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Prevalence of post-operative morbidity risk factors following cardiac surgery in patients with chronic viral hepatitis: a retrospective study

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Abstract. – OBJECTIVE: Current cardiac risk assessments such as EuroSCORE II and the STS-Score do not take liver dysfunction into account. The purpose of this study was to evaluate the prevalence and post-operative morbidity risk factors following cardiac surgery of patients with chronic viral hepatitis.

PATIENTS AND METHODS: The study group consisted of 105 patients with documented chronic viral hepatitis who were subject to elective cardiac surgery from 2001 to 2012. Subjects were evaluated for pre-operative liver dysfunction according to the MELD score.

RESULTS: The average MELD score of the study group was 10.00 ± 6.00. The average EuroSCORE ii of the study group was 2.07% ± 1.62%. The primary post-operative complication was cardiac complications (n=57, 54.3%). Analysis showed significant differences in meld score, bilirubin and smoking. Multivariate logistic regression analysis showed that the variables entering into the model included such risk factors with a significant or near significant ($p < 0.2$) influence on hospital morbidity and consisted in valve vs. coronary artery disease, valve/cad, aortic valve replacement vs. Coronary artery bypass graft, and bilirubin (mg/dl).

CONCLUSIONS: it is vital that liver dysfunction is added to the risk models which are currently utilized to predict the post-operative morbidity of cardiac surgery patients.

Key Words:
Cardiac surgery, Liver dysfunction, Post-operative morbidity, Hepatitis.

Introduction

Whilst many antiviral treatments are currently available, the hepatitis virus infection remains a major health epidemic, typically resulting in chronic hepatitis, cirrhosis and ultimately liver failure[1-3]. The World Health Organization (WHO) reported that an estimated two billion people worldwide have been infected with hepatitis B virus (HBV), more than 360 million have chronic liver infections, and about 620,000 people die every year as a result of hepatitis B virus infection and HBV-related liver disease[3,4]. The WHO also reported that hepatitis C virus (HCV) infection was another major worldwide public health concern among the five hepatitis viruses infections, causing 150 million people to be chronically infected with hepatitis C virus, and more than 350,000 people dying from hepatitis C-related liver diseases each year[4].

Significant advancement in biomedicine and improvements in patient care have ensured cardiac surgery for patients with liver disease; however, the liver disease was reported as a risk factor for mortality and complications after cardiac surgery[5-9]. Moreover, major morbidity ranged from 20 to 60% in group A and 50 to 100% in patients presenting more advanced hepatic disease[10]. Advanced liver dysfunction increased post-operative morbidity because of coagulation disorders, hemostatic disorders and bacterial infection[9,11,12].

Risk models have been created and validated based on the patient's characteristics, such as age, gender, etc. However, current risk scores did not consider liver dysfunction in surgical risk models[5-9], such as the Society of Thoracic Surgeons (STS) system[12] and the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II[13] which have been recognized worldwide and applied in Europe[14], North America[15] and Asia[16]. With the population of liver diseases, specific scores such as Child-Turcotte-Pugh (CTP) class and the model for end-stage liver disease (MELD) score have been used to evaluate the level of liver function[17]. The current

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problem is whether liver dysfunction assessed by CTP or MELD could predict morbidity after cardiac surgery. Thus, we conducted this study to evaluate the prevalence and risk factors of post-operative morbidity after cardiac surgery in patients with chronic viral hepatitis. In addition, an analysis of the relevance of liver dysfunction classified by the MELD score and the simplified MELD score in the prediction of surgical morbidity in patients with chronic viral hepatitis who have undergone cardiac surgery was conducted.

Patients and Methods

Patients and Data Collection

A retrospective analysis of our records selected all patients with hepatitis virus infection who had undergone elective cardiac surgery between March 2001 and November 2012 in our hospital. A total of 105 patients had undergone cardiac surgery, including aortic valve replacement, coronary artery bypass graft or both.

The severity of liver dysfunction was evaluated with the Model for End-Stage Liver Disease (MELD) score[18,19]. In addition, as to subjects who used anticoagulants, a modified score (MELD-XI) was adopted. Furthermore, cardiac function was determined by using echocardiography and the ejection fraction was calculated. Data were also collected on patients' basic characteristics including age, gender, creatinine, bilirubin, overweight and obesity, stroke history, hypertension, chronic obstructive pulmonary disease (COPD), diabetes mellitus, dyslipidemia and smoking status. The outcomes were post-operative outcomes, including cardiac complications, neurological complications, infection, acute renal failure, and arrhythmia.

Statistical Analysis

Continuous variables were presented as mean ± SD or median ± IQR; and categorical variables were expressed by using the proportion. Univariate analysis was performed by Fisher's exact tests for categorical variables and Wilcoxon's rank-sum test for continuous variables. Multivariate logistic regression analysis was performed to identify independent risk factors for hospital mortality after cardiac surgery. Variables entering into the model included those risk factors that had a significant ($p < 0.05$) or near significant ($p < 0.20$) influence on morbidity by the univariate analysis. Crude odds ratio (OR) in univariate analysis and adjusted OR in multivariate logistic regression analysis were calculated. All statistical analyses were performed by using SPSS statistics 16 (SPSS Inc., Chicago, IL, USA). $p < 0.05$ was considered statistically significant.

Results

Basic Patient Parameters Before Surgery

Patients' characteristics prior to surgery are listed in Table I. The mean ± SD of included patients was 58.15 ± 11.01 years, with 39 (37.1%) females and 66 (62.9%) males, in which, 39 (37.1%) were CAD patients, 54 (51.4%) were valve patients and the others (n=12, 11.4%) were both. 43 (41.3%) patients were hepatitis B virus infected, 59 (56.7%) patients were hepatitis C virus infected and 2 (1.9%) were both hepatitis B

Table I. Basic characteristic of patients before surgery.

Pre-operative variables	Results
Number of patients, n	105
Age (years) mean ± SD	58.15 ± 11.01
Male, n (%)	66 (62.9)
Female, n (%)	39 (37.1)
Creatinine, (mg/dL) median ± IQR	0.97±0.48
Bilirubin, (mg/dL) median ± IQR	1.00±0.52
INR median ± IQR	1.17±0.33
Ejection Fraction median ± IQR	55.00±10.00
MELD median ± IQR	10.0±6.00
MELD abs median ± IQR	8.91±5.70
EuroSCORE median ± IQR	1.66%±1.60%
BMI median ± IQR	25.98±6.60
BMI < 25, n (%)	42 (40.0%)
BMI 25-30, n (%)	39 (37.1%)
BMI ≥ 30, n (%)	24 (22.9%)
Hypertension	68 (66.7%)
Diabetes mellitus, n (%)	15 (14.4%)
Dyslipidemia, n (%)	31 (29.5%)
COPD, n (%)	13 (12.5%)
Stroke, n (%)	11 (10.6%)
Hepatitis B, n (%)	43 (41.3%)
Hepatitis C, n (%)	59 (56.7%)
Hepatitis B and C, n (%)	2 (1.9%)
Smoking, n (%)	42 (40.4%)
Myocardia infarction, n (%)	11 (10.5%)
Type of disease-CAD, n (%)	39 (37.1%)
Type of disease-Valve, n (%)	54 (51.4%)
Type of disease- Valve+CAD, n (%)	12 (11.4%)
Arrythmia, n (%)	45 (42.9%)

Note: CAD: coronary artery disease; MELD: model for end-stage liver disease; COPD: chronic obstructive pulmonary disease; EuroSCORE: European System for Cardiac Operative Risk Evaluation.

Table II. Demographics of patients during and after surgery

Intraoperative variables	
Operation: AVR, n (%)	19 (18.1%)
Operation: CABG, n (%)	38 (36.2%)
Operation: combined, n (%)	48 (45.7%)
Aortic cross-clamp (min) median ± IQR	84.50±54.50
CBP time (min) edian ± IQR	112.00±65.00
Post-operative outcomes	
ICU stay (days) median ± IQR	6.00±2.00
Cardiac complications, n (%)	57(54.3%)
Neurological complications, n (%)	3 (2.9%)
Infection, n (%)	4(3.8%)
Respiratory complications, n (%)	11(10.5%)
Acute renal failure, n (%)	3 (2.9%)
Prolonged ventilation, n (%)	11, (10.6%)
Inotropic support, n (%)	77 (73.3%)
Reintervention, n (%)	7 (6.7%)

Note: AVR: aortic valve replacement; CABG: coronary artery bypass.

and C viruses infected. Several risk factors affecting cardiac function were assessed: hypertension (n = 68, 66.7%), diabetes mellitus (n = 15, 14.3%), COPD (n=13, 12.5%), dyslipidemia (n = 31, 29.5%), arrhythmia (n = 45, 42.9 %), overweight (n = 39, 37.1%), and obesity (n = 24, 22.9%). 11 patients (10.6%) had previously documented stroke and myocardial infarction and 42 (40.4%) patients were current smokers.

We, then, evaluated hepatic function by measuring several key parameters. Blood creatinine (median ± IQR) was 0.97 ± 0.48 mg/dL, bilirubin (median ± IQR) was 1.00 ± 0.52 mg/dL. The INR (median ± IQR) was 1.17 ± 0.33 and the ejection fraction (median ± IQR) was 55.00 ± 10.00. As a result, the MELD score (median ± IQR) was 10.0 ± 6.00, and MELD-XI score (median ± IQR) 8.91 ± 5.70 for those who were on anticoagulants. And the EuroSCORE score (median ± IQR) was 1.66% ± 1.60%.

Basic Patient Parameters During and After Surgery

Patients' characteristics during and after surgery are listed in Table II. After evaluating the basal cardiac functions, all patients who have undergone elective surgery with isolated aortic valve replacement (AVR) (n=19, 18.1%), coronary artery bypass (CABG) (n=38, 36.2%) and combined (AVR/CABG) (n=48, 45.7%). The aortic cross-clamp time (median ± IQR) was 84.50±54.50 minutes and the CBP time (median ± IQR) was 112.00±65.00 minutes.

The post-operative outcomes were cardiac complications (n=57, 54.3%), neurological complications (n=3, 2.9%), infection (n=4, 3.81%), acute renal failure (n=3, 2.9%) and respiratory complications (n=11, 10.5%). The ICU stay (median ± IQR) was 6.00±2.00 days. At meanwhile, 11 patients (10.6%) were required to prolong the mechanical ventilation of more than 24 hrs and 77 patients (73.3%) needed inotropic support in the ICU; finally, 7 patients (6.7%) demanded re-interventions, mainly for post-operative bleeding.

Pre-operative Factors and Total Post Surgery Complications

The univariate analysis results of pre-operative factors related to the operative morbidity are presented in Table III. No significant differences were found in terms of age (OR 1.01, 95% CI 0.97-1.04, p = 0.75), gender (OR 0.47, 95% CI 0.20-1.10, p = 0.0), creatinine levels (OR 1.10, 95% CI 0.82-1.46, p = 0.53), INR (OR 1.31, 95% CI 0.86-1.99, p = 0.21), ejection fractions (OR 1.00, 95% CI 0.98-1.03, p = 0.76), MELD scores (>15 vs. <15) (OR 2.20, 95% CI 0.73-6.62, p = 0.16), MELD XI scores (OR 1.07, 95% CI 1.00-1.14, p = 0.06), MELD XI (>7 vs. <7) (OR 1.54, 95% CI 0.69-3.42, p = 0.29), and EuroSCORE (OR >999.99, 95% CI <0.001->999.999, p = 0.14). Significant differences in MELD score (OR 1.09, 95% CI 1.00-1.19, p = 0.04), bilirubin (OR 3.34, 95% CI 1.18-9.46, p = 0.02) and smoking (OR 0.42, 95% CI 0.19-0.94, p = 0.04) were observed when patients with post-operative morbidity were compared with patients without post-operative morbidity.

Pre-operative co-morbidity and Total Post Surgery Complications

Univariate analysis of pre-operative co-morbidity related to operative morbidity was performed and the results are presented in Table IV, from which, we can see that there were no significant differences in diabetes (OR 0.69, 95%CI 0.23-2.09, p = 0.52), dyslipidemia (OR 0.58, 95%CI 0.25-1.35, p = 0.21), BMI (continuous variables) (OR 1.01, 95%CI 0.93-1.09, p = 0.90), BMI (≥30 vs. <25) (OR 1.03, 95% CI 0.36-2.89, p = 0.14), BMI (25-30 vs. <25) (OR 0.89, 95% CI 0.36-2.16, p = 0.95), hypertension (OR 1.85, 95% CI 0.82-4.20, p = 0.14), COPD (OR 4.05, 95% CI 0.85-19.30, p = 0.08), stroke history (OR 7.41, 95% CI 0.91-60.24, p = 0.06), hepatitis C infection (vs. hepatitis B infection) (OR 2.06, 95% CI 0.92-4.62, p = 0.08), hepatitis B and C

Table III. Pre-operative factors and total post surgery complications

Factors		Morbidity YES (N=64)	Morbidity NO (N=41)	Crude OR (95% CI)	p
Age (mean ± SD)		58.42±11.23	57.73±10.79	1.01 (0.97-1.04)	0.7530
Gender	Female	28 (43.7)	11 (26.8)	1.0	0.0827
	Male	36 (56.3)	30 (73.2)	0.47 (0.20-1.10)	
Smoking	NO	43 (67.2)	19 (46.3)	1.0	0.0357
	YES	21 (32.8)	22 (53.7)	0.42 (0.19-0.94)	
Creatinine, (mg/dL)		2.03±6.17	1.16±1.25	1.10 (0.82-1.46)	0.5281
INR		1.75±1.54	1.39±0.79	1.31 (0.86-1.99)	0.2058
Bilirubin, (mg/dL)		1.35±0.83	0.98±0.35	3.34 (1.18-9.46)	0.0231
Ejection Fraction		52.66±15.09	51.74±15.88	1.00 (0.98-1.03)	0.7632
MELD		12.98±7.15	10.21±3.87	1.09 (1.00-1.19)	0.0408
MELD	<15	49 (76.6)	36 (87.8)	1.0	
	≥15	15 (23.4)	5 (12.2)	2.20 (0.73-6.62)	0.1590
MELD XI	11.59±8.79	8.26±5.87	1.07 (1.00- 1.14)	0.0580	
MELD XI	<7	23 (35.9)	19 (46.3)	1.0	0.2884
	≥7	41 (64.1)	22 (53.7)	1.54 (0.69-3.42)	
Euro SCORE		0.022±0.017	0.017±0.014	>999.999 (<0.001->999.999)	0.1441

Note: CAD: coronary artery disease; MELD: model for end-stage liver disease; COPD: chronic obstructive pulmonary disease; EuroSCORE: European System for Cardiac Operative Risk Evaluation.

infection (vs. hepatitis B infection) (OR 0.96, 95% CI 0.06-16.27, $p = 0.97$), myocardial infarction history (OR 0.75, 95% CI 0.21-2.62, $p = 0.65$), valve disease (vs. CAD) (OR 1.89, 95% CI 0.81-4.39, $p = 0.14$) when comparing patients who were subject to post-operative morbidity with those who were not. Nevertheless, there were significant differences in valve/CAD (vs. CAD) (OR 13.33, 95% CI 1.57-112.98, $p = 0.02$), and arrhythmia (OR 2.57, 95% CI 1.12-5.91, $p = 0.02$) in patients who had post-operative morbidity compared to those who had not.

Factors During Surgery and Total Post Surgery Complications

A univariate analysis of factors during surgery related to operative morbidity was conducted. The results of this analysis are presented in Table V. Significant differences were observed in aortic cross-clamp time (OR 1.01, 95% CI 1.00-1.03, $p = 0.03$), CBP time (OR 1.01, 95% CI 1.00-1.02, $p = 0.04$), CABG/AVR (vs. CABG) (OR 3.74, 95% CI 1.48-9.44, $p = 0.01$), but not in AVR (vs. CABG) (OR 1.00, 95% CI 0.33-3.01, $p = 1.00$) when comparing patients who were subject to post-operative morbidity with those who were not.

Multivariate Analysis of Factors Related to Morbidity After Cardiac Surgery

Multivariate logistic regression analysis was performed to identify the risk factors for morbidity. The OR was calculated by adjusting other variables except itself. Variables entering into the model included those risk factors with significant or near significant ($p < 0.2$) influence on hospital morbidity and consisted of valve (vs. CAD) (OR 3.48, 95% CI 1.10-11.00, $p = 0.03$), valve/CAD (vs. CAD) (OR 12.27, 95% CI 1.37-109.77, $p = 0.02$), aortic valve replacement (AVR) (vs. CABG) (OR 0.26, 95% CI 0.07- 0.98, $p = 0.047$), and bilirubin (mg/dl) (OR 3.63, 95% CI 1.05-12.49, $p = 0.04$) (Table VI).

Discussion

Approximately 4 million people in the USA live with chronic hepatitis virus infection[20-22]. Among them, hepatitis B and C virus are the most common types. Because of its high prevalence, cardiac surgeries in the patients with hepatitis virus infection are feasible now and inevitable in the future. Utill et al[23] examined the possibility to treat hepatitis C virus infection with

Table IV. Pre-operative co-morbidity and total post surgery complications

Factors		Morbidity YES (N=64)	Morbidity NO (N=41)	Crude OR (95% CI)	p
Diabetes mellitus	NO	56 (87.5)	34 (82.9)	1.0	0.5150
	YES	8 (12.5)	7 (17.1)	0.69 (0.23-2.09)	
Dyslipidemia	NO	48 (75.0)	26 (63.4)	1.0	0.2064
	YES	16 (25.0)	15 (36.5)	0.58 (0.25-1.35)	
BMI (continuous variables)	26.53±4.95	26.41±4.55	1.01 (0.93-1.09)	0.9004	
BMI	<25	26 (40.6)	16 (39.0)	1.0	0.9492
	25-30	23 (35.9)	16 (39.0)	0.89 (0.36-2.16)	
	≥30	15 (23.4)	9 (22.0)	1.03 (0.36-2.89)	
HTA	NO	19 (29.7)	18 (43.9)	1.0	0.1389
	YES	45 (70.3)	23 (56.1)	1.85 (0.82-4.20)	
COPD	NO	53 (82.8)	39 (95.1)	1.0	0.0795
	YES	11 (17.2)	2 (4.9)	4.05 (0.85-19.30)	
Stroke	NO	54 (84.4)	40 (97.6)	1.0	0.0611
	YES	10 (15.6)	1 (2.4)	7.41 (0.91-60.24)	
Hepatitis	B	22 (34.4)	21 (51.2)	1.0	
	C	41 (64.1)	19 (46.3)	2.06 (0.92-4.62)	0.0798
	B+C	1 (1.6)	1 (2.4)	0.96 (0.06-16.27)	0.9743
Myocardial	NO	36 (87.8)	58 (90.6)	1.0	0.6453
infarction	YES	5 (12.2)	6 (9.4)	0.75 (0.21-2.62)	
Type of disease	CAD	18 (28.1)	20 (48.8)	1.0	
	Valve	34 (53.1)	20 (48.8)	1.89 (0.81-4.39)	0.1392
	Valve+ CAD	12 (18.8)	1 (2.4)	13.33 (1.57-112.98)	0.0175
Arythmia	YES	33 (51.6)	12 (29.3)	1.0	0.0243

Note: COPD: chronic obstructive pulmonary disease.

pegylated interferon and Ribavirin in heart transplantation patients, which showed encouraging results although the number of patients used in the study was small. Our results showed that the main post-operative complications for patients with chronic viral hepatitis after cardiac surgery were cardiac complications (54.3%), which is consistent with another study[24] which showed that cardiac complications were the main post-operative complications for patients with liver disease. However, two other studies showed that renal complications were the post-operative complications found in patients with liver disease[25,26]. Another report showed that hepatic complications were the main post-operative complications for patients with liver disease[27]. However, regardless of the main complication for patients with liver disease that have undergone cardiac surgery, the post-operative complication rate was very high. The MELD score (median ± IQR) was 10.0 ± 6.00, and MELD-XI score (median ± IQR) was 8.91±5.70 for those who used anticoagulants. The results indicate that the patients in this study were of low or moderate liver dysfunction. In spite of this, our work confirms that the post-operative complication rate was very high in patients with hepatitis virus infection. Therefore, the control of hepatitis virus infection before surgery was very important in order to prolong the survival of patients and reduce hospital morbidity.

A univariate analysis of factors related to post-operative morbidity showed significant differences between MELD score, bilirubin and smoking, valve/CAD (*vs.* CAD), and arrhythmia, aortic cross-clamp time, CBP time, CABG/AVR (*vs.* CABG) when comparing patients who were subject to post-operative morbidity with those who were not. These findings indicate that these factors may affect the post-operative complications for patients with hepatitis virus infection who have undergone the cardiac surgery. However, these factors may be influenced by other variables. Consequently, a multivariate logistic re-

Table V. Factors during surgery and total post-surgery complications.

Factors	Morbidity		Crude OR (95% CI)	p
	YES (N=64)	NO (N=41)		
Aortic cross-clamp	98.42±37.93	80.78±36.94	1.01 (1.00-1.03)	0.0256
CBP time	136.78±48.03	115.75±53.09	1.01 (1.00-1.02)	0.0446
Type of operation CABG	18 (28.1)	20 (48.8)	1.0	
AVR	9 (14.1)	10 (24.4)	1.00 (0.33-3.01)	1.0000
combined	37 (57.8)	11 (26.8)	3.74 (1.48-9.44)	0.0053

Note: AVR: aortic valve replacement; CABG: coronary artery bypass

gression analysis was used to find independent risk factors for morbidity. Our analysis showed that only disease types (valve, valve/CAD), aortic valve replacement and bilirubin were independent risk factors for morbidity, which implied that the diseases, the surgical types and the level of bilirubin could affect the post-operative morbidity in patients with hepatitis virus infection.

The EuroSCORE is the best quantitative system to assess the surgical risk factors and provide sound predictions of outcomes[28,29]. However, liver dysfunction was not taken into account in the EuroSCORE formula, despite the well-established impact of hepatic dysfunction on cardiac performance based on available studies about advanced liver dysfunction[13,30]. In the current work, we evaluated the results of cardiac surgery in viral hepatitis patients to find predictors of outcomes and to assess the relevance of the MELD score in the prediction of surgical morbidity. We've found that disease types (valve, valve/CAD), aortic valve replacement and bilirubin were independent risk factors for morbidity. Our results also implied that MELD scores may affect hospital morbidity based on univariate analysis. As to whether the liver dysfunction could affect post-operative morbidity in patients with hepatitis virus infection, our univariate analysis showed that liver dysfunction may affect the post-operative morbidity in patients with hepatitis virus infection. Most studies showed that liver dysfunction could affect the post-operative morbidity in patients with cirrhosis[8,11,24,25,27,31-33], which has been confirmed by our univariate analysis; thus we thought the liver dysfunction could be added to the available models to predict the hospital morbidity for patients with hepatitis virus infection who underwent cardiac surgery.

Conclusions

The results of the present report show that the rate of post-operative complications following cardiac surgery is higher in patients with hepatitis virus infection compared with control patients. In addition, this study has found that disease types including valve, valve/CAD, aortic valve replacement and bilirubin are independent risk factors for morbidity and may affect post-operative morbidity rates in patients with hepatitis virus infection. In addition, the univariate analysis showed that liver function as classified by MELD may affect post-operative morbidity in

Table VI. Multivariate analysis of factors related to morbidity after cardiac surgery.

Factors	Wald Chi-Square	Adjusted OR (95% CI)	p value
Valve (vs. CAD)	4.4957	3.48 (1.10-11.00)	0.0340
Valve+CAD (vs. CAD)	5.0317	12.27 (1.37-109.77)	0.0249
Aortic valve replacement (AVR) (vs. CABG)	3.9340	0.26 (0.07- 0.98)	0.0473
Bilirubin, (mg/dl)	4.1749	3.63 (1.05-12.49)	0.0410

Adjusted by other variables except itself.
Note: CAD: coronary artery disease; AVR: Aortic valve replacement

patients with hepatitis virus infection. This indicates that liver dysfunction should be added to available surgical risk assessment models so as to predict the hospital morbidity for patients with hepatitis virus infection who have undergone cardiac surgery based on our univariate analysis. Future multi-center researches with an increased sample number are required to validate the results of this study.

Financial Disclosure

We declare there is no financial disclosure.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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