therapy, radiotherapy, proton beam radiotherapy, and/or hyperthermia were performed. Thus, multidisciplinary treatment may promote long-term survival in these patients.

The patients in this study had a history of prolonged exposure to chlorinated organic solvent including DCM and DCP. Such chlorinated organic solvents might have played an important role in the development of cholangiocarcinoma. The current study indicates that chlorinated organic solvent-related cholangiocarcinoma developed in workers at several printing companies in Japan in addition to the prototype cases in Osaka [2]. Therefore, occupational cholangiocarcinoma is not limited to a single printing company in Osaka. The previous and current studies have demonstrated that a portion of cholangiocarcinoma cases appear to be caused by chemical exposure. As previously reported, it is necessary to monitor workers who are exposed to chlorinated organic solvents, and regular health examinations may contribute to early detection of occupational cholangiocarcinoma. Further analyses with larger sample sizes are necessary to clarify the mechanism by which occupational cholangiocarcinoma can arise.

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References

1. Kumagai S, Kurumatani N, Arimoto A, Ichihara G. Cholagiocarcinoma among offset colour proof-printing workers exposed to 1,2-dichloropropane and/or dichloromethane. Occup Environ Med. 2013;70:508–10.
2. Kubo S, Nakanuma Y, Takemura S, Sakata C, Urata Y, Nozawa A, et al. Case series of 17 patients with cholangiocarcinoma among young adult workers of a printing company in Japan. J Hepatobiliary Pancreat Sci. 2014;21:479–88.
3. Ministry of Health, Labour and Welfare. Occupational biliary tract cancer cases in Japan. 2013. http://www.mhlw.go.jp/english/policy/employ-labour/labour-standards/Occupational.html
4. World Health Organization Classifications of Tumours. International Agency for Research on Cancer (IARC). In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumours of the digestive system, 4th edn. Lyon: World Health Organization Classifications of Tumours; 2010. p. 195–278.
5. Zen Y, Sasaki M, Fujii T, et al. Different expression patterns of mucin core proteins and cytokeratins during intrahepatic cholangiocarcinogenesis from biliary intraepithelial neoplasia and intraductal papillary neoplasm of the bile duct—an immunohistochemical study of 110 cases of hepatolithiasis. J Hepatol. 2006;44:350–8.
6. Zen Y, Adsay NV, Bardadin K, Colombari R, Ferrell L, Haga H, et al. Biliary intraepithelial neoplasia: an international interobserver agreement study and proposal for diagnostic criteria. Mod Pathol. 2007;20:701–9.
7. Itatsu K, Zen Y, Ohira S, Ishikawa A, Sato Y, Harada K, et al. Immunohistochemical analysis of the progression of flat and papillary preneoplastic lesions in intrahepatic cholangiocarcinogenesis in hepatolithiasis. Liver Int. 2007;27:1174–84.
8. Nakanuma Y, Hoso M, Sanzen T, Sasaki M. Microstructure and development of the normal and pathologic biliary tract in humans, including blood supply. Micro Res Tech. 1997;38:552–70.
9. Parkin DM, Ohshima H, Srivatanakul P, Vatanasapt V. Cholangiocarcinoma: epidemiology, mechanisms of carcinogenesis and prevention. Cancer Epidemiol Biomarkers Prev. 1993;2:537–44.
10. Shaib Y, El-Serag HB. The epidemiology of cholangiocarcinoma. Semin Liver Dis. 2004;24:115–25.
11. Khan SA, Thomas HC, Davidson BR, Taylor-Robinson SD. Cholangiocarcinoma. Lancet. 2005;366:1303–14.
12. Kubo S, Kinoshita H, Hirohashi K, Hamba H. Hepatolithiasis associated with cholangiocarcinoma. World J Surg. 1995;19:637–41.
13. Yamamoto S, Kubo S, Hai S, Uenishi T, Yamamoto T, Shuto T, et al. Hepatitis C virus infection as a likely etiology of intrahepatic cholangiocarcinoma. Cancer Sci. 2004;95:592–5.
14. IARC (International Agency for Research on Cancer). List of classification by cancer sites with sufficient or limited evidence in humans, volume 1 to 105. 2012. http://monographs.iarc.fr/ENG/Classification/index.php
15. Kubo S, Takemura S, Sakata C, Urata Y, Nishioka T, Nozawa A, et al. Changes in laboratory test results and diagnostic imaging presentation before the detection of occupational cholangiocarcinoma. J Occup Health. 2014; http://dx.doi.org/10.1539/joh.14-0002-CS.
16. Abue M, Suzuki M, Tsukamoto K, Aoki M, Kubo S. A case of intrahepatic cholangiocarcinoma with a printing company service history. Tando. (in press, in Japanese with English abstract).
17. Tomimaru Y, Kobayashi S, Wada H, Hama N, Kawamoto K, Eguchi H, et al. Intrahepatic cholangiocarcinoma in a worker at an offset color proof-printing company: an autopsy case report. Hepatol Res. 2014; doi: 10.1111/hepr.12363.

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Regular Article

Efficacy of postoperative anticoagulation therapy with enoxaparin for portal vein thrombosis after hepatic resection in patients with liver cancer

Yo-ichi Yamashita [a,*], Yuki Bekki [a], Daisuke Imai [a], Toru Ikegami [a], Tomoharu Yoshizumi [a], Tetsuo Ikeda [a], Hirofumi Kawanaka [a], Akihiro Nishie [b], Ken Shirabe [a], Yoshihiko Maehara [a]

[a] Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
[b] Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

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ABSTRACT

Backgrounds: Enoxaparin, low-molecular-weight heparin, has become a routine thromboprophylaxis in general surgery.
Study design: A retrospective cohort study was performed in 281 patients who underwent hepatic resections for liver cancers from 2011 to 2013. These patients were divided into two groups; an enoxaparin (-) group (n = 228) and an enoxaparin (+) group (n = 53). Short-term surgical results including venous thromboembolism (VTE) and portal vein thrombosis (PVT) were compared.
Results: In the enoxaparin (+) group, the patients' age (65 *vs.* 69 years; $p = 0.01$) and BMI (22.9 *vs.* 24.4; $p < 0.01$) were significantly higher. According to the symptomatic VTE, symptomatic pulmonary embolism occurred in one patient (0.4%) in the enoxaparin (-) group, but the complication rate was not significantly different ($p = 0.63$). The complication rate of PVT was significantly lower in the enoxaparin (+) group (10 *vs.* 2%; $p = 0.04$). The independent risk factors for PVT were an operation time ≥ 300 minutes (Odds ratio 6.66) and non-treatment with enoxaparin (Odds ratio 2.49).
Conclusions: Postoperative anticoagulant therapy with enoxaparin could prevent PVT in patients who underwent hepatic resection for liver cancers.

Introduction

Venous thromboembolism (VTE) represented by pulmonary embolism (PE) or deep venous thrombosis (DVT) is a significant cause of morbidity and mortality in patients undergoing gastrointestinal surgery for malignancy, and pharmacologic prophylaxis is important [1,2]. One of the major cautions regarding pharmacologic prophylaxis is the risk of major bleeding complication, but a recent systemic review reported that bleeding requiring a change of care occurs in less than 3% of cases [3]. It is well known that several hemostatic alternations are present in patients with liver disease; primary hemostasis is often impaired due to thrombocytopenia and secondary hemostasis can be hampered by the reduced synthesis of coagulation factors [4].

Meta-analysis of the use of low-molecular-weight heparin (LMWH) such as enoxaparin in the prevention of venous thromboembolism in general surgery clearly demonstrates that LMWH is associated with lower rates of VTE than elastic compression without compromising patient safety, and similar safety and efficacy in preventing VTE to unfractionated heparin (UFH) [5]. In Japan, two randomized studies demonstrated that 20 mg enoxaparin taken twice daily has a good safety profile and is effective for the prevention of VTE in patients undergoing total hip and knee replacement [6] and abdominal or pelvic cancer surgery [7].

LMWH has potential advantageous properties such as two-fold or three-fold longer plasma half-life when compared with commercially available UFH at therapeutic doses, and a 90-95% bioavailability following subcutaneous administration [8]. These advantageous properties of LMWH obviate the need for serum concentration monitoring and enable single or double daily dosing [8]. LMWH also showed decreased interaction with platelets, and a significantly lower complication rate (0/333 patients) of heparin-induced thrombocytopenia (HIT) than UFH (9/332 patients) (0 vs. 2.7%; $p = 0.0018$) [9].

Another possible agents for postoperative anticoagulation therapy against VTE is the synthetic factor Xa inhibitor fondaparinux: a randomized clinical trial reported that postoperative fondaparinux (4.6% for VTE) was at least as effective as LMWH (6.1% for VTE) in patients undergoing high-risk abdominal surgery [10]. For prevention against hemorrhagic complications after liver surgery under anticoagulant therapy, we prefer enoxaparin because it has a neutralizer such as protamine.

* Corresponding author. Tel.: +81 92 642 5469; fax: +81 92 642 5482.
E-mail address: yamashi@surg2.med.kyushu-u.ac.jp (Y. Yamashita).

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Portal vein thrombosis (PVT) is a potentially life-threatening complication that occurs after hepatobiliary pancreatic surgery [11,12]. Theoretically, splanchnic vein thrombosis such as PVT cannot be prevented by mechanical prophylaxis by elastic compression leg stockings and/or intermittent pneumatic compression (IPC). PVT was reported to occur in 12 of 22 (55%) patients who underwent laparoscopic splenectomy [13]. Recently, we reported postoperative PVT after hepatic resection occurred in 19 of 208 patients (9.1%), and closely related to delayed recovery of liver function and delayed liver regeneration [14]. Therefore, making an accurate diagnosis and rapidly initiating treatment for PVT are indispensable. However, there are no detailed reports about prophylaxis against PVT after hepatic resection. Accurate anticoagulation drug therapy could prevent PVT after hepatic resection.

We herein report a series of consecutive patients who underwent hepatic resection for liver cancers with or without postoperative enoxaparin administration. We examined the clinical efficacy of enoxaparin for prevention of VTE and PVT.

Methods

Patients

During the 3 years from 2011 through 2013, 287 hepatic resections for liver cancers were performed at the Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University. Six patients were excluded from this study, 3 because they had low platelet counts $\leq 10 \times 10^4/\mu l$, 2 because they had low preoperative % prothrombin time (PT) $\leq 70\%$, and one who received perioperative UFH for strict anticoagulant therapy because of a mechanical cardiac valve. Therefore, 281 patients were included in this study of the clinical efficacy of anticoagulant therapy with enoxaparin. The pathological diagnoses for liver tumors of patients in this series were as follows: 181 hepatocellular carcinoma (HCC), 25 intrahepatic cholangiocarcinomas (ICC), 2 cystadenocarcinoma, 1 sarcoma, and 72 metastatic liver cancers (59 colorectal liver metastasis). All patients undergoing hepatic resection had an Eastern Cooperative Oncology Group Performance status of 0-2.

Perioperative mechanical thromboprophylaxis by elastic compression legs stockings and IPC were applied to all patients. From 2011 to 2012, an anticoagulant drug was administered according to the judgment of each patient's physician in charge. From April 2013 on, patients were routinely administered enoxaparin. All 281 patients were divided into 2 groups the enoxaparin (-) group ($n = 228$), which also had no anticoagulant drug such as UFH or fondaparinux, and the enoxaparin (+) group ($n = 53$).

Surgical Techniques and Peri-operative Management

Details of our surgical techniques and patient selection criteria for hepatic resection against HCC, ICC, and CRM have been reported previously [15–17]. The key factor concerning the indication for hepatic resection is "remnant liver function" to avoid the fatal postoperative liver failure, and patients with an indocyanine green dye retention rate at 15 minutes (ICGR-15) $\leq 40\%$ were selected for hepatic resection [15]. To stabilize the coagulation and fibrinolysis in hepatic resection, 200 mg nafamostat mesilate was given daily, both during and up to 2 days after operation [18], and preoperative steroid (500 mg methylpredonisolone) administration was routinely performed [19]. Intravenous antibiotics for surgical prophylaxis were also given for 2 days after operation.

In almost all hepatic resections, intermittent Pringle's maneuvers, consisting of clamping the portal triad for 15 minutes and then releasing the clamp for 5-minute intervals, or hemivascular occlusions [20] were applied intraoperatively. The CUSA system (Valley Lab, Boulder, CO, USA) has been used with addition of a VIO soft-coagulation system (ERBE Elektromedizin, Tübingen, Germany) [21]. Hepatic venous backflow control [22], which was typically achieved extrahepatically before dividing the liver, and Belghiti's hanging maneuver [23], where a tape was introduced behind the caudate lobe through the groove between the right and middle hepatic vein, were performed as necessary, especially in major hepatic resection. An intraoperative bile leakage test was routinely performed to prevent the postoperative bile leakage [24]. Laparoscopic hepatic resections in the semiprone position were applied to 37 patients in this series [25]. In patients with open hepatic resections ($n = 219$), an epidural catheter was inserted until the 2nd postoperative day; those with laparoscopic hepatic resection ($n = 62$) did not receive an epidural catheter and were not administered nafamostat mesilate perioperatively.

Evaluations of Morbidity Including PVT

Morbidity was evaluated by Clavien's classification of surgical complications, and those with a score of Grade II or more were defined as positive [26]. Postoperative liver failure and bile leakage after liver surgery were evaluated according to the definitions of International Study Group of Liver Surgery [27,28].

At 5-7 days after hepatic resection, enhanced abdominal computed tomography (CT) was routinely performed for each patient to check for intra-abdominal problems such as an abscess around the resected stump or abnormality of hepatic blood flow. Postoperative PVT was evaluated using this enhanced abdominal CT [14].

Details of Postoperative Administration of Enoxaparin

The schedule of postoperative administration of enoxaparin is summarized in Fig. 1. To prevent hemorrhagic complications, subcutaneous injections of enoxaparin 20 mg were applied twice daily after the % PT had recovered to over 70%. Patients without an epidural catheter were given the 1st dose of enoxaparin within 24-36 hours after hepatic resection [6,7]. To prevent spinal epidural hematoma related to the decrease of anticoagulant proteins just after hepatic resection or the coexistence of liver cirrhosis, patients with epidural anesthesia were given their 1st dose of enoxaparin 12 hours after the removal of the epidural catheter. Twice-daily administration of enoxaparin was continued until discharge for at most 14 consecutive days [6,7,29].

Statistical Analysis

We compared the background characteristics, surgical outcomes, tumor-related factors, and short-term surgical results including symptomatic PE, symptomatic DVT, hemorrhagic complications, and postoperative PVT between the patients in the enoxaparin (+) and the enoxaparin (-) groups. Risk factors for postoperative PVT were analyzed in this series. Continuous variables are expressed as means ± SD and were compared using the Student's *t*-test. Categorical variables were compared using either the χ^2 test or Fisher's exact test, as appropriate. Variables at a P value of less than 0.15 on univariate analysis of risk factors for postoperative PVT were subjected to stepwise logistic regression analysis to identify the independent risk factors. All statistical analyses were performed with JMP® Pro 9.0.2 (SAS Institute Inc., Cary, NC). P-values less than 0.05 were considered significant.

Results

Comparisons of Patients' Background Characteristics, Surgical Outcomes, and Tumor-related Factors

The comparison of the patients' background characteristics, surgical outcomes, and tumor-related factors is shown in Table 1. The mean age (65 *vs.* 69 years; $p = 0.01$) and the mean Body Mass Index (BMI) (22.9 *vs.* 24.4; $p < 0.01$) were significantly higher in the enoxaparin (+) group. The ratio of females was higher in the enoxaparin (+) group

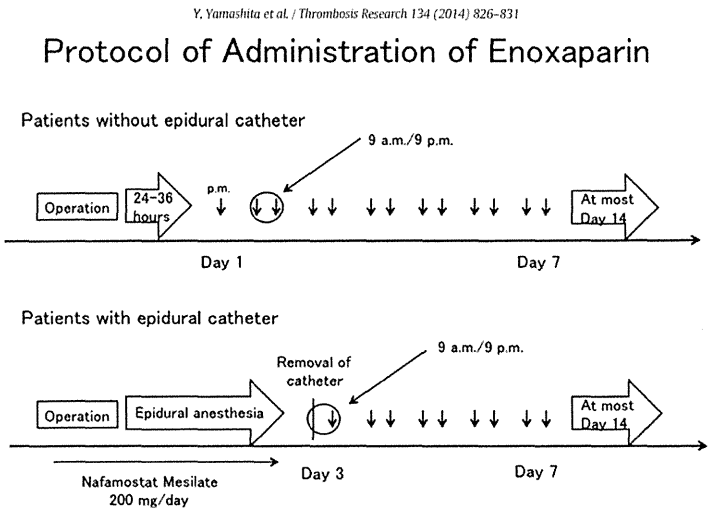

Fig. 1. The schedule of postoperative administration of enoxaparin (20 mg twice daily) is summarized. Patients without epidural catheter received their first dose of enoxaparin within 24-36 hours after hepatic resection. Patients with epidural anesthesia received their first dose of enoxaparin 12 hours after the removal of the epidural catheter. The administration of enoxaparin was continued until discharge for at most 14 consecutive days.

(13 *vs.* 40%), but the difference in ratio was not statistically significant ($p = 0.06$). There was no significant difference in any of the surgical outcomes or tumor-related factors between the two groups. The rates of the existence of histrogical cirrhosis were relatively high in both groups (34 *vs.* 23%; $p = 0.29$).

Comparisons of Short-term Surgical Outcomes

A comparison of short-term surgical outcomes is summarized in Table 2. There was no significant difference in mortality (0 *vs.* 0%; $p = 0.99$), entire morbidity rate (23 *vs.* 30%; $p = 0.29$), and the mean duration of the hospital stay (17 *vs.* 16 days; $p = 0.67$) between the two groups. Symptomatic PE occurred in one patient in the enoxaparin (-) group (0.4%), but the difference of complication rate was not statistically significant ($p = 0.63$). This patient was immediately treated with UFH, and the thrombus in the pulmonary artery disappeared 7 days after UFH treatment. This patient was discharged 25 days after operation with warfarin medication. No patient was complicated by symptomatic DVT in either group. Hemorrhagic complication occurred in one patient in the enoxaparin (-) group (0.4%), and surgical hemostasis with laparotomy was performed. Hemorrhagic complication also occurred in one patient in the enoxaparin (+) group (1.9%). This patient was complicated with a minor hemorrhage from the wound of the surgical drain, and this hemorrhage was immediately stopped by surgical suture under local anesthesia after discontinuance of enoxaparin. The difference in the rate of hemorrhagic complication was not statistically significant ($p = 0.79$). No patients were complicated with HIT in the enoxaparin (+) group.

The complication rate of PVT was significantly higher in the enoxaparin (-) group than that in the enoxaparin (+) group (10 *vs.* 2%; $p = 0.04$). Of course, preoperative abdominal CT confirmed that

Table 1
Background characteristics, surgical outcomes, tumor-related factors.

Variables	Enoxaparin (-) (n = 228)	Enoxaparin (+) (n = 53)	p-Value
Back ground characteristics			
Age	65 ± 12	69 ± 10	0.01
Male/Female	169/29	32/21	0.06
BMI	22.9 ± 3.1	24.4 ± 4	<0.01
DM (%)	47(21%)	9 (17%)	0.37
Total bilirubin (mg/dL)	0.8 ± 0.4	0.8 ± 0.3	0.90
Albumin (%)	4.0 ± 0.5	4.0 ± 0.5	0.94
ICG R15 (%)	13.9 ± 8.9	13.4 ± 7.8	0.72
Child-Pugh: A/B	227/1	53/0	0.27
Liver Damage: A/B	176/52	42:11	0.81
Pit (x 10^4/ĩl)	16.4 ± 6.5	16.7 ± 5.1	0.69
Histological cirrhosis: yes/no	77/151	12/41	0.29
Surgical outcomes			
Surgical time (min)	350 ± 146	343 ± 151	0.74
Surgical blood loss (g)	576 ± 645	593 ± 800	0.87
Transfusion (%)	31 (14%)	4 (8%)	0.23
Major hepatectmy : yes/no	41/181	10/43	0.83
Liver ischemic time (mm)	46 ± 44	41 ± 33	0.45
Laparoscopic procedure (%)	49 (21%)	13 (25%)	0.63
Tumor-related factors			
Tumor size (cm)	3.5 ± 3.1	3.3 ± 2.3	0.73
Number of tumors	1.9 ± 1.5	1.6 ± 1.6	0.35
stage III or IV (%)	95 (45%)	25 (50%)	0.54

Abbreviations:
DM: Diabetis Melitus, ICG R15: indocyanine green retention rate at 15 minutes,

Table 2
Short-term surgical results.

Variables	Enoxaparin (-) (n = 228)	Enoxaparin (+) (n = 53)	p-value
Mortality (%)	0 (0%)	0 (0%)	0.99
Morbidity* (%)	53 (23%)	16 (30%)	0.29
Symptomatic PE (%)	1 (0.4%)	0 (0%)	0.63
Symptomatic DVT (%)	0 (0%)	0 (0%)	0.99
Hemorrhagic complication (%)	1 (0.4%)	1 (1.9%)	0.79
Bile leakage* (%)	8 (4%)	5 (10%)	0.08
Posthepatectomy liver failure* (%)	50 (22%)	8 (16%)	0.31
PVT (%)	23 (10%)	1 (2%)	0.04
Duration of hospital stay (days)	17 ± 15	16 ± 16	0.67

Abbreviations: PE: pulmonary embolism, DVT: deep vein thrombosis, PVT: portal vein thrombosis.
* Morbidity: Clavien-Dindo Grade II or more.
* Bile leakage and posthepatectomy liver failure: Defined by International Study Group of Liver Surgery.

there was no PVT in all patients. The typical cases of postoperative PVT are shown in Fig. 2. In the case shown in Fig. 2A, a partial thrombus of portal vein at the umbilical portion was found after anterior segmentectomy for HCC without the administration of enoxaparin. In the case shown in Fig. 2B, a partial thrombus of the portal vein at the main trunk was found after right lobectomy for HCC without the administration of enoxaparin. Both patients were immediately treated by UFH, and the medication was changed to warfarin after the confirming by enhanced abdominal CT that the PVT had not propagated around 7-14 days after treatment. The PVT disappeared in both patients at enhanced abdominal CT 3 months after operation, at which point warfarin administration was stopped.

Risk Factors for Postoperative PVT

A comparison between the PVT (-) group (n = 257) and the PVT (+) group (n = 24) in terms of patients' background, surgical outcomes, tumor-related factors, and other factors is summarized in Table 3. There were no significant differences in patients' background characteristics between the two groups. The mean age was slightly higher in the PVT (+) group than that in the PVT (-) group (66 *vs.* 67 years), but not significantly (p = 0.16). Concerning the surgical outcomes, the mean surgical time was significantly longer in the PVT (+) group than in the PVT (-) group (342 *vs.* 421 minutes; p = 0.01). The mean liver ischemic time was longer in the PVT (+) group than in the PVT (-) group, but not significantly (43 *vs.* 65 minutes; p = 0.06). Concerning tumor-related factors, HCC-positive rate was significantly higher in the PVT (+) group than in the PVT (-) group (62 *vs.* 88%; p = 0.04). The ratio of patients receiving enoxaparin was significantly lower in the PVT (+) group than in the PVT (-) group (20 *vs.* 4%; p = 0.03).

Independent Risk Factor for Postoperative PVT

The results of the stepwise logistic regression analysis are summarized in Table 4. Surgical time ≥ 360 minutes (odds ratio 6.66, p < 0.01) and non-treatment with enoxaparin (odds ratio 2.49, p = 0.03) were revealed to be independent risk factors for postoperative PVT in our series.

Table 3
Risk factors for postoperative PVT.

Variables	PVT (-) (n = 257)	PVT (+) (n = 24)	p-Value
Back ground characteristics			
Age	66 ± 12	67 ± 11	0.16
Male/Female	185/72	16/8	0.45
BMI	23.2 ± 3.3	23.2 ± 3.6	0.53
DM (%)	53(21%)	3 (13%)	0.37
Total bilirubin (mg/dL)	0.8 ± 0.4	0.7 ± 0.3	0.40
Albumin (%)	4.0 ± 0.5	4.0 ± 0.6	0.88
ICG R15 (%)	13.9 ± 8.8	13.8 ± 8.3	0.64
Child-Pugh: A/B	256/1	24/0	0.88
Liver Damage: A/B	197/60	20/4	0.48
Pit (x 10^4/il)	16.4 ± 6.3	17.1 ± 5.3	0.52
Histological cirrhosis: yes/no	78/179	11/13	0.21
Surgical outcomes			
Surgical time (min)	342 ± 146	421 ± 137	0.01
Surgical blood loss (g)	581 ± 693	599 ± 484	0.32
Transfusion (%)	29(11%)	6 (25%)	0.16
Major hepatectmy : yes/no	45/212	6/18	0.46
Liver ischemic time (mm)	43 ± 41	65 ± 56	0.06
Laparoscopic procedure (%)	59 (23%)	3 (13%)	0.32
Tumor-related factors			
Tumor size (cm)	3.5 ± 3.0	3.7 ± 2.5	0.20
Number of tumors	1.9 ± 1.6	1.6 ± 1.0	0.40
HCC (+) (%)	160 (62%)	21 (88%)	0.04
Other factor			
Enoxaparin (+) (%)	52 (20%)	1 (4%)	0.03

Abbreviations:
PVT; Portal vein thrombosis. DM: Diabetis Melitus, ICG R15; indocyanine green retention rate at 15 minutes.

Discussion

With regard to VTE chemoprophylaxis, surgeons have always needed to balance the risk of peri-operative bleeding complications against the risk of VTE. Liver surgeons have historically withheld peri-operative VTE chemoprophylaxis mainly as a result of the perceived risk of perioperative bleeding, with the hypothesis that transient liver dysfunction after a hepatic resection produces anticoagulation effects. We previously reported that recent advances in surgical techniques in liver surgery accounted for a decrease in the peri-operative bleeding complication rate to as low as 1% [30]. Tzeng CW et al reported that 30-day VTE occurred 163 of 5651 patients (2.9%) with hepatic resection, and was strongly associated with mortality [31]. Therefore, recent years

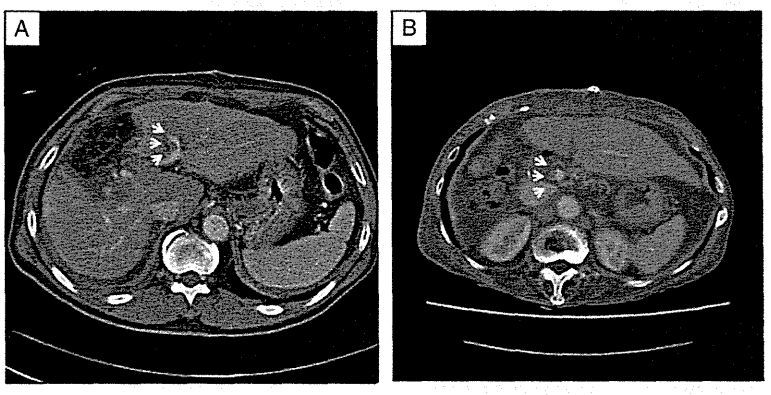

Fig. 2. Typical cases of postoperative PVT after hepatic resection. In Fig. 2A, a partial thrombus of portal vein at the umbilical portion was found after anterior segmentectomy for HCC without the administration of enoxaparin. In Fig. 2B, a partial thrombus of the portal vein at the main trunk was found after right lobectomy for HCC without the administration of enoxaparin.

Table 4
Independent risk factors for PVT.

Variables	Coefficient/SE	Odds ratio	p-value
Surgical time ≥ 360 min.	2.58	6.66	<0.01
Enoxaparin (-)	1.58	2.49	0.03
HCC (+)	1.32	1.68	0.26
Liver ischemic time ≥ 45 min.	0.73	1.35	0.57

have seen a keen interest in chemoprophylaxis as a possible method of reducing postoperative VTE without increasing the risk of bleeding complications in liver surgery.

According to the clinical results of efficacies and risks in Japanese patients (6.7), enoxaparin 20 mg twice daily is the standard regimen for VTE chemoprophylaxis after surgery under the national health insurance in Japan. We applied this regimen for patients who underwent hepatic resections as described in Fig. 1. To minimize the risk of spinal epidural hematoma, we did not concomitantly administrate enoxaparin to patients with epidural anesthesia. VTE and PVT formation would start during operation, however, it is important to start anticoagulant drugs as early as possible. According to the recommendation of Rosencher et al, the removal of the epidural catheter should be over "X + 2Y" hours (X; Tmax, Y; t1/2) after the last application of anticoagulant drugs, and the next application of anticoagulant drugs should be over "8-Tmax" hours later [32]. Concerning the enoxaparin, Tmax is 2.3 hours, t1/2 is 3.2 hours, X + 2Y = 8.7 hours, and 8-X = 5.7 hours [33]. This recommendation should be useful to enable earlier administration of enoxaparin during epidural anesthesia in patients who undergo hepatic resections.

To minimize the risk of bleeding complication, we administered enoxaparin to patients with %PT ≥ 70%. The prolongation of PT demonstrates the decrease of procoagulant proteins, however, cirrhotic patients with low %PT sometimes develop arterial, portal or venous thrombosis which is partly attributed to hypercoagulation [34]. In addition, increasing clinical evidence suggests that the prolonged PT should not be a reason to withhold anticoagulation in patients with cirrhosis or after hepatic resection [35–40]. Despite a postoperative prolongation of the PT, a thrombotic risk in patients after hepatic resection would exist because of a concomitant decline in pro- and anticoagulants which is not reflected in the PT which only assesses pro-coagulant proteins. Therefore, our patients' exclusion criteria of %PT ≤ 70% should be examined further in a detailed clinical study.

Ejaz A et al reported that the preventative effect of UFH for postoperative VTE in hepatic resections was negative in both 90-day DVT (2.1 *vs.* 3.7%; p = 0.33) and 90-day PE (2.1 *vs.* 1,8%; p = 0.81) [41]. Also LMWH (nadroparin or enoxaparin) was previously observed to have no significant preventative effects against postoperative VTE in patients who underwent resections of HCC developed from cirrhosis (1.4 *vs.* 0.6%; p = 0.53) [42]. In our series, the preventative effect of enoxaparin for postoperative symptomatic PE and DVT after hepatic resection was not significant. However, the complication rate of PVT after hepatic resection was significantly decreased by enoxaparin administration (10 *vs.* 2%; p = 0.04).

Postoperative PVT is a potentially life-threatening complication that occurs after hepatobiliary pancreatic surgery, especially in liver transplantation or pancreaticoduodenectomy [11]. In our series, postoperative PVT as evaluated by enhanced abdominal CT on postoperative day 5-7 was evident in 24 patients (8.5%). This is the first report concerning the preventative effects of anticoagulant drugs for PVT after hepatic resection. Theoretically, PVT cannot be prevented by mechanical prophylaxis by elastic compression leg stocking and IPC; therefore, the chemical prophylaxis for PVT is essential. PVT after hepatic resection especially in cirrhotic patients would lead to postoperative liver failure [14], intractable ascites, or gastrointestinal variceal hemorrhage; therefore, the prevention and early diagnosis of, and rapid initiation of treatment for PVT is very important in patients undergoing hepatic resection.

In our series, the independent risk factors for PVT after hepatic resection were surgical time ≥ 360 minutes (odds ratio 6.66, p < 0.01) and non-treatment with enoxaparin (odds ratio 2.49, p = 0.03). The possible causes for the formation of postoperative PVT are stasis of blood flow in portal vein, a hypercoaguable state, and endothelial injury. The significantly longer surgical time in PVT (+) patients would relate to longer liver ischemic time, longer venous stasis time caused by mobilization of liver, and longer and more frequent tractions of the portal vein. These procedures cause stasis of blood flow in the portal vein or endothelial injury of the portal vein. Patients with HCC and cirrhosis are more likely to be in a hypercoagulable state compared to those with other disease entities. Several reports have already mentioned the safety and efficacy of LMWH including enoxaparin for PVT in patients with advanced cirrhosis [43–45], and our new finding of the preventive effect of enoxaparin for postoperative PVT after hepatic resection would support the usefulness of enoxaparin for treatment against PVT.

In conclusion, postoperative anticoagulant therapy with enoxaparin 20 mg twice daily could prevent postoperative PVT in patients undergoing hepatic resection for liver cancers without increase of bleeding complication. The inclusion/exclusion criteria, and the protocol of administering enoxaparin, especially for patients with epidural anesthesia, should be further investigated to achieve the best efficacy of enoxaparin as a prophylactic measure against postoperative VTE in patients who have undergone hepatic resection.

Conflict of Interest

We declare that we have no conflict of interest to disclose.

References

[1] Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:338S–400S.
[2] Leonardi MJ, McGory ML, Ko CY. A systematic review of deep venous thrombosis prophylaxis in cancer patients: implications for improving quality. Ann Surg Oncol 2007;14:929–36.
[3] Leonardi MJ, McGory ML, Ko CY. The rate of bleeding complications after pharmacologic deep venous thrombosis prophylaxis: a systematic review of 33 randomized controlled trials. Arch Surg 2006;141:790–7 [discussion 797–9].
[4] Lisman T, Leebeek FW, Hemostatic alterations in liver disease: a review on pathophysiology, clinical consequences, and treatment. Dig Surg 2007;24:250–8.
[5] Mismetti P, Laporte S, Darmon JY, Buchmüller A, Decousus H. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. Br J Surg 2001;88:913–30.
[6] Fuji T, Ochi T, Niwa S, Fujita S. Prevention of postoperative venous thromboembolism in Japanese patients undergoing total hip or knee arthroplasty: two randomized, double-blind, placebo-controlled studies with three dosage regimens of enoxaparin. J Orthop Sci 2008;13:442–51.
[7] Sakon M, Kobayashi T, Shimazui T. Efficacy and safety of enoxaparin in Japanese patients undergoing curative abdominal or pelvic cancer surgery: results from a multicenter, randomized, open-label study. Thromb Res 2010;125:e65–70.
[8] Weitz JI. Low-molecular-weight heparins. N Engl J Med 1997;337:688–98.
[9] Warkentin TE, Levine MN, Hirsh J, Horsewood P, Roberts RS, Gent M, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 1995;332:1330–5.
[10] Agnelli G, Bergqvist D, Cohen AT, Gallus AS, Gent M. PEGASUS investigators. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. Br J Surg 2005;92:1212–20.
[11] Thomas RM, Ahmad SA. Management of acute post-operative portal venous thrombosis. J Gastrointest Surg 2010;14:570–7.
[12] Miura K, Sato Y, Nakatsuka H, Yamamoto S, Oya H, Hara Y, et al. Catheter-directed continuous thrombolysis following aspiration thrombectomy via the ileocolic route for acute portal venous thrombosis: report of two cases. Surg Today 2013;43:1310–5.
[13] Ikeda M, Sekimoto M, Takiguchi S, Kubota M, Ikenaga M, Yamamoto H, et al. High incidence of thrombosis of the portal venous system after laparoscopic splenectomy: a prospective study with contrast-enhanced CT scan. Ann Surg 2005;241:208–16.
[14] Yoshiya S, Shirabe K, Nakagawara H, Soejima Y, Yoshizumi T, Ikegami T, et al. Portal Vein Thrombosis After Hepatectomy. World J Surg 2014;38:1491–7.
[15] Yamashita Y, Taketomi A, Itoh S, Kitagawa D, Kayashima H, Harimoto N, et al. Long-term favorable results of limited hepatic resections for patients with hepatocellular carcinoma: 20 Years of Experience. J Am Coll Surg 2007;205:19–26.
[16] Yamashita Y, Taketomi A, Morita K, Fukuhara T, Ueda S, Sanefuji K, et al. The impact of surgical treatment and poor prognostic factors for patients with intrahepatic

cholangiocarcinoma: retrospective analysis of 60 patients. Anticancer Res 2008;28:2353–9.
[17] Yamashita Y, Adachi E, Toh Y, Ohgaki K, Ikeda O, Oki E, et al. Risk factors for early recurrence after curative hepatectomy for colorectal liver metastases. Surg Today 2011;41:526–32.
[18] Shimada M, Matsumata T, Shirabe K, Kamakura T, Taketomi A, Sugimachi K. Effect of nafamostat mesilate on coagulation and fibrinolysis in hepatic resection. J Am Coll Surg 1994;178:498–502.
[19] Yamashita Y, Shimada M, Hamatsu T, Rikimaru T, Tanaka S, Shirabe K, et al. Effects of preoperative steroid administration on surgical stress in hepatic resection: prospective randomized trial. Arch Surg 2001;136:328–33.
[20] Chau GY, Lui WY, King KL, Wu CW. Evaluation of effect of hemihepatic vascular occlusion and the Pringle maneuver during hepatic resection for patients with hepatocellular carcinoma and impaired liver function. World J Surg 2005;29:1374–83.
[21] Hirokawa F, Hayashi M, Miyamoto Y, Iwamoto M, Tsunematsu I, Asakuma M, et al. A novel method using the VIO soft-coagulation system for liver resection. Surgery 2011;149:438–44.
[22] Tsujita E, Taketomi A, Kitagawa D, Itoh S, Harimoto N, Gion T, et al. Selective hepatic vascular exclusion for the hepatic resection of HCC. Hepatogastroenterology 2007;54:527–30.
[23] Belghiti J, Guevara OA, Noun R, Saldinger PF, Kianmanesh R. Liver hanging maneuver: a safe approach to right hepatectomy without liver mobilization. J Am Coll Surg 2001;193:109–11.
[24] Yamashita Y, Hamatsu T, Rikimaru T, Tanaka S, Shirabe K, Shimada M, et al. Bile leakage after hepatic resection. Ann Surg 2001;233:45–50.
[25] Ikeda T, Mano Y, Morita K, Hashimoto N, Kayashima H, Masuda A, et al. Pure laparoscopic hepatectomy in semiprone position for right hepatic major resection. J Hepatobiliary Pancreat Sci 2013;20:145–50.
[26] Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187–96.
[27] Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 2011;149:713–24.
[28] Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. Surgery 2011;149:680–8.
[29] Sikorski JM, Hampson WG, Staddon GE. The natural history and aetiology of deep vein thrombosis after total hip replacement. J Bone Joint Surg Br 1981;63:171–7.
[30] Taketomi A, Kitagawa D, Itoh S, Harimoto N, Yamashita Y, Gion T, et al. Trends in morbidity and mortality after hepatic resection for hepatocellular carcinoma: an institute's experience with 625 patients. J Am Coll Surg 2007;204:580–7.
[31] Tzeng CW, Katz MH, Fleming JB, Pisters PW, Lee JE, Abdalla EK, et al. Risk of venous thromboembolism outweighs post-hepatectomy bleeding complications: analysis of 5651 National Surgical Quality Improvement Program patients. HPB (Oxford) 2012;14:506–13.
[32] Rosencher N, Bonnet MP, Sessler DI. Selected new antithrombotic agents and neuraxial anaesthesia for major orthopaedic surgery: management strategies. Anaesthesia 2007;62:1154–60.
[33] Barrowcliffe TE, Johson EA, Thmas DP. Low Molecular Weight Heparin. New York: Wiley; 1992.
[34] Lisman T, Leebeek FW, Hemostatic alterations in liver disease: a review on pathophysiology, clinical consequences, and treatment. Dig Surg 2007;2:250–8.
[35] Tripodi A, Caldwell SH, Hoffman M, Trotter JF, Sanyal AJ. Review article: the prothrombin time test as a measure of bleeding risk and prognosis in liver disease. Aliment Pharmacol Ther 2007;26:141–8.
[36] Louis SG, Barton JS, Riha GM, Orloff SL, Sheppard BC, Pommier RF, et al. The international normalized ratio overestimates coagulopathy in patients after major hepatectomy. Am J Surg 2014;207:723–7 [discussion 727].
[37] Nathan H, Weiss MJ, Solf GA, Stempel M, Dematteo RP, Allen PJ, et al. Pharmacologic prophylaxis, postoperative INR, and risk of venous thromboembolism after hepatectomy. J Gastrointest Surg 2014;18:295–302 [discussion 302–3].
[38] De Pietri L, Montalti R, Begliomini B, Scaglioni G, Marconi G, Reggiani A, et al. Thromboelastographic changes in liver and pancreatic cancer surgery: hypercoagulability, hypocoagulability or normocoagulability? Eur J Anaesthesiol 2010;27:608–16.
[39] Weeder PD, Porte RJ, Lisman T. Hemostasis in Liver Disease: Implications of New Concepts for Perioperative Management. Transfus Med Rev Mar. 15 2014;28:107–13.
[40] Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med 2011;365:147–56.
[41] Ejaz A, Spolverato G, Kim Y, Lucas DL, Lau B, Weiss M, et al. Defining Incidence and Risk Factors of Venous Thromboemolism after Hepatectomy. J Gastrointest Surg 2014;18:1116–24.
[42] Vivarelli M, Zanello M, Zanfi C, Cucchetti A, Ravaioli M, Del Gaudio M, et al. Prophylaxis for venous thromboembolism after resection of hepatocellular carcinoma on cirrhosis: is it necessary? World J Gastroenterol 2010;16:2146–50.
[43] Amitrano L, Guardascione MA, Menchise A, Martino R, Scaglione M, Giovine S, et al. Safety and efficacy of anticoagulation therapy with low molecular weight heparin for portal vein thrombosis in patients with liver cirrhosis. J Clin Gastroenterol 2010;44:448–51.
[44] Villa E, Cammà C, Marietta M, Luongo M, Critelli R, Colopi S, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology 2012;143:1253–60.
[45] Congly SE, Lee SS. Portal vein thrombosis: should anticoagulation be used? Curr Gastroenterol Rep 2013;15:306.

Original Research

$T_1\rho$ Relaxation of the Liver: A Potential Biomarker of Liver Function

Yukihisa Takayama, MD, PhD,[1] Akihiro Nishie, MD, PhD,[2*] Yoshiki Asayama, MD, PhD,[2] Yasuhiro Ushijima, MD, PhD,[2] Daisuke Okamoto, MD, PhD,[2] Nobuhiro Fujita, MD, PhD,[2] Koichiro Morita, MD,[2] Ken Shirabe, MD, PhD,[3] Kazuhiro Kotoh, MD, PhD,[4] Yuichiro Kubo, MD,[5] Tomoyuki Okuaki, MSc,[6] and Hiroshi Honda, MD, PhD[2]

Purpose: To investigate the diagnostic potential of $T_1\rho$ relaxation for assessing liver function, liver fibrosis, or liver necroinflammation in patients with chronic liver disease (CLD).

Materials and Methods: We obtained $T_1\rho$ maps of the liver for 53 patients with or without CLD. We measured the $T_1\rho$ values of the liver and correlated them with the results of laboratory tests and histological examinations. Pearson's correlation coefficients (r) were calculated between the $T_1\rho$ values and blood serum parameters including the retention rates at 15 minutes after an injection of indocyanine green (ICG-R15). Spearman's rank correlation coefficients were calculated between the $T_1\rho$ values and the scores of liver fibrosis or liver necroinflammation.

Results: The $T_1\rho$ values showed significant positive correlations with the serum levels of total bilirubin ($r=0.31$, $P<0.05$), direct bilirubin ($r=0.32$, $P<0.05$), and ICG-R15 ($r=0.46$, $P<0.05$), and significant negative correlations with the serum levels of albumin ($r=-0.33$, $P<0.05$) and γ-glutamyl transpeptidase ($r=-0.28$, $P<0.05$). However, there were no significant correlations between the $T_1\rho$ value and the scores of liver fibrosis ($P=0.95$) or liver necroinflammation ($P=0.86$).

Conclusion: $T_1\rho$ relaxation has potential as a biomarker of liver function in patients with CLD. However, it may not be suitable to estimate liver fibrosis or liver necroinflammation.

Key Words: $T_1\rho$ (T_1rho); liver function; liver fibrosis; liver necroinflammation; chronic liver disease; MRI
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CHRONIC LIVER DISEASE (CLD) is a major worldwide public health problem, and the incidence of CLD is expected to increase due to the aging of the population in many countries and the growing epidemics of obesity, nonalcoholic fatty liver disease or steatohepatitis, alcoholic liver disease, and chronic viral hepatitis (1,2). The progression of liver fibrosis worsens the symptoms related to liver malfunctions (such as jaundice, edema, and bleeding), and it increases the risk of hepatocellular carcinoma (3,4). A needle biopsy is performed for the diagnosis and staging of hepatic fibrosis, but it is an invasive procedure (5,6). Among the latest imaging techniques, magnetic resonance (MR) elastography and ultrasound elastrography are used for the noninvasive assessment of the stage of liver fibrosis (5–7). However, MR elastography requires specific hardware and software, and ultrasound elastography is operator-dependent and has low reproducibility (6–9). A simpler and more objective technique to noninvasively assess the stage of liver fibrosis is clinically desirable.

"$T_1\rho$ relaxation" represents the spin-lattice relaxation time constant in the rotating frame in MR imaging (MRI), and it determines the decay of transverse magnetization in the presence of a "spin-lock" radiofrequency (RF) field (10,11). $T_1\rho$ relaxation is sensitive to macromolecule-water interactions in protein solutions and in biological tissues (12–15). $T_1\rho$ relaxation may serve as a biomarker for biological processes associated with alterations in the macromolecular content properties of tissues (10,11,16–20).

Liver fibrosis, a common feature of liver cirrhosis (LC), involves the accumulation of collagen,

[1]Department of Radiology Informatics and Network, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.
[2]Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.
[3]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Fukuoka, Japan.
[4]Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.
[5]Department of Anatomic Pathology, Pathological Sciences, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.
[6]Philips Electronics Japan, Tokyo, Japan.
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*Address reprint requests to: A.N., Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.
E-mail: anishie@radiol.med.kyushu-u.ac.jp
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Table 1
Characteristics of the 53 Patients

Patients with chronic liver disease	$n=37$
Background of chronic liver disease	
Chronic viral hepatitis B	4
Chronic viral hepatitis C	21
Chronic viral hepatitis B and C	1
Alcohol abuse	1
Primary biliary cirrhosis	1
Nonalcoholic steatohepatitis	1
Chronic liver disease without hepatitis virus infection or alcohol abuse	8
Child-Pugh Classification	
Grade A	30
Grade B	7
Patients without chronic liver disease	**$n=16$**
Without metastatic disease	*3*
With metastatic disease	*13*
Primary site of metastatic tumors	
Gastric gastrointestinal stromal tumor	1
Pancreas cancer	1
Ascending colon cancer	1
Sigmoid colon cancer	1
Rectal cancer	9

proteoglycans, and other macromolecules in the extracellular matrix (1,21,22), and thus $T_1\rho$ relaxation could be a candidate biomarker for liver fibrosis. With a biliary duct ligation (BDL)-induced liver fibrosis rat model, Wang et al (23) reported that $T_1\rho$ relaxation was used successfully to detect early liver fibrosis, and that the liver collagen content was correlated with the degree of elevation of the $T_1\rho$ relaxation. Thus, $T_1\rho$ relaxation can potentially be used noninvasively for detecting and assigning a grade to liver fibrosis (23). Contrarily, Sirlin (24) suggested that $T_1\rho$ relaxation of the liver does not directly reflect liver fibrosis because of the discrepancy between the mechanism of $T_1\rho$ relaxation and the alterations in the extracellular matrix, which is composed of fibril-forming collagen as well as cellular matrices in accord with the progression of liver injury.

Two other recent clinical studies also found that $T_1\rho$ relaxation is useful for the differentiation of LC from normal liver; the $T_1\rho$ values of the liver were prolonged related to the progression of Child–Pugh grade (25,26). We therefore speculated that $T_1\rho$ relaxation could be useful for assessing the severity of liver function rather than the grade of liver fibrosis. The purpose of the present study was to investigate the diagnostic potential of $T_1\rho$ relaxation of the liver for assessing liver function, liver fibrosis or necroinflammation in patients with or without CLD.

MATERIALS AND METHODS

Subjects

This was a retrospective study approved by our Institutional Review Board; it complied with the standards of the Ethics Committee. From May 2012 to July 2013, 144 patients underwent MRI of the liver at our institution because liver tumor(s) were suspected due to CLD or malignant disease in other organs. The criterion for the inclusion of a patient was that serum blood and indocyanine green (ICG) clearance tests were performed 1 week before or after the patient's MRI. Thirteen of the 144 patients had a history of partial hepatectomy or percutaneous RF ablation, and they were included in the study. Ninety-one of the 144 patients were excluded from the study: 26 of the 91 patients had a history of transarterial chemoembolization or infusion chemotherapy before the MRI, and the other 65 patients did not undergo serum blood and/or ICG clearance tests. There were no patients with acute liver injury caused by viral infection, drug, or ischemia. Finally, a total of 53 patients (35 men, 18 women; mean age, 65.2 years; age range, 35–86 years) were enrolled. The patients' characteristics are shown in Table 1.

Imaging Protocols

The MRI was performed on a clinical 3.0T MR system (Achieva TX, Philips Healthcare, Best, The Netherlands) using a 32-channel torso-cardiac phased-array coil. An axial $T_1\rho$ map was generated from 3D $T_1\rho$-prepared images which were scanned during a breath-hold using the turbo field echo and parallel imaging techniques. The imaging parameters were as follows: repetition time = 2.1 msec, echo time = 0.98 msec, field of view = 360 × 306 mm, matrix = 256 × 205, slice thickness = 10 mm, slice gap = 0 mm, number of slices = 3, number of acquisitions = 1, time of spin lock (TSL) = 1/20/40/60 msec, spin-lock pulse frequency = 500 Hz, shot interval = 5000 msec, scan time of $T_1\rho$-prepared image with each TSL = 11.7 seconds. The number of slices was limited to three because of the breath-hold acquisition. Three slices were set at the level of the hepatic hilum.

The longitudinal magnetization was prepared by a nonselective RF pulse train: 90°(x) - TSL/2 (+y) - TSL/2 (-y) - −90°(−x) (27). A spin lock pulse frequency of 500 Hz was set, referring to the literature (21,23,28). The TSL of 60 msec was the maximum length of TSL complying with the limitation of the specific absorption rate (SAR). The shot interval of 5000 msec was set between each slice acquisition, and the *k*-space was filled using low-to-high ordering to avoid affecting the $T_1\rho$ contrast for the next image scan as well as the lower SAR level. $T_1\rho$ mapping was produced with Philips Research Integrated Development Environment (PRIDE) software written in Interactive Data Language (IDL 6.3, ITT, Boulder, CO) on a pixel-by-pixel basis using a monoexponential decay model: $S_{TSL} = S_0 * \exp(-TSL/T_1\rho)$, where S_{TSL} is the signal intensity in $T_1\rho$-prepared images with a certain TSL, and S_0 is that with a TSL of 0 msec. The monoexponential decay model was based on Levenberg–Marquardt algorithm, a previously reported method (29).

Patients' Clinical Data

Laboratory Tests

Blood serum parameters related to liver function, ie, total protein (TP), albumin (Alb), total bilirubin (TB),

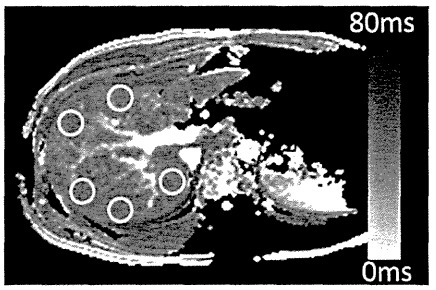

Figure 1. $T_{1\rho}$ measurement on the map. The $T_{1\rho}$ values were measured by placing ROIs as large as possible on the liver parenchyma while avoiding vessels, tumors, and artifacts. Five round or oval ROIs were placed in the right lobe or segment IV of the left lobe.

direct bilirubin (DB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γGTP), total cholesterol (Tcho), serum triglyceride (TG), glucose (Glu), prothrombin activity (PT-INR), and platelet count (Plt) were measured. The ICG clearance tests were performed using 0.5 mg/kg body weight Diagnogreen (Daiichi Pharmaceutical, Tokyo, Japan). Blood samples were collected before and 15 minutes after the Diagnogreen administration, and the retention rates at 15 minutes after the injection (ICG-R15s) were measured. The normal range of ICG-R15s is less than 15%.

Histological Assessments

Forty-two of the 53 patients underwent surgery ($n=39$) or needle biopsy ($n=3$). One pathologist (Y.K.) with 4 years of experience who was unaware of the imaging data reviewed the hematoxylin-eosin-stained glass slides of each patient and referred to the official pathological report to determine the histological findings of the liver parenchyma. When the results were discordant, another experienced pathologist (S.A.) with 14 years of experience was consulted.

The degree of liver fibrosis was classified into five groups according to the New Inuyama Classification: F0 (no fibrosis), F1 (fibrous portal expansion), F2 (bridging fibrosis), F3 (bridging fibrosis with architectural distortion), and F4 (liver cirrhosis) (30,31). Similarly, the grade of necroinflammatory activity was scored as A0 (no necroinflammatory reaction), A1 (mild), A2 (moderate), or A3 (severe) (30,31). The mean interval between the liver MRI and the liver specimen sampling was 40.9 days (range, 1–128 days). The scores of liver fibrosis and liver necroinflammation in the other 11 patients could not be evaluated because of the contraindication of surgery or needle biopsy due to multiple liver metastases or a risk of bleeding caused by severe liver dysfunction.

Imaging Assessment

We measured the $T_{1\rho}$ values of the liver after drawing a total of 15 round or oval regions of interest (ROIs) for each patient. More specifically, five ROIs on each slice of the $T_{1\rho}$ map (Fig. 1) were drawn by two independent radiologists (Y.T. and A.N.) with 13 and 19 years of experience in liver MRI. The radiologists were blinded to the patients' clinical data. The ROIs were made as large as possible on the normal liver parenchyma while still avoiding major vessels, tumors, and artifacts. The range and mean areas of the ROIs of the liver parenchyma were 65.26–401.84 mm^2 and 218.98 mm^2, respectively. All image analyses were performed using MIPAV (Medical Image Processing, Analysis, and Visualization, National Institutes of Health, Bethesda, MD). After we averaged the $T_{1\rho}$ values obtained by the two readers, we analyzed the correlations among the $T_{1\rho}$ values, the laboratory test results, and the scores of liver fibrosis and liver necroinflammation. We also calculated the mean and standard deviations (SDs) of the $T_{1\rho}$ values of the liver in each patient group with different scores of liver fibrosis (F0, F1, F2, F3, and F4) or liver necroinflammation (A0, A1, A2, and A3) (see Table 3 for the details of patient groups).

Statistical Analysis

The intraclass correlation coefficient was used to assess the interreader agreement in measuring the $T_{1\rho}$ values. Pearson's correlation coefficients (r=simple correlation) were calculated between $T_{1\rho}$ values and blood serum parameters, including ICG-R15s. Spearman's rank correlation coefficients (Spearman's ρ) were calculated between $T_{1\rho}$ values and scores of liver fibrosis or liver necroinflammation. Mean $T_{1\rho}$ values among the patient groups with different scores of liver fibrosis or liver necroinflammation were compared by one-way analysis of variance (ANOVA) followed by Tukey's HSD post-hoc test. The

Table 2
T1ρ Values of the Liver and Laboratory Tests

Parameter	Unit	Mean	Range
T1ρ	msec	40.74	31.31–54.89
TP	g/dL	6.91	4.60–8.70
Alb	g/dL	3.81	2.30–5.00
TB	mg/dL	0.95	0.30–2.20
DB	mg/dL	0.25	0.00–1.10
AST	U/L	46.47	16.00–289.00
ALT	U/L	37.72	7.00–194.00
ALP	U/L	298.85	172.00–784.00
γGTP	U/L	64.21	10.00–316.00
Tcho	mg/dL	181.71	102.00–344.00
TG	mg/dL	128.17	37.00–531.00
Glu	mg/dL	106.00	82.00–197.00
PT-INR	INR	1.10	0.91–1.46
Plt	$x10^9/\mu L$	150.96	37.00–434.00
ICG-R15	%	17.56	2.70–79.90

TP: total protein, Alb: albumin, TB: total bilirubin, DB direct bilirubin, AST: aspartate aminotransferase, ALT alanine aminotransferase, ALP: alkaline phosphatase, γGTP: γ-glutamyl transpeptidase, Tcho: total cholesterol, TG: triglyceride, Glu: glucose, PT-INR: prothrombin activity, Plt: platelet count (Plt), and ICG-R15: retention rates at 15 minutes of indocyanine green clearance test

Table 3
Scores and Patient Numbers of Liver Fibrosis and Necroinflammation in 42 Patients

Liver fibrosis score	*n*
F0	18
F1	9
F2	6
F3	4
F4	5
Liver necroinflammation score	***n***
A0	18
A1	12
A2	11
A3	1

statistical analyses were performed with IBM SPSS Statistics 18.0 (IBM Japan, Tokyo) and JMP software v. 9.0 (SAS Institute, Cary, NC). $P<0.05$ was considered significant for each analysis.

RESULTS

Patients' Clinical Data

The summary of $T_1\rho$ values of the liver, laboratory tests, and the scores and patient numbers of liver fibrosis and liver necroinflammation are shown in Tables 2 and 3.

Interreader Agreement

The intraclass correlation coefficient of $T_1\rho$ values between the two readers was 0.980 (95% confidence interval [CI] = 0.97–0.99), indicating excellent concordance in the readers' $T_1\rho$ value measurements (Fig. 2).

Correlations Between $T_1\rho$ Values of the Liver and Laboratory Test Results

The Pearson's correlation coefficients between the $T_1\rho$ values and the laboratory test results are shown in Table 4. The $T_1\rho$ values showed significant positive correlations with TB, DB, and ICG-R15 ($P<0.05$) and significant negative correlations with

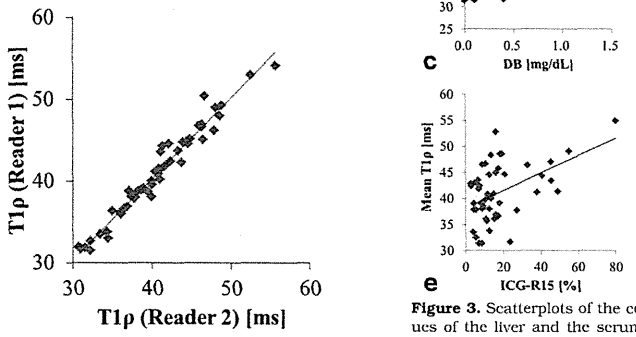

Figure 2. Analysis of interreader agreement. The intraclass correlation was 0.980 (95% CI = 0.97–0.99), indicating the excellent concordance in $T_1\rho$ value measurement between the two readers.

Table 4
Pearson's Correlation Coefficients Between T1ρ Values of the Liver and Laboratory Test Results

Parameter	*r*	95% CI	*P*
TP	−0.09	−0.35–0.19	n.s.
Alb	−0.33	−0.55– −0.07	<0.05
TB	0.31	0.05–0.54	<0.05
DB	0.32	0.18–0.65	<0.05
AST	0.08	−0.19–0.34	n.s.
ALT	−0.09	−0.38–0.22	n.s.
ALP	0.17	−0.11–0.42	n.s.
γGTP	−0.28	−0.51– −0.01	<0.05
Tcho	−0.03	−0.33–0.28	n.s.
TG	−0.09	−0.38–0.22	n.s.
Glu	−0.19	−0.44–0.09	n.s.
PT-INR	0.06	−0.26–0.36	n.s.
Plt	−0.01	−0.28–0.26	n.s.
ICG-R15	0.46	0.22–0.65	<0.01

CI: confidence interval, n.s.: not significant.
Abbreviations as in Table 2.

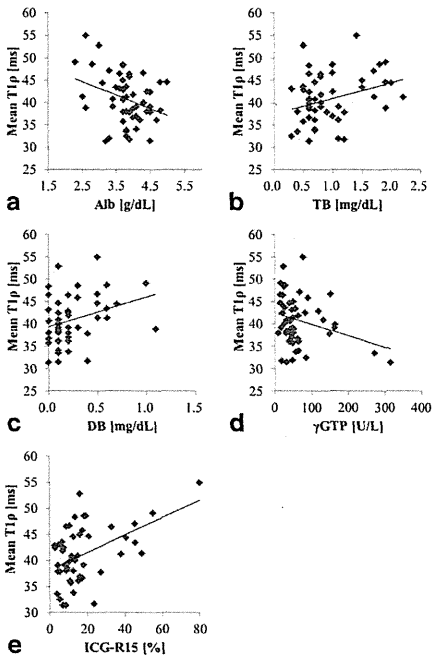

Figure 3. Scatterplots of the correlation between the $T_1\rho$ values of the liver and the serum levels of Alb (a), TB (b), DB (c), γGTP (d), and ICG-R15 (e). A significant correlation was observed in all combinations. Table 4 provides the Pearson's correlation coefficients and *P*-values between $T_1\rho$ values of the liver and the laboratory test results.

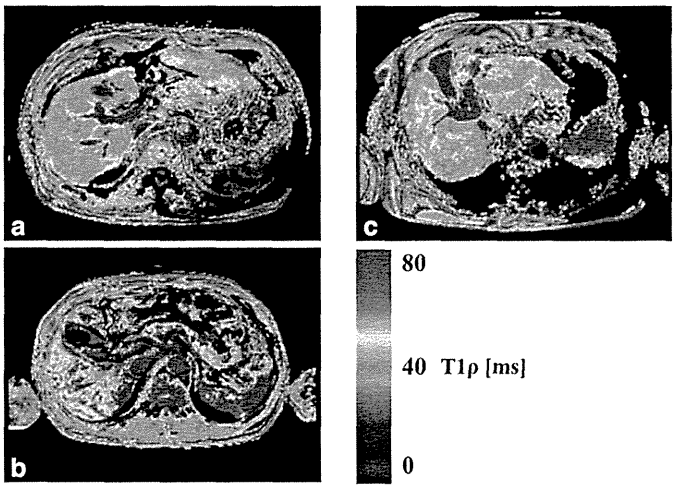

Figure 4. Colored $T_1\rho$ maps. a: A 68-year-old male, mean $T_1\rho$ = 38.5 msec, ICG-R15 = 9.3%. b: A 76-year-old female, mean $T_1\rho$ = 44.7 msec, ICG-R15 = 40.7%. c: A 64-year-old male, mean $T_1\rho$ = 54.1 msec, ICG-R15 = 79.9%. The $T_1\rho$ value of the liver was prolonged with increasing ICG-R15; that is, worsening liver function.

Alb and γGTP ($P < 0.05$). Scatterplots of the correlation between the $T_1\rho$ value of the liver and the serum levels of Alb, TB, DB, and γGTP, and ICG-R15 are shown in Fig. 3. Among those serum parameters, ICG-R15 showed the highest correlation coefficient ($r = 0.46$). Representative images suggesting the relationship between $T_1\rho$ maps of the liver and ICG-R15 are given in Fig. 4.

Correlations Between $T_1\rho$ Values of the Liver and Scores of Liver Fibrosis and Liver Necroinflammation

The $T_1\rho$ values (mean and SDs) in the five patient groups based on liver fibrosis scores were F0 ($n = 18$), 39.91 ± 4.65 msec; F1 ($n = 9$), 41.27 ± 3.01 msec; F2 ($n = 6$), 37.64 ± 7.03 msec, F3 ($n = 4$), 40.62 ± 2.25 msec; and F4 ($n = 5$), 42.16 ± 5.88 msec. There were no significant differences in $T_1\rho$ values among the five groups of different scores of liver fibrosis by one-way ANOVA ($F = 1.03$, $P = 0.40$).

The $T_1\rho$ values (mean and SDs) in the three patient groups based on the liver necroinflammation scores were A0 ($n = 18$), 39.97 ± 4.63 msec; A1 ($n = 12$), 39.96 ± 4.51 msec; A2 ($n = 11$), 39.98 ± 6.78 msec; and A3 ($n = 1$), 39.09 msec. There were no significant differences in $T_1\rho$ values among the three groups by one-way ANOVA ($F = 0.39$, $P = 0.68$). The number of patients in the A3 group was only one, and thus we did not calculate the SDs of the $T_1\rho$ values or perform a pairwise comparison.

$T_1\rho$ values showed no significant correlations with the scores of liver fibrosis (Spearman's $\rho = 0.01$, $P = 0.95$) and liver inflammation (Spearman's $\rho = -0.03$, $P = 0.86$). Scatter graphs illustrating the correlations between the $T_1\rho$ values and score of liver fibrosis or liver necroinflammation of each patient are shown in Fig. 5.

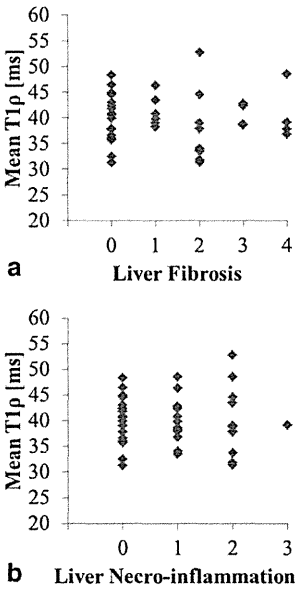

Figure 5. Correlations between the $T_1\rho$ value of the liver and scores of liver fibrosis (a) and liver necroinflammation (b). There were no significant correlations between the $T_1\rho$ values and liver fibrosis (Spearman's $\rho = 0.01$, $P = 0.95$), or between the $T_1\rho$ values and liver necroinflammation (Spearman's $\rho = -0.03$, $P = 0.86$). The numbers of patients in the five patient groups based on liver fibrosis scores and in the three patient groups based on the liver necroinflammation scores are shown in Table 3.

DISCUSSION

The results of the present study showed that $T_1\rho$ relaxation of the liver could be useful to estimate liver function. Two recent clinical studies obtained similar results. One study showed that $T_1\rho$ values of the liver in patients with LC (57.4 ± 7.4 msec) were significantly higher than those of healthy controls (47.8 ± 4.2 msec) (26). Another study demonstrated that the $T_1\rho$ values of the liver increased as the Child-Pugh class increased in patients with LC: class A, 45.4 ± 1.6 msec, class B, 50.0 ± 3.0 msec, and class C, 54.0 ± 3.7 msec (25). There were significant differences between Child-Pugh classes A and B, classes B and C, and classes A and C (25).

Those two studies suggested that $T_1\rho$ relaxation has a potential role as a biomarker for LC. In the present study, ICG-R15 was used to assess the correlation between $T_1\rho$ values and liver function because it is widely used in clinical practice to estimate the liver functional reserve before liver surgery (32,33). Among the blood serum parameters we studied, the ICG-R15 results showed the highest correlation coefficient with the $T_1\rho$ values. The ICG test is influenced by the serum levels of Alb and TB because ICG binds to serum albumin (32,33). The active transfer of ICG into the liver parenchymal cells leads to a rapid disappearance from the plasma, and it appears to be removed solely by the liver; it is secreted into the bile from the parenchymal cells (32). We speculate that $T_1\rho$ relaxation is affected by liver function, especially albumin synthesis, bile transport, and detox.

Other important findings of the present study were that $T_1\rho$ relaxation of the liver was not significantly correlated with liver fibrosis or with necroinflammation. Allkemper et al (25) investigated the correlation between $T_1\rho$ relaxation and the stage of liver necroinflammation, and they concluded that $T_1\rho$ relaxation did not correlate with necroinflammatory activity. Their result was consistent with ours. Importantly, the present study investigated that correlation between $T_1\rho$ values and liver fibrosis including patients with an early stage of liver fibrosis in CLD. We found that $T_1\rho$ relaxation did not correlate with liver fibrosis, and there were no significant differences in $T_1\rho$ values among the patients with five different stages of liver fibrosis. Our results indicated that $T_1\rho$ relaxation might not be useful to detect the early stages of liver fibrosis in CLD. However, our results were obtained from small numbers of patients in each group with different scores of liver fibrosis or liver necroinflammation. A further study is necessary to be validated.

Wang et al (23) described the usefulness of $T_1\rho$ relaxation for the assessment of liver fibrosis using a rat BDL model. Zhao et al (28) also described the usefulness of $T_1\rho$ relaxation for the assessment of liver fibrosis using a rat carbon tetrachloride liver injury model. One possible reason for the discrepancies in the results between these studies with rat models and our present findings is the difference in the environment of liver parenchyma, specifically, acute liver injury versus chronic liver injury (23,28). The present study investigated patients who were suspected to have liver tumors due to CLD or malignant disease in other organs, so that their $T_1\rho$ relaxation might be affected by cholestasis or structural changes in the hepatocytes or liver parenchyma (24).

Another discrepancy regards the mechanisms between $T_1\rho$ relaxation and liver fibrosis. In articular cartilage, $T_1\rho$ relaxation shows a negative correlation with the contents of collagen and proteoglycan (12,20). In LC, in accord with the progression of liver injury, there is an increase in extracellular matrix, composed of fibril-forming collagen as well as cellular matrices (including proteoglycans) (34). We thus suspect that the $T_1\rho$ prolongation in patients with liver dysfunction may be influenced by the depletion of macromolecules or an increase of bulk water rather than the macromolecular accumulation associated with liver fibrosis. It is doubtful that the chemical exchange between bulk water and the hydroxyl and amine groups of proteoglycans affects the $T_1\rho$ relaxation in liver parenchyma in contrast to articular cartilage (13). Biological, chemical, and physical factors may contribute to $T_1\rho$ relaxation.

The promising aspect of $T_1\rho$ relaxation in liver MRI is that it is not affected by other biological changes in liver parenchyma such as the storage of glycogen and the deposition of iron or fat. Deng et al (21) reported that there was no significant difference in liver $T_1\rho$ values between those obtained at the fasting status (43.08 ± 1.41 msec) and postmeal status (42.97 ± 2.38 msec), suggesting that $T_1\rho$ relaxation is not affected by the storage of glycogen in the liver. $T_1\rho$ relaxation also did not correlate with the degree of steatosis or presence of iron load (25). Therefore, $T_1\rho$ relaxation has potential as a biomarker for liver function.

An important point to remember about $T_1\rho$ relaxation is that it is susceptible to B_1 inhomogeneity, as a significant increase in B_1 inhomogeneity-related artifacts degrades the accurate calculation due to the heterogeneous spin-lock pulse distribution (35,36). As noted in previous studies, a solution to this problem is to use a 1.5T MR scanner for the precise calculation of $T_1\rho$ relaxation of the liver. We consider that dual-source RF transmission technology is essential to reduce the B_1 inhomogeneity-related artifacts of the liver when using a 3.0T MR scanner (37,38). Such hardware also helps reduce the limitation of the SAR during the scan.

There were a few other limitations in this study. First, we did not investigate the correlation of $T_1\rho$ relaxation of the liver with scintigraphy with ^{99m}Tc-diethylenetriamine pentaacetic acid-galactosyl-human serum albumin (^{99m}Tc-GSA). ^{99m}Tc-GSA is thought of as the most reliable tool to estimate the liver functional reserve before surgery (39). In the present study, 22 of the 53 patients underwent ^{99m}Tc-GSA scintigraphy, but these data were not included for the analysis because the number of patients was small. Second, the influence of respiratory or cardiac motions was not taken into consideration in the present study. The breath-hold technique was used for respiratory control during the image acquisition

because it enabled fast image acquisition. The respiratory-triggering technique and cardiac electrocardiography gating technique may reduce the influence of respiratory or cardiac motions, but they require further elongation of the scanning time (38). Deng et al (21) reported that respiration motion could lead to artificially high $T_{1\rho}$ values of the liver parenchyma based on even mild spatial misregistration. In addition, the hepatic vein and biliary tract showed high signal intensities. Thus, the vessel contamination might result in unavoidable miscalculation of the $T_{1\rho}$ values of the liver. Third, this was a retrospective study, and the numbers of patients in each group with different scores of liver fibrosis or liver necroinflammation were small. In addition, the etiology of CLD was heterogeneous. A prospective study is necessary to minimize biases due to the number of patients and the etiology of CLD and to validate the diagnostic potential of $T_{1\rho}$ relaxation of the liver.

In conclusion, $T_{1\rho}$ relaxation has potential as a biomarker for the assessment of liver function. However, $T_{1\rho}$ relaxation of the liver may not be suitable to estimate liver fibrosis or liver necroinflammation.

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REFERENCES

1. Faria SC, Ganesan K, Mwangi I, et al. MR imaging of liver fibrosis: current state of the art. Radiographics 2009;29:1615–1635.
2. Kudo M. Hepatocellular carcinoma 2009 and beyond: from the surveillance to molecular targeted therapy. Oncology 2008; 75(Suppl 1):1–12.
3. Starley BQ, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. Hepatology 2010;51:1820–1832.
4. Tsukuma H, Hiyama T, Tanaka S, et al. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. N Engl J Med 1993;328:1797–1801.
5. Manduca A, Oliphant TE, Dresner MA, et al. Magnetic resonance elastography: non-invasive mapping of tissue elasticity. Med Image Anal 2001;5:237–254.
6. Boll DT, Merkle EM. Diffuse liver disease: strategies for hepatic CT and MR imaging. Radiographics 2009;29:1591–1614.
7. Yoshioka K, Hashimoto S. Can non-invasive assessment of liver fibrosis replace liver biopsy? Hepatol Res 2012;42:233–240.
8. Arda K, Ciledag N, Aktas E, Aribas BK, Kose K. Quantitative assessment of normal soft-tissue elasticity using shear-wave ultrasound elastography. AJR Am J Roentgenol 2011;197:532–536.
9. Yin M, Chen J, Glaser KJ, Talwalkar JA, Ehman RL. Abdominal magnetic resonance elastography. Top Magn Reson Imaging 2009;20:79–87.
10. Markkola AT, Aronen HJ, Paavonen T, et al. Spin lock and magnetization transfer imaging of head and neck tumors. Radiology 1996;200:369–375.
11. Santyr GE, Henkelman RM, Bronskill MJ. Spin locking for magnetic resonance imaging with application to human breast. Magn Reson Med 1989;12:25–37.
12. Akella SV, Regatte RR, Gougoutas AJ, et al. Proteoglycan-induced changes in T1rho-relaxation of articular cartilage at 4T. Magn Reson Med 2001;46:419–423.
13. Duvvuri U, Goldberg AD, Kranz JK, et al. Water magnetic relaxation dispersion in biological systems: the contribution of proton exchange and implications for the noninvasive detection of cartilage degradation. Proc Natl Acad Sci U S A 2001;98:12479–12484.
14. Nestrasil I, Michaeli S, Liimatainen T, et al. T1rho and T2rho MRI in the evaluation of Parkinson's disease. J Neurol 2010;257:964–968.
15. Szyperski T, Luginbuhl P, Otting G, Guntert P, Wuthrich K. Protein dynamics studied by rotating frame 15N spin relaxation times. J Biomol NMR 1993;3:151–164.
16. Borthakur A, Gur T, Wheaton AJ, et al. In vivo measurement of plaque burden in a mouse model of Alzheimer's disease. J Magn Reson Imaging 2006;24:1011–1017.
17. Duvvuri U, Poptani H, Feldman M, et al. Quantitative T1rho magnetic resonance imaging of RIF-1 tumors in vivo: detection of early response to cyclophosphamide therapy. Cancer Res 2001; 61:7747–7753.
18. Li X, Benjamin Ma C, Link TM, et al. In vivo T(1rho) and T(2) mapping of articular cartilage in osteoarthritis of the knee using 3 T MRI. Osteoarthritis Cartilage 2007;15:789–797.
19. Takayama Y, Hatakenaka M, Tsushima H, et al. T1rho is superior to T2 mapping for the evaluation of articular cartilage denaturalization with osteoarthritis: radiological-pathological correlation after total knee arthroplasty. Eur J Radiol 2013;82:e192–198.
20. Tsushima H, Okazaki K, Takayama Y, et al. Evaluation of cartilage degradation in arthritis using T1rho magnetic resonance imaging mapping. Rheumatol Int 2012;32:2867–2875.
21. Deng M, Zhao F, Yuan J, Ahuja AT, Wang YX. Liver T1rho MRI measurement in healthy human subjects at 3 T: a preliminary study with a two-dimensional fast-field echo sequence. Br J Radiol 2012;85:e590–595.
22. Wallace K, Burt AD, Wright MC. Liver fibrosis. Biochem J 2008; 411:1–18.
23. Wang YX, Yuan J, Chu ES, et al. T1rho MR imaging is sensitive to evaluate liver fibrosis: an experimental study in a rat biliary duct ligation model. Radiology 2011;259:712–719.
24. Sirlin CB. Science to practice: Can T1rho imaging be used to diagnose and assess the severity of hepatic fibrosis? Radiology 2011;259:619–620.
25. Allkemper T, Sagmeister F, Cicinnati V, et al. Evaluation of fibrotic liver disease with whole-liver T1rho MR imaging: a feasibility study at 1.5 T. Radiology 2014;271:408–415.
26. Rauscher I, Eiber M, Ganter C, et al. Evaluation of T1rho as a potential MR biomarker for liver cirrhosis: comparison of healthy control subjects and patients with liver cirrhosis. Eur J Radiol 2014;83:900–904.
27. Pakin SK, Xu J, Schweitzer ME, Regatte RR. Rapid 3D-T1rho mapping of the knee joint at 3.0T with parallel imaging. Magn Reson Med 2006;56:563–571.
28. Zhao F, Wang YX, Yuan J, et al. MR T1rho as an imaging biomarker for monitoring liver injury progression and regression: an experimental study in rats with carbon tetrachloride intoxication. Eur Radiol 2012;22:1709–1716.
29. Yuan J, Zhao F, Chan Q, Wang YX. Observation of bi-exponential T(1rho) relaxation of in-vivo rat muscles at 3T. Acta Radiol 2012; 53:675–681.
30. Nishie A, Asayama Y, Ishigami K, et al. MR prediction of liver fibrosis using a liver-specific contrast agent: superparamagnetic iron oxide versus Gd-EOB-DTPA. J Magn Reson Imaging 2012;36:664–671.
31. Tomimaru Y, Sasaki Y, Yamada T, et al. Fibrosis in noncancerous tissue is the unique prognostic factor for primary hepatocellular carcinoma without hepatitis B or C viral infection. World J Surg 2006;30:1729–1735.
32. Schneider PD. Preoperative assessment of liver function. Surg Clin N Am 2004;84:355–373.
33. Seyama Y, Kokudo N. Assessment of liver function for safe hepatic resection. Hepatol Res 2009;39:107–116.
34. Bansal MB, Friedman SL. Hepatic fibrogenesis. In: Dooley, JS, Lok A, Burroughs A, Heathcote J, editors. Sherlock's diseases of the liver and biliary system, 12th ed. Hoboken, NJ: Wiley-Blackwell; 2011. p 94–102.
35. Charagundla SR, Borthakur A, Leigh JS, Reddy R. Artifacts in T(1rho)-weighted imaging: correction with a self-compensating spin-locking pulse. J Magn Reson 2003;162:113–121.

36. Witschey WR, 2nd, Borthakur A, Elliott MA, et al. Artifacts in T1 rho-weighted imaging: compensation for B(1) and B(0) field imperfections. J Magn Reson 2007;186:75–85.
37. Takayama Y, Nishie A, Asayama Y, et al. Image quality of Gd-EOB-DTPA-enhanced magnetic resonance imaging of the liver using dual-source parallel radiofrequency transmission technology: comparison with the post-processing correction method for B1 inhomogeneity-induced signal loss. Eur J Radiol 2012;81:3035–3040.
38. Takayama Y, Nishie A, Asayama Y, et al. Three-dimensional T2-weighted imaging for liver MRI: clinical values of tissue-specific variable refocusing flip-angle turbo spin echo imaging. J Magn Reson Imaging 2014 [Epub ahead of print].
39. Sasaki N, Shiomi S, Iwata Y, et al. Clinical usefulness of scintigraphy with 99mTc-galactosyl-human serum albumin for prognosis of cirrhosis of the liver. J Nucl Med 1999;40:1652–1656.

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ORIGINAL ARTICLE

Clinical Outcomes and Prognostic Factors After Surgery for Non-Occlusive Mesenteric Ischemia: a Multicenter Study

Takafumi Yukaya · Hiroshi Saeki · Kenji Taketani · Koji Ando · Satoshi Ida · Yasue Kimura · Eiji Oki · Mitsuhiro Yasuda · Masaru Morita · Ken Shirabe · Yoshihiko Maehara

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Abstract
Background To date, no large-scale study has been undertaken to understand the clinical features of non-occlusive mesenteric ischemia (NOMI) after surgery. We thus performed a multicenter investigation to clarify the clinical outcomes and prognostic factors of NOMI.
Patients and Methods Clinical databases from 22 Japanese facilities were reviewed for evaluation of patients who received surgery for NOMI between 2004 and 2012. NOMI patients (n=51) were divided into two groups: group I (n=28) consisted of patients who survived, and group II (n=23) consisted of patients who did not survived. Prognostic factors were compared between the two groups.
Results NOMI surgery represented 0.04 % of the total number of operations performed in this time period. The overall mortality rate for NOMI surgery was 45 %. Hemodialysis was a significant negative prognostic factor (p=0.027). Preoperative elevation of transaminases, potassium, and white blood cell count, as well as metabolic acidosis and colon ischemia was poor prognostic factors. The mean Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM) score of group I versus group II was 54.5±3.6 and 85.2±4.1, respectively (p<0.001).
Conclusions Currently, NOMI surgery has a 45 % mortality rate. POSSUM scores can be used to predict the clinical outcome of patients who receive NOMI surgery.

Keywords Non-occlusive mesenteric ischemia · Acute mesenteric ischemia · Prognostic factor · Clinical features

Introduction

Non-occlusive mesenteric ischemia (NOMI) consists of intestinal ischemia and/or necrosis in the absence of an organic obstruction within the main trunk of the mesenteric artery or vein.[1] It is currently thought that NOMI is caused by mesenteric vasoconstriction.[2] NOMI has been reported to be the cause of 10 to 30 % of all cases of acute mesenteric ischemia.[2,3] Until recently, NOMI has had a dismal prognosis, with mortality rates between 70 and 90 %.[2,3] NOMI is associated with age, diabetes mellitus, hypertension, and atherosclerosis,[3,4] suggesting that it is a problem of aging.

Selective mesenteric angiography is considered the gold standard for diagnosing acute mesenteric ischemia,[5] and the American Gastroenterological Association has established guideline for the diagnosis and treatment of acute mesenteric ischemia.[6] However, debate regarding angiography and arterial infusion therapy for NOMI exists,[3,7] and the role of surgical treatment for NOMI is controversial.[3,6,9]

Current understanding of NOMI is based on a small number of clinical reports of patients with miscellaneous forms of acute mesenteric ischemia. The largest study to date on patients with a definitive NOMI diagnosis was performed by Ward et al.[9] who reported on 34 patients with NOMI. The aim of this study was to use a multicenter approach to clarify the clinical outcomes and prognostic predictive factors of NOMI.

T. Yukaya (✉) · H. Saeki · K. Taketani · K. Ando · S. Ida · Y. Kimura · E. Oki · M. Yasuda · M. Morita · K. Shirabe · Y. Maehara
Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, 812-8582 Fukuoka, Japan
e-mail: t-yukaya@surg2.med.kyushu-u.ac.jp

Patients and Methods

A retrospective chart review was performed on all patients who underwent surgery at the Department of Surgery and Science, Graduate School of Medical Sciences, Kyusyu University, and 21 related facilities between April 2004 and September 2012. During this period, 114,224 operations (including 12,388 emergency operations) were performed by the 22 institutes. Among them, 51 operations were performed on NOMI patients (0.04 %).

The diagnosis of NOMI was based on operative findings. A definitive diagnosis of NOMI requires the absence of an organic obstruction of the blood vessels distributed in the necrotic intestinal region, segmented discontinuous intestinal ischemic changes, and necrosis.[9–11]

In this study, physicians were asked to fill out a survey form consisting of the following items: patient background [gender, age, underlying disease, surgical division (emergency or scheduled)], laboratory findings at the time of the decision to proceed to surgery, metabolic acidosis upon admission, preoperative hypotension, portal venous gas detected by CT scan, range of ischemic lesion, POSSUM score (predictive mortality rate), additional postoperative treatments (such as prostaglandin E1, continuous hemodiafiltration, polymyxin B-immobilized column direct hemoperfusion, anticoagulant therapy, nitrovasodilators, and octreotide), and prognosis.

NOMI patients were classified into two groups: group I (n=28) consisting of patients who survived to discharge and group II (n=23) consisting of patients who did not. Multiple clinical factors were compared between the two groups.

POSSUM stands for Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity.[12] It was developed by Copeland et al.[12] in 1991 and has since been applied to a number of surgical groups including orthopedics, vascular surgery, head and neck surgery, and GI/colorectal surgery. The POSSUM mortality equation is calculated as follows: $\ln[R/(1-R)] = -7.04 + (0.13 \times \text{physiological score}) + (0.16 \times \text{operative severity score})$, where R is the predicted risk of mortality.[12]

Statistically significant differences were determined using Fisher's exact test and t test. A p value less than 0.05 was considered to be statistically significant. Receiver operator characteristic (ROC) curves and the corresponding area under the curve (AUC) were used to evaluate how the prediction model performed on the study data.

Results

Characteristics and Symptoms of NOMI Patients

A comparison of patient characteristics is shown in Table 1. Males accounted for 51.0 % of all NOMI patients. The median patient age was 78 years (19–94 years), with 19 patients in their 80s. The overall mortality rate was 45 % (n=23). There were no significant differences in gender or age between the two groups.

Hypertension was the most frequent comorbid condition (49 %), followed by cardiovascular disease (47 %) and renal failure (14 %). Four patients were taking digitalis (8 %). There were no significant differences in comorbid conditions (hypertension, cardiovascular disease) or medications between the two groups. However, group II contained significantly more patients on hemodialysis (p=0.027).

Several presenting symptoms were identified. Abdominal pain was the presenting symptom in 30 patients (59 %) and loss of consciousness in 9 (18 %). Seven patients (14 %) were sedated and thus had no presenting complaint. Hematemesis/bloody stool and abdominal distention were present in each

Table 1 Comparison of clinical characteristics between group I and group II

Factors	All (n=51)	Group I (n=28)	Group II (n=23)	p value
Average age	78	75.5±2.3	76.1±2.6	0.856
Gender (Male/Female)	26/25	16/12	10/13	0.404
Comorbid conditions				
Hypertension	25 (49)	14 (50)	11 (50)	0.551
Diabetes mellitus	10 (20)	5 (18)	5 (22)	0.500
Cardiovascular disease	24 (47)	16 (57)	8 (35)	0.970
Ischemic heart disease	11 (22)	7 (25)	4 (17)	0.621
Atherosclerosis	7 (14)	6 (21)	1 (4)	0.112
Arrhythmia	7 (14)	6 (21)	1 (4)	0.112
Congestive heart failure	6 (12)	4 (14)	2 (9)	0.854
Hemodialysis	7 (14)	1 (4)	6 (27)	0.027
Medications				
Digitalis	4 (8)	1 (4)	3 (13)	0.234
Diuretics	10 (20)	9 (32)	1 (4)	0.015

Data listed for comorbid conditions and medications are total number (%)

Group I patients who survived to discharge, *group II* patients who did not survive to discharge

four patients. Finally, 16 patients (32 %) reported no abdominal symptoms.

Laboratory and Radiological Findings of NOMI Patients

A comparison of laboratory findings is shown in Table 2. Aspartate aminotransferase, alanine aminotransferase, potassium, and white blood cell count were higher in group II than those in group I ($p<0.05$).

Metabolic acidosis was present in 29 % of the patients in group I and in 72 % of the patients in group II ($p=0.017$; Table 3). Only one patient underwent angiography, whereas 46 patients underwent computed tomography for preoperative diagnosis. No patient required CT angiography. Portal venous gas was detected in 62 % in group I but in only 30 % of the patients in group II ($p=0.033$). Extensive ischemia (small intestine and colon) was observed in 25 % of the patients in group I and in 61 % of patients in the group II ($p=0.010$). No significant differences were observed in the incidence of preoperative hypotension, the operation time, or the amount of blood lost between the two groups.

Surgery Performed for NOMI

The surgeries performed on the NOMI patients are listed in Table 4. Thirty-two patients (63 %) underwent bowel resection with enterostomy, and eight patients (16 %) underwent intestinal resection with reconstruction. Exploratory laparotomy was performed for 11 patients, 4 of whom (8 %) had no evidence of necrosis and 7 of whom (14 %) had massive necrosis requiring resection. Three patients underwent a second operation for additional bowel resection, because ischemic progression was suspected. Median operation time was 152.6±12.6 min, and median blood loss was 837.7±397.8 mL.

Additional Postoperative Treatments and POSSUM Score

Additional postoperative treatments for NOMI patients are shown in Table 5. Ten patients were treated with prostaglandin E1, nine with continuous hemodiafiltration, three with polymyxin B-immobilized column direct hemoperfusion, and three with anticoagulation therapy. Prostaglandin E1 is a vasodilator; it was used to prevent vasospasm. The first line therapy upon suspicion of NOMI has been angiography and continuous administration of vasodilators, prostaglandin E1, and papavelin. Mitsuyohi et al. reported that high dose intravenous administration of PGE1 was effective in NOMI.[3] Continuous hemodiafiltration was used for remove of inflammatory cytokines and renal replacement.[13] Direct hemoperfusion with polymyxin B-immobilized column was used for remove of endotoxin.[14] The percent of NOMI patients who underwent additional postoperative treatment was 61 % in group I and 26 % in group II ($p=0.014$).

The mean POSSUM scores of groups I and II were 54.5±3.6 and 85.2±4.1, respectively ($p<0.001$; Table 3). All patients with a POSSUM score over 90 were in group II. Furthermore, 22 of the 25 patients with a POSSUM score under 76.1 were in group I. Group I contained a higher percentage of patients with POSSUM scores between 76.1 and 90 who had received additional postoperative treatment ($p=0.024$; Table 6). The treatments were as follows: one patient was treated with anticoagulant therapy, one was treated with direct hemoperfusion with polymyxin B-immobilized column,

Table 2 Comparison of preoperative laboratory findings between group I and group II

Factors		All (n =51)	Group I (n=28)	Group II (n=23)	p value
Serum aspartate aminotransferase	(IU/L)	39 (12–6715)	60±190	738±215	0.011
Serum alanine aminotransferase	(IU/L)	28 (6–996)	28±41	237±46	<0.001
Serum total bilirubin	(mg/dL)	0.8 (0.2–6.8)	1.5±0.5	1.2±0.5	0.300
Serum creatine phosphokinase	(IU/L)	105 (3.4–84106)	970±2,900	8,700±3,300	0.083
Serum blood urea nitrogen	(mg/dL)	32 (12–94)	35.6±3.7	39.7±4.2	0.235
Serum creatinine	(mg/dL)	1.4 (0.4–11.7)	1.7±0.4	2.9±0.5	0.071
Serum albumin	(g/dL)	2.9 (1.3–4.5)	3.0±0.2	2.7±0.2	0.081
Serum sodium	(Eq/dL)	137 (120–155)	137±1.1	138±1.3	0.364
Serum potassium	(Eq/dL)	4.0 (2.2–7.6)	3.9±0.2	4.6±0.2	0.014
White cell count	(/μL)	9,500 (1,490–52,000)	9,700±1,800	16,100±2,000	0.011
Hemoglobin	(mg/dL)	11.8 (7.2–18.1)	11.5±0.4	12.2±0.5	0.152
Hematocrit	(%)	35.4 (21–58)	33.0±1.4	36.1±1.6	0.237
Platelets	($\times10^3$/μL)	16.6 (1.2–36.7)	19.5±1.7	15.5±2.0	0.074

Data listed for all patients are mean values (range). Data listed for group I and group II are mean values±standard deviation

Group I patients who survived to discharge, *group II* patients who did not survive to discharge

Table 3 Comparison of clinical findings between group I and group II

Factor	All	Group I	Group II	*p* value
Metabolic acidosis	17/32 (53)	4/14 (29)	13/18 (72)	0.017
Postoperative hypotension	20/50 (40)	8/27 (30)	12/23 (52)	0.179
Portal venous gas	22/46 (48)	16/26 (62)	6/20 (30)	0.033
Colon ischemia	21/51 (41)	7/28 (25)	14/23 (61)	0.010
Bowel resection >1 m	35/51 (69)	17/28 (61)	18/23 (78)	0.149
POSSUM score (n=47), mean±SD	68.3±3.5	54.5±3.6	85.2±4.1	<0.001
Duration of operation (min; n=51), mean±SD	153±13	149±17	158±19	0.365
Blood count (mL; n=51), mean±SD	838±398	320±530	1,470±590	0.070

Data listed are total number (%)

SD standard deviation, *group I* patients who survived to discharge, *group II* patients who did not survive to discharge

and one was treated with prostaglandin E1 and continuous hemodiafiltration.

Discussion

Acute mesenteric ischemia, including mesenteric arterial embolism, mesenteric arterial thrombosis, NOMI, and mesenteric venous thrombosis, has a poor prognosis with a high in-hospital mortality rate (59–93 %).[2] NOMI is a particularly poorly understood condition marked by progressive intestinal ischemia leading to infarction, sepsis, and death in a high proportion of patients.

NOMI appears to occur secondary to cardiac disease, diabetes mellitus, and chronic dialysis-dependent renal failure.[2,4,14] In this study, 49 % of NOMI patients suffered from hypertension, 47 % from cardiovascular disease, 20 % from diabetes mellitus, and 14 % from dialysis-dependent renal disease. According to previous reports, digitalis is an additional risk factor for NOMI,[3,15,16] perhaps because it induces vasoconstriction and thus increases resistance in peripheral splanchnic vessels. In this study, 8 % of NOMI patients were on digitalis therapy.

Conventional angiography is regarded as the gold standard imaging method in patients with acute mesenteric ischemia.[3,5,6] However, NOMI often occurs in patients with poor or unstable systemic conditions, and angiography may not be possible in many of these patients due to its complexity and invasiveness.[2,17] Catheter angiography is invasive and difficult to perform, so its use is limited to select centers.[2,3,17] Indeed, Bender et al.[18] reported that none of their sample population received angiograms. In this study, only one patient underwent angiography. Hence, angiography is not the primary method for NOMI diagnosis in clinical practice. Mitsuyoshi et al.[3] reported the usefulness of multidetector-row computed tomography for the diagnoses of NOMI. In this study, computed tomography was the primary imaging modality used for NOMI diagnosis.

Histopathologic detection of hemorrhagic and necrotic changes is required for definite diagnosis of NOMI.[12] Unfortunately, pathological examination was not available for 11 study patients who received exploratory laparotomy. In these cases, we used macroscopic findings from the laparotomy to definitively diagnose NOMI. Furthermore, although 40 patients underwent bowel resection, a pathological evaluation of the resected specimen was available for only 25 patients. The findings from all 25 patients met the pathological criteria of a NOMI diagnosis.

Ischemic colitis represents the most common form of gastrointestinal ischemia. Many previous reports have not distinguished NOMI from ischemic colitis. Witternberg et al.[19]

Table 4 Comparison of operative procedures between group I and group II

Operative procedure	All	Group I (n=28)	Group II (n=23)
Intestinal resection with enterostomy	30 (59)	18	12
Intestinal resection with reconstruction (with diverting enterostomy)	2 (4)	1	1
Intestinal resection with reconstruction (without diverting enterostomy)	8 (16)	7	1
Exploratory laparotomy (no findings of intestinal necrosis)	4 (8)	2	2
Exploratory laparotomy (findings of intestinal necrosis)	7 (14)	0	7

Data listed are total number (%)

Group I patients who survived to discharge, *group II* patients who did not survive to discharge

Table 5 Comparison of additional postoperative treatment between group I and group II

Additional postoperative treatment	All (n=51)	Group I (n=28)	Group II (n=23)
Patients who received treatment	23	17 (74)	6 (26)*
Prostaglandin E1	10	7	3
CHDF	9	5	4
PMX	3	2	1
Anticoagulant therapy	3	3	0
Nitrovasodilator	1	1	0
Octreotide	1	1	0
Patients who did not receive treatment	28	11 (39)	17 (61)*

Data listed are total number (%)

CHDF continuous hemodiafiltration, *PMX* polymyxin B-immobilized column direct hemoperfusion, *group I* patients who survived to discharge, *group II* patients who did not survive to discharge

*There was significant difference in postoperative mortality between patients who did or did not receive additional postoperative treatment (p=0.01)

reported differences in the incidence of the underlying vascular etiologies of the two major categories of primary ischemic disease of the bowel. NOMI is a disease primarily of the superior mesenteric artery distribution, whereas ischemic colitis is a disease primarily of the inferior mesenteric artery distribution. We thus excluded cases of bowel ischemia isolated to areas of the colon supplied by the inferior mesenteric artery.

Hemodialysis is a known risk factor for NOMI, because patients with end-stage renal disease have many risk factors for mesenteric ischemia.[7] However, the prognostic impact of hemodialysis on patients who undergo surgery for NOMI has not been evaluated. Our results demonstrate that hemodialysis is a negative prognostic factor for NOMI patients who receive surgery.

Among the 46 patients who underwent computed tomography, portal venous gas was detected in 22 (48 %). Portal venous gas may be found in a variety of conditions.[20] Portal venous gas resulting from bowel ischemia has been shown to be a poor prognostic factor, with an associated mortality rate of 75–90 %.[21] Surprisingly, in our study, patients with portal venous gas had a significantly better prognosis. This finding may be explained by the fact that patients with portal venous gas were diagnosed with severe intestinal necrosis and underwent immediate surgery.

Table 6 Comparison of survival rates between patients who did or did not receive additional postoperative treatment

POSSUM score	With postoperative treatment (n=22)	Without postoperative treatment (n=25)	p value
90≦ (n=11)	0/4 (0)	0/7 (0)	–
76.1≦ and <90 (n=11)	3/3 (100)	1/8 (13)	0.024
<76.1 (n=25)	13/15 (87)	9/10 (90)	0.802
Average POSSUM score	66.9±4.9	69.5±5.2	0.360

Percentages are in parentheses

The area affected by ischemic bowel can range from a few decimeters up to the entire small intestine and colon. Sotriadis J et al.[22] reported that patients with isolated right colon ischemia had a worse outcome than patients with ischemia involving other colon regions. We found that patients with extensive bowel involvement (extending from the small intestine to the colon) had a poorer prognosis. Aliosmanoglu et al.[23] reported that acute mesenteric ischemia involving both the colon and the small intestine resulted in a higher mortality. The high mortality rate in these patients may be due to vasoconstriction of the inferior and superior mesenteric artery territories.

In some cases of NOMI, ischemia progresses after surgery, requiring a second-look surgery to be performed.[8] Ward et al.[8] reported that aggressive re-exploration and delayed intestinal anastomosis improved survival of NOMI patients. In this study, 31 patients (59 %) underwent bowel resection with enterostomy (without anastomosis), 10 patients (20 %) with anastomosis (2 patients with diverting enterostomy), and 3 patients underwent second-look surgery. It can be difficult for surgeons to determine whether to create an anastomosis or an enterostomy during NOMI operations. We found no complications associated with anastomosis formation, suggesting that surgeons appropriately judged the most suitable operative procedure for each patient.

POSSUM scores and the Acute Physiology and Chronic Health Evaluation (APACHE) II are used to evaluate the risk of surgery.[24–26] The POSSUM score is easier to use than APACHE II and has been reported to be superior to APACHE II in predicting mortality in patients admitted to a high-dependency unit after general surgery.[27] To the best of our knowledge, this is the first study to report the prognostic role of the POSSUM score in a series of NOMI patients treated with surgery. We found that a POSSUM score of 76.1 or higher [as determined by the ROC curve (AUC=0.905)] was a predictor of in-hospital mortality.

To date, no published study has focused on additional postoperative treatment of NOMI patients. In this study, patients who received additional postoperative treatments had a better clinical course. However, we found no significant difference in the POSSUM scores of patients who underwent additional postoperative treatment and those who did not (Table 6). Hence, additional postoperative treatment of NOMI patients has the potential to improve prognosis, especially among patients with POSSUM scores between 76.1 and 90.

Patients with NOMI commonly receive intra-arterial infusions of papaverine after surgery. However, angiography is difficult to perform, and access is limited to select centers; hence, intra-arterial infusions of vasodilators can be difficult.