Registered Trials on Stem Cell Therapy in Liver Diseases: a Cross-sectional Study on ClinicalTrials.gov

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Abstract

Background: Stem cells have the ability of self-renewal and differentiation into liver cells, suggesting as a promising therapy for liver diseases. However, the efficacy and safety for clinical application remain unknown for limited number of clinical trials. ClinicalTrials.gov contributes to the development of clinical practice. This study aimed to systematically analyze the registered trials on stem cell therapy in liver diseases based on ClinicalTrials.gov.

Methods: We searched the registered trials on stem cell therapy in liver diseases on ClinicalTrials.gov up to 23 September 2021. We investigated the study type, source of stem cells, and kind of liver diseases of included trials and these characteristics were analyzed by SPSS18.0 software.

Results: Five hundred and fifty-nine registered trials were initially identified on ClinicalTrials.gov and 92 trials were included ultimately. Among them, 84 trials were interventional trials and eight (8.70%) were observational trials. Twenty-four (28.57%) trails aimed to evaluate the efficacy, 16 (19.05%) to evaluate the safety, and 44 (52.38%) to evaluate both. For stem cell source, 73 trials (81.52%) used mesenchymal stem cells (MSCs), including 26 with bone marrow mesenchymal stem cells, 22 with umbilical cord mesenchymal stem cells, 20 with unclassified mesenchymal stem cells, and five with adipose tissue-derived stem cells. For liver disease classification, sixty trials focused on cirrhosis, 16 trials on liver failure, while eight trials on autoimmune liver disease. However, only 22 (23.91%) trials had been completed and four (4.35%) had available results on the website.

Conclusions: Our study suggest that more stem cell therapy trials are needed in liver diseases and sponsors are encouraged to report the results.

Background

Liver diseases is the leading cause of death worldwide, especially in China[1]. Following inflammatory injury, the hepatocytes is damaged, leading to pathological disorder of liver lobular structure. Hepatocytes, with limited regenerative capacity, are injured, necrotic, and replaced by hepatic stellate cell-derived fibroblasts, resulting in the build-up of non-functional collagenous scars. This physiologic adaptation progressively decreases the liver's capacity, such as nutrition metabolism, coagulation factors synthesis, detoxification, leading to end-stage liver diseases (ESLD)[2]. The overall survival of advanced ESLD patients over a 5-year period remains a dismal 35.1%-73%[3–5]. Liver transplantation is still the only curative treatment option for ESLD. However, this procedure is associated with several limitations, including the lack of donors, surgical complications, immunosuppression following transplantation, and high medical cost[6]. New therapeutic approaches such as bioartificial liver, stem cell therapy, and regenerative medicine are being investigated in an attempt to improve the prognosis of patients with ESLD[7].

There has been increasing interest in the transplantation of stem cells as potential treatments for liver disease[8]. Stem cells are cell types distinguished by their ability of self-renewal as well as their capacity

to differentiate into developed progenitor cells that themselves could discriminate into specific matured cells type[9]. Throughout the past decade, various preclinical and clinical studies investigated the capability of stem cells to accelerate liver regeneration, reduce hepatic fibrosis, and restore liver function[10–12]. In spite of this quick development, various essential questions arise which need to be determined[13]. Few studies about the clinical application of stem cells have been performed and its validity, reliability and feasibility for liver disease require more clinical research to confirm.

Clinical trials provided evidence for clinical practice and were widely regarded as the most crucial evidence source of efficacy and safety[14]. Well-designed trials can assist clinical practice and transparency is the key characteristic for well-designed trials[15–17]. Pre-registered in public registries is the most important strategy to ensure transparency[18] and now been required for all trials by the International Committee of Medical Journal Editors (ICMJE). Thus, exploring clinical trials, especially analyzing registered trials will know the progress in such field and be hot spots to help future clinical practice. Many studies have been published to provide comprehensive details about registered trials in ClinicalTrials.gov in several fields[19]. However, there is paucity of published works on the study for stem cell therapy in liver diseases. ClinicalTrials.gov[20] provides publicly accessible date of registered clinical trials, affords the most comprehensive source for identifying and tracking completed or ongoing trials, and is the best way to explore the characteristics of registered trials in particular fields[19]. In this cross-sectional study, we summarize the study design, stem cell source, and liver disease classification regarding the use of stem cells, in registered trials on ClinicalTrials.gov. We conducted the current study to provide a comprehensive analysis of the development of stem cell therapy in liver diseases.

Methods

Search strategy

A cross-sectional study about registered trials for stem cell therapy in liver diseases on ClinicalTrials.gov was carried out, and the searched words were as follows: stem cell, MSCS, ST CELL, mesenchymal stem cells, MSC, bone marrow mesenchymal stem cells, umbilical cord blood stem cells, cord blood stem cell, human umbilical cord blood stem cells, cord blood stem cell transplantation, CBSCT, UCB-MSCS, umbilical cord mesenchymal stem cells, HUCB-MSCS; hepatic disease, liver disease, liver-related disease, diseases of liver or hepatitis, hepatic failure, liver failure, acute-on-chronic liver failure, hypohepatia, liver cirrhosis, cirrhosis, cirrhosis of liver, hepatic cirrhosis, AILD, autoimmune liver disease, ALDS, hepatitis, hepatitis B, liver cancer, hepatoma, hepatic carcinoma, hepatocellular carcinoma. All information was downloaded, and duplicates were removed by Excel (Office 16) according to the trials' national clinical trial (NCT) number.

Selection criteria

We selected trials mainly according to their conditions or study descriptions. Inclusion criteria were: trials on stem cell therapy and only for liver diseases. Exclusion criteria were: trials not related to stem cell; trials not related to liver diseases; trials neither related to stem cell nor liver diseases.

Data extraction

We use a predesigned spreadsheet to collect study data. Eligibility of registered trials is determined by two reviewers (RD and CW), who also independently extract the data. Ambiguous trials are examined by a third reviewer (LJ). Disagreements are resolved by discussion. All the following information is extracted from each study: NCT number, title, the actual start date of the study, study purpose as safety, efficacy or both, study type, register year and start year, enrollment, age and gender of the participants, status, results, sponsors, main funding source, number of funding sources, location, number of centers, study design [interventional study (randomization allocation, intervention methods, intervention models, masking), observational study (model, time perspective)], source of stem cell, kind of liver diseases.

Reporting guideline

This was a cross-sectional study and it was reported according to reporting guideline STROBE[21].

Statistical analysis

The characteristics were analyzed by descriptive methods. The continuous variables were characterized as median and average, and the categorical variables were reported as frequencies and percentages. The study types include interventional trials and observational trials. The start year was when the trial was first posted on ClinicalTrial.gov, including 2002–2006, 2007–2011, 2012–2016, 2017–2021. Whether the results were available or unavailable was also analyzed. The sponsor included university, hospital, industry/company, or others, including some organizations that cannot be included in other categories [Institute, National Center for Global Health and Medicine, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health Clinical Center (CC)]. The main funding resources included industry, or other resources, such as university, individual, and organization that cannot be divided into subtypes. Date analysis was performed using SPSS18.0 software.

Results

Search results and basic characteristics of included trials

Five hundred and fifty-nine registered trials were initially identified on ClinicalTrials.gov. up to 23th September, 2021. Four hundred and sixty-seven trials were excluded and 92 trials were included ultimately (Fig. 1). The characteristics of included trials were shown in Table 1 and the details were shown in the additional file (.xls) (Additional file: The detail of characteristics of the 92 included trials). The trials were started from 2002 to 2021, of which the majority was from 2007 to 2011. The samples ranged from 0 to 320, with the average of 67 and the median of 35. Ninety-one (98.91%) trials did not set gender limitations, while one recruited female only. Thirteen trials did not set age limitations, while 77 (83.70%) included adult only and two included pediatric patients only. Sixty-nine (75.00%) trails were performed in Asia, 13 (14.13%) in Europe, eight (8.70%) in America, and two (2.17%) in Africa.

Eighty-four trials were interventional trials and eight (8.70%) were observational trials. For study status, 48 (52.17%) trials were unknown, 22 completed (23.91%), six recruiting (6.52%), four terminated or withdrawn, and one suspended. Only four (4.35%) trials have available results on Clinical Trials.gov. For sponsors, 45 (48.91%) trials were supported by the university, 23 (25.00%) by the industry/company, 21(22.83%) by the hospital, and three (3.26%) by other institutions.

Table 1
The characteristics of included trials

Characteristics		Number	Percentage (%)
Registered year			
	2002–2006	7	7.61
	2007–2011	34	36.96
	2012–2016	26	28.26
	2017–2021	25	27.17
Enrollment			
	0-100	74	80.43
	100–500	18	19.57
Gender			
	Female only	1	1.09
	Both	91	98.91
Participant age (year)			
	< 18	2	2.17
	≥ 18	77	83.70
	Both	13	14.13
Study type			
	Interventional	84	91.30
	Observational	8	8.70
Status			
	Not recruiting	6	6.52
	Recruiting	11	11.96
	Completed	22	23.91
	Suspended	1	1.09
	Terminated/withdrawn	4	4.35
	Unknown	48	52.17
Study results			

Characteristics		Number	Percentage (%)
	Has results	4	4.35
	No results available	88	95.65
Sponsor			
	University	45	48.91
	Hospital	21	22.83
	Industry/company	23	25.00
	Other	3	3.26
Funding source			
	Industry	23	25.00
	Other	69	75.00
Location			
	America	8	8.70
	Europe	13	14.13
	Asia	69	75.00
	Africa	2	2.17

Study design

Interventional studies

The characteristics of 84 interventional trials were shown in Table 2. For intervention model, 50 trials were designed as parallel assignment, 33 as single group, and one as sequential assignment. For allocation, 35 (41.67%) trials were randomized, while 15 were nonrandomized. For masking, 68 (80.95%) trials were open-labeled, seven single-masked (8.33%), four double-masked (4.76%), two triple-masked (2.38%) and three quadruple-masked (3.57%).

For samples sizes, 68 (80.95%) trials recruited less than 100 participants and 16 (19.05%) recruited more than 100 participants. All trials did not set gender limitations, except one trial included female only. Seventy-three (86.90%) trials recruited adult only and two (2.38%) trials recruited child only, while nine (10.71%) trials recruited both. Sixty-four (76.19%) trials were performed in Asia, which was the most frequently identified study location, followed by 12 in Europe (14.29%), seven in America (8.33%), and one in Africa (1.19%).

Twenty-four (28.57%) trials set their primary outcome as the efficiency and 16 (19.05%) trials set as the safety, while the rest 44 trials (52.38%) did both. For administration route, 28 (33.33%) trial were through peripheral vein, 23 (27.38%) through hepatic artery, and nine (10.71%) through portal vein.

Among interventional trails, 18 (21.43%) trials were completed, ten (11.90%) were still recruiting, six (7.14%) were not recruiting any more, four (4.76%) were terminated or withdrawn, one (1.19%) was suspended, and 45 (53.57%) were unknown. Only four trials have available results on Clinicaltrials.gov. For funding, 40 (58.8%) trails were sponsored by the university, 22 (26.19%) trials by the industry, and 62 (73.81%) unreported.

Table 2
The characteristics of interventional studies

Characteristics	Number	Percentage (%)
Intervention model		
Parallel assignment	50	59.52
Single group assignment	33	39.29
Sequential assignment	1	1.19
Allocation		
Randomized	35	41.67
Nonrandomized	15	17.86
N/A	34	40.48
Masking		
Single	7	8.33
Double	4	4.76
Triple	2	2.38
Quadruple	3	3.57
None (open-label)	68	80.95
Enrollment		
0-100	68	80.95
100–500	16	19.05
Gender		
Both	83	98.81
Female	1	1.19
Participant age (year)		
< 18	2	2.38
≥ 18	73	86.91
Both	9	10.71
Primary purpose		
Efficiency	24	28.57
Safety	16	19.05

Characteristics	Number	Percentage (%)
Both	44	52.38
Intervention		
Hepatic artery	23	27.38
Portal vein	9	10.72
Peripheral vein	28	33.33
Splenic artery	1	1.19
Hepatic artery or portal vein or peripheral vein	8	9.52
Hepatic artery and peripheral vein	1	1.19
Unknown	14	16.67
Status		
Not recruiting	6	7.14
Recruiting	10	11.91
Completed	18	21.43
Suspended	1	1.19
Terminated/withdrawn	4	4.76
Unknown	45	53.57
Results		
Has results	3	3.26
No results available	81	88.04
Sponsor		
University	40	47.62
Hospital	20	23.81
Industry/company	22	26.19
Other	2	2.38
Funding source		
Industry	22	26.19
Other	62	73.81
Location		

Characteristics	Number	Percentage (%)
America	7	8.33
Europe	12	14.29
Asia	64	76.19
Africa	1	1.19

Observational studies

The characteristics of eight observational studies were shown in Table 3. Six trails (75%) recruited less than 100 participants and two recruited more than 100. No trials set gender limitations. Four trails were focused on adults only and another four did not set age limitations. For study location, five (62.50%) trials were conducted in Asia.

Among eight observational trials, three (37.5%) were case-control studies and five (62.5%) were cohort studies. There were three prospective trials, three retrospective trials, and two cross-sectional trials.

For status, four (50.00%) were completed, one (12.5%) is still recruiting, and three (37.50%) were unknown. None reported available results on Clinicaltrials.gov. Five trials were supported by the university, accounting for 62.5%. Only one (12.50%) trail was funded by the industry, while seven (87.50%) did not report clear funding sources.

Table 3
The characteristics of observational studies

Characteristics	Number	Percentage (%)
Enrollment		
0-100	6	75.00
100–500	2	25.00
Participant gender		
Female only	0	0.00
Both	8	100.00
Participant age (year)		
< 18	0	0.00
≥ 18	4	50.00
Both	4	50.00
Observational model		
Case-control	3	37.50
Case-only	0	0.00
Case-crossover	0	0.00
Cohort	5	62.50
Time perspective		
Prospective	3	37.50
Retrospective	3	37.50
Cross-sectional	2	25.00
Status		
Not recruiting	0	0.00
Recruiting	1	12.50
Completed	4	50.00
Terminated/withdrawn	0	0.00
Unknown	3	37.50
Results		
Has results	0	0.00

Characteristics		Number	Percentage (%)
	No results available	8	100.00
Sponsor			
	University	5	62.50
	Hospital	1	12.50
	Industry/company	1	12.50
	Other	1	12.50
Funding source			
	Industry	1	12.50
	Other	7	87.50
Location			
	America	1	12.50
	Europe	1	12.50
	Asia	5	62.50
	Africa	1	12.50

Stem cell source

The Stem cell source of included trials were shown in Table 4. Seventy-three trials (81.52%) used mesenchymal stem cells (MSCs), including 26 with bone marrow mesenchymal stem cells (BM-MSCs), 22 with umbilical cord mesenchymal stem cells (UCMSCs), 20 with unclassified MSCs, and five with adipose tissue-derived stem cells (ADSCs). Besides, there are five (5.43%) trials using peripheral blood stem cells, three (3.26%) using hematopoietic stem cells, and eleven using other stem cells or combined stem cells.

Table 4
The overview of stem cells

Source of stem cells	Number of studies	Percentage (%)
Bone marrow MSCs	26	28.26
Umbilical cord MSCs	22	23.91
Unclassified MSCs	20	21.74
Adipose-derived MSCs	5	5.43
Peripheral blood stem cells	5	5.43
Hematopoietic stem cells	3	3.26
Other stem cells*	11	11.96

*Other stem cells: include autologous endothelial progenitor cell, liver MSC or adult derived human liver stem/progenitor cells, human menstrual blood-derived MSC, allogeneic ABCB5-positive stem cells, adult stem cells, human fetal liver cell, heterologous human adult liver-derived progenitor cells, stem cells from human exfoliated deciduous teeth, stem cell, hepatic stem cell, combination of hematopoietic and mesenchymal stem cell. MSC, mesenchymal stem cells.

Liver diseases classification

The types of diseases involved in the trials were shown in Table 5. Sixty trials were related to the cirrhosis, accounting for 65.22%. There were 16 trials focusing on liver failure, while eight trials were related to autoimmune liver disease (AILD). Other eight trials reported the stem cells applying to liver diseases, including non-alcoholic fatty liver disease (NAFLD), liver cancer, and so on.

For trials about cirrhosis, the BM-MSCs were widely used, accounting for 20.65% (19/92). While the UCMSCs were 15.22% (14/92), the unclassified MSCs were 13.04% (12/92). For the trials about liver failure, four (4.35%) trails were BM-MSCs, four (4.35%) were UCMSCs and four (4.35%) were unclassified MSCs. For the trials about AILD, the UCMSCs accounted for the largest proportions, being four (4.35%), while the BM-MSCs and the hematopoietic stem cells were both one (1.09%), the unclassified MSCs were three (3.26%). mesenchymal stem cells.

Table 5
The overview of hepatic diseases

Disease (n, proportion)	Source of stem cells	Number of studies
Cirrhosis (60, 65.22%)	Bone marrow MSCs	19
	Umbilical cord MSCs	14
	Unclassified MSCs	12
	Adipose-derived MSCs	5
	Peripheral blood stem cells	3
	Hematopoietic stem cells	1
	Other stem cells	6
Liver failure (16, 17.91%)	Bone marrow MSCs	4
	Umbilical cord MSCs	4
	Unclassified MSCs	4
	Adipose-derived MSCs	0
	Peripheral blood stem cells	1
	Hematopoietic stem cells	0
	Other stem cells	3
AILD (8, 8.70%)	Bone marrow MSCs	1
	Umbilical cord MSCs	4
	Unclassified MSCs	3
	Adipose-derived MSCs	0
	Peripheral blood stem cells	0
	Hematopoietic stem cells	1
	Other stem cells	0
Other liver diseases* (8, 8.70%)	Bone marrow MSCs	2
	Umbilical cord MSCs	0
	Unclassified MSCs	2
	Adipose-derived MSCs	0

*Other liver diseases: non-alcoholic fatty liver disease (NAFLD), liver cancer, and so on. AILD, autoimmune liver disease.

Disease (n, proportion)	Source of stem cells	Number of studies
	Peripheral blood stem cells	1
	Hematopoietic stem cells	1
	Other stem cells	2

*Other liver diseases: non-alcoholic fatty liver disease (NAFLD), liver cancer, and so on. AILD, autoimmune liver disease.

Discussion

Clinical trials have played important roles in changing clinical practice and making clinical decisions[22–24]. Analyzing registered trials could provide a comprehensive landscape of progress in a specific field. Thus, increasing number studies have been published to analyze registered trials on Clinicaltrials.gov. Stem cell therapy, as an emerging therapy and an alternative treatment for liver transplantation, has been applied into liver diseases[8]. However, little is known about the characteristics of registered clinical trials regarding this field. Therefore, we performed the current study to analyze registered trials on stem cell therapy in liver diseases, providing the basic characteristics of trials design, location, sponsor, primary purpose, and study results.

A total of 92 registered trials were identified. Among them, there were 84 interventional trials and 8 observational trials, which with a focus on interventional trials is similar to the previous study for drug control and prevention of ventilator-associated pneumonia (VAP)[25]. From 2002 to 2006, only seven trials registered on ClinicalTrials.gov. Nevertheless, more than half trials were registered after 2012, which synchronized with the development of stem cell technology, including stem cell isolation, culture, and transplantation [12]. However, at the beginning of 2007, the growth rate of trials on stem cell therapy in liver diseases was not significant. The reason may be that there were some problems in the clinical application of stem cell therapy, such as ethical issues [26], transplantation efficiency[27], transplantation of timing[28], the number of transplanted cells, or transplantation way[29]. Due to the above reasons, 80.43% registered trials included relatively fewer participants (less than 100), which might increase the potential risk of statistical error[30]. In our study, only 16.30% trials enrolled children, which was similar to the registered ClinicalTrials.gov from 2007 to 2010 that 17% trials enrolled children[20]. This may relate to the challenges of scientific, ethical, and practical issue in children-related trials.

It is very important to report the trials' results. In our study, 23.91% trials had been completed, but only 4.35% reported results on ClinicalTrials.gov, suggesting a lack of transparency[31]. The low percentage of available results was consistent with findings in previous study[19]. The possible explanation might be that researchers paid not enough attention to reporting results and studies sponsored by industry or companies were not likely to report negative results[32]. As a public registry platform, ClinicalTrials.gov is expected to make researches more transparent and reduce reporting bias, and sponsors are encouraged to publish their outcomes on ClinicalTrials.gov with no delay[25]. Feasibility of clinical trials, adequacy of

patients, poor recruitment, patient compliance, lacking funding, unforeseen issues and change project will also affect the progress of trials. In our study, 5.44% trials were suspended, terminated, or withdrawn, which was not high than previous study[20], suggesting more effort need to be made for such field. In our study, 75.00% trials were carried out in Asia, mainly because of high incidence rate of live diseases in Asia.

In our study, most trials were interventional designs. The primary purpose of mostly trials was to evaluate the effectiveness and safety of stem cell therapy. There are many accesses to transplant stem cells into the body, such as peripheral vein, portal vein, hepatic artery, direct injection into the abdominal cavity, liver, spleen, and so on [12]. Hepatic artery injection is the most commonly used method at present. In our study, hepatic artery injection accounted for a higher proportion, about 38.09%, which is consistent with previous results. Moreover, peripheral vein injection is also used in our study, about 44.04%, probably because it is easier to conduct. A total of 59.52% trials were parallel assignment, 41.67% trials randomized, and 80.95% open-labeled. Randomization is a hallmark of trials and randomization with blinding can help reduce bias[33]. In such field, observational trails were relatively rare, because stem cell therapy is not currently widely used in clinical practice.

Many stem cells can play a role in liver damage and be used to treat liver diseases, include hepatic stem cell (HSCs), embryonic stem cell (ESCs), induced pluripotent stem cells (iPSCs), MSCs, peripheral blood stem cells (PBSCs), and so on. Among them, MSCs are pluripotent stem cells that can be isolated from bone marrow, adipose tissue, umbilical cord blood, placenta tissue and other tissues, belonging to adult stem cells. MSCs have the characteristics of proliferation, multidirectional differentiation, anti-inflammatory, immune regulation. Thus, MSCs have been widely used in tissue engineering and regenerative medicine[34, 35]. In our study, MSCs were used in 81.52% of the trials. Several studies have indicated that MSCs can differentiate into hepatocellular like cells under specific conditions and participate in immune regulation, cell proliferation, and injury repair in liver disease[11, 36]. Animal experiments confirmed that MSCs transplantation showed good efficacy and safety in the treatment of liver injury[37–39]. MSCs from different tissues have different therapeutic effects or mechanisms in liver diseases. In recent years, BM-MSCs, ADSCs and UCMSCs are widely used. In our study, a total of 30.95% trials were using BM-MSCs, 5.95% trials using ADSCs, and 26.19% trials using UCMSCs, which account for more than half of all stem cells. MSCs are expected to become an ideal seed cell source in liver diseases due to their abundant sources, convenient materials, easy culture, low immunogenicity and no ethical controversy[40].

Existing domestic and foreign studies have shown that stem cells can be used to treat a variety of liver disease, such as liver failure[41–44], cirrhosis[45–50], liver cancer [51], NAFLD [36, 52], AILD[53–55]. The stem cell therapy is mostly widely studied in liver failure and cirrhosis, which is consistent with our study results. In our study, a total of 71.43% trials were cirrhosis, and 19.05% trials were liver failure. BM-MSCs were the most used in liver cirrhosis and liver failure. The main mechanism of stem cell therapy in liver failure is immune regulation or the production of related cytokines and growth factors to inhibit inflammation, promote the proliferation of remaining stem cells and tissue repair. In cirrhosis, stem cells

can stimulate liver cell proliferation, repair damaged liver tissue, and improve liver fibrosis, but the specific molecular mechanism remains unclear. Stem cells can express IFN-β to alleviate tumor progression and promote hepatocellular carcinoma cell apoptosis. Stem cells play a protective role in liver by improving liver function, promoting lipid metabolism, and reducing oxidative stress to help reverse NAFLD. Stem cell therapy can improve the immune response and thereby ameliorate the liver injury of AILD.

In our study, the limitations should be acknowledged. Firstly, ClinicalTrials.gov does not include all trials because some trials are registered in other trial registers. Secondly, our study is only a cross-sectional study, and only provided the characteristics of the registered trials. The actual strengths and weaknesses of the trials were not assessed, and some missing data may bring bias to this study. Thirdly, we did not check whether the registered trials have published in journals. As ClinicalTrials.gov is not designed to support for date analysis, it limits us to perform date synthesis.

Conclusions

In conclusion, this study provides useful information about registered ClinicalTrials.gov on stem cell therapy trials in liver diseases. This current study is the first study to analysis registered stem cell therapy trials in liver diseases and sponsors are encouraged to report the results. Additional and better trials are needed to provide more evidence of effectiveness and safety.

List Of Abbreviations

end-stage liver diseases (ESLD)

mesenchymal stem cells (MSCs)

bone marrow mesenchymal stem cells (BM-MSCs)

umbilical cord mesenchymal stem cells (UCMSCs)

adipose tissue-derived stem cells (ADSCs)

autoimmune liver disease (AILD)

non-alcoholic fatty liver disease (NAFLD)

hepatic stem cell (HSCs)

embryonic stem cell (ESCs)

induced pluripotent stem cells (iPSCs)

peripheral blood stem cells (PBSCs)

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article and its additional file.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HY and YN designed the study. RD, CW and LJ collected the data. YT and YY analyzed the data. CW and RD interpreted the results and wrote the manuscript. LZ, SF, NT and ZZ performed the statistical analysis and participated in the interpretation of the data, and the critical revision of the manuscript. All authors read and approved the final manuscript.

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Figures

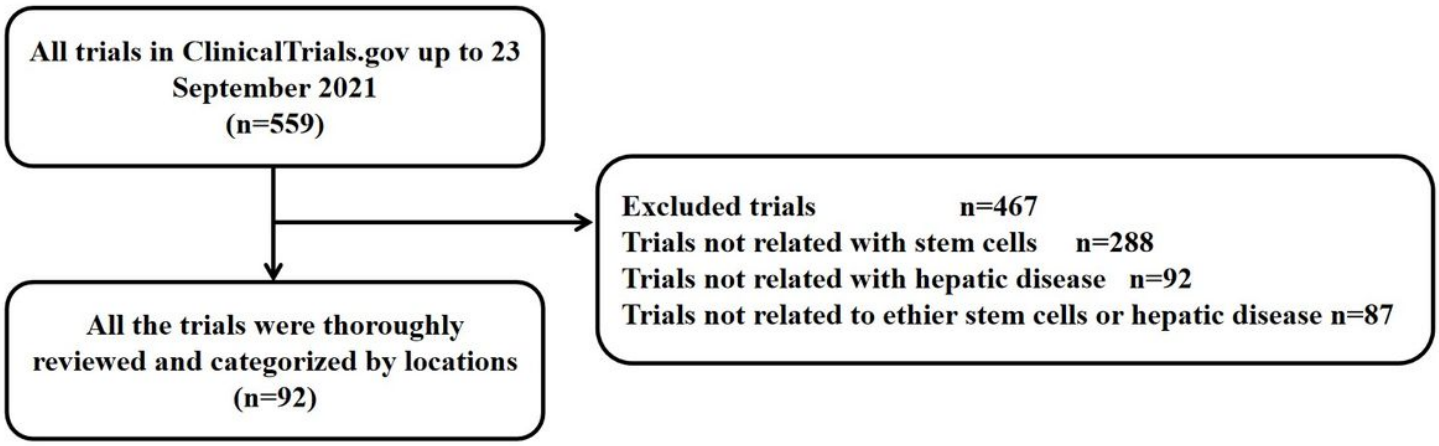

Figure 1. Flowchart of recruited clinical trials registered with ClinicalTrials.gov

Figure 1

See image above for figure legend.

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