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Original article

Bidirectional association between chronic liver disease and chronic kidney disease: a longitudinal study based on CHARLS 2011–2020 data

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ABSTRACT

Introduction and Objectives: Chronic liver disease (CLD) and chronic kidney disease (CKD) are major public health concerns with significant morbidity and mortality worldwide. This study aimed to investigate the bidirectional association between CLD and CKD.

Patients and Methods: We conducted two longitudinal studies using data from the China Health and Retirement Longitudinal Study (CHARLS) between 2011 and 2020. Participants without baseline CKD were analyzed for the risk of CKD associated with CLD, and participants without baseline CLD were assessed for the risk of CLD associated with CKD. Multivariate Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals (95% CIs).

Results: Of 3651 participants without baseline CKD, 575 developed CKD over a median follow-up of 9 years. The incidence of CKD was significantly higher in those with baseline CLD (37.25 vs. 18.08 per 1000 population). Baseline CLD was independently associated with an elevated risk of incident CKD (adjusted HR=1.93; 95% CI: 1.37–2.72; $P < 0.001$). Conversely, of 5530 participants without baseline CLD, 474 developed CLD. Participants with CKD had a significantly higher incidence of CLD (13.56 vs. 8.89 per 1000 population). Baseline CKD was independently associated with an increased risk of incident CLD (adjusted HR=1.68; 95% CI: 1.31–2.16; $P < 0.001$). The bidirectional associations remained robust in sensitivity analyses, and the association persisted across different subgroups.

Conclusions: This study provides evidence of a bidirectional relationship between CLD and CKD. These findings highlight the importance of integrated management strategies targeting both liver and kidney health.

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1. Introduction

Chronic liver disease (CLD) and chronic kidney disease (CKD) are two major global public health challenges, contributing significantly to morbidity, mortality, and healthcare burden worldwide [1,2]. Recent consensus suggests that these diseases should be considered components of an integrated cardiovascular-kidney-metabolic health spectrum, reflecting their extensive mutual interactions and shared risk factors [3]. CLD encompasses a spectrum of liver pathologies, including non-alcoholic fatty liver disease, alcoholic liver disease, viral hepatitis, and cirrhosis, which collectively affect millions of individuals globally [4,5]. CKD, characterized by a progressive decline in renal function, is similarly prevalent, with an estimated global prevalence of 9.1 % in 2017, accounting for 1.2 million deaths annually [6]. Both conditions are associated with substantial economic costs and reduced quality of life, underscoring the need for effective prevention and management strategies [7–9].

Emerging evidence suggests that CLD and CKD may share common risk factors and pathophysiological mechanisms, including metabolic disorders, systemic inflammation, oxidative stress, and vascular dysfunction [10,11]. For instance, non-alcoholic fatty liver disease, the most common cause of CLD, is strongly associated with metabolic syndrome, insulin resistance, and obesity, all of which are also key risk factors for CKD [12–15]. Similarly, CKD is characterized by chronic low-grade inflammation and endothelial dysfunction, which may predispose individuals to liver injury and fibrosis [16]. These shared pathways suggest a potential bidirectional relationship between CLD and CKD, wherein the presence of one condition may increase the risk of developing the other [17].

Abbreviations: 95% CI, 95% confidence interval; BMI, Body mass index; charls, China health and retirement longitudinal study; CKD, Chronic kidney disease; CKD-EPI, Chronic kidney disease epidemiology collaboration; CLD, Chronic liver disease; eGFR, Estimated glomerular filtration rate; eGFRcysc, Cystatin C–based estimated glomerular filtration rate; HR, hazard ratio; RAAS, Renin-angiotensin-aldosterone system; STROBE, Strengthening the reporting of observational studies in epidemiology

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Several cross-sectional and longitudinal studies have explored the association between CLD and CKD, with most focusing on the unidirectional impact of one condition on the other [18]. For example, non-alcoholic fatty liver disease has been identified as an independent risk factor for CKD, with studies reporting a 1.5- to 2-fold increased risk of CKD in individuals with non-alcoholic fatty liver disease compared to those without [10,19]. The severity of liver disease, as indicated by advanced fibrosis or cirrhosis, further amplifies this risk [20]. Conversely, CKD has been associated with an increased risk of liver dysfunction, particularly in the context of uremia and altered drug metabolism in advanced stages of renal disease [21]. However, despite these findings, the bidirectional nature of the relationship between CLD and CKD remains underexplored, especially the association of CKD triggering CLD.

Here, we conducted a longitudinal cohort study using data from the China Health and Retirement Longitudinal Study (CHARLS), a nationally representative survey of middle-aged and older adults in China. Specifically, we aimed to investigate the bidirectional association between CLD and CKD over a 9-year follow-up period. Our study had two primary objectives: (1) to assess the risk of incident CKD associated with baseline CLD, and (2) to evaluate the risk of incident CLD associated with baseline CKD. We hypothesized that CLD and CKD are bidirectionally associated, with the presence of one condition increasing the risk of developing the other.

2. Methods

This study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (Table S1) [22].

2.1. Study population

This study utilized data from the CHARLS, a nationally representative longitudinal survey of Chinese adults aged 45 years and older. CHARLS was initiated in 2011 and includes biennial follow-ups to collect detailed information on demographic, socioeconomic, lifestyle, and health-related factors [23]. For this analysis, we included participants who completed the baseline survey in 2011 and were followed up until 2020. For the two separate analyses, participants with prevalent CKD at baseline were excluded from the analysis assessing the risk of incident CKD associated with baseline CLD, and participants with prevalent CLD at baseline were excluded from the analysis assessing the risk of incident CLD associated with baseline CKD. The final sample sizes were 3651 and 5530 for the two analyses, respectively (Fig. 1).

2.2. Assessment of CLD and CKD

CLD was defined based on self-reported physician diagnoses of chronic liver conditions, including hepatitis, cirrhosis, or other chronic liver diseases. CKD was defined using a combination of self-reported physician diagnoses and laboratory data. Estimated glomerular filtration rate ($eGFR_{cysc}$) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation by cystatin C [24]. CKD was defined as $eGFR_{cysc} < 60$ ml/min/1.73 m^2, consistent with international guidelines [25]. Incident cases of CLD and CKD were identified during follow-up based on new self-reported diagnoses or laboratory measurements meeting the above criteria.

2.3. Covariates

A wide range of demographic, lifestyle, and clinical factors were included as covariates in the analysis. This included age, sex, education level (categorized as illiterate, primary school, middle school, or higher), and marital status (married or not). Lifestyle factors included sleep duration (hours per night), body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), smoking status (current smoker, former smoker, or never smoker), and alcohol consumption (current drinker, former drinker, or never drinker). Clinical factors included the presence of hypertension (self-reported diagnosis or systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) [26], diabetes (self-reported diagnosis or fasting blood glucose ≥ 7.0 mmol/l) [27], hyperlipidemia (self-reported diagnosis or elevated total cholesterol ≥ 5.2 mmol/l) [28], and heart disease (self-reported diagnosis of coronary heart disease, myocardial infarction, or other heart conditions) [29], and baseline $eGFR_{cysc}$.

2.4. Statistical analysis

Baseline characteristics of the study population were summarized using median and interquartile for continuous variables and frequencies and percentages for categorical variables. Differences between groups were assessed using *t*-tests or chi-square tests as appropriate. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95 % confidence intervals (95 % CIs) for the association

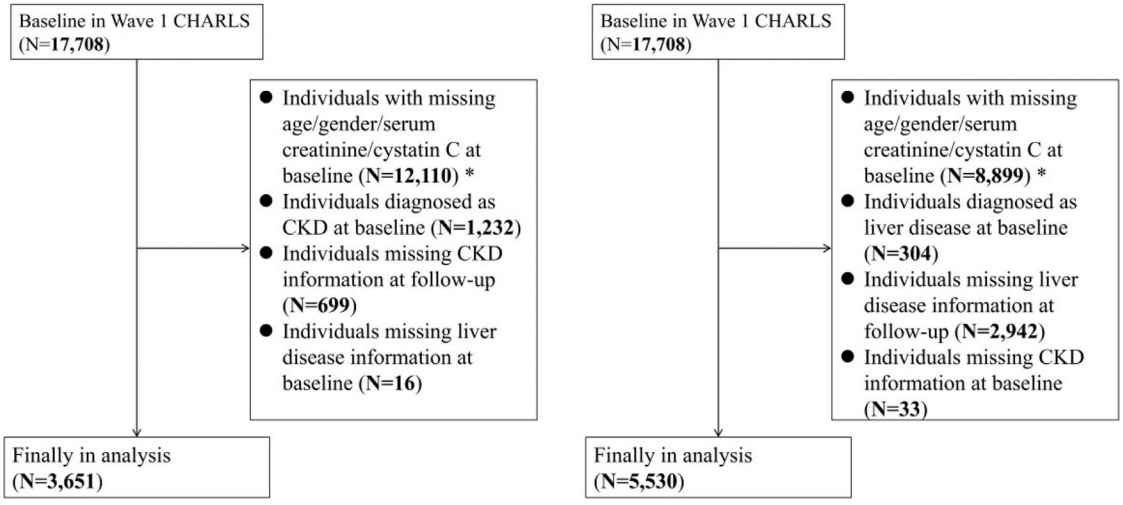

Fig. 1. Participant screening flowchart. a) CLD increases incident CKD risk; b) CKD increases CLD risk.
*Note: We also utilized the 3rd wave of cystatin C to calculate eGFR to synthesize CKD onset and therefore excluded dissimilarity in numbers here.

between baseline CLD and incident CKD, as well as between baseline CKD and incident CLD. Time to event was defined as the time from baseline to the first occurrence of the outcome, loss to follow-up, or the end of the study period in 2020, whichever came first. The proportional hazards assumption was tested using Schoenfeld residuals.

Models were adjusted for potential confounders, including age, sex, education, marital status, sleep duration, BMI, smoking, alcohol consumption, hypertension, diabetes, hyperlipidemia, heart disease, and baseline $eGFR_{cysc}$. Missing data were handled using random forest imputation techniques to minimize bias and improve robustness. Subgroup analyses were performed to examine potential effect modification by key covariates, such as diabetes and hypertension. To assess latent effects, we conducted sensitivity analyses by excluding the first 2 years of follow-up.

All statistical analyses were conducted using Stata version 16.0 (StataCorp, College Station, TX) and *R* software (version 4.2.0). A two-sided *P*-value < 0.05 was considered statistically significant.

2.5. Ethical considerations

The study protocols were approved by the Ethical Review Committee of Peking University (CHARLS: IRB00001052−11015).

3. Results

3.1. Baseline characteristics

The baseline characteristics of included population are summarized in Table 1. For the analysis assessing the association between CLD and incident CKD, a total of 3651 participants were included, of whom 123 (3.4 %) had CLD at baseline. For the analysis assessing the association between CKD and incident CLD, 5530 participants were included, with 1092 (19.7 %) having CKD at baseline. Participants with baseline CLD were more likely to be male (47.2 % vs. 42.4 %), current smokers (29.3 % vs. 27.8 %), and past drinkers (15.4 % vs. 7.1 %) compared to those without CLD. They also had a higher prevalence of diabetes (12.2 % vs. 5.9 %) and hyperlipidemia (21.1 % vs. 10.2 %). Similarly, participants with baseline CKD were older (median age: 66 vs. 57 years), more likely to be female (52.3 % vs. 42.8 %), and had a higher prevalence of hypertension (32.2 % vs. 24.0 %), diabetes (6.3 % vs. 5.3 %), and heart disease (15.8 % vs. 10.4 %) compared to those without CKD. Baseline $eGFR_{cysc}$ was significantly lower in participants with CKD (median: 55 vs. 84 ml/min/1.73 m^2, $P < 0.001$).

3.2. Association between CLD and incident CKD events

Among participants without CKD at baseline, a total of 575 incident cases of CKD occurred during a median follow-up of 9.0 years, with an overall incidence rate of 18.68 per 1000 population (95 % CI: 17.16−20.21) (Table 2). Stratified by CLD status, participants with CLD exhibited a significantly higher incidence rate of CKD (37.25 per 1000 population, 95 % CI: 25.08−49.42) compared to those without CLD (18.08 per 1000 population, 95 % CI: 16.55−19.61). In crude model, CLD was associated with an increased risk of CKD (HR=2.09, 95 % CI: 1.49−2.93, $P < 0.001$). This association remained consistent after adjustment for age and sex (HR=2.09, 95 % CI: 1.49−2.93, $P < 0.001$) and further adjustment for multiple confounders in Model 3 (HR=1.93, 95 % CI: 1.37−2.72, $P < 0.001$) (Table 2).

Conversely, among participants without CLD at baseline, 474 incident cases of CLD were identified, with an incidence rate of 9.80 per 1000 population (95 % CI: 8.92−10.68) (Table 2). Participants with CKD at baseline experienced a significantly higher incidence rate of CLD (13.56 per 1000 population, 95 % CI: 11.21−15.90) compared to those without CKD (8.89 per 1000 population, 95 % CI: 7.95−9.83). CKD was independently associated with an increased risk of developing CLD in all models (Model 1: HR=1.56, 95 % CI: 1.27−1.91, $P < 0.001$; Model 2: HR=1.72, 95 % CI: 1.38−2.14, $P < 0.001$; Model 3: HR=1.68, 95 % CI: 1.31−2.16, $P < 0.001$) (Table 2). Excluding CLD cases from the first two years of follow-up did not change these findings (Table 3).

The Kaplan-Meier survival curves illustrate the cumulative incidence of CKD stratified by CLD status and the cumulative incidence of CLD stratified by CKD status. Participants with baseline CLD showed a significantly higher risk of CKD development compared to those without CLD (log-rank $P < 0.001$). Similarly, participants with baseline CKD demonstrated a significantly higher risk of CLD occurrence compared to those without CKD (log-rank $P < 0.001$) (Fig. 2).

3.3. Subgroup analysis

Subgroup analyses were conducted to evaluate whether the associations between CLD and incident CKD, as well as CKD and incident CLD, were modified by key covariates, including age, sex, diabetes, hypertension, and other baseline characteristics (Fig. 3).

For the association between CLD and incident CKD, the increased risk was consistent across all subgroups. Notably, the association was stronger among current drinkers (HR=3.36; 95 % CI: 1.92−5.88) compared to past (HR=2.12; 95 % CI: 0.84−5.39) and never drinker (HR: 1.28; 95 % CI: 0.75−2.16) ($P_{\text{for interaction}}$: 0.039). No significant interactions were observed for age, sex, or other group ($P_{\text{for interaction}} > 0.05$), indicating that the association between CLD and CKD was robust across these subgroups.

For the association between CKD and incident CLD, the increased risk was also observed across all subgroups. The association was more pronounced in age < 60 years participants (HR=2.18; 95 % CI: 1.63−3.18) compared to those age ≥ 60 (HR=1.45; 95 % CI: 1.00 −2.11) ($P_{\text{for interaction}}$: 0.003). Like the CLD-CKD analysis, no significant interactions were found for other groups ($P_{\text{for interaction}} > 0.05$).

4. Discussion

4.1. Principal findings

This longitudinal study, based on data from the CHARLS from 2011 to 2020, provides robust evidence of a bidirectional association between CLD and CKD. Participants with baseline CLD had a significantly increased risk of developing CKD, while those with baseline CKD were at a higher risk of developing CLD. These associations remained consistent across sensitivity analyses and subgroup analyses, suggesting that the relationship between CLD and CKD is independent of traditional risk factors such as age, sex, diabetes, and hypertension. The findings highlight the importance of integrated management strategies targeting both liver and kidney health, particularly in high-risk populations.

4.2. Comparison with previous studies

Our findings align with and extend previous research on the relationship between liver and kidney diseases. Several cross-sectional studies have reported associations between liver dysfunction and reduced kidney function. For example, Mantovani et al. demonstrated that non-alcoholic fatty liver disease was independently associated with an increased risk of CKD in a meta-analysis of observational studies [19]. Similarly, Musso et al. found that NAFLD was linked to a higher prevalence of CKD, even after adjusting for metabolic risk factors [30]. However, most of these studies were cross-sectional, limiting their ability to establish temporal relationships. Our study addresses this gap by using longitudinal data to demonstrate a bidirectional relationship between CLD and CKD.

Conversely, fewer studies have explored the impact of CKD on liver disease. A study by Tonon et al. reported that kidney injury was associated with worse outcomes in patients with cirrhosis,

Table 1
Characteristics of included participants.

Characteristic	CLD			*P*-value	CKD			*P*-value
	Overall *N* = 3651[1]	None *N* = 3528[1]	Yes *N* = 123[1]		Overall *N* = 5530[1]	None *N* = 4438[1]	Yes *N* = 1092[1]	
Age, year	57 (51, 63)	57 (51, 63)	55 (51, 62)	0.368[2]	58 (51, 65)	57 (50, 63)	66 (58, 72)	<0.001[2]
Age group				0.396[3]				<0.001[3]
< 60 years	2241 (61.4 %)	2161 (61.3 %)	80 (65.0 %)		3121 (56.4 %)	2815 (63.4 %)	306 (28.0 %)	
≥ 60 years	1410 (38.6 %)	1367 (38.7 %)	43 (35.0 %)		2409 (43.6 %)	1623 (36.6 %)	786 (72.0 %)	
Sex				0.298[3]				0.003[3]
Male	1555 (42.6 %)	1497 (42.4 %)	58 (47.2 %)		2421 (43.8 %)	1900 (42.8 %)	521 (47.7 %)	
Female	2096 (57.4 %)	2031 (57.6 %)	65 (52.8 %)		3109 (56.2 %)	2538 (57.2 %)	571 (52.3 %)	
Marriage				0.829[3]				<0.001[3]
Married	3304 (90.5 %)	3192 (90.5 %)	112 (91.1 %)		4942 (89.4 %)	4041 (91.1 %)	901 (82.5 %)	
Other	347 (9.5 %)	336 (9.5 %)	11 (8.9 %)		588 (10.6 %)	397 (8.9 %)	191 (17.5 %)	
Education				0.393[4]				0.006[3]
Less than middle school education	3308 (90.6 %)	3200 (90.7 %)	108 (87.8 %)		5019 (90.8 %)	4002 (90.2 %)	1017 (93.1 %)	
High school and vocational training	311 (8.5 %)	297 (8.4 %)	14 (11.4 %)		462 (8.4 %)	397 (8.9 %)	65 (6.0 %)	
Higher education	32 (0.9 %)	31 (0.9 %)	1 (0.8 %)		49 (0.9 %)	39 (0.9 %)	10 (0.9 %)	
Smoking				0.105[3]				<0.001[3]
Never smoker	2360 (64.6 %)	2288 (64.9 %)	72 (58.5 %)		3510 (63.5 %)	2875 (64.8 %)	635 (58.2 %)	
Past smoker	275 (7.5 %)	260 (7.4 %)	15 (12.2 %)		414 (7.5 %)	311 (7.0 %)	103 (9.4 %)	
Current smoker	1016 (27.8 %)	980 (27.8 %)	36 (29.3 %)		1606 (29.0 %)	1252 (28.2 %)	354 (32.4 %)	
Drinking				0.002[3]				<0.001[3]
Never drinker	2290 (62.7 %)	2223 (63.0 %)	67 (54.5 %)		3465 (62.7 %)	2775 (62.5 %)	690 (63.2 %)	
Past drinker	268 (7.3 %)	249 (7.1 %)	19 (15.4 %)		431 (7.8 %)	300 (6.8 %)	131 (12.0 %)	
Current drinker	1093 (29.9 %)	1056 (29.9 %)	37 (30.1 %)		1634 (29.5 %)	1363 (30.7 %)	271 (24.8 %)	
Sleep duration, h/24 h	6.68 (5.00, 8.00)	6.70 (5.00, 8.00)	6.37 (5.00, 8.00)	0.637[2]	6.41 (5.00, 8.00)	6.62 (5.00, 8.00)	6.00 (5.00, 8.00)	0.001[2]
BMI, kg/m^2	23.0 (21.3, 25.7)	23.0 (21.3, 25.6)	22.9 (21.3, 25.7)	0.778[2]	22.7 (21.0, 25.5)	22.8 (21.2, 25.5)	22.4 (20.4, 25.4)	<0.001[2]
BMI group				0.890[3]				0.259[3]
< 24 kg/m^2	2248 (61.6 %)	2173 (61.6 %)	75 (61.0 %)		3514 (63.5 %)	2804 (63.2 %)	710 (65.0 %)	
≥ 24 kg/m^2	1403 (38.4 %)	1355 (38.4 %)	48 (39.0 %)		2016 (36.5 %)	1634 (36.8 %)	382 (35.0 %)	
Hypertension				0.961[3]				<0.001[3]
None	2724 (74.6 %)	2632 (74.6 %)	92 (74.8 %)		4112 (74.4 %)	3372 (76.0 %)	740 (67.8 %)	
Yes	927 (25.4 %)	896 (25.4 %)	31 (25.2 %)		1418 (25.6 %)	1066 (24.0 %)	352 (32.2 %)	
Hyperlipemia				<0.001[3]				0.953[3]
None	3265 (89.4 %)	3168 (89.8 %)	97 (78.9 %)		5011 (90.6 %)	4022 (90.6 %)	989 (90.6 %)	
Yes	386 (10.6 %)	360 (10.2 %)	26 (21.1 %)		519 (9.4 %)	416 (9.4 %)	103 (9.4 %)	
Diabetes				0.004[3]				0.184[3]
None	3427 (93.9 %)	3319 (94.1 %)	108 (87.8 %)		5226 (94.5 %)	4203 (94.7 %)	1023 (93.7 %)	
Yes	224 (6.1 %)	209 (5.9 %)	15 (12.2 %)		304 (5.5 %)	235 (5.3 %)	69 (6.3 %)	
Heart disease				<0.001[3]				<0.001[3]
None	3243 (88.8 %)	3147 (89.2 %)	96 (78.0 %)		4895 (88.5 %)	3975 (89.6 %)	920 (84.2 %)	
Yes	408 (11.2 %)	381 (10.8 %)	27 (22.0 %)		635 (11.5 %)	463 (10.4 %)	172 (15.8 %)	
Baseline serum creatinine, mg/dl	0.72 (0.63, 0.84)	0.72 (0.63, 0.84)	0.75 (0.64, 0.86)	0.182[2]	0.75 (0.64, 0.87)	0.72 (0.63, 0.84)	0.85 (0.72, 0.99)	<0.001[2]
Baseline cystatin C, mg/dl	0.93 (0.82, 1.02)	0.93 (0.82, 1.02)	0.94 (0.85, 1.04)	0.204[2]	0.96 (0.85, 1.09)	0.93 (0.82, 1.02)	1.24 (1.15, 1.37)	<0.001[2]
Baseline eGFR$_{cysc}$, ml/kg/1.73 m^2	83 (73, 97)	84 (73, 97)	83 (72, 95)	0.348[2]	80 (66, 95)	84 (73, 98)	55 (48, 59)	<0.001[2]

[1] Data were presented as median (interquartile range) and n (%).
[2] Wilcoxon rank sum test.
[3] Pearson's Chi-squared tests.
[4] Fisher's exact test.
Abbreviation: eGFR, estimated glomerular filtration rate; CLD, chronic liver disease; CKD, chronic kidney disease; BMI, body mass index.

Table 2
Bidirectional association of CLD with CKD.

Variables	Case/N	Incidence of per 1000 population	Model 1 HR (95 % CI), *P*-value	Model 2 HR (95 % CI), *P*-value	Model 3 HR (95 % CI), *P*-value
CLD	575/3651	18.68 (95 % CI: 17.16–20.21)			
None	539/3528	18.08 (95 % CI: 16.55–19.61)	1 [Reference]	1 [Reference]	1 [Reference]
Yes	36/123	37.25 (95 % CI: 25.08–49.42)	2.09 (95 % CI: 1.49–2.93), <0.001	2.09 (95 % CI: 1.49–2.93), <0.001	1.93 (95 % CI: 1.37–2.72), <0.001
CKD	474/5530	9.80 (95 % CI: 8.92–10.68)			
None	346/4438	8.89 (95 % CI: 7.95–9.83)	1 [Reference]	1 [Reference]	1 [Reference]
Yes	128/1092	13.56 (95 % CI: 11.21–15.90)	1.56 (95 % CI: 1.27–1.91), <0.001	1.72 (95 % CI: 1.38–2.14), <0.001	1.68 (95 % CI: 1.31–2.16), <0.001

HR, Hazard ratio, 95 % CI, 95 % confidence interval; CLD, chronic liver disease; CKD, chronic kidney disease.
Model 1: unadjusted.
Model 2: adjusted for age and sex.
Model 3: further adjusted for marriage, education, sleep duration, smoking, drinking, hypertension, hyperlipemia, diabetes, heart disease, body mass index, and baseline eGFR$_{cysc}$.

Table 3
Sensitivity analysis excluding the previous two years of incidence.

Variables	Case/N	Model 1 HR (95 % CI), *P*-value	Model 2 HR (95 % CI), *P*-value	Model 3 HR (95 % CI), *P*-value
CLD				
None	488/3477	1 [Reference]	1 [Reference]	1 [Reference]
Yes	30/117	1.94 (95 % CI: 1.34−2.80), <0.001	1.94 (95 % CI: 1.34−2.80), <0.001	1.8 (95 % CI: 1.24−2.61), 0.002
CKD				
None	312/4404	1 [Reference]	1 [Reference]	1 [Reference]
Yes	115/1079	1.56 (95 % CI: 1.26−1.93), <0.001	1.71 (95 % CI: 1.35−2.15), <0.001	1.75 (95 % CI: 1.34−2.27), <0.001

HR, Hazard ratio, 95 % CI, 95 % confidence interval; CLD, chronic liver disease; CKD, chronic kidney disease.
Model 1: unadjusted.
Model 2: adjusted for age and sex.
Model 3: further adjusted for marriage, education, sleep duration, smoking, drinking, hypertension, hyperlipemia, diabetes, heart disease, body mass index, and baseline $eGFR_{cysc}$.

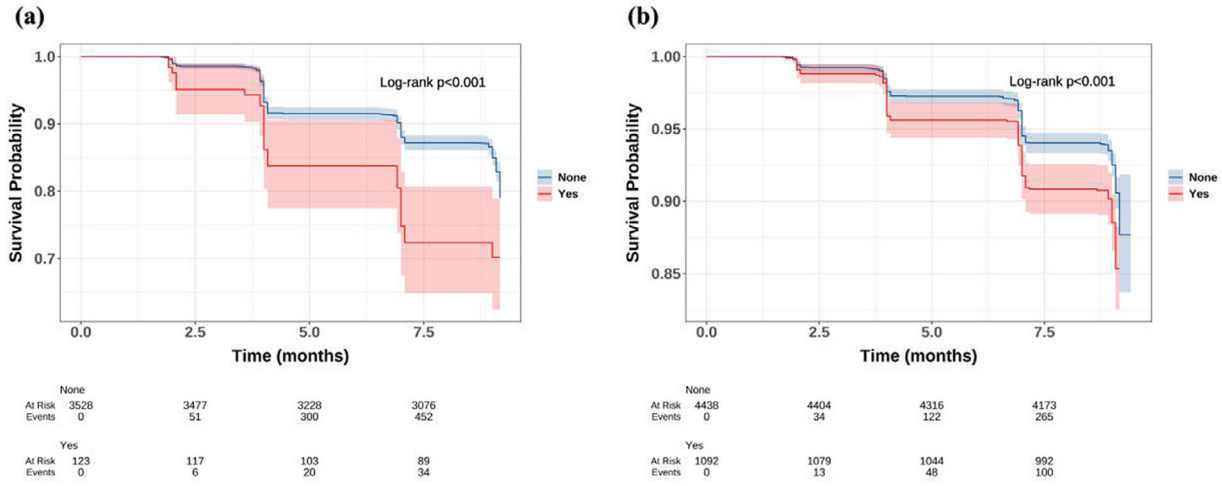

Fig. 2. Survival plot for Cox regression. a) CLD increases incident CKD risk; b) CKD increases CLD risk. Adjusted for age, sex, marriage, education, sleep duration, smoking, drinking, hypertension, hyperlipemia, diabetes, heart disease, body mass index, and baseline $eGFR_{cysc}$.

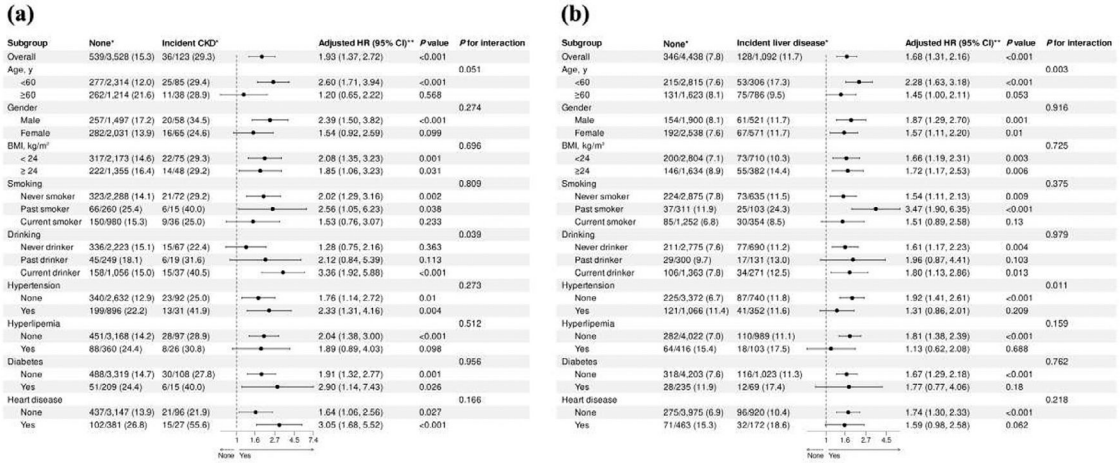

Fig. 3. Forest plots for subgroup analysis. a) CLD increases incident CKD risk; b) CKD increases CLD risk.
* no. of events / total no. (%).
** adjusted for age, sex, marriage, education, sleep duration, smoking, drinking, hypertension, hyperlipemia, diabetes, heart disease, body mass index, and baseline eGFR.

including higher rates of liver-related complications [31]. Our findings build on this evidence by showing that CKD not only exacerbates existing liver disease but also increases the risk of incident CLD in a general population. This bidirectional relationship underscores the interconnected nature of liver and kidney pathophysiology.

4.3. Potential mechanisms

The bidirectional association between CLD and CKD may be explained by several shared pathophysiological mechanisms. Chronic inflammation is a key driver of both conditions. In CLD, systemic inflammation resulting from liver injury can lead to endothelial

dysfunction, oxidative stress, and activation of the renin-angiotensin-aldosterone system (RAAS), all of which contribute to kidney damage [32]. Similarly, CKD is characterized by chronic low-grade inflammation and uremic toxin accumulation, which can impair liver function and promote fibrosis [33].

Metabolic disorders, such as diabetes, obesity, and hypertension, are common risk factors for both CLD and CKD. Insulin resistance and hyperglycemia can exacerbate liver steatosis and fibrosis while also accelerating kidney damage through glomerular hyperfiltration and vascular injury [5]. Furthermore, RAAS activation, a hallmark of CKD, can worsen liver fibrosis by promoting hepatic stellate cell activation and collagen deposition [34].

Another potential mechanism is gut dysbiosis, which has been implicated in both liver and kidney diseases. Alterations in gut microbiota can lead to increased intestinal permeability, allowing bacterial endotoxins to enter the circulation and trigger systemic inflammation. This "gut-liver-kidney axis" may play a critical role in the progression of both CLD and CKD [34,35].

4.4. Strengths and limitations

The strength of this study is that it utilized a large, nationally representative cohort with a long follow-up period, allowing for robust estimation of temporal relationships between CLD and CKD. However, several limitations should be acknowledged. A key limitation is that the definition of chronic liver disease in this study was based on self-reported physician diagnosis from the CHARLS survey and did not distinguish specific etiologies such as NAFLD or MAFLD/MASLD. Therefore, our findings may not fully capture the spectrum or recent nomenclature updates of chronic liver diseases. Second, while $eGFR_{cysc}$ were used to define CKD, the lack of repeated measurements may have led to misclassification of transient kidney dysfunction as CKD. Moreover, lack of information on proteinuria may underestimate the prevalence of CKD. Third, the observational nature of the study precludes causal inference, and unmeasured confounders, such as genetic predisposition or environmental exposures, may have influenced the results. Finally, the findings may not be generalizable to populations outside of China, given the unique demographic and epidemiological characteristics of the CHARLS cohort.

4.5. Implications for clinical practice

The bidirectional relationship between CLD and CKD has important implications for clinical practice. First, clinicians should be aware of the increased risk of CKD in patients with CLD and vice versa. Routine screening for kidney function in patients with liver disease and liver function in patients with CKD may facilitate early detection and intervention. Second, integrated management strategies targeting shared risk factors, such as diabetes, hypertension, and obesity, are essential to prevent the progression of both conditions. Third, the findings highlight the need for multidisciplinary care involving hepatologists, nephrologists, and primary care providers to optimize outcomes for patients with coexisting liver and kidney diseases. Recent evidence has demonstrated that the coexistence of chronic liver disease and chronic kidney disease further increases the risk of major adverse cardiovascular events (MACE), beyond the risk conferred by each condition alone [36,37]. This synergistic effect is likely driven by the overlapping burden of metabolic dysfunction, systemic inflammation, and vascular injury inherent to both diseases. Thus, clinicians should be aware not only of the reciprocal relationship between CLD and CKD, but also of their combined impact on cardiovascular outcomes.

4.6. Future directions

Future research should aim to address the limitations of this study and further elucidate the mechanisms underlying the bidirectional relationship between CLD and CKD. Longitudinal studies with repeated measurements of liver and kidney function are needed to better characterize the temporal dynamics of disease progression. Additionally, studies exploring the role of gut microbiota, systemic inflammation, and metabolic pathways in the liver-kidney axis could provide valuable insights into potential therapeutic targets. Randomized controlled trials evaluating the efficacy of interventions, such as RAAS inhibitors, anti-inflammatory agents, or lifestyle modifications, in reducing the risk of both CLD and CKD are also warranted. Finally, research in diverse populations is needed to determine the generalizability of these findings and to identify population-specific risk factors and interventions.

5. Conclusions

This study demonstrates a bidirectional association between CLD and CKD, highlighting the need for integrated management strategies to prevent and mitigate the progression of these interconnected conditions.

Data availability statement

The data that support the findings of this study are available from the China Health and Retirement Longitudinal Study (CHARLS). Access to this data can be obtained by registering and submitting a request through the official CHARLS website.

Author contributions

FZ and YH designed the study. FZ, YH, and ZXZ analyzed the data. XWZ and YFZ supervised the study. FZ and YH wrote the manuscript, XWZ and YFZ revised the manuscript. All authors read and approved the final manuscript.

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Declaration of interests

The authors declare that they have no relevant financial interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.aohep.2025.102115.

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