**ORIGINAL ARTCILE**

The Southampton Laparoscopic Liver Score: The development and validation of a European multi-centre model to pre-operatively estimate the risk of intra-operative complications during laparoscopic liver resection.

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**ABSTRACT**

**Objective:** To develop and validate a prognostic model for the risk of intra-operative complications during laparoscopic liver resections.

**Background:** There is significant variation in the technical difficulty of laparoscopic liver resections. Previous studies have demonstrated that patient, surgical, tumour and operative variables affect the complexity of laparoscopic liver resections however current difficulty scoring systems only address tumour factors.

**Method:** The prospectively maintained databases of seven European tertiary referral liver centres were compiled for the development and validation of the model. Intra-operative complications were based upon a modified Satava classification. Using the methodology of the Framington Heart Study factors found to independently predict intra-operative complications were attributed points and grouped to represent low, moderate and high risk.

**Results:** Neo-adjuvant chemotherapy, lesion type & size, resection classification and previous open liver resections were found to be independent predictors of intra-operative complications. Those with intra-operative complications had longer hospital stays (4 days vs 5 days p<0.001), a higher complication rates 15.5% vs 32.5% (p<0.001), 30-day mortality 0.3% vs 3.0% (p<0.001) and 90-day mortality 0.8% vs 3.8% (p<0.001). The model was able to predict intra-operative complications (AUC=0.677 (95% C.I. 0.647 – 0.706)) as well as post-operative mortality (Score vs 90-day mortality AUC=0.769 (95% C.I. 0.681 – 0.858)).

**Conclusion:** A comprehensive scoring system based upon patient, surgical and tumour factors from a large, multi-centre, European database has been developed and internally validated that can estimate the risk of intra-operative complications and may aid case selection.

**INTRODUCTION**

Laparoscopic liver surgery (LLS) has been demonstrated to reduce intra-operative blood loss, hospital stay and morbidity whilst maintaining the oncological efficiency of its open counter-part at a similar financial cost (1 - 12). However, there is significant variation in the technical complexity of different procedures (13, 14) and a substantial learning curve to overcome (15 - 18). Previous literature has highlighted the need for a step-wise progression through the learning curve in order to minimise morbidity (19, 20) and this sentiment was reinforced during The European Guidelines Meeting for Laparoscopic Liver Surgery (EGMLLS) (21).

Conversion during LLS should not be viewed as a failure of the operation as in certain circumstances it is necessary for safe progression and to ensure an adequate oncological clearance. However, recent work has demonstrated that those patients whom require conversion to open surgery have significantly worse outcomes than those who have their resections completed laparoscopically. This is especially true if the cause for conversion is an emergency due to an unfavourable intra-operative event (22). Hence, case selection is of paramount importance to ensure that the difficulty of a case is matched to the experience of the surgeon, particularly during the learning curve.

In order that resections of appropriate difficulty maybe selected an objective means of pre-operative stratification of difficulty is required. Ban *et al* (2014) proposed “a novel difficulty scoring system for laparoscopic liver resection” that highlighted five factors that increase the difficulty of resection of liver neoplasms (13). However, this score was developed and validated on the subjective interpretation of difficulty of 86 laparoscopic liver resections at three separate centres by 4 different surgeons. In addition, all participants were from an Asian population with a higher incidence of cirrhosis and Hepatocellular carcinoma (HCC) and lower body mass index (BMI) than would be expected in European populations. In addition, this score has only been validated on Asian populations (23) and so it’s use in European populations should be meet with caution. Recently Kawaguchi *et al* (2017) published a classification of laparoscopic resections that incorporated the location and extent of resection and included technically complex resections as defined by Di fabio et al (14, 24). This classification groups resections by complexity to allow for case selection. However, while this study reports data from a European population it only represents a single institution and only takes into account the type of resection being performed ignoring patient and tumour factors. Whilst these scoring systems correlate well with one another – suggesting that the resection of a small peripheral lesion in the antero-lateral segments is more simple than the resection of a large lesion in the central or postero-superior segments they are both limited by only assessing tumour factors.

Using conversion as a marker of complexity multiple previous studies have highlighted several factors including increasing age; diabetes, high BMI; neo-adjuvant chemotherapy and repeated resection as increasing the complexity of laparoscopic liver surgery (22, 25 - 29). In addition, excessive blood loss has also be found to be associated with worse patient outcomes (30) and should therefore also be considered a marker of intra-operative complexity. Therefore, a large, European, multi-centre study is required to develop and validate a predictive model for the difficulty of laparoscopic liver resections incorporating all factors suggested to increase the difficulty of laparoscopic liver resections.

**AIMS**

To develop and validate a prognostic model for the complexity of laparoscopic liver resections based upon intra-operative complications in a European population that encompasses patient, surgical and tumour characteristics.

**METHODS**

Source of data: An international, multi-centre database of electronically stored, prospectively collected data of 2,856 procedures was compiled for the development and validation of the difficulty score. All consecutive patients undergoing planned pure laparoscopic liver resections, from the first implementation of laparoscopic liver resections in each of the following centres, were included: University Hospital Southampton, Southampton, United Kingdom; San Raffaele Hospital, Milan, Italy; Oslo University Hospital, Oslo, Norway; Ghent University Hospital, Ghent, Belgium; Antoine-Beclere Hospital, Paris, France; University of Navarra Hospital, Pamplona, Spain and Groeninge Hospital, Kortrijk, Belgium. Laparoscopic liver surgery was first undertaken in these centres in 2003, 1997, 1998, 1999, 1999, 2004 and 2011, respectively. Data was collected until 31st October 2016. In each centre the majority of operations were performed by a single surgeon who was responsible for the instigation of the laparoscopic liver programme within that centre and hence this dataset represents procedures from every stage of the learning curve for laparoscopic liver surgery.

Participants: The indications of laparoscopy were similar in all institutions. All patients were discussed in local multi-disciplinary meetings to assess the feasibility of the laparoscopic approach, dependent on disease characteristics, local expertise and available resources. The inclusion criteria for the study were those undergoing planned laparoscopic liver resection for benign or malignant lesions. There were no exclusion criteria based on BMI, increasing age, American Society of Anaesthesia (ASA) grade, number and distribution of lesions and resections extent. Absolute contra-indications to the laparoscopic approach included the need for vascular resection and reconstruction; the need for hepato-jejunostomy; the need for en-bloc multi-visceral resection and resections for hilar cholangiocarcinoma. Patients undergoing planned hybrid / hand-assisted resections; cyst fenestrations / biopsies; resections for living donor hepatectomy and those under 18 were not included. Surgical techniques and intraoperative management were similar in all centres. A pneumoperitoneum of 12-14mmHg and a central venous pressure less than 5cmH20 was maintained during liver transection. The postoperative management protocols were similar in all centres. The local ethics committees of each centre granted approval for the review and auditing of data for research purposes.

Data collected included: patient demographics, medical and surgical history, tumour characteristics, operative details, post-operative inpatient details and 30 and 90-day mortality.The type of resection was categorised into 3 groups (minor, technically major and anatomically major) based upon the classification from the Louisville Consensus 2008 (31) with the additional classification of technically major resections (14, 24). Technically major resections are those that anatomically would be considered minor resections (i.e. involving only 1 or 2 Couinard segments) but are located in areas of the liver that are difficult to access laparoscopically (segments 1, 4a, 7 and 8). Secondary smaller-volume liver resections were classified as concurrent procedures and this category also includes: bowel resection; stoma creation or closure; hernia repair; lymphadenectomy; nephrectomy / adrenalectomy; oophorectomy and MWA/RFA. The post-operative morbidity was based upon the most severe post-operative complication and is graded by the Clavien-Dindo Classification; grades 1-3a representing minor complications that only required medical therapies as treatment, and grades 3b-5 representing complications that required surgical intervention, the use of organ support and fatality (32).

Outcome: The objective marker of a complex operation was an intra-operative complication as per the modified Satava Classification (table 1) (33). Key markers were: blood loss over the normal range, unintentional damage to surrounding structures and conversion to hand-assisted / hybrid / open approaches to complete the operation. In order to establish “blood loss over the normal range” a co-ordinate analysis of a Receiver Operating Characteristic (ROC) curve of blood loss compared to 30-day mortality was used (area under the curve (AUC) was 0.716 (95% confidence interval (C.I.) of 0.574 to 0.857)). This demonstrated an increase in 30-day mortality that corresponded to a blood loss of 775ml and hence this value was used to stratify “normal” or “over the normal range” of blood loss. The study was based on an intension to treat basis and hence any operation planned to be completed laparoscopically was included and conversion was defined as a decision to change the operative approach to hand-assisted / hybrid or laparotomy.

Predictors: To establish which factors are currently regarded as influencing the difficulty of laparoscopic liver resections a comprehensive literature review was performed using Ovid Medline and Pubmed in July 2016. All studies in English with more than 10 patients describing “difficult” resections and those requiring “conversion” during laparoscopic liver surgery were reviewed. The results of this literature review were used to produce of an online survey of 26 factors that was sent directly to 190 established laparoscopic liver surgeons and was disseminated through the E-AHPBA website to its members (see appendix 1 for survey). The survey returned 80 responses (42% response rate) from a mixed cohort of surgeons from Europe, Northern America and Asia with a collective experience of 7,196 laparoscopic liver resections. The results demonstrated that multiple factors including patient, surgical and tumour factors altered the difficulty of laparoscopic liver resections (34) and hence all predictors of difficulty from the literature review were included in the initial univariable analysis. In order to reduce over-fitting of the predictive model factors not found to be statistically significant on univariable analysis were excluded from the subsequent multivariable analysis.

Missing data: We assumed missing data occurred in a random fashion with respect to clinical variables and hence patients were exclude in a list wise fashion prior to the multivariable analysis to allow for complete-case analysis.

Statistical analysis method: The type of resection was categorised into 3 groups: minor, technically major and anatomically major as per DeFabio *et al* (2014) (24). This categorisation was chosen above resection extent (based upon the Brisbane 2000 classification (35)) as it performed better on ROC curve analysis in its ability to predict intra-operative complications (0.632 (95% C.I. 0.605 – 0.658) compared to 0.586 (95% C.I. 0.558 – 0.614) for resection extent). Lesion size was categorised into 3 groups (<3cm, 3-5cm and >5cm) as per the Ban *et al* (2014) classification (13). All other predictors remained as binary variables.

Statistical analysis was performed using IBM SPSS Statistics version 24. Binary analysis was performed using Chi2 and / or Fisher’s Exact test. Analysis of ordinal data with binary outcomes was performed using Mann-Whitney U test. Multivariable analysis was performed using binary logistic regression. The ability of a continuous variable to predict a binary outcome (including testing of the model) was performed using AUC on ROC curve analysis. Spearman Rank correlation, Chi2 and Mann-Whitney U tests were used for analysis of outcomes. All percentages are listed to 1 decimal place and statistical significance was defined by a p value <0.05.

Model building: Univariable analysis of predictors of intra-operative complications was performed on the entire cohort (n=2856 procedures, details of patient characteristics can be found in table 2). Those that were statistically significant (p<0.05) were included in the multivariable analysis. Once the predictors for the multivariable analysis were established a case-wise deletion was performed on those with relevant missing data leaving 2,409 procedures for the subsequent analysis (See flow diagram for movement of patients through the analysis). The randomisation function in SPSS was used as per Arifin (2010) (36) to develop 2 separate cohorts – one for the development and calibration of the scoring system (n= 1,606 (two-thirds)) and a second for the internal validation (n=803 (one-third)).

Using the Framington Heart Study (37) methodology a points system was developed to estimate the risk of an intra-operative complication as it eliminates the need for the practitioner to calculate the cumulative risk (the sum of the regression coefficients multiplied by the degree of separation from the reference base value for each predictor). Using binary logistic regression a regression coefficient was established for each predictor found to be independently associated with an increased risk of an intra-operative complications. Following this predictors were given reference values. Binary variables such as “neo-adjuvant chemotherapy” were simply assigned 0 for absent and 1 for present. As lesion size was grouped the midpoint of each category was used (e.g. 1.5cm representing the midpoint of the group that contained lesions from 0.1 to 2.9cm) with an equal distribution around the midpoint of the middle category (table 3). Following this the difference in terms of regression units between each category and the base reference value was established (Bi(Wij-Wjref)) (table 3). The penultimate step was then to establish the constant (B) that would be the number of regression units that will correspond to one point (or the increased risk associated with neoadjuvant chemotherapy as this was the lowest scoring binary variable). Finally, the points associated with each predictor are established using (table 3):

Pointsij = Bi(Wij - WiREF)/B

The points are rounded to the nearest integer. Once the points system had been established the ability of this model to predict risk was tested against the predictive ability of the logistic model to ensure that no loss of accuracy had occurred (table 5). This was performed by establishing the risk associated with each score that is achieved by multiplying each point by the constant (0.294) and adding the intercept (-3.302) and the base values of the continuous risk factors (lesion size and resection classification) multiplied by their regression coefficients. Therefore the risk associated with each point score is established using (table 5):

Risk = 1 / 1 + exp ( - [-3.302 + (0.186(1.5)) + (0.583(1) + (0.294(score))])

Which can be simplified to = 1 / 1 + exp( - [-2.44 + 0.294(score)])

This same formula is then applied to the results of the logistic model (with Bi(Wij-WjREF) replacing (0.294(score)). The results demonstrated that the points system was representative of the difficulty predicted using the logistic model (table 5). Calibration was performed graphically by the comparison of actual risk of intra-operative complications with the risk predicted by the model for each score. Grouping of scores based on risk of intra-operative complications was performed following calibration into low (<0.1 risk), medium (0.1 – 0.2 risk) and high (0.2 – 0.5 risk). In addition, a further category “Extreme, not to be attempted outside of expert centres” was added to those with a risk greater than 0.5.

Following the development of the scoring system the model was internally validated using the group of patients not used in the development of the scoring system (n=803). The ability of the score to discriminate between patients who had intra-operative complications and those who did not was performed using AUC on ROC curve.

Development vs. Validation: there were no differences between the development group and validation group in terms of inclusion / exclusion criteria and the allocation to each group was performed randomly as per Arifin (2010) (36).

**RESULTS**

Patient demographics and univariable analysis of predictors for intra-operative complications can be found in table 2. Multivariable analysis of statistically significant predictors can be found in table 3. The development of the points system for independently significant predictors of intra-operative complications can be found in table 4. Testing of the ability of the score to predict risk compared to the logistic model can be found in table 5, along with “real-world” scenarios. The risk predicted by the score is graphically represented by y = 0.056x + 0.020 (r2 = 0.992) while actual risk is graphically represented by y = 0.055x – 0.057 with ((r2 = 0.611) (graph 1)). Table 6 demonstrates the post-calibration risk predicted by the score with associated grouping.

Outcome analysis (n = 2,856) demonstrated that 541 patients had operations with intra-operative complications (319 were grade 1 and 222 were grade 2 i.e. conversion to open (table 7)). Those with intra-operative complications had higher post-operative complication rates 32.5% (compared to 15.5% (p<0.001)), longer inpatient stays 5 days (compared to 4 days (p<0.001)), higher 30 day mortality 3.0% (compared to 0.3% (p<0.001)) and higher 90 day mortality 3.8% (compared to 0.8% (p<0.001)).

Testing of the model on the validation cohort (n = 803) found the AUC for score vs difficult operation to be 0.677 (95% C.I. 0.647 – 0.706), AUC for Score vs post-operative complication was 0.611 (95% C.I. 0.580 – 0.642) with increasing scores being associated with an increased frequency of complications (graph 2.). AUC for Score vs 30-day mortality 0.751 (95% C.I. 0.644 – 0.859) with co-ordinate analysis demonstrating a cut-off value of 5 which corresponds to the move from moderate to high risk procedures. Finally, AUC for Score vs 90-day mortality 0.769 (95% C.I. 0.681 – 0.858) with co-ordinate analysis also demonstrating a cut-off value of 5.

**DISCUSSION**

Laparoscopic liver surgery is currently undergoing exponential growth and we envisage that within the next few years more surgeons and centres will be expanding their practice to incorporate this approach into their services. At the EGMLLS it was stressed that the acquisition of a complex skill must be undertaken in a step-wise fashion building complexity into progressive levels until mastery is achieved (21). Traditional advice would suggest starting with minor resections and subsequently proceeding to major resections as experience increases. However, this simplification overlooks many factors that have been demonstrated to affect the difficulty of a laparoscopic liver resection. Hence a simple, objective and robust pre-operative difficulty scoring system that encompasses all the factors proven to increase the difficulty of a laparoscopic liver resection is required in order that a step-wise progression maybe adopted.

The development of the present scoring system is unlike any other as it examined all factors suggested to increase the likelihood of an intra-operative complication during a laparoscopic liver resection and it has been developed and validated in a large European, multi-centre cohort.

The results demonstrate that 5 factors are independently associated with an increased risk of intra-operative complications during laparoscopic liver resection. Resections of malignant lesions, lesion size, neoadjuvant chemotherapy, previous open liver resections and the classification of the operation (which can be viewed as an amalgamation of lesion location and volume of resection) were all found to be independently associated with an increase risk of intra-operative complications during laparoscopic liver resections.

Testing of the model demonstrates that little is lost in terms of accuracy in the conversion of the logistic model to a point score. Thus, with the ease of use the point system this should be adopted in favour of the logistic model. Calibration of the model against actual risk demonstrated that the gradients of the lines of best fit were similar (0.056 for predicted risk compared to 0.055 for actual risk) with the primary difference being the y-axis intercept (0.020 for predicted risk compared to -0.057 for actual risk). Hence the predictive model was re-calibrated (by reducing the predicted risk by 0.075) to a line the risk predicted by the model and the actual risk of an intra-operative complication.

Grouping of scores into similar risk brackets was performed in order to guide surgeons through the learning curve. Previous literature has demonstrated that the learning curve for minor resections is between 20 and 60 procedures (16, 38 - 40) while that for major resections is between 30 and 60 cases (17 - 19, 41 - 43). Therefore, in broad terms those at the beginning of the learning curve (first 40 cases) should be undertaking low-risk procedures (scores 0 – 2, representing a risk of a <0.1 of an intra-operative complication) prior to moving to moderate risk procedures (scores 3 – 5, representing a 0.1 – 0.2 risk of an intra-operative complication) for the second part of the learning curve. High-risk procedures (scores 6 – 9, representing a 0.2 – 0.5 risk of an intra-operative complication) that include complex resections with multiple predictors of difficulty should only be attempted by those who have overcome the learning curve for minor and major resections - having personally performed more than 100 cases with at least 50 being of moderate difficulty. Finally, those in the extreme category should only be considered by leaders of the field and for the majority of surgeons and centres could be considered unsuitable for laparoscopic liver resection. This is in accordance with the guideline provided by the EGMLLS (21).

Analysis of outcome data demonstrates that those who have intra-operative complications had significantly worse outcomes in terms of length of stay (5 days compared to 4 days), a higher complication rate (32.5% compared to 15.5%) and significantly higher 30-day (3.0% compared to 0.3%) and 90-day mortality (3.8% compared to 0.8%).

Our scoring system correlates well with the afore mentioned scores as it demonstrates that the extent and location of the resection, as well as lesion size affects the difficulty of a laparoscopic liver resection. For example, a left lateral sectionectomy represents the cut-off between low and moderate risk groups in the Ban *et al* (2014) classification. In the absence of other risk factors our model would classify this procedure as low risk however the addition of other predictors (for example an increased lesion size) would increase this to moderate risk. At the other end of the spectrum Ban *et al* (2014) classified a simple hepatectomy as the cut-off between moderate and high risk procedures and our score replicates this as the addition of predictors of difficulty to a simple hepatectomy (that alone would be considered moderate risk) would make the procedure high risk. The inclusion of all predictors found to independently increase the likelihood of an intra-operative complication by our model allows for surgeons to precisely gauge the difficulty of a laparoscopic liver resection prior to undertaking the procedure. This in turn should enable appropriate case selection with respect to the current level of experience of the surgeon that may in turn reduce intra-operative complications that have been demonstrated to result in worse patient outcomes (22).

The lack of statistical significance of cirrhosis within our model is noteworthy as the scoring system by Ban *et al* (2014) highlighted that cirrhosis, specifically Child-Pugh B compared to Child-Pugh A, increased the perceived difficulty of a laparoscopic liver resection (13). This may be explained by the higher population incidence of cirrhosis within their study cohort - 82 patients had Child-Pugh A cirrhosis (95.3%) and 4 had Child-Pugh B cirrhosis (4.7%). While in our study only 307 patients had Child-Pugh A cirrhosis (10.7%) and 13 had Child-Pugh B cirrhosis (0.5%) hence reducing the likelihood of statistical significance of cirrhosis within our cohort. A second possible explanation is a selection basis towards simpler cases for those with cirrhosis, however major anatomical resections were not under-represented within this group (being responsible for 56 of 320 procedures (17.5%) compared to 465 of 2,856 procedure (16.3%) in the whole cohort). The final possible explanation for the inconsistencies between the two models is the small cohort used by Ban *et al* (2014) that may have suffered from under-fitting and hence has attributed statistical significance inappropriately. Regardless of the cause it should be stated that with the limited number of patients with cirrhosis within our study cohort the use of this model in populations with higher incidences of cirrhosis should be limited until the score has been validated within a representative population.

The limitations of this study include its retrospective analysis and the lack of data regarding the timing, duration and number of cycles of neoadjuvant chemotherapy. In addition, the inability of the model to perfectly predict an intra-operative complication suggests that other factors which cannot be explained by our calculations are responsible for part of the difficulty of laparoscopic liver resections. Finally, there is an innate selection basis within this study as each individual case was discussed at a local multi-disciplinary team meeting and was deemed suitable for laparoscopic liver resection and hence the most extreme cases in terms of tumour burden / number, anatomical location and need for vascular / biliary reconstruction means that the most challenging cases are yet to be attempted laparoscopically.

**CONCLUSION**

A pre-operative risk scoring system based upon patient, surgical and tumour factors from a large, multi-centre, European database has been developed and internally validated. It may act as a tool to guide case selection based upon a surgeons operative experience and in turn reduce intra-operative complications that have been proven to be of detriment to patient outcome.

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