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Validation of index-based IWATE criteria as an improved difficulty scoring system for laparoscopic liver resection

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ABSTRACT

Background: The original difficulty scoring system was revised after discussion at the 2nd International Consensus Conference on Laparoscopic Liver Resection held in Morioka (Iwate Prefecture) in Japan and renamed the IWATE criteria (a 4-level classification system involving 6 preoperative factors). We used Japanese and French cohorts to validate the IWATE criteria by evaluating their association with the procedure-based difficulty classification proposed by the Institut Mutualiste Montsouris.

Method: Patients who had undergone laparoscopic liver resection at multiple Japanese multi-institutions or the Institut Mutualiste Montsouris were assigned to the multiple Japanese multi-institution ($n = 1{,}867$) or Institut Mutualiste Montsouris cohort ($n = 433$). We analyzed clinical characteristics and outcomes according to the 4-level IWATE criteria difficulties (low, intermediate, advanced, and expert) and evaluated their association with 11 laparoscopic liver resection procedures in the Institut Mutualiste Montsouris classification (low, intermediate, and high levels).

Results: We found significant differences in age, surgical indications, and the 4-level IWATE criteria difficulties between the cohorts (all, $P < .001$). Operation time and blood loss were significantly different among the 4-level difficulties in both cohorts (all, $P < .001$). The rates of conversion, postoperative complications, liver failure, and in-hospital deaths also increased significantly with increasing difficulty (all, $P < .001$). The IWATE criteria classified the three low-level Institut Mutualiste Montsouris procedures in the low-to-intermediate levels, the two intermediate-level procedures in the intermediate-to-advanced levels, and the six high-level procedures in the advanced-to-expert levels.

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Conclusion: We observed associations between the IWATE criteria and intraoperative and postoperative outcomes in the Japanese multi-institution and Institut Mutualiste Montsouris cohorts and thus validated the IWATE system.

Introduction

The number of laparoscopic liver resections (LLRs) has been increasing worldwide owing to the procedure's better short-term outcomes and comparable oncologic outcomes compared with those of conventional open liver resection. The indications for LLR have been gradually expanding in experienced centers.[1–6] The 2nd International Consensus Conference on Laparoscopic Liver Resection (ICCLLR) was held in Morioka (Iwate Prefecture) in Japan to evaluate the current status of LLR and to provide recommendations for its safe dissemination and future development.[7] At the ICCLLR, it was advocated that the preoperative estimation of LLR difficulty is useful for selecting appropriate patients according to the surgeon's experience and skill level and that difficulty classification represents a roadmap of LLRs, ranging from simple to highly difficult procedures.

The difficulty scoring system provided by Ban et al[8] is the first classification system for LLR. The system indexes LLR from 1 to 10 on the basis of 5 preoperative factors (tumor location, extent of hepatic resection, tumor size, tumor proximity to major vessels, and liver function) and classifies LLR into 3 difficulty levels (low, intermediate, and high). The system was validated by the Endoscopic Liver Surgery Study Group (ELSSG), Japan, because the 3 levels were significantly associated with surgical outcomes, including operation time, estimated blood loss, and conversion rate, and with postoperative outcomes, including major complication rates, liver failure and in-hospital death.[9] However, the original difficulty scoring system (a 3-level classification system) had the following problems: no segment 1 in the tumor location category, no separation between segments 4a and 4b (segment 4 only), and no category for hand-assisted laparoscopic surgery (HALS) and the hybrid method. Therefore, the original difficulty scoring system was revised after discussion at the 2nd ICCLLR and renamed the IWATE criteria (an index-based, 4-level classification system [Fig. 1]).[10]

We hypothesized that the IWATE criteria can accurately rank the LLR difficulty as low, intermediate, advanced, or expert on the basis of preoperative variables, as did the original difficulty scoring system. However, the IWATE criteria have not been validated. The IWATE criteria score each LLR procedure from 1 to 12 but do not discriminate between the LLR procedures. Recently, the Institut Mutualiste Montsouris (IMM) group has devised a new LLR classification system (the IMM classification) based on operation time, estimated blood loss, and conversion rate.[11] Unlike the IWATE criteria, the IMM classification system stratifies the difficulty of the 11 LLR procedures into 3 grades (low, intermediate, and high levels).

This study aimed to validate the IWATE criteria and evaluate their associations with various LLR procedures in the IMM classification by using a Japanese multi-institution cohort (JMI) by the ELSSG in Japan and a French IMM cohort.

Methods

Patients

This multi-institution clinical study was conducted at the ELSSG, Japan. We retrospectively analyzed the prospectively collected data of 1,867 patients (JMI cohort) who underwent initial pure LLR for hepatic tumors (hepatocellular carcinoma [HCC], intrahepatic cholangiocarcinoma, metastatic liver tumor, and other malignant and benign liver tumors) between 2010 and 2014 across 43 Japanese institutions. We excluded patients who underwent multiple liver resections, vascular/biliary reconstruction, and concomitant extrahepatic procedures (except cholecystectomy). The median number of LLRs among the 43 institutions was 33 during 5 years (range, 1–191). During the 5-year period, $<$ 50 LLRs were performed at 31 (72%) of the 43 institutions ($n = 727$); $\geq$ 50 LLRs were conducted at the remaining 12 institutions (28%, $n = 1{,}140$). In addition, we analyzed the prospectively collected data of 433 patients (IMM cohort) who underwent pure LLR at IMM between 1995 and 2015. We excluded patients who underwent cyst fenestration, repeated LLRs (except partial resection), multiple liver resections, vascular/biliary reconstruction, and concomitant extrahepatic procedures (except cholecystectomy). In both JMI and IMM cohorts, all patients underwent contrast-enhanced dynamic computed tomography and ultrasonography for the preoperative diagnosis. If a definitive diagnosis could not be made on these imaging findings, gadoxetic acid–enhanced magnetic resonance imaging was additionally performed.

This study was conducted in accordance with the mandates of the Helsinki Declaration and was approved by the institutional review board of each participating institution.

IWATE criteria

The total score was the sum of the following 6 difficulty indices: (1) tumor location (score, 1–5); (2) extent of hepatic resection (score, 0–4); (3) tumor size (score, 0 or 1); (4) proximity to major vessel (score, 0 or 1); (5) liver function (score, 0 or 1); and (6) HALS/hybrid (score, 0 or −1). The 12 difficulty levels were divided into four categories (4-level difficulty), as follows: low (0–3), intermediate (4–6), advanced (7–9) and expert difficulty (10–12; Fig. 1).[10]

Clinical data

We collected baseline preoperative clinical data and operation variables. We used the Clavien–Dindo classification[12] (grade IIIA or greater) for postoperative complications and the International Study Group of Liver Surgery definition for bile leakage[13] and liver failure classification.[14] Tables 1 and 2 list all variables studied.

Definition of liver resection

Anterolateral (AL) segments were defined as Couinaud's segments 2, 3, 4b, 5, and 6; whereas posterosuperior (PS) segments were defined as segments 1, 4a, 7, and 8.[7,11,15] We used the Brisbane 2000 Terminology[16] and the IMM classification[11] to define LLR types. The IMM classification system classified the 11 LLR procedures into 3 grades: grade I (low level), wedge resection and left lateral sectionectomy; grade II (intermediate level), AL segmentectomy and left hepatectomy; and grade III (high level), PS segmentectomy, right posterior sectionectomy, right hepatectomy, central hepatectomy, and extended left/right hepatectomy. Resection of segment 4 was classified as medial sectionectomy in the IWATE criteria and as segmentectomy of posterosuperior segments in the IMM classification.

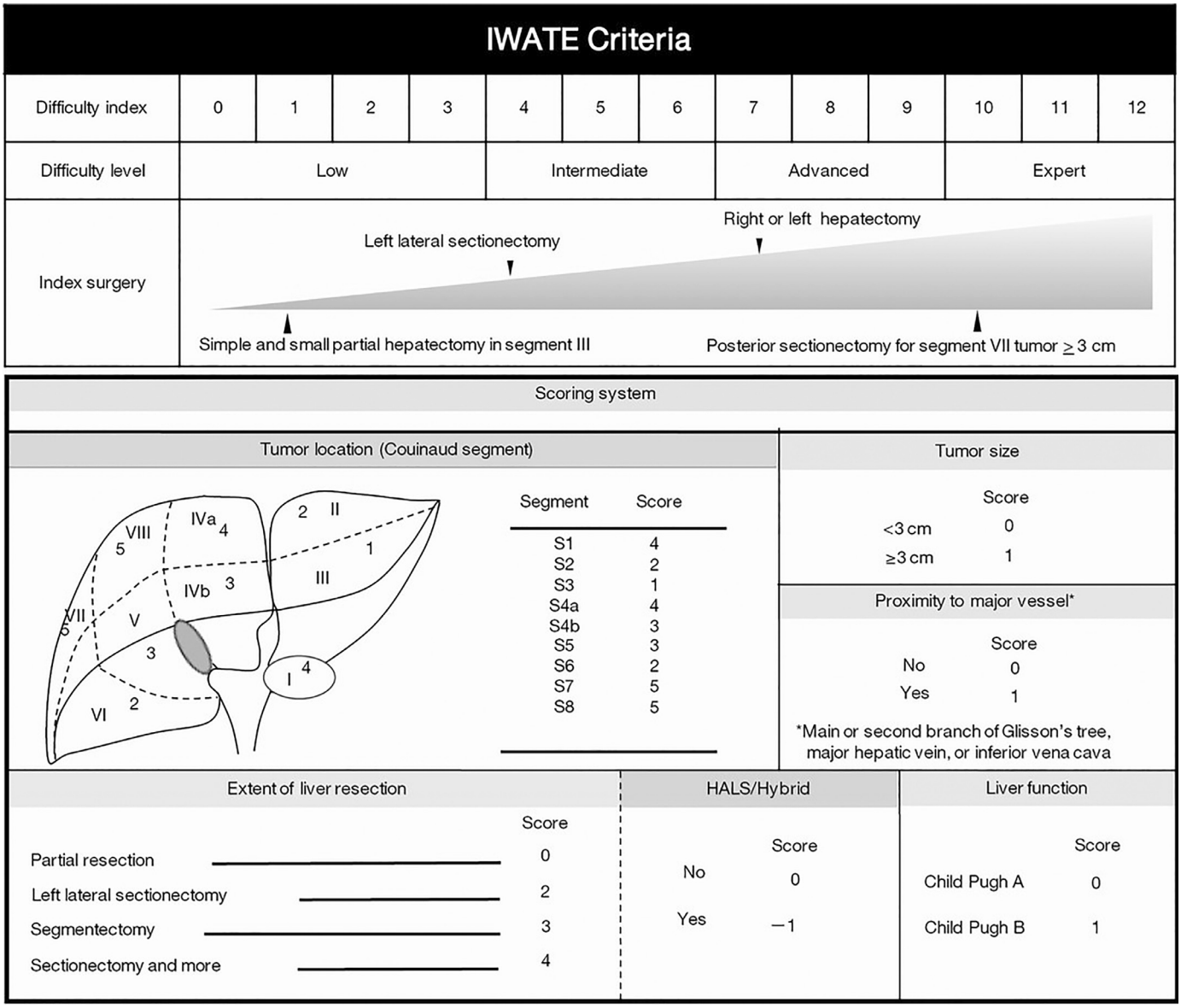

Fig. 1. IWATE criteria proposed at the 2nd International Consensus Conference on Laparoscopic Liver Resection as an improved difficulty scoring system (Reprinted from Wakabayashi,[10] with permission from the AME Publishing Company, Hong Kong). (*Top*) The difficulty level was ranked on a scale of 0–12 on the basis of expert assessments between small and simple partial hepatectomy (simplest LLR procedure) and posterior sectionectomy for segment 7 (tumor size ≥ 3 cm) or more difficult procedures. (*Bottom*) The total score is the sum of the 6 clinical parameters (12-level index): (1) tumor location, (2) extent of hepatic resection, (3) tumor size, (4) proximity to a major vessel, (5) liver function, and (6) HALS/hybrid. This 12-level difficulty index is further stratified into 3 groups: low (0–3), intermediate (4–6), advanced (7–9), and expert (10–12) (4-level difficulties).

Outcomes

We analyzed the clinical characteristics and outcomes after LLR according to the 4-level IWATE criteria difficulties (low, intermediate, advanced, and expert) in the JMI and IMM cohorts. Moreover, we evaluated the association of IWATE criteria with the 11 LLR procedures of the IMM classification.[11]

Statistical analysis

We expressed categorical variables as numerical figures and percentages and compared them among groups by using the Fisher exact test or χ^2 test, as appropriate. We expressed continuous variables as median values (with the range) and compared them by using the Kruskal–Wallis test. Holm's method[17] was used to adjust the *P* values in multiple testing of the demographic variables of the 4 groups. We performed the Cochran–Armitage trend test[18] for categorical variables and Jonckheere–Terpstra trend test[19] for continuous variables of the trends of the intraoperative and postoperative outcomes for stratifying groups from low-to-expert surgical difficulty levels. All statistical analyses were performed using the SPSS v 21.0 (IBM-SPSS, Chicago, IL, USA), JMIP Pro v 13.0.0 (SAS Institute, Cary, NC, USA) software program, and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphic user interface for the R software (The R Foundation for Statistical Computing, Vienna, Austria).[20]

Results

Baseline characteristics

The clinical characteristics and surgical outcomes of the 1,867 and 433 patients in the JMI and the IMM cohorts, respectively, are summarized in Table 1. There were more elderly men in the JMI

Table 1
Clinical characteristics and surgical outcomes of laparoscopic liver resection in two database cohorts.

Variables	JMI cohort ($n = 1,867$)		IMM cohort ($n = 433$)		P value[§]
Age (years)[*]	69	(13–94)	64	(24–89)	< .001[¶]
Sex (M:F)	1211:656		252:181		.009
Hepatic tumors, *n* (%)					< .001
Hepatocellular carcinoma	1,246	(66.7)	40	(9.2)	
Intrahepatic cholangiocarcinoma	47	(2.5)	26	(6.0)	
Metastatic liver tumor	414	(22.2)	277	(70.0)	
Other malignancy	30	(1.6)	28	(6.5)	
Benign tumors	130	(7.0)	62	(14.3)	
Past operation					
Previous surgery[†]	303	(16.2)	253	(58.4)	—
Previous hepatectomy	0	(0)	56	(12.9)	< .001
Conversion to open surgery	52	(2.8)	17	(3.9)	.210
Operation time (min)[*]	264	(37–922)	185	(25–600)	< .001 [¶]
Intraoperative blood loss (cc)[*]	80	(0–11,080)	100	(0–4,500)	.521[¶]
Reoperation	10	(0.5)	14	(3.2)	< .001
Postoperative complications					
Overall[‡]	111	(5.9)	43	(9.9)	.003
Fluid collection (abdominal infection and/or ascites) [‡]	54	(2.9)	25	(5.3)	.004
Bile leakage[‡]	38	(2.0)	18	(4.2)	.015
Respiratory complications[‡]	23	(1.2)	14	(3.2)	.005
Liver failure (ISGLS definition)	28	(1.5)	7	(1.6)	.858
Grade A	16	(0.9)	0	(0)	.097
Grade B	6	(0.3)	0	(0)	.370
Grade C	6	(0.3)	7	(1.6)	.005
In-hospital death	9	(0.5)	5	(1.2)	.105
Hospital stay (days)[*]	9	(3–281)	6	(1–389)	<.001[¶]

[*] Values are median (range).
[†] Only upper abdominal surgery in the JMI cohort.
[‡] Clavien–Dindo classification grade IIIa or greater.
[§] P values were calculated using the Fisher exact test or the χ^2 test.
[¶] P values calculated using the Mann-Whitney U test.
Note: Values in parenthese are percentages unless indicated otherwise.

cohort than in the IMM cohort. HCC was the most frequent LLR indication ($n = 1,246$, 66.7%) in the JMI cohort; whereas metastatic liver tumor was the most frequent LLR indication ($n = 277$, 70.0%) in the IMM cohort. The proportion of patients with high scores for each IWATE criteria index (including extent of hepatic resection, tumor location, tumor size, and proximity to major vessel) was significantly lower in the JMI cohort than in the IMM cohort (Table 2). However, there were no patients with Child–Pugh class B in the IMM cohort. The proportion of the cases classified as low, intermediate, advanced, and expert difficulties significantly differed between the JMI and IMM groups ($P < .001$; see Table 2 for details). Moreover, the rate of reoperation was significantly higher in the IMM cohort than in the JMI cohort. However, we found no significant differences in the incidence of conversion to open surgery or the amount of blood loss. Finally, the incidence of postoperative complications (overall, fluid collection, bile leakage, and liver failure) was lower in the JMI cohort than in the IMM cohort; however, the length of hospital stay was longer for the JMI cohort than for the IMM cohort. We found no significant difference in the in-hospital death rates.

Validation of the IWATE criteria (clinical characteristics and surgical outcomes according to the 4-level IWATE criteria difficulties)

The distribution of difficulty indices, including the extent of hepatic resection, location, size, and proximity to major vessels, corresponded with the difficulty according to the IWATE criteria when using both cohorts (Tables 3 and 4). The variables of the rate of conversion to open surgery (Fig. 2, *A*), operation time (Fig. 2, *B*), and intraoperative blood loss (Fig. 3, *A*) indicated a stepwise increase from low-to-expert difficulty levels (Cochran–Armitage and Jonckheere–Terpstra trend tests, $P < .001$). However, the rate of reoperation was higher for the expert difficulty than for the intermediate difficulty in the IMM cohort, but not in the JMI cohort. The rates of overall postoperative major complication, liver failure, and in-hospital death significantly differed among the 4-level IWATE criteria difficulties when using both cohorts (all, $P < .001$; Fig. 3, *B*; Fig. 4, *A* and *B*).

In both the JMI and IMM cohorts, the rates of overall postoperative complications, postoperative bile leakage, fluid collection, respiratory complications (all, $P < .001$; $P < .001$), liver failure (overall [$P < .001$; $P = .003$], grade C [$P = .001$; $P = .003$]), and in-hospital death ($P < .001$; $P = .011$) significantly increased with stepwise increases from low-to-expert difficulty levels (Cochran–Armitage trend test; Fig. 3, *B*; Fig. 4; and Tables 3 and IV). In the JMI cohort, 73.9% (161/218) of advanced-difficulty procedures and 86.1% (99/115) of expert-difficulty procedures were performed at the 12 high-volume centers (≥50 LLRs over 5 years).

Association of IWATE criteria with 11 LLR procedures in the IMM classification

The low-difficulty level included only the wedge resection of AL segments, which is classified as grade I (low level) in the IMM classification in both cohorts (Table 5). The intermediate difficulty level comprised wedge resections of PS segments and left lateral sectionectomy (IMM grade I) and segmentectomy of AL segments (IMM grade II [intermediate level]). The advanced level included segmentectomy of AL segments and left hepatectomy (IMM grade II) and the six procedures classified as grade III (high level) in the IMM classification. The expert level mainly comprised the six procedures of IMM grade III.

Table 2
Distribution of each index of IWATE criteria* in two database cohorts.

Variables	JMI cohort ($n = 1,867$)		IMM cohort ($n = 433$)		P value‡
Extent of liver resection					< .001
Partial resection	1,169	(62.6)	150	(34.6)	
Anterolateral segments	760	(40.7)	93	(21.5)	
Posterosuperior segments	410	(22.0)	57	(13.2)	
Left lateral sectionectomy	294	(15.7)	35	(8.1)	
Segmentectomy	139	(7.4)	66	(15.3)	
Anterolateral segments	113	(6.1)	43	(10.0)	
Posterosuperior segments	26	(1.4)	23	(5.3)	
Sectionectomy or more	265	(14.2)	182	(42.0)	
Medial sectionectomy	21	(1.1)	1	(0.2)	
Posterior sectionectomy	61	(3.3)	7	(1.6)	
Left hepatectomy	76	(4.1)	26	(6.0)	
Right hepatectomy	58	(3.1)	98	(22.6)	
Central hepatectomy†	41	(2.2)	11	(2.6)	
Extended left hepatectomy	6	(0.3)	12	(2.8)	
Extended right hepatectomy	2	(0.1)	27	(6.2)	
Tumor location					< .001
S1	41	(2.2)	11	(2.5)	
S2	278	(14.9)	42	(9.7)	
S3	343	(18.4)	21	(4.9)	
S4a	111	(5.9)	12	(2.8)	
S4b	86	(4.6)	71	(16.4)	
S5	261	(14.0)	38	(8.8)	
S6	327	(17.5)	31	(7.2)	
S7	163	(8.7)	93	(21.5)	
S8	257	(13.8)	114	(26.3)	
Tumor size					< .001
< 3 cm	1,189	(63.7)	222	(51.3)	
≥ 3 cm	678	(36.3)	211	(48.7)	
Proximity to major vessel					< .001
No	1,525	(81.7)	181	(41.8)	
Yes	342	(18.3)	252	(58.2)	
Liver function					< .001
Child-Pugh A	1,752	(93.8)	433	(100)	
Child-Pugh B	115	(6.2)	0	(0)	
Sum of difficulty score					< .001
1	103	(5.5)	14	(3.2)	
2	275	(14.7)	17	(3.9)	
3	338	(18.1)	48	(11.1)	
4	307	(16.4)	28	(6.5)	
5	367	(19.7)	57	(13.2)	
6	144	(7.7)	40	(9.2)	
7	85	(4.6)	26	(6.0)	
8	83	(4.4)	19	(4.4)	
9	50	(2.7)	27	(6.2)	
10	64	(3.4)	56	(12.9)	
11	51	(2.7)	101	(23.3)	
12	0	(0)	0	(0)	
4-levels difficulty, n (%)					< .001
Low	716	(38.2)	80	(18.5)	
Intermediate	818	(43.8)	124	(28.6)	
Advanced	218	(11.7)	72	(16.6)	
Expert	115	(6.2)	157	(36.3)	

* According to IWATE criteria.[10]
† Includes central bisectionectomy and right anterior sectionectomy.
‡ P values were calculated using the Fisher exact test or the χ^2 test.
Note: Values in parentheses are percentages.

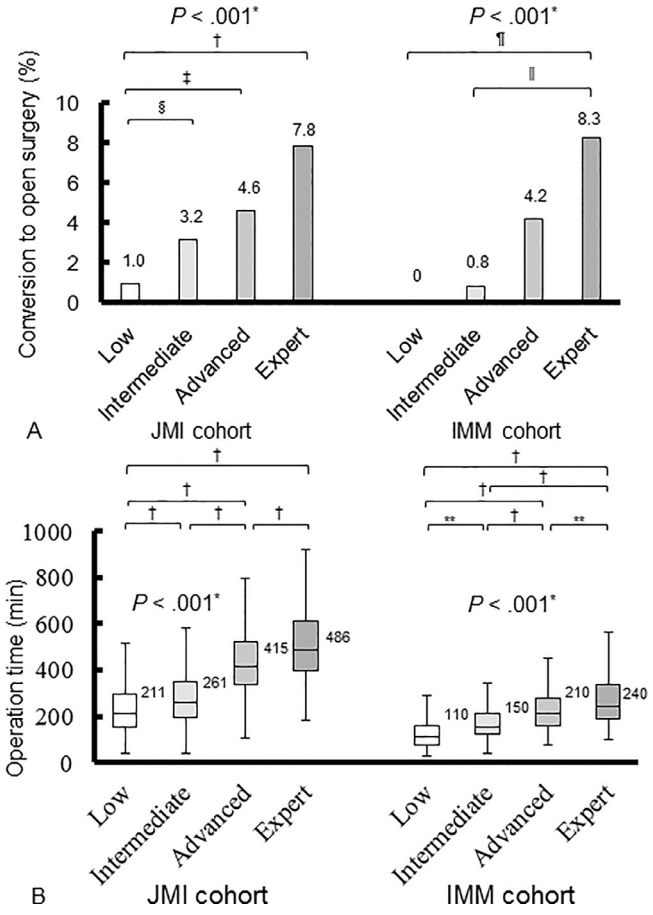

Fig. 2. Surgical outcomes of laparoscopic liver resections grouped according to the 4-level IWATE criteria difficulties in the Japanese multi-institution (JMI) and Institut Mutualiste Montsouris (IMM) cohorts (Part 1). (*A*) Conversion to open surgery and (*B*) operation time.
* P values were calculated using the Fisher exact test or the χ^2 test for categorical variables, and Kruskal-Wallis test for continuous variables.
† $P < .001$.
‡ $P = .008$.
§ $P = .016$.
¶ $P = .027$.
‖ $P = .026$.
** $P = .002$ between-group differences as revealed by the Holm's test.
Note: Conversion rate and operation time significantly increased with a stepwise increase from low-to-expert difficulty levels (Cochran–Armitage trend test and Jonckheere–Terpstra trend test, each $P < .001$).

Discussion

The IWATE criteria predicted the LLR difficulty and the postoperative outcomes in a multi-institution cohort in Japan and in a highly specialized, minimally invasive surgery center in France. Moreover, the IWATE criteria classified the three low-level procedures of the IMM classification in the low-to-intermediate levels, the two intermediate-level procedures of the IMM classification in the intermediate-to-advanced levels, and the six high-level procedures of the IMM classification in the advanced-to-expert levels.

The 1st ICCLLR in Louisville, KY, USA, in 2008 recommended that solitary tumors sized <5 cm located in the AL segments and left lateral sector be amenable to LLR to expand the LLR indications.[15] However, LLR is increasingly being used for major hepatectomy and resection of lesions located in PS segments in highly specialized centers.[4,21–24]. The 2nd ICCLLR in Morioka, Japan, in 2014 recommended that LLR be expanded to major hepatectomy and for lesions in the PS segments, depending on an estimate of its difficulty for safety.[7]

The difficulty scoring system[8] was the first LLR classification system, and the ESLLG in Japan found that it was associated with intraoperative and postoperative outcomes.[9] The IWATE criteria were devised on the basis of the original difficulty scoring system in response to the following three issues that were debated upon in the 2nd ICCLLR: the lack of tumor location at segment 1 (Caudate lobe), the lack of differentiation between segments 4a and 4b, and the lack of the HALS and hybrid methods. The IWATE criteria are the proposal from the international panel of experts' opinion; however, they have not been validated. Therefore, in this study, we aimed to validate the IWATE criteria by using the following two cohorts: the Japanese JMI and the French IMM cohorts. We

Table 3
Clinical characteristics and surgical outcomes of laparoscopic liver resection stratified by the 4-level IWATE criteria difficulties in the JMI Cohort.

Variables	Difficulty*								*P* value
	Low *n* = 716 38.2%		Intermediate *n* = 818 43.8%		Advanced *n* = 218 11.7%		Expert *n* = 115 6.2%		
Age in years [median (range)]	69	(13–89)	69	(22–94)	70	(20–86)	69	(13–94)	.306
Gender (male/female)	461/255		517/301		156/62		77/38		.134
Hepatic tumors, *n* (%)									.012[*,‡]
Hepatocellular carcinoma	476	(66.5)	535	(65.4)	158	(72.5)	77	(67.0)	
Intrahepatic cholangiocarcinoma	6	(0.8)	30	(3.7)	8	(3.7)	3	(2.6)	
Metastatic liver tumor	173	(24.2)	185	(22.6)	33	(15.1)	23	(20.0)	
Other malignancy	11	(1.5)	12	(1.5)	4	(1.8)	3	(2.6)	
Benign tumors	50	(7.0)	56	(6.8)	15	(6.9)	9	(7.8)	
Previous upper abdominal surgery, *n* (%)	146	(20.4)	118	(14.4)	22	(10.1)	17	(14.8)	.001[‡,§]
Extent of liver resection, *n* (%)									< .001[‡,§,¶,‖,**,††]
Partial resection	656	(91.6)	497	(60.8)	16	(7.3)	0	(0)	
Left lateral sectionectomy	60	(8.4)	233	(28.5)	1	(0.5)	0	(0)	
Segmentectomy	0	(0)	70	(8.6)	66	(30.3)	3	(2.6)	
Sectionectomy or more	0	(0)	18	(2.2)	135	(61.9)	112	(97.4)	
Tumor location, *n* (%)									<.001[‡,§,¶,‖,**,††]
S1	0	(0)	35	(4.3)	4	(1.8)	2	(1.7)	
S2	93	(13.0)	154	(18.8)	31	(14.2)	0	(0)	
S3	209	(29.2)	125	(15.3)	9	(4.1)	0	(0)	
S4a	0	(0)	74	(9.0)	22	(10.1)	15	(13.0)	
S4b	38	(5.3)	24	(2.9)	24	(11.0)	0	(0)	
S5	126	(17.6)	81	(9.9)	53	(24.3)	1	(0.9)	
S6	250	(34.9)	43	(5.3)	34	(15.6)	0	(0)	
S7	0	(0)	101	(12.3)	16	(7.3)	46	(40.0)	
S8	0	(0)	181	(22.1)	25	(11.5)	51	(44.3)	
Tumor size, *n* (%)									< .001[‡,§,¶,‖,**,††]
< 3 cm	597	(83.3)	501	(61.2)	73	(33.5)	18	(15.7)	
≥ 3 cm	119	(16.6)	317	(38.7)	145	(66.5)	97	(84.3)	
Proximity to major vessel, *n* (%)									< .001[‡,§,¶,‖,**,††]
No	710	(99.2)	697	(85.2)	87	(39.9)	31	(27.0)	
Yes	6	(0.8)	121	(14.8)	131	(60.1)	84	(73.0)	
Liver function, *n* (%)									.206
Child-Pugh A	681	(95.1)	757	(92.5)	206	(94.5)	108	(93.9)	
Child-Pugh B	35	(4.9)	61	(7.5)	12	(5.5)	7	(6.1)	
Reoperation, *n* (%)	5	(0.7)	2	(0.2)	1	(0.5)	2	(1.7)	.160
Postoperative complications, *n* (%)									
Fluid collection (abdominal infection and/or ascites) [†]	11	(1.5)	20	(2.4)	13	(6.0)	10	(8.7)	< .001[§,¶,‖,**]
Bile leakage[†]	7	(1.0)	11	(1.3)	10	(4.6)	10	(8.7)	< .001[§,¶,‖,**]
Respiratory complication[†]	3	(0.4)	7	(0.9)	7	(3.2)	6	(5.2)	< .001[§,¶,‖,**]
Hospital stay, days [median (range)]	9	(4–105)	9	(3–189)	11	(5–281)	14	(7–116)	< .001[‡,§,¶,‖,**,††]

* According to IWATE criteria.[10]
† Clavien-Dindo classification grade IIIa or greater.
‡ $P < .05$; low versus intermediate by multiple tests using Holm's method.
§ $P < .05$; low versus. advanced by multiple tests using Holm's method.
¶ $P < .05$; low versus expert by multiple tests using Holm's method.
‖ $P < .05$; intermediate versus advanced by multiple tests using Holm's method.
** $P < .05$; intermediate versus expert by multiple tests using Holm's method.
†† $P < .05$; advanced versus expert by multiple tests using Holm's method.

Table 4
Clinical characteristics and surgical outcomes of laparoscopic liver resection stratified by the 4-level IWATE criteria difficulties in the IMM Cohort.

Variables	Difficulty*								*P* value
	Low *n* = 80 18.5%		Intermediate *n* = 124 28.6%		Advanced *n* = 72 16.6%		Expert *n* = 157 36.3%		
Age in years [median (range)]	63	(30–89)	63	(24–89)	65	(25–83)	64	(24–86)	.331
Gender (male/female)	50/30		65/59		42/30		95/62		.452
Hepatic tumors, *n* (%)									< .001§,¶,**
Hepatocellular carcinoma	2	(2.5)	12	(9.7)	6	(8.3)	20	(12.8)	
Intrahepatic cholangiocarcinoma	3	(3.8)	4	(3.2)	7	(9.7)	12	(7.7)	
Metastatic liver tumor	45	(56.2)	73	(58.8)	47	(65.3)	112	(71.3)	
Other malignancy	12	(15.0)	10	(8.1)	2	(2.8)	4	(2.6)	
Benign tumors	18	(22.5)	25	(20.2)	10	(13.9)	9	(5.7)	
Past operation, *n* (%)									
Previous surgery	39	(9.0)	71	(16.4)	38	(8.8)	105	(24.3)	.032¶
Previous hepatectomy	9	(2.1)	10	(2.3)	6	(1.4)	31	(7.2)	.018**
Extent of liver resection, *n* (%)									< .001‡,§,¶,‖,**,††
Partial resection	80	(100.0)	63	(50.8)	7	(9.7)	0	(0)	
Left lateral sectionectomy	0	(0)	35	(28.2)	0	(0)	0	(0)	
Segmentectomy	0	(0)	26	(21.0)	31	(43.1)	9	(5.7)	
Sectionectomy or more	0	(0)	0	(0)	34	(47.2)	148	(94.3)	
Tumor location, *n* (%)									< .001‡,§,¶,‖,**,††
S1	0	(0)	7	(5.7)	4	(5.6)	0	(0)	
S2	6	(7.5)	36	(29.0)	0	(0)	0	(0)	
S3	19	(23.8)	2	(1.6)	0	(0)	0	(0)	
S4a	0	(0)	3	(2.4)	6	(8.3)	3	(1.9)	
S4b	27	(33.8)	11	(8.9)	33	(45.8)	0	(0)	
S5	15	(18.8)	10	(8.1)	13	(18.1)	0	(0)	
S6	13	(16.3)	15	(12.1)	3	(4.2)	0	(0)	
S7	0	(0)	20	(16.1)	9	(12.5)	64	(40.8)	
S8	0	(0)	20	(16.1)	4	(5.6)	90	(57.3)	
Tumor size, *n* (%)									< .001‡,§,¶,‖,**
< 3 cm	74	(92.5)	80	(64.5)	25	(34.7)	43	(27.4)	
≥ 3 cm	6	(7.5)	44	(35.5)	47	(65.3)	114	(72.6)	
Proximity to major vessel, *n* (%)									< .001‡,§,¶,‖,**,††
No	73	(91.3)	90	(72.6)	17	(23.6)	1	(0.6)	
Yes	7	(8.7)	34	(27.4)	55	(76.4)	156	(99.4)	
Liver function, *n* (%)									—
Child-Pugh A	80	(100.0)	124	(100.0)	72	(100.0)	157	(100.0)	
Child-Pugh B	0	(0)	0	(0)	0	(0)	0	(0)	
Reoperation, *n* (%)	1	(1.3)	1	(0.8)	2	(2.8)	9	(5.7)	.005**
Postoperative complications, *n* (%)									
Fluid collection (abdominal infection and/or ascites)†	0	(0)	2	(0.5)	3	(0.7)	20	(4.6)	< .001¶,**
Bile leakage†	0	(0)	0	(0)	3	(0.7)	15	(3.5)	< .001¶,**
Respiratory complications†	0	(0)	0	(0)	1	(0.2)	13	(3.0)	< .001¶,**
Hospital stay, days [median (range)]	4	(1–45)	5	(1–94)	6	(3–34)	9	(3–389)	< .001‡,§,¶,**,††

* According to IWATE criteria.[10]
† Clavien-Dindo classification grade IIIa or greater.
‡ $P < .05$; low versus intermediate by multiple tests using Holm's method.
§ $P < .05$; low versus advanced by multiple tests using Holm's method.
¶ $P < .05$; low versus expert by multiple tests using Holm's method.
‖ $P < .05$; intermediate versus advanced by multiple tests using Holm's method.
** $P < .05$; intermediate versus expert by multiple tests using Holm's method.
†† $P < .05$; advanced versus expert by multiple tests using Holm's method.

deemed the two cohorts appropriate for validation because they were widely different in regard to their indications, rates of sectionectomy, and rate of expert difficulty. These differences in the two cohorts were most likely caused by differences in chronic liver disease rates, leaning curves, and the insurance system coverage between the two cohorts. Indeed, the Japanese national insurance system covered wedge resection and left lateral sectionectomy during the study period. The learning curves were apparent with the longer operative time in the JMI cohort and comparable conversion rates and blood losses between the cohorts, although there were fewer advanced- and expert-level LLRs performed in the JMI cohort. The particularly high incidence of postoperative liver failure and mortality in expert-difficulty procedures in both cohorts might be attributable to a small remnant liver, caused by a high proportion of sectionectomy or more, with increased intraoperative blood loss and postoperative intra-abdominal fluid collection (abdominal infection and/or ascites). We observed that the IWATE criteria could be widely used to score the difficulty of LLRs on the basis of the association of the criteria with intraoperative and postoperative outcomes using the two heterogenic cohorts (Figs. 2, 3, and 4).

The IWATE criteria include the index-based system scoring LLRs from 1 to 12 on the basis of the 6 preoperative variables (Fig. 1). The IMM group[11] reported a procedure-based classification system that stratifies the 11 LLR procedures into 3 levels. However, the index-based IWATE criteria generally stratify the difficulty of various LLR procedures because they classify the low-level IMM classification procedures as lower difficulty and the high-level IMM procedures as higher difficulty. Like the IMM classification system, the IWATE criteria classified segmentectomy as more difficult for PS than for AL segments because it scores the difficulty of PS segments (score, 4–5) as higher than that of AL segments (score, 1–3). The IWATE criteria include the category of Child–Pugh grade A or B as a marker of liver function, but the IMM classification does not. The IWATE criteria divided the high-difficulty procedures in the original difficulty scoring system into advanced- and expert-

Table 5
Association of the IWATE criteria with 11 LLR procedures.

JMI cohort			IMM cohort		
IWATE criteria	11 LLR procedures*		IWATE criteria	11 LLR procedures*	
Low†	Wedge-AL (86.1)	Grade I	Low‖	Wedge-AL (86.0)	Grade I
Intermediate‡	Wedge-PS (96.1), Left lateral (79.3) Seg-AL (61.9)	Grade I Grade II	Intermediate	Wedge-PS (87.7), Left lateral (100) Seg-AL (58.1)	Grade I Grade II
Advanced§	Seg-AL (38.1), Left hep (69.7) Seg-PS (83.0), Right hep (32.8), Right posterior (44.3), Central hep (39.0) Ext-left hep (50.0), Ext-right hep (50.0)	Grade II Grade III	Advanced**	Seg-AL (41.9), Left hep (92.3) Seg-PS (54.2), Ex-left hep (33.3)	Grade II Grade III
Expert¶	Right hep (67.2), Right posterior (50.8), Central hep (61.0), Ext-left hep (50.0), Ext-right hep (50.0)	Grade III	Expert††	Seg-PS (41.7), Right hep (93.9), Ex-right hep (100), Right posterior (100), Central hep (100), Ex-left hep (66.7)	Grade III

* According to the IMM classification.[11]
† Including left lateral (20.4).
‡ Including wedge-AL (13.9), Left hep (19.7), and Right posterior (4.9).
§ Including Wedge-PS (3.9), and Left lateral (0.3).
¶ Including Left hep (10.5), and Seg-PS (17.0).
‖ Including Wedge-AL (14.0), and Seg-PS (0.8).
** Including Wedge-PS (12.3), and Right hep (6.1).
†† Including Left hep (7.7).
Note: Operative procedure (percent) except < 30% was shown.
Wedge-AL, wedge resection of anterolateral segment; *Wedge-PS,* wedge resection of posterosuperior segment; *Left lateral,* left lateral sectionectomy; *Seg-AL,* anterolateral segmentectomy; *Left hep,* left hepatectomy; *Seg-PS,* posterosuperior segmentectomy; *Right hep,* right hepatectomy; *Ex-right hep,* extended right hepatectomy; *Right posterior,* right posterior sectionectomy; *Central hep,* central hepatectomy; *Ex-left hep,* extended left hepatectomy.

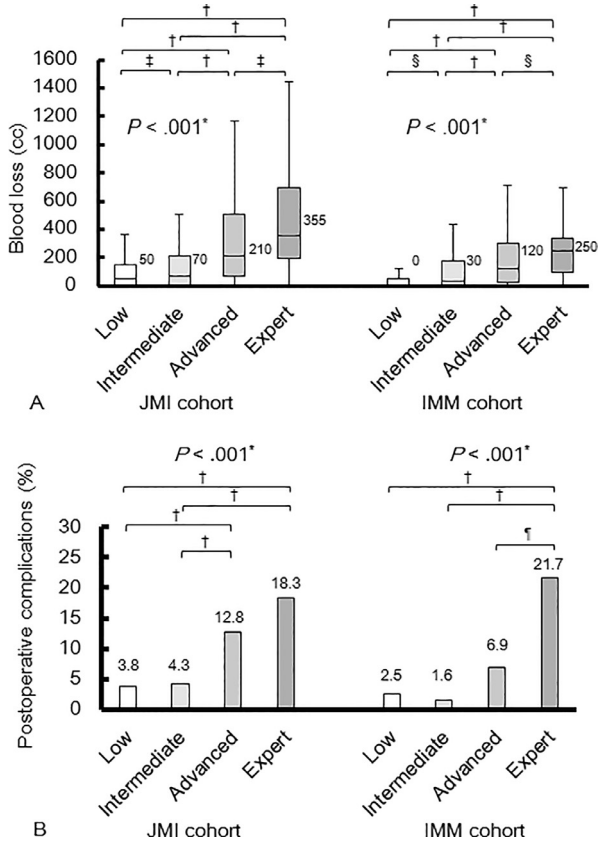

Fig. 3. Surgical outcomes of laparoscopic liver resection grouped according to the 4-level IWATE criteria difficulties in the Japanese multi-institution (JMI) and Institut Mutualiste Montsouris (IMM) cohorts (Part 2). (*A*) blood loss and (*B*) postoperative complications.
**P* values were calculated using the Fisher exact test or the χ^2 test for categorical variables, and Kruskal-Wallis test for continuous variables.
†*P* < .001.
‡*P* = .013.
§*P* = .004.
¶*P* = .029 between-group differences as revealed by the Holm's test.
Note: Blood loss and incidence of postoperative complications increased significantly with a stepwise increase from low-to-expert difficulty levels (Jonckheere–Terpstra trend test and Cochran–Armitage trend test, each, *P* < .001).

difficulty procedures. There were significant differences in the intraoperative and postoperative outcomes between the advanced and expert difficulties. These differences in outcomes among the two difficulty levels would be contribute to meticulous roadmap for skill up of LLR. Thus, we believe that the scoring system of the IWATE criteria is reasonable. First, surgeons should begin performing LLR as a low-difficulty procedure, such as partial resection for peripheral small tumors at segment 3 or 6 in patients with a good liver function. Surgeons should then increase their experience and skill level to treat cases with higher scores, with the extent of liver resection spanning partial resection and left lateral sectionectomy to right or left hepatectomy, ultimately including posterior sectionectomy for segment VII tumor ≥3 cm or more extended resection, as presented in Fig. 1. Furthermore, advanced- and expert-difficulty procedures should be performed in highly specialized centers because of the risk of poor intraoperative and postoperative outcomes. In this study, the number of cases required to advance to the next step was unable to be evaluated. However, two high-volume centers that participated in this study indicated that 60 laparoscopic minor hepatectomies provided adequate experience before the adoption of laparoscopic major hepatomy,[25] and 45 laparoscopic major hepatectomies were required to reduce the operation time.[4] Furthermore, the IWATE criteria newly incorporated the difficulty of segment 1 (score 4, Fig. 1). Our earlier reports indicated that resection of segment 1 had similar outcomes to that of PS segments and a higher rate of major complications than that of AL segments,[26] which corresponded with the proposal from an international panel of experts' opinion. However, the caudate lobe (segment 1) consists of three parts: Spiegel's lobe, the paracaval portion, and the caudate process.[27] In LLR for segment 1, the laparoscopic approach differed among these three parts (left-sided, right-sided, or anterior approach),[28] leading to differences in the difficulty as well. Other studies have reported that in patients with cirrhosis, LLRs were associated with lesser intraoperative blood loss and lower postoperative complication rates than in those with open liver resection.[29,30] However, it is noteworthy that postoperative liver failure develops in patients with poor liver functional reserve, including in those with cirrhosis, even after partial liver resection.[31] Furthermore, both liver cirrhosis and steatohepatitis attributable to neoadjuvant chemother-

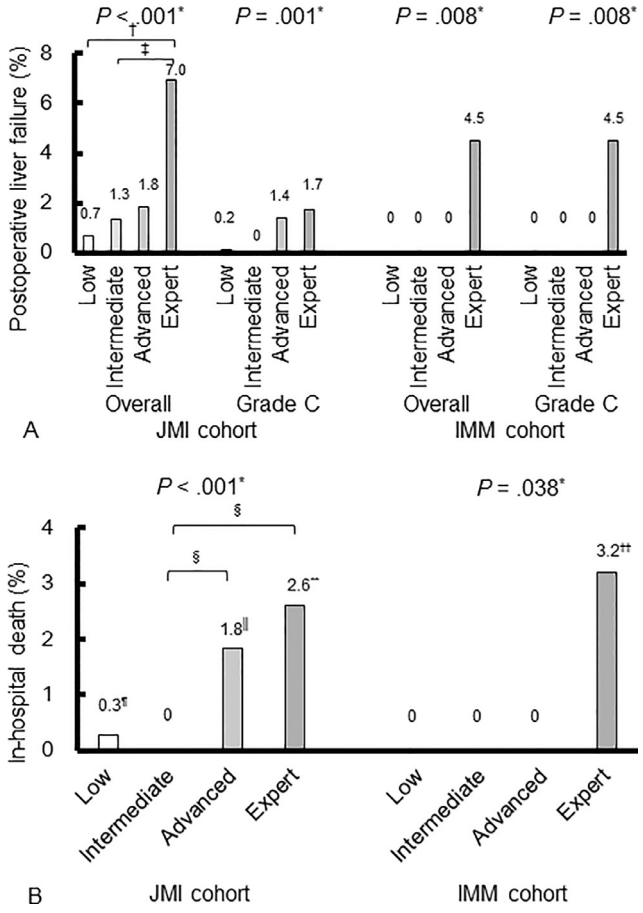

Fig. 4. Surgical outcomes of laparoscopic liver resection grouped according to the 4-level IWATE criteria difficulties in the Japanese multi-institution (JMI) and Institut Mutualiste Montsouris (IMM) cohorts (Part 3). (*A*) postoperative liver failure and (*B*) in-hospital death.

*P values were calculated using the Fisher exact test or the χ^2 test.

†$P < .001$.

‡$P = .005$.

§$P = .011$ between-group differences as revealed by the Holm's test.

¶Liver failure secondary to postoperative bleeding in 1 patient (4 days after surgery), and pneumonia in another (60 days after surgery).

‖Liver failure in 2 patients (29 and 158 days), pancreatitis in 1 (77 days), and pneumonia in 1 (164 days).

**Liver failure in 1 patient (20 days), meningitis in 1 (18 days), and multiorgan failure in 1 (91 days).

††Sepsis in 2 patients (27 days and 43 days, respectively), postoperative bleeding in 1 (6 days), cerebral infarction in 1 (8 days), and unknown in 1 (16 days).

Note: In the JMI and IMM cohorts, the incidences of postoperative liver failure [overall ($P < .001$; $P = .003$), grade C ($P = .001$; $P = .003$)] and in-hospital death ($P < .001$; $P = .011$) all significantly increased with a stepwise increase from low-to-expert difficulty levels (Cochran–Armitage trend test).

apy have recently been suggested to contribute to the difficulty of LLR.[32] Based on these findings, the difficulty division of segment 1 and the involvement of histologic liver injury remain to be resolved.

This study also had some limitations. Because this was a retrospective study, we could not validate another important purpose of the IWATE criteria (ie, to guide surgeons in advancing from simple to highly technical LLRs). However, all surgeons in the JMI cohort who performed LLR had the appropriate level of training or skill. The IWATE criteria need to be further evaluated in other cohorts. On the other hand, the IMM cohort was composed of an expert surgeon's experiences for LLR and covered a long period (11 years), during which the surgical technique evolved. In addition, in this study, the influence of the HALS/Hybrid and Pringle maneuver was not investigated. However, an international multicenter study has indicated that patients who underwent the HALS/Hybrid procedure had a shorter operation time and length of hospital stay than those who underwent pure LLR,[24] which might support the HALS/Hybrid procedure being a -1 score in the IWATE criteria. In fact, Krenzien et al[33] recently validated the IWATE criteria, including the HALS/Hybrid procedure (total: $n = 77$, HALS/Hybrid: $n = 16$); the difficulty level was found to be associated with the operation time, length of hospital stay, and morbidity. The IWATE criteria do not include other important factors, such as high body mass index (obesity), neoadjuvant chemotherapy, repeat liver resection, and concurrent procedures, which may potentially increase the LLR difficulty.[32,34] Nonetheless, our validation of the IWATE criteria, using two cohorts, indicates that the difficulty level can be widely used in low-volume centers and in highly specialized centers.

In conclusion, using the IWATE criteria can help predict the difficulty level of LLR, as evidenced by the association of the intraoperative and postoperative outcomes. Following the IWATE criteria, we recommend a stepwise adoption of LLRs in centers. We also recommend considering the surgeon's learning curve to ensure patients' safety.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.surg.2018.10.012.

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