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Reflected Shadows of Chronic Hepatitis C Virus Infection on its Victims Undergoing Coronary Artery Bypass Grafting Surgery: 10-Years' Experience

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ABSTRACT

Background: Due to the improvement of the treatment lines for the victims of chronic hepatitis C viral (HCV) infection, more survivors elapsed and a larger cohort of patients undergoing coronary artery bypass grafting (CABG) surgery is frequently operated upon. Their hepatic condition represents a surgical challenge because of the higher risk of postoperative complications and mortality.

Objective: This study aimed to trace the impact of chronic HCV infection in patients undergoing CABG in the immediate postoperative period and to identify the predictive risk factors involved in the worse outcomes.

Patients and Methods: This retrospective comparative study included 421 patients presented with ischemic heart disease (IHD) and operated upon by CABG. They were divided into group (A) including chronic HCV infection (196) patients while group (B) including the "free" of HCV infection (225) patients.

Results: Multivariable logistic regression analysis showed that higher model for end-stage liver disease (MELD) score (OR: 3.140 (95% CI: 1.025-10.964); p= 0.019), lower preoperative platelets count (OR: 3.650 (95% CI: 1.166-12.778); p= 0.023), higher preoperative total bilirubin (OR: 1.256 (95% CI: 1.035-1.859); p= 0.021), higher preoperative creatinine (OR: 0.528 (95% CI: 0.345-1.012); p= 0.028) and prolonged cardiopulmonary bypass (CPB) time (OR: 1.145 (95% CI: 0.985-1.925); p= 0.020) were the significant predictors of postoperative morbidity and higher MELD score (OR: 3.220 (95% CI: 1.198-9.130); p= 0.018) and intraoperative blood transfusion (OR: 3.201 (95% CI: 1.595-6.411); p= 0.020) were the significant predictors of perioperative mortality.

Conclusion: Identification and careful evaluation of the predictive risk factors may reduce serious post-surgical adverse outcomes. Greater careful consideration should be offered to patients with preoperative high MELD score, low platelets count, high total bilirubin and high creatinine. We recommend using the MELD score as a risk model in this subset of patients in prediction of the postoperative morbidity and mortality along with the currently used ones, which should involve hepatic dysfunction in its risk scoring system.

Key words: Chronic HCV infection, CABG, HCV.

INTRODUCTION

Viral hepatitis represents a serious national and international medical dilemma. One of the most prevalent and important etiological agents is HCV. It's a member of the Flaviviridae family [(1)]. Its prevalence is 2.5-3 % worldwide. It causes chronic hepatitis C viral infection (chronic HCV infection) with consequent hepatic fibrosis, cirrhosis, liver cell failure and lethal hepatocellular carcinoma and mortality in 175 million people globally [(2)]. Almost 50 % of the deaths assumed to be due to viral hepatitis, which is termed as the seventh leading cause of death worldwide [(3)] and is due to HCV [(4)].

Egypt has HCV infection rates higher than the worldwide ones [(5)]. According to Egypt Demographic and Health Surveys (EDHS) in 2009, it was 14.7 % in 15–59 years citizens and 18 % in rural inhabitants [(6)], and the rate declined to 10 % in 2015 [(7)]. It isn't only the liver that is affected by the chronic HCV infection but also there are multiple extrahepatic affections. The list includes atherosclerosis and cardiovascular disease including coronary (ischemic) heart disease (IHD), carotid artery disease and cerebral strokes. It's also associated with diabetes mellitus (DM), insulin resistance and kidney diseases [(8)].

Although there is much controversy among the reported data concerning the risk of chronic HCV infection as an independent factor initiating the process of atherosclerosis [(9, 10)], different mechanisms were demonstrated explaining its active role. Recent reports suggest both direct and indirect mechanisms. Direct pathway is explained on the basis of vascular wall chronic viral infection, inflammation, direct viral invasion and colonization of the wall plaque and endothelial dysfunction. The indirect pathway is claimed to be a metabolic process via chronic HCV infection interference with both lipid and sugar metabolism resulting in insulin resistance, DM type 2 and hepatic steatosis, which are risk factors of atherosclerosis [(11)].

The proatherogenic effect of chronic HCV infection of the vascular atherosclerotic plaque on the endothelial cells, smooth muscle cells, monocytes, macrophages, and T cells has been proved. Also,

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hepatic steatosis, which is more prevalent in chronic HCV infection patients, is associated with endothelial dysfunction and increased inflammatory mediators [(12)]. Again, it's proved that chronic HCV infection causes chronic stimulation of the immune system liberating different immune mediators and pro-inflammatory cytokines (like fibrinogen, C-reactive protein, interleukin-6 and tumor necrosis factor alfa) resulting in chronic vascular wall inflammation and progressive atherosclerosis [(13)].

Due to the improvement of the treatment lines for the victims of chronic HCV infection, more survivors elapsed and a larger cohort of patients undergoing CABG surgery is frequently operated upon. Their hepatic condition represents a surgical challenge because of the higher risk of complications like bleeding, wound infection and impairment of multiple organs including the kidney, heart and lungs [(14)]. Postoperative hepatic dysfunction is a catastrophic lethal scenario. It's mainly related to cardiopulmonary bypass (CPB) which causes endotoxemia due to injured intestinal mucosa as a result of discrepancy in oxygen supply in the hepatosplanchnic region [(12)].

In respect to the postoperative complications, scoring of chronic HCV infection patients to truly predict the possible adverse events and mortality can be achieved by the model for end-stage liver disease (MELD) score or the Child–Turcotte–Pugh (CTP) classification although -unfortunately- cardiac risk scoring systems whether European System for Cardiac Operative Risk Evaluation (EuroSCORE) II or the Society of Thoracic Surgeons (STS) score don't include the hepatic dysfunction into account [(12)].

This study aimed at tracing the impact and adverse effects of chronic HCV infection in patients undergoing CABG in the immediate postoperative period and to identify the possible accused predictors (risk factors) involved in the worse outcomes.

PATIENTS AND METHODS

Study design

This retrospective comparative study included 421 patients who presented with IHD. They had been operated upon by primary surgical myocardial revascularization (CABG). They were divided into two groups: Group (A) included the "documented" chronic HCV infection (196) patients, while group (B) included the "free" of HCV infection (225) patients. All surgeries were carried out in the operating theatre of the Department of Cardiothoracic Surgery, Faculty of Medicine, Cairo University, that of Beni-Suef University and in El Borg Hospital, Mohandiseen, Giza using standard open-heart surgical procedures. Data of the study were collected for the operated-upon patients in the period between November 2012 and February 2023 from the computer database of the cardiothoracic sections, with the addition of a study of hospital records. In the preoperative, intraoperative, and immediately postoperative phases, all the data were carefully examined**.**

Inclusion criteria: Adult patients with multi-vessel coronary artery disease (CAD), left main or left main-equivalent CAD who were planned for elective primary CABG surgery were included in the study. According to the Canadian Cardiovascular Society's (CCS) classification of angina pectoris, they had anginal pain of degree III.

Exclusion criteria: Patients who required surgical intervention for other pathologies such as mitral valve disease, aortic valve disease, tricuspid valve disease, ascending aortic aneurysm/dissection, left ventricular aneurysm, and ventricular septal defects. The research did not include re-do situations. Patients with hepatocellular carcinoma, acute fulminant hepatitis, MELD scores more than 20, and liver disorders other than HCV infection were also disqualified.

Management protocol:

(1) Preoperatively:

The assessed preoperative variables included age, gender, risk factors of cardiovascular disease e.g. hypertension, smoking, DM, dyslipidemia, post-menopause, and family history of susceptibility to IHD, previous myocardial infarction (MI) and history of cardiac care unit (CCU) admission, history of coronary angioplasty and stenting, chronic obstructive pulmonary disease (COPD), atrial fibrillation (AF), chronic renal disease (defined as a creatinine clearance < 30 ml/min), previous cerebrovascular accidents (CVAs), peripheral vascular disease (defined as the presence of lower limb arterial disease stage I or II according to Leriche and Fontaine classification or a history of vascular surgery), body surface area (BSA)(m^2) and HCV infection and treatment history.

Routine preoperative laboratory investigations including complete blood count (CBC), liver and renal function tests, coagulation profile, serum electrolytes (sodium and potassium), and fasting blood glucose (FBG). Resting 12-lead electrocardiogram (ECG), plain chest X-ray, cardiac catheterization [with estimation of the severity of the CAD lesions using the Gensini score [(15)]] and preoperative baseline transthoracic echocardiography (TTE). By calculating the EuroSCORE II, STS, and MELD scores, risk was assessed. Clopidogril, clexane, and acetylsalicylic acid were stopped 5 days, 12 hours, and 5-7 days before surgery, respectively. All patients were given oral valium in dosages of 5 mg the night before surgery and 10 mg of morphia via injection in the morning.

(2) Intraoperatively:

The assessed operative variables included intraoperative mortality, aortic cross clamping time, CPB time, total operative time, total hemostasis time, number of grafts done, blood glucose level (during and after CPB), metabolic acidosis, hemodynamics, difficulty of weaning off CPB, inotropic support demands, need for intra-aortic balloon pump (IABP) insertion, blood transfusion requirements and post CPB assessment of CBC, liver and renal function tests and coagulation profile.

(3) Conduction of Anesthesia and Operative Technique:

Midazolam 0.03–0.05 $mg.kg^{-1}$, fentanyl 1-2 $mcg.kg^{-1}$, and propofol 1-2 mg.kg-1 were used to produce general anesthesia. Atracurium 0.5 $mg.kg^{-1}$ was used to assist orotracheal intubation. Sevoflurane titrated to an expired minimum alveolar concentration (MAC) between 1-1.5 and a continuous infusion of morphine at 10 to 20 $mcg.kg^{-1}.h^{-1}$ were used to maintain anesthesia. Atracurium and fentanyl dosages were increased as necessary. If hemodynamic instability was detected, it was treated with intravenous bolus doses of fluids, table positioning, and/or norepinephrine boluses of 4–8 mcg per dosage. Hemodynamic instability is defined as systolic blood pressure less than 90 mmHg and/or mean arterial blood pressure less than 60 mmHg. The patients underwent frequent arterial blood gases (ABGs) measurements for pH, electrolytes, and glucose every 15 minutes, as well as frequent ECG monitoring, invasive arterial blood pressure measurement using an arterial catheter connected to a pressure transducer, central venous catheter inserted in the internal jugular vein, nasopharyngeal temperature probe, pulse oximetry, capnography, and urinary catheter. In order to maintain blood glucose levels between 110 and 150 mg/dl, diabetic patients underwent intraoperative tight (strict) glycemic management using a standard intravenous insulin infusion regimen (made by combining 100 units of insulin with 50 ml of 0.9% normal saline).

Heparin (300–400 IU/kg) was administered in the beginning to start the anticoagulation process and subsequent doses were given as needed to keep the active clotting time (ACT) over 400 s throughout the bypass period. Regardless of the overall amount of heparin used, protamine chloride reversed heparin at the conclusion of CPB at a 1:1 ratio of the loading dose. For the whole study population, the operational methodology remained same. The ascending aorta was cross clamped, all patients underwent conventional vertical median sternotomies, warm blood intermittent antegrade cardioplegia was administered every 20 minutes, and CPB was started using aorto-caval cannulation. Priming volumes were usually kept at a minimum of 800-1000 ml. 30-32°C was the average body temperature during CPB. The target mean arterial pressure was set at 60 mmHg, and the pump flow was intended to be between 2.0 and 2.8 $L/min/m^2$. First, 7/0 monofilamentous sutures were used to anastomose the harvested reversed saphenous vein grafts (SVGs) to additional target coronaries in a direct continuous manner. The harvested pedicled left internal thoracic artery (LITA) was then anastomosed to the left anterior descending (LAD) coronary artery using direct continuous 7/0 monofilamentous sutures. After administering a hot shot dosage and unclamping the ascending aorta in order to restore myocardial activity, proximal anastomoses were performed on a beating heart. These procedures involved direct continuous clamping of the partial aortic side occlusion using 6/0 monofilamentous sutures.

(4) Postoperatively:

The assessed postoperative variables included the intensive care unit (ICU) parameters (duration of mechanical ventilation, duration of inotropic support, total blood loss, blood products (packed red blood cells, platelets and fresh frozen plasma) transfusion, blood glucose level, daily laboratory investigations, total duration of ICU stay), immediate postoperative mortality, various adverse complications during hospital stay including MI, coagulopathy, micro-embolization and CVAs, pulmonary embolism, peripheral arterial/venous thromboembolism, low cardiac output syndrome, rhythmic complications, bleeding complications and blood transfusion requirements, pulmonary complications, acute renal failure, deep and superficial wound infections, total hospital stay and routine postoperative TTE. Based on the number of patients who experienced at least one hospital problem, the total hospital complications rate was determined. A new Q wave within 48 hours of surgery or a vanished R wave on the postoperative ECG were also considered signs of perioperative MI, as were creatinine kinase-MB levels that were 5 or more times over the upper limit of normal. A transient ischemic attack (TIA) or a new-onset stroke that lasted for at least 24 hours was considered a CVA. The necessity for two catecholamines >10 mcg/Kg/min was used to characterise low cardiac output syndrome. Any death occurring within the first 30 days after surgery was referred to as perioperative mortality. The existence of a supraventricular, nodal, or ventricular rhythm abnormality was used to characterise rhythmic problems.

Re-exploration to stop bleeding or alleviate cardiac tamponade was used to characterise bleeding problems. The onset of pneumonia, pulmonary atelectasis, and respiratory failure (defined as prolonged mechanical ventilation > 48 hours postoperatively, re-intubation, or tracheostomy) were considered to be pulmonary complications. A spike in creatinine levels (absolute 0.3 mg/dl, percentage 50%) indicating the requirement for renal replacement treatment or for dialysis sessions was deemed to indicate acute renal failure. A surgical

infection within 30 days that spreads beyond the deep tissue plane and has bacteriological samples of positive infected tissues or purulent discharge was described as a deep wound infection. Major morbidity was characterised as any of the following: pulmonary problems, renal failure, deep sternal wound infection, necessity for reoperation, and permanent stroke. When required, platelets and freshly frozen plasma were administered. When a platelet count was less than 70 x $10^3/mm^3$, platelet transfusion was performed [(14)]. According to the STS recommendations, transfused packed red blood cells were employed [(16)].

Ethical Approval:

The investigation was carried out in the operating rooms for cardiothoracic surgery at Cairo University, Beni-Suef University and El Borg Hospital. The study was approved by the Research Ethical Committee (REC) with approval number of FMBSUREC/09042023/Elbatanony. To participate in the study, each patient signed a written informed permission form. The conduction of this study was guided by the Helsinki Declaration for human studies.

Statistical analysis

Using SPSS V. 22.0, the collected data were arranged, tabulated, and statistically analysed. Frequency and percent distributions for qualitative data were computed using the relevant Chi-square test or Fischer's exact test. The t-student test was used to compare mean ± standard deviation (SD), minimum and maximum values for quantitative data. The Spearman's rank correlation coefficient was used to determine the correlation between the parameters. To identify the factors influencing postoperative in-hospital morbidity and perioperative death, multivariable logistic regression analysis was utilised. P values were regarded as significant in all tests when $p < 0.05$.

RESULTS

Preoperative Data:

The study population included 421 patients. Their ages ranged from 43 to 75 years with a median age of 57.5 years. They were 231 (54.87%) males and 190 (45.13%) females. 196 (46.55%) patients represented the HCV group (A) with a mean MELD score of 12.32 ± 1.67, and 225 (53.44%) patients represented the non-HCV group (B). All patients were preoperatively in CCS grade III. Group (A) showed statistically significant differences regarding Gensini score, platelet count, creatinine, international normalized ratio (INR), total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), prothrombin concentration (PC) and partial thromboplastin time (PTT). Differences in hematocrit, gamma-glutamyl transferase (GGT) and albumin were close to significance. However, group (B) showed statistically significant differences as regards hypertension and DM. 37 (8.79%) in both groups needed preoperative IABP insertion for hemodynamic instability (Table 1).

Table (1): Preoperative baseline characteristics

	Group (A)	**Group (B)**	***p* value**
Age (years)	62.45±5.77	61.41±6.21	0.846
Male/Female (%)	109/87 (55.61/44.39%)	122/103 (54.22/45.77%)	0.798
Hypertension (%)	77(39.28%)	137(60.89%)	**0.001**
Smoking (%)	92(46.94%)	100(44.44%)	0.715
DM (%)	74(37.75%)	132(58.67%)	**0.001**
Mean HbA1C (%)	7.92±1.35	7.74±1.16	0.255
Mean FBG (mg/dl)	136.74±32.21	133.45±28.31	0.862
Dyslipidemia (%)	106(54.08%)	119(52.89%)	0.708
Post-menopause (%)	81(41.33%)	95(42.22%)	0.866
Family history of susceptibility to IHD (%)	42(21.43%)	47(20.88%)	0.868
Previous MI (%)	141(71.94%)	159(70.67%)	0.870
Previous CCU admission (%)	136(69.39%)	157(69.78%)	0.923
Previous coronary angioplasty and stenting (%)	103(52.55%)	121(53.77%)	0.814
COPD (%)	16(8.16%)	19(8.44%)	0.934
AF (%)	71(36.22%)	85(37.77%)	0.798
Chronic renal disease (%)	29(14.79%)	16(7.11%)	0.246
Previous CVAs (%)	22(11.22%)	26(11.55%)	0.933
Peripheral vascular disease (%)	15(7.65%)	14(6.22%)	0.806
Mean BSA (m^2)	1.8±0.45	1.7±0.23	0.451
Mean EuroSCORE II (%)	7.69±8.85	7.33±6.20	0.210
Mean STS score (%)	8.51±6.34	8.22±5.63	0.324
Preoperative IABP insertion (%)	19(9.69%)	18(8%)	0.809
Mean LVEF%	54.25±2.56	55.93±2.37	0.689
LM or LM-equivalent CAD (%)	56(28.57%)	68(30.22%)	0.665
Less than 3 CAD (%)	28(14.29%)	23(10.22%)	0.598
Three or more CAD (%)	168(85.71%)	202(89.78%)	0.598
Mean Gensini score	73.25±6.12	64.35±3.69	**0.010**
Mean Hb (gm/dl)	9.41±1.92	12.11±1.56	0.074
Mean hematocrit (%)	29.25±5.51	36.45±4.74	0.050
Mean platelet count ($x10^3/mm^3$)	150.65±20.58	249.51±57.36	**0.001**
Mean total bilirubin (mg/dl)	1.47±0.35	1.01±0.04	**0.011**
Mean ALT (U/l)	65.32±16.21	25.10±6.11	**0.048**
Mean AST (U/l)	63.11±15.63	24.25±5.98	**0.048**
Mean AST/ALT ratio	0.96±0.21	0.96±0.20	0.981
Mean ALP (U/l)	98.54±24.40	34.89±8.61	**0.035**
Mean GGT (U/l)	29.33±7.12	22.87±5.61	0.050
Mean LDH (U/l)	314.71±58.21	291.33±50.76	0.646
Mean albumin (g/dl)	3.25±0.36	3.65±0.87	0.050
Mean creatinine (mg/dl)	1.58±0.22	0.57±0.13	**0.001**
Mean urea (mg/dl)	39.41±9.77	32.30±7.89	0.168
Mean PC (%)	75.88±4.41	86.23±9.87	**0.043**
Mean PTT (sec)	39.78±8.56	27.56±5.25	**0.024**
Mean INR	1.60±0.38	0.9±0.09	**0.001**
Mean Na^+(mmol/l)	135.84±4.48	138.28±4.69	0.864
Mean K^+(mmol/l)	4.24±0.86	4.41±0.54	0.876

DM: diabetes mellitus; HbA1C: hemoglobin A1C; FBG: fasting blood glucose; IHD: ischemic heart disease; MI: myocardial infarction; CCU: cardiac care unit; COPD: chronic obstructive pulmonary disease; AF: atrial fibrillation; CVAs cerebrovascular accidents; BSA: body surface area; EuroSCORE II: European System for Cardiac Operative Risk Evaluation; STS: Society of Thoracic Surgeons; IABP: intra-aortic balloon pump; LVEF%: left ventricular ejection fraction per cent; LM: left main; CAD: coronary artery disease; Hb: hemoglobin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: Gamma-glutamyl transferase; LDH: lactate dehydrogenase; PC: prothrombin concentration; PTT: partial thromboplastin time; INR: international normalized ratio; Na^+: sodium; K^+: potassium.

Operative Data:

Group (A) showed statistically significant differences as regards total operative time, CPB time, total surgical hemostasis time, post CPB fresh blood transfusion, total platelets count, ALP, creatinine, INR, central venous pressure (CVP), total bilirubin, hematocrit, ALT, AST, GGT, PC and PTT. Differences in albumin were close to significance. Group (A) expressed longer aortic cross clamping time, less rates of smooth weaning off CPB and more rates of electrical cardioversion to achieve weaning off it but with statistically insignificant differences. There was no intraoperative mortality in either group. Metabolic acidosis was corrected efficiently prior to transferring the patients to ICU and none had faced persistent acidosis. All the patients received adrenaline infusion 5 mcg/kg/min as a supportive physiological dose for the initial 24 hours postoperatively. To control diabetic vasculopathy, noradrenaline infusion 5-10 mcg/kg/min was further added (Table 2).

Table (2): Operative data.

	Group (A)	**Group (B)**	***p* value**
Mean total operative time (min)	199.46±26.56	164.84±23.45	**0.001**
Mean total CPB time (min)	128.18±16.43	97.56±14.89	**0.021**
Mean total aortic cross clamping time (min)	58.54±8.32	50.23±9.78	0.641
Mean total surgical hemostasis time (min)	53.23±1.96	30.66±0.35	**0.001**
Three or more coronary artery targets (%)	168 (85.71%)	202 (89.78%)	0.598
Less than three coronary artery targets (%)	28 (14.29%)	23 (10.22%)	0.598
Smooth weaning off CPB (%)	174 (88.77%)	206 (91.55%)	0.641
Electrical cardioversion (%)	22 (11.22%)	19 (8.44%)	0.524
Mean blood glucose (during CPB) (mg/dl)	185.61±18.11	186.51±21.51	0.875
*Mean blood glucose (mg/dl)	132.36±17.64	134.56±19.09	0.867
Metabolic acidosis (%)	89 (45.41%)	94 (41.78%)	0.785
Mean ABP (pre CPB) (mmHg)	91.58±11.24	91.11±12.35	0.958
*Mean ABP (mmHg)	89.98±12.56	89.64±12.79	0.965
Mean CVP (pre CPB) (cmH_2O)	13.47±3.10	12.12±3.01	0.213
*Mean CVP (cmH_2O)	14.56±3.51	13.54±1.32	**0.011**
Mean body temperature (pre CPB) (°C)	36.78±0.15	36.37±0.17	0.809
*Mean body temperature (°C)	36.58±0.32	36.29±0.27	0.811
Mean PaO_2 (pre CPB) (%)	400.51±61.12	416.22±64.02	0.568
*Mean PaO_2 (%)	358.25±75.48	387.82±66.04	0.216
*Mean fresh blood transfusion (ml)	809.14±198.12	472.91±115.83	**0.001**
Intraoperative IABP insertion (%)	5 (2.55%)	3 (1.33%)	0.845
Noradrenaline infusion (%)	78 (39.79%)	83 (36.89%)	0.698
*Mean hematocrit (%)	24.36±1.14	30.87±2.56	**0.045**
*Mean platelet count ($x10^3/mm^3$)	123.87±24.69	231.32±42.89	**0.001**
*Mean total bilirubin (mg/dl)	1.53±0.37	1.02±0.07	**0.011**
*Mean ALT (U/l)	69.12±6.56	26.21±6.43	**0.026**
*Mean AST (U/l)	67.85±6.42	26.61±6.45	**0.026**
*Mean ALP (U/l)	128.31±26.14	39.20±9.44	**0.001**
*Mean GGT (U/l)	39.45±9.23	23.64±5.83	**0.047**
*Mean LDH (U/l)	325.87±80.12	301.15±48.33	0.634
*Mean albumin (g/dl)	3.19±0.18	3.58±0.88	0.050
*Mean creatinine (mg/dl)	1.64±0.43	0.61±0.14	**0.001**
*Mean urea (mg/dl)	45.36±11.21	35.22±7.35	0.162
*Mean PC (%)	60.45±5.89	79.89±9.76	**0.036**
*Mean PTT (sec)	46.23±9.89	33.56±5.49	**0.021**
*Mean INR	1.80±0.43	1.00±0.10	**0.001**

CPB: cardiopulmonary bypass; *: post CPB; ABP: arterial blood pressure; CVP: central venous pressure; PaO_2: arterial oxygen tension; IABP: intra-aortic balloon pump; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; LDH: lactate dehydrogenase; PC: prothrombin concentration; PTT: partial thromboplastin time; INR: international normalized ratio.

Postoperative Data: Group (A) showed statistically significant differences as regards total mechanical ventilation duration, inotropic support duration, total blood loss, fresh blood transfusion, platelets transfusion, CVP, total bilirubin, ALT, AST, ALP, GGT, creatinine, PC, PTT, INR, platelet count, reoperation for bleeding, pulmonary complications, pleural effusion, acute renal failure (ARF) occurrence, total ICU stay, total hospital stay and the overall hospital complications rate. Differences in albumin and hematocrit were close to significance. However, perioperative mortality showed no statistically significant difference between both groups (Table 3).

Table (3): Postoperative outcomes

	Group (A)	**Group (B)**	***p* value**
Mean mechanical ventilation duration (hours)	15.65±3.91	7.21±1.80	**0.001**
Mean inotropic support duration (hours)	34.56±6.21	22.57±4.14	**0.001**
Mean total blood loss (ml)	645.55±521.09	420.73±200.42	**0.001**
Mean fresh blood transfusion (ml)	1595.59±550.15	920.12±98.55	**0.001**
Platelets transfusion (%)	181 (92.35%)	17 (7.55%)	**0.001**
FFP transfusion (%)	196 (100%)	219 (97.33%)	0.975
Mean ABP (mmHg) (after inotropes cessation)	95.67±27.86	98.56±26.52	0.979
Mean CVP (cmH_2O) (after inotropes cessation)	10.86±4.52	9.57±2.01	**0.010**
*Mean total bilirubin (mg/dl)	1.79±0.43	1.02±0.05	**0.001**
*Mean ALT (U/l)	119.45±29.43	31.50±7.71	**0.001**
*Mean AST (U/l)	111.21±26.21	29.31±7.20	**0.001**
*Mean ALP (U/l)	139.20±25.11	42.14±10.31	**0.001**
*Mean GGT (U/l)	81.23±15.87	31.17±7.72	**0.038**
*Mean LDH (U/l)	363.07±49.18	341.95±39.27	0.601
*Mean albumin (gm/dl)	3.15±0.11	3.56±0.88	0.050
*Mean creatinine (mg/dl)	1.85±0.36	0.69±0.16	**0.001**
*Mean urea (mg/dl)	49.25±12.41	35.14±8.47	0.140
*Mean PC (%)	71.18±8.74	83.69±10.15	**0.048**
*Mean PTT (sec)	38.88±9.65	29.81±2.19	**0.024**
*Mean INR	1.30±0.31	0.9±0.10	**0.001**
*Mean blood glucose (mg/dl)	131.65±31.18	131.56±31.41	0.881
*Mean platelet count ($x10^3/mm^3$)	148.21±19.25	245.98±53.11	**0.001**
*Mean hematocrit (%)	28.17±4.23	35.87±3.12	0.050
Reoperation for bleeding (%)	36 (18.37%)	20 (8.89%)	**0.001**
IABP insertion (%)	15 (7.65%)	12 (5.33%)	0.754
Perioperative MI (%)	1 (0.51%)	1 (0.44%)	0.864
Pulmonary complications (%)	29 (14.79%)	11 (4.89%)	**0.001**
Pleural effusion (%)	25 (12.76%)	9 (4.00%)	**0.001**
AF (%)	80 (40.81%)	94 (41.77%)	0.798
GIT bleeding (%)	5 (2.55%)	0 (0%)	0.269
ARF (%)	26 (13.27%)	10 (4.44%)	**0.001**
Low COP syndrome (%)	21 (10.71%)	18 (8.00%)	0.765
Stroke (%)	5 (2.55%)	2 (0.88%)	0.712
Deep wound infection (%)	15 (7.65%)	11 (4.89%)	0.689
Superficial wound infection (%)	99 (50.51%)	100 (44.44%)	0.514
Harvested graft site infection (%)	95 (48.47%)	95 (42.22%)	0.505
Mean total ICU stay (hours)	142.12±25.34	45.56±5.79	**0.001**
Mean prior to hospital discharge LVEF%	52.13±1.43	53.23±1.09	0.689
Mean total hospital stay (days)	15.47±1.20	7.15±1.21	**0.001**
Perioperative mortality	14 (7.14%)	10 (4.44%)	0.692
Overall hospital complications rate	76 (38.78%)	67 (29.78%)	**0.001**

FFP: fresh frozen plasma; *: at ICU discharge; ABP: arterial blood pressure; CVP: central venous pressure; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; LDH: lactate dehydrogenase; PC: prothrombin concentration; PTT: partial thromboplastin time; INR: international normalized ratio; IABP: intra-aortic balloon pump; MI: myocardial infarction; AF: atrial fibrillation; GIT: gastrointestinal tract; ARF: acute renal failure; COP: cardiac output syndrome; ICU: intensive care unit; LVEF%: left ventricular ejection fraction per cent.

Postoperative major morbidities were more prevalent in group (A) with variable statistical significance: need for re-operation (p= 0.001), pulmonary complications (p= 0.001), pleural effusion (p= 0.001), deep sternal wound infection (p= 0.689), permanent stroke (p= 0.712) and renal failure (p= 0.001). Multivariable logistic regression analysis showed that higher MELD score, lower preoperative platelets count, higher preoperative total bilirubin, higher preoperative creatinine and prolonged CPB time were the important foreshows embroiled in the postoperative in-hospital morbidity and that higher MELD score and intraoperative blood transfusion were the important predictors involved in the perioperative mortality (Table 4).

Table (4): Predictors of in-hospital morbidity by multivariable logistic regression analysis

Predictor	Odds ratio	P-Value	95% confidence interval
Postoperative Morbidity			
MELD score	3.140	0.019	1.025-10.964
Preoperative platelets count	3.650	0.023	1.166-12.778
Preoperative total bilirubin	1.256	0.021	1.035-1.859
Preoperative creatinine	0.528	0.028	0.345-1.012
Prolonged CPB time	1.145	0.020	0.985-1.925
Perioperative Mortality			
MELD score	3.220	0.018	1.198-9.130
Intraoperative blood transfusion	3.201	0.020	1.595-6.411

OR: odds ratio; CI: confidence interval; MELD: model for end-stage liver disease.

DISCUSSION

IHD patients with seropositive chronic HCV infection subjected to CABG are very liable to develop postoperative hepatic dysfunction associated with higher rates of adverse events, major morbidities, and perioperative mortality [17]. It's highly attributed to the oxygen supply/demand imbalance in the hepatosplanchnic region caused by the CPB that leads to unpreventable hepatic hypoxemia and hepatic endotoxemia by the released pro-inflammatory cytokines. These unfruitful changes adversely affect the diseased hepatocytes [18, 19]. Healthier hepatocytes are protected against shorter periods of hypoxemia, thus hepatic ischemia and the resultant hepatic dysfunction wouldn't occur [18, 20, 21].

This topic had only a limited small-sized samples research work and had not yet been evaluated in a larger cohort [22]. Even fewer studies scarcely addressed the intraoperative and postoperative performance and its impact on the operative and postoperative outcomes [23].

We conducted our study on a relatively large cohort of chronic HCV infection compared to other reported studies; thus, the evolved results would be more consistent and comprehensive. They were 196 patients representing 46.55% of the study groups (group A) opposed to 225 (53.44%) patients representing the control group (group B). **Hsieh *et al.*** [22] reported on 105 patients. **Baran *et al.*** [24] and **Xavier *et al.*** [25] each reported on 60 patients, **Sabry *et al.*** [26] reported on 90 patients and **Abd El Salam *et al.*** [10] reported on 118 patients representing 30.3% of their cohort. **Morisaki *et al.*** [14] reported on 42 patients. **Lin *et al.*** [27] reported on 55 patients. **Filsoufi *et al.*** [28] reported on 27 patients.

Our cohort's demographic and preoperative profile characteristics were like other authors'. Group (A) showed statistically significant differences as regards Gensini score, platelet count, creatinine, INR, total bilirubin, ALT, AST, ALP, PC and PTT. Differences in hematocrit, GGT and albumin were close to significance. These findings reflect the negative effects of chronic HCV infection on the preoperative profile of the surgical candidates that were similarly reported by others [10, 24, 25, 26]. Group (B) showed statistically significant differences as regards hypertension and DM that was consistent with the findings reported by **Butt *et al.*** [29] whose data showed significant high prevalence of IHD among chronic HCV infection patients although they have a more favorable cardiometabolic risk profile. Moreover, group (A) expressed more severe CAD targets lesions with statistically significant Gensini score, a point that agree upon by others [10, 29]. This may reflect the negative adverse effect of chronic HCV infection on coronaries and predict more difficulty challenge intraoperatively. Both groups had statistically insignificant EuroSCORE II and STS score. Although these both scores are worldwide used for surgical risk assessment and postoperative adverse outcomes prediction [30], their lack of criteria of hepatic dysfunction makes them insensitive for this subset of patients with chronic HCV infection [23, 31], as what can be concluded from our findings. Intraoperatively, group (A) expressed statistically significant differences regarding total operative time and CPB time, longer aortic cross clamping time, less rates of smooth weaning off CPB and more rates of electrical cardioversion to achieve

weaning off it but with statistically insignificant differences.

Postoperatively, they experienced statistically significant total mechanical ventilation duration, inotropic support duration, total blood loss, reoperation for bleeding, pulmonary complications, pleural effusion, ARF occurrence, total ICU stay, total hospital stay and the overall hospital complications rate. Others agree with our conclusion where they reported even lower mean EuroSCORE II of 1.12 ± 0.56 and higher postoperative complications rate of 43% [26].

As continuation to the negative adverse effects of chronic HCV infection intraoperatively, group (A) expressed statistically significant differences regarding the total operative time, CPB time, total platelets count, ALP, creatinine, INR, CVP, total bilirubin, hematocrit, ALT, AST, GGT, PC and PTT. Differences in albumin were close to significance. Other researchers reported similar results [24, 25, 26]. Again, group (A) expressed longer aortic cross clamping time despite the submitted efforts to shorten it due to the poorer quality of the targeted coronaries, less rates of smooth weaning off CPB and more rates of electrical cardioversion to achieve weaning off it but with statistically insignificant differences. Other authors reported statistically significant aortic cross clamping time giving no data about weaning off bypass scenarios [24, 25, 26].

The statistically significant total surgical hemostasis time and post CPB fresh blood transfusion (for correction of the statistically significant dropped hematocrit), for group (A) were intentionally done as protective measures against the anticipated adverse effects in the immediate postoperative period. Other investigators reported similar results but for packed red blood corpuscles (RBCs) not fresh blood transfusion and none reported about surgical hemostasis [24, 25, 26].

We believe that proper intraoperative surgical and non-surgical execution namely optimized perfusion flow rate and mean ABP during CPB, proper PaO_2, correction of metabolic acidosis, controlling glucose level, post-CPB fresh blood transfusion and meticulous surgical hemostasis were of utmost importance of favorable operative outcomes and having no intraoperative mortality. These items were seldomly reported in the literature. However, **Baran *et al.*** [24] reported 1.7% mortality.

Chronic HCV infection continued to reflect its negative impacts in the postoperative period where group (A) expressed statistically significant differences regarding the total mechanical ventilation duration, inotropic support duration, total blood loss, fresh blood transfusion, platelets transfusion, CVP, total bilirubin, ALT, AST, ALP, GGT, creatinine, PC, PTT, INR, platelet count, reoperation for bleeding, pulmonary complications, pleural effusion, ARF, total ICU stay, total hospital stay and the overall hospital complications rate. Differences in albumin and hematocrit were close to significance. Postoperative major morbidities were more prevalent in group (A) with variable statistical significance. The most encountered complications were the cardiac, hepatic, pulmonary and renal ones. Other authors reported similar results and even higher overall hospital complications rate [14, 22, 24, 25, 26, 27, 28, 32].

Hsieh *et al.* [22], **Sabry *et al.*** [26] and **Delgado *et al.*** [32] reported cardiac complications as the most evident and postoperative complications rate of 43%, **Sugimura *et al.*** [33] reported hepatic complications, whereas **Thielmann *et al.*** [31] and **Arif *et al.*** [34] reported renal complications. These findings were solely related to the vulnerable hepatocytes to withstand the intraoperative durations of anesthesia, CPB and operative hepatic ischemia. This is in addition to the compromised nutritional status, dysfunctional immune system and coagulopathy [32]. Some authors reported that even minimally impaired hepatocytes would express higher postoperative complications rates [18, 19, 26]. Preoperative thrombocytopenia, thrombasthenia and poor coagulation profile were responsible for the significant postoperative bleeding and re-exploration as agree with others [22, 23, 24, 25, 26, 27, 31]. We had 18.37% re-opening rate while **An *et al.*** [23] reported 25% and **Murashita *et al.*** [35] reported 33%. However, keen postoperative care with suitably adequate fresh blood and platelets transfusion and proper surgical decision timing for the anticipated complications could improve the overall survival as the perioperative mortality showed no statistically significant difference between both groups. Group (A) had 7.14% mortality opposed to 4.44% in group (B).

Baran *et al.* [24] reported 5% mortality, **Xavier *et al.*** [25] reported 8.3% mortality, **Delgado *et al.*** [32] reported 12% mortality and **Lin *et al.*** [27] reported 16.4% mortality.

Multivariable logistic regression analysis showed that preoperative higher MELD score, lower platelets count, higher total bilirubin, higher creatinine and prolonged CPB time were the significant predictors of postoperative in-hospital morbidity and that preoperative higher MELD score and intraoperative blood transfusion were the significant predictors of perioperative mortality. Other investigators reported that age, preoperative MELD score, platelets count, total bilirubin and creatinine are associated with hospital morbidity and mortality [14, 25, 26].

Moreover, **Morisaki *et al.*** [14] and **Sabry *et al.*** [26] reported that age, MELD score and prolonged aortic cross clamping and CPB times were the independent risk factors for significant postoperative morbidity and mortality. However, we couldn't find association between age and postoperative morbidity and mortality as been reported by other authors [22, 23, 24, 27, 31]. Those who report age as a predictor for morbidity and mortality relate it to the higher comorbid effects of prolonged CPB. We do believe that age per se isn't a predictor for morbidity and mortality unless accompanied by other risk factors. **Arif *et al.*** [34] reported MELD score and Euroscore to be associated with increased mortality.

Delgado *et al.* [32] reported that CVP was an independent predictor of immediate short-term mortality. MELD score proved to be a sensitive useful scoring model in patients with chronic HCV infection undergoing CABG. It's simple, objective, comprising of three objective and commonly available laboratory values: INR, total bilirubin and creatinine, including renal function (serum creatinine level) and it has a much wide range of score [6 - 40]. Thus, it's been widely used even more than the CTP score that lacks the previously mentioned pros of the MELD score besides its inability to determine the specific risk for mortality at defined time as it only predicts the status of risk as a low-risk, intermediate risk, or high-risk [25, 26]. However, some authors argue that and they claim that CTP was superior to MELD score as a predictor of postoperative morbidity and mortality [28]. Other authors determined that MELD score exceeding 12-14 was a trustable significant predictor for postoperative morbidity and mortality rates [14, 22, 26, 32].

Delgado *et al.* [32] reported 12% mortality with MELD score of 18. **Xavier *et al.*** [25] reported 8.3% mortality with a mean MELD score of 11 (range: 9-18). These findings are consistent with ours. However, **Lin *et al.*** [27] reported failure of MELD score to predict mortality and that preoperative bilirubin and CABG status were independent predictors of it.

Morisaki *et al.* [14], **Sabry *et al.*** [26], **Lin *et al.*** [27] and **Filsoufi *et al.*** [28] agree with our finding about preoperative low platelets counts as a significant predictor of postoperative morbidity reporting an inverse relationship between the preoperative platelets count and the degree of severity of hepatic dysfunction, yet no clear cutoff value of platelets count was agreed-upon to correlate with the postoperative morbidity incidence. Prolonged CPB time is associated with platelets and coagulation factors depletion, hepatic hypoxemia and endotoxemia [18, 19], contributing to significant postoperative morbidity. Other authors agree with this finding [14, 22, 24, 25, 26, 28].

In agreement with our finding that intraoperative blood transfusion was a significant predictor of perioperative mortality what was confirmed by other authors about the independent association between intraoperative blood transfusion by 1-2 blood units and the higher post on-pump CABG mortality [25].

CONCLUSION

Chronic HCV infection carries multiple risks for IHD patients undergoing CABG. Identification and careful evaluation of the predictive risk factors may reduce serious post-surgical adverse outcomes. Proper preoperative preparation, meticulous intraoperative performance and keen postoperative management are necessary and extremely essential needs to overcome the adverse impacts of chronic HCV infection and improve the postoperative results. Greater careful consideration should be offered to those with preoperative high MELD score, low platelets count, high total bilirubin and high creatinine. We recommend using the MELD score as a risk model in this subset of patients in prediction of the postoperative morbidity and mortality along with the currently used ones, which should involve hepatic dysfunction in its risk scoring system.

Study Limitations: It is a retrospective study. The studied comparable cohort involved patients with chronic HCV infection only not involving other hepatitis viral infections. Patients with liver cirrhosis weren't in the scope of the study. Long-term survival and mortality rates couldn't be done due to lack of patients' long follow-up compliance. However, it was carried out on a relatively large cohort of moderate degree of hepatic dysfunction victims currently representing a great sector of CABG cases. Thus, the evolved results would be comprehensive and applicable.

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REFERENCES

1. **Cooke G, Lemoine M, Thursz M *et al.* (2013):** Viral hepatitis and the Global Burden of Disease: a need to regroup. J Viral Hepat., 20: 600–601.
2. **Petruzziello A, Marigliano S, Loquercio G *et al.* (2016):** Global epidemiology of hepatitis C virus infection: An up-date of the distribution and circulation of hepatitis C virus genotypes. World J Gastroenterol., 22: 7824–7840.
3. **Stanaway J, Flaxman A, Naghavi M *et al.* (2016):** The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. Lancet, 388 (10049): 1081-1088.
4. **Mohd Hanafiah K, Groeger J, Flaxman A *et al.* (2013):** Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology, 57: 1333–1342.
5. **Cornberg M, Razavi H, Alberti A *et al.* (2011):** A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel. Liver International, 31 (2): 30–60.
6. **El-Zanaty F, Way A (2009):** Egypt Demographic and Health Survey 2008, (Ministry of Health, Cairo, Egypt). https://www.scirp.org/(S(lz5mqp453edsnp55rrgjct55.))/reference/ referencespapers.aspx?referenceid=1382248
7. **El-Zanaty F, Associates [Egypt], ICF International: Egypt Health Issues Survey (2015):** Cairo, Egypt and Rockville, Maryland, USA: Ministry of Health and Population and ICF International, Pp: 234. https://dhsprogram.com/publications/publication-fr313-dhs-final-reports. cfm
8. **Cacoub P, Gragnani L, Comarmond C *et al.* (2014):** Extrahepatic manifestations of chronic hepatitis C virus infection. Dig Liver Dis., 46: 165–173.
9. **Petta S, Maida M, Macaluso F *et al.* (2016):** Hepatitis C virus infection is associated with increased cardiovascular mortality: a metanalysis of observational studies. Gastroenterology, 150: 145–155.

10. **Abd El Salam R, Nabil B, Saber M *et al.* (2016):** Prevalence of Hepatitis C Virus Seropositivity and Its Impact on Coronary Artery Disease among Egyptian Patients Referred for Coronary Angiography. Cardiology Research and Practice, 16: 1623197. http://dx.doi.org/10. 1155/2016/1623197.
11. **Negro F (2014):** Facts and fictions of HCV and comorbidities: steatosis, diabetes mellitus, and cardiovascular diseases. J Hepatol., 61: 69–78.
12. **Hussein A, Abdel Ghany M, Mahmoud H (2020):** Short- and long-term outcomes following percutaneous coronary intervention in hepatitis C virus seropositive patients. The Egyptian Heart Journal, 72: 44. https://doi.org/10.1186/s43044-020-00079-9.
13. **Roed T, Kristoffersen U, Knudsen A *et al.* (2014):** Increased prevalence of coronary artery disease risk markers in patients with chronic hepatitis C–a cross-sectional study. Vasc Health Risk Manag., 10: 55–62.
14. **Morisaki A, Hosono M, Sasaki Y (2010):** Risk factor analysis in patients with liver cirrhosis undergoing cardiovascular operations. Ann Thorac Surg., 89: 811–818.
15. **Neeland I, Patel R, Eshtehardi P *et al.* (2012):** Coronary angiographic scoring systems: an evaluation of their equivalence and validity. American Heart Journal, 164: 547–552.
16. **Ferraris V, Brown J, Shore-Lesserson L *et al.* (2011):** Update to the society of thoracic surgeons and the society of cardiovascular anesthesiologists' blood conservation clinical practice guidelines. Ann Thorac Surg., 91:944–982.
17. **Meng F, Yin X, Ma X *et al.* (2013):** Assessment of the value of serum cholinesterase as a liver function test for cirrhotic patients. Biomed Rep., 1: 265–268.
18. **Abo El Fetouh F, Salah M, Mostafa M *et al.* (2009):** The effects of hypothermic vresus normothermic cardiopulmonary bypass on hepatic blood flow. Egypt J Cardiothorac Anesth., 3: 14–22.
19. **Thoren A, Elam M, Richsten S (2001):** Jejunal mucosal perfusion is well maintained during mild hypothermic cardio pulmonary bypass in humans. Anesth Analg., 92: 5–11.
20. **Okano N, Miyoshi S, Owada R *et al.* (2002):** Impairment of hepatosplanchnic oxygenation and increase of serum hyaluronate during normothermic and mild hypothermic cardiopulmonary bypass. Anesth Analg., 95: 278–286.
21. **Takala J (1996):** Determinants of splanchnic blood flow. Br J Anaesth., 77: 50–58.
22. **Hsieh W, Chen P, Gradinariu G *et al.* (2013):** Postoperative morbidity in patients with chronic viral hepatitis undergoing cardiac surgery: a retrospective study. J Card Surg., 8: 68. doi: 10.1186/1749-8090-8-S1-P68
23. **An Y, Xiao Y, Zhong Q (2007):** Open-heart surgery in patients with liver cirrhosis: indications, risk factors, and clinical outcomes. Eur Surg Res., 39: 67–74.
24. **Baran C, Cakici M, Ozcinar E *et al.* (2018):** Clinical results of cardiac surgery in patients with chronic hepatitis C and their role in risk models: A case-control study. Thorac Cardiovasc Surg., 66 (04): 328-332.
25. **Xavier S, Norris C, Ewasiuk A *et al.* (2020):** The impact of cirrhosis in patients undergoing cardiac surgery: a retrospective observational cohort study. Can J Anesth/Can Anesth., 67: 22–31.
26. **Sabry A, Fouad H, Hashem A *et al.* (2017):** Risk factors in adult patients with chronic hepatitis C virus undergoing cardiac surgery with cardiopulmonary bypass: a prospective study. Research and Opinion in Anesthesia & Intensive Care, 4: 213–225.
27. **Lin C, Lin F, Wang S *et al.* (2005):** Cardiac surgery in patients with liver cirrhosis. Ann Thorac Surg., 79: 1551–1554.
28. **Filsoufi F, Salzberg S, Rahmanian P *et al.* (2007):** Early and late outcome of cardiac surgery in patients with liver cirrhosis. Liver Transpl., 13: 990–995.
29. **Butt A, Xiaoqiang W, Budoff M *et al.* (2009):** Hepatitis C virus infection and the risk of coronary disease. Clinical Infectious Diseases, 49 (2): 225–232.
30. **Siregar S, Groenwold R, De Heer F *et al.* (2012):** Performance of the original EuroSCORE. Eur J Cardiothorac Surg., 41: 746–754.
31. **Thielmann M, Mechmet A, Markus N *et al.* (2010):** Risk prediction and outcomes in patients with liver cirrhosis undergoing open-heart surgery. Eur J Cardiothorac Surg., 38: 592–599.
32. **Lopez-Delgado J, Esteve F, Javierre C *et al.* (2013):** Short-term independent mortality risk factors in patients with cirrhosis undergoing cardiac surgery. Interact Cardiovasc Thorac Surg., 16: 332–338.
33. **Sugimura Y, Toyama M, Katoh M *et al.* (2012):** Analysis of open heart surgery in patients with liver cirrhosis. Asian Cardiovasc Thorac Ann., 20: 263–268.
34. **Arif R, Seppelt P, Schwill S *et al.* (2012):** Predictive risk factors for patients with cirrhosis undergoing heart surgery. Ann Thorac Surg., 94: 1947–1952.
35. **Murashita T, Komiya T, Tamura N *et al.* (2009):** Preoperative evaluation of patients with liver cirrhosis undergoing open heart surgery. Gen Thorac Cardiovasc Surg., 57: 293–297.