TRANSTHORACIC ECHOCARDIOGRAPHY AS A PREDICTOR OF PERIOPERATIVE MORBIDITY AND MORTALITY

DR CHEONG CHAO CHIA

MGE 130013

DISSERTATION SUBMITTED IN FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF ANESTHESIOLOGY

FACULTY OF MEDICINE
UNIVERSITY OF MALAYA
KUALA LUMPUR

2016

UNIVERSITY MALAYA

ORIGINAL LITERARY WORK DECLARATION

Name of Candidate:

CHEONG CHAO CHIA

[redacted]

Registration Matric Number: MGE 130013

Name of Degree: Master of Anaesthesiology and Intensive Care Medicine

Title of Project Paper/ Research Project/ Dissertation ("this Work") :

TRANSTHORACIC ECHOCARDIOGRAPHY AS PREDICTOR OF PERIOPERATIVE MORBIDITY AND MORTALITY

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ABSTRACT

Objective: To identify risk factors (patient's characteristic, surgical and anaesthesia factors) associated to adverse outcome post-hepatectomy. Also, to assess will performing pre-operative transthoracic echocardiogram will change outcome of surgery and circumstances when pre-operative echocardiogram should be considered.

Methods: This was a retrospective cohort study done on 92 patients who have had hepatic resection surgery done under Hepatobiliary Surgery team from Jan 2010 to July 2016. Patient's characteristic, demographic, pre-operative echocardiography parameters such as left ventricular ejection fraction, diastolic dysfunction of left heart, left ventricular hypertrophy were assessed and associated with development of adverse event post-op, days of ventilation, hospital stay and ICU stay. Association of echocardiogram parameters were also analysed against organ failure (acute kidney failure, liver failure and major adverse cerebrovascular and cardiovascular event MACCE). Predictors contributing to adverse event post hepatectomy was analysed. Analysis method include chi square cross tabulation, non-parametric Mann Witney test, Kruskal Wallis test, and multivariate regression analysis with SPSS version 23.

Result: There was no significant association when preforming pre-operative echocardiogram or otherwise with primary outcome (development of post-operative adverse event), ICU stays or days of ventilation or any morbidity (MACCE, acute kidney failure and acute liver failure). However, if major estimated blood loss, prolonged operation time, high lactate level, perioperative pack cell transfusion, performing pre-operative echocardiography become significantly related to pre-operative adverse event ($p=0.018$).

Conclusion: Clinical decision to perform pre-operative echocardiogram or otherwise should not be predicted based on patient's cardiac risk factor or premorbid alone.

Consideration should be given to major complex hepatectomy requiring prolonged operation time, surgery with high estimated blood lost and major fluid shift. Larger prospective cohort study involving collaboration from hepatobiliary surgical team should be carried out in future.

Keyword: hepatectomy, echocardiogram, left ventricular ejection fraction, diastolic dysfunction left heart, left ventricular hypertrophy.

ABSTRAK

Objektif: Untuk mengenal pasti risiko (ciri-ciri pesakit, factor pembedahan and bius) yang berkenaan menyebabkan komplikasi selepas pembedahan *hepatectomy*. Selain daripada itu, untuk mengenalpasti sama ada menjalankan prosedur *echocardiography* pra-pembedahan akan mengubah keputusan pembedahan dan dalam situasi yang mana echocardiography patut dipertimbangkan.

Metode: Kajian ini adalah sebuah analisis retrospektif yang dijalankan atas 92 orang pesakit pembedahan *hepatectomy* bawah jagaan Unit Pembedahan Hepaobiliary di Pusat Perubatan Universiti Malaya dari Januari 2010 hingga Julai 2016. Ciri-ciri demographi, *echocardiograpy* sebelum pembedahan seperti *left ventricular ejection fraction, diastolic dysfunction left heart, left ventricular hypertrophy* dinilai dan hubungan dengan komplikasi selepas pembedahan, bilangan hari ventilasi, bilangan hari penginapan bawah unit jagaan rapi dan hospital.

Hubungan parameter echocardiogram juga dikaji dengan kegagalan organ (kegagalan buah pinggang, kegagalan hati dan *major adverse cerebrovascular and cardiovascular event, MACCE)*. Factor-factor yang menyebabkan komplikasi selepas pembedahan hati dikaji. Data dikumpulkan di dalam SPSS versi 23 dan dianalisa menggunakan ujian statistic- *chi square cross tabulation*, ujian *non-parametric Mann Witney*, ujian *Kruskal Wallis* dan ujian *multivariate regression*.

Keputusan: Tidak ada hubung kait antara menjalankan *echocardiography* sebelum pembedahan dengan kejadian komplikasi selepas pembedahan, bilangan hari penginapan ICU, bialangan hari ventilasi dengan morbiditi (MACCE, kegagalan buah pinggang, kegagalan hati). Walau bagaimana, jikalau pembehahan dikaitkan dengan kehilangan darah berlebihan , tempoh pembehahan yang panjang, paras *lactate* yang tinggi,

keperluan pemindahan darah, menjalankan *echocardiography* sebelum pembedahan menjadi faktor yang penting berhubungkait dengan komplikasi selepas operasi (p=0.018).

Kesimpulan: Keputusan klinikal sama-ada untuk menjalankan *echocardiogram* sebelum pembedahan ataupun tidak tidak patut dipertimbangkan dari segi faktor risiko daripada segi kesihatan dan kercergasan jantung sahaja. Pertimbangan patut berdasarkan sama-ada operasi yang bakal dijalankan kompleks, mengambil masa yang panjang, pembedahan melibatan kehilangan darah yang banyak dengan peralihan cecair badan secara mendadak. Kajian prospektif yang bakal melibatkan lebih banyak pesaki dengan kerjasama pihak pembedahan hati dengan hempedu patut dipertimbangkan pada masa depan.

Kata kunci: Keyword: hepatectomy, echocardiogram, left ventricular ejection fraction, diastolic dysfunction left heart, left ventricular hypertrophy.

ACKNOWLEDGEMENTS

I would like to express my greatest gratitude to Dr. Loh Pui San for her guidance and advice in preparation of this dissertation. This study would not be completed without their support and continuous encouragement. I would also like to thanks the staff from Record Office UMMC in assisting old medical record retrieval and data collection. In addition, greatest appreciation also goes to Echocardiography unit for retrieval of patient's result. Lastly, my gratitude goes to Dr. Mohammad Ashraful Islam who assisted me so much in data analysis.

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IVC	Inferior vena cava
CVP	Central venous pressure
ICU	Intensive care unit
ECHO	Echocardiography
LVEF	Left ventricular ejection fraction
EBL	Estimated blood loss
LVH	Left ventricular hypertrophy
LV	Left ventricle
RIFLE	Risk injury failure lost end stage kidney disease
MACCE	Major adverse cerebrovascular and cardiovascular event
NYHA	New York Heart Association

1.0 INTRODUCTION

Hepatic resection surgery is now the treatment of choice for colorectal hepatic metastasis without evidence of more distant spread and remains commonest indication for hepatic resection surgery. [1] It is a term reserved for the group of procedures that involves the operative resection of a region of the liver. [2]

Hepatic resection is known to be associated with major hemodynamic changes and massive blood loss intraoperatively especially during surgical liver mobilisation, liver bed resection, vessel (inflow and outflow) occlusion method and low central venous pressure technique. [3][1]. *Justin T et al.* reported that intra operative blood loss and transfusion requirement are risks factor for operative mortality following partial hepatectomy. [2] Despite advances in surgical techniques, estimated blood lost from hepatectomy remains approximately 0.5 to 1 L or more than 1 L especially in major hepatectomy. [4] Therefore, non-operative technique including low central venous pressure is continued to be used to aid reduction in bleeding.

Operative techniques include i) hepatic inflow occlusion method which temporary occlusion of portal vein and hepatic artery during parenchymal resection (Pringle manoeuvre). [3] ii) hepatic outflow occlusion method which is clamping of supra- and infra- hepatic IVC, iii) parenchymal transection technique. [2] Vascular isolation technique is associated with major hemodynamic shift. This may result in decrease in cardiac output of up to 10% and increase in left ventricular afterload of up to 20-30%, potentially causing hemodynamic compromise[1]. In a sole study evaluating total hepatic outflow occlusion (IVC clamping) by *Belgiti* et al , there is a significant increase in operative hemodynamic instability, ischemic duration, operative time, and hospital stay in with a trend towards a higher complication rate; particularly a higher risk of symptomatic pulmonary emboli.[5]

Non-operative techniques include i) reducing central venous pressure ii) haemodilution iii) use of pharmacological agents including tranexenemic acid and aprotinin. [6]The mechanisms behind low CVP will reduce impedance for hepatic venous system to IVC and subsequently reduce hepatic venous volume and pressure, allowing reduced retrograde venous bleeding during transection and improved coagulative effect from electrosurgical device. [2] Targeted CVP is less than 5 mm Hg is advocated in multiple studies and shown to reduce major blood loss associated morbidity and mortality. [7].Methods used to decrease CVP intraoperatively include decreased intravenous fluid and volume, morphine, systemic nitroglycerin infusion.[7, 8] A caution in CVP

reduction is drop in arterial perfusion pressure which need concomitant use of vasopressor. Any measure to lower CVP should not jeopardize arterial perfusion. [9]

Echocardiography has been utilised widely in patients with active cardiac conditions going for non-cardiac surgery to aid in risk stratification. American Society of Echocardiography has not clearly defined indication for resting echocardiogram, except for high risk vascular procedure. [10]

ASA/ACA taskforce cardiac risk assessment categorised hepatectomy into surgery with intermediate cardiac risk (1-5%) and recommended non-invasive cardiac evaluation if it changes management. [11]

2014 ACC/AHA do not recommended routine pre-operative echocardiography for patient undergoing intermediate risk intraabdominal surgery (Level B evidence). [12] Mukherjee et al. proposed in addition to patient premorbid, functional status and surgical risk should all be considered in evaluating non-invasive cardiac risk assessment pre-operatively. [13]

In addition to pre-operative assessment of left ventricular function, transthoracic echocardiogram performed before hepatic resection surgery also enables assessment of cardiomyopathy from alcohol and nutritional toxicity. [3]. Echocardiography also enables detection of pulmonary hypertension include tricuspid regurgitation and enlarge right atrium and right ventricle. [3] Presence of regional wall abnormalities also predict cardiovascular morbidity and mortality , and will indicate invasive cardiac assessment before major elective surgery. [13] Detection of valve abnormalities especially of aortic stenosis will influence intraoperative management and affect post-operative outcome with higher 30-days mortality and increase incidence of postoperative myocardial infarction. [14]

2.0 OBJECTIVE

Primary objective – To investigate risk factors contributing to the development of post-hepatectomy adverse outcomes, prolonged ventilation (> 1 day), prolonged ICU stay and mortality (in hospital, one month and one year) and whether performing pre-operative echocardiography changes outcome of surgery.

Secondary – To investigate associations between ECHO findings, pre-operative demographic and intraoperative parameters (estimated blood loss, blood transfusion, intraoperative fluid, lactate, low central venous pressure CVP) and adverse outcomes.

3.0 METHODOLOGY

After obtaining medical ethic board approval, medical records of patients underwent hepatic resection surgery under general anaesthesia between Jan 2010 and August 2016 in UMMC were reviewed with collaboration from medical record office.

A total of 118 patients underwent hepatic resection surgery but out of which 26 medical records were either missing, incomplete or did not meet inclusion criteria. Exclusion criteria include carcinoid tumour, surgery under regional anaesthesia and emergency hepatectomy secondary to trauma.

Information on demography, pre-operative comorbidities, pre-operative investigation, parameters measured in echocardiography, operative details, adverse postoperative event, outcome of surgery were obtained in a data collection form (Appendix 1).

Echocardiogram parameters were defined as:

1. Normal LVEF - American Cardiology Guideline defined normal left ventricular ejection fraction range from 50% to 70%. LVEF less than 40% indicate cardiomyopathy and heart failure, LVEF 41% to 50% is considered borderline with patients might have previous heart attack. In addition, high ejection fraction (> 70%) indicates cardiomyopathy is found to have increased morbidities. [15]

2. Diastolic dysfunction- presence of abnormal relaxation of heart especially in geriatric population had been shown to be significantly associated with adverse event in vascular surgery.[16]

3. Regional Wall Motion Abnormality – presence predict increased risk of perioperative and postoperative myocardial infarction.

4. Left ventricular hypertrophy- 2D targeted M mode increased measurement of LV dimensions and increased LV mass[17]

Perioperative parameters were defined as:

1. Laboratory parameters [18]:
   a) Hypoalbuminemia (serum albumin < 40 g/dl)
   b) Thrombocytopenia (platelet < 150 x 10^9 /L)
   c) Hyperbilirubinemia (serum bilirubin > 20 µmol/L)
   d) Hyperglycaemia (random blood sugar > 11.1 mmol/L)

2. Extent of resection [18]:
   a) Major resection: right or left hepatectomy or ≥ single segmentectomy
   b) Minor resection: < 3 segments hepatectomy and non-anatomical resection

3. Extrahepatic vascular pedicle ligation: dissection and ligation of the ipsilateral hepatic artery and portal vein within the hilus of the liver[18]

4. Concomitant extrahepatic procedure: example diaphragm repair, radiofrequency ablation, colectomy excluding cholecystectomy

5. Intraoperative hypotension is defined as mean arterial blood pressure 20% less than baseline

6. Major blood loss: blood loss > 1 L

Outcomes measured:

1. Primary outcome: Post-operative adverse event (occurrence of ≥ 1 adverse event) following elective hepatectomy [16]

Perioperative outcomes: days of ICU stay, days of ventilation, in-hospital mortality, one month and one year mortality

2. Secondary outcome: morbidity/ individual adverse event

Definition of adverse event:

1. Acute kidney injury is based on RIFLE definition of abrupt reduction of kidney function of i) increase in serum creatinine ≥ 26.4 μmol/L, ii) increase in serum creatinine 1.5-fold from baseline or iii) oliguria of < 0.5 cc/kg/hr for consecutive of 6 hours. [19]
2. Transient rise in serum hepatic transaminase and alkaline phosphatase levels as result of hepatocellular damage is common but persistently elevated and increasing level suggest ongoing hepatic ischemia and progression to acute fulminant hepatitis. [20]
3. MACCE (Major adverse cardiac and cerebrovascular event) defined as non-fatal cardiac arrest, acute myocardial infarction, congestive heart failure, new cardiac arrhythmia, angina, stroke, cardiovascular death or cerebrovascular death. [21]
4. Requirement for postoperative intubation of greater than 24 hours was categorised as prolonged intubation. [16]

Statistical analysis:

Association between patients that had pre-operative echocardiography against continuous variables (days of ICU stay, days of hospital stay and days of ventilation were tested against normality of distribution and were analysed with Mann-Whitney U test.

Association between adverse event and echocardiography measures of LVEF, diastolic dysfunction, left ventricular hypertrophy and presence of regional wall motion abnormalities were analysed using Pearson chi-square test with Yates correction.

Multivariate logistic regression analysis was performed to identify independent factors associated with adverse outcome. The same analysis was used to estimate propensity score for echocardiography. Characteristic found to be associated with an adverse outcome to the $P \leq 0.05$ were included.

Clinical significance guided initial choice of covariates: age, sex, types of surgery, comorbid disease, epidural anaesthesia, periods of low central venous pressure, periods of hypotension, intra-operative fluid, colloid and pressor use.

Data which is normally distributed is presented as mean ± standard deviation, or median (25% - 75% interquartile range) when not normally distributed.

Incidence or outcomes were presented as percentage of whole or a group, and 95% confidence interval (95 CI) are presented as outcomes, where appropriate.

4.0 Result

4.0.1 Demography study

Demographics of cohort for 92 patients who underwent hepatectomy from Jan 2010 to July 2016 are displayed in Table 1.

Table 1: The demographic of all patients (n=92)

Patient characteristics (n=92)	
Underwent pre-operative TEE, n (%)	73 (79.3)
Male (%)/ Female (%)	56 (61)/ 36 (39)
Age; mean (SD), years	58 (11.5)
Weight; mean (SD), kg	64 (12.9)
BMI; mean (SD), kgm^2	24.5 (4.4)
Pathology; n (%)	
- Hepatocellular carcinoma	37 (40.2)
- Benign liver tumour	8 (8.7)
- Secondary liver tumour	47 (51.1)
Comorbid; n (%)	
a) Hypertension	50 (54.3)
- Controlled	35 (38)
- Poorly controlled	15 (16.3)
b) Diabetes mellitus	27 (29)
- Controlled	14 (58.3)
- Poorly controlled	12 (41.6)
c) Dyslipidaemia	29 (31.5)
d) Hepatitis B co-infection	26 (28.3)
e) Hepatitis C co-infection	1 (1.1)
f) Liver cirrhosis	
Child's A	83 (90.2)
Child's B	8 (8.7)
Child's C	1(1.1)
g) Chronic kidney disease	61 (66.3)
Stage 1	7 (11.4)
Stage 2	39 (63.9)
Stage 3	14 (22.9)
Stage 4	1 (1.6)

h) Ischemic Heart Disease Prior PCI Medical therapy only	9 (9.8) 6 (66.6) 3 (33.4)
i) Pulmonary disease	3 (3.2)
j) Disseminated cancer	8 (8.7)
k) Chronic smoker	38 (41.3)
l) Alcoholic	23 (25)
m) Cholangitis	5 (5.4)
n) Obstructive jaundice	10 (10.9)
Pre-operative status; n (%)	
a) ASA status ASA 1 ASA 2 ASA 3	 30 (32.6) 60 (65.2) 2 (2.2)
b) NYHA status NYHA class I NYHA class II	 46 (50%) 46 (50%)
c) Functional status Independent Partially dependent	 90 (97.8) 2 (2.2)

Total 92 cases with mean age of patient population 58 years old. There are about 61% male and 39% female patients. Most hepatic resection surgery was done for underlying metastatic liver tumour (51.1%) and primary hepatoma (40.2%).

Patients are at mean age group of 58 who have co-morbid such as hypertension (54%) by which 16.3% uncontrolled, diabetes mellitus (29%), dyslipidaemia (31.5%) and chronic kidney disease (63% stage II), as such render them at risk of cardiovascular adverse event.

9.8% patient has ischemic heart disease and amongst them only 66% had prior percutaneous coronary intervention and stent insertion done.

28.3% of cases have hepatitis B co- infection. Most hepatic resection surgery cases are done for Child A (90.2%) who has functionally good liver function reserve. 25% of patient is chronic alcoholic and may have alcoholic liver disease.

41.3% of patient are either ex-smoker or active smoker with 3.2% with pulmonary disease. Majority are in ASA II with mild systemic disease.

Table II: Pre-operative intervention and surgical demographic

Intervention pre-op; n (%)	
a) Chemotherapy	26 (28.3)
b) Radio ablation	7 (7.6)
c) Portal Vein Embolization	5 (5.4)
d) PTBD	6 (6.5)
Extent of surgery; n (%)	
a) Extended resection (> 4 segments, contiguous or not)	33 (35.9)
b) > 3 segmental resections	6 (6.5)
c) < 3 segmental resections	34 (37)
d) Wedge resection	16 (17.4)
e) Local resection	3 (3.3)
Surgical access; n (%)	
a) Open	84 (91.3)
b) Laparoscopic	6 (6.5)
c) Laparoscopic convert open	2 (2.2)

Trans-arterial chemoembolization (TACE) that combines function of de-arterialisation of tumour and selective delivery of chemotherapeutic agent to liver had shown statistical significant survival benefits in patient with hepatocellular carcinoma and is superior over systemic chemotherapy.[22] 28% patients had underwent either systemic or TACE prior to surgery. 7.6 % has radiofrequency ablation of tumour, 5.4% underwent portal vein embolization and 6.5% had percutaneous trans-biliary drainage prior to surgery.

Portal vein embolization is one of the methods used to stimulate growth of future remnant liver and to ensure adequate liver reserve prior to liver resection. [23]

55.9% patients underwent extended liver resection that involve more than 4 segments whist majority of liver resection is accessed by open incision.

Table III: Complications of hepatic resection surgery and mortality

Morbidity; n (%)	
Acute kidney injury	18 (19.6)
Liver failure	15 (16.3)
a) Acute fulminant liver failure	11 (12.0)
b) Decompensated liver failure	4 (4.3)
Coagulopathy	15 (16.3)
Sepsis/ septic shock	17 (18.5)
Cardiac event	12 (13)
a) Acute coronary syndrome	5 (5.4)
b) Malignant arrhythmia	7 (7.6)
Bile leak	7 (7.5)
Pulmonary complication	
a) Atelectasis	9 (9.8)
b) Pneumonia	8 (8.7)
c) Pleural effusion	3 (3.3)
Ischemic stroke	2 (2.2)
Upper Gastrointestinal Bleed	4 (4.3)
28 day re-operation	7 (7.6)
Mortality	
In hospital mortality	4 (4.3)
30 days mortality	6 (6.5)

Acute kidney injury develops in 19.6% post hepatectomy.

16.3 % of patients developed acute liver failure or decompensation post hepatic resection surgery.

Similarly, 16.3% patient developed coagulopathy along with deterioration of liver function. Coagulopathy also developed following major intraoperative bleeding or blood transfusion more than 4000ml and consumption of coagulation factor following severe infection/sepsis. [24]

13% developed cardiac adverse event either as acute coronary syndrome (5.4%) or malignant arrhythmia (7.6%).

Majority of patient were extubated day 0 post op (52.2%) or day 1 post op (30%). Prolonged intubation had shown to increase risk of pulmonary complications. 9.8% patient developed atelectasis with hypoxemia and radiographically changes. 8.7% developed pneumonia day 3-5 post op. Pleural effusion developed in 3.3% of patients which can be reactive related to surgical manipulation or hepatic hydrothorax as this group of patient show no sign of infection.

In hospital mortality and 30 day mortality following hepatectomy is 4.3% and 6.5% respectively.

4.0.2 Analysis of 92 cases of hepatectomy divided into 2 groups (those who had pre-operative echocardiography done versus those with no pre-operative echocardiography done) and comparison between difference in outcome

Analysis of 92 patients, of whom 79% (n= 73) had pre-operative echocardiography done before surgery. Patients who did or did not done ECHO had significant difference in measured characteristic. Patients who done ECHO are generally older generations with greater comorbid disease and those undergoing major hepatectomy.

Table IV: Comparison of primary outcome (length of ICU stay, length of hospital stay and days of ventilation) between patient with echocardiogram and no echocardiogram done pre-operatively (n=92)

Variable	Median (IQR)	Z-stat**	p-value
Length of ICU stay (days) Done ECHO No ECHO done	 2.0 (2.0) 1.0 (1.0)	 -1.273	 0.203
Length of hospital stay (days) Done ECHO No ECHO done	 7 (6) 7 (7)	 -0.451	 0.652
Days of ventilation (days) Done ECHO No ECHO done	 1 (1) 0 (1)	 -0.409	 0.682

* continuous variables are expressed as median and interquartile range

** Mann-withney test

There is no significant difference in length of ICU stay, length of hospital stay or days or ventilation between patient who had pre-operative echocardiogram and no echocardiogram done before hepatectomy.

Table V: Comparison between primary outcome (in hospital, 30 days and one year mortality, development of adverse outcome) and secondary outcome (morbidity) between patient with echocardiogram and no echocardiogram done pre-operatively (n=92)

Variable	Done ECHO n (%)	No ECHO done n (%)	Chi Square	p-value

In hospital mortality Yes No	 3 (4.1) 70 (95.9)	 1 (5.2) 18 (94.8)	0.048	0.99©
30 day mortality Yes No	 4 (5.4) 69 (94.6)	 3 (15.7) 16 (84.3)	2.280	0.152©
One year mortality Yes No	 20 (32.3) 42 (67.7)	 3 (17.6) 14 (82.4)	1.380	0.367©
Primary adverse outcome ≥1 adverse outcome No adverse outcome	 44 (60.2) 29 (39.8)	 7 (36.8) 12 (63.2)	3.351	0.067
Acute kidney injury Yes No	15 (20) 58 (80)	3 (16) 16 (85)	0.217	0.756
Liver failure Yes No	61 (83.6) 12 (16.4)	16 (84.2) 3 (15.8)	0.005	0.99 ©
MACCE Yes No	10 (13.7) 63 (76.3)	2 (10.5) 17 (89.5)	0.134	0.99 ©
Bile leak Yes No	3 (4.1) 70 (95.9)	4 (21.1) 15 (78.9)	6.15	0.031©
Upper Gastrointestinal Bleed Yes No	2 (2.7) 71 (97.3)	2(10.5) 17 (89.5)	2.198	0.188©

©Fisher exact test

There was no statistically significant difference in occurrence of adverse post-operative outcome in patients who had perioperative echocardiography done (p=0.067). Bile leak

was found to be significantly different in those that had pre-operative echocardiography done (p=0.031)

Otherwise, there was no significant difference in 30 days, in hospital and one year mortality between patients who had pre-operative echocardiogram done versus not done.

4.0.3 Univariate and multiple regression model to predict significant risk factor that influence primary outcome (n=92)

Univariate analysis was performed to identify risk factors associated with adverse event post hepatectomy.

Table VI: Comparison of demographic/ laboratory variables between 2 groups*

	Presence of adverse event (n= 51)	No adverse event (n=41)	p value
Age, years	59 (12)	59 (17)	0.579
Gender, male	34 (66.7%)	22 (53.7%)	0.204
BMI	24 (6)	23 (4)	0.595
Malignant liver lesion (liver metastasis or primary hepatoma)	46 (90.2%)	38 (92.7%)	0.728
Hypertension	29 (56.9%)	21 (51.2%)	0.589
Diabetes mellitus	17 (33.3%)	10 (24.4%)	0.349
Cirrhotic liver	6 (11.8%)	3 (7.3%)	0.72
Hepatitis B co-infection	11 (21.6%)	15 (36.6%)	0.112
Ischemic heart disease	6 (11.8%)	3 (7.3%)	0.178
Pulmonary disease	2 (3.9%)	1 (2.4%)	0.99
Disseminated cancer	3 (12.2%)	5 (5.9%)	0.46 ©
Chronic smoker	24 (47.1%)	14 (34.1%)	0.211
Alcoholic	15 (29.4%)	8 (19.5%)	0.276
ASA ≥ 2	38 (74.5%)	24 (58.5%)	0.23
Adjuvant chemo/TACE	11 (21.6%)	15 (36.6%)	0.112
Hypoalbuminemia (serum albumin < 40g/dl)	30 (58.8%)	23 (56.1%)	0.793
Hemoglobin (g/dL)	13.4 (2.2)	12.6 (2.8)	0.101
Platelet count < 150	11 (21.6%)	4 (9.8%)	0.127
Bilirubin > 20	9 (17.6%)	3 (7.3%)	0.144
RBS > 11.1 mmol/L	7 (14.6%)	1 (2.7%)	0.130©

*continuous variables are expressed as median and interquartile range , otherwise figure represent number of patients with percentage in parentheses

© Fisher exact test

Table VII: Comparison of surgical/anaesthesia variables between 2 groups*

	Presence of adverse event (n= 51)	No adverse event (n=41)	P value
Major resection	24 (47.1%)	15 (36.6%)	0.312
Vascular ligation	36 (70.6%)	21 (21.2%)	0.057
Extra hepatic procedure	22 (42.1 %)	14 (34.1%)	0.38
Major blood loss (> 1 L) (n, mean)	37 (1400 ml)	16 (700 ml)	0.001 **
Hypotensive period (min)	240	180	0.179
Urine output < 0.5ml/kg/hr	9 (17.6%)	4 (9.8%)	0.28
Severe hypothermia (< 35 degree)	18 (41.5%)	17 (35.3%)	0.54
Epidural	12 (23.5)	6 (14.6)	0.285
Op Time (min)	480	420	0.007**
Blood (unit)	1	0	0.017**
Highest lactate (mmol/l)	4.3	3.3	0.019**
Total fluid (ml)	4000	3500	0.027**

*continuous variables are expressed as median and interquartile range, otherwise figure represent number of patients with percentage in parentheses

** significant parameters

Univariate analysis showed median op time of 480 min, median blood loss of 1400 ml, perioperative blood transfusion and higher lactate level during resection with higher amount of perioperative fluid usage were predictors which significantly associated with post-operative adverse event.

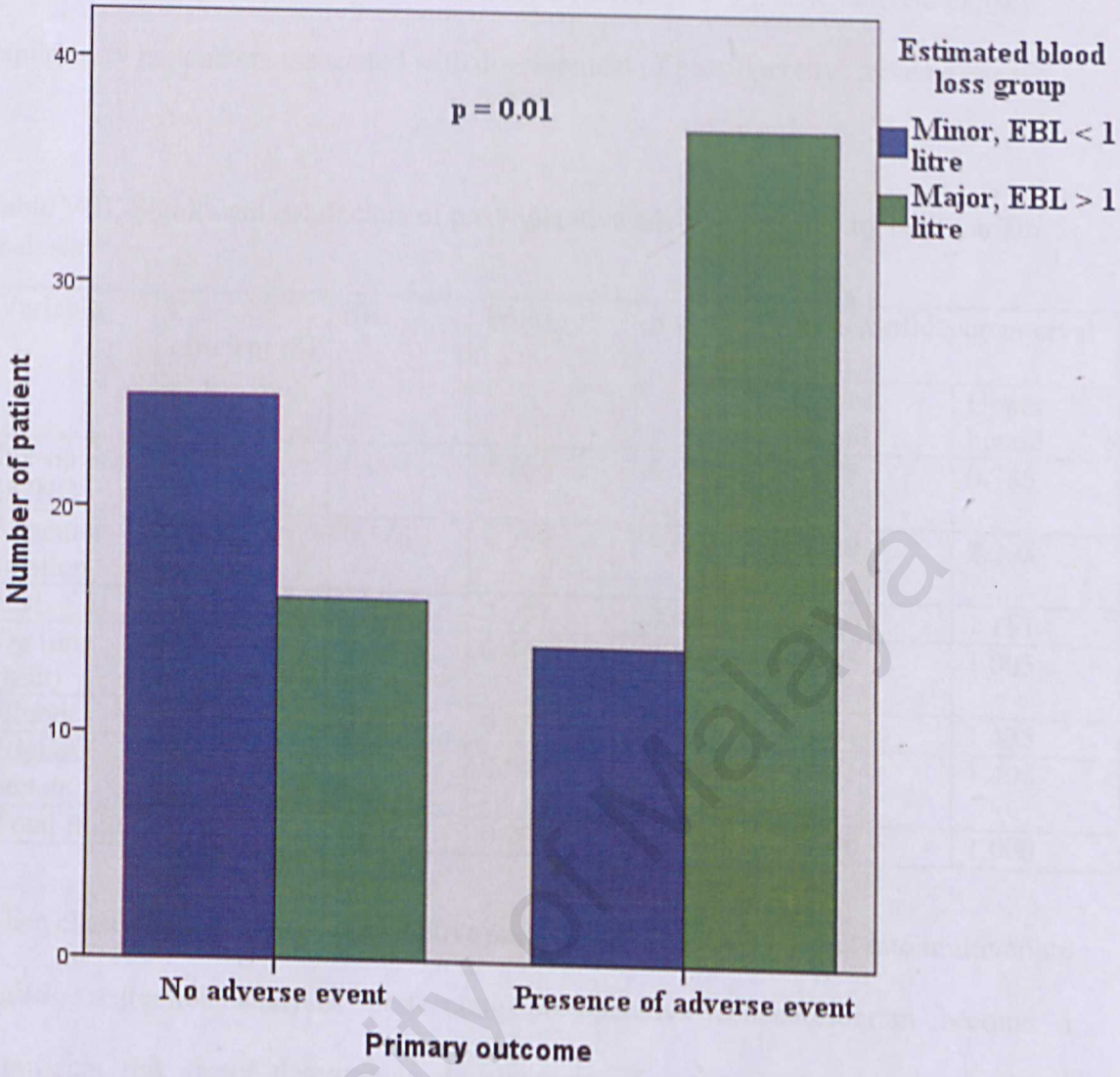

Figure 1: Association of Estimated Blood Lost with Post-operative Adverse Event

Multivariate analysis of covariates with α-level (p-value) < 0.1 is included to explain explanatory parameters associated with development of post-operative adverse event.

Table VIII: Significant risk factors of post-operative adverse outcome by multivariate analysis

Variable	Co-efficient (β)	SE	Wald χ^2	p value	95% confidence interval for β	
					Lower bound	Upper bound
Pre-op ECHO	-1.432	0.607	5.566	0.018	0.073	0.785
Vascular ligation	-0.278	0.546	0.259	0.611	0.260	2.208
EBL ≥ 1L	-1.033	0.599	2.977	0.084	0.110	1.151
Op time (min)	2.001	0.002	0.449	0.503	0.998	1.005
Blood	0.046	0.157	0.086	0.770	0.769	1.425
Highest lactate	0.102	0.123	0.688	0.407	0.871	1.408
Total fluid	0.000	0.000	0.206	0.650	1.000	1.000

When clinically significant pre-operative and surgical variables was put into multivariate logistic regression analysis, performing pre-operative echocardiogram become a significant risk factor determining development of post-operative adverse outcome (p=0.018).

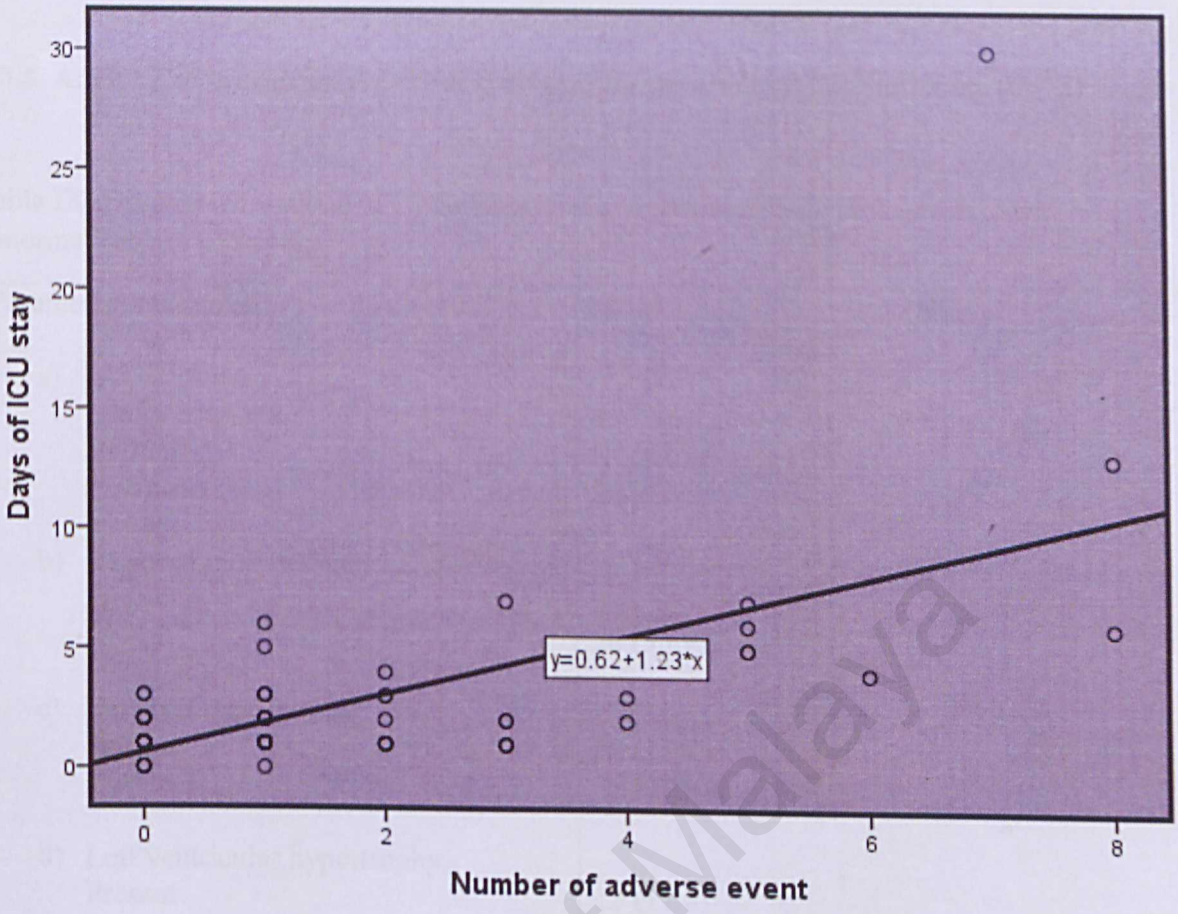

Figure 2: Correlation between number of post-operative adverse event and length of ICU stay

Pearson correlation between number of post-operative adverse event and length of ICU stay shows a strong association between number of post-operative adverse event and days of ICU stay (p=0.000, Pearson correlation 0.646)

4.0.4 Analysis of pre-operative echocardiography parameters with outcome (n=73)

Table IX: Descriptive statistic of 73 patients who underwent pre-operative ECHO and abnormal cardiac pathology

Parameters measured	
a) LVEF	
< 50%	4 (5.4)
50-70%	38 (52.2)
> 70%	31 (42.4)
b) Regional motion abnormality	
Present	3 (4.1)
Absent	70 (95.9)
c) Diastolic dysfunction	
Present	18 (25.7)
Absent	55 (75.3)
d) Left ventricular hypertrophy	
Present	13 (17.8)
Absent	60 (82.2)

Table X: Comparison of perioperative outcomes between LVEF groups (n=73)*

Variable (days)	LVEF			Kruskal-Wallis	p value
	< 50 % (n=4)	50-70% (n=38)	>70% (n=31)		
ICU stay	4 (3)	1 (1)	1 (1)	9.823	0.007*
Ventilation days	1 (4)	0 (1)	0 (1)	0.696	0.404
Hospital stay	12.5 (9)	7 (5)	6 (7)	1.997	0.368

* continuous variables are expressed as median and interquartile range

Analysis of 73 patients showed statistically significant prolonged days of ICU stay in patients with LVEF < 50% and >70% (p=0.007). Ventilation days and hospital stay were observed to be also longer in patient with LVEF < 50%.

Table XI: Comparison of perioperative outcomes between LVEF groups (n=73)

Variable	LVEF		Chi square	p value
	50-70 % n (%)	< 50% or > 70% n (%)		
30-day mortality				
Yes	3 (7.8)	1 (2.8)	0.893	0.616©
No	35 (92.2)	34 (97.2)		
One year mortality				
Yes	13 (44.8)	7 (21.2)	3.939	0.047*
No	16 (55.2)	26 (78.8)		
Primary outcome				
≥ 1 adverse outcome	18 (60.0)	24 (55.8)	0.127	0.722
No adverse outcome	12 (40.0)	19 (44.2)		
Liver failure				
Decompensated liver failure	1 (2.6)	2 (5.7)	8.2	0.042*
Acute liver failure	6 (15.8)	3 (8.6)		
Transient transaminitis	16 (42.1)	25 (71.4)		
No	15 (39.5)	5 (14.3)		
Acute kidney failure				
Yes	10 (26.3)	5 (14.3)	1.615	0.204
No	28 (73.7)	30 (85.7)		
MACCE				
Yes	7 (18.4)	4 (11.4)	0.696	0.404
No	31 (81.6)	31 (88.6)		

Abnormal left ventricular ejection fraction was found to be associated with one year hospital mortality (p= 0.047) and development of liver failure (decompensation or acute liver failure) (p= 0.042). It was found to be weakly associated with acute kidney injury.

However, development of MACE (major adverse cardiac event) was not significantly associated with abnormal LVEF.

Abnormal diastolic dysfunction can come with a normal LVEF. A meta-analysis of 14 studies conducted by American College of Cardiology concluded that presence of diastolic dysfunction on pre-operative echocardiogram was associated with higher post-operative mortality and major adverse cardiac event (MACE) regardless of LVEF. [25]

Table XII: Comparison of perioperative outcome between diastolic dysfunction groups* (n=73)

Variable (days)	Diastolic dysfunction		Z- stat**	P value
	Yes (n= 18)	No (n=55)		
ICU stay	1 (1)	1 (1)	0.327	0.744

* continuous variables are expressed as median and interquartile range

** Mann- Whitney test

Table XIII: Comparison of perioperative outcome between diastolic dysfunction groups (n=73)

Variable	Diastolic dysfunction		Chi Square	P value
	Yes n (%)	No n (%)		
30 day mortality				
Yes	2 (3.6)	2 (11.1)	1.463	0.25 ©
No	53 (96.4)	16 (88.9)		
One year mortality				
Yes	14 (31.1)	6 (35.3)	0.099	0.753
No	31 (68.9)	11 (64.2)		
Primary outcome				
≥1 adverse event	30 (54.5)	13 (72.2)	1.751	0.186
No	25 (45.5)	5 (27.8)		
Acute kidney injury	11 (20)	4 (22.2)	0.041	0.99 ©
Yes	44 (80)	14 (77.8)		
No				
Liver failure	8 (14.5)	4 (22.2)	0.582	0.446
Yes	47 (85.5)	14 (77.8)		
No				

MACCE Yes No	7 (12.7) 48 (87.3)	4 (22.2) 14 (77.8)	0.955	0.447

25.7% of patients in whom who had echocardiography done was found to have diastolic dysfunction. It was observed patient with diastolic dysfunction is twice more likely develop one or more adverse outcome compared to patient with normal diastolic dysfunction (45.5 % [25] vs. 27.7%. [5]). This association, however is not significant (p=0.186).

In this study, diastolic dysfunction was not a significant predictor of any MACCE or end organ failure.

Table XIV: Comparison of perioperative outcome between left ventricular hypertrophy groups* (n=73)

Variable (days)	Left ventricular hypertrophy		Z- stat**	P value
	Yes (n= 13)	No (n=60)		
ICU stay	1(3)	1 (1)	-0.417	0.677
Ventilation days	0 (3)	0 (1)	-0.439	0.661
Hospital stay	6.5 (5)	7 (8)	-0.631	0.528

* continuous variables are expressed as median and interquartile range

** Mann- Whitney test

Table XV: Comparison of perioperative outcome between left ventricular hypertrophy groups* (n=73)

Variable	Left ventricular hypertrophy		Chi Square	P value
	Yes n (%)	No n (%)		
30 day mortality				
Yes	2 (15.4)	2 (3.3)	2.996	0.143
No	11 (84.6)	58 (96.7)		
1 year mortality				
Yes	2 (10.0)	9 (21.4)	1.213	0.478
No	18 (90.0)	33 (78.6)		
Reintubation				
Yes	3 (23.1)	2 (3.3)	6.528	0.037©*
No	10 (76.9)	58 (96.7)		
Readmission to ICU	2 (15.4)	1 (1.7)	5.102	0.08©
Yes	11 (84.6)	59 (98.3)		
No				
Acute kidney injury				
Yes	4 (30.7)	11 (18.3)	1.012	0.448
No	9 (69.3)	49 (81.7)		
Acute liver failure				
Yes	3 (23.1)	9 (15.0)	0.507	0.438©
No	10 (76.9)	51 (85.0)		
MACCE				
Yes	2 (15.4)	9 (15.0)	0.001	0.99
No	11 (84.6)	51 (55.0)		

In our study, left ventricular hypertrophy was found to be associated with rate of reintubation (p=0.037) . There was no significant association between hospital stay, ICU stay , MACCE and end organ failure (acute kidney injury, liver failure).

5.0 DISCUSSION

There was no consensus guideline up to date in performing perioperative echocardiography for hepatectomy. In our study, only 73 out of 92 patients had perioperative echocardiography done. Patient who underwent hepatic resection is in mean age of 58 years old with 67% ASA 2 and above. Indication of hepatic resection mainly secondary to hepatoma or secondary liver tumour excision. Majority of our study population has comorbid such as hypertension (16.2% of whom poorly controlled), diabetes mellitus and chronic kidney disease which are risk factor of major adverse cardiovascular and cerebrovascular event post-operative.

In this study, performing perioperative echocardiogram prior to hepatic resection surgery was not shown to influence days of ventilation, days of ICU and in-hospital stay. Perioperative echocardiogram also does not influence mortality or occurrence of post-operative adverse event.

This is in concordance with studies ACC/AHA 2007 Guideline on Perioperative Cardiovascular Evaluation and Care for Non-cardiac Surgery statement that resting echocardiography has relatively weak evidence in predicting post-operative outcomes even in patients with active cardiac conditions and poor functional status. [11]

Nevertheless, consideration for pre-operative echocardiogram cannot be view from perspective of patient's comorbid alone. Consideration should also be made on extent of resection and vascular occlusion technique employed by surgeon.

Univariate study of contributory factors contributing adverse event and ICU stay post op includes estimated blood lost, operative time, perioperative blood transfusion, lactate level during hepatic resection and amount of fluid given. Some factors are in line with major bigger studies done in Hong Kong by *Poon et. al.* including estimated blood lost, perioperative blood transfusion[18].

Our study identified highest lactate level during hepatic resection to be independent and significant (p=0.019) risk factor contribute to post-operative adverse event. This finding is parallel to a retrospective study by *Wiggans et al.* which concluded that initial post-operative lactate concentration is a useful predictor and patients with normal lactate level are unlikely to suffer from significant liver or renal failure and may not require intensive care monitoring. [26]

Traditionally, hepatic resection adopts restricted fluid therapy to lower CVP as a measure to reduce bleeding. Our study identified higher volume of intra-operative fluid given leads to worse outcome. To date, no study had been conducted to investigate effect of type and volume of fluid in hepatectomy.

Multivariate analysis of clinically significant risk factors demonstrated performing pre-operative ECHO is a significant risk factor (p= 0.018) in pot-operative adverse event. In fact, usage of trans-oesophageal echocardiography had extend to intraoperative tool for not only hemodynamic monitoring, but also for ability to provide information of liver anatomy, liver vessels and patency of inferior vena cava during hepatic resection surgery. [27]

Abnormal left ventricular ejection fraction was shown to significantly affect one year survival in vascular surgery but no apparent increase in perioperative mortality and perioperative cardiac complication. [28] American College of Cardiology in a cohort study of high LVEF (> 70%) conducted on 23187 veterans shown U shaped relationship between LVEF and outcomes, and those with high ejection fraction associated with higher mortality and admission rate. Impact of LVEF > 70% on perioperative outcome was yet to be studied in any major journal.

In our study, we found significant higher days of ICU stay (p=0.007) and 1 year mortality(p=0.047) in patients with LVEF < 50%. There was also increased risk of

developing liver failure (p=0.042) but not renal failure or MACCE between patients with abnormal LVEF compared to normal LVEF.

Meta-analysis of 14 studies conducted by Journal of American College of Cardiology conducted in 2015, prognostic role of diastolic dysfunction was studied against post-operative mortality, major adverse cardiac events and days of ventilation. The study concluded that presence of diastolic dysfunction, independent of systolic function was associated with higher perioperative mortality and adverse cardiac event.[16] In our study which consists of 73 patients who had ECHO done, larger proportion of adverse outcome was found in those with abnormal diastolic dysfunction, no significant parameters were found in relevance to abnormal diastolic dysfunction.

Prolonged hypertension was known to lead to target organ response of left ventricular hypertrophy. Increased left ventricular mass index in ECHO indicated increased myocardial oxygen demand caused by increased myocardial wall tension which leads to myocardial perfusion insufficiency and potential myocardial infarction.[29] Low central venous pressure anaesthesia (CVP < 5 mm Hg) in major hepatic resection can reduce blood lost and transfusion requirement but low CVP will inadvertently lead to hypotension.[30] Loss of blood pressure autoregulation during hypotension predispose kidney to hypotensive episode during hepatic resection surgery.

In our study, larger proportion of patients with left ventricular hypertrophy detected from pre-operative ECHO found to develop acute kidney injury post-operative despite association was not significant.

LIMITATIONS

This study is a retrospective cohort study whereby bounded by missing records and data. A larger prospective cohort involving audit database involving bigger number of cases should be included.

Elective hepatectomy were conducted after proper case selection which result in small number of high risk cases with poor pre-operative cardiac function, liver function, advanced age and comorbid illness. Cases selection criteria may be extended prospectively in advent of surgical and anaesthesia advancement.

Certain operative parameters such as duration of Pringle manoeuvre and vascular clamping time which are deemed to be of importance in other series of major hepatectomy audit done in Japan, Hong Kong and Western countries are not properly documented in surgical notes.

Pre-operative computed tomography finding of tumour site and number of tumours was included as surgical parameter in investigating hepatic resection surgery outcome in United Kingdom. This information was unable to be incorporated due to incomplete radiology documentation of pre-operative CT scan.

Anaesthesia operative notes did not specifically account fluid infusion rate which can be pertinent into more objective reflection of intra-operative fluid usage over time.

RECOMMENDATIONS

Audit involving surgical, cardiology, intensive care medicine and anaesthesiology unit should be planned to involve a bigger database to determine significant risk factors that affect outcome of hepatic resection.

8.0 CONCLUSION

Decision whether to perform pre-operative echocardiogram should not be judged based on patient's comorbid, NYHA status and cardiac risk assessment alone. Consideration should be taken into consideration extent of hepatic resection, operative time, major vascular ligation, possibility of liver mobilisation, extend of blood loss and how extensive fluid shift involved.

Peak serum lactate level is predictive of adverse outcome by indicating residual functional liver reserve, target end organ damage and need to be monitor throughout during hepatic resection.

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Data Collection Form Sheet

Transthoracic Echocardiography and perioperative mortality in Hepatic Resection Surgery

Subject Number :
Date of Data Collection:

Patient's Profile a

Patient Data

Age:

Weight: kg Height: cm BMI:

ASA:

Premorbid:	(known case of)		
Hypertension	Y/N	(controlled/ uncontrolled)	
Diabetes	Y/N	(controlled/ uncontrolled)	
Dyslipidemia	Y/N		
Liver cirrhosis	Y/N	Child Pugh	A / B / C
Chronic renal disease	Y/N		
Ischemic heart disease	Y/N		
Structural heart disease	Y/N		
Peripheral vascular disease	Y/N		

Date of hepatic resection surgery: _____

Echocardiogram done: Y/N , if Yes

Echocardiogram Indices

Left venticular efection fraction	%		(normal > 55%)
Left atrium dilatation	Y/N		
Left ventricle dilatation	Y/N		
Regional wall motion abnormaly	Y/N	if yes,	territories:
Left ventricular diastolic function			
E/A ratio			(1-2)
Aortic stenosis:	Y/N	if yes,	grading: _____
Mitral stenosis:	Y/N	if yes,	grading: _____
Aortic regurgitation:	Y/N	if yes,	grading: _____
Mitral regurgitation:	Y/N	if yes,	grading: _____

Pulmonary hypertension:		
	Right atrium dilatation	Y/N
	Right ventricle dilatation	Y/N
	Presence of tricuspid regurgitation	Y/N

PASP mmHg

Congenital heart disease: Y/N if yes, pathology: _____

Operative details

Sugery: _____

Tumor location: _____

Vascular occlusion: _____

Estimated blood loss: ml

Duration of low CVP (2-5mm Hg) : min

Volume of pack cell tranfused: ml

Outcome

Length of ICU stay:

Length of Hospital Stay:

Need of pressor support post op:

End organ perfusion post op:

Acute kidney injury	Y/N
Acute liver failure	Y/N
Sepsis	Y/N
Perioperative myocardial infarction	Y/N
Biliary leak	Y/N
Decompensated liver disease *	Y/N

Post operative survival 30 days
1 year

* include ascites, hepatic encephalopathy, upper gastrointestinal bleed