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ORIGINAL ARTICLE

Risk factors for hepatic insufficiency after major hepatectomy in non-cirrhotic patients

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Summary *Background:* Although recent advances in surgical techniques and perioperative management have reduced the morbidity and mortality after hepatectomy, hepatic insufficiency after major hepatectomy remains an important concern. This study aimed to clarify the risk factors for post-hepatectomy liver insufficiency.
Methods: We enrolled 103 consecutive patients who underwent major hepatectomy which was defined as resection of four or more segments. Hepatic insufficiency is defined as an increase in serum total bilirubin after hepatectomy of 7 mg/dL or more, or death from multiple organ failure. We compared the patient disposition, demographics, perioperative factors such as surgical method, combined procedure, morbidity and so on between the patients with or without hepatic insufficiency.
Results: Hepatic insufficiency occurred in 14 patients (14%) and six of them died during the hospital stay (6%). Risk factors by univariate analysis were the percentage of hepatic parenchyma to be resected ($P = .025$), combined procedure ($P = .008$) and postoperative morbidity excluding hepatic insufficiency ($P < .001$). A combined procedure ($P = .036$) and postoperative morbidity excluding hepatic insufficiency ($P = .002$) were a significant risk factor by multivariate analysis.
Conclusion: Unless remaining liver after hepatectomy has enough volume, combined procedure may account for hepatic insufficiency, which can follow the development of postoperative morbidity.

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1. Introduction

Preoperative strict criteria in patient-selection for major hepatectomy, and recent advances in surgical techniques and perioperative management have reduced the morbidity and mortality after surgery. However, post-hepatectomy liver insufficiency, although uncommon, is one of the life-threatening complications and remains an important concern. Especially after major hepatectomy, which is defined as resection of four or more segments,[1] hepatic insufficiency is subject to develop.[2] We occasionally encounter the patients in whom serum bilirubin continuously increases after major hepatectomy and some of them die of fatal liver failure at our hospital. Intrahepatic cholestasis is a type of hepatic insufficiency in the absence of biliary obstruction. This ranges from mild hepatic insufficiency, characterized by transient hyperbilirubinemia (HB) that does not alter the expected postoperative course, to fatal liver failure resulting in multiple organ failure requiring intensive treatment. Percutaneous transhepatic portal vein embolization (PTPE) is known to be one of the methods of preventing this complication. Nevertheless, our former report suggested that patients who underwent major hepatectomy combined with skeletonization of the hepatoduodenal ligament for biliary tract disease with jaundice were subject to HB even after PTPE.[3] This study focused on the risk factors for post-hepatectomy liver insufficiency following HB.

2. Methods

2.1. Patient selection

This study compared the clinicopathologic factors between the patients with or without hepatic insufficiency. From April 2002 through June 2017, 103 consecutive patients underwent resection of four or more segments at the Department of Hepato-Biliary-Pancreatic Surgery, Miyazaki University Hospital and were enrolled in this study. Surgical procedures included right hemihepatectomy in 72, right hepatectomy with middle hepatic vein (MHV) resection in 22 and right and left trisectionectomy in 5 and 4, respectively. Our criteria for major hepatectomy are as follows: first, indocyanine green retention rate at 15 min (ICGR15) of 10 or less[4]; second, the percentage of hepatic parenchyma to be resected (HPR%) under 65%; third, remnant maximal removal rate of galactosyl human serum albumin (GSA-Rmax) by technetium-99 m (^{99m}Tc)-GSA scintigraphy over 0.15.[5] HPR% is defined as normal parenchymal volume to be resected as a percentage of total liver volume excluding tumor volume. The patients received a diagnosis of primary hepatic cancer ($n = 42$), biliary neoplasm ($n = 37$), metastatic liver cancer ($n = 18$) or other miscellaneous diseases ($n = 6$). Forty-three patients underwent concomitant biliary procedures, which were extrahepatic bile duct resection and reconstruction with lymphadenectomy in the hepatoduodenal ligament. Four patients received a combined procedure, such as total gastrectomy in 1, pancretodudenectomy in 1, right nephrectomy in 1 and resection and reconstruction of the right hepatic artery in 1. PTPE was performed in 45 patients before hepatectomy. Our criteria for PTPE are ICGR15 between 10 and 20,[4] HPR% over 65% and remnant GSA-Rmax under 0.15.[5] The patients in whom the above two values, excluding ICGR15, did not improve 3–6 weeks after PTPE were excluded from surgical indication of major hepatectomy. Hepatic insufficiency is defined as an increase in serum total bilirubin after hepatectomy of 7 mg/dL or more,[6] or death from multiple organ failure. Postoperative mortality was defined as death within 90 days of operation or during the same hospital stay. Postoperative morbidity was defined as grade III or more according to the classification proposed by Dindo and colleagues,[7] excluding hepatic insufficiency, which developed in 33 patients, bile leak (n = 11), perihepatic abscess (n = 7), intraabdominal hemorrhage (n = 4), disseminated intravascular coagulation (n = 4), portal vein thrombus (n = 2), liver abscess (n = 1), gastrointestinal hemorrhage (n = 1), intestinal perforation (n = 1), acute renal failure (n = 1) and refractory abscess (n = 1). Some morbidities were multifactorial and a single event was difficult to be identified, thus the first or main event was selected. Informed consent for this retrospective analysis was obtained by the opt-out method, and this study was approved by the institutional review board at Miyazaki University in March, 2017 (approved number #2016-179).

2.2. Clinical parameters

To investigate the clinical parameters associated with an occurrence of hepatic insufficiency after major hepatectomy, we compared the following data between the patients with or without hepatic insufficiency: age, gender, disease, underlying liver disease, ICGR15, HPR%, remnant GSA-Rmax, surgical method, combined procedure, duration of operation, blood loss volume, duration of portal pedicle clamping and postoperative morbidity except hepatic insufficiency. The underlying liver diseases were chronic hepatitis (n = 29), jaundice (n = 18), non-alcoholic fatty liver disease (n = 7), blue liver associated with chemotherapy including oxaliplatin (n = 9), and normal liver (n = 40). The medical records of eligible patients were evaluated until 90 days after surgery, including surgeon's notes, radiologic imaging, surgical and pathology reports, and discharge summaries.

2.3. Statistical analysis

Clinical parameters were expressed as the number (percentage) or median (range). Our missing data analysis procedures used complete-case analysis. Comparisons between groups were made using the χ^2 test for categorical variables and the Mann–Whitney *U*-test for continuous variables. Multivariate logistic regression analysis was also conducted to determine the risk factors associated with the development of hepatic insufficiency. All *P*-values were based on a two-sided test, and a P-value $< .05$ was considered to be significant. Statistical analyses were performed using SPSS software version 18.0 for Windows (SPSS, Chicago, IL).

3. Results

Hepatic insufficiency developed in 14 patients (14%) and six of them died during the same hospital stay (6%). The HPR% (54% vs 49%, $P = .025$), combined procedure (21% vs 1%, $P = .008$) and postoperative morbidity except hepatic insufficiency (79% vs 25%, $P < .001$), were significantly larger in the patients with hepatic insufficiency than in those without it by univariate analysis (Table 1). No factors for hepatic function, such as ICGR15, remnant GSA-Rmax were significantly different between the two groups. There were no significant differences in the disease, underlying disease, duration of operation and blood loss volume between the two groups. By multivariate analysis, a combined procedure ($P = .036$) and postoperative morbidity excluding hepatic insufficiency ($P = .008$) were significantly different risk factors (Table 2).

Table 2 Risk factors for hepatic insufficiency by multivariate analysis.

	SE	Odds ratio	95%CI	P value
HPR% (%)	.050	1.063	.963–1.173	.224
Combined procedure (%)	1.329	16.206	1.198–219.179	.036
Postoperative morbidity except hepatic insufficiency	.734	9.406	2.232–39.636	.002

SE standard error, *CI* confidence interval, *HPR%* percentage of hepatic parenchyma to be resected.

4. Discussion

The International Study Group of Liver Surgery (ISGLS)[8] defined postoperative liver failure as an increased international normalized ratio (INR) of prothrombin time (PT) and HB according to the normal limits of the local laboratory on or after postoperative day 5. The severity of post-hepatectomy liver failure was graded based on its effects on clinical management; grade A requires no change in the patient's clinical management; grade B requires deviation from the usual management, but does not require invasive therapy; grade C requires invasive treatment.[8] Before ISGLS criteria, Balzan et al[9] advocated that the association of PT <50% and serum bilirubin >50 μmol/L on postoperative day 5 (the 50-50 criteria) was an accurate predictor of more than 50% mortality rate after hepatectomy. The bilirubin level is perhaps the least likely variable to be biased after hepatectomy and is the most widely accepted biochemical indicator of hepatic insufficiency. Although PT is a reliable marker of the synthetic function of the liver, it can be biased by transfusion of fresh-frozen plasma after hepatectomy. Therefore, we defined hepatic insufficiency in this study as an increase in serum total bilirubin after hepatectomy of 7 mg/dL or more according to the criteria of Mullen et al[6] or death from multiple organ failure requiring invasive treatment corresponding to grade C by the ISGLS criteria.

Our results indicate that a combined procedure is one of the risk factors for hepatic insufficiency after major hepatectomy by univariate and multivariate analysis, which is consistent with the results of some prior studies.[6,10] Mullen et al[6] reported that a concomitant major intraabdominal procedure at the time of major hepatectomy was a substantial independent predictor of liver-related mortality. Jarnagin et al[10] also reported that concomitant additional major procedures significantly increased operative mortality in patients who underwent resection of three or more segments of the liver. In contrast, Elias et al[11] reported that simultaneous hepatectomy and intestinal anastomosis appeared to be safe

Table 1 Risk factors for hepatic insufficiency by univariate analysis.

	Hepatic insufficiency (n = 14)	Control (n = 89)	*P* value
Age (years)	67 ± 14	65 ± 11	.608
Gender (male/female)	11/3	59/30	.540
Disease (PHC/Bil/Meta/Others)	5/7/1/1	37/30/17/5	.719
Underlying liver disease (CH/Jaundice/NAFLD/Blue/Normal)	3/4/3/0/4	26/14/4/9/36	.079
ICGR15 (%)	12.5 ± 6.2	12.2 ± 9.3	.903
HPR% (%)	54 ± 7	49 ± 11	.025
Remnant GSA-Rmax	.28 ± .04	.30 ± .09	.480
Surgical method (RHH/RHwM/RTS/LTS)	12/1/0/1	60/21/5/3	.342
Combined procedure (%)	21	1	.008
Duration of operation (minutes)	642 ± 228	546 ± 147	.146
Blood loss volume (ml)	3170 ± 2340	2105 ± 2355	.119
Duration of portal pedicle clamping (minutes)	54 ± 62	50 ± 37	.824
Postoperative morbidity except hepatic insufficiency (%)	79	25	<.001

PHC primary hepatic cancer, *Bil* biliary neoplasm, *Meta* metastatic liver cancer, *CH* chronic hepatitis, *NAFLD* nonalcoholic fatty liver disease, *Blue* blue liver associated chemotherapy, ICGR15 indocyanine green retention rate at 15 min, *HPR%* percentage of hepatic parenchyma to be resected, *GSA-Rmax* maximal removal rate of galactosyl human serum albumin by scintigram, *RHH* right hemihepatectomy, *RHwM* right hepatectomy with middle hepatic vein resection, *RTS* right trisectionectomy.
LTS left trisectionectomy, *HB* hyperbilirubinemia.

for synchronous liver metastases from colorectal cancer. However, from the result of this study, the authors believe that two-stage surgery can be safer in major hepatectomy with gastrointestinal, colorectal surgery, or surgical indication should be reconsidered in combined pancreatic resection to prevent imminent liver insufficiency. In this study, hepatic insufficiency did not develop in only one patient who underwent right hemihepatectomy and right nephrectomy for renal cell carcinoma invading to the right liver extensively, so combined nephrectomy might be safe in major hepatectomy.

Increase in HPR% was the second risk factor by univariate analysis in this study. Shoup et al[12] reported that volumetric analysis of the percentage of liver remaining after resection correlated with the peak bilirubin level measured postoperatively. They also demonstrated major resection with $\leq$25% of the liver remaining more than tripled the risk of hepatic dysfunction. Shirabe et al[13] also reported that the expected remaining liver volume appears to be a good predictor of liver insufficiency in patients who undergo a right hemihepatectomy. Other factors regarding hepatic function, such as ICGR15 and remnant GSA-Rmax, were not associated with post-hepatectomy liver insufficiency in our study, which may be ascribed to the patient-selection criteria before surgery in our institution. In other words, we have already excluded the patients with bad values for hepatic function during the last two decades; therefore, few patients experience post-hepatectomy liver insufficiency because of the grade of preoperative hepatic dysfunction. We emphasize that proper patient selection and preservation of an obligatory volume of remaining liver are mandatory.

Postoperative morbidity excluding hepatic insufficiency was one of the risk factors for post-hepatectomy liver insufficiency by univariate and multivariate analysis in our study. Our former report[3] advocated that postoperative complications are a significant risk factor for post-hepatectomy liver insufficiency following HB. In our study, eight of 14 patients with hepatic insufficiency recovered from it and did not die. Six of 8 patients had grade IIIa or more complications according to Clavien-Dindo classification, such as arterial hemorrhage, duodenal ulcer bleeding, intraabdominal abscess or bile leak. They underwent endoscopic or interventional radiological treatments and recovered from it. Therefore, a difference between survivors and deaths might be a response to the treatments for severe complications. A postoperative "second hit", such as infection, massive bleeding[14] or sepsis, has been demonstrated to decrease Kupffer cell function and increase toxic cytokines, both of which can inhibit hepatocyte proliferation.[15–17] Leukocyte-Kupffer cell interaction is thought to trigger a local inflammatory response leading to the release of TNF-α and IL-6, which then act on hepatocytes leading to proliferation.[15] Administration of endotoxin to hepatectomized rats results in massive necrosis and up to 50% mortality,[16] possibly by interfering with Kupffer cell activation via this leucocyte-Kupffer cell interaction. Endotoxin release from blood-borne bacteria appears to have a direct action on hepatocytes resulting in decreased mitochondrial function. Intraperitoneal injection of lipopolysaccharide in mice has been found to inhibit liver regeneration by suppression of proliferative pathways via upregulation of TGF-β.[17] Liver insufficiency can adversely cause sepsis because of dysfunction of Kupffer cells or a decrease in synthesis of acute phase proteins. Nevertheless, even if the initial liver dysfunction after major hepatectomy has been sustained, the subsequent recovery of liver function depends on the postoperative condition. Severe intestinal endotoxemia commonly results in excessive inflammatory responses, with serious hepatic necrosis, further severe hepatitis and even induces acute liver failure.[18]

Chemotherapy for colorectal liver metastases is associated with an increased risk of regimen-specific liver injury.[19,20] Clinical studies have shown that steatotic grafts increases complications after liver transplantation.[21,22] However, our results did not demonstrate that the underlying liver disease was one of the risk factors for post-hepatectomy liver failure. This is probably because we already exclude the patients with severe liver dysfunction due to these underlying diseases by strict criteria which is composed of ICGR15, remnant GSA-Rmax, HPR% under 65% and combined PTPE.

In conclusion, a combined procedure with major hepatectomy may account for hepatic insufficiency, which can follow the development of postoperative morbidity, unless the remaining liver volume after hepatectomy is enough to prevent this severe complication even after PTPE. Because of the limitations of small sample size and the single-institution nature of this study, further prospective or multi-institutional joint research with large sample size more than 1000 will be necessary to clarify the detail mechanism of post-hepatectomy liver insufficiency. We expect that this study will contribute to the decision of selecting major hepatectomy combined with additional procedures for patients with multimorbidities.

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Disclosure statement

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Conflict of interest

There is no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.asjsur.2018.03.002.

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