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Review article

Concomitant vs staged orthotopic liver transplant after cardiac surgical procedures

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ABSTRACT

Background: In patients who require orthotopic liver transplant (OLT), cardiac surgery may be needed to optimize preoperative cardiac status for OLT. The aim of this systematic review was to evaluate patient characteristics and outcomes of those undergoing staged versus concomitant cardiac procedures with OLT.
Methods: An electronic search was performed to identify all case reports and series, from which patient-level data was extracted regarding cardiac procedures associated with OLT. After assessment for inclusion and exclusion criteria, 26 articles were pooled for systematic review.
Results: Overall, 49 patients were included in the analysis, of whom 12 (24%) underwent staged procedures and 37 (76%) underwent concomitant procedures. The median age was lower in the staged group [staged: 51 (IQR, 43.8–59.2) years vs. concomitant: 60 (IQR, 55.0–64.0) years, $p = .02$]. Other baseline characteristics were comparable between the two groups. For staged procedures, the median time between heart procedures and OLT was 2 (IQR, 1.0–3.5) months. The most commonly reported cardiac procedures were coronary artery bypass graft (CABG) [staged: 4/12 (33.3%) vs. concomitant: 21/37 (56.8%), $p = .28$], aortic valve replacement (AVR) [staged: 3/12 (25.0%) vs. concomitant: 19/37 (51.2%), $p = .21$], and transcatheter aortic valve replacement (TAVR) [staged: 4/12 (33.3%) vs. concomitant: 0/37 (0%), $p = .002$]. Regarding outcomes, there was a significantly shorter post-OLT hospital stay for those who had staged procedures versus those who had concomitant procedures [staged: 8 (IQR, 5–13) days vs. concomitant: 17 (IQR, 14–24) days, $p = .007$]. However, both groups had similar in-hospital mortality rates [staged: 1/12 (8.3%) vs. concomitant: 4/37 (10.8%), $p = 1.0$]. Overall survival stratified between the two groups was comparable.
Conclusions: Patients who underwent the staged approach had a shorter post-transplant hospital stay, but comparable survival with respect to those who underwent concomitant cardiac procedures and OLT.

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1. Introduction

Orthotopic liver transplantation (OLT) has become a routinely performed procedure to treat end stage liver disease (ESLD); however, organ shortages continue to be a major obstacle for this patient population. According to the Organ Procurement and Transplantation Network (OPTN), in 2010, 16,000 people were awaiting OLT while only 6000 received a liver allograft [1]. For those with a co-existing cardiac comorbidity awaiting OLT, surgical treatment may be necessary to optimize preoperative cardiac status before OLT as cardiovascular complications are the leading cause of death following OLT [2]. The severity of cardiac disease can exclude patients from OLT and therefore treatment before OLT may be necessary to increase candidacy. The goals of pre-OLT assessments are to risk assess a patient's ability to undergo liver transplantation and subsequent transplant complications as well as to identify cardiopulmonary diseases in the patient that may severely complicate the transplant course [3]. While undergoing extensive pre-OLT cardiac testing, some patients are found to have cardiac abnormalities that require surgical intervention in order to withstand the stress of transplantation.

This study is needed as information is still lacking on approaches and strategies to address indications for cardiac surgery in patients with liver disease who require OLT. The purpose of this systematic review was to look at common indications for heart surgery in patients who are undergoing OLT and highlight the current management strategies, patterns and outcomes.

2. Methods

2.1. Literature search strategy

A thorough systemic electronic search was performed in October 2018 using Cochrane Controlled Trials Register, Ovid Medline, Cumulative Index of Nursing and Allied Health Literature (CINAHL), and Scopus. To achieve the maximum sensitivity of the search strategy, the following combined terms were used: "coronary artery bypass" OR "CABG" OR "revasculari*" OR "bypass" OR "TAVR" OR "transcatheter aortic valve replacement" OR "TAVI" OR "cardiac surgery" OR "thoracic surgery" OR "heart surgery" OR "valve replacement" OR "heart valve prosthesis" OR "heart valve implantation" OR "prosthesis implantation" AND "orthotopic liver transplan*" OR "OLT" OR "hepatic transplan*". The reference lists of all eligible studies were reviewed for further identification of potentially relevant studies and assessed using the inclusion and exclusion criteria.

2.2. Selection criteria

Eligible articles for the present systematic review included those that focused on patients who underwent heart surgery before or during OLT. Patients <18 years of age were excluded. With respect to staged procedures, only patients who underwent the cardiac procedure and OLT within a maximum of one year were selected to be part of this subgroup. When institutions published duplicate studies with overlapping individual patient data, only the most complete reports were included. To ensure that our results were reflective of current practice, literature published from 1995 onwards was included. Due to a paucity of research on the topic, only case reports and series were included. Reports not published in the English language and those not involving human subjects were excluded.

2.3. Data extraction and critical appraisal

Patient-level data were extracted from article texts, tables, and figures. For patients who underwent staged operations, perioperative data and postoperative outcomes were reflective of the second procedure (OLT). Any discrepancies between the reviewers were resolved by discussion and consensus. When data were not available, attempts were made to contact the corresponding authors to obtain the relevant data for the current study.

2.4. Statistical analysis

Baseline characteristics and demographics were reported using descriptive statistics, including medians and interquartile ranges (IQR) for continuous variables and percentages for categorical variables. Continuous variables were compared using Wilcoxon rank-sum test, while categorical variables were analyzed using chi-square test. Individual patient survival and outcome data from each case report and series were combined to produce a Kaplan-Meier survival curve. A subgroup analysis was also performed to compare outcomes between the concomitant and staged groups. All analyses were performed with R software, version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). *P* values <.05 were considered statistically significant (Fig. 1).

3. Results

3.1. Baseline pre-cardiac surgery demographics

Overall, 49 patients were included in the analysis, of whom 12 (24%) underwent staged cardiac surgical intervention and OLT while 37 (76%) underwent concomitant cardiac surgery with OLT (Table 1). The median age was significantly lower in the staged group [staged: 51.0 (IQR, 43.8–59.2) years vs. concomitant: 60.0 (IQR, 55.0–64.0) years, $p = .02$]. For staged procedures, the median time between heart procedures and OLT was 2.0 (IQR, 1.0–3.5) months. Within the staged group, two patients had cardiac surgery and OLT performed during the same hospitalization; a 20 h interval lapsed between procedures for one patient and for the other, OLT was performed 32 days following heart surgery. Further details on the pre-cardiac surgery baseline characteristics are outlined in Table 1.

3.2. Indications and perioperative characteristics

The most common indications for cardiac surgery included coronary artery disease (CAD) [staged: 4/12 (33.3%) vs. concomitant: 21/37 (56.8%), $p = .28$], aortic stenosis [staged: 2/12 (16.7%) vs. concomitant: 16/37 (43.2%), $p = .19$], and aortic regurgitation [staged: 4/12 (33.3%) vs. concomitant: 3/31 (8.1%), $p = .09$]. The most commonly reported cardiac procedures were coronary artery bypass graft (CABG) [staged: 4/12 (33.3%) vs. concomitant: 21/37 (56.8%), $p = .28$], surgical aortic valve replacement (SAVR) [staged: 3/12 (25.0%) vs. concomitant: 19/37 (51.2%), $p = .21$], and transcatheter aortic valve replacement (TAVR) [staged: 4/12 (33.3%) vs. concomitant: 0/37 (0%), $p = .002$]. There were no significant differences with regards to intraoperative transfusions, however usage of fresh frozen plasma was somewhat higher in the concomitant group [staged: 7.5 (IQR, 4.2–15.0) units vs. concomitant: 16.0 (IQR, 13.8–25.8) units, $p = .24$]. The usage of platelets tended to be higher in the staged group without statistical significance [staged: 20.0 (IQR, 12.5–25.0) units vs. concomitant: 8.0 (IQR,

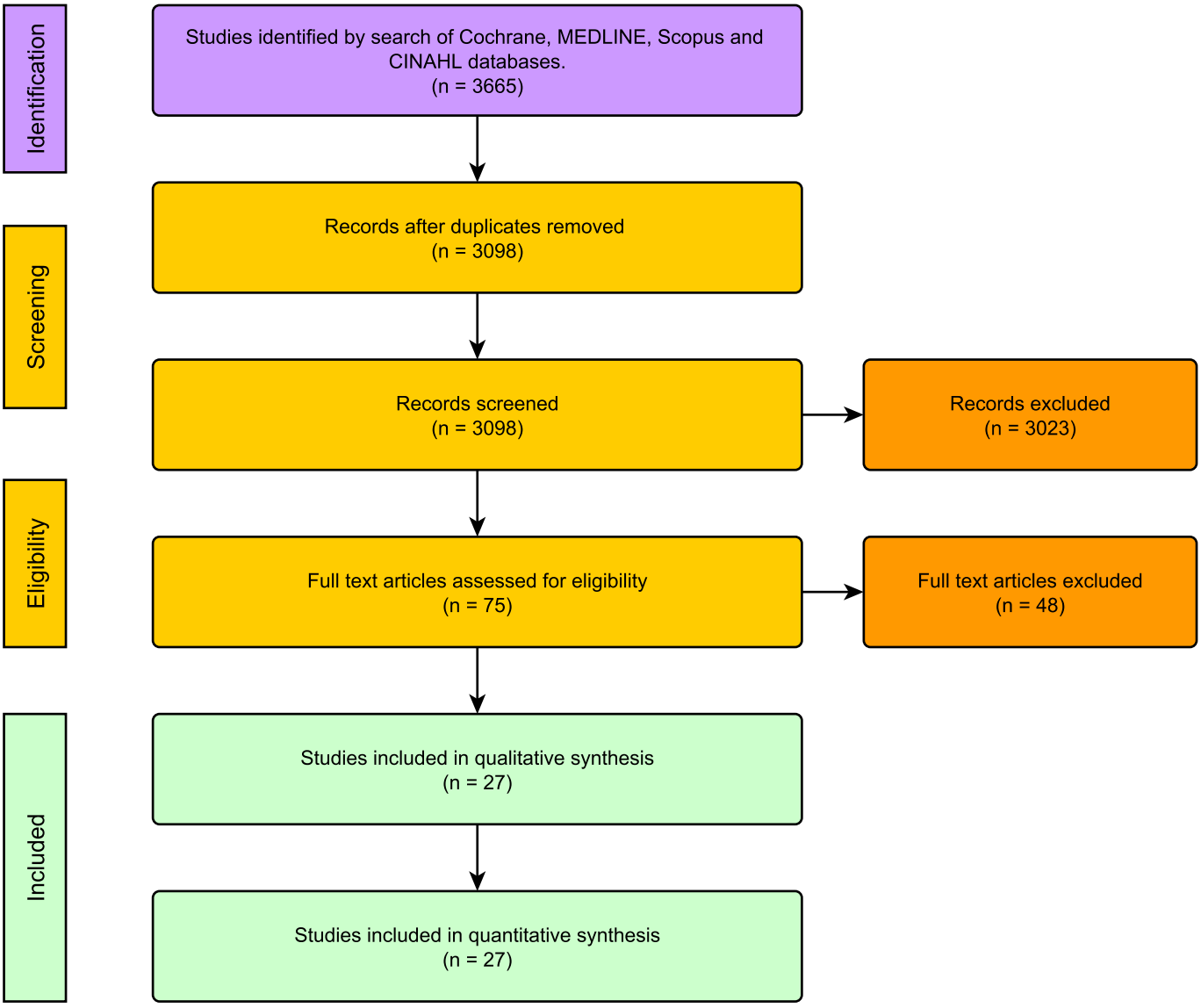

Fig. 1. PRISMA schematic diagram of the search strategy. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

Table 1
Baseline patient characteristics.

Variable	Concomitant ($n = 37$)	Staged ($n = 12$)	Total ($n = 49$)	p-value
Age (years), median [IQR]	60.0 [55.0, 64.0]	51.0 [43.8, 59.2]	58.0 [50.0, 63.0]	0.02
Male, n (%)	31 (83.8)	10 (90.9)	41 (85.4)	0.92
Left ventricular ejection fraction (%), median [IQR]	60.0 [55.0, 65.0]	60.0 [55.0, 61.0]	60.0 [55.0, 65.0]	0.43
MELD score, median [IQR]	18.0 [13.0, 26.0]	26.0 [16.0, 29.0]	18.5 [13.5, 26.8]	0.48
Child-Turcotte-Pugh Class				0.01
Class A, n (%)	0 (0.0)	2 (33.3)	2 (8.3)	0.09
Class B, n (%)	8 (44.4)	0 (0.0)	8 (33.3)	0.13
Class C, n (%)	10 (55.6)	4 (66.7)	14 (58.3)	1
Comorbidities				
Alcohol abuse, n (%)	10 (27.0)	2 (16.7)	12 (24.5)	0.73
Renal failure, n (%)	8 (21.6)	1 (8.3)	9 (18.4)	0.55
Nephrolithiasis, n (%)	1 (2.7)	1 (8.3)	2 (4.1)	0.99
Atrial fibrillation, n (%)	6 (16.2)	2 (16.7)	8 (16.3)	1
Aortic valve endocarditis, n (%)	2 (5.4)	2 (16.7)	4 (8.2)	0.53
Hypersplenism, n (%)	2 (5.4)	2 (16.7)	4 (8.2)	0.53
History of rheumatic fever, n (%)	1 (2.7)	1 (8.3)	2 (4.1)	0.99
Platelet count (per nL), median [IQR]	77.0 [68.0, 109.0]	51.5 [38.2, 59.5]	60.0 [48.5, 85.0]	0.07
Prothrombin time (seconds), median [IQR]	15.1 [14.8, 15.8]	18.6 [16.0, 21.5]	16.3 [15.0, 18.7]	0.29
Albumin (g/dL), median [IQR]	2.6 [2.5, 2.7]	3.0 [2.8, 3.3]	2.8 [2.6, 3.1]	0.11
Total bilirubin (mg/dL), median [IQR]	2.6 [2.2, 2.7]	1.7 [1.7, 2.2]	2.0 [1.7, 2.6]	0.29
Creatinine (mg/dL), median [IQR]	2.0 [1.4, 2.8]	1.6 [1.3, 1.9]	1.8 [1.4, 2.3]	0.45

Table 2
Surgery characteristics.

Variable	Concomitant (n = 37)	Staged (n = 12)	Total (n = 49)	p-value
Cardiac Indication				
Coronary artery disease, n (%)	21 (56.8)	4 (33.3)	25 (51.0)	0.28
Aortic stenosis, n (%)	16 (43.2)	2 (16.7)	18 (36.7)	0.19
Aortic regurgitation, n (%)	3 (8.1)	4 (33.3)	7 (14.3)	0.09
Mitral regurgitation, n (%)	1 (2.7)	0 (0.0)	1 (2.0)	1
Tricuspid regurgitation, n (%)	1 (2.7)	0 (0.0)	1 (2.0)	1
Pulmonary embolism, n (%)	1 (2.7)	0 (0.0)	1 (2.0)	1
Procedure				
Coronary artery bypass graft, n (%)	21 (56.8)	4 (33.3)	25 (51.0)	0.28
Surgical aortic valve replacement, n (%)	19 (51.2)	3 (25.0)	22 (44.9)	0.21
Transaortic valve replacement, n (%)	0 (0.0)	4 (33.3)	4 (8.2)	0.002
Liver Transplant				
Diagnoses at transplant				
Liver cirrhosis, n (%)	23 (62.2.)	9 (75.0)	32 (65.3)	0.64
Hepatocellular carcinoma, n (%)	9 (24.3)	3 (25.0)	12 (24.5)	1
Non-alcoholic steatohepatitis, n (%)	4 (10.8)	1 (8.3)	5 (10.2)	1
Hepatitis B, n (%)	3 (8.1)	2 (16.7)	5 (10.2)	0.76
Hepatitis C, n (%)	9 (24.3)	2 (16.7)	11 (22.4)	0.88
Hepatitis, unspecified, n (%)	4 (10.8)	1 (8.3)	5 (10.2)	1
Other, n (%)	4 (10.8)	1 (8.3)	5 (10.2)	1
Signs and Symptoms				
Ascites, n (%)	7 (77.8)	5 (45.5)	12 (60.0)	0.31
Encephalopathy, n (%)	5 (55.6)	4 (36.4)	9 (45.0)	0.68
Esophageal varices, n (%)	3 (33.3)	5 (45.5)	8 (40.0)	0.93
Variceal bleeding, n (%)	3 (33.3)	3 (27.3)	6 (30.0)	1
Jaundice, n (%)	2 (22.2)	1 (9.1)	3 (15.0)	0.85
Intraoperative transfusion				
Fresh frozen plasma (units), median [IQR]	16.0 [13.8, 25.8]	7.5 [4.2, 15.0]	14.5 [6.2, 25.8]	0.24
Packed red blood cell (units), median [IQR]	13.5 [9.2, 38.0]	21.0 [11.5, 23.0]	14.0 [8.0, 25.0]	0.80
Platelets (units), median [IQR]	8.0 [6.5, 24.5]	20.0 [12.5, 25.0]	8.0 [6.0, 30.0]	0.90
Intraoperative aprotinin administration, n (%)	3 (8.1)	1 (8.3)	4 (8.2)	1

6.5–24.5) units, $p = .90$]. The usage of packed red blood cells [staged: 21.0 (IQR, 11.5–23.0) units vs. concomitant: 13.5 (IQR, 9.2–38.0) units, $p = .80$], was not significantly between the two groups. Indications and perioperative characteristics are detailed in Tables 2 and 3.

3.3. Estimated survival and outcomes for staged vs concomitant heart procedures for OLT

There was a significantly shorter post-OLT hospital stay for those who had staged procedures versus those who had concomitant procedures [staged: 8 (IQR, 5–13) days vs. concomitant: 17 (IQR, 14–24) days, $p = .007$]. While both groups had a comparable in-hospital mortality rate [staged: 1/12 (8.3%) vs. concomitant: 4/37 (10.8%), $p = 1.0$] the overall mortality rate was higher in the concomitant group [staged: 1/12 (9.1%) vs. concomitant: 7/37 (24.1%), $p = .47$] following OLT; however, no significant difference was noted. Kaplan-Meier analysis on patient survival in the staged vs. concomitant groups is shown in Fig. 2. During the two years post-OLT, the difference in estimated survival was not significant between the groups (staged group 83% vs. concomitant group 63%, p = .4).

4. Discussion

Overall, this analysis has identified some important trends and patterns in cardiac management before OLT. It appears that most patients underwent heart surgery at the time of OLT and that CABG was the most common procedure performed. Surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR) were also common, with TAVR performed only in the staged group. Those in the staged group also tended to be younger. Both groups had a comparable in-hospital mortality rate and although no significant difference was noted, the overall mortality rate was 20% higher in the concomitant group following OLT. Mortality rates following cardiac surgery in the staged group were not reported. Assuming non-zero mortality after cardiac procedures, survival rates reported for the staged group may be artificially higher.

Several pathophysiological changes occur in patients with cirrhosis (termed cirrhotic cardiomyopathy) that include reduced ventricular responses to stress, increased cardiac output, low systemic vascular resistance and bradycardia (7) which can lead to potential cardiac complications during or after OLT.

One of the biggest obstacles in performing heart surgery in patients with severe liver disease before OLT is the risk of decompensated liver

Table 3
Outcomes.

Variable	Concomitant (n = 37)	Staged (n = 12)	Total (n = 49)	p-value
Hospital stay (days), median [IQR]	17.0 [14.0, 24.2]	8.0 [5.0, 12.5]	14.0 [9.0, 19.0]	0.007
Follow-up time post-transplant (months), median [IQR]	4.6 [0.8, 18.3]	2.2 [0.5, 11.3]	3.1 [0.6, 15.5]	0.48
Hemorrhage, n (%)	1 (2.7)	1 (8.3)	2 (4.1)	0.99
Reoperation, n (%)	2 (5.4)	2 (16.7)	4 (8.2)	0.53
In-hospital mortality, n (%)	4 (10.8)	1 (8.3)	5 (10.2)	1
Overall mortality, n (%)	7 (24.1)	1 (9.1)	8 (19.5)	0.47

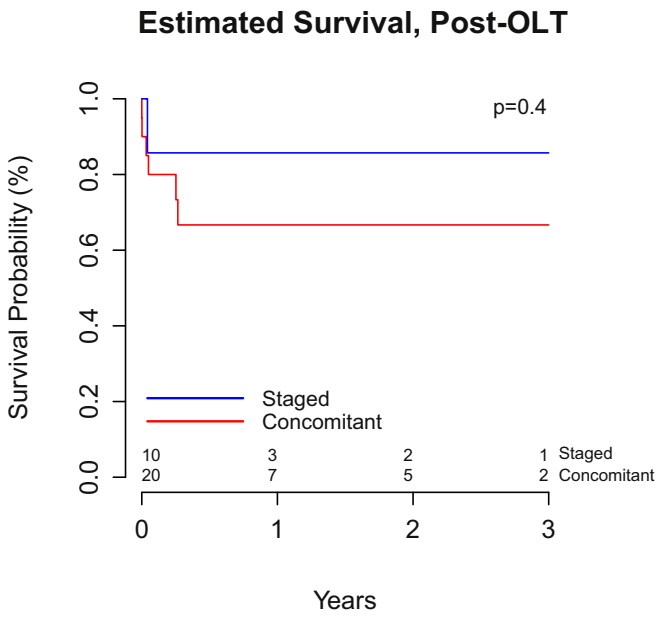

Fig. 2. Kaplan Meier curves indicating estimated survival post-OLT stratified by staged vs. concomitant procedures.

failure associated with cardiopulmonary bypass (CPB)(8). In evaluating patients before placing them on CPB, baseline characteristics such as Child-Turcotte-Pugh (CTP) class of liver cirrhosis, Model for End-Staged Liver Disease (MELD), preoperative total plasma bilirubin and EuroSCORE need to be considered as this has an effect on the long-term outcomes of patients, while recognizing that those with class A are more likely to tolerate CPB (9). Filsoufi et al. reported an operative mortality of 26% for cardiac procedures in patients with a CTP class B (score 7–9) and a MELD score of 14; there was a 67% mortality rate in those with class C (score 10–15) [4]. Suman et al. also found that CTP class and MELD scores were significantly associated with hepatic decompensation and mortality after cardiac surgery using CPB in patients with cirrhosis. Surgery can be conducted safely in patients with a CTP score ≤ 7 while patients with a CTP score ≥ 8 had a significant risk for mortality [5]. Additionally, the adjunct of portal pressures might help risk stratify for staged procedures to determine the risk of decompensation after cardiac interventions (Barcelona staging).

The overall prevalence of CAD in those with chronic liver disease (CLD) has been reported to be 13–16% with the highest prevalence in patients aged over 50 years [2]; this percentage is expected to grow as the age of the population continues to increase in addition to the rising non-alcoholic steatohepatitis (NASH) indication for OLT. These findings overlap with the relatively high percentage of patients who had CAD in this cohort. One recent study showed that approximately 26% of transplant candidates presented with moderate to severe coronary narrowing and those with moderate to severe CAD were more likely to be men [2]. Furthermore, half of OLT recipients had hypertension or diabetes, and more than half had ≥2 coronary risk factors other than age with a high prevalence of CAD. Guidelines suggest that if significant coronary artery stenosis (>70% stenosis) is detected, revascularization should be attempted prior to OLT; therefore, coronary artery stenting is increasingly performed prior to OLT [3]. Bare metal stents have been preferred to avoid the need for long-term dual antiplatelet therapy (clopidogrel and aspirin rather than aspirin alone) that is likely to delay the OLT [3]. However, when extensive multi-vessel disease is identified prior to OLT, a CABG rather than stenting will be required.

The most common procedures performed in our cohort were CABG and aortic valve replacement. One patient included in our study who underwent off pump CABG had satisfactory outcomes. It has been suggested that for patients indicated for CABG, off-pump CABG may be performed for patients undergoing sequential CABG and OLT as using the off-pump technique has been associated with better hemodynamic profiles such as fewer coagulation disorders [6]. Procedures that included concomitant off-pump CPB and non-cardiovascular surgeries did not increase mortality or postoperative morbidities; however, outcomes with this approach based on larger studies are not known [7,8]. The risks and benefits of on-pump versus off-pump CPB for CABG should be carefully weighed in assessing patients before the procedure; if possible, a shorter duration of CPB as opposed to off-pump CABG can be implemented with the extent of underlying liver dysfunction assessed accordingly [9].

Aortic valve replacement was another common procedure performed as many patients with an indication for OLT presented with aortic stenosis. The use of less invasive techniques for addressing valve disease such as TAVR have also been increasingly adopted to help reduce exposure to CPB [10]. The reported use of TAVR before OLT is consistently performed in a staged fashion according to this analysis. Transfemoral and transapical TAVR have been performed with satisfactory outcomes in patients with mild to moderate liver disease. However, for those with advanced liver disease, large-scale outcomes using this procedure are not available [11]. Alternative procedures for aortic valve repair such as balloon valvuloplasty are not seen as the best option for older patients because of the relatively higher in-hospital mortality, 3-year mortality of 53% and a higher rate of patients who eventually needed surgery [12]. While surgical aortic valve replacement can be performed simultaneously with OLT, a staged approach if possible may be preferable for those who are symptomatic in need of urgent cardiac surgery [13].

This review has several key limitations and must be interpreted with care. Differences existed in patient selection as no data was separately available on cardiac surgery mortality for staged patients, likely under-representing the true mortality and morbidity in this group. We acknowledge that this is a fundamental limitation that cannot be addressed due to an inability to extract sufficient detail from the pooled data. Due to a lack of granularity, we were unable to stratify outcomes according to specific cardiac indications and baseline characteristics. Publication bias, as well as the small number of patients, limits the statistical power of the analysis.

There are currently no management algorithms or protocols associated with cardiac surgery before or during OLT. Since patient outcomes in our study were more or less comparable, this may suggest that a more patient-specific approach can be taken for patients when choosing a staged vs concomitant strategy. Assessments including CTP class, MELD scores, and, potentially, portal pressure measurements need to be taken into consideration when evaluating potential OLT recipients. Although the overall mortality rate was higher in the concomitant group, no significant differences were noted perhaps due to the small sample size. The optimal time for performing cardiac surgeries prior to OLT still remains to be identified. Therefore, future studies including a larger patient cohort that investigate the optimal time between cardiac intervention and liver transplant would help supplement the outcomes identified in this research. These results have practical implications as they have identified key patterns in current strategies taken for managing and treating patients with significant heart disease before OLT.

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