J Gastrointest Surg (2009) 13:325–333
DOI 10.1007/s11605-008-0711-8

ORIGINAL ARTICLE

# Prognostic Impact of Surgical Complications and Preoperative Serum Hepatocyte Growth Factor in Hepatocellular Carcinoma Patients After Initial Hepatectomy

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Received: 26 June 2008 / Accepted: 18 September 2008 / Published online: 10 October 2008


**Abstract**
*Introduction* The relationship between postoperative complications and survival after hepatectomy is not completely understood. The purpose of this study was to determine if surgical complications would have a prognostic impact and to identify any difference of the prognostic factors between a complication group and complication-free group for hepatocellular carcinoma (HCC) patients after initial hepatectomy.
*Patients and Methods* One hundred consecutive HCC patients were analyzed in this study. Operative variables and liver functional markers were compared between the complication group and complication-free group. The diagnostic accuracy for predicting complications was evaluated by the receiver operating characteristic (ROC) curve. The Kaplan–Meier method with log-rank test was employed for survival analysis. Univariate and multivariate analyses were performed to identify the prognostic factors in each group.
*Results and discussion* A total of 45 complications in 32 patients were observed according to the modified Clavien classification. The albumin, γ-glutamyl transferase, choline esterase, indocyanine green retention rate at 15 min ($ICGR_{15}$), hyaluronic acid, prealbumin, hepatocyte growth factor (HGF), HH15, and LHL15 levels before hepatectomy, operative time, and blood loss were significantly different between the two groups. Multivariate analysis revealed that γ-glutamyl transferase, $ICGR_{15}$, and HGF were independent risk factors for postoperative complications. The values of the areas under the ROC curve for predicting complications proved the significance of the predictions. Although the recurrence-free survival rates were not significantly different, the overall survival rates were significantly different between the two groups. Univariate and multivariate analyses for the overall survival rate showed that the stage of the HCC and HGF for the complication group and tumor size for the complication-free group were independent prognostic factors for overall survival.
*Conclusion* Postoperative surgical complications could have a prognostic impact on overall survival in HCC patients after initial hepatectomy. Serum HGF could be a factor connected to complications and survival in this group.

**Keywords** Hepatectomy · Hepatocyte growth factor · Hepatocellular carcinoma · Complication · Prognosis

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## Introduction

The incidence of hepatocellular carcinoma (HCC) has been increasing internationally due to epidemic viral hepatitis.[1,2] Liver resection is one of the best curative therapies for HCC patients who maintain good liver function,[1,2] and assessment of liver functions before surgery is important to avoid liver dysfunction or liver failure.[3–5] Many indicators have been used for the assessment of liver function such as the Child–Pugh score,[3] indocyanine green retention rate at

15 min ($ICGR_{15}$),[3] $^{99m}$Tc-galactosyl serum albumin (GSA),[4] and serum hyaluronic acid (HA) levels.[5] Knowledge of these preoperative evaluations, in addition to the improvement of surgical techniques and devices, helps surgeons to perform safe hepatectomy in modern surgery. The mortality in the 1980s was reported to be approximately 10% for major hepatectomy, but has now been reduced to only a few percent.[6,7]

Although the mortality rate in liver surgery has decreased, surgical complications may be inevitable to some degree. If the operative procedure and perioperative management with an appropriate surgical plan are completed without errors, surgical complications should become minimal. In this circumstance, surgical complications could be mostly related to the host condition. Viral-associated HCC develops in the process of disease progression such as chronic hepatitis and liver cirrhosis[8,9] when liver function deteriorates in parallel. Therefore, HCC patients are vulnerable to complications associated with surgical stress.

Many perioperative variables, such as tumor factors (tumor size, number of tumors, extension of the tumor, and vascular invasion), clinical factors (age, liver damage, and α-fetoprotein [AFP]), and operative factors (surgical curability and margin), are related to recurrence and the survival rate after hepatectomy.[10] The cause of death in HCC patients is usually either cancer-related or liver failure-related. Good liver function has the potential to prolong survival due to more chances to receive additional salvage therapy.[11] Therefore, liver function may play an important role in predicting not only postoperative complications but also survival after hepatectomy. However, the relation between postoperative complications and survival after hepatectomy is not completely understood.

Hepatocyte growth factor (HGF) is found in the sera of patients with fulminant liver failure[12] and promotes hepatocyte proliferation, including that of hepatocellular carcinoma cells.[13] Clinically, HGF levels are well-correlated with the worsening of liver disease.[8,9] High HGF levels in the cirrhotic liver correlate with the presence of hepatocellular carcinoma and overall prognosis.[9] We have also reported that the preoperative HGF level correlates with postoperative liver dysfunction.[5] Therefore, HGF is very important not only for mitogenic activity but also as a clinical indicator to predict cancer development, the severity of liver disease, and liver dysfunction after hepatectomy. However, the significance of HGF in predicting postoperative complications in liver surgery has not been clarified yet.

We surveyed patients who had complications after initial hepatectomy and compared them to patients who were discharged on schedule to identify risks for complications after hepatectomy. Furthermore, we hypothesized that the deteriorated patient condition might be a major reason for complications and result in a different clinical prognosis. The aim of this study was to identify prognostic factors among patients who had complications and those who were complication-free after initial hepatectomy in 100 consecutive HCC patients.

## Patients and Methods

### Patients

Between January 2001 and December 2005, 100 hepatocellular carcinoma patients who underwent hepatectomy were enrolled in this study with informed consent. Mortality was defined as any death in the hospital within 90 days after operation. Postoperative complications were defined and classified by the modified Clavien classification system.[14] Briefly, grade I was any deviation from the normal postoperative course without any special treatment. Grade II was requiring pharmacological treatment with drugs. Grade III was requiring surgical or radiological intervention with (IIIb) or without (IIIa) general anesthesia. Grade IV was a life-threatening complication involving single (IVa) or multiple (IVb) organ dysfunction. Grade V was the death of the patient. Of the complications ranked grade IV or higher, liver failure/insufficiency was defined as a serum bilirubin concentration of more than 10 mg/dL for more than 2 days. Portal vein thrombosis and pulmonary effusion were diagnosed either by ultrasound sonography or computed tomography with enhancement. Pneumonia was diagnosed either by respiratory symptoms with X-ray examination or proof of bacteria. Venous thrombosis was defined by a sudden respiratory distress symptom with decreased peripheral oxygen saturation regardless of proof of a thrombus. Angina pectoris/acute myocardial infarction was defined as chest pain and by electrocardiographic examination. Renal insufficiency was defined by oliguria (less than 400 mL/day) with sustained serum creatine elevation of more than 1.1 mg/dL. Although no mechanical ileus that required nasointestinal tube drainage occurred, paralytic ileus was observed with oral intake of less than 500 mL/day for more than 3 days. Gastrointestinal bleeding was diagnosed by endoscopic examination. Wound infection/dehiscence was defined as any wound that split open regardless of proof of bacteria. Ascites was defined as fluid discharge of more than 300 mL/day for more than 3 days.

We divided the patients into two groups. The complication group consisted of 32 patients who had complications of any grade during the hospital stay. The complication-free group consisted of 68 patients who were discharged within 14 days after hepatectomy. The study design conformed to

the ethical guidelines of the Declaration of Helsinki and obtained informed consent with individual signature prior to registry.

### Assessment of Clinical and Operative Variables

Routine laboratory tests conducted before hepatectomy included those for $ICGR_{15}$, hyaluronic acid as a liver fibrotic marker, prealbumin as a rapid turnover protein, HGF, AFP, PIVKAII, and GSA (HH15, LHL15). Intraoperative data and any complications during hospital stays were recorded. Tumor size, number, and vascular invasion were recorded by pathological examinations. All laboratory tests were conducted in the early morning on the day of assessment.

### Surgical Procedure

All liver resections were basically performed with Pringle maneuver techniques after more than 300 mL of intraoperative bleeding. No hepatic flow was controlled if intraoperative bleeding was less than 300 mL. A Cavitron ultrasonic aspirator (CUSA) was used for liver parenchymal dissection. Either an argon laser beam coagulator or a saline-linked monopolar electric cautery was used to achieve hemostasis. Antibiotics were administered at 30 min before laparotomy and every 3 h during the operation. Absorbable sutures (Vicryl or PDS, Johnson & Johnson Gateway, Piscataway, NJ, USA) were used for all sutures and ties except for skin closure. Skin was closed with either nylon sutures or a skin stapler. Periwound skin was washed with 500 mL of warm saline before skin closure. Either a closed-type subphrenic or hepatoduodenal drain was placed after hepatectomy and removed 2 or 3 days later.

### Statistical Analysis

For statistical analyses, demographic and perioperative laboratory tests were extracted from the database and the differences between the groups were compared using the chi-square test followed by a post hoc 2×2 Fisher exact test, when needed. Logistic regression analysis was used to identify the most relevant risks of complication. Factors determining overall survival were assessed using the Kaplan–Meier method with comparison of the log-rank test and univariate or multivariate analysis using the Cox proportional hazards regression model. The calculations were performed using the StatView 5.0 software package (Abacus Concepts, Berkeley, CA, USA) or SPSS 15.0 (SPSS, Chicago, IL, USA). The receiver operating characteristic (ROC) curve for calculating the area under the ROC curve (AUC) was determined using the MedCalc software package (Version 8.0.1.0, Mariakerke, Belgium). All results are expressed as the mean values± standard deviations (SD). $p<0.05$ was considered to be statistically significant.

## Results

In our 100 consecutive hepatectomies for HCC, 45 complications were observed in 32 patients, although 38 of the complications in 26 patients were minor ones (Table 1). Serious grade V complications consisted of two liver failures, one myocardial infarction, and one gastrointestinal hemorrhage. Although one patient recovered after intensive care, he was classified as having grade IVb liver failure and renal failure. Clinical and operative variables were compared between the two groups (Table 2). Although age, sex, the type of virus, pathological background, stage of the HCC, bilirubin, prothrombin time, tumor markers, tumor size, number of tumors, vascular invasion, and type of hepatectomy were not significantly different between the groups, the albumin ($p=0.010$), γ-glutamyl transferase ($p=0.002$), choline esterase ($p=0.008$), $ICGR_{15}$ ($p=0.007$), HA ($p=0.003$), prealbumin ($p=0.004$), HGF ($p=0.005$), HH15 ($p=0.001$), and LHL15 ($p=0.021$) levels before hepatectomy, operative time ($p=0.003$), and blood loss ($p=0.001$) were significantly different. Multivariate analysis revealed that γ-glutamyl transferase ($p=0.002$), $ICGR_{15}$ ($p=0.047$), and HGF ($p=0.003$) were independent risk factors for postoperative complications in our series (Table 3). The area under the ROC curve (AUC) was calculated for three factors (Fig. 1) and all of them were significantly different (γ-glutamyl transferase: $p=0.005$; $ICGR_{15}$: $p=0.002$; HGF: $p<0.001$).

The recurrence-free survival curve and overall survival curve are shown in Fig. 2. Although the recurrence-free survival was not significantly different between the two groups ($p=0.108$), the overall survival probability was significantly different ($p=0.036$). Mean overall survival times were 58.94±4.14 months in the complication-free group and 39.07±5.75 months in the complication group. Univariate (Table 4) and multivariate (Table 5) analyses were performed to identify significant impacts on overall survival among clinical and operative variables in each group independently. Univariate analysis using the Cox proportional hazards model in the complication group revealed that the pathological background ($p=0.031$), stage of the HCC ($p=0.004$), HGF ($p=0.015$), AFP ($p=0.004$), PIVKAII ($p=0.005$), tumor size ($p=0.004$), vascular invasion ($p=0.041$), and blood loss ($p=0.006$) were significant risk factors in this group. On the other hand, in the complication-free group, albumin ($p=0.024$), $ICGR_{15}$ ($p=0.001$), prealbumin ($p=0.001$), tumor size ($p=0.001$), and blood loss ($p=0.018$) were significant risk factors. Multivariate analysis of these factors in the complication group showed that the stage of

**Table 1** Postoperative Complications in 32 Patients

| Complications | Total number | Grade of surgical complication | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | I | II | IIIa | IIIb | IVa | IVb | V |
| Liver/biliary | | | | | | | | |
| Liver failure/insufficiency | 4 | | | | | 1 | 1 | 2 |
| Bile leak | 2 | | | 2 | | | | |
| Portal vein thrombosis | 2 | | 2 | | | | | |
| Pulmonary | | | | | | | | |
| Pleural effusion (symptomatic) | 6 | 2 | 2 | 2 | | | | |
| Pneumonia | 2 | | 2 | | | | | |
| Cardiovascular | | | | | | | | |
| Venous thrombosis | 2 | | 2 | | | | | |
| Angina pectoris/myocardial infarction | 1 | | | | | | | 1 |
| Genitourinary | | | | | | | | |
| Renal insufficiency/failure | 2 | | 1 | | | | 1 | |
| Gastrointestinal | | | | | | | | |
| Ileus | 3 | | | 3 | | | | |
| Gastrointestinal hemorrhage | 2 | | | 1 | | | | 1 |
| Miscellaneous | | | | | | | | |
| Wound infection/dehiscence | 8 | 6 | 2 | | | | | |
| Ascites | 11 | 4 | 5 | 2 | | | | |
| Total number (complications/patients) | 45/32 | 38/26 | | | | 7/6 | | |

Grades of surgical complications are according to modified Clavien classification

**Table 2** Clinical and Operative Variables in HCC Patients After Initial Curative Hepatectomy

| Variables | Complication ($n$=32) | Complication-free ($n$=68) | $p$ value |
|---|---|---|---|
| Age (years) | 64.69±8.65 | 61.87±10.45 | 0.189 |
| Sex (male/female) | 26:6 | 50:18 | 0.391 |
| Etiology (B/C/NBNC) | 18:13:1 | 43:19:6 | 0.101 |
| Background (CH/LC/N) | 9:21:2 | 27:32:9 | 0.199 |
| Stage (I/II/III/IV) | 5:10:12:5 | 17:22:20:9 | 0.707 |
| Albumin (g/dL) | 3.73±0.43 | 3.95±0.44 | 0.010* |
| Bilirubin (mg/dL) | 0.92±0.39 | 0.84±0.36 | 0.243 |
| Prothrombin time (%) | 93.19±17.44 | 98.59±12.15 | 0.081 |
| γ-Glutamyl transferase (IU/L) | 140.05±108.36 | 87.54±81.15 | 0.002* |
| Choline esterase (IU/L) | 193.74±71.13 | 233.25±79.97 | 0.008* |
| $ICGR_{15}$ (%) | 18.32±9.14 | 13.73±8.73 | 0.007* |
| Hyaluronic acid (ng/mL) | 264.25±251.65 | 162.12±142.61 | 0.003* |
| Prealbumin (mg/dL) | 13.96±6.79 | 18.75±7.76 | 0.004* |
| HGF (ng/mL) | 0.43±0.22 | 0.33±0.14 | 0.005* |
| AFP (ng/mL) | 5,254.56±17,866.77 | 2,164.15±11,688.14 | 0.236 |
| PIVKAII (mAU/mL) | 4,718.72±16,174.82 | 4,955.79±19,361.02 | 0.947 |
| HH15 | 0.652±0.095 | 0.593±0.074 | 0.001* |
| LHL15 | 0.902±0.055 | 0.924±0.037 | 0.021* |
| Tumor size (cm) | 4.69±3.31 | 4.54±3.44 | 0.820 |
| Tumor number | 1.97±1.44 | 1.69±1.21 | 0.267 |
| Vascular invasion (negative/positive) | 16:16 | 36:32 | 0.783 |
| Type of resection (Hr0 or HrS/Hr1/Hr2/Hr3) | 19:4:6:3 | 42:15:9:2 | 0.063 |
| Operation time (min) | 425.91±279.06 | 298.23±96.01 | 0.003* |
| Blood loss (mL) | 1,308.78±1,474.34 | 562.17±503.54 | 0.001* |

*HCC*: hepatocellular carcinoma, *B*: HBV, *C*: HCV, *NBNC*: non-B and non-C hepatitis, *CH*: chronic hepatitis, *LC*: liver cirrhosis, *N*: normal liver, $ICGR_{15}$: indocyanine green retention rate at 15 min, *AFP*: alpha fetoprotein, *PIVKAII*: protein induced by vitamin K absence or antagonist II, *HH15*: clearance index, *LHL15*: receptor index, *Hr0*: partial resection, *HrS*: subsectionectomy, *Hr1*: sectionectomy, *Hr2*: hemihepatectomy, *Hr3*: trisectionectomy

*$p<0.05$

**Table 3** Logistic Regression Analysis for Contributing to Risk of Complications After Liver Resection in HCC Patients

| Variables | | Odds ratio | 95%CI | *p* value |
|---|---|---|---|---|
| Albumin (g/dL) | >4.0 | 1 | 0.245–5.929 | 0.819 |
| | ≤4.0 | 1.204 | | |
| γ-Glutamyl transferase (IU/L) | <100 | 1 | 2.216–33.278 | 0.002* |
| | ≥100 | 8.587 | | |
| Choline esterase | ≥200 | 1 | 0.092–2.736 | 0.425 |
| | <200 | 0.502 | | |
| $ICGR_{15}$ (%) | <10 | 1 | 1.026–35.500 | 0.047* |
| | ≥10 | 6.034 | | |
| Hyaluronic acid (ng/mL) | <130 | 1 | 0.026–1.097 | 0.062 |
| | ≥130 | 0.168 | | |
| Prealbumin (mg/dL) | ≥15 | 1 | 0.591–11.788 | 0.204 |
| | <15 | 2.639 | | |
| HGF (ng/mL) | <0.35 | 1 | 2.392–65.979 | 0.003* |
| | ≥0.35 | 12.562 | | |
| HH15 | <0.60 | 1 | 0.210–4.315 | 0.951 |
| | ≥0.06 | 0.953 | | |
| LHL15 | ≥0.9 | 1 | 0.665–16.331 | 0.144 |
| | <0.9 | 3.295 | | |
| Operation time (min) | <300 | 1 | 0.704–11.218 | 0.143 |
| | ≥300 | 2.810 | | |
| Blood loss (mL) | <600 | 1 | 0.125–2.437 | 0.432 |
| | ≥600 | 0.551 | | |

*HCC*: hepatocellular carcinoma, *$ICGR_{15}$*: indocyanine green retention rate at 15 min, *HGF*: hepatocyte growth factor, *HH15*: clearance index, *LHL15*: receptor index
*$p<0.05$

the HCC ($p=0.036$) and HGF ($p=0.006$) were significant independent risk factors for overall survival, but in the complication-free group, tumor size ($p=0.015$) was the only significant independent risk factor for overall survival.

## Discussion

We showed in this study that perioperative complications could be risk factors indicative of overall prognosis. Among

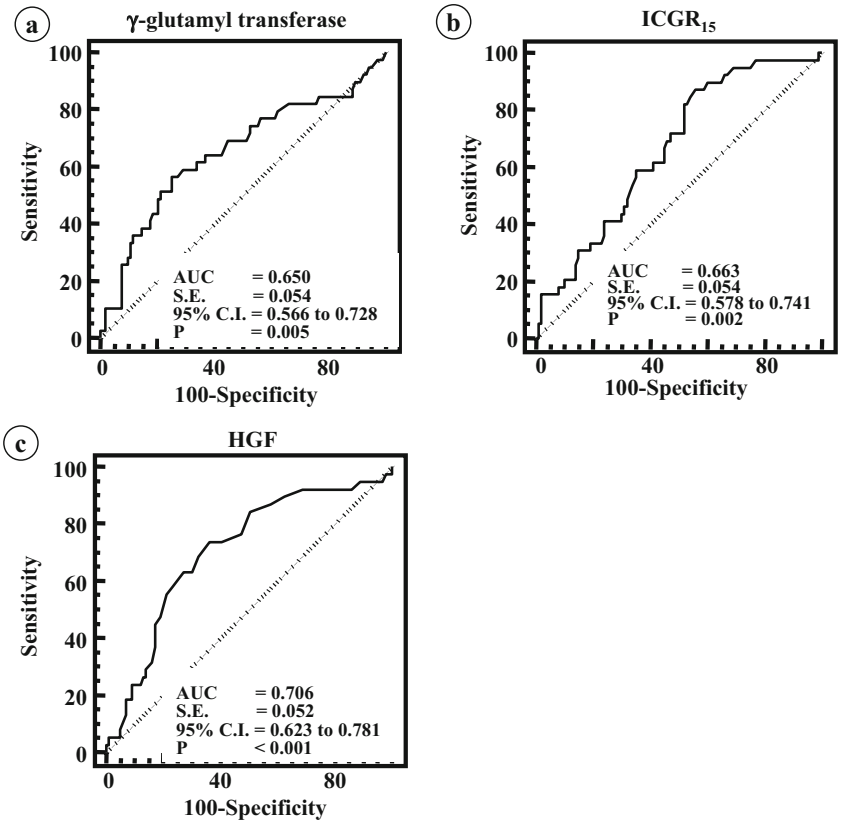


**Figure 1** ROC curves of γ-glutamyl transferase (**a**), $ICGR_{15}$ (**b**), and HGF (**c**) for predicting complications after initial hepatectomy for HCC patients. *AUC* area under the ROC curve, *S.E.* standard error, *C.I.* confidence interval. $p<0.05$ was considered to be significant.

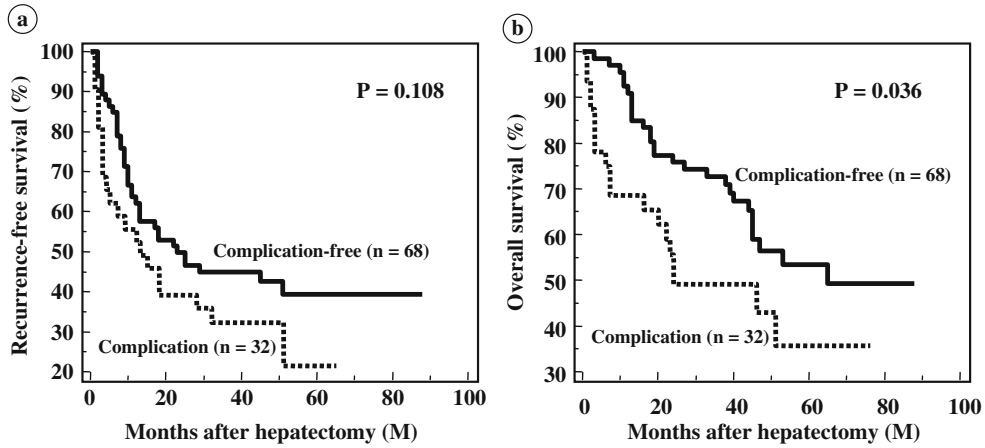


**Figure 2** Recurrence-free survival curve (**a**) and overall survival curve (**b**) after initial hepatectomy for 100 HCC patients in the complication group ($n$=32, *dotted line*) and complication-free group ($n$=68, *solid line*). Mean recurrence-free times in the complication group and the complication-free group were 25.64±4.69 and 43.26±4.74 months, respectively ($p$=0.108). Mean overall survival times in the complication group and the complication-free group were 39.07±5.75 and 58.94±4.14 months, respectively ($p$=0.036).

the clinical and operative variables, γ-glutamyl transferase, $ICGR_{15}$, and HGF were independent risk factors for postoperative complications. Furthermore, HGF was an independent prognostic factor in the complication group in addition to the stage of the HCC. On the other hand, tumor size was the only independent prognostic factor in the complication-free group. Our study indicated a close relation between postoperative complications and overall survival in HCC patients after initial hepatectomy.

Morbidity and mortality after hepatectomy have been reduced by recent surgical procedures.[6,11,15] However, the quality of postoperative complications is still being debated. In fact, morbidity due to hepatectomy varied from 10% to 50% in a past study.[16] The variability of the morbidity in the literature was due to a lack of proper definition of surgical complications.[17] Recently, a definition of surgical complications has been proposed with a clear classification. The modified Clavien classification of surgical complications is a well-organized system in which any deviation from the normal perioperative course can be recorded.[14] Based on this classification, bias with regard to surgical complications in our study could be minimized.

Under minimal bias of surgical complications, morbidity reflects the balance between the patient's condition and surgical skill or management. The large case study of Blumgart and colleagues found that the number of resected segments and estimated blood loss were high risk factors for morbidity and mortality after hepatectomy.[18] Another study of 100 major hepatic resections also showed that blood transfusion, which was associated with blood loss, was a risk factor for morbidity after surgery.[19] These reports indicated that there was more bleeding and longer operation time in more severe cases in which the patient's condition might deteriorate and become vulnerable to surgical complications. Although our results showed that operation time and blood loss lost significance in multivariate analysis, in univariate analysis they were significantly different, which was partly consistent with previous reports. Furthermore, the hepatic background in the complication-free group tended to be less cirrhotic, which could make it easier control bleeding than in the complication group, although there was no significant difference between the groups. We, however, could not rule out the possibility that we employed less-invasive hepatic resection in cirrhotic cases and more aggressive hepatic resection in normal cases. As long as we conducted our routine liver resection for HCC patients, the intrinsic patient condition was a more significant risk factor for postoperative complications in our 100-case series than operative variables. Therefore, it is possible that we could not have prevented most postoperative complications in our series even if our surgical approach were reconsidered to reduce morbidity. In other words, postoperative complications are dependent on the patient's condition and cannot be totally avoided.

Furthermore, our study showed the prognostic impact of postoperative complications for HCC patients, although disease-free survival was not significantly different. The prognosis of the HCC patient after hepatectomy partially depends on the liver function,[11] which is associated with increased opportunities for various treatments. The longer overall survival in the complication-free group indicated that fundamental liver function in this group was better than that in the complication group. In fact, comparison of clinical variables between the two groups indicated that liver function in the complication-free group was much better than that of the complication group. Therefore, the survival difference between the groups was most likely due to the difference of fundamental liver function. If surgical complications randomly occurred due to technical errors, liver functions should have been similar between the

**Table 4** Univariate Analysis for Clinical Factors Contributing to Overall Survival After Liver Resection in HCC Patients

| Variables | | Complication ($n$=32) | | | | Complication-free ($n$=68) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | $n$ | Hazard ratio | 95%CI | $p$ value | $n$ | Hazard ratio | 95%CI | $p$ value |
| Age (years) | <65 | 13 | 1 | 0.634–4.828 | 0.280 | 35 | 1 | 0.438–2.294 | 0.994 |
| | ≥65 | 19 | 1.749 | | | 33 | 1.003 | | |
| Sex | Men | 26 | 1 | 0.466–4.567 | 0.516 | 50 | 1 | 0.262–2.273 | 0.638 |
| | Women | 6 | 1.459 | | | 18 | 0.772 | | |
| Etiology (NBNC, B/C) | N, B | 19 | 1 | 0.460–3.284 | 0.681 | 49 | 1 | 0.279–1.801 | 0.469 |
| | C | 13 | 1.229 | | | 19 | 0.709 | | |
| Background (N, CH/LC) | N, CH | 11 | 1 | 1.085–5.552 | 0.031* | 36 | 1 | 0.593–3.870 | 0.386 |
| | LC | 21 | 2.455 | | | 32 | 1.514 | | |
| Stage (I, II/III, IV) | I, II | 15 | 1 | 1.801–22.972 | 0.004* | 39 | 1 | 0.990–6.181 | 0.052 |
| | III, IV | 17 | 6.433 | | | 29 | 2.474 | | |
| Albumin (g/dL) | ≥4.0 | 9 | 1 | 0.412–4.086 | 0.656 | 34 | 1 | 1.143–6.850 | 0.024* |
| | <4.0 | 24 | 1.297 | | | 34 | 2.798 | | |
| Bilirubin (mg/dL) | <1.0 | 24 | 1 | 0.559–4.705 | 0.373 | 51 | 1 | 0.738–4.128 | 0.205 |
| | ≥1.0 | 8 | 1.622 | | | 17 | 1.745 | | |
| Prothrombin time (%) | ≥90 | 20 | 1 | 0.590–4.273 | 0.360 | 52 | 1 | 0.560–3.390 | 0.485 |
| | <90 | 12 | 1.588 | | | 16 | 1.378 | | |
| γ-Glutamyl transferase (IU/L) | <100 | 12 | 1 | 0.799–7.845 | 0.115 | 52 | 1 | 0.615–3.447 | 0.392 |
| | ≥100 | 20 | 2.504 | | | 16 | 1.457 | | |
| Choline esterase (IU/L) | ≥200 | 17 | 1 | 0.519–3.761 | 0.508 | 46 | 1 | 1.933–10.418 | 0.001* |
| | <200 | 15 | 1.397 | | | 22 | 4.488 | | |
| $ICGR_{15}$ (%) | <10 | 5 | 1 | 0.491–28.439 | 0.203 | 42 | 1 | 0.957–6.314 | 0.062 |
| | ≥10 | 27 | 3.736 | | | 26 | 2.457 | | |
| Hyaluronic acid (ng/mL) | <130 | 11 | 1 | 0.712–8.786 | 0.152 | 39 | 1 | 1.868–11.168 | 0.001* |
| | ≥130 | 21 | 2.501 | | | 29 | 4.568 | | |
| Prealbumin (mg/dL) | ≥15 | 12 | 1 | 0.856–10.588 | 0.585 | 45 | 1 | 2.075–12.015 | 0.001* |
| | <15 | 20 | 3.011 | | | 23 | 4.993 | | |
| HGF (ng/mL) | <0.35 | 20 | 1 | 1.424–29.258 | 0.015* | 50 | 1 | 0.937–5.288 | 0.069 |
| | ≥0.35 | 12 | 6.456 | | | 18 | 2.226 | | |
| AFP (ng/mL) | <100 | 20 | 1 | 1.615–12.671 | 0.004* | 47 | 1 | 0.499–2.786 | 0.707 |
| | ≥100 | 12 | 4.524 | | | 21 | 1.179 | | |
| PIVKAII (mAU/mL) | <100 | 16 | 1 | 1.766–24.099 | 0.005* | 39 | 1 | 0.657–3.384 | 0.339 |
| | ≥100 | 16 | 6.524 | | | 29 | 1.491 | | |
| HH15 | <0.60 | 13 | 1 | 0.335–5.063 | 0.703 | 35 | 1 | 0.336–3.028 | 0.987 |
| | ≥0.06 | 19 | 1.301 | | | 33 | 1.009 | | |
| LHL15 | ≥0.9 | 13 | 1 | 0.134–2.106 | 0.368 | 54 | 1 | 0.398–5.317 | 0.571 |
| | <0.9 | 19 | 0.532 | | | 14 | 1.454 | | |
| Tumor size (cm) | <5 | 19 | 1 | 1.645–15.717 | 0.004* | 53 | 1 | 2.137–12.790 | 0.001* |
| | ≥5 | 13 | 5.085 | | | 13 | 5.228 | | |
| Tumor number | Single | 18 | 1 | 0.834–7.505 | 0.101 | 40 | 1 | 0.900–5.267 | 0.084 |
| | Multiple | 14 | 2.502 | | | 28 | 2.177 | | |
| Vascular invasion | Negative | 16 | 1 | 1.052–10.804 | 0.041* | 36 | 1 | 0.831–4.892 | 0.122 |
| | Positive | 16 | 3.371 | | | 32 | 2.016 | | |
| Type of resection (Hr0,S/Hr1–3) | Hr0,S | 19 | 1 | 0.545–3.974 | 0.446 | 42 | 1 | 0.369–2.726 | 0.995 |
| | Hr1–3 | 13 | 1.471 | | | 26 | 1.003 | | |
| Operation time (min) | <300 | 12 | 1 | 0.764–7.516 | 0.134 | 40 | 1 | 0.198–2.107 | 0.468 |
| | ≥300 | 20 | 2.396 | | | 28 | 0.645 | | |
| Blood loss (mL) | <600 | 13 | 1 | 1.795–35.245 | 0.006* | 44 | 1 | 1.146–10.853 | 0.018* |
| | ≥600 | 19 | 7.953 | | | 24 | 3.526 | | |

*HCC*: hepatocellular carcinoma, *B*: HBV, *C*: HCV, *NBNC*: non-B and non-C hepatitis, *CH*: chronic hepatitis, *LC*: liver cirrhosis, *N*: normal liver, $ICGR_{15}$: indocyanine green retention rate at 15 min, *HGF*: hepatocyte growth factor, *AFP*: alpha fetoprotein, *PIVKAII*: protein induced by vitamin K absence or antagonist II, *HH15*: clearance index, *LHL15*: receptor index, *Hr0*: partial resection, *HrS*: subsectionectomy, *Hr1*: sectionectomy, *Hr2*: hemihepatectomy, *Hr3*: trisectionectomy

*$p$<0.05

**Table 5** Multivariate Analysis for Contributing to Overall Survival After Liver Resection in HCC Patients

| Variables | | Hazard ratio | 95%CI | *p* value |
|---|---|---|---|---|
| Complication ($n$=32) | | | | |
| Stage (I, II/III, IV) | I, II | 1 | 1.301–3896.771 | 0.036* |
| | III, IV | 72.212 | | |
| HGF (ng/mL) | <0.35 | 1 | 4.146–5421.990 | 0.006* |
| | ≥0.35 | 149.935 | | |
| AFP (ng/mL) | <100 | 1 | 0.119–157.582 | 0.423 |
| | ≥100 | 4.335 | | |
| PIVKAII (mAU/mL) | <100 | 1 | 0.252–18.559 | 0.482 |
| | ≥100 | 2.161 | | |
| Tumor size (cm) | <5 | 1 | 0.009–2.414 | 0.179 |
| | ≥5 | 0.147 | | |
| Blood loss (mL) | <600 | 1 | 0.650–106.304 | 0.103 |
| | ≥600 | 8.312 | | |
| Complication-free ($n$=68) | | | | |
| Albumin (g/dL) | ≥4.0 | 1 | 0.278–10.507 | 0.562 |
| | <4.0 | 1.710 | | |
| Choline esterase (IU/L) | ≥200 | 1 | 0.074–6.846 | 0.766 |
| | <200 | 0.710 | | |
| Hyaluronic acid (ng/mL) | <130 | 1 | 0.745–18.819 | 0.109 |
| | ≥130 | 3.744 | | |
| Prealbumin (mg/dL) | ≥15 | 1 | 0.412–38.993 | 0.232 |
| | <15 | 4.008 | | |
| Tumor size (cm) | <5 | 1 | 1.377–21.299 | 0.015* |
| | ≥5 | 5.416 | | |
| Blood loss (mL) | <600 | 1 | 0.255–6.916 | 0.736 |
| | ≥600 | 1.328 | | |

*HCC*: hepatocellular carcinoma, *CI*: confidence interval, *HGF*: hepatocyte growth factor, *AFP*: alpha fetoprotein, *PIVKAII*: protein induced by vitamin K absence or antagonist II
*$p<0.05$

groups. In such a case, no survival impact would be observed and our results could not have been obtained. Therefore, complications could become a prognostic factor as long as the surgical technique and management are properly conducted.

In the complication group, HGF was one of the independent prognostic factors besides the stage of the disease. The serum HGF level represents the severity of clinical liver disease.[8,9] HGF is correlated with pathological fibrosis and the presence of hepatocellular carcinoma.[9] Severe pathological fibrosis could be a cause of perioperative complications and the presence of HCC leading to a poor prognosis. In the complication group, high HGF indicated disease deterioration with poor liver function. Additional therapy for recurrence in this group was difficult due to poor liver function. Basically, HGF function in the normal liver could play an important role for hepatocyte survival and tissue remodeling.[20] However, our study and others seem to show controversial results in the clinical setting. This indicates that the liver is desensitized to HGF signals for some reason when liver disease deteriorates. Therefore, a high HGF level in a diseased patient does not have a biological effect on the diseased liver. This suggests that the function of c-*met*, as an HGF receptor, may decrease or the activity of HGF itself may be reduced. Receptor abnormality[21] and the inactive form of HGF[22] are considered to be potential mechanisms of the HGF elevation in liver disease, including HCC. In some way, the mechanism quenching HGF from the serum fails and the signals never go through the hepatocytes. On the other hand, cancer cells, apart from the normal hepatocytes, might respond to mitogenic activity of HGF, which might promote disease progression and affect overall survival.

## Conclusion

We surveyed 100 consecutive HCC patients who had initial hepatectomy. Postoperative complications were recorded with the modified Clavien classification. We have shown that postoperative surgical complications could be a prognostic factor for overall survival in our study. Furthermore, a high serum HGF level could be a risk factor for complications and overall survival in this group, although we observed no difference of recurrence-free time between the groups due to the small number of subjects on this study. A large number of multiple center trials should be designed to clarify the prognostic value of the preoperative HGF level in the future.

**Acknowledgments** We thank Kim Barrymore for his help in preparing this manuscript. This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, no. 20591615 to T. Mizuguchi.

## References


1. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999;340:745–750. doi:10.1056/NEJM199903113401001.
2. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907–1917. doi:10.1016/S0140-6736(03)14964-1.
3. Schneider PD. Preoperative assessment of liver function. Surg Clin North Am 2004;84:355–373. doi:10.1016/S0039-6109(03)00224-X.
4. Kwon AH, Ha-Kawa SK, Uetsuji S, Kamiyama Y, Tanaka Y. Use of technetium 99m diethylenetriamine-pentaacetic acid-galactosyl-human serum albumin liver scintigraphy in the evaluation of preoperative and postoperative hepatic functional reserve for hepatectomy. Surgery 1995;117:429–434. doi:10.1016/S0039-6060(05)80063-7.
5. Mizuguchi T, Katsuramaki T, Nobuoka T, Kawamoto M, Oshima H, Kawasaki H et al. Serum hyaluronate level for predicting subclinical liver dysfunction after hepatectomy. World J Surg 2004;28:971–976. doi:10.1007/s00268-004-7389-1.
6. Vauthey JN, Pawlik TM, Abdalla EK, Arens JF, Nemr RA, Wei SH et al. Is extended hepatectomy for hepatobiliary malignancy justified? Ann Surg 2004;239:722–730. doi:10.1097/01.sla.0000124385.83887.d5.
7. Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK et al. Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. Ann Surg 2004;240:698–708. doi:10.1097/01.sla.0000143808.63039.51.
8. Shiota G, Okano J, Kawasaki H, Kawamoto T, Nakamura T. Serum hepatocyte growth factor levels in liver diseases: clinical implications. Hepatology 1995;21:106–112.
9. Yamagamim H, Moriyama M, Matsumura H, Aoki H, Shimizu T, Saito T et al. Serum concentrations of human hepatocyte growth factor is a useful indicator for predicting the occurrence of hepatocellular carcinomas in C-viral chronic liver diseases. Cancer 2002;95:824–834. doi:10.1002/cncr.10732.
10. Ikai I, Arii S, Kojiro M, Ichida T, Makuuchi M, Matsuyama Y et al. Reevaluation of prognostic factors for survival after liver resection in patients with hepatocellular carcinoma in a Japanese nationwide survey. Cancer 2004;101:796–802. doi:10.1002/cncr.20426.
11. Kaibori M, Matsui Y, Hijikawa T, Uchida Y, Kwon AH, Kamiyama Y. Comparison of limited and anatomic hepatic resection for hepatocellular carcinoma with hepatitis C. Surgery 2006;139:385–394. doi:10.1016/j.surg.2005.08.035.
12. Gohda E, Tsubouchi H, Nakayama H, Hirono S, Takahashi K, Koura M et al. Human hepatocyte growth factor in plasma from patients with fulminant hepatic failure. Exp Cell Res 1986;166:139–150. doi:10.1016/0014-4827(86)90514-8.
13. Breuhahn K, Longerich T, Schirmacher P. Dysregulation of growth factor signaling in human hepatocellular carcinoma. Oncogene 2006;25:3787–3800. doi:10.1038/sj.onc.1209556.
14. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–213. doi:10.1097/01.sla.0000133083.54934.ae.
15. Poon RT, Fan ST. Hepatectomy for hepatocellular carcinoma: patient selection and postoperative outcome. Liver Transpl 2004;10:S39–S45. doi:10.1002/lt.20040.
16. Llovet JM, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma. Semin Liver Dis 2005;25:181–200. doi:10.1055/s-2005-871198.
17. Martin RC 2nd, Brennan MF, Jaques DP. Quality of complication reporting in the surgical literature. Ann Surg 2002;235:803–813. doi:10.1097/00000658-200206000-00007.
18. Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg 2002;236:397–406. doi:10.1097/00000658-200210000-00001.
19. Pol B, Campan P, Hardwigsen J, Botti G, Pons J, Le Treut YP. Morbidity of major hepatic resections: a 100-case prospective study. Eur J Surg 1999;165:446–453. doi:10.1080/110241599750006686.
20. Huh CG, Factor VM, Sanchez A, Uchida K, Conner EA, Thorgeirsson SS. Hepatocyte growth factor/c-met signaling pathway is required for efficient liver regeneration and repair. Proc Natl Acad Sci U S A 2004;101:4477–4482. doi:10.1073/pnas.0306068101.
21. D'Errico A, Fiorentino M, Ponzetto A, Daikuhara Y, Tsubouchi H, Brechot C et al. Liver hepatocyte growth factor does not always correlate with hepatocellular proliferation in human liver lesions: its specific receptor c-met does. Hepatology 1996;24:60–64.
22. Arakaki N, Kawakami S, Nakamura O, Ohnishi T, Miyazaki H, Ishii T et al. Evidence for the presence of an inactive precursor of human hepatocyte growth factor in plasma and sera of patients with liver diseases. Hepatology 1995;22:1728–1734.