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Model to predict major complications following liver resection for HCC in patients with metabolic syndrome

Giammauro Berardi[1,2], **Francesca Ratti**[3], **Carlo Sposito**[4], **Martina Nebbia**[5], **Daniel M. D'Souza**[6], **Franco Pascual**[7], **Epameinondas Dogeas**[8], **Samer Tohme**[8], **Francesco E. D'Amico**[9], **Remo Alessandris**[9], **Ilaria Simonelli**[10], **Celeste Del Basso**[2], **Nadia Russolillo**[11], **Amika Moro**[12], **Guido Fiorentini**[3,13], **Matteo Serenari**[14], **Fernando Rotellar**[15], **Giuseppe Zimmitti**[16], **Simone Famularo**[17], **Tommy Ivanics**[18], **Daniel Hoffman**[19], **Edwin Onkendi**[20], **Yasmin Essaji**[21], **Santiago Lopez Ben**[22], **Celia Caula**[22], **Gianluca Rompianesi**[23], **Asmita Chopra**[24], **Mohammed Abu Hilal**[16], **Guido Torzilli**[17], **Gonzalo Sapisochin**[18], **Carlos Corvera**[19], **Adnan Alseidi**[19], **Scott Helton**[21], **Roberto I. Troisi**[23], **Kerri Simo**[24], **Claudius Conrad**[25], **Matteo Cescon**[14], **Sean Cleary**[13], **Choon H.D. Kwon**[12], **Alessandro Ferrero**[11], **Giuseppe M. Ettorre**[2], **Umberto Cillo**[9], **David Geller**[8], **Daniel Cherqui**[7], **Pablo E. Serrano**[6], **Cristina Ferrone**[5], **Vincenzo Mazzaferro**[4], **Luca Aldrighetti**[3], **T. Peter Kingham**[1]

[1]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York, USA

[2]Department of Surgery, San Camillo Forlanini Hospital, Rome, Italy

[3]Hepatobiliary Surgery Division, San Raffaele Hospital, Milan, Italy

[4]Department of Oncology and Hemato-Oncology, University of Milan and Department of Surgery, HPB Surgery and Liver Transplantation, Istituto Nazionale Tumori IRCCS, Milan, Italy

[5]Department of Surgery, Massachusetts General Hospital, Boston, Massachusetts, USA

[6]Department of Surgery, McMaster University, Hamilton, Canada

[7]Department of Surgery, Paul Brousse Hospital, Villejuif, Paris, France

[8]Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

[9]Department of Surgery, University of Padua, Padua, Italy

[10]Laltrastatistica Consultancy and Training, Biostatistics Department, Rome, Italy

[11]Department of Surgery, Mauriziano Hospital, Turin, Italy

[12]Department of Surgery, Cleveland Clinic, Cleveland, Ohio, USA

[13]Department of Surgery, Mayo Clinic, Rochester, New York State, USA

[14]Hepato-biliary Surgery and Transplant Unit, IRCCS Sant'Orsola Hospital, University of Bologna, Bologna, Italy and Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy

Correspondence: Giammauro Berardi, Department of General, Hepatobiliary and Pancreatic Surgery, Liver Transplantation Service, San Camillo Forlanini Hospital, Circonvallazione Gianicolense 87, Rome 00152, Italy. gberardi2@scamilloforlanini.rm.it.

[15]HPB and Liver Transplant Unit, Clinica Universidad de Navarra, University of Navarra. Institute of Health Research of Navarra (IdisNA), Pamplona, Spain

[16]Department of Surgery, Poliambulanza Foundation Hospital, Brescia, Italy

[17]Hepatobiliary Surgery Division, Humanitas University and Research Hospital- IRCCS, Rozzano - Milano. Italy

[18]Abdominal Transplant and HPB Surgical Oncology, Division of General Surgery, Toronto General Hospital

[19]Department of Surgery, University of California, San Francisco, California, USA

[20]Department of Surgery, Texas Tech University Health Sciences Center, Lubbock, Texas, USA

[21]Department of Surgery, Virginia Mason Hospital and Seattle Medical Center, Seattle, Washington, USA

[22]Department of Surgery, Hospital Universitari Dr Josep Trueta de Girona, Girona, Spain

[23]Department of clinical medicine and surgery, division of HPB, minimally invasive and robotic surgery, transplantation service, Università Federico II, Naples, Italy.

[24]Department of Surgery, Promedica, Toledo, Ohio, USA

[25]Department of Surgery, Saint Elizabeth Medical Center, Boston, Massachusetts, USA

Abstract

Background: Metabolic syndrome (MS) is rapidly growing as risk factor for HCC. Liver resection for HCC in patients with MS is associated with increased postoperative risks. There are no data on factors associated with postoperative complications.

Aims: The aim was to identify risk factors and develop and validate a model for postoperative major morbidity after liver resection for HCC in patients with MS, using a large multicentric Western cohort.

Materials and Methods: The univariable logistic regression analysis was applied to select predictive factors for 90 days major morbidity. The model was built on the multivariable regression and presented as a nomogram. Performance was evaluated by internal validation through the bootstrap method. The predictive discrimination was assessed through the concordance index.

Results: A total of 1087 patients were gathered from 24 centers between 2001 and 2021. Four hundred and eighty-four patients (45.2%) were obese. Most liver resections were performed using an open approach (59.1%), and 743 (68.3%) underwent minor hepatectomies. Three hundred and seventy-six patients (34.6%) developed postoperative complications, with 13.8% major morbidity and 2.9% mortality rates. Seven hundred and thirteen patients had complete data and were included in the prediction model. The model identified obesity, diabetes, ischemic heart disease, portal hypertension, open approach, major hepatectomy, and changes in the nontumoral parenchyma as risk factors for major morbidity. The model demonstrated an AUC of 72.8% (95% CI: 67.2%–78.2%) (https://childb.shinyapps.io/NomogramMajorMorbidity90days/).

Conclusions: Patients undergoing liver resection for HCC and MS are at high risk of postoperative major complications and death. Careful patient selection, considering baseline characteristics, liver function, and type of surgery, is key to achieving optimal outcomes.

INTRODUCTION

Metabolic syndrome (MS) is a cluster of inter-related risk factors, including abdominal obesity, dyslipidemia, hypertension, and insulin resistance. The prevalence of MS is increasing worldwide and currently represents one of the major health issues in Western countries, reaching rates of 25% in Europe and 43% among adults more than 60 years old in the United States.[1,2] NAFLD is the hepatic manifestation of MS, and ranges from simple steatosis to steatohepatitis and ultimately to fibrosis and cirrhosis.[3] Patients affected by MS have a 2–4 fold higher risk of developing HCC than the general population.[4] Surgical treatments such as liver resection and liver transplantation are the best available options for patients with HCC as they offer long-term survival and are considered potentially curative.[5] Though mortality and morbidity rates have significantly decreased in high volume centers over the last 2 decades, liver resection for HCC in patients with MS remains associated with a 3-fold increased risk of mortality and a 2-fold increased risk of postoperative morbidity, depending on the severity of patients' comorbidities and parenchymal changes.[6–9] In addition to obesity, these patients also have multiple comorbidities such as type-2 diabetes, atherosclerosis, cardiovascular disease, chronic kidney disease, polycystic ovarian syndrome, obstructive apnea syndrome, and extrahepatic malignancies.[10] As a result, patients are at higher risk of liver-related, cardiovascular, and all-cause mortality and morbidity. Selecting appropriate patients with MS and HCC who need surgery is necessary to avoid unfavorable postoperative outcomes. There are, however, no data on which factors should be considered to select these patients.

This study aimed to review a large multicenter Western database of liver resections for HCC in patients with MS and evaluate the postoperative outcomes focusing on complications and death. Furthermore, we aimed to investigate predictive factors of morbidity after surgery and develop and validate a prediction model.

MATERIALS AND METHODS

Between January 2001 and January 2021, data from 24 institutions (12 European and 12 North American) experienced in the treatment of hepatobiliary malignancies were collected. Patients' demographics, disease presentation, surgical approach, type of resection performed, intraoperative data, short-term outcomes, pathology report, and oncological outcomes were reviewed.

Patients were included only if fulfilling the following inclusion criteria: (1) receipt of pure laparoscopic, hand-assisted, robot-assisted, or open liver resection for histologically proven hepatocellular carcinoma; (2) a preoperative diagnosis of MS, defined by 3 out of 5 of the following criteria[11,12]: (a) abdominal obesity [body mass index (BMI) ≥ 30 kg/m^2 or waist circumference > 102 cm in men and > 88 cm in women][13]; (b) triglycerides > 150 mg/dl; (c) high-density lipoprotein cholesterol <40 mg/dl in men and <50 mg/dl

in women; (d) type-2 diabetes or glucose intolerance (fasting glucose > 110 mg/dl); (e) hypertension (blood pressure > 130/85 mm Hg); (3) older than 18; (4) anatomical and non-anatomical hepatectomies; and (5) up to one additional liver ablation. The following exclusion criteria were applied: (1) resections of HCC on viral, alcoholic (> 40 g/d, > 21 drinks per week for men and > 14 drinks per week for women),[14] or autoimmune diseases, as well as hemochromatosis and Wilson's disease; (2) fibrolamellar HCC or mixed hepatocellular-cholangiocellular carcinoma; (3) extrahepatic metastases; (4) exploratory laparoscopy/laparotomy without liver resection; (5) main portal vein, hepatic artery, biliary duct, or inferior vena cava invasion requiring major reconstructions.

The primary endpoint was to build predictive models for postoperative major morbidity and death. As secondary endpoints, the short-term outcomes focusing on overall morbidity and mortality within 90 days of surgery were investigated. As a sensitivity analysis, outcomes according to type of hepatectomy were explored.

Institutional Review Board (IRB) approval was obtained from the coordinating center (no. 16–801, approved December 7, 2020); data transfer agreement and IRB approval were included and requested for all participating institutions. According to the centers' policies, every case was discussed in a multidisciplinary setting, and informed consent for surgery was obtained from each patient.

Definitions

Minimally invasive liver resections were considered laparoscopic or robotic-assisted procedures, including conversion to open, according to an intention-to-treat principle. Portal hypertension was defined as the radiological presence of significant splenomegaly, umbilical vein recanalization, portosystemic shunts, and preoperative platelet count <100,000/mm^3.[15] Whenever HVPG was available, a 10 mm Hg cutoff was considered as significant portal hypertension.[16] Patients' comorbidities were graded using the Charlson Comorbidity Index.[17] Major liver resections were defined as the resection of 3 segments or more. Morbidity was graded according to the Clavien-Dindo classification and the Comprehensive Complication Index.[18,19] Major morbidity was defined as a grade 3 or more complication according to Clavien-Dindo classification.[19] Postoperative ascites was defined as a drainage output of more than 10/mL/kg/24 h.[20] Posthepatectomy liver failure and bile leakage were graded according to the International Study Group on Liver Surgery definition.[21,22] A margin of <1 mm was considered an R1 resection. Data on the nontumoral liver tissue were collected: specifically, degree of fibrosis, steatosis, lobular inflammation, and hepatocellular ballooning were graded according to the NAFLD Activity Score (NAS).[23] Furthermore, the European Association for the Study of the Liver (EASL) definition was used to categorize the nontumoral liver parenchyma as follows[24]: (1) NAFL when steatosis alone plus one of lobular or portal inflammation or ballooning was present; (2) NASH, when steatosis was associated with lobular or portal inflammation and ballooning; (3) cirrhosis, when F4 fibrosis was diagnosed; (4) normal parenchyma, when none of the above-mentioned conditions was satisfied.

Statistical analysis

Continuous data were expressed as the mean ± SD or, when appropriate, as median (interquartile ranges) for nonparametric distribution. Categorical data were expressed as numbers and percentages. The distribution of variables was analyzed using the Kolmogorov-Smirnov test.

Logistic regression was used to build a predictive model for 90 days major morbidity. Patients with missing data were excluded. Univariable logistic regression analyses were performed to evaluate the unadjusted association of patients' and disease's characteristics (gender, age, BMI, comorbidities, previous surgery, portal hypertension, MELD score, nontumoral liver parenchyma) and surgery (type of approach and type of hepatectomy) with 90-day major morbidity. A prediction model was then built considering all the variables with a P value <0.200 at univariable analyses. Results were presented as OR with the corresponding 95% CI and robust standard errors estimation was performed to take into account centers' clustering. The prediction model was then built based on the multivariable logistic regression. Based on the multivariable model, a nomogram was constructed. This nomogram provides a graphical representation of the risk factors associated with 90 days major morbidity and enables calculating the risk of postoperative complications for individual patients. The model's performance was evaluated by internal validation through the bootstrap method choosing n = 1000 resamplings. Internal validation was chosen over splitting the sample to reduce the chance of generating models with suboptimal performance (ie, models with unstable and same performance as obtained with half the sample size).[25]

The predictive discrimination of the model was assessed through the AUC, which is equivalent to the concordance index (c-index), and the values were interpreted according to Hosmer and Lemeshow.[26] The calibration curve and the Hosmer-Lemeshow test were used to assess the model's goodness of fit. In addition, the Brier score was reported: lower values indicate a higher accuracy of the model. Univariable logistic regression analysis was performed to analyze risk factors for mortality at 90 days. A P value <0.05 was considered statistically significant. Statistical analyses were performed using the R version 4.1.1. The multivariable logistic regression analysis, the nomogram construction, and the calibration plots were performed using the "rms" package (version 5.1–3.1; https://cran.r-project.org/web/packages/rms/). Hosmer-Lemeshow test were performed with the "Hltest.R."

RESULTS

One thousand eighty-seven patients with a mean age of 68.7 ± 9.3 were collected and reviewed (Table 1). Four hundred eighty-four patients (45.2%) were obese. Most patients presented with hypertension (78.1%), diabetes (56.4%), and dyslipidemia (54.3%). The majority (94.6%) of patients were classified as Child-Pugh A and the median MELD score of the study population was 8 (interquartile range: 6–9).

Most liver resections were approached by open technique (59.1%), and 743 patients (68.3%) underwent a minor hepatectomy (Table 2). Thirty-one patients (2.9%) died within 90 days from surgery, and 376 (34.6%) developed postoperative complications (Tables 3,

4). One hundred and fifty patients (13.8%) developed major complications. Ascites and posthepatectomy liver failure were diagnosed in 9.8% and 3.2% of patients, respectively. The median hospital stay was 6 (interquartile range: 5–9) days, and 8.5% of patients were readmitted after discharge. Pathology reports showed an R0 resection rate of 91.2%. Nontumoral liver parenchyma evaluation demonstrated normal parenchyma in 337 (38.7%) patients while NAFL, NASH and cirrhosis was diagnosed in 91 (10.4%), 160 (18.3%), and 284 (32.6%) respectively.

Nomogram to predict 90 days major morbidity

Among 1087 patients, 713 (65%) had complete data and were included in the prediction models. No multi-collinearity was observed. The model identified open approach ($P = 0.026$), major hepatectomy ($P < 0.001$), and portal hypertension ($P = 0.004$) as statistically significant risk factors for postoperative major morbidity. Concerning nontumoral parenchyma, cirrhosis was associated with 2.64 times higher odds of major morbidity compared to normal parenchyma (OR = 2.64, 95% CI: 1.36–5.14; $P = 0.004$). Furthermore, NASH patients had higher odds of having major morbidity at 90 days compared to normal parenchyma patients (OR = 1.79, 95% CI: 1.00–3.19; $P = 0.048$). The pair-wise comparisons showed a significant difference between cirrhosis compared to NAFL patients (OR = 3.66, 95% CI: 1.21–11.06; $P = 0.021$) or compared to NASH patients (OR = 2.63, 95% CI: 1.07–6.48; $P = 0.036$). The discrimination power was 75.1% (95% CI: 69.8%–80.4%) and at internal validation, after bootstrapping, the model showed a corrected AUC of 72.8% (95% CI: 67.2%–78.2%). The model is graphically presented as nomogram in Figure 1. An online calculator is available at https://childb.shinyapps.io/NomogramMajorMorbidity90days/.

Calibration was evaluated by plotting the predicted probability of morbidity and the actual outcomes (Figure 2). The model was less accurate in estimating high probabilities, but the calibration curve showed good concordance between the predicted probability and the actual probability. The Hosmer-Lemeshow test yielded a nonsignificant statistic ($P = 0.226$) and the Brier score was equal to 0.102.

Only univariable analysis was performed for 90-day mortality due to the small number of events (n = 22/713, 3.1%) precluding the construction of reliable multivariable model. Portal hypertension (OR = 3.49, 95% CI: 1.22–8.81; $P = 0.012$), MELD score ≥ 9 (OR = 3.2, 95% CI: 1.36–7.86; $P = 0.008$) as well as major hepatectomies (OR = 3.84, 95% CI: 1.62–9.76; $P = 0.003$) were associated with postoperative mortality (Table 5).

The type of hepatectomy was associated with post-operative outcomes (Supplemental Table http://links.lww.com/HEP/A52). Patients undergoing major hepatectomies had significantly higher morbidity (48.7% vs. 27.3%; $P < 0.001$) and mortality rates (6.1% vs. 1.7%; $P = 0.001$), as well as a higher chance of developing postoperative liver failure (7.4% vs. 1.0%; $P = 0.002$) and bile leaks (9.6% vs. 2.3%; $P = 0.011$) as compared to patients undergoing minor resections. Hospital stay was also longer (7 vs. 6 d; $P < 0.001$) and a greater proportion of patients were readmitted after discharge (13.7% vs. 7.3%; $P = 0.013$).

DISCUSSION

Liver resection for HCC in patients with MS is associated with high rates of postoperative morbidity and mortality.[6] A nomogram to improve patients' selection for surgery may help decrease complications and should therefore be implemented in hepatobiliary centers managing these patients. Indeed, preoperative knowledge of factors associated with postoperative major morbidity could help surgeons identify individuals at high risk for surgery, address modifiable variables, and evaluate and discuss with the patient potential alternatives, risks, benefits, and expectations of treatment.

As viral hepatitis is significantly decreasing in recent years due to the efficacy of new generation drugs and vaccinations, NAFLD has become the leading cause of chronic liver diseases in Western countries.[27] The evolving parenchymal changes induced by NAFLD (steatosis, fibrosis, cirrhosis) lead to the development of precancerous lesions and a yearly incidence of HCC as high as 2.6%.[28] Furthermore, both MS and NAFLD promote the development of primary liver malignancies regardless of fibrosis or cirrhosis, given the pathological proinflammatory environment, the altered endocrine and immunological signaling, and the metabolic and oxidative stress.[29,30] Recent advancements in surgical techniques and technology, as well as the improvements in preoperative evaluation of patients and liver function, have resulted in a decline in the perioperative mortality and morbidity of liver surgery, which currently represents one of the potentially curative treatment options for patients with HCC.[7] Despite this, patients with MS and early-stage HCC amenable to surgical resection have increased risks of postoperative complications, representing a unique category of patients and a surgical challenge. In 2012, a large population study based on the National Surgical Quality Improvement Program (NSQIP) database from the United States showed that patients with MS undergoing hepatectomy for both benign and malignant diseases developed postoperative complications in 29% of cases, and 9% of them died within 30 days.[31] More recently, Paro et al[32] confirmed that patients with MS have higher odds of postoperative morbidity and mortality and, in turn, lower odds of achieving textbook outcomes following hepatectomy. Furthermore, patients were at higher risks of being readmitted to the hospital after discharge. Cauchy et al[6] in a study with 62 patients undergoing surgery showed a 11% mortality rate and a 58% morbidity rate. In a relatively larger study comparing 152 NAFLD and 844 non-NAFLD patients, Koh et al[8] corroborated these results disclosing a 54.6% versus 30.8% morbidity rate in NAFLD and non-NAFLD patients, respectively, with a major morbidity rate of 16.2% versus 8.1%. Compared to nonmetabolic related liver diseases, patients with NAFLD have significantly worse postoperative outcomes. Wakai and colleagues compared 17 patients with HCC on NAFLD, 61 with underlying hepatitis B disease, and 147 with underlying hepatitis C. Patients with NAFLD had a 59% morbidity rate as compared to 28% in hepatitis C and 31% in hepatitis B patients. Furthermore, mortality was also higher with a rate of 12% in NAFLD patients as compared to 0.7% in hepatitis C and 3.3% in hepatitis B.[9] In our cohort from Western tertiary-referral centers, we observed a 34.6% morbidity and 2.9% mortality at 90 days, with 13.8% of patients experiencing major complications. These results are promising, especially considering that all of our patients, as opposed to those of the above-mentioned study, were diagnosed with HCC and that 17.5% and 32.6% had significant fibrosis or

cirrhosis, respectively, therefore harboring increased postoperative risks. Notwithstanding, morbidity and mortality are still high and might be ameliorated by preoperatively selecting patients at the highest risk for surgery.

Comorbidities in MS play an essential role in increasing the chance of postoperative complications. Diabetes, obesity, dyslipidemia, cardiovascular, and respiratory diseases frequently coexist in this syndrome, framing the patient as a high-risk individual from a surgical standpoint.[33,34] Indeed, MS has been recognized as a predictor of adverse postoperative outcomes in bariatric, colorectal, pancreatic, and endocrine surgery.[35–37] A high number of patients were overweight or obese in our study, with an overall high mean BMI, diabetes, hypertension, and dyslipidemia. This further highlights the complexity of managing patients with HCC on MS: indeed, in addition to the tumor itself and the decreased liver function, these individuals have the additional negative predictive factor of presenting with multiple comorbidities. In our model, diabetes and obesity were associated with postoperative major complications. Appropriate diet, exercise, and pharmacotherapy should not only be employed to prevent NAFLD and the development of malignancies but also to improve the outcomes when surgery is considered.[38] Previous studies have shown that preoperative exercise and diet alteration of proteins intake without the concomitant increase of the lipids intake are effective tools to improve short-term and long-term outcomes in cancer patients with MS.[39,40] In this setting, clinicians should consider preoperative nutrition consult and rehabilitation support to eventually improve outcomes.

For patients with early-stage HCC undergoing surgery, advanced liver cirrhosis and portal hypertension are adverse prognostic factors for both short-term and long-term outcomes.[41,42] In our study, we confirmed that the presence of clinically significant portal hypertension was associated with increased major morbidity and mortality and should therefore be preoperatively assessed in patients with MS undergoing surgery. Preoperative liver function is mostly assessed with the MELD score and Child-Pugh classifications. These scores were originally developed in patients with cirrhosis. Because our study includes both patients with and without cirrhosis, the ALBI score would be more appropriate. Unfortunately, this was available only for 438 out of the 1087 patients. This is probably related to the fact that the ALBI is currently adopted in few of the centers included in our study. Indeed, despite being developed on a Western series of patients,[43] this score has been mainly validated and used in the East.[44–47]

There is a significant association between postoperative complications in NAFLD and the extent of liver resections. A systematic review and meta-analysis in 2010 reported that patients with at least 30% steatosis had significantly increased risks of morbidity and mortality following major hepatic resections.[7] A more recent study including both benign and malignant liver tumors showed that following major resections, patients with MS had a 37% and 32% chance of postoperative morbidity and serious morbidity, respectively, and a 2.7% chance of mortality.[48] We confirmed that major hepatectomies were associated with high rates of complications and death and were among the strongest predictors of poor surgical outcomes. Indeed, posthepatectomy liver decompensation is a significant issue for patients with HCC that is further worsened in cases of major resections; depending on the preoperative clinical assessment and the estimation of the future liver remnant and

its regeneration capacity, the extent of resections should be weighed against the potential drawbacks that major surgery implies. A parenchymal sparing approach should be preferred whenever possible and certainly in patients with impaired liver function and comorbidities, still maintaining oncological adequacy.

Another potentially modifiable risk factor in the hands of the surgeon is the type of surgical approach. Since its introduction, minimally invasive liver surgery has been associated with improved postoperative outcomes, including morbidity and hospital stay, especially in the setting of HCC and liver cirrhosis.[49–51] In our study, we identified that surgical approach, either laparoscopic or robotic-assisted, was associated with decreased major morbidity. Patients with MS potentially benefit from a minimally invasive approach but are frequently obese and have pulmonary or cardiovascular comorbidities, limiting the application of laparoscopy or robotics. In our opinion, a minimally invasive approach should strongly be considered in these patients as the benefits may outweigh the risks of conversion. In this setting, referral to tertiary centers where laparoscopy or robotics have been implemented should be considered.

MS and NAFLD are associated with various histopathological changes, ranging from normal parenchyma to significant fibrosis and cirrhosis. These modifications are potentially related to different rates of complications that are currently under investigation worldwide. Of note, previous studies have shown that in patients with noncirrhotic NAFLD livers, morbidity following liver resection is similar to patients with liver cirrhosis.[30,52,53] However, no correlation with histopathological data has been reported so far. To our knowledge, this is the first study demonstrating the association between nontumoral liver parenchyma changes and morbidity following surgery in patients with MS. The collaboration between experienced centers allowed gathering precise pathological data to address important clinical questions. First, cirrhotic livers were associated with almost a 3-fold increase in major complications compared to patients with normal parenchyma, similarly to what has been already reported in the literature.[42,54–56] Second, even initial parenchymal changes such as steatosis and NASH showed to have a detrimental effect on major complications following hepatectomy. This result, although intuitive, it is the first of its kind given the data and represents an important message in the field. As 75% of patients with MS showed some sort of parenchymal disease and 32.6% had cirrhosis, the preoperative knowledge of such changes might be useful in selecting patients undergoing liver resection, especially if a major operation is planned. Despite this, pathological information of nontumoral liver parenchyma requires a preoperative biopsy which is neither recommended by international guidelines nor performed in most centers worldwide. In this setting, we suggest implementing noninvasive diagnostic measurements of liver steatosis and fibrosis (serum biomarkers, MRI, fibroscan) to stratify the surgical risk for each patient, eventually improving the selection of surgical candidates and allowing for a clear patient-clinician discussion and informed consent. Indeed, the main application of the model proposed in the current study is to support a clear and thorough discussion with the patient on risks and benefits of the procedure, to clarify expectations and to guide clinicians addressing the informed consent properly.

This is a retrospective study, and selection bias might limit the data quality and results. Variables such as comorbidities can be hard to retrieve and categorize, especially in a multicenter study involving 24 centers. We only allowed the inclusion of patients satisfying at least 3 of the 5 diagnostic criteria for MS, therefore improving the homogeneity of our population. Recently, a new definition of metabolic-associated fatty liver disease was proposed:[57,58] collection of data for the present study was ongoing when this new definition was proposed. Metabolic-associated fatty liver disease should be further investigated and validated to standardize terminology in the literature. Our study is the largest available on the topic, collecting patients from 24 institutions from Western countries where MS represents a major healthcare problem. Furthermore, this is the first study reporting risk factors for postoperative major morbidity of this high-risk subset of patients. The reproducibility of our results is limited to Western countries as Asian populations have both different body compositions and different surgical policies regarding HCC. MS is, however, not only a Western disease as it is rapidly growing also in Eastern countries. Results of surgery in this setting are warranted. Weight and BMI are limited measures to truly assess the outcomes of patients undergoing surgery. Sarcopenia and body composition are more powerful predictors of outcomes and are currently assessed in different surgical settings.[38] However, sarcopenia was not considered in the current study as few centers have employed this marker in clinical practice. The prediction model presented in this study excluded patients with missing variables rather than using multiple imputations and used internal validation with the bootstrapping method. Missing data were considered to be missing completely at random in the present study, therefore being noninformative to our primary aim. We acknowledge that missing completely at random is rare and that significant information might be hidden in data that were not available in our database. For this reason, external validation of our model is required, preferably in a prospective fashion and in large populations.

CONCLUSIONS

MS is a rising disease in Western countries and will eventually represent the major cause of HCC. Patients with HCC on MS have multiple comorbidities and different degrees of liver function. In this setting, liver resection is at high risk for postoperative complications and death, and the selection of patients is mandatory to improve the outcomes. Patients' characteristics such as, BMI, diabetes, ischemic heart disease the presence of portal hypertension, and the status of nontumoral liver parenchyma should be carefully considered before surgery. Minor resections and minimally invasive approaches should be preferred whenever possible to decrease the chance of postoperative complications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

CONFLICT OF INTEREST

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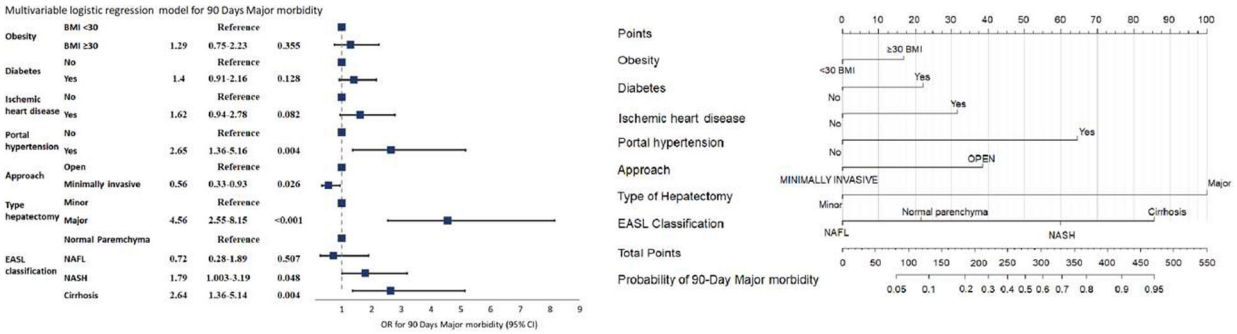

FIGURE 1.

Multivariable model and nomogram to predict 90 days major morbidity following surgery for hepatocellular carcinoma on metabolic syndrome. The nomogram maps the predicted probability of 90 days postoperative major morbidity in a scale of 0–550. For each covariate, please draw a vertical line upwards and note down the corresponding points (ie, major hepatectomy = 100 points). This is repeated for each covariate ending with a total score that corresponds to a predicted probability of morbidity at the bottom of the nomogram. Please visit https://childb.shinyapps.io/NomogramMajorMorbidity90days/. Model equation on logarithmic scale was equal to: −3.2+0.26*Obesity(BMI ≥ 30)+0.34*Diabetes +0.48*Ischemic heart disease+0.98*Portal Hypertension–0.58*Approach(minimally invasive)+1.52*type of hepatectomy(major)+(if EASL classification = NAFL the coefficient was −0.32; if EASL classification = NASH the coefficient was +0.58; if EASL classification = Cirrhosis the coefficient was +0.97). Lower and upper confidence limit of the constant: −4.04 to −2.55. Abbreviations: BMI, body mass index; EASL, European Association for the Study of the Liver.

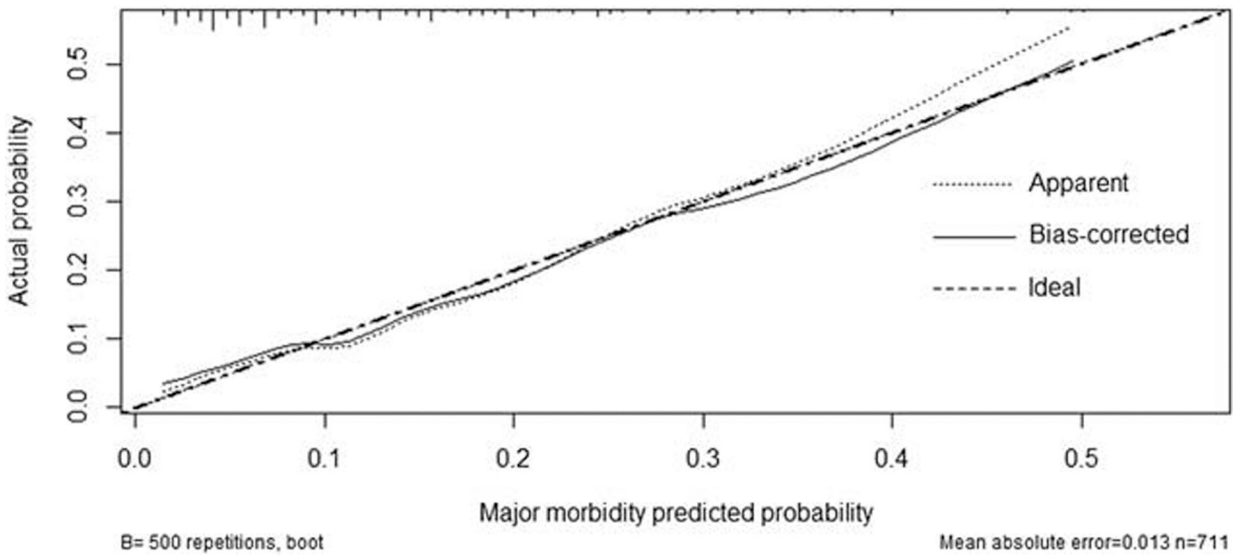

FIGURE 2.

Calibration plot of the nomogram. Ideal line estimated probabilities correspond to the actual observed; apparent line, prediction capability of the model obtained after data analysis; bias-corrected line, prediction capability of the model obtained after bootstrap correction. Vertical lines at the top of the figure represent number of patients.

TABLE 1

Patients' characteristics

	n = 1087, n (%)	Missing data
Age (y)	68.7 (± 9.3)	0
Gender, female/male	305/782	0
Geographic area		0
Europe	667 (61.4)	
North America	420 (38.6)	
BMI (kg/m^2)	29.4 (± 5.32)	22
Obesity (BMI ≥ 30 kg/m^2)	484 (45.2)	17
ASA score	3 (2–3)	48
Charlson comorbidity index	6 (5–7)	390
Hypertension	844 (78.1)	6
Diabetes	610 (56.4)	6
Ischemic heart disease	217 (20.1)	9
Congestive cardiac failure	61 (5.7)	12
Respiratory disease	172 (16)	11
Dyslipidemia	587 (54.3)	7
Child-Pugh score		199
A	840 (94.6)	
B	47 (5.3)	
C	1 (0.1)	
MELD score	8 (6–9)	74
ALBI score		649
1	255 (58.2)	
2	174 (39.7)	
3	9 (2.0)	
Portal hypertension	97 (10.4)	156
Preoperative ascites	27 (2.7)	97
Preoperative varices	77 (8)	123
Previous treatment		2
Locoregional (TACE-TARE-RFA)	122 (11.2)	
Liver resection	25 (2.3)	
Previous supramesocolic surgery	189 (17.7)	18
Preoperative hemoglobin (g/dL)	13.4 (± 1.88)	66
Preoperative AST (μ/L)	36 (25–55)	75
Preoperative ALT (μ/L)	34 (23–51)	74
Preoperative GGT (μ/L)	74 (42–138)	386
Preoperative bilirubin (mg/dL)	0.7 (0.5–1)	30
Preoperative INR	1.1 (1–1.19)	28
Preoperative creatinine (mg/dL)	0.9 (0.77–1.16)	25
Preoperative albumin (g/L)	4 (3.6–4.3)	343

	n = 1087, n (%)	Missing data
Preoperative platelets (10^3/mm^3)	202 (153–266)	20
Preoperative platelets <100,000/mm^3	80 (7.5)	
Preoperative AFP (ng/mL)	9.4 (3.6–63)	144
Preoperative AFP > 200 ng/mL	144 (15.3)	
Number of lesions	1 (1–1)	12
Size of lesions (mm)	48 (31 −75)	12

Note: Continuous data were expressed as mean ± SD or median (25th–75th percentile).

Abbreviations: AFP, alfafetoprotein; ALBI, albumin-bilirubin; ALT, alanine transaminase; ASA, American Society of Anesthesiology; AST, aspartate transaminase; BMI, body mass index; GGT, gamma-glutamyl transferase; INR, international normalized ratio; MELD, Model for End Stage Liver Disease; RFA, radiofrequency ablation; TACE, transarterial chemoebolization; TARE, transarterial radioembolization.

TABLE 2

Intraoperative data

	n = 1087, n (%)	Missing data
Year of operation		0
2001–2011	273 (25.1)	
2012–2015	328 (30.2)	
2016–2018	293 (26.9)	
2019–2021	193 (17.8)	
Approach		0
Open	642 (59.1)	
Laparoscopic	391 (36.0)	
Robotic assisted	54 (5.0)	
Type of hepatectomy		0
Minor	743 (68.3)	
Major	344 (31.7)	
Type of resection		0
Wedge	291 (26.8)	
Segmentectomy	198 (18.2)	
Bisegmentectomy[a]	118 (10.9)	
Left lateral sectionectomy	79 (7.3)	
Left medial sectionectomy	8 (0.7)	
Right anterior sectionectomy	6 (0.6)	
Central hepatectomy	12 (1.1)	
Left hepatectomy	82 (7.6)	
Right hepatectomy	193 (17.7)	
Left extended hepatectomy	11 (1)	
Right extended hepatectomy	42 (3.9)	
Pringle	607 (56.4)	10
Total pringle time (min)	35 (20–55)	49
Blood loss (mL)	300 (100–600)	139
Blood transfusions	130 (12.4)	38
Operative time (min)	236 (170–304)	120

Note: Continuous data were expressed as median (25th–75th percentile).

[a]Bisegmentectomy other than the ones listed in the table.

TABLE 3

Postoperative data

	n = 1087, n (%)	Missing data
90 d mortality	31 (2.9)	0
90 d morbidity	376 (34.6)	0
Major morbidity (Clavien-Dindo ≥ III)	150 (13.8)	2
Comprehensive complication index	22.6 (20.9–37.1)	5
Postoperative ascites	107 (9.8)	0
Liver failure	35 (3.2)	0
Bile leak	55 (5.0)	0
Sepsis	29 (2.6)	0
Superficial surgical site infection	23 (2.3)	0
Pleural effusion	57 (5.2)	0
Pneumonia	43 (4.0)	0
Deep vein thrombosis/pulmonary embolism	14 (1.3)	0
Myocardial infarction	10 (0.9)	0
Atrial fibrillation	31 (2.9)	0
Urinary tract infection	21 (1.9)	0
Acute kidney injury	31 (2.9)	0
Hemorrhage	24 (2.2)	0
Other	114 (10.5)	0
POD 1 bilirubin (mg/dL)	1.1 (0.7–1.58)	448
POD 1 INR	1.2 (1.12–1.36)	418
POD 1 platelets (10^3/mm^3)	173 (133–223)	329
POD 3 bilirubin (mg/dL)	1.2 (0.8–1.75)	460
POD 3 INR	1.2 (1.1–1.36)	474
POD 3 platelets (10^3/mm^3)	161 (121–207)	372
POD 5 bilirubin (mg/dl)	1 (0.7–1.6)	652
POD 5 INR	1.2 (1.1–1.3)	687
POD 5 platelets (10^3/mm^3)	184 (141–243)	552
Hospital stay (d)	6 (5–9)	5
Readmission	81 (8.5)	136
R1 resection	95 (8.8)	12

Note: Continuous data were expressed as median (25th–75th percentile). Abbreviations: INR, international normalized ratio; POD, postoperative day.

TABLE 4

Logistic regression analysis for 90-day major morbidity

	90 D major morbidity (%, n/N)	Univariable analysis			Multivariable analysis		
	13.4 (95/713)	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Gender							
Female	11.7 (25/214)		Reference				
Male	14.1 (70/499)	1.23	0.83–1.84	0.303			
Age							
Years		1.00	0.98–1.03	0.895			
Obesity (BMI ≥ 30)							
No	10.7 (44/413)		Reference			Reference	
Yes	17.0 (51/300)	1.72	1.07–2.76	0.025	1.29	0.75–2.23	0.355
Hypertension							
No	11.6 (18/158)		Reference				
Yes	13.8 (77/556)	1.22	0.84–1.78	0.304			
Diabetes							
No	9.9 (31/312)		Reference			Reference	
Yes	16.0 (64/401)	1.72	1.109–2.69	0.017	1.40	0.91–2.16	0.128
Respiratory disease							
No	12.8 (77/601)		Reference				
Yes	16.1 (18/112)	1.30	0.75–2.26	0.344			
Ischemic heart disease							
No	12.3 (71/579)		Reference			Reference	
Yes	17.9 (24/134)	1.56	0.99–2.46	0.054	1.62	0.94–2.78	0.082
Dyslipidemia							
No	13.0 (39/299)		Reference				
Yes	13.5 (56/414)	1.04	0.60–1.80	0.880			
Previous surgery							
No	12.9 (77/599)		Reference				
Yes	15.8 (18/114)	1.27	0.50–3.25	0.617			
Portal hypertension							
No	12.3 (79/640)		Reference			Reference	

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	90 D major morbidity (%, n/N)	Univariable analysis			Multivariable analysis		
	13.4 (95/713)	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Yes	21.9 (16/73)	1.99	1.11–3.59	0.021	2.65	1.36–5.16	0.004
MELD score							
< 9	12.0 (58/485)		Reference				
≥ 9	16.2 (37/228)	1.43	0.74–2.75	0.289			
Approach							
Open	17.9 (68/380)		Reference			Reference	
Minimally invasive	8.1 (27/333)	0.4	0.22–0.73	0.003	0.56	0.33–0.93	0.026
Type hepatectomy							
Minor	8.3 (40/483)		Reference			Reference	
Major	23.9 (55/230)	3.48	1.97–6.16	< 0.001	4.56	2.55–8.15	< 0.001
Nontumoral parenchyma							
Normal parenchyma NAFL	10.5 (31/294)		Reference			Reference	
	7.3 (6/82)	0.67	0.24–1.90	0.451	0.72	0.28–1.89	0.507
NASH	14.7 (19/129)	1.47	0.70–3.06	0.309	1.79	1.00–3.19	0.048
Cirrhosis	18.8 (39/208)	1.96	1.27–3.02	0.002	2.64	1.36–5.14	0.004

Abbreviations: BMI, body mass index; MELD, Model for End Stage Liver Disease.

TABLE 5

Logistic regression analysis for 90-day mortality

	90 D mortality (%. n/N)	Univariable analysis		
	3.1 (22/713)	OR	95% CI	*P*
Gender				
Female	29 (62/214)		Reference	
Male	36.5 (182/499)	1.47	0.57–4.53	0.451
Age				
Years		1.01	0.96–1.06	0.812
Obesity (BMI ≥ 30)				
No	2.2 (9/413)		Reference	
Yes	4.3 (13/300)	2.03	0.87–4.99	0.107
Hypertension				
No	3.9 (6/155)		Reference	
Yes	2.9 (16/558)	0.73	0.29–2.07	0.524
Diabetes				
No	1.6 (5/312)		Reference	
Yes	4.2 (17/401)	2.71	0.99–7.45	0.052
Respiratory disease				
No	3 (18/601)		Reference	
Yes	3.6 (4/112)	1.2	0.34–3.29	0.746
Ischemic heart disease				
No	2.9 (17/579)		Reference	
Yes	3.7 (5/134)	1.28	0.41–3.31	0.632
Dyslipidemia				
No	3.3 (10/299)		Reference	
Yes	2.9 (12/414)	0.86	0.37–2.07	0.734
Previous surgery				
No	3.3 (20/599)		Reference	
Yes	1.7 (2/114)	0.52	0.08–1.80	0.378
Portal hypertension				
No	2.5 (16/640)		Reference	
Yes	8.2 (6/73)	3.49	1.22–8.81	0.012
MELD score				
< 9	1.9 (9/485)		Reference	
≥ 9	5.7 (13/228)	3.2	1.36–7.86	0.008
Approach				
Open	3.4 (13/380)		Reference	
Minimally invasive	2.7 (9/333)	0.78	0.32–1.84	0.581
Type hepatectomy				
Minor	1.7 (8/483)		Reference	
Major	6.1 (14/230)	3.84	1.62–9.76	0.003

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	90 D mortality (%. n/N)	Univariable analysis		
	3.1 (22/713)	OR	95% CI	*P*
Nontumoral parenchyma				
Normal parenchyma	3.1 (9/294)		Reference	
NAFL	0 (0/82)	—	—	—
NASH	3.1 (4/129)	1.01	0.27–3.17	0.983
Cirrhosis	4.3 (9/208)	1.43	0.55–3.73	0.455

Abbreviations: BMI, body mass index; MELD, Model for End Stage Liver Disease.