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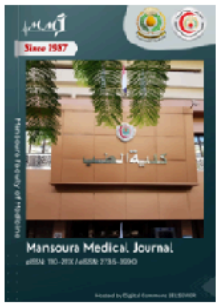

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Study of Serum bilirubin in relation to stable chronic coronary artery disease severity and outcome after percutaneous intervention

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ORIGINAL STUDY

Study of Serum Bilirubin in Relation to Stable Chronic Coronary Artery Disease Severity and Outcome After Percutaneous Intervention

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Abstract

Background: **Bilirubin is an endogenous antioxidant, and increased physiological concentrations reduce the severity of coronary artery disease with better prognosis after percutaneous coronary intervention (PCI).**

Objective: **Assess serum bilirubin level in patients with stable chronic coronary artery disease and correlate it with the severity of this disease and outcome after PCI.**

Patients and methods: **Cross-sectional prospective observational study included 203 patients with stable chronic coronary artery disease divided into two groups according to bilirubin: group I less than or equal to 0.6 mg/dl group II more than 0.6 (up to 1.2 mg/dl). Hundred cases underwent elective coronary angiography and PCI with full clinical examination, laboratory tests: total serum bilirubin, creatinine, lipid profile, ECG, echocardiography, and follow up of major adverse cardiac and cerebral endpoint (MACCE) after 6 months and 1 year.**

Results: **A highly significant increase in SYNTAX score, total MACCE after 6 months, especially heart failure (HF), also total MAACE after 12 months especially revascularization, HF, and cerebrovascular stroke in cases with bilirubin less than or equal to 0.6 mg/dl with a higher incidence than other groups with a highly significant negative correlation between bilirubin and T wave abnormalities, HF, and MACCE after 6 months, revascularization, HF, cerebrovascular stroke, and MACCE after 12 months., also there was a significant negative correlation between bilirubin and ST-segment elevation, RWMA, SYNTAX score, myocardial infraction after 6 months.**

Conclusion: **Serum bilirubin level in stable chronic coronary artery disease is correlated with SYNTAX score and severity of disease and could be used to predict the incidence of MAACE after PCI.**

Keywords: Chronic coronary syndrome, Major adverse cardiac and cerebral endpoint, Percutaneous coronary intervention, Serum bilirubin

1. Introduction

Cardiovascular disease caused by atherosclerosis is the leading cause of morbidity and mortality in both modern and developed countries. It is a chronic disease caused by a chronic inflammation of the arterial wall, which begins as endothelial dysfunction and then progresses to inflammation and deposition as well as peroxidation of lipids (Jebari-Benslaiman *et al.*, 2022).

Bilirubin is an effective endogenous antioxidant is known as the scavenger of reactive oxygen radicals and it has been hypothesized that increased physiological concentrations of serum bilirubin level might reduce atherogenic risk (Kang *et al.*, 2013; Turfan *et al.*, 2013). Also, bilirubin has been shown to be clinically beneficial in the treatment of inflammatory diseases (Yao *et al.*, 2019).

In addition, some reports show that intracellular bilirubin modulates extracellular bilirubin uptake or elevates HO-1, a cellular enzyme related to endogenous bilirubin synthesis, to reduce ectopic oxaditve stress and increase endothelial function (Liu *et al.*, 2017) also bilirubin may also be inhibitory to the

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inflammatory process leading to atherosclerosis and has been shown to have an inverse relationship with markers of inflammation, including C-reactive protein, neutrophil–leucocyte ratio, and red cell distribution width (Akboga *et al.*, 2015).

Percutaneous coronary intervention (PCI) is the most common intervention for coronary artery disease with very low complications, indicated to improve symptoms and quality of life when performed for chronic coronary artery disease (Means *et al.*, 2017; Piccolo *et al.*, 2015).

2. Aim

The aim of the present study was to assess serum bilirubin levels in patients with stable chronic coronary artery disease and correlate it with the severity of this disease, also follow up of these patients to detect the reflection of serum bilirubin value on the outcome of coronary artery disease after percutaneous intervention.

3. Patients and methods

Type of study: it is a prospective cross-sectional observational study.

3.1. Patients selection

The study involved 203 patients with mean age 58.92 ± 9.205 with stable chronic coronary artery disease admitted to Cardiology Department in Mansoura Specialized Medical Hospital for elective coronary angiography and PCI during the period from June 2021 to May 2022 included in the study.

3.1.1. Inclusion criteria

All patients with stable chronic artery disease presented with either:

(1) Stable angina.
(2) Old myocardial infraction.

3.1.2. Exclusion criteria

The patients with any of the following conditions had been excluded from the study:

(1) Patient with chronic liver disease.
(2) Patients with blood disorders: anemia (especially hemolytic anemia), hemorrhagic disorders, or leukemia.
(3) Systemic malignancy.
(4) Suspicion of thromboembolic disease.
(5) Patient with congestive heart failure (HF).
(6) Acute coronary syndrome.
(7) Patients with advanced renal impairment.

3.2. Ethical considerations

(1) Study protocol was approved by research board and ethical Committee at Mansoura Faculty of Medicine.
(2) Informed written consent was obtained from each participant sharing in the study.

3.3. Methods

All patients were subjected to through history taking regarding age, chest pain type, and severity Canadian Society of Cardiology class (CCS), dyspnea and its NYHA class, coronary artery disease risk factors, other cardiac symptoms as orthopnea palpitation and syncope. Full clinical examination including pulse, blood pressure, temperature, neck veins, pallor, jaundice, hepatosplenomegaly, ascites, neurological, and chest examination.

Investigations including 12 lead ECG for ischemic changes and arrhythmias, echo Doppler study for resting systolic wall motions, diastolic dysfunction, and ejection fraction. Laboratory testing for serum bilirubin, serum creatinine liver functions including serum albumin SGOT and SGPT lipid profile.

Coronary angiography and percutaneous intervention PCI were performed through the femoral or radial approach according to the standard technique. The coronary angiograms results were reviewed by three independent and experienced interventional cardiologists, blinded to all data to assess SYNTAX score and degree of coronary artery stenosis and PCI procedure outcome.

Follow up: the patients were followed in the outpatient clinic and phone call at monthly intervals regarding major adverse cardiac and cerebral endpoints (MACCE), including revascularization, coronary artery bypass grafting (CABG), HF, myocardial infarction, cerebral stroke or death that were reported at 6 month and 1 year.

4. Results

Our study comprised 203 patients categorized into 156 (76.8 %) males and 47 (23.2 %) females presented with stable chronic coronary artery disease and were admitted for elective coronary angiography and PCI. Their age ranges from 29 to 84 years old with mean age of 58.92 ± 9.205.

4.1. Statistical analysis

The clinical and laboratory data were recorded on an 'investigation report form.' These data were tabulated, coded, and then analyzed using the computer program SPSS (Statistical package for social science), version 20, to obtain descriptive and analytical data.

Population were divided according to their total bilirubin level into two groups; group I in which bilirubin less than or equal to 0.6 mg/dl ($N = 103$) and group II in which bilirubin more than 0.6 (up to 1.2 mg/dl) ($N = 100$), the mean age of group I was 59.39 ± 9.059 and mean age of group II was 58.43 ± 9.375 with no statically significant difference was found between them regarding age. Regarding sex 78.6 % of group I was male and 21.4 % was female, while group II 75 % was male and 25 % was female with no statistically significant difference between two groups regarding sex, however it shows male predominance (78.6 %, 75 %) in groups I and II, respectively.

Comparative analysis between risk factors in both groups there was a significant increase in percentage of patients with positive family history of cardiovascular disease in the group of serum bilirubin less than or equal to 0.6 as compared to group with serum bilirubin more than 0.6 ($P = 0.037$) while nonsignificant difference in other risk factors (hypertension, diabetes mellitus, smoking, or dyslipidemia) ($P > 0.5$; Table 1).

There was a significant increase in CCS class IV in the group with serum bilirubin less than or equal to 0.6 mg versus group with serum bilirubin more than 0.6 mg ($P = 0.029$; Table 2). Regarding ECG and ECHO data, there were significant increase in ST-segment elevation, T wave inversion, and arrhythmias, and RWMA in the group with serum bilirubin less than or equal to 0.6 versus group with serum bilirubin more than 0.6 mg and nonsignificant changes in other parameters (Table 3). SYNTAX score was higher in the group with low serum bilirubin versus the group with high serum bilirubin (Table 3).

Regarding the comparison of MACCE after 6 months between two studied groups, it was higher in cases with bilirubin less than or equal to 0.6 mg/dl than those with elevated serum bilirubin more than 0.6 mg/dl, especially total MACCE and HF between two groups was highly statistically significant ($P < 0.001$), no death or CABG occur within first 6 months in two groups. Comparison of MACCE after 12 months between two studied groups, it was found that they were higher in cases with bilirubin less than or equal to 0.6 mg/dl than those with elevated serum bilirubin more than 0.6 mg/dl and was highly statistically significant ($P < 0.001$) especially total MACCE, revascularization, HF, and

Table 1. Comparison between two studied groups regarding risk factors.

Risk factor	Group I (bilirubin ≤0.6 mg/dl) ($N = 103$) [n (%)]	Group II (bilirubin >0.6 mg/dl) ($N = 100$) [n (%)]	Test of significance	P value
Hypertension	65 (63.1)	63 (63.0)	$\chi^2 = 0.001$	$P = 0.987$
Diabetes	51 (49.5)	54 (54.0)	$\chi^2 = 0.409$	$P = 0.523$
Smoking	48 (46.6)	45 (45.0)	$\chi^2 = 0.052$	$P = 0.819$
Dyslipidemia	39 (37.9)	38 (38.0)	$\chi^2 = 0.001$	$P = 0.984$
Positive family history for CV disease	34 (33)	20 (20)	$\chi^2 = 4.398$	$P = 0.036$*

χ^2, χ^2 test.
*Statistically significant P value less than or equal to 0.05.

Table 2. Comparison between the studied groups regarding chest pain class according to Canadian society of cardiology classification.

	Group I (bilirubin ≤0.6 mg/dl) ($N = 103$) [n (%)]		Group II (bilirubin >0.6 mg/dl) ($N = 100$) [n (%)]		Test of significance	P value
CCS class						
No chest pain	3	2.9	1	1		
CCS class I	3	2.9	1	1		
CCS class II	2	1.9	10	10	$\chi^2 = 10.781$	$P = 0.029$*
CCS class III	12	11.7	20	20		
CCS class IV	83	80.6	68	68		

χ^2, χ^2 test; CCS, Canadian cardiovascular Society.
*Statistically significant P value less than or equal to 0.05.

Table 3. Comparison of the two studied groups regarding ECG changes, ECHO data, and SYNTAX score.

	Group I (bilirubin ≤0.6 mg/dl) ($N = 103$)	Group II (bilirubin >0.6 mg/dl) ($N = 100$)	Test of significance	P value
ECG				
	n (%)	n (%)		
ST-segment elevation	8 (7.8)	–	$\chi^2 = 8.086$	$P = 0.007$*
ST segment depression	66 (64.1)	63 (63)	$\chi^2 = 0.025$	$P = 0.873$
T wave abnormality	42 (40.8)	18 (18)	$\chi^2 = 12.642$	$P \leq 0.001$**
Arrhythmias	33 (32.0)	54 (54)	$\chi^2 = 9.992$	$P = 0.002$*
Echo				
RWMA	43 (41.7)	27 (27)	$\chi^2 = 4.885$	$P = 0.027$*
E/A ratio				
Mean ± SD	0.85 ± 0.31	0.89 ± 0.42	$Z = -0.060$	$P = 0.952$
Median (minimum–maximum)	0.75 (0.43–2)	0.75 (0.42–3)		
EF%				
Mean ± SD	60.77 ± 7.93	61.9 ± 6.07	$Z = -0.086$	$P = 0.931$
Median (minimum–maximum)	62 (35–73)	62.5 (40–79)		
SYNTAX				
Mean ± SD	17.92 ± 7.88	13.89 ± 7.79	$Z = -3.638$	$P \leq 0.001$**
Median (minimum–maximum)	18 (2–37)	12.5 (1–36)		

χ^2, χ^2 test; EF, ejection fraction; RSWMA, resting segmental wall motion abnormalities; Z, Mann–Whitney test.
*Statistically significant P value less than or equal to 0.05.
**Highly statistically significant P value less than 0.001.

Table 4. Comparison between two studied groups regarding MACCE after 6 and 12 months from percutaneous coronary intervention.

	Group I (bilirubin ≤0.6 mg/dl) ($N = 103$) [n (%)]	Group II (bilirubin >0.6 mg/dl) ($N = 100$) [n (%)]	Test of significance	P value
MACCE after 6 months	16 (15.5 %)	–	$\chi^2 = 16.863$	$P \leq 0.001$**
Components of MACCE after 6 months				
revascularization	1 (1.0)	–	$\chi^2 = 0.976$	$P = 0.323$
CABG	–	–		
MI	2 (1.9)	–	$\chi^2 = 1.961$	$P = 0.498$
HF	13 (12.6)	–	$\chi^2 = 13.485$	$P \leq 0.001$**
CVS	1 (1.0)	–	$\chi^2 = 0.976$	$P = 0.323$
Death	–	–		
MACCE after 12 months	46 (44.7)	2 (2)	$\chi^2 = 51.145$	$P \leq 0.001$**
Components of MACCE after 12 months				
Revascularization	11 (10.7)	–	$\chi^2 = 11.291$	$P \leq 0.001$**
CABG	–	–		
MI	3 (2.9)	1 (1)	$\chi^2 = 0.961$	$P = 0.327$
HF	25 (24.3)	1 (1)	$\chi^2 = 24.606$	$P \leq 0.001$**
CVS	12 (11.7)	–	$\chi^2 = 12.382$	$P \leq 0.001$**
Death	–	–		

χ^2, χ^2 test; CABG, coronary artery bypass grafting; CVS, cerebrovascular stroke; HF, heart failure; MI, myocardial infraction.
*Statistically significant P value less than or equal to 0.05.
**Highly statistically significant P value less than 0.001.

cerebrovascular stroke (CVS) between two groups with no death or CABG occur within first 12 months in two groups (Table 4).

There were highly statistically significant negative correlations between serum total bilirubin and T wave abnormalities in ECG, HF after 6 months, MACCE after 6 months, revascularization after 12 months, HF after 12 months, CVS after 12 months, and MACCE after 12 months, also there were significant statistically negative correlation between serum total bilirubin and ST-segment elevation in ECG, RWMA in ECHO, SYNTAX score, myocardial infraction after 6 months (Table 5).

5. Discussion

The most important results of our study are that in spite of no difference in age, sex, and risk factors between the two studied groups that, high serum bilirubin more than 0.6 mg and low serum bilirubin

Table 5. Correlation between serum bilirubin and different study variables.

	Serum bilirubin	
	r	*P*
ST-segment elevation	−0.213	0.002*
T wave	−0.244	<0.001**
RWMA	−0.159	0.024*
SYNTAX	−0.177	0.011*
MI after 6 months	−0.154	0.028*
HF after 6 months	−0.315	<0.001**
MACCE after 6 months	−0.348	<0.001**
Revascularization after 12 months	−0.291	<0.001**
HF after 12 months	−0.390	<0.001**
CVS after 12 months	−0.289	<0.001**
MACCE after 12 months	−0.589	<0.001**

CV, cardiovascular; CVS, cerebrovascular stroke; DBP, Diastolic blood pressure; HF, heart failure; MI, myocardial infraction; *r*, Spearman's correlation; SBP, Systolic blood pressure.
*Statistically significant *P* value less than or equal to 0.05.
**Highly statistically significant *P* value less than 0.001.

less than 0.6 mg different parameters of severity of coronary artery disease in patients with chronic coronary syndrome as CCS class, ECG changes, SWMA by ECHO, and SYNTAX score by angiography were higher in the group with lower serum bilirubin less than 0.6 mg confirming the protective value of serum bilirubin in atherosclerotic heart disease.

Our results regarding risk factors are concordant with Kim *et al.* (2015) with the exception of a significant increase in positive family history of CVD in our study, while Yao *et al.* (2015) found similar results to ours except in dyslipidemia that was significantly higher in low serum bilirubin group.

Our finding regarding the ECG is that lower serum bilirubin is associated with more T wave inversions, ST-segment elevation and arrhythmias, and more severe stable coronary artery disease.

Our results regarding the EF are similar to Kim *et al.* (2015) and Gao *et al.* (2019) who found nonsignificant difference in EF in the group with low versus high bilirubin.

On assessment of SYNTAX score in the two studied group a significantly higher score was found in the group with low as compared to high total bilirubin ($P < 0.001$). This result is similar to that of Yu *et al.* (2017) also Turfan *et al.* (2013) found that higher SYNTAX score group have lower total serum bilirubin and this means that serum bilirubin is inversely related to the severity of stable coronary artery disease.

Follow-up of the two studied groups for MACCE after 6 months following PCI demonstrated that a highly significant incidence of total MACCE (15.5 vs. 0 %) ($P < 0.001$), especially HF (12.6 vs. 0 %) ($P < 0.001$) in the group with low serum bilirubin and nonsignificant change in revascularization, myocardial infraction, and CVS, no death or CABG in both groups.

On the other hand, follow-up of patients 12 months after PCI showed a highly significant increase of total MACCE (44.6 vs. 2 %) ($P < 0.001$), including revascularization (10.7 vs. 0 %), HF (24.3 vs. 1 %), and CVS (11.7 vs. 0 %) ($P < 0.001$) in the group with low versus high total bilirubin while nonsignificant myocardial infraction incidence and no death or CABG was recorded.

Our findings are partly consistent with Yu *et al.* (2017), who found a higher incidence of MACE in the low total bilirubin group (12.8 vs. 4.9 %, $P < 0.05$). Elevated total bilirubin can predict the long-term prognosis of patients with stable angina pectoris (odds ratio = −2.315, 95 % confidence interval −0.017 to −0.001, $P = 0.021$) significantly higher event-free survival rate in the patients with higher bilirubin levels (95.1 vs. 87.2 %, $P < 0.05$).

Kim *et al.* (2015) demonstrated that low serum total bilirubin level was associated with cardiac death and MACCE in patients undergoing PCI, which is partially consistent with our results regarding total MACCE and myocardial infraction but different in the incidence of death, revascularization, and HF development.

5.1. Limitations of the study

(1) A single-center study.
(2) The small number of patients included and this was due to selection criteria, which exclude patients with liver disease and other comorbid conditions which affect serum bilirubin.
(3) Lack of long-term follow-up of these patients to detect prognostic significant of serum bilirubin level on cardiovascular outcome for more than 1 year.

5.2. Overall conclusions of our study are

(1) Higher serum bilirubin level is associated with statically lower CCS class.
(2) Higher serum bilirubin level is associated with a significantly lower occurrence of ECG changes as a ST-segment elevation, arrhythmias, and T wave abnormalities.
(3) Echocardiographic data showed more RWMA in patients with lower serum bilirubin.
(4) Regarding angiographic data, a higher SYNTAX score was found in patients with lower serum bilirubin.

(5) Follow-up of our patients showed a significant increase in total MACCE and HF after 6 months while a significant increase in total MACCE and revascularization, HF, and CVS after 12 months in patients with lower serum bilirubin.
(6) A significant negative correlation between serum bilirubin and T wave, ST-segment elevation, and arrhythmias in ECG, RWMA in ECHO, SYNTAX score by angiography, myocardial infraction, HF, MACCE after 6 months, revascularization, HF, CVS, and MACCE after 12 months which proves incremental increase in the beneficial effect of antioxidant effects of higher serum bilirubin (within normal physiological level).

Conflicts of interest

None declared.

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