Journal of Inflammation Research

Dovepress
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ORIGINAL RESEARCH

The Inflammation Effect in the Association Between Bilirubin and Chronic Kidney Disease in Patients with Type 2 Diabetes: A Retrospective Cohort Study

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Background: The associations of bilirubin (BIL) and systemic inflammation with chronic kidney disease (CKD) remain unclear. This study examined associations among BIL, systemic inflammation, and CKD progression in type 2 diabetes patients, assessing systemic inflammation's mediating role.

Methods: This retrospective cohort study included 1215 subjects. The exposure was baseline BIL concentrations, while inflammation-related indicators including systemic inflammatory response index (SIRI) and systemic immune-inflammation index (SII). The main outcome was the first event of CKD progression, characterized by a decrease in the estimated glomerular filtration rate (eGFR) stage, with a sustained ≥25% decline in eGFR from baseline, confirmed by two consecutive measurements ≥3 months apart. Cox proportional hazards models assessed associations between BIL, systemic inflammation, and CKD progression. Subgroup and sensitivity analyses were also conducted. Restricted cubic splines (RCS), and mediation analysis were performed to assess the nonlinear associations and mediating role of systemic inflammation.

Results: During a median follow-up duration of 2.00 years (interquartile range: 1.03–2.84 years), 153 participants exhibited progression of CKD. The RCS analysis indicated nonlinear associations between both total bilirubin (TBIL, P for nonlinear < 0.001) and indirect bilirubin (IBIL, P for nonlinear < 0.001) with CKD progression. Cox regression models showed the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for TBIL and IBIL were 0.92 (95% CI: 0.89, 0.96) and 0.90 (95% CI: 0.85, 0.94), respectively. Subgroup and sensitivity analyses reinforced the findings, demonstrating consistent outcomes across demographic groups and under varied analytical conditions. The modest mediating effects were observed for SIRI (5.21%) and SII (5.50%) with TBIL, and for SIRI (7.17%) and SII (6.92%) with IBIL. However, these correlations were not observed with direct bilirubin (DBIL).

Conclusion: Lower BIL levels (especially IBIL) were inversely associated with CKD progression risk in type 2 diabetes, with systemic inflammation partially mediating this relationship.

Keywords: bilirubin, inflammation, chronic kidney disease, type 2 diabetes, cohort study

Introduction

Chronic kidney disease (CKD) has escalated into a pressing global health crisis. According to the latest Global Burden of Disease (GBD) study,[1] CKD affected approximately 788 million adults aged ≥20 years globally, reflecting an age-standardized prevalence of 14.2% in 2023. The mortality burden is equally alarming, with CKD ranking as the ninth leading cause of death globally in 2023, accounting for 1.48 million deaths. The burden of diabetes-associated CKD constitutes a common and disabling condition, linked to elevated morbidity and healthcare costs. Based on the

https://doi.org/10.2147/JIR.S578233
Received: 6 November 2025
Accepted: 20 December 2025
Published: 19 January 2026

International Diabetes Federation (IDF), 9.3% of the global population—approximately 463 million people—were living with diabetes in 2019.[2] Among individuals with diabetes, over 25% show evidence of CKD, and projections suggest 40% will develop CKD at some point in their lifetime.[3] As global diabetes prevalence rises, the incidence of diabetes-related CKD is similarly increasing.[3,4] Thus, identifying the risk factors that drive CKD progression in people with diabetes is critical for developing effective prevention strategies.

Bilirubin (BIL) should be regarded not merely as a byproduct of hemoglobin degradation but also as a critical antioxidant and hormone that facilitates lipid metabolism.[5] Evidence suggests that individuals with Gilbert syndrome—characterized by mild elevations in serum BIL levels—exhibit a reduced risk of developing several "diseases of civilization", including metabolic syndrome and type 2 diabetes.[6] Furthermore, research has highlighted the potent antioxidant properties of BIL and its unique role in lowering the risk of CKD progression, underscoring its multifaceted biological significance. Despite BIL's strong antioxidant properties, it paradoxically elevates the risk of renal calcium oxalate crystal deposition—an effect driven by promoting renal tubular apoptosis, enhancing oxalate secretion, and facilitating crystal formation and aggregation.[7] Another result from a biopsy-focused investigation[8] revealed a negative correlation between serum BIL concentrations and diabetic nephropathy progression risk, although BIL was not identified as a standalone factor—contrasting with prior research.[9] Furthermore, numerous epidemiological studies and a recent meta-analysis have focused on the simple correlation between BIL and renal disease, generally showing a linear inverse association between BIL levels and CKD risk.[10–12] Moreover, several prospective studies did not distinguish between BIL subtypes (indirect bilirubin [IBIL] and direct bilirubin [DBIL]),[13,14] leaving insufficient evidence on effective predictors and biological mechanisms connecting BIL to CKD progression in diabetic populations.

Inflammation is widely recognized as both a pivotal driver of CKD[15–18] and a pathognomonic feature of its pathophysiology.[19,20] Research indicates that BIL possesses significant anti-inflammatory and antioxidant characteristics, making it a potentially valuable therapeutic candidate for relieving inflammatory and immune-related conditions.[21–23] Consequently, inflammation could be a factor in influencing the relationship between BIL levels and the progression of CKD. Systemic inflammation response index (SIRI) and systemic immune-inflammation index (SII) have been widely used to measure systemic inflammation activity, illustrating the interplay between inflammatory and immune responses.[24] Previous research has demonstrated their effectiveness in evaluating the severity of local inflammation and systemic immune status, contributing to the prediction of various clinical outcomes.[25,26] They have gained recognition as significant indicators of the prognosis of diabetes and the diabetic kidney diseases.[27,28] Currently, the mediating role of systemic inflammatory biomarkers in the association between BIL levels and CKD progression remains poorly understood.

This study aimed to investigate the dose-response relationship between serum BIL levels and CKD progression in patients with type 2 diabetes, specifically to identify which BIL subtype may exert a key role. Furthermore, we sought to explore whether and how systemic inflammatory biomarkers mediate the observed associations.

Methods

Study Population

Previously reported in comprehensive detail,[29] this observational cohort study was systematically executed within the substudy of the Tianjin Medical University Chu Hsien-I Memorial Hospital's longitudinal research initiative examining Factors Associated With Pathogenic Mechanisms and Clinical Outcomes in Diabetic Kidney Disease. Specifically, A total of 3191 adult patients with type 2 diabetes who had their first hospitalization were recruited from the Tianjin Medical University Chu Hsien-I Memorial Hospital between January 1, 2017 and September 25, 2021. This study used a complete-case analysis approach, where only participants with complete data for all variables were included in the analysis. Participants with hepatobiliary disorders (eg, gallstones, liver cancer or failure, hepatitis or liver cirrhosis), malignant hematologic disorders (eg, hemodialysis, hemolysis, or leukemia), severe renal dysfunction (eg, eGFR <15 mL/min/1.73 m^2, renal failure or renal replacement therapy), or lacking follow-up information, were excluded. Ultimately, 1215 individuals were deemed eligible, the screening process is detailed in Figure 1. The study has obtained ethical approval from the Tianjin Medical University Chu Hsien-I Memorial Hospital (approval number ZXYJNYYkMEC2023-50), and

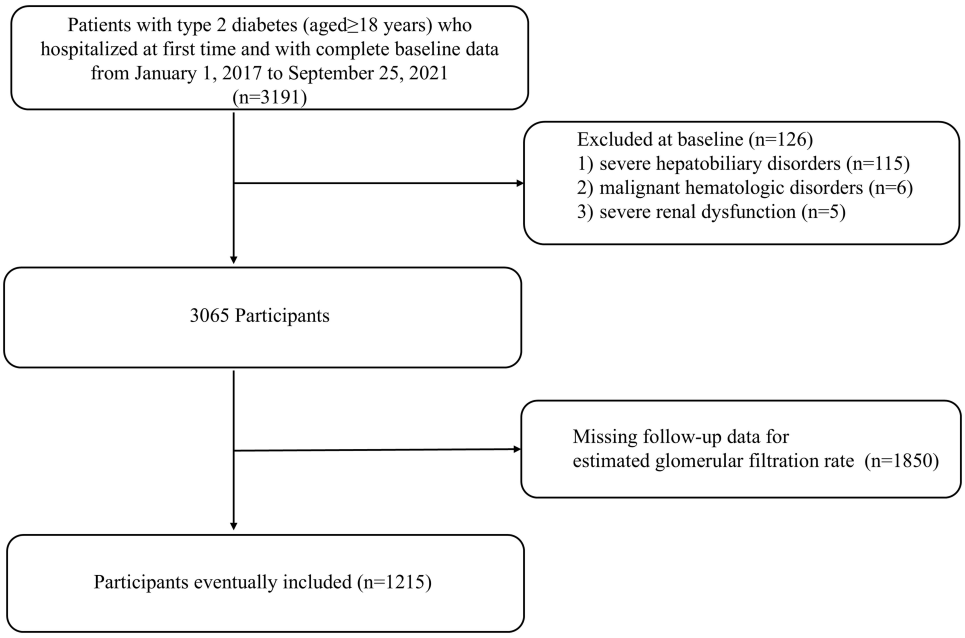

Figure 1 Flow chart of study participants.

adhered to ethical principles outlined in the Helsinki Declaration. Informed consent from individual patients was waived for this retrospective, non-interventional study. All patient data were anonymized and handled with strict confidentiality to ensure the protection of personal privacy and rights.

Study Procedure

Assessment of Exposure and Outcome

The exposure considered was baseline serum TBIL, including its subtypes IBIL and DBIL. The outcome was the first occurrence of CKD progression, defined as a decline in eGFR stage (eg, G1 ≥ 90, G2 60–89, G3a 45–59, G3b 30–44, G4 15–29, and G5 <15 mL/min/1.73 m^2) and a sustained ≥25% decline in eGFR from baseline, confirmed by two consecutive measurements ≥3 months apart.[30,31] The study follow-up concluded on September 25, 2023. For each participant, the final observation date was either the date on which the CKD progression occurred or the last eGFR record before the set deadline.[32]

Assessment of Systemic Inflammation Biomarkers

Biochemical tests and complete blood cell counts were performed using routine automated analyzers. The systemic inflammation biomarkers derived from blood counts were calculated as follows: SIRI = neutrophil counts × monocyte counts / lymphocyte counts; SII = platelet counts × neutrophil counts / lymphocyte counts; NLR = neutrophil counts / lymphocyte counts; PLR = platelet counts / lymphocyte counts; LMR = lymphocyte counts / monocyte counts.[33]

Assessment of Covariates

Baseline data for participants were collected to account for potential confounding factors. This included variables significant in univariate Cox analysis ($P < 0.05$, supplementary Table 2), as well as demographic characteristics and variables identified from relevant literature.[9,32] The use status of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEi/ARBs), statins, insulin therapy, and SGLT2 inhibitors (SGLT2i) was traced via the hospital's electronic prescription system. Specifically, these covariates included age, gender, body mass index (BMI), hemoglobin A1c (HbA1c), systolic blood pressure, log-triglycerides, diabetes duration, low density lipoprotein cholesterol (LDL-cholesterol), uric acid, alanine aminotransferase (ALT), statin use (yes or no), ACEi/ARBs use (yes or no), and insulin therapy (yes or no).

https://doi.org/10.2147/JIR.S578233

Statistical Analyses

Description of the Characteristics

Data are expressed as means ± standard deviations (SD). The baseline characteristics were analyzed across TBIL tertiles employing appropriate statistical methods, such as analysis of variance (ANOVA), Kruskal–Wallis rank sum tests, or χ^2 tests. The triglyceride was converted to logarithmic form for analysis. All analyses were performed using R version 4.2.3 (R Foundation) and SPSS version 26.0 (IBM). $P < 0.05$ was deemed statistically significant.

Association of BIL, Systemic Inflammation, and CKD Progression Risk

The hazard ratios (HRs) and their associated 95% confidence intervals (CIs) for the association between BIL levels, systemic inflammation, and the risk of CKD progression were calculated utilizing the Cox proportional hazards model. The validation of the proportional hazards assumption was conducted through the examination of Schoenfeld residuals prior to the analysis. Furthermore, Multiple linear regression models were utilized to estimate β coefficients and 95% CIs for alterations in BIL levels corresponding to each unit increase in systemic inflammation markers. An analysis of collinearity revealed that there is no collinearity present among the variables. The investigation into the dose-response relationship involving BIL, systemic inflammation, and the progression of CKD was conducted through the application of a multivariable-adjusted RCS curve with four knots (5th, 35th, 65th, and 95th percentile). This approach improved the smoothness of the curve while effectively reducing the risk of overfitting.[34] Subgroup analyses based on sex, age group, and BMI were performed, and multiplicative interactions between BIL levels and subgroup variables were evaluated.

Mediation Analysis

Mediation analyses were conducted using the "mediation" package in R 4.2.3. This was performed using Cox proportional hazards models to explore the potential mediating role of systemic inflammation in the association between BIL and renal outcome risk, adjusting for all covariates mentioned above, including age, gender, BMI, HbA1c, systolic blood pressure, log-triglycerides, diabetes duration, LDL-cholesterol, uric acid, ALT, statin use (yes or no), ACEi/ARBs use (yes or no), and insulin therapy (yes or no). The 95% CI of these estimates was computed using the bootstrap method (500 samples). The presence of an intermediary effect is defined as meeting all of the following rules, with significant total, direct, and indirect effects.[35] The proportion of the mediation effect of systemic inflammation on the total effect of BIL on the outcome was estimated.

Sensitivity Analyses

Sensitivity analyses were conducted to assess the robustness of the primary findings. First, the multivariate model was further adjusted for baseline eGFR. Secondly, baseline hemoglobin, also known to be associated with the exposure factor, was included in the adjustments of the multivariate model. Thirdly, adjustments were made for the use of sodium-glucose cotransporter 2 inhibitors (SGLT2i). Finally, conventional clinical trials often use composite endpoints for CKD progression (eg, doubling of serum creatinine, eGFR less than 15 mL/min/1.73 m^2, or kidney replacement therapy). However, these events are rare and often occur late. To assess the impact of BIL on renal function at an earlier disease stage, the renal outcome was redefined as the progression of eGFR category alone from baseline stage.

Results

Participant Characteristics

Clinical and laboratory data for participants, segmented by TBIL tertiles, are presented in Table 1. Of the 1215 eligible individuals, 536 (44.12%) were female and 679 (55.88%) male, with an average age of 56.12 ± 12.47 years. None of the patients had serum BIL levels in the toxic range. As TBIL tertiles increased, there were decreases in age and baseline albumin-to-creatinine ratio (UACR), and an increase in baseline eGFR. Participants in higher tertiles also exhibited significantly lower levels of neutrophils, platelets, PLR, and SII. No statistically significant differences were observed in the frequency of drug use, except for statin use.

Table 1 Baseline Characteristics of Participants Stratifying by the Tertiles of Total Bilirubin

	Tertiles of Total Bilirubin			P Value
	Tertiles 1 (n=410)	Tertiles 2 (n=397)	Tertiles 3 (n=408)	
Male, n (%)	163 (39.76)	225 (56.68)	291 (71.32)	<0.001
Age, years	58.10±11.88	56.40±11.83	53.85±13.30	<0.001
BMI, kg/m^2	26.85±3.96	26.99±4.23	26.94±4.01	0.882
Diabetic duration, years	11.88±8.17	10.68±8.11	9.44±7.81	<0.001
History of diabetes, n (%)	240 (77.17)	241 (76.27)	246 (76.88)	0.963
Systolic blood pressure, mmHg	135.98±17.31	134.02±17.49	135.44±18.68	0.273
Diastolic blood pressure, mmHg	79.21±9.98	80.32±10.35	82.28±11.25	<0.001
HbA1c, %	8.75±2.05	8.78±2.00	8.76±1.90	0.976
Triglyceride, mmol/L	1.76 (1.30,2.68)	1.70 (1.25,2.31)	1.55 (1.12,2.35)	0.006
Total cholesterol, mmol/L	5.20±1.55	5.17±1.42	5.04±1.49	0.297
LDL-cholesterol, mmol/L	3.49±1.10	3.50±1.01	3.40±0.99	0.338
HDL-cholesterol, mmol/L	1.12±0.29	1.11±0.28	1.08±0.26	0.197
Baseline eGFR, mL/min/1.73 m^2	89.81±25.65	98.14±20.16	101.37±19.22	<0.001
Baseline UACR, mg/g	14.21 (7.11,100.21)	10.21 (5.84,38.55)	9.48 (5.18,28.59)	<0.001
Uric acid, μmol/L	339.88±97.57	341.32±91.54	349.57±101.50	0.307
Hemoglobin, g/L	131.34±14.64	141.02±14.94	147.43±15.53	<0.001
Neutrophil counts, 10^9/L	4.01±1.23	3.77±1.11	3.80±1.13	0.006
Monocyte counts, 10^9/L	0.48±0.13	0.48±0.12	0.48±0.13	0.976
Lymphocyte counts, 10^9/L	2.06±0.64	2.04±0.60	1.98±0.54	0.134
Platelet counts, 10^9/L	240.34±55.15	229.36±55.77	215.92±54.58	<0.001
NLR	2.08±0.76	1.96±0.69	2.01±0.66	0.051
LMR	4.46±1.41	4.42±1.29	4.32±1.29	0.290
PLR	124.68±36.84	119.45±36.51	114.62±34.00	<0.001
SIRI	1.00±0.45	0.94±0.43	0.97±0.43	0.136
SII	497.89±205.30	448.52±187.60	435.30±181.81	<0.001
ALT, U/L	21.49±14.11	26.81±23.42	29.67±23.75	<0.001
AST, U/L	21.68±11.53	23.85±14.27	27.32±17.68	<0.001
GGT, U/L	28.64±21.46	36.56±36.96	42.68±43.25	<0.001
Total bilirubin, μmol/L	8.41±1.54	12.36±1.09	19.71±5.21	<0.001
Indirect bilirubin, μmol/L	5.94±1.70	9.28±1.41	14.96±4.25	<0.001
Direct bilirubin, μmol/L	2.47±0.99	3.09±1.05	4.76±1.86	<0.001
Insulin use, n (%)	238 (58.05)	223 (56.17)	222 (54.41)	0.577
Statin use, n (%)	273 (66.59)	258 (64.99)	235 (57.60)	0.018
ACEi/ARBs use, n (%)	159 (38.78)	147 (37.03)	132 (32.35)	0.142
SGLT2i use, n (%)	110 (26.83)	111 (27.96)	126 (30.88)	0.417
GLP-1RA use, n (%)	59 (14.39)	54 (13.60)	56 (13.73)	0.941

Notes: Data are expressed as mean ± SD, median (IQR), or n (%).

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-creatinine ratio; NLR, neutrophil to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PLR, platelet to lymphocyte ratio; SIRI, systemic inflammatory response index; SII, systemic immune-inflammation index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers; SGLT2i, sodium-glucose cotransporter 2 inhibitors; GLP-1RA, glucagon-like peptide 1 receptor agonists.

BIL and CKD Progression Risk

During a median follow-up of 2.00 years (interquartile range: 1.03–2.84 years), 153 participants experienced CKD progression. The baseline levels of TBIL and IBIL were markedly reduced in patients who experienced progression in renal outcomes (supplementary Table 1). Additionally, elevated concentrations of TBIL and IBIL were notably linked to a reduced likelihood of CKD progression in the unadjusted model. Upon controlling for possible confounding variables, these inverse relationships persisted consistently (Table 2). The adjusted HRs (95% CIs) for the progression of CKD per 1 μmol/L increase in TBIL and IBIL were 0.92 (95% CI: 0.89, 0.96) and 0.90 (95% CI: 0.85, 0.94), respectively.

Table 2 HRs (95% CIs) for Progression of CKD Based on the Bilirubin Levels

	Crude Model		Adjusted Model	
	HR (95% CI)	**P Value**	**HR (95% CI)**	**P Value**
Total bilirubin				
Continuous (per unit)	0.92 (0.88,0.95)	<0.001	0.92 (0.89,0.96)	<0.001
Categorical				
Tertiles T1 (≤10.50)	Reference	–	Reference	–
Tertiles T2 (10.50–14.50)	0.54 (0.37,0.78)	0.001	0.52 (0.35,0.76)	0.001
Tertiles T3 (>14.50)	0.37 (0.25,0.57)	<0.001	0.39 (0.25,0.61)	<0.001
Indirect bilirubin				
Continuous (per unit)	0.89 (0.86,0.94)	<0.001	0.90 (0.85,0.94)	<0.001
Categorical				
Tertiles T1 (≤7.80)	Reference	–	Reference	–
Tertiles T2 (7.80–11.00)	0.53 (0.37,0.76)	0.001	0.47 (0.31,0.68)	<0.001
Tertiles T3 (>11.00)	0.33 (0.22,0.51)	<0.001	0.32 (0.20,0.50)	<0.001
Direct bilirubin				
Continuous (per unit)	0.14 (0.82,1.03)	0.917	0.97 (0.86,1.09)	0.637
Categorical				
Tertiles T1 (≤2.60)	Reference	–	Reference	–
Tertiles T2 (2.60–3.80)	0.99 (0.69,1.43)	0.966	1.24 (0.86,1.81)	0.254
Tertiles T3 (>3.80)	0.73 (0.48,1.12)	0.151	0.90 (0.58,1.42)	0.656

Notes: Crude model: none adjusted. Adjusted model included following covariates at baseline: age, sex, body mass index, hemoglobin A1c, systolic blood pressure, log-triglycerides, duration of diabetes, LDL-cholesterol, uric acid, alanine aminotransferase, use of statin (yes or no), use of ACE inhibitors or angiotensin receptor blockers (ACEi/ARBs) (yes or no) and insulin treatment (yes or no).
Abbreviations: CKD, chronic kidney disease; HRs, hazard ratios; 95% CI, 95% confidence intervals.

Similarly, these correlations persisted when TBIL and IBIL were categorized into tertiles. RCS analyses indicated nonlinear associations between both TBIL (P for nonlinear < 0.001) and IBIL (P for nonlinear < 0.001) with renal outcomes, but these correlations were not observed with DBIL (P for nonlinear = 0.338) (Figure 2).

Sensitivity Analyses

The sensitivity results were similar to that of the primary analysis (supplementary Table 5). Particularly, in the analysis using progression of eGFR category from baseline as the outcome, 304 participants reached the outcome during the median follow-up period of 1.90 years (interquartile range: 0.90–2.69 years). A similar result—showing that elevated concentrations of TBIL and IBIL were significantly associated with a lower risk of CKD progression—was obtained compared with the primary analysis (supplementary Table 5).

Supplementary Fig 1 displays comprehensive subgroup analyses stratified by gender, age, and BMI. After adjusting for all covariates, the associations between BIL (TBIL and IBIL) and CKD progression risk were significant in males with a BMI ≥ 24 kg/m^2 (all P < 0.05), while the association between DBIL and CKD progression was not significant across all subgroups (all P for interaction > 0.05).

Systemic Inflammation and CKD Progression Risk

Supplementary Table 3 details the associations between systemic inflammation and CKD progression risk, controlled for all mentioned confounders. An elevated level of systemic inflammation was positively correlated with an increased risk of CKD progression. The adjusted HRs of systemic inflammation markers SIRI, SII, NLR, and LMR for CKD progression were 2.05 (95% CI: 1.43, 2.96), 1.28 (95% CI: 1.10, 1.50), 1.43 (95% CI: 1.14, 1.79), and 0.81 (95% CI: 0.70, 0.94), respectively. RCS analyses demonstrated linear associations of SIRI and SII with renal outcomes (P for nonlinearity > 0.05, Figure 2).

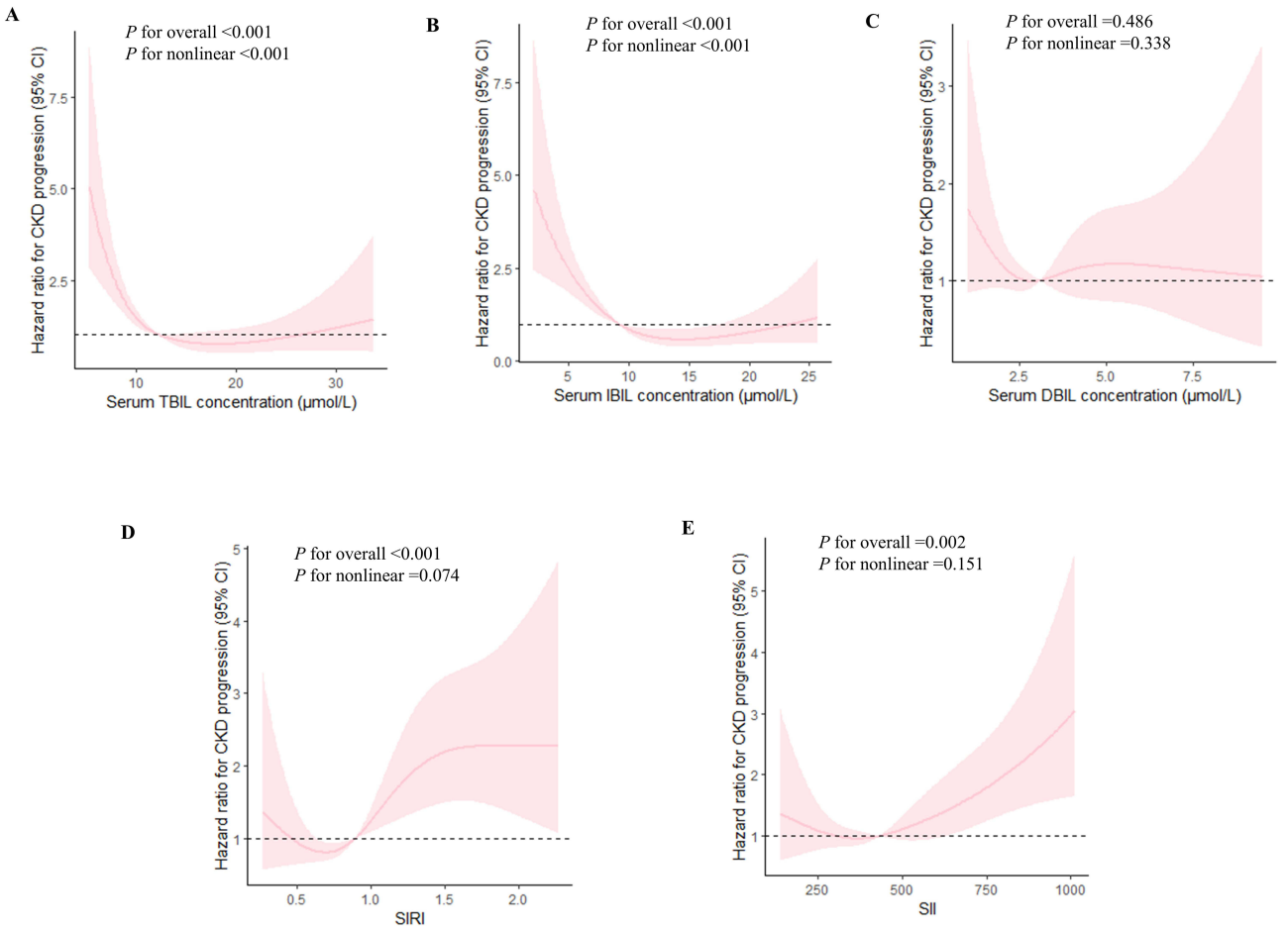

Figure 2 Analysis of adjusted RCS model in relation to bilirubin, systemic inflammation and CKD progression. RCS between CKD progression and TBIL (**A**), IBIL (**B**), or DBIL (**C**). RCS between CKD progression and SIRI (**D**) or SII (**E**). The following covariates at baseline were incorporated into the RCS model with four knots (5th, 35th, 65th, and 95th percentile): age, sex, body mass index, hemoglobin A1c, systolic blood pressure, log-triglycerides, duration of diabetes, LDL-cholesterol, uric acid, alanine aminotransferase, use of statin (yes or no), use of ACE inhibitors or angiotensin receptor blockers (ACEi/ARBs) (yes or no) and insulin treatment (yes or no). Solid and long dashed lines represent the estimated regression hazard ratios (HR) and its 95% confidence interval (95% CI).

Abbreviation: RCS, restricted cubic spline; CKD, chronic kidney disease; TBIL, total bilirubin; IBIL, indirect bilirubin; DBIL, direct bilirubin; SIRI, systemic inflammatory response index; SII, systemic immune-inflammation index.

BIL and Systemic Inflammation

Multiple linear regression was employed to assess the correlation between BIL and inflammation. After adjusting for relevant covariates, TBIL and IBIL were negatively correlated with increased systemic inflammation. Specifically, the β and their corresponding 95% CIs were as follows: for TBIL, $\beta = -0.01$ for SIRI (95% CI: −0.01, −0.00) and $\beta = -2.89$ for SII (95% CI: −4.85, −0.94); for IBIL, $\beta = -0.01$ for SIRI (95% CI: −0.01, -0.00) and $\beta = -4.14$ for SII (95% CI: −6.52, −1.83) (supplementary Table 4).

Mediating Effect Analysis

Systemic inflammation showed statistically significant but modest mediating effects on the relationship between BIL (TBIL and IBIL) and CKD progression risk (Figure 3). According to the definition of mediation effect, only SIRI and SII passed the test of mediation model. Specifically, after adjusting for same covariates, the indirect effects of SIRI on the associations of TBIL and IBIL with renal outcomes were -0.36×10^{-3} (95% CI: -0.89×10^{-3}, -0.08×10^{-3}) and -0.57×10^{-3} (95% CI: -1.46×10^{-3}, -0.20×10^{-3}), respectively. Similarly, the indirect effects of SII on the associations of TBIL and IBIL with renal outcome were -0.38×10^{-3} (95% CI: -1.03×10^{-3}, -0.08×10^{-3}) and -0.55×10^{-3} (95% CI: -1.32×10^{-3}, -0.13×10^{-3}), respectively. The proportion of the SIRI-mediated effect on the association with renal

https://doi.org/10.2147/JIR.S578233

outcomes was 5.21% for TBIL and 7.17% for IBIL. Similarly, SII-mediated proportions were 5.50% for TBIL and 6.92% for IBIL.

Discussion

In this study, we investigated the association between serum BIL concentrations and CKD progression in patients with type 2 diabetes. Our results revealed a significant inverse association between TBIL and IBIL levels and CKD progression, whereas no such association was observed for DBIL. These findings were robustly supported by subgroup and sensitivity analyses. Dose-response analyses further uncovered nonlinear relationships between TBIL/IBIL levels and CKD progression. Moreover, mediation analysis indicated that systemic inflammation played a modest mediating role in the association between BIL and CKD progression.

Recent studies have redefined BIL as an endocrine signaling molecule with demonstrated cardiorenal and metabolic protective effects. These benefits are mediated through dual modulation of lipid metabolism and inflammatory pathways.[36] Specifically, BIL suppresses complement activation, inhibits pro-inflammatory factors, and reduces lipid peroxidation,[37] establishing it as a key regulator of cellular homeostasis. The renal protective effects of BIL are partially explained by its role as a selective PPARα agonist. Through direct binding to this nuclear receptor, BIL upregulates fatty acid oxidation genes, thereby reducing renal steatosis and improving lipid profiles in diabetic kidney disease.[36] The recent work by Adeosun et al further elucidates the BIL-biliverdin reductase A-PPARα axis as a central regulator of lipid homeostasis, suppressing de novo lipogenesis while promoting fatty acid β-oxidation.[38] This mechanism provides a plausible explanation for the observed inverse correlation between BIL levels and CKD progression.

Epidemiological studies consistently show that individuals with moderately elevated BIL levels exhibit reduced risk of chronic inflammatory diseases, including diabetes and CKD.[39,40] While most longitudinal studies have not differentiated BIL subtypes,[41,42] our analysis reveals crucial distinctions: both TBIL and IBIL, but not DBIL, independently predict CKD progression. The nonlinear relationship between IBIL levels and renal outcomes suggests a threshold effect, with optimal protection occurring at moderately elevated concentrations. Prespecified subgroup analyses identified males

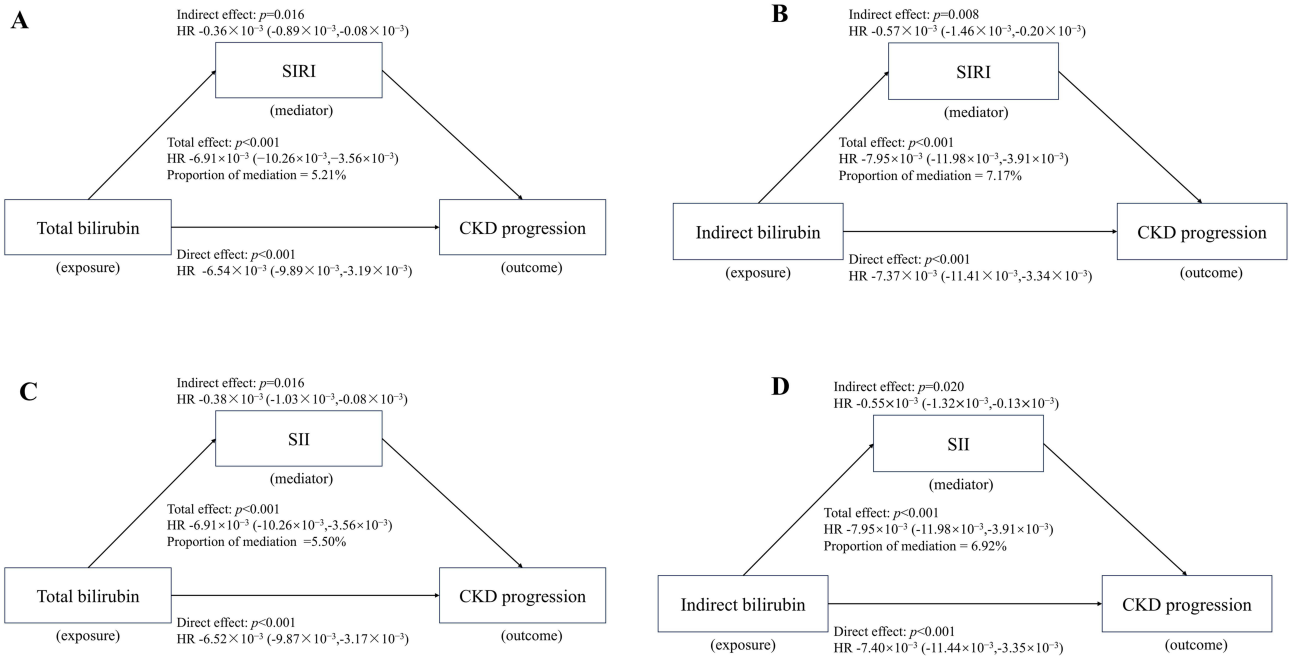

Figure 3 Analysis of the mediation by SIRI (**A** and **B**) and SII (**C** and **D**) of the associations of bilirubin with CKD progression. Mediating role of SIRI in the association between total bilirubin (**A**) indirect bilirubin (**B**) and CKD progression. Mediating role of SII in the association between total bilirubin (**C**) indirect bilirubin (**D**) and CKD progression. The 95% CI of these estimates was computed using the bootstrap method (500 samples). In all mediation analyses, adjustments were made for the following covariates: age, sex, body mass index, hemoglobin A1c, systolic blood pressure, log-triglycerides, duration of diabetes, LDL-cholesterol, uric acid, alanine aminotransferase, use of statin (yes or no), use of ACE inhibitors or angiotensin receptor blockers (ACEi/ARBs) (yes or no) and insulin treatment (yes or no).
Abbreviation: CKD, chronic kidney disease; SIRI, systemic inflammatory response index; SII, systemic immune-inflammation index.

with BMI ≥ 24 kg/m^2 as deriving particular benefit from higher BIL levels, suggesting BIL's potential as an early prognostic indicator in this high-risk population. These findings align with similar observations in coronary heart disease studies,[43] supporting BIL's role as a broader cardiometabolic risk modulator.

Lipid homeostasis[44] and inflammatory activation[45] are established central drivers of diabetes-induced CKD. In recent years, blood-cell-derived inflammatory indices—such as the SIRI and SII—have been increasingly utilized as prognostic tools in various inflammation-associated conditions including diabetes.[46] Conversely, mildly elevated TBIL has garnered attention for its potential renal protective effects in diabetic kidney disease.[47] Consistent with prior analyses of NHANES data (2009–2018),[48] the present study demonstrated that most inflammatory markers correlated inversely with BIL levels and positively with CKD progression. Notably, this study extends previous observations by employing mediation analysis to elucidate potential mechanisms underlying BIL's inverse association role. We identified that novel inflammatory markers SIRI and SII—reflecting systemic inflammatory status—partially mediated the association between BIL and renal outcomes. While BIL's function as a reactive oxygen species scavenger is well documented, its anti-inflammatory properties are increasingly recognized.[49] Preclinical evidence suggests that IBIL may exert stronger CKD protection due to superior antioxidant capacity. Unlike DBIL, lipophilic IBIL readily crosses cell membranes, neutralizing intracellular oxidative stress and directly inhibiting NADPH oxidase and NF-κB signaling.[50] This aligns with clinical observations that Gilbert's syndrome—characterized by elevated IBIL—confers cardiorenal protection. Thus, our mediation analysis provides new clinical cohort evidence supporting that elevated BIL concentrations may contribute to the preservation of renal function through anti-inflammatory mechanisms.

The present study conducted a comprehensive analysis of the relationship between BIL and renal outcomes, with particular emphasis on differentiating the effects of BIL subtypes. Our findings demonstrate that the potentially protective association is primarily attributable to IBIL, providing new insights into BIL's complex role in renal pathophysiology. Importantly, we identified a nonlinear dose-response relationship between BIL levels (TBIL/IBIL) and CKD progression, indicating that moderately elevated serum BIL confers a reduced risk of renal function decline—contrasting with conventional perspectives that link only extreme BIL concentrations (either markedly high or low) to adverse health indicators such as hepatic dysfunction. Furthermore, systemic inflammatory biomarkers (SIRI/SII) partially mediated the BIL-CKD association, though the proportion mediated was modest (5–7%), consistent with emerging evidence suggesting synergistic roles of inflammation and oxidative stress in CKD progression. BIL's antioxidant capacity may thus function as a buffer against inflammatory injury rather than a sole determinant, highlighting its potential as a multifactorial modulator in diabetic kidney disease.

The study also has limitations that deserve consideration. Firstly, our endpoint definition (eGFR decline ≥25% with stage progression) may capture short-term renal function fluctuations influenced by acute factors (eg, medication changes or intercurrent illness). The median follow-up of 2.00 years limits the ability to assess long-term CKD progression. Future work should use harder endpoints (eg, end stage renal disease) over longer periods. Secondly, the primary analysis was based on the Cox proportional hazards model, with adjustment for key baseline confounders and certain medications including statin use, ACEi/ARBs, insulin therapy, and SGLT2i. However, in practical clinical scenarios, there remains a potential for unmeasured or imperfectly measured time-varying factors (eg, lifestyle factors). Therefore, prospective validation in cohorts with deep phenotyping is warranted. Thirdly, although systemic inflammation (eg, SIRI/SII) exhibited a statistically significant mediating role in the BIL–CKD association, the modest mediating proportion (5–7% of the total effect) indicates that inflammation likely accounts for only a partial component of this relationship. Lastly, the study is limited by its retrospective nature, single-center design, and lack of external validation, which constrain causal inference and generalizability; thus, the proposed causal chain requires verification via multi-center prospective studies or experimental models.

Conclusion

This study revealed that elevated TBIL, particularly IBIL, showed a nonlinear inverse association with CKD progression in type 2 diabetes. While inflammation partially mediated this link, BIL's antioxidative properties likely play a central role. Future studies should validate BIL's prognostic utility in diverse CKD populations and explore its therapeutic potential.

Statement

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (see Supplementary Files for the STROBE checklist).

Data Sharing Statement

All datasets generated during the current study are available from the corresponding author on reasonable request.

Ethics Approval Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Tianjin Medical University Chu Hsien-I Memorial Hospital (approval number ZXYJNYYkMEC2023-50). The need for informed consent was waived due to the retrospective nature of the study. All patient data were anonymized and handled with strict confidentiality to ensure the protection of personal privacy and rights.

Acknowledgments

We are grateful to the Tianjin Key Medical Discipline (Specialty) Construction Project (TJYXZDXK-032A).

Author Contributions

All authors made a significant contribution to the work reported.

YYC, SSW and XNC: Writing - original draft, Conceptualization, Investigation, Data curation, Methodology, Supervision, Formal Analysis, Validation.

BS, YC and XYL: Writing - review & editing, Conceptualization, Investigation, Data curation, Methodology, Supervision, Validation.

LMC: Writing - review & editing, Conceptualization, Investigation, Supervision, Validation, Funding acquisition, Resources.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was funded by National Science and Technology Major Projects “Cancer, Cardiovascular, Respiratory, and Metabolic Diseases Prevention and Treatment Research” (Number: 2023ZD0509203), the National Natural Science Foundation of China (Number: 82370842), the Natural Science Foundation of Tianjin (Numbers: 23JCZDJC00640 and 24JCQNJC01310), Scientific Research Funding of Tianjin Medical University Chu Hsien-I Memorial Hospital (Number: ZXY-ZDSYSZD2022-2) and the Science & Technology Development fund of Tianjin Education Commission for Higher Education (Number: 2020KJ189).

Disclosure

The authors declare no conflicts of interest.

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