Background: Relationship between outcomes of major hepatectomy and the mortality rate predicted by National Clinical Database risk calculator (NCD-RC) was examined.

Methods: Patient demographics and postoperative morbidity and mortality were compared between 30-day and in-hospital mortality rates among 55 patients who underwent major hepatectomies. The cut-off value for high-risk mortality was set at 5%. Patients were divided into four groups: A) no severe complications and low predictive mortality rate (woML), B) severe complications or mortality, and low mortality rate (wML), C) no severe complications and high mortality rate (woMH), and D) severe complications or mortality, and high mortality rate (wMH).

Results: Morbidity higher than CD III occurred in 17 patients (28%) and 30-day and in-hospital mortality in none and two (3%), respectively. The in-hospital mortality rate was significantly higher for male patients (p<0.01). Age, elderly patients, diseases, and co-morbidity did not significantly differ among groups. Although bile leakage was common in group wML, there were no in-hospital deaths. All surgical procedures performed in group wMH were right hepatectomy with bile duct resection (RH-BDR) for biliary
malignancy, and two died of hepatic failure; however, the incidence of RH-BDR was not significantly higher than those in other groups.

Conclusions: Preoperative mortality rate predicted by NCD-RC was not always consistent with outcomes in actual clinical settings and further improvements are needed. In case of RH-BDR for biliary malignancy with high predictive mortality rate, careful decision making for liver function and perioperative management are required.
Original article

Institutional utilization of postoperative mortality predicted by a nationwide survey-based risk calculator in patients who underwent major hepatectomy

Short title: Risk calculator for major hepatectomy
Abstract

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Keywords: National Clinical Database, risk calculator, perioperative factors, mortality rate, major hepatectomy
**Background**

Liver resection is currently the best curative treatment modality for patients with hepatobiliary malignancies and the safety of major hepatectomy for patients with various liver diseases has markedly improved with reduced mortality rates due to adequate preoperative evaluations of the extent of hepatectomy, precise assessments of the functional liver reserve, and advances in perioperative management (1-3). The prognosis of patients after hepatectomy is influenced by age, their general status, co-morbidities, and the organ functional reserve. The relationships among these parameters have been also recently examined (4-6) and, unexpected postoperative morbidity, such as hepatic failure, and related mortality were observed.

A big data analysis recently provided evidence-based predictions in various medical fields, including major surgery (7, 8), and the established scoring system is expected to be clinically useful. The National Clinical Database (NCD) in Japan was initiated by a nationwide registration system in the field of general surgery in 2011 and has produced NCD-based research works, (9, 10). NCD-risk calculator (RC) to predict expected mortality based on large cohort data was developed for a number of major surgical procedures, including hepatectomy. (9) Despite this risk evaluation, we still need to decide indications for hepatectomy using conventional indications depending on the functional liver reserve.

To reevaluate the significance of NCD-RC and reconsider our strategy for major hepatectomy, the relationship between perioperative parameters or in-hospital outcomes and the expected risk ratio of NCD-RC was examined in 61 patients who underwent major hepatectomy in the past 5 years.
Methods

Patients

This retrospective study concomitantly collected data from 61 patients, representing all patients who underwent major hepatectomy for hepatobiliary diseases at the Division of Hepato-biliary-pancreas Surgery, Department of Surgery, University of Miyazaki Faculty of Medicine, Japan between April 2015 and June 2020, in order to evaluate the recent macro-chair system. Surgery was typically indicated for all patients with the Child-Pugh A status. All patients were medically fit for major laparotomy, showed no signs of preoperative dissemination or distant metastases, and had tumors that were anatomically confined to within the liver. Further examinations were performed in cases of biliary malignancy. Nine patients (15%) with colorectal liver metastases received multiple anti-cancer drugs for multiple liver metastases until surgery.

Surgical indication based on liver function for major hepatectomy

The liver volume to be resected was estimated based on 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) Radical hepatectomy was performed to remove hepatic tumors without leaving any residual tumor. All study protocols were approved by the Ethics Review Board of the 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 the present study, and the authors declare no conflicts of interest.

Clinicopathological parameters, surgical data, tumor staging, and subgroups of postoperative survival
The following clinical parameters were recorded: patient demographics, including age, sex, liver diseases, background liver diseases, co-morbidities, and surgical data; the extent of hepatectomy, blood loss, transfusion, surgery time, combined procedures; postoperative complications, and the incidence of a Clavien-Dindo classification higher than III or mortality. The incidence of mortality within 30 days and hepatectomy-related in-hospital mortality were calculated using the formula for major hepatectomy on the Japan NCD website (http://www.ncd.or.jp/about/feedback.html) in Japan.

Patients were divided into the following groups: 1) no severe complications (CD≥III) and a low predictive 30-day or in-hospital mortality rate (group woML), 2) severe complications or mortality, and low mortality rate (group wML), 3) no severe complications and a high mortality rate (group woMH), and 4) severe complications or mortality, and a high mortality rate (group wMH).

Statistical analysis

Continuous data are expressed as means ± standard deviations (SD). Data from different groups were compared using a one-way analysis of variance, followed by the Student’s t-test or Dunnett’s multiple comparison test. In a univariate analysis, categorical data using the cut-off value were analyzed using the chi-squared test or Fisher’s exact test. Two-tailed values of \( p < 0.05 \) were considered to be 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 a mean age of 68.5±10.0 years (range; 39-86 years). Background liver diseases included a normal liver in four patients (7%), chemotherapy-associated liver dysfunction in nine (15%), chronic viral hepatitis in 17 (29%; cirrhosis in none), 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 on 16 patients (25%), right hepatectomy with bile duct resection (RH-BDR) on eight (13%), right trisectionectomy on one (2%), left hepatectomy on 12 (20%), left hepatectomy with bile duct resection on 14 (23%), left trisectionectomy on one (2%), left hepatectomy with pancreaticoduodenectomy on four (7%), and central hepatectomy (segments 4, 5, and 8) on five (8%). In-hospital morbidity and morbidity higher than CD III were observed in 37 (61%) and 17 (28%) patients, respectively, and 30-day and in-hospital mortality in none and two (3%), respectively. Thirty-day and in-hospital mortality rates calculated by NCD-RC in the present study were 2.25±2.21% (range; 0.1-10.5%) and 2.37±3.05% (range; 0.3-15.9%), respectively.

Relationship with mortality estimated by NCD-RC

Age correlated with 30-day mortality (r=0.377, p=0.003) and was associated with in-hospital mortality (r=0.240, p=0.062). Table 1 shows the relationships between patient demographics and the results of NCD-RC. In-hospital mortality rates were significantly higher in male patients than in female patients (p<0.01). Age was divided into 3 groups, and 30-day mortality was significantly higher (p<0.05), while in-hospital mortality was slightly higher in elderly patients. The 30-day mortality rate was slightly higher, while the in-hospital mortality
rate was significantly higher (p<0.01) in patients with systemic circulatory, cerebral, renal, and respiratory diseases. Furthermore, the in-hospital mortality rate was significantly higher (p<0.01) in patients with chronic respiratory diseases. Background liver diseases did not correlate with 30-day or in-hospital mortality rates. Thirty-day and in-hospital mortality rates did not significantly differ among each type of major hepatectomy.

Thirty-seven patients (61%) in group woML were examined. Mean age was 67.8±8.7 years old (range; 45-84 years old). Eighteen (49%) and two (5%) elderly patients were 70-79 and older than 80 years old, respectively. Table 2A-C shows the relationships among preoperative patient demographics, co-morbidity, surgery or postoperative outcomes, and mortality rates predicted by NCD-RC. The cut-off value for high-risk mortality before hepatectomy was set at 5%.

**Patient characteristics associated with high risk mortality by NCD-RC**

Table 2A-C shows the relationship between perioperative results and predictive mortality rate by NCD-RC in group wML (n=13 (21%)), group woMH (n=7 (11%)), and group wMH (n=4 (6.5%)). No significant differences were observed in age or the number of elderly patients (divided by <70, 70-79, and >79 years old) among the groups. Furthermore, no significant differences were noted in the incidence of males, background liver diseases, or main hepatobiliary diseases. Preoperative co-morbidity rates were slightly lower in patients without severe postoperative complications (27% in group woML and 23% in group woMH) than in those with complications (57% in group wML and 50% in group wMH), whereas the incidence of preoperative co-morbidity did not significantly differ among groups.

In group wML, the type of hepatectomy varied and there were no in-hospital deaths. In group woMH, the type of hepatectomy also varied and neither organ failure nor in-hospital death was observed. All surgical procedures performed in group wMH were RH-BDR for
biliary malignancy. Two patients died of hepatic failure within 30 days. Another two patients developed hepatectomy-unrelated complications after hepatectomy and recovered. Thirty-day mortality rates before hepatectomy predicted by NCD-RC were 1.4±1.1% in group woML, 1.6±1.1% in group wML, 5.5±2.6% in group woMH, and 6.6±2.0% in group wMH, with significantly higher rates in the latter two groups (p<0.01). In-hospital mortality rates before hepatectomy predicted by NCD-RC were 1.6±1.0% in group woML, 1.2±0.6% in group wML, 8.1±6.3% in group woMH, and 3.4±1.1% in group wMH, respectively, with significantly higher rates in the latter two groups (p<0.01).
Discussion

The outcomes of patient undergoing major hepatectomy for hepatobiliary malignancies are mainly influenced by the functional liver reserve (1-3, 13-15). Previous studies indicated that co-existing factors, such as patient demographics, co-morbidities, preoperative liver function, surgical outcomes, and postoperative complications, also affect postoperative outcomes (4-6). Although the surgical outcomes of elderly patients have generally improved, major hepatectomy in patients older than 85 years old is still challenging (16). In the first author’s experiences, the upper range of high age was an 86 years female patient undergoing the extended RH-BDR for cholangiocarcinoma and an 87 years female patient undergoing pancreaticoduodenectomy for pancreatic carcinoma, who had no severe complications at the hospital stay (not published). The next major consideration is co-morbidities, such as heart, respiratory, renal, and metabolic diseases, which are common in elderly patients older than 60 years old (5-7, 16). In case the anesthetic tolerance is preserved such as an ASA classification (16-18), the operation under general anesthesia is possible. For major hepatectomy, the tolerance has not been elucidated and the operation time or complication risk rate are usually considered in each.

In the present study, we reviewed the relationship between NCD-RC for major hepatectomy and the clinical results obtained at our institute. NCD-RC was developed to compare mortality to that of each institute and, therefore, the better prognosis than mortality predicted by NCD-RC is favorable. In case of worse prognosis, the plan-do-check-act cycle to improve institutional results is required at the NCD website (http://www.ncd.or.jp/about/feedback.html). Since the mortality rate of all cases in the present study appeared to be low, 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 study. This patient had adequate liver function and underwent preoperative portal vein embolization (PVE). PVE is performed to avoid postoperative hepatic failure following major right hepatectomy (19, 20). In our experience, if the functional liver reserve decreases after PVE, scheduled hepatectomy is generally abandoned. In our patient, no significant changes were observed in post-PVE liver function. Blood loss was 1100 mL and there were no complications during surgery; however, the remnant liver showed partial congestion at segment 4 due to kinking of the middle hepatic vein. Inflammation developed between days 2 and 5, but immediately improved with the administration of antibiotics. However, hepatic and renal failure gradually progressed and the patient died on day 47 despite early intensive care interventions. Two in-hospital mortalities occurred among patients considered to be at a high risk of mortality by NCD-RC (n=11). The actual mortality ratio among these patients was 18% and, based on this result, the prediction by NCD-RC appeared to be accurate. Patients with good outcomes also received routine management regardless of a high risk of mortality predicted by NCD-RC. The complete utilization of NCD-RC for each patient may be difficult preoperatively. After the publication of NCD-RC, the cut-off level of mortality rate was not understandable and, however, the over 5% mortality was referred as the cut-off level without firm evidence. Ant preoperative protocol, decision or content of hepatectomy procedures and postoperative managements have not been changed in this series. Therefore, the present study was an intermediate or pilot analysis to assess NCD-RC data obtained to date.

At this latest stage, 17 patients developed postoperative complications (higher than CD-III) and 13 in group wML had procedure-related complications that were not fatal and treatable by interventions from institutional staff. Since the management of predicted complications has been 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 older than 80 years old could not be clarified in this study. Since Japan and other developed countries now have super aging societies, the selection or avoidance of major hepatectomy with extended procedures in elderly patients should be avoided. In the present study, all four patients who died (6.5% of all those undergoing major hepatectomy) underwent RH-BDR or anastomosis for advanced biliary malignancies. Major hepatectomy for perihilar biliary diseases may be still a high-risk procedure leading to lethal complications or in-hospital death (21-23). It is important to consider the pitfalls of procedures that lead to lethal complications or hepatic failure and this information needs to be provided to patients before surgery.

The American College of Surgeons (ACS) NSQIP surgical risk calculator is an online tool that is used worldwide for preoperative informed consent and was established prior to NCD-RC (5, 8). However, to the best of our knowledge, the usefulness of this calculator to evaluate accuracy in each patient remains unclear. NCD-RC is based on nationwide real data on Japanese patients and 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 specialists for high-level surgical procedures approved by the Japanese Society of Hepato-Biliary-Pancreatic Surgery was initiated in 2011 (10, 24), the number of specialists at our institute or in our region is smaller than in other prefectures in Japan. Transection times under inflow occlusion procedures were still slightly longer in the present study; therefore, transection skills and management during hepatectomy need to be improved by increase of effort to secure patients indicating high-risk mortality predicted by NCD-RC. The ACS calculator consisted of 13 parameters and, however, preoperative parameter was several as pneumonia, cardiac complication, readmission, return to OR, facility and so on. These were not specified to each surgical
procedure. Hepatectomy-specified NCD-RC consisted of 23 preoperative and estimated procedure parameters that independent risk factors by actual 7732 data and the validation set analysis was performed. A comparison of these systems revealed that NCD-RC was slightly more precise. Although a simpler system is often reliable, comparison of these would be necessary before deciding operative indication if necessary.

The limitations of the present study need to be addressed. 1) A retrospective cohort analysis nevertheless NCD-RC was referred only in patients with serious co-morbidities, 2) difficult understanding of relationship between actual complications higher than CDIII and the mortality rate predicted by NCD-RC, and 3) unclear decision making regarding the surgical procedure or extent of liver resection.

Nomogram to decide hepatectomy is desirable.

Conclusions

We herein examined the relationships between 30-day and in-hospital mortality rates predicted by NCD-RC in Japan and the demographics and clinicopathological and surgical records of patients with hepatobiliary malignancies who underwent major hepatic resection. A predicted high morbidity (higher than CD III) or mortality rate did not always match the preoperative mortality rate. Although the present predictions by NCD-RC may be used for informed consent, it is still controversial to rely on predictions of outcomes in each patient. Improvements in the adjusted risk calculator for liver surgery are needed by collecting with every period of time using a large cohort.

Supplementary Information

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 contributions
AN was responsible for and designed the present study. NI made a data archive and statistically analyzed. MH, KY, TH, TN, DS, RS, YU, TW, and KN collected data on each patient. 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 the published article and its supplementary information files.

Ethics approval and consent to participate
All study protocols were approved by the Ethics Review Board of the 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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References

1. Yamamoto J, Okada S, Shimada K, Okusaka T, Yamasaki S, Ueno H, Kosuge T. Treatment strategy for small hepatocellular carcinoma: Comparison of long-term results after percutaneous ethanol injection therapy and surgical resection. Hepatology 2001;34(4):707-4

2. Poon RT, Fan ST. Hepatectomy for hepatocellular carcinoma: patient selection and postoperative outcome. Liver Transplantation 2004;10(2):39-45

3. Tung-Ping Poon R, Fan ST, Wong J. Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. Ann Surg 2000;232:10-24.

4. Tanaka S, Ueno M, Iida H, Kaibori M, Nomi T, Hirokawa F, Ikoma H, Nakai T, Eguchi H, Kubo S. Preoperative assessment of frailty predicts age-related events after hepatic resection: a prospective multicenter study. J Hepatobiliary Pancreat Sci. 2018;25(8):377-87.

5. Tzeng CW, Cooper AB, Vauthey JN, Curley SA, Aloia TA. Predictors of morbidity and mortality after hepatectomy in elderly patients: analysis of 7621 NSQIP patients. HPB (Oxford). 2014;16(5):459-68.

6. Schiergens TS, Stielow C, Schreiber S, Hornuss C, Jauch KW, Rentsch M, Thasler WE. Liver resection in the elderly: significance of comorbidities and blood loss. J Gastrointest Surg. 2014;18(6):1161-70.

7. Ma KW, Cheung TT, She WH, Chok KSH, Chan ACY, Dai WC, Lo CM. Risk prediction model for major complication after hepatectomy for malignant tumour - A validated scoring system from a university center. Surg Oncol. 2017;26(4):446-52.
8. Beal EW, Lyon E, Kearney J, Wei L, Ethun CG, Black SM, Dillhoff M, Salem A, Weber SM, Tran TB, Poultsides G, Shenoy R, Hatzaras I, Krasnick B, Fields RC, Buttner S, Scoggins CR, Martin RCG, Isom CA, Idrees K, Mogal HD, Shen P, Maithel SK, Pawlik TM, Schmidt CR. Evaluating the American College of Surgeons National Surgical Quality Improvement project risk calculator: results from the U.S. Extrahepatic Biliary Malignancy Consortium. HPB (Oxford). 2017;19(12):1104-11

9. Kenjo A, Miyata H, Gotoh M, Kitagawa Y, Shimada M, Baba H, Tomita N, Kimura W, Sugihara K, Mori M. Risk stratification of 7,732 hepatectomy cases in 2011 from the National Clinical Database for Japan. J Am Coll Surg. 2014;218(3):412-22.

10. Miura F, Yamamoto M, Gotoh M, Konno H, Fujimoto J, Yanaga K, Kokudo N, Yamaue H, Wakabayashi G, Seto Y, Unno M, Miyata H, Hirahara N, Miyazaki M. Validation of the board certification system for expert surgeons (hepato-biliary-pancreatic field) using the data of the National Clinical Database of Japan: part 1 - Hepatectomy of more than one segment. J Hepatobiliary Pancreat Sci. 2016;23(6):313-23.

11. Takasaki T, Kobayashi S, Suzuki S, Muto H, Marada M, Yamana Y, Nagaoka T. Predetermining postoperative hepatic function for hepatectomies. Int Surg 180;65:309-13.

12. Kubota K, Makuuchi M, Kusaka K, Kobayashi T, Miki K, Hasegawa K, Harihara Y, Takayama T. Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. Hepatology. 1997;26(5):1176-81.

13. Kamiyama T, Nakanishi K, Yokoo H, Kamachi H, Tahara M, Yamashita K, Taniguchi M, Shimamura T, Matsushita M, Todo S. Perioperative management of hepatic resection toward zero mortality and morbidity: analysis of 793 consecutive cases in a single institution. Am Coll Surg. 2010;211(4):443-9.
14. Ge PL, Du SD, Mao YL. Advances in preoperative assessment of liver function. Hepatobiliary Pancreat Dis Int. 2014;13:361-70

15. van Mierlo KM, Schaap FG, Dejong CH, Olde Damink SW. Liver resection for cancer: New developments in prediction, prevention and management of postresectional liver failure. J Hepatol. 2016;65(4):1217-31.

16. Nanashima A, Abo T, Nonaka T, Fukuoka H, Hidaka S, Takeshita H, Ichikawa T, Sawai T, Yasutake T, Nakao K, Nagayasu T. Prognosis of patients with hepatocellular carcinoma after hepatic resection: are elderly patients suitable for surgery? J Surg Oncol. 2011;104(3):284-91.

17. Hoffmann K, Hinz U, Stravodimos C, Knoblich T, Schön MR, Büchler MW, Mehrabi A. Risk assessment for liver resection. Surgery. 2018;164(5):998-1005.

18. Tang TY, Zong Y, Shen YN, Guo CX, Zhang XZ, Zou XW, Yao WY, Liang TB, Bai XL. Predicting surgical site infections using a novel nomogram in patients with hepatocellular carcinoma undergoing hepatectomy. World J Clin Cases. 2019;7(16):2176-88.

19. Makuuchi M, Le Thai B, Takayasu K, Takayama T, Kosuge T, Gunvén P, Yamazaki S, Hasegawa H, Ozaki H. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. Surgery 1990;107(5):521–7.

20. Nagino M, Nimura Y, Kamiya J, Kondo S, Uesaka K, Kin Y, Hayakawa N, Yamamoto H. Changes in hepatic lobe volume in biliary tract cancer patients after right portal vein embolization. Hepatology 1995;21(2):434–9.

21. Chaudhary RJ, Higuchi R, Nagino M, Unno M, Ohtsuka M, Endo I, Hirano S, Uesaka K, Hasegawa K, Wakai T, Uemoto S, Yamamoto M. Survey of preoperative management protocol for perihilar cholangiocarcinoma at 10 Japanese high-volume centers with a combined experience of 2,778 cases. J Hepatobiliary Pancreat Sci. 2019;26(11):490-502.
22. Akashi K, Ebata T, Mizuno T, Yokoyama Y, Igami T, Yamaguchi J, Onoe S, Nagino M. Surgery for perihilar cholangiocarcinoma from a viewpoint of age: Is it beneficial to octogenarians in an aging society? Surgery. 2018;164(5):1023-9.

23. Franken LC, Schreuder AM, Roos E, van Dieren S, Busch OR, Besselink MG, van Gulik TM. Morbidity and mortality after major liver resection in patients with perihilar cholangiocarcinoma: A systematic review and meta-analysis. Surgery. 2019;165(5):918-28.

24. Otsubo T, Kobayashi S, Sano K, Misawa T, Ota T, Katagiri S, Yanaga K, Yamaue H, Kokudo N, Unno M, Fujimoto J, Miura F, Miyazaki M, Yamamoto M. Safety-related outcomes of the Japanese Society of Hepato-Biliary-Pancreatic Surgery board certification system for expert surgeons. J Hepatobiliary Pancreat Sci. 2017;24(5):252-61
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 |         | 1.9±2.9/2.4±2.2/ 4.5±5.7     |         |
| **Systemic co-morbidity (no/yes)(n=42/19)** | 2.05±2.37/2.68±1.80       | 0.057   | 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       | 0.66    | 2.02±2.69/3.79±4.07           | <0.01   |
| **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                            |         | 1.3                            |         |
| Left hepatectomy (LH) (n=12) | 1.82±2.87                     |         | 2.21±3.12                     |         |
| LH with BDR (n=14) | 2.56±2.45                     |         | 1.71±1.06                     |         |
| LH with pancreaticoduodenectomy (n=4) | 3.73±2.28                     |         | 1.15±1.07                     |         |
| Left trisectionectomy (n=1) | 1.5                            |         | 3.4                            |         |
| Central segmentectomy 458 (n=5) | 0.86±0.76                     |         | 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 mortality 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        | nil              | nil                   | 0.3                             | 1.1                               |
| 6 | ICC     | HT                        | LH          | yes      | ileus                     | 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      | bile leak                 | nil              | nil                   | 1.8                             | 1.1                               |
| 9 | PHC     | nil                       | LH-BDR      | yes      | ileus                     | nil              | nil                   | 0.8                             | 0.6                               |
| 10| PHC     | nil                       | LH-BDR      | yes      | bile leak                 | nil              | nil                   | 0.5                             | 0.3                               |
| 11| CLM     | nil                       | LH-BDR      | yes      | bile leak, DGE            | nil              | nil                   | 1.4                             | 0.9                               |
| 12| PHC     | COPD                      | LH-BDR      | yes      | bile leak                 | nil              | nil                   | 1.5                             | 2.1                               |
| 13| PHC     | HT                        | LH-PD       | yes      | pancreatic fistula        | 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 heptatectomy, 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                      | RH          | nil   | UTI                       | nil             | nil                  | 6.1                              | 15.9                                 |
| 2       | HCC                      | RH          | nil   | nil                       | nil             | nil                  | 4.8                              | 15.3                                 |
| 3       | CLM                      | RH          | nil   | enteritis, ascites        | nil             | nil                  | 2.4                              | 6.3                                  |
| 4       | HCC                      | RH          | nil   | hyponatremia, DGE         | nil             | nil                  | 3.3                              | 5.8                                  |
| 5       | HCC                      | LH          | nil   | nil                       | nil             | nil                  | 10.5                             | 11.7                                 |
| 6       | PHC                      | LH-PD       | nil   | nil                       | nil             | nil                  | 6.2                              | 0.8                                  |
| 7       | PHC, PC                  | LH-PD       | nil   | nil                       | 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                      | RH-BDR      | yes   | Hepatic failure           | nil             | yes                  | 6.9                              | 2.8                                  |
| 2       | PHC                      | RH-BDR      | yes   | Aspiration pneumonia,    | nil             | nil                  | 5.0                              | 5.0                                  |
| 3       | ICC                      | RH-BDR      | yes   | Enteritis, UTI            | nil             | nil                  | 9.4                              | 3.5                                  |
| 4       | PHC                      | RH-BDR      | yes   | Hepato-renal failure      | nil             | yes                  | 5.0                              | 2.4                                  |

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