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Defining the complexity of liver transplant: the development of a scoring system to assess recipient risk

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Contents

Statement of originality

This is a statement certifying that the content within this thesis is my own work. This thesis has not been submitted for any other degree or purpose.

I certify that the intellectual content of this thesis is the product of my own work, and all assistance received throughout the preparation of this thesis and all sources have been acknowledged.

Victor Yu

Dated 27th September 2025

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Authorship attribution statement

Chapter II of this thesis has been prepared for publication in *Transplantation Reviews*. I designed the study, gathered and analysed data and wrote the manuscripts. DP and AP provided support with analysis and drafting of manuscripts. CP provided supervision and review of both methodology and writing of manuscripts.

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As lead supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Carlo Pulitano

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Declarations

Generative AI statement

No content produced by generative AI tools has been used in the preparation of this thesis

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Abbreviations

For the purposes of journal publication, each individual manuscript chapter contains its own list of abbreviations. The following list contains all abbreviations used throughout the thesis.

BMI	body mass index
CCI	Charlson comorbidity index
CI	confidence interval
CT	computed tomography
DBD	donation after brain death
DCD	donation after circulatory death
EBL	estimated blood loss
ECD	extended criteria donor
GF	graft failure
GS	graft survival
HCC	hepatocellular carcinoma
HD	high difficulty
ICU	intensive care unit
IC	intraoperative complication
ID	intermediate difficulty
IVC	inferior vena cava
LD	low difficulty
LT	liver transplantation
MD	mean difference
MELD	Model for End-stage Liver Disease
MRI	magnetic resonance imaging
NMP	normothermic machine perfusion
NPV	negative predictive value

OS	overall survival
OR	odds ratio
OT	operating time
PPV	positive predictive value
PVT	portal venous thrombosis
ROC	receiver operating characteristics
SBP	spontaneous bacterial peritonitis
TIPS	transcutaneous intrahepatic portosystemic shunt

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Publications

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Abstracts

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Presentations

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Abstract

Liver transplantation (LT) is the definitive treatment for end-stage liver disease and other significant life-limiting disorders, with a widening range of indications in the face of developments in immunosuppression and perioperative care. Procedurally, LT is technically complex and at present, the assessment of the patient from a surgical standpoint is subjective and unquantified. The optimisation of this surgical assessment serves to improve perioperative factors including resource allocation, inform patient discussions and provide objectivity to the multidisciplinary assessment of a transplant recipient. This thesis delves into surgical difficulty in LT by developing an appropriate measure, exploring its predictive factors and incorporating these into a score with pre-transplant clinical utility.

I. General introduction

Ethical principles in liver transplantation and risk benefit assessment

LT is a life-changing procedure which serves as the definitive treatment for end-stage liver disease, extending both quantity and quality of life, with a five-year survival of over 80% (1). It is however, a significant and technically complex treatment which confers great risk and morbidity. Furthermore, there exists discordance between availability of donors and the number of patients who may potentially derive benefit from transplantation, an imbalance which is being further stressed by increasing indications for transplantation. Assessment of the risks and benefits of LT requires a consideration of a multitude of patient, disease, technical and social factors.

The major challenge in assessing patients for potential liver transplantation pertains to the medical ethical principle of justice. In the context of a shortfall of available donor organs to meet demands of LT, transplant centres face a need to balance utility against individual equity, by offering transplant to patients who would derive significant survival benefit and precluding transplant from those who have minimal expected benefit (i.e. concurrent life-limiting illnesses which minimise expected life extension from transplant) or those whose disease is not so severe that the significant risks of this massive procedure would be outweighed. These “survivorship thresholds” or minimal listing criteria form the basis of many transplant and ethical guidelines (2, 3), including in Australia and New Zealand (4). Given these complexities in the risk-benefit assessment of LT, and the stakeholders beyond the single patient, more so than many other medical treatments, the need to optimise and maximise each and every transplant is paramount.

Unique to LT in its role in organ failure as the sole definitive treatment option in end-stage liver disease, in contrast to for example, renal failure, where dialysis can provide a stable bridging or even long-term therapeutic strategy. Therefore, patients who require liver transplant have only finite time to wait for an available and appropriate organ - consideration must be given to the urgency of transplantation. Furthermore, the manifestations of diseases of the liver are highly heterogenous and complex, with no single objective measure which captures disease severity nor urgency. The Model for End-Stage Liver

Disease (MELD) score can relatively accurately predict mortality from liver failure (5) and is utilised in prioritisation in most cases however cannot be readily applied to patients who require transplantation but will not necessarily die from liver failure, such as in the case of hepatocellular carcinoma (HCC), where other scores and assessments are required (6, 7).

Presently, a wide range of considerations are required in the individual assessment of a potential transplant recipient prior to listing, in addition to the considerations of waitlist management. Each of the factors considered in this assessment often have complex relationships with other factors, with the ultimate goal of providing this life-saving procedure to those most likely to derive benefit.

Aspects of surgical complexity

The focus of this thesis is centred on the surgical assessment of the transplant recipient, which contributes one significant portion of a multifactorial, multidisciplinary assessment prior to listing. Surgical assessment for patients in any context can be broadly defined by a fitness to undergo a proposed procedure, which comprises a review of patient and disease factors as well as technical factors. The two former factors are thoroughly in context of overall risk-benefit assessments which already occur within the multidisciplinary discussions prior to listing however the technical aspects are not necessarily well appreciated.

Evaluating the technical aspects of an operation for a specific patient ultimately involves raising key questions – how will the surgeon approach the procedure (such as entry incision and access, patient positioning, techniques to control major vasculature and perform reconstructions)? What technical challenges are anticipated (risks of bleeding and difficult haemostatic control, aberrant anatomy, risks of damaging crucial nearby structures)? How can the procedure be optimised (availability of experienced staffing, second surgeon on standby, cell salvage)? Overall, the goal of a surgical assessment is to review these factors in order to determine appropriateness to proceed and address expected concerns and challenges with required resources and discuss anticipated course.

Surgical complexity is therefore in itself a complex entity, with no universally agreed upon definition for what constitutes difficult surgery. In literature difficulty of surgery is often defined by surrogate measures that are indicative that a difficult operation has taken place. Most common variables utilised include bleeding and operative time (8-10) however others utilise record of intraoperative complications (11-13), deviations from the expected procedure (14) or even retrospective subjective surgeon opinions (15). Ultimately these definitions are arbitrary, heterogenous and it is unlikely to be possible to derive a universally agreed measure. Moreover, such arbitrary definitions should be cautiously interpreted for its role – does surgical difficulty have real impact on the patient and can this factor be modifiable to improve care? Overall, the definitions need to be tailored to specific procedure and the goal of assessing difficulty – whether that be to guide suitability of cases for training, availability of resources or impacts to patient outcomes.

Technical challenges in liver transplantation

LT presents a formidable surgical challenge and is therefore sensitive to factors affecting technical complexity. There is no single ideal standard approach to LT, and the transplant surgeon must be prepared to be adaptable and resourceful. In broad terms, the native liver must be encountered, cleared of its attachments and excised whole, and the donor organ reimplanted in a timely fashion. Two inflows (main hepatic artery and portal vein) and two outflows (hepatic veins/inferior vena cava and common bile duct) are required to be anastomosed in this process, with a variety of potential aberrancies and anatomical abnormalities. Each of these inflows and outflows represent major vasculature, which is susceptible to haemorrhage, thrombosis and potential overall haemodynamic compromise to the patient, with the exception of the bile duct whose propensity to leak or stricture can have devastating long-term complications. In addition to these are patient factors: body habitus, adhesions from prior surgery, portosystemic shunts from obstruction of portal venous flow, recanalization of vestigial veins, coagulopathy amongst others.

Clearly. LT represents a highly technically demanding and complex operation, and subsequently sensitive to difficulties being compounded by patient factors. Therefore, an understanding of the nature of these factors contributing to increased difficulty has important ramifications for the success of LT. At present, assessment of a patient undergoing LT involves a multidisciplinary approach. Surgical risk assessment represents one part of a broader evaluation of a patient to be deemed appropriate for listing for transplantation. Although many of these individual assessments are guided by objective criteria, such as MELD scores to predict mortality risk of disease, surgical assessment has been largely performed as an informal, experience based clinical judgement, left to the potentially subjective perspective of an individual surgeon who may not necessarily be the operating surgeon.

Aims and scope of thesis

The aims of this thesis are to develop an improved, quantitative framework for the surgical assessment of potential LT recipients to inform peri-operative decision making and planning. The goals of this surgical assessment framework are to be generalisable to all potential adult liver transplant recipients and have clinical utility in discussions for transplantation listing, resource allocation and optimisation of transplant outcomes.

The primary objectives in achieving this aim are to: 1) define surgical complexity in liver transplantation and develop acceptable surrogate variables as objective measures of complexity; 2) assess the significance of surgical complexity on the outcomes of LT, particularly short-term survival, graft survival and requirement for resources; 3) review patient characteristics which may be examined pre-operatively to predict surgical complexity; and 4) analyse the relationship between pre-operative patient characteristics, intraoperative surgical complexity and outcomes of LT to develop a score which may be utilised in the assessment of patients.

Thesis structure

The first chapter of this thesis provides an overview of surgical complexity and its manifestations in practice and its relevance to clinical parameters, in context of liver transplantation (LT). Each subsequent chapter represents a manuscript prepared, submitted or accepted for publication at the time of thesis submission. Chapter II, entitled *"Surgical risk assessment in liver transplantation – technical challenges, considerations and predicting intraoperative difficulty"* is a narrative-style literature review which aims to discuss the pertinent literature around surgical risk assessment in LT. The findings of this literature review prompted an investigation into the role of clarifying the history of prior abdominal surgery and its intraoperative impact, performed as a retrospective study and presented as a manuscript in Chapter III, entitled "*Delineating prior abdominal surgery and its intraoperative impact in liver transplantation*". The main body and focus of this thesis are within a retrospective study and analysis of outcomes of 10-years of liver transplantation to develop a risk stratification score to aid surgical assessment in the pre-operative setting. This is presented as a manuscript in Chapter IV, entitled "Predicting surgical difficulty in liver transplantation – a scoring system to stratify risk". A final chapter includes a discussion and summation of the findings revealed within this thesis as well as a discussion surrounding future directions of study needed within this field.

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II. Surgical risk assessment in liver transplantation – technical challenges, considerations and predicting intraoperative difficulty

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Keywords:

Liver transplantation; Risk factors; End stage liver disease; Intraoperative complication

Abbreviations:

CT – computed tomography

DBD – donation after brain death

DCD – donation after circulatory death

ECD – extended criteria donor

GS – graft survival

IVC – inferior vena cava

LT – liver transplantation

MELD – Model for End-stage Liver Disease

MRI – magnetic resonance imaging

NMP – normothermic machine perfusion

OS – overall survival

PVT – portal venous thrombosis

SBP – spontaneous bacterial peritonitis

TIPS – transcutaneous intrahepatic portosystemic shunt

ABSTRACT

Liver transplantation (LT) provides the definitive treatment for end-stage liver disease in a wide range of its aetiology but in all contexts confers great risk, associated with high morbidity and mortality. In the face of advances in perioperative management and immunosuppressive therapies, indications for LT have expanded and evolved and so too the complexity of patients being listed, which potentially compounds existing risks. The pre-operative assessment of LT involves complex and nuanced multidisciplinary discussions, with which surgical risk review serves an important role; however, this assessment is poorly quantified and potentially unreliable. The ability to predict intraoperative difficulty, particularly in the context of increasing patient complexity, serves to optimise perioperative resource management, better inform patient discussion, guide marginal organ allocation and ultimately improve patient outcomes following LT. We review the pertinent aspects of surgical risk assessment in LT and evaluate the evidence base for risks of intraoperative difficulty.

INTRODUCTION

Liver transplantation (LT) is the only definitive treatment for end-stage liver disease but remains a highly technically challenging and resource-demanding procedure, associated with high morbidity and mortality (1). Since the first pioneering procedures performed by Starzl in 1963 (2), significant developments have been made in surgical technique, medical optimisation and overall care. LT remains a life-changing treatment for many patients and remains the standard of treatment for end-stage liver disease, patients with hepatocellular carcinoma (HCC) and acute liver failure(3), with an evolving space of potentially broadening indications.

In recent times, substantial progress in outcomes of LT have been made, primarily in the form of availability of improved immunosuppressive agents (such as tacrolimus and mycophenolate) reducing acute rejection rates, as well as advances in perioperative care, such as improved infection control, anaesthetic and transfusion protocols and point-of-care coagulation testing (such as thromboelastography) (4). Subsequently, LT is now offered to a broader population, including older patients and those with significant comorbidities. In addition to these patients, the improved safety of LT has led to an expansion in its indications. For instance, patients with hepatocellular carcinoma (HCC) within Milan criteria (5) or cholangiocarcinoma (6) are now well accepted indications, as well as acute liver failure, including those previously deemed too unstable are now routinely considered.

Chiefly, the major source of transplantable livers throughout the world is deceased donation, either via the brain death (DBD) or circulatory death route (DCD) (7, 8). The availability of organs for potential recipients is therefore unpredictable and the quality variable, being heavily dependent on donor characteristics and the sequence of events leading to their availability as a donor. Subsequently, there exists a significant supply-demand mismatch for suitable donor organs. Increases in the prevalence of chronic liver disease and broadening of indications for LT have further stressed these demands (9). Organ preservation techniques such as ex-situ normothermic machine perfusion (NMP) have shown promise in mitigating some of the variability and unpredictability of donors. These organ preservation techniques aim to maintain the liver within physiological and metabolically active limits, allow for real-

time assessment of graft function for suitability for implantation and potentially offer improved outcomes in marginal organs such as DCD or other extended criteria donors (ECD) (10).

From a technical standpoint, LT is a formidable challenge, calling for excision of the often scarred and hypertrophied organ, gaining access and control to the great vessels and ensuring precise re-anastomosis, all in a metabolically deranged and coagulopathic patient. Surgical techniques vary, depending on patient, disease and surgeon factors but typically requires accurate reconstruction of the inferior vena cava (IVC), portal vein, hepatic artery and bile duct. Technical complications including arterial and venous thromboses, haemorrhage or strictures of the bile duct can result in catastrophic consequences for the patient, often requiring major reintervention such as re-operation, and is associated with significant morbidity and mortality. In an operation which is already associated with considerable risks, factors which impact technical difficulty logically has downstream effects on patient and graft outcomes and can potentially determine suitability for implantation of marginal grafts – however this is poorly quantified in literature. Several studies to date have examined predictors for intraoperative difficulty however this data is retrospective, lacks external validation and their predictive accuracy is uncertain (11, 12).

Ultimately, the utility of an ability to predict surgical difficulty in LT cannot be understated, particularly for transplant teams to inform and plan appropriately. Firstly, it informs and guides perioperative planning, particularly the need for additional resources and staffing in high-risk cases, such as the availability of a second senior surgeon. Risk stratification of surgical difficulty could also potentially be implemented into organ allocation decision-making, such as avoidance of allocating marginal grafts to patients who are deemed to be of high surgical risk. Finally, any indicators for surgical difficulty will assist in informing and counselling patients on their perioperative risks and allow for better expectation setting following high-risk surgery.

For these reasons, we aim to seek clarity on understanding the factors which contribute to a surgically challenging LT procedure. In this review, we will discuss the pertinent aspects of surgical planning and

defining difficulty, explore the current understanding of factors associated with surgical difficulty, identify gaps in existing predictive tools and outline directions for further study.

CURRENT ASSESSMENT OF POTENTIAL LIVER TRANSPLANT RECIPIENTS

The perioperative evaluation of LT candidates relies on a multidisciplinary team reviewing a range of patient, donor and waitlist variables. The Model for End-Stage Liver Disease (MELD) score is the principal tool used to prioritise transplantation urgency, given its relative accuracy in predicting short-term mortality (13) and is typically considered in conjunction with waitlist times, compatibility (ABO blood group), surgical feasibility and risk, survival and benefit assessment in context of patient and disease processes.

Surgical suitability assessment typically involves an evaluation of recipient anatomy to assess feasibility of orthotopic transplantation with cross-sectional imaging (either CT or MRI) forming the cornerstone of this assessment. Patients are assessed for body habitus, aberrant anatomy which may warrant deviation from routine practice (such as planned interposition or jump grafts) and portal vein patency and flow, which confers significant impact on the ultimate blood supply of the transplanted organ. There is variability in assessment between centres but typically note is made of any additional high risk surgical features such as significant prior surgical history, prior spontaneous bacterial peritonitis, portal vein thrombosis and re-transplantation. However, these findings are variable, the delineation of patients at risk of surgical difficulty subjective and, overall, there are no clear guidelines to the impact of these risk factors on the patient's overall outcomes nor the suitability for marginal grafts. In many centres an informal assessment is made to deem a patient a 'high risk' surgical candidate and it is unclear whether there is any meaningful guidance or impact on risk mitigation strategies, patient discussions or perioperative planning. Given the heterogeneity and breadth of the LT recipient, and in the face of limited organ resources, subjective assessment of surgical suitability based on such criteria is grossly inadequate.

DEFINING AND PREDICTING SURGICAL DIFFICULTY IN LT

Defining 'difficulty' in surgery is inevitably fraught with subjectivity and ultimately measured with arbitrary surrogates. These surrogates are variably defined based on the specific operation being performed however in most studies this includes operating time, estimated blood loss as well as operative specific measures (such as conversion to open in laparoscopic approaches) or intraoperative complications.

Two groups to date have offered forward definitions of a difficult LT, both utilising surrogate measures of bleeding and operating time but differing on the specifics of their measurement. Table 1 highlights the key findings in these studies including proposed definitions of difficulty, identified risks as well as impact of difficulty on patient outcomes. Both studies were carried out in a retrospective fashion and their results are yet to be validated with an external cohort.

Azoulay's group utilised median values for operating time (defined as total operating time), cold ischemia time and number of packed blood cell transfusions to define intraoperative difficulty (12). High risk predictors of difficulty included prior abdominal surgery, disposition and splenomegaly (in association with either hepatomegaly or hepatic atrophy). Notably, re-do transplantations were excluded from analysis and the authors assessed a range of characteristics including donor variables, which were considered in their assessment of intraoperative difficulty. Given the unpredictability of donor variables, the utility of this in a pre-operative assessment setting is limited.

Ausania et al. defined LT difficulty using operating time (measured only from incision to arterial reperfusion) and estimated blood loss (adjusted for patient body weight). Factors identified to be associated with difficulty were retransplantation, planned portal vein thrombectomy, prior upper abdominal surgery, spontaneous bacterial peritonitis (SBP) and prior variceal bleeding. The authors included these findings into a score to stratify risk however, the sensitivity and specificity of this score was low (30% and 88% respectively), limiting the utility of their findings in a clinical setting. Neither

group demonstrated any significant impact to overall patient survival with the former study identifying an association with reduced graft survival at 1-year.

Overall, these findings are heterogeneous and inconsistent – both in their use of surrogate measure and defining surgical difficulty as well as their ability to accurately predict patients at risk of high surgical difficulty. Surrogate measures used in the studies to date are generalised measures and fail to consider LT-specific intraoperative difficulties, which may not necessarily be accounted for by operating time or bleeding – including unplanned utilisation of jump grafts, delayed abdominal closure or hepaticojejunostomy. Many of the factors identified in each study individually to be associated with risk of intraoperative difficulty were not replicated in the other – including patient disposition, anatomical considerations and consequences of portal hypertension. Previous abdominal surgery was the only concurring risk factor, indicative of correlation with increased surgical difficulty, however the delineation of what constitutes prior surgery is again inconsistent. Owing to these limitations, the ultimate clinical utility of these studies is limited – clearly more robust and validated data is required to warrant implementation of a standardised surgical risk assessment.

FACTORS ASSOCIATED WITH SURGICAL DIFFICULTY

Given the overall paucity of data and potential incongruency of findings surrounding predictors of surgical difficulty in LT, we aimed to discuss the evidence surrounding known high-risk factors. We reviewed both factors currently typically included in the pre-transplant surgical assessment as well as those considered within the current literature which have been considered or investigated to be potential risks.

Prior abdominal surgery

The patient requiring liver transplantation who has undergone previous abdominal surgery is not infrequently encountered (14). Although outcomes of patient and graft survival do not appear to be significantly impacted, previous abdominal surgery has been shown repeatedly to impact intra-operative

complexity, particularly longer operating time, and increased transfusion requirements (11, 12, 15). These findings are in keeping with previous abdominal surgery in a range of other procedures including bariatric surgery (16), pancreatectomy (17), bowel resection (18) and hepatic resection (19). The need for extensive adhesiolysis and unclear delineation of anatomy in these patients complicates many aspects of liver transplant with the need to balance risks of over-dissection and inadvertent injury with access and adequate views for hepatectomy and implantation.

The impact of prior surgery can be further refined based on anatomical location, method of entry, significance of procedure and temporal relation to LT. In one cohort, patients were subdivided into upper and lower abdominal surgery, with the upper abdominal group further subdivided into high or low impact, based on the type of procedure performed (20). Patients who had previously undergone upper abdominal surgery required significantly greater volumes of red cell transfusions, more extensive adhesiolysis and were at higher risk for requiring abdominal packing. Those who had undergone high impact upper abdominal surgery were also observed to have higher rates of arterial conduit use, potentially as a result of extensive adhesions rendering the hepatic artery proper not amenable to anastomosis. Notably, these results were more significant for patients who had abdominal surgery within 90 days of transplant.

Clearly, the major effect of prior abdominal surgery is the development of adhesions and subsequently increases the complexity in accessing the target anatomy. Patients who have undergone significant surgery in the right upper quadrant of the abdomen, through open access rather than laparoscopic, particularly with recency, appear to be significant factors in intraoperative complexity for liver transplant. Combari-Ancellin and colleagues compared liver transplantation difficulty following open and laparoscopic liver resection - they found patients who had undergone a laparoscopic approach associated with less postoperative adhesions compared to open, whose postoperative fields were marked by dense adhesions at transplantation (21). Similar outcomes were reported in a similar study by Kim et al (22). Interestingly, associations between post-operative haematoma and the formation of highly vascular adhesions have been reported in the literature, potentially complicating the difficulty of future adhesiolysis and surgical access (23). Although not an absolute contraindication to transplant, the

presence of these factors should be carefully considered in patient selection and perioperative planning, particularly the timing of surgery to reduce cold graft ischemia time given these patients will likely require longer overall operating time.

Re-transplantation

Given the documented associations with higher morbidity and mortality, re-do liver transplantation should be discussed separately to other forms of prior abdominal surgery. The most common indications for re-transplantation are primary non function (PNF), arterial thrombosis and chronic rejection(24). Surgery following LT has been associated worse outcomes, particularly in the context of emergency abdominal surgery, where morbidity is as high as 30% and mortality 1% (20). In one study of repeat transplants, patients receiving their third or more LT, overall survival rates were 82%, 80%, 75% and 71% at one-, three-, five- and ten-year endpoints respectively (25). In a direct study comparing primary and secondary LT, re-do LT had significantly worse survival rates of 59% compared to 82% at 12 months (26).

Significantly, re-do LT has been demonstrated to be associated overall with increased operation duration and blood transfusions when compared with primary LT (27). It is unclear whether the presence of extensive adhesions plays a significant role in these cases, particularly in the context of long-term immunosuppression in the post-LT patient however it is evident that these patients represent a more technically challenging procedure. The timing of re-do LT can impact the density and extent of adhesion formation and thus the difficulty of dissection. Re-do LT has also been associated with other technical challenges, including increased likelihood of requiring complex anastomoses, such as SMV jump grafts, aorto-hepatic arterial conduits and biliary-enteric anastomoses (33% compared to 4% of primary-LT) (28). The re-transplant candidate should also be carefully considered from an anatomical perspective - patients with arterial thromboses have the potential to develop a number of arterial collaterals (24).

Concomitant surgery

In select cases, there is a need for concomitant surgery in addition to LT given the significant risks of surgery associated with advanced liver disease. Patients with end-stage liver failure undergoing cardiac or abdominal surgery have been demonstrated to have up to six-fold increased mortality risks in the immediate post-operative period compared to those without (29). This is likely due to a range of factors including compromised hepatic synthetic function resulting in higher risks of decompensation, bleeding and infectious complications (30, 31). Consequently, patients requiring LT with indications for other major surgery often either have their secondary procedures delayed or concomitantly with LT.

Three cohorts of patients undergoing concomitant surgery with LT have been examined previously, with the most common concomitant procedures being cardiac (coronary artery bypass grafts, valve replacements), gastrointestinal (colonic resection, gastrectomy) and splenic (splenectomy), compared against patients who underwent only LT (32-34). There were no statistically significant differences in all cohorts in terms of their graft survival and short-term surgical outcomes such as length of stay and readmission. Total operative time was noted to be higher in concomitant LT, reporting 451 vs 355 min in the LT only group. One group examining concomitant cardiac surgery with LT reported a significantly lower survival rate in the combined group with survival periods of 1, 5 and 10 years at 90 vs 62%, 79 vs 55% and 70 vs 45% respectively for control vs combined.

Although select concomitant surgery with LT does not appear to significantly affect short-term post-operative outcomes, these patients undergo appreciably longer operating time. There is a risk that concomitant surgery therefore skews the delineation of which patients constitute a complex surgical candidate. Overall, these represent select, uncommon cases, reflected by the small cohorts reported in literature.

Portal hypertension and portal vein thrombosis

The presence of portal hypertension can result in the formation of significant collateralisation of vessels, in the form of oesophageal, gastric varices and recanalization of umbilical vein. These all present a significant peri-operative risk, as these non-anatomical shunts carry large volumes of portal blood and are particularly prone to bleeding. The presence of previous variceal bleeding in particularly has been associate with increased intraoperative bleeding and longer operating times(11).

Trans-jugular intrahepatic portosystemic shunt (TIPS) has been widely used to treat complications of portal hypertension prior to transplant. While TIPS procedure aims to reduce the flow through the collaterals thus theoretically decreasing bleeding risk, the literature has not demonstrated statistically significant reduction of administered blood products (35). There appears to be no significant differences in perioperative outcomes of transfusion requirements (TIPS 3 units IQR 0-7 vs no TIPS 5 units IQR 2-8) and operating time (TIPS 348±13 min vs no TIPS 337±10 min) between patients with and without prior TIPS(36).

Although portal hypertension is often significantly improved following LT, splenomegaly and hypersplenism may persist, resulting in excessive portal pressures and decreases in hepatic artery inflow, potentially resulting in poor graft perfusion(37). Commonly, patients with significant splenomegaly undergo splenectomy during LT which has been associated with increased operative time and bleeding. There is also the consideration of post-splenectomy infection and further thrombosis. One group describes the practice of partial splenectomy during liver transplant, with demonstrated improvements in hepatic arterial and portal venous flows, as well as reduced post-operative hypersplenism and requirement for embolization(38). Notably these improvements in flow were accompanied by increases in both operating time and intraoperative blood loss.

The presence of portal hypertension and associated splenomegaly is therefore associated with increased intraoperative complexity. Given routine imaging prior to most elective transplant scenarios, there is likely benefit to reviewing the presence of splenectomy and portal hypertension prior to surgery and planning subsequent intra-operative and post-operative management.

Portal vein thrombosis (PVT) in the transplant recipient is now commonly encountered, particularly in view of the increased disease severity of modern candidates. The recorded incidence of PVT has great range, varying from 0.6% to 64.1% depending on diagnosis and patient selection(39, 40). PVT has demonstrated adverse effects on outcomes, including reduced graft survival, particularly as the new graft is highly dependent on adequate portal flow for perfusion(41). Significantly from a technical standpoint, the presence of PVT is associated with prolonged implantation time. Despite previously being a contraindication to transplant, a number of techniques have been developed to limit its impact, including medical therapy, intraoperative techniques, and pre-operative endovascular procedures(42). Importantly, patients with known preoperative PVT are frequently commenced on anticoagulant therapy, which in conjunction with their liver disease increases perioperative bleeding risks(43, 44).

The optimal outcome of a physiological, direct portal venous to portal venous anastomosis cannot always be achieved intra-operatively as PVT limits the availability and quality of portal vein for anastomosis in reducing flow for the new graft. A wide range of techniques have been employed, from intra-operative portal vein thrombectomy (41), jump grafts to SMV (40, 45), jump grafts to other collaterals (46, 47) and, arterialisation (48). Many of these techniques, particularly the use of jump grafts and additional anastomoses significantly increases the risks of complications in LT. A classification of PVT has been proposed to guide surgical decision-making depending on the level of severity (49). Patients with higher grades of occlusion of the portal vein are more likely to require more complex vascular reconstructions including jump grafts, whilst lower grades of occlusion are safely managed without intervention or thrombectomy (50). Despite many of these strategies, performing LT on patients with PVT carries significant risk – perioperative mortality overall in these patients is reported at 13%, and up to 28% for those with thrombus burden extending to the superior mesenteric vein (39).

Clearly, PVT presents the surgeon with a formidable challenge. Longer operating times, increased bleeding and more complex anastomoses should be expected, even if pre-operative recanalization procedures have been performed. The role of routine abdominal imaging in the form of multi-phase

abdominal CT cannot be understated in detecting the severity of PVT and adequate preparations for the entire transplant team including surgeon, where possible, should be ensured.

Need for jump-grafts

Complex vascular conditions can present a technical challenge to the surgeon at time of LT. The principal indications for complex vascular reconstructions such as arterial and venous jump grafts occur in a range of circumstances. The risks involved with jump grafts are primarily associated with the increased number of anastomoses formed, as each is independently at risk of failure and thrombosis.

Indications for arterial jump grafts typically include anomalous recipient arterial anatomy (51), coeliac axis stenosis and median arcuate ligament syndrome, which chiefly results in a reduced inflow onto the native hepatic artery. The use of donor iliac arterial conduits to infrarenal aorta and occasionally supracoeliac aorta are well documented when these indications are present (52).

Conversely, the chief indication for venous jump grafts is PVT. Typically, jump grafts are performed to the distal-most, non-thrombosed vein, ideally native portal vein. Other documented sites of venous jump grafts include superior mesenteric vein (45), alternative recipient veins or collaterals and rarely arterialisation of the portal vein (53). Importantly, in cases where there a mismatch in size between the donor graft and recipient, there can be significant discrepancies between vessel sizes. Small recipients with larger donors can encounter problems with insufficient inflows from portal vein and hepatic artery, resulting in poor graft function. Regardless of indication, the use of jump grafts is associated with a significantly higher complication rate, with portal vein grafts shown to be associated with higher rates of re-thrombosis (54, 55).

The ability to perform these complex vascular reconstructions is notably also dependent on the donor surgery, particularly in harvesting useable and appropriate venous and arterial grafts. Although artificial conduits have been used in the past, they have been associated with increased risks of thrombosis and

infection (52). Where challenging anatomy is predicted or significant PVT is present, the availability of appropriate donor vascular grafts should be prioritised.

Donor-recipient graft size mismatch

Although significant donor and recipient graft size mismatch is uncommon in adult liver transplants its potential perioperative impacts demand the surgeons' attention. In addition to the potential requirements for high-risk jump grafts as a result of portal vein and hepatic artery size discrepancies, significant mismatch requires modifications to perioperative management. Principally, there are two circumstances which should be considered here, small-for-size grafts and large-for-size grafts (56).

Small-for-size grafts, in addition to being insufficient for normal hepatic function, are at higher risks for PNF. The mechanisms for this are complex however one described process is 'portal hyperperfusion', wherein the small graft is injured by high portal inflow from the recipient (57-60). Employed techniques to manage this high flow state have been described, including the use of splenic artery ligation (61), splenectomy (62), and porto-systemic shunts (63, 64), amongst others.

Large-for-size grafts are also at higher risks of PNF; however, the proposed mechanism is insufficient portal flow, resulting in impaired hepatic microcirculation (65-67). Proposed solutions for these cases include hemi-hepatectomy following the completion of vascular anastomoses to reduce hepatic venous outflow occlusion (68). Furthermore, large volume grafts can significantly increase intra-abdominal pressures, resulting in cardio-respiratory and subsequently global perfusion compromise. These patients are not uncommonly left open or closed by mesh before a subsequent complete abdominal closure(56).

CONCLUSIONS

Preoperative evaluation for LT remains a complex nuanced and multidisciplinary process which requires consideration of patient, organ and logistical factors. In the face of expanding indications and

patient base potentially undergoing LT, careful surgical assessment is necessary to inform both patient and treating teams, allow for peri-operative planning and optimisation of long-term outcomes in cases deemed high risk and potentially guide organ allocation. Current surgical assessment models are limited and inconsistent in their findings and more data is required to accurately risk stratify surgical difficulty in LT.

TABLES AND FIGURES

Table 1 – Comparison of studies to date defining and identifying predictors of surgical difficulty in LT.

Study	Ausania et al. 2022	Azoulay et al. 2021
n	101/515	88/467
Difficulty surrogate measure	Operating time (skin to arterial reperfusion) Estimated blood loss (ml/kg)	Operating time (total) Transfusion requirements (PC) Cold ischemia time
Factors assessed	Age Sex BMI Indication MELD Prior variceal bleed Prior abdominal surgery	Age Sex BMI Indication (including re-transplantation) MELD Prior variceal bleed Prior upper abdominal surgery

	Prior HCC treatment (Ablation/TACE) TIPS PVT Ascites Disposition Splenomegaly Caudate lobe hypertrophy Hepatosplenomegaly Liver atrophy + splenomegaly Recanalisation of umbilical vein BAR score DRI score			Prior HCC treatment (Ablation/TACE) TIPS (including malposition) PVT Ascites SBP Planned portal vein thrombectomy Planned veno-venous bypass Planned non-standard arterial anastomosis Encephalopathy Donor type Donor age Donor arterial anatomical variation Surgeon experience		
Identified risk factors (OR, 95% CI, *p*)	Re-transplantation Upper abdominal surgery Planned thrombectomy SBP Variceal bleeding	4.34 (2.03 – 9.30) 2.16 (1.29 – 3.62) 3.42 (1.75 – 6.68) 1.99 (1.13 – 3.49) 1.40 (1.02 – 2.40)	0.001 0.003 0.001 0.017 0.051	Disposition (ICU) Previous abdominal surgery Hepatosplenomegaly Liver atrophy + splenomegaly	2.7 (1.2 – 4.0) 2.2 (1.1 – 4.3) 2.2 (1.2 – 4.0) 2.5 (1.2 – 5.2)	0.02 0.03 0.01 0.02
1-year OS (% difficult/% control, *p*)	87.5 (94.5), $p = 0.088$			94 (93), $p = 0.94$		

1-year GF (% difficult/% control, *p*)	82.6 (82.6), $p = 0.016$	94 (92), $p = 0.89$

PC- packed cells; BMI – body mass index; MELD – model for end-stage liver disease; TIPS – transcutaneous intrahepatic portosystemic shunt; SBP – spontaneous bacterial peritonitis; BAR – balance of risk score; DRI – donor risk index; CI – confidence interval; OS – overall survival; GF – graft failure

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III. Delineating prior abdominal surgery and its intraoperative impact in liver transplantation

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CONFLICT OF INTEREST

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Liver transplantation; Retrospective studies; Intraoperative complication; Surgical procedures, operative; Blood loss, surgical; Laparoscopy

Abbreviations:

BMI – body mass index

CCI – Charlson Comorbidity Index

CI – confidence interval

GF – graft failure

HCC – hepatocellular carcinoma

ICU – intensive care unit

LT – liver transplantation

MELD – Model for End-stage Liver Disease

MD – mean difference

OS – overall survival

OR – odds ratio

OT – operating time

PC – packed cell transfusion requirement

ABSTRACT

Purpose: Prior abdominal surgery is associated with increased complexity of liver transplantation (LT), but this remains a broad term, encompassing simple laparoscopic surgery to complex liver resections. We sought to quantify the nature of prior abdominal surgery and its intraoperative impact in LT.

Methodology: Retrospective review was performed of all adult LT performed between 2012 and 2023. Patients were divided into cohorts based on number of abdominal entries, the anatomical location of prior abdominal surgery (re-transplant, hepatobiliary, other abdominal and no surgery) as well as method of entry (open, laparoscopic). Primary outcomes were total operating time (OT) and packed cell transfusion requirements (PC). Secondary outcomes measured included length of stay, 30-day re-operation rates, graft failure and overall survival at 1-year.

Results: A total of 771 patients were included. Mean operative time for patients who had no prior abdominal surgery was 33.05±111min and was significantly lower than those who had undergone re-transplantation (410.9±149.7, $p<0.001$), hepatobiliary surgery (386.5±119.8, $p<0.001$) or any abdominal surgery requiring open approach (391.4±124.4, $p=0.013$). Transfusion requirements without prior surgery were 5.24±4.9units, lower than those who had undergone re-transplantation (11.78±12.6, $p<0.001$), hepatobiliary (7.57±5.2, $p<0.001$) or open surgery (8.49±10.2, $p<0.001$). Similar associations were not seen in patients who had only undergone previous laparoscopic abdominal surgery (OT, 355.7±121.8, $p=0.06$; PC, 5.81±6.0, $p=0.338$), nor those who had abdominal surgery distant to the right upper quadrant (OT, 360.3±117.8, $p=0.019$; PC, 6.02±5.6, $p=0.109$). The number of prior abdominal entries was positively associated with OT (B=25.7, $R^2= 0.194$, F=29.95, $p<0.001$) and PC (B=1.4, $R^2=0.175$, F=23.95, $p<0.001$).

Conclusions: Patients who have previously undergone re-transplant, hepatobiliary and open surgery have significantly increased operative time and blood loss in LT. Notably, laparoscopic surgery or surgery distant to the right upper quadrant was not associated with worse intraoperative parameters. Detailed pre-operative surgical assessment is paramount in identifying and planning for these high-risk patients.

INTRODUCTION

History of prior surgery in most contexts confers an increased intraoperative risk in consequent surgery (1-3) and is therefore a standard part of surgical assessment. In highly technically complex procedures such as liver transplantation (LT), this increased intraoperative risk may be compounded into increased demands for the operating surgeon, operative resources and potentially worse outcomes for the patient. Prior abdominal surgery has been previously quantifiably shown to be associated with increased operating time and blood loss in the context of major hepatic surgery, including liver resection(4), hepatectomy in LT (5, 6) and LT in general (7-9)

However, the term ‘prior abdominal surgery' represents a heterogeneous cohort of patients who present having undergone innumerably varied forms of surgery. For instance, many patients may have commonly undergone mostly benign procedures such as appendicectomy or elective hernia repair, which should clearly present a distinct entity from liver resection for hepatocellular carcinoma (HCC). Moreso, the advent and widespread adoption of minimally invasive surgical techniques in laparoscopy and robotics have furthered the propensity for reducing impact of surgery within the intraperitoneal space. No longer is a full laparotomy required to perform for example a Hartmann’s procedure or resection of small bowel.

Definitions of prior surgery in the literature has to date been poorly delineated, utilising this term to classify any of the range of aforementioned operations, and yet earmarked at a risk factor for surgical complexity in LT. Some studies have utilised anatomical space to help limit this, such as the use of ‘upper abdominal surgery’ however it remains poorly qualified and quantified (8). The aim of this study is to clarify the forms of prior abdominal surgery against their impacts to intraoperative outcomes in LT.

PATIENTS AND METHODS

All consecutive transplants performed by eight experienced transplant surgeons between January 2012 and July 2023 at our high-volume transplant centre (Royal Prince Alfred Hospital) were considered for this study. Data were collected retrospectively from chart review and a prospectively maintained database. The study was conducted in accordance with the ethical principles stipulated by the Declaration of Helsinki and reviewed and approved with a waiver of consent by the institutional Human Research Ethics Committee.

All patients were analysed for pre-operative demographic (age, sex, body mass index [BMI], Charlson Comorbidity Index [CCI] (10), disposition at time of transplant, indication, Model for End-Stage Liver disease [MELD] score (11)) and biochemical (serum haemoglobin, platelet count, fibrinogen) and transplantation characteristics (multi-organ, split-liver, donor type).

Abdominal surgery was classified based on the number of abdominal procedures previously carried out, nature or anatomical location of each prior procedure (categorised into re-transplantation, hepatobiliary and other abdominal) and approach (categorised into open or minimally-invasive, i.e. laparoscopic or robotic). Where patients had undergone multiple previous procedures, the most significant operation was used to cohort: open over laparoscopic, hepatobiliary over other abdominal.

Primary outcomes were total operating time measured from skin incision to closure and intraoperative blood transfusion requirement measured by absolute number of packed cell transfusions. Secondary outcomes were length of stay, 30-day re-operation rate and 1-year survival and graft failure rates.

Continuous variables were expressed as means/standard deviations and medians/interquartile ranges as appropriate whilst categorical variables were expressed with frequencies and proportions. Univariate analysis was performed using one-way ANOVA and independent t-tests for continuous variables and Chi-square tests were for categorical variables, with p-values <0.05 considered statistically significant. Linear regression was performed to assess for relationships between continuous variables. Variables with significant association with the primary endpoints of OT and PC (defined as $>75^{th}$ percentile) on

univariate analysis ($p<0.1$) were included in multivariate logistic regression analysis to assess for collinearity and expressed as adjusted odds ratios (aOR). All statistical analysis was performed using Statistical Package for Social Science (SPSS version 31.0, IBM, USA).

RESULTS

A total of 771 transplants were included in the analysis from 742 patients. Baseline characteristics compared between patients with and without prior history of abdominal surgery are shown in Table 1. A total of 319 patients within the cohort had a history of abdominal surgery. Our patient cohort varied from no prior surgery to up to 4 prior abdominal procedures. The number of prior abdominal procedures was positively associated with increased operating time ($B = 25.7$, $R^2 = 0.194$, $F = 29.95$, $p<0.001$) and packed cell transfusion requirement ($B = 1.4$, $R^2 = 0.175$, $F = 23.95$, $p<0.001$).

Method of entry

Patients with prior history of abdominal surgery were divided into cohorts based on the method of entry (open, laparoscopic/robotic) and compared against each other and no surgery. Open abdominal surgery had been previously performed on a total of 200 and laparoscopic surgery on 119 transplants within our cohort. Baseline demographics were compared between cohorts and displayed in Table 2.

Primary outcomes of OT and PC were compared and displayed in Table 3. Prior open surgery was associated with increased overall operating time (391.4±124.4 min) and transfusion requirement (8.49±10.2 units), compared to both laparoscopic (OT, $p=0.013$; PC, $p=0.010$) and no surgery (OT, $p<0.001$; PC, $p<0.001$). Patients who had undergone previous open surgery were also secondarily found to have longer overall hospital length of stay (27.8±23.3 vs 24.5±21.1 days, $p=0.005$), significantly greater 30-day reintervention rates (27.6 vs 19.1%, $p<0.001$) and worse overall survival (86.0 vs 94.5%, $p<0.001$) at 1-year post-operatively.

Prior laparoscopic surgery was not associated with any significant differences in operating time nor transfusion requirements compared with no surgery (OT, 355.7±121.8 vs 335.0±111.1 min, p=0.06; PC 5.81±6.0 vs 5.24±4.9 units, p=0.338). Post-operative outcomes of length of stay, re-intervention and survival at 1-year were equivalent to those who had never undergone abdominal surgery.

Anatomy of prior abdominal surgery

Patients were also divided into cohorts based on the anatomical location of prior surgery and compared against no prior surgery. Baseline characteristics for these cohorts are displayed in Table 4. Within the study cohort, 45 patients underwent re-transplantation, 129 with prior hepatobiliary surgery and 145 with prior other abdominal surgery. Outcomes compared between the cohorts are displayed in Table 5.

Re-do transplantation was associated with greatest risk with significantly increased OT (410.9±149.7, MD 75.98 min, p<0.001) and PC (11.78±12.62, MD 6.54 units, p<0.001). Patients who had re-do transplants secondarily had prolonged post-operative hospitalisation (31.9±28.8 vs 24.5±21.1 days, p=0.016), higher re-intervention rates (44.4 vs 19.1%, p<0.001) and reduced overall survival at 1-year (71.1 vs 94.5%, p<0.001)

Hepatobiliary surgery, independent of re-do transplantation was associated with prolonged operating times (386.45±149.7, MD 51.50, p<0.001) and increased transfusion requirements (7.57±5.24, MD 2.33 units, p<0.001). Overall survival at 1-year was worse in this cohort (88.4%) however other outcomes of length of stay or re-intervention rates were no different to baseline.

Each cohort of prior surgery was entered into a regression model to adjust for covariates (Table 66). Multivariate regression analysis revealed prior open (aOR 1.73, 95%CI 1.14-2.62, p=0.011) and hepatobiliary (aOR 1.96, 95%CI 1.26-3.04, p=0.003) as predictors for prolonged operating time (≥ 412 minutes). Prior open surgery (aOR 1.49, 95%CI 1.02-2.28, p=0.041) and re-transplantation (aOR 2.41, 95%CI 1.23-4.73, p=0.011) were predictors for increased transfusion requirements (≥ 8 units).

DISCUSSION

The results of this study are concordant with previous associations between history of abdominal surgery with increased operating times and transfusion requirements in LT. However, our data highlights the need for specificity in reporting prior abdominal surgery, with *re-transplantation*, *hepatobiliary* and *open surgery* as the only relevant forms of surgical history contributing meaningfully to intraoperative variables.

Our study findings demonstrate strong associations between re-transplantation with both intraoperative complexity and higher re-intervention rate (within 30-days, 44.4% vs 19.1%, $p<0.001$) and lower overall survival (OS 1-year 71.1% vs 94.5%, $p<0.001$). These results appear to be consistent with the wider literature (12-14), again redemonstrating the immense risks of re-do transplantation. Patients who are listed for second and third transplants require careful consideration of perceived benefits and expected recovery in context of these findings.

Of particular note are the findings of the significant impact of prior hepatobiliary surgery as well as open abdominal surgery, independent of re-transplant, on intraoperative variables. These patients are of increased requirements for both intraoperative transfusions and prolonged operating time when compared to no surgery or other forms of prior surgery, including laparoscopic or other abdominal. Surgical assessment in LT should be appropriately detailed to delineate the specific forms of prior surgery as this has now been shown to impact the overall operation. Identifying these cases in a pre-transplant assessment setting has utility in guiding perioperative planning, including preparing blood bank resources and ensuring adequate staffing.

There were inherent differences between the cohorts of patients who had prior surgery against those who had not – those without a prior history of abdominal surgery had higher disease severity compared to those with, demonstrated by higher mean MELD scores (21.2 vs 19.6, $p=0.015$), lower platelet (96.8 $x10^9$ vs 113.9 $x10^9$, $p=0.005$) and fibrinogen counts (2.49 vs 2.18, $p<0.001$). Despite these differences, both operating time and transfusion requirements were higher in patients who had undergone prior

surgery, again demonstrating its impact in intraoperative variables independent of other disease factors such as coagulopathy.

Significantly are the findings of the low impact on intraoperative variables conferred by a history of laparoscopic surgery. There were no significant intraoperative differences between patients who had undergone prior laparoscopic surgery compared to those who had no prior surgery. This may suggest that, where possible in patients who are potentially expected to become LT recipients, a minimally invasive approach should be considered over open. Given this study is limited by its retrospective design and observational nature, it is not possible to draw further conclusions on these. Furthermore, there is evidence that the timing of prior abdominal surgery may impact the development of adhesions and therefore intraoperative impact – patients who had undergone surgery less than 90 days prior to transplant were at increased risks (15), a variable which was not captured within our study. Future studies are warranted to investigate whether minimally invasive abdominal surgery (particularly in cases of HCC resection) over open surgery as well as timing of surgery can improve intraoperative and post-operative variables in future transplant.

CONCLUSION

Some forms of prior abdominal surgery are risk factors for increased operating time and transfusion requirements during LT. This risk should not be generalised to all forms of abdominal surgery, with prior transplantation, hepatobiliary or any open approach surgery associated with the highest risk, whilst prior laparoscopic surgery was not associated with increased risk.

TABLES AND FIGURES

Table 1 – Baseline characteristics compared between patients with or without prior history of any abdominal surgery

Outcome	Prior surgery	No prior surgery	*p*
n	319	452	
Age, years	54.5 (11.6)	53.4 (11.2)	0.203
Sex, male (%)	202 (63.3)	328 (72.6)	**0.006**
Indication for transplantation			**0.002**
Alcohol-related liver disease	46 (14.4)	101 (22.3)	
Hepatocellular carcinoma	61 (19.1)	65 (14.4)	
Hepatitis C	37 (11.6)	79 (17.5)	
Metabolic dysfunction-associated steatotic liver disease	38 (11.9)	55 (12.2)	
Primary sclerosing cholangitis	33 (10.3)	29 (6.4)	
Other	104 (32.6)	123 (27.2)	
BMI, kg/m^2	28.4 (6.0)	28.7 (5.4)	**0.389**
MELD Score	19.6 (8.5)	21.0 (9.1)	**0.015**
Charlson Co-morbidity Index	5 (2)	5 (2)	0.727
Haemoglobin, g/L	112.3 (25.7)	110.6 (23.6)	0.362

Platelet count, x10^9/L	113.9 (92.5)	96.8 (74.7)	**0.005**
Fibrinogen, g/L	2.5 (1.4)	2.3 (1.2)	**<0.001**
Disposition at transplant, *n* (%)			0.290
Home	179 (56.1)	241 (53.3)	
Occasional inpatient	34 (10.7)	63 (13.9)	
Hospital bound	78 (24.5)	97 (21.5)	
ICU	28 (8.8)	51 (11.3)	
Multi-organ transplant, *n* (%)			0.181
Liver only	300 (94.0)	431 (95.4)	
Liver-Kidney	18 (5.6)	16 (3.5)	
Liver-Other	1 (0.3)	5 (1.1)	
Split-liver donor, *n* (%)	43 (13.5)	67 (14.3)	0.599
Donor type, DBD, *n* (%)	302 (94.7)	411 (90.9)	0.052

Table 2 – Baseline characteristics compared between patients with previous open or laparoscopic or no abdominal surgery

Outcome	Open	Laparoscopic	None	*p*
n	200	119	452	
Age, years	53.1 (12.4)	56.7 (9.8)	53.4 (11.2)	**0.010**
Sex, male (%)	124 (62.0)	78 (65.5)	328 (72.6)	**0.020**
Indication for transplantation				**0.004**
Alcohol-related liver disease	30 (15.0)	16 (13.4)	101 (22.3)	
Hepatocellular carcinoma	35 (17.5)	26 (21.8)	65 (14.4)	
Hepatitis C	22 (11.0)	15 (12.6)	79 (17.5)	
Metabolic dysfunction-associated steatotic liver disease	19 (9.5)	19 (16.0)	55 (12.2)	
Primary sclerosing cholangitis	20 (10.0)	13 (10.9)	29 (6.4)	
Other	74 (37.0)	30 (25.2)	123 (27.2)	
BMI, kg/m^2	27.6 (5.9)	29.6 (6.1)	28.7 (5.4)	**0.007**
MELD Score	20 (9)	19 (8)	21 (9)	**0.034**
Charlson Co-morbidity Index	5 (2)	5 (1)	5 (2)	0.820
Haemoglobin, g/L	110.8 (25.8)	114.6 (25.5)	110.6 (23.6)	0.281

Platelet count, x10^9/L	117.4 (103.5)	107.9 (70.1)	96.8 (74.7)	**0.011**
Fibrinogen, g/L	2.7 (1.5)	2.2 (1.1)	2.3 (1.2)	**<0.001**
Disposition at transplant, *n* (%)				0.342
Home	109 (54.5)	70 (65.1)	241 (53.3)	
Occasional inpatient	20 (25.1)	14 (14.9)	63 (13.9)	
Hospital bound	49 (44.9)	29 (26.7)	97 (21.5)	
ICU	22 (11.0)	6 (12.3)	51 (11.3)	
Multi-organ transplant, *n* (%)				0.088
Liver only	184 (92.0)	116 (97.5)	431 (95.4)	
Liver-Kidney	15 (7.5)	3 (2.5)	16 (3.5)	
Liver-Other	1 (0.5)	0 (0)	5 (1.1)	
Split-liver donor, *n* (%)	28 (14.0)	15 (16.8)	67 (14.3)	0.821
Donor type, DBD, *n* (%)	191 (95.5)	111 (93.3)	411 (90.9)	0.117

Table 3 – Comparison of intraoperative and post-operative outcomes following LT between patients with prior open, laparoscopic or no abdominal surgery

Outcome	Open	*p* (vs lap)	*p* (vs none)	Laparoscopic	*p* (vs none)	None	*p* (all)
n	200			119		438	
Operating time, min	391.4 (124.4)	**0.013**	**<0.001**	355.7 (121.8)	0.060	335.0 (111.1)	**<0.001**
PRBC, units	8.49 (10.2)	**0.010**	**<0.001**	5.81 (6.0)	0.338	5.24 (4.9)	**<0.001**
Length of stay, days (IQR)							
ICU-specific	7.8 (8.7)	0.430	0.078	6.9 (10.3)	0.891	6.8 (7.6)	0.494
Ward	20.0 (19.3)	**0.002**	0.061	13.9 (11.2)	**0.023**	17.7 (17.0)	**0.008**
Total	27.8 (23.3)	**0.005**	**0.037**	20.9 (16.4)	0.078	24.5 (21.1)	**0.016**
Return to OT, within 30-days, *n* (%)	55 (27.6)	**<0.001**	**0.003**	13 (10.9)	0.060	82 (19.1)	**<0.001**
Overall survival at 1-year (%)	172 (86.0)	0.068	**<0.001**	109 (91.6)	0.350	427 (94.5)	**0.001**
Graft failure at 1-year (%)	5 (2.5)	0.315	0.288	2 (1.7)	0.245	15 (3.3)	0.596

Table 4 – Baseline variables compared between patients with re-transplant, previous hepatobiliary, other abdominal or no abdominal surgery

Outcome	Re-transplant	Hepatobiliary	Other abdominal	None	*p*

n	45	129	145	452	
Age, years	47.3 (15.4)	55.7 (11.7)	55.6 (9.2)	53.4 (11.2)	**<0.001**
Sex, male (%)	29 (64.4)	84 (65.1)	89 (61.4)	328 (72.6)	**0.048**
Indication for transplantation					**<0.001**
Alcohol-related liver disease	9 (20.0	10 (7.8)	27 (18.6)	101 (22.3)	
Hepatocellular carcinoma	8 (17.8)	39 (30.2)	14 (97)	65 (14.4)	
Hepatitis C	3 (6.7)	11 (8.5)	23 (15.9)	79 (17.5)	
Metabolic dysfunction-associated steatotic liver disease	2 (4.4)	11 (8.5)	25 (17.2)	55 (12.2)	
Primary sclerosing cholangitis	4 (8.9)	17 (13.2)	12 (8.3)	29 (6.4)	
Other	19 (42.2)	41 (31.8)	44 (30.3)	123 (27.2)	
BMI, kg/m^2	25.1 (5.1)	28.6 (6.7)	29.2 (5.3)	28.7 (5.4)	**<0.001**
MELD Score	23 (10)	18 (9)	20 (7)	21 (9)	**<0.001**
Charlson Co-morbidity Index	4 (2)	5 (2)	5 (1)	5 (2)	**0.016**
Haemoglobin, g/L	103.1 (29.3)	117.3 (25.3)	110.7 (24.0)	110.6 (23.6)	**0.004**
Platelet count, $x10^9/L$	112.8 (96.8)	124.6 (102.9)	101.6 (79.5)	96.8 (74.7)	**0.003**

Fibrinogen, g/L	3.1 (1.7)	2.7 (1.4)	2.2 (1.2)	2.2 (1.2)	**<0.001**
Disposition at transplant, *n* (%)					**<0.001**
Home	15 (33.3)	5 (3.9)	8 (5.5)	51 (11.3)	
Occasional inpatient	13 (28.9)	33 (25.6)	32 (22.1)	97 (21.5)	
Hospital bound	6 (13.3)	16 (12.4)	12 (8.3)	63 (13.9)	
ICU	11 (24.4)	75 (58.1)	93 (64.1)	241 (53.3)	
Multi-organ transplant, *n* (%)					0.133
Liver only	42 (93.3)	125 (96.9)	133 (91.7)	431 (95.4)	
Liver-Kidney	3 (6.7)	3 (2.3)	12 (8.3)	16 (3.5)	
Liver-Other	0 (0)	1 (0.8)	0 (0)	5 (1.1)	
Split-liver donor, *n* (%)	3 (6.7)	20 (15.5)	20 (13.8)	67 (14.8)	0.489
Donor type, DBD, *n* (%)	44 (97.8)	123 (95.3)	135 (93.1)	411 (90.9)	0.173

Table 5 - Intraoperative variables and post-operative outcomes compared between patients with previous re-transplantation, hepatobiliary, other abdominal against no surgery

Outcome	Re-transplantation	*p*	Hepatobiliary	*p*	Other abdominal	*p*
n	45		129		145	

Operating time, min	410.93 (149.7)	**<0.001**	386.45 (119.8)	**<0.001**	360.33 (117.8)	**0.019**
Mean difference	75.98		51.50		25.38	
PRBC, units	11.78 (12.62)	**<0.001**	7.57 (5.24)	**<0.001**	6.02 (5.55)	0.109
Mean difference	6.54		2.33		0.79	
Length of stay, days (IQR)						
ICU-specific	10.4 (7.9)	0.083	6.86 (9.0)	0.339	7.1 (9.9)	0.428
Ward	21.5 (26.3)	**0.003**	16.9 (15.3)	0.460	17.3 (14.5)	0.423
Total	31.9 (28.8)	**0.016**	23.8 (20.0)	0.359	24.4 (19.3)	0.478
Return to OT, within 30-days, *n* (%)	20 (44.4)	**<0.001**	20 (15.5)	0.244	29 (20.0)	0.308
Overall survival at 1-year (%)	32 (71.1)	**<0.001**	114 (88.4)	**0.008**	135 (93.1)	0.222
Graft failure at 1-year (%)	1 (2.2)	0.346	3 (2.3)	0.283	3 (2.1)	0.271

Table 6 – Univariate and multivariate regression analysis of prior abdominal surgical approach and anatomy as predictors for prolonged operating time and increased transfusion requirements

	Univariate	**Multivariate**
Operating time (75th percentile/412min)		

Variable	**OR (95% CI)**	***p***	**R^2**	**OR (95% CI)**	***p***	**R^2**
Open	2.26 (1.59 – 3.21)	**<0.001**	0.026	1.73 (1.14 – 2.62)	**0.011**	0.037
Laparoscopic	1.02 (0.65 – 1.60)	0.926	0.000			
Re-transplantation	2.11 (1.14 – 3.94)	**0.018**	0.007	1.61 (0.789 – 3.30)	0.190	
Hepatobiliary	2.23 (1.50 – 3.33)	**<0.001**	0.019	1.96 (1.26 – 3.04)	**0.003**	
Other abdominal	0.99 (0.66 – 1.52)	0.989	0.000			
Packed cell transfusion requirement (75^{th} percentile/8 units)						
Open	1.83 (1.30 – 2.57)	**<0.001**	0.015	1.49 (1.02 – 2.28)	**0.041**	0.024
Laparoscopic	0.79 (0.50 – 1.23)	0.290	0.001			
Re-transplantation	3.23 (1.78 – 6.02)	**<0.001**	0.018	2.41 (1.23 – 4.73)	**0.011**	
Hepatobiliary	1.20 (0.80 – 1.81)	0.370	0.001			
Other abdominal	0.94 (0.63 – 1.41)	0.769	0.000			

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IV. Predicting surgical difficulty in liver transplantation – a scoring system to stratify risk

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CONFLICT OF INTEREST

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Keywords:

Liver transplantation; Retrospective studies; Risk factors; End stage liver disease; Intraoperative complication

Abbreviations:

BMI – body mass index

CCI – Charlson comorbidity Index

EBL – estimated blood loss

GF – graft failure

HCC – hepatocellular carcinoma

HD – high difficulty

ICU – intensive care unit

IC – intraoperative complication

ID – intermediate difficulty

IVC – inferior vena cava

LD – low difficulty

LT – liver transplantation

MELD – Model for End-stage Liver Disease

NPV – negative predictive value

OS – overall survival

OR – odds ratio

OT – operating time

PPV – positive predictive value

PVT – portal venous thrombosis

ROC – receiver operating characteristics

SBP – spontaneous bacterial peritonitis

ABSTRACT

Introduction: Patients undergoing liver transplantation (LT) are routinely assessed for surgical difficulty, but the predictability of these assessments is unreliable and are unquantified. We aimed to identify and quantify risk factors for surgical complexity in LT to inform decision making and assist in peri-operative planning.

Methodology: We retrospectively examined all adult liver transplants performed at a single centre between 2012 and 2023. Surgical difficulty was defined by three surrogate measures; operating time, estimated blood loss, and intraoperative complications. Patients were allocated points based on their percentiles for each surrogate and stratified into low (LD), intermediate (ID) and high (HD) difficulty cohorts. Cohorts were compared based on demographic, biochemical, surgical and radiological data. Univariate and multivariate logistic regression was performed to calculated odds ratios (OR) with $p<0.05$ considered statistically significant

Results: A total of 771 transplants were included in the study (LR; n=225, IR; n=346, HR; n=200). Patients in the HD cohort were associated with worse overall survival (OS; HD 85.5% vs ID 93.7% vs LD 96.4%, p<0.001) and graft failure (GF; HD 6.5% vs ID 2.0% vs LD 0.9%, p<0.001) at 1-year as well as longer hospital length of stay and surgical complications. Factors predictive of surgical difficulty were multiple prior abdominal surgical procedures (>1, OR 1.94, p<0.05), prior open hepatobiliary surgery (OR 3.86, p<0.05), re-transplantation (OR 5.89, p<0.05) and prior spontaneous bacterial peritonitis (OR 3.04, p<0.05)

Conclusions: We identified four key variables associated with significant risk for surgical complexity in LT. These risk factors have been incorporated into a score in a pre-operative setting to adequately inform patient of risks and plan perioperative resources accordingly.

INTRODUCTION

Improvements to techniques, perioperative care and immunosuppression have resulted in improved outcomes following liver transplantation (LT). This has then led to the expansion of life-saving transplants to include patients who may have been previously considered too high risk including re-do transplantation, cholangiocarcinoma and portal vein thrombosis [1]. These factors add complexity to an already technically demanding procedure, the nature of which is poorly defined in literature. In most LT centres, patients are routinely screened pre-operatively for presumed high risk variables such as prior abdominal surgery, re-transplantation and anatomical variances but there is no standardised or quantifiable assessment of surgical difficulty.

Attempts to define and quantify risk factors leading to surgical difficulty in LT have been limited and yielded discordant findings. Azoulay et al. offered a definition of difficulty based on intraoperative metrics and identified a number of associated risk factors both pre-operative (previous abdominal surgery and ICU-bound at time of transplant) as well as intraoperative (split-graft use, non-standard arterial reconstruction and porto-systemic shunt ligation) [2]. Whilst these factors potentially predict poorer outcomes, interpreting their utility in the pre-operative setting is limited and was based only on first-transplant liver-only patients, negating many of the highly complex cases now performed. Another group, Ausania et al. identified re-transplantation, prior upper abdominal surgery, planned thrombectomy, prior spontaneous bacterial peritonitis and variceal bleeding as objective predictors for difficulty [3]. These factors were implemented into a score with pre-operative utility, providing a cut-off for patients who are likely to be low risk – however it is arguably the ability to predict high-difficulty cases requiring additional intraoperative resources which would be of highest utility.

Despite these known risks, the selection and prioritisation of patients for LT is still primarily guided by medical factors such as the Model for End-Stage Liver Disease (MELD) score which remains the standard for organ allocation [4]. Whilst MELD can predict short-term mortality [5], it utilises only biochemical laboratory variables and does not account for the technical nuances and intraoperative risks associated with transplantation. Two patients with similar MELD scores can differ vastly in their

surgical risk profile and as such, can oversimplify and under-recognise high-risk cases in surgical planning, which do not currently have any objective criteria to guide risk stratification.

This gap underpins the need for adjunctive tools to better capture and stratify surgical complexity. The ability to accurately predict cases with significant intraoperative difficulty is of utmost importance – particularly in perioperative planning, optimising post-operative outcomes and potentially patient and organ allocation. We aimed to stratify difficulty and quantify risks predictive of technical complexity in LT to aid in these parameters.

PATIENTS AND METHODS

All consecutive transplants performed by eight experienced transplant surgeons between January 2012 and July 2023 at our high-volume transplant centre (Royal Prince Alfred Hospital) were considered for this study. Data were collected retrospectively from chart review and a prospectively maintained database. Patients at our centre typically undergo transplant assessment prior to discussion at a multidisciplinary meeting prior to listing. Patients deemed to be at unacceptable risk based on limited benefit of transplantation, anaesthetic or surgical risk were declined according to Transplantation Society of Australia and New Zealand (TSANZ) guidelines. Patients undergoing whole and split-liver deceased donor transplantation were included, as were patients undergoing simultaneous multi-organ transplants (kidney-liver, kidney-liver-pancreas and liver-lung). No patients in our cohort underwent living donor transplantation. The study was conducted in accordance with the ethical principles stipulated by the Declaration of Helsinki and reviewed and approved with a waiver of consent by the institutional Human Research Ethics Committee.

Surgical technique

LT was carried out in a manner at the discretion of the operating transplant surgeon. Typically, this was through an upper mid-line laparotomy with right sub-costal extension with or without left sub-costal extension. No veno-venous bypass or portosystemic shunting was employed. Hepatic arteries

were ligated before portal venous clamping, and any portal vein thrombectomy was performed at this time. Most transplants were performed with en-bloc removal of the IVC and bicaval end to end anastomosis, however some surgeons employed end-to side cavo-cavostomy (piggy-back) and some employed side to side cavo-cavostomy unless en-bloc IVC resection was required due to a close tumour or intraoperative IVC damage. Re-vascularisation was mostly portal vein first after an end-to-end anastomosis, followed by the arterial anastomosis and arterial re-vascularisation. Some cases at the discretion of the surgeon were revascularized on vein and artery at the same time. Direct end-to-end common bile duct anastomosis was performed unless hepatico-jejunostomy was indicated. A dedicated transplant anaesthesia team managed the patient intraoperatively with thromboelastometry used to guide blood product transfusion.

Study definitions, variables and outcomes

In order to determine surgical difficulty retrospectively, we devised an index based on three surrogate variables which were determined to be empirically important and available; operating time (OT), estimated blood loss (EBL) and surgical intraoperative complication (IC). These variables were utilised to stratify the study patients into low, intermediate and high difficulty LT. The primary outcome of the study was to examine pre-operative variables which could reliably predict whether a liver transplant was associated with surgical difficulty as defined by the difficulty index.

OT was measured in minutes and were subdivided into total operating time (skin incision to closure), hepatectomy time (skin incision to liver out), implantation time (liver out to arterial reperfusion) and closure time (arterial reperfusion to skin closure - used for bile duct anastomosis and bleeding control). Patients who underwent multiple procedures (such as combined liver-kidney transplant) included only the liver transplant portion of the operation in their total operating time, from skin incision to completion of implantation and not necessarily to skin closure. EBL was measured as a combination of transfusion requirements - volume of red cell transfusion plus volume of cell salvage returned to patient, measured in mL. IC was defined as any unexpected intraoperative deviation from the standard technique, including delayed closure, unplanned hepaticojejunostomy and unplanned venous or arterial jump grafts

which would typically demand the presence of an additional surgeon. Non-surgical intraoperative complications such as reperfusion hyperkalaemia cardiac arrest were therefore not included. Ultimately, we aimed to present a definition which would adequately represent cases that require specific additional resources or needs and therefore any predictors of difficulty could reliably guide peri-operative planning.

Percentiles were calculated for OT and EBL and patients were designated points based on their total OT, EBL and IC – 1 point for patients who were ≥50th percentile and 2 points for patients ≥75th percentile. Patients were designated 1 point for any defined intraoperative surgical complication. Patients with 0 points were indexed as low difficulty (LD), 1 – 2 as intermediate difficulty (ID) and 3 – 5 as high difficulty (HD).

All patients were analysed for pre-operative demographic (age, sex, body mass index [BMI], Charlson Comorbidity Index [CCI], disposition, transplant indication, Model for End-Stage Liver Disease [MELD] score), biochemical (serum haemoglobin, platelet, fibrinogen, bilirubin, liver enzymes, albumin and creatinine), surgical (previous abdominal surgery – delineated by anatomical location, approach and number, prior SBP, prior treatment for HCC, re-do transplantation), radiological (presence of PVT, spleen and liver diameter) and transplantation characteristics (multi-organ, split-liver, concomitant surgery, donor type, age).

Secondary outcomes measured included intensive care unit (ICU) and total length of stay as well as 30-day complications, defined by the Clavien-Dindo classification [6]. We also measured graft failure and mortality rates with all transplants included in the study having minimum follow up of 1-year.

Statistical analysis

Continuous variables were expressed as means/standard deviations and medians/interquartile ranges as appropriate whilst categorical variables were expressed with frequencies and proportions. Univariate analysis was performed using one-way ANOVA for continuous variables and Chi-square tests were for categorical variables, with p-values <0.05 considered statistically significant. Variables with significant

association in predicting the endpoint of surgical difficulty on univariate analysis ($p < 0.1$) were included in multinomial logistic regression analysis to account for covariates and expressed as adjusted odds ratios (aOR). All statistical analysis was performed using Statistical Package for Social Science (SPSS version 29.0, IBM, USA).

RESULTS

A total of 771 transplants performed on 742 patients were included in our study. Baseline demographic, biochemical and surgical parameters are recorded, which were all considered potential factors contributing to surgical difficulty and included in statistical analysis. Median and 75th percentiles were calculated for each surrogate variable of EBL, OT and IC and patients were subsequently stratified based on their point allocation as defined by Table 1.

Primary Outcomes

A total of 220 transplants were stratified into the LD category, 351 into ID and 200 into HD. There were no significant differences noted between groups in terms of baseline demographic characteristics including age, sex, transplant indication, BMI, CCI, donor type or multi-organ transplantation (Table 2). Re-transplantation was performed in a total 45 cases, with 39 patients undergoing second transplant and 6 patients undergoing third transplantation.

Univariate analysis revealed a number of factors associated with difficulty, displayed in Table 3, including MELD score (HD 22 vs ID 19 vs LD 18, $p<0.001$; OR 2.74 (95% CI 1.83 – 4.10) [MELD > 24]), platelet count (HD 72x10^9 vs ID 81 vs LD 84, $p=0.018$; OR 1.63 (1.09 – 2.46) [PLT < 100]), bilirubin (HD 76 vs ID 63 vs LD 55 umol/L, $p<0.001$; OR 1.48 (0.98 – 2.23) [Bili > 100]), presence of PVT on imaging (HD 13.0% vs ID 8.0% vs LD 6.4%, $p=0.017$; OR 5.45 (2.20 – 13.55), previous SBP (HD 9.0% vs ID 5.1% vs LD 2.7%, $p=0.017$, OR 3.61 (1.40 – 9.28)) and disposition (hospital bound, HR 31.5% vs IR 20.5% vs LR 18.2%, $p<0.001$; OR 2.01 (1.37 – 2.97) [any hospitalisation]).

Surgical history was associated with intraoperative difficulty including type (prior open hepatobiliary surgery, HD 33% vs ID 22.5% vs LD 13.6%, p<0.001; OR 3.63 (2.03 – 6.49)) and method of entry (open, HD 37.5% vs ID 26.2% vs LD 15.5%, p<0.001). Re-transplantation was also associated with surgical difficulty (HD 10.5% vs ID 5.7% vs LD1.8%, p<0.001; OR 6.48 (2.19 – 19.23)). No donor factors demonstrated an independent effect on intraoperative LT difficulty.

Four independent variables were identified as predictors of difficult surgery on multivariable analysis, shown in Table 3; multiple prior abdominal surgical procedures (>1; adjusted OR [aOR] 1.92, CI 1.02–3.61, p<0.05), prior open hepatobiliary surgery (independent of prior LT; aOR 3.86, CI 1.76-8.46, p<0.001), re-transplantation (aOR 5.89, CI 1.77-19.51, p<0.05) and prior SBP (aOR 3.04, CI 1.14-8.08, p<0.05). The overall model was statistically significant (X^2=89.05, R^2=0.116, p<0.001) and goodness of fit test confirmed on Pearson and Deviance Test.

Secondary Outcomes

Difficulty groups were further analysed for their outcomes and displayed in Table 4. Overall survival (OS) was lower and graft failure (GF) higher at 1-year in the HD group (OS; HD 85.5% vs ID 93.7% vs LD 96.4%, log-rank Mantel-Cox p<0.001; GF; HD 6.5% vs ID 2.0% vs LD 0.9%, log-rank Mantel-Cox p <0.001). Kaplan-Meier curves demonstrating OS and GF at 1-year post-LT are displayed in Figure 1 and 2 respectively.

Re-operation rates also differed between groups, with HD associated with the highest rates at 33.5% (compared to ID 16.5% and LD 11.8%). Patients in the HD group had longer total hospital stays (HD 22 vs ID 18 vs LD 18 days, p<0.001) without significant differences in ICU specific length of stay.

Subdivided operating times of hepatectomy, implantation and closure were also compared between difficulty cohorts to determine if a particular phase of the operation was particularly affected in high difficulty surgery (Table 5). All phases were significantly prolonged in the HD group (hepatectomy 180 min [HD] vs 95 min [LD]; implantation 97 min [HD] vs 60 min [LD]; closure 192 min [HD] vs 106 min [LD]).

Risk Score

Utilising the results from multinomial logistic regression, we assigned points to each risk variable corresponding to the coefficient. Ultimately, we devised a score to identify both patients at increased risk of high difficulty surgery as well as those who were not likely to have intraoperative difficulty (Table 6). We performed receiver operating characteristic (ROC) curve analysis to determine the accuracy of our proposed score with an area under the curve of 0.65. Coordinates generated from the ROC curve provided values of sensitivity and specificity from which we calculated negative (NPV) and positive predictive values (PPV) for each corresponding score (Table 7). Overall, a score of less than 2 (or absence of any risk factors) predicts with 78.84% NPV against possibility of high difficulty LT and a score of 10 or more predicts with 98.13% PPV of risk of high difficulty only LT.

DISCUSSION

Our results ultimately reveal four major variables as strong predictors for significant intraoperative difficulty in LT: *multiple previous abdominal procedures*, *prior open hepatobiliary surgery, prior liver transplantation*, and *prior spontaneous bacterial peritonitis*. Predicting the patient who will be difficult intraoperatively has until now been chiefly reliant on clinical judgement. Our findings provide utility in the pre-operative setting to allow transplant teams to assess patients by ruling in and out with relative confidence risk of surgical difficulty. This is the largest patient cohort assessed for surgical difficulty in LT to date.

Unlike previously proposed measures [3], our score utilises a range, rather than a strict cut-off, which can safely predict those patients who are very unlikely to present surgical difficulty (therefore avoiding any additional preparations) as well as those who are very likely to be intraoperatively difficult. Notably, no patient in out cohort exhibited all four identified high-risk characteristics. In our proposed scoring system, a score of < 2 (or absence of any risk factors) predicts with nearly 80% certainty against high difficulty surgery, whilst a score of ≥ 10 is highly predictive of high difficulty surgery. Practically, this

should allow transplant teams to efficiently differentiate patients who will likely require additional support and resources intraoperatively. Patients with an equivocal score (between 2 and 10, i.e. 1-2 risk variables present) should have discussions around potentially increased risks.

More importantly, our results have established that patients with high surgical difficulty in LT are a cohort who are at risk of unfavourable outcomes, with worse short-term overall and graft survival, prolonged hospitalisation and risk of significant complications. Patients identified as high risk should therefore have every effort made to optimise peri-operative care. Specifically, this could include the allocation of an experienced senior surgeon and a second surgeon on standby for high-risk cases, which has potentially shown a reduction in complications and need reintervention [7, 8] and preparing blood banks and anaesthetic teams to time and stock adequate blood products in advance. Ideally, high risk cases should also be carried out in optimised conditions, including daylight hours, to mitigate complication rates [9]. Finally, our results may allow transplant teams to risk stratify organ allocation in the decision to accept marginal donors – patients at risk of surgical difficulty and consequently longer operating times may not be suitable for marginal grafts which could be subject to further ischemic insults. If marginal grafts are to be safely used in these cases, they will likely need to be optimised supporting the need for access to machine perfusion [10].

Overall, our data demonstrates concordance with previous studies in identifying prior abdominal surgery, re-transplantation and SBP as strong predictors for intraoperative difficulty in LT [2, 3]. Unsurprisingly, re-do LT represents the highest risk for intraoperative difficulty, with nearly six-fold increased odds compared to no prior transplant (OR 5.89, 95%CI 1.77-19.51, $p<0.05$), and these findings are concordant with prior studies [11]. These cases present significant surgical challenge as a result of potentially unexpected anatomy, adhesions and viability of vessels for reimplantation and are associated with increased morbidity and mortality [12-14]. Both prior surgery and SBP [15] are also associated with the formation of visceral adhesions which can contribute to prolonging hepatectomy as well as blood loss, correlating with our results [16, 17].

We refined ‘prior abdominal surgery’, acknowledging the breath of procedures this represents in our cohort, deeming it poorly representative that all such procedures were treated as equivalent entities in terms of their contribution to intraoperative LT difficulty. We stratified prior abdominal surgery by anatomical location (hepatic, biliary, upper abdominal and other) and method of entry (open or minimally invasive) with the expectation that minimally invasive procedures distant to LT would have reduced impact on the LT operation, a hypothesis supported in other literature [18-20]. Our findings were consistent, with both open and hepatobiliary surgical history along with multiple abdominal entries independently predicting surgical difficulty. We excluded re-transplantation within this variable to ensure no collinearity –results demonstrating that any patients who have previously undergone open hepatobiliary surgery, regardless of prior transplant status, are at a three-fold increase in odds of intraoperative difficulty at LT. Routine pre-operative cross-sectional multiphase CT were also reviewed, given prior associations between portal venous thrombosis and requirement for thrombectomy with difficult transplant [2, 3, 21]. However, whilst we found significant association on univariate analysis (HR 13% vs LR 2.7%; IR 7.8%, $p<0.001$), these results were not significant on multivariate analysis (OR 1.26, 95%CI 0.61-2.60, $p=0.54$). This may reflect the relatively small cohort of patients at our facility who had undergone LT with concurrent PVT.

Ultimately, our results provide a useful predictor of intraoperative complexity for transplant teams. These results offer a valuable insight in shared decision-making between clinicians and patients, particularly in quantifying and individualising patient risks and setting expectations for patients in their recovery – which can be used in addition to traditional discussions which may have centred around MELD-estimated survival benefit.

The main limitations of this study are inherent to its retrospective design and risk factors remain observational. There may be potential candidates whose risk was determined to be excessive and excluded from transplant and therefore this study’s results cannot be extrapolated to determine futility. Our surrogates for difficulty are ultimately arbitrary and much debate has surrounded the ideal definition of a difficult transplant, though similar metrics have been previously used [18, 22]. We utilised transfusion requirements in our definition as this was thought to have the greatest impact in

perioperative care and assist in predicting requirements of blood bank and use of cell salvage. This variable may be impacted by pre-existing coagulopathy, but our results did not find any significant associations between biochemical indicators for coagulopathy with difficulty.

Future studies should test the validity of our proposed score by prospectively risk stratifying and comparing against intraoperative difficulty to determine its true accuracy and utility in other transplant cohorts. The score could also be compared against clinically perceived high-risk cases to determine if it outperforms surgeon clinical judgement. Efforts should also be made to investigate methods of mitigating these identified risks; although variables such as re-do transplantation and abdominal surgery are not modifiable, there may be a role in delaying LT to reduce the impact of adhesions [23]. Any randomised trials investigating risk-mitigating interventions should correlate changes to intraoperative difficulty with short and long-term post-operative outcomes, including survival.

CONCLUSION

Surgical difficulty in LT is associated with poorer outcomes including worse early graft and patient survival. Four variables have been quantified to be predictive of high risk for difficult LT and should be considered in transplant assessments to aid perioperative planning, risk/outcome discussions and resource allocation.

TABLES AND FIGURES

Table 1 – Cutoff percentile values for surrogate measures of difficulty with corresponding point allocations. Points were allocated once for each category. ≤ 50th percentiles in any category were allocated 0 points.

Surrogate	**Percentile values**		
	≤ 50th percentile	**> 50th percentile**	**> 75th percentile**
Estimated blood loss (*mL*, packed cell transfusion + cell salvage)	< 1707	1707	3109
Total operating time (*min*)	< 338	338	411
Intraoperative complication	N/A	Unplanned surgical complication (delayed closure, jump-graft, hepaticojejunostomy)	N/A
Point allocation	**0**	**1**	**2**

Table 2 –Baseline and pre-operative factors stratified by difficulty cohorts. All continuous variables are reported as median (IQR) unless otherwise specified.

Pre-operative variables	**Difficulty Cohorts**	***p value***

	Low **(0)**	**Intermediate** **(1-2)**	**High** **(3-5)**	
n	220	351	200	
Age, years	57 (15)	56 (12.6)	56 (11.8)	0.580
Male sex, *n* (%)	144 (65.5)	248 (70.7)	138 (69.0)	0.426
Indication for transplantation Alcohol-related liver disease Hepatocellular carcinoma Hepatitis C Metabolic dysfunction-associated steatotic liver disease Primary sclerosing cholangitis Hepatitis B Other	 37 (16.8) 43 (19.5) 30 (13.6) 18 (8.2) 18 (8.2) 11 (5.0) 63 (28.6)	 67 (19.1) 54 (15.4) 54 (15.4) 53 (15.1) 30 (8.5) 16 (4.6) 78 (22.2)	 43 (21.5) 29 (14.5) 32 (16.0) 23 (11.5) 14 (7.0) 14 (7.0) 46 (23.0)	0.635
BMI, kg/m^2	27 (7)	29 (6.8)	29 (5.8)	0.676
MELD Score	18 (9)	19 (11)	22 (12.3)	**< 0.001**
Charlson Co-morbidity Index	5 (3)	5 (2)	5 (2)	0.056

Haemoglobin, g/L	113 (32)	112 (34)	110 (33)	0.248
Platelet count, $x10^9$/L	84 (78)	81 (71)	72 (60)	**0.018**
Fibrinogen, g/L	2 (1.4)	2 (1.5)	2 (1.1)	**0.005**
Bilirubin, umol/L	55 (96)	63 (106)	76 (119)	**< 0.001**
AST, U/L	68 (75)	70 (72)	67 (57)	0.313
ALT, U/L	44 (58)	49 (55)	48 (51)	0.101
Albumin, g/L	34 (10)	32 (10)	33 (9)	0.570
Creatinine, umol/L	75 (29)	78 (33)	81 (40)	0.630
Portal venous thrombosis on imaging, *n* (%)	14 (6.4)	28 (8.0)	26 (13.0)	**0.017**
Spleen diameter on imaging, mm	150 (42)	158 (46)	160 (40)	0.161
Liver diameter on imaging, mm	160 (35)	150 (52)	232 (103.5)	**0.012**
Any prior abdominal surgery, *n* (%)	71 (32.3)	159 (45.3)	104 (52.0)	**< 0.001**
Number of prior abdominal surgical procedures, n	0 (1)	0 (1)	1 (1)	**< 0.001**
Type of prior abdominal surgery, *n, %*				

Any open hepatobiliary	13 (5.9)	30 (8.5)	28 (14.0)	**0.023**
Any hepatobiliary	30 (13.6)	79 (22.5)	66 (33.0)	**< 0.001**
Method of surgical entry, *n* (%)				**< 0.001**
Open	34 (15.5)	92 (26.2)	75 (37.5)	
Laparoscopic	31 (14.1)	61 (17.4)	27 (13.5)	
Re-transplantation, *n* (%)	4 (1.8)	20 (5.7)	21 (10.5)	**0.001**
Other minimally invasive treatments, *n* (%)	72 (32.7)	90 (25.6)	40 (20)	0.066
Prior spontaneous bacterial peritonitis, *n* (%)	6 (2.7)	18 (5.1)	18 (9.0)	**0.017**
Disposition at transplant, *n* (%)				**< 0.001**
Home	138 (62.7)	192 (54.7)	90 (45.0)	
Occasional inpatient	23 (10.5)	53 (15.1)	21 (10.5)	
Hospital bound	40 (18.2)	72 (20.5)	63 (31.5)	
ICU	19 (8.6)	34 (9.7)	26 (13.0)	
Multi-organ transplant, *n* (%)				0.725
Liver only	207 (94.1)	337 (96.0)	187 (93.5)	
Liver-Kidney	11 (5.0)	10 (2.8)	14 (7.0)	

Liver-Pancreas-Kidney Liver-Other	0 (0) 2 (0.9)	1 (0.3) 3 (0.9)	0 (7.0) 0 (7.0)	
Split-liver donor, *n* (%)	38 (17.3)	37 (10.5)	35 (17.5)	**0.026**
Donor type, DBD, *n* (%)	205 (93.2)	325 (92.6)	183 (91.5)	0.804
Donor age, years	47 (27)	50 (29)	47 (28)	0.246
Donor BMI, kg/m^2	26 (6.6)	26 (5)	25 (6)	0.250

Table 3 – Predictors of high surgical difficulty (HD vs LD) on univariate and multivariate logistic regression

	Univariate		**Multivariate**	
Variable	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Male sex	1.17 (0.78 – 1.77)	0.44		
MELD (> 24)	2.74 (1.83 – 4.10)	< 0.001	1.60 **(**0.84 – 3.07)	0.153
Platelets (< 100)	1.63 (1.09 – 2.46)	0.018	1.00 (0.99 – 1.00)	0.133
Bilirubin (> 100)	1.48 (0.98 – 2.23)	< 0.001	1.00 (1.00 – 1.00)	0.062
Fibrinogen (> 2.3)	2.27 (1.50 – 3.44)	0.005	0.82 (0.66 – 1.00)	0.060

Disposition at transplant (any hospitalisation)	2.01 (1.37 – 2.97)	< 0.001	1.24 (0.58 – 2.69)	0.579
Multi-organ transplant	0.90 (0.41 – 2.00)	0.80		
Multiple prior abdominal surgery (> 1)	2.94 (1.68 – 5.13)	< 0.001	**1.94 (1.03 – 3.65)**	**0.039**
Prior open hepatobiliary surgery (excl. transplant)	3.63 (2.03 – 6.49)	< 0.001	**3.86 (1.76 – 8.46)**	**< 0.001**
Other minimally invasive procedures	1.95 (1.25 – 3.04)	0.004	1.28 (0.85 – 1.93)	0.231
Re-transplantation	6.48 (2.19 – 19.23)	< 0.001	**5.89 (1.77 – 19.51)**	**0.004**
Prior spontaneous bacterial peritonitis	3.61 (1.40 – 9.28)	0.008	**3.04 (1.14 – 8.08)**	**0.030**
Portal venous thrombosis on imaging	5.45 (2.20 – 13.55)	< 0.001	1.26 (0.61 – 2.60)	0.542
Split-liver donor	1.02 (0.61 – 1.68)	0.95		
Donor type (DBD)	0.79 (0.38 – 1.62)	0.52		

OR – odds ratio; DBD - donor after brain death

Table 4 – Secondary outcomes stratified by difficulty groups.

Outcome	**Difficulty Cohorts**			***p value***
	Low (0)	**Intermediate (1-2)**	**High (3-5)**	

n	220	351	200	
Graft failure, *n* (%)				
1-year	2 (0.9)	7 (2.0)	13 (6.5)	**0.001**
2-years	2 (0.9)	8 (2.3)	13 (6.5)	
Death, any cause, *n* (%)				
1-year	8 (3.6)	22 (6.3)	29 (14.5)	**< 0.001**
2-year	11 (5.0)	29 (8.3)	31 (15.5)	
Return to OT, within 30 days, *n* (%)	26 (11.8)	52 (14.8)	67 (33.5)	**< 0.001**
Length of stay, days (IQR)				
ICU-specific	4 (4)	5 (4)	6 (6)	0.261
Ward	13 (13)	12 (12)	14 (18)	**< 0.001**
Total	18 (15)	18 (13)	22 (21)	**< 0.001**

Table 5 – Univariate analysis of subdivided phases of operating time across difficulty groups.

Variable	**HD**	**ID**	**LD**	**Total**	**MD (HD vs LD)**	**MD (%)**	***p***
Hepatectomy	180.2	128.8	94.9	132.6	85.2	64.3	< 0.001

Reperfusion	98.6	72.6	60.1	75.2	36.5	48.5	< 0.001
Closure	191.7	143.3	105.9	145.3	85.8	59.1	< 0.001

HD – high difficulty; ID – intermediate difficulty; LD – low difficulty; MD - mean difference

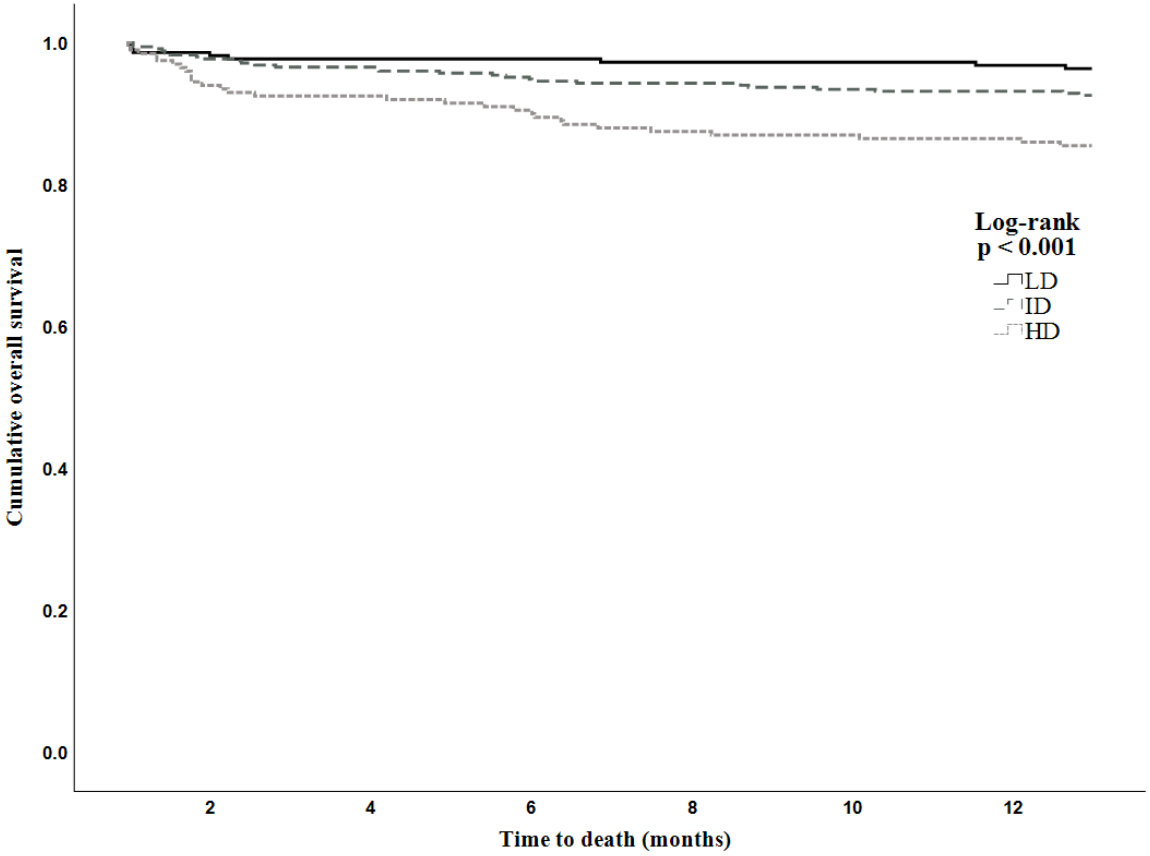
Table 6 – Odds ratios for high-difficulty LT on multinomial logistic regression, with score allocations are derived from the coefficients of the lower limit of confidence intervals of odds ratios.

Variable	**Odds ratio**	**95% CI**	***p value***	**Score**
Multiple prior abdominal surgery (> 1)	1.94	1.03 – 3.65	0.039	2
Prior open hepatobiliary surgery (excl. transplant)	3.86	1.76 – 8.46	< 0.001	4
Re-transplantation	5.89	1.77 – 19.51	0.004	6
Prior spontaneous bacterial peritonitis	3.04	1.14 – 8.08	0.030	3
MELD > 24	1.60	0.84 – 3.07	0.153	N/A
Portal venous thrombosis on imaging	1.26	0.61 – 2.60	0.542	N/A
Maximum score = 15				

Table 7 – Sensitivity, specificity, negative (NPV) and positive predictive values (PPV) for the LT-difficulty risk score

Score	Sensitivity	Specificity	NPV	PPV
2	41.0	77.0	78.84	38.44
3	33.0	84.1	78.18	42.09
4	25.0	87.7	76.95	41.59
5	20.0	91.4	76.54	44.89
6	19.0	91.9	76.41	45.1
7 – 9	6.0	98.1	74.87	52.52
≥ 10	1.5	99.99	74.35	98.13

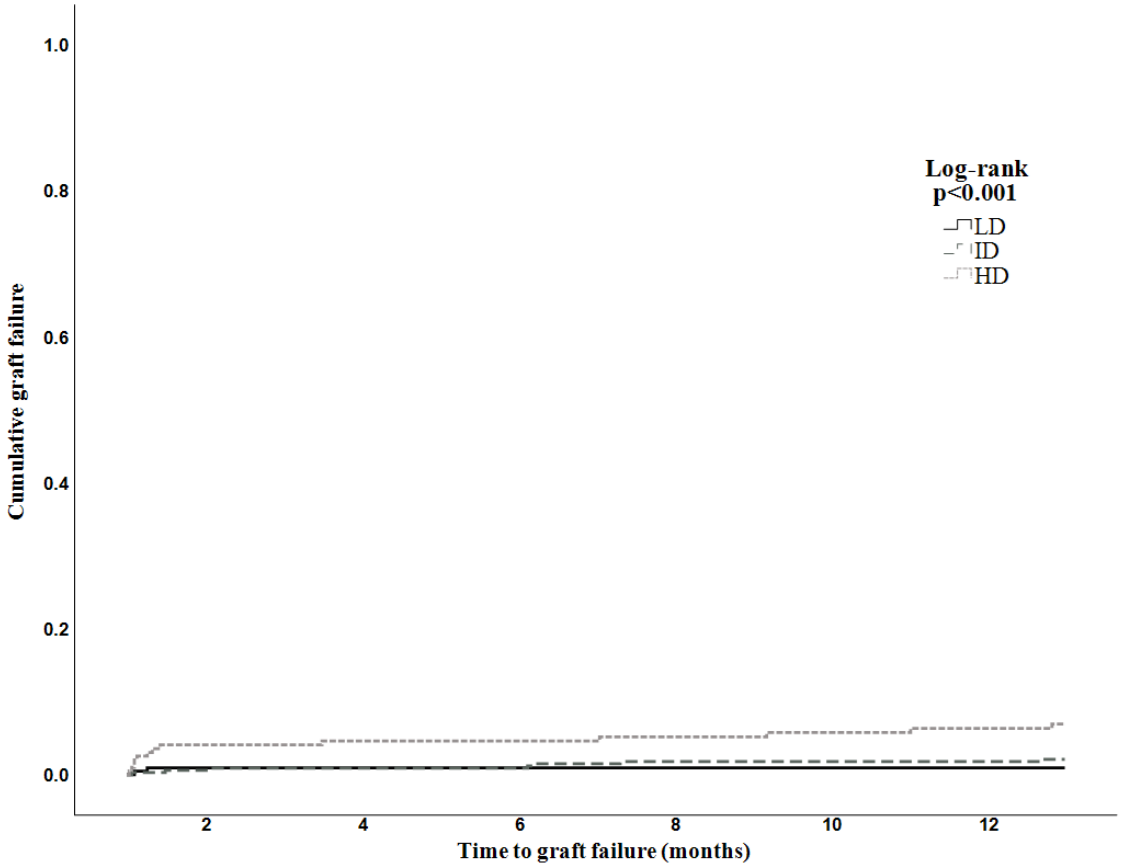
Figure 1 – Kaplan-Meier curve of overall survival at 1-year post-LT compared between difficulty groups



Patients at risk

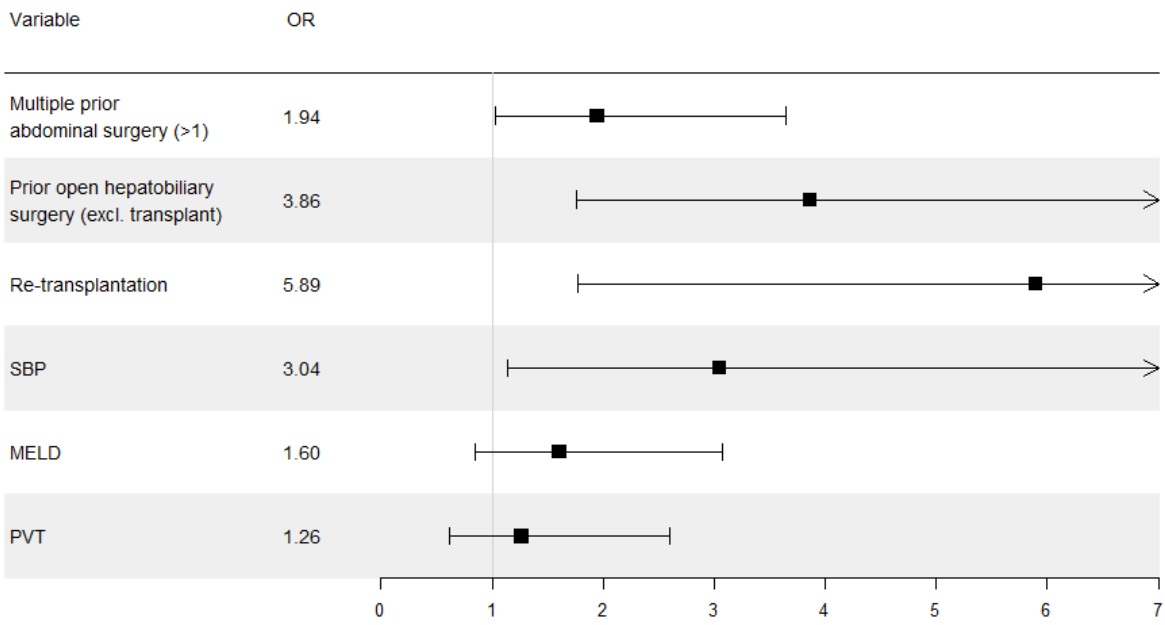
LD	220	215	215	214	214	214	106
ID	351	339	336	331	329	327	163
HD	200	185	184	176	174	173	86

Figure 2 – Kaplan-Meier curve of graft failure at 1-year post-LT compared between difficulty groups



Patients at risk							
LD	220	213	213	211	211	211	105
ID	351	336	333	326	323	321	160
HD	200	177	175	167	164	162	80

Figure 3 – Forest plot of odds ratios for high difficulty LT on multinomial logistic regression



SBP = spontaneous bacterial peritonitis; MELD = model for end-stage liver disease; PVT = portal venous thrombosis

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IV. Concluding remarks

Summary of findings

Throughout this thesis, an in-depth exploration into the aspects which contribute to surgical difficulty in LT has been performed. In Chapter I, a discussion into the ethical principles of transplant assessment in LT and the need behind maximising the outcomes of these precious organs underpins the rationale of the investigations carried out in the remainder of the thesis. This was followed by Chapter II, an extensive narrative review into current literature surrounding surgical assessment and prediction of difficulty in LT. A discussion surrounding how one of the major risk factors, prior abdominal surgery, was poorly delineated drove the retrospective study performed in Chapter III. The study and analysis performed in Chapter IV summates these findings by identifying several important and key risk factors in difficult surgery, incorporating them into a scoring system which can be utilised in a pre-operative assessment context.

From these findings we have addressed the need for an objective and quantitative framework to perform surgical risk assessment in the pre-operative setting for LT. The identified risk factors of *multiple previous abdominal procedures*, *prior open hepatobiliary surgery, prior liver transplantation*, and *prior spontaneous bacterial peritonitis* and their corresponding risk scores should be closely evaluated for in all future LT workup assessments. Most importantly, these patients represent a cohort of transplants who are at significant risk of detrimental outcomes including lower overall short-term survival, higher rates of graft failure, extended hospitalisation and increased requirements for re-intervention.

The ability to delineate both cases which are of extremely high risk as well as those who are relatively low risk should also provide practical utility. High risk cases warrant allocation of additional resources to support likely intraoperative difficulties, which may be represented by all facets of the transplant team – second surgeon available, blood bank stockpiling and cell-salvage, experienced anaesthetic and nursing operating room staff and transplant familiar ICU teams. Cases expected to be low risk may be conversely utilised as training cases or in rare cases of simultaneous transplant within one centre be

prioritised so as to not cause undue systematic stresses. Logistical considerations of transportation and cold ischemia/preservation time can also be guided by the findings of this score.

In addition to these practical considerations, at a minimum, these results should shape discussions and conversations between transplant clinicians, patients and their stakeholders. Ultimately, patients with elevated risk of intraoperative difficulty in LT need to be well informed, both of the fact itself and of its potential consequences to recovery.

Future directions

The findings from this thesis alone clearly provide sufficient evidence and utility to support peri-operative decision making in LT. However as with all data which has any real-world clinical application, our results should generate more questions and hypotheticals than the ones initially being attempted to be answered.

Should and do our results alter the algorithm in which potential recipients of LT are listed for transplantation, including how these patients are assess on their perceived benefit and expected life expectancy? Are there better criteria, given that some patients are clearly exposed to much greater surgical risks, which can guide which organs are appropriate for each patient, based on their risk profile? Should patients with significantly elevated surgical risk be reconsidered for transplant, given they will have potentially worse outcomes and reduced survival? What measures can be taken to reduce the harms which can occur to patients who are surgically difficult in order to maximise their long-term results and extract the greatest benefit from the invaluable resource that is a donated liver? How well are we informing patients, families and their relevant stakeholders at present with respect to their expected outcomes, time in hospital, further interventions and trajectory of recovery? These are questions which are best served answered by future studies and investigations, which can incorporate the exciting and perpetually evolving face of transplantation research, such as developments in normothermic machine perfusion, alternative treatments for hepatitis B and improvements in immunosuppression.

The predictive risk factors and score devised from this thesis will warrant testing in a clinical context for validation prior to widespread usage. In future studies, the devised risk assessment score can be prospectively applied to other liver transplant cohorts, as well as compared to standard subjective, surgeon-based assessments to evaluate its predictive ability and utility. Irrespective of this, patients and transplant teams can now be better informed of outcomes, either in the absence or presence of these risk factors.

Finally, beyond objective measures of failures and successes in LT lies a human and their experiences. Many studies in transplantation are focused on the survival outcomes of both patient and graft, but, given the far-reaching stakeholders in transplantation and the propensity for difficult surgery to impact said patients, there is a need to maintain and demonstrate its impact on quality of life. Future studies should include metrics of quality of life and patient reported outcomes, which can further inform the patient undergoing LT.

Conclusion

Ultimately, the complex interplay of factors contributing to a successful liver transplant cannot be completely resolved by an all-encompassing score or guideline. Patients requiring this life-saving treatment require individualised assessment and multidisciplinary input. Regardless, the findings of this thesis identify significant factors which, whether utilised to inform risk, guide resource management or determine listing need to be considered and addressed in a pre-operative setting prior to embarking on transplantation.

Appendices

Appendix I: Visual abstract

Predicting surgical difficulty in liver transplant – a scoring system to predict risk. Visual abstract accompaniment to Chapter IV for submission to *Transplantation*.