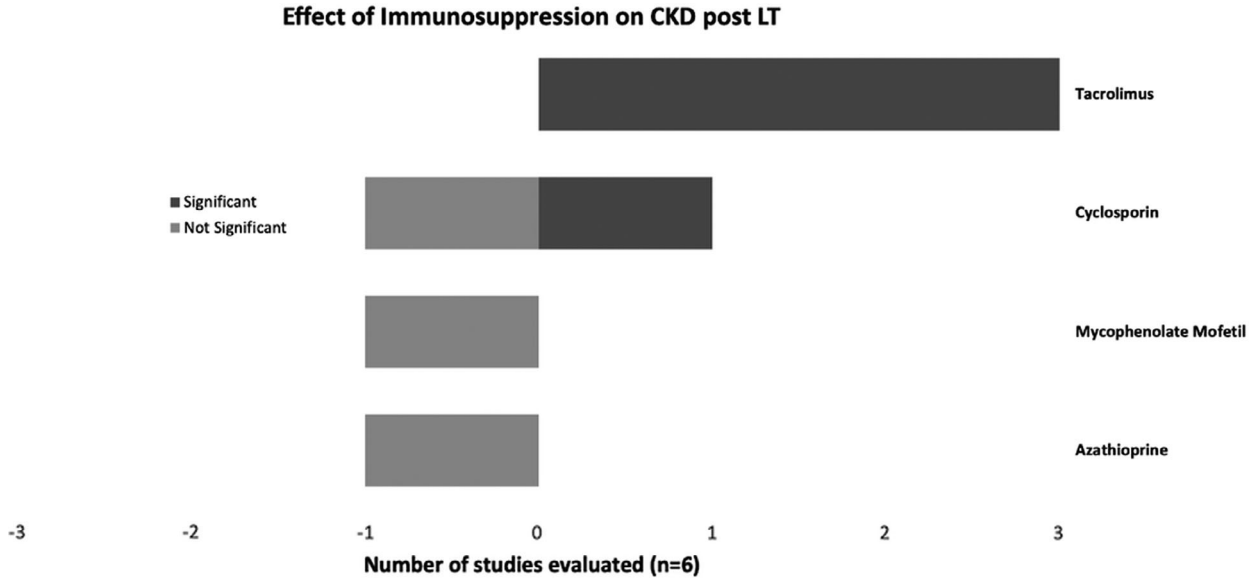

Figure 3 Summary of studies on effect of immunosuppression on chronic kidney disease after liver transplantation.

comparing between patients with stage 4 and 5 CKD to patients without CKD after LT, there was a significant increase in mortality (HR 3.23, CI 1.74–5.98, $P < 0.01$). However, in studies by Allen *et al.* and Ramachandran *et al.*, stage 3 CKD after LT was not significantly associated with increased mortality ($P = 0.27$ and $P = 0.51$, respectively) [13,41]. Furthermore, Sharma *et al.* [31] reported that stage 4 and 5 CKD was also associated with increased mortality compared to patients with stage 3 CKD (HR 2.90, CI 1.30–6.40, $P = 0.008$).

Discussion

A greater proportion of LT recipients have been reported to develop CKD when compared to heart and lung transplant recipients [45,46]. Our meta-analysis of 44 383 post-LT patients summarizes the published literature on the cumulative incidence and risk factors associated with post-LT CKD, as well as its association with all-cause mortality. We found that more than a quarter of patients had CKD at 1 year after LT and the rates increased to two-fifths at 5 years. Most of the patients who developed CKD at 1 year after LT had stage 3 CKD, and <0.5% of the patients had stage 5 CKD at 1 year post-LT. Additionally, female gender, perioperative AKI, diabetes, and older age were risk factors significantly associated with CKD post-LT. Furthermore, only stage 4 or 5 CKD was associated with significantly increased mortality.

While the advanced stages of CKD can result in higher mortality, much remains uncertain in stage 3 CKD patients. Although a pooled estimate of stage 3 CKD was unavailable due to sparsity in reporting, Allen *et al.* [13] and Ramachandran *et al.* [41] found stage 3 CKD to have no significant impact on mortality. Additionally, Sharma *et al.* reported that stage 4 and 5 CKD were also associated with increased mortality compared to patients with stage 3 CKD (HR 2.90, CI 1.30–6.40, $P = 0.008$) [31]. Therefore, while it is unclear if kidney dysfunction after LT and its relationship to poor outcome is associative or causative, prevention of CKD progression should be a key goal of post-LT care. In addition to increased risk of mortality in more advanced stages of CKD, worsened kidney function after LT may also eventually lead to need for dialysis or kidney transplantation.

Choice and dosage of immunosuppression has been widely reported to affect kidney function post-LT [47–49]. However, among the included studies, there was insufficient homogeneity to allow meaningful assessment as to whether immunosuppression choice affected the occurrence of post-LT CKD. Most of the included studies were retrospective, and many had included various renal sparing immunosuppression regimens already in patients at risk of post-LT CKD [31,36,37], acting as a possible confounder. In addition, several landmark studies looking specifically at the effect of immunosuppression regimens on post-LT

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CKD were not included as they did not use the MDRD to quantify CKD [47–50].

Currently, most studies regarding the occurrence of CKD in post-LT patients included patients with pre-transplant kidney dysfunction. This includes previous large scale multicenter studies by Allen *et al.* [13] and Ojo *et al.* [2]. However, the majority of patients included for analysis had normal kidney function prior to transplant (Table S1), suggesting that the majority of patients developed CKD after LT [13]. In our meta-analysis, six studies examined the rate of new-onset CKD post-LT without the inclusion of patients with pre-LT CKD [28,29,32,36,37,39]. To account for sources of variance arising from studies involving patients with pre-LT CKD, a sensitivity analysis of patients with normal kidney function revealed the rate of CKD development to be 34.87%, 47.73%, and 54.01% at 1, 3, and 5 years after LT, respectively, which provides comparable estimates to that before sensitivity analysis. These consistent estimates therefore validates the high incidence of new-onset CKD in LT recipients and highlights the need for future studies to identify the role of personalized renal sparing strategies in preventing new-onset CKD, especially among higher risk populations including older, female LT recipients or those with perioperative AKI.

Strengths and limitations

To our knowledge, this is the first meta-analysis to study cumulative incidence of CKD post-LT. As available evidence surrounding post-LT CKD is mostly in the form of cohort studies due to the clinical nature of the disease, this systematic review and meta-analysis would form a stronger body of evidence from pooled results from the included studies. CKD defined by eGFR using commonly used formulas such as Cockcroft-Gault or MDRD may not be as precise in LT recipients; however, the latter has been found to be most accurate [2]. Furthermore, although the CKD Epidemiology Collaboration (CKD-EPI) equation has been proposed to be more accurate than the MDRD equation in the general population, previous studies have suggested that eGFR obtained by the MDRD equation may be closer to the true GFR than that obtained by the CKD-EPI equation in cirrhotic patients from liver transplant registries [51]. Of note, MDRD remains one of the recommended equations for eGFR reporting in adults by the National Kidney Disease Education Program [52]. More importantly, most studies in the earlier part of the decade reported eGFR using the MDRD equation. Thus, MDRD was chosen over CKD-EPI to ensure inclusion of a larger number of studies. By standardizing CKD definition by eGFR calculated by MDRD, we sought to decrease the heterogeneity and provide a potentially more accurate surrogate of renal function in our study. However, our systematic review and meta-analysis has a few limitations. First, pooling rates specifically from studies that used the MDRD formula to estimate GFR resulted in the exclusion of some large studies [4,47–50]. Second, most studies included patients with kidney dysfunction prior to LT, and only six studies [28,29,32,36,37,39] included specifically patients who had no CKD before LT. Nevertheless, on sensitivity analysis, the cumulative incidence of new-onset CKD post-LT in patients who had no CKD pre-LT were comparable to the estimates before sensitivity analysis. Additionally, further analysis on the effects of variables such as race, pre-LT dialysis, and dialysis duration on the cumulative incidence of CKD post-LT could not be conducted due to a paucity of data among the included studies. Future analysis with a larger number of Asian studies is also warranted to further evaluate the CKD post-LT trends between geographical regions. Lastly, we were unable to incorporate differing indications for transplantation and immunosuppressive regimen and its effect on CKD due to inconsistent reporting among studies.

Conclusion

In summary, CKD remains a common complication after LT, with a majority of patients diagnosed with stage 3 CKD. Although only a small fraction of these patients may go on to develop a need for dialysis and/or kidney transplantation, CKD in its more advanced stages (stages 4 and 5) is associated with significantly increased mortality. Thus, measures should be promptly taken to delay progression of CKD to the more advanced stages, which are associated with adverse outcomes.

Authorship

MDM, CHN and EXXT: conceptualization. SYL, RW, DJHT, CHN and WHL: data curation. CHN, DJHT and NS: formal analysis. MDM and EXXT: supervision. WHL, NS, EW, AV, MSS, JF, MDM and EXXT: validation. SYL, RW, DJHT, CHN, WHL, MDM and EXXT: writing, original draft. SYL, RW, DJHT, CHN, JQ, WHL, NS, EW, AV, MSS, JF, MDM and EXXT: writing, review and editing.

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Conflicts of interest

The authors have declared no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Summary of included articles.

Table S2. Risk of bias assessment of included articles.

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