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Predictors of Complications After Liver Surgery: a Systematic Review of the Literature

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Abbreviations: ALT: alanine transferase, ASA: American Society of Anesthesiologists, AST: aspartate transferase, BMI: body mass index, CI: confidence interval, COPD: chronic obstructive pulmonary disease, ECOG: Eastern Cooperative Oncology Group, HR: hazard ratio, INR: international normalized ratio, MELD: model for end-stage liver disease, NAFLD: non-alcoholic fatty liver disease, OR: odds ratio, POD: postoperative day, RR: risk ratio

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Abstract

Background

Numerous potential predictors of adverse outcomes have been reported but their performance and utilization in practice seem heterogenous. This study aimed to systematically review the literature on the role and value of predictors of complications after hepatectomy.

Methods

A systematic review following the PRISMA guidelines was performed. Studies on liver transplant were excluded. Only studies assessing overall or major complications were included.

Results

A total of 10'965 abstracts were screened. After application of exclusion criteria, 72 articles including 68'480 patients were included. A total of 72 markers with 48 pre-, 9 intra- and 15 postoperative factors were identified as predictors of complications. Preoperative and intraoperative predictive markers retrieved several times with the highest odds ratios (OR) were ASA score (OR range: 1.3-7.5, significant in 8 studies) and intraoperative need for red blood cell transfusion (OR range: 1.2-17.1, significant in 24 studies), respectively.

Discussion

Numerous markers have been described to predict the complication risk after hepatectomy. Because of their intrinsic characteristics, most markers such as ASA score and need for red blood cell transfusion are of limited clinical interest. There is a clear need to identify new biomarkers and to develop scores that could easily be implemented in clinical practice.

Keywords: hepatectomy; risk factors; morbidity; outcomes; markers.

Introduction

Liver surgery is key in the treatment of various primary and secondary liver tumors, whose incidence is rising, as well as for various benign diseases [1,2]. Following improvement in perioperative management, advances in anesthesia, progress in surgical technique, and development of minimally invasive surgery, postoperative outcomes have improved over these last decades [3–5]. However, reported mortality and morbidity rates after hepatectomy remain around 2-4% and 20-45%, respectively [3,6–10].

Postoperative morbidity leads to prolonged hospital stay, adverse effects on quality of life, increased resource expenditure, greater medical costs and possibly even poor long-term survival in oncologic patients [11–14]. Identification of patients at greater risk of developing postoperative complications is paramount in order to anticipate or at least reduce the impact of complications [9,15,16]. The ideal predictive marker should be performant, early indicative, inexpensive, and easy to measure in daily clinical practice.

The aim of the present study was to systematically review the current literature to identify pre-, intra-, and postoperative markers that independently predict postoperative complications after liver resection.

Methods

Search

A systematic search on MEDLINE/PubMed, Embase, Web of Science, Google Scholar, Ovid, and Cochrane Library for articles published from database implementation until January 2020 was performed. Grey literature such as abstracts, proceedings, or reports was also considered. Grey literature was searched using Google Scholar and cross-referencing. The following medical search headings and keywords were used: “liver resection” OR “surgical procedures” OR “operation” AND “complication” AND “marker” OR “predictor” OR “surrogate” in non-MeSH terms; and “hepatectomy” OR “surgery” AND “morbidity” AND “risk factor” in MeSH terms. Only human studies published in English or French languages as full-text articles were included [17]. Bibliographies of selected articles were also assessed to find relevant studies that might not have been identified during initial database search (cross-referencing). Two authors (GL, GRJ) performed the initial search and compared their findings.

Outcomes of interest

Outcomes of interest were markers of post-hepatectomy complications. Nature of the markers could be clinical, biological, radiological, or pathological. Pre-, intra-, or postoperative markers were considered. Predictive scores including different parameters were also included. American Society of Anesthesiologists (ASA) and Eastern Cooperative Oncology Group (ECOG) scores were classified into clinical markers and not predictive scores [18,19].

Inclusion criteria

Only studies reporting ≥50 hepatectomies were included. Types of surgery were defined as minimally invasive (laparoscopy or robotic surgery) and open surgery. Moreover, liver resections were classified as anatomical or non-anatomical using the Brisbane 2000 Terminology of Liver Anatomy and Resections [20]. In studies including other procedures associated to hepatectomy, at least 50 hepatectomies alone accounting for a minimum of 50% of the overall surgeries should have been performed to be included in this review. The number of 50 patients was chosen to ensure that multivariable analysis was derived from a significant sample. Studies had to report overall or major complication rate with a clear definition.

Exclusion criteria

Studies on liver transplantation were excluded. Other exclusion criteria were studies reporting only specific complications (e.g., acute kidney injury only or infectious complications only), and studies lacking multivariable analysis of the markers for overall or major complications. Year of the performed surgery, extent of resection, volumetric measurements, and indocyanine green tests were not considered in this analysis as these items have been extensively studied and validated [7,21–26].

Data extraction

Reported odds ratios (OR), hazard ratios (HR), risk ratios (RR), beta coefficient regressions, mean differences with confidence intervals (CI) and p-values were extracted from the different studies. It was specified whether complications were defined according to Clavien classification (overall: grades 1-5, minor: grades 1-2, major: grades >2) [27] or not ("other").

Quality assessment, heterogeneity, and publication bias

The quality of studies was assessed using the Newcastle-Ottawa scale for cohort studies [28]. This scale consists of 3 domains, including selection of cohort, comparability of cohort, and outcome assessment. Domains are further divided into 9 items, with star allocation to each item to enable semi-quantitative assessment of study quality. The total score ranges between 0 to 9 stars. A high score corresponds to a high quality (**supplementary Table 1**).

Heterogeneity of included studies was measured using Cochrane I^2. Publication bias was assessed with funnel plot. These last 2 measures were realized for the 2 outcomes that were cited multiple times and had the highest OR to avoid including studies multiple times.

Results

After the initial search, 10’966 records were retrieved. Among them 10’861 had to be excluded on the basis of title and abstract. Finally, 72 studies (5 prospective and 67 retrospective) including a total of 68’480 patients were analyzed (**Fig. 1**). A total of 72 factors were found to be predictors of complications following hepatectomy. These markers were divided as follows: preoperative clinical markers (n=24), preoperative biological markers (n=20), preoperative radiological markers (n=2), preoperative scores (n=2), intraoperative markers (n=9), postoperative clinical markers (n=1), postoperative biological markers (n=4), postoperative scores (n=2), and postoperative pathological markers (n=8). Confounders variables such as surgical reconstruction and neoadjuvant chemotherapy were present in 22 [3,9,22,24,25,29–45] and 19 [24,32–36,38,42–44,46–54] studies, respectively.

Preoperative markers

All preoperative markers with their OR range are summarized in **Tables 1 and 2**. A graphical representation of the preoperative items can be found in **Figure 2**.

Preoperative clinical markers

Details of included studies assessing preoperative clinical markers [3,7,13,21,22,24,29,31,37–39,41,43,44,46–49,51–69] are shown in **supplementary Table 2**. Regarding age, thresholds of 60 and 70 years were found in 2 studies [46,55]. High body mass index (BMI) was predictive of complication with cut-offs of 28 [43] and 30 kg/m^2 [21,61]. Two studies issued from the American College of Surgeons National Quality Improvement Program (ACS-NSQIP) included >10’000 patients [7,53]. He *et al.* [7] found that primary hepatic or biliary malignancy as indication was an independent risk factor of complications (n=13’227). Tohme *et al.* [53] identified age, ASA score, diabetes mellitus, smoking, chronic obstructive pulmonary disease low performance status prior to surgery, bleeding disorder, malignancy, and >10% weight loss within 6 months of the operation as other independent clinical surrogate markers (n=12’987).

Preoperative biological markers

Supplementary Table 3 summarizes in detail all preoperative biological markers [3,13,24,25,30,32,35,42,45,47,48,52–54,59,62,63,70–77]. Albumin was the most frequently identified preoperative laboratory value predictive of complications (thresholds of 3 and 3.5 g/dL) [3,35,47,52–54,70]. Preoperative bilirubin was another biological marker statistically significant in 5 studies (>1 mg/dL, 1.5x normal bilirubin) [30,42,48,53,71]. Platelet count with thresholds <100 and <150 G/l was also identified as predictor of major and overall complications [25,53597273]. Cheng *et al.* [13] in a study including 360 patients found that high international normalized ratio (INR) was strongly predictive of complication (OR: 63.2, 95% CI: 5.2-761.8, p=0.001).

Preoperative radiological markers

Two studies identified liver stiffness (calculated using Fibroscan) and sarcopenia (defined by the total psoas muscle area calculated using CT-scan) as radiological markers of adverse outcomes [16,78].

Preoperative scores

Preoperative scores were also found as predictors of complications in 4 studies (**supplementary Table 4**) [23,59,79,80]. Most of the studies used the standard Child-Turcotte-Pugh score [23,79–81].

Intraoperative markers

Nine different intraoperative characteristics predicted postoperative complications in 50 studies and are summarized in **Table 3** (for details of the studies see **supplementary Table 5**). Intraoperative transfusion was reported in 23 studies [22,25,29,32,33,36,38,40,44,47–51,53,58,68,72,79,82–85], with only 2 studies setting a cutoff at 600 ml. Estimated blood loss was another predictor of postoperative complication with thresholds ranging from 400 ml to 2500 ml (**supplementary Table 6**) [3,13,15,23,43,46,50,56,57,62,63,65,67,70–73,77,80,86,87]. Another frequently mentioned intraoperative prognostic factor was operative duration (thresholds from 180 to 360 minutes)

[15,23,37,44,45,47,53,64,66,69–71,74,82,88]. Pedicular clamping time was associated with postoperative morbidity in 8 studies with cut-offs of 20, 30, 40, or 60 minutes [34,43,48,57,79,82,83,85]. A randomized controlled trial compared close suction abdominal drainage (n=52) *versus* no drainage (n=52) after elective hepatic resection for various chronic hepatic diseases [67]. The authors reported an increased morbidity associated with drainage (RR: 4.4, 95% CI: 1.7-11.6, p=0.002). **Figure 3** sums up graphically the most predominant intraoperative markers.

Postoperative markers

Postoperative clinical markers

Red blood cell transfusion was not only found to be predictive of postoperative complications when transfused intraoperatively, but also when administered postoperatively (**Table 5, supplementary Table 7**) [47,65].

Postoperative biological markers

Table 4 and **supplementary Table 7** summarize the various biological predictors [9,22,43,50,60,65,89]. Each biological marker except lactate was found significant in only one study.

Postoperative scores

Rahbari *et al.* [50] reported 2 scores predictive of postoperative morbidity. One is derived from the definition of posthepatectomy liver failure [90] defined by the International Study Group of Liver Surgery (increased INR and hyperbilirubinemia on or after postoperative day 5, OR: 5.6, 95% CI: 2.7-11.6, p<0.001). The other score was the Model for End-stage Liver Disease (MELD) score [91] on postoperative day 5 (OR: 2.1, 95% CI: 1.4-3.0, p=0.001, **Table 4, supplementary Table 7**).

Postoperative pathological markers

All 8 pathological markers are displayed in **Table 4** and **supplementary Table 7** [26,33,34,36,38,57,59,65,77,79,87].

The median Newcastle-Ottawa scale of all included studies was 7 (IQR 7-8, **supplementary Table 1**). Funnel plot of studies that found ASA score or need of intraoperative red blood cell transfusion as risk factors for complication is shown in **supplementary Figure 1**. Related Cochrane I^2 measuring heterogeneity was 51%.

Discussion

The present systematic review included 72 articles with 72 markers of complication after hepatectomy identified. Overall quality of the evidence was judged poor as only 5 of the 72 included studies were prospective. The present review showed that numerous predictors of complications have been described. Among the predictors that were highlighted several times, the 2 preoperative markers with the highest OR were ASA score and liver cirrhosis (**Fig. 2**).

Regarding preoperative predictors, data were scarce. For example, for the predictive items that were the most frequently found such as age, ASA score or albumin, only few studies (9, 8, and 7 studies, respectively) among the abundant literature on this topic identified these markers as significant predictors of complication on multivariable analysis. Looking at the preoperative items identified several times and with the highest OR, ASA score (highest OR 7.5) was significant in 8 out of 19 studies, whereas liver cirrhosis (highest OR 6.5) was only positive in 4 out of 10 studies. More solid evidences are needed for certain predictors to preoperatively recommend their routine use as marker of complications after liver resection. Moreover, preoperative predictors of complications are essential and paramount to identify, as they would allow preoperative or intraoperative strategies to decrease or prevent postoperative morbidity. The next step would be to design studies incorporating preoperative nomograms or scores derived from these predictors that would assess potential strategies to mitigate postoperative complications based on the preoperative risk.

Few highlighted predictors are modifiable. However, it is important to control these factors as best as possible in order to decrease the complication risk. Smoking cessation and weight loss in case of BMI >25 kg/m^2 should be recommended preoperatively. In case of malnutrition, preoperative nutritional status can be improved. Moreover, comorbidities such as hypertension or diabetes should be well controlled to preoperatively optimize patients for surgery.

Intraoperative transfusion was the intraoperative predictor associated with the highest reported OR (17.1). Among the 23 studies that identified intraoperative transfusion as predictor of complications, only 1 was prospective [48] and 2 reported a threshold of 600 mL [40,85]. This marker was strongly associated with postoperative complications and might be used as risk predictor of morbidity in clinical practice. Operative duration was also associated with postoperative complications in 15 studies. Occurrence of these factors intraoperatively should raise surgeon concern regarding the risk of postoperative complication. Nevertheless, no follow-up algorithm based on these markers was proposed. Additionally, intra- and postoperative predictors are less helpful, as they do not allow any preoperative or surgical modifications to prevent postoperative morbidity.

Available systematic reviews on the topic are scare, with one single publication only [92]. The present study specifically focused on studies analyzing predictive markers of overall morbidity and major complications, as postoperative complications impact long-term outcomes [11–14]. The study by Lim *et al.* assessed the risk prediction models in liver surgery based on the different outcomes and the role of these models in clinical practice [92]. Due to different selection criteria from the review by Lim *et al*. and recent published articles, 33 new articles were included in the present study adding important novel data in liver surgery. Twenty-one additional risk factors of morbidity after liver resection were newly described, providing a total of 72 pre-, intra-, and postoperative predictive factors. These recently published articles enabled to confirm certain previously described predictive factors of morbidity and to add some new markers that enlarge the list of predictors. Thus, transfusion and blood loss were further validated as strong predictors of complications. Moreover, ASA score, which was not described as morbidity marker in the review by Lim *et al.* (only 2 studies found it as an independent predictor), was found to be an independent predictor in 8 studies in the present review. This suggests that even though this score contains some subjective parts, it might be used as a clinical preoperative risk predictor of complications. Five years after the review by Lim *et al.*, the important number of newly published articles on this subject shows that surgeons are working to define factors able to predict postoperative complications and that an ideal predictive marker has not been described yet. For example, a recent study (published after our literature review) showed that an early postoperative gain of weight ≥3.5 kg was associated with major complications [93].

The present study compiled many predictors of complications (n=72). Qualities of the studies were heterogeneous and usefulness of the assessed markers of complications was variable. A valuable marker for clinical practice should ideally be easy to measure, inexpensive and indicative as early as possible to anticipate, prevent, or reduce the impact of postoperative complications [94]. These criteria are fulfilled for most of the preoperative clinical and intraoperative markers that are routinely assessed in liver surgery patients. Most of biological markers are part of the regular assessment and are inexpensive (e.g., gamma-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, albumin, creatinine, urea nitrogen, or cholesterol). On the contrary, some laboratory values are more expensive, such as procalcitonin or hepatocyte growth factor, as well as postoperative pathological factors which require more resources and time. An important point to mention is that the impact on clinical practice of the included markers was not assessed. This review showed that several markers had predictive value in terms of complications, but that objective postoperative management algorithms once a marker was present do not currently exist.

The main limitation of this study lies in the heterogeneity of the included articles (study populations, indications for hepatectomy, hepatectomy techniques, postoperative management). Moreover, postoperative complications were not uniformly defined among included studies. Only 23 of them (33%) referred to the Clavien classification system [27].

In summary, this review identified 72 potential predictors of complications after liver surgery. Overall, level of evidence of the available data was low. Identified biomarkers, their impact (OR) and threshold were highly heterogenous which stresses the need to further explore the question in large-scale prospective studies. In addition, these results emphasized the importance to identify new potent biomarkers with stronger impact on decision-making, allowing to guide postoperative surveillance or to select patients at higher risk who could benefit from specific therapeutic measures, aiming to mitigate their risk of complications. These points need to be investigated by dedicated prospective trials.

Author Contributions

Study conception and design: IL, ND and GRJ, data acquisition and literature review: GL and GRJ, critical review of included articles: GL, IL, ND and GRJ, analysis and interpretation of data: GL, IL, ND and GRJ, drafting of the manuscript: GL and GRJ, critical revision and approval of the final version of the manuscript: GL, IL, ND and GRJ.

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Conflict of Interest

Authors declare no Conflict of Interest for this article.

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Figure Legends

Fig. 1. PRISMA flow chart of the review.

Fig. 2. Preoperative markers of postoperative complications with odds ratio (OR) range.

Fig. 3. Intraoperative markers of postoperative complications with odds ratio (OR) range.

Table 1. Preoperative clinical markers of postoperative complications after hepatectomy

Marker	*References*	*OR range*
Age	(13,22,46,52,53,55–58)	1.0-4.5[Σ]
ASA score	(24,29,31,46,47,53,59,60)	1.3-7.5[Σ]
Gender	(3,31,51)	1.4-2.6[Σ]
Body mass index (kg/m^2)	(21,43,48,61)	1.2-2.6
Smoking	(47,53)	1.4-1.7
Chronic obstructive pulmonary disease	(44,53,54)	1.8-3.1
Diabetes mellitus	(38,48,53,62)	1.2-6.4[Σ]
Cardiovascular disease	(37,63)	1.3-1.3
Coronary artery disease	(38)	4.8[#]
Hypertension	(38)	2.9[#]
Previous cardiac surgery	(54)	2.8
Previous hepatic surgery	(51,64)	2.4-5.8[Σ]
Any comorbidity	(3,65,66)	1.4-4.0
Preoperative risk score	(55)	8.0[#]
ECOG score	(46)	1.9-4.6
Liver cirrhosis	(48,58,67,68)	1.6-6.5[Σ]
Jaundice	(39)	13.0[Δ]
Preoperative cholecystitis or cholangitis	(41)	9.1
Primary hepatic malignancy as indication	(7,69)	1.5-3.3
Low performance status	(53)	1.5
Bleeding disorder	(53)	1.4
>10% weight loss within 6 months	(53)	1.3
Malignancy	(29,53)	1.1
Preoperative chemotherapy	(49,51)	3.5-5.5[Σ]

[Σ] HR/RR were included in the OR range, [#] HR, [Δ] RR

ASA : American Society of Anesthesiologists, ECOG : Eastern Cooperative Oncology Group

Table 2. Preoperative biological, radiological, and score as markers of postoperative complications after hepatectomy

Marker	*References*	*OR range*
Biological		
Low albumin level	(3,35,47,52–54,70)	1.4-3.5
High bilirubin level	(30,42,48,53,71)	1.1-6.4
High bilirubin and AP levels	(32)	∅
Low platelet count	(25,53,59,72,73)	1.2-3.1$^{\Sigma}$
High AST	(24,53,54,74)	1.1-2.0
High ALT	(75)	2.0
High transaminase levels	(48)	1.8$^{\#}$
High AP level	(47,53)	1.3-4.9
High partial thromboplastin time	(47	2.0
Low prothrombin activity	(45)	1.1
High INR	(13)	63.2
High AST to platelet count ratio index	(13)	4.2
High gamma-glutamyl transferase	(76)	8.6
High hepatocyte growth factor	(76)	12.6
Low cholesterol	(62)	- 0.01042$^{\beta}$
High urea nitrogen level	(62,74)	0.05785-6.913x10$^{-3\ \beta}$
High creatinine level	(3)	1.8
Low galactose elimination capacity	(63)	2.1-2.2
Low hematocrit	(53)	1.2
Low cholinesterase level	(77)	0.0
Radiological		
Liver stiffness (Fibroscan)	(78)	7.3
Sarcopenia (CT-scan)	(16)	3.1
Score		
Child-Turcotte-Pugh (CPT)	(23,79,80)	5.0$^{\#}$
Modified CPT score*	(59)	1.4

$^{\Sigma}$ HR/RR were included in the OR range
$^{\#}$ HR, $^{\beta}$ Beta coefficient regression
*Because most patients with hepatic encephalopathy are not considered candidates for resection, a modified Child score incorporating the preoperative platelet count instead of encephalopathy was created.
AP : alkaline phosphatase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, INR: international normalized ratio

Table 3. Intraoperative predictive factors of postoperative complications after hepatectomy

Markers	*References*	*OR range*
Long operative duration (minutes)	(15,23,37,44,45,47,53,64,66,69–71,74,82,88)	1.0-8.7
Long transection time (minutes)	(43)	1.9
Laparotomy	(46)	2.0
Thoracotomy	(71,82)	1.8-2.0
Pedicular clamping time	(34,43,48,57,79,82,83,85)	1.5-2.9$^{\Sigma}$
Abdominal drainage	(67)	4.4$^{\Delta}$
Non-radicality	(66)	2.6
Estimated blood loss	(3,13,15,23,43,46,50,56,57,62,63,65,67,70–73,77,80,86,87)	1.0-7.5$^{\Sigma}$
Transfusion	(22,25,29,32,33,36,38,40,44,47–51,53,58,68,72,79,82–85)	1.2-17.1$^{\Sigma}$

$^{\Delta}$ RR

$^{\Sigma}$ HR/RR were included in the OR range

Table 4. Postoperative predictive factors of postoperative complications after hepatectomy

Markers		*References*	*OR range*
Clinical	Blood transfusion	(47,65)	1.4-1.5
Biological	High procalcitonin	(9)	20.2
	Albumin drop	(60)	1.1-1.1[#]
	High bilirubin	(22)	10.0-83.3
	High lactate	(43,89)	2.0
Score	Post Hepatectomy Liver Failure *	(50)	5.6
	High MELD on POD 5	(50)	2.1
Pathological	Milan criteria	(59	3.9
	Positive nodes	(79)	3.7[#]
	Steatosis	(33,36,65)	1.3-3.4[Δ]
	Fibrosis and NAFLD activity score grade	(57)	5.7[#]
	Non-alcoholic steatohepatitis	(38)	6.0[#]
	Cirrhosis of the remaining liver	(26,77)	5.1
	Abnormalities nontumoral liver	(34,87)	1.6-1.6[Δ]
	Maximum size of metastases	(34)	3.0[Δ]

*as defined by the International Study Group of Liver Surgery (ISGL): increased INR and hyperbilirubinemia on or after postoperative day 5

[#]HR, [Δ]RR

MELD: Model for End Stage Liver Disease, POD: Postoperative Day, NAFLD: Non-Alcoholic Fatty Liver Disease

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