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Development and validation of a comprehensive model to predict complications after hepatectomy

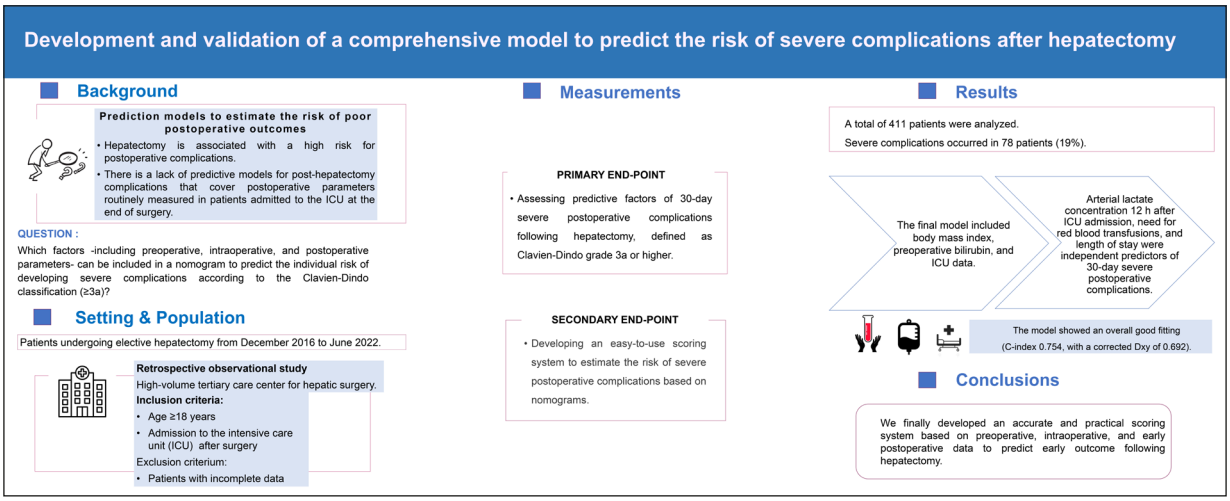
R. GASPARI[1,2], F. ARDITO[3,4], P.C. PAFUNDI[5], A.W. AVOLIO[3,6], P. ACETO[1,2], E. ADDUCCI[1,2], M. PALLOCCHI[1], E. PARENTE[1], L. SOLLAZZI[1,2], M. ANTONELLI[1,2], F. GIULIANTE[3,4]

[1]Department of Emergency, Anesthesiological and Reanimation Sciences, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[2]Department of Basic Biotechnological Science, Intensive and Peri-operative Clinics, Università Cattolica del Sacro Cuore, Rome, Italy
[3]Department of Gastroenterological, Endocrine, Metabolic and Nephro-urological Sciences, General Surgery and Hepatobiliary Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[4]Department of Translational Medicine and Surgery, Università Cattolica del Sacro Cuore, Rome, Italy
[5]Epidemiology and Biostatistics Research Core Facility, Gemelli Science and Technology Park, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[6]Department of Gastroenterological, Endocrine, Metabolic and Nephro-urological Sciences, General Surgery and Transplantation Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

Rita Gaspari and Francesco Ardito equally contributed to the study as first authors

Abstract. – OBJECTIVE: Despite advances in perioperative care, hepatectomy remains associated with morbidity rates of up to 40%. Currently, available nomograms for predicting severe post-hepatectomy complications do not include early postoperative data. This retrospective observational study aimed to determine whether the parameters routinely measured in patients admitted to the Intensive Care Unit (ICU) after hepatectomy could represent risk factors for severe morbidity and to propose a nomogram scoring system to predict severe postoperative complications.

PATIENTS AND METHODS: 411 adult patients who underwent elective hepatectomy at a high-volume tertiary care center for hepatic surgery from December 2016 to June 2022 were enrolled. The primary outcome was the assessment of predictors of 30-day severe postoperative complications following hepatectomy, defined as Clavien-Dindo grade 3a or higher. As a secondary outcome, we aimed to develop an



Graphical Abstract. Visual summary of the main steps of the research project discussed in the article.

Corresponding Author: Paola Aceto, MD, Ph.D; e-mail: paola.aceto@unicatt.it; pa.aceto@gmail.com

easy-to-use scoring system to estimate the risk of severe postoperative complications.

RESULTS: Severe complications occurred in 78 patients (19%). The final model included body mass index, preoperative bilirubin level, and ICU data (i.e., pH, lactate clearance, arterial lactate concentration 12 hours after ICU admission, need for packed red blood cell transfusions, and length of stay). Notably, the latter three variables were proven to be independent predictors of the outcomes. The model showed an overall good fit (C-index=0.754, corrected Dxy=0.692). A calibration plot using bootstrap internal validity resampling confirmed the stability of the model (mean absolute error=0.017, root mean square error of approximation=0.00051).

CONCLUSIONS: We developed an accurate and practical scoring system based on preoperative and early postoperative data to predict poor outcomes after hepatectomy. Further external validation on larger series could lead to the integration of such a tool in the routine clinical practice to support patients' management and early warning during ICU stay.

Key Words:
Liver surgery, Intensive care, Lactates, Lactate clearance, Blood transfusion, Predicting models.

Introduction

The enhancement of surgical techniques and perioperative management have allowed surgeons to perform even more complex elective hepatectomies and extend the indications to patients with advanced parenchymal diseases such as steatosis, cirrhosis, or post-chemotherapy damage[1,2].

However, hepatectomy is associated with a high risk for postoperative complications. The complication rate, according to the Clavien-Dindo classification[3], remains high even in high-volume centers (20-40%)[4]. Recently, there has been a growing interest in developing comprehensive and well-calibrated prediction models to estimate the risk of poor postoperative outcomes. Most models[5-7] have been established to predict post-hepatectomy liver failure (PHLF), and few have been proposed for Clavien-Dindo complications[8,9]. Moreover, many models have only focused on preoperative and intraoperative factors[6-9]. There is a lack of predictive models for post-hepatectomy complications that cover postoperative parameters routinely measured in patients admitted to the intensive care unit (ICU) at the end of surgery.

This study aimed to assess the risk factors for severe morbidity, including preoperative, intraoperative, and postoperative parameters, and to propose a nomogram to predict the individual risk of developing severe complications according to the Clavien-Dindo classification.

Patients and Methods

Design and Population

This was a large-scale, single-center, retrospective study of patients who underwent elective hepatectomy at the Hepatobiliary Surgery Unit of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS (Rome, Italy) between December 2016 and June 2022. We included patients aged ≥18 years who were admitted to the ICU after surgery. Patients with incomplete data were excluded from this study.

The approval for this study (ID: 5073) was provided by the Ethics Committee of Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, on 25 July 2022. The study was conducted in accordance with the 1976 Declaration of Helsinki and its latest amendments and reported following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines[10]. Written informed consent was obtained from all patients.

Anesthesia Protocol

The anesthesia protocol was standardized. Anesthesia was induced with propofol (2 mg/kg), fentanyl (3 mcg/kg) and maintained with sevoflurane (age-adjusted 1 minimum alveolar concentration in a 40% air-oxygen mixture) and infusion of remifentanil (dose ranging from 0.05-0.2 mcg/Kg/min). Muscle relaxation was induced with rocuronium (0.6 mg/kg) and maintained with additional boluses (0.15 mg/kg). Mechanical ventilation was set to keep end-tidal carbon dioxide between 35 and 45 mmHg (tidal volume of 6-8 mL of ideal body weight). Routine hemodynamic monitoring included heart rate and electrocardiogram (D2-V5 derivations), pulse oximetry, and invasive pressure through cannulation of the radial artery.

At the time of skin incision, all patients received an infusion of Rehydrating Electrolyte Solution (RES) at 3 ml/kg/h (i.e., basal fluid infusion). A fluid bolus (250 ml) of RES was administered in case of mean arterial pressure (MAP) <65 mmHg, cardiac index (CI) <2.5 L/min/m^2, and stroke volume variation (SVV) >13%. If MAP was <65 mmHg with CI ≥2.5 L/min/m^2, regardless of SVV, continuous infusion of norepinephrine was

started at a dose of 0.1 mcg/kg/min and titrated to achieve a MAP ≥65 mmHg; after reaching MAP ≥65 mmHg, SVV was optimized (if ≥13) with RES bolus after the end of liver resection phase or during liver resection only in case of urine output <1 ml/kg/h. Continuous dobutamine infusion was considered the first-line intervention when CI <2.5 L/min/m^2, MAP <65 mmHg, and SVV ≤13% (**Supplementary Figure 1**). Hemodynamics were managed using the FloTracTM/VigileoTM system (Vigilance Monitor Edwards Life Sciences, Irvine, CA, USA) according to the protocol described in **Supplementary Figure 1**[11,12]. Human albumin (20 g/L) was administered only to treat clinically documented hypoalbuminemia (<2.8 g/dL). Packed red blood cells (PRBCs) were transfused to maintain a hemoglobin concentration ≥8 g/dL (≥9 g/dL in patients with a history of ischemic heart disease).

After surgery, patients with one or more comorbidities or those undergoing extensive parenchymal resection or surgical procedures lasting for more than six hours were transferred to the ICU.

Surgical Procedure

Liver resection was defined according to the International Hepato-Pancreato-Biliary Association terminology[13]. Resections ≥3 segments were classified as major hepatectomies. Minor complex hepatectomies included ≥3 parenchymal-sparing liver resections for metastases. The surgical technique used for hepatectomy was previously described[14-17]. Parenchymal transection was performed with the Cavitron ultrasonic surgical aspirator (CUSA 200; Valleylab, Boulder, CO, USA) and wet bipolar forceps. Hemostasis and biliostasis were achieved using absorbable clips (Absolok AP200 and AP300; Ethicon, Johnson & Johnson Medical Devices Companies, Pratica di Mare, Italy) or with 3/0-4/0 absorbable and non-absorbable stitches on the hepatic vein branches. The intermittent Pringle maneuver was used only when bleeding hindered a clear view of the operative field[17]. In case of minimally invasive hepatectomy, the patient was placed in either supine or middle left lateral position according to the tumor location, with the surgeon between the legs. Five trocars were then inserted. Hepatectomy was performed using an 80-degree articulating vessel sealer (Aesculap Caiman; B. Braun, Tuttlingen, Germany) and CUSA.

Data Collection and Definitions

Demographic data included age, sex, body mass index (BMI), American Society of Anesthesiology Physical Classification, comorbidities, pre-existing parenchymal liver diseases, and Model for End-Stage Liver disease (MELD).

Intraoperative parameters included the surgical approach, the extent of hepatectomy, surgical time, cumulative duration of the Pringle Maneuver, blood loss, need for PRBC transfusions, and inotropic support. Hemodynamic and metabolic profiles were recorded at ICU admission and 12 hours later. The arterial lactate concentration (aLC) was measured in blood samples drawn from the radial artery using heparinized syringes at 37°C (Nova Biomedical Corporation, Waltham, MA, USA). Lactate clearance was defined as follows[18]: [(aLC_ICU admission – aLC_12 hours after ICU admission) / aLC_ICU admission] × 100. The number of patients transfused with PRBCs during the initial postoperative 12 hours was also recorded.

Outcome parameters included 30-day postoperative complications according to the Clavien-Dindo classification (1-2 *vs.* 3a-5 grade)[3]. PHLF was evaluated according to the International Study Group of Liver Surgery definition[5]. Length of stay (LoS) in the ICU and hospital were also collected.

End-Points

The primary endpoint was the assessment of predictive factors for severe postoperative complications 30 days after hepatectomy, defined as Clavien-Dindo grade ≥3a[8,9]. The secondary endpoint was the development of an easy-to-use scoring system to estimate the risk of severe postoperative complications based on nomograms.

Statistical Analysis

To the best of our knowledge, this is the first study to develop a potential score for predicting postoperative complications, including ICU data. There is no generally accepted approach for estimating the sample size for the derivation of score prediction models. Hence, we based the derivation on the inclusion of several covariates in the multivariable model in compliance with the rule of at least ten events per candidate variable[19], and the TRIPOD guidelines[20]. This led to the inclusion of over 400 patients.

Appropriate descriptive statistics were used. Qualitative variables were expressed as absolute and relative percentage frequencies. Quantitative variables were reported as mean and standard deviation (SD) or median and interquartile range (IQR). Gaussian distribution was assessed using the Shapiro-Wilk test. Multiple imputations with Lasso Regression methods focused on mean data were applied to quantitative variables, whilst

classification trees for imputation by "rpartC" function were used for qualitative data[21].

Univariable and multivariable logistic regression models were used to identify independent predictors of Clavien-Dindo complications grade ≥3a to be included in the score. We computed the Odds Ratios (ORs) and 95% Confidence Intervals (CIs) of candidate predictors of severe postoperative complications using univariate logistic regression models. Predictors to be included in the multivariable model were selected based on univariable analysis ($p<0.05$ or suggestive, i.e. $0.05\leq p<0.10$) and expert opinion[20]. Methods used for performance assessment, calibration, and internal validation are described in the **Supplementary File**.

We then developed a scoring system to predict the outcome, providing an integer value to each predictor included in the score based on the β-coefficient of each variable in our sample[22].

In-depth, the regression coefficients of the model are converted into scores through appropriate mathematical transformations and plotted into a nomogram as a predictive model tool[22]. For each independent variable, a straight line perpendicular to the Points axis (through a ruler) is made at that point, and the intersection point represents the score under the value of the independent variable. The corresponding points for the independent variables can be calculated for each patient. We can get total points that trace the outcome probability axis using a perpendicular line.

Statistical significance was set at $p<0.05$. Suggestive p-values were also reported ($0.05\leq p<0.10$). Statistical analyses were performed using R software, version 4.2.3 (CRAN®, R Core 2022, Wien, Austria).

Results

General Characteristics of the Study Sample

Of the 420 patients admitted to the ICU, nine were excluded due to incomplete clinical records. In total, 411 patients were included in this study (**Supplementary Figure 2**). Patient demographic characteristics and comorbidities are shown in Table I.

Most patients underwent surgery for colorectal cancer metastases (56.9%), followed by hepatocellular carcinoma (14.8%). The median duration of surgery was 569 min (IQR 457.5-600), and the interventions were almost equally distributed between minor and major/minor complex.

Table I. General characteristics of the study sample (N=411). Qualitative variables are expressed as absolute and relative percentage frequencies, whilst quantitative data as median and interquartile range (IQR).

Demographics	
Age, years	67 (60-74)
Sex	
M	273 (66.4)
F	138 (33.6)
BMI, kg/m^2	25.0 (22.4-28.0)
BMI, n (%)	
<18.5 kg/m^2	14 (3.4)
18.5-29.9 kg/m^2	338 (82.2)
≥30 kg/m^2	59 (14.4)
ASA, n (%)	
1-2	281 (68.3)
3-4	130 (31.7)
Comorbidities, n (%)	
Diabetes	69 (16.8)
Hypertension	229 (55.7)
Ischemic cardiopathy	47 (11.4)
COPD	72 (17.5)
Others	145 (35.3)
Fibrosis	136 (33.1)
Fibrosis Grade	
Absent-Mild	392 (95.4)
Moderate-Severe	19 (4.6)
Steatotic liver disease	99 (24.1)
Steatosis Grade	
Absent-Mild	395 (96.1)
Moderate-Severe	16 (3.9)
Cirrhosis	39 (9.5)
Preoperative data	
Creatinine, mg/dL	1.0 (1.0-1.1)
Bilirubin, mg/dL	1.0 (1.0-1.1)
INR	1.04 (1.01-1.09)
MELD	7 (7-8)
Hemoglobin, g/dL	12.9 (11.7-14.0)
Intraoperative data	
Blood loss, mL	400 (200-600)
PRBCs transfused patients, n (%)	78 (19)
Norepinephrine use, n (%)	35 (8.5)
Surgery type, n (%)	
Colorectal Cancer Metastases	234 (56.9)
Hepatocellular Carcinoma	61 (14.8)
Intrahepatic Cholangiocarcinoma	37 (9.0)
Benign	25 (6.1)
Other cancer metastases	23 (5.6)
Hilar-cholangiocarcinoma	21 (5.1)
Gallbladder cancer	10 (2.4)
Surgery duration, minutes	509.0 (397.5-600.0)
Anesthesia duration, minutes	569.0 (457.5-660.0)
Pringle duration, minutes	82.0 (42.5-123.0)
Surgery class, n (%)	
Minor	216 (52.6)
Major/Minor Complex	195 (47.4)
Laparotomy, n (%)	308 (74.9)

M: Males; F: Females; BMI: body mass index; ASA: American Society of Anesthesiology; COPD: Coronary Obstructive Pulmonary Disease; INR: international normalized ratio; MELD: Mayo End stage Liver Disease; PRBCs: packed red blood cells.

Sixty-three patients had simultaneous colorectal (73%), ovarian (9.5%), or other cancers (17.5%).

At ICU admission, the median aLC was 4.9 mmol/L (IQR 2.6-7.2), with a median pH of 7.36 (IQR 7.32-7.4) and hemoglobin below normal ranges.

Twelve hours after ICU admission, aLC decreased to a median value of 2 mmol/L (IQR 1.2-3.2), with a median clearance of 51.1 (IQR 26.2-69), whereas pH increased (median 7.44, IQR 7.41-7.47). Almost all patients had a positive fluid balance (87.1%), and PRBC transfusion was required in 13.1% of cases.

In our series, Clavien-Dindo 1-2 grade complications occurred in 51.8% and 29.2% of patients, respectively, while Clavien-Dindo grade ≥3a occurred in 19% of patients (Table II).

Table II. Post-surgical data and complications in the study sample (N=411). Qualitative variables are expressed as absolute and relative percentage frequencies, whilst quantitative data as median and interquartile range (IQR).

Laboratory parameters in ICU	
At admission	
Lactates, mmol/L	4.9 (2.6-7.2)
pH	7.36 (7.32-7.40)
Hemoglobin, g/dL	11.4 (9.9-12.6)
12 h after ICU admission	
aLC, mmol/L	2.0 (1.2-3.2)
Lactate clearance, mL/min	51.1 (26.2-69.0)
pH	7.44 (7.41-7.47)
Hemoglobin, g/dL	10.7 (9.5-12.1)
ICU length of stay, days, median (range)	1 (1-14)
Fluid balance, mL	1,500 (474.5-2,415)
PRBCs transfused patients, n (%)	54 (13.1)
Norepinephrine use, n (%)	35 (8.5)
Clavien-Dindo complications, n (%)	
1	213 (51.8)
2	120 (29.2)
3°	27 (6.6)
3b	33 (8.0)
4°	10 (2.4)
4b	5 (1.2)
5	3 (0.7)
Clavien-Dindo complications ≥3°, n (%)	78 (19)
30-day mortality, n (%)	3 (0.7)
90-day mortality, n (%)	6 (1.5)

ICU: Intensive Care Unit; PRBCs: packed red blood cells; aLC: arterial lactate concentration.

Potential Predictors of Severe Postoperative Complications

On univariable analysis, lower BMI was suggestively associated with severe complications (OR 0.95, 95% CI 0.89-1.01; p=0.084), alongside higher preoperative bilirubin levels (OR 1.41, 95% CI 0.95-2.10; p=0.089). In fact, 35.7% of underweight patients (5/14) developed severe complications *vs.* 18.9% of normal/overweight patients (64/338) and only 15.2% of obese patients (9/59).

Intraoperative data showed that greater blood loss and the need for PRBC transfusion were significantly associated with a higher risk of Clavien-Dindo grade ≥3a (OR 1.00, 95% CI 0.99-1.00; p<0.001 and OR 3.71, 95% CI 2.14-6.43; p<0.001, respectively). Major surgery and laparotomy revealed a significantly higher risk of severe complications (OR 2.16, 95% CI 1.30-3.59; p=0.003 and OR 2.32, 95% CI 1.18-4.60; p=0.015, respectively). A similar finding was observed for the duration of surgery. Among ICU parameters on admission, higher aLC was associated with a higher risk of severe complications (OR 1.12, 95% CI 1.05-1.20; p<0.001), while higher hemoglobin levels were associated with a lower risk (OR 0.81, 95% CI 0.71-0.93; p=0.002). Twelve hours after ICU admission, higher aLC (OR 1.41, 95% CI 1.24-1.59), lactate clearance (OR 0.99 95% CI 0.98-1.00; p=0.003), longer ICU LoS (OR 2.72, 95% CI 1.77-4.18; p<0.001), positive fluid balance (OR 1.00, 95% CI 0.99-1.01; p=0.005), and blood transfusion (OR 3.69, 95% CI 2.00-6.82; p<0.001) were associated with a higher risk of severe Clavien-Dindo complications (Table III).

Predictive Performance of Models

Three subsequent models were then developed. The first included all significant/suggestive predictors. Among ICU parameters, only ICU LoS was independently associated with the outcome (OR 2.03, 95% CI 1.20-3.45; p=0.008), while a suggestive role was observed for aLC 12 h after ICU admission (OR 1.30; 95% CI 0.98-1.72; p=0.066) (Table IV).

The accuracy of this model, although a relatively good C-index (0.775), was flanked by a Brier score of 0.123 (confirming good accuracy). However, the strict relationship between the C-index and Somers' Dxy rank correlation (0.417 when corrected after the bootstrap calibration procedure with 100 replicates) indicates an over-optimistic model; thus, more variables could be ruled out owing to poor contribution. Further calibration curves using the bootstrap internal validity resampling method provided evidence that the model was overfitted. In particular, we obtained a mean absolute error (MAE) of 0.031 and a root mean squared error (RMSE) of 0.00256 (**Supplementary Figure 3**).

The coefficients of the regression model were then converted into scores through appropriate mathematical transformations and plotted as a

Table III. Assessment of potential predictors of Clavien-Dindo severe complications (N=411). Qualitative variables are expressed as absolute and relative percentage frequencies, whilst quantitative data as median and interquartile range (IQR). In bold significant data, in italics the suggestive ones ($0.05 \leq p < 0.10$).

	Clavien-Dindo ≥3a n=78	Clavien-Dindo <3a n=333	Univariable analysis OR (95% C.I.); *p*
Age, years	67 (52-73)	66 (59-74)	1.00 (0.98; 1.03); 0.735
Female sex	29 (37.2)	109 (32.7)	1.22 (0.73; 2.03); 0.455
BMI, kg/m^2	24.2 (21.6-27.6)	25.3 (22.5-28.0)	0.95 (0.89; 1.01); 0.084
Comorbidities, n (%)			
Diabetes	12 (15.4)	57 (17.1)	0.88 (0.45; 1.73); 0.713
Hypertension	47 (60.3)	182 (54.7)	1.26 (0.76; 2.08); 0.371
Ischemic cardiopathy	10 (12.8)	37 (11.1)	1.18 (0.56; 2.48); 0.670
COPD	11 (14.1)	61 (18.3)	0.73 (0.36; 1.47); 0.379
Fibrosis			
Absent-Mild (ref.)	74 (94.9)	318 (95.5)	-
Moderate-Severe	4 (5.1)	15 (4.5)	1.15 (0.37; 3.55); 0.813
Steatotic liver disease			
Absent-Mild (ref.)	75 (96.2)	320 (96.1)	-
Moderate-Severe	3 (3.8)	13 (3.9)	0.98 (0.27; 3.54); 0.981
Cirrhosis	9 (11.5)	30 (9.0)	1.32 (0.60; 2.90); 0.494
Preoperative data			
Creatinine, mg/dL	1.00 (1.00-1.01)	1.00 (1.00-1.04)	1.11 (0.25; 4.85); 0.887
Bilirubin, mg/dL	1.00 (1.00-1.15)	1.00 (1.00-1.10)	1.41 (0.95; 2.10); 0.089
INR	1.05 (1.00-1.09)	1.04 (1.00-1.08)	3.86 (0.18-84.16); 0.390
MELD	7 (7-8)	7 (7-8)	1.10 (0.96; 1.25); 0.159
Hemoglobin, mg/L	12.7 (11.4-13.5)	13.0 (11.8-14.1)	**0.86 (0.75; 0.99); 0.038**
Intraoperative data			
Blood loss, mL	500 (300-800)	350 (200-600)	**1.00 (0.99; 1.00); <0.001**
PRBCs transfused patients	30 (38.5)	48 (14.4)	**3.71 (2.14; 6.43); <0.001**
Surgery duration, minutes	555 (452.8-630.0)	495 (389-585)	**1.00 (1.00; 1.01); 0.001**
Norepinephrine use, n (%)	9 (11.5)	26 (7.8)	1.54 (0.69; 3.43); 0.291
Anesthesia duration, minutes	615 (512.8-690.0)	555 (449-645)	**1.00 (1.00; 1.01); 0.001**
Pringle duration, minutes	83.5 (44.2-138.7)	82 (42-121)	1.00 (0.99; 1.01); 0.425
Surgery class			
Minor	29 (37.2)	187 (56.2)	-
Major/Minor Complex	49 (62.8)	146 (43.8)	**2.16 (1.30; 3.59); 0.003**
Laparotomy	67 (85.9)	241 (72.4)	**2.32 (1.18; 4.60); 0.015**
Parameters at admission in ICU			
aLC, mmol/L	5.6 (3.6-8.5)	4.4 (2.5-6.8)	**1.12 (1.05; 1.20); <0.001**
pH	7.36 (7.31-7.40)	7.36 (7.32-7.40)	0.23 (0.01; 0.81); 0.421
Hemoglobin, g/dL	10.4 (9.3-12.0)	11.6 (10.0-12.6)	**0.81 (0.71; 0.93); 0.002**
Parameters 12 h after ICU admission			
aLC, mmol/L	2.8 (1.8-5.5)	1.8 (1.2-2.9)	**1.41 (1.24; 1.59); <0.001**
Lactate clearance, mL/min	42.0 (11.0-57.9)	52.6 (28.6-70.1)	**0.99 (0.98; 1.00); 0.003**
pH	7.43 (7.40-7.47)	7.44 (7.41-7.46)	**0.01 (0.00; 0.40); 0.019**
Hemoglobin, g/dL	10.3 (9.1-11.3)	10.8 (9.6-12.3)	**0.83 (0.72; 0.96); 0.015**
ICU length of stay, days (median, range)	1 (1-3)	1 (1-14)	**2.72 (1.77; 4.18); <0.001**
Fluid balance, mL	1,941 (1,050-2,841)	1,338 (374-2,350)	**1.00 (0.99; 1.01); 0.005**
PRBCs transfused patients, n (%)	22 (28.2)	32 (9.6)	**3.69 (2.00; 6.82); <0.001**
Norepinephrine use, n (%)	9 (11.5)	26 (7.8)	1.54 (0.69; 3.43); 0.291

M: Males; F: Females; BMI: body mass index; ASA: American Society of Anesthesiology; COPD: Coronary Obstructive Pulmonary Disease; INR: international normalized ratio; MELD: Mayo End-stage Liver Disease; PRBCs: Packed red blood cells; ICU: Intensive Care Unit; CI: Confidence Interval; OR: Odd Ratio; aLC: arterial lactate concentration.

nomogram (**Supplementary Figure 4**), which showed a negligible contribution from several parameters.

We then fitted a second model erasing the aforementioned variables, which disclosed the following independent predictors: ICU LoS (OR 2.15, 95% CI 1.29-3.57; p=0.003) and aLC at 12 hours (OR 1.23; 95% CI 1.06-1.44; p=0.006) (Table IV). However, even in this case, the model did not show an overall good fit, with a C-index of 0.762 but a low corrected Dxy rank correlation (0.440), suggesting a

Table IV. Multivariable predictive models for Clavien-Dindo severe complications (n=411). In bold significant data, in italics the suggestive ones ($0.05 \leq p < 0.10$).

	Multivariable Analysis OR (95% C.I.); p		
	Model 1	**Model 2**	**Model 3**
Preoperative data			
BMI, kg/m^2	0.95 (088; 1.12); 0.180	0.95 (0.88; 1.02); 0.161	0.94 (0.88; 1.01); 0.098
Bilirubin, mg/dL	1.19 (0.72; 1.97); 0.493	1.24 (0.75; 2.04); 0.402	1.25 (0.76; 2.06); 0.375
Hemoglobin, g/dL	0.96 (0.79; 1.16); 0.671		
Intraoperative data			
Blood loss, mL	1.00 (0.99; 1.00); 0.793		
PRBCs transfused patients	1.65 (0.75; 3.66); 0.214		
Surgery			
Anesthesia duration, minutes	1.00 (0.99; 1.00); 0.646		
Major/Minor Complex Surgery (Ref. Minor)	1.20 (0.65; 2.23); 0.557	1.30 (0.73; 2.32); 0.372	
Laparotomy	1.20 (0.55; 2.65); 0.644		
Parameters at admission in ICU			
aLC, mmol/L	0.95 (0.81; 1.11); 0.527		
Hemoglobin, g/dL	0.94 (0.73; 1.23); 0.678	0.92 (0.72; 1.18); 0.518	
Parameters 12 h after ICU admission			
aLC, mmol/L	1.30 (0.98; 1.72); 0.066	**1.23 (1.06; 1.44); 0.006**	**1.26 (1.08; 1.46); 0.002**
Lactate clearance, mL/min	1.00 (0.99; 1.01); 0.628	0.99 (0.99; 1.00); 0.157	0.99 (0.99; 1.00); 0.186
pH	0.80 (0.00; 20.8); 0.374	0.05 (0.00; 10.5); 0.271	0.04 (0.00; 7.64); 0.230
Hemoglobin, g/dL	1.09 (0.84; 1.42); 0.513	1.06 (0.83; 1.35); 0.657	
ICU length of stay, days	**2.03 (1.20; 3.45); 0.008**	**2.15 (1.29; 3.57); 0.003**	**2.14 (1.30; 3.52); 0.003**
Fluid balance, mL	1.00 (1.00; 1.01); 0.958		
PRBCs transfused patients	1.69 (0.72; 3.96); 0.223	1.86 (0.81; 4.26); 0.144	**2.14 (1.04; 4.42); 0.040**

BMI: body mass index; PRBCs: Packed red blood cells; ICU: Intensive Care Unit; CI: Confidence Interval; OR: Odd Ratio; aLC: arterial lactate concentration.

potentially low contribution from the other covariates. The related nomogram suggested that we ruled out surgical class and hemoglobin level, both on ICU admission and at 12 h (**Supplementary Figure 5**).

The third and final model included BMI, preoperative bilirubin level, and ICU data (pH, lactate clearance, aLC 12 h after ICU admission, PRBC administration, and LoS, with the last three identified as independent predictors of outcome) (see Table IV). The model showed an overall good fit (C-index=0.754, corrected Dxy=0.692). The calibration plot confirmed the stability of the model (MAE=0.017, RMSE=0.00051) and a small deviation from the reference (Figure 1). The related nomogram showed the highest contribution to ICU LoS, followed by aLC 12 h after ICU admission. Notably, lower BMI was associated with a higher risk of severe complications (Figure 2). For example, the probability of the occurrence of a severe complication exceeds 95%, with a score ≥8.

Discussion

Predictive scores offer clinicians the indication to apply mitigation strategies to reduce the overall risk[23]. The models developed to date to predict the likelihood of post-hepatectomy complications primarily focused on preoperative and intraoperative parameters[6-9]. Recently, high interest in the hepatologic literature has been raised by a French model[7] predictive of post-hepatectomy liver failure in cirrhotic patients. The model, showing a C-statistic equal to 0.73, was developed using pre-operative and intra-operative data from 343 liver-resected patients (six centers).

Our final model aimed to quantify the overall risk of hepatic failure and other complications after resection surgery in the neoplastic patient, besides BMI, preoperative bilirubin, and other intraoperative data, including some parameters measured 12 h after ICU admission (blood lactates, need for PRBC transfusions, and ICU LoS). The model revealed the highest C-statistic and the highest goodness of fit compared to previous ones.

Notably, the inclusion of early postoperative parameters may enhance the performance of the overall algorithm and improve postoperative patient management from ICU admission.

Our final model included parameters measured 12 h after ICU admission, including lactate

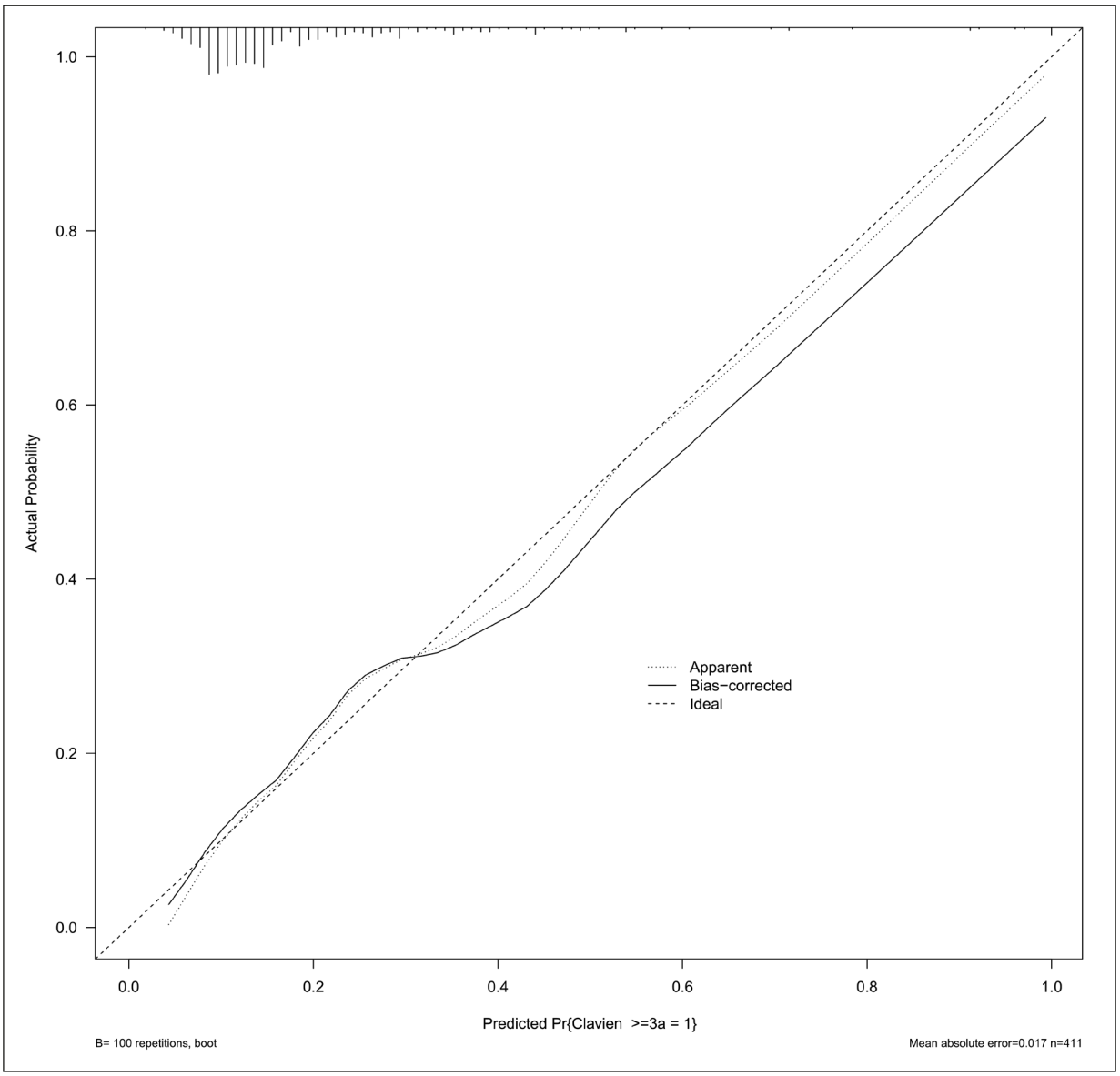


Figure 1. Calibration plot of the final model using bootstrap internal validity resampling method, randomly sampling 100 returnable cases. The lateral axis shows the predicted probability of severe complications for each patient, while the vertical axis shows the actual probability of severe complications for each patient. It is ideal if the straight line exactly coincides with the dotted line.

levels, need for PRBC transfusions, and ICU LoS. BMI and preoperative bilirubin levels were also considered. The model had a good overall fit. Subsequent transformation into a nomogram scoring system allowed for individualized and easy-to-use risk estimation.

Blood lactate levels result from the dynamic balance between lactate production and clearance. A high blood lactate level is usually linked to either peripheral hypoperfusion or tissue hypoxia, especially when associated with metabolic acidosis[24]. It has been previously reported[25-30] that higher lactate levels at the end of hepatectomy are associated with adverse outcomes. Over the past decade, in other clinical contexts, the study of lactate kinetics has proved[18,31,32] to be a reliable prognostic predictor. Although the overall long-term prognosis of liver resected patients is mainly related to oncological determinants, the implications of perioperative management should be considered[33]. In this setting, the association between postoperative lactate clearance and prognosis has been evaluated only in a few small studies[34,35] and with controversial findings. Moreover, blood lactate, or

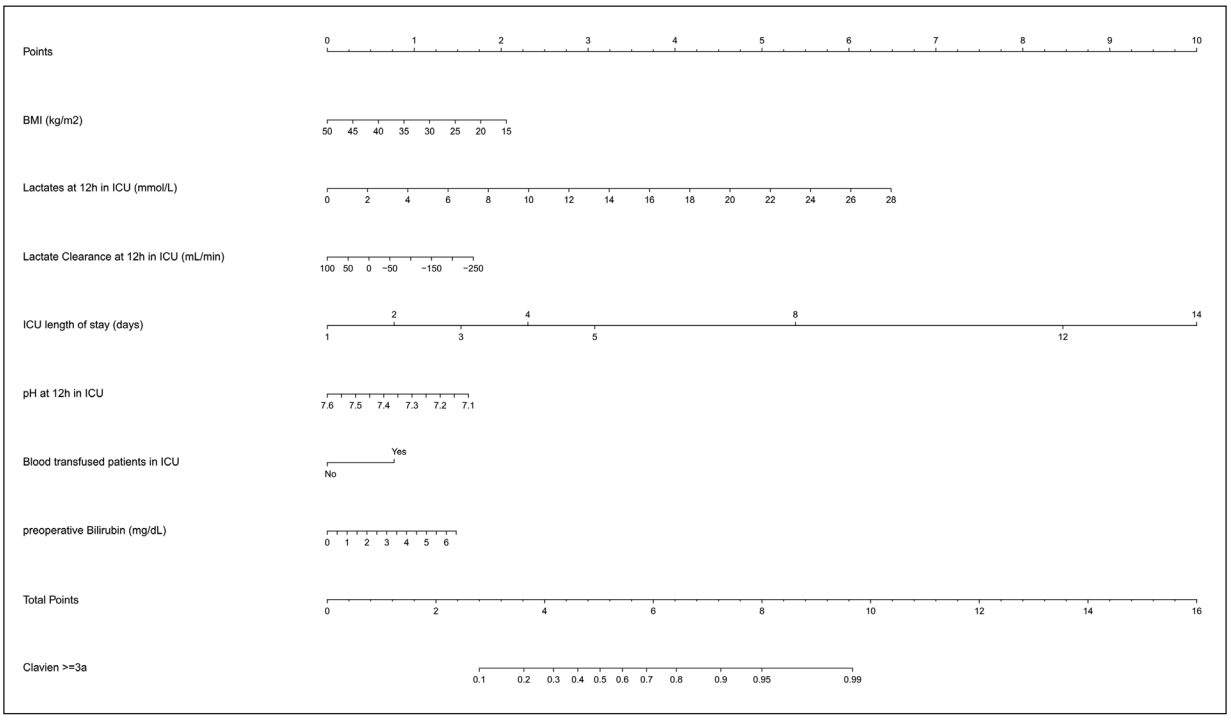


Figure 2. Nomogram displaying the probability of the occurrence of a severe complication (Clavien-Dindo grade ≥3a). The upper points help assign the correct score to each variable, whilst the total points in the bottom part of the nomogram, alongside the predicted probability in the last line, allow the assignment of the predicted probability of a severe complication according to the total score.

its clearance, has not yet been included in predictive models of post-hepatectomy complications.

In our study, a higher lactate level 12 hours after ICU admission was identified as an independent predictor of severe post-hepatectomy complications. This finding, along with the lower lactate clearance observed in the univariate analysis, could suggest a failure in the metabolic power of the liver. In fact, factors such as reduced blood flow to the liver caused by the Pringle maneuver[36], extensive liver resection, or pre-existing parenchymal damage could alter liver function and lead to severe post-hepatectomy complications; however, this was not observed in the present study.

In contrast, in the univariate analysis, we observed a significant association between severe complications and increased intraoperative blood loss, as well as more patients transfused during surgery and in the first 12 h of ICU admission. However, the lower preoperative hemoglobin levels at ICU admission in patients with severe complications may have contributed to the increased transfusion requirements.

Intraoperative blood loss has already been reported[37,38] as a potential risk factor for unfavorable outcomes. Notably, high lactate levels 12 hours after ICU admission, low pH, greater need for PRBC transfusions, and larger fluid therapy may be linked to peripheral hypoperfusion. However, the lack of real data on oxygen consumption makes these hypotheses speculative.

The patient who requires blood transfusion, in our models, is a patient with an independent risk of major complications. A blood transfusion may be a surrogate parameter of a challenging surgical procedure, which is itself related to negative outcomes[39]. This finding is in line with the evidence obtained by the authors of the French study[7] on the prediction of liver failure in resected cirrhotic patients, although, in the final French model, the count of the blood units was removed due to the competition with other variables. It should be noted that multicentric studies with different cases per center may suffer from center-related bias.

Accordingly, technical difficulty indicated by the duration of surgery, complexity of hepatic resection, and surgical approach were associated with the degree of complications. Nevertheless, in our series, the risk of severe complications increased by 3.7 times for each PRBC unit transfused in the ICU.

Interestingly, our data suggest that lower BMI may lead to a higher risk of severe complications. This finding confirms that BMI may be used as a surrogate marker of malnutrition and/or frailty in liver surgery and transplantation settings[40-42].

As regards the presence of steatotic liver disease, identified by imaging or biopsy[43], no differences were found in relation to postoperative complications despite some evidence[44] demonstrating that moderate steatosis increases ischemia-reperfusion injury, making the liver more susceptible to Pringle maneuver.

Our nomogram suggests that we should carefully monitor patients with a longer ICU stay, even after ICU discharge, who have had slower normalization of blood lactate levels and a greater need for PRBC transfusion.

To the best of our knowledge, this is the first large comprehensive study to investigate the role of preoperative, intraoperative, and early postoperative factors in predicting poor outcomes after hepatectomy.

Limitations

However, this study has some limitations. First, this was a single-center retrospective analysis. Second, there was a population bias due to the different indications for hepatic surgery and criteria for ICU admission, including preexisting comorbidities, duration, and/or complexity of surgery. The prevalence of cirrhosis was lower than that in other series. This may impair the direct translation of the model to highly selected populations. However, we believe that the impact of these limitations is negligible owing to the large volume of hepatectomies performed in our center.

Conclusions

Using a comprehensive approach involving pre-, intra-, and early postoperative factors potentially associated with the outcome, we developed a prediction model to quantify the risk of complications according to the Clavien-Dindo classification after hepatectomy. Finally, knowledge of risk factors will guide healthcare decision-makers to manage resources for the treatment of these patients in the postoperative period.

ORCID ID

Gaspari Rita: 0000-0003-0141-3686
Ardito Francesco: 0000-0003-1596-2862
Pafundi Pia Clara: 0000-0002-0310-3529
Avolio Alfonso Wolfango: 0000-0003-2491-7625
Aceto Paola: 0000-0002-0228-0603
Adducci Enrica: 0000-0002-8977-762X
Pallocchi Matteo: 0000-0001-8134-2309
Parente Emiliano: 0009-0006-1724-859X
Sollazzi Liliana: 0000-0002-2973-6236
Antonelli Massimo: 0000-0003-3007-1670
Giuliante Felice: 0000-0003-2087-2589.

Conflicts of Interest

The authors declare that they have no conflict of interest to disclose.

Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki of 1975 (as revised in 2013), and the protocol was reviewed and approved by the Ethics Committee of Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy (ID: 5073) on 25 July 2022.

Informed Consent

Written informed consent was obtained from all patients.

Informed Consent

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Data Availability

Data are available on reasonable request from RG (e-mail: rita.gaspari@unicatt.it).

Authors' Contributions

Rita Gaspari: conceptualization, methodology, data acquisition, analysis and interpretation, writing the original draft and revised version, approval of the final version. Francesco Ardito: conceptualization, methodology, data acquisition, analysis and interpretation, drafting and critical revision of the manuscript, approval of the final version. Pia Clara Pafundi: methodology, statistical analysis, drafting and critical revision of the manuscript, approval of the final version. Alfonso Wolfango Avolio: conceptualization, methodology, acquisition, analysis and interpretation of data, drafting and critical revision of the manuscript, approval of the final version. Paola Aceto: conceptualization, methodology, analysis and interpretation of data, drafting and critical revision of the manuscript, approval of the final version. Enrica Adducci: data acquisition and interpretation, critical revision of the manuscript, approval of the final version. Matteo Pallocchi: data acquisition and interpretation, critical revision of the manuscript, approval of the final version. Emiliano Parente: data acquisition and interpretation, critical revision of the manuscript, approval of the final version. Liliana Sollazzi: conceptualization, data interpretation, critical revision of the manuscript, approval of the final version. Massimo

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