Perioperative Risk Predictors of Cardiac Outcomes in Patients Undergoing Liver Transplantation Surgery

Anas Safadi, MD; Mohamed Homsi, MD; Waddah Maskoun, MD; Kathleen A. Lane, MS; Inder Singh, MD; S.G. Sawada, MD; Jo Mahenthiran, MD

Background—Cardiac risk assessment for perioperative outcomes of liver transplantation patients is limited. We examined the outcomes of an older intermediate-cardiac-risk group of patients undergoing liver transplantation surgery.

Methods and Results—Patients who had liver transplantation surgery between 2001 and 2005 were studied. The 3 outcomes analyzed were nonfatal myocardial infarction, death, and either outcome within the first 30 days after the liver transplantation surgery. Of 403 patients (mean age, 52±9 years; 67% male), 106 (26%) were diabetic, 84 (21%) were hypertensive, and 173 (43%) had a history of smoking. There were 48 total events (12%), 25 myocardial infarctions (7%), and 38 deaths (9%) recorded during the perioperative period. From the final multivariate model, history of coronary artery disease, prior stroke, and postoperative sepsis predicted greater risk (P=0.014; odds ratio [OR], 4.0; 95% confidence interval [CI], 1.3 to 11.8; OR, 6.6; 95% CI, 1.3 to 33.8; and P<0.001; OR, 7.5; 95% CI, 3.3 to 17.1, respectively). Use of perioperative β-blockers was protective (P=0.004; OR, 0.20; 95% CI, 0.1 to 0.6) for combined cardiac outcomes. For the outcome of death on multivariate analysis, postoperative sepsis and increased interventricular septal thickness predicted risk (P<0.001; OR, 8.6; 95% CI, 3.5 to 20.9, and P=0.027; OR, 2.8; 95% CI, 1.1 to 7.2, respectively), whereas the use of perioperative β-blockers was again protective (P=0.012; OR, 0.07; 95% CI, 0.01 to 0.56).

Conclusion—In our study of cardiac risk assessment for liver transplantation surgery, history of stroke, coronary artery disease, postoperative sepsis, and increased interventricular septal thickness were markers of adverse perioperative cardiac outcomes, whereas use of perioperative β-blockers was significantly protective. (Circulation. 2009;120:1189-1194.)

Key Words: echocardiography ■ liver ■ prognosis ■ risk factors ■ surgery ■ transplantation

The number of liver transplantations done each year continues to grow, with improvement in outcomes yielding a greater treatment demand.1 Liver transplantation has emerged over the past several decades as a viable treatment option for patients with fulminant hepatic failure and end-stage liver disease.1 There is an expected rise in the prevalence of coronary artery disease (CAD) in patients with increased cardiac risk factors (obesity, diabetes mellitus, hypertension, and hyperlipidemia); these risk factors have been shown to increase post–liver transplantation surgery (LTS) complications.2 In addition, excluding recurrent disease, graft loss resulting from technical complications, and malignancies, CAD is the most common cause of complications post LTS, with a greater risk of cardiac deaths and ischemic events in LTS patients as compared to age- and sex-matched general populations.2 As reported by Plotkin et al,3 patients with known CAD have a significantly increased morbidity and mortality with this surgery. Patients undergoing this procedure continue to get older; therefore, the prevalence of CAD will likewise increase. Currently, the estimated prevalence of CAD in patients with end-stage liver disease is up to 27%, clearly exceeding the general healthy population.4 The cardiac risk stratification is of great interest in LTS patients as those with known CAD have worse outcomes, there is a paucity of organ donation, and there is a greater resource expenditure for the entire process.5

Clinical Perspective on p 1194

Hence, the cardiac perioperative risk assessment of these patients is an increasingly important clinical requirement before transplantation surgery and will likely have a strong impact on postoperative outcomes. Presently, cardiac risk assessment for perioperative outcomes is limited, and there are conflicting results on the utility of stress testing for risk stratification.5 In 1 study, stress echocardiography did not reliably identify patients at high cardiac risk during liver transplantation; another showed that a normal stress myocardial perfusion study identified patients at very low risk for early and late cardiac events despite having high-risk profiles.5,6 Defining risk in this population remains challenging with no optimal cardiovascular risk stratification strategy available.7 Lester et al7 reported that there are no formal

Received January 18, 2009; accepted July 17, 2009.
From the Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis.
Correspondence to Jo Mahenthiran, MD, FACC, Associate Professor of Clinical Medicine, Krannert Institute of Cardiology, Room D4078, 1801 N Senate Blvd, Suite E400, Indianapolis, IN 46202–1228. E-mail jmahenth@iupui.edu
© 2009 American Heart Association, Inc.
Circulation is available at http://circ.ahajournals.org DOI: 10.1161/CIRCULATIONAHA.108.847178
guidelines to help in this process, but generally, patients who are >45 years of age or who have history of diabetes mellitus, peripheral vascular disease, or >2 standard cardiac risk factors should undergo some type of formal cardiovascular testing. Since current guidelines do not distinguish LTS as high risk, higher stress state of surgery (ie, high risk of bleeding), and the unreliability of noninvasive stress testing for risk assessment, we sought to further evaluate the prognostic markers of perioperative cardiac outcomes in older intermediate coronary artery risk patients undergoing LTS at our institution.

Methods

We evaluated 413 patients who underwent LTS between 2001 and 2005 at Indiana University. The study protocol is a retrospective clinical experience of all patients who were seen for cardiac risk assessment and subsequently underwent LTS. Most patients were seen by a cardiologist and/or referred for a stress test before undergoing surgery. It is routine practice at our institution to have patients undergo a stress examination before their LTS. Patient with all conventional known atherosclerotic risk factors were analyzed. The primary events analyzed were the incidence of nonfatal myocardial infarction (MI), death, or combined events within the first 30 days after the LTS (perioperative period). The electronic chart on each patient was reviewed to collect follow-up data, including demographics, medical history, medications use (both before and after transplantation), stress test results, ECG findings, echocardiography variables, and postoperative outcomes. Follow-up data were incomplete on 10 patients (2.4%); therefore, our final study group consisted of 403 patients. Most patients (356 of 403, 89%) underwent dobutamine stress echocardiography as part of their perioperative cardiac risk assessment as per our standard laboratory protocol with wall motion analysis at rest and with stress of all coronary territories. An abnormal stress echocardiogram was defined by the presence of a new stress-induced wall motion abnormality. All stress echocardiography studies were interpreted as an individual clinical study blinded to our present analysis on outcomes. All stress echocardiograms were interpreted as an individual clinical study blinded to our present analysis on outcomes. All stress echocardiograms were interpreted as an individual clinical study blinded to our present analysis on outcomes. All stress echocardiograms were interpreted as an individual clinical study blinded to our present analysis on outcomes.

Statistical Analysis

All independent variables were screened in separate univariate logistic regression models for each outcome of postoperative MI, death, and combined events. Variables with a value of \( P \leq 0.15 \) from the univariate model were included in the multivariate analysis. A value of \( P \leq 0.15 \) was chosen as the cutoff because a lower probability value cutoff has the possibility of failing to identify variables that may be important in the multivariate setting; it is possible that a collection of variables, each of which is weakly associated with the outcome, can become significant when taken together. Logistic regression model was performed with both stepwise selection and forward selection to identify the final models for each outcome with all variables significant at \( P \leq 0.05 \). In cases of small sample sizes, exact logistic regression was used. This analysis strategy was repeated in the subset of subjects with stress tests, in those with hypertension, and in subjects with diabetes mellitus. Event-free survival curves were constructed from the Kaplan–Meier product-limit method. Log-rank tests were used to compare the event-free survival times of those with and without perioperative \( \beta \)-blocker use. Survival analysis was added to look at time to event in more detail.

Results

The baseline characteristics of our patient population are shown in Table 1. Of the 403 patients studied, 25 (6.6%)
experienced an MI, 38 (9.4%) died, and 48 (11.9%) experienced either outcome within the first 30 days. Univariate predictors for each outcome (MI, death, or their combination) were analyzed and are shown in Table 2. For MI, the univariate variables that were considered significant included a history of stroke, postoperative sepsis, and diuretic use ($P = 0.005$; odds ratio [OR], 7.9; 95% confidence interval [CI], 1.9 to 33.9; $P = 0.04$; OR, 3.37; 95% CI, 1.05 to 10.8; and $P = 0.035$; OR, 0.42; 95% CI, 0.18 to 0.94, respectively).

For death, significantly more pertinent variables entered the multivariate analysis model, including gender, history of CAD, prior alcohol use, abnormal stress test, wide QRS, abnormal interventricular septal thickness, preoperative nonsteroidal antiinflammatory drug use, postoperative sepsis, and perioperative β-blocker use. The significant univariate predictors of combined events were several and were similar to the death outcome (see Table 2) with the notable addition of history of prior stroke and diuretic use.

Results from the final multivariate models are shown in Table 3. For MI, significant risk was associated with history of stroke ($P = 0.008$; OR, 7.5; 95% CI, 1.7 to 32.7). There was increased risk for death alone in patients with postoperative sepsis and increased interventricular septal thickness ($P < 0.001$; OR, 8.6; 95% CI, 3.5 to 20.9; and $P = 0.027$; OR, 2.8; 95% CI, 1.1 to 7.2), whereas the use of perioperative β-blockers was found to be protective ($P = 0.012$; OR, 0.07; 95% CI, 0.01 to 0.56). From the final multivariate model for combined outcomes, history of CAD, prior stroke, and postoperative sepsis predicted greater risk ($P = 0.014$; OR, 4.0; 95% CI, 1.3 to 11.8; $P = 0.025$; OR, 6.6; 95% CI, 1.3 to 33.8; and $P < 0.001$; OR, 7.5; 95% CI, 3.3 to 17.1, respectively), whereas perioperative β-blockers were protective ($P = 0.004$; OR, 0.20; 95% CI, 0.1 to 0.6). The Kaplan–Meier survival curve estimates for the combined outcomes of death and MI showed early protection from perioperative use of β-blockers in patients undergoing LTS (see the Figure). Noninvasive stress testing provided additional information for risk stratification of these LTS patients, most notably with very high specificity and negative predictive value for predicting preoperative risk of cardiac outcomes with LTS (see Table 4).


Table 4. Stress Test Data of Early Postoperative Adverse Cardiac Events Among LTS Patients (Subjects With Stress Tests)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal MI within 30 d</td>
<td>0.80</td>
<td>0.95</td>
<td>0.11</td>
<td>0.93</td>
</tr>
<tr>
<td>Death within 30 d</td>
<td>0.15</td>
<td>0.95</td>
<td>0.23</td>
<td>0.92</td>
</tr>
<tr>
<td>Death/nonfatal MI within 30 d</td>
<td>0.14</td>
<td>0.95</td>
<td>0.27</td>
<td>0.89</td>
</tr>
</tbody>
</table>

**Discussion**

Screening and cardiac risk stratification for liver transplantation surgery continues to be a dilemma for many centers nationwide. This is likely because of conflicting data available for noninvasive stress testing and the lack of specific guideline recommendations. Currently, there are wide variations in the center-specific protocols utilized for cardiac risk stratification of LTS patients. Compared with other transplantation surgeries, liver transplantation can induce marked perioperative hemodynamic and hypercoagulability alterations that can adversely affect outcomes in patients with known CAD. Therefore, we sought to identify prognostic markers and perioperative risk for cardiac outcomes in patients undergoing LTS to better assist in risk stratification of this population. Of note, nonfatal MI was defined through the use of troponin positivity. Because these patients were intubated and sedated, a clinical history could not be obtained. Shammas et al. reported that only a minority of patients (14%) who undergo noncardiac surgery have signs or symptoms of myocardial ischemia; therefore, measurement of cardiac biomarkers (preferably troponin) is the preferred method for diagnosing MI.

Although we analyzed for many variables considered strong cardiac risk factors (ie, diabetes mellitus, hypertension, age), we found that only history of CAD and stroke significantly increased perioperative cardiac outcomes in this 30-day period. It is noteworthy to point out that early mortality outcomes after LTS are usually due to infection or allograft failure and are not cardiovascular in nature. In fact, short-term perioperative outcomes for both MI and cardiac death were found to be <3% in 1 study. Zoghbi et al. pointed out that late cardiovascular-related mortality is often seen in patients with a history of CAD or known risk factors, with a reported mortality of 16% to 22% within 5 years of transplantation. Our study showed that a positive stress test was a univariate predictor of risk for cardiac outcomes within the perioperative period (early mortality). Moreover, we found that patients who had increased interventricular septal thickness were at risk of increased death. This is likely a surrogate marker for left ventricular hypertrophy, which has been shown to have negative prognostic implications with increased risk for all-cause mortality and cardiovascular disease morbidity and mortality. In addition, Haider et al. showed that increased left ventricular hypertrophy was associated with increased risk for sudden death after accounting for known risk factors. Therefore, patients with these findings are likely at higher risk than an age-matched cohort with the same clinical risk profile.

In addition to the positive findings discussed, many pertinent negative findings deserve mention. From a pharmacological perspective, medications such as statins were not found to be statistically significant. Likewise, other demographic features such as history of hypertension, hyperlipidemia, diabetes mellitus, race, and echocardiographic variables (ie, ejection fraction, fractional shortening, left atrial dilation) or ECG findings (ie, wide QRS, QT prolongation) were not found to be statistically significant on multivariate analysis.

The use of noninvasive stress testing as a diagnostic tool for risk stratification remains controversial; the literature seems to be conflicting in terms of both the optimum stress imaging modality in this population and the utility in predicting outcomes. In the former, Plevak recommended dobutamine stress echocardiography as the stress imaging modality of choice, whereas others have shown that stress-induced wall motion abnormality did not correlate with cardiac catheterization findings in the majority of these patients. Williams and colleagues showed that dobutamine stress echocardiography positivity did not correlate with intraoperative cardiac events in patients undergoing LTS. Recently, Harinstein et al. showed that dobutamine stress echocardiography as a screening test for obstructive CAD in liver transplantation patients has very poor sensitivity (13%). Our study has the largest number of patients studied retrospectively and showed that an abnormal stress echocardiography was not associated with adverse cardiac outcomes (on multivariate analysis). In conjunction with the available literature to date, we found that a normal stress test had a very high negative predictive value (>90%) in all patients undergoing LTS. Our results are similar to previously reported findings of poor sensitivity and positive predictive capabilities of dobutamine stress echocardiography in these patients undergoing LTS. Therefore, according to our results, patients undergoing LTS would likely benefit only from noninvasive stress testing to help identify those patients who are at very low risk for negative cardiac outcomes in the LTS perioperative period.

Perioperative β-blockers during LTS for cardiac outcome risk reduction have not been evaluated in the literature to date in this population. The American College of Cardiology/American Heart Association guidelines state that several randomized trials have been published that have not demonstrated the efficacy of β-blockers. The guidelines indicate that the weight of evidence is in favor of perioperative β-blockers during noncardiac surgery in high-risk patients with possible harm in lower-risk patients. Our study showed a significant reduction in perioperative adverse cardiac outcomes with the use of β-blockers in LTS patients, suggesting that this cohort is likely at a higher risk for cardiac events. Chopra et al. explained that during the perioperative period a significant catecholamine surge occurs, producing elevations in heart rate and blood pressure; in addition, experimental models showed that increased vasomotor reactivity, rupture of coronary plaques, and thrombus formation are heightened during the perioperative period, ultimately leading to increased cardiovascular events. β-Blockers
attenuate both the sympathetic and neuroendocrine responses to stress perioperatively; they balance myocardial oxygen supply and demand mismatch, reduce inflammatory markers and free radicals, and stabilize atherosclerotic plaques. These mechanisms likely explain the decreased perioperative cardiac events in our LTS population. Our study demonstrates that the use of β-blockers protected perioperative LTS patients from adverse cardiac outcomes. This population and surgery, considered intermediate by standard risk stratification, are more likely a higher-than-perceived-risk group and consequently derived benefit from this therapy. Although, as per our study, β-blockers seem to provide significant protection from perioperative cardiac outcomes during LTS; this finding needs to be further evaluated in a randomized outcome trial before any firm conclusions can be made.

Because noninvasive stress testing remains controversial in this population, it would be prudent to evaluate whether cardiac catheterization and subsequent prophylactic revascularization of these higher-risk patients would improve cardiac outcomes. Cardiac catheterization was done on a limited number of patients (96 of 413, 23%); therefore, revascularization (done on only 8 patients) and its effects on perioperative outcomes were not specifically evaluated. In the general population, multiple trials have shown no benefit in prophylactic revascularization compared with medical therapy in stable patients undergoing surgery (even major vascular surgery). McFalls et al concluded that coronary artery revascularization before elective vascular surgery did not significantly alter the long-term outcome and hence recommended against prophylactic revascularization. Further studies evaluating the benefit of prophylactic revascularization in this specific population undergoing LTS are needed before any definite recommendations can be made.

Our study has several limitations. Because it is a retrospective study, there is likely to be heterogeneity and bias in the medical therapy and cardiac testing options of this group. The results of the study also can be affected by the patient selection process, preoperative risk stratification strategy, and postoperative care. This was a cohort study that evaluated this specific liver transplantation population and not specific individuals, which is a limitation of the study. In addition, liver transplantation programs have different algorithms for risk stratification with differing outcomes; hence, findings in our specific population may not accurately be extrapolated to a mixed general population of patients scheduled to undergo LTS.

Conclusions

Our study of a large intermediate-cardiac-risk cohort undergoing a high-risk LTS suggests that a history of CAD, prior stroke, postoperative sepsis, and increased intraventricular septal thickness were important risk predictors of early postoperative adverse cardiac outcomes. These patients also derived significant protection with the use of perioperative β-blockers regardless of their clinical risk profile. In addition, noninvasive stress testing by dobutamine stress echocardiography is an important risk stratification method of further risk prediction, with a normal stress study providing a high degree of negative predictive value. These findings provide insight into this specific population, and additional prospective, randomized studies are needed before any firm conclusions or recommendations can be made.

Disclosures

None.

References

Liver transplantation surgery has become widespread, but knowledge of the appropriate perioperative cardiac risk assessment of this patient population remains limited. Current literature is controversial and clinical outcomes data are lacking. We evaluated the largest cohort to date to better define cardiac risk and to identify prognostic markers for those patients undergoing liver transplantation surgery. The present clinical study should help lead to a standardized approach to cardiac risk evaluation of patients undergoing a liver transplantation surgery. This, in turn, should lead to better patient outcomes and improved resource allocation. Several areas are controversial, including the role of preoperative noninvasive stress testing, use of perioperative β-blockers, surgical risk, and identification of variables that can be associated with adverse cardiac outcomes. We found that perioperative β-blocker use was protective from adverse cardiac outcomes. Furthermore, noninvasive stress testing was most useful for identifying a low-risk group of patients with a very high negative predictive value. History of coronary disease, stroke, increased interventricular septal thickness, and postoperative sepsis were all associated with adverse cardiac outcomes. Current models of risk assessment underestimate these patients, and our study suggests that they do not fit the traditional model and are likely at a higher risk for perioperative cardiac events. This study has helped clarify many of the clinical issues and should provide a strong foundation to develop future prospective randomized trials.
Perioperative Risk Predictors of Cardiac Outcomes in Patients Undergoing Liver Transplantation Surgery
Anas Safadi, Mohamed Homsi, Waddah Maskoun, Kathleen A. Lane, Inder Singh, S.G. Sawada and Jo Mahenthiran

Circulation. 2009;120:1189-1194; originally published online September 14, 2009; doi: 10.1161/CIRCULATIONAHA.108.847178
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/120/13/1189