THE ROLE OF SERIAL LACTATE AND LIVER ENZYME DYNAMICS IN PREDICTING POST HEPATECTOMY LIVER FAILURE

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DECLARATION

I, Vuyolwethu Sonwabile Soldati, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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Dr Vuyolwethu Sonwabile Soldati

Signed on the 30th day of June 2021

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LIST OF TABLES AND FIGURES

ABBREVIATIONS

AKI	Acute kidney injury
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
BMI	Body mass index
CCI	Comprehensive complication index
CRCLM	Colorectal cancer liver metastases
GGT	Gamma-glutamyl transferase
HCC	Hepatocellular carcinoma
HIV	Human immunodeficiency virus
HPB	Hepato-pancreatico-biliary
ICU	Intensive care unit
INR	International normalised ratio
ISGLS	International Study Group of Liver Surgery
NET	Neuro-endocrine tumour
PHLF	Post-hepatectomy liver failure
UCT	University of Cape Town

ABSTRACT

Background: Post-hepatectomy liver failure (PHLF) is an important cause of morbidity and mortality following liver resection. Current prognostic models only allow for the detection of PHLF on post-operative day 5. Earlier detection and intervention may improve outcomes. To date, no studies have evaluated serial post-operative lactate and liver function tests (LFT) to predict PHLF.

Aim: This study evaluated the prognostic utility of serial lactate concentrations and LFTs to predict PHLF following hepatectomy.

Methods: All major liver resections (≥3 Couinaud segments) undertaken at Groote Schuur Hospital and UCT Private Academic Hospital from May 2018 to April 2021 were included. Lactate levels were measured 4-hourly for the first 24 hours post hepatectomy and daily LFTs for the first 5 days. Associations between baseline patient characteristics and lactate dynamics in PHLF as well as the predictive value of lactate, INR and bilirubin were determined.

Results: Forty-seven patients, mean age 56.5 (±13.2) years, of whom 24 were males were assessed. Five (10.6%) patients had PHLF and were older (67.4 ± 12.2) and were predominantly men (80%). The presence of diabetes was significantly associated with PHLF (β (SE) 2.97 (1.09), p =0.007) as were intra-abdominal collections (β (SE) 2.68 (1.18), p =0.023). In univariate analysis, lactate levels measured 16 hours post-operatively were marginally associated with PHLF (β (SE) 1.68 (0.85), p =0.054). In multivariate analyses where diabetes and collections were adjusted for, INR and total bilirubin were significantly associated with PHLF on day 3 (β (SE) 0.27 (0.11), p =0.022; and β (SE) 33.51 (12.05), p = 0.008 respectively).

Conclusion: Lactate as marker for PHLF is promising but requires further investigation in a larger sample size. In this study, diabetes was associated with the development of PHLF and should be considered as a pre-operative risk factor, while a day 2 bilirubin and day 3 INR could predict PHLF.

Literature review

Liver resection

Over the past decade, epidemiological transitions have resulted in an increased need for hepatic resection. At present, primary liver cancer is estimated to be the sixth most common cancer globally, contributing significantly to cancer mortality(1, 2). Hepatocellular carcinoma (HCC) comprises 75-90% of all primary hepatic malignancies, and it is the fourth most common malignancy in Africa(2, 3). In sub-Saharan Africa (SSA), HCC is the second most common cancer in males and the fourth most common in females (4). Liver metastases may occur secondary to several types of malignancies, in particular gastrointestinal tumours, with colorectal cancer most often associated with liver metastases (5). These shifts in epidemiological patterns and expanding indications for liver intervention, have seen an increase in hepatic interventions, including hepatic resection, either alone or with hyperthermic tumour ablation for both primary hepatobiliary and secondary metastatic tumours (6-10). Despite improved surgical techniques and better peri-operative care, liver resections still pose both intra- and post-operative challenges (11, 12). These inherently complex surgical procedures, in particular major resections, defined as resection of three or more Couinaud segments, are characterized by relatively high morbidity and mortality rates. Several studies which included patient cohorts treated in the 1980s and 1990s report mortality rates as high as 30% for liver resection (13-16). With more emphasis on patient risk modification, advancements in operative and anaesthetic techniques and improved perioperative care has seen perioperative mortality rates declining from 30% to 1-3% in high-volume centres and 5–10% in population-based analyses, morbidity rates remain high (12, 17). Timeous detection of complications to facilitate early intervention during the post-operative period is imperative for optimal results.

Post hepatectomy liver failure

With better operative techniques and better understanding of the functional liver anatomy, operative mortality for patients undergoing liver resection has reduced in frequency with post-operative hepatic failure now being reported as the most common cause of post-operative mortality (7, 12, 15, 18). Where major liver resection has been associated with mortality rates of up to 30%, PHLF accounts for more than 60% of post-operative deaths (13-15). The incidence of PHLF varies between institutions, quoted at 1.2% to 32%, in recent literature, but averaging at 8% in high volume centres (19). This wide range points to the differences in patient populations and performed procedures. This may also be influenced by different units using different definitions of PHLF. Decrease in PHLF in the last years is due to the improvement in surgical techniques and in intensive care medicine. Risk factors of the patient population seem to have a big influence on the occurrence of PHLF (19).

The exact mechanism of PHLF, primarily the result of hepatocyte growth factor dysregulation is still being investigated. Following surgical resection, hepatic regeneration is initiated by the increased expression of transcription factors in response to sheer stress on the vascular endothelium. These transcription factors stimulate the release of nitric oxide (NO) by the sinusoidal endothelial cells, which in turn enables a cascade responsible for sensitization of hepatocytes to hepatocyte growth factors contributing for hepatic regeneration (20-22). In the event of severe sheer stress on the endothelium, the same cascade responsible for regeneration will result in necrosis and damage to existing hepatocytes. Dysregulation of inflammatory cytokines such as Interleukin-6 (IL-6) and Tumour Necrosis Factor-α (TNF-α) has been suggested as contributing factors to the development of PHLF (23, 24).

Several definitions for PHLF have been proposed (12). The International Study Group of Liver Surgery (ISGLS) has suggested a definition of PHLF (Table 1a), which has since been validated and is currently the most commonly used definition, which facilitates data comparisons (25, 26). In brief PHLF is defined as an acquired deterioration in the ability of the liver to maintain its synthetic, excretory and detoxifying functions, which are characterised by an increased INR (or need for clotting factors to maintain INR) and hyperbilirubinemia on or after day 5. In patients with normal pre-operative liver function increases in INR and hyperbilirubinemia are assessed according to cut off levels defined by the local laboratory. If INR and/or serum bilirubin concentration were increased pre-operatively, PHLF is defined by an increasing INR and increasing serum bilirubin on or after day 5 (compared with the values of the previous day). Other obvious causes for the observed biochemical and clinical alterations such as biliary obstruction should be ruled out. This definition has recently been validated (26). As with all anticipated complications, timeous detection of PHLF remains imperative.

Prevention of PHLF with careful pre-operative assessment of patients undergoing hepatectomy is important, especially in major liver resections. Pre-operative hepatic volumetric analysis, using cross-sectional imaging, to calculate the volume of the future liver remnant (FLR) as a percentage of the total parenchymal volume should be performed in major resections where a marginal FLR is expected (27). Stand-alone volumetric assessment is sufficient in the absence of underlying liver disease with reasonable consensus that a FLR volume of 25% with intact blood supply and venous and biliary drainage is sufficient for preservation of post-operative function and for post-resection regeneration (28). In the presence of underlying parenchymal disease, for example cirrhosis and chemotherapy-associated liver injury (CALI) a functional analysis needs to be added and the FLR needs to be increased as a function of the dysfunction. The Child Turcotte Pugh (CTP) and Model for End-

Stage Liver Disease (MELD) scoring systems are routinely used in the pre-operative assessment of patients with underlying cirrhosis set to undergo hepatic resection (17, 29). The CTP was originally designed for another purpose and despite some studies suggesting a low predictive value, the CTP is still frequently used (29). Several studies have validated the use of the MELD scoring system, with higher scores associated with increased mortality following hepatectomy (27). Dynamic scintigraphy and MRI-based function assessment methods have also been proposed (30, 31). Analyte tests are the most commonly used measure of hepatic function in clinical practice due to their low cost and ease to perform. They give indirect indications of liver function and include measurements of cell permeability or damage (liver enzymes), synthetic capability (coagulation parameters and albumin) and metabolic integrity (bilirubin) (32). Most of the tests, however, are non-specific and serum levels are influenced by factors other than liver function.

There are several patient-related factors that are associated with PHLF, including diabetes mellitus, obesity, chemotherapy-associated steatohepatitis (CASH), fibrosis and cirrhosis, malnutrition, renal insufficiency, hyperbilirubinemia, thrombocytopenia, lung disease, and age >65 year (10, 17, 33). A growing body of literature cites diabetes mellitus as a significant predicative factor for the development of PHLF (12, 34). Studies suggest that poor immune function, altered liver metabolism and pre-existing hepatic steatosis may act as co-factors with diabetes, conferring an increased mortality rate (34-36). The development of PHLF in the setting of CASH is described in several studies, largely as a result of the hepatotoxicity of chemotherapeutic and biologic agents (36-38).

In addition to patient-related factors, the risk of PHLF is influenced by the nature and extent of the surgical procedure. The development of PHLF is associated with significant intra-operative estimated blood loss (>1200mL) and need for intra-operative transfusion,

prolonged ischaemia of the FLR (Pringle manoevre), prolonged operating time (>240min) excessive dissection of portal triad and hepatoduodenal ligament and resection of >50% of liver volume with consequent small remnant liver volume (10, 12, 39-42). Similarly, post-operative events, including post-operative haemorrhage, bile leak and post-operative infection, are associated with an increased risk for the development of PHLF (7, 43). The presence of these associated surgical risk factors, pre-, intra- and post-operatively, influence the outcomes of patients undergoing hepatic resections and should be considered in the perioperative period.

Post-operative prognostic models form a central role in the prediction and detection of post-operative liver failure, which has resulted in the development of several scoring systems, of which the International Study Group of Liver Surgery (ISGLS) and 50–50 criteria are the most widely used (25, 44, 45). These, however, only detect PHLF by post-operative day 5. Hyder *et al.* developed a scoring system that combined Clavien-Dindo grade of complications, INR, bilirubin and creatinine levels on post-operative day 3, which demonstrated a linear association between increased risk scores and post-operative mortality (46).

Few studies have evaluated the kinetics of LFTs after liver resection and only one study has used the ISGLS definition of PHLF (27, 47, 48). The inability of current scoring systems to provide an earlier indication that a patient is at risk of PHLF, and which could prompt earlier intervention, is problematic. Serum procalcitonin (PCT) has been used as a post-operative predictor for the development of complications in several surgical specialties. An observational study by Aoki *et al.* reported serum PCT to be an accurate early predictor of post-operative complications following hepatic resection, peaking within 2 post-operative days in 85% of patients (49). It was however not specifically for PHLF.

Lactate as a predictor for post-hepatectomy liver failure

Lactate is a carbohydrate and its levels increase with increased metabolism during exercise and with catecholamine stimulation. Glucose-6-phosphate is anaerobically converted to pyruvate and then to lactate via the Embden-Meyerhof pathway. Lactate eventually exits the cells and is transported to the liver and oxidized back to pyruvate before conversion to glucose via the Cori cycle. However, all tissues can metabolize lactate, converting it to pyruvate which enters the Krebs cycle functioning as an energy source. (Figure 1) Rising lactate levels could reflect decreased oxygenation of tissue in general but could also be due to impaired metabolism in the liver (50).

Arterial lactate concentration at the end of a hepatectomy has been shown to be an accurate predictor of postoperative outcome. Vibert *et al.* validated the use of end-operative arterial lactate concentration following hepatectomy as an early predictor of post-operative complications (51). These results were echoed by Watanabe *et al.* who found arterial lactate concentration on admission to ICU to be an independent predictor of morbidity and mortality following hepatic resection(52). The cut-off value for lactate concentration above which morbidity and mortality is significantly higher still needs to be determined. One of the criticisms of these studies was the variability in the time after surgery at which the lactate was measured, with some studies using the highest intra-operative lactate, while others assessed a lactate level anytime from the start of abdominal closure to 4 hours post-operatively (53). The kinetics of arterial lactate levels following hepatectomy and its possible value in predicting the risk for PHLF has not been assessed. In this thesis we investigate the hypothesis that the dynamics of serial post-operative lactate levels may be more reliable than a single lactate level in predicting PHLF.

PUBLICATION READY MANUSCRIPT

THE ROLE OF SERIAL LACTATE AND LIVER ENZYME DYNAMICS IN PREDICTING POST HEPATECTOMY LIVER FAILURE

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Key words

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INTRODUCTION

Hepatic resection remains the gold standard for curative-intended treatment of both primary and secondary liver malignancies (54). With expanding and better defined indications for liver resection and an increase in the incidences of primary liver malignancies, specifically hepatocellular and colorectal cancer with associated liver metastases, there has globally been an increase in the number of liver resections performed (6-8, 10). Several studies which included patient cohorts treated in the 1980s and 1990s report mortality rates as high as 30% for liver resection (13-16) .With more emphasis on patient risk modification, advancements in operative and anaesthetic techniques and improved perioperative care, recent published data have shown mortality rates 1-3% in high-volume centres, but still 5–10% in population-based studies (12, 17, 42).

Better operative techniques and understanding of functional liver anatomy, has resulted in a reduction in operative mortalities. Post-operative liver failure has (PHLF) become the most common cause of post-operative mortality accounting for more than 60% of post-operative deaths (7, 12-15, 18). The International Study Group of Liver Surgery (ISGLS) definition of PHLF is the most commonly used (25). PHLF is defined as an acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterised by an increased INR (or need for clotting factors to maintain INR) and hyperbilirubinemia on or after day 5 in the absence of other obvious causes for the biochemical and clinical alterations such as biliary obstruction. In patients with normal pre-operative liver function, increases in INR and hyperbilirubinemia are assessed according to cut off levels defined by the local laboratory. If INR and/or serum bilirubin concentration were increased pre-operatively, PHLF is defined by an increasing INR and increasing serum bilirubin on or after day 5 (compared with the values of the previous day).

There are no tools for earlier diagnosis of PHLF that would allow earlier intervention. Lactate levels increase as a result of decreased oxygenation of tissue in general, but also specifically with liver dysfunction due to impaired metabolism in the liver (50). Arterial lactate concentration at the end of elective hepatectomy has been shown to be an accurate predictor of postoperative outcome (51). However, the kinetics of serial arterial lactate levels following hepatectomy and its possible value in predicting the risk for PHLF has not been assessed. In this article we investigate the hypothesis that the dynamics of serial post-operative lactate levels may be more reliable than a single lactate level in predicting PHLF.

Patients and methods

Patients undergoing elective major liver resection at Groote Schuur and UCT Private Academic Hospital between May 2018 and April 2021 were eligible for participation in the study. Informed, written consent was obtained from each participant. The study was approved by the Human Research Ethics Committee of the University of Cape Town (HREC 758/2017) and has been performed according to the principles outlines in the Helsinki Declaration.

Demographic characteristic and baseline clinical variables were recorded (Table 2). In addition, we report on the indication for liver resection, previous hepatectomy, pre-operative chemotherapy. Operative variables recorded include surgical approach (open or laparoscopic), extent of liver resection, associated biliodigestive anastomosis, synchronous procedure (e.g. colorectal resection), ischaemic time of the FLR, total operation time, parenchymal transection time, estimated intra-operative blood loss, intraoperative transfusion requirements, intraoperative fluid administration (calculated as millilitres per minute of surgery) and inotrope use. All patients were post-operatively monitored in a high care unit before discharge to a routine surgical ward. Complications were recorded and graded according to the Accordion grade, Comprehensive Complication Index (CCI) and 90-day mortality was reported (55, 56). Post hepatectomy liver failure and post hepatectomy bile leak were defined and graded using the respective ISGLS definitions (Table 1a and b) (25, 57). Final histology, including any histological signs of underlying disease, such as cirrhosis or CALI were reported.

Biochemistry

Pre-operative biochemistry collected included a full blood count (FBC), International Normalizing Ratio (INR), sodium, potassium, urea and creatinine (U&E), liver function tests (LFT), tumour markers and hepatitis studies (Table 3a).

FBC; U&E; LFT and INR were collected daily for the first 5 post-operative days. Arterial blood gas analyses which include serum lactate, were performed at closure of the abdomen following liver resection, and thereafter 4 hourly for 24 hours.

Data management and statistical analysis

All data were entered into REDCap electronic data capturing software licensed to the University of Cape Town. Statistical analysis was performed using SPSS statistics (version 26.0, IBM, USA). Statistical significance was set as $p < 0.05$. Continuous data were reported as mean ± SD or mean ± SEM, non-parametric data as median and interquartile range and discreet data as percentages. Associations between baseline patient characteristics and preoperative variables with PHLF were assessed in univariate models. Following bivariate analysis, confounding variables were included in multivariate analysis.

RESULTS

Patient characteristics

Forty-seven patients were included in the study (Figure 2) with the patient demographics and characteristics summarized in Table 2. The mean age at time of the study was 56.5 years (±SD 13.2), 47% of patients being female with no significant difference in gender. Colorectal cancer liver metastases (CRCLM) was the most common indication for surgery (55.3 %) followed by cholangio- and hepatocellular carcinoma (19% respectively). All patient undergoing resection for CRCLM received preoperative chemotherapy. The majority of patients (62.7%) had one or more co-morbidities, as detailed in Table 2. The pre-operative and serial post-operative biochemical profiles of the whole patient cohort as well as patients with and without PHLF are shown in Tables 3a-c. The intra-operative and serial post-operative blood gas analyses which includes the lactate levels of the whole patient cohort as well as patients with and without PHLF are shown in Tables 4a&b.

Baseline demographic and clinical characteristics that were statistically significantly associated with PHLF are shown in Table 5a. Age ($p = 0.05$), diabetes ($p = 0.007$), post-operative intra-abdominal collections (0.023), the need for surgical or endoscopic intervention ($p = 0.048$) correlated with the development of PHLF.

In the univariate analysis the lactate levels at 16 hours, INR levels on days three to five, total bilirubin concentration on days two to five and pH at 24 hours were statistically significantly associated with the development of PHLF as shown in Table 6. In the multivariate analyses as shown in table 7, there was no association found between serial post-operative lactate the

development of PHLF. However, an early rise in Total Bilirubin on day 2 and INR on day 3, was statically significantly predictive for the development of PHLF.

Five (10.6%) patients developed PHLF (Table 9). The all-cause mortality rate at 90 days was 10.6% with PHLF accounting for 20% of all mortalities (Table 10).

Discussion

This study evaluated the role of serial post-operative lactate measurements in predicting the development of PHLF according to the ISGLS definition, in patients undergoing major liver resection. We could not demonstrate an association between serial lactate measurements and the development of PHLF. Age and diabetes were shown to be pre-operative predictors for PHLF, while collections and the need for endoscopic or surgical intervention post operatively were shown to predict PHLF. Bilirubin levels and INR could predict PHLF from the third post-operative day.

To our knowledge this the only study that has looked at serial lactates and their role in predicting PHLF. Although our sample size is relatively small, lactate shows potential as a predictor for PHLF as shown in our univariate analysis. Arterial lactate concentration at the end of elective hepatectomy has been shown to be an accurate predictor of postoperative outcome. Vibert *et al.* (2015) validated the use of end-operative arterial lactate concentration following hepatectomy as an early predictor of post-operative complications. These results were echoed by Watanabe *et al.* (2007), who found arterial lactate concentration on admission to ICU to be an independent predictor of morbidity and mortality following hepatic resection (51, 52). One of the criticisms of these studies was the variability in the time after surgery at which the lactate was measured, with some studies using the highest intra-operative lactate, while others assessed a lactate level anytime from the start of abdominal closure to four hours post-operatively (53).

Our findings of a significant correlation between and age and diabetes with PHLF are in keeping with the literature. An increasing age is associated with PHLF with an age over sixty-

five, seen as a risk factor for PHLF (12, 44). A growing body of literature cites diabetes mellitus as a significant predicative factor for the development of PHLF (12, 34). Studies suggest that poor immune function, altered liver metabolism and pre-existing hepatic steatosis may act as co-factors with diabetes, conferring an increased mortality rate (34-36).

The presence of intra-abdominal collections post-operatively was a significant predictor for PHLF in our series. While we differentiated between intra-abdominal collections and bile leak, we did not sub-divide collections according to aetiology. Our findings are however consistent with current evidence which suggests that some post-operative complications, including post-operative haemorrhage, bile leak and infection, are associated with an increased risk for the development of PHLF (7, 43).

There is currently no reported association in the literature between the development of PHLF and endoscopic or surgical intervention. In terms of endoscopic intervention, this may be due to an over-diagnosis of PHLF in patients with an obstructive cause. We however kept these patients in the PHLF arm as their bilirubin and INR remained elevated post endoscopic intervention. The need for surgical intervention post hepatectomy was significantly associated with PHLF regardless of the findings and intervention performed. Again, some of these patients may be a duplication of the group with abdominal collections, however intra-abdominal collections were not the only indication for surgical intervention.

In our study, we used the ISGLS definition of PHLF. We found that, patients diagnosed with PHLF on post-operative day five, had a statistically significantly raised INR and Total Bilirubin

from post-operative day three to five. A single study suggests that a day one INR could predict PHLF category C patients (47).

The limitations of this study include the retrospective analysis, however data was sourced from a prospectively maintained database. Secondly, our numbers are limited and this due to a variety of reasons such as, resource limitations, late presentations reducing the number of patients eligible for curative resection, and one year of the study running through the COVID period. However, the standard methodology, continuity of treatment by a dedicated single center multidisciplinary hepato-pancreato-biliary team and detailed patient documentation help to minimize confounders and increase the validity of the data allowing for a robust analysis.

In conclusion, we have shown that serial lactate levels have potential in predicting PHLF and should be evaluated in a larger study. Age and diabetes are pre-operative risk factors for the development of PHLF. Post-operative collections or the need for endoscopic or surgical re-intervention are associated with PHLF. Bilirubin levels and INR may be able to diagnose PHLF from post-operative day three. This needs to be validated in further studies.

Table 1a The ISGLS consensus definition and severity grading of PHLF (reproduced from Rahbari *et al.*, 2011)

Definition	
A postoperatively acquired deterioration in the ability of the liver (in patients with normal and abnormal liver function) to maintain its synthetic, excretory, and detoxifying functions, characterized by an increased INR (or need of clotting factors to maintain normal INR) and hyperbilirubinemia (according to the normal cut-off levels defined by the local laboratory) on or after postoperative day 5. If INR or serum bilirubin concentration is increased preoperatively, PHLF is defined by an increasing INR (decreasing prothrombin time) and increasing serum bilirubin concentration on or after postoperative day 5 (compared with the values of the previous day). Other obvious causes for the observed biochemical and clinical alterations such as biliary obstruction should be ruled out.	
Grading	
Grade A	PHLF with abnormal laboratory parameters but requiring no change in the clinical management of the patient.
Grade B	PHLF resulting in a deviation from the regular clinical management but manageable without invasive treatment.
Grade C	PHLF resulting in a deviation from the regular clinical management and requiring invasive treatment.

Table 1b The ISGLS definition and severity grading of bile leak (reproduced from Koch *et al,* 2011)

Definition	
Fluid with bilirubin level at least 3 times serum level in the abdominal drain or intra-abdominal fluid on or after post-operative day three.	
Grading	
Grade A	No or minimal change in patient management
Grade B	Leakage lasting more than a week or any intervention required apart from laparotomy
Grade C	Laparotomy was required

Table 2. Patient characteristics recorded in 47 participants.

RECORDED CHARACTERISTIC	ALL PARTICIPANTS 47	NON PHLF 42 (89.3%)	PHLF 5 (10.7%)
Demographics			
Age (years)	56.5 (13.2)	55.2 (25.2)	67.4 (12.2)
Gender - female	23 (48.9 %)	22 (52.4 %)	1 (20 %)
Body mass index (kg/m^2)	25.3 (4.9)	25.2 (4.6)	26.4 (8.1)
Co-morbidities			
Diabetes	6 (12.8 %)	3 (7.1 %)	3 (60.0 %)
Hypertension	18 (38.3 %)	13 (31.0 %)	5 (100 %)
Retroviral disease (RVD)	3 (6.4 %)	3 (7.1 %)	-
Hepatitis B	7 (14.8%)	7 (16.7 %)	-
Hepatitis C	1 (2.1%)	1 (2.4 %)	-
None	18 (38.3.0 %)	18 (42.9 %)	-
Preoperative chemotherapy	26 (55.3 %)	26 (61.9%)	-
Indication for hepatectomy			
Bile duct stricture	2 (4.3 %)	2 (4.8 %)	-
Biliary cystadenoma	1 (2.1 %)	1 (2.4 %)	-
Cholangiocarcinoma	7 (14.9 %)	7 (16.7 %)	-
Colorectal liver metastases	26 55.3 %	22 (52.4 %)	4 (80.0 %)
Hepatocellular carcinoma	7 (14.9 %)	6 (14.3 %)	1 (20.0 %)
Hydatid	1 (2.1 %)	1 (2.4 %)	-
Liver cyst	1 (2.1 %)	1 (2.4 %)	-
Neuroendocrine secondaries	2 (4.3 %)	2 (4.8 %)	-

Continuous variables expressed as mean (± standard deviation), median (interquartile range) or proportions as appropriate

Table 3a. Biochemical profiles of all participants post-operatively.

PARAMETER	PRE-OP	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5
Hb(g/dL)	12.4 (2.3)	10. 9 (1.9)	9.6 (1.8)	9.5 (1.7)	9.2 (1.5)	9.5 (1.4)
INR	1.09 (0.15)	1.46 (0.28)	1.55 (0.31)	1.31 (0.23)	1.21 (0.21)	1.25 (0.23)
Urea (mmol/L)	5.5 (3.9-6.6)	5.4 (4.2-8.4)	6.4 (3.9-9.8)	6.7 (3.6-11.6)	7.1 (3.9-11.3)	7.0 (3.7-12.4)
Creatinine (mmol/L)	71 (61-87)	79 (62-125)	82 (62-118)	76 (55-96)	71 (52-96)	72 (51-111)
Sodium (mmol/L)	139 (4)	136 (4)	133 (4)	133 (4)	134 (5)	135 (6)
Potassium (mmol/L)	4.4 (0.6)	4.6 (0.7)	4.7 (0.8)	4.3 (0.7)	4.1 (0.6)	4.2 (1.1)
Albumin (g/L)	31 (5)	29 (6)	28 (5)	28 (5)	37 (51)	29 (6)
Total Bilirubin (umol/L)	12 (9)	27 (21)	30 (25)	28 (24)	27 (23)	26 (24)
Conjugated Bili (umol/L)	6 (7)	16 (17)	18 (15)	18 (16)	19 (19)	18 (20)
Unconjugated Bili (umol/L)	7 (4)	11 (9)	11 (13)	9 (11)	8 (6)	6 (4)
ALT (U/L)	24 (18-44)	358 (221-560)	275 (183-462)	193 (102-324)	142 (86-231)	97 (70-144)
AST (U/L)	30 (23-48)	464 (281-752)	280 (170-450)	143(95-194)	77 (56-119)	50 (39-72)
ALP* (U/L)	122 (91-202)	96 (61-132)	109 (74-144)	115 (78-159)	125 (101-152)	141 (109-176)
GGT* (U/L)	86 (46-288)	67 (47-196)	80 (43-79)	66 (43-152)	75 (75-152)	121 (71-190)

*Non parametric data reported as median (interquartile range); parametric data expressed as mean (± standard deviation); POST-OP: postoperatively; Hb: Hameoglobin; INR: Internationalised ratio; ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase; GGT: gamma0glutamyltransferase; g/dL: grams per decilitre; mmol/L: millimoles per litre; g/L: grams per litre; umol/L: micromoles per litre; U/L: Units per litre

Table 3b. Post-operative biochemical profiles of participants **without PHLF** (n=38).

PARAMETER	PRE-OP	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5
Hb (g/dL)	12.4 (2.3)	10.9 (1.8)	9.5 (1.8)	9.3 (1.8)	9.0 (1.2)	9.3 (1.5)
INR	1.10 (0.16)	1.45 (0.29)	1.52 (0.29)	1.26 (0.16)	1.15 (0.13)	1.21 (0.19)
Urea (mmol/L)	5.5 (4.1-6.9)	5.4 (4.2-8.0)	5.6 (3.8-9.6)	6.3 (3.6-10.5)	6.4 (3.9-10.7)	6.4 (3.7-11.8)
Creatinine (mmol/L)	74 (61-85)	77 (61-104)	81 (62-100)	73 (55-91)	67 (52-87)	62 (49-85)
Sodium (mmol/L)	139 (4)	136 (4)	133 (4)	134 (4)	135 (5)	135 (6)
Potassium (mmol/L)	4.3 (0.5)	4.7 (0.7)	4.7 (0.7)	4.3 (0.7)	4.1 (0.5)	4.3 (1.0)
Albumin (g/L)	41 (6)	29 (6)	28 (5)	28 (5)	38 (53)	29 (6)
Total Bilirubin (umol/L)	12 (9)	26 (22)	27 (23)	25 (20)	22 (18)	22 (20)
Conjugated Bili (umol/L)	7 (8)	16 (18)	16 (14)	16 (17)	16 (19)	18 (21)
Unconjugated Bili (umol/L)	7 (4)	11 (9)	10 (11)	8 (8)	6 (3)	7 (7)
ALT (U/L)	24 (19-46)	339 (220-597)	276 (165-488)	187 (91-250)	138 (74-162)	94 (35-87)
AST (U/L)	30 (24-50)	457 (70-629)	266 (162-450)	123 (95-197)	73 (54-101)	49 (36-71)
ALP (U/L)	131 (91-223)	98 (57-152)	109 (73-162)	115 (78-162)	123 (97-158)	142 (108-175)
GGT (U/L)	87 (48-317)	67 (47-210)	78 (44-191)	66 (43-170)	75 (51-170)	120 (66-178)

Non parametric data reported as median (interquartile range); parametric data expressed as mean (± standard deviation); POST-OP: postoperatively; Hb: Haemoglobin; INR: Internationalised ratio; ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase; GGT: gamma-glutamyltransferase; g/dL: grams per decilitre; mmol/L: millimoles per litre; g/L: grams per litre; umol/L: micromoles per litre; U/L: Units per litre

Table 3c. Post-operative biochemical profiles of participants **with PHLF** (n=5).

PARAMETER	PRE-OP	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5
Hb (g/dL)	12.3 (2.3)	10. 7 (1.9)	10.2 (1.5)	10.2 (0.9)	10.2 (1.7)	10.5 (0.4)
INR	1.03 (0.11)	1.51 (0.24)	1.68 (0.40)	1.62 (0.42)	1.57 (0.36)	1.53 (0.28)
Urea (mmol/L)	5.7 (3.8-6.4)	8.0 (3.4-8.9)	9.9 (6.0-12.8)	11.9 (6.4-18.0)	12.0 (5.3-19.2)	12.3 (5.6-16.3)
Creatinine (mmol/L)	85 (54-120)	170 (67-207)	135 (86-294)	150 (75-398)	113 (72-409)	117 (64-334)
Sodium (mmol/L)	140 (3)	136 (3)	134 (4)	133 (5)	137 (6)	137 (6)
Potassium (mmol/L)	4.2 (1.0)	4.4 (0.8)	4.7 (0.7)	4.5 (1.0)	3.9 (1.1)	3.7 (0.8)
Albumin (g/L)	42 (3)	28 (5)	29 (6)	30 (3)	30 (3)	29 (4)
Total Bilirubin (umol/L)	12 (6)	33 (18)	49 (37)	54 (35)	59 (32)	57 (30)
Conjugated Bili (umol/L)	5 (3)	16 (6)	30 (16)	35 (24)	46 (23)	42 (21)
Unconjugated Bili (umol/L)	10 (5)	17 (16)	20 (23)	19 (23)	18 (14)	11 (7)
ALT (U/L)	28 (13-50)	472 (285-524)	271 (226-339)	198 (106-275)	146 (58-195)	106 (41-122)
AST (U/L)	27 (23-55)	759 (480-986)	389 (237-467)	176 (165-236)	135 (108-141)	91 (43-111)
ALP (U/L)	111 (78-150)	75 (68-101)	100 (87-130)	115 (51-116)	137 (122-145)	135 (111-254)
GGT (U/L)	59 (27-185)	63 (34-106)	93 (34-104)	105 (31-124)	104 (45-152)	156 (86-304)

Non parametric data reported as median (interquartile range); parametric data expressed as mean (± standard deviation); POST-OP: postoperatively; Hb: Haemoglobin; INR: Internationalised ratio; ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase; GGT: gamma-glutamyltransferase; g/dL: grams per decilitre; mmol/L: millimoles per litre; g/L: grams per litre; umol/L: micromoles per litre; U/L: Units per litre

Table 4a. Arterial blood gas values obtained post-operatively.

PARAMETER	POST-OP	4 HOURS	8 HOURS	12 HOURS	16 HOURS	20 HOURS	24 HOURS
pH	7.33 (0.07)	7.36 (0.54)	7.36 (0.65)	7.31 (0.43)	7.38 (0.05)	7.39 (0.05)	7.39 (0.05)
PCO2	5.5 (0.8)	5.2 (1.0)	5.1 (0.9)	5.1 (1.1)	5.1 (1.0)	5.1 (0.9)	5.1 (0.8)
HCO_3^-	22 (4)	22 (4)	22 (3)	22 (4)	23 (4)	24 (3)	23 (3)
Lactate	3.0 (2.0-4.8)	3.1 (1.5-4.0)	3.0 (1.7-4.3)	2.1 (1.4-3.3)	1.9 (1.2-2.7)	1.6 (1.4-2.2)	2.0 (1.4-2.7)
Base Excess	-2.6 (-5.9--1.1)	-14.5 (-6.8-0.2)	-1.9 (-6.2--0.3)	-1.5 (-4.7-0.5)	-1.8 (-4.3-2.1)	-1.6 (-3.4-1.8)	-1.6 (-3.4-1.8)

Non parametric data reported as median (interquartile range); continuous variables expressed as mean (± standard deviation); POST-OP: postoperatively; INR: Internationalised ratio; ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase; GGT: gamma0glutamyltransferase

Table 4b. Arterial blood gas values obtained post-operatively

WITHOUT PHLF						
PARAMETER	**POST-OP**	**4 HOURS**	**8 HOURS**	**12 HOURS**	**16 HOURS**	**20 HOURS**
pH	7.33 (0.07)	7.36 (0.47)	7.36 (0.59)	7.31 (0.46)	7.38 (0.48)	7.39 (0.04)
PCO2	5.4 (0.8)	5.3 (1.0)	5.1 (0.9)	5.2 (1.1)	5.1 (1.04)	5.1 (0.8)
HCO_3^-	22 (4)	22 (4)	23 (4)	22 (4)	23 (4)	24 (3)
Lactate	3.0 (1.9-4.8)	3.3 (1.5-4.1)	1.9 (1.4-2.9)	1.9 (1.4-2.9)	1.7 (1.2-2.6)	1.5 (1.3-1.9)
Base Excess	-3.3 (-6.2--1.1)	-2.3 (-15.5--2.3)	-1.5 (-4.7—0.2)	-2.4 (-4.7-0.2)	-1.7 (-3.8-2.0)	-1.6 (-3.4-1.8)
PHLF						
PARAMETER	**POST-OP**	**4 HOURS**	**8 HOURS**	**12 HOURS**	**16 HOURS**	**20 HOURS**
pH	7.33 (0.06)	7.34 (0.98)	7.34 (0.11)	7.34 (0.11)	7.35 (0.98)	7.35 (0.06)
PCO2	5.5 (0.6)	4.8 (0.8)	4.7 (0.7)	5.0 (1.2)	4.9 (1.2)	5.2 (0.5)
HCO_3^-	21 (3)	21 (3)	20 (4)	21 (7)	21 (7)	22 (4)
Lactate	3.3 (2.0-4.0)	3.6 (2.6-4.8)	3.2 (2.4-7.2)	3.3 (2.2-6.4)	3.3 (2.2-5.5)	2.5 (1.9-3.7)
Base Excess	-3.6 (-7.3--0.6)	-4.8 (-11.0--2.2)	-5.3 (-11.3 - - 0.8)	-2.9 (-7.2-11.0)	-6.6 (-10.3-2.6)	-3.8 (-7.3-2.6)

Non parametric data reported as median (interquartile range); continuous variables expressed as mean (± standard deviation); POST-OP: postoperatively; INR: Internationalised ratio; ALT: alanine transaminase; AST: aspartate transaminase

Table 5a Baseline demographic and clinical characteristics that were statistically significantly associated with PHLF.

RECORDED CHARACTERISTIC	β (SE)	p
Demographics		
Age (years)	12.16 (6.11)	0.052
Co-morbidities		
Diabetes	2.97 (1.09)	0.007
Post operative course		
Intra-abdominal collection	2.68 (1.18)	0.023
Surgical intervention required	2.30 (1.17)	0.049
Endoscopy	2.16 (1.09)	0.048

β: standardized beta coefficient; SE: standard error; PHLF: post post-hepatectomy liver failure

Table 5b Baseline intra-operative findings

RECORDED CHARACTERISTIC	β (SE)	p
Blood loss	-172.97 (501.22)	0,732
Crystalloid	19.12 (28420.72)	0,999
Colloid	-1.36 (1.16)	0,333
Blood	-2.89 (1.20)	0,384
Total Fluids	0.27 (2.52)	0.913
No Segments resected	0.31 (0.39)	0,440
Vasc Control to FLR	1.61 (1.33)	0.227
Vasc Control of “to be resected liver” HA	19.31 (13397.65)	0.999
Vasc Control of “to be resected liver” PV	19.26 (15191.52)	0.999

β: standardized beta coefficient; SE: standard error; PHLF: post post-hepatectomy liver failure; FLR: Future liver remnant; HA: Hepatic Artery; PV: Portal Vein

Table 6. Univariate analysis between biochemistry parameters and PHLF.

	B (SE)	p
LACTATE		
Post op	-0.46 (1.21)	0,702
4 hours	0.34 (1.15)	0,765
8 hours	0.88 (1.49)	0,556
12 hours	1.60 (1.18)	0,181
16 hours	**1.68 (0.85)**	**0,054**
20 hours	0.85 (0.52)	0,111
24 hours	1.67 (1.37)	0,233
INR		
Day 1	0.06 (0.14)	0.663
Day 2	0.15 (0.15)	0,298
Day 3	**0.36 (0.09)**	**0,001**
Day 4	**0.41 (0.09)**	**0,000**
Day 5	**0.31 (0.11)**	**0,006**
pH		
Post op	-0.00 (0.33)	0,919
4 hours	-0.02)0.03)	0,412
8 hours	-0.02 (0.03)	0,500
12 hours	0.04 (0.21)	0,851
16 hours	-0.04 (0.03)	0,150
20 hours	-0.04 (0.02)	0,072
24 hours	**-0.09 (0.04)**	**0,039**
TOTAL BILLIRUBIN		
Day 1	21.57 (11.54)	0,068
Day 2	**28.42 (10.57)**	**0,010**
Day 3	**36.07 (9.23)**	**0,001**
Day 4	**34.66 (10.01)**	**0,001**
Day 5	**36.13 (11.36)**	**0,003**
CONJUGATED BILLIRUBIN		
Day 1	13.04 (6.83)	0,063
Day 2	**18.38 (8.31)**	**0,033**
Day 3	**29.44 (9.21)**	**0,003**
Day 4	**25.67 (11.34)**	**0,030**
Day 5	**26.89 (11.87)**	**0,037**
UNCONJUGATED BILLIRUBIN		
Day 1	9.91 (6.01)	0,107
Day 2	**11.06 (5.36)**	**0,047**
Day 3	**11.59 (2.80)**	**0,000**
Day 4	**4.93 (2.25)**	**0,036**
Day 5	6.33 (6.84)	0,111

β: standardized beta coefficient; SE: standard error; POST-OP: postoperatively; INR: Internationalised ratio; ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase; GGT: gamma0glutamyltransferase; significant associations shown in bold.

Table 7. Multivariate analysis between biochemical parameters and PHLF*

	B (SE)	p
Lactate		
Post-op	-1.03 (1.34)	0,450
4 Hour	-2.04 (1.08)	0,065
8 Hour	-1.15 (1.47)	0,441
12 Hour	-0.81 (1.16)	0,492
16 Hour	-0.03 (0.85)	0,973
20 Hour	0.37 (0.56)	0,506
24 Hour	0.61 (1.44)	0,675
INR		
Day 1	0.08 (0.16)	0.594
Day 2	0.13 (0.17)	0,452
Day 3	**0.31 (0.11)**	**0,008**
Day 4	**0.43 (0.12)**	**0,001**
Day 5	**0.33 (0.13)**	**0,015**
TOTAL BILLIRUBIN		
Day 1	11.60 (13.98)	0.683
Day 2	**37.53 (11.84)**	**0,003**
Day 3	**41.74 (10.95)**	**0,000**
Day 4	**40.39 (11.38)**	**0,001**
Day 5	**43.05 (12.63)**	**0,002**
CONJUGATED BILLIRUBIN		
Day 1	**17.65 (7.76)**	**0,028**
Day 2	**23.82 (8.75)**	**0,010**
Day 3	**33.25 (9.93)**	**0,002**
Day 4	**26.35 (12.96)**	**0,050**
Day 5	**36.34 (13.91)**	**0,015**
UNCONJUGATED BILLIRUBIN		
Day 1	**14.98 (6.71)**	**0,032**
Day 2	**14.02 (5.68)**	**0,019**
Day 3	**11.26 (3.16)**	**0,001**
Day 4	5.19 (2.57)	0,052
Day 5	7.72 (4.60)	0,105

β: standardized beta coefficient; SE: standard error; POST-OP: postoperatively; INR: Internationalised ratio; ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase; GGT: gamma0glutamyltransferase; significant associations shown in bold. *Adjusted for the presence of diabetes

Table 8. Post-operative complications of patients who developed PHLF (n=5).

PT	SURGICAL COMPLICATIONS			INTERVENTIONS			NON-SURGICAL COMPLICATIONS	SEVERITY		
	COLLECTION	**BILE LEAK**	**WOUND DEHISCENCE**	**RADIOLOGICAL INTERVENTION**	**ENDOSCOPIC INTERVENTION**	**RE-OPERATION**	**DESCRIPTION**	**ACCORDION**	**HOSPITAL STAY (DAYS)**	**FINAL PHFL GRADE**
1	**Y**	Y	N	**Y**	**Y**	N	renal dysfunction	6	190	C
2	**Y**	N	N	N	**Y**	N	renal dysfunction, delirium, DVT	3	33	B
3	**Y**	N	**Y**	**Y**	N	**Y**	renal dysfunction	2	27	B
4	**Y**	N	N	**Y**	N	N	renal dysfunction	3	22	A
5	**Y**	N	N	**Y**	N	N	delirium, hyponatraemia	3	17	B

PT: patient; Y=yes, N=no; DVT: deep vein thrombosis

Table 9. Post hepatectomy liver failure (ISGLS) assessment in 5 patients.

PATIENT 1	**GRADE A**	**GRADE B**	**GRADE C**
Specific Treatment			*
Hepatic Function		*	
Renal Function			*
Pulmonary Function		*	
Additional Evaluation		*	
Overall PHLF Grade			*
PATIENT 2	**GRADE A**	**GRADE B**	**GRADE C**
Specific Treatment		*	
Hepatic Function		*	
Renal Function	*		
Pulmonary Function	*		
Additional Evaluation		*	
Overall PHLF Grade		*	
PATIENT 3	**GRADE A**	**GRADE B**	**GRADE C**
Specific Treatment		*	
Hepatic Function			*
Renal Function	*		
Pulmonary Function	*		
Additional Evaluation		*	
Overall PHLF Grade		*	
PATIENT 4	**GRADE A**	**GRADE B**	**GRADE C**
Specific Treatment	*		
Hepatic Function	*		
Renal Function	*		
Pulmonary Function	*		
Additional Evaluation	*		
Overall PHLF Grade	*		
PATIENT 5	**GRADE A**	**GRADE B**	**GRADE C**
Specific Treatment	*		
Hepatic Function		*	
Renal Function		*	
Pulmonary Function	*		
Additional Evaluation		*	
Overall PHLF Grade		*	

Table 10. All-cause mortality in 47 patients undergoing hepatectomy.

MORTALITY RATE (n=5)	**10.6 %**
CAUSE OF DEATH	
Cardiovascular complications	20 %
Renal complications	40 %
Non-surgical related septicaemia	20 %
Post- hepatectomy liver failure	20 %

Figure 1. Cori Cycle

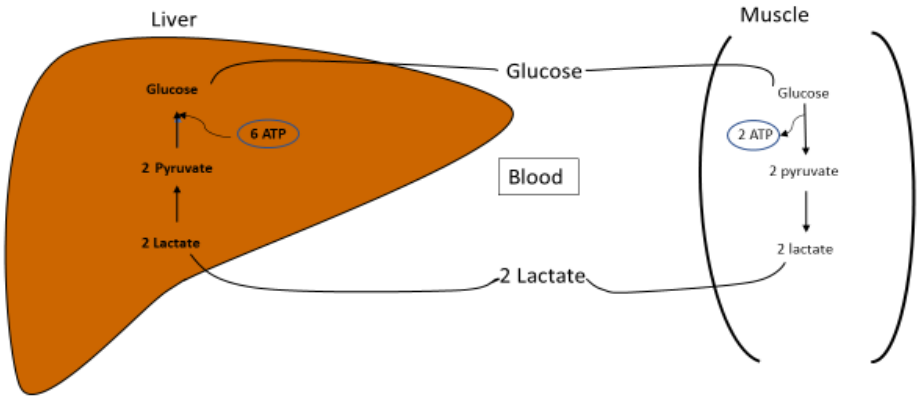
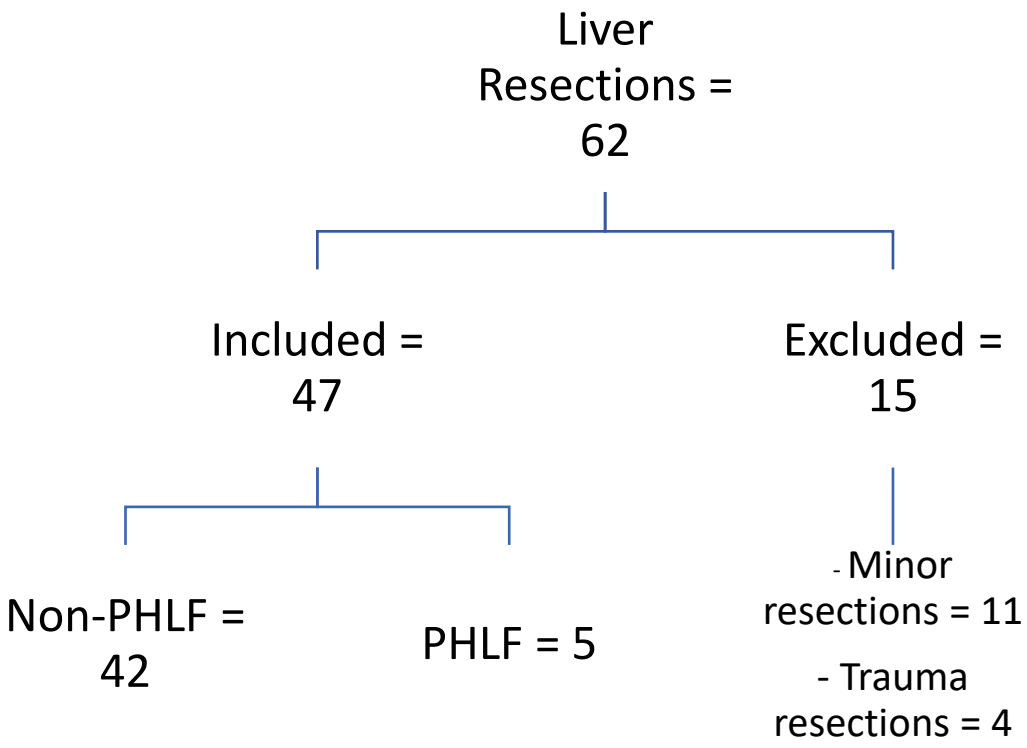


Figure 2. Patient selection



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Appendices

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.7.22
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	29/7/21

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

HUMAN RESEARCH ETHICS COMMITTEE
28 JUL 2021
HEALTH SCIENCES FACULTY UNIVERSITY OF CAPE TOWN

Please clarify your plan for research-related activities during COVID-19 lockdown

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	28th July 2021		
HREC REF Number	758/2017	Current Ethics Approval was granted until	15th Nov 2019
Protocol title	A prospective observational study investigating the kinetics of routine liver function tests and arterial lactate concentrations after hepatectomy and their relationship to the development of postoperative liver failure		
Principal Investigator	Dr Marc Bernon		
Department / Office Internal Mail Address	E23 Room 19, New Main Building, Groote Schuur Hospital mm.bernon@uct.ac.za		
1.1 Does this protocol receive US Federal funding?		☐ Yes	✓ No

2. Protocol status (tick ✓)

✓	Research-related activities are ongoing
☐	Data collection is complete, data analysis only

Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		50
Total number of records or specimens collected, reviewed or stored since last progress report		50
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	✓ Yes	☐ No

4. Signature

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Signature of PI	M. M. Bernon	Date	28th July 2021