Am J Transl Res 2022;14(8):5848-5858
www.ajtr.org /ISSN:1943-8141/AJTR0141847

Original Article

Umbilical cord blood-derived mesenchymal stem cells transplantation decreases incidence of liver cancer in end-stage liver disease patients: a retrospective analysis over 5 years

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Received January 19, 2022; Accepted July 21, 2022; Epub August 15, 2022; Published August 30, 2022

Abstract: Objective: To investigate effects of umbilical cord blood-derived mesenchymal stem cells (UC-MSCs) transplantation on the risks of liver cancers in end-stage liver disease (ESLD) patients. Methods: Data of 45 ESLD patients received UC-MSCs transplantation (UC-MSCs group) and 50 ESLD patients received non-UC-MSCs transplantation (non-UC-MSCs group) were retrospectively analyzed, and they were followed up for 5 years. Results: The incidence of liver cancer was much lower in UC-MSCs group than that in the non-UC-MSCs group (12% vs 2.2%, P=0.008). The survival rate of patients was significantly higher in the UC-MSCs group than that in the non-UC-MSCs group during the five years follow-up (P=0.043). The inflammation and fibrosis scores were lower in the UC-MSCs group than those in the non-UC-MSCs group (P<0.036). Compared with the non-UC-MSCs group, the UC-MSCs group showed largely improved liver cirrhosis degree and lower Child-Pugh scores (P<0.05). Conclusions: UC-MSCs transplantation is able to decrease the risks of liver cancers in ESLD patients, which might work by inhibiting inflammation.

Keywords: Umbilical cord blood-derived mesenchymal stem cells, transplantation, liver cancer, end-stage liver disease patients, retrospective analysis

Introduction

End-stage liver disease (ESLD) is the final stage of a liver disease, which largely increases possibility of liver cancers and results in high morbidity and mortality in the world [1]. ESLD is characterized by the cirrhosis and the age of patients with ESLD tends to be younger [1, 2]. Several etiologies including alcohol abuse, infections of chronic hepatitis B virus (HBV) and hepatitis C virus are involved in liver cirrhosis, which often shows fibrosis and a profound chronic systemic inflammatory response [3, 4]. Moreover, inappropriate therapy on inflammation may cause a variety of complications in liver cirrhosis patients [4]. The conventional therapies including radiotherapy, chemotherapies, and anti-cancer drugs based conservative treatment against liver cirrhosis are not satisfied to heal the disease and harbor high risks to develop into liver cancer [5]. Orthotopic liver transplantation is thought to be an effective therapy to treat liver cirrhosis, while it is limited for broad use due to immunological rejection and the scarcity of donor sources [6]. Therefore, a more effective and safe strategy against liver cirrhosis should be investigated to reduce severity of the disease.

Several studies indicated that long-term inflammation and fibrosis in the liver might be the reason that liver cirrhosis causes liver cancer [7, 8]. Thus, suppression of inflammation and fibrosis might be one of solutions for reducing the risks of liver cancer. Stem cell transplantation was found to remarkably reduce the severity of inflammation and fibrosis [1]. Stem cell transplantation technology was established in the 1950s [9]. Each year, numerous stem cell transplantation cases were reported globally

[10]. It has been demonstrated that stem cell transplantation is an effective strategy in treating a variety of diseases including severe and refractory autoimmune diseases (AD), non-rhabdomyosarcoma soft tissue sarcomas, kidney diseases, and multiple sclerosis and immune-mediated neurological diseases [11-14]. Distinct types of stem or progenitor cells were reported to be used in transplantation, among them, the hematopoietic stem cells (HSC) derived from peripheral-blood are marked with CD34 and umbilical cord blood-derived mesenchymal stem cells (UC-MSCs) were most often used [15]. Umbilical cord blood (UCB) and serum were reported to exert essential role in ocular diseases. Serum in the form of eye drops was useful to be applied topically onto the ocular surface, which could efficiently treat anterior segment disorders such as dry eye syndrome or corneal epithelial defects with different etiologies [16]. Additionally, as stem cells, UCB could differentiate into various mature cells, including corneal and retinal cells, which have been proposed as a replacement therapy for the treatment of retinal and optic nerve diseases [16]. Therefore, the potential utilization of stem cells transplantation to treat various diseases has attracted more and more attention.

Emerging evidences indicate that transplantation of stem cells including HSCs and MSCs is an effective strategy to treat liver cirrhosis [6]. It was demonstrated that treatment with stem cell transplantation in liver cirrhosis patients showed promising results, for example, the autologous infusion of CD34+ cells improved the serum albumin level and the Child-Pugh score in ESLD patients [6]. However, studies using MSCs to treat liver cirrhosis with long-term follow-up outcomes post transplantation remain very limited. Moreover, whether MSCs transplantation could result in liver cancer remains unclear. Thus, in our study, a retrospective analysis was performed towards the 5-year survival of the ESLD patients that underwent UC-MSCs transplantation to figure out the effect of UC-MSCs transplantation on liver cirrhosis and prevention of liver cancer, with the hope to provide new insights into the role of stem cell transplantation in prevention of liver cancer.

Materials and methods

Case selection

The data of ESLD patients treated with UC-MSCs transplantation (UC-MSCs group) and those didn't receive UC-MSCs transplantation (non-UC-MSCs group) from June 2013 to June 2016 at Sichuan Provincial People's Hospital were retrospectively analyzed and they were followed up for 5 years after discharge by our team. ESLD patients were confirmed by hepatic decompensation according to the guidelines defined by the Chinese Society of Hepatology and Chinese Society of Infectious Diseases. The study was reviewed and approved by the Ethics Committee of Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital for stem cell research. Written informed consents were obtained from all the participants or their legal surrogates.

Inclusion criteria: Patients getting anticoagulation injection showed prothrombin time (PT) change less than 5 seconds. Exclusion criteria: Patients who were pregnant or lactating women; patients had hepatocellular carcinoma, bacterial peritonitis, human immunodeficiency virus (HIV) infection or any other life-threatening infection (e.g., hepatitis B virus and hepatitis C virus), recurrent gastrointestinal hemorrhage, portal thrombosis with main portal trunk obstruction, sponge blood vessel, superior mesenteric vein occlusion, or severe intestinal congestion, ascites and resistance to diuretic therapy or developed abdominal compartment syndrome, hepatic encephalopathy; patients without complete clinical and follow-up data.

Preparation and identification of UC-MSCs

UC-MSCs were prepared as described in a previous study [17]. For culture of UC-MSCs, the umbilical cord from donors was cut into 1-mm^3 pieces and filtered through a 1.5 mm mesh. Filtered umbilical cord pieces were seeded in 150-cm^2 flask, followed by adding DMEM/F12 complete medium. The culture medium was refreshed every 3 to 4 d, and non-adherent cells were removed. The UC-MSCs were separated by trypsin digestion and cultured when cell confluency reached 80-90%. UC-MSCs were identified and quantified by flow cytometry

(FACScalibur, BD Inc., San Jose, CA, USA). Antibodies including anti-human CD34-PE, anti-human CD45-PE, anti-human CD73-PE, anti-human CD90-PE, anti-human CD105-PE were purchased from eBioscience. The morphology (measured by light microscope, TS-100/100-F, Nikon) and mycoplasma contamination condition (C0297S, Beyotime Biotechnology, Shanghai, China) as well as proliferation ability (C0009S, MTT Cell Proliferation and Cytotoxicity Assay Kit, Beyotime Biotechnology, Shanghai, China) were determined. All results from above assays showed that the UC-MSCs were successfully obtained and could be used for following treatments (**Figure 1**).

Treatment method

All the patients received same routine treatment, including routine liver protection, enhancing immunity, reducing portal pressure, nutritional support, maintaining smooth stool, and parallel diet education to keep the disease stable. Regular antiviral therapy (telbivudine or entecavir) was provided according to the relative indications. ESLD-related complications were dealt with in accordance with relevant norms and guidelines [18-20]. All the patients were followed up for 5 years after treatment.

In the non-UC-MSCs group, patients did not receive stem cell transplantation but were treated by routine strategy of ESLD as above.

In the UC-MSCs group, patients were administered with polyene phosphatidyl choline (0.3-0.4 g/(kg·d)) and magnesium isoglycyrrhizinate (3-4 mg/(kg·d)) for liver protection, α1-thymosin (1.6 mg/d) for immunity enhancement, somatostatin (24-hour continuous infusion at 250 mg/h) and propranlolum (10-20 mg/d) for decreasing portal vein pressure. Patients were transplanted with UC-MSCs ($1.79\pm1.66\times10^6$) via either hepaticartery or portal vein. During transplantation procedure, the portal vein pressure was carefully assessed and monitored. A low molecular weight heparin of anticoagulant (Sanofi-Aventis, Paris, France) was treated at postoperative day 3 to prevent portal vein thrombosis [20].

Outcome measures

All the patients were followed up at 3, 6, 12, 36, and 60 months post treatment by clinical visits.

The general clinical data and surgical information were collected for all patients, and postoperative complications and recurrences were recorded.

The results of blood test, liver function examination (ALT, AST, albumin and total bilirubin), coagulation time analyses (prothrombin time (PT) and activated partial thromboplastin time (aPPT)), immunological detection and tumor marker examinations were recorded and analyzed.

The malignant tumors were ruled out using contrast-enhanced ultrasound, computed tomography (CT) scan and vascular angiography.

The Knodell scoring system was used for scoring liver inflammation and fibrosis. Ascites were recorded and classified as absent (score 0), slight (score 1), moderate (score 2), and severe (score 3).

Samples used for pathological analysis was collected using liver biopsy with ultrasound or during surgery. All pathological results were checked and confirmed by at least two experienced pathologists.

Statistical analysis

The statistical analysis was performed using GraphPad Prism (version 5.0 for Windows). Continuous variables with normal distribution were presented as mean ± SD and analyzed by analysis of variance (ANOVA), or the repeated measures ANOVA with LSD test. Survival analysis was performed by Kaplan-Meier method. Univariate analysis was performed by Cox regression analysis. A P value of <0.05 was considered to be statistically significant.

Results

The clinical characteristics of patients

As shown in **Table 1**, there was no significant difference in sex, age, body weight, body height, cause of liver cirrhosis, grade of Child-Pugh score and complication incidence between the UC-MSCs group and non-UC-MSCs group (all $P>0.05$). Some co-morbids were observed including varicose veins (class 1, 12.0%), varicose veins (class 2, 20.0%), varicose veins (class 3, 18.0%), ascites (46.0%), hypersplenism (40.0%), hepatic encephalopathy (12.0%),

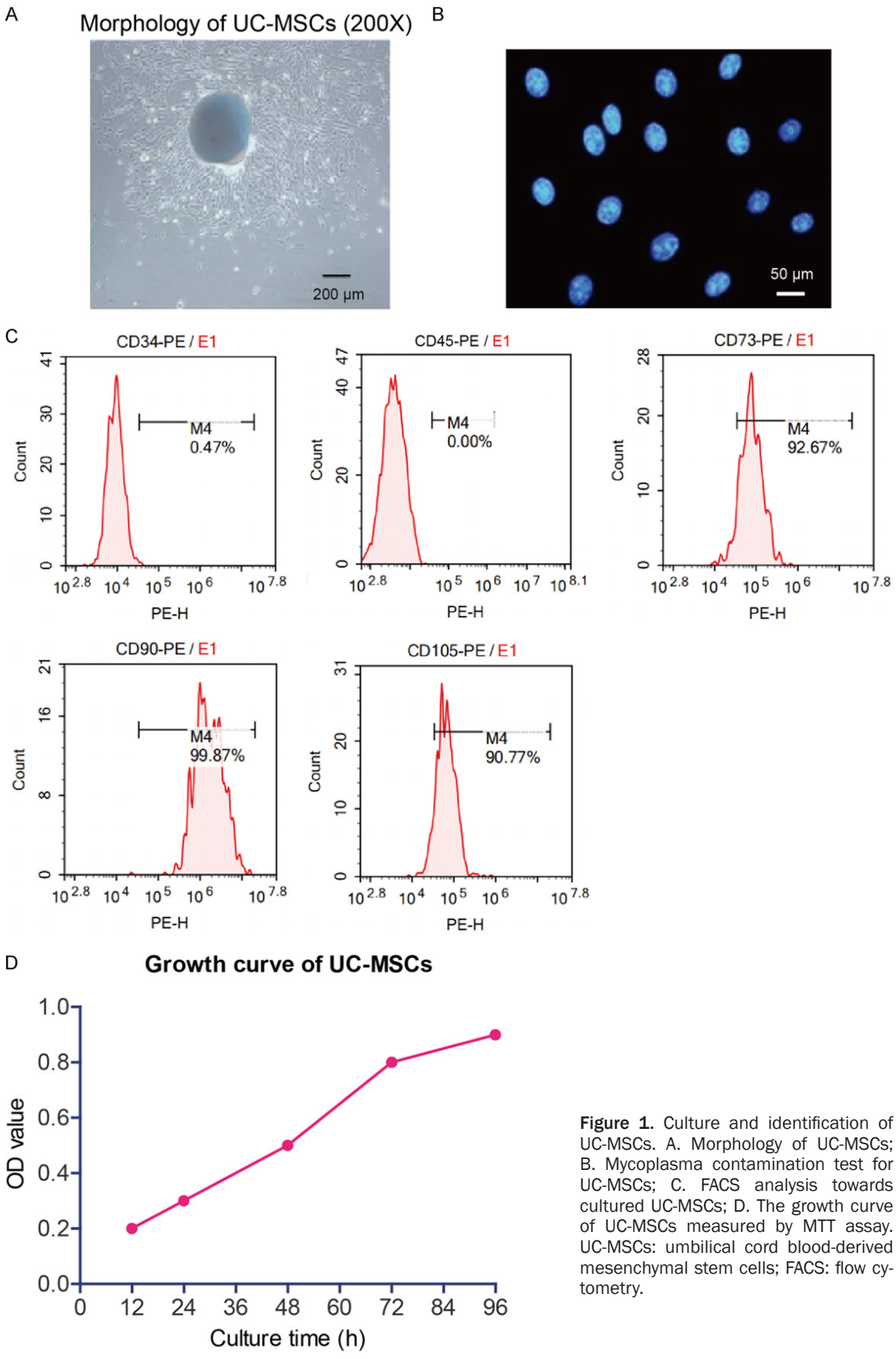

Figure 1. Culture and identification of UC-MSCs. A. Morphology of UC-MSCs; B. Mycoplasma contamination test for UC-MSCs; C. FACS analysis towards cultured UC-MSCs; D. The growth curve of UC-MSCs measured by MTT assay. UC-MSCs: umbilical cord blood-derived mesenchymal stem cells; FACS: flow cytometry.

Table 1. Clinical characteristic of patients with cirrhosis of non-UC-MSCs transplantation and patients with cirrhosis following UC-MSCs transplantation

Variable	non-UC-MSCs group (n=50)	UC-MSCs group (n=45)	*P* Value
Sex (n, %)			
Male	29 (58.0%)	35 (77.8%)	0.563
Female	21 (42.0%)	10 (22.2%)	0.632
Age (years)	49.9±3.56	48.2±6.34	0.351
Body weight (kg)	63.4±5.88	62.8±8.23	0.128
Body height (cm)	164.0±10.33	165.8±9.21	0.078
Aetiology (n, %)			0.379
Hepatitis B cirrhosis	38 (78.0%)	31 (68.9%)	
Hepatitis C cirrhosis	3 (6.0%)	7 (15.6%)	
Alcoholic cirrhosis	8 (20.0%)	5 (11.1%)	
Autoimmune cirrhosis	1 (2.5%)	2 (4.4%)	
Child-Pugh class (n)			0.013
A (5-6)	9 (18.0%)	5 (11.1%)	
B (7-9)	35 (70.0%)	23 (51.1%)	
C (≥10)	6 (12.0%)	17 (37.8%)	
Surgery history	Partial spleen embolism, Splenectomy + portico devascularization, gastroesophageal vein ligation	Partial spleen embolism, Splenectomy + portico devascularization, gastroesophageal vein ligation	
Complications (n, %)			
Varicose veins (class 1)	6 (12.0%)	5 (11.1%)	0.893
Varicose veins (class 2)	10 (20.0%)	7 (15.6%)	0.573
Varicose veins (class 3)	15 (30.0%)	22 (48.9%)	0.059
Ascites	23 (46%)	13 (28.9%)	0.086
Hypersplenism	20 (40.0%)	24 (53.3%)	0.193
Hepatic encephalopathy	6 (12.0%)	4 (8.9%)	0.621
Hepatorenal syndrome	2 (4.0%)	2 (4.4%)	0.686
Surgery history	12 (6.0%)	15 (33.3%)	0.312

hepatorenal syndrome (4.0%), and surgery (6.0%). Both groups were performed surgeries including partial spleen embolism, splenectomy + portico devascularization, and gastroesophageal vein ligation.

UC-MSCs decreased incidence of the liver cancer

To investigate effects of UC-MSCs on the incidence of the liver cancer in ESLD patients, the number of liver cancer patients in non-UC-MSCs and UC-MSCs groups was calculated. It was found that the incidence of liver cancer patients in the non-UC-MSCs group (12%) was significantly higher than that in the UC-MSCs group (2.2%) (**Figure 2**).

Survival rate analysis

To examine survival situation of the ESLD patients with and without UC-MSCs transplantation, the survival curves were generated. In the non-UC-MSCs group, two patients died from severe jaundice and hypohepatia, and one from hypoproteinemia and hepatorenal syndrome. In the UC-MSCs group, one patient died from hepatorenal syndrome and multiple organ failure, and another one died from hepatorenal syndrome. The survival rate in the UC-MSCs group (43/45) was higher than that in the non-UC-MSCs group (57/50), but the difference was not significant. So, UC-MSCs transplantation might increase survival percentage in ESLD patients (**Figure 3**).

Interestingly, the survival rate in male patients was higher than female patients in non-UC-MSCs transplantation group (**Figure 3A**); on the contrary, the survival rate in female patients was higher than male patients in UC-MSCs group (**Figure 3B**), though the differences were insignificant (both P<0.05).

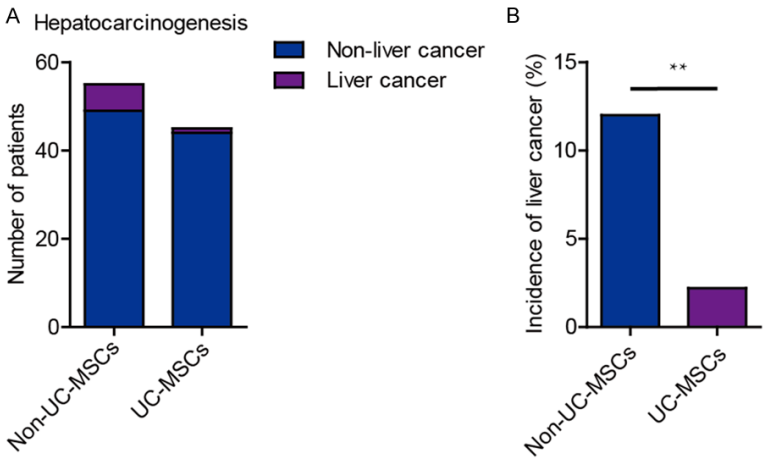

Figure 2. UC-MSCs transplantation decreased incidence of liver cancer. A. Number of liver cancer patients in ESLD patients; B. The incidence of liver cancer in ESLD patients (**P<0.01). UC-MSCs: umbilical cord blood-derived mesenchymal stem cells; ESLD: end-stage liver disease.

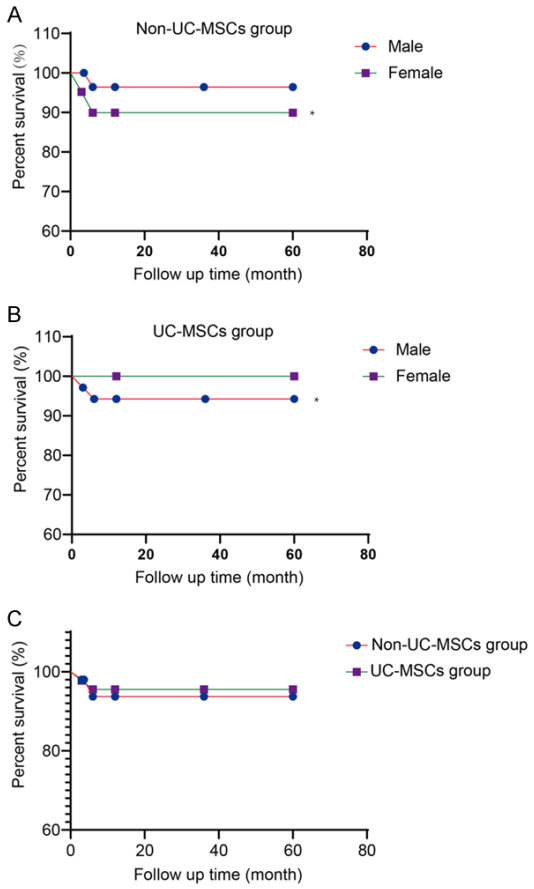

Figure 3. Survival analysis of patients underwent UC-MSCs transplantation during the 5-year follow-up. A. The survival curves stratified by gender of non-UC-MSCs transplanted ESLD patients (*P<0.05); B. The survival curves stratified by gender of UC-MSCs transplanted ESLD patients (*P<0.05); C. The survival percentage in patients treated with UC-MSCs transplantation was higher than that in patients with UC-MSCs transplantation (P>0.05). UC-MSCs: umbilical cord blood-derived mesenchymal stem cells; ESLD: end-stage liver disease.

Inflammation and fibrosis scores of ESLD patients with and without UC-MSCs transplantation

To evaluate the inflammation and fibrosis during follow-up period for ESLD patients with and without UC-MSCs transplantation, the inflammation and fibrosis scores using Ishak system were calculated. It was shown that inflammation score decreased over the follow-up time, and inflammation score of UC-MSCs transplantation ESLD patients was lower than non-UC-MSCs transplantation patients in late follow-up period (12, 36, and 60 month) (**Figure 4A**). For fibrosis, it was found that the fibrosis score was decreased over the time in ESLD patients with UC-MSCs transplantation, while it was increased over the time in ESLD patients without UC-MSCs transplantation (**Figure 4B**). Interestingly, inflammation score in UC-MSCs transplantation patients was higher than that in non-UC-MSCs transplantation ESLD patients at the beginning of transplantation, while the inflammation score in UC-MSCs transplantation ESLD patients was lower than that in non-UC-MSCs transplantation ESLD patients at 60th month of follow-up. Taken together, it was plausible that UC-MSCs transplantation could relieve the liver inflammation and fibrosis compared with patients without UC-MSCs transplantation.

The Child-Pugh score was one of the most important indexes to assess severity of liver cirrhosis [5]. To further investigate the effects of the UC-MSCs transplantation on cirrhosis in ESLD patients, a Child-Pugh class analysis was executed. It was shown that the number of patients with Child-Pugh class A was increased while the number of patients with Child-Pugh class B was decreased over the follow-up time, and the number of patients with Child-Pugh class C was declined first then climbed up in

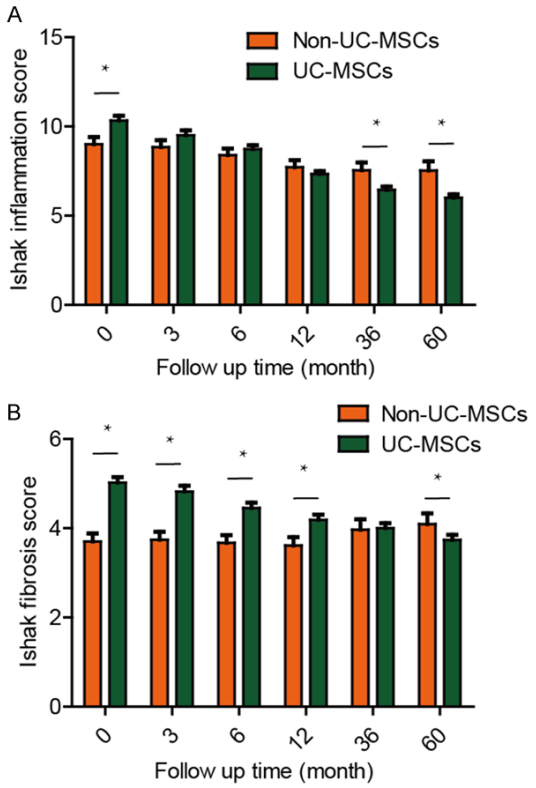

Figure 4. Inflammation and fibrosis scoring using Ishak system after treatment. A. Ishak inflammation scoring for non-UC-MSCs and UC-MSCs transplanted ESLD patients (*P<0.05); B. Ishak fibrosis scoring for non-UC-MSCs and UC-MSCs transplanted ESLD patients (*P<0.05). UC-MSCs: umbilical cord blood-derived mesenchymal stem cells; ESLD: end-stage liver disease.

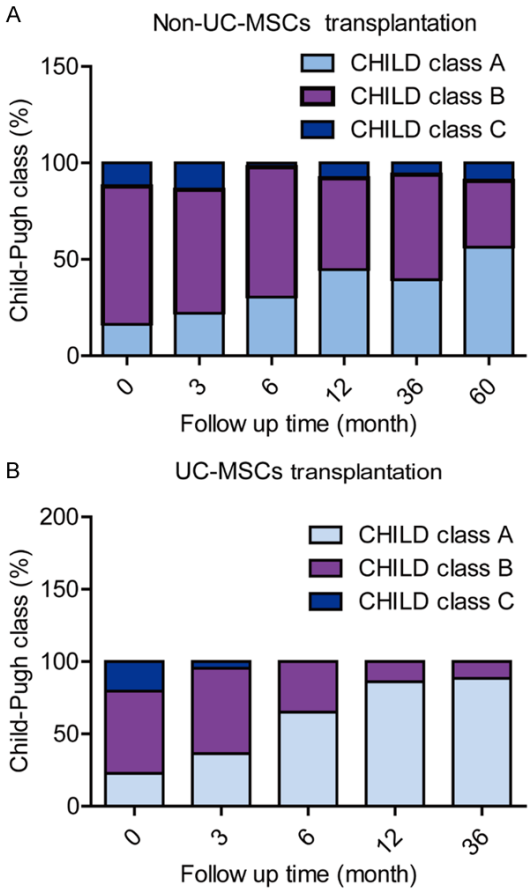

Figure 5. Child-Pugh classification of the ESLD patients after treatment. A. Child-Pugh classification in non-UC-MSCs transplanted ESLD patients; B. Child-Pugh classification in ESLD patients following UC-MSCs transplantation. UC-MSCs: umbilical cord blood-derived mesenchymal stem cells; ESLD: end-stage liver disease.

non-UC-MSCs transplanted ESLD patients (**Figure 5A**). For UC-MSCs transplanted ESLD patients, it was indicated that the number of patients with Child-Pugh class A was quickly increased, while the number of patients with Child-Pugh class B and C was quickly decreased, and especially, there was no patients with Child-Pugh class C after 12nd month of follow-up (**Figure 5B**). Therefore, compared with non-UC-MSCs transplanted patients, UC-MSCs transplantation potentially improved liver cirrhosis in ESLD patients.

Complications analysis of patients with UC-MSCs transplantation

The complications of ESLD patients after UC-MSCs transplantation was analyzed in the study. As show in **Figure 6**, 9 (17.78%) patients showed upper gastrointestinal bleeding; 2 (4.44%) patients developed into hepatorenal syndrome; 2 (4.44%) patients were observed to be hepatic encephalopathy; 3 (6.67%) patients developed into portal thrombosis; 2 (4.44%) patients showed hypohepatia; most of patients (27/45, 60.00%) had no serious complications (one case showed both portal thrombosis and hypohepatia). These results indicated that this technology for treating ESLD patients was relatively safe.

Discussion

Untreated cirrhosis has high possibility to result in liver cancer due to long-term chronic inflammation, while improper therapeutic solutions of liver cirrhosis could not reduce risks of development of liver cancer [21, 22]. For end-stage

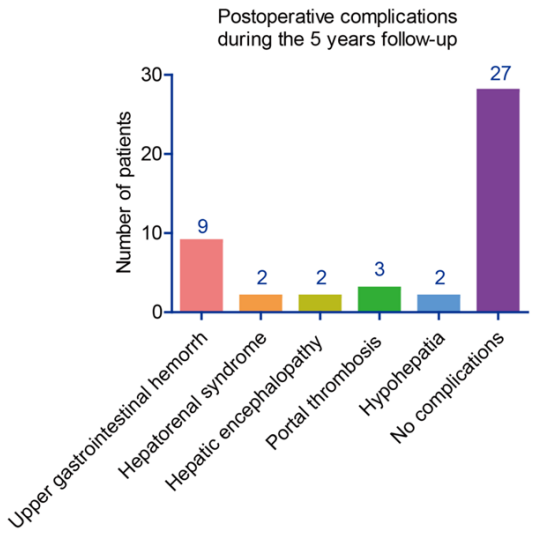

Figure 6. Postoperative complications during the 5 years follow-up in ESLD patients treated with UC-MSCs transplantation. UC-MSCs: umbilical cord blood-derived mesenchymal stem cells; ESLD: end-stage liver disease.

liver cirrhosis, the liver transplantation is treated as the only definite strategy, while the limited number of donors, high costs of surgery, and requirement of long-term administration of immunosuppressive agents hamper its broad application [6]. As one of new strategies treating liver cirrhosis, stem cell transplantation has attracted more and more attention [23]. Stem cells based therapies have been confirmed to have promising effects on end-stage of liver cirrhosis by our group and others [24, 25]. However, to the best of our knowledge, few published reports analyzed the cancer incidence post transplantation. Thus, the present study focused on effects of UC-MSCs transplantation on liver cancer incidence in ELDS patients and possible mechanisms.

Interestingly, we found that the incidence of liver cancer in ELDS patients was largely reduced by UC-MSCs transplantation compared with non-UC-MSCs transplantation (**Figure 2**). Similarly, UC-MSCs were found to exert certain effects on several types of cancers, for example, Han *et al*. found that UC-MSCs significantly inhibited proliferation of PC-3 prostate cancer cells through activation of JNK and downregulation of PI3K/AKT signaling [26]. In glioma, Fan et al. found that UM-MSCs might serve as a novel cellular vehicle for delivering therapeutic molecules in therapies against glioma [27]. Reduction of the liver cancer incidence may be linked to increase of the survival percentage. Indeed, it was found that UC-MSCs slightly increased survival percentage compared with non-UC-MSCs group in ESLD patients in our study (**Figure 3**). Interestingly, we observed that the clinical outcomes might be related to gender (**Figure 3**). There are also several studies which showed that clinical characteristics after stem cell transplantation are related to gender index [28, 29]. However, the underlying mechanism of UC-MSCs transplantation in reduction of liver cancer incidence remains unclear.

Chronic inflammation is closely related to live injury and concurrent regeneration, which may result in sequential advancement of fibrosis, cirrhosis, and finally liver cancer [30]. Another unique characteristic of liver cancer is that liver cancer is greatly associated with liver fibrosis [31]. The close relationship between liver cancer and inflammation and fibrosis provokes us to figure out the underlying mechanism of reducing liver cancer incidence of UC-MSCs. Interestingly, we found that Ishak inflammation and fibrosis scores were decreased over the follow-up time in ESLD patients with UC-MSCs transplantation, and these two parameters were lower in ESLD patients with UC-MSCs transplantation than in patients without UC-MSCs transplantation (**Figure 4**). It was also demonstrated that UC-MSCs transplantation largely improved liver cirrhosis of ESLD patients (**Figure 5**). Thus, it is plausible that UC-MSCs transplantation reduces incidence of liver cancer via improving liver inflammation, fibrosis and cirrhosis.

Although UC-MSCs transplantation has several benefits for liver disease patients, the complications post transplantation should be noted. It was found that leukemia patients had great risk to suffer from early and late complications after UC-MSCs transplantation [32]. In patients with refractory lupus nephritis, fever and gastrointestinal tract symptoms were common complications after UC-MSCs transplantation [33]. In the present study, it was found that several patients had different complications including upper gastrointestinal bleeding, hepatorenal syndrome, hepatic encephalopathy, portal thrombosis, and hypohepatia (**Figure 6**). Therefore, it was proposed to diagnose these

complications as early as possible for liver diseases who received UC-MSCs transplantation.

However, there are some limitations in this study such as the limited case number and the data were respectively analyzed which may cause some biases. Therefore, more efforts should be investigated towards increasing the number of patients and follow-up time to further verify the therapeutic benefits of UC-MSCs transplantation in treating ESLD and decreasing risks of causing liver cancer.

In conclusion, we found that UC-MSCs transplantation could largely decrease incidence of liver cancer, which should be linked to increase of the survival percentage. Mechanistically, we found that UC-MSCs transplantation could decrease liver inflammation and fibrosis, and improve liver cirrhosis in ESLD patients compared with non-UC-MSCs transplanted patients, and this may be associated with the finding that the UC-MSCs transplantation caused reduction of liver cancer incidence. Few complications were observed in UC-MSCs transplantation patients, which should be aware to improve survival of the patients.

Acknowledgements

The study was supported by the Major Research Plan of Sichuan Science and Technology Department Province (grant number: 2018-SZ0110), the Project of Science & Technology Department of Sichuan Province Key R & D Plan (major science and technology projects) (grant number: 2018HH0062), the Scientific Research Project of Sichuan Provincial Department of Health (grant number: 18PJ498), the School of Medicine, University of Electronic Science and Technology of China, Sichuan Provincial People's Hospital Youth Talent (grant number: 2015QN17, 2017QN08), the National Basic Research Program of China (grant number: 2015CB964703), and Chengdu City Science and Technology Bureau Key R & D Support Plan, Technological Innovation R & D Project (grant number: 2019-YFYF-00131-SN), Chengdu City Science and Technology Bureau Technological Innovation R & D Project (grant number: 2021-YF05-01008-SN), the Scientific Research Program of Sichuan Medical Association (grant number: S21018), Sichuan Medical Association Scientific Research Program (NO: S21018).

Disclosure of conflict of interest

None.

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