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Review Article

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Is Cardiac Surgery Safe in Patients with Previous Liver Transplantation? A Narrative Review

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Abstract

Background

Liver transplant patients have increased risk of developing cardiovascular disease and the outcome of these patients following cardiac surgery has been reported in small series of patients. The aim of this review was to examine and report safety outcomes of liver transplant patients undergoing cardiac surgery.

Methods

Literature review was conducted using three databases from inception to June 2023. Multiple search terms were used and limited to English language. Nine relevant articles were included. Outcomes of interest were short-term mortality, long-term survival, liver graft failure, major morbidity and infection in liver transplant recipients undergoing cardiac surgery.

Results

Cardiac risk factors (diabetes mellitus, hypertension, hyperlipidemia) were prevalent in liver transplant patients. 30-days mortality ranged across the studies from zero to 23.8%. 1-year survival ranged from 74-91% and 5-years survival ranged from 33-69%. Commonest causes of death were cardiac and sepsis. Predictors of mortality were preoperative encephalopathy, pulmonary hypertension, blood transfusion and postoperative increase in creatinine and bilirubin levels. Liver allograft rejection ranged from zero to 4.7% with no predictors reported. Liver dysfunction was seen in 33-46% of patients, and all were transient with recovery at the time of hospital discharge. Major morbidities were commonly reported and included respiratory and renal failure. Infection rates ranged from zero to 38% and the most common reported sites were pneumonia, sepsis, and surgical site infections.

Conclusion

Cardiac surgery can be performed in liver transplant patients with good short- and long-term results and acceptable morbidities.

Keywords: Liver Transplant, Cardiac Surgery, Graft Failure, Liver Rejection, Immunosuppression.

1. Introduction

Orthotopic liver transplantation (OLT) is the treatment of choice for end-stage liver disease (ESLD) in appropriate candidates. Significant cardiovascular disease is considered a contraindication to liver transplantation because of the operative risks, the potential for reduced survival rate, and the limited transplant resources. In the past two decades, the mean age at OLT has progressively increased and currently more than 2/3 of patients receiving transplants are above 50 years old. This trend has been accompanied by an increase in the number of OLT candidates with pre-existing cardiovascular pathology [1]. Patients with ESLD and above age of 50 years old waiting for liver transplant surgery were studied using coronary angiography which showed a prevalence of severe coronary artery disease (>70% stenosis) of 16.2%. Even after eliminating patients with prior history of coronary artery disease (angina, myocardial infarction, revascularization) the prevalence was 13.3% with Diabetes mellitus (DM) being the most important risk factor for developing coronary artery disease [2]. It has been reported that patients who underwent liver transplant with a follow-up of 82 months had 17.3% death rate attributed to primary cardiovascular event and 12% were coronary specific event. The strongest pre-transplant predictors of mortality were age, Framingham risk score, pre-existing coronary artery disease, pre-existing hyperlipidemia. The strongest post-transplant predictors of mortality were new-onset hypertension, and new-onset diabetes mellitus post transplantation. New-onset hypertension developed in 40% of patients post liver transplant and new-onset DM in 22% of patients and new-onset hyperlipidemia in 36.8% of patients in that study [1].

Consequently, the number of liver transplant patients with

cardiac risk factors or new risk factors been referred to cardiac surgery is increasing with only limited outcome measures have been previously reported [3]. first reported on three patients with liver transplants to undergo coronary artery bypass graft surgery (CABG). All three cases tolerated the procedure well without liver decompensation, infection, excessive bleeding, or impaired wound healing. Since then, more single center studies reported their experience with liver transplant patients undergoing cardiac surgery [4-12]. The aim of this review was to examine and report the short- and long-term outcomes of liver transplant recipients undergoing cardiac surgery. Prevalence of liver graft failure and long-term survival were also examined and discussed. Understanding these outcomes will lead to the development of preventative strategies and improved outcomes in these patients.

2. Methods

Literature review was conducted in PubMed, Google scholar, Embase databases from inception to 1st June 2023. Literature search was limited to English language only. The following search terms were used [cardiac surgery and liver transplant], [cardiac surgery and abdominal solid organ transplant], [valve surgery and liver transplant], [coronary artery bypass and liver transplant], [liver failure and cardiac surgery], [immunosuppression and cardiac surgery]. All titles were screened, and relevant abstracts were extracted. All relevant articles were then reviewed, analyzed, and summarized. Individual references from the reference list of each relevant article were also manually searched to expand the search criteria. Case reports and small case series of less than 10 patients were excluded from the study. In the event of duplicate publications from same authors or institution, the largest study was included only. Studies examining the outcomes of cardiac surgery on patients with abdominal solid organ transplantation (ASOT) were included in the study if individual data were available for liver transplant subset. The number of relevant articles meeting the above criteria included in this analysis was nine articles [4-12]. Outcomes of interest were short-term mortality, predictors of mortality, long-term survival, liver graft failure, major morbidity post-operatively and infections. Outcome variables were tabulated in relevant tables with reference to each published article. Short-term mortality was defined as 30-Day mortality following cardiac surgery. Liver graft failure referred to liver graft failure that required a re-transplantation or ended up in a mortality. Liver graft dysfunction was defined as transient deterioration in liver function as measured by elevation in liver function tests that resolved subsequently. Infectious complications referred to surgical site infections (sternum and leg wound) whether deep or superficial, pneumonia or sepsis. Ethical approval was not required, and no informed consent was needed as this was a narrative review of published articles.

3. Results

3.1 Prevalence of Risk Factors in Liver Transplant Patients Undergoing Cardiac Surgery

Table 1 is the summary of the included articles. As shown, majority of patients are males (58%-89%) in their 5th-6th decade of life. Interval from liver transplantation to cardiac surgery ranged from 30 months to 96 months. Cardiac risk factors were prevalent with Diabetes mellitus (DM) occurring in 25-75% of liver transplant patients, hypertension occurring in 67-94% of patients, hyperlipidemia occurring in 29-62% of liver transplant patients and history of coronary artery disease occurring in 10-40% of cases. The incidence of endocarditis ranged from zero to 24% and renal failure was seen in 17-47% of liver transplant patients. Child-Pugh class was only described in one paper [8]. MELD score (Model for end-stage Liver disease) that is used widely in predicting mortality in patients undergoing liver transplants was reported in two studies only [8,10]. All articles included were retrospective observational studies of single center with exception of one study which was a retrospective analysis of Health care cost and utilization project nationwide inpatient sample [9].

Variable	Mitruka [4]	Prabhakar [5]	Deb [6]	Filsoufi [7]	Ota [8]	Vargo[9]	Harrington [10]	Farag [11]	Kohmoto [12]
Year of publication	1997	1998	2006	2007	2013	2016	2017	2017	2018
Patients number	17	15	13	12	61	738	43	21	18
Type of study	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Center	Single	Single	Single	Single	Single	Nationwide database	Single	Single	Single
Control group	No	No	No	No	No	Yes	No	Yes	No
Mean Age (years)	56	53	52	68	62	58	60	55	63
Male Gender	76%	87%	NR	58%	74%	66%	79%	71%	78%
Type of cardiac surgery	CABG,valve, other.	CABG, valve + combination	CABG, valve + combination	CABG, valve + combination	CABG, valve + combination	CABG, valve + combination	CABG, valve + combination	CABG, valve + combination	CABG, valve + combination
Interval from liver transplant to cardiac surgery	53 months	30.4 months	79 months	56 months	5.4 years	NR	63 months	4.5 years	8 years
Diabetes mellitus	47%	47%	43%	58%	75%	25%	48%	71%	72%
Hypertension	94%	67%	87%	83%	69%	NR	NR	81%	89%
Hyperlipidemia	NR	NR	62%	NR	30%	NR	29%	48%	NR
Coronary artery disease	35%	40%	26%	33%	23%	24%	10%	29%	33%
Endocarditis	6%	20%	NR	Zero	10%	NR	NR	24%	NR

Renal failure	NR	47%	46%	17%	31%	34%	30%	43%	NR
Immunosuppression therapy	NR	NR	Triple: 34% Double: 57% Single: 9%	Triple: 17% Double: 25% Single: 58%	NR	NR	NR	NR	NR
Child class	NR	NR	NR	NR	A: 54% B: 46%	NR	NR	NR	NR
MELD score (mean)	NR	NR	NR	NR	13.5	NR	11.2	NR	NR

Table 1: Summary of the included studies and the baseline demographic reported.
NR: not reported.
CABG: Coronary artery bypass graft surgery.
MELD: Model for end-stage liver disease.

3.2 30-Days Mortality and Long-Term Survival in Liver Transplant Patients Following Cardiac Surgery

30-Days mortality (table 2) ranged across the studies examined from zero to 23.8% with four studies showing no mortalities and another four studies showed 30-Days mortality between 6-7% only [4-10,12]. The two commonest causes of death were cardiac and sepsis. Follow-up time post cardiac surgery ranged from 20 to 51 months with survival at follow-up ranged from 57% to 94% (table 2). Reported 1-year survival ranged from 74-91% and reported 5-years survival ranged from 33-69%. Predictors of mortality (table 3) were reported in only three studies [8,10,11]. These predictors were: preoperative encephalopathy, pulmonary hypertension, intra-op blood transfusion, postoperative peak in creatinine level and postoperative increase in Bilirubin level.

Author/year	Number of patients	30-Days mortality	Causes of death	Follow-up	Long-term survival
Mitruka 4/ 1997	17	Zero	1 case at follow up from sepsis	Mean=20 months	94% at 20 months
94% at 20 months	94% at 20 months	Zero	2 deaths at follow-up: 1 from cardiac cause and 1 respiratory failure	2 deaths at follow-up: 1 from cardiac cause and 1 respiratory failure	86.7% at 26.5 months follow-up
Deb 6/2006	13	Zero	4 deaths at follow-up: 1: GI bleed 2: sepsis 3: Hepatitis C 4: Unknown	Mean=39 months	69.2% survival at 39 months 1-year survival: 77% 5-years survival: 69%
Filsoufi 7/2007	12	Zero	Not reported	Median=3.9 years	67% survival at 3.9 years follow up. 1-year survival: 91% 5-years survival: 67%
Ota 8/2013	61	6.6%	1. respiratory (8.2%) 2.cerebrovascular (6.6%) 3. cardiac (5%) 4. Cancer (3.3%) 5. Infection (1.6%) 6. Unknown (18%)	Mean=3.1 years	57.4% survival at mean follow up of 3.1 years. 1-year survival: 82.4% 5-years survival: 50.2%
Vargo 9/2016	738	7.2%	Not reported.	No follow-up	Not reported

Harrington 10/ 2017	43	7%	Not reported.	Median 3.4 years	1-year survival: 90% 5-years survival: 51% 10-years survival 35%
Farag 11/2017	21	23.8%	1. Sepsis 2. Cardiac	Median 32 months	Survival at follow-up was 62% 1-year survival: 74% 5-years survival: 66% 10-years survival: 56%
Kohmoto 12/ 2018	18	6%	Cardiac	Median 51 months	Survival at follow-up: 89% 3-years survival: 61% 5-years survival: 33% 10-years survival: 17%

Table 2: Short-term mortality and long-term survival in liver transplant patients undergoing cardiac surgery.
GI: gastrointestinal.

Author/year	Predictors of mortality
Ota [8]/2013	**Preoperative encephalopathy (OR 5.2) and pulmonary hypertension (OR 3.5)**
Harrington [10] / 2017	**Post-operative peak creatinine level (OR 1.8)**
Farag [11]/2017	**Post-operative increase in Bilirubin (HR 1.3), intra-operative transfusion (HR 1.0).**

Table 3: Predictors of short and long-term mortality in liver transplant patients undergoing cardiac surgery.
OR: odds ratio.
HR: Hazard ratio.

3.3 Allograft Rejection, Liver Dysfunction and Major Morbidity Following Cardiac Surgery

Allograft rejection rates ranged from zero to 4.7% (table 4). Five studies showed no allograft rejection while the other studies showed rejection rates between 3-4.7% [4-9,11,12]. No predictors of liver rejection post cardiac surgery have been reported previously. Liver allograft dysfunction (which is defined as elevation of liver function tests post-operatively) was reported in three studies with incidence of 33-46%. All liver dysfunctions were transient and recovered at the time of hospital discharge [5-7]. Encephalopathy was reported in only two studies with incidence of 6% and 20%, respectively [4,8]. No predictors of liver dysfunction were reported previously. Major morbidities such as respiratory failure and renal failure were commonly reported in published series. The incidence of respiratory failure reported was 6.6% to 23.5% and incidence of renal failure reported was 6-36% (table 4).

Author/year	Number of patients	Graft rejection rate	Renal failure	Respiratory failure	Morbidity-3
Mitruka [4]/ 1997	17	Zero	6%	23.5%	Encephalopathy (6%)
Prabhakar [5] /1998	15	Zero	20%	6.6%	Liver allograft dysfunction (40%): resolved on discharge.

Deb [6]/2006	13	Zero	Not reported	Not reported.	Liver allograft dysfunction (46%): resolved on discharge.
Filsoufi [7]/2007	12	Zero	8%	17%	Liver allograft dysfunction (33%): resolved on discharge.
Ota [8]/2013	61	3%	11.5% dialysis (6.6%)	18%	Encephalopathy (20%) Ascites (11.5%)
Vargo [9]/2016	738	4%	36%	Not reported	Not reported
Harrington [10] /2017	43	Not reported	21%	14%	Re-exploration for bleeding (9%)
Farag [11]/2017	21	4.7%	19%	9.5%	Re-exploration for bleeding (9.5%)
Kohmoto [12] /2018	18	Zero	17%	11.1%	No re-exploration for bleeding.

Table 4: Major morbidity and liver graft rejection rates in liver transplant patients undergoing cardiac surgery.

3.4 Infection rates and sites of infections in liver transplant patients undergoing cardiac surgery

Postoperative infections in liver transplant patients undergoing cardiac surgery (table 5) ranged from zero to 38%. Two studies showed no post-operative infection [5,6]. The most common reported sites were pneumonia, septicemia, and surgical site infections (SSI).

Author/year	Number of patients	Infection rate	Site of infection
Mitruka [4] / 1997	17	17.6%	1. pneumonia 2. leg wound infection 3. UTI No mediastinitis/no sepsis.
Prabhakar [5]/1998	15	Zero	None
Deb [6]/2006	13	Zero	None
Filsoufi [7]/2007	12	8.3%	Superficial sternal wound infection. No deep sternal infection/ no sepsis.
Ota [8]/2013	61	25%	1.Pneumonia 2.sepsis
Vargo [9]/2016	738	11.2%	Pneumonia (SSI not reported).
Harrington [10]/2017	43	14%	Not reported.
Farag [11]/2017	21	38.1%	1. SSI 2. sepsis 3. pneumonia 4. UTI
Kohmoto [12]/2018	18	5.5%	Pneumonia No SSI

Table 5: Infection rates and sites of infection in liver transplant patients undergoing cardiac surgery.
UTI: urinary tract infection.
SSI: surgical site infection.

4. Discussion

4. 1 Liver Transplant and Cardiovascular Disease

Liver transplant patients have an increased morbidity and mortality compared with a matched healthy population. This is partially related to pre-existing cardiovascular disease risk factors and partially related to the immunosuppression therapy used. Reducing this risk is of paramount importance to improve long term survival of liver transplant patients. Epidemiological studies have shown that liver transplant is associated with an increased prevalence of cardiac risk factors including hypertension, DM, hyperlipidemia, and obesity. This led to an increased cardiovascular event rate that ranged from 9.4% at 5 years to 25% at 10 years following transplantation. Cardiovascular disease accounts for 21% of deaths of liver transplant recipients surviving more than 3 years [13]. As shown in table 1, hypertension was prevalent among the studies reviewed and occurred in up to 94% of liver transplant patients undergoing cardiac surgery. Hypertension following

liver transplantation is a consequence of immunosuppression (glucocorticoids) and of renal disease. DM was also prevalent in liver transplant patients undergoing cardiac surgery (table 1) with up to 75% of these patients having DM at the time of cardiac surgery. Several factors predispose to the development of DM following liver transplantation such as age, obesity, hepatitis C viral infection and immunosuppression therapy (corticosteroids and Calcineurin inhibitors). Hyperlipidemia is also seen in up to 62% of liver transplant recipients undergoing cardiac surgery (table 1) and occurs secondary to obesity and immunosuppression therapy (Glucocorticoids, Sirolimus) [14]. The aim of this review is to summarize the main results of data published over 4 decades with particular emphasis on the outcome data, operative mortality, and long-term survival. This review will help clinicians in drawing the proper decision in the management strategies when presented with liver transplant patients requiring cardiac surgery.

4.2 Mortality and its Predictors in Liver Transplant Patients Following Cardiac Surgery

30-Days mortality ranged across the studies examined from zero to 23.8% with four studies showing no mortalities and another four studies showed 30-Days mortality between 6-7% only [4, 7-10,12]. The two commonest causes of death in the liver transplant patients were cardiac and sepsis. Reported 1-year survival ranged from 74-91% and reported 5-years survival ranged from 33-69%. Predictors of mortality (table 3) were reported in only three studies [8,10,11]. These predictors were: preoperative encephalopathy, pulmonary hypertension, intra-op blood transfusion, postoperative peak in creatinine level and postoperative increase in Bilirubin level. Two studies have matched liver transplants to controls using a variety of matching techniques [9,11]. Vargo et al, reported that liver transplant patients undergoing cardiac surgery had significantly higher 30-days mortality compared to controls (7.2% vs 3.3%). However, no long-term follow-up survival was reported in that study [9]. Farag et al reported significantly higher 30 Days mortality in liver transplant patients compared to controls (23.8% vs. 5.7%) with long-term mortality also significantly higher in the liver transplant group (38.1% vs 11.4%) over a median follow-up time of 32 months [11]. Two studies analyzed their mortality outcomes using MELD score [8,10].

The MELD score was a linear regression model calculated from serum bilirubin, international normalized ratio (INR) and serum creatinine (range value from 6-40). It was originally adopted in liver transplantation for allocation purposes and proved to be a good predictor of waiting list mortality and post-liver transplant mortality calculation. Ota et al reported that the pre-operative MELD score for those who died in-hospital or late postoperatively were significantly higher than the score for others (In-hospital mortality 23.7 vs 13.1) and (late deaths 15.2 vs 12.3) [8]. The optimal cut-off MELD value was 13.5 (sensitivity 56%, specificity 67.6%). Survival rate for patients with MELD score < 13.5 was significantly higher than for those with MELD score >13.5 both at 1 year (94% vs 52%) and 5 years (67% vs 46%). In contrast, survival rate when stratified by Child-Pugh class (A vs B) was not significantly different at 1 year (83.5% vs. 81% at 1 year) and at 5 years (57% vs 40%). Harrington et al, reported the optimal cut-off value for pre-operative MELD score to predict late death was >13.8 (sensitivity 53%, specificity 89%) while the optimal cut-off value for post-operative MELD score to predict late death was >17 (sensitivity 67%, specificity 79%) [10].

Patients with preoperative MELD score of ≤13.8 had significantly greater survival than those with MELD score >13.8. Patients with post-operative MELD score ≤17 had greater survival than those with > 17. However, both studies had lower sensitivity and specificity of the tests to be used as a risk scoring model for mortality in liver transplant recipients undergoing cardiac surgery. Even the most widely used EURO II score for mortality prediction in cardiac surgery was shown as underestimate for prediction of the 30-days mortality in liver transplant patients undergoing cardiac surgery [8,10]. There is currently only limited data on the 30-days mortality for liver transplant patients undergoing cardiac surgery that will potentially guide the development of useful mortality predictor model in the future specific to liver transplant patients.

4.3 Liver Allograft Rejection and Dysfunction Following Cardiac Surgery

Liver allograft rejection rates ranged from zero to 4.7% (table 4). Five studies showed no allograft rejection while the other studies showed rejection rates between 3-4.7% [4-9,11,12]. No predictors of liver rejection post cardiac surgery have been reported previously. Liver allograft dysfunction was reported in three studies with incidence of 33-46%. All liver dysfunctions were transient and recovered at the time of hospital discharge [5-7]. Early liver graft dysfunction in patients undergoing liver transplant surgery was said to occur in 5.2-38.7% of patients with liver graft survival significantly lower in patients with early graft dysfunction. Strong predictors for early graft dysfunction in liver transplant surgery were bilirubin and INR on day 7 post liver transplantation [15]. Farag et al compared liver transplant patients undergoing cardiac surgery to a matched control group and showed that post-operative Bilirubin level was significantly higher than control (2.8 vs 1.04 mg/dL) and mean post-operative albumin was significantly lower in liver transplant group (29.5 vs 34.2) [11]. Of note that liver graft dysfunction was a transient phenomenon post cardiac surgery, and all recovered at the time of hospital discharge (table 3). Encephalopathy was reported in only two studies with incidence of 6% and 20%, respectively. No predictors of liver dysfunction were reported previously [4,8].

4.4 Major Morbidities and Postoperative Infection Following Cardiac Surgery

Major morbidities such as respiratory failure and renal failure were commonly reported in published series. The incidence of respiratory failure reported was 6.6% to 23.5% and incidence of renal failure reported was 6-36% (table 4). Postoperative infections in liver transplant patients undergoing cardiac surgery are of particular concern to cardiac surgeons as these patients are on chronic immunosuppression therapy and steroids with impaired wound healing and secondary infections. As shown in table 5, infection rates ranged from zero to 38%. Two studies showed no post-operative infection [5,6]. The most common reported sites were pneumonia, septicemia, and surgical site infections (SSI). Farag et al, compared liver transplant patients

to matched controls following cardiac surgery and reported that infection was significantly higher in liver transplant patients than controls (38% vs 13%) [11]. The difference in the reported rates of postoperative infections could be related to the different use of immunosuppression regimen, the urgency of the operation, prevalence of endocarditis and cardiac risk factors in the population studied (e.g., renal failure, DM, obesity) and whether stress dose steroids were given to some or most of the liver transplant patients at the time of cardiac surgery.

4.5 Management Strategies in Liver Transplant Patients Undergoing Cardiac Surgery

Key features in the perioperative management of liver transplant patients include appropriate management of immunosuppression, multidisciplinary approach, minimizing liver toxic agents and close monitoring of the liver function tests postoperatively with close monitoring of the immunosuppression medications to avoid toxicity. Multidisciplinary approach (cardiac surgeons, intensivists, anesthetists, transplant clinicians and infectious disease specialists) is of great importance when managing liver transplant patients. Developing risk scoring models can identify liver transplant recipients at higher risk of mortality and morbidity preoperatively that may help in allocating the best treatment strategies and resources appropriately.

5. Limitations of the Study

Although this is a comprehensive review of the outcome of liver transplant recipients undergoing cardiac surgery, the review has several limitations. Firstly, the references used were observational studies and were mostly single center studies. Secondly, there was no prospective study and no randomized trial performed in these study population that was reported and as such, these studies will have inherent selection bias associated with them. Thirdly, although the general principles of management for the liver transplant patients following cardiac surgery were applied in the various studied used, the management strategies differed between centers with lack of standardization between them. This might have biased the results of observed outcomes and partially explain the differences in outcomes seen between the studies examined.

6. Conclusion

Cardiac surgery can be safely performed in patients with prior liver transplants with good short-term morbidity and mortality. Long-term survival results are encouraging. Understanding these observations may lead to improved outcomes in the future and improve detection and management strategies aiming at reducing the adverse outcomes. The use of scoring systems such as MELD may be useful in predicting adverse events in liver transplant patients undergoing cardiac surgery.

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none declared.

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Ethical approval and informed consent

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