A Clinic Study on Long-term Efficacy and Safety of Autologous Peripheral Blood Stem Cell Transplantation in Patients with Decompensated Hepatitis B Cirrhosis

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ABSTRACT

Objective • To investigate the long-term safety and efficacy of autologous peripheral blood stem cell transplantation (APBSCT) in treating decompensated hepatitis B cirrhosis.

Methods • In this study, a retrospective analysis was conducted on a cohort of 84 patients diagnosed with decompensated hepatitis B cirrhosis between January 2011 and December 2012. The patients were categorized into two groups based on their treatment approach: the transplantation group, consisting of 34 cases who received APBSCT in addition to medical treatment, and the comprehensive medical treatment (CMT) group, comprising 50 cases who solely received CMT. EPI Data software was used for data input and verification. Survival curves were drawn by Kaplan-Meier method and analyzed by log-rank test. Paired t test and independent sample t test were used for intra-group and inter-group mean comparison of measurement data, respectively. The Mann-Whitney U test is used for non-normally distributed data.

Results • After the ten-year follow-up period, it was found that overall survival (OS) in the transplantation group was markedly higher than that in the CMT group (56% vs. 16%, P < .001). Albumin (ALB), prothrombin time (PT), and indocyanine green retention at 15 min (ICG R15) were significantly improved in sequence at 4 to 12 weeks of early treatment in APBSCT group; subsequently, the Acoustic radiation force impulse (ARFI) index and spleen length significantly decreased at 48 weeks. Compared with the CMT group, ALB and PT levels in the APBSCT group continued to recover and eventually stabilize at normal or low-risk levels at subsequent follow-ups up to 8 years. The ten-year prevalence of hepatocellular carcinoma (HCC) in the APBSCT group was markedly lower than that in the CMT group (26% vs. 62%; P = .025). Moreover, APBSCT significantly reduced ascites (χ² = 6.997, P = .041) and was not associated with any significant adverse events during APBSCT. Based on clinical evidence, APBSCT is a safe and effective treatment for decompensated hepatitis B cirrhosis, resulting in a favorable long-term prognosis with no significant adverse events.

Conclusions • APBSCT is a relatively safe and effective treatment for decompensated hepatitis B cirrhosis. (Altern Ther Health Med. [E-pub ahead of print.])

INTRODUCTION

In China, the hepatitis B virus (HBV) is the predominant etiological factor leading to the development of cirrhosis. The chronicity of HBV infection can result in the progression towards decompensated hepatitis B cirrhosis, which is characterized by a multitude of complications including gastrointestinal bleeding, hepatorenal syndrome, hepatic encephalopathy, and ascites. The aforementioned complications are widely observed and significantly impact the unfavorable prognosis of the disease. At present, the efficacy of available treatment options, such as antiviral and antifibrotic therapies, is limited. Although liver transplantation therapy is acknowledged as the most effective approach for end-stage liver disease, its utilization is constrained by a scarcity of donors, exorbitant expenses, and postoperative complications. Nevertheless, the field of regenerative medicine has emerged as a promising avenue for research in the treatment of this
Patients

MATERIALS AND METHODS

Patients

This study was permitted by the Institutional Ethics Committee of Ningbo No. 2 Hospital, Zhejiang Province in China. The patients were enrolled from January 01, 2011, to December 30, 2012, and the follow-up period was until June 30, 2022. Two cohorts of patients with HBV-related decompensated cirrhosis were followed up, all of whom were hospitalized during the same period. The control group was treated with conventional therapy (CMT, n = 50) while the transplantation group received APBSCT combined with CMT (APBSCT, n = 34). Both groups were predominantly male, with a male-to-female ratio of 1.5 (30 males and 20 females) in the CMT group and 2.1 (23 males and 11 females) in the APBSCT group, respectively. The mean age at enrollment was 50.10 ± 11.02 years in the APBSCT group and 51.14 ± 9.70 years in the CMT group. Clinical data were obtained via medical record retrieval systems or follow-up interviews. The inclusion criteria of APBSCT group were: (i) HBV-associated decompensated cirrhosis, age 18-65 years; (ii) at least six months of antiviral therapy and HBV-DNA < 1.0×10^6 IU/mL; (iii) no plasma, albumin, or other blood product transfusions in the month before study inclusion; and (iv) CTP scores ≥7. The exclusion criteria were: (i) combined cirrhosis with other etiologies (e.g., other viral hepatitis, autoimmune liver disease, fatty liver, alcoholic liver disease, genetic metabolic liver disease, etc.); (ii) HCC or other malignancies; (iii) end-stage cirrhosis with severe complications (Grade II or higher hepatic encephalopathy, active upper gastrointestinal bleeding, hepatorenal syndrome, or bacterial infection); (iv) cardiac, pulmonary, or renal failure; and, (v) alcohol abuse or abstinence for less than six months.

Diagnoses and interventions

Chronic hepatitis B was diagnosed by combining pathogenic tests, biochemical examinations, and patient history. Decompensated cirrhosis was verified by ultrasound or computed tomography and upper gastrointestinal endoscopy. Patients in both cohorts underwent medical treatment according to the 2011-2022 guidelines. They were treated with nucleoside analog antiviral (e.g., entecavir or lamivudine combined with adefovir), antifibrotics, hepatoprotective (silymarin and polyenyl phosphatidylcholine), and symptomatic supportive therapy. Complications such as ascites, gastrointestinal bleeding, hepatic encephalopathy, and hepatorenal syndrome were also managed during the study.

Before transplantation, the APBSCT group received rhG-CSF (400ug/d; Kirin, Japan) for four consecutive days, and ultrasound monitoring of the spleen was performed during mobilization. Stem cells were obtained on the day after the last injection. About 50 ml (10^7-10^8/Kg) of peripheral blood mononuclear cells (PBMCs) were acquired by leukocyte isolation using the blood cell separator (Com. Tec model, Fresenius Kabi AG, Germany). The CD34+ cells were analyzed by flow cytometry. The purified CD34+ stem cells were ensured to be no less than (2-4) × 10^7/ml each time and injected into the hepatic artery via femoral artery intubation within 2 hours. The patient was extubated...
postoperatively, the puncture site was dressed with pressure for 6 hours and bed rest for 24 hours. During the follow-up period after transplantation, the treatment included liver care, management of various complications, and symptomatic supportive treatment.

Liver functional reserve assay

The hepatic functional reserve index (indocyanine green retention at 15 min [ICG R15]) is an important indicator for the assessment of patient survival, liver transplantation requirements, and preoperative liver functions.25 It reflects the number of hepatic viable cells and hepatic blood flux.23 It has been reported that ICG R15 level positively correlates with portal pressure and the extent of liver fibrosis and is a standard method for quantifying liver function reserves.26 It reflects liver reserve functions by the retention rate of indole in blood at 15 min. Patients were fasted and injected with a single dose of 0.5 mg/kg ICG R15 (Jishi Pharmaceutical Co., Ltd., China). The liver function reserve analyzer automatically measured the concentration of ICG R15 by applying a DDG-3300K nasal photoreceptor probe to the nose. The usual range of ICG R15 is 0%-10%, the range for chronic hepatitis is 15%-20%, and 35% indicates cirrhosis.23

Acoustic radiation force impulse (ARFI) imaging assay

The ultrasound machine emits a focused ultrasound beam to the hepatic region-of-interest (ROI), generating longitudinal compressions and transverse vibrations to create shear waves. It uses a specific electronic system to capture low-frequency shear wave information and convert it into shear wave velocity (SWV), which is expressed in meters/second (m/s). Measurements are performed under ultrasound guidance, 2-3 cm below the hepatic pericardium, avoiding intrahepatic bile ducts and vasculature. The measurements are repeated ten times to obtain the median. The hepatic ARFI index in normal adults ranges from 1.0-1.3 m/s without gender differences.27 A range of between 1.6-2.0 m/s suggests early cirrhosis, and greater than 2.0 m/s suggests advanced cirrhosis.28

Outcome measures

Basic information for all patients (patient name, hospitalization number, gender, age, symptoms, hepatic biochemical indexes, and abdominal B-mode ultrasound) was recorded, with death or liver transplantation as a follow-up endpoint for at least ten years. Follow-up schedule was: outpatient follow-up, questionnaire, and telephone follow-up were used, with one outpatient visit per month for the first six months and an average of one outpatient, questionnaire, or telephone visit every three months after that. After two years, the follow-up was once a year until June 30, 2022. The follow-up included symptoms and signs, laboratory tests, complications, and time to death or liver transplantation. Several indicators, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (ALB), total bilirubin (TBIL), and prothrombin time (PT) were measured early in treatment (0, 4, 12, 24 weeks) and long-term (1, 2, 4, 8 years). Changes in liver ARFI index and spleen size were assessed in both groups (0, 4, 12, 24, and 48 weeks) after treatment. Liver function reserve index (indocyanine green retention at 15 min [ICG R15]) was also tested in both groups at 0, 4, 12 and 24 weeks. Death information was obtained from case records and confirmed by telephone. Ultrasound or computed tomography was performed to confirm HCC.

Statistical analysis

Data entry and validation were performed using the EPI DATA software (Chinese Center for Disease Control and Prevention, Chinese version, China). Survival curves were plotted using the Kaplan-Meier method and analyzed by the log-rank test. Measurement data are expressed as mean ± standard deviation (σ). Intra-group and inter-group comparisons of means were performed by paired t-test and independent sample t-test, respectively. The Mann-Whitney U test was used for non-normally distributed data. The SPSS software (IBM SPSS Statistics 26.0) was used for analyses, and a 2-sided P < .05 was set as the threshold for statistical significance.

RESULTS

Patient's baseline information

A total of 84 patients were included in the present study, and the patient enrollment and screening process is illustrated in Figure 1. There were no significant differences in gender, age, pre-treatment levels of patient body mass index (BMI), ALT, AST, TBIL, ALB, PT, ICG R15, spleen size, and liver ARFI values between the two groups, as shown in Table 1.

Patient survival rate

The Kaplan-Meier survival curves of the patients are illustrated. The difference in two-year overall survival (OS) outcomes between the CMT and APBSCT groups (88% vs. 97.1%) was not significant. However, the APBSCT group exhibited a significantly higher 8-year OS rate (56%) compared to the CMT group (18%) (P < .001). The results suggest that APBSCT has a positive impact on long-term survival in the entire study cohort. See Figure 2.

Biochemical indicators after APBSCT treatment

Biochemical markers, including ALT, AST, TBIL, ALB, and PT were used to evaluate the prognosis of the patients. Before treatment, there were no significant differences in the levels of these markers between the two groups. As shown in Table 1, the levels of ALT, AST, and TBIL did not show any significant changes in either group (P > .05). In contrast, ALB and PT levels in the APBSCT group gradually improved starting from week four and remained at desirable or low-risk levels up to eight years post-transplantation. See Table 1, Table 2, Table 3.

The study results indicated that there were no significant differences in ALB and PT levels between the CMT and APBSCT groups during the early stages of treatment (weeks
### Table 1. Subject Demographics and Baseline Data

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Male/Female</th>
<th>Age (year)</th>
<th>ALT(IU/L)</th>
<th>AST(IU/L)</th>
<th>ALB(g/L)</th>
<th>TBIL(μmol/L)</th>
<th>ICG R15(%)</th>
<th>PT(s)</th>
<th>PTA (%)</th>
<th>PT(A)</th>
<th>PTA(A)</th>
<th>ALB(g/L)</th>
<th>ICG R15 15-min Retention Rate (%)</th>
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</thead>
<tbody>
<tr>
<td>CMT</td>
<td>50</td>
<td>30/20</td>
<td>51.44±9.70</td>
<td>40.35±18.70</td>
<td>28.94±17.80</td>
<td>29.82±16.80</td>
<td>61.93±30.67</td>
<td>18.14±20.31</td>
<td>34.27±13.37</td>
<td>0.43±0.12</td>
<td>0.19±0.04</td>
<td>34.27±13.37</td>
<td>28.94±17.80</td>
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</tr>
<tr>
<td>APBSCT</td>
<td>34</td>
<td>23/11</td>
<td>50.10±11.02</td>
<td>54.45±25.77</td>
<td>40.96±10.48</td>
<td>18.75±10.34</td>
<td>61.44±26.08</td>
<td>31.58±18.26</td>
<td>34.27±13.37</td>
<td>0.43±0.12</td>
<td>0.19±0.04</td>
<td>34.27±13.37</td>
<td>28.94±17.80</td>
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</tr>
</tbody>
</table>

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; ARFI, Acoustic pulse radiation force imaging velocity.

### Table 2. Short-Term Liver Function Biochemistry and Prothrombin Time Measurement

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Male/Female</th>
<th>Spleen thickness (mm)</th>
<th>Spleen length (mm)</th>
<th>ARFI(m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT</td>
<td>50</td>
<td>30/20</td>
<td>53.0±8±09.54</td>
<td>158.4±27.07</td>
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<td>APBSCT</td>
<td>34</td>
<td>23/11</td>
<td>47.3±9±09.21</td>
<td>148.6±28.37</td>
<td>2.56±0.39</td>
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</tbody>
</table>

**Abbreviations:** TBIL, total bilirubin; ICG R15, 15-minute retention rate of indocyanine green; PT, prothrombin time; PTA, prothrombin activity; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALB, albumin; ARFI, Acoustic pulse radiation force imaging velocity.

### Table 3. Long-Term Liver Function Biochemistry and Prothrombin Time Measurement

<table>
<thead>
<tr>
<th>Group</th>
<th>Project</th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 12</th>
<th>Week 24</th>
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<tbody>
<tr>
<td>APBSCT</td>
<td>TBL</td>
<td>54.45±33.87</td>
<td>49.85±18.99</td>
<td>46.28±12.84</td>
<td>37.06±6.83</td>
<td>27.95±12.87</td>
</tr>
<tr>
<td>ALT(IU/L)</td>
<td>31.58±18.26</td>
<td>36.53±21.38</td>
<td>34.02±19.69</td>
<td>29.74±22.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST(IU/L)</td>
<td>57.4±24.37</td>
<td>58.6±25.12</td>
<td>59.4±20.71</td>
<td>59.4±22.64</td>
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<td></td>
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<tr>
<td>PT(s)</td>
<td>21.8±10.47</td>
<td>21.8±10.47</td>
<td>17.8±20.91</td>
<td>16.8±20.91</td>
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<tr>
<td>CMT</td>
<td>TBL</td>
<td>60.7±39.46</td>
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<tr>
<td>ALT(IU/L)</td>
<td>31.58±18.26</td>
<td>36.53±21.38</td>
<td>34.02±19.69</td>
<td>29.74±22.22</td>
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</tr>
<tr>
<td>AST(IU/L)</td>
<td>57.4±24.37</td>
<td>58.6±25.12</td>
<td>59.4±20.71</td>
<td>59.4±22.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT(s)</td>
<td>21.8±10.47</td>
<td>21.8±10.47</td>
<td>17.8±20.91</td>
<td>16.8±20.91</td>
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</tr>
</tbody>
</table>

**Abbreviations:** TBL, total bilirubin; ICG R15, 15-minute retention rate of indocyanine green; PT, prothrombin time; PTA, prothrombin activity; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALB, albumin; ARFI, Acoustic pulse radiation force imaging velocity.

### Figure 1. Patient Enrollment Design Chart.

### Figure 2. Ten-Year Survival Curve of APBSCT Group and Control Group

**Abbreviations:** LT, Liver Transplantation

0, 4, 12, and 24) as shown in Table 2. However, ALB levels in the APBSCT group showed a significant increase over time, with a marked increase at 4, 12, and 24 weeks compared to the baseline levels ([28.45 ± 5.75] μg/L) (P < .05). In addition, ALB levels were significantly higher in the APBSCT group at 12 and 24 weeks than at 4 weeks ([30.48 ± 4.94] μg/L, P < .05). The APBSCT group also showed significant increases in ALB levels at 4, 12, and 24 weeks compared to the CMT group (P < .05). On the other hand, PT levels in the APBSCT group decreased significantly over time. Specifically, PT levels at 12 and 24 weeks were significantly lower than the baseline ([28.48 ± 4.94] s, P < .05). This decrease was statistically significant compared to the control group during the same period (P < .05). Long-term follow-up (1, 2, 4, and till 8 years) revealed that the ALB and PT levels in the APBSCT group were significantly different from those in the CMT group in the same year. As presented in Table 3, ALB levels in the APBSCT group continued to increase in years 1 and 2, decreased slightly in year 4, and eventually stabilized at the desired level till year 8. Meanwhile, PT levels in the APBSCT group remained stable from years 1 to 4 and maintained a low-risk level till year 8.

**Synthetic reserve functions of the liver**

Table 4 summarizes the ICG R15 results. The APBSCT group exhibited significantly lower ICG R15 levels at 12...
weeks (39.37 ± 15.24) and 24 weeks (34.84 ± 8.24) compared to pre-transplant levels and concurrent control group. These findings suggest that APBSCT has the potential to improve the hepatic synthetic reserve function in patients, and this benefit can be observed at an early stage.

**ARFI index and spleen size**

In order to investigate whether APBSCT therapy could ameliorate hepatic fibrosis and portal vein pressure and if stem cell therapy could increase the risk of hypersplenism, we examined the changes in liver ARFI index (Table 5) and spleen size (Table 6) in both groups at 0, 4, 12, 24, and 48 weeks. The ARFI index in the APBSCT group was 2.03 ± 0.45 m/s at 48 weeks, which was significantly lower than pre-transplantation [2.50 ± 0.39 m/s, P < .01] and concurrent controls [2.54 ± 0.42 m/s, P < .05] as shown in Table 5. Although there was a trend towards reduction in spleen thickness in the APBSCT group, it was not significant. However, there were significant differences in spleen length at 48 weeks [127.42 ± 32.94 mm] compared to before transplantation [148.69 ± 28.37 mm, P < .01] and concurrent controls [141.63 ± 30.96 mm, P < .05] as shown in Table 6.

**Clinical outcomes and complications**

All patients in the study were able to tolerate the treatment regimen without experiencing serious infections, bleeding, or liver function deterioration. The most common adverse events observed were mild symptoms such as hypothermia, musculoskeletal pain, and fatigue, which were attributed to the administration of rhG-CSF and transplantation. Upon discontinuing the treatment, these symptoms disappeared. In Table 7, a significant regression of ascites was observed in 6 out of 7 patients in the APBSCT group (85.71%) compared to 21 out of 39 patients in the CMT group (61.76%) during the 8-year follow-up period (P < .05).

The causes of death in both groups are presented in Table 8. In the transplantation group, 57% (8/14) of the patients died due to complications, 29% (4/14) from HCC, and 7% from non-liver-related causes (1/14), and one case of tuberculosis infection. In control patients, 46% (19/41) died from complications, 20% (8/41) died from liver failure, 32% (13/41) died from HCC, and 2% (1/41) died from stroke. Although fewer patients in the APBSCT group died from liver failure (7%) than in the control group (20%), there was no statistical difference between the two groups. The difference in the proportion of HCC-associated deaths between the groups was also insignificant (P > .05). Table 9 summarizes the prevalence of HCC, which was significantly lower in the APBSCT group (26%) than in the CMT group (62%) (P = .025). The mean age of onset of HCC between the APBSCT group (53.22 ± 7.76 years) and the CMT group (51.23 ± 8.34 years) did not show any significant difference (P = .711).

**DISCUSSION**

In this retrospective cohort study involving 84 patients, it has been determined that APBSCT represents a secure and efficacious therapeutic approach for individuals with decompensated hepatitis B cirrhosis. This treatment modality yields a favorable long-term prognosis, devoid of any notable adverse events. The integration of conventional medical therapy with APBSCT results in sustained and augmented therapeutic advantages, without any discernible rise in toxicity. These findings underscore the enduring stability, effectiveness, and safety of APBSCT.

**Stem cells, which are of significance in cell therapy, have potential risks.** Mesenchymal stem cells (MSCs) ameliorate inflammation and fibrosis during liver tissue remodeling by supporting and synergizing with hematopoietic stem cells (HSCs). Clinically, PBSCs, which are more or less like HSCs,
due to their relatively low risk and easy availability, have made tremendous progress in treatment of various conditions with poor prognostic outcomes and relapsing refractory diseases (e.g., malignant lymphoma, diabetes, and multiple myeloma). There are reports about the ability of APBSCT to treat cirrhosis, such as PBSCs promote hepatocyte regeneration and extracellular matrix (ECM) remodeling in rat liver cirrhosis; APBSCT reduces MELD score and significantly improves the 5-year survival without increasing the risk of HCC. However, with advances in anti-HBV drugs, patients may have better survival rates than before. More retrospective studies should be performed to assess the efficacy and risks of APBSCT.

Our previous study confirmed that APBSCT improves portal hemodynamics and hepatic function reserves in decompensated hepatitis B cirrhosis patients. The follow-up time was one year. We further investigated the clinical outcomes of patients after ten years. Patients who received APBSCT in combination with conventional therapy (e.g., entecavir or lamivudine combined with adeovir) showed a significant long-term survival advantage and exhibited better outcomes with regards to reduction of ascite incidences. Moreover, the ALB and PT levels in the APBSCT group also improved relative to baseline at weeks 4, 12, and 24, as evidenced by significantly higher ALB and lower PT levels. These levels remained significant when compared with the control. These findings imply that APBSCT promotes the reduction of liver inflammation and recovery of coagulation in the early stage. Patients with advanced cirrhosis are accompanied by multiple complications and pathological manifestations, such as reduced hepatic functional reserves and increased hepatic portal pressure. ICG R15 is a standard method for quantifying liver functional reserves and is more accurate than the CTP score. In this study, ICG R15 levels in the APBSCT group were markedly improved at week 24, later than the point in time when ALB and PT levels began to recover. The hepatic ARFI index was positively correlated with portal vein pressure. It reflects the degree of liver fibrosis and cirrhosis. To establish whether APBSCT therapy alleviates hepatic fibrosis and portal vein pressure and whether stem cell transplantation increases hypersplenism risk, we evaluated the ARFI index and spleen size. There were marked improvements in ARFI index and spleen lengths in the APBSCT group at 48 weeks, which was later than the onset of the recovery of ICG R15 levels. Moreover, we assessed the long-term efficacy of APBSCT in patients with decompensated hepatitis B cirrhosis. It was established that ALB and PT levels in the APBSCT group continued to recover and stabilize at desirable levels during the subsequent follow-up of up to 8 years. Therefore, APBSCT can delay the progression of decompensated hepatitis B cirrhosis at an early stage with stable long-term efficacies. However, these results are not directly related to APBSCT, which involves multiple mechanisms. Stem cell therapy for cirrhosis involves multiple mechanisms, including regulation of liver immune microenvironment via secretion of multiple cytokines, suppression of inflammatory responses, stimulation of hepatic oocyte proliferation, and paracrine regulation. It has been reported that APBSCT has long-term anti-fibrosis effects, which can directly induce the apoptosis of hepatic stellate cells (HSCs), secrete hepatocellular growth factors (HGF), granulocyte colony-stimulating factor (G-CSF), matrix protein metalloenzyme 9 (MMP-9) and other antifibrotic substances to reduce extracellular matrix deposition, thereby inhibiting liver tissue fibrosis. However, it has not been established which mechanism is dominant. Neoplastic hepatocytes are crucial for maintaining the physiological homeostasis of the liver. Hepatocyte growth factor (HGF) is the most crucial protein factor that promotes hepatocyte proliferation and liver repair. Hematocellular oval cells (HOCs) are precursor/stem cells of hepatocytes. When the liver is severely damaged, HOCs are activated and differentiate to generate hepatocytes and bile duct cells to participate in liver repair. The stromal-cell-derived factor-1alpha (SDF-1α), also known as chemokine CXCL12, is an essential activator of HOCs. Stem cells secrete SDF-1α to activate HOCs and promote hepatocyte regeneration.

Regarding the long-term safety of APBSCT, causes of death, incidences of HCC, and mean age of onset were determined. Patients in both groups died mainly from cirrhosis complications; fewer in the APBSCT group died from liver failure (7%) than in the control (20%), but there was no statistical difference. Differences in HCC-associated mortality rates between the groups were not significant, which is consistent with previously reported results. We established that the prevalence of HCC was significantly low in the APBSCT group (26%), relative to the control group (62%). These findings indicate that medical treatment combined with APBSCT can effectively delay the progression of decompensated hepatitis B cirrhosis to HCC. Advanced hepatitis B-associated deaths are mainly from cirrhosis and HCC, and cirrhosis is a risk factor for HCC. The patient should be closely monitored so that the best time for treatment is not missed. It has been reported that the incidence of HCC within five years of autologous bone marrow cell therapy for compensated cirrhosis was 26.3%. Our results showed that 27.0% of patients in the APBSCT group progressed to HCC over ten years. Differences in outcomes were attributed to variations in sample size, serologic responses between study samples, or antiviral therapy.

We firstly addressed concerns about the long-term efficacy and safety of APBSCT in patients with decompensated hepatitis B cirrhosis. The combination of conventional medical therapy and APBSCT yields sustained and enhanced therapeutic benefits, which was of great value for future clinical treatment.

To our knowledge, this is the first study to investigate the long-term efficacy and safety of APBSCT in patients with decompensated hepatitis B cirrhosis. The results of our study indicate that the combination of conventional medical therapy and APBSCT can provide long-lasting and improved
therapeutic benefits. These findings have important implications for developing future clinical treatment strategies. However, the mechanism by which autologous peripheral blood stem cell therapy repairs or reverses damaged liver cells is still not fully understood. Besides the sample size, limited number of patients, and the relatively short follow-up period, the long-term outcomes of APBSCT in decompensated hepatitis B cirrhosis should be clarified through large-scale prospective clinical trials. Furthermore, the biological effects of mesenchymal stem cells on hepatic progenitors in acute-on-chronic liver failure needs to be further investigated. In conclusion, we elucidated the long-term prognosis of decompensated hepatitis B cirrhosis patients through a 7-year follow-up and multiple liver function indicators. In summary, APBSCT is a relatively long-term, safe, and effective treatment option. In future, studies with larger sample sizes should be conducted to collect long-term clinical data and prospective cohort trials to confirm our findings.

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**AUTHOR DISCLOSURE STATEMENT**

The authors have no potential conflicts of interest to report relevant to this article.

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XZ and JH designed the study and performed the experiments, DZ, LH and WL collected the data, XZ and JD prepared the manuscript. All authors read and approved the final manuscript.

**REFERENCES**