Probability of Postoperative Complication after Liver Resection: Stratification of Patient Factors, Operative Complexity, and Use of Enhanced Recovery after Surgery

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BACKGROUND: The current study aimed to assess the performance of the 3-level complexity classification that stratified liver resection procedures into 3 complexity grades (grade I, low; grade II, intermediate; and grade III, high complexity) and to evaluate whether the Enhanced Recovery after Surgery (ERAS) protocol improves postoperative outcomes for each complexity grade.

STUDY DESIGN: Consecutive patients undergoing open liver resection and laparoscopic liver resection at Lausanne University Hospital during 2010 to 2020 were assessed.

RESULTS: A total of 437 patients were included. Operative time, estimated blood loss, and length of hospital stay increased significantly, with a stepwise increase of the grades from I to III in open liver resection and laparoscopic liver resection (all, $p < 0.05$). The same trend for Comprehensive Complication Index was found in open liver resection ($p < 0.005$). Age ($p = 0.004$), 3-level complexity classification (grade II vs I; $p = 0.001$; grade III vs I; $p < 0.001$), no use of the ERAS protocol ($p = 0.016$), and biliary reconstruction ($p < 0.001$) were significant predictors for postoperative complication, defined as Comprehensive Complication Index $\geq$ 26.2 in a multivariable logistic regression analysis. The prediction model incorporating the 4 factors had a calculated Concordance Index of 0.735 and 0.742 based on the bootstrapping method. The use of ERAS protocol was associated with lower probability of postoperative complication for each complexity grade and age.

CONCLUSIONS: The use of ERAS protocol can decrease the probability of postoperative complication for each surgical complexity of liver resection and patient age. This finding emphasized the importance of tailoring perioperative management according to surgical complexity and patient age to improve outcomes after liver resection. (J Am Coll Surg 2021;233:357−368.

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Abbreviations and Acronyms

AUC	=	area under the curve
CCI	=	Comprehensive Complication Index
ERAS	=	Enhanced Recovery after Surgery
LLR	=	laparoscopic liver resection
OLR	=	open liver resection
OR	=	odds ratio

Recent advances in surgical technique and perioperative management have improved postoperative outcomes in patients undergoing liver resection.[1,2] The incidence of postoperative complication after liver resection remains high compared with other oncologic operations.[3] To predict postoperative outcomes, the minor/major classification has been used traditionally to categorize liver resection procedures into 2 complex levels. The nomenclature of minor and major liver resections was originally introduced by Tung in 1979.[4] In the study, major liver resection was defined as resection of 2 or more sections, which were equivalent to Couinaud segments II+III, IV, V+VIII, or VI+VII. Recently, most studies have defined the term *major liver resection* as the resection of 3 or more contiguous segments.[5] However, studies reported that the minor/major classification did not effectively stratify liver resection procedures in terms of surgical complexity and postoperative outcomes.[6-8] The new 3-level complexity classification for laparoscopic liver resection (LLR), which categorized 11 LLR procedures as being of low, intermediate, or high grade, was proposed on the basis of a study using a French cohort in 2018.[6] Subsequently, it was validated for LLR in a Japanese multi-institution cohort and an Italian multi-institution cohort[9,10] and for open liver resection (OLR) in a North American cohort and a Japanese cohort.[5,9]

The Enhanced Recovery after Surgery (ERAS) programs was advocated to improve postoperative outcomes and allow cost reduction, and has been used for abdominal, orthopaedic, urologic, and gynecologic operations.[11-17] Our institution had been using the ERAS protocol for patients undergoing liver resection since July 2013 and showed benefits of the liver ERAS protocol.[18,19] However, the effect of the ERAS protocol is unclear in the context of various surgical complexity levels and other factors associated with postoperative complication.

The current study aimed to assess the performance of the 3-level complexity classification for LLR and OLR in a Swiss cohort and to evaluate whether the ERAS protocol was effective for improving postoperative outcomes after each complexity level of liver resection.

METHODS

Patient selection

The study analyzed prospectively recorded baseline characteristics and surgical outcomes of 437 consecutive patients who underwent OLR or LLR for malignant or benign liver tumors at Lausanne University Hospital between January 2010 and February 2020. Institutional indication criteria of LLR was generally based on the Second International Consensus Conference.[20] At the beginning, we indicated liver lesions that were resected using nonanatomic wedge resection and left lateral sectionectomy as laparoscopic approach, and gradually expanded the indication for LLR to anatomic resection and hemihepatectomy. Contraindications for laparoscopic liver resection are as follows: perihilar cholangiocarcinoma or need for liver resection with biliary reconstruction and history of upper abdominal operation. Since July 2013, all patients with liver resection were managed according to liver ERAS. This study was approved by the local ethics committee (registration number CER-VD 2020-02649). Written informed consent was obtained from all patients.

Surgical procedures

OLR was performed under general anesthesia and epidural analgesia. J-shape incision without thoracotomy was performed systematically. Parenchymal transection was performed using a Cavitron ultrasonic surgical

Table 1. Enhanced Recovery after Surgery Protocol

ERAS single item	ERAS protocol
Preoperative	
Counseling and education	Preadmission counseling and written information at the outpatient clinic*
Fasting	Clear fluids until 2 h before operation, solids 6 h before operation
Carbohydrate drink	800 mL the evening before operation and 400 mL 2 h before operation
Premedication	No premedication
Thromboprophylaxis	Low-molecular-weight heparin 12 h before operation and during hospitalization, and IPC
Oral bowel preparation	No routine use
Intraoperative	
PONV prophylaxis	Droperidol + ondansetron ± betamethasone if no contraindication
Hypothermia prevention	Active warming with air blanket
Antibiotic prophylaxis	Cefuroxime 1.5 g at induction
Balanced IV fluids	Intraoperative crystalloids, quantity depending on the operation, avoiding salt and water overload Postoperative crystalloids 1000 mL for the first 24 h then 500 mL/24 h for the first postoperative days
Postoperative	
Nasogastric tube	No routine use
Postoperative analgesia	Epidural or systemic morphine and paracetamol (if no hepatic failure) and metamizole Oral oxycodone-naloxone (when epidural is removed, usually on POD 3). NSAID from POD 5 instead of metamizole
Abdominal drain	No routine abdominal drainage
Urinary catheter	Removal on POD 3
Nutrition	Free fluid 4 h after operation Normal diet from POD 1 2 nutritional supplements per day
Laxative	Oral magnesium hydroxide twice a day until day of hospital discharge
Mobilization	Out of bed at least 2 h on the day of operation From POD 1 at least 8 h out of bed
Systematic audit	Systematic audit, meeting every 3 mo

*Preadmission counseling is performed by the Enhanced Recovery after Surgery (ERAS)-dedicated nurse and consists mainly of information on the ERAS protocol and the patient log book.
IPC, intermittent pneumatic compression; POD, postoperative day; PONV, postoperative nausea and vomiting.

aspirator (CUSA EXel+TM; Integra LifeSciences) and an ultrasonically activated device (Harmonic HD 1000i; Johnson & Johnson). LLR was performed under general anesthesia without peridural. A balloon-tipped trocar was inserted at supraumbilical place, and 3 or 4 trocars were placed in total. Parenchymal transection was performed using a Cavitron ultrasonic surgical aspirator, an ultrasonically activated device, and bipolar forceps (Micro France CEV134; Integra Lifesciences). Intermittent inflow occlusion (Pringle maneuver) was performed if necessary (eg for high risk of bleeding and uncontrollable bleeding).[21]

Institutional Enhanced Recovery after Surgery program

The ERAS protocol for liver operation has been applied since July 2013. The ERAS protocol was initially designed by the local ERAS team and included a list of diverse pre-, intra-, and postoperative items that were based on our previous study (Table 1).[18] This ERAS liver protocol was later validated by a panel of international liver surgeons based on a Delphi process and by the ERAS Society, and was published in 2016 as official ERAS guidelines.[18]

Definitions

Anterolateral segments are defined as Couinaud segments II, III, IVb, V, and VI, and posterosuperior segments are defined as Couinaud segments I, IVa, VII, and VIII.[6,20,22] Surgical complexity of liver resection procedures was stratified using the 3-level complexity classification, which classifies 11 different liver resection procedures as grade I (low complexity), grade II (intermediate complexity), or grade III (high complexity) (Fig. 1).[5,6,9,23] *Wedge resection* was defined as "resection of less than one Couinaud segment for removal of a tumor less than 3 cm in diameter" and *segmentectomy* was defined as "resection of less than one Couinaud segment for removal of a tumor at

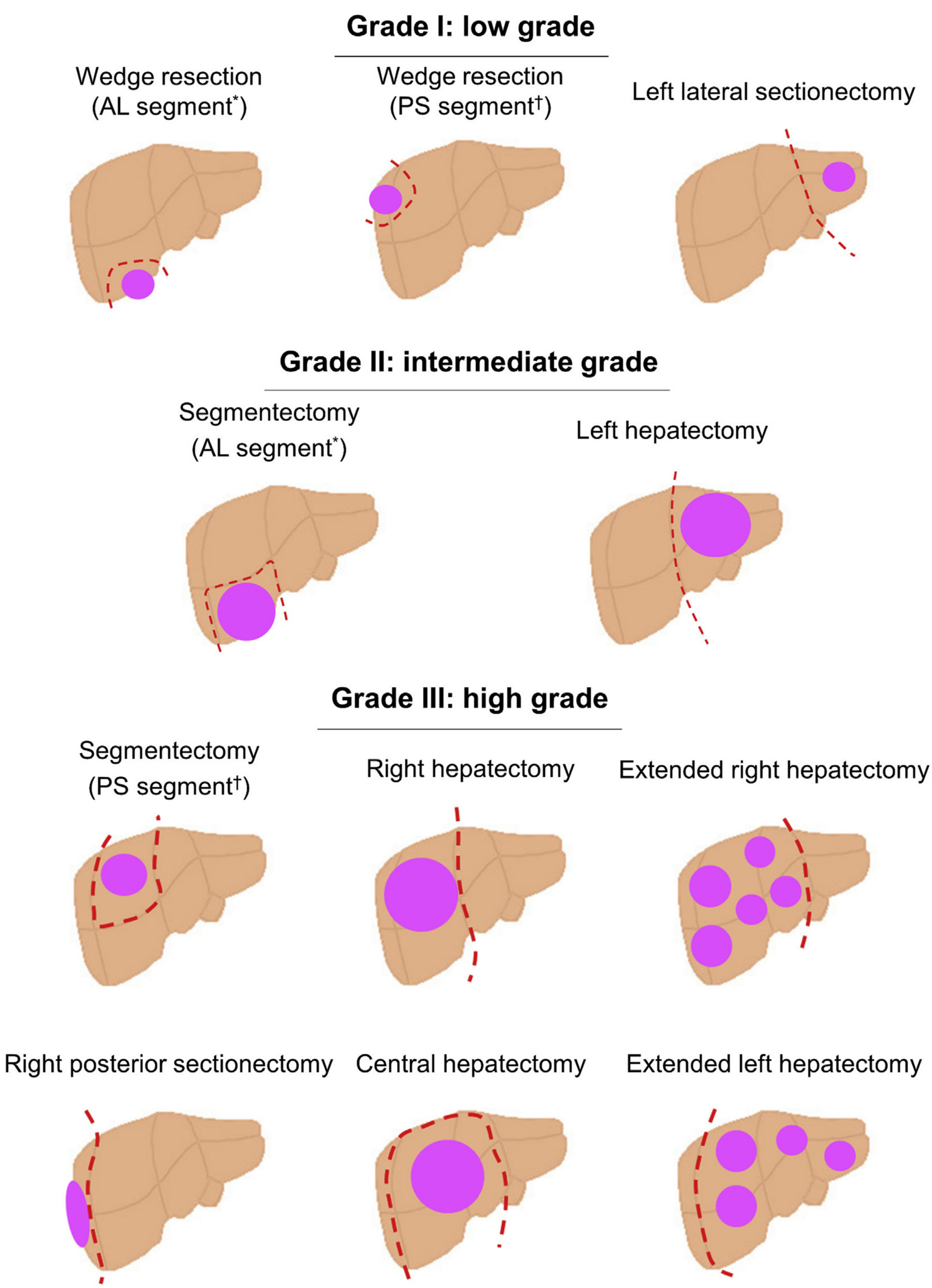

Figure 1. Three-level complexity classification. *Anterolateral (AL) segments are defined as Couinaud segments 2, 3, 4b, 5, and 6. †Posterosuperior (PS) segments are defined as Couinaud segments 1, 4a, 7, and 8. (Reprinted from Kawaguchi and colleagues[23] with permission from Wiley.

least 3 cm in diameter or anatomical removal of one Couinaud segment."[5,8] Major liver resection was defined as the resection of more than 3 contiguous Couinaud segments according to the minor/major classification.[5,8,24] When 2 or more areas of the liver were resected, the higher grade was applied to the patient; for example, patients undergoing right hepatectomy (grade III and major resection) and wedge resection of segment III (grade I and minor resection) were categorized as grade III and major resection. We defined morbidity and death that occurred within 90 days after operation as postoperative complication and mortality, respectively. Postoperative complications were graded using the Clavien classification,[25] and cumulative morbidity was measured using the Comprehensive Complication Index (CCI).[26]

Comparison of 2 classifications

The performance of the 3-level classification was compared with that of the minor/major classification for stratifying liver resection procedures with respect to surgical and postoperative outcomes. To test whether the 3-level complexity classification performed better than the minor/major classification, the areas under the receiver operating characteristic curves (AUCs) were compared.

Statistical analysis

Categorical variables were expressed as n (%) and were compared between groups using Fisher exact test or the chi-square test, as appropriate. Continuous variables were expressed as median (interquartile range) and were compared using the Kruskal-Wallis test for 3 groups. CCI scores was expressed as mean (SD), and were compared among groups using the ANOVA test for 3 groups. The 3-level complexity classification and the minor/major classification were evaluated using the receiver operating characteristic curve analysis, and AUCs were compared to evaluate the performance of each classification using the method described by Kanda.[27] Median value was used as the threshold for estimated blood loss and duration of operation (estimated blood loss of 600 mL and duration of operation of 283 minutes). A CCI score of 26.2, which corresponds to 1 postoperative complication of Clavien classification grade IIIa, was used as the threshold between high (CCI score $\geq$ 26.2) and low (CCI score $<$ 26.2) complication severity.[5] A logistic regression model analysis was used to predict the incidence of complication (CCI score $\geq$ 26.2). Odds ratios (ORs) and 95% CIs were calculated for each factor. The multivariable prediction model was developed and validated based on the TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) statement.[28] The predictive performance of the logistic regression model was internally validated using the bootstrapping method.[29] Harrell's C-statistic of the identified model was calculated using 100 bootstrap samples. A p value $<$ 0.05 was considered significant. Statistical analyses were performed using JMP Pro, version 15.0.0 (SAS Institute) and SAS, version 9.4 (SAS Institute).

Table 2. Demographic and Clinicopathologic Characteristics of Patients

Characteristic	Data (n = 437)
Patient factors	
Age, y, median (IQR)	64 (55–71)
Sex, m/f, n	266/171
BMI, kg/m^2, median (IQR)	24.7 (22.2–27.8)
ASA PS classification $\geq$ 3, n (%)	125 (28.6)
WHO performance states classification, n	
0	271
1	152
2	12
3	2
Cirrhosis, n (%)	65 (14.9)
ERAS protocol, n (%)	350 (80.1)
Diagnosis, n (%)	
Hepatocellular carcinoma	60 (13.7)
Intrahepatic cholangiocarcinoma	42 (9.6)
Hilar cholangiocarcinoma	6 (1.4)
Liver metastasis	240 (54.9)
Gallbladder cancer	13 (3.0)
Echinococcosis	40 (9.2)
Adenoma	11 (2.5)
Other	25 (5.7)
Classification of liver resection, n (%)	
3-level complexity classification	
Grade I	99 (22.7)
Grade II	110 (25.2)
Grade III	228 (52.2)
Minor/major classification, n (%)	
Minor liver resection	217 (49.7)
Major liver resection	220 (50.3)
Surgical factor, n (%)	
Open liver resection	361 (82.6)
Laparoscopic liver resection	76 (17.4)
Neoadjuvant chemotherapy	208 (47.6)
Biliary reconstruction	41 (9.4)
Portal vein resection	20 (4.6)
Drain placement	184 (42.1)

ASA PS, American Society of Anesthesiologists physical status; ERAS, Enhanced Recovery after Surgery; IQR, interquartile range.

RESULTS

Study population

From January 2010 to February 2020, a total of 437 consecutive patients underwent OLR and LLR. Demographic and clinicopathologic characteristics are shown in Table 2. Of the 437 patients, 361 patients (82.6%) underwent OLR and 76 patients (17.4%) underwent LLR. Indications for liver resection were mainly liver metastases (54.9%) and hepatocellular carcinoma (13.7%). On the basis of the 3-level

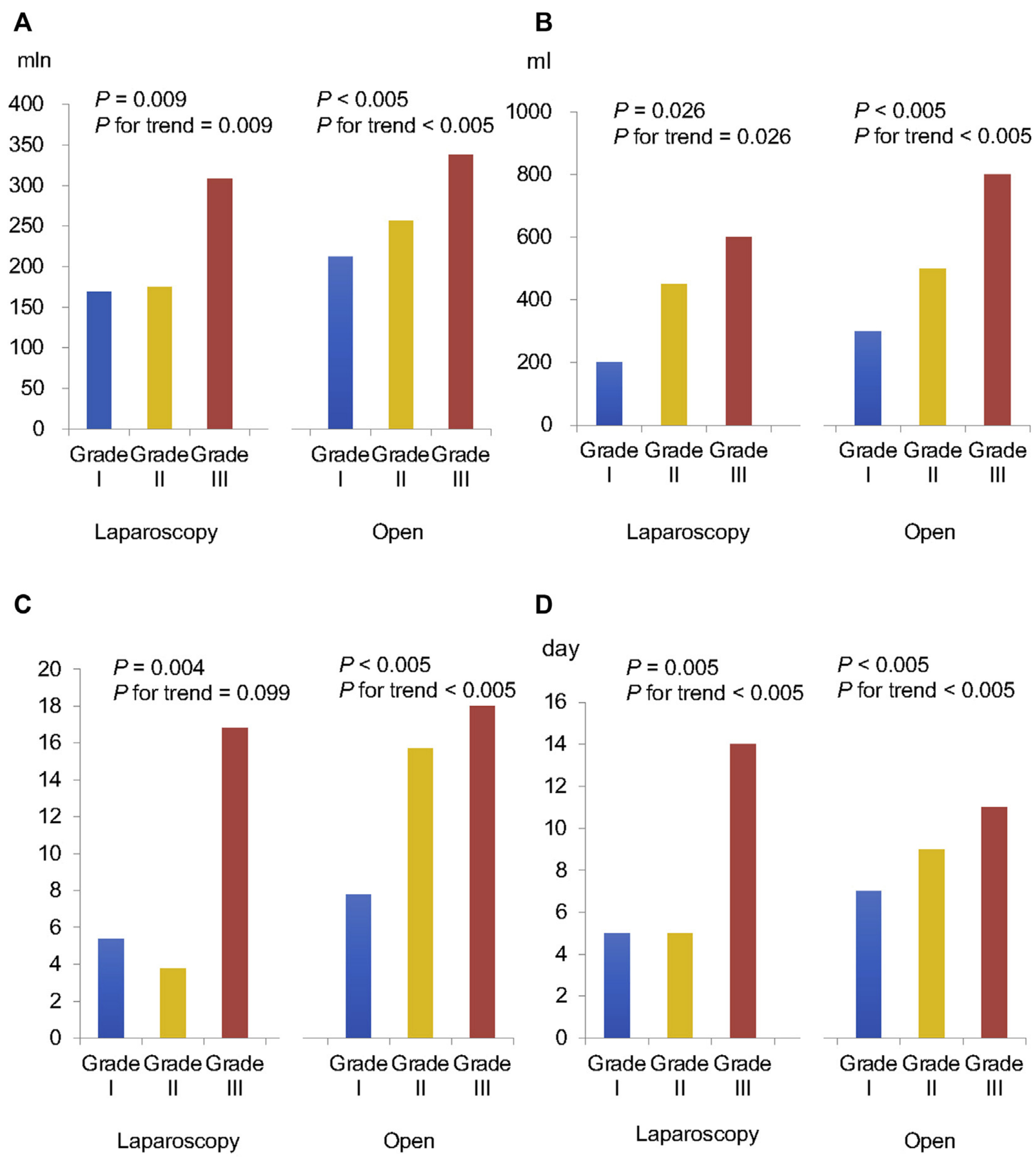

Figure 2. Surgical and postoperative outcomes by 3-level complexity classification. (A) Operative time, (B) estimated blood loss, (C) Comprehensive Complication Index (CCI), and (D) length of hospital stay. Median for (A, B, and D), and mean (SD) for (C) are shown. In patients undergoing laparoscopic liver resection, operative time ($p = 0.009$), estimated blood loss ($p = 0.026$), and length of hospital stay ($p < 0.005$) increased significantly, with a stepwise increase of the grades from I to III using the Kruskal-Wallis test. In patients undergoing open liver resection procedures, operative time, estimated blood loss, CCI, and length of hospital stay were significantly different among the 3 grades (all, $p < 0.05$) and increased significantly, with a stepwise increase of the grades from I to III (all, $p < 0.05$). CCI scores were compared among groups using ANOVA test for 3 groups.

complexity classification, 99 patients (22.7%) underwent grade I procedures, 110 patients (25.1%) underwent grade II procedures, and 228 patients (52.2%) underwent grade III procedures. A total of 350 patients (80.1%) underwent OLR and LLR with the ERAS program.

Surgical and postoperative outcomes stratified by 3-level complexity classification

Surgical and postoperative outcomes in OLR and in LLR stratified by 3-level complexity classification are shown in Figure 2. In patients undergoing LLR, operative time (p = 0.009), estimated blood loss (p = 0.026), CCI (p = 0.004), and length of hospital stay (p = 0.005) were significantly different among the 3 grades. In addition, operative time (p = 0.009), estimated blood loss (p = 0.026), and length of hospital stay (p < 0.005) increased significantly, with a stepwise increase of the grades from I to III. Similarly, in patients undergoing OLR procedures, operative time, estimated blood loss, CCI, and length of

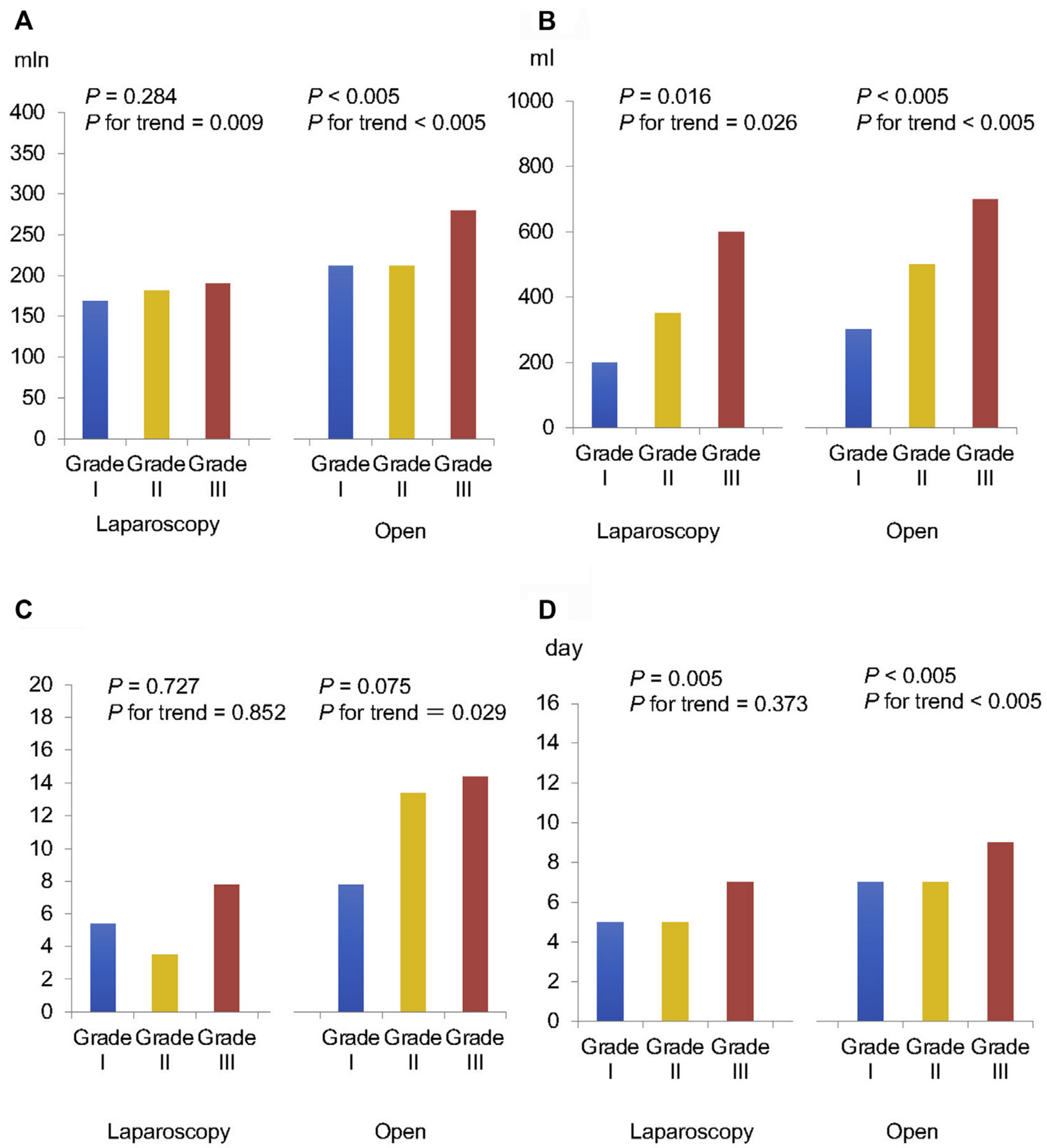

Figure 3. Surgical and postoperative outcomes of minor liver resection alone by 3-level complexity classification. (A) Operative time, (B) estimated blood loss, (C) Comprehensive Complication Index (CCI), and (D) length of hospital stay. Median for (A, B, and D), and mean (SD) for (C) are shown. Of the 217 patients who underwent minor liver resection, 100 (46.1%) underwent grade I procedures, 69 (31.8%) underwent grade II procedures, and 48 (22.1%) underwent grade III procedures. In patients undergoing laparoscopic liver resection, estimated blood loss (p = 0.016) and length of hospital stay (p = 0.005) were significantly different among the 3 grades using the Kruskal-Wallis test. Operative time (p = 0.009) and estimated blood loss (p = 0.026) increased significantly, with a stepwise increase of the grades from I to III. In patients undergoing open liver resection, operative time (p < 0.005), estimated blood loss (p < 0.005), and length of hospital stay (p < 0.005) were significantly different among the 3 grades. Operative time, estimated blood loss, CCI, and length of hospital stay increased significantly, with a stepwise increase of the grades from I to III (all, p < 0.05). CCI scores were compared among groups using ANOVA test for 3 groups.

hospital stay were significantly different among the 3 grades (all, $p < 0.05$), and increased significantly, with a stepwise increase of the grades from I to III (all, $p < 0.05$).

Mean CCIs for grade II procedures were significantly lower in patients undergoing LLR than in patients undergoing OLR (3.8 vs 15.7; $p = 0.001$), and mean CCIs for grade I procedures and for grade III procedures did not differ significantly between patients undergoing LLR and patients undergoing OLR (grade I: 5.4 vs 7.8; $p = 0.168$; grade III: 16.8 vs 18.0; $p = 0.831$).

Because the analysis included patients who had and did not have ERAS protocol, similar analysis was only repeated in patients who had ERAS protocol. The distribution of CCI scores stratified by the 3-level complexity classification and surgical approach (LLR vs OLR) was in line with the analysis of all patients (eFig. 1).

Surgical and postoperative outcomes including minor liver resection only

To evaluate whether surgical and postoperative outcomes of minor liver resection were different by the 3 grades, we repeated the similar analysis only for patients undergoing minor liver resection (Fig. 3). Of the 217 patients who underwent minor liver resection (OLR, n = 153; LLR, n = 64), 100 (46.1%) underwent grade I procedures, 69 (31.8%) underwent grade II procedures, and 48 (22.1%) underwent grade III procedures. In patients undergoing LLR, estimated blood loss ($p = 0.016$) and length of hospital stay ($p = 0.005$) were significantly different among the 3 grades. Operative time ($p = 0.009$) and estimated blood loss ($p = 0.026$) increased significantly, with a stepwise increase of grades from I to III. In patients undergoing OLR, operative time ($p < 0.005$), estimated blood loss ($p < 0.005$), and length of hospital stay ($p < 0.005$) were significantly different among the 3 grades. Operative time, estimated blood loss, CCI, and length of hospital stay increased significantly, with a stepwise increase of grades from I to III (all, $p < 0.05$).

Areas under the curve for the 3-level complexity and minor/major classifications

The AUC for estimated blood loss was significantly higher for the 3-level complexity classification than for the minor/major classification ($p = 0.004$) (Table 3). The AUCs for operative time and CCI did not differ significantly between the 2 classifications.

Predictors for postoperative complication

Because the 3-level complexity classification performed better than the minor/major classification for stratifying surgical complexity, a logistic regression model analysis was performed using the 3-level complexity classification for categorizing liver resection procedures. A univariable logistic regression model analysis showed that patient's age ($p = 0.005$), 3-level complexity classification ($p < 0.001$), no use of ERAS protocol ($p = 0.043$), biliary reconstruction ($p < 0.001$), venous resection ($p < 0.001$), open liver resection ($p = 0.003$), and drain placement ($p = 0.008$) were significantly associated with CCI $\geq$ 26.2. Of these factors, patient's age (OR 7.5; 95% CI, 1.7 to 31.7; $p = 0.004$), 3-level complexity classification (grade II vs grade I, OR 3.6; 95% CI, 1.4 to 9.2; $p = 0.005$; grade III vs grade I, OR 4.2; 95% CI, 1.7 to 10.3; $p < 0.001$), no use of ERAS protocol (OR 2.0; 95% CI, 1.1 to 3.5; $p = 0.016$), and biliary reconstruction (OR 4.5; 95% CI, 2.0 to 10.2; $p < 0.001$) were significant predictive factors for CCI $\geq$ 26.2 in a multivariable analysis (Table 4).

Table 3. Comparison of 3-Level Complexity Classification with Minor/Major Classification Using Receiver Operating Characteristic Curve Analysis

	AUC		
Variable	**3-level complexity classification**	**Minor/major classification**	**p Value**
Estimated blood loss	0.734	0.676	0.004
Operative time	0.741	0.745	0.838
CCI score	0.632	0.623	0.745

AUC, area under the curve; CCI, Comprehensive Complication Index.

Internal validation of the regression model and prediction of postoperative complication

The regression model incorporating the 4 significant predictive factors (ie age, 3-level complexity classification, use of ERAS protocol, and biliary reconstruction) was shown as follows; $\text{Log}\,[p/(1-p)] = -4.667 + 0.0277 \times (\text{age}) + 1.400 \times (\text{3-level classification, grade II} = 1 \text{ and grade I} = 0) + 1.617 \times (\text{3-level classification, grade III} = 1 \text{ and grade I} = 0) + 1.716 \times (\text{hepaticojejunostomy, yes} = 1 \text{ and no} = 0) + 0.615 \times (\text{use of ERAS protocol, no} = 1 \text{ and yes} = 0)$, p = predicted probability of postoperative complication $\geq$ CCI 26.2. This prediction model had a calculated Concordance Index of 0.735 (95% CI, 0.682 to 0.789) and 0.742 (95% CI 0.737 to 0.746) based on the bootstrapping method, which showed a relatively good discrimination. Calibration plots for this model using 100 bootstrap samples showed that the predicted proportions of postoperative complication was within 5% of the margin of error (eFig. 2). Our model showed that in patients who had ERAS protocol and liver resection without biliary reconstruction, the probability of complication (CCI $\geq$ 26.2) increased, with an

Table 4. Univariable and Multivariable Analysis for Predicting Postoperative Complication (Comprehensive Complication Index ≥ 26.2)

		Univariable			Multivariable	
		Complications				
Variable	Total patients, n	n	%	p Value	Odds ratio (95% CI)	p Value
Sex				0.877	—	—
Male	266	61	22.9		—	—
Female	171	38	22.2		—	—
Age, y (continuous)	—	—	—	0.005	7.5 (1.7−31.7)	0.004
ASA PS classification ≥3	—	—	—	0.095	—	—
Yes	125	34	27.2		—	—
No	312	64	20.5		—	—
WHO PS classification ≥2				0.065	—	—
Yes	14	6	42.9		—	—
No	423	92	21.7		—	—
Cirrhosis				0.053	—	—
Yes	65	20	30.8		—	—
No	372	78	21.0		—	—
3-level complexity classification						
Grade I	99	6	6.1	—	1.0 (ref)	—
Grade II	110	24	21.8	0.002	3.6 (1.4−9.2)	0.005
Grade III	228	67	29.4	< 0.001	4.2 (1.7−10.3)	< 0.001
ERAS protocol				0.043	—	—
Yes	350	72	20.6		1.0 (ref)	0.016
No	87	26	30.0		2.0 (1.1−3.5)	—
Biliary reconstruction				< 0.0013	—	—
Yes	41	24	58.5		4.5 (2.0−10.2)	< 0.001
No	396	74	18.7		1.0 (ref)	—
Portal vein resection				< 0.001	—	—
Yes	20	12	60.0		2.2 (0.7−6.7)	0.162
No	417	86	21.7		1.0 (ref)	—
Surgical approach				0.003	—	—
LLR	76	8	10.5		1.0 (ref)	0.271
OLR	361	91	25.2		1.6 (0.7−3.7)	—
Diagnosis				0.144	—	—
Benign	76	22	28.9		—	—
Malignant	361	76	21.1		—	—
Drain placement				0.008	—	—
Yes	184	52	28.3		1.1 (0.7−1.9)	0.636
No	253	46	18.2		1.0 (ref)	—

ASA, American Society of Anesthesiologists; ERAS, Enhanced Recovery after Surgery, LLR, laparoscopic liver resection, OLR, open liver resection; PS, physical status; ref, reference.

incremental increase of age (Fig. 4A). Regardless of the age of patients, the probability of complication (CCI ≥ 26.2) was the highest in patients undergoing grade III procedures, intermediate in patients undergoing grade II procedures, and lowest in patients undergoing grade I procedures. Figures 4B through D show that the use of ERAS protocol decreased the probability of complication (CCI ≥ 26.2) in patients undergoing grade I procedures (Fig. 4B), grade II procedures (Fig. 4C), and grade III procedures (Fig. 4D). For a 60-year-old patient, the use of ERAS protocol decreased the probability of complication (CCI ≥ 26.2) from 8.4% to 4.7% in grade I procedures, from 27.1% to 16.7% in grade II procedures, and from 31.6% to 20.0% in grade III procedures.

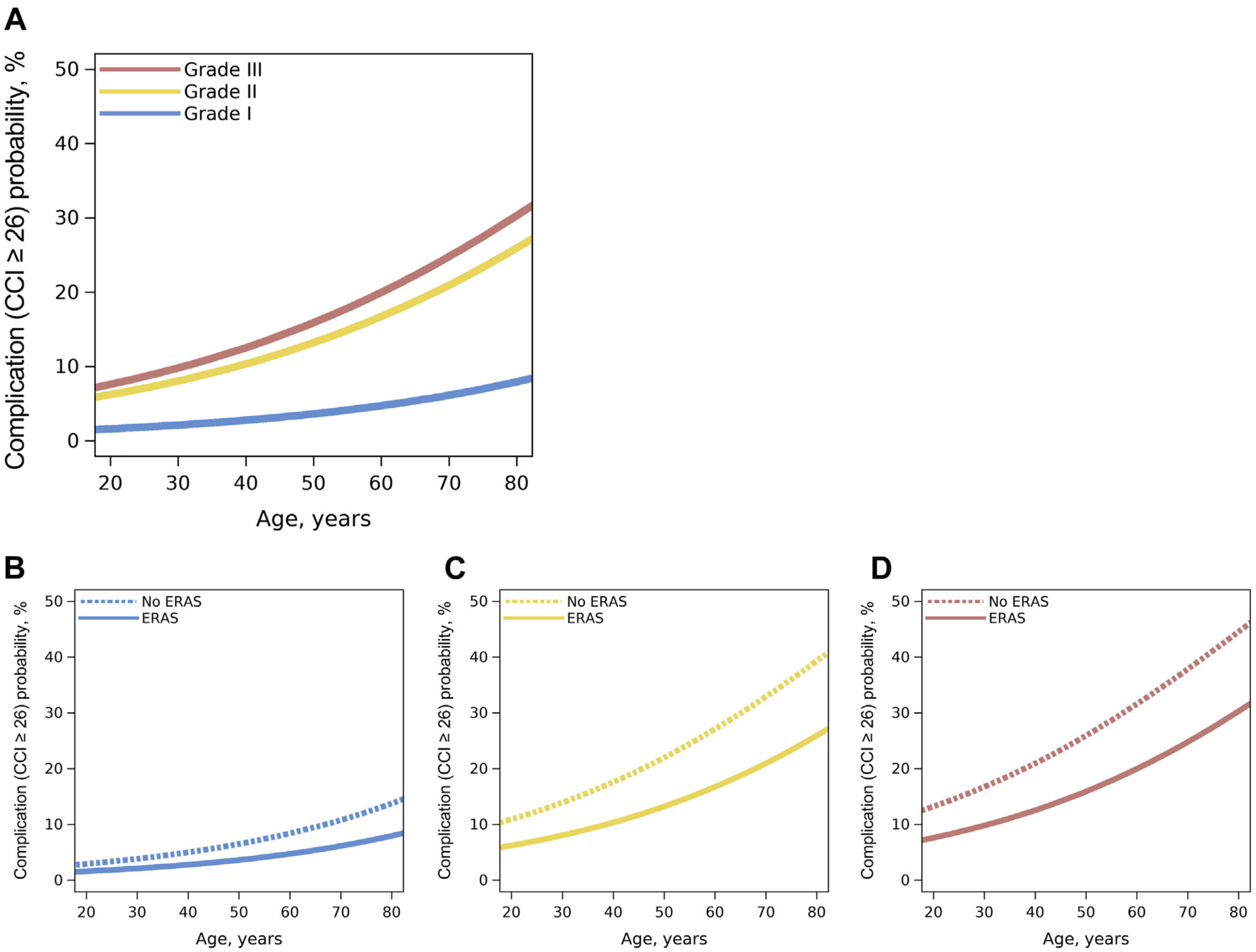

Figure 4. Probability of postoperative complication stratified by 3-level complexity classification and age with or without use of Enhanced Recovery after Surgery (ERAS) protocol. (A) Probability of postoperative complication by 3-level complexity classification and age in patients who received ERAS protocol. (B, C, D) Use of ERAS protocol was associated with lower probability of postoperative complication (Comprehensive Complication Index $\geq$ 26.2), irrespective of age, in patients undergoing resection of grade I procedures (B), grade II procedures (C), and grade III procedures (D).

DISCUSSION

The findings of the current study suggest that the recently reported 3-level complexity classification of LLR and OLR performed better than the minor/major classification with respect to surgical outcomes in patients at a European institution. Our regression model for predicting postoperative complications (CCI $\geq$ 26.2) incorporated the 4 factors (ie age, 3-level complexity classification, use of ERAS protocol, and biliary reconstruction), and showed good discrimination for predicting patients with a high probability of postoperative complication. Importantly, the current study highlighted that the 3-level complexity classification stratified the incidence of postoperative complications and use of ERAS protocol decreased the incidence of postoperative complication, regardless of patient age.

The presented regression model incorporated the recently reported 3-level complexity classification. The 3-level complexity classification[6] was designed for LLR on the basis of a cohort in a single French institution to guide surgical complexity of LLR, because the traditional minor/major classification had limitations for stratifying surgical complexity of liver resections.[9] The minor/major classification was useful for indicating the risk of liver failure. Recent advancement in liver volume calculation enabled accurate estimation of preoperative liver volume and postoperative future liver remnant volume, contributing to decreased risk of postoperative liver failure.[30] As such, the new liver resection classification associated with surgical complexity can be useful for training and planning. It allows planning liver resection procedures, tailoring management after liver resection, and comparing intergroup differences of surgical complexity in cohort studies. The 3-level complexity classification was recently validated using multi-institution data, including patients who underwent LLR at 43 Japanese institutions[9] and using 1,752 patients from the Italian Group of Minimally invasive Liver Surgery registry.[10] Although the 3-level classification was originally designed for LLR, a recent bi-institution study in the US and Japan found that the 3-level classification also applies for OLR. It was correlated with surgical and postoperative outcomes and performed better than other classifications for liver resection. The current study, based on a Swiss cohort, supported that the 3-level complexity classification did correlate with surgical and postoperative outcomes in patients undergoing either LLR or OLR (Fig. 1). In the subgroup analysis including patients who underwent minor liver resection only, the 3-level complexity classification showed a stepwise increase of surgical and postoperative outcomes. This clearly suggests a limitation of the minor/major classification because the category of minor liver resection includes heterogenous liver resection procedures in terms of surgical complexity and postoperative complication.

ERAS protocol was proposed to temper patient response to surgical stress and so decrease postoperative complications.[31] Our group had demonstrated the clinical and economic benefit of ERAS in patients undergoing colorectal surgery.[32] Other groups reported that use of the ERAS protocol improved postoperative outcomes after liver resection.[19,33,34] The current study confirmed that the use of ERAS protocol decreased the incidence of postoperative complication for all complexity levels of liver resection procedures. Specifically, the model presented suggests that use of ERAS protocol effectively decreases complication probability in older patients undergoing complex liver resection procedures. Use of ERAS protocol is only a modifiable factor in this regression model. As such, the current study might be useful for identifying patients with a high probability of postoperative complications developing and for selecting patients who should follow ERAS protocol with a high compliance.

Several studies reported that postoperative complication rate was lower in patients undergoing LLR than in patients undergoing OLR.[35-37] A univariable logistic regression analysis confirmed this finding because the probability of postoperative complication was significantly higher in OLR than in LLR patients. Interestingly, OLR (vs LLR) was no longer a predictive factor for postoperative complication using a multivariable logistic regression analysis after adjusting for other predictive factors, including the 3-level complexity classification. This implies that the incidence of postoperative complication might not be different between LLR and OLR after adjustment for surgical complexity. In fact, the incidence of postoperative complication did not differ significantly between patients undergoing LLR with grade I and III procedures and patients undergoing OLR with grade I and III procedures (Fig. 2). In contrast, the incidence of postoperative complication after grade II procedures was lower in patients undergoing LLR than in patients undergoing OLR. This finding emphasizes the importance of liver resection classification associated with surgical complexity and postoperative outcomes for comparing intergroup difference in cohort studies.

Some limitations of the current study have to be addressed. First, this is a retrospective study in a single high-volume institution in Switzerland. The proportion of LLR was low because a laparoscopic approach had only been used frequently since 2017. Finally, some data about the compliance of ERAS protocol were missing. Of note, high compliance with ERAS protocol is associated with success of ERAS implementation[38] and compliance with ERAS protocol might have influenced the effect of ERAS on postoperative outcomes.

CONCLUSIONS

This 3-level complexity classification was useful for stratifying surgical complexity and postoperative outcomes in patients undergoing OLR and LLR. The use of ERAS protocol can decrease the probability of postoperative complication for each surgical complexity of liver resection and patient age. These findings emphasize the importance of tailoring perioperative management according to surgical complexity and patient age to improve outcomes after liver resection.

Author Contributions

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Analysis and interpretation of data: Kobayashi, Kawaguchi

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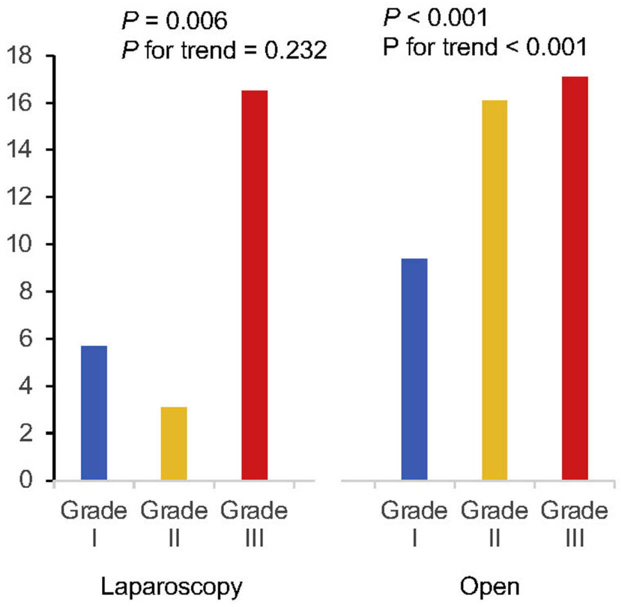
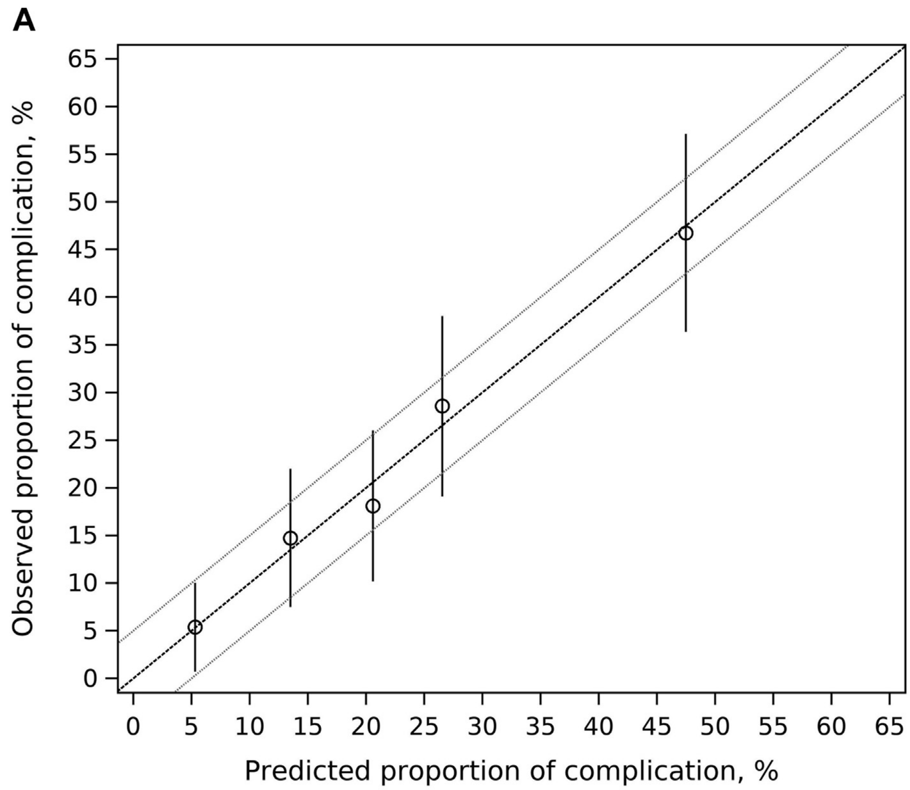
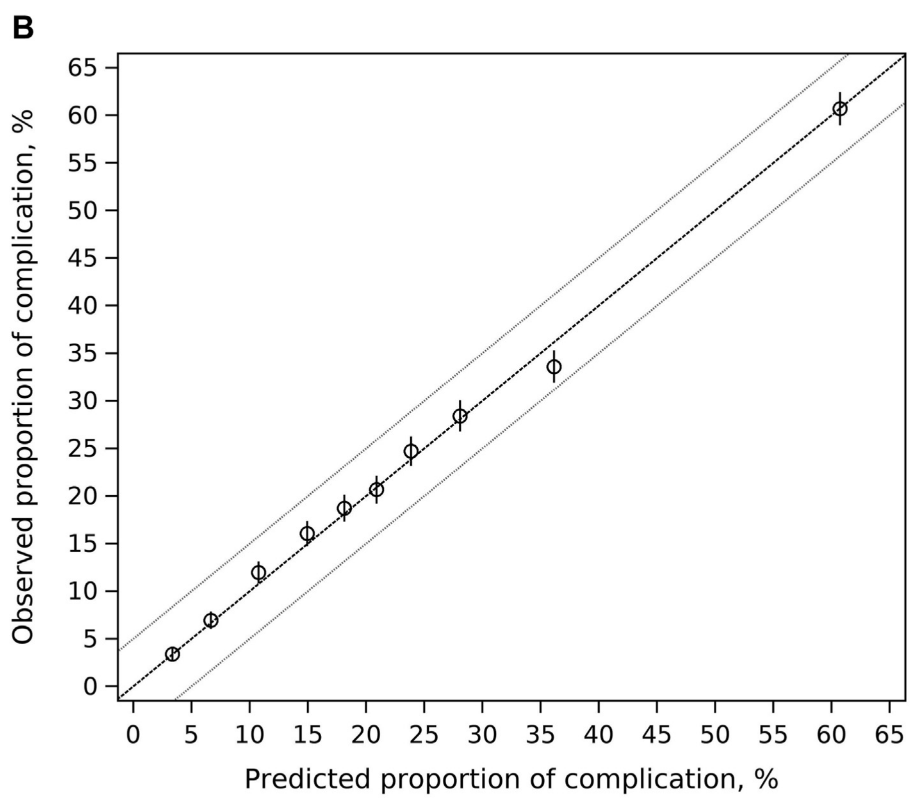


eFigure 1. Comprehensive Complication Index (CCI) by 3-level complexity classification only in patients who had Enhanced Recovery after Surgery (ERAS) protocol. CCI scores were significantly different in both patients undergoing laparoscopic liver resection and open liver resection (OLR) using ANOVA test for 3 groups. In patients undergoing OLR procedures, CCI increased significantly, with a stepwise increase of the grades from I to III ($p < 0.05$).





eFigure 2. Calibration plots of the logistic model using (A) the original cohort and (B) the bootstrap method.