CLINICAL STUDY

The predictive value of risk indices for cardiac complications in living donor liver transplantation

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ABSTRACT

BACKGROUND AND AIMS: The American College of Surgeons' National Surgical Quality Improvement Program (NSQIP) risk tool and Revised Cardiac Risk Index (RCRI) are recommended tools for cardiovascular assessment before non-cardiac surgery to predict early postoperative cardiac morbidity and mortality. Their predictive value for postoperative cardiovascular morbidity and mortality after liver transplantation is unknown. We aimed to evaluate the validity of these two risk tools to predict early (30-day) cardiovascular complications and in-hospital all-cause mortality.

METHODS: Patients who underwent living donor liver transplantation were retrospectively analyzed. Consecutive 278 adult patients were included and their NSQIP and RCRI scores were calculated.

RESULTS: Cardiovascular morbidity occurred in 5 (1.8 %) patients. In-hospital all-cause mortality occurred in 18 (6.4 %) patients. None-of the patients died from cardiac complications. Causes of cardiac morbidity were as follows; acute coronary syndrome in 1 patient, intraoperative cardiac arrest with successful resuscitation in 1 patient, heart failure in 3 patients. Neither the NSQIP nor the RCRI score were associated with cardiovascular morbidity. Only RCRI medium-high score, DM and Nonalcoholic steatohepatitis as transplant indications were associated with in-hospital all-cause mortality (p = 0.001).

CONCLUSIONS: The NSQIP risk calculator and RCRI scores failed to accurately predict the risk of perioperative cardiac complications *(Tab. 3, Ref. 30)*. Text in PDF *www.elis.sk*.

KEY WORDS: preoperative cardiac assessment, cardiac morbidity, cardiac mortality, revised cardiac risk index, NSQIP risk index.

Abbreviations: ACC/AHA – American College of Cardiology/American Heart Association, ASA – American Society of Anesthesiologists, ACS – acute coronary syndrome, CAD – coronary artery disease, CI – confidence intervals, CVD – cardiovascular disease, DM – diabetes mellitus, ESC/ESA – European Society of Cardiology/European Society of Anesthesiology, FS – functional status, HT – hypertension, LDLT – living donor liver transplantation, LT – liver transplantation, MELD – model for end stage liver disease, NASH – nonalcoholic steatohepatitis, NSQIP – The American College of Surgeons' National Surgical Quality Improvement Program, RCRI – revised cardiac risk index

Introduction

Since the first successful liver transplantation (LT) in 1967 by Starzl et al, orthotopic LT has become gold standard therapy for

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many liver diseases (1). With the advances in surgical techniques and new immunosuppressive drugs, survival rates have been improved (1). These advances have enlarged the indications for LT. Current LT recipients are older and have more comorbidities (1). Traditional cardiovascular risk factors may accompany patients with cirrhosis. Although older studies speculated that liver diseases might have a protective effect against coronary artery disease (CAD) (2), prevalence of CAD is similar between cirrhotic patients and general population (3, 4, 5). More importantly, cardiovascular complications play a major part in morbidity and mortality after LT (6, 7).

Clinical risk indices are recommended to be used for reducing the risk of perioperative cardiac complications (8, 9, 10). For this purpose, 2014 American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology/European Society of Anesthesiology (ESC/ESA) guidelines on non-cardiac surgery, cardiovascular assessment and management recommend using revised cardiac risk index (RCRI) or the American College of Surgeons' National Surgical Quality Improvement Program (NSQIP) model (11, 12). Performances of these two risk models are unknown for patients undergoing living donor liver transplantation (LDLT). In our study, we aimed to investigate the performance of these risk models in predicting perioperative cardiac morbidity and mortality.

Methods

Patients who have undergone adult LDLT at Florence Nightingale Hospital Liver Transplantation Unit between January 2012 and May 2016 were retrospectively analyzed for < 30-day cardiovascular morbidity and mortality, and in-hospital all-cause mortality. Consecutive 278 patients were included in our study. Patients who were under 18 years old and underwent deceased donor liver transplantation or dual liver-kidney transplantation were excluded. All patients had an electrocardiogram and transthoracic echocardiography in our initial evaluation. Patients with an indication to LT had a work-up according to European Association for the Study of the Liver clinical practice guidelines (13).

Demographic and clinical parameters were collected from our patient database: Gender, age at the time of LT, primary indication for LT, creatinine, diabetes mellitus on insulin (DM), history of CAD, history of heart failure, history of cerebrovascular disease, MELD at the time of LT, tobacco use, hypertension, cardiac testing modalities. Prevalence and causes < 30-day cardiovascular morbidity (acute coronary syndrome (ACS), congestive heart failure, complete heart block, cardiac arrest) and mortality, and in-hospital all-cause mortality were also recorded.

RCRI which comprises six variables (type of surgery, history of CAD, history of heart failure, history of cerebrovascular disease, DM and pre-operative creatinine level > 2 mg/dL) and NSQIP risk score which comprises five variables (type of surgery, functional status (FS), pre-operative creatinine level > 1.5 mg/dL, American Society of Anesthesiologists (ASA) class and age) were calculated (12 ,13).

RCRI was divided into 3 groups according to estimated rate of myocardial infarction, heart failure, ventricular fibrillation, cardiac arrest or complete heart block: < 1 % low risk; 1–5 % medium risk and ≥ 5 % high risk. NSQIP model score was also divided into 3 groups according to estimated risk probability for perioperative myocardial infarction or cardiac arrest: < 1 % low risk; 1–5 % medium risk and ≥ 5 % high risk.

The study was undertaken with the approval of the local research ethics committee and in accordance with the Declaration of Helsinki of the World Medical Association.

Statistical analysis

Demographic and laboratory data are presented as medians and interquartile range (IQR) for continuous variables. Patients were divided into three groups according to their outcome: Group 1: Patients with cardiovascular morbidity, Group 2: Patients with in-hospital all-cause mortality, Group 3: Patients without cardiac complications or in-hospital all-cause mortality. The number of patients who have high risk according to NSQIP risk score and RCRI score was very low, thus we divided the patients further into two categories for statistical analysis: Patients with low risk and patients with medium – high risk. These categorical variables were compared with cardiac complications and in-hospital all-cause mortality using Chi-square test or Fisher's exact test (when chi-square test assumptions do not hold due to low expected cell counts). The Mann–Whitney U test was used to compare the continuous variables. The correlation between the risk indices and the occurrence of in-hospital all-cause mortality and cardiovascular morbidity was assessed using Spearman correlation. A two-sided p value less than 0.05 is considered statistically significant within a 95 % confidence interval (CI). All analyses were performed using SPSS v.21.0 for Windows (SPSS, Inc., Chicago, Illinois, USA).

Results

Retrospectively consecutive 278 patients with a mean age of 53.5 (20–75) years were included in this study. Demographic and clinical characteristics and primary indication for transplantation are shown in Table 1. Table 2 shows the liver-specific, general and cardiac clinical risk indices in our patient population.

None of the patients had prior heart failure and cerebrovascular disease. Cardiovascular complications occurred in 5 (1.8 %) patients: Heart failure occurred in 3 patients, acute ST segment

Tab. 1. Demographic and clinical characteristics of the patients.

Characteristic	n = 278
Gender (Female), n (%)	79 (28.4)
Age (years), median (range)	53.5 (20–75)
Age ≥ 60 years, n (%)	73 (26.3)
DM, n (%)	46 (16.5)
HT, n (%)	17 (6.1)
Creatinine (mg /dL), median (range)	0.8 (0.36–2.6)
CAD, n (%)	9 (3.2)
Tobacco use, n (%)	98 (35.3)
Primary indication for transplant	n (%)
Hepatocellular carcinoma	66 (23.7)
Hepatitis B	59 (21.2)
Cryptogenic	44 (15.8)
Hepatitis C	32 (11.5)
Alcohol	25 (9.0)
NASH	21 (7.6)
Other	31 (11.2)

DM – diabetes mellitus, HT – hypertension, CAD – coronary artery disease, NASH –nonalcoholic steatohepatitis

Tab. 2. Clinical risk indices in the study population.

n = 278	
MELD, median (range)	16 (6–35)
MELD ≥ 20, n (%)	66 (23.7)
ASA class	n (%)
Class-3	265 (95.3)
Class-4	12 (4.3)
Class-5	1 (0.4)
FS	n (%)
FS-1	250 (89.9)
FS-2	25 (9)
FS-3	3 (1.1)
NSQIP index score	n (%)
Low	180 (64.7)
Medium-high	98 (35.2)
RCRI	n (%)
Low	223 (80.2)
Medium-high	55 (19.7)

MELD – model for end-stage liver disease, ASA – American Society of Anesthesiologists, FS – functional status, NSQIP – National Surgical Quality Improvement Program, RCRI – Revised cardiac risk index

Tab. 3. Association of the RCRI and NSQIP risk tools with the patient outcomes.

Variables	Group 1 (Patients with cardiac complications) n=5	Group 2 (Patients with in-hospital all-cause mortality) n=18	Group 3 (Patients without cardiac complications or mortality) n=255	p	
RCRI score, n				0.258[a]	0.000[b]
Low	3	8	212		
Medium -high	2	10	43		
NSQIP index score, n				>0.99[a]	0.061[b]
Low	3	8	169		
Medium -high	2	10	86		

[a] p values are comparing Group 1 to Group 3, [b] p values are comparing Group 2 to Group 3. MELD: model for end-stage liver disease, DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, NSQIP: National Surgical Quality Improvement Program, RCRI: Revised cardiac risk index

elevation myocardial infarction in 1 patient and perioperative cardiac arrest with successful resuscitation in 1 patient. Acute ST elevation myocardial infarction occurred in a patient with known CAD. The patient had undergone coronary angiography before liver transplantation and the stent, which was implanted in left anterior descending artery 4 years ago, was patent. Stent thrombosis occurred on postoperative day 5. Coronary angiography was performed in the patient with perioperative cardiac arrest and displayed normal coronary arteries. None of the patients died from cardiac mortality. In-hospital all-cause mortality occurred in 18 (6.4 %) patients. Infection accounted for 33.3 % of all deaths within 30 days, followed by graft failure (16.6 %), hemorrhage (11. 1%), renal failure (11.1 %), and other causes (27.9 %).

There was a positive weak correlation between RCRI score and in-hospital all-cause mortality (r = 0.245, p = 0.000). No correlation was found between cardiac complications and RCRI score. No correlation was found between NSQIP risk score and both with cardiac complications and in-hospital all-cause mortality.

Patients were divided into three groups according to their outcome: Group 1: Patients with cardiovascular morbidity, Group 2: Patients with in-hospital all-cause mortality, Group 3: Patients without cardiac complications or in-hospital all-cause mortality. Table 3 demonstrates the association between the patient groups and the RCRI and NSQIP risk tools. Patients with in-hospital all-cause mortality had higher RCRI medium-high scores than those of patients without cardiovascular morbidity or mortality (p = 0.000). No significant difference was found between these three patient groups according to NSQIP risk scores. Comparing patient groups, the female/male ratio was similar between groups (3.8 % vs 1 % in Group 1, 6.3 % vs 6.5 % in Group 2, and 89.9 % vs 92.5 % in Group 3, respectively; p = 0.287). Age was similar (58 (49–72) years for Group 1, 55 (29–69) years for Group 2, and 53 (20–75) for Group 3; p = 0.367) in groups. Additionally, the number of patients who were ≥ 60 years old did not differ between the 3 groups (p = 0.768). No significant difference was found between median MELD scores (17 (10–24) in Group 1, 17 (9–30) in Group 2, and 16 (6–35) in Group 3; p = 0.761). Patients with DM were at higher risk for in-hospital all-cause mortality (17.4 % vs 4.3 %; p = 0.004). However, patients with DM had a similar rate of cardiovascular complications than nondiabetics (2.6 % vs 1.8 %, respectively; p = 0.549). Interestingly, the presence of hypertension did not associate with cardiovascular complications (0 % vs 1.9

%; p > 0.99) or in-hospital all-cause mortality (5.9 % vs 6.5 %; p > 0.99). Group 1 patients had higher rates of history of CAD than those of Group 3, but this was not statistically significant (20 % vs 2.4 %; p = 0.128). Similarly, Group 2 patients had higher history of CAD rates than those of Group 3, however, not statistically significant (11.1 % vs 2.4 %; p = 0.091). Creatinine levels were similar (0.9 mg/dL (0.6–1.1) for Group 1, 0.7 mg/dL (0.5–2.1) for Group 2, and 0.8 mg/dL (0.36–2.6) for Group 3; p = 0.788) in groups. Tobacco use was similar between groups (40 % for Group 1, 44.4 % for Group 2, and 34.5 % for Group 3; p = 0.678). Patients were divided as nonalcoholic steatohepatitis (NASH) vs. non-NASH according to their primary indication for transplantation. Patients with in-hospital all-cause mortality (Group 2) had higher rates of NASH patients than those without cardiovascular complications or mortality (Group 3) (22.2 % vs 6.7 %; p = 0.039). However, there was no relationship according to NASH etiology between Group 1 and Group 3 (0 % vs 6.7 %; p > 0.99).

Discussion

In this retrospective study, we investigated the predictive value of two recommended tools, RCRI and NSQIP risk score in patients undergoing LDLT. Risk calculators are developed mainly for two reasons: 1- avoiding further investigations and unnecessary delays in operation (14, 15); 2- optimizing preoperative pharmacological treatment to lower postoperative morbidity. NSQIP risk score and RCRI are the two risk indices recommended by ACC/AHA guidelines10. RCRI is an older risk calculator than NSQIP risk score. In a systematic meta-analysis of 24 studies including 792,740 patients, RCRI showed moderate discrimination to predict cardiac complications (16). VanWagner et al studied a prognostic model for the prediction of early postoperative cardiovascular disease (CVD) mortality in a large population (n=54,697). The study showed that in univariate analysis mean RCRI scores were significantly higher in early CVD mortality group than those in no CVD mortality group (17). Hoftman et al evaluated the predictive role of RCRI in their kidney transplantation cohort including 1652 patients (18). Our study is the first study in the literature investigating the predictive role of RCRI and NSQIP risk scores for early cardiovascular complications in patients undergoing LDLT. In our study, both risk scores failed to predict early cardiac complications after LDLT. Only RCRI medium-high score, DM and

NASH as transplant indication were associated with in- hospital all-cause mortality. The reason could be most of our patients had low risk RCRI scores (80.2 %), because they had a relatively low DM prevalence (16.5 %) and low creatinine levels (2.2 % of the patients had a creatinine level > 2 mg/dL), also none-of-them had history of heart failure or cerebrovascular disease, and history of CAD was 3.2 %.

Cardiovascular complications are the most common cause of non-graft related post-transplant death19. However, a recent systematic review by Konerman et al reported that in liver transplantation early (≤ 6 month) cardiovascular complication incidence could range from 1 % to 41 %. This review also demonstrated in multivariate analyses that older age and background cardiac disease were persistently associated with higher risk of CV events post-LT20. Our study population had a median age of 53.5 years and 26.3 % of patients were ≥ 60 years old, similar to the studies included in this review.

Nicolau-Raducu et al reported in their cohort of 389 patients, 3.9 % of patients' had ACS in the first month (20). In their cohort, ACS was significantly associated with age, history of CAD and pre-transplant vasopressor use. The mean age was 55 years and 29 % of patients were ≥ 60 years old, and history of CAD was 6 %. Snipelisky et al followed up 506 patients for more than 3 years (21). In their cohort, 8 patients experienced cardiac related mortality. Acute myocardial infarction was rare in their cohort (6 patients in 6 month). In our study, ACS occurred only in 1 patient. The reasons for low incidence of ACS in our cohort were probably due to low DM prevalence and low rates of CAD history and renal failure. Also, our patient group differs from other studies with including only living donor liver transplantation recipients. All of our patients had a recent cardiovascular evaluation, which is usually within 6 weeks, and an elective operation may prevent serious decompensation of the recipient. Differences in donor and surgical characteristics could be another reason.

In the first years after LT, the presence of CAD had caused up to 50 % mortality and 80 % morbidity (22). This high morbidity and mortality rate caused CAD patients were excluded from waiting lists in some clinics. But recent studies showed very low perioperative cardiac complication rates in CAD patients. Skaro et al investigated the impact of CAD on outcomes after liver transplantation (23). In their retrospective study of 386 consecutive liver transplanted patients, they analyzed the follow-up data with a median follow-up of 4.21 years. They concluded that the presence of CAD was not associated with postoperative ACS, cardiac mortality and heart failure. An et al investigated the prevalence of CAD in 1045 patients and reported very low rates (3) adverse cardiac events in 57 CAD patients) (4). Wray et al investigated outcomes of 630 patients undergoing LT who underwent angiography prior to transplantation (5). They reported treated CAD patients with optimal medical and invasive strategies, post-LT survival was similar for the patients with and without CAD in their cohort. However, Konerman et al reviewed 29 studies representing 57,493 patients, and reported that 7 in 23 studies demonstrated history of cardiac disease as a predictor of cardiovascular events in post-transplant period. But only 2 of these studies were conducted in the early post-transplant period (21). History of CAD was not a predictor of cardiac complications and in- hospital all-cause mortality in our study. First, we had only nine (3.2 %) patients with history of CAD, most of the previous studies had 6–7.6 % CAD history rates (24, 25, 26). Second, we had a low cardiovascular complication rate of 1.8 %, and no cardiovascular mortality in early post-transplant period. The reason could be our recipient selection criteria, which has lead to low rates of recipient with history of CAD. Additionally, in LDLT, patients experience less hemodynamic changes intraoperatively from those undergoing deceased donor LT and this may have a differential effect on cardiac events. VanWagner et al conducted a study among 32810 LT recipients, 368 Patients experienced major adverse cardiovascular events < 30 day, and 3.3 % of these patients had living donor, 4.4 % of these patients had DCD donor, but no statistics were conducted on the difference between LDLT patients and non-LDLT patients (26).

MELD score was found an independent predictor of cardiovascular complications after liver transplantation in several studies (18, 20, 25, 27). VanWagner et al studied 54697 liver transplantation patients with mean MELD 19, and on univariate analysis patients with CVD mortality had significantly higher mean MELD scores than those of without CVD mortality (18). Also, MELD score was a multivariate predictor of 30-day cardiovascular mortality post-LT. In a recent systematic review, MELD score was the third independent predictor of cardiovascular outcomes, following older age and history of CAD21. The studies included in this review had mean MELD scores between (19–22) however our median MELD score was (16). Our relatively low MELD scores could be another reason for low cardiovascular complication rates after LT.

Diabetes and NASH are often thought as increased risk for cardiac outcomes. Our study had 16.5 % DM prevalence and 7.6 % of the patients had NASH as a transplant indication. Although DM and NASH were not prominent predictors for cardiovascular outcomes in most of the previous studies, NASH prevalence was similar, but DM prevalence was relatively low compared to other studies (29, 30). In our study, DM and NASH were associated with in- hospital all-cause mortality, but not with cardiovascular complications.

In our study, a relatively large number of LDLT patients were included and there was no missing data required for estimating the risk on revised RCRI and NSQIP model. The major limitation was cardiac troponin levels after surgery. But electrocardiogram and echocardiography to determine postoperative volume status are routine in our practice, so we hardly missed myocardial infarction. Troponin elevations without chest pain and/or dynamic electrocardiographic change can show myocardial injury but not myocardial infarction, so there would be no change in medical treatment. Another limitation, the current analysis may be limited due to our total number of complications, although not insignificant, it was too low to perform a multivariate logistic regression; therefore, the effects of independent variables could not be excluded. Also, due to the differences in peri-operative and donor factors between LDLT and deceased donor transplantation, these data may not represent the majority of LT patients.

Conclusion

Cardiac complications after living donor liver transplantation were not common, and non-cardiac reasons were the leading cause of death after surgery in our study group. Neither the NSQIP index nor the RCRI score predicted perioperative cardiovascular complications after living donor liver transplantation. Special risk assessment tools are required for this special population in order to improve patient outcomes and identify patients at highest risk for these outcomes.

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