ORIGINAL RESEARCH

Total Bilirubin in Prognosis for Mortality in End-Stage Renal Disease Patients on Peritoneal Dialysis Therapy

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***Background*—**Evidence regarding bilirubin's antioxidant properties and predictive roles is growing. However, it is unclear whether serum bilirubin would have a prognostic impact on survival of patients with regular peritoneal dialysis.

***Methods and Results*—**We used the Taiwan Renal Registry Data System utilizing its 2005-2012 data set. Data from patients on regular peritoneal dialysis were retrieved. The primary end point of observation was 3-year mortality. A total of 3704 patients (mean age 53.5 years, 44% male) were enrolled, and these patients were divided according to baseline serum total bilirubin levels (<0.3, 0.3-0.4, 0.4-0.5, 0.5-0.6, >0.6 mg/dL). Serum total bilirubin level was linearly related to age, incidence of hypertension, and type 2 diabetes mellitus. At the end of the observation period with a mean follow-up of 2.12±1.07 years, 1095 (30.6%) deaths were detected. Serum total bilirubin level and 3-year mortality rate presented a U-shaped relationship. Those with serum total bilirubin 0.5 to 0.6 mg/dL had the lowest 3-year mortality rate (24%). After adjustment for age, sex, underlying systemic disorders, medications, and laboratory discrepancies, serum total bilirubin still played an independent role for predicting 3-year mortality.

***Conclusions*—**Baseline serum total bilirubin level is significantly associated with 3-year mortality among patients receiving regular peritoneal dialysis. **(*J Am Heart Assoc*. 2017;6:e007507. DOI: 10.1161/JAHA.117.007507.)**

Key Words: bilirubin • dialysis • prognosis

Patients with end-stage renal disease are at higher risk for overall mortality regardless of the renal replacement therapy modality chosen, including hemodialysis (HD) and peritoneal dialysis (PD). According to the nationwide survey for renal disease in Taiwan, the 10-year survival rate of both HD and PD patients is ≈30%. Cardiovascular and infectious diseases account for the major causes of death among patients requiring dialysis. Despite advances in treatment technology, the survival of HD and PD patients with different patient demographic characteristics has declined in recent decades.[1] The risk factors for mortality among dialysis patients, including age, low serum albumin, dose of dialysis (Kt/V), and creatinine clearance rate per week have long been recognized.[2] Moreover, hyponatremia, hypomagnesemia, and overhydration have been associated with increased mortality among PD patients.[3-5] There is a need to optimize the prediction of the clinical trajectory of these patients, and a search for other biomarkers that could delineate the clinical outcomes of PD patients is ongoing. Numerous novel biomarkers have been advocated for this purpose, such as alkaline phosphatase.[6] Nevertheless, several unexplored biomarkers exist.

Serum bilirubin is derived from biliverdin via biliverdin reductase, which is found in all tissues, especially in the macrophages of the liver and spleen. Bilirubin is a normal end product of the heme metabolism pathway. It plays an important role in detecting jaundice. Although a high serum level is associated with a high mortality rate among jaundice patients, bilirubin has been discovered to have antioxidant properties, whether conjugated or unconjugated,[7] free or protein bound.[8] Bilirubin exerts its beneficial effect by cellular protection via the biliverdin reductase antioxidant cycle.[9] Heme oxygenase-1-induced bilirubin was recently found to protect endothelial cells against high glucose–induced damage.[10] Based on this favorable characteristic, it was postulated that a high total bilirubin level

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Clinical Perspective

What Is New?

- The nationwide Taiwan Renal Registry Data System demonstrated the relationship between serum total bilirubin level and all-cause mortality among patients with end-stage renal disease undergoing chronic peritoneal dialysis.
- Although the relationship was not a perfect linear pattern, we found a specific range of level of serum total bilirubin that was associated with the lowest mortality rate.

What Are the Clinical Implications?

- Serum total bilirubin level could be a novel biomarker for predicting survival among peritoneal dialysis patients.
- Deviation of serum total bilirubin level deserves further investigation for underlying etiology and pathology, with the goal toward improving the survival rate of such a group of patients.

within physiological range could have a beneficial effect on patient health. Previous studies observed that the serum total bilirubin level predicted the progression of chronic kidney disease, showing better renal outcomes among groups with higher serum total bilirubin.[11,12] A negative correlation with daily amount of urine protein was also identified.[13] The incidence of end-stage renal disease among patients with IgA nephropathy was inversely correlated with the serum bilirubin level.[14] A similar conclusion was also reached regarding cardiac outcomes, where a higher level of total bilirubin was associated with fewer major adverse cardiovascular events among patients with cardiac syndrome X.[15] A higher level of serum bilirubin was also found to be associated with higher functional independence in the elderly population.[16] As a result, serum bilirubin level might be another novel biomarker for predicting the clinical outcomes of patients with end-stage renal disease who undergo PD. Recently, our research team found that total bilirubin level was associated with mortality among patients undergoing long-term hemodialysis.[17] The relationship between serum bilirubin level and survival in PD patients remains unclear. This study aimed to investigate the predictive ability of serum total bilirubin level in patients requiring PD.

Methods

Due to the policy of Taiwan Society of Nephrology for confidentiality of each individual patient, the data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

This study was approved by the ethics committee of the Taipei Medical University Institutional Review Board (No. N201610006). The requirement that subjects give informed consent was waived. The National Health Insurance of Taiwan covers more than 99% of the Taiwanese people and facilitates the promotion of health and disease control among residents of Taiwan. This observational study was conducted using the Taiwan Renal Registry Data System, which comprises a nationwide cohort of patients with renal diseases. Information regarding patients was retrieved from medical centers or individual dialysis clinics. We used the 2005-2012 data set. Patients with end-stage renal disease who underwent PD were included in our study.

Clinical Data Collection

Clinical information was collected, including age, sex, comorbidities, medications, dialysis duration, and baseline laboratory investigations before starting dialysis. Serum laboratory tests were performed under fasting status. Persons with a history of malignancy, a history of a transient shift to HD, of ages <20 or >90 years, with total bilirubin levels <0.1 or >1.2 mg/dL, who were serum positive for hepatitis B virus or hepatitis C virus, or who showed abnormal liver enzyme tests (alanine aminotransferase >40 IU/L or aspartate aminotransferase >40 IU/L) were excluded from analysis (Figure 1).

Group Stratification

Patients were divided into 5 groups: ≤0.3, 0.3-0.4, 0.4-0.5, 0.5-0.6, and >0.6 mg/dL according to the baseline serum total bilirubin level.

Observation End Point

The primary end point of this study was 3-year all-cause mortality. All patients were followed up until death or December 31, 2012. Patient mortality was reported by each medical center or PD clinic and confirmed by the mortality record of the National Health Insurance.

Statistical Analysis

Numeric parameters are presented as mean±standard deviation, and categorical variables are expressed as percentages. Comparison of numeric parameters between groups was performed using Student t test, and categorical variables were compared with the chi-squared or Fisher exact test. Survival analysis between groups was performed using the Kaplan-Meier method with the log-rank test. The mortality hazard ratio was evaluated using Cox regression models with

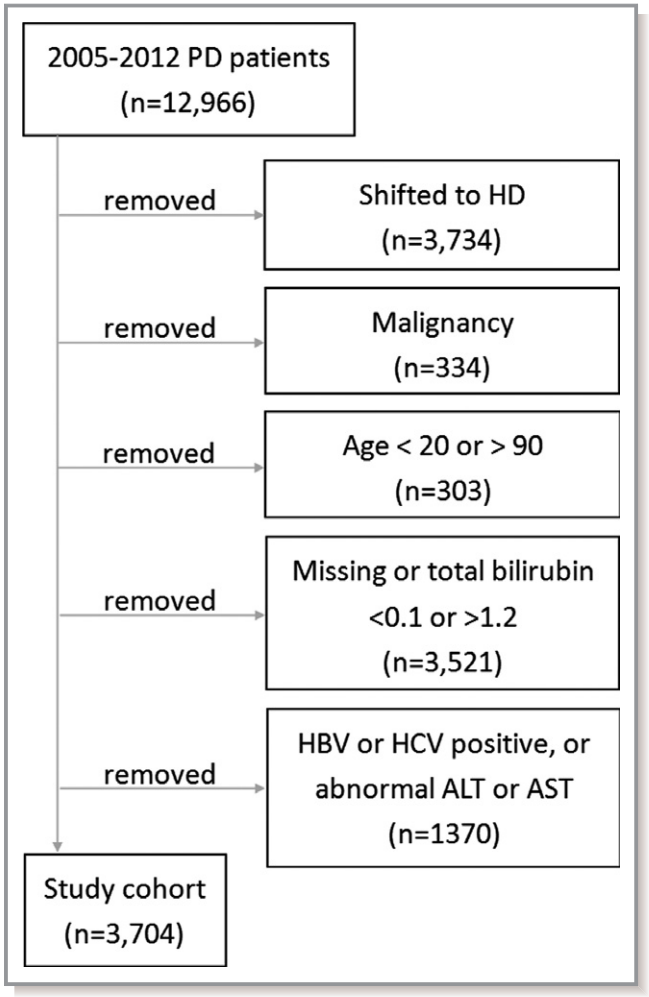

Figure 1. Study flow chart. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; HD, hemodialysis; PD, peritoneal dialysis.

adjustments for age, sex, underlying diseases (including hypertension, type 2 diabetes mellitus, congestive heart failure, left ventricular hypertrophy, history of stroke, coronary artery disease, and history of acute myocardial infarction), and laboratory discrepancies, which refer to parameters that had statistically significant differences between groups by analysis of variance for continuous variables, ie, *P* for trend <0.05. The hazard ratio and 95% confidence interval were calculated. Statistical analyses were performed with JMP10 statistics software (SAS Institute, Cary, NC). A $P<0.05$ was considered statistically significant.

Results

Patient Demographics

A total of 3704 PD patients were enrolled in the study (mean age 53.5±15.0 years; mean PD duration 2.12±1.07 years). Patient distribution into different groups was as follows: 916 (24%) total bilirubin <0.3 mg/dL; 1179 (31%) 0.3-0.4 mg/dL; 691 (19%) 0.4-0.5 mg/dL; 437 (12%) 0.5-0.6 mg/dL; 481 (14%) total bilirubin >0.6 mg/dL. The baseline characteristics are shown in Table 1. Briefly, higher total bilirubin levels were associated with advanced age, male sex, and a lower prevalence of type 2 diabetes mellitus and hypertension. Moreover, higher total bilirubin levels were statistically, but may not be clinically, significantly related to higher serum liver enzymes and iron parameters. Nevertheless, increased total bilirubin was associated with lower levels of uric acid and lipid profiles. All patients met the recommended dialysis dose (weekly dialysis dose (Kt/V)>1.7).

Clinical Outcomes

The mean follow-up period was 2.12±1.07 years. At the end of the observation period, 1095 (29.6%) mortalities were noted, which represented the mean mortality of the whole study group. As shown in Figure 2, the lowest mortality rate was noted in the 0.5 to 0.6 mg/dL total bilirubin group, which demonstrated a 24% mortality during the observation period. The relationship between serum total bilirubin level and 3-year mortality among PD patients depicted a “U-shaped” curve with a nadir range at 0.5 to 0.6 mg/dL.

Serum total bilirubin level was associated with overall mortality. As shown in Figure 3, the survival analysis using the Kaplan-Meier model showed a significant difference between the groups (log rank $P=0.0069$). After adjustment for age, sex, underlying systemic diseases, laboratory investigations, and dialysis dose, multivariate analysis using the Cox regression model demonstrated total bilirubin level to be an independent predictor of all-cause mortality among patients undergoing PD (Table 2). In addition to serum total bilirubin level, Cox regression analysis demonstrated that age, diabetes mellitus status, serum albumin level, white blood cell count, hemoglobin, and cholesterol level were statistically associated with survival (Table 3).

To evaluate the accuracy of predicting 3-year mortality from serum total bilirubin, receiver operator characteristic analysis was performed, which revealed the best cutoff point for serum total bilirubin level to be 0.371 mg/dL. The area under curve from this cutoff point analysis was 0.5346, as shown in Figure 4.

Discussion

To the best of our knowledge, our study is the first article that presents the relationship between serum total bilirubin level and mortality among PD patients. In this retrospective study, serum total bilirubin level was identified as another useful biomarker for predicting the clinical course of PD patients. Unsurprisingly, our cohort data showed that PD patients

Table 1. Baseline Characteristics of All PD Patients

Variable	Whole Group	Total Bilirubin, mg/dL					*P* for Trend
		<0.3	0.3 to 0.4	0.4 to 0.5	0.5 to 0.6	>0.6	
Number	3704	916	1179	691	437	481	
Age, y	53.5±15.0	52.8±15.6	52.9±14.7	53.6±14.7	55.0±14.3	54.7±15.3	0.0146
Male, n (%)	1630 (44)	350 (38)	497 (42)	300 (43)	231 (53)	252 (52)	<0.0001
DM, n (%)	1342 (36)	370 (40)	412 (35)	240 (35)	154 (35)	166 (35)	0.0166
HTN, n (%)	1717 (46)	422 (46)	612 (52)	304 (44)	192 (44)	187 (39)	<0.0001
CHF, n (%)	294 (8)	87 (9)	88 (7)	53 (8)	33 (8)	33 (7)	0.3024
LVH, n (%)	228 (6)	70 (8)	79 (7)	42 (6)	17 (4)	20 (4)	0.3148
CVA, n (%)	127 (3)	28 (3)	42 (4)	20 (3)	20 (5)	17 (4)	0.7287
CAD, n (%)	183 (5)	45 (5)	64 (5)	34 (5)	18 (4)	22 (5)	0.5722
MI, n (%)	89 (2)	16 (2)	35 (3)	20 (3)	9 (2)	9 (2)	0.5623
HTN drugs, n (%)	3113 (83)	765 (84)	1005 (85)	586 (85)	368 (84)	389 (81)	0.0023
PD duration, y	2.12±1.07	2.11±1.05	2.18±1.07	2.08±1.08	2.13±1.06	2.06±1.08	0.0738
Laboratory data							
Total bilirubin, mg/dL	0.41±0.17	0.21±0.05	0.35±0.04	0.46±0.03	0.56±0.03	0.74±0.10	<0.0001
Ccr, mL/min	5.48±1.92	5.51±2.00	5.47±2.07	5.43±1.67	5.42±1.77	5.60±1.93	0.6531
Weekly Kt/V	2.12±0.37	2.10±0.37	2.13±0.36	2.16±0.36	2.11±0.36	2.09±0.39	0.0161
AST, IU/L	20.0±6.60	19.1±6.60	19.6±6.50	20.2±6.70	21.2±6.50	21.2±6.6	<0.0001
ALT, IU/L	19.0±6.70	18.5±6.50	18.8±6.70	19.3±6.80	19.6±7.10	19.4±6.6	0.0089
Uric acid, mg/dL	7.07±1.28	7.18±1.28	7.09±1.29	7.04±1.32	7.01±1.26	6.93±1.24	0.0003
Ferritin, ng/mL	316.8±221.9	325.2±229.7	314.2±219.4	318.8±224.8	319.6±213.5	301.8±216.2	0.6262
TIBC, μg/dL	256.8±46.3	248.2±47.3	253.7±43.2	258.1±43.9	264.7±47.0	271.9±49.6	<0.0001
Fe, μg/dL	74.3±26.7	69.4±25.3	74.8±25.2	77.6±26.3	76.0±30.1	75.8±28.9	<0.0001
Cholesterol, mg/dL	198.1±38.4	198.8±40.0	197.9±36.6	198.8±40.5	197.3±36.6	197.0±38.5	0.1387
Triglyceride, mg/dL	171.5±107.0	179.1±117.4	169.9±101.7	167.5±105.3	168.2±99.5	169.5±107.5	0.0031
Albumin, g/dL	3.70±0.43	3.67±0.45	3.73±0.42	3.71±0.43	3.71±0.42	3.68±0.45	0.004
Glucose, mg/dL	125.7±52.7	127.6±50.4	124.0±54.1	125.4±50.9	126.6±61.5	126.1±47.3	0.4194
Hematocrit, %	30.78±3.65	30.24±3.76	30.67±3.55	31.13±3.76	31.09±3.31	31.29±3.66	<0.0001
Ca, mg/dL	9.10±0.77	9.03±0.78	9.13±0.79	9.11±0.73	9.09±0.71	9.16±0.78	0.0321
P, mg/dL	5.07±1.13	5.13±1.20	5.05±1.09	4.99±1.07	5.07±1.07	5.09±1.20	0.0861
ALK-P, μ/L	108.5±88.0	117.8±95.8	107.7±83.3	109.6±88.1	103.8±98.9	95.4±69.0	0.0011
i-PTH, pg/mL	268.6±205.7	266.4±205.7	265.3±199.5	272.5±206.9	272.1±210.8	271.9±214.9	0.9287
Ca*P	45.9±11.0	45.8±11.4	45.8±10.8	45.4±10.5	46.1±10.5	46.8±12.2	0.3306

ALK-P indicates alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAD, coronary artery disease; Ccr, clearance rate of creatinine; CHF, congestive heart failure; CVA, cerebrovascular accident; DM, diabetes mellitus; HTN, hypertension; i-PTH, intact parathyroid hormone; Kt/V, dialysis adequacy; LVH, left ventricular hypertrophy; MI, myocardial infarction; PD, peritoneal dialysis; TIBC, total iron-binding capacity.

generally had poor chances of survival (mean 3-year survival ≈70%) and that serum total bilirubin level may act as an independent predictor of all-cause mortality in these patients. The relationship between serum total bilirubin level and mortality rate demonstrated a U-shaped tendency, with the lowest event rate among those with serum total bilirubin level between 0.5 and 0.6 mg/dL. To our knowledge this is the first report investigating the connection between serum total bilirubin level and survival rate among patients who undergo regular PD. Slightly elevated bilirubin level was found to be associated with lower incidence of cardiovascular disease and all-cause mortality in adults.[18] Nevertheless, extremely elevated bilirubin level represents a pathological process and translates to a higher mortality rate. Our study might

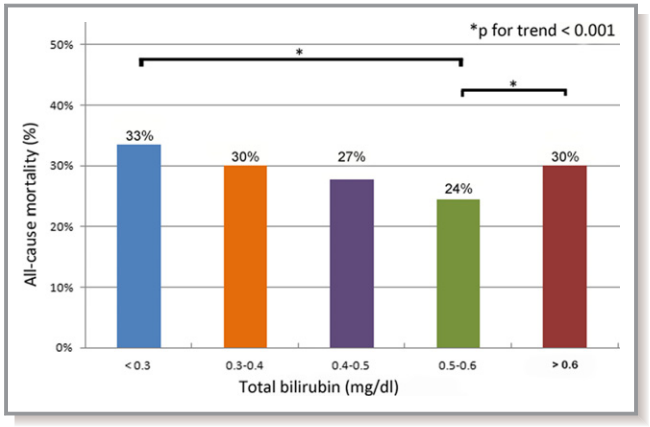

Figure 2. Mortality rates of peritoneal dialysis patients according to baseline serum total bilirubin levels.

provide a "sweet range" that indicates the level at which bilirubin could serve as a prognostic sign.

According to recent investigations by other researchers, the reported 3-year mortality rate of various different races is

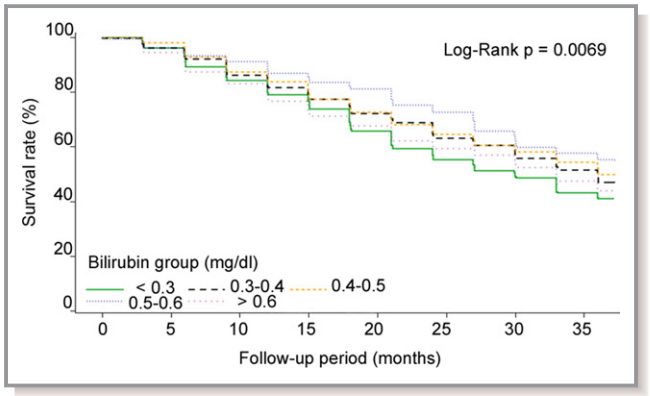

Figure 3. Kaplan-Meier analysis of each study group by baseline serum total bilirubin level.

≈30±5%.[4,6,19-21] The 3-year overall mortality rate of our whole PD cohort was similar to the cohorts in previous studies. Demographic and clinical characteristics were gathered. Based on these findings, serum total bilirubin can be predictive of PD patient mortality. Moreover, it is cost effective and easy to use.

In the late 1980s, bilirubin was found to have antioxidant and cytoprotective effects via the scavenging of peroxyl radicals generated through various biochemical reactions.[22] Each molecule of conjugated bilirubin could scavenge 1 molecule of hypochlorous acid,[7] a strong oxidant, in the environment. Consequently, subsequent investigators searched for evidence to support the notion that higher serum bilirubin levels can lead to favorable outcomes. A meta-analysis showed the inverse relationship between serum bilirubin and atherosclerosis in men.[23] Favorable outcomes were also observed in the cerebral and renal systems.[12,16] Our findings expanded the utility of bilirubin as a prognostic factor in a wider variety of diseases.

The behavior of bilirubin from a cellular point of view has been scrutinized in recent years. In an animal model bilirubin suppressed atherosclerotic plaque formation by disrupting endothelial vascular cell adhesion molecule-1 or intercellular adhesion molecule-1-mediated leukocyte migration and by scavenging reactive oxygen species, which offers potential cardioprotective effects and possibly survival advantage.[24] The anti-inflammatory property of bilirubin in our study can be partially observed from the negative linear relationship with uric acid, which was found to be associated with inflammatory biomarkers.[25] Another animal study demonstrated that bilirubin accelerated the degradation of macrophage surface ATP-binding cassette transporter A1, a transmembrane cholesterol transporter involved in apolipoprotein A1–mediated cholesterol efflux, resulting in favorable circumstances against atherosclerotic plaque formation.[26]

Table 2. Multivariable Adjustment for Survival Analysis of PD Patients

Total bilirubin, mg/dL	n (%)	Crude HR	*P* Value	Adjusted HR*	*P* Value	Adjusted HR†	*P* Value	Adjusted HR‡	*P* Value
<0.3	916 (24%)	1.49 (1.24-1.79)	<.0001	1.64 (1.36-1.97)	<.0001	1.61 (1.34-1.94)	<.0001	1.59 (1.27-1.99)	<.0001
0.3 to 0.4	1179 (31%)	1.18 (0.98-1.41)	0.0784	1.29 (1.07-1.54)	0.0073	1.33 (1.10-1.59)	0.0027	1.38 (1.11-1.72)	0.0044
0.4 to 0.5	691 (19%)	1.20 (0.99-1.47)	0.0699	1.26 (1.04-1.54)	0.021	1.28 (1.05-1.56)	0.0154	1.37 (1.08-1.74)	0.0087
0.5 to 0.6	437 (12%)	Ref		Ref		Ref		Ref	
>0.6	481 (14%)	1.36 (1.07-1.74)	0.0125	1.43 (1.12-1.82)	0.0040	1.39 (1.09-1.77)	0.0080	1.44 (1.08-1.92)	0.0132
All	3704 (100%)	0.97 (0.94-1.00)	0.0227	0.95 (0.93-0.98)	0.0015	0.95 (0.92-0.98)	0.0008	0.95 (0.92-0.98)	0.0043

HR indicates hazard ratio; PD, peritoneal dialysis; Ref, reference group.

*Adjusted with age, sex.

†Adjusted with age, sex, diabetes mellitus, hypertension, heart failure, left ventricular hypertrophy, cerebrovascular accident, coronary artery disease, history of myocardial infarction, and antihypertensive agents.

‡Adjusted with those named above plus aspartate aminotransferase, alanine aminotransferase, ferritin, iron, uric acid, total iron binding capacity, albumin, hemotocrit, calcium, phosphorus, intact-parathyroid hormone, alkaline phosphatase, Kt/V (a measure of dialysis adequacy).

Table 3. Cox Regression Analysis for Risk Factors of Death in PD Patients

	Crude HR	95% CI	*P* Value	Adjusted HR	95% CI	*P* Value
Age (increase per year of age)	1.037	1.033 to 1.041	<0.001	1.038	1.023 to 1.053	<.0001
Diabetes mellitus	1.771	1.601 to 1.958	<0.001	1.148	0.771 to 1.712	0.4981
Coronary artery disease	0.881	0.709 to 1.093	0.2474	1.148	0.509 to 2.589	0.74
Albumin (increase per 0.1 g/dL)	0.904	0.894 to 0.914	<0.001	0.945	0.904 to 0.987	0.0113
Hemoglobin (increase per 1 g/dL)	0.955	0.918 to 0.994	0.0256	0.858	0.735 to 1.002	0.0525
WBC (increase per 1000/μL)	1.116	1.095 to 1.139	<0.001	1.095	1.024 to 1.171	0.0076
Cholesterol (increase per 10 mg/dL)	0.962	0.949 to 0.975	<0.001	0.966	0.915 to 1.021	0.2108

CI indicates confidence interval; HR, hazard ratio; PD, peritoneal dialysis; WBC, white blood cell.

There are distinct differences between dialysis and nondialysis patients with regard to metabolic syndrome. For example targeting low-density lipoprotein level is still beneficial in lowering cardiovascular-related mortality in nondialysis patients with chronic kidney disease,[27] but this was not observed in dialysis patients,[28] especially when cardiovascular disease is present.[29] In addition, the metabolic effect of bilirubin was also demonstrated. It was found to have a protective effect against obesity, with a beneficial antioxidant effect,[22,30,31] and to improve atherosclerosis.[24] However, very high bilirubin levels are associated with higher mortality rates because of "reverse epidemiology," probably due to the nonadjustable confounding effect of malnutrition and inflammation in HD patients with low body mass index. In PD patients, residual urine markers should be assessed because pathological disease states may have existed for years, such as in patients with advanced chronic kidney disease. Second, PD patients may gain weight after starting PD therapy due to glucose absorption from dialysis fluid through the peritoneal membrane.[32] Therefore, metabolic syndrome or obesity may become a clinically important issue in PD patients, and we found that bilirubin had a protective antioxidant role in PD patients.

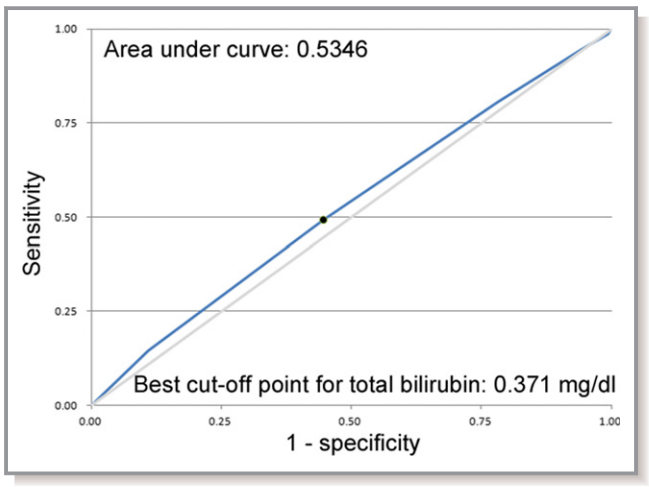

Figure 4. Receiver operator characteristic curve analysis for serum total bilirubin level regarding 3-year mortality prediction among peritoneal dialysis patients.

The cause of the elevated serum bilirubin levels remains unclear, but a possible explanation was addressed in a previous publication in which it is reported that serum bilirubin levels are linked to a TA-repeat *UGT1A1*28* polymorphism in the promoter region of the hepatic bilirubin uridine diphosphate-glucuronosyltransferase (*UGT1A1*) gene, which is the main gene responsible for bilirubin degradation and predicts long-term cardiovascular events and mortality in chronic hemodialysis patients.[33]

Limitations

The study has several limitations. First, the precise cause of death of each patient could not be identified clearly, although the mortality events were confirmed by data from the National Health Insurance. Second, we did not separate conjugate and unconjugated bilirubin, nor did we collect data regarding the reticulocyte count or blood smear. Thus, we could not exclude the possibility of hemolysis, spherocytosis, or other pathologic processes. The objective of this observational study was to search for a trend and trajectory between serum bilirubin level and mortality outcome. It is necessary in future studies investigating bilirubin-related survival to scrutinize the actual cause of death for each individual and various bilirubin levels. Third, the residual renal function and the PD complications (eg, peritonitis, gastrointestinal complications, electrolyte imbalance, peritoneal sclerosis) of each patient undergoing peritoneal dialysis could not be obtained in detail, both of which may have affected overall survival and made statistical adjustment impossible.

Conclusion

The serum total bilirubin level is related to the 3-year mortality rate among PD patients. Serum total bilirubin has beneficial

effects at a relatively elevated level. However, extremely high serum bilirubin levels are harmful, as are extremely low levels. Thus, total serum bilirubin can be another biomarker for predicting survival among PD patients. Further cellular, biochemical, and molecular studies are necessary to clarify the beneficial effects of bilirubin.

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Disclosures

None.

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