Synchronous splenectomy and hepatectomy for patients with hepatocellular carcinoma and hypersplenism: A case-control study

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AIM: To investigate whether the use of synchronous hepatectomy and splenectomy (HS) is more effective than hepatectomy alone (HA) for patients with hepatocellular carcinoma (HCC) and hypersplenism.

METHODS: From January 2007 to March 2013, 84 consecutive patients with HCC and hypersplenism who underwent synchronous hepatectomy and splenectomy in our center were compared with 84 well-matched patients from a pool of 268 patients who underwent hepatectomy alone. The short-term and long-term outcomes of the two groups were analyzed and compared.

RESULTS: The mean time to recurrence was 21.11 ± 12.04 mo in the HS group and 11.23 ± 8.73 mo in the HA group, and these values were significantly different (P = 0.001). The 1-, 3-, 5-, and 7-year disease-free survival rates for the patients in the HS group and the HA group were 86.7%, 70.9%, 52.7%, and 45.9% and 88.1%, 59.4%, 43.3%, and 39.5%, respectively (P = 0.008). Platelet and white blood cell counts in the HS group were significantly increased compared with the HA group one day, one week, one month and one year postoperatively (P < 0.001). Splenectomy and micro-vascular invasion were significant independent prognostic factors for disease-free survival. Gender, tumor number, and recurrence were independent prognostic factors for overall survival.

CONCLUSION: Synchronous hepatectomy and hepatectomy potentially improves disease-free survival rates and alleviates hypersplenism without increasing the surgical risks for patients with HCC and hypersplenism.

Key words: Hepatocellular carcinoma; Hypersplenism; Splenectomy; Hepatectomy; Case-control study
Core tip: The optimal approach for treating patients suffering from hepatocellular carcinoma (HCC) and hypersplenism is not well established. In the present study, synchronous hepatectomy and hepatectomy improved disease-free survival rates and alleviated hypersplenism without increasing the surgical risk for patients with HCC and hypersplenism.

INTRODUCTION

Hypersplenism, secondary to portal hypertension, is commonly associated with hepatocellular carcinoma (HCC) in cirrhotic patients, resulting in anemia, leucopenia, and thrombocytopenia. Given the poor preoperative situation, increased surgical risks and poor long-term survival, hypersplenism is considered a contraindication for HCC patients undergoing liver resection. The guidelines of the American Association for the Study of Liver Disease recommended that splenectomy be performed in cirrhotic patients with preserved liver function. However, splenic immune function decreases with the development of HCC. Nomura et al. reported that splenectomy improved liver fibrosis and led to beneficial immunological changes in cirrhotic patients with hepatitis, and splenectomy was also suggested to improve antitumor responses. In addition, splenectomy is advocated as an effective treatment for hypersplenism and portal hypertension, as this procedure improves low white blood cell (WBC) and platelet counts and reduce portal vein pressure. The selection criteria and surgical techniques have been refined, and the outcome of patients undergoing liver resection has improved, with 5-year survival rates after resection reported to exceed 50%.[12-14] However, the best method for treating patients suffering from HCC and hypersplenism is currently not well established.

We carefully performed synchronous hepatectomy and splenectomy (HS) in patients with HCC and hypersplenism with preserved liver function. The aim of this case-control study was to investigate whether the use of synchronous hepatectomy and splenectomy was better than hepatectomy alone (HA) for patients with HCC and hypersplenism.

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Table 1 Demographic data of the hepatectomy and splenectomy group and the hepatectomy alone group

| Variable                        | HS group | HA group | P value |
|---------------------------------|----------|----------|---------|
| Number of patients (n)          | 84       | 84       |         |
| Age (yr)                        | 49.32 ± 10.483 | 51.01 ± 10.830 | 0.306   |
| Gender (M/F)                    | 69:15    | 69:15    | 1.000   |
| HBsAg (positive/negative)       | 71:12    | 72:12    | 0.828   |
| AFP (ng/mL)                     |          |          | 0.633   |
| ≤ 400                           | 54       | 51       |         |
| > 400                           | 30       | 33       |         |
| White blood cell count (10^9/L) | 3.96 ± 4.11 | 4.60 ± 4.41 | 0.332   |
| Platelet count (10^4/L)         | 61.43 ± 42.113 | 68.93 ± 17.677 | 0.134   |
| Splenomegaly                    | 12:46:36 | 14:53:27 | 0.380   |
| (mild/moderate/severe)          |          |          |         |
| Child-Pugh class (A)            | 84       | 84       |         |
| Number of tumors                | 11       | 11       | 1.000   |
| Single                          | 73       | 73       |         |
| Multiple                        |          |          |         |
| Diameter of tumor (cm)          | 4.18 ± 2.134 | 4.26 ± 1.996 | 0.809   |
| ≤ 5                             | 13       | 18       | 0.320   |
| > 5                             | 71       | 66       |         |
| Micro-vascular invasion         | Yes      | Yes      | 0.722   |
| No                              | 20       | 22       |         |
|                                | 64       | 62       |         |

HS: Hepatectomy and splenectomy; HA: Hepatocyte alone; AFP: Alpha-fetoprotein; HBsAg: Hepatitis B surface antigen.

MATERIALS AND METHODS

Case-control study

From January 2007 to March 2013, 84 consecutive patients with HCC and hypersplenism who underwent hepatectomy and splenectomy (the HS group) in the Department of Liver Surgery and Liver Transplantation Center of the West China Hospital of Sichuan University were retrospectively enrolled.

The HA group consisted of 84 patients selected from a pool of 268 patients who underwent HA for HCC and hypersplenism during the same period and met the selection criteria for hepatectomy and splenectomy. The cases and controls were well matched at a 1:1 ratio between the HS group and the HA group for the following variables: age, gender, hepatitis B surface antigen (HBsAg), alpha-fetoprotein (AFP), WBC and platelet (PLT) counts, splenomegaly, number of tumors, tumor size and micro-vascular invasion (MVI). To reduce bias, contemporary case controls were selected in a consecutive manner, and patients who received splenectomy after primary hepatectomy were excluded from the case-control study. The mean duration of follow-up was 35.87 ± 16.16 mo in the HS group and 33.45 ± 17.94 mo in the HA group. All of the enrolled patients were categorized as having Child-Pugh A liver function. The demographic data of the two patient groups are presented in Table 1.

The following data were collected for all cases and controls: length of hospital stay, follow-up time, minor and major complications (Dindo et al. classification...
of surgical complications), type of liver resection (major vs minor), intraoperative bleeding, number of transfusions and time to recurrence. Data regarding total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and WBC and PLT counts were collected one day, one week, one month, and one year after the operation. The short- and long-term outcomes of the two groups were analyzed and compared.

All study subjects were informed of the benefits and risks of surgery in detail. Written informed consent for patient information to be stored in the hospital database and used for research was obtained from all patients.

**Indications for splenectomy**

Hypersplenism was defined as: (1) the portal vein greater than or equal to 1.0 cm in diameter; (2) the presence of hepatic cirrhosis and splenic thickness greater than or equal to 4.0 cm, as measured by radiographic examination; and (3) PLT and WBC counts less than 80 × 10⁹/L and 3.0 × 10⁹/L, respectively, obtained the week prior to surgery. Patients who suffered from splenomegaly with hypersplenism and/or splenomegaly that was classified as greater than class I (spleen enlarged beyond left subcostal margin and palpable) were treated by splenectomy.

**Patient follow-up**

All of the patients received follow-up monitoring 1 mo after the operation, every 3 mo thereafter during the first 3 years and then every 6 mo in subsequent years. All enrolled patients received regular follow-up monitoring until death or termination of the study. Disease status was assessed according to serum liver biochemistries, AFP levels, hepatitis B virus (HBV)-DNA levels and radiological examination. One or two types of radiological examination, such as ultrasound, contrast-enhanced ultrasound, contrast-enhanced computed tomography (CT), and magnetic resonance imaging, were chosen based on the specific situation. Tumor recurrence was diagnosed based on the identification of a new lesion in at least two radiological examinations and increased AFP levels. The final follow-up visit occurred at the end of July 2014, unless the patient had died prior to that time. The overall median follow-up time was 33 mo (5-86 mo).

**Statistical analysis**

Continuous variables are expressed as mean ± standard deviation and were compared between groups using the t-test or Mann-Whitney U test for variables with an abnormal distribution. Categorical data were compared using the χ² test or Fisher's exact test. The overall survival rates were analyzed using the Kaplan-Meier method, and the differences were analyzed using the log-rank test. The Cox proportional hazard model was used for univariate and multivariate analyses of prognostic factors after surgery. Two-tailed P values < 0.05 were considered statistically significant. Calculations were performed using the SPSS package (SPSS, Inc. 1989-1995, Chicago, IL).

**RESULTS**

According to the case-match design, age, gender, HBsAg, AFP, WBC and PLT counts, splenomegaly, tumor number, tumor size and MVI were similar between the two groups of patients (Table 1). A total of 33 patients died in the HA group, whereas 26 patients died in the HS group. The length of hospital stay, follow-up time, type of liver resection (major vs minor), intraoperative bleeding, and number of transfusions during the perioperative period did not significantly differ between the two groups (Table 2). The mean time to recurrence was 21.11 ± 12.04 mo in the HS group and 11.23 ± 8.73 mo in the HA group, and these values were significantly different (P = 0.001). Subgroup analyses indicated that 8 of 35 patients suffered early recurrence (time to recurrence less than 12 mo) in the HA group, whereas 31 of 48 patients in the HA group experienced early recurrence (P < 0.001).

**Surgical complications**

No treatment-related mortality was noted in either group (Table 3). Complications above grade II were defined as severe complications and were analyzed. In the HS group, two patients developed pleural effusion and received pleurocentesis. In addition, two patients were diagnosed with intra-abdominal bleeding and underwent re-laparotomy. As a result of hypotension and shock, two patients were resuscitated and required ICU management. In the HA group, one patient de-
Table 3  Surgical complications classified by Clavien classification for the two groups.

| Clavien classification | HS group | HA group | P value |
|------------------------|----------|----------|---------|
| Grade I (fever/pain/vomiti/ wound infection/ ascites/ hypokalemia) | 21 | 22 | 0.532 |
| Grade II (transfusion/infection/ coagulopathy/liver failure) | 6 | 10 | 0.187 |
| Grade IIa | 2 | 1 | |
| Grade IIb | 2 | 0 | |
| Grade III | 2 | 3 | |
| Grade V | - | - | |
| Total | 33 | 36 | 0.532 |

Two patients had pleural effusion and received pleurocentesis; Two patients were diagnosed with intra-abdominal bleeding and underwent re-laparotomy; Two patients were resuscitated and needed ICU management due to the hypotension and shock; One patient had pleural effusion and received pleurocentesis; Two patients suffered type 1 respiratory failure and 1 patient suffered hypotension and shock, all of whom needed ICU management. HS: Hepatectomy and splenectomy; HA: Hepatectomy alone.

Synchronous splenectomy and hepatectomy for HCC

Disease-free survival rate: The 1-, 3-, 5-, and 7-year disease-free survival rates for patients in the HS group and HA group were 86.7%, 70.9%, 52.7%, and 45.9% and 88.1%, 59.4%, 43.3%, and 39.5%, respectively. Disease-free survival was enhanced in the HS group compared with the HA group (P = 0.008; Figure 1).

Overall survival rate: The 1-, 3-, 5-, and 7-year overall survival rates for patients in the HS group and HA group were 90.4%, 77.9%, 65.9%, and 45.2% and 85.7%, 70.0%, 58.3%, and 54.7%, respectively. No significant difference in overall survival was noted between the two groups (P = 0.187) (Figure 2).

Laboratory tests after surgery

Total bilirubin, ALT, AST, and PLT and WBC counts were similar in both groups prior to surgery (Table 4). After surgery, the PLT and WBC counts in the HS group were significantly increased compared with the HA group (P < 0.001) (Figure 3A and B). The levels of TBIL and ALT were significantly increased in the HS group compared with the HS group on postoperative day one (P < 0.05) but then decreased to levels similar to those observed in the HS group at one week, one month and one year after the operation (Figure 3C and D). In addition, the serum AST levels did not differ between the two groups in the short-term or long-term period after surgery (P > 0.05).

Prognostic factors for patients with HCC and hypersplenism

Disease-free survival: Splenectomy (HR = 0.531; 95%CI: 0.341-0.828; P = 0.005) and MVI (HR = 2.642, 95%CI: 1.685-4.143; P < 0.001) were identified as significant independent prognostic factors for disease-free survival using univariate and multivariate analyses (Table 5).

Overall survival: Univariate analysis indicated that the following four variables were statistically significant prognostic factors associated with overall survival in patients with HCC and hypersplenism: gender (female, P = 0.020), tumor number (multiple, P = 0.041),...
Table 4  Laboratory tests of the two groups after surgery

| Variable          | Pre-operation | 1 d       | 1 wk       | 1 mo       | 1 yr       |
|-------------------|---------------|-----------|------------|------------|------------|
|                   | HS            | HA        | P value    | HS         | HA        | P value    | HS         | HA        | P value    | HS         | HA        | P value    |
| TBIL (μmol/L)     | 17.94 ± 7.34  | 16.62 ± 6.63 | 0.451     | 22.34 ± 8.52  | 32.72 ± 27.14 | 0.026     | 24.04 ± 10.90  | 34.06 ± 48.89 | 0.216     | 15.12 ± 5.28  | 15.87 ± 6.70  | 0.858     | 17.20 ± 6.21  | 18.61 ± 5.82  | 0.314     |
| ALT (IU/L)        | 39.50 ± 16.89 | 39.24 ± 14.54 | 0.059     | 213.85 ± 187.27 | 348.00 ± 342.49 | 0.036     | 112.00 ± 101.69 | 169.57 ± 154.49 | 0.058     | 43.49 ± 23.78  | 49.41 ± 21.62  | 0.860     | 39.82 ± 17.85  | 41.11 ± 34.93  | 0.038     |
| AST (IU/L)        | 39.92 ± 15.69 | 47.16 ± 27.63 | 0.162     | 244.49 ± 186.49 | 321.81 ± 314.90 | 0.194     | 80.64 ± 77.33  | 64.19 ± 37.23  | 0.246     | 49.41 ± 21.62  | 44.22 ± 22.31  | 0.306     | 47.69 ± 27.75  | 48.00 ± 48.75  | 0.973     |
| PLT count (10^9/L)| 61.43 ± 42.11 | 68.95 ± 17.68 | 0.134    | 98.54 ± 33.27  | 67.11 ± 21.67   | <0.001    | 230.95 ± 114.93 | 74.63 ± 26.05   | <0.001    | 214.48 ± 102.03 | 73.24 ± 24.12  | <0.001    | 199.97 ± 58.19 | 68.08 ± 56.52  | <0.001    |
| WBC count (10^9/L)| 3.96 ± 1.11   | 4.60 ± 4.41  | 0.352     | 16.30 ± 5.38   | 11.79 ± 4.07   | <0.001    | 10.93 ± 4.27   | 6.14 ± 2.74   | <0.001    | 6.48 ± 1.71   | 4.25 ± 1.41   | <0.001    | 5.96 ± 1.46   | 4.88 ± 2.02 | <0.001     |

Both PLT and WBC counts in the HS group were alleviated and were significantly higher when compared to those in the HA group at one day, one week, one month and one year postoperatively (<0.001) (Figure 3A and B). While levels of the TBIL and ALT were much higher in the HA group than in the HS group on postoperative day one (<0.05), and then descended as similar as the HS group (Figure 3C and D). The level of AST did not differ between the two groups. TBIL: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PLT: Platelet; WBC: White blood cell.

DISCUSSION

Perioperative bleeding control and postoperative liver failure are the major concerns for cirrhotic patients with HCC and hypersplenism[4,5,7]. However, splenectomy has been suggested as a method to overcome these problems, as this procedure can reduce serum bilirubin levels and improve liver function[11]. In addition, PLT counts increase immediately after splenectomy, thereby potentially reducing intraoperative bleeding and surgical risk[20,21]. In the present case-control study, TBIL and ALT levels were reduced at one day and one week postoperatively in patients undergoing synchronous hepatectomy and splenectomy compared to those treated by hepatectomy alone. In addition, intraoperative bleeding and severe surgical complications were similar between the two groups. Furthermore, the disease-free survival was significantly increased in the HS group compared with the HA group, suggesting that synchronous hepatectomy and splenectomy are safe and beneficial for patients with HCC and hypersplenism.

Interestingly, synchronous hepatectomy and splenectomy decreased tumor recurrence and prolonged the interval to recurrence; however, this technique was not beneficial to the overall survival of patients with HCC and hypersplenism. The reduction of TGF-β levels after splenectomy was shown to lead to decreased recruitment of T regulatory (Treg) cells via the TGF-β-miRNA-34a-CCL22 pathway[26,31], which may reduce the ability of HCC cells to evade immune defenses and inhibit tumor
metastasis. Intricate immunosuppressive mechanisms, such as abnormal T cell receptor-CD3 complex, tumor-induced tolerance, suppression of NK cells, and impaired T cell function, may also be altered by splenectomy, thereby temporarily inducing tumor regression. However, sustained hepatitis viral infection results in inflammation and inflammatory microenvironments that promote fibrosis, cirrhosis and even permanent oncogenesis. As demonstrated in the present study, most patients were characterized as hepatitis b antigen-positive; thus, the outcomes of the case-control groups were not significantly different (P = 0.187).

In addition, numerous reports suggest that patients can significantly benefit from splenectomy. Hepatic resection increases portal hypertension, which is potentially associated with upper gastrointestinal hemorrhage. Splenectomy reduces 20%-30% of the portal vein inflow, thereby greatly decreasing portal hypertension. A total of four patients in the HS group experienced an episode of upper gastrointestinal hemorrhage after liver resection, whereas seven patients in the HA group experienced hemorrhage. In addition, WBC and PLT counts were significantly increased compared with the HA group one day, one week, one month and one year postoperatively (P < 0.001) (A and B); Total bilirubin and ALT levels were significantly increased in the HA group compared with the HS group on postoperative day one (P < 0.05) and then decreased to levels similar to those observed in the HS group (C and D); E: The AST levels did not differ between the two groups. HS: Hepatectomy and splenectomy; HA: Hepatectomy alone; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PLT: Platelet; WBC: White blood cell.
The study had several limitations. First, given that it was not a randomized study, selection bias may be inherent to the study. To reduce this bias, we selected contemporary case controls in a consecutive manner and excluded patients who received splenectomy after primary hepatectomy. Second, the number of subjects was relatively small. A large randomized control study is thus needed to confirm the role of HS in improving disease-free survival for patients with HCC and hypersplenism.

In conclusion, our results suggest that synchronous hepatectomy and hepatectomy may improve disease-free survival rates and alleviate hypersplenism without an increased surgical risk for patients with HCC and hypersplenism.

COMMENTS

Background

Given its poor preoperative characteristics, increased surgical risks and poor long-term survival, hypersplenism is considered a contraindication for hepatocellular carcinoma (HCC) patients undergoing liver resection. Moreover, the optimal method to treat patients suffering from HCC and hypersplenism is not well established. Therefore, the authors conducted this case-control study to investigate whether the use of synchronous hepatectomy and splenectomy was better than hepatectomy alone for patients with HCC and hypersplenism.

Research frontiers

The immunophysiology of the spleen in cirrhotic patients has not been fully characterized. Splenectomy potentially restores lymphocyte function and induces tumor regression when coupled with immunotherapy.

Innovations and breakthroughs

Synchronous splenectomy may play a prophylactic role against hepatocellular carcinoma recurrence after liver resection.

Applications

The use of synchronous hepatectomy and splenectomy may improve disease-free survival and alleviate hypersplenism without increasing the surgical risk for patients with HCC and hypersplenism.

Terminology

The immunosuppressive mechanisms of HCC, including defective antigen presentation, tumor-induced tolerance, impaired CD4+ T cell function, suppression of natural killer cells, recruitment of immunosuppressive myeloid and lymphoid cell populations and the up-regulation of immune checkpoint pathways, are intricate and further interfere with the development of a meaningful anti-tumor response.

Peer review

This is an interesting study that aims to determine the role of splenectomy and hepatectomy for patients with hepatocellular carcinoma and hypersplenism.

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