Observational Study

Liver fibrosis is a major risk factor for liver regeneration
A comparison between healthy and fibrotic liver

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Abstract

Background: Blood flow factors, such as congestion or ischemia after hepatectomy, have a significant impact on liver regeneration, but with the popularization of precise hepatectomy technology, segmental hepatectomy without congestion or ischemia has become the preferred treatment. Our aim is to investigate the factors affecting liver regeneration after hepatectomy without blood flow changes, and to provide clinical evidence for surgeons on the timing of second hepatectomy for cirrhosis patients with hepatocellular carcinoma (HCC).

Methods: This study retrospectively analyzed data from patients who underwent right hepatectomy without middle hepatic vein (MHV) in West China Hospital between January 2016 and January 2018. Eighteen living-donors without MHV as normal group and 45 HCC patients, further classified into 3 subgroups based on the severity of fibrosis using the Scheuer system. Demographic data, pre- and postoperative liver function indexes, and remnant liver volume (RLV) were retrospectively compared. We also analyzed the remnant liver regeneration rate (RLRR) post-operatively in each group. The significant indexes in univariate analysis were further analyzed using both receiver operating characteristic (ROC) analysis and multivariate regression analysis.

Results: Liver regeneration occurred in both living-donor and HCC groups after hepatectomy; the RLRRs at 1 month were 59.46±10.39% and 57.27±4.77% (P = .509), respectively. Regeneration in the cirrhosis group occurred more slowly and less completely compared with that in other groups. The regeneration rate in the first 6 months showed rapid increase and the RLRR reached above 70% in cirrhosis group. Multivariate and ROC analyses revealed that Alb and the hepatic fibrosis grade in the early postoperative period were significant predictors of remnant liver regeneration.

Conclusion: The liver regenerated in all HCC patients; however, regeneration was significantly slower and less complete compared with the normal liver, especially in the patients with cirrhosis. Therefore, it can be concluded that the degree of liver fibrosis is a major predictor of liver regeneration. Furthermore, the optimal time for second resection in recurrent HCC patients with cirrhosis was 6 months after the first operation.

Abbreviations: Alb = Albumin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, Cre = creatinine, CT = computed tomographic, Hb = hemoglobin, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, ICG = indocyanine green, INR = International normalized ratio, LR = liver resection, MHV = middle hepatic vein, MRE = magnetic resonance electrography, PHLF = posthepatic liver failure, Plt = platelet, POD = postoperative day, PRLV = postoperative remnant liver volume, PT = prothrombin time, RFA = radiofrequency ablation, RLRR = remnant liver regeneration rate, RLV = remnant liver volume, ROC = receiver operating characteristic, RR = re-resection, SLT = salvage liver transplantation, TACE = transcatheter arterial chemoembolization, Tbil = total bilirubin, TLV = total liver volume.

Keywords: fibrosis, hepatocellular carcinoma, liver regeneration, living donor, right hepatectomy

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide[1]; more than half of the incidence of HCC in the world occurs in China.[2] Epidemiological studies in China have revealed that more than 80% of HCC cases were preceded by chronic hepatitis B virus (HBV), which is characterized by histopathological developments, such as fibrosis and cirrhosis.[3]

Unlike other organs, a normal liver has enormous regeneration capacity. After liver resection (LR), residual liver tissue, with basic normal structure and sufficient blood supply, will be able to restore itself to its original size, and liver function may return to normal.[4,5] According to the European Association for the Study of the Liver guidelines, surgical therapy for HCC is still the mainstay of all HCC treatment, leading to the best outcomes of any treatment available in well-selected candidates.[6] LR is the preferred surgical treatment for HCC with fibrosis or cirrhosis because of the limitation of donor pool and the high medical cost for liver transplantation.[7,8] However, excessive hepatectomy in...
patients with cirrhosis often leads to liver failure, making it difficult for patients to survive the perioperative period without liver transplantation.

To avoid liver failure after LR, and its associated risk of fatality, a great deal of clinical research has focused on liver regeneration. Current studies suggest that the rate of liver regeneration is primarily related to blood flow into the liver, which may be related to portal vein pressure and hepatic artery velocity. However, with improvements in surgical technique, there is no congestion or ischemia in the residual liver after operation. Thus, it is necessary to study factors of liver regeneration without blood flow changes. When blood flow changes are excluded, it is presumed that liver fibrosis or cirrhosis may affect the rate of liver regeneration. The pathogenesis of liver fibrosis and cirrhosis is a lengthy process and the severity of the clinical manifestations varies. It is difficult to apply cirrhosis as a risk factor in a clinical setting, because most patients with hepatocellular carcinoma, caused by HBV, have more or less fibrosis. Therefore, it is necessary to study the relationship between the degree of fibrosis and the rate of regeneration. There are a few reports on the rate of liver regeneration with varying degrees of fibrosis; these reports often lack the control of normal liver regeneration. In our study, the remnant liver of living donor liver transplantation after hepatectomy was used as a control group to obtain a normal liver regeneration rate. We used the Scheuer grading system to determine the degree of liver fibrosis in HCC patients, and we monitored the post-operative liver conditions to ascertain other factors affecting the regeneration of the residual liver.

2. Materials and methods

2.1. Patients and data sources

HCC patients and living-donors, who had undergone right hepatectomy without middle hepatic vein (MHV) between January 2016 and January 2018 at West China hospital of Sichuan University, China, were enrolled in this retrospective study (Fig. 1). The Institutional Review Board of West China Hospital of Sichuan University gave its final approval to perform surgery only after informed consent was obtained from patients and/or their legal guardians.

The medical records of living donors were obtained from the Chinese Liver Transplant Registry (CLTR: http://cltr.cotr.cn). Inclusion criteria for donor selection were as follows: aged 18 to 60 years, healthy, ABO compatible, lineal relatives within three generations or spouses, and an estimated remnant liver volume (preoperative estimated total liver volume - estimated graft volume) >35% of the total liver volume (TLV).

Forty-five HCC patients who had received right hepatectomy without MHV (the MHV trunk was preserved in the remnant liver) were included in this retrospective study. HCC diagnosis and liver fibrosis stage were confirmed by histopathological examination of a surgical sample. All of the patients with HCC were further divided into three subgroups based on the pathological fibrosis degree, using the Scheuer grading system. The presence of Albumin (Alb), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum bilirubin level, coagulation function, platelet (Plt), tumor volume, and remnant liver volume (RLV, calculated by subtracting the resected liver weight from the TLV) were considered when selecting HCC patients for surgery. Only PLT > 70g/L, RLV > 35% (RLV > 45% in cirrhosis patients) of functional liver volume (FLV, TLV-tumor volume), Child-Pugh A, a follow-up time greater than twelve months, available abdominal computed tomographic (CT) every 1 to 3 months, and patients with HBV infection were included.

In both HCC and living donor groups, the data drawn from electronic medical records included the age, sex, height, weight, liver biopsy result, postoperative complications, length of postoperative hospitalization, as well as pre and 1st to 7th postoperative day (POD) blood values: hemoglobin (Hb), total bilirubin (Tbil), ALT, AST, PLT, creatinine (Cre), prothrombin
time (PT), and International normalized ratio (INR). We also estimated the preoperative TLV, tumor volume, and postoperative RLV after 1, 3, 6, and 12 months by contrast-enhanced computed tomography (CT) during the follow-up period.

2.2. Liver volume measurements

All the living donors and HCC patients underwent a three-dimensional helical CT or contrast-enhanced CT examination to measure the TLV, tumor volume, and right liver volume with/without the MHV prior to surgery. Follow-up contrast-enhanced CT scans were performed every 1 to 3 months in both groups. CT volumetric analysis of TLV, tumor volume, FLV, RLV and postoperative remnant liver volume (PRLV) were calculated at different intervals by a semiautomatic three-dimensional imaging analysis program after marking the liver contours on cross-section images. We also calculated the postoperative remnant liver regeneration rate (RLRR, PRLV/FLV × 100%) in each group. The resected liver volume of donors was used as the resected liver weight because the liver has nearly the same density as water.[11] Postoperative changes in liver regeneration in both groups were compared according to the histological degree of liver fibrosis.

2.3. Grading of liver fibrosis

A liver biopsy of the resected specimen was performed to evaluate the severity of liver fibrosis, via the Scheuer grading system, in all of the HCC patients.[12] Liver fibrosis was graded from S0 through S4 (Fig. 2); the 45 HCC patients were further classified into 3 subgroups based on the assigned grade using the Scheuer system: patients with liver fibrosis grade S0-S1 (mild fibrosis group, n = 14); patients with liver fibrosis grade S2-S3 (advanced fibrosis group, n = 15); and patients with liver fibrosis grade S4 (cirrhosis group, n = 16).

2.4. Statistical analysis

Statistical analyses were performed using the SPSS program (version 23.0 for Windows, SPSS Inc., US). After testing for normal distribution using Kurtosis and Skewness tests, descriptive variables were expressed as a mean ± standard deviation or as a median (ranges). Qualitative variables were expressed as frequencies. Student’s t test, Mann–Whitney U test, and repeated measures analysis of variance (ANOVA) were used for continuous variables. Categorical parameters were compared using the X² test or Fisher exact test, as appropriate. Significant variables in the univariate analyses were further analyzed using both receiver operating characteristic (ROC) analysis and multivariate logistic regression.
regression to identify the most important factors. A \( P \) value < .05 was considered statistically significant.

3. Results

3.1. Baseline data of patients

A total of 45 HCC patients with HBV and 18 living donors who underwent right hepatectomy without MHV were included in this study. Table 1 shows the demographic and baseline data of all patients. Among them, the mean age, sex, body mass index (BMI), Hb, WBC, Cre, and Alb were similar among the 4 groups (\( P > .05 \)). The preoperative liver function indexes, including ALT, AST, PT, and Tbl, were excluded in the baseline comparison because of the effect of fibrosis on these indicators. No significant differences in the tumor diameter, serum AFP, and intraoperative variables (blood loss, blood transfusion, operation time) were observed between groups (\( P > .05 \)).

3.2. Postoperative characteristics

The serial changes in liver function parameters (ALT, AST, Tbl, PT) after hepatectomy for the living-donor and fibrosis groups are shown in Figure 3. ALT, AST, Tbl, and PT were elevated in
both donor and HCC groups on POD 1 or 2 but normalized by the end of week one. The mean peak value of ALT (361.31 vs 856.67 ml/L, P > .99), AST (404.81 vs 328.33 U/L, P = .893), Tbil (47.51 vs 59.20 μmol/L, P = .821), and PT (15.79 vs 15.01 s, P > .99) were similar in the living-donor and fibrosis groups. A comparison of the postoperative clinical data between the living-donor and fibrosis groups is shown in Table 2. No life-threatening complications or posthepatectomy liver failure (PHLF) occurred in either group. Most patients experienced only minor complications (Clavien classification grade I or II).

### 3.3. Volume related parameters

The volumetric data are summarized in Table 3 and the RLV regeneration of living-donor and HCC subgroups are illustrated in Figure 4. The RLV ratio of the living-donor and fibrosis patients were 40.04 ± 2.04% and 46.51 ± 5.22% (P = .009) of the original FLV after surgery, respectively. The remnant liver volume grew rapidly, resulting in an increase to 59.46 ± 10.39% and 71.62 ± 8.36% of FLV at 1 and 3 months in the living-donor group, and 57.27 ± 4.77% and 68.19 ± 7.36% of FLV in the fibrosis group, respectively. Although liver regeneration in the early postoperative period (≤3 months) was slower in fibrosis patients than in living-donors, it was not statistically significant (POD 30 RLV, 656.01 ± 68.36 vs 711.63 ± 119.50, P = .323; POD 90 RLV, 781.27 ± 99.53 vs 856.67 ± 76.43, P = .191). Thereafter, the remnant liver volume at 6 months (mean 593.28 vs 851.46 ml, P = .015) and 12 (mean 1057.25 vs 895.97 ml, P = .002) months showed a significant difference in liver regeneration between the living-donors and fibrosis patients.

The remnant liver of the living-donors increased to 88.52 ± 9.76% of the FLV by 1 year. Concurrently, the liver volume increase in patients with fibrosis S0-S1 (mild fibrosis group), S2-S3 (advanced fibrosis group) and S4 (cirrhosis group) was 87.76 ± 13.41%, 77.50 ± 13.92%, and 69.46 ± 4.86%, respectively (P = .043). The results showed a significant difference in liver regeneration according to the liver fibrosis degree, and the regeneration rate decreased as the severity of hepatic fibrosis increased as shown in Figure 4. Although the cirrhosis group had gradual remnant liver growth during the first 6 postoperative months (791.63 ± 84.83 ml at 6 months), no enlargement was found thereafter. The RLV in this group remains at approximately 750 ml at 12 months postoperatively, but the patients are all leading a normal life. Additionally, three of the patients in the cirrhosis group had a decrease in RLV after 6 months. No complete restoration was found during the follow-up of the cirrhosis group.

### Table 2

| Characteristics | Living-donor Group (n=18) | Mild Fibrosis (n=14) | Advanced Fibrosis (n=15) | Cirrhosis (n=16) | P value |
|-----------------|---------------------------|---------------------|--------------------------|-----------------|---------|
| Postoperative Complications (n) | | | | | |
| Clavien-Dindo ≤ Grade 2 | 16 (88.9%) | 14 (100.0%) | 14 (93.3%) | 14 (87.5%) | | |
| Clavien-Dindo > Grade 2 | 2 (11.1%) | – | 1 (7.7%) | 2 (12.5%) | | |
| Bilary leakage | 1 (5.6%) | – | 1 (6.7%) | 1 (6.3%) | | |
| Abdominal hemorrhage | – | – | – | 1 (6.3%) | | |
| Ascites | 2 (11.1%) | 1 (7.1%) | 2 (13.3%) | 4 (25.0%) | | |
| Wound infection | – | – | 1 (6.7%) | 1 (6.3%) | | |
| Pulmonary infection | 1 (5.6%) | 2 (14.3%) | – | 1 (6.3%) | | |
| Urinary tract infection | 2 (11.1%) | 1 (7.1%) | 2 (12.5%) | | | |
| Systemic Inflammation | 1 (5.6%) | 1 (7.1%) | 2 (13.3%) | 1 (6.3%) | | |
| Postoperative hospital stay time (mean±SD, days) | 8.60±4.35 | 5.92±2.23 | 7.15±1.95 | 12.00±4.31 | | |

### Table 3

| Volumetric Assessment | Living-donor Group (n=18) | HCC Group (n=45) | P value | Patients with HCC |
|-----------------------|---------------------------|----------------|---------|------------------|
| Preoperative TLV, ml (mean±SD) | 1204.46±117.53 | 1730.32±193.82 | .000 | Mild Fibrosis (n=14) |
|                        |               |               |         | Advanced Fibrosis (n=15) |
| Tumor volume, ml (mean±SD) | – | 578.34±101.88 | – | Cirrhosis (n=16) |
| Preoperative FLV, ml (mean±SD) | 1204.50±117.53 | 1150.98±139.33 | .753 | P value |
| Postoperative RLV, ml (mean±SD) | 475.16±43.82 | 532.04±61.21 | .053 | Mild Fibrosis (n=14) |
| POD 30 RLV, ml (mean±SD) | 711.63±119.50 | 656.01±68.36 | .323 | Advanced Fibrosis (n=15) |
| POD 90 RLV, ml (mean±SD) | 856.67±76.43 | 781.27±99.53 | .191 | Cirrhosis (n=16) |
| POD 180 RLV, ml (mean±SD) | 963.28±59.20 | 851.46±111.78 | .015 | P value |
| POD 360 RLV, ml (mean±SD) | 1057.25±44.74 | 885.97±154.08 | .002 | Mild Fibrosis (n=14) |
| POD 0 RLR, (mean±SD, %) | 40.04±5.04 | 46.51±5.22 | .000 | Advanced Fibrosis (n=15) |
| POD 30 RLR, (mean±SD, %) | 49.46±10.30 | 57.27±4.77 | .509 | Cirrhosis (n=16) |
| POD 90 RLR, (mean±SD, %) | 71.62±8.36 | 68.19±7.36 | .364 | P value |
| POD 180 RLR, (mean±SD, %) | 73.72±8.42 | 74.30±8.30 | .194 | Mild Fibrosis (n=14) |
| POD 360 RLR, (mean±SD, %) | 88.52±9.76 | 78.24±13.18 | .101 | Advanced Fibrosis (n=15) |

FLV = functional liver volume, HCC = hepatocellular carcinoma, RLR = remnant liver regeneration rate (RLV/FLV × 100%), POD = postoperative day, RLV = remnant liver volume, TLV = total liver volume. 
Pvalue, P value between the living-donor, mild fibrosis, advanced fibrosis and cirrhosis group.
Changes in remnant liver volume by liver fibrosis after right hepatectomy for living donors and hepatocellular carcinoma subgroups.

The univariate analysis shown in Table 4 indicates that the following 3 variables were statistically significant prognostic factors associated with the regeneration rate of residual liver at 6 months post-operation: Alb (P=.006), PT (P=.032), and grade of hepatic fibrosis (P<.001). Furthermore, based on the multivariate analysis, the grade of hepatic fibrosis (95% CI: 4.901–262.048, P<.001) and Alb (95% CI: 0.643–0.992, P=.042) were the most important predictor of remnant liver regeneration rate on the 180th day after right hepatectomy (Table 5).

Figure 5 shows the ROC curves using both Alb and the grade of hepatic fibrosis to predict the remnant liver regeneration rate. The area under the Alb curve was .731 (P<.001, 95% confidence interval (95% CI): .600 to .863), the optimal cutoff was 43.50/g/L with sensitivity of 75.88% and specificity of 72.41%. The area under the grade of hepatic fibrosis was .949 (P<.001, 95% CI: .889 to 1.000) and the optimal cutoff was 1.5 with sensitivity of 96.55% and specificity of 89.66. It also indicated that the hepatic fibrosis grade is more closely associated with the combined Alb–hepatic fibrosis grade (AUR=.969, 95% CI: .929 to 1.000, P<.001) in predicting the remnant liver regeneration.

### Table 4

| Variables                  | All Included Patients (n=63) | | HCC Patients (n=45) | |
|----------------------------|-------------------------------| | | | |
| Relative Risk (95% CI)     | P                             | | Relative Risk (95% CI) | P |
| Age (mean±SD, years)       | 1.014 (0.968–1.062)           | .566 | 1.002 (0.991–1.055) | .939 |
| Male                       | 2.018 (0.620–6.569)           | .244 | 0.885 (0.189–4.142) | .876 |
| BMI (mean±SD, kg/m²)       | 0.992 (0.940–1.0172)          | .927 | 1.016 (0.845–1.220) | .867 |
| Child-Pugh score (mean±SD) | 1.000 (0.606–1.769)           | .000 | 0.536 (0.031–4.186) | .667 |
| Tbl (mean±SD, µmol/L)      | 0.980 (0.902–1.066)           | .639 | 0.937 (0.842–1.043) | .234 |
| Alb (mean±SD, g/L)         | 0.835 (0.734–0.950)           | .006 | 0.923 (0.811–1.051) | .226 |
| PT (mean±SD, s)            | 2.197 (1.069–4.516)           | .032 | 1.286 (0.570–2.902) | .546 |
| Hb (mean±SD, g/dl)         | 0.997 (0.962–1.034)           | .876 | 0.981 (0.941–1.022) | .361 |
| AST mean±SD, u/L           | 0.978 (0.956–0.999)           | .042 | 1.020 (0.962–1.0093) | .832 |
| ALT (mean±SD, µmol/L)      | 1.016 (0.996–1.038)           | .157 | 0.989 (0.977–1.019) | .843 |
| Plt (mean±SD,100/L)        | 0.999 (0.993–1.006)           | .781 | 0.998 (0.991–1.005) | .533 |
| WBC (mean±SD,100/L)        | 1.099 (0.786–1.537)           | .580 | 0.865 (0.582–1.287) | .476 |
| Cre (mean±SD, µmol/L)      | 1.013 (0.968–1.060)           | .590 | 1.002 (0.950–1.056) | .945 |
| APRI                       | 2.777 (0.961–8.024)           | .059 | 1.100 (0.369–3.280) | .864 |
| FIB-4                      | 1.377 (0.897–2.112)           | .998 | 1.065 (0.708–1.602) | .764 |
| Living-donor group         | NS                            | | NS | | |
| Mild fibrosis group        | 0.044 (0.005–0.368)           | .004 | 0.008 (0.001–0.028) | .004 |
| Advanced fibrosis group    | 10.969 (2.188–54.085)         | .004 | 5.667 (1.090–29.688) | .039 |
| Grade of hepatic fibrosis  | 30.0 (3.588–25.804)           | .002 | 16.071 (1.870–138.149) | .011 |
| Serum AFP >400 ng/mL       | NS                            | | 22.114 (4.155–117.691) | <.001 |
| Tumor size (mean±SD, cm)   | NS                            | | 0.786 (0.227–2.716) | .703 |
| Number of tumor ≥2 (%)     | NS                            | | 0.909 (0.689–1.198) | .497 |

15minGFR = indocyanine green retention test at 15 minutes, AFP = alpha-fetoprotein, Alb = albumin, ALT = Alanineaminotransferase, APRI = AST to PT ratio index, AST = aspartate aminotransferase, BMI = body mass index, Cre = Creatinine, FIB-4 = fibrosis index based on factor 4 (Age, ALT, AST, Plt), Hb = hemoglobin, Plt = platelet, PT = prothrombin time, Tbl = total bilirubin, WBC = white blood cell.

### Table 5

The variables in the multivariate analysis for regeneration rate of residual liver on 180th Days.

| Variables                  | Relative risk (95% CI) | P       |
|----------------------------|------------------------|---------|
| Grade of hepatic fibrosis  | 35.839 (4.901–262.048) | <.001   |
| (ST, 50.51,62.51,63,64 group)|                       |         |
| Alb (mean±SD,g/L)          | .799 (0.643–0.992)     | <.042   |

Alb = albumin.

4. Discussion

Previous studies have addressed the controversial issue of cirrhotic liver regeneration. In 1962, Pack et al[13] demonstrated rapid regeneration of the remnant liver in 4 cirrhotic patients with HCC after major hepatectomy. Conversely, Lin et al[14] did not detect any increase in the liver remnant after hepatectomy in five cirrhotic patients. Thereafter, some studies have reported that cirrhotic liver has the ability to regenerate, albeit more slowly and less completely.[3,15,16] Only Shirabe et al[17] showed no association between fibrosis and regeneration. In our study,
liver regeneration gradually and significantly decreased according to the severity of fibrosis (Fig. 4).

Early studies reveal that in patients with a normal liver, the liver remnant returns to its original size about 6 months after extensive LR\cite{13,18,19} but it takes 9 to 12 months in cirrhosis patients.\cite{19} Recent studies have reported different results. Pascher et al\cite{20} and Yokoi et al\cite{21} reported that the liver volume of the donors increased to 72% and 79.8% of its TLV by 6 months and 85% and 97.2% of TLV in 12 months, respectively. Another study by Pomfret et al\cite{22} demonstrated that the RLV reached 83% of the TLV 1 year after right-lobe donation. In 2018, Jang et al\cite{23} demonstrated a negative relationship between the degree of liver stiffness, measured by magnetic resonance elastography (MRE), and the liver regener-

Figure 5. Normal liver, S0-S1, S2-S3 and S4 are 0, 1, 2, 3, respectively, so CUTOFF=1.5 indicates that S2-S3 and S4 will significantly affect the rate of liver regeneration.

Figure 6. Serial CT scans after right hepatectomy without MHV in living-donor patient. A, preoperative CT scan. B, 3 months after hepatectomy. C, 6 months after hepatectomy. D, 12 months after hepatectomy. MHV = middle hepatic vein.
Our study results concur with this and show that hepatic fibrosis has a negative impact on liver regeneration, as shown in Figure 3. Living-donor liver volume increased by 79.72±8.42% and 88.52±9.76% at 6 months and 12 months, respectively; however, the regeneration ability is impaired in HBV-related HCC patients, and the mean regeneration rate at 6 and 12 months was 74.30±8.30% and 78.24±13.18%, respectively. Some studies have reported that key factors (tumor necrosis factor α, interleukin-6 and hepatocyte growth factors) influence liver regeneration; these factors are significantly lower in cirrhotic livers than in normal livers.[27] This could explain the decreased regeneration capacity of the cirrhotic liver seen in this study.

Both donors and HCC patients showed an increase in liver volume after hepatectomy, and the regeneration rate was rapid in the first 6 months. Interestingly, 3 patients in the cirrhosis group showed a slight decrease in liver volume after 3 months. Similar findings were observed in a previous study.[28] In 1987, Nagasue et al.[19] reported that in one in four liver cirrhosis patients with HCC, the size of the liver remnant was restored nearly to 500 m³ 4 months after right hepatectomy, but no enlargement was found thereafter. Therefore, we assume that no enlargement occurred in some patients with cirrhosis.

Even though advances in surgery and perioperative management have improved the prognosis of HCC patients, recurrence, generally in the hepatic remnant, occurs in 60% to 100% of cases after curative resection.[29–31] A previous study revealed that effective treatment of recurrences is imperative to improve survival rates.[32] There are a variety of therapeutic approaches for intrahepatic recurrent HCC, including salvage liver transplantation (SLT), re-resection (RR), transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA). Of these, RR and SLT have been considered to be the most effective, potentially curative, therapies for recurrent HCC.[33,34] Due to the shortage of organ donors and the strict selection criteria, RR is the mainstay curative treatment option for recurrent HCC.[33,35] Adequate regeneration of the remnant liver volume and liver reserve are indispensable for re-resection in early recurrent (recurrence within 12 months) HCC patients. Thus, it is important to define which specific time point after the initial resection will offer an adequate remnant liver volume and liver function in early recurrent HCC patients. Currently, there is no consensus regarding the time interval for subsequent LR in early recurrent HCC patients. In our study, regeneration in the first 6 months after initial right hepatectomy showed a phase of rapid increase, and there was no significant difference in RLRR between the normal and HCC livers (Fig. 4). The remaining liver

![Figure 7](image-url)

**Figure 7.** Serial CT scans after right hepatectomy without MHV in HCC patients. A, preoperative CT scan. B, 3 months after hepatectomy. C, 6 months after hepatectomy. D, 12 months after hepatectomy. HCC = hepatocellular carcinoma, MHV = middle hepatic vein.
volume in the mild, advanced, and cirrhosis groups regen-erated to a mean value of 76.54%, 73.53%, and 72.83% of the FLV at 6 months after surgery, respectively. Besides, slower and incom-plete regeneration was found 6 months after hepatectomy in HCC patients. Therefore, we recommend that RR be performed 6 months after right hepatectomy in early recurrent HCC patients, if possible; for those patients who recruit within the 6 months, we recommend TACE/RFA as a bridge before RR in order to prevent the occurrence of PHLF and small-for-size syndrome. Accurate assessment of the remnant liver reserve before surgery is essential for a better prognosis. At present, most studies evaluate the safety of hepatectomy by measuring the RLV, Child-Pugh score, or indocyanine green (ICG) retention test; these studies do not include the severity of fibrosis. Each of these methods has their own merits as well as limitations[21,36–40] and a combined evaluation (Child-Pugh score, ICG retention test at 15 minutes, ALT, AST, RLV, and the severity of fibrosis) of the remnant liver reserve could improve the prognosis of HCC patients, and reduce the incidence of PHLF and mortality. Recent studies have investigated the relationship between serological biomarkers, imaging examinations, transient elastography, and pathological liver fibrosis grade.[3,41–43] These will enable practitioners to assess the degree of fibrosis prior to surgery and acquire a safer remnant liver volume for HCC patients with different fibrosis stages.

Unlike previous studies, the HCC patients in this study were divided into 3 subgroups based on their degree of hepatic fibrosis as determined by pathological examination, the gold standard for staging liver fibrosis.[13] Both groups underwent a right hepatectomy without MHV. However, this study has several limitations, the most important of which is its retrospective nature. The relatively small number of patients and follow-up times in our study limited the number of variables. In the present study, the precise evaluation of liver fibrosis was a key step in demonstrating the negative relationship between hepatic fibrosis and regeneration capacity, but sampling error is inevitable. Further studies are required to validate the impact of the degree of fibrosis on the regeneration of liver volume.

In conclusion, liver regeneration is influenced by the severity of liver fibrosis. Both donors and HCC patients showed regeneration after hepatectomy (Figs. 6 and 7). We also found that slower and incomplete regeneration occurred in the cirrhotic liver group, but complete regeneration of the remnant liver is possible in cirrhotic patients. The grade of liver fibrosis and Alb can predict the rate of liver regeneration after precise hepatectomy. The correlation between the degree of fibrosis and liver regeneration capacity provides an important reference for ensuring a safer remnant liver volume, leading to enhanced treatments, decision-making, and prognostic evaluations.

Author contributions
Jia-Yin Yang proposed the study. Yiliyaer Aierken performed the research and wrote the first draft. AY, Ling-Xiang Kong, Bo Li, Xi-Jiao Liu and Su Lu collected and analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts.

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