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Association of Remnant Liver Ischemia With Early Recurrence and Poor Survival After Liver Resection in Patients With Hepatocellular Carcinoma

Jai Young Cho, MD, PhD; Ho-Seong Han, MD, PhD; YoungRok Choi, MD; Yoo-Seok Yoon, MD, PhD; Sungho Kim, MD; Jang Kyu Choi, MD; Jae Seong Jang, MD; Seong Uk Kwon, MD; Haeryoung Kim, MD, PhD

IMPORTANCE The remnant liver after hepatectomy may have inadequate blood supply, especially following nonanatomical resection or vascular damage.

OBJECTIVE To evaluate whether remnant liver ischemia (RLI) may have an adverse effect on long-term survival and morbidity after liver resection in patients with hepatocellular carcinoma.

DESIGN, SETTING, AND PARTICIPANTS This study was a retrospective analysis at Seoul National University Bundang Hospital. Remnant liver ischemia was graded on postoperative computed tomographic scans in 328 patients who underwent hepatectomy for hepatocellular carcinoma between January 1, 2004, and December 31, 2013.

MAIN OUTCOMES AND MEASURES Remnant liver ischemia was defined as reduced or absent contrast enhancement during the venous phase. Remnant liver ischemia was classified as minimal (none or marginal) or severe (partial, segmental, or necrotic).

RESULTS Among 328 patients (252 male and 76 female; age range, 26-83 years [mean age, 58.2 years]), radiologic signs of severe RLI were found in 98 patients (29.9%), of whom 63, 16, and 19 had partial, segmental, or necrotic RLI, respectively. These patients experienced more complications and longer hospital stay than patients with minimal RLI. Preoperative history of transarterial embolization (odds ratio [OR], 1.77; 95% CI, 1.02-3.03; *P* = .04), use of the Pringle maneuver (OR, 1.96; 95% CI, 1.08-3.58; *P* = .03), and longer operative time (OR, 1.003; 95% CI, 1.002-1.005; *P* < .001) were independent risk factors for severe RLI. Early recurrence rates within 6 (60.2% vs 9.6%) or 12 (79.6% vs 18.7%) months after hepatectomy were higher in patients with severe RLI than in patients without RLI (*P* < .001). Severe remnant liver ischemia was an independent risk factor for overall survival (OR, 6.98; 95% CI, 4.27-11.43; *P* < .001) and disease-free survival (OR, 5.15; 95% CI, 3.62-7.35; *P* < .001).

CONCLUSIONS AND RELEVANCE Preventive management and technical refinements in hepatectomy are important to decrease the risk of RLI and to improve survival of patients with hepatocellular carcinoma.

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Supplemental content

Author Affiliations: Department of Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea (Cho, Han, Y. Choi, Yoon, S. Kim, J. K. Choi, Jang, Kwon); Department of Pathology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea (H. Kim).

Corresponding Author: Ho-Seong Han, MD, PhD, Department of Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 300 Gumi-Dong, Bundang-Gu, Seongnam-Si, Gyeonggi-Do, Seoul 463-707, Korea (hanhs@snubh.org).

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide. Although it is more prevalent in Asia and Africa, its incidence is increasing in Western countries.[1,2] Although hepatic resection is a widely accepted treatment option for patients with good liver function, the high incidence of postoperative recurrence remains a serious problem.[3,4] The high risk of recurrence is likely because of the high incidence of intrahepatic metastasis and multicentric occurrence of de novo HCC.[5] Anatomical hepatectomy (AH) was reported to be preferred for HCC because of the tumor's tendency to invade the portal veins and spread along their intrasegmental branches.[6] Although the outcomes of AH and non-AH (NAH) or limited hepatic resection have been compared, the conclusion was unclear.[7]

Advanced surgical techniques and improvements in imaging technologies have facilitated surgical approaches involving the resection of individual hepatic segments.[6,8] However, unintentional damage to a segment's inflow or outflow vessel can result in liver hypoperfusion or ischemia of tissue supplied by the damaged vessel.[9] Surgical stress, such as hepatic ischemic injury, was reported to promote liver metastasis in animal models.[10,11] Although some research has focused on ischemic damage of the liver after hepatectomy, these studies mainly addressed the consequences of intraoperative temporary hepatic blood inflow occlusion or ischemic reperfusion injury.[12,13] Until now, few reports have examined the clinical relevance of remnant liver ischemia (RLI) after partial hepatectomy and the oncologic outcomes of affected patients. Therefore, the objective of our study was to assess the incidence of and risk factors for RLI and its effect on patient survival, long-term oncologic outcomes, and disease recurrence after hepatectomy in patients with HCC.

Key Points

Question Will remnant liver ischemia after partial hepatectomy affect the oncologic outcomes of patients?

Findings In this database study that included 328 patients who underwent hepatectomy for hepatocellular carcinoma, severe remnant liver ischemia was an independent risk factor for overall survival and disease-free survival.

Meaning Preventive management and technical refinements in hepatectomy are important to decrease the risk of remnant liver ischemia and to improve survival of patients with hepatocellular carcinoma.

Methods

Study Population and Definitions

We conducted a retrospective analysis of a prospective database of 378 consecutive patients who underwent hepatectomy for HCC at the Department of Surgery, Seoul National University Bundang Hospital, Seoul, Republic of Korea, between January 1, 2004, and December 31, 2013. Of 378 patients, 50 were excluded from the study because of the absence of contrast-enhanced computed tomographic (CT) images within 1 month after surgery. The study was approved by the Seoul National University Bundang Hospital Institutional Review Board. Written informed consent was obtained from each patient by the surgical team. Patient demographic characteristics, preoperative laboratory values, surgical procedures, perioperative outcomes, tumor histopathologic findings, and follow-up data were retrieved from the patients' medical records.

Postoperative complications were graded according to the Clavien classification of morbidity severity.[14-16] If a patient had more than 2 complications, only the complication with the highest grade was analyzed. Complications exceeding grade IIIa were classified as major complications, which included any complications requiring surgical or radiologic intervention, management in an intensive care unit, or readmission after discharge.

All patients with cirrhosis had histologically confirmed F4 or F3 fibrosis, as determined by a pathologist.[17-19] Postoperative complications were reviewed for 30 days, and postoperative mortality was defined as death within 90 days after surgery. Liver resection was defined according to the Brisbane 2000 system terminology.[20,21] The extent of hepatectomy was defined as major (>3 segments) or minor.

Operative Procedures

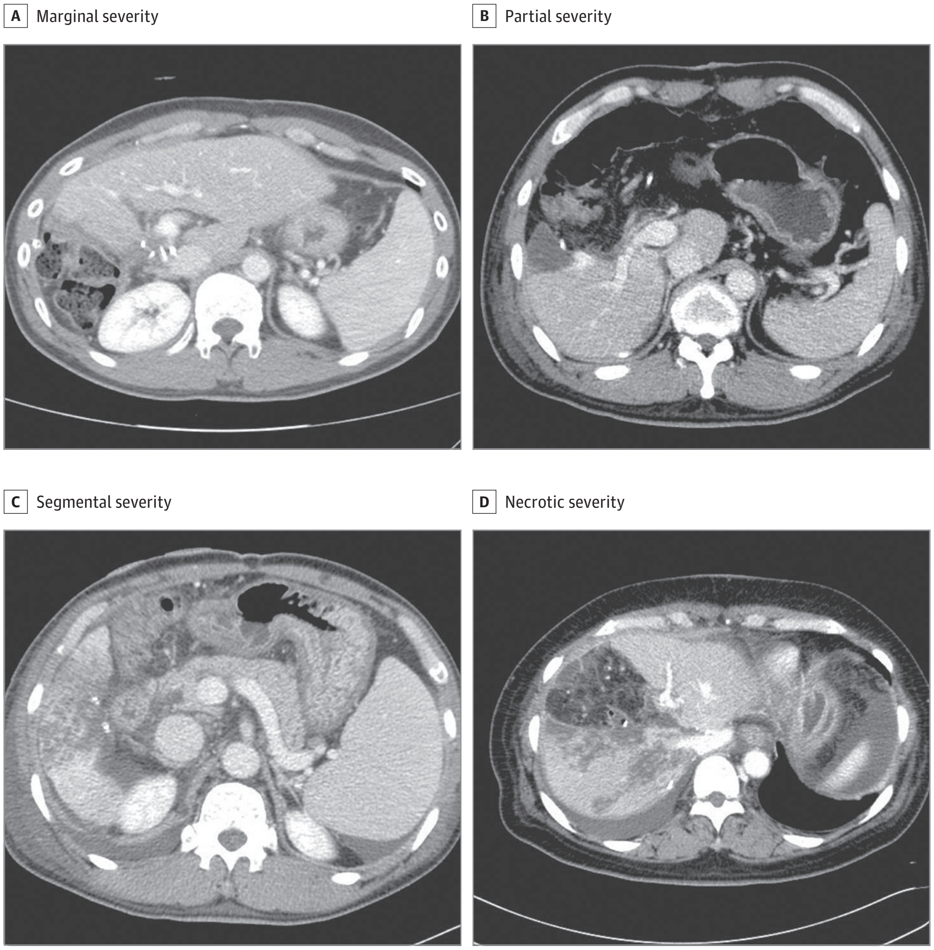
The absence of severe portal hypertension and an adequate hepatic reserve are prerequisites for surgery in patients with HCC. Anatomical hepatectomy was the preferred type of resection if indicated. The type of resection was selected based on the depth of the lesions, the number of lesions, the proximity to major vascular structures, and the hepatic reserve. Major liver resection was considered if the remaining liver function was expected to be adequate for a deep-seated lesion. Liver function was evaluated in terms of the indocyanine green retention rate at 15 minutes and CT volumetry. If the estimated volume of the future remnant liver was insufficient for right hepatectomy, preoperative portal vein embolization was performed.

The indications for laparoscopic liver resection were similar to those for open liver resection in terms of the preoperative assessment of liver function, type of liver resection, and postoperative care.[22] However, laparoscopic approaches were not usually considered in patients with tumors exceeding 5 cm in diameter and tumors invading or adjacent to the main portal pedicle or inferior vena cava, as well as patients with central lesions in the suprahepatic junction adjacent to the major hepatic vein.[23]

Anatomical hepatectomy was defined when the corresponding lobar, sectional, or segmental branch of the Glisson pedicle was resected for hemihepatectomy, sectionectomy, or segmentectomy. Large tumorectomy or wedge resection was defined as NAH regardless of the resected liver volume.

For AH, the resection limits on the liver surface were defined by ischemic demarcation after selective clamping or ligation of the corresponding Glisson pedicle. In right hemihepatectomy, the liver was usually fully mobilized from the inferior vena cava, and multiple small hepatic veins were clipped and divided. The portal pedicles were dissected outside the liver parenchyma, and the portal venous branch, the

Figure 1. Representative Computed Tomographic Images of Remnant Liver Ischemia



Marginal, partial, segmental, and necrotic severities of remnant liver ischemia are shown.

hepatic arterial branch, and the bile duct were isolated and transected. Anatomical major liver resection was occasionally performed using the Glisson pedicle approach. The Pringle maneuver was not used in AH resections but was usually used in NAH resections to reduce bleeding.[24]

CT Protocol and Definition of RLI

To measure RLI, all CT images obtained within 1 month after surgery were evaluated. Contrast-enhanced helical CT scans were obtained using CT scanners with at least 16 detector rows (Brilliance; Philips Healthcare). Patients were given 2 mL of iopromide per kilogram of body weight intravenously at a rate of 3 mL/s via the antecubital vein. Imaging was performed in the portal venous phase with a scan delay of 60 seconds after enhancement in the descending aorta reached 150 Hounsfield units. The CT images were routinely obtained with the patient in the supine position during a single breath hold. Unenhanced and 2 contrast-enhanced–phase CT scans were obtained. Images from all CT phases (noncontrast, arterial, and portal) were analyzed. All images were reviewed on a picture archiving and communication system monitor (PACS 3.0.9.1; Infinitt). The cases were randomly intermixed, and patient identifiers were concealed when the CT images were analyzed.

The usual radiologic criteria for the assessment of liver hypoperfusion and necrosis on CT were adopted.[9,25] In brief, RLI was defined as reduced or absent contrast enhancement during the portal phase, and the severity was graded as marginal, partial, segmental, or necrotic. Necrotic RLI was defined as the absence of parenchymal and vascular contrast enhancement, in addition to the presence of air in the liver tissue (**Figure 1**). Patients were also grouped according to the severity of ischemia as minimal (none or marginal) or severe (partial, segmental, or necrotic). To reduce interobserver and intraobserver variability, the cases were randomly intermixed, and patient identifiers were concealed while CT features were analyzed.

Statistical Analysis

Continuous variables were compared between groups using independent-samples *t* tests, and categorical variables were compared between groups using χ^2 tests. The survival rates were calculated using the Kaplan-Meier method, and the differences between groups were assessed using a log-rank test. A Cox proportional hazards regression model was used for multivariable survival analysis to determine the significance of the predictive variables that were found to be significant on univariate analysis. All analyses were performed using statistical software (SPSS for Windows, version 18.0; SPSS Inc). In all tests, $P < .05$ was considered significant.

Results

Demographic Characteristics and Incidence of RLI

Of the 328 patients who underwent liver resection for HCC, 252 were male and 76 were female. Their ages ranged from 26 to 83 years (mean age, 58.2 years). The predominant etiology of liver disease was hepatitis B (241 patients [73.5%]). According to the definitions, 204 patients (62.2%) exhibited signs of RLI, which was graded as marginal in 106, partial in 63, segmental in 16, and necrotic in 19. Based on these grades, patients were categorized as those with minimal RLI (230 patients [70.1%]) or severe RLI (98 patients [29.9%]). Anatomical hepatectomy was performed in 208 patients (63.4%). The incidence of severe RLI was similar between patients who underwent AH or NAH (29.8% [62 of 208] vs 30.0% [36 of 120], $P = .97$). The incidence of RLI was also similar between patients who underwent major or minor liver resection (33.3% [35 of 105] vs 28.3% [63 of 223], $P = .62$). The types of resection and the incidence of severe RLI are listed in eTable 1 in the Supplement. Severe RLI was most frequent after central bisectionectomy (70.6% [12 of 17]) and was rare after left lateral sectionectomy (11.8% [4 of 34]). All types of resection were associated with RLI, although its incidence varied.

Risk Factors for Severe RLI After Hepatectomy

We analyzed the risk factors for severe RLI after hepatectomy. Univariate analysis showed that a history of transarterial chemoembolization (TACE), Child-Pugh classification, use of the Pringle maneuver, intraoperative transfusion, results of serum albumin and serum alanine aminotransferase, and operative time were risk factors for severe RLI (eTable 2 in the Supplement). The multivariable analysis showed that a history of TACE (odds ratio [OR], 1.77; 95% CI, 1.03-3.04; $P = .04$), use of the Pringle maneuver (OR, 1.96; 95% CI, 1.08-3.58; $P = .03$), and longer operative time (OR, 1.003; 95% CI, 1.002-1.005; $P < .001$) were independent risk factors for severe RLI after hepatectomy (**Table 1**).

Influence of RLI on Morbidity After Hepatectomy

The overall complication rate (43.9% [43 of 98] vs 18.7% [43 of 230], $P < .001$) and the major complication rate (34.7% [34 of 98] vs 12.6% [29 of 230], $P < .001$) were higher in patients with severe RLI than in patients with minimal RLI. Bile leakage after hepatectomy was more frequent in patients with severe RLI (6.1% [6 of 98] vs 1.7% [4 of 230], $P = .04$). The mean (SD) hospital stay was longer in patients with severe RLI than in patients with minimal RLI (15.2 [18.1] vs 9.8 [15.2] days, $P = .002$).

Influence of RLI on Disease Recurrence and Long-term Outcome After Hepatectomy

After a mean follow-up of 44 months (range, 1-125 months), overall survival of the 328 patients was 98.5% (323 of 328) at 1 year, 92.5% (281 of 328) at 3 years, and 89.0% (292 of 328) at 5 years. Disease-free survival was 97.6% (320 of 328) at 1 year, 95.4% (313 of 328) at 3 years, and 85.7% (281 of 328) at 5 years. Patients with severe RLI had higher recurrence rates within 6 months (60.2% [197 of 328] vs 9.6% [31 of 328], $P < .001$) and within 12 months (79.6% [261 of 328] vs 18.7% [61 of 328], $P < .001$) after hepatectomy compared with patients with minimal RLI.

Univariate analysis of all 328 patients showed that RLI, T stage, Child-Pugh classification, open surgery, intraoperative transfusion, the presence of a satellite nodule, gross tumor type, and histologically confirmed cirrhosis were poor prognostic factors for overall patient survival (eTable 3 in the Supplement). Sex, RLI, T stage, previous TACE, AH, the presence of a satellite nodule, microscopic vascular invasion, gross tumor type, and the indocyanine green retention rate at 15 minutes were the prognostic factors for disease-free survival.

The results of the multivariable analysis showed that severe RLI (OR, 6.98; 95% CI, 4.27-11.43; $P < .001$), open surgery (OR, 1.76; 95% CI, 1.10-2.82; $P = .02$), and multinodular confluent or infiltrative gross tumor type (OR, 2.72; 95% CI, 1.13-6.71; $P = .03$) were independent risk factors for overall survival (**Table 2**). A T stage of T3 or T4 (OR, 1.71; 95% CI, 1.07-2.72; $P = .03$), severe RLI (OR, 5.15; 95% CI, 3.62-7.35; $P < .001$), NAH resection (OR, 1.57; 95% CI, 1.13-2.19; $P = .01$), and microscopic vascular invasion (OR, 1.60; 95% CI, 1.13-2.314; $P = .01$) were independent risk factors for disease-free survival.

The median 5-year overall survival was significantly lower in patients with severe RLI than in patients with minimal RLI (31.1% [102 of 328] vs 84.7% [278 of 328], $P < .001$) (**Figure 2**A). Likewise, the median 5-year disease-free survival was significantly lower in patients with severe RLI than in patients with minimal RLI (8.3% [28 of 328] vs 49.1% [161 of 328], $P < .001$) (Figure 2B). Overall survival (85.5% vs 83.7% vs 34.3% vs 30.9% vs 20.2%; $P < .001$) and disease-free survival (54.4% vs 43.1% vs 6.4% vs 0.0% vs 0.0%; $P < .001$) decreased with increasing severity of RLI (**Figure 3**).

Table 1. Multivariable Analysis of the Risk Factors for Remnant Liver Ischemia After Hepatectomy

Variable	OR (95% CI)	*P* Value
Previous TACE	1.77 (1.03-3.04)	.04
Child-Pugh classification B or C	1.57 (0.57-4.35)	.38
Use of the Pringle maneuver	1.96 (1.08-3.58)	.03
Intraoperative transfusion	1.11 (0.60-2.06)	.75
Serum albumin level	0.75 (0.36-1.57)	.45
Serum ALT level	1.004 (0.998-1.011)	.20
Longer operative time	1.003 (1.002-1.005)	<.001

Abbreviations: ALT, alanine aminotransferase; OR, odds ratio; TACE, transarterial chemoembolization.

Discussion

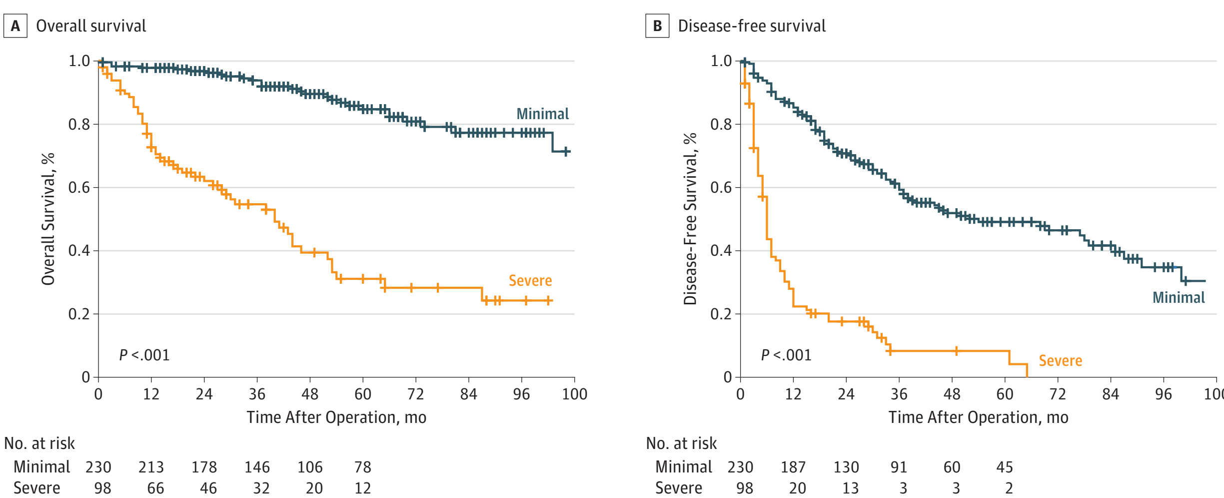
Complete surgical resection is necessary for curative treatment of HCC. However, intrahepatic recurrence is common after HCC resection. The results of several experimental studies have suggested that growth of any residual tumor may be

Table 2. Multivariable Analysis of the Prognostic Factors Associated With Overall Survival and Disease-Free Survival

	Overall Survival		Disease-Free Survival	
Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Male sex	NA	NA	0.84 (0.57-1.25)	.39
ICGR at 15 min >10%	NA	NA	1.25 (0.90-1.73)	.19
Stage T3 or T4	1.66 (0.88-3.13)	.12	1.71 (1.07-2.72)	.03
Previous TACE	NA	NA	0.95 (0.67-1.35)	.78
Child-Pugh classification B or C	1.36 (0.77-2.42)	.29	NA	NA
Severe remnant liver ischemia	6.98 (4.27-11.43)	<.001	5.15 (3.62-7.35)	<.001
Open surgery	1.76 (1.10-2.82)	.02	NA	NA
Intraoperative transfusion	0.98 (0.61-1.58)	.95	NA	NA
Nonanatomical resection	NA	NA	1.57 (1.13-2.19)	.008
Presence of a satellite nodule	1.17 (0.63-2.19)	.62	0.80 (0.51-1.27)	.35
Microscopic vascular invasion	1.16 (0.50-1.42)	.51	1.60 (1.13-2.31)	.008
Multinodular confluent or infiltrative gross tumor type	2.76 (1.13-6.71)	.03	0.81 (0.34-1.94)	.64
Histologically confirmed cirrhosis	1.23 (0.74-2.04)	.43	NA	NA

Abbreviations: ICGR, indocyanine green retention rate; NA, not applicable; OR, odds ratio; TACE, transarterial chemoembolization.

Figure 2. Comparison of Overall Survival and Disease-Free Survival



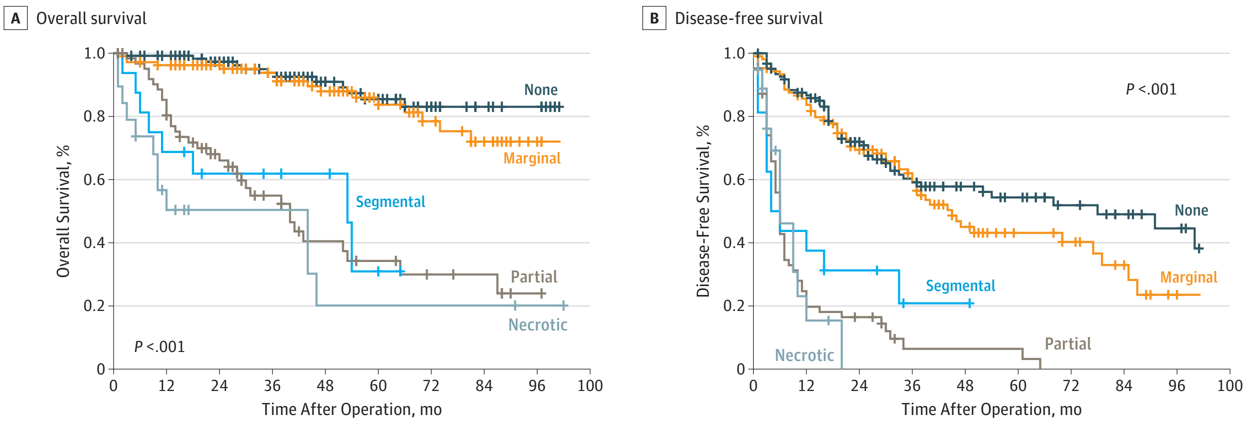
Compared are patients with minimal vs severe remnant liver ischemia after hepatectomy for hepatocellular carcinoma.

enhanced by hepatectomy, although the mechanism responsible for this enhanced tumor growth remains poorly defined.[26] Although there are a few reports of RLI after resection or transplantation,[9] its effect on tumor growth is unclear.

This study showed that some degree of RLI occurred in 60.9% (203 of 328) of patients after hepatectomy and that severe RLI occurred in 29.9% (98 of 328) of patients. Theoretically, RLI should not occur if resection is performed along the exact anatomical plane of the liver. However, severe RLI occurred in 29.8% (62 of 208) of patients after AH, although the incidence of severe RLI was not significantly different between patients who underwent AH or NAH or between patients who underwent major or minor liver resection. Severe RLI was most frequent after central bisectionectomy and rarely occurred after left lateral sectionectomy, suggesting that RLI is correlated with the complexity of hepatectomy. Anatomical liver resection follows the line of ischemic demarcation after specific inflow control, which is the plane of transection. However, imaging studies have demonstrated that the boundaries between the different liver segments are not constant and do not follow flat planes but instead form curved shapes.[27,28] Therefore, the transection plane may not correspond exactly to the intersegmental boundary in many cases of AH. As a consequence, any devascularized parenchymal tissue will remain in situ.

The risk factors for RLI have not yet been reported, to our knowledge. The multivariable analysis conducted in our study showed that previous TACE, use of the Pringle maneuver during hepatectomy, and longer operative time were independent risk factors for severe RLI after hepatectomy. An associa-

Figure 3. Association of the Severity of Postoperative Remnant Liver Ischemia With Overall Survival and Disease-Free Survival



A. No. at risk

	0	12	24	36	48	60
None	124	115	93	76	52	41
Marginal	106	98	85	70	53	35
Partial	63	47	33	21	13	9
Segmental	16	11	8	6	5	1
Necrotic	19	8	5	5	2	2

B. No. at risk

	0	12	24	36	48	60
None	124	101	67	48	35	29
Marginal	106	86	63	43	25	16
Partial	63	12	9	2	2	2
Segmental	16	6	4	1	1	0
Necrotic	19	2	0	0	0	0

Remnant liver ischemia was classified as none, marginal, partial, segmental, or necrotic. A, The classification data are 85.5% vs 83.7% vs 34.3% vs 30.9% vs 20.2% ($P < .001$) for overall survival. B, The data are 54.4% vs 43.1% vs 6.4% vs 0.0% vs 0.0% ($P < .001$) for disease-free survival.

tion between use of the Pringle maneuver and significant ischemic damage has been documented in other studies.[12,29] The Pringle maneuver may reduce intraoperative bleeding during hepatectomy, but it also affects postoperative liver function. Moreover, ischemia or reperfusion injury by an intermittent Pringle maneuver could contribute to RLI. Therefore, the Pringle maneuver should only be used when necessary. Previous TACE was not a risk factor for poor survival but was an independent risk factor for developing RLI. Although TACE is frequently used as an optional treatment for HCC, it may have adverse effects, including ischemia-induced neoangiogenic reactions after an increase in vascular endothelial growth factor secretion.[30]

The rates of complications, especially bile leakage, after hepatectomy were higher in patients with severe RLI. It was previously reported that a complicated surgical procedure is an independent risk factor for bile leakage.[31] Hepatectomies in which the resection plane is close to the major Glisson sheath or the hepatic hilum (eg, right anterior sectionectomy, central bisectionectomy, and total caudate lobectomy) were associated with a high risk of postoperative bile leakage.[32] Such high-risk procedures may affect the major Glisson sheath around the hepatic hilum and decrease flow through the Glisson sheaths.

It is not surprising that patients with severe RLI experienced more complications and that their hospital stay was longer than that in patients with minimal RLI. Patients with severe RLI also had a higher recurrence rate and lower overall and disease-free survival rates after hepatectomy compared with patients with minimal RLI. The severity of RLI was also correlated with worsening prognosis in a stepwise manner. The effects of postoperative complications on long-term survival after hepatectomy have been investigated, but the influence of postoperative RLI on overall and disease-free survival has not been extensively evaluated.[33-36] The mechanisms underlying the worse prognosis of patients with severe RLI are poorly understood. An immunological study[37] showed that liver ischemic injury can lead to lymphocyte dysfunction and various types of stress, including liver ischemia, promote the release of cytokines and chemokines (eg, tumor necrosis factor, interleukin 6, and interleukin 8).[38] If this period of suppressed immunity is prolonged by severe RLI, it may lead to increased growth of occult micrometastases. In the ischemic tissue, angiogenic stimuli may be activated, which can also stimulate tumor growth.[26]

Limitations

In the present study, the negative effect of RLI on the survival rate was higher compared with other well-known risk factors. This influence is possible owing to selection bias because hepatectomy is usually performed in selected patients without a high risk of recurrence or poor liver reserve function, including gross vascular invasion, multiple HCCs, severe cirrhosis, or intractable portal hypertension.

Conclusions

Based on the results of this study, particularly the prognosis of severe RLI and the risk factors for developing RLI, we believe that the overall and disease-free survival rates of patients with HCC undergoing hepatectomy could be improved by reducing the operative time and avoiding the Pringle maneuver. Furthermore, if possible, TACE before hepatectomy is not recommended in resectable HCC. Medical treatment to reduce ischemic injury and immunologic modulation therapy in patients with severe RLI could improve patient survival. Ongoing quality and technical refinements in hepatectomy for HCC should be directed toward the prevention of postoperative RLI. There is still room for improving the overall and disease-free survival rates after hepatectomy in patients with HCC.

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Study concept and design: Cho, Han, J. K. Choi, Kwon.
Acquisition, analysis, or interpretation of data: Y. Choi, Yoon, S. Kim, J. K. Choi, Jang, H. Kim.
Drafting of the manuscript: Cho, S. Kim, J. K. Choi, Kwon.
Critical revision of the manuscript for important intellectual content: Han, Y. Choi, Yoon, Jang, H. Kim.
Statistical analysis: Cho, S. Kim.
Administrative, technical, or material support: Y. Choi, Jang, Kwon, H. Kim.
Study supervision: Han, Yoon.

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