Liver transplantation is widely accepted as an effective therapy for hepatoma. Perioperative dynamic observation of coagulation function is important for graft-receivers. This study was to explore perioperative changes of coagulation functions in the local advanced liver cancer patients who received liver transplantation. Clinical data of 31 local advanced liver cancer patients, underwent liver transplantation from September 2003 to January 2007, were analyzed. Platelet (PLT) counting, prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (Fib) and international normalized ratio (INR) before operation, at anhepatic phase and the first week after operation were analyzed to evaluate coagulation function. The coagulation functions of most patients were normal before operation. The six parameters varied significantly at anhepatic phase and on most days of the first week after operation when compared with the preoperative levels (p < 0.05). The elevation of PT, APTT, TT and INR and the decrease of Fib and PLT were more apparent at anhepatic phase when compared with the preoperative levels [PT: (19.51 ± 3.78) s vs. (14.16 ± 1.46) s; APTT: (77.01 ± 30.51) s vs. (40.19 ± 4.11) s; TT: (27.50 ± 15.10) s vs. (19.46 ± 3.05) s; INR: 1.61 ± 0.37 vs. 1.11 ± 0.16; Fib: (1.73 ± 0.70) g/L vs. (3.38 ± 1.00) g/L; PLT: (108 ± 60) x 10^9/L vs. (184 ± 108) x 10^9/L, p < 0.01]. In the first week after operation, the elevated PT, APTT, TT and INR levels decreased gradually, APTT was even lower than the preoperative level [(32.05 ± 6.50) s vs. (40.19 ± 4.11) s, p < 0.01]. These changes appeared usually 1–2 days after operation. Decreased PLT and Fib regained slowly at the first week after operation when compared with the preoperative levels [Fib: (2.13 ± 0.53) g/L vs. (3.38 ± 1.00) g/L, p < 0.01; PLT: (145 ± 90) x 10^9/L vs. 184 ± 108) x 10^9/L, p < 0.05], but the values were normal. According to stratification analysis, the hypocoagulability was more obvious in the patients with moderate or severe cirrhosis and those with Child-Pugh class B than in their counterparts. The coagulation functions of local advanced liver cancer patients shift from hypocoagulatory to hypercoagulatory or normal in perioperative period, therefore, prevention of bleeding should be focused on at anhepatic phase and 1–2 days after operation while prevention of thrombosis should be focused on after the first week after operation. The degree of liver cirrhosis and Child-Pugh score could help to evaluate postoperative coagulation disorder.

Liver transplantation is widely accepted as an effective therapy for advanced liver cancer.1 According to incomplete summary, more than 5,000 cases of liver transplantation had been performed till Jan. 2005, of which liver transplantation for treatment of advanced liver cancer had accounted for about 40%.2 Managing the changes of coagulation functions is important in perioperative management after liver transplantation,3 therefore, dynamic observation of coagulation functions will not only help to direct the infusion of blood products and administration of drugs but also help to prevent postoperative complications, such as bleeding and thrombosis. Researchers at home and abroad had observed the changes of coagulation functions in the perioperative period of liver transplantation, but reports concerning the changes of coagulation functions of the local advanced liver cancer patients in the perioperative period of liver transplantation are rare. This study retrospectively analyzed coagulation indexes, including platelet (PLT) counting, prothrombin time (PT), activated partial platelet time (APTT), fibrinogen (Fib), thrombin time (TT) and international normalized ratio (INR), of 31 local advanced liver cancer patients before liver transplantation, at the anhepatic phase and at the first week after operation in order to explore the changes of coagulation functions and provide theoretical basis for coagulation treatment of local advanced liver cancer patients in the perioperative period of liver transplantation.

**Materials and Methods**

Inclusive criteria for medical cases. The criteria for subject selection were as follow: (1) local advanced liver cancer patients who received liver transplantation (local advanced liver cancer was designated as liver cancer with intra-hepatic dissemination, or...
that with recurrent sites after hepatectomy, or that uncontrolled by non-operative therapy, or that with tumor thrombus in the first-order or main branches of portal vein without extra-hepatic metastasis; (2) patients with hepatocellular carcinoma (HCC) verified by postoperative pathology; (3) liver cancer patients survived for more than 6 months after liver transplantation; (4) those with complete record of coagulation indexes in perioperative period; (5) those with secondary abdominal surgery but excluded other reasons such as hemorrhage.

Clinical data. According to the above criteria, 31 liver cancer patients who received liver transplantation in Cancer Center of Sun Yat-sen University from Sep. 2003 to Jan. 2007 were selected. Among the patients, 27 were men and 4 were women with a median age of 48 (range, 25–68). Results of preoperative liver function examination were listed as follow: AST: 0–40 U/L in 16 (51.61%) patients; 41–80 U/L in 10 (32.26%) patients, and above 81 U/L in 5 (16.13%) patients. ALT: 0–45 U/L in 11 (35.48%) patients, 46–90 U/L in 12 (38.71%) patients, and above 91 U/L in 8 (25.81%) patients. Child-Pugh class: 23 (74.19%) patients in class A and 8 (25.81%) in class B. Postoperative pathology examination revealed that 15 (48.39%) patients had minor liver cirrhosis, 13 (41.49%) patients had moderate cirrhosis, and 3 (9.68%) patients had severe cirrhosis.

Fast resection of donor liver tissue using an in situ hypothermic perfusion technique was performed, with uw solution used as both perfusion solution and storage solution. The average time for donor liver preservation in cold ischemia was 10.89 h. Modified piggyback liver transplantation (cavalplasty) was performed under the condition of tracheal intubation combined with intravenous general anesthesia. The operation time was (7.97 ± 1.71) h with an anhepatic phase of (53.09 ± 8.64) min. During liver transplantation, no coagulation drugs were administered for the patients. Concentrated red cells, fresh frozen plasma and platelets were transfused regarding to the bleeding monitoring situation. On the operation day or in the 1st week after operation, blood products or haemostatics were used regarding to the drainage monitoring results. Of the 31 patients, 4 (12.90%) only used blood products, 4 (12.90%) only used haemostatics, 8 (25.81%) used both of them, and 15 (48.39%) used none of them. Blood products (mainly included fresh frozen plasma and platelets) or haemostatics (mainly included antifibrinolytic drugs, anti-fibrinogen and anti-thrombin drugs) were mostly used on the operation day or the first day after operation.

Coagulation indexes and measurement methods. The coagulation indexes, including PLT, PT, APTT, Fib, TT and INR, were observed before operation, at the anhepatic phase and at the 1st week after operation. The reference values were listed in Table 1. The peripheral venous blood in fasting was extracted with a vacuum test tube before operation, at the anhepatic phase, on the operation day and at the first, second, third, fifth and seventh days after operation. Of the extracted blood, 2 mL was mixed with 0.109 mmol/L sodium citrate (1:9) for anti-coagulation and analyzed by French Stago auto thrombus/hemostasis analyzer for PT, APTT, Fib, TT and INR; another 2 mL was mixed with 3.0 mg EDTA-K2 for anti-coagulation and analyzed by STKS blood counter system (Beckman Counter, US) for PLT.

Statistical analysis. All data were presented as mean ± SE and analyzed by SPSS10.0 statistical analysis software. A p value of less than 0.05 was considered significant. Changes of coagulation functions of the local advanced liver cancer patients receiving liver transplantation in perioperative period were analyzed by single-factor ANOVA for inter-group comparison, and LSD-t test for inter-group pairing comparison. For only three patients had severe cirrhosis, they were incorporated with moderate cirrhosis patients into severe-moderate cirrhosis group. Independent samples t test was used for grouping analysis.

Results

The results of six coagulation indexes of the local advanced liver cancer patients receiving liver transplantation were listed in Table 1. Although some of the indexes before operation were beyond the reference values, the overall levels still stayed in normal ranges. Significant changes were observed in the 6 indexes before operation as compared with those at the anhepatic phase and after operation (p < 0.05). PT, APTT and TT was prolonged, INR was elevated, and Fib and PLT were decreased most significantly at the anhepatic phase (p < 0.05). In the week after operation, the prolonged PT, APTT and TT were shortened gradually and the elevated INR was returned. APTT was

Table 1 Perioperative changes of coagulation functions of the 31 local advanced liver cancer patients receiving liver transplantation

<table>
<thead>
<tr>
<th>Time point</th>
<th>PT (s)</th>
<th>INR</th>
<th>APTT (s)</th>
<th>TT (s)</th>
<th>Fib (g/L)</th>
<th>PLT (x10⁹/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference value</td>
<td>10.50–13.50</td>
<td>0.85–1.20</td>
<td>22.50–34.00</td>
<td>14.00–21.00</td>
<td>1.80–4.00</td>
<td>100–300</td>
</tr>
<tr>
<td>Before operation</td>
<td>14.16 ± 1.46</td>
<td>1.11 ± 0.16</td>
<td>40.19 ± 4.11</td>
<td>19.46 ± 3.05</td>
<td>3.38 ± 1.00</td>
<td>184 ± 108</td>
</tr>
<tr>
<td>Anhepatic phase</td>
<td>19.51 ± 3.78b</td>
<td>1.61 ± 0.37b</td>
<td>77.01 ± 30.51b</td>
<td>27.50 ± 15.10b</td>
<td>1.73 ± 0.70b</td>
<td>108 ± 60b</td>
</tr>
</tbody>
</table>

PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; TT, thrombin time; Fib, fibrinogen; PLT, platelet. All values are presented as mean ± SD of the 31 patients. *p < 0.05, **p < 0.01, vs. preoperative levels.
significantly shorter during this week than before operation ($p < 0.01$). These changes were happened mostly 1–2 days after operation. Decreased Fib and PLT recovered slowly and significant differences were still found in them in the 1st week after operation as compared with the levels before operation ($p < 0.01$ and $p < 0.05$, respectively).

The results of six coagulation indexes of the 31 patients stratified by hepatic cirrhosis and Child-Pugh class were listed in Tables 2 and 3. As compared with the levels in minor cirrhosis group, PT, APTT and TT were longer, INR was higher, while Fib and PLT were lower in severe‑moderate cirrhosis group. Some changes were significant ($p < 0.01$ or $p < 0.05$), which happened mostly at the 1st day after operation. As stratified by Child-Pugh score, similar changes were showed, especially the changes of PT, TT, Fib and PLA, which also happened mostly at the 1st day after operation.

### Discussion
Liver synthesizes most coagulation factors and anti-coagulation substances, and thus plays an essential role in coagulation activities in the body by maintaining balance between coagulation and anti-coagulation, and between fibrinolysis and anti-fibrinolysis. Bleeding and thrombosis always appear as the overriding factors in determining the success of liver transplantation $^5,^6$. The liver functions in transplantation recipients are damaged at different levels before operation. Heavy damage caused by operation, long duration of operation, large volume of blood transfusion and liquid infusion, and injuries from the anhepatic phase and reperfusion phase lead to changes of coagulation functions. Numerous researches at home and abroad $^7$-$^11$ found coagulation dysfunction appeared as the liver
transplantation continued, reaching the summit at the anhepatic phase and reperfusion phase. The degree of coagulation dysfunction during operation parallels to the degree of liver function disorder before operation. But the literature often focuses on the operation period, and reports concerning the peri-operation period are rare, not to say those reports on liver transplantation for liver cancer patients. Liver cancer patients also suffer from various complications such as cirrhosis and portal hypertension. Hypercoagulability (Trousseau syndrome) often exists in tumor patients due to the unique characteristics of tumors. Liver cancer patients not only suffer from Trousseau syndrome, they also show hyperfibrinolysis. Biguzzi et al. and Zhou et al. found that the levels of pro-coagulation and fibrinolysis-related factors in plasma, such as thrombomodulin (TM), endothelial protein C receptor (EPCR), tissue factor (TF), urokinase type plasminogen activator (uPPT) and urokinase type plasminogen activator receptor (uPTR), were elevated in liver cancer patients. These researches imply that liver cancer patients may have unique characteristics regarding to the changes of coagulation functions.

In the present study, 31 local advanced liver cancer patients showed different levels of cirrhosis and liver dysfunction. Some even showed hypocoagulability, in which PT, APTT and TT were prolonged and INR was elevated, whereas PLT and Fib were decreased. However, the degree of cirrhosis was mostly minor or moderate (90.32%). Patients with AST and ALT levels elevated 2-fold of normal levels before operation accounted for 16.13% and 25.81% respectively. Most patients (74.19%) were subjected to Child-Pugh class A before operation; no class C was noted. These people were still in the compensational period with coagulation indexes in the normal range on average. During liver transplantation, especially at the anhepatic phase, the hypocoagulability reached a summit and the values of PT, APTT, TT, INR, PLT and Fib showed significant differences, compared with those before operation (p < 0.01). At the 1st week after operation, the prolonged PT, APTT and TT and elevated INR returned. At the seventh day after operation, the values of PT and INR fell back to those before operation, and the values of APTT and TT were lower than those before operation with significant difference for APTT (p < 0.01). It implies that the liver functions recovered gradually and the patients endured a transition from hypocoagulability to normal coagulation or hypercoagulability which mostly happened at the first or second day after operation. In the meantime, the levels of Fib and PLT were lower than those before operation and recovered slowly. One week after operation, the levels of Fib and PLT were still significantly lower than those before operation (p < 0.05), but the average levels of them already recovered to normal range. Zhang et al. investigated the coagulation functions of 100 patients receiving liver transplantation and found that hypocoagulability was apparent at the anhepatic phase. The hypocoagulability observed by them was more severe than that observed by us, however, they have selected advanced liver cirrhosis patients with coagulation indexes higher than those in our study. Yang et al. investigated the coagulation functions of cirrhosis patients and liver cancer patients before operation till 72 h after operation, and found that cirrhosis group showed hypercoagulability while liver cancer group had normal coagulation functions before operation, the hypercoagulability was apparent in the new-liver period in both groups, especially in cirrhosis group, and the coagulation indexes escalated gradually. Their results of changes of coagulation functions in liver cancer patients are consistent with our results.

In the present study, stratification analyses showed that the hypocoagulability in peri-operation period was more apparent in the patients with severe cirrhosis and high Child-Pugh scores, and this situation was mostly noted at the first or second day after operation. As the donor liver recovered its functions in the body, the hypocoagulability was corrected and the coagulation indexes were consistent among stratified subgroups. Only some of the six indices showed significant changes in stratification analyses, which might be contributed by few severe cirrhosis patients and few Child-Pugh class B patients in our study. As a consequence, the cirrhosis level and Child-Pugh scores were significant for evaluating postoperative coagulation dysfunction in local advanced liver cancer patients receiving liver implantation.

We had only investigated perioperative changes of coagulation functions in 31 local cancer patients receiving liver transplantation. No early stage liver cancer patients and non-liver cancer patients had been involved in our study. Moreover, the influence of tumor stage on the coagulation functions and whether the perioperative changes in early stage liver cancer patients are consistent with the changes in local advanced liver cancer patients are uncertain. Hei et al. found that the changes of coagulation functions were similar in 8 severe hepatitis patients and 11 liver cancer patients during liver transplantation; however, more coagulation substances were administered for severe hepatitis patients. These results suggest that extensive researches and comparative analysis should be further carried on regarding to coagulation functions of patients receiving liver transplantation.

In conclusion, because of the characteristics of the disease and the influence from liver transplantation, the coagulation functions of local advanced liver cancer patients transit from hypocoagulability to normal or hypercoagulability in perioperative period. The hypocoagulability reaches the summit at the anhepatic phase and changes at the first or second day after operation with a tendency to normal or hypercoagulability as the donor liver recovers its functions. At the anhepatic phase, on the operation day, and at the first or second day after operation, the patients have a bleeding tendency, while one week after operation, thrombosis should be prevented. Moreover, cirrhosis level and Child-Pugh scores may be helpful for evaluating the coagulation dysfunction after operation.

References

Perioperative changes of coagulation functions in the local advanced liver cancer patients receiving liver transplantation


