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42,573 cases of hepatectomy in China: a multicenter retrospective investigation

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Hepatectomy is currently routinely performed in most hospitals in China. China owns the largest population of liver diseases and the biggest number of liver resection cases. A nationwide multicenter retrospective investigation involving 112 hospitals was performed, and focused on liver resection for patients with hepatocellular carcinoma (HCC). 42,573 cases of hepatectomy were enrolled, and 18,275 valid cases of liver resection for HCC patients were selected for statistical analysis. The epidemiology of HCC, distribution of hepatectomy, postoperative complications and prognosis were finally analyzed. In the 18,275 HCC patients, 81% had hepatitis B virus infection and 10% had hepatitis C virus infection. 38% of the HCC patients had normal Alphafetoprotein (AFP) level, and other 35% had an AFP level lower than 400 ng mL^{-1}. In the study period, 97% of the hepatectomy for HCC were treated with open surgery, and 23.81% had vascular exclusion techniques. The operation time was (191.7±105.6) min, the blood loss was (546.0±562.8) mL, and blood transfusion was (543.0±1,035.2) mL. The median survival for HCC patients was 631 days, with 1-, 3-, and 5-year overall survival of 73.2%, 28.8% and 19.6%, respectively. Liver cirrhosis, multiple nodules, tumor thrombosis and high AFP level were risk factors that affect postoperative survival.

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INTRODUCTION

China has the most population of liver diseases, and performed the most cases of liver resection in the whole world. Liver cancer is one of the most prevalent life-threatening diseases in China, and hepatectomy is the major therapy for this malignancy (Lau and Lai, 2008). Liver resection is currently routinely performed in most municipal or provincial hospitals in China. However, surgical technique and operative indication were not consistent in different institutions, due to different levels of development and medical education in China, although the Chinese Chapter of International Hepato-Pancreato-Biliary Association and the Liver Surgery Group, Surgical Branch of the Chinese Medical Association have drafted guideline for diagnosis and therapy for hepatocellular carcinoma (HCC) (Association, 2013; Association, 2017; Chen and Zhang, 2017).

The Barcelona Clinic Liver Cancer (BCLC) staging system is the most commonly accepted system worldwide to choose therapy for HCC. However, there was still controversy about this standard, as a lot of clinical studies provided different evidences for the treatment of HCC. The EASL (European Association for Study of Liver) (Bruix et al., 2001) and AASLD (American Associations for Study of Liver Diseases) (Bruix et al., 2011) also published guidelines for HCC management in 2001 and 2011, respectively. Japan and Hong Kong also formulated national or regional guideline for HCC treatment. Nevertheless, controversy existed for all these guidelines or comments. Therefore, the international guideline for HCC treatment still needs to be improved, and requires stronger evidences from clinical studies.

Compared with the western world, HCC patients in China have the following distinct characteristics (Chen, 1994; Zhang et al., 2016): (i) more than 80% of the patients with HCC had hepatitis B virus infection and liver cirrhosis; (ii) many patients presented big or huge tumor at their first consultation to the clinics; (iii) liver transplantation could not be widely performed owing to lack of liver donor and high hospitalization cost. Therefore, we need our own guideline for the treatment of HCC in China fitting characteristics to obtain a better therapeutic prognosis. Tongji Hospital of Huazhong University of Science and Technology has its unique experience and has achieved ideal prognosis in treating huge HCC (Chen et al., 2006a; Zhang et al., 2016), HCC with tumor thrombosis (Chen et al., 2006b; Luo et al., 2015), and HCC with metastasis or portal hypertension (Chen et al., 2005; Chen et al., 2006b; Xiao et al., 2015).

The Chinese experience and clinical evidences are essential to set up the national guideline in China and to provide comments for international guideline. However, we do not have reported nationwide data to investigate the status of treatment of HCC. Therefore, we initiated this study, under the support of the Surgical Branch of the Chinese Medical Association. This study was the first nation-wide multicenter retrospective clinical study, intending to investigate the current status of hepatectomy in China, especially to declare liver resection for HCC.

RESULTS

Epidemiology of hepatectomy for patients with liver diseases

From January 2008 to December 2013, we screened a total of 42,573 patients performed hepatectomy in 112 medical institutions in China. The patients lack of important data were excluded, and finally 33,700 patients were considered as valid cases (Figure 1). In all these valid cases, 28,315 (84%) patients were male, and 5,385 (16%) patients were female. The median age was 54.4 years, with the oldest age 92 years. The average age was (52.60±13.45) years. In these 33,700 valid cases, 67% were HCC, 9% were liver hemangioma, 7% were cholangicarcinoma, 4% were hepatolithiasis, 4% were metastatic liver cancer, 1% were focal nodular hyperplasia, 1% were carcinoma of gallbladder, and the left portion were other diseases such as liver adenoma, hepatoblastoma, and verminosis (Figure 2).

Epidemiology of hepatectomy for patients with hepatocellular carcinoma

Patients diagnosed with HCC were enrolled in this study. In the 33,700 valid patients, 20,545 were diagnosed with HCC. After clinicians' selection, 18,275 patients with relative integrated clinical data and following up data were recruited for analysis, and others were excluded with the exclusion criteria as described in the method section (Figure 1).

The preoperative characteristics for these HCC patients were shown in Table 1. In all these 18,275 patients with HCC, 15,351 (84%) patients were male, and 2,924 (16%) patients were female. The median age was 52.0 years, with the oldest age 91 years. The average age was (51.70±11.94) years.

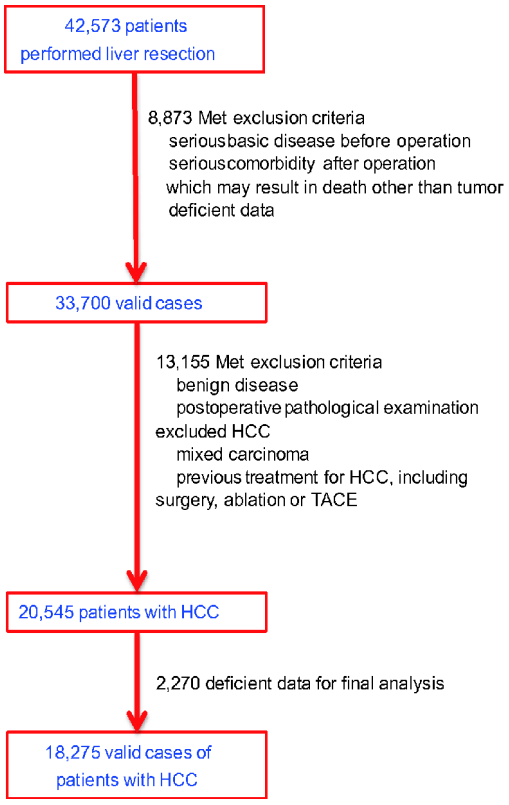

Figure 1 Flow diagram of patients enrollment.

Hepatitis related cirrhosis is the main cause of HCC in China. Therefore, hepatitis B virus (HBV) and hepatitis C virus (HCV) infection were emphasized in this study. 80.50% patients had HBV infection, while only 3.84% had HCV infection. 80.12% patients with HCC had liver cirrhosis (with 8.85% severe cirrhosis, 28.33% moderate cirrhosis, and 42.95% slight cirrhosis). Hepatic portal hypertension was induced by liver cirrhosis, and 8.00% patients in these patients with HCC presented portal hypertension. 80.73% patients had one single tumor, 14.05% patients had two nodules, and 5.14% had three or more than three nodules. Alphafetoprotein (AFP) level was increased in 61.89% of patients with HCC, with 34.74% had an AFP level of 20–400 ng mL^{-1} and 27.16% over 400 ng mL^{-1}.

Surgery data of hepatectomy for patients with hepatocellular carcinoma

Preoperatively, the liver function was evaluated by Child-Pugh scoring system. In all patients performed hepatectomy, 88.59% was Child-Pugh A stage, and 10.94% was Child-Pugh B stage, while few patients with Child-Pugh C stage was performed hepatectomy (Table 1). 96.84% patients were performed open surgery, while only 3.16% patients were performed laparoscopic liver resection during the study period. R0 resection was performed in 90.93% of the HCC patients, the remnant 7.59% patients were R1 resection and 1.48% patients were R2 resection (Table 2).

Different techniques of blood stream occlusion were applied to control bleeding during hepatectomy for 3,786 (23.81%) of the total 15,898 patients with open surgery. Pringle maneuver was most commonly used during hepatectomy, and was performed in 1,985 (12.49%) patients. The application of other vascular exclusion techniques was distributed as follows: 581 (3.65%) patients with total hepatic vascular exclusion, 208 (1.31%) patients with inferior vena cava exclusion, 306 (1.92%) patients with partial hepatic inflow exclusion plus partial hepatic outflow exclusion, 297 (1.87%) patients with hemihepatic vascular occlusion, 40 (0.25%) patients with total hepatic blood flow occlusion to

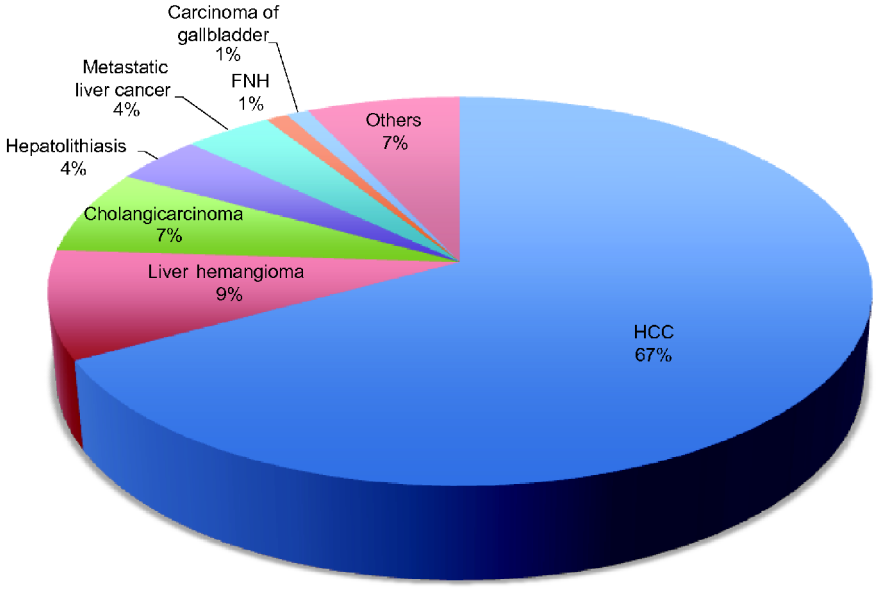

Figure 2 Components of diseases for the whole population underwent hepatectomy. FNH, focal nodular hyperplasia.

Table 1 Preoperative characteristics

	Value (n=18,275)
Age (year)	51.7±11.94
Sex (male), no. (%)	15,351 (84)
HBsAg positive, no. (%)	12,838 (80.50)
HCV, no. (%)	503 (3.84)
Liver cirrhosis, no. (%)	
Without	2,756 (19.88)
Slight	23 (42.95)
Moderate	35 (28.33)
Severe	29 (8.85)
Portal hypertension, no. (%)	1,203 (8.00)
No. of tumor, no. (%)	
0	10 (0.10)
1	11,238 (80.73)
2	1,956 (14.05)
≥3	716 (5.14)
AFP, no. (%)	
<20	5,217 (38.11)
20–400	4,756 (34.74)
≥400	3,718 (27.16)
Child-pugh stage, no. (%)	
A	14,165 (88.59)
B	1,750 (10.94)
C	75 (0.47)

Table 2 Surgery data[a)]

	Value (n=18,275)
Type of surgery, no. (%)	
open	15,898 (96.84)
laparoscopy	519 (3.16)
Type of resection, no. (%)	
R0	9,600 (90.93)
R1	801 (7.59)
R2	156 (1.48)
Type of occlusion for open surgery, no. (%)	
Total	3,786 (23.81)
Pringle maneuver	1,985 (12.49)
Total HV exclusion	581 (3.65)
Chen's exclusion	369 (2.32)
IVC exclusion	208 (1.31)
Partial hepatic inflow exclusion plus partial hepatic outflow exclusion	306 (1.92)
Hemi-HV occlusion	297 (1.87)
Total HV occlusion to maintain patency of IVC	40 (0.25)
Type of occlusion for laparoscipic surgery, no. (%)	
Total	482 (24.12)
Pringle maneuver	166 (8.3)
Total HV exclusion	116 (5.81)
Chen's exclusion	100 (5.00)
IVC exclusion	39 (1.95)
Partial hepatic inflow exclusion plus partial hepatic outflow exclusion	50 (2.50)
Hemi-HV occlusion	7 (0.35)
Total HV occlusion to maintain patency of IVC	4 (0.20)
Tumor thrombus, no. (%)	
Portal vein	783 (4.06)
Hepatic vein	102 (0.56)
IVC	26 (0.14)
Bile duct	83 (0.45)
Operative time (min)	191.7±105.6
Intraoperative blood loss (mL)	102 (0.56)
Transfusion requirements	
Patients transfused, no. (%)	1,849 (10.12)
Packets red cell (mL)	543±103.6

a) HV, hepatic vein; IVC, inferior vena cava.

maintain patency of inferior vena cava.

482 (24.12%) patients had vascular occlusion for the other 1,998 patients performed with laparoscopic liver resection or conversation surgery. In this portion of patients, the distribution of vascular exclusion techniques was quite different: 166 (8.3%) patients with Pringle maneuver; 116 (5.81%) patients with total hepatic vascular exclusion, 39 (1.95%) patients with inferior vena cava exclusion, 50 (2.50%) patients with partial hepatic inflow exclusion plus partial hepatic outflow exclusion, seven (0.35%) patients with hemihepatic vascular occlusion, four (0.20%) patients with total hepatic blood flow occlusion to maintain patency of inferior vena cava.

Tumor thrombus was critical in determining surgery and predicting prognosis. In the 18,275 cases of HCC patients with liver resection, 783 (4.06%) patients presented portal vein tumor thrombosis, 102 (0.56%) patients had hepatic vein tumor thrombosis, 26 (0.14%) patients had inferior vena cava tumor thrombosis, and 83 (0.45%) had bile duct tumor thrombosis.

The intraoperative parameters including operative time, blood loss and transfusion were shown in Table 2.

Postoperative complications

The common postoperative complications were assessed as follows (Table 3): 164 patients presented wound infection, 424 cases had pleural effusion that did not require aspiration, while the other 122 pleural effusion cases required aspiration, 718 patients showed ascites which was the most common complication after liver resection, 134 cases had pulmonary infection, 38 cases had biliary leakage, 75 cases had intra-abdominal haemorrhage, 52 cases had liver failure, 32 cases had renal failure, 20 cases had pulmonary dysfunction, 28 cases showed MODS, and 31 cases dead within

Table 3 Postoperative complications

	Value (n=18275)
Overall complications, no. (%)	1,838 (26.74)
Grade I, no. (%)	
Wound infection	164 (2.39)
Grade II, no. (%)	
Pleural effusions (not requiring aspiration)	424 (6.17)
Peritoneal effusions	718 (10.45)
Pulmonary problems	134 (1.95)
Total minor complications (Grade I+II), no. (%)	1,440 (20.95)
Grade III, no. (%)	
Pleural effusions (requiring aspiration)	122 (1.77)
Bilioma/bile leak	38 (0.55)
Intra-abdominal bleeding	75 (1.09)
Grade IV, no. (%)	
Grade IV a (single organ dysfunction)	104 (1.51)
Grade IV b (multiorgan failure)	28 (0.41)
Grade V, no. (%)	
Death	31 (0.45)
Total major complications (Grade III+IV+V), no. (%)	398 (5.79)

30 days postoperatively. The severity data of postoperative complications are shown in Table 3, according to Clavien's classification.

Prognosis of hepatocellular carcinoma after hepatectomy

6,222 patients were followed up in the whole population of 18,275 patients with HCC, and the median survival time was 631 days after hepatectomy. The 1, 3, 5 years overall survival was 73.2%, 28.8% and 19.6%, respectively (Figure 3A). Male patients showed no significant difference with females, in rates of median survival and 1, 3, 5 years overall survival (Figure S1 in Supporting Information).

The overall survival of patients with HBV or HCV infection had no significant difference with those patients without hepatitis virus infection, although hepatitis is the main cause of HCC in China (Figure 3B and C). The high level of liver cirrhosis was correlated with poor overall survival (Figure 4A). The median survival time of patients without liver cirrhosis was 652 days, significantly longer than that for patients with light, moderate, severe liver cirrhosis as 516 days, 339 days and 340 days, respectively (P<0.001). The patients with single tumor also had significant longer survival time (median survival 675 days), when compared with patients with multiple tumors (median survival 592 days) (P<0.05) (Figure 4B).

For patients with normal AFP level, the median survival time was 1085 days, which was significantly longer than that of the whole study population and those with abnormal AFP level (P<0.001). The overall survival for patients with HCC was negatively correlated with the level of AFP (Figure 4C).

Patients with tumor thrombosis also predicted poor survival, as expected (Figure 5). The median survival time for patients without portal vein tumor thrombosis, hepatic vein tumor thrombosis, and bile duct tumor thrombosis were 612 days, 686 days and 701 days, significantly longer than those for patients with tumor thrombosis (481 days, 545 days, and 527 days, respectively) (P<0.001).

In order to investigate whether open or laparoscopic liver resection effects prognosis, we compared the overall survival for patients with open surgery and laparoscopic surgery (Figure S2 in Supporting Information). The median survival time for open surgery was 631 days, which was comparable with that for laparoscopic surgery (683 days). In addition, the overall survival also showed no significant difference between open surgery and laparoscopic surgery.

DISCUSSION

HCC is one of the most common cancers in China, and hepatectomy is widely accepted as a curative therapy for this malignancy. Hepatectomy was initially performed in a few hospitals in China at the beginning of the 1950s. It is currently routinely performed in most hospitals in this developing country, after decades of development. This study was the first nationwide investigation of the surgical treatment for patients with HCC in China, and reported the maximum number of cases worldwide. The results presented herein have broad range of clinical implications and will be helpful for surgeons in the field of hepato-pancreato-biliary surgery and clinicians in the related field.

In this study, we recorded 42,573 cases of patients with hepatectomy in 3 years nationwide. Among these patients, 20,545 were diagnosed with HCC, which was common in southeastern China. The following epidemiologic characteristics were reported, which were essential for clinicians and public health service. Male patients (84%) with HCC were more than five times as much as female (16%). The average age for the whole HCC population was 51.7 years. 80.5% of the HCC patients had HBV infection, while only 3.84% had HCV infection. HBV infection rate in the HCC cases with hepatectomy was higher than the worldwide level (Lai et al., 2003). 80.12% patients with HCC had liver cirrhosis, and 61.89% showed abnormal AFP level.

The 5-year overall survival in this study might be lower than those reported previously. This study included data from many centers, and some of them might achieve a worse prognosis, which might lead to a decline in overall efficacy. In addition, a small portion of patients with Child-pugh grade C were included in prognosis analysis, which might be as-

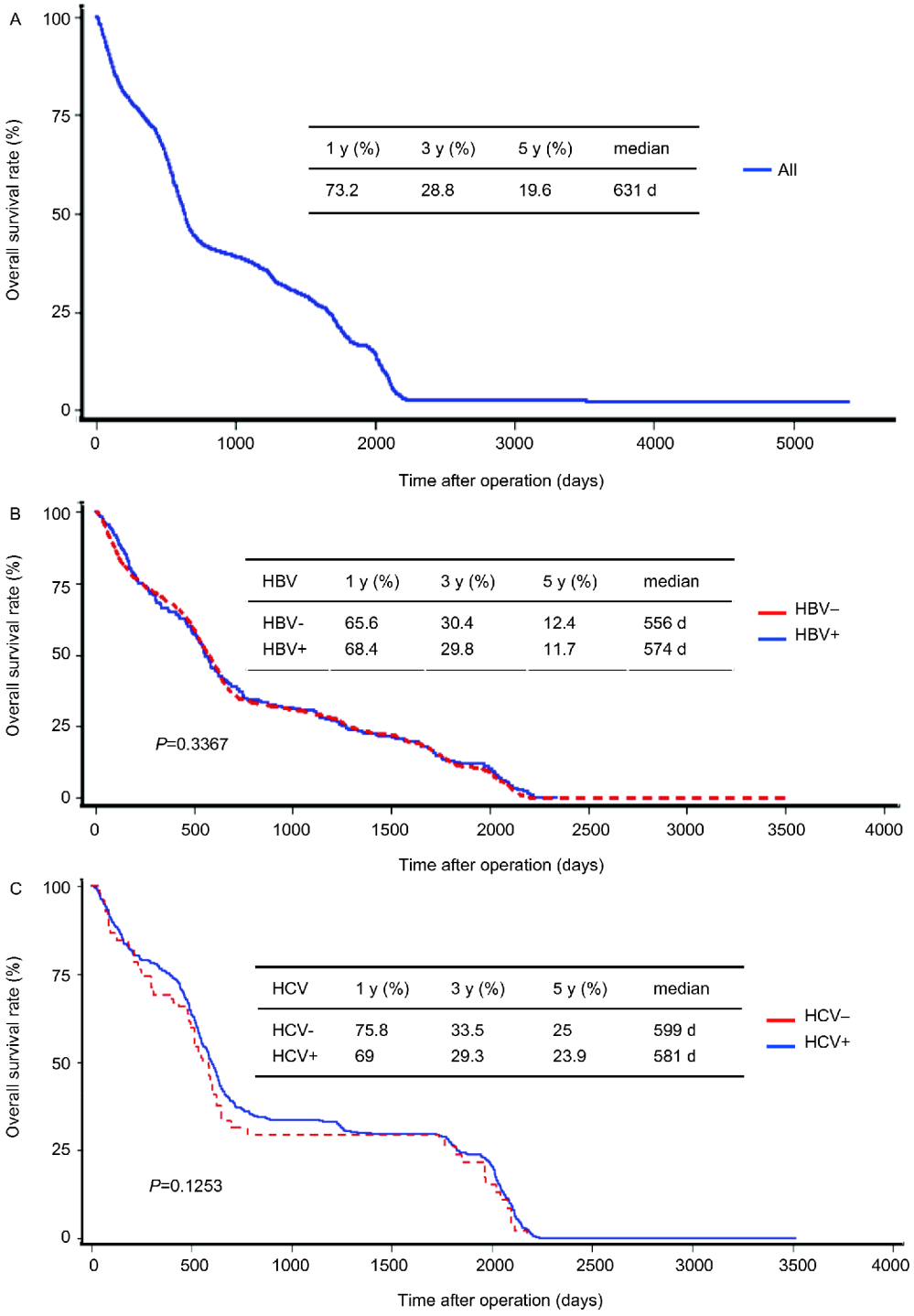

Figure 3 (Color online) Survival curve for HCC patients after hepatectomy. A, Overall survival were analyzed for the whole postoperative patients with HCC. Survival for patients with/without HBV infection (B) or HCV infections (C) were compared and analyzed. The median survival time, 1-year survival rate, 3-year survival rate, and 5-year survival rate for each group were described in the corresponding tables.

sociated with a decreased outcome.

In the study period, 96.84% of the surgical patients with HCC were performed with open surgery, while only 3.16% of them were performed laparoscopic liver resection (LLR). This result was in accordance with the development of laparoscopic liver resection in China. In 2014, a questionnaire survey initiated by Prof. Xiao-ping Chen to 61 experienced hepatic surgery centers across the country was completed, and indicated that LLR developed very slowly before 2013, with 118 to 580 cases per year for all liver diseases including benign tumor and malignancy (unpublished data). In the developing period, surgeons had been wondering whether

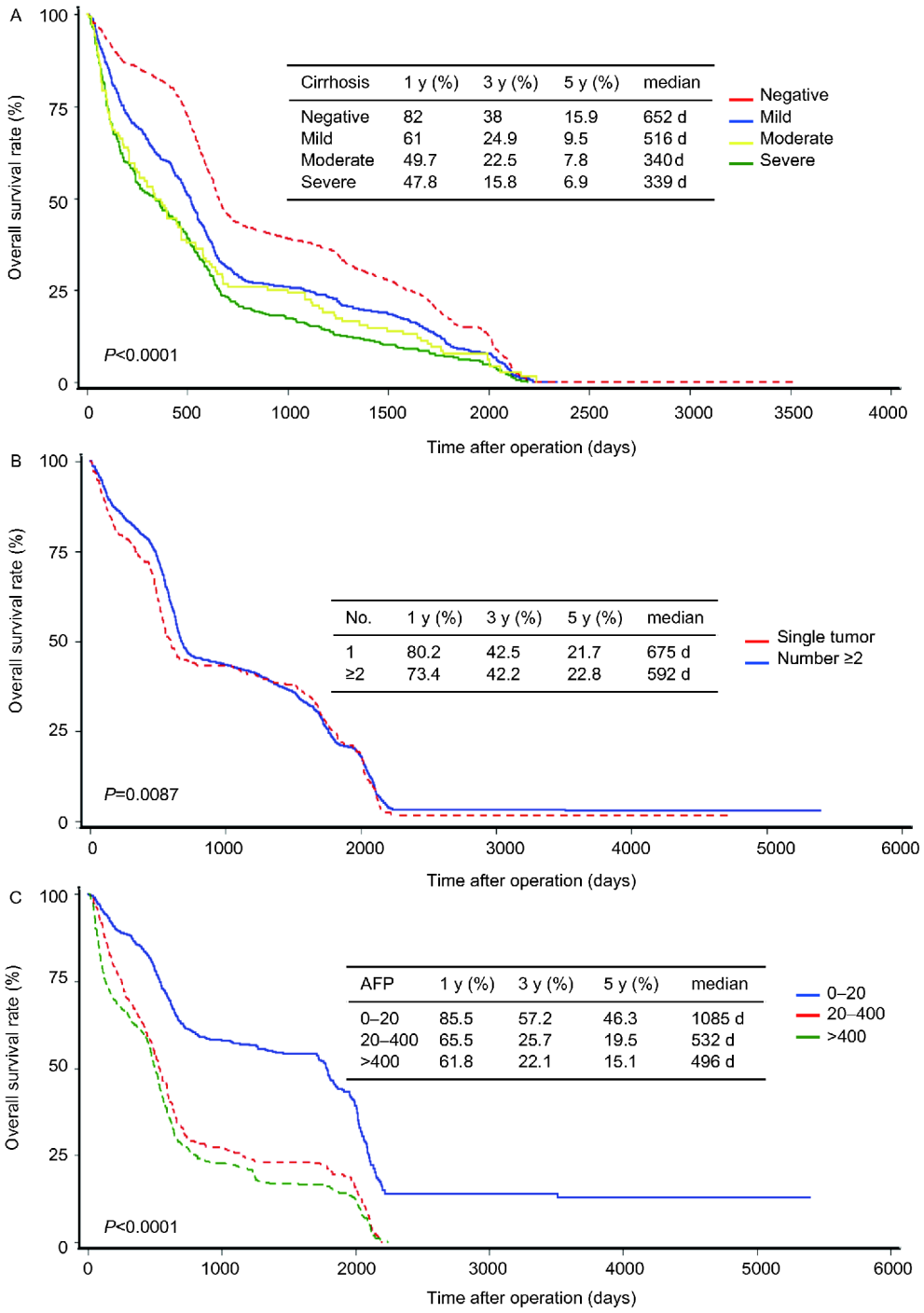

Figure 4 (Color online) Survival for HCC patients after hepatectomy were separately analyzed according to levels of liver cirrhosis (A), number of tumor nodules (B), and AFP levels (C). The median survival time, 1-year survival rate, 3-year survival rate, and 5-year survival rate for each group were described in the corresponding tables.

LLR could obtain curative result as open surgery. This study provided nationwide evidence that there was no significant difference between LLR and open hepatectomy on post-operative long-term survival, and thus supported the wide spread of laparoscopic liver resection for selected patients with HCC.

Intraoperative bleeding is undoubtedly a main concern during liver resections, as mortality and morbidity are clearly correlated with the amount of blood loss (Hanazaki et al., 2002; Jarnagin et al., 2002). Vascular exclusion is commonly applied to control intraoperative bleeding during hepatectomy to reduce transfusion and complications. In our investigation, 23.81% patients were applied with vascular exclusion for open surgery, and 24.12% for LLR, indicating

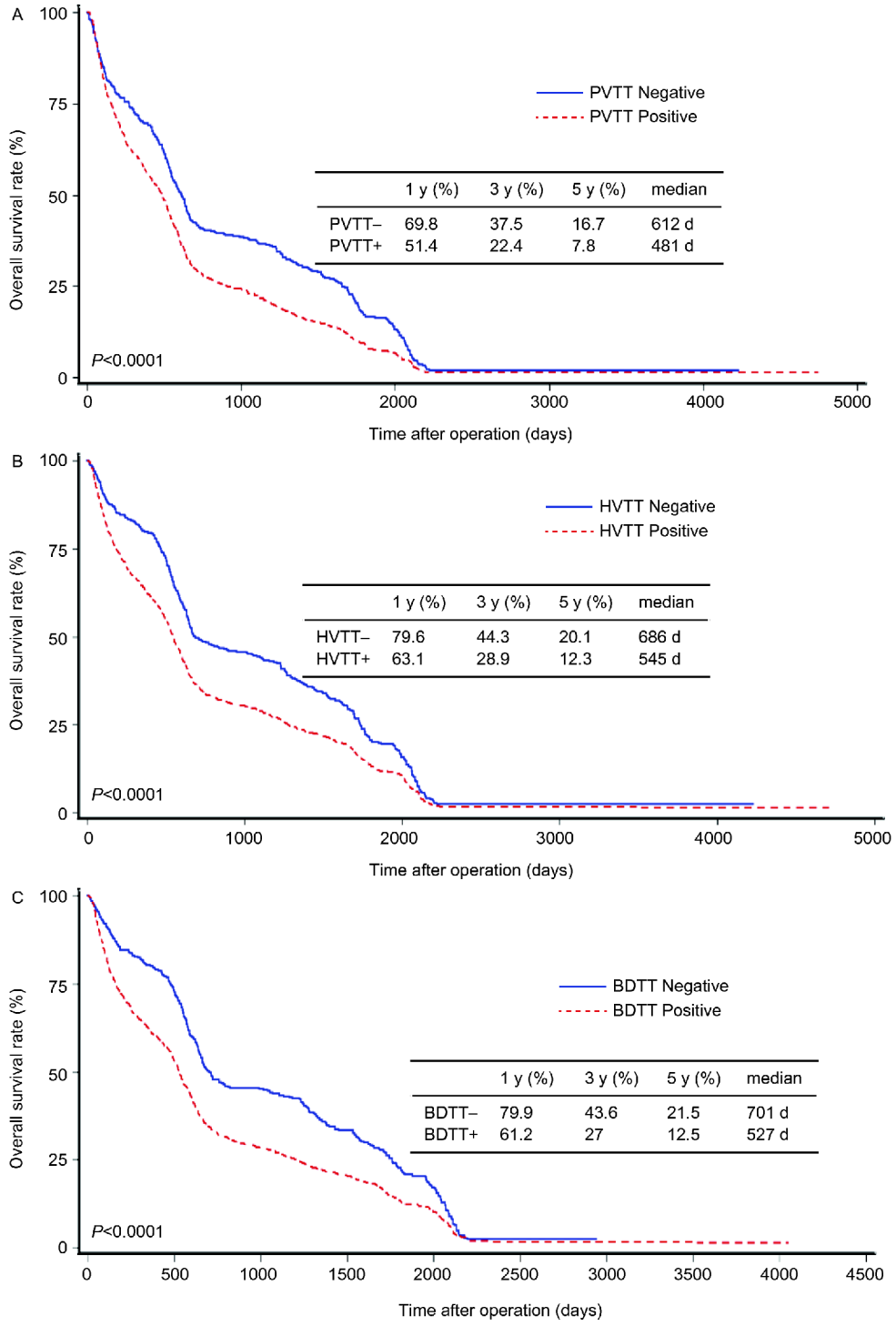

Figure 5 (Color online) Survival for HCC patients with tumor thrombosis. Survivals for patients with tumor thrombosis in portal vein (A), hepatic vein (B) and bile duct (C) were compared with those for patients without tumor thrombosis. The median survival time, 1-year survival rate, 3-years survival rate, and 5-years survival rate for each group were described in the corresponding tables.

the necessity of bleeding control for both open and laparoscopic liver resection. However, total hepatic vascular exclusion was more frequently applied in LLR, while Pringle maneuver was less favored, when compared with that in open surgery. It must be taken into consideration that surgeons may choose different vascular exclusion techniques when required, based on the patient's condition, anatomy, source of hemorrhage, and individual experience.

HBV infection is the main course of HCC in China. In this study, 81% of patients with HCC had HBV infection, and 80% patients had liver cirrhosis. HBV or HCV infection did not affect postoperative survival, while liver cirrhosis in-

dicated poor prognosis. The higher severity of liver cirrhosis was correlated with poorer survival. To explain this phenomena, we hypothesized that: (i) liver cirrhosis may lead to death other than tumor; (ii) different types of cirrhosis existed, including HBV-related cirrhosis, HCV-related cirrhosis, schistosome-related cirrhosis, alcohol-related cirrhosis and others. In the study period, anti-viral therapy has not been routinely conducted for HBV related HCC. Recent study reported that anti-HBV treatment prolonged survival for HCC patients with HBV and reduced postoperative recurrence (Papatheodoridis et al., 2015; Zhang et al., 2015). Therefore, we believe that HBV-related HCC patients can greatly benefit from anti-virus therapy and achieve better prognosis compared to HCC patients without HBV infection, provided that anti-virus therapy had been routinely performed for patients with HBV-related HCC.

Number of tumors is another factor that affects therapy decision and prognosis. The median survival for patients with single tumor was 675 days, longer than that for patients with multiple tumors (592 days). However, it did not show statistical significance. Therefore, patients with multiple tumors can get good prognosis under the condition that the tumors can be resected, indicating that HCC with multiple tumors is not a contraindication for hepatectomy. In Tongji Hospital, up to 20% of all liver resections for HCC were performed for multiple tumors (Chen et al., 2006b).

Tumor thrombosis is a high risk factor for poor prognosis which is supposed to be emphasized in therapeutic decision making. In this study, patients with tumor thrombosis in portal vein, hepatic vein and bile duct had significant shorter overall survival, compared with those without tumor thrombosis. However, selected HCC patients with tumor thrombosis got benefit from surgery, even though it predicted poor long survival (Chen et al., 2006b; Luo et al., 2015).

High AFP level also predicts poor prognosis, especially when APF is higher than 400 ng mL^{-1}. In the whole population of HCC patients, 38.11% had normal APF level, and the other 34.74% had an AFP level lower than 400 ng mL^{-1}. This result indicated that clinicians had to carefully diagnose HCC for patients with normal or relatively increased AFP level, as early diagnosis of HCC for these patients could result in better prognosis than those with high AFP level and easier to make a diagnosis.

In summary, the results in this study provided evidences that liver cirrhosis, high APF level and tumor thrombosis were predictors of poor prognosis for patients with HCC.

There are several limitations in this study which need further discussion and exploration. It is a retrospective study which involved 112 institutions with different levels of surgical techniques. Bias may exist, as surgeons in different institutions owned different ranks of experience and techniques in treating liver diseases. In addition, a portion of the patients had insufficient data or lost to follow-up. However, this study objectively presented the current national status of hepatectomy in China. Further research may focus on prospective clinical study, aiming at improving long time survival through technique renewal and therapeutic strategy optimization.

MATERIALS AND METHODS

Study design and oversight

This study was a multicenter, retrospective clinical investigation. This study was approved by the Ethics Committee for Clinical Pharmacology in Tongji Medical College, and all the information of patients was kept confidential. The investigators who collected the original clinical data were blind of the study design and did not take part in data analysis. The experienced clinicians went through the original data, and excluded the invalid cases, based on serious lack of important data that may cause bias or obvious incorrect case record such as essential error data on treatment or diagnosis. The major cases of patients lack of important data are as follows: (i) data for grouping, such as gender, number of tumors, location of tumors; (ii) data about diagnosis, or confused diagnosis; (iii) pathology data; (iv) type of resection; (v) data with logical error.

Study participants

Between January 2008 and December 2013, a total of 42,573 patients from 112 medical institutions underwent hepatectomy were screened in this study in China. All valid cases were included for epidemiology analysis. As this study mainly focused on HCC in China, patients diagnosed with HCC were finally recruited for further analysis.

Patients with the following characteristics were excluded: (i) postoperative pathological examination excluded HCC; (ii) mixed carcinoma, such as HCC mixed with cholangiocarcinoma; (iii) previous treatment for HCC, including surgery, ablation or TACE; (iv) serious underlying disease before operation; (v) serious comorbidity after operation which may result in death other than tumor, (vi) deficient data.

Data collection

The following basic characteristics were collected for each patient: age, gender, condition of hepatitis B surface antigen (HBs-Ag), hepatitis C virus antibody (HCV-Ab), liver cirrhosis, the size and number of tumors, tumor thrombosis. Preoperative examination including Child-Pugh staging, AFP (ng mL^{-1}), CEA (ng mL^{-1}), total bilirubin (μmol L^{-1}), albumin (g L^{-1}), prothrombin time, and international normalized ratio (INR) were collected. In addition, the in-

traoperative features including type of liver resection, R0, R1 or R2 resection, volume of blood loss and blood transfusion, the duration of surgery, the techniques of blood occlusion were also analyzed.

The following postoperative complications were collected: incision infection, arrhythmia, pulmonary infection, urinary tract infection, thorax infection, abdominal infection, bile leakage, hepatic insufficiency, renal insufficiency, pulmonary embolism, multiple organ dysfunction syndrome (MODS), and death.

Patients were followed up by telephone inquiry or clinic visit, and 1-, 3-, and 5-year overall survival rates were analyzed. The time to recurrence or overall survival were used as study endpoints.

Clinical diagnosis and definitions

Liver cirrhosis was diagnosed based on medical history, physical examination, ultrasound findings, and/or histopathology. The evaluation of present hepatic function was based on Child-Pugh scoring system (Pugh et al., 1973). Hepatic insufficiency was defined as prothrombin activity < 50% and serum bilirubin > 50 μmol L^{-1} on postoperative day 5 (Vauthey et al., 2002). The diagnosis of hepatic encephalopathy was clinically-based, upon exclusion of confusion, coma, and other differentials, with hyperammonaemia as the most remarkable symptom (Haga et al., 2011). Hepatorenal syndrome occurred in patients with cirrhosis, ascites, in the absence of shock, with serum creatinine >133 μmol L^{-1}, upon improvement in serum creatinine at least 2 d after diuretic withdrawal and volume expansion with albumin, in the absence of current or recent treatment with nephrotoxic drugs, and in the absence of parenchymal kidney disease (Goodman, 2007).

R0 resection referred to no cancer cells being residual on the surgical resection margins by a microscope and naked eyes. Residual tumor at the resection margin was divided into microscopic (R1 resection) and macroscopic (R2 resection).

Biliary leakage was defined as catheter drainage with bilirubin content higher than normal plasma levels. Ascites was defined as abdominal fluid output > 500 mL d^{-1} or ascites that required medical treatment. The incidence and severity of the perioperative complications were analyzed by the classification of surgical complication (Dindo et al., 2004; Lau, 2002). Hospital stay was defined as the time after operation until hospital discharged.

The presence of preoperative portal hypertension (PHT) was defined as (i) esophageal varices detectable at endoscopy or (ii) splenomegaly with a platelet count $<100\times10^3$ mm^{-3} according to the BCLC group criteria (Llovet et al., 1999). Perioperative mortality was defined as death in the hospital during the initial admission for surgery or death within 30 days after hepatic resection. Postoperative liver dysfunction was assessed by using the "50–50 criteria" (Balzan et al., 2005): serum bilirubin exceeding 50 μmol L^{-1} (3 mg dL^{-1}) and prothrombin time less than 50% on postoperative day 5.

The severity of each complication was classified according to Clavien's classification (Dindo et al., 2004). Briefly, the classification of surgical complications was mainly based on whether the patient required pharmacological treatment (grade II, otherwise grade I), surgical, endoscopic or radiological intervention (grade III), or presented life-threatening complication (grade IV), or was dead (grade V).

Statistical analysis

Statistical analysis was performed by the third-party institution, LinkDoc company (Beijing), with statisticians who were blind of the study design. Continuous variables were expressed as mean and standard deviation, and differences between groups were compared by the independent-samples *t*-test or Mann-Whitney *U*-test, as appropriate; categorical variables were reported as number of cases and prevalence, and differences between groups were compared by the chi-square test or Fisher's exact test, as appropriate. The patients' overall survival was calculated using the Kaplan-Meier method, and their comparison was performed using the log-rank test. The multivariate analysis was performed using the Cox regression model. $P<0.05$ was considered significant in all analysis. Statistical analysis was carried by SAS 17.0 software.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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SUPPORTING INFORMATION

Institutions involved in this study

Figure S1 Survival curve for male and female patients with HCC after hepatectomy. The median survival time, 1 year survival rate, 3 years survival rate, and 5 years survival rate for each group were described in the corresponding table.

Figure S2 Survival curve for HCC patients following open surgery or laparoscopic liver resection. The median survival time, 1 year survival rate, 3 years survival rate, and 5 years survival rate for each group were described in the corresponding tables.

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