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Does Risk Calculator by Nationwide Survey Match The Postoperative Outcome in Patients Who Underwent Major Hepatectomy?

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Abstract

Background: To clarify significance of the present National Clinical Database risk calculator (NCD-RC) for hepatectomy in Japan, relationship between perioperative parameters or outcomes in major hepatectomy and the mortality rate by NCD-RC was examined.

Methods: Patient demographics, co-morbidity, surgical records, postoperative morbidity or mortality were examined and compared to the 30 days- or in-hospital-mortality rate among 55 patients with hepatobiliary diseases who underwent hemi- or more-extended hepatectomy and central (segment 458) hepatectomy. The cut-off percent for high risk mortality before hepatectomy was set at 5% in this period.

Results: In-hospital morbidity over CD III was 17 (28%), The 30-day mortality and in-hospital mortality was nil and two (3%), respectively. Male patient showed significantly higher in-hospital mortality rate ($p<0.01$). In the 37 patients (group *woML)*, mean age was 67.8±8.7 years old ranging 45 and 84. Others included A) with severe complications or mortality in whom low mortality rate (*group wML*, n=13), B) without severe complications neither mortality in whom high mortality rate (*group woMH*, n=7), and C) with severe complications or mortality in whom high mortality rate (*group wMH*, n=4 (6.5%)). Age, distribution of elderly patients, gender, the hepatobiliary diseases and the prevalence of preoperative co-morbidity were not significantly different between groups. In the *group wML*, the bile leakage was dominant and, however, the in-hospital death was not observed. In the *group wMH*, all operations were right hepatectomy with bile duct resection (RH-BDR) for biliary malignancy and two died of hepatic failure and, however, the prevalence of RH-BDR was not significantly higher in comparison with other groups.

Conclusions: Predictive mortality rate by risk calculator under nationwide survey did not always match with patient outcomes in the actual clinical setting and further improvement will be required. In case of RH-BDR for biliary malignancy with high predictive rate, the careful perioperative managements is important under the present nationwide database.

Background

Liver resection is currently considered the best curative treatment modality for patients with hepatobiliary malignancies and the safety of major hepatectomy in patients with various background liver diseases has improved markedly with reduced mortality rates based on adequate preoperative evaluation of the extent of hepatectomy, precise evaluation of functional liver reserve and advances in perioperative management (1–3). Patient prognosis after hepatectomy is influenced by patient age, general status, co-morbidity or organ functional reserve as well. The relationship with these parameters have been also recently examined (4–6) and, however, unexpected postoperative morbidity as hepatic failure and related mortality were still observed at this stage.

Recently, the big data analysis show the evidence-based prediction in various medical fields including major surgery (7, 8) and the established scoring system is supposed to be clinically useful. The National Clinical Database (NCD) in Japan has been started by the nation-wide registration system in the field of general surgery since 2011 and produced NCD-based research works, (9, 10) which was epoch-making in a decade. In this period, NCD-risk calculator (RC) to predict expected mortality based on these large cohort data has been made in various major operations including hepatectomy. (9) By referring this risk evaluation, we have still continue to decide indications for hepatectomy using the conventional institutional indication due to functional liver reserve and, however, we sometimes experience discrepancy.

To reevaluate the significance of NCD-RC and reconsider our strategy in major hepatectomy, the relationship between perioperative parameters or in-hospital outcomes and the expected risk ratio of NCD-RC in 61 patients who underwent major hepatectomy for the recent 5 years to improve patient survival by further management in the perioperative period.

Methods

Patients

This retrospective study collected data from 61 patients, representing all patients who underwent major hepatectomy for hepatobiliary diseases in the Division of Hepato-biliary-pancreas Surgery, Department of Surgery, University of Miyazaki Faculty

of Medicine, Japan between April 2015 and June 2020 to evaluate under the recent director's system. Surgery was typically indicated for all patients with Child-Pugh A status. All patients were medically fit for major laparotomy, showed no signs of preoperative dissemination or distant metastases and displayed tumors anatomically confined to within the liver. Each patient basically underwent routine preoperative imaging, including whole-abdomen computed tomography (CT) or magnetic resonance imaging (MRI). Further examinations were added in case of the biliary malignancy or any other. No defined protocol of neoadjuvant chemotherapy was applied before hepatectomy for prevention of tumor recurrence and, however, nine patients (15%) of colorectal liver metastases were received multiple anti-cancer drugs for multiple liver metastases until operation.

Operative indication by liver function for major hepatectomy

The liver volume to be resected was estimated according to the indocyanine green retention rate at 15 min (ICGR15) using the formula of Takasaki *et al* (11) The expected liver volume for resection, excluding the tumor, was measured by CT volumetry (12) Transection of the hepatic parenchyma was routinely performed using the Kelly-clamp crushing technique and an ultrasonic dissector was used only around the large Glissonian pedicle (13) Radical hepatectomy was performed to remove the hepatic tumor without leaving any residual tumor. All study protocols were approved by the Ethics Review Board of University of Miyazaki Faculty of Medicine (#O-0778 accepted on September 10, 2020). Mortality and morbidity data were collected from our department database and provided by collaborating hospitals. No financial support was received for this study, and the authors declare no conflicts of interest.

Clinicopathological parameters, surgical data, tumor staging, and subgroups of postoperative survival

We recorded the following clinical parameters: patient demographics including age, gender, liver diseases, background liver, co-morbidities, surgical data; extent of hepatectomy, blood loss, transfusion, operation time, combined procedure; postoperative complications; content of complications, prevalence of Clavien-Dindo classification over III or mortality. Prevalence of mortality within 30 days and the hepatectomy related in-hospital mortality were calculated by formula for major hepatectomy on the Japan NCD website (*http://www.ncd.or.jp/about/feedback.html*) in Japan.

Statistical analysis

Continuous data are expressed as mean ± standard deviation (SD). Data of different groups were compared using one-way analysis of variance, followed by student's *t*-test or Dunnett's multiple comparison test. In univariate analysis, categorical data were analyzed using the chi-square test or Fisher's exact test. Two-tailed values of $p<0.05$ were considered significant. Statistical analyses were performed using SPSS software (SPSS, IBM Company Headquarters, Chicago, IL).

Results

Patient demographics

The study group included 44 males (72%) and 17 females with mean ages of 68.5±10.0 years (ranging 39-86 years). Background liver diseases included normal liver in four patients (7%), chemotherapy-associated liver dysfunction in nine (15%), chronic viral hepatitis in 17 (29%; cirrhosis in nil) and obstructive jaundiced liver in 31 (51%). Diseases included hepatocellular carcinoma in 17 patients (29%), intrahepatic cholangiocarcinoma in 13 (21%), chronic liver metastasis in 9 (15%), biliary cancers in 18 (30%) and others in four. Right hepatectomy was performed in 16 patients (25%), right hepatectomy with bile duct resection in eight (13%), right trisectionectomy in one (2%), left hepatectomy in 12 (20%), left hepatectomy with bile duct resection in 14 (23%), left trisectionectomy in one (2%), left hepatectomy with pancreaticoduodenectomy in four (7%) and central hepatectomy (segment 4, 5 and 8) in five (8%). In-hospital morbidity and morbidity over CD III was 37 (61%) and 17 (28%), respectively. The 30-day mortality and in-hospital mortality was nil and two (3%), respectively. The 30-day mortality rate and in-hospital mortality rate calculated by NCD-RC in the present series were 2.25±2.21% (ranging 0.1-10.5%) and 2.37±3.05% (ranging 0.3-15.9%), respectively.

Relationship with the estimated mortality by NCD-RC

The age was significantly correlated with the 30-day mortality (r=0.377, p=0.003) and, tended to be correlated with in-hospital mortality but not significant (r=0.240, p=0.062), respectively. Table 1 summarized the relationship between patient demographics and results by NCD-RC. Male patient showed significantly higher in-hospital mortality rate in compared to female (p<0.01). Age was divided into 3 groups and elderly patients significantly showed higher the 30-day mortality (p<0.05) and the in-hospital mortality also tended to be higher in elderly patients but no significant difference. Existence of systemic circulatory, cerebral, renal and respiratory diseases tended to show higher 30-day mortality rate without significance, and significantly showed higher in-hospital mortality rate (p<0.01). Existence of chronic respiratory diseases significantly showed higher in-hospital mortality rate (P<0.01). Background liver diseases were not significantly associated with 30-day or in-hospital mortality rate, either. The 30-day and in-hospital mortality rate was not significantly different in each type of major hepatectomy, respectively.

The 37 patients (61%) without severe morbidity (CD>II) or mortality who had low predictive 30-day or in-hospital mortality rate by NCD-RC (*group woML*) were examined. Age was 67.8±8.7 with ranging 45 and 84 years old (y.o.). Elderly patients of 70-79 and over 80 y.o. was 18 (49%) and two (5%). Table 2 showed the relationship between preoperative patient demographics, co-morbidity, operation or postoperative results, and predictive mortality rate by NCD-RC. The cut-off percent for high risk mortality before hepatectomy was set at 5%.

Patient features of highly estimated mortality by NCD-RC

Table 2, 3 and 4 showed preoperative parameters including age, gender, main hepatobiliary diseases, type of hepatectomy, CD-high (over III), postoperative major complications, mortality and the preoperative predictive mortality rates by NCD-RC were indicated in each situation with severe morbidity or with high risk mortality rates, except no morbidity, mortality nor high risk rates in 37 patients as above. These were divided in three groups as follows; A) with severe complications or mortality in whom low mortality rate by NCD-RC (*group wML,* n=13 (21%)), B) without severe complications neither mortality in whom high mortality rate (*group woMH,* n=7 (11%)), and C) with severe complications or mortality in whom high mortality rate (*group wMH,* n=4 (6.5%)) as Table 2-4. Patient age were not significantly different as 67.8±8.7 y.o., 66.4±13.7, 72±7.6 and 75.3±10.9, respectively, and the number of elderly patients (divided by <70, 70-79 and >79 y.o.) was not significantly different between groups (p=0.48). Prevalence of male was not significantly different between groups (p=0.99). Prevalence of the background liver injury and the main hepatobiliary diseases were not significantly different between groups, respectively (p=0.47 and 0.76). Although the preoperative co-morbidity rates in patients without postoperative severe complications (27% in the *group woML* and 23% in the *group woMH*) tended to be lower in comparison with that with complications (57% in the *group wML* and 50% in the *group wMH*), the prevalence of preoperative co-morbidity were not significantly different between groups (p=0.31).

In the *group wML*, type of hepatectomy was various and the bile leakage and the in-hospital death was not observed. In the *group woMH*, type of hepatectomy was various and organ failures or in-hospital death was not observed. In the *group wMH*, all operations were right hepatectomy with bile duct resection (RH-BDR) for biliary malignancy. Two patients died of hepatic failure over 30 days. Other two patients had hepatectomy-unrelated complications were occurred after hepatectomy and recovered. The prevalence of RH-BDR tended to be higher (p=0.089) but not significantly different. The predictive 30-day mortality rate before hepatectomy by NCD-RC was 1.4±1.1% in the *group woML*, 1.6±1.1% in the *group wML*, 5.5±2.6% and 6.6±2.0% in the *group wMH*, respectively and the latter two groups significantly showed higher percent (p<0.01). The predictive in-hospital mortality rate before hepatectomy by NCD-RC was 1.6±1.0% in the *group woML*, 1.2±0.6% in the *group wML*, 8.1±6.3% and 3.4±1.1% in the *group wMH*, respectively and the latter two groups significantly showed higher percent (p<0.01).

Discussion

Patient outcomes undergoing major hepatectomy for hepatobiliary malignancies was mainly influenced by functional liver reserve (1–3, 14–16). Co-existing factors such as patient demographics, co-morbidity, preoperative liver function, surgical results and postoperative complications seemed to be associated with postoperative outcomes (4–6) In the daily real world clinically, the elderly patient age, particularly over 80 years, was firstly concerned. Although the surgical results for elderly patients has been improved in a mass group, major hepatectomy in patient over 85 years would be still challenging (17). By the first author's experiences, the upper limit of high age was a 86 years female patient undergoing the extended right hepatectomy with bile duct

resection for cholangiocarcinoma and a 87 years female patient undergoing pancreaticoduodenectomy for pancreatic carcinoma, who had no severe complications at the hospital stay (not published). Certainly, we realize that these two patients were selected and champion cases who with a high physical quality but no preoperative severe co-diseases. The next major concern is co-morbidity as heart, respiratory, renal or metabolic diseases, which is common in elderly patients over 60 years (5–7, 17) In case the anesthetic tolerance is preserved such as an ASA classification (17–19), the operation under general anesthesia is possible. For major hepatectomy, the definite tolerance has not been elucidated and the operation time or complication risk rate are usually considered in each patient.

In the present study, we reviewed the correlation or divergence between NCD-RC for major hepatectomy and the real results at our institute. NCD-RC itself has been established to compare mortality to that of each institute and, therefore, the better prognosis than mortality by NCD-RC is favorable. In case of worse prognosis, the plan-do-check-act cycle to improve institutional results would be required at the NCD website (http://www.ncd.or.jp/about/feedback.html*).* As the mortality rate of the entire cases in the present series might be lower, we had better keep the present quality for major hepatectomy. However, the real mortal patient died of hepatic failure has not been predicted by the low mortality rate by NCD-RC in one patient who underwent right hepatectomy for perihilar cholangiocarcinoma in the present series. This patient had an adequate liver functions and the preoperative portal vein embolization (PVE) was added. PVE has been established to avoid postoperative hepatic failure in case of major right hepatectomy (20, 21) If the functional liver reserve failed after PVE, the scheduled hepatectomy is usually abandoned in our experiences. In the present patient, post-PVE liver function was not altered significantly and the permitted resected volume by Takasaki's formula was maintained (11) Blood loss was 1100 mL and the problematic events was not found during operation and, however, the remnant liver showed a partial congestion at segment 4 by kinking of the middle hepatic vein. Inflammatory findings occurred at between day 2 and 5, but immediately improved by administration of antibiotics. Unfortunately, the hepatic and renal failure were gradually progressed after this event and the patient died at day 47 nevertheless of early intensive care interventions. While, patients with good outcomes also received our routine managements regardless high mortality was expected by NCD-RC. Utilization of NCD-RC in each patient seems to be difficult preoperatively. After publication of NCD-RC, the cut-off level of morality rate was not understandable and, however, the over 5% mortality was referred as the cut-off level without firm evidences. Ant preoperative protocol, decision or content of hepatectomy procedures and postoperative managements have not been changed in this series. This study is an intermediate or pilot analysis to evaluate the NCD-RC data since now.

At this latest stage, total 17 patients had postoperative complications (over CD-III) and 13 patients as the *group wML* showed the procedure-related complications not leading to lethal results, which can be improved by the technical means and experiences of institutional staff. As the managements for these predictive complications has been almost established at our institute, these 13 patients might be recovered without severe situation or in-hospital death. By comparing preoperative factors which may be related to NCD-RC mortality rate, the significant associated factor including the high age over 80 y.o. could not be clarified in this study. At the time of a progressing aging society in Japan or other developed countries, selection or avoidance of major hepatectomy with extended procedures in high age patients should be difficult. In the present study, we noticed that all dead patients (four patients, 6.5% of all undergoing major hepatectomy) underwent right hepatectomy with bile duct resection or anastomosis for advanced stage of biliary malignancies. Major hepatectomy for perihilar biliary diseases may be still a high risk operation leading to lethal complications or in-hospital death (22–24). We must always need to know pitfalls in procedures leading to lethal complication or hepatic failure in such a case and this information would be provided to patients before operation.

The American college of surgeon (ACS) NSQIP surgical risk calculator is a worldwide famous online tool for preoperative informed consent, which has been established prior to NCD-RC (5, 8). However, usefulness of this calculator is still uncertain to evaluate accuracy in each patient to our knowledge. NCD-RC is based on the Japanese patients' nationwide real data and the each registration seems to be very strictly kept in each institute. Thus, it may be better to apply for evaluation our own situations in Japan. The remnant associated factor is a level of surgeon's procedures to regulate blood loss, operating time and skills. Although the board-certification system of specialist for high level operations approved by the Japanese Society of Hepato-Biliary-Pancreatic Surgery has begun since 2011 (10, 25), the specialist is not enough at our institute or region so far in comparison to other prefectures in Japan. Transection time under inflow occlusion procedure tended to be still longer in this

series, transection skill or other careful managements during hepatectomy must be advanced more by increase of effort to secure patients indicating high risk mortality by NCD-RC.

Conclusions

We analyzed relationships between 30 day- and in-hospital mortality rate by NCD-RC in Japan and patient demographics, clinicopathological and surgical records in hepatobiliary malignant patients who had undergone major hepatic resection. The high morbidity or mortality rate was not always matched with predictive mortality rate. One patient, whom the predictive mortality rate was low, died of postoperative hepatic failure due to inflammatory event once after right hepatectomy with bile duct resection in perihilar cholangiocarcinoma. Although the present prediction can be used for informed consent and, however, it is still controversial to rely on prognostic prediction in each patient. Improvement of adjusted risk calculator for liver surgery is expected by a future cohort.

Abbreviations

NCD-RC
National Clinical Database-risk calculator, NSQIP:National Surgical Quality Improvement Program, CD:Clavien Dindo, PVE:preoperative portal vein embolization, CT:computed tomography, MRI:magnetic resonance imaging

Declarations

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Author's contribution

AN has a responsibility of this study and made a study design. NI made a data archive and calculated. MH, KY, TH, TN, DS, RS, YU, TW, and KN collected each patient data. All authors read and approved the final version of the manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Ethics approval and consent to participate

All study protocols were approved by the Ethics Review Board of University of Miyazaki Faculty of Medicine (#O-0778 accepted on September 10, 2020).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1
Relationship between patient demographics or operative procedures, and the predictive mortality rates by NCD-RC

	The 30-day mortality rate (%)	P-value	In-hospital mortality rate (%)	P value
Sex (male/female) (n = 44/17)	2.19 ± 2.04/2.39 ± 2.66	0.60	2.88 ± 3.43/1.07 ± 0.87	< 0.01
Age (years; <70/70–79/≥80)(n = 28/27/6)	1.6 ± 1.8*/2.3 ± 2.1/5.0 ± 2.2	0.057	1.9 ± 2.9/2.4 ± 2.2/ 4.5 ± 5.7	< 0.01
Systemic co-morbidity (no/yes)(n = 42/19)	2.05 ± 2.37/2.68 ± 1.80	0.66	1.67 ± 1.98/3.91 ± 4.30	< 0.01
Respiratory co-diseases (no/yes)(n = 49/12)	2.24 ± 2.30/2.28 ± 1.87		2.02 ± 2.69/3.79 ± 4.07	
Background diseases (normal/CASH/chronic hepatitis/ obstructive jaundice) (n = 4/9/17/31)	0.7 ± 0.59/1.16 ± 0.91/ 2.47 ± 2.65/2.65 ± 2.21		1.53 ± 1.22/1.69 ± 1.82/ 4.1 ± 5.11/1.72 ± 1.14	
Type of hepatectomy				
Right hepatectomy (RT) (n = 16)	1.94 ± 1.74		3.7 ± 4.98	
RT with bile duct resection (BDR) (n = 8)	3.38 ± 1.88		2.29 ± 1.35	
Right trisectionectomy (n = 1)	0.6			
Left hepatectomy (LH) (n = 12)	1.82 ± 2.87			
LH with BDR (n = 14)	2.56 ± 2.45			
LH with pancreaticoduodenectomy (n = 4)	3.73 ± 2.28			
Left trisectionectomy (n = 1)	1.5			
Central segmentectomy 458 (n = 5)	0.86 ± 0.76		1.3	
			2.21 ± 3.12	
			1.71 ± 1.06	
			1.15 ± 1.07	
			3.4	
			1.32 ± 0.68	

CASH, chemotherapy associated steatohepatitis

* p < 0.05 vs 70–79 and over 80 years old, respectively.

Table 2 Relationship between perioperative results and predictive morality rate by NCD-RC

A) Cases with severe complications or mortality in whom low mortality rate was predicted by NCD-RC

	Disease	Preoperative co-morbidity	Hepatectomy	CD high*	Postoperative complication	30-day mortality	in-hospital mortality	NCD-RC calculated 30-day MR (%)	NCD-RC calculated in-hospital MR (%)
1	HCC	HT	RH	yes	bile leak	nil	nil	2.4	1.3
2	PHC	HT	RH-BDR	yes	bile leak	nil	nil	4.2	1.1
3	ICC	HT	RH-BDR	yes	bile leak	nil	nil	2.1	1.1
4	CLM	nil	RTS	yes	bile leak	nil	nil	0.6	1.3
5	HL	COPD, HT	LH	yes	bile leak, abscess ileus	nil	nil	0.3	1.1
6	ICC	HT	LH	yes	bile leak	nil	nil	1.8	1.4
7	HCC	CI	LH	yes	bile leak	nil	nil	2.3	2.7
8	ICC	nil	LH-BDR	yes	ileus	nil	nil	1.8	1.1
9	PHC	nil	LH-BDR	yes	bile leak	nil	nil	0.8	0.6
10	PHC	nil	LH-BDR	yes	bile leak, DGE	nil	nil	0.5	0.3
11	CLM	nil	LH-BDR	yes	bile leak	nil	nil	1.4	0.9
12	PHC	COPD	LH-BDR	yes	pancreatic fistula	nil	nil	1.5	2.1
13	PHC	HT	LH-PD	yes		nil	nil	1.2	0.6

CD; Clavien-Dindo, *; including III, IV and V, NCD-RC; national clinical database-risk calculator, M; male, F; female, HCC; hepatocellular carcinoma, PHC; perihilar cholangiocarcinoma, ICC; intrahepatic cholangiocarcinoma, CLM; colorectal liver metastasis, HL; hepatolithiasis, HT; hypertension, COPD; chronic obstructive pulmonary disease, CI; cerebral injury, RH; right hepatectomy, BDR; bile duct resection, PD; pancreaticoduodenectomy, DGE; delayed gastric empty, MR; mortality rate

B) Cases without severe complications neither mortality in whom high mortality rate was predicted by NCD-RC

	Disease	Preoperative co-morbidity	Hepatectomy	CD-H*	Postoperative complication	30-day mortality	in-hospital mortality	NCD-RC calculated 30-day MR (%)	NCD-RC calculated in-hospital MR (%)
1	HCC	COPD, CI	RH	nil	UTI	nil	nil	6.1	15.9
2	HCC	High dose Steroid use	RH	nil	nil	nil	nil	4.8	15.3
3	CLM	COPD, HT	RH	nil	nil	nil	nil	2.4	6.3
4	HCC	Heavy smoker, HT	RH	nil	enteritis, ascites	nil	nil	3.3	5.8
5	HCC		LH	nil	nil	nil	nil	10.5	11.7
6	PHC	nil	LH-PD	nil	nil	nil	nil	6.2	0.8
7	PHC, PC	HT, pancreatitis	LH-PD	nil	hyponatremia, DGE	nil	nil	5.0	0.9

See Table 2A, PC; pancreatic carcinoma, UTI; urinary tract infection

C) Cases with severe complications or mortality in whom high mortality rate was predicted by NCD-RC

	Disease	Preoperative co-morbidity	Hepatectomy	CD-H*	Postoperative complication	30-day mortality	in-hospital mortality	NCD-RC calculated 30-day MR (%)	NCD-RC calculated in-hospital MR (%)
1	GBC	Heavy smoker	RH-BDR	yes	Hepatic failure	nil	yes	6.9	2.8
2	PHC	HT, COPD	RH-BDR	yes	Aspiration pneumonia,	nil	nil	5.0	5.0
3	ICC	HT	RH-BDR	yes	Enteritis, UTI	nil	nil	9.4	3.5
4	PHC	HT, CI	RH-BDR	yes	Hepato-renal failure	nil	yes	5.0	2.4

See Table 2A, GBC; gallbladder carcinoma, GI; gastrointestinal