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META-ANALYSIS

A meta-analysis on the prevalence of chronic kidney disease in liver transplant candidates and its associated risk factors and outcomes

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SUMMARY

Pre-liver transplant (LT) chronic kidney disease (CKD) has emerged as a leading cause of post-operative morbidity. We aimed to report the prevalence, associated risk factors, and clinical outcomes in patients with pre-LT CKD. Meta-analysis and systematic review were conducted for included cohort and cross-sectional studies. Studies comparing healthy and patients with s pre-LT CKD were included. Outcomes were assessed with pooled hazard ratios. 15 studies were included, consisting of 82,432 LT patients and 26,754 with pre-LT CKD. Pooled prevalence of pre-LT CKD was 22.35% (CI: 15.30%–32.71%). Diabetes mellitus, hypertension, viral hepatitis, and non-alcoholic fatty liver disease, and older age were associated with increased risk of pre-LT CKD: (OR 1.72 CI: 1.15–2.56, $P = 0.01$), (OR 2.23 CI: 1.76–2.83, $P < 0.01$), (OR 1.09; CI: 1.05–1.13, $P < 0.01$), (OR 1.73; CI: 1.10–2.71 $P = 0.03$), and (MD: 2.92 years; CI: 1.29–4.55years; $P < 0.01$) respectively. Pre-LT CKD was significantly associated with increased mortality (HR 1.38; CI: 1.2–1.59; $P < 0.01$), post-LT end-stage renal disease and post-LT CKD. Almost a quarter of pre-LT patients have CKD and it is significantly associated with post-operative morbidity and mortality. However, long-term outcomes remain unclear due to a lack of studies reporting such outcomes.

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Introduction

Advancements in the field of liver transplantation (LT) have yielded drastic improvements in short-term graft and patient survival outcomes [1,2]. However, the development of chronic kidney disease (CKD) before liver transplant persists as a complicated, multifaceted issue leading to a multitude of adverse outcomes including inferior graft survival, increased infection, increased health care cost, and longer duration of stay

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[3-7]. Patients with pre-LT CKD suffer increased intra-operative blood loss and haemostatic abnormalities, bearing a 15% increased risk of post-operative mortality [8,9]. Common contributing factors of pre-LT CKD include haemodynamic instability, viral or bacterial infection and excessive use of nephrotoxic drugs, which may lead to prolonged ischaemic or toxic insults to the kidney [9-12]. Use of calcineurin inhibitors (CNI) post-LT may also contribute to post-LT renal failure [9,13].

A rising prevalence of pre-LT CKD can be attributed to the larger proportion of LT patients suffering from manifestations of metabolic syndrome such as diabetic nephropathy, following the emergence of non-alcoholic steatohepatitis (NASH) as a leading cause of chronic liver disease and indicator for liver transplant [14-16]. Additionally, as a consequence of implementation of model for end-stage liver disease (MELD) score used for liver allograft allocation, there is an increased incidence of renal dysfunction amongst liver transplant candidates and increased donor liver prioritization to patients with renal dysfunction [15,17,18,19].

While CKD after liver transplant has been discussed extensively [6], studies describing renal dysfunction in the setting of liver disease before transplant are scarce [2]. Hence, this review aims to synthesize available evidence concerning the prevalence and post-operative outcomes of patients with CKD pre-LT using definition of CKD as per Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines. Additionally, the risk factors associated with CKD in LT candidates were evaluated. Results may aid physicians in identifying high-risk patients to predict and improve liver graft prognosis.

Methods

Search strategy

This meta-analysis was conducted with adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement for its synthesis [20]. A search was conducted via two electronic databases, Medline, and Embase, for relevant articles. The search strategy utilized was (*exp renal insufficiency, chronic/or (CAPD or CCPD or APD or end-stage renal or end-stage kidney or end-stage renal or end-stage kidney or ESRF or ESKF) or (chronic kidney or chronic renal or CKF or CKD or CRF or CRD).tw.) or (hemofiltration or haemofiltration or hemodialysis or haemodialysis) AND (exp Liver Transplantation/ or ((hepatic* or liver*) and (graft* or transplan* or transplantation)) or (sklt or slkt or clkt or cklt).tw.) AND ((pre* or before or prior or past or preced* or previous*).tw)*. The search was conducted on 22 February 2021 and no date restrictions were applied. A manual sieve of titles and abstracts was conducted on the included articles, and duplicates were removed via EndNote Reference Manager X9.

Eligibility and data extraction

The main inclusion criteria of articles were the description of prevalence and outcomes of CKD in pre-liver transplant patients. Only original articles were included. Study designs including retrospective cohorts, prospective cohorts, and cross-sectional studies were included. The exclusion criteria consisted of articles not written in English, or studies in the form of commentaries, editorials, reviews, and case studies. Two authors (VXYT and RRYH) independently performed the title and abstract sieve and full-text review based on the inclusion criteria. Discrepancies were resolved through the decision of an independent third author (PWLT).

Two authors (VXYT and RRYH) independently extracted relevant data from each article into a structured proforma. Extracted data included country of study, age, definition of CKD, CKD staging, BMI, MELD at listing, diabetes mellitus, hypertension, aetiology of liver disease, and clinical outcomes. Outcomes of interest included the pooled prevalence of CKD in pre-LT patients, risk factors, and post-operative outcomes, such as mortality, post-operative CKD, end-stage kidney disease (ESKD), and acute kidney injury (AKI). CKD was defined as an estimated glomerular filtration rate (eGFR) of <60 ml/minute, persisting for more than 3 months, in accordance with the KDIGO 2012 Guidelines or by ICD-9-CM codes [21]. 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 as defined by the guidelines [21]. Value estimates were derived through formulas when the mean and standard deviation were not provided [22].

Statistical analysis and quality assessment

All analysis were conducted in R (RStudio 1.3.1073) using the *meta* and *metaprop* command. When there were insufficient studies for a meta-analysis, the results were summarized systematically. A proportional meta-analysis was first conducted using a generalized linear mix model with Clopper-Pearson intervals to stabilize the variance as it has been established to offer the most accurate estimate in single-arm meta-analysis [23]. Heterogeneity measures including I^2 and Cochran's Q-

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test values, where an I^2 value of 25%, 50%, and 75% represented low, moderate, and high degree of heterogeneity respectively [24]. Heterogeneity was considered significant in a Cochran's Q test with P-value of ≤0.10 or a I^2>40% [24,25]. Regardless of heterogeneity score, all analyses were conducted in random effects. An assessment of publication bias was not carried out considering the scarcity of an accurate measurement tool for single-arm meta-analysis [26]. Next, the Mantel-Haenszel method and Paule-Mandel estimator was used to perform a meta-analysis of dichotomous variables to calculate pooled odds ratio (OR). The Paule-Mandel method is one of the most accurate method for pooling dichotomous variables [27]. Continuous variables and outcomes were analysed using the inverse variance method and DerSimonian-Laird estimator to calculate the pooled mean difference (WMD). Lastly, hazard ratio (HR) were pooled using inverse variance method in random effects. Quality assessment and risk of bias was conducted by two independent authors (VXYT and RRYH) using the Joanna Briggs Institute (JBI) Critical Appraisal Tool and is presented in the supplementary material. The JBI tool determines the extent to which studies have addressed the possibility of bias in its design, conduct and analysis [28].

Results

Summary of included articles

Our search strategy identified an initial 3429 articles, of which 2940 were excluded based on title and abstract. Duplicates were removed and 46 articles underwent full-text review. 15 articles met the inclusion criteria (Fig. 1). Several articles were excluded due to the varying definition of renal impairment and sparsity in reporting [29-33]. The included studies were conducted from 1991 till 2017 with a cumulative sum of 82,432 LT patients. The population samples consisted of liver transplant recipients identified by the respective institutions. They originated from nine different countries with five from USA [5,14,18,34,35] three from Japan

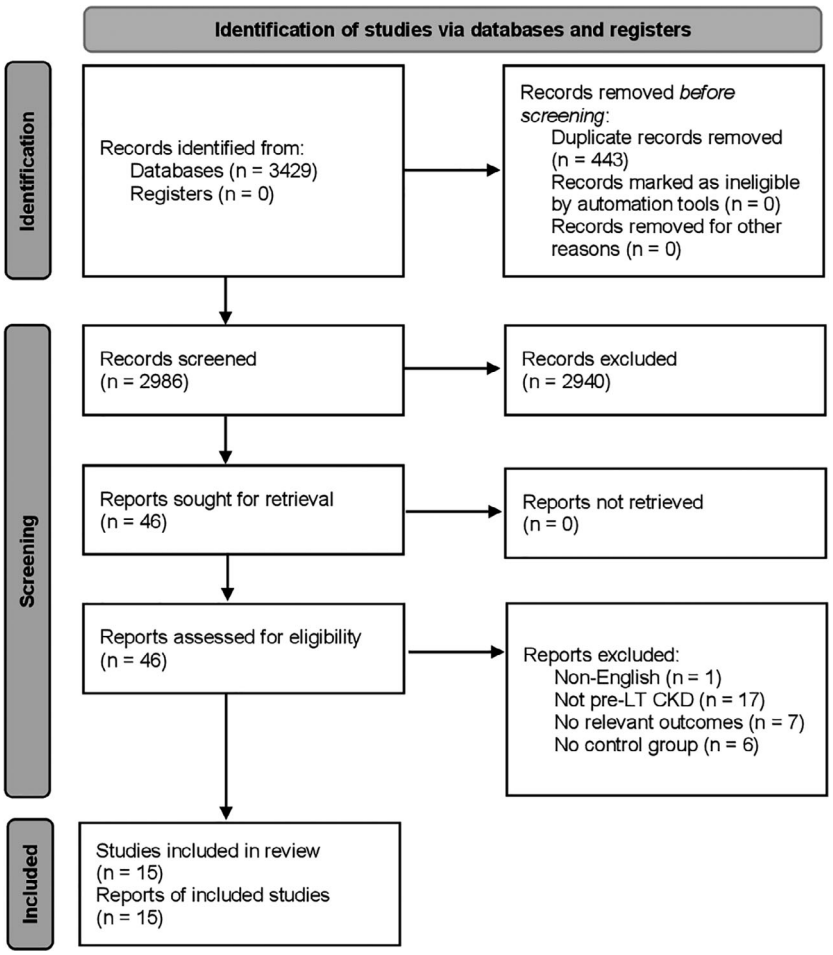

Figure 1 PRISMA flow diagram of systematic review.

[2,9,36] one from Korea [37], one from Taiwan [6], one from Germany [17], one from Brazil [38], one from Turkey [39], one from Italy [40], and one from Switzerland [13]. Mean age of CKD patients ranged from 46.8 years to 58.7 years, while mean age of non-CKD patients ranged from 46.3 years to 56.3 years. The range of quality was 7–10 using the JBI quality assessment tool. A summary of the included articles and their characteristics is provided in the Table S1.

Prevalence and associated factors of CKD before LT

Of the 82,432 patients who underwent liver transplantation, 26,793 were diagnosed with pre-LT CKD. Pooled analysis revealed an overall prevalence of 22.35% (CI: 15.29%–32.71%; Fig. 2). A sensitivity analysis excluding patients on preoperative renal-replacement therapy found 26.60% (CI: 17.61%–38.05%) of 1539 patients to have pre-LT CKD. Additionally, a sensitivity analysis excluding studies which recruited patients before the LT allocation according to MELD score found a CKD prevalence of 20.7% (CI: 14.06%–29.44%) in 41344 pre-LT patients [41-44]. Only three articles reported the breakdown rates of CKD stages. Horvatits *et al* reported a 7.1%, 9.1%, and 15.4% prevalence of stage 3, 4, and 5 CKD, respectively [17], while Nishi *et al*. reported a 15.4%, 3.6%, and 1.1% prevalence of stage 3, 4, and 5 CKD respectively [2], and Ojo *et al*. reported a 19.4% and 7.4% prevalence of stage 3 and > stage 4 CKD respectively [35].

An analysis of risk factors including population characteristics, concomitant illnesses, and liver disease aetiology was conducted as summarized in Table 1. Age was significantly higher in the CKD group (MD: 2.92 years CI: 1.29–4.54 years, $P < 0.01$). Patients with diabetes mellitus and hypertension had significantly higher odds of CKD (OR: 1.72; CI: 1.54–2.56; $P = 0.01$ and OR: 2.23; CI: 1.76–2.83; $P < 0.01$), respectively. Patients with aetiologies including viral hepatitis and non-alcoholic fatty liver disease (NAFLD) had significantly higher odds of concurrent CKD (OR: 1.09 CI: 1.05–1.13; $P < 0.01$ and OR: 1.73; CI: 1.10–2.72; $P = 0.03$ respectively). Risk factors, such as male gender, cardiovascular diseases, alcoholic hepatitis, and AKI were associated with increased odds of CKD, but these were not statistically significant.

Clinical outcomes

Mortality

Pre-LT CKD patients were found to have higher post-LT mortality (HR: 1.38; CI: 1.20–1.59; $P < 0.01$, Fig. 3). Cullaro *et al*. reported higher post-transplant mortality in patients with Stages 4 and 5 CKD: HR 1.16; CI: 1.08–1.25; HR 1.42, CI: 1.28–1.58; and HR 1.42; CI: 1.31–1.54 for CKD stages 3, 4, and 5 respectively [14].

Acute kidney injury (AKI) after LT

The differing definitions of AKI disallowed a pooled analysis of prevalence of AKI post-LT in patients with pre-LT CKD. Narciso *et al*. defined AKI according to the acute kidney injury network (AKIN) recommendations [45], while Inoue *et al*. defined it as an increase in serum creatinine level of 0.5 mg/dl above baseline [36], and Süleymanlar *et al*. as a 1.5 mg/dl or 100% rise in serum creatinine above baseline [39]. Narciso *et al*., Inoue *et al*. and Süleymanlar *et al*. reported the incidence of post-LT acute kidney injury (AKI) in pre-LT CKD patients to be 84%, 25%, and 45.5%, respectively [36,38,39].

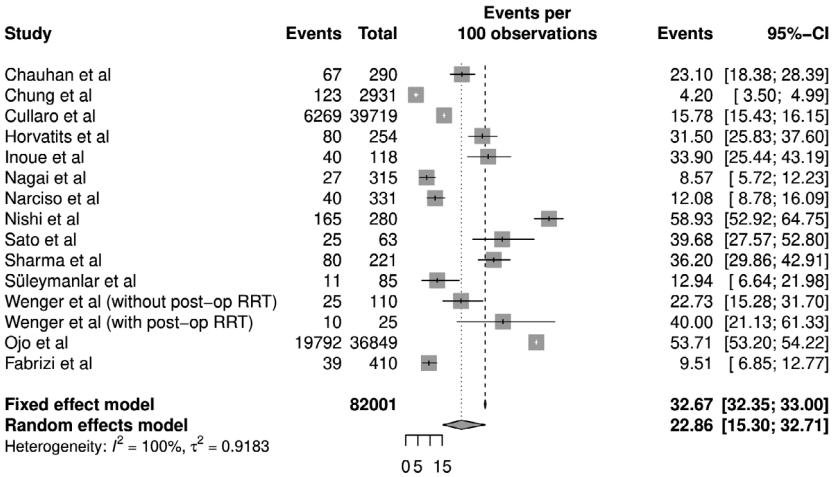

Figure 2 Forest plot of overall prevalence of pre-LT CKD in liver transplant patients.

Table 1. Risk factors for Pre-LT CKD.

	Total	Effect size	95% Confidence interval	*P*-value
Weighted mean difference				
Age	43879	2.92	1.29–4.55	**<0.01**
BMI	425	0.15	−0.89–1.20	0.97
MELD	40538	−4.49	−4.66 to −4.33	0.59
Odds ratios				
Male gender	43854	1.45	0.69–3.04	0.27
Diabetes mellitus	43879	1.72	1.15–2.56	**0.01**
Hypertension	4025	2.23	1.76–2.83	**<0.01**
Cardiovascular diseases	3221	2.98	0.02–412.1	0.22
Alcoholic Hepatitis	43391	1.05	0.515–2.12	0.85
Viral Hepatitis	43454	1.09	1.05–1.13	**<0.01**
NAFLD	40419	1.73	1.10–2.78	**0.03**
HCC	1031	0.76	0.37–1.58	0.25
AKI	534	1.69	0.25–11.18	0.36
Acute liver failure	621	0.85	0.0–8274893	0.92

Significant *P*-values are indicated in bold.

AKI, acute kidney injury; BMI, body mass index; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; pre-LT RRT, pre-liver transplant renal-replacement therapy; WMD, weighted mean difference.

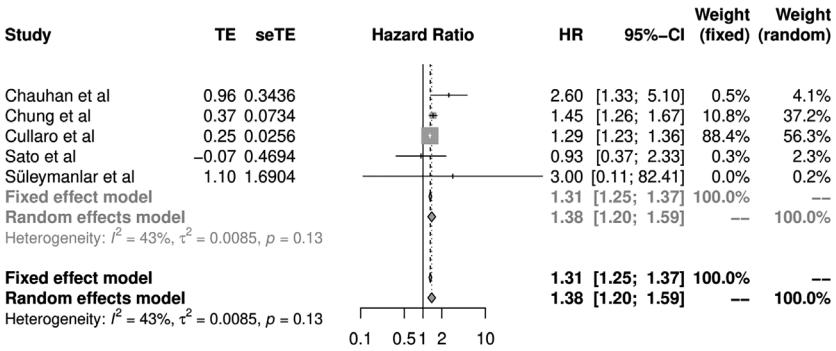

Figure 3 Forest plot of mortality in pre-LT CKD patients in hazard ratios.

Chronic kidney disease (CKD) after LT

Ojo *et al.* reported that stage 3 and stage 4 CKD pre-LTs were associated with a relative risk of 2.54 and 3.78 for post-LT CKD, respectively [35]. Nishi *et al.* identified pre-LT CKD of stages 4 or 5 to be significantly associated with stages 4 and 5 CKD post-LT on multivariate analysis (HR 8.93, CI: 1.00–70.19; $P = 0.05$) [2]. Lee *et al.* found that a higher pre-LT eGFR was associated with reduction in CKD after LT (HR: 0.97; CI: 0.96–0.98; $P < 0.001$) [37].

Three studies, Chauhan *et al.*, Narciso *et al.* and Sharma *et al.* reported the incidence of post-LT ESKD among pre-LT CKD patients as 68.0%, 25.0%, and 15.0%, respectively [5,18,38]. Narciso *et al.* and Sharma *et al.* excluded patients on pre-LT renal-replacement therapy. However, varying diagnostic criteria of ESKD were used in all three articles. Chauhan *et al.* used ICD9 coding or documentation of maintenance renal-replacement therapy (RRT), Narciso *et al.* used National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines of eGFR <15ml/min per 1.73 m^2 or permanent need of dialysis, while Sharma *et al.* defined ESKD as eGFR <30 ml/min persisting for ≥ 3 months or initiation of RRT or listing of renal transplants. Narciso *et al.* identified pre-LT CKD to be independently associated with post-LT ESKD (HR = 3.78; CI: 1.47–8.22). Although Chauhan and colleagues included patients with ESKD in their study, they have also separately described pre-LT Stage 3 CKD to be significantly associated with post-LT ESKD, after adjusting for effects of AKI (HR = 4.8; CI: 2.0–11.8; $P = 0.001$).

With regards to post-transplant kidney dialysis, Nagai *et al.* reported the incidence of post-LT dialysis required

in patients with and without pre-LT CKD, with the inclusion of patients on pre-LT dialysis. In that study, pre-LT CKD patients had significantly higher odds of requiring post-LT dialysis (OR = 5.59; CI: 1.27–24.7; P = 0.02) [34].

Discussion

In our study on CKD in patients on the LT waitlist, we found that about almost a quarter of potential LT candidates have CKD. This is higher than that expected in the general population, where CKD has been reported to affect 8% and 16% of the general population [46]. CKD in pre-LT cirrhotic patient could be contributed by complications of advanced liver disease, such as type 2 hepatorenal syndrome or IgA nephropathy [47-49]. Moreover, the prevalence of CKD among patients with liver cirrhosis has risen from 7.8% in 2002 to 14.6% in 2017 [14], possibly contributed by the rise in prevalence of CKD-associated comorbidities, such as diabetes and cardiovascular disease [50]. Due to improved care of patients with decompensated liver cirrhosis, patients may survive longer and thus increase the chance of CKD development while on the LT waitlist. In cirrhotic patients on the LT waitlist, liver allograft allocation is also at present mostly dependent on the MELD score.

We found that there is a large variability in prevalence of CKD pre-LT in the studies included, ranging from 4.2% to 58.93%. The increasing trend of CKD prevalence over the years may account for its variability in the prevalence of pre-LT CKD in the studies included, which have variable study periods ranging from 1990 to 2018. Additionally, geographical location and differences in methods of renal function measurement may account for the high variability of prevalence of pre-LT CKD [12,51]. Hence, this large variability should be taken into account when interpreting the data in the context of the local setting.

Expectedly, we found that factors, such as older age, diabetes, hypertension, viral hepatitis, and NAFLD as the cause of liver cirrhosis were significantly associated with CKD pre-LT. Interestingly, MELD was not found to be associated with pre-LT CKD. The MELD score is based on creatinine, bilirubin, INR (international normalized ratio), serum sodium and can be influenced by disease aetiology. Currently, NAFLD is shown to be significantly associated with CKD as compared with previously where viral hepatitis was the main cause of transplant rather than NAFLD. The MELD score of patients with viral hepatitis, however, is largely influenced by bilirubin and INR as opposed to renal dysfunction in NAFLD. As in previous meta-analyses, we found that the presence of CKD pre-LT has a major impact on mortality. Similarly, our review of included articles found an association between pre-LT CKD and post-LT ESKD [12,50,52]. However, the differing definitions of CKD prevented a pooled analysis that was unaccounted for in the previous meta-analysis [12]. In our study, a pooled analysis was possible as we ensured standardized CKD definitions across all included studies, as per the KDIGO guidelines. A systematic review of post-LT ESKD thus reveals the rate of post-LT ESKD to be 25%–68% in patients with pre-LT CKD [12]. Furthermore, Ruebner and colleagues have reported that in 86 patients with pre-LT persistent eGFR <30 ml/min undergoing LT, about a third had ESKD at and death at 3 years (31% and 37% respectively) [29]. Patients often experience a decrease in eGFR by 10 ml/min immediately post-LT [53].

Clinical implications

Our meta-analysis on the prevalence of CKD in potential LT recipients shows that almost a quarter of them have CKD pre-LT. Given that the proportion of LT candidates with CKD is expected to increase further, prudent pre, perioperative- and post-operative management strategies to lessen the frequency and severity of renal failure are crucial to reducing the risk of adverse post-operative outcomes [18]. Pre-operative approaches include good control of metabolic and cardiovascular risk factors, and minimizing renal insults where possible. Perioperatively, minimal blood loss, avoiding hypotension or hypovolaemia, and surgical considerations such as the piggy-back technique may be considered [13,54]. Post-operative management involves minimal or if possible complete avoidance of nephrotoxic medication to preserve existing renal function [9,13]. Identification of patients with risk factors of ESKD, such as DM, hypertension, age, viral or NASH cause of cirrhosis will be useful to identify patients at higher risk of post-LT ESKD who will benefit from pre-emptive measures to decrease risk of CKD progression post-LT.

Strengths and limitations

To the best of our knowledge, this is the largest meta-analysis of 82,022 patients, which reports the prevalence, risks factors and post-LT outcomes in patients with pre-LT CKD. There are several limitations of this review. Firstly, there was a lack of studies reporting

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more uncommon outcomes, such as post-transplant ESKD, 1-year progression of CKD and post-transplant dialysis requirement. It was thus not possible to conduct a pooled meta-analysis for these outcomes, which could have yielded significant findings. Additionally, the paucity of studies reporting prevalence and outcomes of pre-LT CKD according to CKD stage prevents adjustments according to extent of renal injury. Moreover, as most of these studies were observational, and each may have used varied renal sparing protocols in management of post-LT CKD, this could have also contributed to heterogeneity.

Another limitation of the study was the heterogeneity of immunosuppressive therapy regimen used in the included studies. As such, it was not possible to investigate the association between the various immunosuppression drugs and transplant outcomes. Studies included also did not further stratify the aetiology of CKD in patients included; thus, further analyses on the effect of type of CKD on post-LT outcomes were impossible. Nevertheless, our study has several novel additions to existing limited literature on pre–LT CKD. In this study, we have reported that more than one-fifth of potential LT recipients have CKD. In keeping with previous meta-analysis [12], our study has confirmed that pre-LT CKD is associated with all-cause mortality post-LT. Moreover, we have identified factors that were associated with increased pre-LT CKD.

Conclusion

This study reports a high prevalence of pre-operative CKD in patients undergoing liver transplant. Age, diabetes mellitus, hypertension, non-alcoholic fatty liver disease, and viral hepatitis are significant risk factors for pre-LT CKD. This meta-analysis and systematic review found patients with CKD to have a higher risk of post-operative complications including mortality, end-stage renal disease, Stage 4 CKD and required dialysis. Due to the paucity of data, future studies should aim to investigate these long-term outcomes and also effect of SLKT in a subset of these patients.

Authorship

VXYT, RRYH, PWLT, EXXT, and CHN contributed to the acquisition of data, analysis and interpretation of data and drafted the article. DJHT, YO, EYT, DH, EXXT, AV, MM: aided in revising the article critically for important intellectual content. All authors read and gave final approval of the version to be submitted.

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Conflicts of interests

None of the authors declares any conflict of interest.

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All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. No writing assistance was obtained in the preparation of the manuscript. The manuscript, including related data, figures, and tables has not been previously published and that the manuscript is not under consideration elsewhere.

Data availability statement

All articles in this manuscript are available from Medline and Embase.

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.

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