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Serum Bilirubin Association with Estimated Glomerular Filtration Rate and Other Risk Factors Among Chronic Kidney Disease Patients

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Abstract: Chronic kidney disease is one of the most serious public health burdens globally, with significant morbidity, mortality, and reduced in patient life expectancy. Although the current marker of kidney disease is the glomerular filtration rate (GFR), the serum creatinine used for GFR determination is influenced by many factors. Therefore, it has become increasingly important to search for possible additional parameters related to estimated glomerular filtration rate to enhance early detection of disease progression. A hospital-based cross-sectional study was conducted at Jimma University Medical Center to evaluate serum bilirubin parameter and its correlation with eGFR in the chronic kidney disease patients on follow-up. Using consecutive sampling technique, a total of 140 CKD follow-up patients were recruited into the current study. Then, data were collected using interviewer-based structured questionnaires, record reviews, and physical examinations. Data were analyzed by SPSS version 25.0. The correlation between eGFR as well as other explanatory variables with serum bilirubin (total and direct) concentrations was examined by Pearson's correlation analyses. Univariate and multivariate linear regression were used to test predictors of serum bilirubin (total and direct bilirubin). Subjects of this study included (54.3% [n = 76]) men and (45.7% [n = 64]) women, respectively. The mean (SD) age of study subjects was 51.04±9.02 years with a minimum and maximum age of being 30 and 70 years old, respectively. A positive correlation was found between serum bilirubin and eGFR; total bilirubin ($r = 0.868$, $P < 0.001$), direct bilirubin ($r = 0.641$, $P < 0.001$). BMI was negatively correlated ($r = -0.221$, $P < 0.009$) with serum bilirubin value. Moreover, the eGFR value was positively associated ($\beta = 0.04$, $P =< 0.001$) with serum total bilirubin among study participants. As a conclusion, estimated glomerular filtration rate were positively correlated with both serum total and direct bilirubin. Furthermore, eGFR was positively associated with serum total and direct bilirubin in the study subjects, whereas BMI was negatively associated with serum bilirubin in CKD participants. Therefore, low serum bilirubin (total and direct bilirubin) and increased body mass index are independent risk factors for disease progression in patients with CKD.

Keywords: Total Bilirubin, Direct Serum Bilirubin, Chronic Kidney Disease, eGFR

1. Background

Chronic kidney disease is an abnormality of the structure and function of the kidneys, explained by a GFR<60mL/min/1.73m^2 for at least three months [1]. It is a common non-communicable disease that currently affects approximately 850 million people worldwide, 78% of whom live in low and middle-income countries [2]. Cardiovascular disease is the most common complication of CKD, with its prevalence rising to 74% in CKD patients [3]. Many sub-Saharan African countries face double-burden (economic and human resource) challenges in treating CKD and its complications [4].

The prevalence of the disease has increased rapidly in Africa, with 11% in Tunisia, 34.7% in Morocco, and 83.7% in Tanzania, respectively [5]. In Ethiopia, the prevalence of chronic kidney

disease is estimated to be 17.3% [6]. Although many causes of CKD have been proposed, the two most common causes accounting for two-thirds of CKD are diabetes mellitus (44%) and hypertension (29%) respectively [7]. Several studies have indicated that kidney disease is characterized by increased oxidative stress even in the early stages of CKD [8]. The causes of the inflammatory process in CKD include increased production of pro-inflammatory cytokines, uremic toxins, decreased defense mechanism, recurrent infections, metabolic acidosis, and the dialysis procedure [9, 10].

In addition, cytokine and growth factor release affects glomerular histology through expansion of mesangial cells and subsequent glomerulosclerosis [11, 12]. Serum bilirubin is an endogenous antioxidant derived from the catabolism of heme [13]. Most (80%) plasma bilirubin comes from the hemoglobin of senescent erythrocytes in reticuloendothelial cells, and the remaining 20% comes from the breakdown of other heme proteins such as cytochrome, myoglobin, and catalase from other tissues [14]. Recent studies suggest that serum bilirubin has strong antioxidant activity [15]. Both direct and indirect bilirubin Inhibit the enzymatic activity of NADPH oxidase and inhibition of superoxide (O_2^-) free radical production in vascular endothelial cells and renal tubular cells [16].

Several epidemiological studies suggest that higher serum bilirubin concentrations in the physiological range reduce the risk of chronic kidney disease. A current cross-sectional study in Japan suggests that patients with lower serum bilirubin have a higher risk of developing advanced CKD in both men and women [17]. Another similar study from Tokyo Japan on diabetic nephropathy demonstrated that serum bilirubin was significantly associated with eGFR [18]. Similarly, a study in southern India showed that patients with CKD and other comorbidities such as diabetes had lower serum total and direct bilirubin [19]. A comparative study in Korea showed that serum total bilirubin concentrations were inversely associated with eGFR and CKD stages in diabetic and non-diabetic patients [20]. Elevated serum bilirubin is associated with a reduced risk of developing stage III CKD in diabetic patients of longitudinal study in Turkey [21].

A cohort study in China proposes that direct bilirubin has anti-complement effects and protects tissues from inflammatory damage in animal models [22]. However, this study did not show the association between serum bilirubin and eGFR values in CKD patients. Another prospective cohort study in Korea showed that moderately elevated serum bilirubin was associated with better kidney progression and had beneficial effects on renal fibrosis [23]. Similarly, a finding from the Republic of Korea indicated that patients with low serum bilirubin had a greater risk of transplant rejection and a lower glomerular filtration rate than patients with high serum bilirubin [24].

A study from Australia indicates that elevated plasma bilirubin protects against systemic oxidative stress in the vascular component of CKD patients [25]. Multiple studies have demonstrated that glomerular filtration rate (GFR) has been used for early screening, diagnosis and monitoring of kidney function [26]. However, eGFR is measured by clearance techniques that use substances such as creatinine as markers of filtration [27]. Serum creatinine used for eGFR determination is itself influenced by various factors including muscle mass, demographic factors, and dietary intake [43]. These factors are responsible for the variability and decrease in the sensitivity of eGFR to detect disease progression in CKD patients [28].

Despite evidence showing that a lower level of serum bilirubin is an independent risk factor for renal disease, whether serum bilirubin is simply a biomarker of disease progression or have a true pathogenic role in kidney function among chronic kidney disease patients remains inconclusive. Moreover, to the best of our knowledge, this study is the first study in Ethiopia to assess serum bilirubin and its correlation with the estimated glomerular filtration rate in the progression of chronic kidney disease among CKD patients. Consequently, searching for parameters that correlate with eGFR contribute is an additional option for early screening and monitoring of the disease progression that results in reducing hospitalization, complication, early death from the disease, and minimize economic burdens required in the treatment of renal failure in CKD patients. Therefore, a recent study aimed to evaluate serum bilirubin and its association with eGFR in chronic kidney disease patients during follow-up in kidney clinics (JUMC, 2021).

2. Methods and Materials

2.1. Study Setting and Design

This is an institution-based cross-sectional study design conducted at Jimma University Medical Center from November 5, 2021, to January 13, 2022. The hospital is located in the town of Jimma in southwestern Ethiopia, 354 kilometers away from Addis Ababa, the capital of Ethiopia. The Jimma University Medical Center has a 660-bed capacity and serves a school district population of approximately 20 million. According to the health management information system and the hospital chronic follow-up registration data, about 350 CKD patients were followed up in 3 outpatient chronic follow-up wards.

2.2. Study Participants

The source population was patients with chronic kidney disease who had hospital records of diagnosis of CKD with follow-up at the JUMC. Inclusion criteria were all CKD patients who had visited JUMC during the study and were willing to participate in the study. CKD patients with hemolytic anemia, malaria, acute and chronic liver disease, malignant disease, patients with musculoskeletal deformities, and critically ill patients who unable to cooperate were excluded.

2.3. Sample Size Determination and Sampling Techniques

The sample size was determined by a single population proportion formula, prevalence of hypo bilirubinemia in patients with renal disease (p=15.2), 95% CI, 5% precision, considering a 10% non-response rate. 140 CKD participants

were recruited using consecutive sampling techniques.

2.4. Data Collections and Measurement Procedure

Data were collected using questionnaires, anthropometric measurements, record reviews, physical examinations, and blood samples. The accuracy of the questionnaire was tested in 5% of the total sample in the follow-up of diabetic patients. Interviewer-administered structured questionnaires were used to collect sociodemographic profiles, behavior-related information, and medical histories of eligible participants. A physical examination was also performed, including measurements of height, weight, and blood pressure. Body mass index (BMI) was calculated using weight and height computed as weight in kilograms divided for height in meter. BMI is classified as follows: BMI ≤ 18.5 Kg/m^2 underweight, BMI = 18.5-24.9 Kg/m^2 normal weight, BMI = 25-29.9 Kg/m^2 overweight and BMI ≥ 30 Kg/m^2 obese [30].

Blood pressure was measured in a standardized fashion three times using the Omron digital BP measuring device (HEM907, Kyoto, Japan) on the right upper arm after participants had been seated and resting quietly for at least five minutes with feet on the ground and back supported. The average of three measurements was used to determine blood pressure values. Consider analyzing the mean of systolic and diastolic blood pressure, as recommended by the World Health Organization. Therefore, if systolic blood pressure ≥140mmHg and diastolic blood pressure ≥90mmHg are considered hypertension, respectively [31].

2.5. Laboratory Measurements

Venous blood (5 mL) was drawn from each patient to determine serum creatinine and bilirubin (total and direct bilirubin) levels. The sample was measured in a single laboratory using an automated clinical chemistry analyzer (Coobas400; Horiba France, Longjumeau Cedex, France). Internal quality was ensured by running control test every day before analyzing patients' sera. GFR was estimated using the CKD-EPI formula using serum creatinine values, age, gender, and race. Estimated GFR was calculated by the 2009 CKD-EPI equation [32]. For females with, SCr≤ 0.7 mg/dl: GFR = 166 x $(SCr/0.7)^{-0.329}$ $(0.993)^{age}$ and females with, SCr> 0.7 mg/dl: GFR = 166 × $(SCr /0.7)^{-1.209}$ x $(0.993)^{age.}$ For males with, SCr≤ 0.9 mg/dl: GFR = 163 x $(SCr / 0.9)^{-0.411x}$ $(0.993)^{age}$ and males with, SCr> 0.9 mg/dl: GFR = 163 × $(SCr / 0.9)^{-1.209}$ x $(0.993)^{age.}$

The stages of eGFR are classified according to a classification system established by the National Kidney Foundation's Classification of the Kidney Disease Outcomes Quality Initiative (KDOQI). Stage-I=eGFR of ≥90 mL/min/1.73m^2, Stage-II=eGFR of 60-89 mL/min/1.73m^2, Stage-IIIA=eGFR of 45-59mL/min/1.73m^2, Stage-IIIB=eGFR of 30–44.9 mL/min/1.73 m^2, Stage-IV=eGFR of 15-29 mL/min/1.73 m^2, and Stage-V≤15 eGFR of mL/min/1.73 m^2.

2.6. Statistical Analysis

After the data collection was completed, the Epi data version 3.1 software was for data entry, and then exported to SPSS version 25 software for analysis. The normality of the data was tested by Kolmogorov-Shapiro Willi's test. All continuous and normally distributed data are expressed as mean ± standard deviation, while continuous and non-normal data are expressed as interquartile range or median. Categorical data are expressed as proportions or percentages. Pearson and Spearman's correlation was calculated to see the correlation between serum bilirubin (total and direct) with various factors. Univariate and multivariate linear regression models were performed to test the significance of the association. Variables associated at p-value<0.05 were considered as statistically significant.

3. Result

3.1. Sociodemographic Characteristics and Health-Related Behavior of Participants

A total of 140 study participants were recruited for this study. The subjects included (54.3% [n=76]) men and (45.7% [n=64]) women, respectively. The mean (SD) age of CKD patients was 51.04 ± 9.02 years, with a minimum and maximum age of 30 and 70 years, respectively. The majority of study participants were between the ages of 30-59 (81.43% [n=114]) and 18.57% [n=26]) were 60 and older. Most of the study participants resided in rural (55.7% [n=78]) whereas the rest resided in urban (44.3% [n=62]). Most of the study participants resided in rural (55.7% [n=78]) whereas the rest resided in urban (44.3% [n=62]). Majority of the study subjects were never smoker (89.3% [n=125]) whereas (10.7% [n=15]) were smokers (Table 1).

Table 1. *Sociodemographic and health-related behavior of study participants (N=140).*

Variables Categories		Frequency (N=140)	(%)
Sex:	Male	76	54.30
	Female	64	45.70
Age category	30-59 age group	114	81.43
	≥60 age group	26	18.57
Marital status:	Single	5	3.60
	Married	120	85.70
	Divorced	15	10.70
Educational status:	Illiterate	81	57.90
	Primary school	27	19.30
	Secondary school	23	16.40
	College/Unv	4	2.90
	Graduate	5	3.60
Residence:	Urban	62	44.30
	Rural	78	55.70
Occupation:	Farmer	93	66.40
	Merchant	26	18.60
	Gov'temployed	12	8.60
	Daily Labor	7	5.00
	Other	2	1.40
Smoking Status	Never smoke	125	89.30
	Former smoker	14	10.0
	Recent smoker	1	0.70
Alcohol Consumption	Yes	9	6.40
	No	131	93.60

3.2. Classification of Study Participants by Stages CKD

In this study, CKD patients were divided into five [5] stages calculated according to the CKD-EPI equation. A substantial number of CKD patients were identified in stage IV (29.3% [n=41]) succeeded by stage-II CKD, which included (25.7% [n=36]) participants (Figure 1).

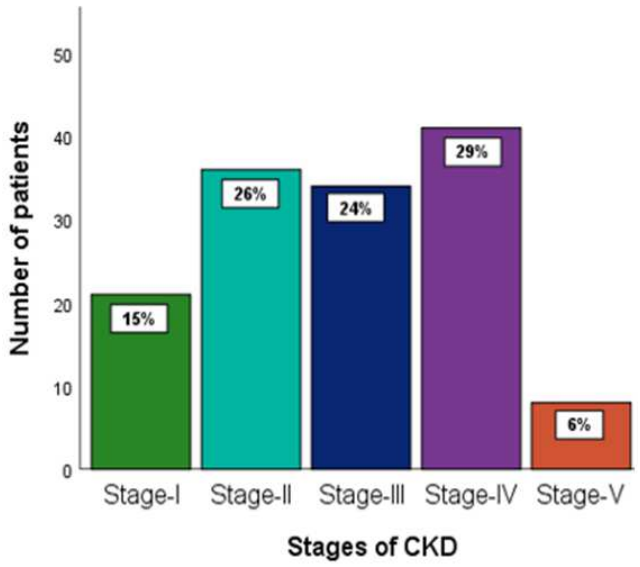

Figure 1. *The percentage of CKD stages among study patients.*

3.3. Biochemical Measurements Among Chronic Kidney Disease Patients

The mean value of serum total bilirubin was 0.7±0.14 mg/dl whereas the average value of direct bilirubin was 0.1 ± 0.06 mg/dl. The mean estimated glomerular filtration rate (eGFR) was 52.11±30.12 mL/min/1.73m^2, with a minimum value of 9.6mL/min/1.73m^2 and a maximum value of 108mL/min/1.73m^2. Furthermore, the mean values of serum creatinine and blood urea nitrogen among participants in this study were 2.1±1.21 and 65.8±25.8 mg/dL, respectively (Table 2).

Table 2. *The mean value of different biochemical parameters in CKD patients (N=140).*

Variables	Mean ±SD
Serum creatinine (mg/dl)	2.1±1.21
Blood urea nitrogen (mg/dl)	65.8±25.8
Estimated glomerular filtration rate (eGFR) (mL/min/1.73m^2)	52.1±30.12
Body mass index (kg/m^2)	22.7±1.57
Systolic blood pressure (mmHg)	124.4±10.11
Diastolic blood pressure (mmHg)	89.2±7.32
Direct bilirubin (mg/dl)	0.1±0.06
Total bilirubin (mg/dl)	0.7±0.14

Data are presented as mean ±Standard deviation

3.4. Clinical Data and Biochemical Parameters Across CKD Stages

Among all study participants, (47.9% [n=105]) had pre-existing hypertension and (25% [n=35]) had known diabetes mellitus (DM). In the study, only 6.4% had a family history of kidney disease. A large number of CKD patients with pre-existing hypertension were identified in stage IV (23.6% [n=33]), followed by stage III CKD (12.9% [n=18]) individuals with known hypertension individuals. Similarly, participants with pre-existing diabetes mellitus with (10.7% [n=15]) were found in stage-IV CKD followed by stage III with (5.7% [n=8]) known diabetic patients. In addition, values for systolic blood pressure, diastolic blood pressure, body mass index, estimated glomerular filtration rate, blood urea nitrogen, and serum creatinine increased with increasing chronic kidney disease stage (Table 3).

Table 3. *Distribution of various factors across CKD stages among study participants (N=140).*

Variables	Grouping of participants by CKD stage					
	Categories	Stage-I	Stage-II	Stage-III	Stag- IV	Stag- V
History of DM	Yes (N=35)	5 (3.6%)	3 (2.1%)	8 (5.7%)	15 (10.7%)	4 (2.9%)
	No (N=105)	16 (11.4%)	33 (23.6%)	26 (18.6%)	26 (18.6%)	4 (2.9%)
History of Hypertension	Yes (N=67)	4 (2.9%)	5 (3.6%)	18 (12.9%)	33 (23.6%)	7 (5.0%)
	No (N=73)	17 (12.1%)	31 (22.1%)	16 (11.4%)	8 (5.7%)	1 (0.7%)
Family History of Kidney diseases:	Yes (N=9)	1 (0.7%)	2 (1.4%)	0 (0%)	6 (4.3%)	0 (0%)
	No (N=131)	20 (14.3%)	34 (24.3%)	34 (24.3%)	35 (25%)	8 (5.8%)
Body Mass Index (kg/m^2)		22.16±1.7	22.69±1.38	22.82±1.71	22.65±1.57	23.91±0.9
Systolic Blood Pressure (mmHg)		120	119	128	130	135
Diastolic Blood Pressure (mmHg)		80	85.5	90.5	96	97
Serum Total Bilirubin (mg/dl)		.85±.07	.76±.071	.65±.068	.53±.054	.46±.04
Serum Creatinine (mg/dl)		0.97	1.17	1.87	3.2	4.57
Blood Urea Nitrogen (mg/dl)		42.3±12.6	49.3±16.2	61.3±14.6	86.8±17.6	113.3±18
eGFR (mL/min/1.73m^2)		100±5.3	75±9.63	43.5±9.6	22.4±3.94	12.5±1.87

DM=Diabetes Mellitus, eGFR=estimated glomerular filtration rate. Values are expressed as the mean (SD) for normally distributed and continuous variables, and as the median for non-normal and continuous variables. Categorical data was presented as proportion or percentage

3.5. Correlation Between Serum Bilirubin (TB&DB) and Explanatory Variables

Based on Pearson's correlation analysis, there was a significant positive correlation (r=0.868, P<0.001) between serum total bilirubin and eGFR value among CKD patients. Spearman's correlation also showed a significant positive correlation (r=0.641, P<0.001) between direct bilirubin and eGFR value of the study subjects. However, systolic blood pressure, diastolic blood pressure, BMI, and age were negatively correlated with serum bilirubin (TB&DB) in patients with CKD (Table 4).

Table 4. *The correlation analysis between serum bilirubin (TB&DB) and different factors among CKD patients (N=140).*

Variables	Serum total bilirubin		Serum direct bilirubin	
	Pearson correlation (r)	P-value	Spearman's correlation (r)	P-value
eGFR	0.868	<0.001*	0.641	<0.001*
BMI	-0.221	0.009*	-0.233	0.006*
SBP	-0.561	<0.001*	-0.449	<0.001*
DBP	-0.459	<0.001*	-0.396	<0.001*
Age	-0.450	<0.001*	0.438	<0.001*

*Correlation is significant at p-value<0.05 (two-tailed). BMI=Body mass index
eGFR=estimated glomerular filtration rate, SBP=Systolic blood pressure, DBP=Diastolic blood pressure.

Scatter plot also showed the correlation between eGFR value and serum total bilirubin (Figure 2).

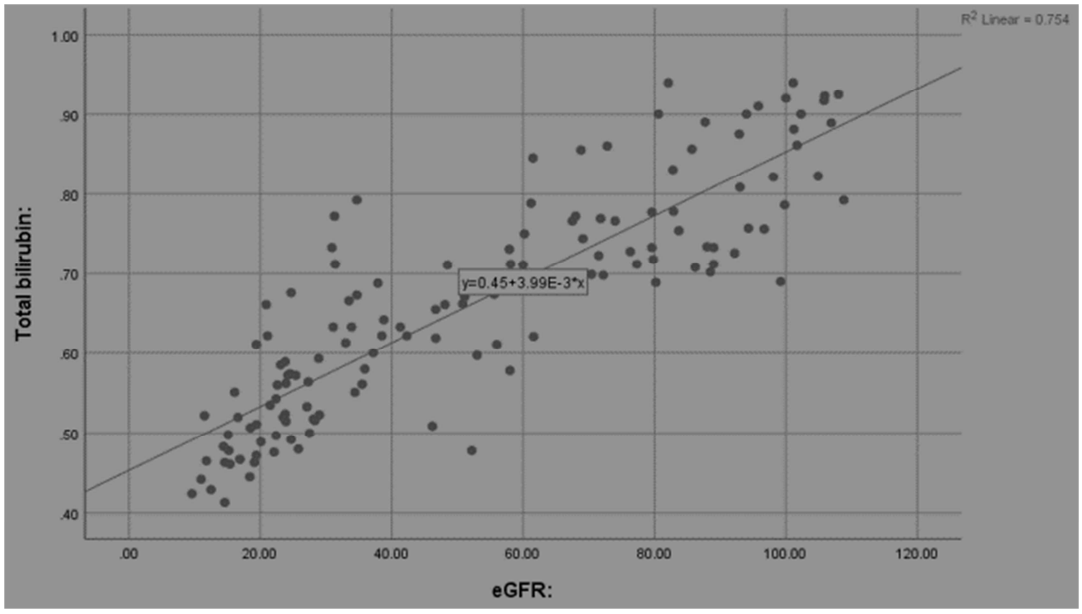

Figure 2. *Scatter plot shows the linear positive correlation between serum total bilirubin and eGFR value.*

3.6. Association of Explanatory Variables with Dependent Variables

Univariable linear regression analyses were done to test the association between a single explanatory variable and each outcome variable (Serum total bilirubin). In univariable linear regression analysis, factors including age (β = -0.007, p>0.001), history of hypertension (β = -0.138, p=0.01), diabetes mellitus (β = -0.08, p=0.03), systolic blood pressure (β = -0.08, p<0.001), and diastolic blood pressure (β = -0.009, p<0.001), were negatively associated with serum total bilirubin. Moreover, eGFR has statistically positive association (β=0.04, p=0.0023) with serum total bilirubin.

Table 5. *Factors associated with serum total bilirubin in CKD study participants (N=140).*

Lists of explanatory variables	Outcome variable (STB) β (95%CI)	P-value
Age (year)	-0.001	0.422
History of HTN	-0.003	0.889
History of DM	-0.018	0.148
Body Mass Index (kg/m^2)	-0.007	0.023*
SBP (mmHg)	-0.002	0.746
DBP (mmHg)	-0.002	0.606
eGFR (min/mL/1.73m^2)	0.04	<0.001*

*Significant association at p-value <0.005
DM= Diabetes mellitus, HTN= Hypertension

Then, candidate variables were taken to stepwise multiple linear regression. In multivariable linear regression, eGFR

has a statistically positive association (β=0.04, P=<0.00) with serum total bilirubin. But body mass index has a negative association (β = -0.007, p=0.023) with serum total bilirubin after being adjusted for another confounder (Table 5).

4. Discussion

To the best of our knowledge, this study is the first study in Ethiopia to assess serum bilirubin and its correlation with estimated glomerular filtration rate in the progression of chronic kidney disease among CKD patients on follow-up. Overall, 140 study participants were involved in the current study. This study showed that serum total bilirubin was significantly positively correlated with eGFR (r=0.868, P<0.001) amongst CKD patients. In this subject, direct bilirubin was also positively correlated with eGFR (r=0.641, P<0.001).

Consistent with the present study, a finding from the United Kingdom showed a strong positive correlation between serum total bilirubin and eGFR values in CKD patients (r=0.92, P<0.0001). Additionally, their study also found a statistically significant positive correlation (r=0.76, P<0.0001) between direct bilirubin and eGFR [19].

A study in Tokyo, Japan is also consistent with recent findings, showing that serum total bilirubin and indirect bilirubin, respectively, were positively correlated with eGFR values (r=0.223, P=0.013; r=0.244, P=0.007) [18].

Another supporting finding from Korea also showed a positive correlation between serum total bilirubin concentration and eGFR in all subjects (r=0.128, P=0.001) [20]. Likewise, studies conducted in Japan agree with this finding and show a weak positive correlation between direct serum bilirubin and eGFR (r=0.181, P<0.001) amongst the study participants [32].

In our study the value of eGFR was positively associated (β=0.04, P=<0.001) with serum total bilirubin. Statistically, this can be explained as a one-unit increase in eGFR results in approximately a 0.04 increase in serum total bilirubin in CKD patients. When the stage of CKD is increasing, the value of serum bilirubin (both TB&DB) is decreasing. Therefore, patients with lower eGFR or advanced CKD had lower mean serum bilirubin. Therefore, patients with lower eGFR or advanced CKD had lower mean serum bilirubin.

Consistent with this finding, a study from China found that serum bilirubin was significantly and independently associated with eGFR values (β=0.011, P=0.001) [32]. This fact shows that CKD patients with low eGFR value or advanced stage of CKD have lower serum bilirubin than near normal eGFR value. The proposed mechanism is that serum bilirubin inhibits the upregulation of endothelial adhesion molecules and also has anti-complement properties that prevent inflammation, the development of atherosclerosis, and the onset/progression of CKD [33].

Similarly, study from the British Journal of Biomedical Sciences also support this finding. According to this result, serum total bilirubin levels showed significant positive association (R^2=0.90, P<0.05) with eGFR value. This can be explained as, holding other explanatory variables constant, the 90% variability in eGFR is determined by serum total bilirubin levels and thus serum level of total bilirubin is an independent predictor of eGFR values in renal diseases [19].

Another study in Tokyo is consistent with the current findings. According to their study, patients with CKD stage-V had significantly lower median serum bilirubin values (0.3mg/dL, P<0.01) than in those with CKD stage III-IV (0.4 mg/dL, P < 0.01) among the study population [34].

In this study, body mass index was significantly negatively correlated with serum total bilirubin (r = -0.221, P=0.09). BMI was also negatively correlated with direct bilirubin (r = -0.233, P=0.006) amongst the study participants. In addition, this study showed that BMI was significantly negatively correlated with total serum bilirubin in CKD subjects (β-0.007, P=0.023).

Consistent with the current findings, the Slovenian study reported a significant negative correlation between body mass index and total serum bilirubin (r=–0.287, P=0.013) (36). Similarly, another study from Slovenia agreed with this finding and showed that BMI was significantly associated with (β = -0.436, P<0.05) and serum total bilirubin [36].

A study in Italy was also consistent with the current findings and suggested that BMI was inversely correlated with total serum bilirubin (β = -0.08, P=0.001) [37]. The proposed mechanism is that overexpression of heme oxygenase 1 (HO 1) leads to a marked increase in adiponectin, an anti-inflammatory adipokine. Overexpressed HO-1 also inhibits adipocyte expansion and levels of inflammatory cytokines TNF-α, IL-1β, and IL-6 in obese individuals [38].

Contrary to recent findings, the Japanese Medical School study found a negative correlation between serum total bilirubin concentration and eGFR value (β-0.186, P=0.038). According to their findings, indirect bilirubin was also negatively correlated with eGFR values in CKD patients (β-0.196, P=0.027) [18]. This discrepancy in findings may be due to differences in the study population, as the study population at the Japanese medical school was only for type 1 diabetes.

Another conflicting finding was reported in Korea, showing that serum bilirubin was inversely correlated with eGFR values in both diabetic and non-diabetic CKD patients (β = -0.14, P<0.001) [39]. This difference may be due to differences in study design and study population. South Korea's study design was a prospective observational study design with only stage-III and stage-IVCKD study population.

5. Conclusion

According to the current findings, serum total and direct bilirubin levels in patients with chronic kidney disease decreased with increasing CKD stage. Serum total bilirubin and direct bilirubin values were positively correlated with eGFR values. Furthermore, eGFR was significantly

positively correlated with serum total and direct bilirubin in CKD patients, whereas BMI was significantly negatively associated with serum bilirubin in CKD patients. Therefore, low serum bilirubin (total and direct bilirubin) and increased body mass index are independent risk factors for disease progression in patients with CKD.

6. Limitation of This Study

A single measurement of serum creatinine and serum bilirubin might not be sufficiently accurate for confirming the correlation and association between serum bilirubin and explanatory variables. Furthermore, the study subjects were recruited at a single hospital; therefore, the patient selection was limited, and the sample size was relatively small and not representative of the national target population.

7. Recommendations

Based on our findings, it is suggested to incorporate serum bilirubin parameters as one of the routine laboratory tests to predict the progression of CKD disease. Further multicenter studies with large sample sizes are needed to definitively examine the relationship between serum bilirubin and eGFR and other variables.

List of Abbreviations

BMI: Body mass index
CKD: Chronic kidney disease
DM: Diabetes mellitus
eGFR: Estimated glomerular filtration rate
HO: Heme oxygenase
HTN: Hypertension
IL-1β: Interleukin one beta
IL-6: Interleukin six
JUMC: Jimma University Medical Center
TNF-α: Tomer necrosis factor alpha

Declarations

Authors' Contributions

Fikadu Seyoum: is a Principal investigator of the research made substantial contribution to the design of the work, data entry, analysis, interpretation, result writing, and manuscript preparation.

Belay Zewdie: Act as advisor in guiding, commenting research paper and also, he contributed to manuscript editing and revising activities.

Availability of Data and Materials

The dataset generated during/or analyzed during the current study are not publicly available due to the papers written using this dataset have not been published but are available from corresponding authors on reasonable request.

Computing Interest

All the authors do not have any possible conflicts of interest.

Ethical Approval and Consent for Participation

Before participating in the study, all subjects signed informed consent. The study was approved by Institutional Ethics review board (IERB) of the first affiliated Jimma University with IERB No. IHRPG1/6/2022. The study was conducted in accordance with the Helsinki declaration.

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