Supplementary Table 1 The summary of the clinical studies involving injection of mesenchymal stem cells in hepatobiliary diseases

Ref.	N	Cell type and source	Etiology	Administration Route	Dose	Dose Interval	Follow-up	Outcome
Shi *et al*[S1]	24	Allogeneic UC-MSCs	HBV-ACLF	Peripheral vein	5×10^5 cells/kg	Multiple	72 wk	Increased survival Reduced MELD score
Li *et al*[S2]	11	Allogeneic UC-MSCs	HBV-ACLF	Hepatic artery	10^8 cells/patient	Single	96 wk	Improved liver function tests and MELD score
Xu *et al*[S3]	30	Allogeneic UC-MSCs	HBV-ACLF	Peripheral vein	10^5 cells/kg	Multiple	48 wk	Improved liver function tests and MELD score

Zhang *et al*[S4]	30	Allogeneic UC-MSCs	HBV	Peripheral vein	5×10^5 cells/kg	Multiple	52 wk	Improved liver function tests, MELD score and ascites
Wang *et al*[S5]	7	Allogeneic UC-MSCs	PBC	Peripheral vein	5×10^5 cells/kg	Multiple	48 wk	Improvement ın GGT and ALP but not in other tests
El-Ansary *et al*[S6]	15	Autologous BM-MSCs	HCV	Peripheral vein	10^6 cells/kg	Single	24 wk	Partial improvement in liver function tests and MELD score
Xu *et al*[S7]	20	Autologous BM-MSCs	HBV	Hepatic artery	$0.75 \pm 0.50 \times 10^6$ cells/patient	Single	24 wk	Increased serum TGF-β, reduced

								IL-6 and TNF-α
Salama *et al*[S8]	20	Autologous BM-MSCs	HCV	Peripheral vein	1×10^6 cells/kg	Single	24 wk	Improved liver function tests
Götze *et al*[48]	3	Allogeneic AD-MSCs	ALF and/or ACLF	Peripheral vein	$2.0\text{-}7.8 \times 10^7$ cells/patient	Multiple	56-88 d	Improved liver function tests and reduced liver stiffness
Mohamadnejad *et al*[S9]	14	Autologous BM-MSCs	HBV, Cryptogenic, PBC, AIH, HCV	Peripheral vein	1.2×10^8-2.95×10^8 cells/patient	Single	52 wk	Observed no significant change

Pan *et al*[S10]	80	Autologous BM-MSCs	HBV, Cryptogenic, PBC, AIH, HCV	Peripheral vein, Hepatic artery	5×10^6-2×10^8 cells/patient	Single	24-48 wk	Partial improvement in liver function tests and MELD scores
Lin *et al*[S11]	110	Allogeneic BM-MSCs	HBV	Peripheral vein	10^5-10^6 cells/kg	Multiple	24 wk	Improved liver function tests and MELD score
Jang *et al*[S12]	11	Autologous BM-MSCs	Alcohol	Hepatic artery	5×10^7 cells/patient	Multiple	12 wk	Histologic improvement in 54% and improvement in CPT score
Suk *et al*[S13]	37	Autologous BM-MSCs	Alcohol	Hepatic artery	5×10^7 cells/patient	Multiple	24 wk	Reduced fibrosis,

					improved CPT score

BM-MSC: Bone marrow derived mesenchymal stem cells, AD-MSC: Adipose derived mesenchymal stem cells, UC-MSC: Umblical cord derived mesenchymal stem cells, HBV: Hepatitis B Virus, HCV: Hepatitis C virus, ALF: acute liver failure, ACLF: Acute on chronic liver failure, PBC: Primary biliary cirrhosis, MELD: Model for end stage liver disease score, GGT: Gamma glutamyl transferase, CPT: Child-Pugh-Turcot Score, TGF-β: Transforming growth factor β, TNF-α: Tumor necrosis factor-α, IL-6: Interleukin-6.

Supplementary Table 2 The summary of the preclinical models where adipose derived mesenchymal stem cells were used for the treatment of hepatobiliary disease models

Ref.	**Animal**	**Model**	**Type of SC**	**Injection**	**Cell number**
Banas *et al*[41]	Mouse	CCl_4-induced ALF	Xenogeneic AD-MSCs	Tail vein	1.5×10^6 cells/animal
Gardin *et al*[S14]	Dog	Natural occuring liver disease	Autologous AD-MSCs	Portal vein	5×10^5 cell/kg
Pascual-Miguelañez *et al*[S15]	Rat	CCl_4-induced ALF	Allogeneic AD-MSCs	Tail vein	10^6 cells/animal

Pan *et al*[S16]	Rat	High-fat-diet-induced NAFLD	Allogeneic AD-MSCs	Portal vein	2×10^6 cells/animal
Liao *et al*[S17]	Rat	High-fat-diet-induced NAFLD	Allogeneic AD-MSCs	Portal vein	2×10^6 cells/animal
Seki *et al*[S18]	Mouse	Steatohepatitis-induced cirrhosis	Allogeneic AD-MSCs	Splenic subcapsule	10^5 cells/animal
Ge *et al*[47]	Pig	Ischemia reperfusion injury+ partially hepatectomy	Allogeneic AD-MSCs	Liver parenchyme	10^6 cells/kg
Guo *et al*[S19]	Mouse	CCl_4-induced ALF	Xenogeneic AD-MSCs	Tail vein	$2\text{-}3 \times 10^6$ cells/animal
Saito *et al*[S20]	Mouse	Ischemia reperfusion injury+partially hepatectomy	Xenogeneic AD-MSCs	Tail vein	10^5 cells/animal

Sun *et al*[S21]	Rat	Ischemia reperfusion injury+partially hepatectomy	Autologous AD-MSCs	Tail vein	1.2×10^6 cells/animal
Seki *et al*[S22]	Rat	Ischemia reperfusion injury+partially hepatectomy	Allogeneic AD-MSCs	Penile vein	2×10^6 cells/animal
Iseki *et al*[S23]	Mouse	CCl_4-induced liver fibrosis	Xenogeneic BM-MSCs	Tail vein	5×10^4 cells/animal

AD-MSC: Adipose derived stem cells, BM-MSC: Bone marrow derived mesenchymal stem cells, CCL_4: Carbon tetrachloride, NAFLD: Non-alcoholic fatty liver disease.

SUPPLEMENTARY REFERENCES

S1. **Shi M**, Zhang Z, Xu R, Lin H, Fu J, Zou Z, Zhang A, Shi J, Chen L, Lv S, He W, Geng H, Jin L, Liu Z, Wang FS. Human mesenchymal stem cell transfusion is safe and improves liver function in acute-on-chronic liver failure patients. *Stem Cells Transl Med* 2012; **1**: 725-731 [PMID: 23197664 DOI: 10.5966/sctm.2012-0034]

S2. **Li YH**, Xu Y, Wu HM, Yang J, Yang LH, Yue-Meng W. Umbilical Cord-Derived Mesenchymal Stem Cell Transplantation in Hepatitis B Virus Related Acute-on-Chronic Liver Failure Treated with Plasma Exchange and Entecavir: a 24-Month Prospective Study. *Stem Cell Rev Rep* 2016; **12**: 645-653 [PMID: 27687792 DOI: 10.1007/s12015-016-9683-3]

S3. **Xu WX**, He HL, Pan SW, Chen YL, Zhang ML, Zhu S, Gao ZL, Peng L, Li JG. Combination Treatments of Plasma Exchange and Umbilical Cord-Derived Mesenchymal Stem Cell Transplantation for Patients with Hepatitis B Virus-Related Acute-on-Chronic Liver Failure: A Clinical Trial in China. *Stem Cells Int* 2019; **2019**: 4130757 [PMID: 30863450 DOI: 10.1155/2019/4130757]

S4. **Zhang Z**, Lin H, Shi M, Xu R, Fu J, Lv J, Chen L, Lv S, Li Y, Yu S, Geng H, Jin L, Lau GK, Wang FS. Human umbilical cord mesenchymal stem cells improve liver function and ascites in decompensated liver cirrhosis patients. *J Gastroenterol Hepatol* 2012; **27 Suppl 2**: 112-120 [PMID: 22320928 DOI: 10.1111/j.1440-1746.2011.07024.x]

S5. **Wang L**, Li J, Liu H, Li Y, Fu J, Sun Y, Xu R, Lin H, Wang S, Lv S, Chen L, Zou Z, Li B, Shi M, Zhang Z, Wang FS. Pilot study of umbilical cord-derived mesenchymal stem cell transfusion in patients with primary biliary cirrhosis. *J Gastroenterol Hepatol* 2013; **28 Suppl 1**: 85-92 [PMID: 23855301 DOI: 10.1111/jgh.12029]

S6. **El-Ansary M**, Abdel-Aziz I, Mogawer S, Abdel-Hamid S, Hammam O, Teaema S, Wahdan M. Phase II trial: undifferentiated versus differentiated autologous mesenchymal stem cells transplantation in Egyptian patients with HCV induced liver cirrhosis. *Stem Cell Rev Rep* 2012; **8**: 972-981 [PMID: 21989829 DOI: 10.1007/s12015-011-9322-y]

S7. **Xu L**, Gong Y, Wang B, Shi K, Hou Y, Wang L, Lin Z, Han Y, Lu L, Chen D, Lin X, Zeng Q, Feng W, Chen Y. Randomized trial of autologous bone marrow mesenchymal stem cells transplantation for hepatitis B virus cirrhosis: regulation of Treg/Th17 cells. *J Gastroenterol Hepatol* 2014; **29**: 1620-1628 [PMID: 24942592 DOI: 10.1111/jgh.12653]

S8. **Salama H**, Zekri AR, Medhat E, Al Alim SA, Ahmed OS, Bahnassy AA, Lotfy MM, Ahmed R, Musa S. Peripheral vein infusion of autologous mesenchymal stem cells in Egyptian HCV-positive patients with end-stage liver disease. *Stem Cell Res Ther* 2014; **5**: 70 [PMID: 24886681 DOI: 10.1186/scrt459]

S9. **Mohamadnejad M**, Alimoghaddam K, Bagheri M, Ashrafi M, Abdollahzadeh L, Akhlaghpoor S, Bashtar M, Ghavamzadeh A, Malekzadeh R. Randomized placebo-controlled trial of mesenchymal stem cell transplantation in decompensated cirrhosis. *Liver Int* 2013; **33**: 1490-1496 [PMID: 23763455 DOI: 10.1111/liv.12228]

S10. **Pan XN**, Zheng LQ, Lai XH. Bone marrow-derived mesenchymal stem cell therapy for decompensated liver cirrhosis: a meta-analysis. *World J Gastroenterol* 2014; **20**: 14051-14057 [PMID: 25320545 DOI: 10.3748/wjg.v20.i38.14051]

S11. **Lin BL**, Chen JF, Qiu WH, Wang KW, Xie DY, Chen XY, Liu QL, Peng L, Li JG, Mei YY, Weng WZ, Peng YW, Cao HJ, Xie JQ, Xie SB, Xiang AP, Gao ZL. Allogeneic bone marrow-derived mesenchymal stromal cells for hepatitis B virus-related acute-on-chronic liver failure: A randomized controlled trial. *Hepatology* 2017; **66**: 209-219 [PMID: 28370357 DOI: 10.1002/hep.29189]

S12. **Jang YO**, Kim YJ, Baik SK, Kim MY, Eom YW, Cho MY, Park HJ, Park SY, Kim BR, Kim JW, Soo Kim H, Kwon SO, Choi EH, Kim YM. Histological improvement following administration of autologous bone marrow-derived mesenchymal stem cells for alcoholic cirrhosis: a pilot study. *Liver Int* 2014; **34**: 33-41 [PMID: 23782511 DOI: 10.1111/liv.12218]

S13. **Suk KT**, Yoon JH, Kim MY, Kim CW, Kim JK, Park H, Hwang SG, Kim DJ, Lee BS, Lee SH, Kim HS, Jang JY, Lee CH, Kim BS, Jang YO, Cho MY, Jung ES, Kim YM, Bae SH, Baik SK. Transplantation with autologous bone marrow-derived mesenchymal stem cells for alcoholic cirrhosis: Phase 2 trial. *Hepatology* 2016; **64**: 2185-2197 [PMID: 27339398 DOI: 10.1002/hep.28693]

S14. **Gardin C**, Ferroni L, Bellin G, Rubini G, Barosio S, Zavan B. Therapeutic Potential of Autologous Adipose-Derived Stem Cells for the Treatment of Liver Disease. *Int J Mol Sci* 2018; **19** [PMID: 30558283 DOI: 10.3390/ijms19124064]

S15. **Pascual-Miguelañez I**, Salinas-Gomez J, Fernandez-Luengas D, Villar-Zarra K, Clemente LV, Garcia-Arranz M, Olmo DG. Systemic treatment of acute liver failure with adipose derived stem cells. *J Invest Surg* 2015; **28**: 120-126 [PMID: 25517764 DOI: 10.3109/08941939.2014.987407]

S16. **Pan F**, Liao N, Zheng Y, Wang Y, Gao Y, Wang S, Jiang Y, Liu X. Intrahepatic transplantation of adipose-derived stem cells attenuates the progression of non-alcoholic fatty liver disease in rats. *Mol Med Rep* 2015; **12**: 3725-3733 [PMID: 26018346 DOI: 10.3892/mmr.2015.3847]

S17. **Liao N**, Pan F, Wang Y, Zheng Y, Xu B, Chen W, Gao Y, Cai Z, Liu X, Liu J. Adipose tissue-derived stem cells promote the reversion of non-alcoholic fatty liver disease: An in vivo study. *Int J Mol Med* 2016; **37**: 1389-1396 [PMID: 26986083 DOI: 10.3892/ijmm.2016.2528]

S18. **Seki A**, Sakai Y, Komura T, Nasti A, Yoshida K, Higashimoto M, Honda M, Usui S, Takamura M, Takamura T, Ochiya T, Furuichi K, Wada T, Kaneko S. Adipose tissue-derived stem cells as a regenerative therapy for a mouse steatohepatitis-induced cirrhosis model. *Hepatology* 2013; **58**: 1133-1142 [PMID: 23686813 DOI: 10.1002/hep.26470]

S19. **Guo DL**, Wang ZG, Xiong LK, Pan LY, Zhu Q, Yuan YF, Liu ZS. Hepatogenic differentiation from human adipose-derived stem cells and application for mouse acute liver injury. *Artif Cells Nanomed Biotechnol* 2017; **45**: 224-232 [PMID: 26838674 DOI: 10.3109/21691401.2016.1138495]

S20. **Saito Y**, Shimada M, Utsunomiya T, Ikemoto T, Yamada S, Morine Y, Imura S, Mori H, Sugimoto K, Iwahashi S, Asanoma M. The protective effect of adipose-derived stem cells against liver injury by trophic molecules. *J Surg Res* 2013; **180**: 162-168 [PMID: 23117122 DOI: 10.1016/j.jss.2012.10.009]

S21. **Sun CK**, Chang CL, Lin YC, Kao YH, Chang LT, Yen CH, Shao PL, Chen CH, Leu S, Yip HK. Systemic administration of autologous adipose-derived mesenchymal stem cells alleviates hepatic ischemia-reperfusion injury in rats. *Crit Care Med* 2012; **40**: 1279-1290 [PMID: 22336724 DOI: 10.1097/CCM.0b013e31823dae23]

S22. **Seki T**, Yokoyama Y, Nagasaki H, Kokuryo T, Nagino M. Adipose tissue-derived mesenchymal stem cell transplantation promotes hepatic regeneration after hepatic ischemia-reperfusion and subsequent hepatectomy in rats. *J Surg Res* 2012; **178**: 63-70 [PMID: 22482751 DOI: 10.1016/j.jss.2012.02.014]

S23. **Iseki M**, Kushida Y, Wakao S, Akimoto T, Mizuma M, Motoi F, Asada R, Shimizu S, Unno M, Chazenbalk G, Dezawa M. Muse Cells, Nontumorigenic Pluripotent-Like Stem Cells, Have Liver Regeneration Capacity Through Specific Homing and Cell Replacement in a Mouse Model of Liver Fibrosis. *Cell Transplant* 2017; **26**: 821-840 [PMID: 27938474 DOI: 10.3727/096368916X693662]