ORIGINAL ARTICLE

The significance of underlying cardiac comorbidity on major adverse cardiac events after major liver resection

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Abstract

Background: The risk of postoperative adverse events in patients with underlying cardiac disease undergoing major hepatectomy remains poorly characterized.

Methods: The NSQIP database was used to identify patients undergoing hemihepatectomy and trisectionectomy. Patient characteristics and postoperative outcomes were evaluated.

Results: From 2005 to 2012, 5227 patients underwent major hepatectomy. Of those, 289 (5.5%) had prior major cardiac disease: 5.6% angina, 3.1% congestive heart failure, 1% myocardial infarction, 54% percutaneous coronary intervention, and 46% cardiac surgery. Thirty-day mortality was higher in patients with cardiac comorbidity (6.9% vs. 3.7%, P = 0.008), including the incidence of postoperative cardiac arrest requiring cardiopulmonary resuscitation (3.8% vs. 1.2%, P = 0.001) and myocardial infarction (1.7% vs. 0.4%, P = 0.011). Multivariate analysis revealed that functional impairment, older age, and malnutrition, but not cardiac comorbidity, were significant predictors of 30-day mortality. However, prior percutaneous coronary intervention was independently associated with postoperative cardiac arrest (OR 2.999, P = 0.008).

Conclusion: While cardiac comorbidity is not a predictor of mortality after major hepatectomy, prior percutaneous coronary intervention is independently associated with postoperative cardiac arrest. Careful patient selection and preoperative optimization is fundamental in patients with prior percutaneous coronary intervention being considered for major hepatectomy as restrictive fluid management and low central venous pressure anesthesia may not be tolerated well by all patients.

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Introduction

Postoperative cardiovascular complications remain a significant concern in surgical patients, accounting for one-third of postoperative deaths, prolonged hospitalization, and increased medical costs.[1] Preoperative cardiac disease is a well-known risk factor associated with poor surgical outcomes following vascular[2,3] and colorectal surgery.[4–6] The risk of mortality increases 5-fold in patients with prior ischemic heart disease undergoing non-cardiac surgery.[7]

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While advancements in surgery and anesthesia have lead to a dramatic improvement in post-hepatectomy mortality from 20% to nearly 0% over the last 3 decades,[8–10] the morbidity associated with complex liver resections remains considerable. In an Italian study evaluating 1500 consecutive patients undergoing hepatectomy, the authors observed a morbidity of 22.5%.[11] Similarly, a study using the American College of Surgeon National Surgical Quality Improvement Program database reported a morbidity of 22.6% within 30 days following hepatectomy and found that previous cardiac disease and chronic obstructive pulmonary disease (COPD) were the only comorbidities associated with post-hepatectomy morbidity.[12] However, the aforementioned study included patients who underwent minor hepatectomy and did not specifically examine postoperative cardiac complications as an endpoint. Thus, it remains unclear how major hepatectomy can be tolerated in patients with underlying cardiac comorbidity. Given the intraoperative considerations during major liver surgery, specifically related to the need to maintain a low central venous pressure through fluid restrictive strategies and occasionally through the use of vasopressors,[13] we sought to investigate the role of underlying cardiac comorbidity on postoperative outcomes following major hepatectomy using a large multi-institutional database.

Methods

Data source

The American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) is a nationally validated, outcomes based and risk-adjusted program used to assess the quality of surgical care in participating academic and community hospitals. The ACS NSQIP database assesses preoperative risk factors, operative data, and 30-day postoperative morbidity and mortality. The ACS NSQIP Participant User File was queried to identify patients who underwent major hepatectomy from January 1, 2005 to December 31, 2012. Current procedural terminology (CPT) codes were used to determine major liver resection, including CPT codes 47122 (trisectionectomy), 47125 (total left lobectomy), or 47130 (total right lobectomy). Only index procedures with CPT codes meeting the inclusion criteria were included.

Patients were stratified based on presence or absence of cardiac co-morbidity. Cardiac co-morbidities included newly diagnosed or acute exacerbation of congestive heart failure one month prior to surgery, myocardial infarction in the 6 month period prior to surgery, previous percutaneous coronary intervention, previous major cardiac procedure, and angina within one month before surgery. Previous cardiac surgery includes coronary artery bypass graft surgery, valve replacement or repair, repair of atrial or ventricular defects, greater thoracic vessel repair, cardiac transplant, left ventricular aneurysmectomy, and insertion of left ventricular assist device. Not included are pacemaker or automatic implantable cardioverter defibrillation (AICD) insertions.

Main outcome measures

Postoperative variables analyzed include rates of 30-day mortality, return to the operating room within 30 days of index procedure, length of stay, and complications within 30 days of index procedure. Complications collected in ACS NSQIP include surgical site infection, deep incisional surgical site infection, organ space infection (i.e. intra-abdominal abscess), wound dehiscence, pneumonia, unplanned intubation, pulmonary embolism, prolonged mechanical ventilation (>48 h), stroke, coma, cardiac arrest requiring cardiopulmonary resuscitation (CPR), acute myocardial infarction either intraoperatively or within 30 days of surgery, bleeding requiring blood transfusion, deep vein thrombosis, sepsis, and acute renal failure.

Statistical analysis

Categorical variables were presented as counts (percentages) and compared using chi-square or Fisher's exact tests. Continuous variables were presented as means (standard deviation) and compared using Student t-test or Mann–Whitney test, where applicable. Univariate and multivariate logistic regressions were performed to determine factors associated with postoperative 30-day mortality and cardiac arrest requiring CPR. All statistical analyses were performed using SPSS version 22.0 (IBM, Chicago, IL, USA) and STATA version 13.1 (StataCorp, College Station, TX, USA). Statistical significance was set at $p < 0.05$.

Results

From 2005 to 2012, 5227 patients underwent major hepatectomy. Of those, 289 (5.5%) had history of major cardiac disease: 16 (5.6%) angina, 9 (3.1%) congestive heart failure, 3 (1%) myocardial infarction within 6 months prior to surgery, 156 (54%) percutaneous coronary intervention (PCI), and 132 (46%) cardiac surgery. Table 1 shows the frequencies of underlying cardiac co-morbidities in the entire cohort.

Patients were stratified into two groups based on presence or absence of cardiac co-morbidity. Differences in baseline patient characteristics between the two groups are detailed in Table 2. Those with underlying cardiac comorbidity tended to be older in age (mean 69 vs. 57 years, $P < 0.001$) and male (76.1% vs. 49.1%, $P < 0.001$). Patients with underlying cardiac comorbidity also had co-existing co-morbidities including diabetes, COPD, peripheral vascular disease, and prior transient ischemia accident or cerebrovascular accident. There were no differences in body mass index, smoking status, functional status, alcohol use, impaired sensorium, and preoperative sepsis.

The incidence of postoperative complications based on underlying cardiac disease is shown in Table 3. The 30-day mortality (6.9% vs. 3.7%, $P = 0.008$) was significantly higher in those with underlying cardiac co-morbidity. Overall postoperative

Table 1 Frequency of preoperative cardiac co-morbidities in patient undergoing major hepatectomy

	Frequency (n, %) N = 5227
CHF	9 (0.17)
MI (within 6 months prior to surgery)	3 (0.08)
Prior PCI	156 (3.96)
PCS	142 (3.6)
Angina	16 (0.41)

Abbreviation: CHF, congestive heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; PCS, prior cardiac surgery.

Table 2 Preoperative patient baseline characteristics of patients who underwent major hepatectomy stratified by cardiac co-morbidity

	No cardiac co-morbidity (n = 4938)	Cardiac co-morbidity (n = 289)	P-value
Age (mean, SD)	57 (13)	69 (9)	<0.001
Male	2419 (49.1)	220 (76.1)	<0.001
Race			
White	3498 (73)	232 (82)	0.01
Black	384 (8)	11 (3.9)	
Hispanic	209 (4.4)	8 (2.8)	
Asian	341 (7.1)	12 (4.2)	
Other	360 (7.5)	20 (7.1)	
Diabetes	701 (14.2)	102 (35.3)	<0.001
Smoker	773 (15.7)	47 (16.3)	0.803
ETOH (n = 3947)	95 (2.6)	10 (3.5)	0.444
Dyspnea	370 (7.5)	45 (15.6)	<0.001
Partial/Total functional dependence	76 (1.5)	9 (3.1)	0.051
History of COPD	121 (2.5)	16 (5.5)	0.003
Ascites	56 (1.1)	5 (1.7)	0.387
Esophageal varices (n = 3942)	8 (0.2)	0 (0)	0.427
HTN on medication	2165 (43.8)	233 (80.6)	<0.001
PVD (n = 3942)	25 (0.7)	13 (4.5)	<0.001
Rest pain (n = 3942)	1 (0)	0 (0)	1.000
Dialysis (n = 3942)	15 (0.3)	1 (0.3)	0.598
Impaired sensorium (n = 3942)	3 (0.1)	1 (0.3)	0.262
History of TIA (n = 3942)	52 (1.4)	19 (6.6)	<0.001
CVA (n = 3942)	64 (1.6)	15 (5.2)	<0.001
BMI (mean, SD)	27.6 (6.2)	28.3 (5.9)	0.083
Preop radiotherapy in last 90 days	22 (0.91)	3 (1.04)	0.746
Preop chemo in last 90 days	394 (10.8)	20 (6.94)	0.045
Preop sepsis	100 (2.0)	7 (2.43)	0.647
Preop albumin (mean, SD)	3.9 (0.571)	3.7 (0.56)	<0.001
Operating time min	270 (160)	269 (123)	0.930

Abbreviation: Preop, preoperative; CVA, cerebrovascular accident; TIA, transient ischemic accident; PVD, peripheral vascular disease; HTN, hypertension; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

Table 3 Postoperative outcomes after major hepatectomy

	No cardiac co-morbidity (n = 4938)	Cardiac co-morbidity (n = 289)	P-value
30-day mortality	182 (3.7)	20 (6.9)	0.008
LOS (mean, SD)	9.1 (8.9)	11.6 (11.7)	0.001
Deep wound infection	69 (1.4)	4 (1.4)	1.000
Intra-abdominal abscess	400 (8.1)	21 (7.3)	0.658
Dehiscence	52 (1.1)	2 (0.7)	0.768
Pneumonia	194 (3.9)	20 (6.9)	0.016
Reintubation	213 (4.3)	28 (9.7)	<0.001
Any cardiac complication	78 (1.6)	14 (4.8)	<0.001
Cardiac arrest	58 (1.2)	11 (3.8)	0.001
Myocardial infarction	20 (0.4)	5 (1.7)	0.011
Postoperative bleeding	939 (19)	37 (12.8)	0.01
DVT	134 (2.7)	6 (2.1)	0.706
Systemic sepsis	351 (7.1)	21 (7.3)	0.906
Septic shock	171 (3.5)	16 (5.5)	0.072
ARI	61 (1.2)	7 (2.42)	0.084
ARF	93 (1.9)	15 (5.2)	0.001

Abbreviation: DVT, deep vein thrombosis; LOS, length of stay; ARI, acute renal insufficiency; ARF, acute renal failure requiring dialysis.

cardiac complications were higher in those with underlying cardiac disease than those without (4.8% vs. 1.6%, $P < 0.001$), including postoperative cardiac arrest (3.8% vs. 1.2%, $P = 0.001$) and myocardial infarction (1.7% vs. 0.4%, $P = 0.011$). Respiratory complications were more common in patients with underlying cardiac disease: pneumonia (6.9% vs. 3.9%, $P = 0.016$) and re-intubation (9.7% vs. 4.3%, $P < 0.001$). Total hospital length of stay was slightly longer in the group with underlying cardiac comorbidity (mean 11.6 vs. 9.1 days, $P = 0.011$).

Multivariate logistic regression was performed to determine predictors of 30-day mortality, and cardiac arrest requiring cardiopulmonary resuscitation (CPR). While underlying cardiac comorbidity was not a predictor of 30-day mortality, older age, functional status, and poor nutrition were predictors of early postoperative mortality (Table 4). Furthermore, after adjusting for confounding patient factors, previous PCI was a significant predictor of postoperative cardiac arrest requiring CPR (OR 2.999, 95% CI: 1.329–6.766, $P = 0.008$) following major hepatectomy (Table 5). In order to investigate further the potential interaction between previous PCI and postoperative renal dysfunction (as a potential surrogate of strict intraoperative fluid restriction), we performed a subset analysis of previous PCI patients with and without postoperative renal dysfunction (acute renal insufficiency or failure) and found a marginally higher rate of postoperative cardiac arrest in the former group (25% vs. 5.4%, $P = 0.084$).

Discussion

Our study demonstrates that although preoperative cardiac comorbidity is not associated with 30-day mortality in general after major hepatectomy, history of PCI is associated with a three-fold increase risk of any cardiac complication and specifically of cardiac arrest requiring cardiopulmonary resuscitation. We also found that older age and decreased serum albumin were

Table 4 Multivariate logistic regression – predictors of 30-day mortality after major hepatectomy

	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P-value
Age	1.053 (1.040–1.067)	<0.001	1.041 (1.024–1.057)	<0.001
Female	0.578 (0.432–0.774)	<0.001	0.842 (0.580–1.222)	0.366
Diabetes	2.196 (1.598–3.017)	<0.001	1.273 (0.829–1.955)	0.269
COPD	2.967 (1.675–5.254)	<0.001	2.057 (0.989–4.278)	0.053
Any cardiac comorbidity	1.942 (1.204–3.132)	0.006	0.940 (0.531–1.662)	0.832
Functional impairment	5.695 (3.200–10.137)	<0.001	2.553 (1.217–5.358)	0.013
Ascites	2.765 (1.176–6.499)	0.020	1.391 (0.528–3.662)	0.504
PVD	2.158 (0.656–7.099)	0.205	–	
CVA	2.908 (1.374–6.155)	0.005	1.441 (0.596–3.484)	0.417
Preoperative Albumin	0.314 (0.253–0.388)	<0.001	0.334 (0.257–0.433)	<0.001

Abbreviation: COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval; PVD, peripheral vascular disease; CVA, cerebrovascular accident.

Table 5 Multivariate logistic regression – predictors of cardiac arrest requiring cardiopulmonary resuscitation after major hepatectomy

	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P-value
Age	1.057 (1.035–1.080)	<0.001	1.051 (1.023–1.080)	<0.001
Female	0.506 (0.306–0.838)	0.008	0.806 (0.441–1.473)	0.484
Diabetes	2.623 (1.572–4.377)	<0.001	1.316 (0.684–2.529)	0.411
COPD	3.654 (1.554–8.594)	0.003	2.313 (0.840–6.368)	0.105
PCI	4.209 (1.956–9.057)	<0.001	2.999 (1.329–6.766)	0.008
PCS	2.682 (1.054–6.828)	0.038	0.951 (0.321–2.819)	0.929
Functional impairment	3.910 (1.391–10.994)	0.010	2.134 (0.661–6.901)	0.205
Ascites	1.249 (0.171–9.146)	0.826	–	
PVD	1.891 (0.254–14.032)	0.533	–	
CVA	2.837 (0.867–9.282)	0.085	–	
Preoperative albumin	0.443 (0.302–0.618)	<0.001	0.511 (0.331–0.785)	0.002

Abbreviation: COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval; PCI, percutaneous coronary intervention; PCS, prior cardiac surgery; PVD, peripheral vascular disease; CVA, cerebrovascular accident.

independent predictors of postoperative mortality and cardiac morbidity. Our study is the first to demonstrate an association between percutaneous coronary intervention and postoperative cardiac arrest following major hepatectomy, implying that these patients with previous PCI may represent a potentially identifiable cohort of patients with limited physiologic reserve and ability to withstand the stress of these complex operations. Thus, while preoperative cardiac comorbidity in general and specifically history of prior cardiac surgery were not found to be associated with postoperative cardiac complications following major hepatectomy, patients with prior PCI should undergo rigorous preoperative cardiac evaluation in order to identify areas of optimization prior to major hepatectomy.

To our knowledge, two studies have specifically evaluated the impact of cardiac disease on post-hepatectomy outcomes. In a single-institution study from the United States consisting 1206 consecutive patients undergoing partial hepatectomy (11.4% with coronary artery disease), the authors reported similar rates of complications (39.9% vs. 32.6, P = 0.108) and mortality (5.8% vs. 4.8%) between those with coronary artery disease and those without coronary artery disease.[14] On the other hand, a Japanese study consisting of 23 patients with underlying cardiac disease and 451 patients without cardiac disease reported a significant increase in cardiac complications (24% vs. 0%, $P < 0.001$) and postoperative mortality (16% vs. 3%, $P < 0.001$) following hepatectomy in patients with underlying cardiac disease.[15] However, these single-institution series were limited by the inclusion of mostly minor hepatectomies in their cohorts, thereby limiting the applicability of the results in patients undergoing hemihepatectomies and trisectionectomies.

One interesting finding in the current study is that prior PCI was strongly associated with cardiac complications. Prior coronary stenting is a well-established risk factor associated with major adverse cardiac events.[1,16–19] More recently, however, Holcomb and colleagues demonstrated that the incremental risk of cardiac complications significantly decreases when surgery is performed more than 6 months following coronary stenting: the incremental risk of cardiac complications stabilizes at 1% beyond 6 months following coronary stenting.[20] Although NSQIP excludes those with prior percutaneous coronary intervention within 6 months of hepatectomy, we still found that those with history prior PCI (>6 months before the liver resection) had a cardiac complication rate of 6.4% as well as a three-fold increase risk of cardiac arrest. One can infer that underlying coronary disease, the complexity of liver surgery, and a fluid restrictive strategy maintaining a low CVP and perhaps necessitating vasopressors are all synergistic drivers of major adverse cardiac complications in patients undergoing major liver resection.

Several techniques have been shown to reduce intraoperative bleeding and blood transfusion during hepatectomy. Several systemic review and meta-analyses have demonstrated that low CVP anesthesia was associated with a modest reduction in blood transfusion in patients undergoing hepatectomy.[21,22] Another technique is clamping of the infrahepatic inferior vena cava during hepatectomy, which can lower CVP but can be associated with higher rates of thromboembolic events and ischemia associated liver injury.[23] Furthermore, stroke volume variation is another valuable index that can be used to intraoperatively assess intravascular fluid status. In a study consisting of 93 patients undergoing living right donor hepatectomy, low stroke volume variation was a significant predictor of intraoperative bleeding of >700 ml, even after adjusting for hemodynamic parameters such as heart rate and systemic vascular resistance.[24] Nevertheless, additional prospective protocols should be carried out in the future to determine the optimal anesthetic techniques to reduce blood loss and transfusion requirements during hepatectomy.

Interestingly, patients with prior PCI and postoperative renal impairment had a 25% incidence of postoperative cardiac arrest. It is hard to know whether postoperative renal impairment was a result of extensive intraoperative fluid restriction or a result of the postoperative cardiac arrest itself (as NSQIP does not provide a chronologic sequence of postoperative complications), but still this observation generates the hypothesis that prior PCI and significant intraoperative fluid restriction (sufficient to lead to postoperative renal impairment) might represent an ominous combination during major hepatectomy.

In the current study, less than 0.1% of patients (n = 3) had acute myocardial infarction within the 6-months preceding surgery. While recent acute myocardial infarction and drug-eluting stents are considered contraindications to elective non-cardiac surgery as the risk of postoperative myocardial re-infarction is as high as 11.6%,[16] some cases reports have shown that intra-aortic balloon pump (IABP) can be used for elective liver surgery in patients with recent acute myocardial infarction. For example, Okadome and colleagues described the use of IABP in the resection of a 12-cm hepatocellular tumor in a patient with multivessel coronary artery disease detected during preoperative surgical evaluation. Because coronary artery stenting would necessitate prolonged dual anti-platelet therapy that would delay operative oncologic intervention, the patient underwent a successful IABP-assisted hepatectomy.[25] Similarly, Oliver *et al.* also reported a patient with a remote history of coronary artery disease with recurrent myocardial ischemia during preoperative assessment for colorectal liver metastasis. Instead of pursuing coronary artery bypass grafting, which would have delayed operative intervention of liver metastasis, the patient similarly underwent a successful liver resection with intraoperative IABP.[26] Thus, IABP may be an alternative circulatory assist device that can be used in elective non-cardiac surgery to increase myocardial perfusion and cardiac output in carefully selected patients.

This study has several important limitations. First, this is a retrospective analysis of a clinical registry and therefore hepatectomy-specific complications such as biloma and liver insufficiency were not available. Second, the type of stent used (bare-metal stent vs. drug-eluting stent) as well as the use of anti-platelet therapy in perioperative setting in this cohort could not be determined using this database, an important factor that warrants further investigation as it remains unclear whether continuation or cessation of antiplatelet therapy (i.e. aspirin) would have had an impact on postoperative outcomes.[16,18] Currently, the American College of Cardiology/American Heart Association Task Force have recommended that elective noncardiac surgery should be delayed by at least 30 days after bare metal stent or 365 days after drug-eluting stent implantation for coronary revascularization.[27] However, anti-platelet management during elective non-cardiac surgery remains equivocal and at the discretion of clinicians involved in the care of the patient to weigh the relative risk of bleeding with that of stent thrombosis. Lastly, 90-day mortality as opposed to the provided 30-day mortality may be a more accurate measure of the true risk of death after surgery.

In conclusion, patients with underlying cardiac comorbidity, particularly those with prior percutaneous coronary intervention, have a modest increase in postoperative adverse cardiac events and specifically cardiac arrest following major hepatectomy. This observation may be secondary to the fluid restrictive management used to achieve low central venous pressure during major hepatectomy. Careful patient selection, rigorous preoperative cardiology evaluation and potential optimization, as well as sophisticated anesthesiologic management with dual cardiologic and hepatic surgery expertise is necessary in patients with cardiac disease being considered for major hepatectomy.

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Conflicts of interest

None declared.

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