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REVIEW

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Stem cell therapy for hepatocellular carcinoma and end-stage liver disease

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Abstract

Hepatocellular carcinoma (HCC) is a major health problem worldwide, especially for patients who are suffering from end-stage liver disease (ESLD). The ESLD is considered a great challenge for clinicians due to the limited chance for liver transplantation, which is the only curative treatment for those patients. Stem cell-based therapy as a part of regenerative medicine represents a promising application for ESLD patients. Many clinical trials were performed to assess the utility of bone marrow-derived stem cells as a potential therapy for patients with liver diseases. The aim of the present study is to present and review the various types of stem cell-based therapy, including the mesenchymal stem cells (MSCs), BM-derived mononuclear cells (BM-MNCs), CD34 + hematopoietic stem cells (HSCs), induced pluripotent stem cells (iPSCs), and cancer stem cells.

Though this type of therapy achieved promising results for the treatment of ESLD, however still there is a confounding data regarding its clinical application. A large body of evidence is highly required to evaluate the stem cell-based therapy after long-term follow-up, with respect to the incidence of toxicity, immunogenicity, and tumorigenesis that developed in many patients.

Keywords HCC, Liver, MSCs, Stem cell and end stage

Introduction

Hepatocellular carcinoma (HCC) is the most common cause of cancer-related death all over the world. It ranked third for mortality and fifth in incidence according to the World Health Organization's (WHO) statistics in 2020 [1]. The incidence of HCC achieved about a 75% rise in the last two decades, and it is continuously increasing, where males are three times more likely to be affected than females [2]. It is expected that more than one million deaths due to liver cancer will occur by 2030 [3].

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There are many risk factors for HCC that differ between developed and developing countries. E.g., chronic hepatitis B virus (HBV) infection and aflatoxin B1 (AFB1) are the major risk factors for liver cancer in developing regions [4, 5], while hepatitis C virus (HCV) [6] and non-alcoholic fatty liver disease (NAFLD) are the major risk factors for liver cancer in developed countries [7].

The outcome of HCC patients is usually poor, as surgery is suitable only for early-stage patients who represent 5–15% of the patients, in which the risk of postoperative complications is more common due to diminished hepatic regenerative capacity, whereas the treatment strategy for patients with intermediate-stage liver cancer is mainly trans-arterial chemoembolization (TACE), which achieves only a 23% improvement in the 2-year survival rate [8].

In the last 15 years, there are numerous molecular-targeted drugs that have been approved by the FDA for the treatment of patients with advanced HCC. These drugs included kinase inhibitors such as sorafenib

(2008), regorafenib (2017), lenvatinib (2018), and cabozantinib (2019). Also, angiogenesis inhibitors such as ramucirumab (2019) and bevacizumab (2020), as well as immune checkpoint inhibitors including pembrolizumab (2018), atezolizumab (2020), and nivolumab (2020) [9]. However, still the incidence of recurrence and mortality rates are steadily increasing, where the efficacy of these drugs is modest and can extend the survival rates for only a few months in advanced HCC patients [10]. In addition to the emergence of drug toxicity or inefficacy that emerged after long-term use [11].

Liver transplantation is an ideal option of treatment for selected patients with HCC; however, lacking donors, high cost, and prolonged administration of immunosuppressive drugs make it of limited use [12, 13]. As a result, still there is no effective line of therapy that could improve the prognosis and the outcome of patients suffering from HCC [11]. However, the emerging stem cell therapy could open a new avenue for HCC patients especially those with end-stage liver disease (ESLD). Many types of research are developing now to maintain the optimum conditions for producing an effective and potent stem cell therapy for HCC patients. Hence, the aim of the current study was to review the various types of stem cell-based therapy including mesenchymal stem cells (MSCs), cancer stem cells (CSCs), autologous bone marrow-derived cells, and induced pluripotent stem cells (iPSCs).

Stem cells definition and classification

Stem cells are unspecialized cells that can differentiate into different types of cells, in addition to their ability of self-renewal in order to maintain stem cell populations in different tissues [14]. Stem cells can be classified according to the differentiation potential into totipotent, pluripotent, multipotent, and unipotent cells [15]. The most potent one which has the highest differentiation potential is the totipotent stem cell. These totipotent stem cells are the early blastomeres that are formed 1–3 days after oocyte fertilization, and they can form both embryo and extraembryonic structures [16]. The next type is the pluripotent stem cells (PSCs), which can differentiate into all germ layers. It is formed of the embryonic stem cells (ESCs) which constitute the inner cell mass of the blastocyst (formed 4–14 days after fertilization). These PSCs are capable of the formation of ectoderm, mesoderm, and endoderm, but not extraembryonic structures [17]. After that, these cells are converted to multipotent stem cells, which can differentiate into only all cell types of one germ lineage, while the unipotent stem cells can differentiate only into one cell type [16, 18].

Another classification of stem cells depends upon the origin of the cells; this classification includes (1) embryonic stem cells (ESCs), which are derived from the inner cell mass of the blastocyst, and (2) adult stem cells, which are present in the whole body after development. The latter are multipotent stem cells that function to maintain healing, growth, and replacement of any dead or lost cells [14, 19, 20]. An important type of adult stem cells is the mesenchymal stem cells (MSCs), which act for replenishment and renewing of the tissues in which they reside. They are present mainly in the bone marrow, adipose tissue, hair follicle, and dental pulp [21]. Signals that are controlling stem cell specialization can be divided into external signals, such as physical contact between cells or chemical secretion of certain chemokines by the surrounding tissue, whereas the internal signals are regulated through specific genes in the MSCs [14]. Though MSCs have a limited capacity for differentiation, recent evidence has shown the possibility of restoring the pluripotent differentiation capacity in adult stem cells by forcing the expression of four transcription factors (TFs) that characterize a pluripotent cell [22]. These TFs allow reprogramming of the MSCs and therefore the formation of induced pluripotent stem cells (iPSCs) that can differentiate into the three embryonic layers [15, 23]. The iPSCs have promising applications in regenerative medicine, as it has been now successfully recruited for the treatment of stroke [24], macular degeneration [25], osteoarthritis [26], diabetes, and neurodegenerative diseases [27]. Additionally, it has been investigated for the treatment of many types of cancers including glioma, breast, and hepatic cancer [28–30].

Cancer stem cells (CSCs) in hepatocellular carcinoma

HCC is considered a complex disease formed of heterogenous cell populations that vary in their molecular, biological, and immunological characteristics. Consequently, this heterogeneity could have a potential effect on the disease recurrence, resistance to treatment, and the clinical outcome of the patients [9, 31]. An accumulated body of evidence suggested that the heterogeneity within HCC is due to a subpopulation of progenitor cells called CSCs. These cells have the capability of self-renewal and plasticity, which allow it to differentiate into different types of cells. Accordingly, these unique features render these liver CSCs (LCSCs) to be responsible for the tumorigenesis, angiogenesis, and metastasis that eventually lead to tumor recurrence and drug resistance [32, 33]. Moreover, Zheng and his colleagues performed the combined transcriptomic and functional analysis at a single-cell level in HCC patients. They found a diversity of LCSCs subpopulations that varies in their molecular, functional, and phenotypic characteristics, which is responsible for the intertumoral heterogeneity that occurs in HCC [34].

Hence, it is important to target these LCSCs in order to improve patients' response to treatment and survival outcomes [35, 36].

Characterization of the LCSCs

Extensive research was performed to investigate the identification and characterization of the LCSCs by fluorescence or magnetic-activated cell sorting, through the expression of many surface markers including CD133, CD44, CD90, CD24, CD34, CD47, C-kit, cytokeratin 19 (CK19), epithelial cell adhesion molecule (EpCAM), and intercellular adhesion molecule-1 (ICAM-1) [9, 33, 37–40]. It was demonstrated by Yang et al. that increased serum levels of LCSCs markers including cytokeratin 19 (CK19), KRABCG2, CD133, nestin, and CD44 associated significantly with angiogenesis and inferior outcome of HCC patients [41]. Additionally, it was found that CK19, c-kit, ABCG2, and ALDH have an important role in maintaining tumorigenesis and resistance to radiotherapy or chemotherapy by regulating the expression of drug-efflux-related genes [42–44].

Circulating CSCs

Another entity concerning CSCs research is the study of circulating CSCs in liquid biopsy for assessing the diagnosis, prognosis, and survival rates of the patients. In this regard, it was observed that increased plasma levels of $CD45^{-}$ $ICAM1^{+}$ LCSCs in HCC patients associated significantly with poor clinical outcomes [45]. Additionally, the plasma level of circulating EpCAM + LCSCs was found to be a useful predictor biomarker for postoperative HCC relapse [46, 47]. Moreover, Guo et al. reported a panel of LCSCs markers formed of EpCAM, CD90, CD133, and CK19 that could efficiently have a role in the early diagnosis and early recurrence of HCC after resection [48].

Targeting the LCSCs in clinical practice

In the past few years, research has been directed towards targeting the LCSCs through developing anti-surface marker antibodies, oncolytic viruses, epigenetic regulators, and small molecule inhibitors that could selectively affect the LCSCs [49]. The small-molecule inhibitors were directed against certain signaling pathways that regulate the stemness and proliferation of the LCSCs such as Wnt/β-catenin (OMP-18R5 and OMP-54F28) [50, 51], Notch pathway (PF-03084014) [52], TGF-β pathway (LY2157299) [53], and Hedgehog signaling pathway (LED225 [ClinicalTrials.gov. NCT02151864)]), while the anti-surface markers included targeting the CD133 through oncolytic measles viruses (MV-141.7 and MV-AC133) [54] and anti-EpCAM (VB4-845) [55]. Other studies assessed the role of epigenetic control inhibitors on the tumorigenesis and aggressiveness of LCSCs such as zebularine (DNMT1 inhibitor) [56] and SBHA (HDAC inhibitor) [57]. Other clinical trials (ClinicalTrials.gov. NCT02279719) were also conducted including the combination of napabucasin (a STAT3 inhibitor) and sorafenib, or amcasertib (a NANOG inhibitor) and sorafenib, where NANOG is a transcriptional factor that maintains embryonic stem cells pluripotency [9]. Though all the previously mentioned studies achieve a primary suppression of HCC, especially when combined with chemotherapeutic agents, however, all the targeted markers and molecular pathways in LCSCs are similar to the other normal stem cell populations. Hence, eradication of LCSCs may also affect the normal hepatic stem cells which would result in the reduction of hepatic regeneration capacity and consequently liver failure. Therefore, proper identification and specification of the LCSCs remain a challenging matter, and further research is highly required to accurately identify and target the LCSCs [9, 48].

LCSCs and immunotherapy

Accumulating evidence suggested that the aggressiveness of the LCSCs is due to their poor immunogenicity which allows them to evade immunosurveillance through their interaction with the tumor microenvironment and the inhibition of different immune cells [9]. Therefore, many recent studies tried to assess the utility of these cells in immunotherapy including the development of dendritic cell (DC) vaccine pulsing with CD133 (ClinicalTrials.gov. NCT02049489). In this trial, patients showed an efficient cytotoxic T-cell response against $CD133^{+}$ LCSCs that inhibited tumor growth [58]. Another study was performed by Choi et al. who induced a potent immune cytotoxic T-cell response against $CD44^{+}$ $EpCAM^{+}$ LCSCs using DCs pulsed with CD44 and EpCAM peptides [59]. Other immunotherapeutic modalities which currently under trials are the engineered chimeric antigen receptor (CAR) T cells. One of these studies was the development of CD133-directed CAR T cells in the treatment of patients with advanced HCC [60]. Though these studies provided a good clinical response in controlling the tumor growth and achieving complete remission, the encountered cytotoxicity including the decreased levels of hemoglobin, platelets, and lymphocytes still needs to be resolved [60].

Clinical applications of MSCs in liver diseases

The allogenic MSCs

The MSCs are pluripotent non-hematopoietic stem cells that can be isolated from several sources including liver, umbilical cord, placenta, muscle, skin, synovial membrane, amniotic fluid, and tooth root [61, 62]. The MSCs

commonly express surface markers including CD73, CD105, and CD90, while they are lacking the expression of CD45, CD34, CD14 or CD11b, CD79α or CD19, and HLA-DR [63]. Various experimental studies and clinical trials had been conducted to investigate the therapeutic utility of MSCs in different diseases including multiple sclerosis (MS), corneal disease, myocardial infarction, Crohn's disease, amyotrophic lateral sclerosis, and acute respiratory distress syndrome (ARDS) [64–66]. Also, it had been approved in many counties for preclinical and clinical purposes for the treatment of, e.g., graft-versus-host disease (GVHD) in the USA [67] and for the treatment of traumatic or degenerative osteoarthritis in Korea [68].

Some studies assessed the intravenous injection of umbilical cord-derived MSCs (UC-MSCs) in patients with primary biliary cirrhosis (PBC). They reported that the UC-MSCs treatment is a safe and efficient therapy, as there were reduced serum levels of alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT). However, there were no significant changes in serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), albumin, prothrombin time activity, and immunoglobulin M levels [69, 70]. Other clinical trials demonstrated that intravenous infusion of UC-MSCs in patients with liver cirrhosis and HBV injured liver was safe, tolerable, and increased the survival rates of the patients [71–74]. On the other hand, Nevens et al. conducted an open-label phase II clinical study (EudraCT 2016–001177-32) on 24 patients with acute-on-chronic liver failure (ACLF) treated with human MSCs (HepaStem) transplantation. They reported improved survival with no adverse events related to therapy [75]. Similarly, Lin et al. performed an open-label non-blinded randomized controlled study on 110 patients with HBV-related ACLF infused with $1.0–10\times10^5$ cells/kg allogeneic bone marrow-derived mesenchymal stem cells (BM-MSCs) and followed up for 6 months. Patients treated with the BM-MSCs showed reduced mortality rates due to decreased incidence of infection and improved liver function compared to the control group [76]. These data provide evidence that the BM-MSCs could be a potential safe and feasible therapeutic option for HBV-related ACLF patients.

Though exogenous stem cell therapy is considered by different companies all over the world for sale, its safety and efficacy are still major challenges in large-scale clinical trials that lead to the inapplicability of allogenic MSCs [77]. These challenges included mainly the immunogenic incompatibility that developed either early or secondary after repeated infusions due to the accumulation of inflammatory cells and mediators such as interferon-γ [78, 79]. Other technical problems associated with the allogenic MSCs are poor-quality control and lack of stability, in addition to the inconsistent heterogeneity, differentiation, and migratory capacity of the cells [80, 81].

The autologous MSCs therapy

To date, cellular therapy including MSCs has become a promising therapeutic strategy for patients with decompensated liver disease [82]. In fact, the MSCs have many advantages that make them a unique line of treatment for those patients with ESLD. As these cells were obtained from the patient himself, therefore, all the differentiated cells will carry the same genetic profile of the patient. In addition, MSCs are characterized by low immunogenicity because they express low levels of major histocompatibility complex-1 (*MHC-I*) molecules, so they overcome the immune rejection occurred with liver transplantation [12, 83].

Furthermore, the delivered MSCs exert an inhibitory effect on HCC through different mechanisms including restoration of functioning hepatocytes, antifibrotic, antiapoptotic, and antioxidative effects. Additionally, it was found that these effects were potentiated through co-treatment of the MSCs with melatonin [84, 85]. Also, they exert anti-inflammatory function through increasing the secretion of interleukin-10 (*IL-10*), indoleamine 2,3-dioxygenase (*IDO*), prostaglandin 2 (*PGE2*), transforming growth factor (*TGF)-β3*, and hepatocyte growth factor (*HGF*) [86]. Moreover, the MSCs have an antitumor effect via inhibition of the Wnt signaling pathway [87]. Another important mechanism is the immunomodulation characteristic of MSCs as they suppress the immune response through inhibiting T-cell activation and proliferation, as well as inducing macrophages shift from M1 to M2 [88, 89]. Also, the increased levels of anti-inflammatory mediators lead to suppressing the effector T cells and stimulating the regulatory T cells through increasing *FOXP3*, *CTLA4*, and *GITR* expression [90, 91]. Therefore, Zhang and his colleagues performed a clinical trial (no. ChiCTR2000037732), in which they injected six doses of MSCs 1×10^6/kg bodyweight intravenously for patients with ABO-incompatible liver transplantation (ABO-i LT). They found that MSC transfusion could efficiently reduce the risk of acute rejection similar to that of rituximab treatment. Additionally, MSCs are preferred as an immunosuppressive approach for ABO-i LT because there is no risk of infection and biliary complications that might be associated with rituximab [92].

Another concern regarding MSCs therapy is the ability of these cells to move in the direction of the inflammatory or damaged area to make tumor homing [25]. This attraction is maintained through the increased production of certain factors by the tumor cells including IL-6, platelet-derived growth factor subunit B

(PDGFB), vascular endothelial growth factor (VEGF), and transforming growth factor beta-1 (TGF-b1) [93, 94]. Recently, it was reported that some chemokines have a major role in MSCs tumor homing including C-X-C motif chemokine receptor 4 (CXCR4), CCR1, CXCR5, CXCR6, CCR7, and CCR9 [95–97]. These migratory and homing properties of MSCs allow them to be a promising vehicle for the delivery of anticancer molecules. This strategy was applied through either loading the MSCs with drug molecules or nanoparticle carriers. In this regard, Zhao et al. assessed the efficacy of adipose-derived MSCs (AD-MSCs) loaded with superparamagnetic iron oxide-coated gold nanoparticles (*SPIO@AuNPs*) in HCC cell line and in mice with induced liver injury. They reported a successful homing of *SPIO@AuNP*-loaded AD-MSCs in the hepatic tissue, which make the AD-MSCs a potential specific delivery of therapeutic agents in patients with liver diseases [98]. Another approach was developed through genetic modification of MSCs to stimulate the expression of tumor suppressor genes or anticancer proteins [99]. Schug and his team demonstrated that genetically engineered MSCs could significantly decrease tumor proliferation and increase survival rate in mice treated with *SMAD-NIS-MSCs* through *TGFB1*-induced *SMAD* promoter activity [100]. However, these techniques are studied experimentally in vivo and still not recruited for clinical applications in liver cancer patients.

In the past few years, many clinical trials have been performed to assess the efficiency of autologous MSCs in the treatment of liver diseases [101–104]. Among these trials was that done by Suk et al., who reported that BM-MSCs therapy could improve liver function and Child–Pugh score in patients with liver cirrhosis compared to the control group. They did not find any adverse event associated with the BM-MSCs administration for 12-month follow-up period [102]. Another clinical trial was performed by Sakai and his team (ClinicalTrials.gov. NCT01062750), where they used autologous adipose tissue-derived stem cells (ADRCs) for intrahepatic arterial infusion in patients with liver cirrhosis. The results showed that ADRCs therapy could efficiently and safely repair liver cirrhosis [103].

Though the autologous MSCs-based therapy provides a promising strategy for regenerative treatment of liver disease, there are many limitations encountered. These limitations are the emerged chromosomal instability, emboli formation, and inducing immune reaction, in addition to the incidence of unwanted differentiation and tumor formation [105, 106]. Other reported limitations were the low migration and poor survival of the transplanted MSCs, which directed researchers to consider other stem cells for the treatment of liver diseases [107, 108].

Autologous bone marrow-derived cells

Bone marrow (BM)-derived CD34 + hemopoietic stem cells (HSCs) or whole mononuclear cells (BM-MNCs) were considered an attractive therapeutic approach for ESLD patients [109]. It had been reported that transplantation of autologous BM-MNCs is a safe and feasible option for patients with decompensated alcoholic liver diseases. Additionally, the end-stage liver disease (MELD) scores and liver function were improved; however, there was an insufficient regenerative capacity [110, 111]. These results are comparable to that reported by Lyra et al., who concluded that infusion of BM-MNCs via hepatic artery could significantly increase albumin level and improve the Child–Pugh score, while there was no change in the MELD score [112]. Another study is done by Mohamadnejad et al. (ClinicalTrials.gov. NCT01120925), who compared intraportal infusion of CD133 + cells, BM-MNCs, and placebo group. They found that there was a transient improvement in the MELD score in patients receiving CD133 + cells after a follow-up period of 3 months, while there was no improvement in the MELD score after 6 months of follow-up period. Also, they concluded that there was no significant improvement in the MELD score of patients infused with MNCs neither after 3 nor 6 months of follow-up [113].

Indeed, most of the performed clinical trials reported a benefit of autologous BM stem cell transplantation after a maximum of 1 year [83]. However, in a recent study done by Kim et al. [114], who followed up patients for five years after autologous BM stem cell transplantation. They observed the development of malignant tumors in 36.8% (7/19) of the patients, in the form of HCC in 26.3% (5/19), lymphoma in 5.3% (1/19), and colon cancer in 5.3% (1/19) of the patients. Zekri et al. reported that intraportal infusion with CD34 + CD133 + cells, followed by peripheral IV infusion of in vitro-differentiated MSCs within 1 week, and repeated infusion after 3 months achieved a beneficial therapeutic effect on the patients, with minimal adverse events and prolonged clinical efficacy [115]. Similarly, many other studies reported that G-CSF-mobilized $CD133^{+}$ stem-progenitor cells (SPCs) could induce transient improvement in ESLD patients with no detectable adverse events [116–118].

On the other side, Chruscinski and his colleagues observed high mortality and morbidity rates in patients with HSTs liver transplantation after follow-up for a long period. They concluded that HSTs could not be considered for clinical applications at this time due to increased incidence of multiorgan failure and toxicity after discontinuation of the immunosuppressive regimen [119]. Similarly, Margini et al. concluded that the therapeutic effect of HSCs is only temporary, which suggests that HSCs act

through producing trophic support rather than trans-differentiation [116].

Induced pluripotent stem cell (iPSC)

Induced pluripotent stem cells (iPSCs) are produced from adult somatic cells (usually fibroblast) that have been genetically reprogrammed to differentiate into pluripotent ESC [120]. This reprogramming occurs by transfection with four transcription factors called Yamanaka factors (OSKM; Oct4, Sox2, Klf4, and c-Myc) [108]. These iPSCs were developed to overcome the challenges accompanying the application of other types of stem cells. As they provide a reproducible and reliable source of expandable, bankable, and engraftable hepatocyte-like cells (HLCs), which can be repeatedly used for clinical treatments [121]. Additionally, Antarianto et al. reported that using HLCs differentiated from iPSCs in vitro is more mature with lower cell–ECM adhesion, spatial cell distribution, albumin secretion, and CYP450 expression than HLCs that differentiated from MSCs in decellularized liver scaffold [122].

Many experimental studies reported the functionality and feasibility of iPSCs in different liver diseases including acute liver failure and liver fibrosis [123, 124]. Moreover, advanced therapeutic technology was developed in the field of gene editing modality that utilized the iPSCs for treating patients with metabolic liver diseases. These genetically engineered iPSCs showed promising success in disease modeling and gene correction in different hereditary liver diseases including Crigler-Najjar disease or alpha-1 antitrypsin (A1AT) deficiency, Wilson's disease, familial hypercholesterolemia, glycogen storage disease type 1, Niemann-Pick type C, and hemophilia B [125–132]. Though there are many clinical trials in phases I or II being conducted on several diseases including cardiovascular and neurological disorders [133, 134], however, no trials concerned with liver diseases were registered until now [135]. Indeed, there are many critical aspects which should be considered before transferring these cells safely for clinical applications including the long-term stability and tolerability. In addition to the increased risk of immunological reaction and tumorigenesis especially in those with genetic modification [121, 136].

Conclusion

In conclusion, stem cell-based therapy achieved promising results regarding improving liver function, MELD score, and overall survival rates of the patients. However, most of these trials were performed on a small number of patients for short-term follow-up. Though this cellular-based therapy appears to be safe and tolerable especially the autologous type, still the biological behavior of these cells could not be expected in the long run regarding the toxicity, immunogenicity, and tumorigenesis that had been developed in many patients. Therefore, this stem cell-based therapy should be evaluated after long-term follow-up, taking into consideration the site and route of administration as well as the nature of transplanted cells according to the type of liver injury and the presence of other comorbidities. Finally, still further research is highly required to overcome the challenges that occur after a long-term therapy, as this will open a new avenue and rescue a great number of patients who had no options for treatment other than liver transplantation.

Abbreviations

ACLF	Acute-on-chronic liver failure
AD-MSCs	Adipose-derived MSCs
AFB1	Aflatoxin B1
A1AT	Alpha-1 antitrypsin
ALP	Alkaline phosphatase
ARDS	Acute respiratory distress syndrome
BM-MNCs	Bone marrow mononuclear cells
BM-MSCs	Bone marrow-derived mesenchymal stem cells
CART	Chimeric antigen receptor T cells
CSCs	Cancer stem cells
CXCR4	C-X-C motif chemokine receptor 4
CK19	Cytokeratin 19
DCs	Dendritic cells
ECM	Extracellular matrix
EpCAM	Epithelial cell adhesion molecule
ESCs	Embryonic stem cells
ESLD	End-stage liver disease
GGT	Gamma-glutamyl transferase
G-CSF	Human granulocyte colony-stimulating factor.
GVHD	Graft-versus-host disease
HBV	Chronic hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HLCs	Hepatocyte-like cells
HSCs	Hemopoietic stem cells
HepaStem	Human MSCs
HGF	Hepatocyte growth factor
IDO	Indoleamine 2,3-dioxygenase
IL-10	Interleukin-10
iPSCs	Induced pluripotent stem cells
ICAM-1	Intercellular adhesion molecule-1
LCSCs	Liver cancer stem cells
MELD	Model for end-stage liver disease
MHC-1	Major histocompatibility complex-1
MS	Multiple sclerosis
MSCs	Mesenchymal stem cells
NAFLD	Non-alcoholic fatty liver disease
PDGFB	Platelet-derived growth factor subunit B
PGE2	Prostaglandin 2
PBC	Primary biliary cirrhosis
PSCs	Pluripotent stem cells
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SPIO@AuNPs	Superparamagnetic iron oxide-coated gold nanoparticles
SPCs	Stem-progenitor cells
TACE	Trans-arterial chemoembolization
TFs	Transcription factors
TGF-β3	Transforming growth factor-β3
TGF-b1	Transforming growth factor beta-1
UC-MSCs	Umbilical cord-derived MSCs
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

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MSA collect the data and wrote the manuscript, and ANZ supervised the work and revised the final manuscript.

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Declarations

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