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Original Article

ORIGINAL ARTICLE

Prevalence and outcomes of chronic liver disease in patients receiving dialysis: systematic review and meta-analysis

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ABSTRACT

Background. Patients receiving dialysis for end-stage kidney disease (ESKD) commonly co-exhibit risk factors for hepatic impairment. This systematic review and meta-analysis aimed to quantify the coexistence of chronic liver disease (CLD) and characterize risk factors and outcomes.

Methods. We searched the following databases from inception to May 2021: CINAHL, Cochrane Library, Embase, Kings Fund Library, MEDLINE and PubMed. The protocol was pre-registered on PROSPERO (study ID: CRD42020206486). Studies were assessed against three inclusion criteria: adults (>18 years) with ESKD receiving dialysis, primary outcome involving CLD prevalence and publications in English. Moderator analysis was performed for age, gender, study size and publication year. Sensitivity analysis was performed where applicable by removing outlier results and studies at high risk of bias.

Results. Searches yielded 7195 articles; of these 15 met the inclusion criteria. A total of 320 777 patients were included. The prevalence of cirrhosis and non-alcoholic fatty liver disease (NAFLD) was 5% and 55%, respectively. Individuals with CLD had 2-fold higher mortality than those without {odds ratio [OR] 2.19 [95% confidence interval (CI) 1.39–3.45]}. Hepatitis B [OR 13.47 (95% CI 1.37–132.55)] and hepatitis C [OR 7.05 (95% CI 4.00–12.45)], but not diabetes, conferred increased cirrhosis risk. All studies examining NAFLD were judged to be at high risk of bias. We found no data on non-alcoholic steatohepatitis (NASH). Deaths from CLD, cancer and infection were greater among cirrhotic patients.

Conclusions. CLD is prevalent in dialysis patients. Hepatitis B and C confer increased risk of CLD. The impact of NAFLD and NASH cirrhosis requires further study. CLD is associated with an increased risk of mortality in this setting.

Keywords: dialysis, ESRD, haemodialysis, peritoneal dialysis, systematic review

INTRODUCTION

End-stage kidney disease (ESKD) and chronic liver disease (CLD) share common cardiometabolic and pathogenic risk factors. For example, diabetes mellitus (DM) is one of the leading causes of ESKD worldwide [1] and, in addition to other metabolic risk factors, is a common finding in patients with non-alcoholic fatty liver disease (NAFLD). NAFLD, the most common liver

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disorder in the Western world, affects 17–46% of adults [2]. NAFLD progresses to non-alcoholic steatohepatitis (NASH) in ∼20% of cases [3]. NASH can lead to liver fibrosis and cirrhosis [4] and, with a increasing prevalence predicted over the next decade, is soon expected to overtake chronic infection with hepatitis B and C as the leading cause of cirrhosis worldwide [5–7]. Nevertheless, hepatitis B and C remain prevalent particularly within haemodialysis (HD) populations globally despite improvements in infection control, uptake of hepatitis B vaccines and the emergence of novel therapeutic options for hepatitis C [8–10].

The prevalence of combined advanced liver and kidney impairment is increasing, as evidenced by increasing numbers of simultaneous liver–kidney transplant referrals over the past 2 decades [11]. This is partly due to increased emphasis on kidney impairment in liver transplant scoring systems, but the increasing prevalence of liver and kidney disease in the context of DM and obesity is also a probable contributor.

Despite the increasing burden of combined liver and kidney dysfunction, relatively little attention has been paid to this patient group, despite high risks of haemodynamic instability, malnutrition, bleeding and infection [12]. The primary aim of this systematic review and meta-analysis was to summarize available evidence on the prevalence of CLD in patients treated with dialysis. It also assessed known aetiological factors, severity of CLD and clinical outcomes. This is the first systematic review and meta-analysis to evaluate CLD not limited to viral hepatitis and outcomes in dialysis patients.

MATERIALS AND METHODS

The systematic review and meta-analyses were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [13]. The methods were preregistered on PROSPERO (study ID: CRD42020206486).

Search strategy and review process

The search strategy is available from https://www.crd.york.ac.uk/PROSPEROFILES/206486_STRATEGY_20201008.pdf. In brief, a combination of terms for ESKD, HD, peritoneal dialysis (PD), liver disease and outcomes was used. Articles were searched across the following databases from inception until 4 May 2021: CINAHL, Cochrane Library, Embase, Kings Fund Library, MEDLINE and PubMed. A total of 7181 records were retrieved with a further 14 identified through lateral searches. After removing duplicates, 5808 papers were screened by the first author against the following inclusion criteria: adults (>18 years) with ESKD treated with dialysis, primary outcome related to the prevalence of CLD (defined as the presence of hepatic inflammation, steatosis, fibrosis or cirrhosis) and publication in English.

A total of 93 articles were selected for full-text review. Two authors (O.S. and S.R.) screened articles independently for consensus on inclusion. Discrepancies were resolved through discussion with members of the study team (S.S. and K.F.). A total of 15 studies met the inclusion criteria and were used in the analysis [14–28] (see Figure 1). Detailed reasons for exclusion were noted.

Baseline study data summarizing study characteristics are outlined in Table 1. All data extracted are incorporated into this article and the online supplementary material.

Outcome measures

The primary clinical outcome measure of interest was the prevalence of CLD among patients treated with dialysis. Other secondary outcome measures included differences in mortality rates of patients treated with dialysis both with and without coexistent CLD and differences in mortality from cardiovascular disease, infection, malignancy and liver disease. Other prespecified measurements of interest included rates of comorbidities associated with an increased risk of CLD (DM, obesity and viral hepatitis), the proportion of patients with systemic inflammation, anaemia and depression and the underlying aetiology and severity of liver disease.

Risk of bias assessment

Risk of bias assessment was performed by two authors (O.S. and H.U.) independently using the Newcastle–Ottawa Scale (NOS) as recommended by Cochrane [29, 30]. This tool includes assessment of the quality of patient selection, comparability and exposure. Results were then discussed and discrepancies were resolved by consensus.

Statistical methods

Data analysis was undertaken using Review Manager 5 software, version 5.4 (Cochrane Collaboration, London, UK) and MetaEssentials: workbooks for meta-analysis, version 1.5 (Erasmus Research Institute of Management, Rotterdam, The Netherlands) [31]. All relevant data from individual studies were extracted and pooled manually. A random effects model was applied to the data undergoing meta-analysis in order to account for heterogeneity and the impact of differing sample sizes within the populations of interest [32]. Data pertaining to clinical outcomes were handled using odds ratios (ORs) with 95% confidence intervals (CIs). Statistical heterogeneity between combined studies was measured using the I^2 test, which defines the percentage of total variation across studies due to heterogeneity rather than chance [33]. Levels of heterogeneity are typically defined as follows: low (<25%), moderate (25–75%) and high (>75%). Moderator analysis was performed for age, gender, study size and year of publication only, due to insufficient data on other shared risk factors. Sensitivity analyses were performed where applicable by removing outlier results and studies at high risk of bias to assess the robustness of synthesized results.

RESULTS

Study and patient characteristics

This meta-analysis selected 15 studies published between 1992 and 2021 (Figure 1). Baseline study characteristics are outlined in Table 1. Six studies were performed in East Asia [15, 16, 20–22, 28], five in Europe [14, 17, 19, 25, 26], two in the USA [18, 24] and one in North Africa [27]. One study was multinational [23]. Follow-up ranged from 1 to 15 years (two studies were cross-sectional). The number of included patients was 320 777. The mean age of participants ranged from 49 to 71 years. The proportion of male participants ranged from 43 to 68%. Only two studies [18, 23] described participant ethnicity. Seven studies [14, 18, 19, 25–28], including the largest study involving 291 663 patients drawn from a 5% random sample of US Medicare beneficiaries [18], involved HD patients only; four [17, 20, 22, 24] involved (PD) patients only. The remaining four studies [15, 16, 21, 23] involved both PD and HD patients. Three studies evaluated patients on dialysis with NAFLD [25–27]. The remaining studies evaluated patients with cirrhosis. A total of 21 523 patients had cirrhosis. Information on cirrhosis diagnosis came from abstraction from coding records, patient databases and clinical notes in 98% and from review of histological, clinical or

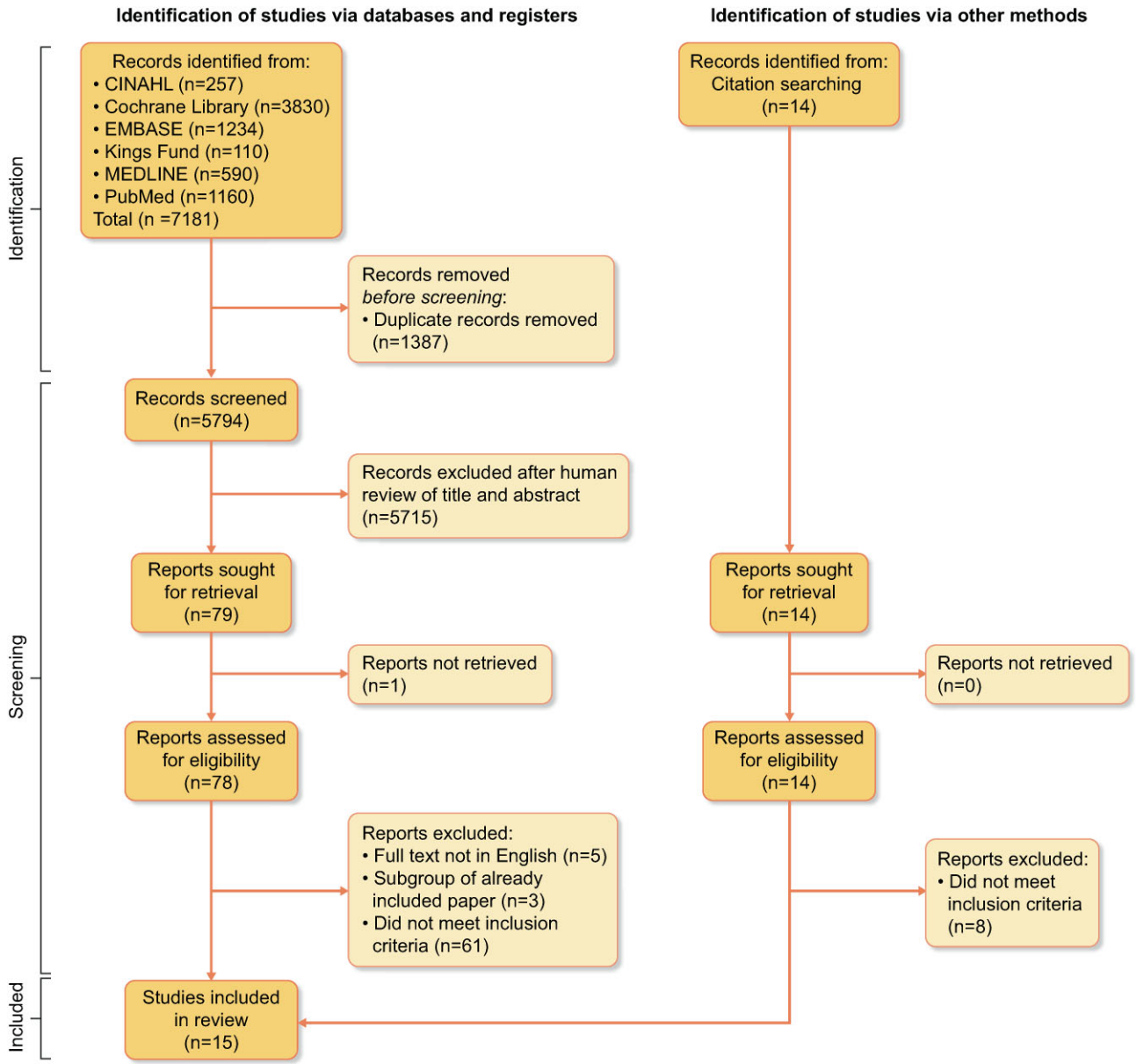

FIGURE 1: Study selection flowchart.

radiological findings in 2%. NAFLD was identified in 119 patients based on ultrasound or FibroScan imaging findings.

Risk of bias

Risk of bias was assessed using the NOS (Supplemental Tables S1–S3). Eleven studies were of high quality, with a score ≥7. Four scored ≤6 [24–27] and therefore were at high risk of exhibiting bias. Sensitivity analyses were performed, where applicable, to examine data excluding studies exhibiting high risk of bias (Supplemental Table S4). All studies evaluating NAFLD exhibited a high risk of bias.

Prevalence of CLD among patients with ESKD receiving dialysis

The prevalence of cirrhosis ranged from 2 to 11%. The overall pooled prevalence of cirrhosis across studies using a random effects model was 5% (Figure 2). There was no significant difference in prevalence between those treated with HD (5%) and PD (5%). Sensitivity analyses performed excluding outlier, case–control and case series studies did not yield significantly different results (Supplemental Figure S3 and Supplemental Table S4). Seven studies assessed cirrhosis severity [14, 15, 17, 20–22, 24]. A total of 60% had Child–Pugh A, 23% Child–Pugh B and 17% Child–Pugh C cirrhosis (Table 2). Cirrhosis aetiology was only available from a minority of studies but was pooled from the six studies where there were available data [15, 17, 19, 21, 22, 24]. A total of 35% had cirrhosis secondary to hepatitis B, 32% secondary to hepatitis C and 17% secondary to alcohol-related liver disease. The aetiology of cirrhosis was undefined in 15% of patients across these six studies (Table 3). Heterogeneity across these studies was high ($I^2 = 98\%$). Sensitivity analyses excluding studies at high risk of bias did not yield significantly different results in terms of the severity and aetiology of cirrhosis or heterogeneity (Supplemental Table S4).

Table 1. Study and participant characteristics

Study	Country	Length of follow-up	Study period	Population source		Patients included, *n*	Demographics					Study design	Inclusion criteria	Exclusion criteria	Method of liver disease diagnosis
							Age (years)	Male (%)	Ethnicity	HD (%)	PD (%)				
Artru 2019 [14]	France	2 years	2000–2014	All patients in Nephronor database, Nord Pas du Calais	Regional population	7658	70.5	58.1	Not described	100	0	Cohort study	>18 years, HIV negative, no previous transplant	None described	Histological, clinical or radiological findings
Chien 2012 [16]	Taiwan	7.6 years (PD) 6.9 (HD)	1999–2008	Taiwan National Health Insurance Research Database	National population database	12 054	59.5	46.6	Not described	93.7	6.3	Cohort study	>18 years, >90 days on dialysis	Kidney transplant (prior to or during follow up), multiple modality switches	ICD-9 CM codes
Che-Yi 2016 [15]	China	6 years	2004–2013	China Medical University Hospital	Single hospital population	425[a]	62.5	64.7	Not described	80	20	Cohort study	>3 months on dialysis	Patients receiving HDF	ICD-9 CM codes
[b]	Taiwan	Up to 15 years	1996–2011	Longitudinal Health Insurance Database for Catastrophic Illness Patients of the Taiwan National Health Research Institute	National population database	1395[c]	60.3	62.1	Not described	80	20	Cohort study	ESKD with liver cirrhosis	None described	
Deshpande 2019 [18]	USA	1 year	2005–2016	5% random sample of USA Medicare beneficiaries receiving inpatient or outpatient care	National population database	291 663	67.3	55	55% White, 32.5% Black, 3.0% Asian, 5.8% Hispanic, 1.4% Native American	100	0	Cohort study	ESKD treated with dialysis with HCV infection/cirrhosis	None described	ICD-9 or ICD-10 CM codes
De Vecchi 2002 [17]	Italy	3.2 years (CLD) 2.8 years (controls)	1985–1999	Nephrology Department, University of Milan	Single hospital population	62[d]	57.3	67.7	Not described	0	100	Case control study	ESKD treated with PD	None described	Histological, clinical or radiological findings
Espinosa 2001 [19]	Spain	8 years	1992–1999	5 dialysis units, Cordoba	Regional population	175	53.2	53.1	Not described	100	0	Cohort study	Treatment with thrice weekly standard HD	<6 months on HD, HCV negative initially but then developed hepatitis, HbeAg positive	Histological, clinical or radiological findings
Huang 2011 [20]	Taiwan	3.3 years (CLD) 2.6 years (controls)	1984–2008	Department of Nephrology, Taichung Veterans General Hospital	Single hospital population	90[e]	48.9	43.3	Not described	0	100	Case control study	ESKD treated with PD	None described	Histological, clinical or radiological findings

Table 1. Continued.

Study	Country	Length of follow-up	Study period	Population source		Patients included, *n*	Demographics					Study design	Inclusion criteria	Exclusion criteria	Method of liver disease diagnosis
							Age (years)	Male (%)	Ethnicity	HD (%)	PD (%)				
Kim 2016 [21]	South Korea	2.9 years (CLD) 3.2 years (controls)	2000–2011	Gachon University Gil Medical Center, Korea	Single hospital population	1069	55	56	Not described	69.4	30.6	Cohort study	ESKD treated with dialysis	<18 years, recovery of native kidney function, kidney transplant during follow-up period, incomplete medical records	Clinical or radiological findings
Lee 2017 [22]	South Korea	4.8 years (CLD) 6.4 years (controls)	2007–2014	Dong-A University Hospital, Busan	Single hospital population	295	59.1	59	Not described	0	100	Case control study	>18 years, PD catheter *in situ*	HD catheter sited prior to treatment with PD	Histological, clinical or radiological findings
Marcelli 1996 [23]	USA	Up to 5 years	1986–1991	US Renal Data System	National population database	2900	59.9	53.7	White only	78.8	21.2	Cohort study	White patients starting dialysis	Patients who died within 30 days of starting RRT	USRDS database
	Italy	Up to 5 years	1986–1991	Lombardi Dialysis and Transplant Registry	Regional population	1296	55.9	62.1	White only	69.3	30.7	Cohort study	White patients starting dialysis	Patients who died within 30 days of starting RRT	RLDT database
Marcus 1992 [24]	USA	2.1 years	1980–1990	Division of Nephrology, University of Michigan	Single hospital population	9[e]	Not described	Not described	Not described	0	100	Case series	Chronic liver disease and ascites at time of starting PD	None described	Histological, clinical or radiological findings
Mikolasevic 2015 [25]	Croatia	1.5 years	Not specified	Department of Nephrology, Dialysis and Kidney Transplantation, Rijeka	Single hospital population	94	69.1	54.3	Not described	100	0	Cohort study	Treatment with thrice weekly HD 4–5 h per session	Active HBV/HCV infection, alcohol abuse, other liver diseases, hepatotoxic medications, failed transient elastography, AKI or metastatic cancer, kidney transplant during follow-up period	Transient elastography
Stolic 2016 [26]	Serbia	Cross-sectional study	Not specified	HD patients at Clinical Center Kragujevac	Single hospital population	72	All > 65	56.9	Not described	100	0	Cross-sectional study	>65 years, ESKD treated with HD, previous liver USS imaging	<3 months on HD, hospitalization within last 6 months, infection with hepatotrophic virus, DM, previous HPB surgery, BMI >30, statin/glucocorticoid therapy	USS comparison of echogenicity of right kidney/spleen with liver

Table 1. Continued.

Study	Country	Length of follow-up	Study period	Population source		Patients included, *n*	Demographics					Study design	Inclusion criteria	Exclusion criteria	Method of liver disease diagnosis
							Age (years)	Male (%)	Ethnicity	HD (%)	PD (%)				
Nakayama 2000 [28]	Japan	6 years	1993–1999	16 dialysis centres mostly in Tokyo	Regional population	1470	55.4	60.5	Not described	100	0	Cohort study	ESKD treated with HD	None described	Clinical or radiological findings
Behairy 2021 [27]	Egypt	Cross-sectional study	2018–2019	2 dialysis centres in Egypt	Regional population	50	48.6	60	Not described	100	0	Cross-sectional study	>18 years, thrice weekly HD > 6 months, 4 h per session	HBV/HCV/HIV positive, decompensated or known liver disease, alcohol intake, diabetes mellitus, BMI >30, use of drugs known to induce liver steatosis	Transient elastography

[a]A total of 425 patients included in final analyses however prevalence data based on data from 9975 patients prior to propensity matching.
[b]Where data from Chien *et al.* [16] are also analysed, these data have not been included due to risk of double counting.
[c]A total of 1395 patients included in final analyses, however group selected from 5365 patients prior to propensity matching.
[d]A total of 41 controls and 21 cirrhotic PD patients included in the final analysis from 381 patients prior to matching.
[e]A total of 60 controls and 30 cirrhotic PD patients included in the final analysis from 728 prior to matching.
[f]A total of 9 patients included in the final analysis with prevalence data calculated from information about the total number of records reviewed ($n = 465$).

Study or subgroup	Prevalence (%)	SE	Cirrhosis, *n*	No cirrhosis, *n*	Weight (%)	Prevalence (%) IV, random (95% CI)	Year
Haemodialysis							
Nakayama	3.53	0.48	52	1418	7.8	3.53 (2.59–4.47)	2000
Espinosa	5.71	1.75	10	165	4.8	5.71 (2.28–9.14)	2001
Chien	6.23	0.23	703	10590	8.1	6.23 (5.78–6.68)	2012
Kim	4.45	0.75	33	709	7.3	4.45 (2.98–5.92)	2016
Artru	3.97	0.22	304	7354	8.1	3.97 (3.54–4.40)	2019
Deshpande	6.74	0.05	19661	291663	8.2	6.74 (6.64–6.84)	2019
Subtotal (95% CI)			20763	311899	44.3	5.09 (3.77–6.41)	
Heterogeneity: $\tau^2 = 2.30$; $\chi^2 = 201.56$; df = 5 (P < 0.00001); $I^2 = 98\%$							
Test for overall effect: Z = 7.58 (P < 0.00001)							
Peritoneal dialysis							
Marcus	1.94	0.64	9	456	7.5	1.94 (0.69–3.19)	1992
De Vecchi	5.51	1.17	21	360	6.3	5.51 (3.22–7.80)	2002
Huang	4.12	0.74	30	698	7.3	4.12 (2.67–5.57)	2011
Chien	5.26	0.81	40	721	7.1	5.26 (3.67–6.85)	2012
Kim	3.36	1	11	316	6.7	3.36 (1.40–5.32)	2016
Lee	11.18	1.84	33	262	4.6	11.18 (7.57–14.79)	2017
Subtotal (95% CI)			144	2813	39.5	4.81 (2.99–6.63)	
Heterogeneity: $\tau^2 = 4.10$; $\chi^2 = 30.10$; df = 5 (P < 0.00001); $I^2 = 83\%$							
Test for overall effect: Z = 5.18 (P < 0.00001)							
Mixed haemodialysis and peritoneal dialysis populations							
Marcelli	1.86	0.21	78	4118	8.1	1.86 (1.45–2.27)	1996
Che-Yi	5.39	0.23	538	9437	8.1	5.39 (4.94–5.84)	2016
Subtotal (95% CI)			616	13555	16.2	3.62 (0.16–7.08)	
Heterogeneity: $\tau^2 = 6.18$; $\chi^2 = 128.46$; df = 1 (P < 0.00001); $I^2 = 99\%$							
Test for overall effect: Z = 2.05 (P = 0.04)							
Total (95% CI)			21523	328267	100	4.75 (3.57–5.93)	
Heterogeneity: $\tau^2 = 4.44$; $\chi^2 = 763.47$; df = 13 (P < 0.00001); $I^2 = 98\%$							
Test for overall effect: Z = 7.88 (P < 0.00001)							
Test for subgroup differences: $\chi^2 = 0.61$; df = 2 (P = 0.74); $I^2 = 0\%$							

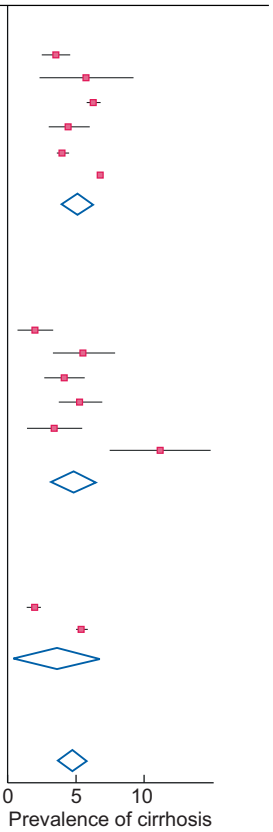

FIGURE 2: Prevalence of cirrhosis in dialysis patients by modality. SE: standard error; IV: inverse variance; df: degrees of freedom; I^2: total variability due to heterogeneity.

Table 2. Severity of cirrhosis in ESKD patients

Study		Child–Pugh A, *n*	Child–Pugh B, *n*	Child–Pugh C, *n*	Total, *N*
Haemodialysis					
Che-Yi 2016 [15] (HD cohort)[a]		199	59	82	340
Kim 2016 [21] (HD cohort)		15	13	5	33
Artru 2019 [14]		150	52	11	213
	Subtotal (*n*)	364	124	98	586
	%	62	21	17	
Peritoneal dialysis					
Marcus 1992 [24]		0	7	2	9
De Vecchi 2002 [17]		10	5	6	21
Huang 2011 [20]		16	12	2	30
Che-Yi 2016 [15] (PD cohort)[a]		48	17	20	85
Kim 2016 [21] (PD cohort)		6	3	2	11
Lee 2017 [22]		20	10	3	33
	Subtotal (*n*)	100	54	35	189
	%	53	29	18	
Total		464	178	133	775
% Overall		60	23	17	

[a]Data on severity only provided for CMUH cohort.

The overall prevalence of NAFLD across studies using a random effects model was 55% (Figure 3). Heterogeneity across these studies was low ($I^2 = 0\%$). It was not possible to perform sensitivity analyses for this subgroup, as all studies exhibited a high risk of bias.

Mortality risk and the effect of CLD in ESKD receiving dialysis

Patients with CLD had a >2-fold higher likelihood of mortality compared with those without CLD [OR 2.19 (95% CI 1.39–3.45)]

Table 3. Aetiology of cirrhosis in ESKD patients

Study		HBV, *n*	HCV, *n*	ArLD, *n*	Multifactorial disease (HBV/HCV/ArLD combination), *n*	Other, *n*	Unknown, *n*	Total, *N*
Haemodialysis								
Espinosa 2001 [19]			9		1			10
Che-Yi 2016 [15] (HD cohort—full dataset)[a]		500	478	253			225	1456
Kim 2016 [21] (HD cohort)		25		5	3			33
	Subtotal (*n*)	525	487	258	4		225	1499
	%	35	32	17	<1		15	
Peritoneal dialysis								
Che-Yi 2016 [15] (PD cohort—full dataset)[a]		117	117	66			64	364
De Vecchi 2002 [17]		4	9	1	2		5	21
Kim 2016 [21] (PD cohort)		8	1	0	2			11
Lee 2017 [22]		16	9	5			3	33
Marcus 1992 [24]		1		5		1	2	9
	Subtotal (*n*)	146	136	77	4	1	74	438
	%	33	31	18	<1	<1	17	
Total		671	623	335	8	1	299	1937
Overall %		35	32	17	<1	<1	15	

HBV: hepatitis B; HCV: hepatitis C; ArLD: alcohol-related liver disease.
[a]All Che-Yi data included (no risk of duplication).
Data from Artru, Deshpande, Nakayama, Huang excluded as incomplete data set on aetiology of cirrhosis.

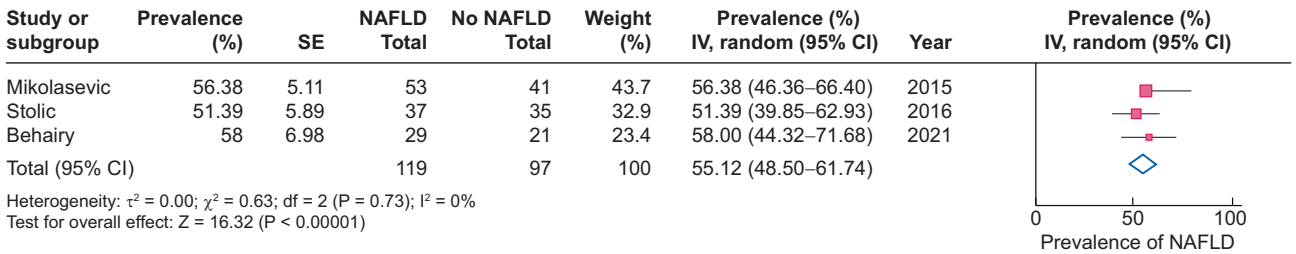

FIGURE 3: Prevalence of NAFLD in dialysis patients. SE: standard error; IV: inverse variance; df: degrees of freedom; I^2: total variability due to heterogeneity.

(Figure 4). In the cirrhosis group, the OR for death was 1.90 (95% CI 1.20–3.00) and in the NAFLD group (one study), the OR for death was 18.78 (95% CI 4.11–85.82) (Figure 4). The heterogeneity observed in the analyses for the cirrhosis group was high ($I^2 = 88\%$) and remained so ($I^2 = 88\%$) in the sensitivity analysis, which excluded outlier studies [19, 20], with minimal change in the OR for death (Supplemental Table S4). Data on the mortality risk of cirrhosis among dialysis patients were also described in three other studies [16, 21, 23], but these data were excluded, as the raw data were unobtainable. In these three studies, cirrhosis conferred a significant increased risk of mortality, despite adjustment for other comorbidities. The severity of cirrhosis and its relationship with mortality were measured in four studies [14, 15, 17, 24]. An increasing severity of cirrhosis (classified by the Child–Pugh score or the presence of liver disease decompensation) was associated with increased mortality in the studies where this information was available (Supplemental Table S5).

Patients with cirrhosis had an increased risk of death compared with those without, from infection [OR 2.17 (95% CI 1.51–3.11)], cancer (including hepatocellular carcinoma) [OR 5.42 (95% CI 1.01–28.96)] and liver disease [OR 28.46 (95% CI 16.52–49.03)], but not from cardiovascular disease [OR 0.96 (95% CI 0.54–1.73)] (Supplemental Figure S1).

Risk factors

Both hepatitis B [OR 13.47 (95% CI 1.37–132.55)] and hepatitis C [OR 7.05 (95% CI 4.00–12.45)] conferred an increased risk of cirrhosis, although this was not the case with DM [OR 1.19 (95% CI 0.97–1.46)] (Supplemental Figure S2).

Moderator analyses

Meta-regression was performed to consider the effect of age, gender, study size and year of study publication on cirrhosis prevalence in dialysis patients (Supplemental Figures S4–S7). The year of study publication was significantly associated with cirrhosis prevalence ($P = 0.027$), with increasing prevalence found in more recently published studies. Age, gender and study size were not significantly associated with cirrhosis prevalence. Other moderator analyses planned a priori were not performed due to the small number of studies assessing the variables of interest [34].

Assessment for publication bias

Publication biases were considered by examining funnel plot asymmetry (Supplemental Figure S8). There was no evidence of

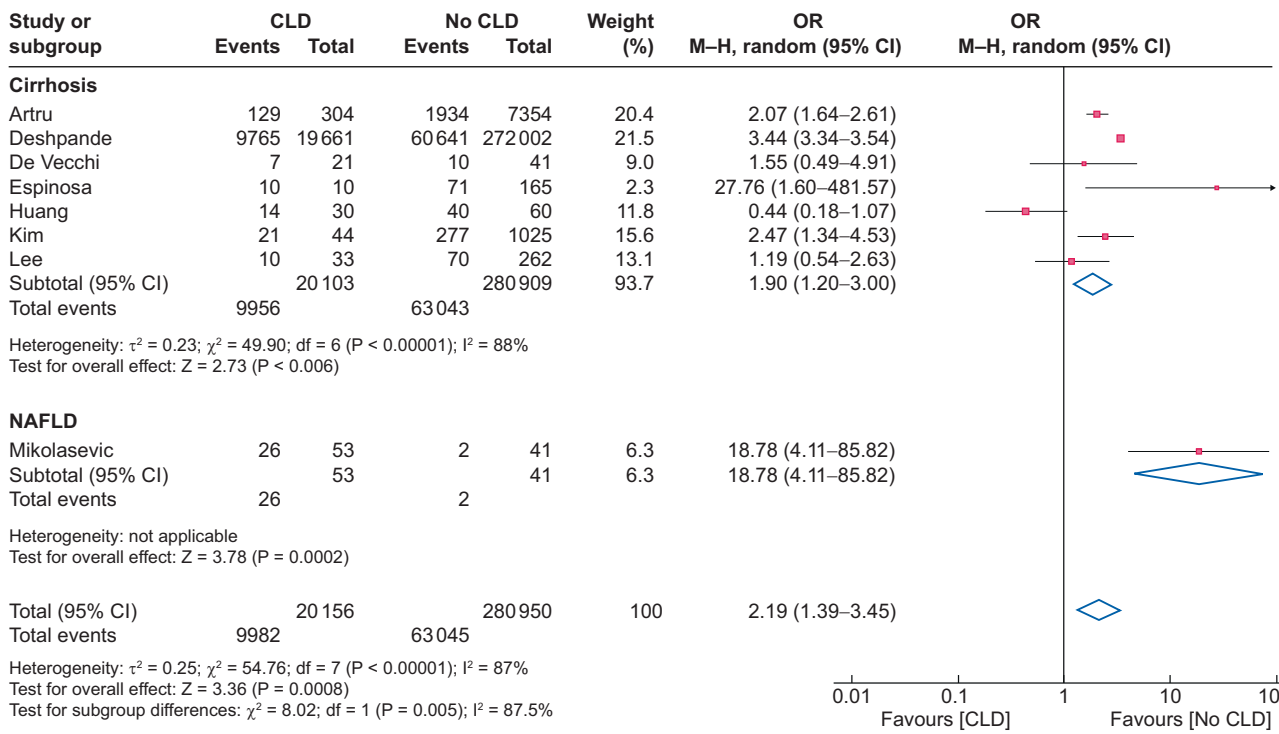

FIGURE 4: Association between death in dialysis patients with and without cirrhosis or NAFLD. M-H: Mantel–Haenszel; df: degrees of freedom; I^2: total variability due to heterogeneity.

publication bias in the reporting of CLD across studies (Egger regression test P = 0.058).

DISCUSSION

This systematic review and meta-analysis assessed the prevalence of CLD in patients treated with dialysis. Risk factors for CLD in dialysis patients were explored, along with associations with all-cause mortality and cardiovascular, infectious, cancer and liver mortality. Cirrhosis and NAFLD prevalence was 5 and 55%, respectively. Outcomes for dialysis patients with CLD were worse, with a >2-fold higher likelihood of mortality for patients with CLD compared with those without.

We found a stronger association with mortality for NAFLD than for cirrhosis, although this should be interpreted with significant caution. It is based on data from a single study with a high risk of bias and small sample size (Figure 4). Patients with cirrhosis were at increased risk of death from infection, cancer and liver disease, but not from cardiovascular disease. In most studies, the exact cause of liver death was not detailed.

Risk of infectious death in cirrhosis patients receiving dialysis was lower than previously described among all patients with cirrhosis [35]. This may relate to high rates of infectious death among dialysis patients without cirrhosis. Additionally, deaths attributed to liver disease may have been due to bacterial infection, a well-recognized trigger for liver decompensation [36].

Interestingly, DM did not confer an increased risk of cirrhosis, although there was a trend towards significance. The high rates of hepatitis observed in these populations may have masked the impact of DM.

It is currently unclear what proportion of dialysis patients have undiagnosed CLD. Liver enzymes are often normal in advanced CLD [37], and the majority of patients with NASH in the general population remain undiagnosed [38]. The difficulties in obtaining a diagnosis of CLD and the impact of the method of liver disease diagnosis on coded diagnostic information may explain the high level of heterogeneity observed across studies. This may be a factor in the differences in prevalence rates of cirrhosis observed in two of the largest studies in this analysis. The prevalence was 4.0% (95% CI 3.5–4.4) in Artru *et al.* [14] but was 6.7% (95% CI 6.6–6.8) in Deshpande *et al.* [18]. Differences in dialysis vintage may also be an important factor. This parameter was reported in five studies [19, 22, 25, 26, 28] and ranged between 5 and 7 years.

In patients not on dialysis, Child–Pugh A cirrhosis is associated with better outcomes and Child–Pugh C cirrhosis with the worst [39, 40]. An increasing severity of cirrhosis in patients with ESKD, as evidenced by a higher Child–Pugh classification or the presence of decompensated liver disease, was similarly associated with poorer outcomes. Furthermore, patients with decompensated cirrhosis with coexistent advanced kidney disease (e.g. those with hepatorenal syndrome) have a very poor short-term prognosis without liver transplantation [41] and may not have survived the minimum period on dialysis to meet study inclusion criteria. This may have led to an underestimation of survival rates in this systematic review, as six studies included in this review considered only patients who had been dialysing for a minimum period of 30 days–6 months [15, 16, 19, 23, 26, 27]. Other studies that abstracted registry data may not have included inpatients initiating dialysis who did not survive to hospital discharge. In addition, patients with decompensated cirrhosis may not have been deemed suitable for long-term dialysis if they were not considered potential candidates for liver transplantation.

Where the cause of liver disease was available, two-thirds had cirrhosis secondary to hepatitis B or C, although these analyses were influenced by the results of a large Taiwanese data set [15]. As a result, hepatitis B and C were the most relevant factors for the development of cirrhosis in dialysis patients in this systematic review. However, these results may not be generalizable to current populations where patients are now vaccinated against hepatitis B virus and treatments to eradicate hepatitis C are easily accessible.

There were no data on NASH cirrhosis or obesity, despite the increasing impact of these conditions on the global burden of CLD [42]. Therefore the impact of NASH cirrhosis among dialysis populations remains to be determined. Three articles with small sample sizes reported on the prevalence of NAFLD in the dialysis setting and indicated that the prevalence of NAFLD in dialysis patients was greater than that in the general population [2]. The true prevalence of NAFLD may be even higher in dialysis populations, as two of these three studies excluded patients with obesity and DM [26, 27]. It was not possible to establish NAFLD as a risk factor for cardiovascular mortality as part of this study due to insufficient data.

The studies involving patients with cirrhosis and ESKD exhibited significant heterogeneity. This is likely to have been influenced by reporter bias, the variation in the prevalence of cirrhosis and hepatitis B and C in the populations studied based on geographical location, variations in follow-up times and the different study sample sizes. No significant evidence of publication bias was identified. Sensitivity analyses that excluded the studies with a high risk of bias did not alter heterogeneity or interpretation of the overall data on cirrhosis prevalence. It was not possible to perform moderator analyses to adequately explore possible factors that may explain the high level of heterogeneity observed (other than age, gender, study size and year of publication), as there was insufficient consistency on the reporting of other characteristics of interest (at least 10 observations per characteristic are recommended for a moderator analysis to be performed) [34]. The year of study publication was associated with an increasing reported prevalence of cirrhosis, reflecting the increasing numbers of patients with combined kidney and liver dysfunction and potentially improved diagnosis. A requirement for future studies to report on risk factors for liver disease, including DM, obesity and ethnicity, would enable better stratification of patients at high risk of NAFLD and NASH cirrhosis.

This is the first systematic review and meta-analysis to evaluate CLD in dialysis patients. While offering the largest evidence synthesis to date, some caveats apply when interpreting the findings. These mainly relate to the degree of heterogeneity observed across studies, which, as discussed, we could only explore in a limited fashion because of scarce reporting of moderators of interest. Hence some of the analyses outlined in our PROSPERO preregistration document were not possible to pursue. These included relationships with anaemia, hypoalbuminemia, quality of life, hospital admission and length of hospital stay. All these variables could provide important information about current clinical status, morbidity and patient-reported outcomes. However, the strengths of this review include the provision of evidence-based assessments for the co-occurrence of CLD and ESKD and, importantly, in detailing its impact on mortality in this patient group. The review also highlights important avenues for future research, especially on the impact of NAFLD and NASH in dialysis patients. Both NAFLD and NASH [43, 44] are associated with DM, obesity, hypertension and systemic inflammation, all of which are commonly encountered in the dialysis population [45]. Given the high prevalence of NAFLD we have observed, further investigation is required on the role of NAFLD and NASH in systemic inflammation in ESKD, the risk of developing cirrhosis among dialysis patients with NAFLD and NASH and their impact on outcomes, including mortality.

In conclusion, this systematic review and meta-analysis has demonstrated that CLD is an important comorbidity associated with increased risks of mortality in this already vulnerable patient group. Close collaborative work between nephrologists and hepatologists to manage these patients is required, alongside further studies to identify those at highest risk of developing these complications and to define the additional burdens they impose on dialysis patients.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented have not been published previously in whole or part, except in abstract format.

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