論文9

ORIGINAL ARTICLE

Risk Model for Distal Gastrectomy When Treating Gastric Cancer on the Basis of Data From 33,917 Japanese Patients Collected Using a Nationwide Web-based Data Entry System

Nobuhiro Kurita, MD, PhD, Hiroaki Miyata, MD, PhD,†‡ Mitsukazu Gotoh, MD, PhD,†‡ Mitsuo Shimada, MD, PhD,† Satoru Imura, MD, PhD,§ Wataru Kimura, MD, PhD,† Naohiro Tomita, MD, PhD,† Hideo Baba, MD, PhD,† Yukou Kitagawa, MD, PhD,† Kenichi Sugihara, MD, PhD,* and Masaki Mori, MD, PhD**

Objective: To establish a risk model for distal gastrectomy in Japanese patients with gastric cancer.

Background: Risk stratification for distal gastrectomy in Japanese patients with gastric cancer improves surgical outcomes.

Methods: The National Clinical Database was constructed for risk determination in gastric cancer-related gastrectomy among Japanese individuals. Data from 33,917 gastric cancer cases (1737 hospitals) were used. The primary outcomes were 30-day and operative mortalities. Data were randomly assigned to risk model development (27,220 cases) and test validation (6697 cases) subsets. Stepwise selection was used for constructing 30-day and operative mortality logistic models.

Results: The 30-day, in-hospital, and operative mortality rates were 0.52%, 1.16%, and 1.2%, respectively. The morbidity was 18.3%. The 30-day and operative mortality models included 17 and 21 risk factors, respectively. Thirteen variables overlapped: age, need for total assistance in activities of daily living preoperatively or within 30 days after surgery, cerebrovascular disease history, more than 10% weight loss, uncontrolled ascites, American Society of Anesthesiologists score ($\geq$ class 3), white blood cell count more than 12,000/μL or 11,000/μL, anemia (hemoglobin: males, <13.5 g/dL; females, <12.5 g/dL; or hematocrit: males, <37%; females <32%), serum albumin less than 3.5 or 3.8 g/dL, alkaline phosphatase more than 340 IU/L, serum creatinine more than 1.2 mg/dL, serum Na less than 135 mEq/L, and prothrombin time-international normalized ratio more than 1.25 or 1.1. The C-indices for the 30-day and operative mortalities were 0.785 (95% confidence interval, 0.705–0.865; $P < 0.001$) and 0.798 (95% confidence interval, 0.746–0.851; $P < 0.001$), respectively.

Conclusions: The risk model developed using nationwide Japanese data on distal gastrectomy in gastric cancer can predict surgical outcomes.

Keywords: distal gastrectomy, gastric cancer, National Clinical Database, risk model of mortality, surgical outcome

(*Ann Surg* 2015;262:295–303)

Age-adjusted mortality of gastric cancer has decreased in most countries; however, it remains the fourth most common cause of cancer death worldwide.[1] Treatment for gastric cancer has received special consideration in East Asia because of its high incidence.[2] Surgery is the most effective treatment approach for gastric cancer. According to the Japanese gastric cancer treatment guidelines, standard surgery for curable advanced gastric cancer is more than two-thirds (subtotal) gastrectomy with D2 dissection.[3] This procedure has been performed without pancreatosplenectomy, which has been shown to be responsible for high mortality and morbidity.[4] In general, the gastrectomy procedures, including lymphadenectomy for early and advanced gastric cancer, have been accepted and performed as standard procedures in most hospitals that participate in the Japanese Gastric Cancer Association.[5] The Japanese Gastric Cancer Association collected data regarding the survival outcomes of 13,626 patients with primary gastric cancer treated at 208 participating hospitals in 2002 and showed that the direct death rate (30-day mortality) was 0.48%.[5] In addition, a nationwide survey by the Japanese Society of Gastrointestinal Surgery (JSGS), which included 24,100 cases treated at 1775 institutions in 2006 and 2007, found that the mortality rates varied from 0.4% to 1.1% depending on the hospital volume.[6] The outcomes appear to be better than those reported in Western countries[7–10]; however, further improvement is still possible.

The National Clinical Database (NCD), which commenced patient registration in January 2011, is a web-based data entry system linked to the surgical board certification in Japan. In this study, we focused on the NCD division of gastrointestinal surgery,[11–13] which uses patient variables and definitions that are almost identical to those used by the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP).[14] Traditionally, various governing bodies, including ACS-NSQIP, have used the 30-day patient mortality as a benchmark to assess the quality of both hospital and surgeon performances in virtually all major surgical procedures. However, we recently reported that mortality based only on known data at 30 days is misleading, and it greatly underestimates the actual perioperative mortality by up to 50% compared with that at 90 days for various procedures (eg, pancreaticoduodenectomy, hepatectomy, and total gastrectomy).[11–13] Thus, the risks for 30- and 90-day in-hospital mortalities should be analyzed together with parameters similar to those used in ACS-NSQIP for patients undergoing distal gastrectomy. To formulate risk models for the 30-day and operative mortalities associated with distal gastrectomy, we evaluated data from 33,917 gastric cancer cases entered in NCD and tested the performance of the model for open and laparoscopic gastrectomy.

METHODS

Study Population

NCD is a nationwide project performed with the cooperation of the board certification system for surgery in Japan. Submission of cases to NCD is a prerequisite for all member institutions of both the Japan Surgical Society and the JSGS, and only registered cases can be used for board certification.[15] Information related to more than 1,200,000 surgical cases treated at more than 3500 hospitals was

From the *Japanese Society of Gastroenterological Surgery, Tokyo, Japan; †Japanese Society of Gastroenterological Surgery, Database Committee, Tokyo, Japan; ‡National Clinical Database, Tokyo, Japan; and §Japanese Society of Gastroenterological Surgery, Working Group of Database Committee, Tokyo, Japan.

Disclosure: None of the authors has any conflicts of interest or sources of funding relevant to this study to declare.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).

Reprints: Nobuhiro Kurita, MD, PhD, The Japanese Society of Gastroenterological Surgery, 104-0041 Chuouku Sintomi, 1-14-1 Central East Bldg 5F, Tokyo, Japan. E-mail: gogokuri@qc4.so-net.ne.jp.

ISSN: 0003-4932/15/26202-0295
DOI: 10.1097/SLA.0000000000001127

collected in 2011. The common input items in the JSGS guidelines have been registered from 2045 institutions. To ensure data traceability, NCD staff work with individuals who approve the data, those in the departments responsible for the annual reporting of case data, and individuals who enter the data via a web-based data management system. The staff also validates data consistency consecutively based on random inspections of the institutions.

In this study, we focused on the specific NCD section for gastrointestinal surgery, which uses variables and definitions that are almost identical to those employed by ACS-NSQIP (http://site.acsnsqip.org/wp-content/uploads/2013/10/ACSNSQIP.PUF_.UserGuide.2012.pdf#search = 'user+guide+for+the+2012+ACS+NSQIP'). Briefly, potential independent variables included patient demographics, pre-existing comorbidities, preoperative laboratory values, and operative data. The demographic variables of age, sex, smoking status, and alcohol drinking status were considered. The patients were categorized according to whether they were transferred directly by ambulance or not. General factors such as preoperative functional status [independent, partially dependent, and totally dependent based on a patient's ability to perform activities of daily living (ADL) at 30 days and immediately before surgery] and body mass index were also considered. The American Society of Anesthesiologists (ASA) physical status classification system was evaluated. We also considered pre-existing comorbidities, including cardiovascular status (eg, congestive heart failure, coronary diseases, hypertension, previous cardiac surgery, and peripheral vascular disease), respiratory status (eg, dyspnea, ventilator dependence, pneumonia, and chronic obstructive pulmonary disease), renal status (eg, acute renal failure and dialysis), hematological status (eg, bleeding disorders and preoperative blood transfusion), oncological status (eg, disseminated cancer, chemotherapy, and radiotherapy), preoperative blood transfusion, chronic corticosteroid use, ascites, sepsis, diabetes, presence of an open wound, and pregnancy. The laboratory parameters included in the analysis were white blood cell count, hemoglobin level, hematocrit, platelet count, prothrombin time-international normalized ratio, and activated partial thromboplastin time, as well as the serum levels of albumin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, urea nitrogen, creatinine, sodium, hemoglobin A_{1c}, and C-reactive protein.

This study focused on 30-day outcomes (if a patient had been discharged after their initial admission) based on a direct 30-day time point assessment. The outcomes included 23 rigorously defined morbidities (including the following categories: wound, respiratory system, urinary tract, central nervous system, cardiac, and other preoperative conditions) as well as mortality. NCD registered the surgical cases from each department in the gastroenterological surgery section, which required the detailed input of items for 8 procedures that represented the performance of surgery in each specialty. All the variables and definitions, as well as the inclusion criteria for NCD, are accessible on the NCD Web site (http://www.ncd.or.jp/). NCD supports an E-learning system to ensure consistent data entry by participants. The NCD staff also answers all inquiries regarding data entry (approximately 80,000 inquiries in 2011) and regularly lists some of these as "Frequently Asked Questions" on the Web site.

The presence of distal gastrectomy in patients with gastric cancer was performed between January 1, 2011 and December 31, 2011 at 1737 institutions in Japan. The NCD records of patients who did not give permission to use their records were excluded from this analysis. Records with missing data in terms of age, sex, or status at 30 days after surgery were also excluded. We selected patients who had undergone distal gastrectomy for gastric cancer, including those who underwent cholecystectomy during the same operation. The exclusion criteria were any other associated surgeries that affected the outcomes based on the surgical criteria for distal gastrectomy applied in Japan after distal gastrectomy and/or gall bladder cancer (Fig. 1). Data were excluded for 41 patients who had undergone simultaneous distal pancreatectomy and 87 patients who had undergone splenectomy (30-day mortalities, 0% and 3.4%, respectively). After data cleaning, the data from 33,917 patients with gastric cancer treated at 1737 hospitals throughout Japan were used to develop the risk model (Fig. 1).

End Points

The primary outcome measures were the 30-day and operative mortalities. "Operative mortality" was defined as death during the index hospitalization, regardless of the length of hospital stay ($\leq$90 days), as well as death after hospital discharge and 30 days or less from the surgery date.

Statistical Analysis

We used SPSS (version 20; IBM Corp., Armonk, NY) for the data analyses. Data were randomly divided into 2 subsets with a split of 80/20, where 1 set was used for model development (27,220 cases) and the other for validation (6697 cases). There were no significant differences in the profiles of the variables between the model development and validation sets, according to univariate analysis using Fisher exact tests and unpaired Student *t* tests. The 2 sets of logistic models (30-day mortality and operative mortality) were constructed for data set development using forward stepwise selection of predictors with a $P < 0.05$ for inclusion. A goodness-of-fit test was performed to assess how well the model could discriminate between patient survival and death. The receiver operating characteristic (ROC) curves for 30-day and operative mortalities were created for the validation data set. An ROC curve is a plot of a test's true positive rate (sensitivity) versus its false-positive rate (1 − specificity). Each point on the ROC curve indicates a pair of false- and true-positive rates that is achieved using a particular threshold to dichotomize the predicted probabilities. Model calibration (the degree to which the observed outcomes matched the predicted outcomes from the model across a group of patients) was

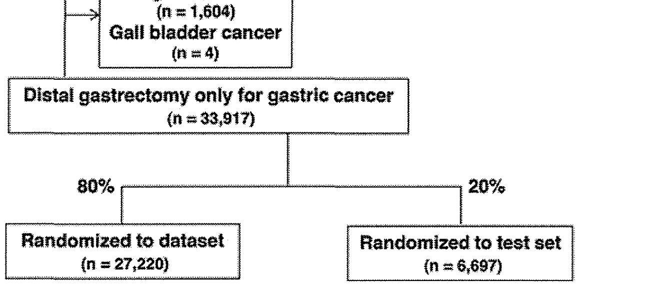

FIGURE 1. Study population selection process. We selected cases where the patients underwent distal gastrectomy for gastric cancer, including patients who simultaneously underwent cholecystectomy. The exclusion criteria were any other associated surgery that could affect the outcomes after distal gastrectomy and/or gall bladder cancer.

examined by comparing the observed and predicted averages with each of 10 equally sized subgroups, which were arranged in order of increasing patient risk.

RESULTS

Risk Profile of the Study Population

The NCD patient population (patients with gastric cancer who underwent distal gastrectomy: n = 33,917) had a mean age of 69.0 (standard deviation = 11.8) years, and 66.5% of the patients were males. Among this population, 1.4% of the patients arrived at the hospital by ambulance and 0.9% required emergency surgery. An abbreviated risk profile of the study population is shown in Table 1. In brief, 8.9% of the patients had an ASA classification of 3 to 5; 0.7% and 0.8% had total dependency during ADLs within 30 days after surgery or preoperatively, respectively; 4.7% needed some assistance with ADLs before surgery; 18.2% had a body mass index more than 25 kg/m^2; and 4.7% had experienced weight loss more than 10%. In terms of pre-existing comorbidities, 33.3% of the patients had hypertension, 15.1% had diabetes mellitus, 3.6% had chronic obstructive pulmonary disease, 0.8% required preoperative dialysis, 3.9% had cerebrovascular disease, 1.1% had ascites, and 2.8% required blood transfusion. Distal gastrectomy with associated cholecystectomy was performed in 10.3% of the patients.

Outcome Rates

The 30-day, in-hospital, and operative mortality rates for distal gastrectomy in the treatment of gastric cancer among the 2011 NCD population were 0.52%, 1.16%, and 1.2%, respectively.

The postoperative morbidities are summarized in Table 2. The overall morbidity in the distal gastrectomy population was 18.3%, and grade II or higher complications, as defined by the Clavien–Dindo Classification of Surgical Complications system,[16] were observed in 11.5% of the patients. Surgical complications included surgical site infection in 4.3% of the patients, anastomotic leakage in 2.1%, and pancreatic fistula (grades A, B, and C) in 1.6%. Nonsurgical complications included pneumonia in 2.0% of the patients, acute renal failure in 0.3%, central nervous system events in 0.5%, and cardiac events in 0.3%.

The following variables were significantly more frequent in the 30-day and operative mortality groups compared with the nonmortality group: reoperation within 30 days, overall complications, surgical complications (except bile leakage in the 30-day mortality group), and nonsurgical complications. In the 30-day mortality group, the incidences of unplanned intubation, pulmonary embolism, cardiac events, and septic shock were increased compared with those in the operative mortality group. In contrast, the incidence of postoperative infectious complications (ie, surgical site infection, bile leakage, pneumonia, and urinary tract infection) increased in the operative mortality group.

Model Results and Performance

Two different risk models were developed. The final logistic models with odds ratios (ORs) and 95% confidence intervals (CIs) are shown in Table 3. The scoring system for the mortality risk models based on the logistic regression equation was as follows:

$$\text{Predicted mortality} = e(\beta 0 + \sum \beta i Xi)/1 + e(\beta 0 + \sum \beta i Xi),$$

where βi is the coefficient of the variable Xi in the logistic regression equation provided in Table 3 for 30-day mortality and 90-day in-hospital mortality. Xi = 1 if a categorical risk factor is present and 0 if it is absent. For the age categories, Xi = 1, if the patient age is less than 59 years; Xi = 2, for 60 to 64 years; Xi = 3, for 65 to 69 years; Xi = 4, for 70 to 74 years; Xi = 5, for 75 to 79 years; and Xi = 6, for 80 years or more. The 2 groups shared 13 overlapping variables: age, need for total assistance in ADL before surgery or within 30 days after surgery, history of cerebrovascular disease, weight loss more than 10%, uncontrolled ascites, ASA score class 3 or more, white blood cell count more than 12,000/μL or 11,000/μL, anemia (hemoglobin: males, <13.5 g/dL; females, <12.5 g/dL; or hematocrit: males <37%; females <32%), serum albumin less than 3.5 or 3.8 g/dL, alkaline phosphatase more than 340 IU/L, serum creatinine more than 1.2 mg/dL, serum Na less than 135 mEq/L, and prothrombin time-international normalized ratio more than 1.25 or 1.1. The independent variables for only 30-day mortality were habitual alcohol consumption, preoperative pneumonia, history of myocardial infarction, and untreated bleeding disorder. The independent variables for only operative mortality were the presence of respiratory distress, disseminated cancer, chronic corticosteroid use, emergency surgery, low platelet count ($<12 \times 10^4/\mu$L), aspartate aminotransferase more than 40 IU/L, increased level of total bilirubin (>2 mg/dL), and activated partial thromboplastin time more than 40 seconds.

Model Performance

To evaluate the model performance, we evaluated the area under the ROC curve (AUC) and the model calibration across risk groups. The ROC curves for both models are shown in Figure 2. The AUC was 0.785 for the 30-day mortality [95% confidence interval (CI), 0.705–0.865; $P < 0.001$] and 0.798 for the overall operative mortality (95% CI, 0.746–0.851; $P < 0.001$). Figure 3 shows the calibration of the models, which illustrates how well the rates for the predicted events matched those of the observed events among the patient risk subgroups.

We evaluated the model performance in open and laparoscopic distal gastrectomy cases (n = 22,039 and 11,878 cases, respectively). The preoperative risk factors were significantly higher in open cases than those in laparoscopic cases (Table 4; Supplemental Digital Content available at http://links.lww.com/SLA/A750). The 30-day and operative mortalities in the open cases were significantly high than those in the laparoscopic cases (Table 5; Supplemental Digital Content available at http://links.lww.com/SLA/A751). This was also the case with morbidity. The ROC curves obtained when both models were applied to the open and laparoscopic cases are shown in Figure 4 (Supplemental Digital Content available at http://links.lww.com/SLA/A752). The AUC was 0.746 for the 30-day mortality (95% CI, 0.628–0.863; $P < 0.001$) and 0.787 for the overall operative mortality (95% CI, 0.717–0.856; $P < 0.001$) in the laparoscopic cases. The AUC was 0.791 for the 30-day mortality (95% CI, 0.756–0.827; $P < 0.001$) and 0.831 for the overall operative mortality (95% CI, 0.808–0.853; $P < 0.001$) in the open cases.

DISCUSSION

The nationwide database used in this study was constructed from the data related to 33,917 cases treated at 1737 hospitals, which comprise most of the Japanese institutions that perform gastric cancer surgery. In this study, the postoperative morbidity, 30-day mortality, and postoperative mortality were 18.3%, 0.52%, and 1.2%, respectively. This is the first report in Japan to present 30-day and operative mortality risk models for distal gastrectomy, which were developed using data from the nationwide web-based data entry system of NCD. The variables examined were selected from among those considered in ACS-NSQIP. The 30-day and operative mortality models included 17 and 21 significant variables, respectively, and the C-indices for the 30-day and operative mortalities in the validation sets were 0.785 and 0.798, respectively, thereby supporting the good predictive abilities of the models.

TABLE 1. Key Preoperative Risk Factors and Surgical Outcomes

Characteristics	Entire Study Population (n = 33,917)		Distal Gastrectomy Outcome Groups: 30-d Mortality (n = 176)			Distal Gastrectomy Outcome Groups: Operative Mortality (n = 409)		
	n	%	n	%	*P*	n	%	*P*
Demographics								
Age, mean (SD), yr	69 (11.8)		76.4 (11.2)		<0.001	76.4 (11.2)		<0.001
Males	22,558	66.5	130	73.9	0.039	301	73.6	0.002
Ambulance transport	474	1.4	12	6.8	<0.001	33	8.1	<0.001
Preoperative risk assessment								
General								
ADL before 30 d: total assistance	227	0.7	12	6.8	<0.001	27	6.6	<0.001
Preoperative ADL: total assistance	264	0.8	14	8.0	<0.001	33	8.1	<0.001
Preoperative ADL: any assistance	1604	4.7	45	25.6	<0.001	121	29.6	<0.001
Body mass index >25 kg/m^2	6153	18.2	28	15.9	0.49	60	14.7	0.07
Habitual alcohol consumption	8113	23.9	41	23.3	0.92	75	18.3	0.008
Current smoker (within a year)	6721	19.8	32	18.2	0.63	75	18.3	0.49
Brinkman index >400	9201	27.1	43	24.4	0.44	104	25.4	0.47
Diabetes	5131	15.1	43	24.4	0.001	84	20.5	0.003
Pulmonary								
Preoperative pneumonia	147	0.4	9	5.1	<0.001	17	4.2	<0.001
Chronic obstructive pulmonary disease	1206	3.6	14	8.0	0.006	41	10.0	<0.001
Respiratory distress	743	2.2	18	10.2	<0.001	51	12.5	<0.001
Cardiac								
Congestive heart failure	262	0.8	8	4.5	<0.001	15	3.7	<0.001
Myocardial infarction	188	0.6	7	4.0	<0.001	13	3.2	<0.001
Angina pectoris	442	1.3	9	5.1	<0.001	20	4.9	<0.001
Previous percutaneous coronary intervention	846	2.5	16	9.1	<0.001	30	7.3	<0.001
Previous cardiac surgery	408	1.2	6	3.4	0.02	13	3.2	0.002
Previous peripheral vascular disease surgery	169	0.5	5	2.8	0.002	9	2.2	<0.001
Hypertension	11,293	33.3	75	42.6	0.010	165	40.3	0.003
Renal								
Acute renal failure	23	0.1	0	0.0	1.00	2	0.5	0.003
Preoperative dialysis	268	0.8	7	4.0	<0.001	15	3.7	<0.001
Central nervous system								
Previous cerebrovascular disease	1329	3.9	28	15.9	<0.001	53	13.0	<0.001
Nutritional/immune/other								
Weight loss >10%	1599	4.7	34	19.3	<0.001	80	19.6	<0.001
Ascites	372	1.1	15	8.5	<0.001	34	8.3	<0.001
Ascites without control	298	0.9	13	7.4	<0.001	29	7.1	<0.001
Disseminated cancer	584	1.7	16	9.1	<0.001	46	11.2	<0.001
Chronic steroid use	287	0.8	1	0.6	1.00	13	3.2	<0.001
Bleeding disorder without treatment	148	0.4	7	4.0	<0.001	13	3.2	<0.001
Preoperative transfusions	944	2.8	26	14.8	<0.001	51	12.5	<0.001
Chemotherapy	453	1.3	4	2.3	0.30	8	2.0	0.27
Radiotherapy	45	0.1	0	0.0	1.00	1	0.2	0.42
Sepsis	57	0.2	3	1.7	0.003	7	1.7	<0.001
Emergent surgery	316	0.9	16	9.1	<0.001	35	8.6	<0.001
ASA ≥Grade 3	3008	8.9	62	35.2	<0.001	152	37.2	<0.001
ASA Grade 5	33	0.1	2	1.1	0.013	3	0.7	0.007
Cholecystectomy	3499	10.3	15	8.5	0.528	43	10.5	0.879
Preoperative laboratory data								
White blood cells								
>9000/mL	1933	5.7	29	16.5	0.015	66	16.1	<0.001
>11,000/mL	601	1.8	16	9.1	<0.001	32	7.8	<0.001
Hemoglobin, males: <13.5 g/dL; females: <12.5 g/dL	14,642	43.2	129	73.3	<0.001	294	71.9	<0.001
Hematocrit, males: <37% females: <32%	10,467	30.9	108	61.4	<0.001	250	61.1	<0.001
Platelets								
<8 × 10^4/mL	175	0.5	5	2.8	0.029	9	2.2	<0.001
<12 × 10^4/mL	932	2.7	13	7.4	0.001	38	9.3	<0.001
Serum albumin <3.8 g/dL	8730	25.7	99	56.3	<0.001	255	62.3	<0.001

(*Continues*)

TABLE 1. Key Preoperative Risk Factors and Surgical Outcomes (*Continued*)

	Entire Study Population (n = 33,917)		Distal Gastrectomy Outcome Groups: 30-d Mortality (n = 176)			Distal Gastrectomy Outcome Groups: Operative Mortality (n = 409)		
Characteristics	n	%	n	%	*P*	n	%	*P*
AST >40 IU/L	2064	6.1	20	11.4	0.007	56	13.7	<0.001
ALP >340 IU/L	2540	7.5	30	17.0	<0.001	61	14.9	<0.001
Total bilirubin >2 mg/dL	285	0.8	2	1.1	0.66	10	2.4	0.003
BUN >20 mg/dL	5201	15.3	52	29.5	<0.001	135	33.0	<0.001
Creatinine >1.2 mg/dL	2231	6.6	32	18.2	<0.001	76	18.6	<0.001
Serum Na								
<130 mEq/L	179	0.5	11	6.3	0.061	19	4.6	<0.001
<135 mEq/L	1068	3.1	32	18.2	<0.001	70	17.1	<0.001
Hemoglobin A_{1c} >6.5%	2035	6.0	8	4.5	0.520	20	4.9	0.40
CRP >1.0 mg/dL	2696	7.9	44	25.0	<0.001	118	28.9	<0.001
PT-INR								
>1.1	4748	14.0	63	35.8	<0.001	142	34.7	<0.001
>1.25	966	3	21	12	<0.001	42	10	<0.001
APTT > 40 seconds	902	2.7	13	7.4	<0.001	39	9.5	<0.001

ALP indicates alkaline phosphatase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; PT-INR, prothrombin time-international normalized ratio; SD, standard deviation.

TABLE 2. Prevalence of Morbidity With Distal Gastrectomy Outcomes

	Entire Study Population (n = 33,917)		Distal Gastrectomy Outcome Groups: 30-d Mortality (n = 176, 0.52%)			Distal Gastrectomy Outcome Groups: Operative Mortality (n = 409, 1.2%)		
Postoperative Outcomes	n	%	n	%	*P*	n	%	*P*
Readmission within 30 d	553	1.6	3	1.7	0.765	7	1.7	0.843
Reoperation within 30 d	633	1.9	29	16.9	<0.001	80	19.6	<0.001
Postoperative complications								
Overall	6193	18.3	148	84.1	<0.001	329	80.4	<0.001
≥Grade II	3893	11.5	138	78.4	<0.001	303	74.1	<0.001
Surgical complications								
Surgical site infection	1458	4.3	31	17.6	<0.001	89	21.8	<0.001
Superficial incisional	668	2.0	9	5.1	0.008	42	10.3	<0.001
Deep incisional	288	0.8	8	4.5	<0.001	35	8.6	<0.001
Organ space	910	2.7	27	15.3	<0.001	72	17.6	<0.001
Wound dehiscence	182	0.5	6	3.4	<0.001	26	6.4	<0.001
Anastomotic leak	696	2.1	25	14.2	<0.001	73	17.8	<0.001
Pancreatic fistula	542	1.6	17	9.7	<0.001	37	9.0	<0.001
Bile leakage	102	0.3	2	1.1	0.099	13	3.2	<0.001
Nonsurgical complications								
Pneumonia	687	2.0	35	19.9	<0.001	122	29.8	<0.001
Unplanned intubation	293	0.9	77	43.8	<0.001	136	33.3	<0.001
Prolonged ventilation >48 hr	299	0.9	59	33.5	<0.001	129	31.5	<0.001
Pulmonary embolism	26	0.1	4	2.3	<0.001	5	1.2	<0.001
Acute renal failure	89	0.3	25	14.2	<0.001	55	13.4	<0.001
Urinary tract infection	150	0.4	5	2.8	0.001	21	5.1	<0.001
Events in central nervous system	164	0.5	32	18.2	<0.001	60	14.7	<0.001
Cardiac events	118	0.3	75	42.6	<0.001	88	21.5	<0.001
Septic shock	138	0.4	38	21.6	<0.001	75	18.3	<0.001

Many studies have aimed to develop methods that predict the risk of perioperative mortality following gastric resection in the Western hemisphere[17–20] and in Asian countries.[21] All these previous studies used data from either a single institution or a nationwide database.[17–21] The most commonly used nationwide databases in the Western hemisphere are the population-based National Inpatients Sample[17,18] and ACS-NSQIP.[20] However, the National Inpatients Sample data set is an administrative data set, which lacks operative factors such as the procedure duration, bleeding volume, and extent of lymph node resection, and it also lacks other important factors such as ASA status, preoperative nutritional status, extent of weight loss, palliative versus curative resection, and use of neoadjuvant therapy. The risk models created using ACS-NSQIP variables have been shown to be quite effective for predicting mortality in

TABLE 3. Risk Models for 30-Day Mortality and Operative Mortality After Distal Gastrectomy

	30-d Mortality					Operative Mortality				
Variables	b Coefficient	Odds Ratio	95% CI		*P*	b Coefficient	Odds Ratio	95% CI		*P*
Age category	0.184	1.202	1.062	1.361	0.004	0.283	1.327	1.217	1.446	<0.001
ADL										
Before 30 d: total assistance	1.083	2.955	1.418	6.159	0.004					
Preoperative: total assistance						1.099	3.001	1.856	4.852	<0.001
Habitual alcohol consumption	0.453	1.573	1.047	2.362	0.029					
Preoperative pneumonia	1.019	2.769	1.171	6.549	0.02					
Respiratory distress						0.869	2.385	1.634	3.482	<0.001
Myocardial infarction	1.14	3.127	1.282	7.63	0.012					
Previous cerebrovascular disease	0.734	2.084	1.248	3.48	0.005	0.575	1.777	1.228	2.572	0.002
Weight loss >10%	0.82	2.271	1.437	3.589	<0.001	0.785	2.192	1.592	3.018	<0.001
Ascites without control	1.091	2.978	1.404	6.315	0.004	1.018	2.767	1.638	4.674	<0.001
Disseminated cancer						1.063	2.896	1.897	4.42	<0.001
Chronic steroid use						1.026	2.789	1.454	5.35	0.002
Bleeding disorder without treatment	1.17	3.223	1.205	8.622	0.02					
Emergent surgery						0.618	1.856	1.026	3.357	0.041
ASA ≥class 3	0.668	1.95	1.288	2.953	0.002	0.648	1.912	1.453	2.518	<0.001
White blood cells										
>11,000/mL						0.934	2.545	1.591	4.071	<0.001
>12,000/mL	1.299	3.666	1.837	7.314	<0.001					
Hemoglobin										
Males: <13.5 g/dL females: <12.5 g/dL	0.596	1.814	1.136	2.897	0.013					
Hematocrit										
Males: <37% females: <32%						0.364	1.439	1.089	1.901	0.01
Platelets <12 × 10^4/mL						0.696	2.006	1.3	3.093	0.002
Serum albumin										
<3.5 g/dL	0.395	1.485	0.979	2.252	0.063					
<3.8 g/dL						0.555	1.741	1.303	2.326	<0.001
Aspartate aminotransferase >40 IU/L						0.416	1.516	1.06	2.169	0.023
Alkaline phosphatase >340 IU/L	0.772	2.164	1.384	3.386	0.001	0.442	1.556	1.113	2.173	0.01
Total bilirubin >2 mg/dL						0.969	2.634	1.204	5.764	0.015
Creatinine >1.2 mg/dL	0.573	1.773	1.124	2.796	0.014	0.59	1.803	1.328	2.448	<0.001
Serum Na <135 mEq/L	0.908	2.48	1.528	4.025	<0.001	0.812	2.251	1.612	3.146	<0.001
PT-INR										
>1.1						0.423	1.527	1.175	1.985	0.002
>1.25	0.708	2.03	1.162	3.549	0.013					
APTT > 40 seconds						0.455	1.576	1.05	2.366	0.028
Intercept	−7.393				<0.001	−6.996				<0.001

APTT indicates activated partial thromboplastin time; PT-INR, prothrombin time-international normalized ratio.

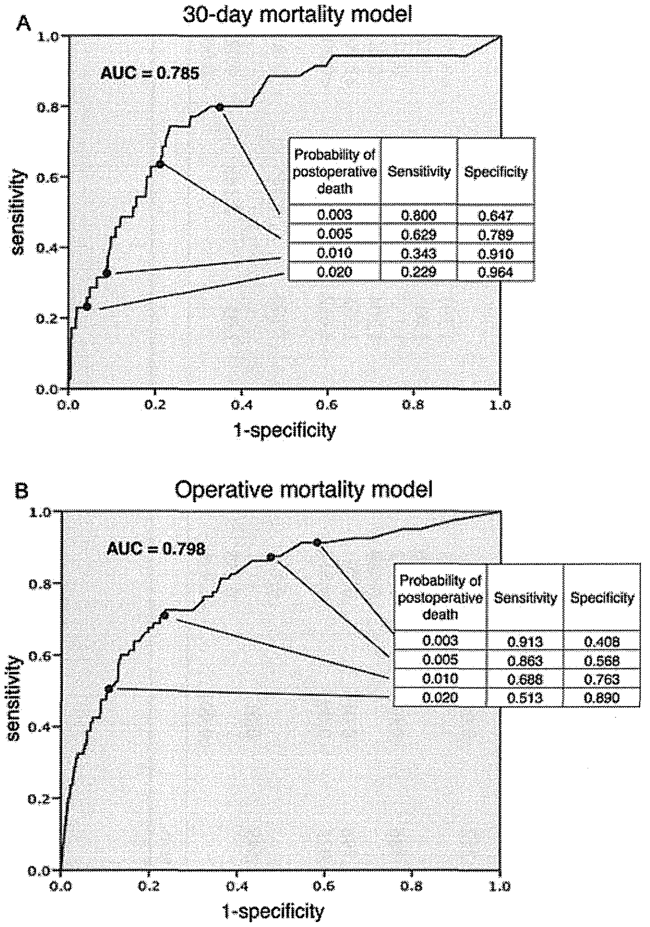

FIGURE 2. ROC curves of the (A) 30-day mortality model and (B) operative mortality model. The AUC was 0.785 for the 30-day mortality (95% CI, 0.705–0.865; $P < 0.001$) and 0.798 for the overall operative mortality (95% CI, 0.746–0.851; $P < 0.001$).

various procedures and for improving surgical quality in participating hospitals.[14] However, Borja-Cacho et al[22] showed that the current ACS-NSQIP variables do not have a good predictive capacity for major complications after major oncological resection, and thus they advocated the use of additional disease-specific and operation-specific variables to obtain more accurate predictions of the 30-day postoperative outcome. NCD uses variables similar to those employed in ACS-NSQIP but with some modifications that allow it to represent not only the 30-day mortality but also the in-hospital mortality 90 days or less after surgery. The Japanese system of universal health care allows most patients who undergo surgery to be cared for in the same hospital that performed the operation until the patient can independently function in terms of ADL.[23,24] With this adjustment to include longer-term mortality, the operative mortality rate of patients treated by distal gastrectomy increased to twice the 30-day mortality rate (1.2% vs 0.52%, respectively).

There are 2 major distinct gastrectomy procedures: distal and total gastrectomy. The surgical procedures for resection and anastomosis are quite different, and the outcomes of the respective procedures are reported in the JSGS annual report (30-day mortality/operative mortality: subtotal gastrectomy, 0.6%/1.3%; total gastrectomy, 1.0%/2.3%).[25] In this study, we focused only on patients who had undergone distal gastrectomy for gastric cancer. Out of the 17 and 21 risk factors in the 30-day and operative mortality models, respectively, 13 variables shared similar characteristics. Previously, many of these factors have been shown to affect perioperative mortality in patients who undergo gastric resections for malignancy.[17–22] The results of our study clearly showed that common and independent variables affected the mortality risk in the early (30-day mortality) and late (90-day in-hospital mortality) postoperative periods. The variables that predicted the 30-day mortality only and not the operative mortality comprised those that influence relatively early death after surgery, such as habitual alcohol consumption, preoperative pneumonia, myocardial infarction, and untreated bleeding disorder. The variables that predicted operative mortality only are those that influence late death after surgery, such as any respiratory distress, disseminated cancer, chronic corticosteroid use, emergency surgery, low platelet count, and high levels of aspartate aminotransferase, total bilirubin, and activated partial thromboplastin time. The variables that predicted both the 30-day and operative mortalities are those that influence both early and late death after surgery. In particular, the laboratory variables (eg, white blood cell count, serum albumin, and prothrombin time-international normalized ratio) that captured the risk of both early and late mortality appeared to be related to substantially abnormal levels in the 30-day mortality group. Further analysis is needed to determine the variables that are relevant to the respective morbidities leading to mortality, but these results provide insight into the specific preoperative risk variables responsible for the early or late mortality of patients who undergo distal gastrectomy.

This study had several limitations, which need to be addressed in future studies. First, the reported mortality and morbidity rates in our study would have been influenced by cancer stage, extent of lymphadenectomy (eg, D1, D1, and D2),[8,9,10,26–28] curative ability of the surgery,[29,30] hospital volume,[31,32] and institutional experience.[33] In addition, we only analyzed the variables that could be obtained before surgery. Although these risk models predicted the mortality well for open or laparoscopic approaches, the effects of these variables on outcomes should be assessed in a future study using a propensity score matching system. Second, some reports have described preoperative scoring systems that predict surgical risks, such as the Physiologic and Operative Severity Score for the enUmeration of Mortality and Morbidity and the Estimation of Physiologic Ability and Surgical Stress for general surgery.[34,35] However, although these systems are useful for general surgery, some modifications would be required for specific operative procedures.[36] The NCD is currently being used to investigate the accuracy of these models for Japanese patients who undergo gastrectomy. Third, although our analysis used the nationwide database, the study population was limited to a single race. Therefore, our results should be evaluated on the basis of comparisons with patients from other countries using the same variables and definitions. Thus, we are currently planning a mutual collaboration with ACS-NSQIP.

CONCLUSIONS

We report the first risk stratification study based on the NCD for distal gastrectomy in cancer treatment. The NCD database allowed us to determine interinstitutional differences in outcomes and the factors that affect these differences. This system will contribute to an improved quality control in surgical practice and it should also be useful in counseling and for obtaining informed consent from patients.

ACKNOWLEDGMENTS

The authors thank all the data managers and hospitals that participated in the NCD project for their great efforts in entering the data analyzed in this study. They also thank Prof. Hideki Hashimoto and Noboru Motomura, MD, for providing direction in the foundation

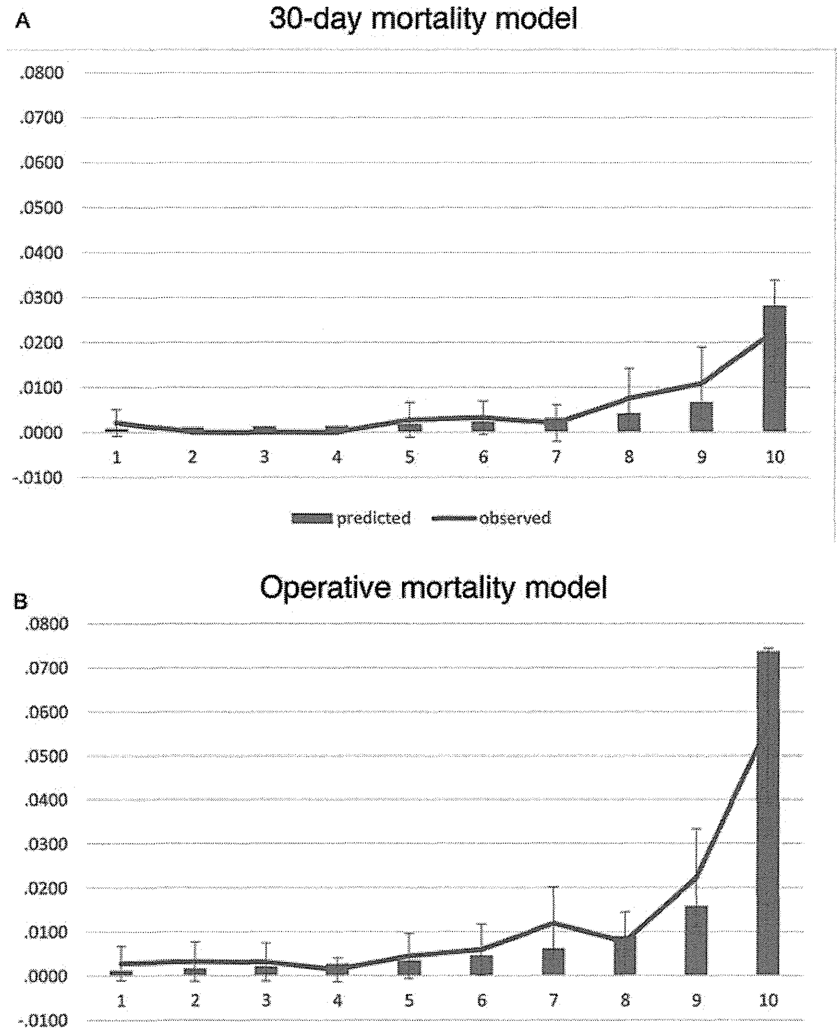

FIGURE 3. Calibrations of the 30-day mortality model (A) and operative mortality model (B). The calibrations of the models illustrate how well the rates of the predicted events matched those of the observed events among the patient risk subgroups. The error bar represents 95% confidence interval.

of NCD, and they thank the working members of the JSGS database committee (Masayuki Watanabe, MD; Satoru Imura, MD; Fumihiko Miura, MD; Hiroya Takeuchi, MD; Ichiro Hirai, MD; Yoshio Takesue, MD; Hiroyuki Suzuki, MD; Megumi Ishiguro, MD; Hiroyuki Konno, MD; Makoto Gega, MD; Nagahide Matsubara, MD; and Akihiko Horiguchi, MD). They also acknowledge Hiroyuki Konno, MD, for his important suggestions regarding this article.

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin.* 2012;62:10–29.
2. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127:2893–2917.
3. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer.* 2011;14:113–123.
4. Sasako M. Risk factors for surgical treatment in the Dutch Gastric Cancer Trial. *Br J Surg.* 1997;84:1567–1571.
5. Nashimoto A, Akazawa K, Isobe Y, et al. Gastric cancer treated in 2002 in Japan: 2009 annual report of the JGCA Nationwide Registry. *Gastric Cancer.* 2013;16:1–27.
6. Suzuki H, Gotoh M, Sugihara K, et al. Nationwide survey and establishment of a clinical database for gastrointestinal surgery in Japan: Targeting integration of a cancer registration system and improving the outcome of cancer treatment. *Cancer Sci.* 2011;102:226–230.
7. Songun I, Putter H, Kranenbarg EM, et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomized nationwide Dutch D1D2 trial. *Lancet Oncol.* 2010;11:439–449.
8. Cuschieri A, Fayers P, Fielding J, et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. *Lancet.* 1996;347:995–999.
9. Bonenkamp JJ, Hermans J, Sasako M, et al. Extended lymph-node dissection for gastric cancer. *N Engl J Med.* 1999;340:908–914.
10. Degiuli M, Sasako M, Ponti A, et al. Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer. *Br J Surg.* 2014;101: 23–31.
11. Kimura W, Miyata H, Gotoh M, et al. A pancreaticoduodenectomy risk model derived from 8575 cases from a national single-race population (Japanese) using a web-based data entry system: the 30-day and in-hospital mortality rates for pancreaticoduodenectomy. *Ann Surg.* 2014;259:773–780.
12. Kenjo A, Miyata H, Gotoh M, et al. Risk stratification of 7732 hepatectomy cases in 2011 from the National Clinical Database for Japan. *J Am Coll Surg.* 2014;218:412–422.
13. Watanabe M, Miyata H, Gotoh M, et al. Total gastrectomy risk model: data from 20,011 Japanese patients in a nationwide internet-based database. *Ann Surg.* 2014;260:1034–1039.
14. Hall BL, Hamilton BH, Richards K, et al. Does surgical quality improve in the American College of Surgeons National Surgical Quality Improvement Program: an evaluation of all participating hospitals. *Ann Surg.* 2009;250:363–376.
15. Miyata H, Gotoh M, Hashimoto H, et al. Challenges and prospects of a clinical database linked to the board certification system. *Surg Today.* 2014;44:1991–1999.
16. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien–Dindo classification of surgical complications: five-year experience. *Ann Surg.* 2009;250: 187–196.

17. Smith JK, McPhee JT, Hill JS, et al. National outcomes after gastric resection for neoplasm. *Arch Surg.* 2007;142:387–393.
18. Dhir M, Smith LM, Ullrich F, et al. A preoperative nomogram to predict the risk of perioperative mortality following gastric resections for malignancy. *J Gastrointest Surg.* 2012;16:2026–2036.
19. Oñate-Ocaña LF, Cortés-Cárdenas SA, Aiello-Crocifoglio V, et al. Preoperative multivariate prediction of morbidity after gastrectomy for adenocarcinoma. *Ann Surg Oncol.* 2000;7:281–288.
20. Grossmann EM, Longo WE, Virgo KS, et al. Morbidity and mortality of gastrectomy for cancer in Department of Veterans Affairs Medical Centers. *Surgery.* 2002;131:484–490.
21. Park DJ, Lee HJ, Kim HH, et al. Predictors of operative morbidity and mortality in gastric cancer surgery. *Br J Surg.* 2005;92:1099–1102.
22. Borja-Cacho D, Parsons HM, Habermann EB, et al. Assessment of ACS-NSQIP's predictive ability for adverse events after major cancer surgery. *Ann Surg Oncol.* 2010;17:2274–2282.
23. Ikegami N, Yoo BK, Hashimoto H, et al. Japanese universal health coverage: evolution, achievements, and challenges. *Lancet.* 2011;378:1106–1115.
24. Hashimoto H, Ikegami N, Shibuya K, et al. Cost containment and quality of care in Japan: is there a trade-off? *Lancet.* 2011;378:1174–1182.
25. Konno H, Wakabayashi G, Udagawa H, et al. Annual Report of National Clinical Database in Gastroenterological Surgery 2011–2012. *Jpn J Gastroenterol Surg.* 2013;46:952–963.
26. Wu CW, Hsiung CA, Lo SS, et al. Randomized clinical trial of morbidity after D1 and D3 surgery for gastric cancer. *Br J Surg.* 2004;91:283–287.
27. Sasako M, Sano T, Yamamoto S, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med.* 2008;359: 453–462.
28. Degiuli M, Sasako M, Ponti A. Italian Gastric Cancer Study Group. Morbidity and mortality in the Italian Gastric Cancer Study Group randomized clinical trial of D1 versus D2 resection for gastric cancer. *Br J Surg.* 2010;97: 643–649.
29. Söreide JA, van Heerden JA, Burgart LJ, et al. Surgical aspects of patients with adenocarcinoma of the stomach operated on for cure. *Arch Surg.* 1996;131:481–486.
30. Mahar AL, Coburn NG, Singh S, et al. A systematic review of surgery for noncurative gastric cancer. *Gastric Cancer.* 2012;(suppl 1):S125–S137.
31. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med.* 2002;346:1128–1137.
32. Mahar AL, McLeod RS, Kiss A, et al. A systematic review of the effect of institution and surgeon factors on surgical outcomes for gastric cancer. *J Am Coll Surg.* 2012;214:860–868.
33. Degiuli M, Sasako M, Calgaro M, et al. Morbidity and mortality after D1 and D2 gastrectomy for cancer: interim analysis of the Italian Gastric Cancer Study Group (IGCSG) randomised surgical trial. *Eur J Surg Oncol.* 2004;30: 303–308.
34. Copeland GP, Jones D, Walters M. POSSUM: a scoring system for surgical audit. *Br J Surg.* 1991;78:355–360.
35. Haga Y, Wada Y, Takeuchi H, et al. Estimation of physiologic ability and surgical stress (E-PASS) for a surgical audit in elective digestive surgery. *Surgery.* 2004;135:586–594.
36. Wang H, Chen T, Wang H, et al. A systematic review of the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity and its Portsmouth modification as predictors of postoperative morbidity and mortality in patients undergoing pancreatic surgery. *Am J Surg.* 2013;205:466–472.

Interactive CardioVascular and Thoracic Surgery 21 (2015) 151–156
doi:10.1093/icvts/ivv109 Advance Access publication 29 April 2015

ORIGINAL ARTICLE – CONGENITAL

Cite this article as: Hoashi T, Miyata H, Murakami A, Hirata Y, Hirose K, Matsumura G *et al.* The current trends of mortality following congenital heart surgery: the Japan Congenital Cardiovascular Surgery Database. Interact CardioVasc Thorac Surg 2015;21:151–6.

The current trends of mortality following congenital heart surgery: the Japan Congenital Cardiovascular Surgery Database

Takaya Hoashi*, Hiroaki Miyata, Arata Murakami, Yasutaka Hirata, Keiichi Hirose, Goki Matsumura, Hajime Ichikawa, Yoshiki Sawa and Shinichi Takamoto

The Japan Cardiovascular Surgery Database Organization, Osaka, Japan

* Corresponding author. The Japan Cardiovascular Surgery Database Organization, 5-7-1, Fujishiro-dai, Suita, Osaka 565-8565, Japan. Tel: +81-6-68335012; fax: +81-6-68727486; e-mail: thoashi@surg1.med.osaka-u.ac.jp (T. Hoashi).

Received 6 February 2015; received in revised form 24 March 2015; accepted 2 April 2015

ORIGINAL ARTICLE

Abstract

OBJECTIVES: Whereas surgical outcomes of congenital heart surgery have improved during the past two decades, there are still measurable postoperative mortalities in this field. This study is aimed at evaluating the current situation of mortality following congenital heart surgery.

METHODS: Data on all registered 28 810 patients in The Japan Congenital Cardiovascular Surgery Database (JCCVSD) between 2008 and 2012 were analysed, except for patients with degenerative cardiomyopathy including dilated, restrictive and hypertrophic cardiomyopathy, and pathologically or histologically malignant cardiac tumours. The number of registered cases increased every year, and reached ~9000 cases in 2012. The median age at surgery was 0.8 years (range, 0–82). More than half of the patients (54%) who underwent surgery were <1 year old, and 6.0% of all patients were over 18 years old (adults). In this study, all mortalities within 90 days after the operation and mortality at discharge beyond 90 days of hospitalization were defined as '90-day and in-hospital mortality'.

RESULTS: The 30-, 90-day and in-hospital mortality rates were 2.3, 3.5 and 4.5%, respectively. The mean and median durations from surgery to death were 61 ± 89 and 28 days (range, 0–717), respectively. Whereas 658 mortalities (51%) occurred within 30 days of surgery, 265 (21%) occurred later than 90 days after surgery. A total of 3630 patients (13%) were hospitalized for more than 90 days after the operation; of those, 3365 patients survived at discharge (93%). Cardiac problems were the most frequent causes of death after the surgery at any point in time, and 7.1 per 1000 patients died at over 30 days after the operation due to solely cardiac.

CONCLUSIONS: The investigation of JCCVSD revealed that about a half of mortalities occurred later than 30 days; hence 90-day and in-hospital mortality would be a good discriminator that accurately represented the current situation of mortality after congenital heart surgery. Mortalities long after the operation due to post-cardiotomy heart failure without any other lethal complications were still not rare.

Keywords: Congenital heart disease • Surgery • Database • Extracorporeal membrane oxygenation

INTRODUCTION

Whereas a great improvement in the surgical outcomes of congenital heart surgery has been achieved during the past two decades, there are still measurable postoperative mortalities in this field. In addition, for the further evolution of surgical procedures or treatments for each anatomical group, therapeutic options such as left ventricular assist devices, heart transplantation and cardiac regenerative therapy must be offered to rescue patients falling victim to postoperative heart failure.

The Japan Congenital Cardiovascular Surgery Database (JCCVSD), which is the nationwide congenital heart surgery database registry system, was established in 2008 [1]. The accuracy of follow-up outcomes was confirmed by a site audit [2], and now >90% of congenital heart operations performed in Japan are enrolled in the database. Utilizing this database, we have reviewed the timing, cause and trends of death after congenital heart surgery in Japan in order to assess the current situation and the necessity of further treatment options for post-cardiotomy heart failure.

MATERIALS AND METHODS

Japanese Cardiovascular Surgery Database Organization Committee granted permission to access and analyse the data collected in the JCCVSD with a waiver of informed consent.

Of the patients registered on the JCCVSD between 2008 and 2012, 28 810 patients were selected as study subjects, mainly by fundamental diagnosis (Supplementary material, File S1) [3]. Patients with myocardial degenerative disease including dilated, restrictive and hypertrophic cardiomyopathy, a cardiac tumour or complications after heart transplantation were excluded from this study (Supplementary material, File S2).

The characteristics of the 28 810 enrolled patients are summarized in Table 1. The number of admitted institutions was 17 in 2008, 68 in 2009, 93 in 2010, 102 in 2011 and 111 in 2012; thus, the number of registered cases increased every year and reached ~9000 cases in 2012. The median age at surgery was 0.8 years (range, 0–82). More than half of the patients (54%) who underwent surgery were <1 year old, and 6.0% of all patients were over 18 years old (adults). The surgery was electively scheduled for 84.6% of the patients, 11.3% of the cases were scheduled urgently and 4.1% were emergently performed.

Definitive surgery was defined as the last surgery that was planned according to each anatomical property, and so it included not only complete biventricular repair, but also partial biventricular repair or Fontan operations with or without fenestration. The prevalence rates of the definitive operation with cardiopulmonary bypass (CPB), the palliative operation with CPB, the definitive operation without CPB and the palliative operation without CPB were 64, 13, 7.0 and 15%, respectively.

Prevalence of patients by risk adjustment in the congenital heart surgery system (RACHS) ([4], Supplementary material, File S3) categories were as follows: risk category 1 in 13% of patients, category 2 in 33%, category 3 in 34%, category 4 in 7.7%, category 5 in 0.1% and category 6 in 2.6% of patients.

Table 1: Patient characteristics

Total number of patients (*n*)	28 810	
Male:female (*n*)	14 412:13 105	
Age at operation [mean ± SD, median (range)]	4.4 ± 10.0	0.8 (0–81)
	n	(%)
Generation		
Neonate	4760	(16.5)
Infant	10 778	(37.4)
Child	11 523	(40.0)
Adult	1734	(6.0)
Unknown	15	(0.1)
Year of operation (number of registered institutions)		
2008 (17)	982	(3.4)
2009 (68)	3403	(11.8)
2010 (93)	7051	(24.5)
2011 (102)	8389	(29.1)
2012 (111)	8985	(31.2)
Situation		
Elective	24 360	(84.6)
Urgent	3256	(11.3)
Emergency	1194	(4.1)
Type		
Definitive, with CPB	18 532	(64.3)
Palliative, with CPB	3833	(13.3)
Definitive, without CPB	2019	(7.0)
Palliative, without CPB	4426	(15.4)
RACHS risk category		
1	3454	(12.9)
2	8922	(33.2)
3	9008	(33.5)
4	2078	(7.7)
5	16	(0.1)
6	707	(2.6)
Uncategorized	2689	(10.0)

CPB: cardiopulmonary bypass; RACHS: risk adjustment in congenital heart surgery system.

Definition of 90-day and in-hospital mortality

The database forced medical practitioners to enter the discharge date within 90 days after the last surgery and the life prognosis at postoperative day 90, so that mortality up to and including postoperative day 90 was completely recorded. If patients were in the hospital for more than 90 days after the operation, the entering of the discharge date and life prognosis was voluntary. However, 3616 of 28 810 patients (13%) were in the hospital beyond postoperative day 90, and the life prognoses at discharge were recorded for all patients.

In addition, only 3.1% of all mortalities occurred after discharge. All these patients were discharged within 90 days after the last operation and their death was identified by the confirmation of life prognosis at 90 days after the last surgery. Therefore, in this study, all mortalities within 90 days after the operation and mortality at discharge beyond 90 days of hospitalization were defined as '90-day and in-hospital mortality'.

Definition of the cause of death

The cause of death was determined by the treating physicians according to their clinical impressions when considering the postoperative course, which was objectively assessed according to the clinical chart of the intensive care unit, operative records, echocardiograms, catheterizations and clinical summaries. Then, the principal clinical issue contributing to the patient's death was determined as the cause of death, which was not necessarily the same as the preterminal event occurring immediately before death. Because the identification of the sole cause of death was usually difficult, all possible causes [i.e. (i) cardiac, (ii) lung, (iii) infection, (iv) central nervous system damage, (v) renal and other issues] could be concomitantly recorded.

Post-cardiotomy extracorporeal membrane oxygenation cannulation

Extracorporeal membrane oxygenation (ECMO) cannulation and decannulation have been added as surgical procedures since 2010. During the study period, paediatric left ventricular assist systems were not available, and there had been only 2 donors under 15 years of age for paediatric heart transplantation, nevertheless, the Organ Transplant Law in Japan was revised and enforced in 2010.

Study methods

Evaluated variables in this study were as follows: (a) timing and cause of death after surgery; (b) differences in mortality rates by generation, surgical year, RACHS risk category and operation type; and (c) prognostic outcomes for post-cardiotomy ECMO support.

Preoperative risk factors that were required to be entered into the database are listed in the Supplemental Material. Risk factor analysis was conducted using the Pearson's χ^2 test and data were analysed using the JMP software version 10 (SAS Institute, Cary, NC), USA. Differences were considered statistically significant when the P-value was <0.05.

RESULTS

Timing and cause of death after surgery

Of all the 28 810 patients enrolled in the database, 1293 mortalities (4.5%) were identified (Fig. 1). The 30-day and 90-day mortality rates were 2.3 and 3.5%, respectively. Forty of the mortalities (3.1%) occurred after discharge. The mean and median durations from the last operation to death were 61 ± 89 days and 28 days (range, 0–717), respectively. Whereas 658 mortalities (51%) were observed within 30 days of the last surgery, 352 (27%) were from 30 days to 90 days, and 265 (21%) were observed more than 90 days after the last surgery.

The causes of death after surgery were often multifactorial (Table 2). Of all 1293 mortalities, 546 mortalities (42%) were related solely to cardiac issues; thus any other lethal problems such as lung issues, infections, central nervous system damage or renal issues were not related. Solely lung issues was the second most frequent cause of death, which included acute respiratory distress syndrome, pulmonary hypertension crisis or persistent pulmonary hypertension without such problems as left heart issues, pulmonary bleeding or thromboembolism, and so on. Infection was the sole cause of death in 99 patients (7.7%), and central nervous system damage was the sole cause of death in 41 patients (3.2%). Table 2 also demonstrates the different trends in the causes of death by displaying the timing of death. Although cardiac issues were the most common causes of death during the entire period, the prevalence of mortalities caused by cardiac issues decreased as time passed, and mortalities caused by infection increased.

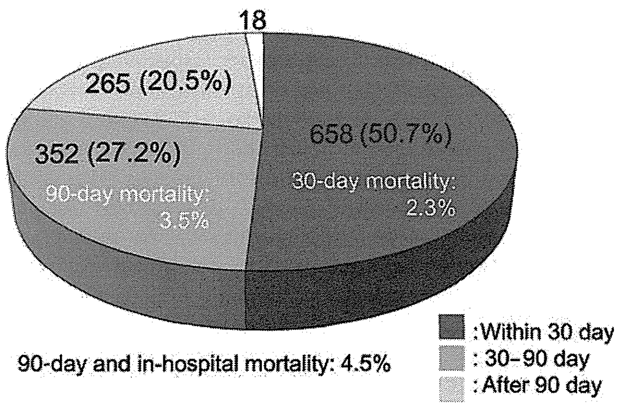

Figure 1: Timing of death after surgery. The areas in red, orange and yellow represent the amount and prevalence of mortality within 30 days after surgery, between 30 and 90 days after surgery, and more than 90 days after surgery, respectively.

Table 2: Causes of death after surgery (multiple reasons allowed)

Mortality	All	Beyond 30 days	Beyond 90 days
N	1293	617	265
Cause of death [n (%)]			
Cardiac	776 (60.0)	329 (53.3)	121 (45.7)
Cardiac-only	546 (42.2)	205 (33.2)	72 (27.2)
Lung	376 (29.1)	199 (32.3)	85 (32.1)
Lung-only	169 (13.0)	90 (14.6)	48 (18.1)
Infection	225 (17.4)	155 (25.1)	73 (27.5)
Infection-only	99 (7.7)	62 (10.0)	29 (10.9)
CNS damage	85 (6.6)	31 (5.0)	11 (4.2)
CNS damage-only	41 (3.2)	7 (1.1)	1 (0.4)
Renal	7 (0.5)	6 (1.0)	5 (1.9)
Others	237 (18.3)	142 (23.0)	70 (26.4)

CNS: central nervous system.

Differences in mortality rate by preoperative variables

The differences between the number of patients and mortality rates by generation are shown in Fig. 2A. The postoperative mortality rate of surgery in the neonatal period was 12% (547/4760) and exhibited the highest rate of all four generations ($P < 0.001$). On the other hand, postoperative mortality rates of surgery in children over 1 year of age (1.6%, 188/11 523) and adults over 18 years of age (2.4%, 42/1734) were significantly lower when compared with the other three generations.

The chronological changes of the enrolled patient number and mortality rate by surgical year are shown in Fig. 2B. The number of enrolled patients increased yearly, whereas the mortality rate varied each year varied, ranging from 4.2 to 5.9%. In 2012, 376 of the 9361 patients enrolled were deceased and the mortality rate was 4.2%, which was almost the same trend as in 2011.

The differences between the numbers of patients and the mortality rates by RACHS risk category are shown in Fig. 3. The risk grade category and the mortality rate had a statistically strongly positive, linear correlation ($R^2 = 0.951$, $P < 0.001$), except for risk category 5, where the repair of truncus arteriosus and an interrupted aortic arch was performed. There were only 16 patients who received these procedures during the entire study period.

The differences between the numbers of patients and the mortality rates by surgical situation and type are shown in Fig. 4. Whether CPB was required or not, the mortality rate of palliative surgery was significantly higher than that of definitive surgery (800/8259 = 9.7% vs 493/22 526 = 2.2%, $P < 0.001$). With regard to the former, the mortality rate of palliative surgery with CPB was significantly higher than that of the same surgery without CPB (416/3833 = 10% vs 384/4426 = 8.7%, $P < 0.001$) (Fig. 4A). With regard to surgical situation, emergency surgery resulted in a mortality rate of >20% (255/1194 = 21.4%), while that of elective surgery was 2.8% (682/24 360) (Fig. 4B).

Prognostic outcomes of post-cardiotomy extracorporeal membrane oxygenation cannulation

Between 2010 and 2012, 108 of the registered 24 425 patients (0.4%) required ECMO cannulation during the perioperative period. Of those, 41 patients survived to discharge after successful ECMO decannulation (38.0%). The mean and median durations

ORIGINAL ARTICLE

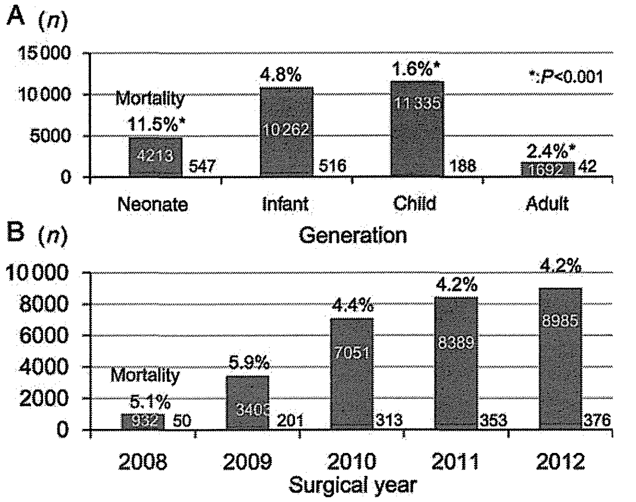

Figure 2: Differences between the number of patients and the mortality rate stratified by generation (**A**), or surgical year (**B**). The blue bar represents the number of surviving patients, and the red bar represents deceased patients. *P < 0.001.

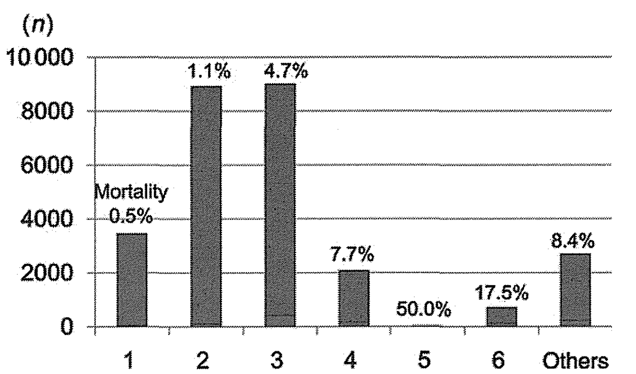

Figure 3: Differences between the number of patients and the mortality rate by risk adjustment in the congenital heart surgery system (RACHS) risk category. The blue bar represents the number of surviving patients, and the red bar represents deceased patients.

from ECMO cannulation to death in the remaining 67 patients were 42.8 ± 66.2 days and 18 days (range, 0–299), respectively.

DISCUSSION

The Japanese Association for Thoracic Surgery Committee has reported the results of thoracic and cardiovascular surgery, including congenital heart surgery, annually since 1986, and is famous for the establishment on a national scale of the annual statistics overview because of the high response rate to the survey [5]. On the other hand, an individual case registration system, according to the authorized nomenclature for the diagnosis and surgical procedure, was mandated to compare the outcomes accurately with other nationwide or international databases [6]. Although each category based on a risk-adjusted tool did not match, 30-day, 90-day, and 90-day and in-hospital mortality rates after congenital heart surgery in Japan were 2.3, 3.5 and 4.5%, respectively, during the past 5 years, which compared favourably with the Congenital Heart Surgery Database of the Society of Thoracic Surgeons, the European Association for Cardio-thoracic Surgery or a combination of the two [7–9]. The number of operations and postoperative mortality rates have currently stabilized at ∼9000 cases per year and <5.0% during the last 2 years, respectively.

Two specific medical situations of Japan were demonstrated in this study. First, 111 institutions performed ∼7000 congenital open heart surgeries using CPB in 2012. There are <10 institutions in Japan where >200 congenital open heart surgeries were annually performed; thus, the other 5000 cases were carried out at the remaining 100 institutions. Although this database system cannot allow for a more detailed investigation of the relationship between the case volumes, case complexities and mortality rates of each institution, it is noteworthy that the overall nationwide surgical outcomes were acceptable even if such a large amount of small programmes exist [10].

Although a case-matched comparison study could not be conducted because of the different definitions of operative mortality, another unique situation in Japan is the long duration from

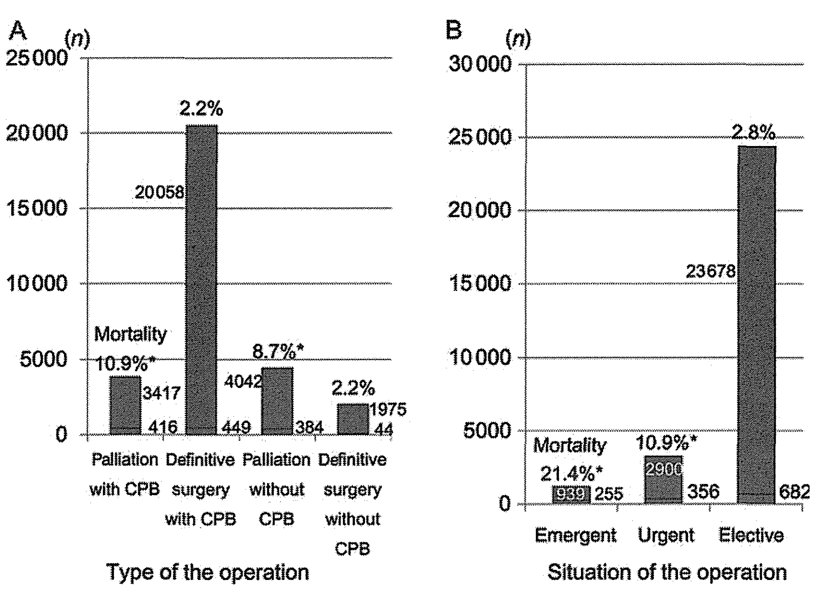

Figure 4: Differences between the number of patients and the mortality rate stratified by type of operation (**A**) and operative situation (**B**). The blue bar represents the number of surviving patients, and the red bar represents deceased patients. CPB: cardiopulmonary bypass. *P < 0.001.

operation to death [11–13]. Indeed, half of all mortalities were observed 30 days after surgery, and the median duration from operation to death was 28 days. With full medical cost coverage of patients born with congenital heart disease until 18 years of age, by the support of disabled children from the public health care system in Japan, parents and caregivers can make the greatest efforts possible to cure all children. As a result, extended intensive care continues for patients with post-cardiotomy complications, and a considerable number of patients are finally cured and discharged from the hospital long after surgery. In fact, out of the 3630 patients (13%) hospitalized for more than 90 days after the operation, 3365 patients survived at discharge (93%).

Cardiac problems were the most frequent cause of death after surgery at any point in time, and 7.1 per 1000 patients died after postoperative day 30 due solely to cardiac problems, which means that there are still some patients who died owing to post-cardiotomy heart failure without any other lethal complications after long-term intensive care. Except for some medically developed countries, advanced therapeutic options such as heart transplantation or long-term use of ventricular assistance devices are not available for post-cardiotomy heart failure in the paediatric population [14]. Patients who developed post-cardiotomy heart failure were treated with conventional therapy methods like medication, catheterization or surgical intervention, and temporary extracorporeal membrane oxygenation support with limited therapeutic effects. Finally, the Organ Transplant Law in Japan was revised and enforced in 2010, which legally and ethically allowed for paediatric heart transplantation. Donations from brain-death cadavers under 15 years old are now possible without written declaration of the donors themselves. Although there have only been two donors so far, an increase is expected [15]. In addition, an investigator-initiated trial of the EXCOR® paediatric ventricular assist device (Berlin Heart, Inc., Berlin, Germany) is now ongoing in Japan for bridge-to-heart transplants or recovery use [16, 17].

Study limitations

Limitations of this study were as follows. At first, the number of enrolled institutions significantly increased during the studied 5 years; therefore, only a small percentage of institutions reported their data during a part of the early study period. Even in the later study period, however, ~90% of all congenital heart surgeries was reported to this database. Second, a registry of post-cardiotomy ECMO use after congenital heart surgery should be established [18, 19]. Thirdly, although registration of the cause of death was mandated, cardiac issues included not only ventricular dysfunction, but also arrhythmia, cardiac tamponade, haemodynamic instability caused by unrepaired intracardiac lesions, sudden pulmonary overcirculation after single ventricle palliations, and so on.

With the large number of data in this database system, more detailed information about specific diagnosis/operative procedure is expected to be analysed. Also, further scientific analysis of the discrepancy between 30-day mortality and 90-day and in-hospital mortality by each diagnosis and procedure in addition to the RACHS score is mandatory.

In conclusion, significant discrepancy between 30-day mortality and 90-day and in-hospital mortality was demonstrated from analysis of the JCCSD. Patients who died long after the operation due to post-cardiotomy heart failure without any other complications are not rare.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

Conflict of interest: none declared.

REFERENCES

[1] Miyata H, Murakami A, Tomotaki A, Takaoka T, Konuma T, Matsumura G *et al.* Predictors of 90-day mortality after congenital heart surgery: the first report of risk models from Japan congenital cardiovascular surgery database (JCCVSD). J Thorac Cardiovasc Surg 2014;148:2201–6.

[2] Tomotaki A, Miyata H, Hashimoto H, Murakami A, Ono M. Results of data verification of the Japan congenital cardiovascular database, 2008 to 2009. World J Pediatr Congenit Heart Surg 2014;5:47–53.

[3] STS Congenital Database Full Specifications Version 2.50. http://www.sts.org/sites/default/files/documents/pdf/Congenital_DataSpecs_250.pdf (February 2015, date last accessed).

[4] Jenkins KJ, Gauvreau K, Newburger JW, Spray TL, Moller JH, Iezzoni LI. Consensus-based method for risk adjustment for surgery for congenital heart disease. J Thorac Cardiovasc Surg 2002;123:110–8.

[5] Amano J, Kuwano H, Yokomise H. Thoracic and cardiovascular surgery in Japan during 2011: annual report by The Japanese Association for Thoracic Surgery. Gen Thorac Cardiovasc Surg 2013;61:578–607.

[6] Jacobs JP, Maruszewski B, Kurosawa H, Jacobs ML, Mavroudis C, Lacour-Gayet FG *et al.* Congenital heart surgery databases around the world: do we need a global database? Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2010;13:3–19.

[7] Jacobs JP, Jacobs ML, Maruszewski B, Lacour-Gayet FG, Tchervenkov CI, Tobota Z *et al.* Initial application in the EACTS and STS congenital heart surgery databases of an empirically derived methodology of complexity adjustment to evaluate surgical case mix and results. Eur J Cardiothorac Surg 2012;42:775–9.

[8] O'Brien SM, Clarke DR, Jacobs JP, Jacobs ML, Lacour-Gayet FG, Pizarro C *et al.* An empirically based tool for analyzing mortality associated with congenital heart surgery. J Thorac Cardiovasc Surg 2009;138: 1139–53.

[9] Jacobs ML, Jacobs JP, Franklin RC, Mavroudis C, Lacour-Gayet F, Tchervenkov CI *et al.* Databases for assessing theoutcomes of the treatment of patients with congenital and paediatric cardiacdisease—the perspective of cardiac surgery. Cardiol Young 2008;18:101–15.

[10] Welke KF, O'Brien SM, Peterson ED, Ungerleider RM, Jacobs ML, Jacobs JP. The complex relationship between pediatric cardiac surgical case volumes and mortality rates in a national clinical database. J Thorac Cardiovasc Surg 2009;137:1133–40.

[11] Kansy A, Tobota Z, Maruszewski P, Maruszewski B. Analysis of 14,843 neonatal congenital heart surgical procedures in the European Association for Cardiothoracic Surgery Congenital Database. Ann Thorac Surg 2010;89: 1255–9.

[12] Jacobs JP, O'Brien SM, Pasquali SK, Jacobs ML, Lacour-Gayet FG, Tchervenkov CI *et al.* Variation in outcomes for risk-stratified pediatric cardiac surgical operations: an analysis of the STS congenital heart surgery database. Ann Thorac Surg 2012;94:564–71.

[13] Overman DM, Jacobs JP, Prager RL, Wright CD, Clarke DR, Pasquali SK *et al.* Report from the Society of Thoracic Surgeons National Database Workforce: clarifying the definition of operative mortality. World J Pediatr Congenit Heart Surg 2013;4:10–2.

[14] Canter CE, Shaddy RE, Bernstein D, Hsu DT, Chrisant MR, Kirklin JK *et al.* Indications for heart transplantation in pediatric heart disease: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young; the Councils on Clinical Cardiology, Cardiovascular Nursing, and Cardiovascular Surgery and Anesthesia; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation 2007;115:658–76.

[15] Ueno T, Fukushima N, Sakaguchi T, Ide H, Ozawa H, Saito S *et al.* First pediatric heart transplantation from a pediatric donor heart in Japan. Circ J 2012;76:752–4.

[16] Hetzer R, Alexi-Meskishvili V, Weng Y, Hübler M, Potapov E, Drews T *et al.* Mechanical cardiac support in the young with the BerlinHeart EXCOR pulsatile ventricular assist device: 15 years' experience. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2006;9:99–108.

ORIGINAL ARTICLE

[17] Almond CS, Morales DL, Blackstone EH, Turrentine MW, Imamura M, Massicotte MP *et al*. Berlin Heart EXCOR pediatric ventricular assist device for bridge to heart transplantation in US children. Circulation 2013;127:1702–11.

[18] Merrill ED, Schoeneberg L, Sandesara P, Molitor-Kirsch E, O'Brien J Jr, Dai H *et al*. Outcomes after prolonged extracorporeal membrane oxygenation support in children with cardiac disease—Extracorporeal Life Support Organization registry study. J Thorac Cardiovasc Surg 2014;148: 582–8.

[19] Mascio CE, Austin EH III, Jacobs JP, Jacobs ML, Wallace AS, He X *et al*. Perioperative mechanical circulatory support in children: an analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. J Thorac Cardiovasc Surg 2014;147:658–64.

J Hepatobiliary Pancreat Sci (2015) 22:721–727
DOI: 10.1002/jhbp.276

ORIGINAL ARTICLE

Long-term and perioperative outcomes of laparoscopic versus open liver resection for hepatocellular carcinoma with propensity score matching: a multi-institutional Japanese study

Takeshi Takahara · Go Wakabayashi · Toru Beppu · Arihiro Aihara · Kiyoshi Hasegawa · Naoto Gotohda · Etsuro Hatano · Yoshinao Tanahashi · Toru Mizuguchi · Toshiya Kamiyama · Tetsuo Ikeda · Shogo Tanaka · Nobuhiko Taniai · Hideo Baba · Minoru Tanabe · Norihiro Kokudo · Masaru Konishi · Shinji Uemoto · Atsushi Sugioka · Koichi Hirata · Akinobu Taketomi · Yoshihiko Maehara · Shoji Kubo · Eiji Uchida · Hiroaki Miyata · Masafumi Nakamura · Hironori Kaneko · Hiroki Yamaue · Masaru Miyazaki · Tadahiro Takada

Published online: 1 July 2015

The author's affiliations are listed in the Appendix.

Correspondence to:
Takeshi Takahara, Department of Surgery, Iwate Medical University School of Medicine, 19-1 Uchimaru, Morioka, Iwate 020-8505, Japan.
Email: takahara@iwate-med.ac.jp

DOI: 10.1002/jhbp.276

Abstract

Background The aim of this study was to compare the long-term outcomes and perioperative outcomes of laparoscopic liver resection (LLR) with those of open liver resection (OLR) for hepatocellular carcinoma (HCC) between well-matched patient groups.

Methods Hepatocellular carcinoma patients underwent primary liver resection between 2000 and 2010, were collected from 31 participating institutions in Japan and were divided into LLR (n = 436) and OLR (n = 2969) groups. A one-to-one propensity case-matched analysis was used with covariates of baseline characteristics, including tumor characteristics and surgical procedures of hepatic resections. Long-term and short-term outcomes were compared between the matched two groups.

Results The two groups were well balanced by propensity score matching and 387 patients were matched. There were no significant differences in overall survival and disease-free survival between LLR and OLR. The median blood loss (158 g vs. 400 g, $P < 0.001$) was significantly less with LLR, and the median postoperative hospital stay (13 days vs. 16 days, $P < 0.001$) was significantly shorter for LLR. Complication rate (6.7% vs. 13.0%, $P = 0.003$) was significantly less in LLR.

Conclusion Compared with OLR, LLR in selected patients with HCC showed similar long-term outcomes, associated with less blood loss, shorter hospital stay, and fewer postoperative complications.

Keywords Hepatocellular carcinoma · Laparoscopic liver resection · Long-term survival · Open liver resection · Propensity score matched analysis

Introduction

The advancements of laparoscopic procedures in liver surgery have proceeded slowly given the inherent risks for massive bleeding associated with liver resection [1]. The First International Consensus Conference on Laparoscopic Liver Surgery convened in Louisville in 2008 [2], since then, the number of laparoscopic liver resection (LLR) reported has increased steadily worldwide and the greatest diffusion of LLR occurred in East Asia, North America, and Europe [3, 4]. Moreover, the number of hepatocellular carcinoma (HCC) cases to which LLR is applied has increased steeply over the past 5 years, especially in Asia and Europe [5, 6]. However, no randomized controlled trials

(RCTs) have been published and the available data derive from multiple case series, case-control studies, reviews, and meta-analyses published over the last several years.

For new surgical procedures to become widely adopted as standard operations, they should first be compared with established procedures and shown to be superior in at least some respects [7]. Despite its lateness to embrace laparoscopy, liver surgery is now gaining momentum in this paradigm shift. Following improvements in technology and equipment, LLR should now be considered a safe option, if performed by experienced surgeons. Additionally, dramatic improvements in the safety of hepatic resection, based on an increased understanding of liver anatomy and better preoperative radiologic imaging, have facilitated this transition. Thus, adoption of the laparoscopic approach for the surgical treatment of hepatic lesions is now progressively expanding. However, unfortunately, it is impossible to reach an accurate conclusion regarding benefits and risks of LLR over open liver resection (OLR) in the absence of RCTs.

Propensity score matched analysis has become increasingly used in retrospective cohorts to reduce the impact of treatment-selection bias in the comparison of treatment to a non-randomized control using observational data [8, 9]. This type of evaluation has been proven to decrease selection bias in retrospective studies and allows comparison between different surgical procedures. Several studies have demonstrated that LLR for HCC is less invasive and can provide similar disease-free survival (DFS) and overall survival (OS) compared with OLR [10–17]. However, most of these studies were based on retrospective analyses of case-matched studies or meta-analyses of non-randomized studies. The aim of the present study was therefore to compare the long-term oncological outcomes and the perioperative outcomes of LLR with those of OLR for HCC, using propensity score matching (PSM) of relatively large data collected from 31 institutions in Japan.

Patients and methods

This multicenter clinical study was conducted by the "Project Committee of the Endoscopic Surgery" of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. We retrospectively reviewed 3405 patients who underwent primary liver resection for HCC from 2000 to 2010, who were gathered by 31 Japanese institutions in the Endoscopic Liver Surgery Study Group. The patients were divided into LLR (n = 436) and OLR (n = 2969) groups. The diagnosis of HCC was confirmed by histologic examination of resected specimens in all patients.

This study was approved by the ethics committee of the Japanese Society of Hepato-Biliary-Pancreatic Surgery, as well as one from each Institutional Review Board, and conducted in accordance with the mandates of the Helsinki Declaration.

Propensity score analysis

To avoid confounding differences due to baseline varieties between laparoscopic and open approaches, we performed a propensity score-matched subset. Propensity score analysis was used to build a matched group of patients for comparison of oncological and short-term outcomes between LLR and OLR groups. The propensity scores were generated with the preoperative characteristics, including sex, age, underlying liver disease (hepatitis B surface antigen (HBs-Ag) and anti-hepatitis C virus antibody positivity), tumor size, tumor number, serum α-fetoprotein and des-gamma-carboxy prothrombin levels, indocyanine green retention rate at 15 min (ICGR 15 min), extent of liver damage (decide according to the Criteria of the Liver Cancer Study Group of Japan) [18, 19], Child–Pugh score, difficult tumor location (yes, no), and distant metastasis (yes, no). Difficult tumor location was defined as postero-superior segments of the liver (segment 1, 7, 8 and the superior part of segment 4) [20]. Surgical procedures were classified according to the Brisbane 2000 nomenclature of liver resection [21]. In this study, hemihepatectomy, trisectionectomy, central bisectionectomy, right anterior sectionectomy, right posterior sectionectomy, and medial sectionectomy were defined as major hepatectomy, while wedge resection and left lateral sectionectomy were as minor hepatectomy. The wedge resection was only non-anatomical resection. The predicted probability of preprocedural stains was calculated by fitting a logistic regression model, using all preoperative relevant clinical variables as shown in Table 1. PSM was performed using a 1:1 ratio without replacement by caliper-matching on the estimated propensity score. The value of the caliper was calculated by 0.25 × (the standard deviation (SD) of log (the propensity score (PS)/ 1-PS)). Receiver operating characteristic (ROC) curves were used to assess the accuracy of PSM, as a predictor of LLR indicated by a propensity score.

Comparison between the two matched groups

The study criteria for comparing the two matched groups were the following: (i) clinicopathologic data of each matched group; (ii) intraoperative and surgical results. Morbidity was graded according to the Clavien-Dindo classification and Grade IIIa or greater complications were counted between the two matched groups. Further, we investigated each perioperative outcome of patients who underwent major hepatectomy or minor hepatectomy in each matched group; and (iii) long-term oncologic outcomes in aspects of OS and DFS.

Table 1 Comparison of baseline characteristics

Covariates	LLR (*n* = 436)	OLR (*n* = 2969)	*P*	Matched-LLR (*n* = 387)	Matched-OLR (*n* = 387)	*P*
Gender						
Female	142 (32.6%)	644 (21.7%)		125 (32.30%)	126 (32.56%)	
Male	294 (67.4%)	2325 (78.3%)	<0.001	262 (67.70%)	261 (67.44%)	0.939
Age (year)	66.48 ± 9.87	66.68 ± 9.64	0.69	66.42 ± 9.84	66.19 ± 9.96	0.741
Height	160.2 ± 9.12	161.0 ± 8.67	0.073	160 ± 9.19	160.9 ± 8.72	0.21
Weight	59.0 ± 11.25	60.5 ± 11.18	0.012	59.0 ± 10.92	60.0 ± 11.11	0.203
HBV positive	99 (22.7%)	663 (23.1%)	0.886	91 (23.51%)	100 (25.84%)	0.453
HCV positive	222 (51.0%)	1473 (51.3%)	0.932	195 (50.39%)	198 (51.16%)	0.829
Liver damage						
A	347 (80.51%)	2244 (75.94%)		312 (80.62%)	311 (80.36%)	
B	73 (16.94%)	533 (18.04%)		65 (16.80%)	70 (18.09%)	
C	11 (2.55%)	178 (6.02%)	0.009	10 (2.58%)	6 (1.55%)	0.552
Child–Pugh	5.34 ± 0.66	5.34 ± 0.66	0.944	5.33 ± 0.64	5.32 ± 0.61	0.774
ICG R15	15.8 ± 10.9	15.8 ± 9.12	0.949	15.7 ± 11.0	16.5 ± 9.93	0.292
Number	1.16 ± 0.50	1.47 ± 1.09	<0.001	1.17 ± 0.52	1.21 ± 0.54	0.246
Size (mm)	28.7 ± 15.2	40.2 ± 26.0	<0.001	28.8 ± 15.1	28.8 ± 15.0	0.992
Difficult location	96 (22.1%)	1447 (50.2%)	<0.001	82 (21.19%)	80 (20.67%)	0.86
Distant meta	3 (0.69%)	11 (0.37%)	0.332	3 (0.78%)	1 (0.26%)	0.316
AFP (ng/ml)	9.45 (4.35, 65.25)	14.3 (5.1, 133)	0.027	9.3 (4.3, 61.9)	13.5 (5, 100)	0.067
DCP (mAU/ml)	47 (23, 210)	81 (25, 637)	0.206	48 (24, 225)	42 (21, 195.9)	0.206
Major hepatectomy	46 (10.55%)	952 (32.21%)	<0.001	42 (10.85%)	36 (9.30%)	0.474
Minor hepatectomy	341 (78.21%)	1384 (46.82%)	<0.001	299 (77.26%)	305 (78.81%)	0.602

AFP α-fetoprotein, *DCP* des-gamma-carboxy prothrombin, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *ICG* indocyanine green

Statistical analysis

PSM and the other statistical analyses after PSM were performed by Stata 13 (Stata Corporation, College Station, TX, USA). In analyses and comparisons of preoperative covariates and clinical parameters after PSM, Student's *t*-test or Wilcoxon rank sum test for continuous variables, and χ^2 test or Fisher's exact test for categorical variables were used. All categorical data were expressed as number or frequency (%), and all continuous data were as mean ± standard deviation, or median (25, 75% quartile deviation). The DFS period was calculated from the date of surgery to the recurrence of HCC. Survival rates were estimated using the Kaplan–Meier methods and the log-rank test for the *P*-value for OS and DFS. The Cox proportional hazards regression was used to calculate the hazard ratio (HR) and 95% confidence interval for univariate and multivariate analyses. A *P*-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

Table 1 summarizes the baseline characteristics of the overall cohort and that selected after PSM. In the overall cohort, most of the LLR patients were females (32.6% vs. 21.7%), the mean height of the LLR patients was lower than that of the OLR patients, most of the LLR patients had Liver damage A (80.51% vs. 75.94%), the number and size of the tumor in the LLR patients were significantly less and smaller than in the OLR patients, most of the LLR patients had non-difficult location of the tumor (77.9% vs. 49.8%), and minor hepatectomy had been performed in most of the LLR patients (78.21% vs. 46.82%). After PSM both groups were well balanced for all variables, as shown in Table 1. The ROC area under the curve of the propensity score for undergoing LLR was 0.786 (Figs S1,S2).

Clinicopathological outcomes

Between the LLR and OLR groups after PSM, the background of the liver about the staging of the fibrosis according to new Inuyama classification of chronic hepatitis [22], microvascular invasion, positive pathological surgical margin, and the tumor stage according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer, were almost similar (Table 2).

Table 2 Comparison of clinicopathological outcomes after propensity score matching (PSM)

	Matched–LLR (n = 387)	Matched–OLR (n = 387)	p
Background of liver			
F3–F4	232 (61.7%)	211 (59.6%)	0.562
A2–	90 (33.21%)	99 (43.23%)	0.021
Differentiation			
Well	59 (15.57%)	85 (22.49%)	
Moderately	266 (70.18%)	236 (62.43%)	
Poorly	44 (11.61%)	53 (14.02%)	0.031
Vascular invasion			
va1–va2	4 (1.04%)	1 (0.26%)	0.18
vp1–vp2	48 (12.5%)	58 (15.03%)	
vp3	2 (0.52%)	1 (0.26%)	0.51
vv1–vv2	12 (3.13%)	21 (5.47%)	0.111
b1–b2	3 (0.79%)	1 (0.26%)	0.311
Pathological surgical margin (+)	18 (4.68%)	17 (4.43%)	0.869
TNM classification			
Stage I	97 (25.06%)	96 (24.81%)	
Stage II	227 (58.66%)	210 (54.26%)	
Stage III	55 (14.21%)	73 (18.86%)	
Stage IVa or IVb	8 (2.06%)	8 (2.06%)	0.269

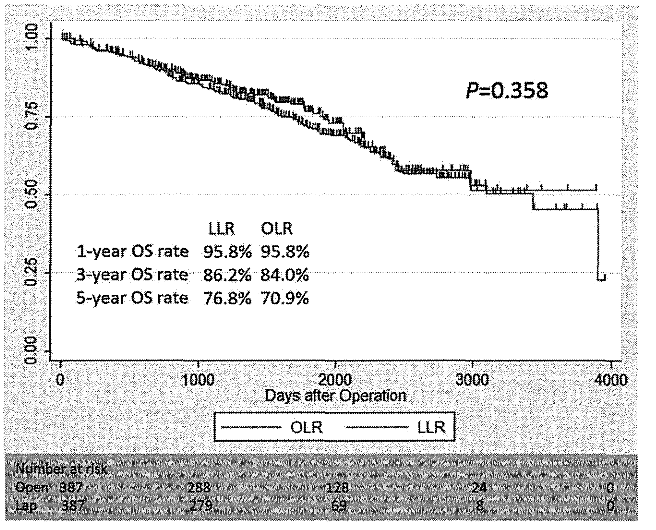

Fig. 1 Kaplan–Meier survival curve comparing overall survival (OS) in the propensity score matching (PSM) cohort

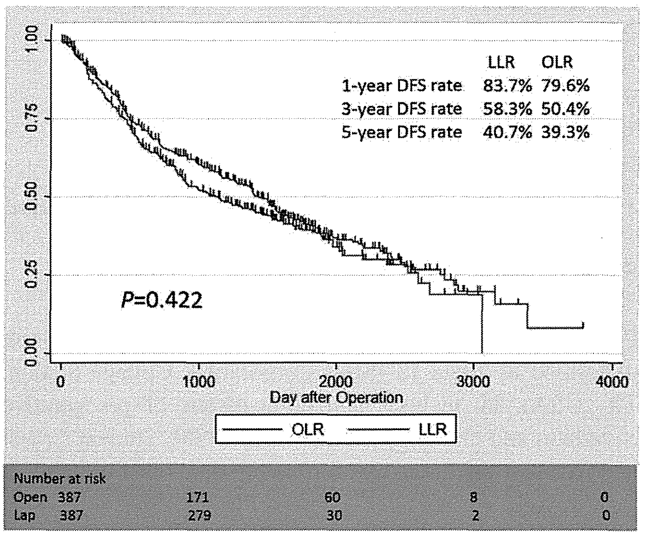

Fig. 2 Kaplan–Meier survival curve comparing disease-free survival (DFS) in the propensity score matching (PSM) cohort

Long-term oncologic outcomes

We performed Kaplan–Meier analyses for OS and DFS curves, as shown in Figures 1 and 2. The median observation period in the LLR group was 46.7 months (25% quartile deviation: 31.4 months, 75%: 60.5 months), and one in the OLR group was 51.7 months (25%: 31.8 months, 75%: 75.8 months). The cumulative 1-, 3- and 5-year OS rates were 95.8, 86.2 and 76.8% in the LLR group, 95.8 and 84.0, and 70.9% in the OLR group. On the other hand, the cumulative 1-, 3- and 5-year DFS rates were 83.7, 58.3 and 40.7% in the LLR group, 79.6 and 50.4, and 39.3% in the OLR group, respectively. There were no significant differences in OS (P = 0.358) and DFS (P = 0.422) between the matched two groups.

Perioperative outcomes

In the LLR group after PSM, the median blood loss (158 g) was significantly less (P < 0.001) than in the OLR group (400 g), and the median postoperative hospital stay (13 days) for the LLR patients was significantly shorter (P < 0.001) than for the OLR patients (16 days), while the operation time in the LLR group (294.4 ± 158.8 min) was significantly longer than in the OLR group (271.0 ± 130.0) (P = 0.025). Conversion from LLR to OLR or Hybrid or hand-assisted laparoscopic surgery occurred in 25 patients (6.5%). Complications over Grade IIIa according to the Clavien-Dindo classification after LLR included ascites (n = 7), intraperitoneal abscess (n = 4), pleural effusion (n = 2), bile leak (n = 5), and liver failure (n = 2), while ones after OLR included ascites (n = 12), intraperitoneal abscess (n = 4), pleural effusion (n = 5), bile leak (n = 9), and liver failure (n = 7). Postoperative complication rates in the LLR group were significantly lower than in the OLR group (6.7% vs. 13.0%, P = 0.003). The frequency of intraoperative accident was almost the same between the two groups. Mortality at 30 postoperative days was none, at 90 days was 0.26% (n = 1) in the LLR group, while at 30 days it was 0.26% (n = 1), and at 90 days it was 1.03% (n = 4) in the OLR group (Table 3).

Discussion

A comprehensive meta-analysis of 26 studies comparing LLR with OLR revealed that there were advantages associated with LLR, such as reduced blood loss, decreases in overall and liver-specific complications, and shorter postoperative hospital stays, although LLR procedures were associated with longer operating time, and moreover, it found that the oncological outcomes were not different from OLR [23]. Likewise the large study analyzing 31 papers comparing LLR (1146 patients) to OLR (1327 patients) came to the same conclusions for benefits of LLR over OLR, with equivalent cancer outcomes [24]. Another meta-analysis about surgical and oncological outcomes following LLR versus OLR for HCC included 10 studies comprising 627 patients [25]. The 10 studies were six case-control and four retrospective analyses; no RCTs were included. The laparoscopic group had significantly less blood loss by 223.17 ml ($P < 0.001$), less need for transfusions ($P = 0.007$), shorter hospital stay by 5.05 days ($P < 0.001$) and fewer postoperative complications ($P = 0.002$). However, these results were not produced by RCTs and were affected more or less by the selection-bias of LLR. To date, several reports have been published using PSM, confirming short-term advantages and comparable oncological outcomes in LLR patients compared with OLR patients for HCC. Common short-term advantages by LLR were less intraoperative blood loss and a shorter hospital stay [26, 27]. However, these studies included a relatively small number of patients after PSM.

Table 3 Comparison of perioperative outcomes after propensity score matching (PSM)

	Matched–LLR (n = 387)	Matched–OLR (n = 387)	P
Blood loss (ml)	158 (50, 450%)	400 (170, 675%)	<0.001
RCC transfusion	28 (7.24%)	38 (9.82%)	0.198
FFP transfusion	17 (4.44%)	30 (7.85%)	0.049
Operation time (min)	294.4 ± 158.8	271.0 ± 130.0	0.025
Hospital stay (days)	13 (9, 18)	16 (11, 25)	<0.001
Conversion			
Pure → Hybrid or HALS	7 (1.81%)	–	
Pure → Open	7 (1.81%)	–	
Hybrid or HALS → Open	11 (2.84%)	–	
Accident			
Bleeding	9 (2.33%)	14 (3.79%)	
Injury of other organs	0	0	
Others	1 (0.26%)	0	0.313
Complications	26 (6.72%)	50 (12.99%)	0.003
Ascites	7	12	
Intraperitoneal abscess	4	4	
Pleural effusion	2	5	
Bile leak	5	9	
Liver failure	2	7	
Wound infection	1	4	
Bleeding	1	1	
Others	4	8	
30 days mortality	0	1 (0.26%)	0.317
90 days mortality	1 (0.26%)	4 (1.03%)	0.178

FFP fresh frozen plasma, *HALS* hand-assisted laparoscopic surgery, *RCC* red cell concentration

Although we can easily assess the malignancy of HCC using tumor size, number, and the levels of serum tumor markers, and the liver functional reserve examining the extent of liver damage and Child–Pugh score, it is difficult to evaluate the complexity of the hepatic resection. We evaluated the difficulty of hepatic resection by finding difficult tumor locations for LLR demonstrated by Cho et al. [20], and additionally we divided the hepatic resection into the major hepatectomy, minor hepatectomy and others. Practically in the overall cohort, there were significant differences not only in tumor size and tumor number but also in the difficult location and in the frequency of the major or minor hepatectomy between LLR and OLR for HCC (Fig. S3).

In each institution there are various selection criteria of LLR for HCC, and the criteria might be affected by the learning curve of the surgical skill of LLR. And so, we intend to treat all preoperative relevant clinical variables as the covariates to build the propensity score. Forty-nine LLR patients were not matched because PSM was statistically performed using a 1:1 ratio on the estimated propensity score. Nevertheless, our study includes the large number of 387 patients and 387 patients for HCC in LLR and OLR, respectively, after the background characteristics of each patient were almost identical.

Regarding the long-term survival of two matched groups, median observation periods were not comparable between the two groups because the timing that LLR had been introduced was different in each institution. Regarding the histopathological outcomes, the degree of inflammation of the background liver and the differentiation of the tumor in the matched-open group were worse than those in the matched-lap group. These results were limitations in our retrospective study. However, it is difficult to assess the impact of primary hepatic resection on the OS in HCC treatment. The result that DFS as well as OS in the well-matched groups was statistically even in the comparison of the oncological outcomes, was noteworthy.