

ORIGINAL ARTICLE

The relationship between serum bilirubin level with interleukin-6, interleukin-10 and mortality scores in patients with sepsis

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Abstract

Context: Bilirubin has been shown to influence the mechanisms of both apoptosis and inflammation.

Aims: The aim of the following study is to investigate the relationship between the serum bilirubin level with sepsis progression.

Settings and Design: A total of 20 patients from intensive care unit were included for this study.

Materials and Methods: Patients were divided into two groups: Patients diagnosed with sepsis according to the American College of Chest Physicians/Society of Clinical Care Medicine consensus conference criteria ($n = 10$) and patients treated for various other diagnoses ($n = 10$). Blood samples were collected for both groups at the time of origin (defined as the time of diagnosis) and 24 and 48 h after diagnosis. Serum interleukin (IL)-6, IL-10 and bilirubin levels were analyzed and compared. Acute physiology and chronic health evaluation (APACHE) II and sepsis related organ failure (SOFA) scores of the patients were also evaluated.

Statistical Analysis Used: We used Statistical Package for Social Sciences (SPSS for Windows, version 17.0, SPSS Inc. 233 South Wacker Drive, Chicago) for statistical analysis.

Results: At all-time intervals, serum IL-6, IL-10 and total, direct and indirect serum bilirubin levels were significantly higher in the sepsis group ($P < 0.05$); APACHE II and SOFA scores were also significantly higher. Both SOFA scores and serum IL-10 levels were positively correlated with bilirubin levels 24 h after diagnosis ($P < 0.05$, $r = -0.76$).

Conclusions: Although levels of bilirubin and other associated parameters were higher for the sepsis group, only SOFA score and bilirubin levels were correlated. Because bilirubin is already a SOFA parameter, this correlation was not considered as clinically significant.

Key words: Acute physiology and chronic health evaluation, bilirubin, interleukin-6, interleukin-10, sepsis

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Introduction

Sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs. Sepsis may lead to shock, multiple organ failure and death, especially if not recognized early and treated promptly. Sepsis remains the primary cause of death from infection despite advances in modern medicine.^[1] Therefore, sensitive and specific laboratory tests are needed to guide clinicians in

achieving early diagnoses, monitoring therapeutic responses and developing treatment models if necessary.

Bilirubin is one of the end-products of heme catabolism and occurs as a result of the activity of heme oxygenase and bilirubin reductase.^[2] The relationship between

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bilirubin and sepsis is not clear, but hemolysis, cholestasis and hepatic dysfunction may cause hyperbilirubinemia in septic patients. Impaired absorption, transport and clearance of bilirubin, as well as, hepatic and hepatocellular injury cause hepatic dysfunction. In sepsis, hypotension and reduced hepatic blood flow cause Kupffer cell dysfunction, ischemia (particularly cells in central zones) and subsequent damage with reperfusion.^[3]

In patients with acute respiratory distress syndrome induced sepsis, hyperbilirubinemia is associated with poor prognosis and mortality. Previous studies found that the 1-week mortality rate was significantly higher in these patients.^[4,5] However, in one study,^[5] clinical factors may have influenced serum bilirubin levels.

Bilirubin suppresses post-ischemic myocardial dysfunction, has a negative correlation with insulin resistance and type 2 diabetes and has protective effects against lipopolysaccharide (LPS) induced hepatic injury. Bilirubin also improves carrageenan-induced local inflammation and vascular endothelial cell adhesion molecule (VCAM) related airway inflammation and blocks VCAM-1 dependent lymphocyte migration. These findings suggest that bilirubin is a cytoprotective molecule.^[6-9] However, recent studies have reported that bilirubin is associated with apoptosis and inflammation, both mechanisms related to sepsis pathogenesis. Bilirubin is known to induce apoptosis via mitochondrial pathways and activation of N-Methyl-D-aspartate receptors.^[10,11] Previous studies have also suggested that bilirubin has a negative correlation with C-reactive protein levels and may inhibit the expression of inducible nitric oxide, as well as, the secretion of phospholipase A2 and NO; therefore, bilirubin may have anti-inflammatory effects.^[8,12,13]

Bilirubin levels may be useful in demonstrating progression from systemic inflammatory response syndrome to severe sepsis. Therefore, the present study investigates bilirubin, which is known to have apoptotic, anti-inflammatory and anti-oxidant properties and its association with serum interleukin (IL)-6, IL-10 and scores measuring patient morbidity and mortality.

Materials and Methods

After receiving approval from the faculty ethics committee, 20 intensive care unit (ICU) patients diagnosed with sepsis or other diseases and between the ages of 18 and 75, were included. All patients were receiving synchronized intermittent mechanical ventilation (tidal volume: 6-8 ml/kg, f: 12-14, I/E: 1/2). Informed consent was obtained from the patients' relative. The patients were classified into two groups: Patients diagnosed with sepsis according to the American College of Chest Physicians/Society of Clinical Care Medicine consensus

conference criteria ($n = 10$); and patients treated for other reasons ($n = 10$). Patients with a history of hepatobiliary diseases, jaundice, hepatitis B virus/hepatitis C virus sero positivity, renal failure, drug overdose, hemolytic anemia, hypoxia, severe hemodynamic instability and/or possible brain death were excluded.

Blood samples were taken at 3 time intervals: The time of origin (defined as the day of sepsis diagnosis), 24 and 48 h after diagnosis. Serum IL-6, IL-10 and total, direct and indirect bilirubin levels were evaluated; acute physiology and chronic health evaluation (APACHE) II and sepsis related organ failure (SOFA) scores were also evaluated.

Blood samples were centrifuged at 3000/rpm for 5 min and then kept at -80°C . Human IL-6 and IL-10 commercial kits (Invitrogen, California, USA) and fully automated enzyme-linked immunosorbent assay Dynex Technologies Headquarters 14340 Sullyfield Circle Chantilly, VA 20151-1621 USA) were used for IL-6 and IL-10 measurements (pg/ml). To determine bilirubin levels, rapidlab 348 (Siemens, Chapel Lane Swords County Dublin, Ireland) was used (mg/ml).

We used Statistical Package for Social Sciences (SPSS for Windows, version 17.0) for statistical analysis. Findings were described as median (min-max). The Wilcoxon Signed Rank Test was used for comparison within groups. Gender was evaluated by Fisher's-Exact, Chi-Square test. For comparing between groups, the Mann Whitney U-test was used. To identify correlations, Pearson's and Spearman's correlation tests were performed. $P < 0.05$ were considered to be significant.

Results

The demographic characteristics of the patients were not statistically different. In the sepsis group, five patients had urosepsis, three had sepsis following abdominal infection and two patients had pulmonary origin [Table 1].

Within the groups, serum IL-6 levels were not statistically different for all time intervals [Tables 2 and 3]. Serum IL-10 levels were not statistically different for different time intervals [Tables 2 and 3]. However, serum IL-6 levels were higher in the sepsis group compared to the control group at all-time intervals (respectively, $P = 0.008$, $P = 0.005$ and $P = 0.041$) [Figure 1]. Serum IL-10 levels were higher in the sepsis group compared with the control group at all-time intervals (respectively, $P = 0.001$, $P = 0.028$ and $P = 0.029$) [Figure 2]. Serum total and direct bilirubin levels were higher in the sepsis group compared to the control group at all-time intervals ($P = 0.001$) [Figure 3], indirect bilirubin levels were higher in the sepsis group compared to the control group at all-time intervals (respectively, $P = 0.001$, $P = 0.002$ and $P = 0.001$).

Patients with sepsis had higher APACHE II compared to the control group ($P = 0.001$) [Figure 4]. SOFA scores also had higher in the sepsis group compared to the control group ($P = 0.001$) [Figure 5 and Table 4]. Serum IL-10 levels and SOFA scores of septic patients were correlated 24 h after diagnosis ($r = -0.76$, $P = 0.01$). Only SOFA scores were correlated with serum total bilirubin levels ($r = 0.72$,

$P = 0.017$) and serum direct bilirubin ($r = 0.74$, $P < 0.014$) 24 h after diagnosis.

Discussion

Bilirubin can be measured by performing routine biochemical tests in ICU and other units; measurement is thought to aid in early diagnosis of sepsis and to provide some information about clinical progression and prognosis. Therefore, we investigated the association between sepsis and hyperbilirubinemia and also between hyperbilirubinemia and APACHE II and SOFA scores in septic patients without primary hepatobiliary diseases.

Experimental and clinical studies have found increased serum and tissue IL-6 and IL-10 levels and strong correlations between plasma IL-10 levels and APACHE II and multiple organ dysfunction scores. Plasma IL-6 levels have also been shown to have predictive value for sepsis survival.^[14-17] Similarly, we found that IL-6 and IL-10 levels were higher in the sepsis group compared to the control group.

In one study, the authors injected LPS to subjects and created a sepsis model to investigate the relationship between infection and bilirubin. At 18 h after LPS injection, sinusoidal uptake, hepatic concentration and canalicular excretion of bilirubin were lower in endotoxemic groups compared to control groups.^[18] In a study of 19 patients with intraabdominal infection but no primary hepatobiliary diseases, total bilirubin levels were substantially higher 12 h after diagnosis in patients with septic shock.^[19] Our findings were consistent with these studies. In our study, sepsis patients had hyperbilirubinemia 24 h after diagnosis.

High bilirubin levels may indicate a poor prognosis; however, recent studies suggest a negative correlation between bilirubin levels and atherosclerosis and ischemic heart disease and it is observed that patients with high bilirubin levels had less atherosclerotic events than patients with normal bilirubin levels.^[4,5,20,21] Two clinical studies have investigated the association between bilirubin levels and certain diseases that may cause morbidity in

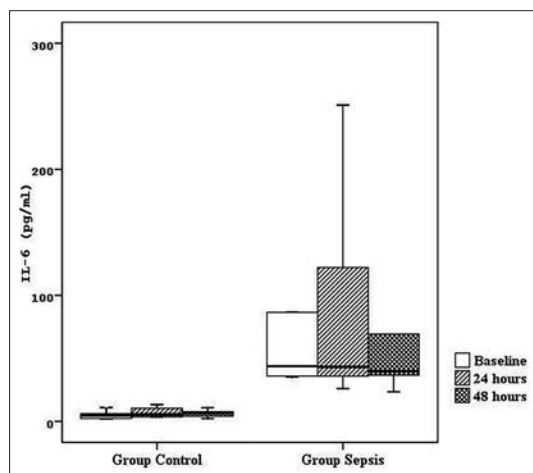


Figure 1: Serum interleukin-6 levels

Table 1: Demographic data of patients

Groups	Median (minimum-maximum)		Statistical analysis (P)
	Group control	Group sepsis	
Age (year)	72 (18-75)	69 (19-75)	0.53
Gender (F/M)	6/4	5/5	1.00
The number of patients treated with mechanical ventilation	10/10	10/10	
Cause of admission to intensive care unit	Ischemic CVD (5)	Ischemic CVD (4)	
	Intracerebral hemorrhage (3)	Intracerebral hemorrhage (1)	
	Pulmonary edema (1)	Intestinal perforation (3)	
	Pulmonary embolism (1)	Aspiration pneumonia (2)	
Source of sepsis		Urinary (5)	
		Abdominal (3)	
		Pulmonary (2)	

CVD=Cardiovascular disease

Table 2: Comparison of data according to baseline values

Group	Variable	Median (minimum-maximum)			Baseline (P)	
		Baseline	24 h	48 h	24 h	48 h
Control	IL-6	4.70 (1.83-13.75)	5.40 (3.20-13.32)	6.75 (2.27-18.00)	0.49	0.40
	IL-10	3.55 (1.20-5.34)	4.10 (1.30-5.80)	3.60 (1.43-5.70)	0.66	0.53
	T. Bil	0.56 (0.25-1.06)	0.79 (0.07-0.98)	0.71 (0.30-1.00)	0.14	0.06
Sepsis	IL-6	43.73 (35.06-248.32)	43.21 (26.02-250.98)	39.78 (23.43-412.00)	0.58	0.22
	IL-10	26.18 (10.19-57.95)	17.75 (10.81-147.13)	15.46 (10.32-145.97)	0.71	0.72
	T. Bil	1.88 (1.38-2.60)	1.93 (1.40-4.12)	1.96 (1.42-5.03)	0.14	0.22

IL=Interleukin; T. Bil=Total bilirubin

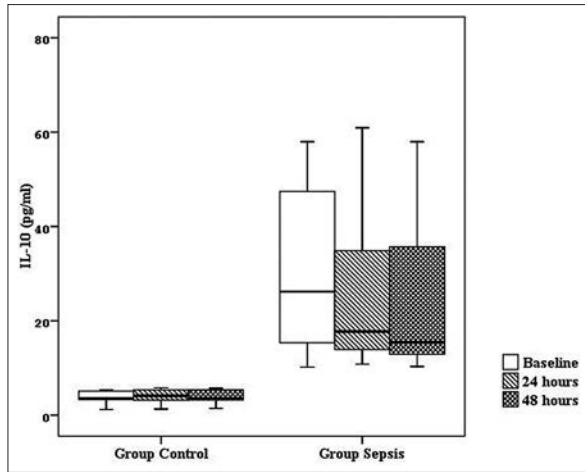


Figure 2: Serum interleukin-10 levels

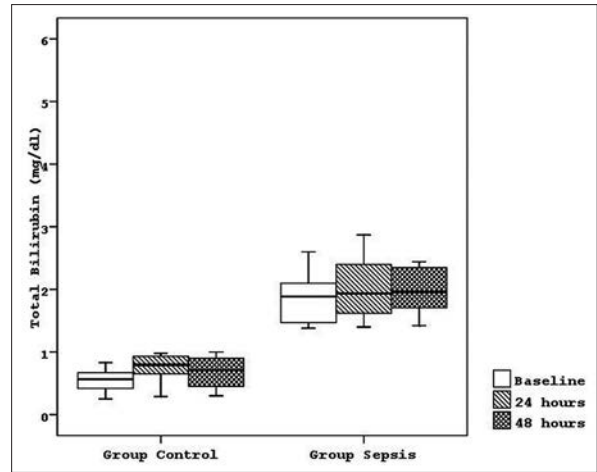


Figure 3: Serum total bilirubin levels

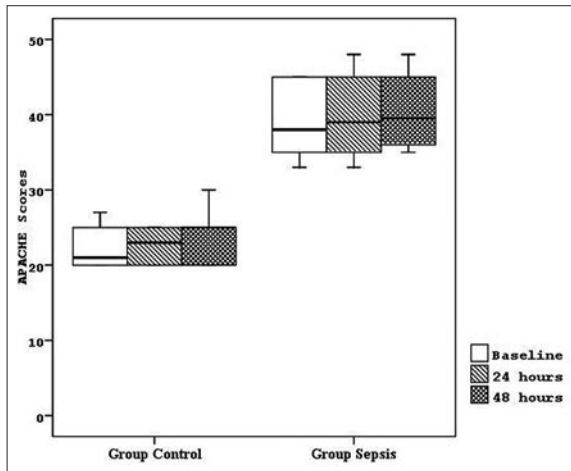


Figure 4: Acute physiology and chronic health evaluation scores

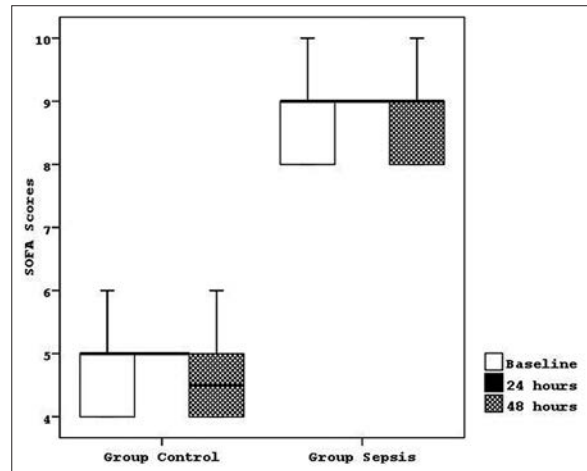


Figure 5: Sepsis related organ failure scores

Table 3: Comparison of percentage change compared to baseline values

Variable	Median (minimum-maximum)		P
	Group control	Group sepsis	
IL-6			
0-24 h	0.62 (0.05-2.31)	0.08 (0.02-2.31)	0.07
0-48 h	0.65 (0.14-3.47)	0.16 (0.01-0.78)	0.02
IL-10			
0-24 h	0.43 (0.00-3.59)	0.44 (0.13-3.08)	0.55
0-48 h	0.48 (0.28-3.50)	0.30 (0.16-3.05)	0.44
T. Bil			
0-24 h	0.46 (0.07-0.94)	0.09 (0.03-0.96)	0.64
0-48 h	0.21 (0.05-0.55)	1.15 (0.02-1.39)	0.95

IL=Interleukin; T. Bil=Total bilirubin

Table 4: Comparison of score change compared to baseline values

Variable	Median (minimum-maximum)		P
	Group control	Group sepsis	
Acute physiology and chronic health evaluation			
0-24 h	0.5 (2-3)	1.5 (1-4)	0.12
0-48 h	1 (2-5)	2.5 (2-4)	0.92
Sepsis-related organ failure assessment			
0-24 h	0 (0-1)	0 (0-1)	0.61
0-48 h	1 (0-1)	0.5 (0-1)	0.66

neonates with low birth weight. Bilirubin levels were found to be lower in patients with retinopathy of prematurity, intraventricular hemorrhage, necrotizing enterocolitis, respiratory distress syndrome and bronchopulmonary dysplasia. Bilirubin was also thought to have anti-oxidant effects.^[22,23]

Rodrigues *et al.*^[10] prepared neuron cultures taken from 17 to 18 day old rat fetuses and administrated unconjugated bilirubin to evaluate the effect of bilirubin on apoptosis. In neurons exposed to bilirubin, excessive secretion of cytochrome c from the mitochondria and its accumulation in the cytosol were observed. It was also observed that even small increments in bilirubin levels activated caspase-3 and caused full length substrate poly (ADP

ribose polymerase degradation. In another experimental study, exogenous bilirubin was shown to block VCAM-1 dependent lymphocyte migration via suppression of free oxygen radicals; it was also shown to improve VCAM related *in vivo* airway inflammation.^[9]

Previous studies have also reported that high bilirubin levels reduce endotoxin-induced inflammation, NO production via inhibition of nicotinamide adenine dinucleotide phosphate oxidase, microvascular leukocyte adhesion and pulmonary VCAM-1 dependent leukocyte migration.^[8,9,24,25] In subjects with experimental endotoxemia, administration of exogenous bilirubin improved clinical outcomes and also inhibited LPS-induced leukocyte-endothelial interaction and leukocyte accumulation. Moreover, gene expression of endothelial adhesion molecules and inflammatory mediators, such as IL-1 β and tumor necrosis factor- α , decreased significantly; thus, bilirubin has been suggested to have anti-inflammatory effects.^[26] In our study, no correlation was found between bilirubin levels and IL-6 and IL-10 levels in septic patients, perhaps due to the lack of long-term, molecular follow up for inflammation. To the best of our knowledge, there is no other study that investigates the relationship between bilirubin and cytokine levels and hence this aspect of our study cannot be discussed.

APACHE II and SOFA scores are commonly used in ICUs to determine prognosis and mortality of patients with sepsis. APACHE II score is calculated the 12 physiological variables: (Age, temperature, mean arterial pressure, pH arterial, heart rate, respiratory rate, sodium, potassium, creatinine, hematocrit, white blood cell count, Glasgow Coma Scale). The SOFA was developed in 1994 during a consensus conference. Six organ systems (respiratory, cardiovascular, renal, hepatic, central nervous, coagulation) were selected based on a review of the literature and the function of each is scored from 0 (normal function) to 4 (most abnormal), giving a possible score of 0-24.^[27] APACHE II and SOFA scores were higher in the sepsis group, as is consistent with the literature. Studies have reported that there is a correlation between APACHE II and SOFA scores and IL-6 and IL-10.^[28,29] We did not observe a similar correlation in our study, perhaps due to the use of different sampling time intervals and the shorter duration of our study (48 h). Studies have suggested that the correlation between IL-6 and APACHE II and III occurs 3-7 days after diagnosis of sepsis, or 1 day after severe sepsis. The correlation between IL-10 and APACHE scores occurs within 1-3 days after the onset of severe sepsis.^[29-31] A study by Oda *et al.*^[32] evaluated IL-6 levels of patients with SIRS and sepsis and reported that peak IL-6 levels correlated with maximal SOFA levels. However, SOFA scores reached their maximum levels approximately 2.5 days after IL-6 levels peaked. Because our blood sampling intervals differed from literature, we did not find any correlation between SOFA scores and serum IL-6 levels. However, we did find

a correlation between SOFA scores and IL-10 levels 24 h after diagnosis and this finding was consistent with the literature.^[33] We also found a correlation between bilirubin levels and SOFA scores, but bilirubin is already a SOFA parameter, so this result was not considered clinically significant.

Bilirubin, a frequently used parameter in clinical units, is affected by hepatic infections and has a role in apoptosis and inflammation. We investigated whether bilirubin may be used in monitoring sepsis prognosis. We found that serum IL-6 and IL-10 levels, as well as APACHE II and SOFA scores, were significantly higher in patients with sepsis when compared with a control group, but no correlations between bilirubin and other important sepsis parameters were found. Our study has major limitations, including a small number of patients and failure to select a specific patient population for the control group. Therefore, further studies with larger populations and specific control groups are necessary.

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