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Liver injury associated with acute respiratory distress syndrome and the prospects of mesenchymal stromal cells therapy for liver failure

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ABSTRACT

The pathogenesis of acute respiratory distress syndrome (ARDS) includes neutrophilic alveolitis, alteration of alveolar epithelium and endothelium, formation of hyaline membranes and microvascular thrombosis, which results in an acute hypoxemic respiratory failure. ARDS results in major structural and cellular changes in organs and organ systems. It causes liver dysfunction in critical patients through paracrine action of cytokines and other pro-inflammatory mediators as well as hypoxemia, oxidative stress, toxins and hypoperfusion.

Coronavirus disease 2019 (COVID-19)-associated ARDS affects liver through the development of systemic inflammatory response syndrome and hypoxia as well as cytokine storm. Liver injury manifests itself as increased plasma levels of hepatic transaminases and cholestatic liver enzymes. Stem cell therapy is one of the promising modern methods for treating ARDS-induced liver failure.

Many studies showed the ability of multipotent mesenchymal stromal cells (MMSCs) to differentiate into functional hepatocyte-like cells, which were then successfully used for liver regeneration. MMSCs were proven to be able to prevent the apoptosis of hepatocytes, as well as have anti-fibrotic and anti-inflammatory activity which allows their successful use in the treatment of ARDS-induced liver injury.

KEY WORDS: *acute respiratory distress syndrome; COVID-19; multipotent mesenchymal stromal cells; liver injury; liver failure*

Coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), directed the attention of the scientists to the research of effective methods for the treatment of its complications. Patients with the severe form of COVID-19 most commonly develop acute respiratory distress syndrome (ARDS). Said pathology also can be caused by polytrauma, sepsis, influenza virus infection etc. ARDS is a symptom complex of acute respiratory failure, which is characterised by a severe hypoxemia, non-cardiogenic pulmonary oedema, diffuse alveolar damage and pulmonary cellular infiltration. ARDS is also associated with microvascular thrombosis, increased endothelial and alveolar epithelial permeability, decreased alveolar clearance and the formation of hyaline membranes. The diffuse pulmonary damage occurs during the first acute phase. Afterwards it either resolves or progresses and results in interstitial fibrosis [1-4].

Liver injury is the most common ARDS complication [5]. In severe cases, it results in liver failure, which is characterised by jaundice, ascites, liver encephalopathy and hypocoagulation [6]. Nowadays the only existing method of liver failure treatment is liver transplantation. Nevertheless, the lack of donor organs, high mortality during waiting time and post-surgery complications limit the use of this method [7].

Finding the optimal treatment methods of ARDS-caused liver impairment is a highly relevant task of modern biomedical research, especially considering a long-term COVID-19 pandemic. Special attention is given to cellular therapy methods that use multipotent mesenchymal stromal cells (MMSCs). MMSCs are adult stem cells, which take part in the renewal and regeneration of organism tissues and have the ability to differentiate into a variety of somatic cell lines. The main abilities of MMSCs are symmetric and asymmetric division, high proliferative potential, adhesion, fibroblast-like morphology and easily induced adipogenic, chondrogenic and osteogenic differentiation [8-12]. According to the International Society for Cellular Therapy criteria MMSCs are immunophenotyped with the use of flow cytometry by measuring the presence of positive cluster of differentiation (CD)105, CD90 and CD73 markers and the absence of CD45, CD34, CD14, CD11b, CD79α or CD19 haematopoietic markers and human leukocyte antigens (HLA) class II [13].

Numerous preclinical researches and clinical trials have demonstrated the safety and the efficacy as well as immunomodulatory, anti-inflammatory, anti-fibrotic and regenerative impact of MMSCs-based therapy [8-12; 14-21].

The purpose of this article is to review the modern scientific data on the developmental mechanisms of ARDS and ARDS-associated liver injury and the use of cellular therapy methods, specifically MMSCs, for the successful treatment of ARDS-caused liver failure.

ACUTE RESPIRATORY DISTRESS SYNDROME

ARDS is a severe respiratory failure caused by a non-cardiogenic pulmonary oedema [1, 22]. ARDS pathogenesis includes diffuse alveolar damage (DAD) which consists of alveolar epithelial injury, neutrophilic infiltration, alveolar macrophage activation, cytokines and chemokines production, plasma extravasation, procoagulant activity and fibrin deposition, hyaline membranes formation, myofibroblast proliferation and intraalveolar fibrosis [5; 22].

ARDS mortality ranges from 35 % to 46 % [23] and is most commonly caused by the progressive multiple organ failure as opposed to refractory hypoxemia. ARDS is considered as a pulmonary manifestation of multiple organ dysfunctions. The severity of non-pulmonary ARDS-associated multiple organ failure increased with the rise of hypoxemia level [24].

The main causes of ARDS can be divided into two pathophysiological categories: the direct pulmonary pathogenesis (bacterial and viral pneumonia, inhalation trauma, aspirational pneumonitis and thoracic trauma including pulmonary parenchymal trauma) and indirect extrapulmonary pathogenesis (extrathoracic sepsis, trauma, shock, burns, blood transfusion, pancreatitis and multiorgan transplantation) [25-30].

One of the main factors causing a severe blood and tissue oxygenation impairment during DAD is the formation of protein-rich oedema of the breathing pathways because of the damage of alveolar-capillary membrane. DAD can occur not only as a result of a direct lung injury (e.g., pneumonia) but can also be a pulmonary manifestation of a variety of systemic immunoregulatory disorders such as sepsis. Thus, ARDS pathogenesis is linked to the changes of local and systemic immunity and immune responses. The liver plays an important role in these processes [5].

ARDS-ASSOCIATED LIVER INJURY

The liver plays a major role in the regulation of metabolic homeostasis. It takes part in the synthesis and processing of lipids, carbohydrates, proteins and bile acids. Thus, the impairment of liver function influences other organs through the disruption of their energy supply [31].

The liver plays a key role in toxin and drug metabolism, systemic inflammatory response regulation and immune protection. It eliminates endotoxins, circulating bacteria, intravascular coagulation products and bioactive molecules. It synthetises acute phase proteins (APPs), complement components, pro-inflammatory cytokines and chemokines as well as eicosanoids. The liver contains a major number of residential immune cells. The normal functioning of this organ is essential for the protection of lungs and their post-injury renewal [5].

The hepatobiliary system has the ability to inactivate and detoxicate proinflammatory cytokines, vasoactive mediators and eicosanoids in systemic circulation, thus protecting the lungs and other organs from being injured. The elevated levels of cytokines such as interleukin (IL)-8, IL-1β, epithelial neutrophil activating peptide (ENA-78), tumor necrosis factor alpha (TNF-α), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α) and eicosanoids such as thromboxane and leukotrienes have a direct cytotoxic effect on alveolar epithelial and endothelial cells and are able to activate local innate immune response and increase thrombocyte aggregation in the lungs. All of them promote the development of DAD [32, 33].

Liver-produced APPs have anti-bacterial and phagocytic activities, antioxidant effect, anti-proteolytic action as well as the ability to control haemostasis. But at the same time, they along with hepatic pro-inflammatory mediators are able to cause pulmonary oedema, alveolar epithelial and endothelial damage, oxidative stress, neutrophils entering lungs, the elevation of pulmonary pro-inflammatory mediator levels, alveolar macrophage activation and coagulation stimulation [5].

Hepatocellular injury results in the loss of clearing function of the li-ver, the dysfunction of immune response, the occurrence of such systemic complications as coagulopathy, increased infection risk, hypoglycaemia, increased inflammatory response, encephalopathy and the impairment of extra-hepatic organs, specifically lungs [34].

Acute lung injury impairs liver function through hypoxemia, systemic inflammatory response activation and cardiovascular changes [35-37].

The local inflammation of the alveolar space in patients with ARDS results in acute phase response in the liver which does not depend on bacterial dissemination but occurs as a result of pro-inflammatory signal molecules (IL-1, IL-6 and TNF-α), produced by pulmonary immunocytes. Such cytokines leave the lungs to join systemic circulation and influence the liver expression of such acute-phase proteins as C-reactive protein, α-1 antitrypsin, serum amyloid A protein etc., which in their turn are able to return to the lungs and cause a pulmonary inflammation as a result of alveolar macrophage activation [32, 38, 39].

Bacteria in lungs and liver can influence immune system cells directly through the activation of Toll-like receptors (TLRs) and indirectly through their metabolites and signal molecules such as pathogen-associated molecular patterns (PAMP). Activated alveolar macrophages and Kupffer cells release pro-inflammatory cytokines, which promote the initiation and progression of lung and liver injury and the activation of systemic inflammatory process [40-42].

Liver dysfunction manifests itself as the elevation of liver enzyme levels (gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), aspartate transaminase (AST), and alanine transaminase (ALT)) and bilirubin in blood plasma, the decrease of albumin and coagulation factors plasma levels and the increase of prothrombin time (PT) [43, 44].

As a result of liver dysfunction, the ability of liver to remove bacteria and their products as well as the inflammation mediators such as PAMP and cytokines from the bloodstream decreases which leads to the elevation of the blood levels of these molecules. Such pro-inflammatory molecules are able to cause or increase lung injury through TLR-4-mediated activation of intravascular and alveolar macrophages [45-50].

Hyperbilirubinemia negatively influences the lungs, causing the decrease of surface-active abilities of alveolar surfactant. High bilirubin levels also result in oxidative stress, apoptosis and inflammatory response, which increases ARDS development. Hyperbilirubinemia is used as ARDS biomarker and is one of mortality markers in patients with ARDS [51]. The liver produces a range of hormones, specifically insulin-like growth factor, angiotensinogen and thrombopoietin that influence ARDS development [52-54].

The link between liver and lungs, mediated by APPs, is important for the integration of systemic and pulmonary responses, regulation of immune response for the normalisation of homeostasis and post-injury organism renewal. Disbalance of that link is an important factor in the initiation and progression of ARDS and the occurrence of multi-organ failure [42; 55].

LIVER INJURY CAUSED BY COVID-19-ASSOCIATED ARDS

ARDS is the leading cause of death of patients with COVID-19 [56]. Research conducted in Jinyintan Hospital (Wuhan, PRC) discovered that 67–85 % critically ill patients with SARS-CoV-2 infection develop ARDS. The mortality of ARDS patients was 61.5 % total [57]. Research conducted in Wuhan Central Hospital discovered that COVID-19 patients with moderate and severe ARDS had the mortality of 70 % [58].

COVID-19 patients often have associated liver injury. Liver is the second most injured organ in COVID-19 patients after lungs [59-62]. Hepatocytes can be damaged because of direct cytotoxicity caused by SARS-CoV-2 virus replication in liver, because of systemic inflammatory response syndrome (SIRS), cytokine storm that occurs during severe COVID-19, or as a result of hypoxic changes caused by respiratory disorders [63-68].

COVID-19-associated liver injury is characterised by a moderate form of microvesicular steatosis, Kupffer cell activation, lobular and portal inflammation, apoptotic and necrotic foci and the elevation of ALT and AST plasma levels [63, 64, 69-72]. In numerous instances, two separate phases of liver injury were observed: the initial increase of transaminase (ALT and AST) levels, followed by elevation of cholestatic liver enzymes (ALP and GGT) levels [73].

According to Chen et al. who examined 99 Wuhan patients, 43.4 % of them had elevated ALT, AST and lactate dehydrogenase levels [74]. Guan et al. who examined 1099 Chinese COVID-19 patients discovered the elevated AST and ALT levels in 18.2 % and 19.8 % of patients with mild form and 39.4 % and 28.1 % of patients with severe form of C_{0-} VID-19 [75]. Wang et al. have established that ALT and AST levels of COVID-19 intensive care patients were much higher than those of non-intensive case patients, which proves that liver injury occurs more often in patients with the severe form of COVID-19 than in those with the mild form [76]. Xie et al. conducted a research of liver injury in COVID-19 patients without any liver comorbidities. They discovered that 31.6 %, 35.4 % and 5.1 % of said patients had elevated levels of ALT, AST and bilirubin, respectively [77].

According to the data obtained from 5700 New York patients, 58.4 % of them had the level of AST>40 U/l, 39 %, level of ALT >60 U/l and 2.1 % of them were diagnosed with acute liver injury as a result of AST or ALT levels being increased by 15 or more times [78].

Wang et al. after reviewing clinical data of 228 COVID-19 patients who had no previous chronic liver diseases, discovered that 29.4 % of those patients had elevated ALT, AST, ALP, GGT and total bilirubin levels upon administration and 56.3 % of them exhibited liver function impairment during hospitalisation [79].

According to numerous systemic meta-analyses and literature reviews 14.8–53 % of COVID-19 patients have elevated ALS and AST, 35 % of them have elevated total bilirubin level, 6.1 % have elevated ALP level and 21.1 % have elevated GGT level [65, 80-84].

COVID-19 associated ARDS is able to cause hypoxic hepatitis. More than 90 % hypoxic hepatitis cases are caused by cardiac failure, respiratory failure and sepsis. Acute respiratory failure, ischemia, hypovolemia and shock lead to liver tissue hypoxia, dying of hepatocytes and centrilobular necrosis [85-87]. Ischemic-hypoxic liver injury is associated with metabolic acidosis, hypercalcemia, changing of mitochondrial membrane permeability and high plasma concentration of aminotransferases [88]. As a result of hypoxemia and hypercapnia during ARDS, right ventricle dysfunction occurs, caused by a high pulmonary vascular resistance. It leads to the elevation of central venous pressure, which in its turn causes blood stasis in liver and congestive hepatopathy [85-87, 89-91].

THE CORRECTION OF LIVER FUNCTION WITH THE USE OF STEM CELLS

Stem cell therapy is a modern method of liver diseases treatment. It uses hematopoietic, induced pluripotent and multipotent mesenchymal stem cells (MMSCs). All of these cells are able to differentiate into hepatocyte-like cells [92-98]. Stem cells are proven to have tropism to the regions of inflammations in the recipient organism, thus after being intravenously injected they have the ability to migrate and accumulate in the areas of injuries or pathological changes [99]. Among different stem cell types, perinatal MMSCs have numerous advantages for clinical use. Comparing to embryonic and adult stem cells, MMSCs derived from perinatal tissues have higher availability, efficiency, multipotency, regenerative potential and a lower risk of infection [100].

Unlike embryonic or induced pluripotent stem cells, MMSCs derived from perinatal tissues have repressed oncogenes, which makes them non-oncogenic. Unlike adult stem cells, perinatal MMSCs are less immunogenic as a result of their low antigen major histocompatibility complex (MHC) I and low or absent antigen MHC II expression which makes them protected from being attacked by recipients' natural killer cells during allogeneic transplantation [101]. MMSCs derived from umbilical cord and amnion produce numerous cytokines i.e., interleukins, growth factors, prostaglandin E2, leukaemia inhibitory factor. By using biologically active secretome substances with angiogenic, anti-apoptotic, antioxidant and mitogenic effects, MMSCs stimulate the regeneration of injured tissues and organs [102].

MMSCs can be isolated from numerous human organs and tissues, e.g., bone marrow, umbilical cord and cord blood, adipose tissue etc [103, 104]. They have the ability to differentiate into different cell lines, i.e., chondroblasts, osteoblasts and adipocytes [105, 106].

MMSCs can also be differentiated into hepatocytes, which can be further used for liver regeneration. In order to cause the differentiation, MMSCs are inducted with the hepatocyte growth factor (HGF), epidermal growth factor, oncostatin M, leukaemia inhibitory factor, dexamethasone, insulin-transferrin-selenium or nicotinamide. The differentiation of MMSCs into hepatocytes can be stimulated by the extracellular matrix of the liver. Co-culturing of MMSCs with liver cells can also induce their differentiation into hepatocyte-like cells [93-97].

MMSCs are proven to have anti-fibrotic activity. They prevent transdifferentiation of hepatic stellate cells (Ito cells) into fibrogenic myofibroblasts, which produce extracellular matrix proteins (EMP) and cause liver fibrosis. MMSCs are able to secrete such factors as transforming growth factor beta-3 (TGF-β3), TNF-α, IL-10, HGF and nerve growth factor (NGF), which lower collagen synthesis by inducing Ito cell apoptosis. Conditioned medium of MMSCs, added to Ito cells, is able to inhibit their proliferation [107]. MMSCs produce matrix metalloproteinases (MMP)-9 and MMP-13 that are able to disintegrate EMP. MMSCs are also able to prevent liver fibrosis through the decrease of pro-fibrotic F4/80+ macrophages infiltration [108-109].

It is known that MMSCs are able to inhibit inflammatory processes in the liver through the modulation of production of pro-inflammatory cytokines and other pro-inflammatory molecules by liver immunocytes thus acting as hepatoprotectors. MMSCs lower the number of $CD4^+T^-$lymphocytes, $Gr\text{-}1^+$neutrophiles, $CD11b^+$ F4/80+macrophages, inhibit the expression of proinflammatory TNF-α, interferon gamma (IFN-γ), IL-4 and Fas ligand (FasL) cytokines by $CD4^+$ lymphocytes and Kupffer cells, and increase the production of immunosuppressive and hepatoprotective IL-10 [110-112].

The use of MMSCs had a hepatoprotective effect on the murine liver injury inducted by Concanavalin A, which manifested itself as a decrease of serum transaminases levels, alleviation of hepatocyte necrosis and a decrease of pro-inflammatory and pro-apoptotic cytokines TNF-α and IFN-γ production by liver immunocytes [111, 113].

Zhang Y et al., discovered that the systematic injection of MMSCs, derived from human umbilical cord, has an inhibitory effect on hepatocellular apoptosis, stimulates liver regeneration and the compensation of its function and increases the survival of rats with acute liver failure, caused by D-galactosamine and lipopolysaccharide [7].

CLINICAL EFFECTIVENESS OF CELL THERAPY IN PATIENTS WITH LIVER INJURY

Numerous clinical researches conducted on patients with acute and chronic liver injuries have proven the effectiveness and safety of MMSC-based therapy [14-21; 114-117].

Shi et al. [115] and Zhang et al. [117] used the intravenous administration of allogeneic MMSCs, obtained from umbilical cord, for the treatment of patients with liver failure caused by chronic hepatitis B. Both of the researches showed the restoration of liver function (i.e., increased levels of serum albumin, cholinesterase, prothrombin activity and decrease of total bilirubin and ALT levels), improved survival of treated patients compared to control groups and the absence of adverse reactions to MMSCs.

Xu et al. used the injection of autologous bone marrow-derived MMSCs into hepatic artery as a treatment method of liver cirrhosis, associated with chronic hepatitis B. Their research showed the decrease of IL-6, IL-17 and TNF-α levels [19].

Li et al. administered umbilical cord-derived MMSCs into hepatic artery for the treatment of patients with liver failure caused by hepatitis B, which resulted in the normalisation of serum albumin, ALT, AST, total and direct bilirubin levels and prothrombin time of the treated patients [116].

Lin et al. in their randomised controlled trial administered allogeneic bone marrow-derived MMSCs to patients with liver failure caused by hepatitis B, which led to a decrease of serum bilirubin level [21].

Amin et al. have performed an intrasplenic autologous transplantation of bone marrow-derived MMSCs to the patients with liver cirrhosis caused by hepatitis C. The result was a normalisation of liver function, i.e., the decrease of total bilirubin, AST and ALT levels and prothrombin time and the increase of albumin serum level [14]. El-Ansary et al. conducted phase II clinical trial during which patients with liver cirrhosis caused by hepatitis C were intravenously given non-differentiated autologous bone marrow-derived MMSCs as well as MMSCs, differentiated into hepatocyte-like cells. The result was the elevation of serum prothrombin and albumin and the lowering of bilirubin levels [114].

Salama et al. established the positive influence of autologous bone marrow-derived MMSCs, injected intravenously, on the course of liver cirrhosis associated with hepatitis C [17].

Jang et al. performed the injection of autologous bone marrow-derived MMSCs into hepatic artery for the treatment of alcoholic liver cirrhosis. They observed the decrease of fibrosis markers such as transforming growth factor beta-1, collagen 1 and smooth muscle alpha-actin as well as positive histological liver changes [16]. The ability of bone marrow-derived MMSCs to reduce the formation of liver fibrosis was also proven in a phase II randomised trial conducted by Suk et al [20].

CONCLUSION

The therapy of ARDS and its complication is getting more relevant because of COVID-19 pandemic. The analysis of modern scientific data shows that the most common ARDS complication is liver injury. One of the newest methods of liver failure treatment is cell therapy. Stem cells have a major regenerative, anti-inflammatory and immunomodulatory potential. Adding cellular therapy methods to treatment protocols of patients with liver failure caused by ARDS will increase their quality of life and optimise health outcomes.

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REFERENCES:

1. *Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al.* Definition Task Force ARDS. Acute respiratory distress syndrome. Jama, 2012; **307(23)**: 2526-2533. https://doi.org/10.1001/jama.2012.5669
2. *Bourenne J, Carvelli J, Papazian L.* Evolving definition of acute respiratory distress syndrome. J Thorac Dis. 2019; **11(3)**:S390. https://doi.org/10.21037/jtd.2018.12.24
3. *Thille AW, Esteban A, Fernandez-Segoviano P, et al.* Comparison of the Berlin definition for acute respiratory distress syndrome with autopsy. Am J Respir Crit Care Med. 2013; **187**:761-7 https://doi.org/10.1164/rccm.201211-1981OC
4. *Kamyshnyi A, Krynytska I, Matskevych V, Marushchak M, Lushchak O.* Arterial hypertension as a risk comorbidity associated with COVID-19 pathology. Int J Hypertens. 2020; **2020**:8019360. https://doi.org/10.1155/2020/8019360
5. *Herrero R, Sánchez G, Asensio I, López E, Ferruelo A, Vaquero J, et al.* Liver–lung interactions in acute respiratory distress syndrome. Intensive Care Med Exp. 2020; **8(1)**:1-13. https://doi.org/10.1186/s40635-020-00337-9
6. *Cai Y, Zou Z, Liu L, Chen S, Chen Y, Lin Z, Chen Y.* Bone marrow-derived mesenchymal stem cells inhibits hepatocyte apoptosis after acute liver injury. Int J Clin Exp. 2015; **8(1)**: 107.
7. *Zhang Y, Li Y, Li W, Cai J, Yue M, Jiang L, et al.* Therapeutic effect of human umbilical cord mesenchymal stem cells at various passages on acute liver failure in rats. Stem Cells Int. 2018; 2018. https://doi.org/10.1155/2018/7159465
8. *Lopes-Pacheco M, Robba C, Rocco PRM, Pelosi P.* Current understanding of the therapeutic benefits of mesenchymal stem cells in acute respiratory distress syndrome. Cell Biol Toxicol. 2020; **36(1)**:83-102. https://doi.org/10.1007/s10565-019-09493-5
9. *Tsuchiya A, Kojima Y, Ikarashi S, Seino S, Watanabe Y, Kawata Y, et al.* Clinical trials using mesenchymal stem cells in liver diseases and inflammatory bowel diseases. Inflamm Regen. 2017; **37(1)**: 1-15. https://doi.org/10.1186/s41232-017-0045-6
10. *Xiao K, Hou F, Huang X, Li B, Qian ZR, Xie L.* Mesenchymal stem cells: current clinical progress in ARDS and COVID-19. Stem Cell Res Therapy. 2020; **11(1)**:1-7. https://doi.org/10.1186/s13287-020-01804-6
11. *Wang YH, Wu DB, Chen B, Chen EQ, Tang H.* Progress in mesenchymal stem cell–based therapy for acute liver failure. Stem Cell Res Therapy. 2018; **9(1)**:1-9. https://doi.org/10.1186/s13287-018-0972-4
12. *Hu C, Wu Z, Li L.* Pre-treatments enhance the therapeutic effects of mesenchymal stem cells in liver diseases. JCMM. 2020; **24(1)**:40-49. https://doi.org/10.1111/jcmm.14788
13. *Dominici MLBK, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini FC, Krause, DS, et al.* Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006; **8(4)**:315-317. https://doi.org/10.1080/14653240600855905
14. *Amin MA, Sabry D, Rashed LA, et al.* Short-term evaluation of autologous transplantation of bone marrow-derived mesenchymal stem cells in patients with cirrhosis: Egyptian study. Clin Trans. 2013; **27(4)**:607-612. https://doi.org/10.1111/ctr.12179
15. *Wang L, Li J, Liu H, et al.* Pilot study of umbilical cord-derived mesenchymal stem cell transfusion in patients with primary biliary cirrhosis. J Gastroenterol Hepatol. 2013; **28(1)**:85-92. https://doi.org/10.1111/jgh.12029
16. *Jang YO, Kim YJ, Baik SK, et al.* Histological improvement following administration of autologous bone marrow-derived mesenchymal stem cells for alcoholic cirrhosis: a pilot study. Liver Int. 2014; **34**:33-41. https://doi.org/10.1111/liv.12218
17. *Salama H, Zekri AR, Medhat E, et al.* 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. https://doi.org/10.1186/scrt459
18. *Wang L, Han Q, Chen H, et al.* Allogeneic bone marrow mesenchymal stem cell transplantation in patients with UDCA-resistant primary biliary cirrhosis. Stem Cells Dev. 2014; **23**:2482-2489. https://doi.org/10.1089/scd.2013.0500

19. *Xu L, Gong Y, Wang B, et al.* 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. https://doi.org/10.1111/jgh.12653
20. *Suk KT, Yoon JH, Kim MY, et al.* Transplantation with autologous bone marrow-derived mesenchymal stem cells for alcoholic cirrhosis: Phase 2 trial. Hepatology. 2016; **64**:2185-2197. https://doi.org/10.1002/hep.28693
21. *Lin BL, Chen JF, Qiu WH, et al.* Allogeneic bone marrow-derived mesenchymal stromal cells for hepatitis B virus-related acute-onchronic liver failure: a randomized controlled trial. Hepatology. 2017; **66**:209-219. https://doi.org/10.1002/hep.29189
22. *Matthay MA, Ware LB, Zimmerman GA.* The acute respiratory distress syndrome. J Clin Investig. 2012; **122(8)**: 2731-2740. https://doi.org/10.1172/JCI60331
23. *Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al.* Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. Jama. 2016; **315(8)**: 788-800. https://doi.org/10.1001/jama.2016.0291
24. *Kallet RH, Lipnick MS, Zhuo H, Pangilinan LP, Gomez A.* Characteristics of nonpulmonary organ dysfunction at onset of ARDS based on the Berlin definition. 2019. https://researcherprofiles.org/profile/5784350630992403
25. *Michael AM, Zemans RL, Zimmerman GA, et al.* Acute respiratory distress syndrome. Nat Rev Dis Primers. 2019; **5**:18. https://doi.org/10.1038/s41572-019-0069-0
26. *Thompson BT, Chambers RC, Liu KD.* Acute respiratory distress syndrome. N Engl J Med. 2017; **377**:562-72. https://doi.org/10.1056/NEJMra1608077
27. *Papazian L, Aubron C, Brochard L, Chiche J-D, Combes A, Dreyfuss D, et al.* Formal guidelines: management of acute respiratory distress syndrome. Ann Intensive Care. 2019; **9(1)**:1-18. https://doi.org/10.1186/s13613-019-0540-9
28. *Raghavendran K, Napolitano LM.* Severe Acute Respiratory Distress Syndrome, An Issue of Critical Care Clinics-E-Book. 2011; **27(3)**:429-437. https://doi.org/10.1016/j.ccc.2011.05.006
29. *Raghavendran K, Napolitano LM.* ALI and ARDS: challenges and advances. Crit Care Clin. 2011, **27(3)**:429. https://doi.org/10.1016/j.ccc.2011.05.012
30. *Amato MB, Meade MO, Slutsky AS, et al.* Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med. 2015; **372**:747-55. https://doi.org/10.1056/NEJMsa1410639
31. *Rui L.* Energy metabolism in the liver. Compr Physiol. 2014; **4**:177-197. https://doi.org/10.1002/cphy.c130024
32. *Guillot A, Tacke F.* Liver macrophages: old dogmas and new insights. Hepatology communications. 2019; **3(6)**:730-743. https://doi.org/10.1002/hep4.1356
33. *Kolaczkowska E, Jenne CN, Surewaard BGJ, Thanabalasuriar A, Lee W-Y, Sanz M-J, et al.* Molecular mechanisms of NET formation and degradation revealed by intravital imaging in the liver vasculature. Nat Commun. 2015; **6(1)**:1-13. https://doi.org/10.1038/ncomms7673
34. *Wang Y, Liu W, Liu X, Sheng M, Pei Y, Lei R, et al.* Role of liver in modulating the release of inflammatory cytokines involved in lung and multiple organ dysfunction in severe acute pancreatitis. Cell Biochem Biophys. 2015; **71(2)**:765-776. https://doi.org/10.1007/s12013-014-0261-5
35. *Yang P, Formanek P, Scaglione S, Afshar M.* Risk factors and outcomes of acute respiratory distress syndrome in critically ill patients with cirrhosis. Hepatol Res. 2019; **49(3)**:335-343. https://doi.org/10.1111/hepr.1324
36. *Patterson EK, Yao LJ, Ramic N, Lewis JF, Cepinskas G, McCaig L, et al.* Lung-derived mediators induce cytokine production in downstream organs via an NF-κB-dependent mechanism. Mediators of inflammation. 2013. https://doi.org/10.1155/2013/586895
37. *Karcz M, Bankey B, Schwaiberger D, Lachmann B, Papadakos PJ.* Acute respiratory failure complicating advanced liver disease. In: Seminars in respiratory and critical care medicine. Thieme Medical Publishers. 2012; 96-110. https://doi.org/10.1055/s-0032-1301738
38. *Weber M, Lambeck S, Ding N, Henken S, Kohl M, Deigner HP, et al.* Hepatic induction of cholesterol biosynthesis reflects a remote adaptive response to pneumococcal pneumonia. The FASEB Journal. 2012; **26(6)**:2424-2436. https://doi.org/10.1096/fj.11-191957
39. *Quinton LJ, Blahna MT, Jones MR, Allen E, Ferrari JD, Hilliard KL, et al.* Hepatocyte-specific mutation of both NF-κB RelA and STAT3 abrogates the acute phase response in mice. J Clin Investig. 2012; **122(5)**:1758-1763. https://doi.org/10.1172/JCI59408
40. *Enaud R, Prevel R, Ciarlo E, Beaufils F, Wieërs G, Guery B, et al.* The gut-lung axis in health and respiratory diseases: a place for inter-organ and inter-kingdom crosstalks. Front Cell Infect Microbiol. 2020; **10**:9. https://doi.org/10.3389/fcimb.2020.00009
41. *Albillos A, Gottardi A, de Rescigno M.* The gut-liver axis in liver disease: pathophysiological basis for therapy. J Hepatol. 2020; **72(3)**:558-577. https://doi.org/10.1016/j.jhep.2019.10.003
42. *Young RP, Hopkins RJ, Marsland B.* The gut–liver–lung axis. Modulation of the innate immune response and its possible role in chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol. 2016; **54(2)**:161-169. https://doi.org/10.1165/rcmb.2015-0250PS
43. *Horvatits T, Drolz A, Trauner M, Fuhrmann V.* Liver injury and failure in critical illness. Hepatology. 2019; **70(6)**:2204-2215. https://doi.org/10.1002/hep.30824
44. *Lescot T, Karvellas C, Beaussier M, Magder S.* Acquired liver injury in the intensive care unit. Anesthesiology. 2012; **117(4)**:898-904. https://doi.org/10.1097/ALN.0b013e318266c6df
45. *Dickson RP.* The lung microbiome and ARDS. It is time to broaden the model. 2018. https://doi.org/10.1164/rccm.201710-2096ED
46. *Mukherjee S, Hanidziar D.* More of the gut in the lung: how two microbiomes meet in ARDS. Yale J Biol Med. 2018; **91(2)**:143-149.
47. *Dickson RP, Singer BH, Newstead MW, Falkowski NR, Erb-Downward JR, Standiford TJ, et al.* Enrichment of the lung microbiome with gut bacteria in sepsis and the acute respiratory distress syndrome. Nat Microbiol. 2016; **1(10)**:1-9. https://doi.org/10.1038/nmicrobiol.2016.113
48. *de Jong PR, González-Navajas JM, Jansen NJG.* The digestive tract as the origin of systemic inflammation. Crit Care. 2016; **20(1)**:1-12. https://doi.org/10.1186/s13054-016-1458-3
49. *Massey VL, Poole LG, Siow DL, Torres E, Warner NL, Schmidt RH, et al.* Chronic Alcohol Exposure Enhances Lipopolysaccharide-Induced Lung Injury in Mice: Potential Role of Systemic Tumor Necrosis Factor-Alpha. Alcohol Clin Exp Res. 2015; **39(10)**:1978-1988. https://doi.org/10.1111/acer.12855
50. *Massey VL.* Potential role of the gut/liver/lung axis in alcohol-induced tissue pathology. Biomolecule. 2015; **5(4)**:2477-2503. https://doi.org/10.3390/biom5042477
51. *Dizier S, Forel J-M, Ayzac L, Richard J-C, Hraiech S, Lehingue S, et al.* Early hepatic dysfunction is associated with a worse outcome in patients presenting with acute respiratory distress syndrome: a post-hoc analysis of the ACURASYS and PROSEVA studies. PLoS One. 2015; **10(12)**:e0144278. https://doi.org/10.1371/journal.pone.0144278
52. *Wang Z, Li W, Guo Q, Wang Y, Ma L, Zhang X.* Insulin-like growth factor-1 signaling in lung development and inflammatory lung diseases. Biomed Res Int. 2018; 2018. https://doi.org/10.1155/2018/6057589
53. *Kobayashi K, Horikami D, Omori K, Nakamura T, Yamazaki A, Maeda S, et al.* Thromboxane A 2 exacerbates acute lung injury via promoting edema formation. Scientific reports. 2016; **6(1)**:1-12. https://doi.org/10.1038/srep32109
54. *Cuccurullo A, Greco E, Lupia E, De Giuli P, Bosco O, Martin-Conte E, et al.* Blockade of thrombopoietin reduces organ damage in experimental endotoxemia and polymicrobial sepsis. PLoS One. 2016; **11(3)**:e0151088. https://doi.org/10.1371/journal.pone.0151088
55. *Hilliard KL, Allen E, Traber KE, Yamamoto K, Stauffer NM, Wasserman GA, et al.* The lung-liver axis: a requirement for maximal innate immunity and hepatoprotection during pneumonia. Am J Respir Cell Mol Biol. 2015; **53(3)**:378-390. https://doi.org/10.1165/rcmb.2014-0195OC

56. *Nardo AD, Schneeweiss-Gleixner M, Bakail M, Dixon ED, Lax SF, Trauner M*. Pathophysiological mechanisms of liver injury in COVID-19. Liver Int. 2021; **41(1)**:20-32. https://doi.org/10.1111/liv.14730
57. *Huang C, Wang Y, Li X, et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; **395**:497-506. https://doi.org/10.1016/S0140-6736(20)30183-5
58. *Liu Y, Sun W, Li J, et al*. Clinical features and progression of acute respiratory distress syndrome in coronavirus disease. medRxiv. 2020. https://doi.org/10.1101/2020.02.17.20024166
59. *Hu LL, Wang WJ, Zhu QJ, Yang L*. Novel coronavirus pneumonia related liver injury: etiological analysis and treatment strategy. Chin J Hepatol. 2020; **28**:E001-E001. https://doi.org/10.3760/cma.j.issn.1007-3418.2020.02.001
60. *Zu ZY, Jiang MD, Xu PP, Chen W, Ni QQ, Lu GM, et al*. Coronavirus disease 2019 (COVID-19): A perspective from China. Radiology. 2020. https://doi.org/10.1148/radiol.2020200490
61. *Ren M Jie L, Jun S, Subrata G, Liang-Ru Z, Hong Y, et al*. Implications of COVID-19 for patients with pre-existing digestive diseases. Lancet Gastroenterol Hepatol. 2020. https://doi.org/10.1016/S2468-1253(20)30076-5
62. *Li J, Fan JG*. Characteristics and mechanism of liver injury in 2019 coronavirus disease. Journal of clinical and translational hepatology. 2020; **8(1)**:13. https://doi.org/10.14218/JCTH.2020.00019
63. *Wang Y, Liu S, Liu H, et al*. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID- 19. J Hepatol. 2020. https://doi.org/10.1016/j.jhep.2020.05.002
64. *Wang Y, Lu F, Zhao J*. Reply to: Correspondence relating to "SARSCoV- 2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19". J Hepatol. 2020. https://doi.org/10.1016/j.jhep.2020.06.028
65. *Zhang C, Shi L, Wang FS*. Liver injury in COVID-19: management and chal-lenges. Lancet Gastroenterol Hepatol. 2020; **5**:428-30. https://doi.org/10.1016/S2468-1253(20)7-13005
66. *Liu J, Li S, Liu J, et al*. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020; **55**:102763. https://doi.org/10.1016/j.ebiom.2020.102763
67. *Kucharski AJ, Russell TW, Diamond C, et al*. Early dynamics of transmission and control of COVID-19: a mathematical modelling study. Lancet Infect Dis. 2020; **20**:553-558. https://doi.org/10.1016/S1473-3099(20)30144-4
68. *Ridruejo E, Soza A*. The liver in times of COVID-19: What hepatologists should know. Annals of hepatology. 2020; **19(4)**:353-358. https://doi.org/10.1016/j.aohep.2020.05.001
69. *Cai Q, Huang D, Yu H, et al*. COVID-19: Abnormal liver function tests. J Hepatol. 2020. https://doi.org/10.1016/j.jhep.2020.04.006
70. *Lax SF, Skok K, Zechner P, et al*. Pulmonary arterial thrombosis in covid-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. Ann Intern Med. 2020. https://doi.org/10.7326/M20-2566
71. *Ji D, Qin E, Xu J, et al*. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. J Hepatol. 2020. https://doi.org/10.1016/j.jhep.2020.03.044
72. *Sonzogni A, Previtali G, Seghezzi M, et al*. Liver histopathology in severe COVID 19 respiratory failure is suggestive of vascular alterations. Liver Int. 2020; **40**:2110-2116. https://doi.org/10.1111/liv.14601
73. *Bernal-Monterde V, Casas-Deza D, Letona-Giménez L, et al*. SARSCoV- 2 Infection Induces a Dual Response in Liver Function Tests: Association with Mortality during Hospitalization. Biomedicines. 2020; **8**:328. https://doi.org/10.3390/biomedicines8090328
74. *Chen N, Zhou M, Dong X, et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; **395**:507-513. https://doi.org/10.1016/S0140-6736(20)30211-7
75. *Guan W, Ni Z, Hu Y, et al*. Clinical characteristics of coronavirus disease 2019 in China. N. N Engl J Med. 2020; **382**:1708-1720. https://doi.org/10.1016/j.jemermed.2020.04.004
76. *Wang D, Hu B, Hu C, et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus infected pneumonia in Wuhan, China. JAMA. 2020; 323:1061-1069. https://doi.org/10.1001/jama.2020.1585
77. *Xie H, Zhao J, Lian N, Lin S, Xie Q, Zhuo H*. Clinical characteristics of non ICU hospitalized patients with coronavirus disease 2019 and liver injury: a retrospective study. Liver Int. 2020; **40**:1321-1326. https://doi.org/10.1111/liv.14449
78. *Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, DavidsonKW, et al*. Presenting characteristics comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA. 2020. https://doi.org/10.1001/jama.2020.6775
79. *Wang J, Zhu L, Xue L, Liu L, Yan X, Yan X, et al*. Risk factors of liver injury in patients with coronavirus disease 2019 in Jiangsu, China: A retrospective, multi center study. Journal of Medical Virology. 2021; **93(6)**:3305-3311. https://doi.org/10.1002/jmv.26663
80. *Kulkarni AV, Kumar P, Tevethia HV, et al*. Systematic review with meta-analysis: liver manifestations and outcomes in COVID-19. Aliment Pharmacol Ther. 2020; 52. https://doi.org/10.1111/apt.15916
81. *Yadav DK, Singh A, Zhang Q, et al*. Involvement of liver in COVID- 19: systematic review and meta-analysis. Gut. 2020. https://doi.org/10.1136/gutjn l-2020-322072
82. *Kumar-M P, Mishra S, Jha DK, et al*. Coronavirus disease (COVID- 19) and the liver: a comprehensive systematic review and meta-analysis. Hepatol Int. 2020. https://doi.org/10.1007/s12072-020-10071-9
83. *Paliogiannis P, Zinellu A*. Bilirubin levels in patients with mild and severe Covid-19: A pooled analysis. Liver International. 2020; **40**:1787-1788. https://doi.org/10.1111/liv.14477
84. *Parasa S, Desai M, Chandrasekar VT, et al*. Prevalence of Gastrointestinal Symptoms and Fecal Viral Shedding in Patients With Coronavirus Disease 2019. JAMA Netw Open. 2020; **3**:e2011335. https://doi.org/10.1001/jamanetworkopen.2020.11335
85. *Waseem N, Chen P-H*. Hypoxic Hepatitis: A Review and Clinical Update. J Clin Transl Hepatol. 2016; **4**:263-268. https://doi.org/10.14218/JCTH.2016.00022
86. *Horvatits T, Trauner M, Fuhrmann V*. Hypoxic liver injury and cholestasis in critically ill patients. Curr Opin Crit Care. 2013; **19**:128-132. https://doi.org/10.1097/MCC.0b013e32835ec9e6
87. *Henrion J*. Hypoxic hepatitis. Liver Int. 2012; **32**:1039-1052. https://doi.org/10.1111/j.1478-3231.2011.02655.x
88. *Li J, Li RJ, Lv GY, Liu HQ*. The mechanisms and strategies to protect from hepatic ischemia-reperfusion injury. Eur Rev Med Pharmacol Sci. 2015; **19**:2036-2047.
89. *Fayssoil A, Mustafic H, Mansencal N*. The Right Ventricle in COVID-19 Patients. J Clean Prod. 2020; 130. https://doi.org/10.1016/j.amjcard.2020.06.007
90. *Horvatits T, Drolz A, Trauner M, Fuhrmann V*. Liver Injury and Failure in Critical Illness. Hepatology. 2019; **70**:2204-2215. https://doi.org/10.1002/hep.30824
91. *Vieillard-Baron A, Naeije R, Haddad F, Bogaard HJ, Bull TM, Fletcher N, et al*. Diagnostic workup, etiologies and management of acute right ventricle failure. Intensive care medicine. 2018, **44(6)**:774-790. https://doi.org/10.1007/s00134-018-5172-2

92. *Kang H, Kim MY, Eom YW, Baik SK*. Mesenchymal stem cells for the treatment of liver disease: present and perspectives. Gut and liver. 2020; **14(3)**:306. https://doi.org/10.5009/gnl18412
93. *Eom YW, Shim KY, Baik SK*. Mesenchymal stem cell therapy for liver fibrosis. Korean J Intern Med. 2015; **30**:580-589. https://doi.org/10.3904/kjim.2015.30.5.580
94. *Yin L, Zhu Y, Yang J, Ni Y, Zhou Z, Chen Y, et al*. Adipose tissue-derived mesenchymal stem cells differentiated into hepatocyte-like cells in vivo and in vitro. Mol Rep Med. 2015, **11(3)**:1722-1732. https://doi.org/10.3892/mmr.2014.2935
95. *Kadota Y, Yagi H, Inomata K, Matsubara K, Hibi T, Abe Y, et al*. Mesenchymal stem cells support hepatocyte function in engineered liver grafts. Organogenesis. 2014; **10(2)**:268-277. https://doi.org/10.4161/org.27879
96. *Mou XZ, Lin J, Chen JY, Li YF, Wu XX, Xiang BY, et al*. Menstrual blood-derived mesenchymal stem cells differentiate into functional hepatocyte-like cells. Journal of Zhejiang University SCIENCE B. 2013; **14(11)**:961-972. https://doi.org/10.1631/jzus.B1300081
97. *Wu XB, Tao R*. Hepatocyte differentiation of mesenchymal stem cells. HBPD INT. 2012; **11(4)**:360-371. https://doi.org/10.1016/s1499-3872(12)60193-3
98. *Han YJ, Kang YH, Shivakumar SB, Bharti D, Son YB, Choi YH, et al*. Stem cells from cryopreserved human dental pulp tissues sequentially differentiate into definitive endoderm and hepatocyte-like cells in vitro. Int J Med Sci. 2017; **14(13)**:1418. https://doi.org/10.7150/ijms.22152#
99. *Kidd S, Spaeth E, Dembinski JL, Dietrich M, Watson K, Klopp A, et al*. Direct evidence of mesenchymal stem cell tropism for tumor and wounding microenvironments using in vivo bioluminescent imaging. Stem cells. 2009; **27(10)**:2614-2623. https://doi.org/10.1002/stem.187
100. *Wang J, Cen P, Chen J, Fan L, Li J, Cao H, et al*. Role of mesenchymal stem cells, their derived factors, and extracellular vesicles in liver failure. Stem Cell Res Ther. 2017; **8**:137. https://doi.org/doi.org/10.1186/s13287-017-0576-4
101. *Prakash MD, Miller S, Randall-Demllo S, Nurgali K*. Mesenchymal stem cell treatment of inflammation-induced cancer. Inflamm Bowel Dis. 2016; **22(11)**:2694-2703. https://doi.org/10.1097/MIB.0000000000000900
102. *Kumar P, Kandoi S, Misra R, Vijayalakshmi S, Rajagopal K, Verma RS*. The mesenchymal stem cell secretome: a new paradigm towards cell-free therapeutic mode in regenerative medicine. Cytokine Growth Factor Rev. 2019; **46**:1-9. https://doi.org/10.1016/j.cytogfr.2019.04.002
103. *Zarrabi M, Mousavi SH, Abroun S, Sadeghi B*. Potential uses for cord blood mesenchymal stem cells. Cell Journal (Yakhteh). 2014; **15(4)**:274.
104. *Ribeiro A, Laranjeira P, Mendes S, Velada I, Leite C, Andrade P, et al*. Mesenchymal stem cells from umbilical cord matrix, adipose tissue and bone marrow exhibit different capability to suppress peripheral blood B, natural killer and T cells. Stem Cell Res Ther. 2013; **4(5)**:1-16. https://doi.org/10.1186/scrt336
105. *Kim G, Eom YW, Baik SK, Shin Y, Lim YL, Kim MY, et al*. Therapeutic effects of mesenchymal stem cells for patients with chronic liver diseases: systematic review and meta-analysis. Journal of Korean Medical Science. 2015; **30(10)**:1405-1415. https://doi.org/10.3346/jkms.2015.30.10.1405
106. *Secunda R, Vennila R, Mohanashankar AM, Rajasundari M, Jeswanth S, Surendran R*. Isolation, expansion and characterisation of mesenchymal stem cells from human bone marrow, adipose tissue, umbilical cord blood and matrix: a comparative study. Cytotechnology. 2015; **67(5)**:793-807. https://doi.org/10.1007/s10616-014-9718-z
107. *Huang B, Cheng X, Wang H, et al*. Mesenchymal stem cells and their secreted molecules predominantly ameliorate fulminant hepatic failure and chronic liver fibrosis in mice respectively. J Transl Med. 2016; **14**:45. https://doi.org/10.1186/s12967-016-0792-1
108. *Liu YC, Zou XB, Chai YF, et al*. Macrophage polarization in inflammatory diseases. Int J Biol Sci. 2014; **10**:520-529. https://doi.org/10.7150/ijbs.8879
109. *Ali G, Mohsin S, Khan M, et al*. Nitric oxide augments mesenchymal stem cell ability to repair liver fibrosis. J Transl Med. 2012; **10**:75. https://doi.org/10.1186/1479-5876-10-75
110. *Gazdic M, Arsenijevic A, Markovic BS, Volarevic A, Dimova I, Djonov V, et al*. Mesenchymal stem cell-dependent modulation of liver diseases. Int J Biol Sci. 2017; **13(9)**:1109. https://doi.org/10.7150/ijbs.20240
111. *Heymann F, Hamesch K, Weiskirchen R, et al*. The concanavalin A model of acute hepatitis in mice. Lab Anim. 2015; **49(1)**:12-20. https://doi.org/10.1177/0023677215572841
112. *Ryu KH, Kim SY, Kim YR, et al*. Tonsil-derived mesenchymal stem cells alleviate concanavalin A-induced acute liver injury. Exp Cell Res. 2014; **326**:143-154. https://doi.org/10.1016/j.yexcr.2014.06.007
113. *Zhu X, He B, Zhou X, et al*. Effects of transplanted bone-marrow-derived mesenchymal stem cells in animal models of acute hepatitis. Cell Tissue Res. 2013; **351**:477-486. https://doi.org/10.1007/s00441-012-1524-3
114. *El-Ansary M, Abdel-Aziz I, Mogawer S, et al*. Phase II trial: undifferentiated versus differentiated autologous mesenchymal stem cells transplantation in Egyptian patients with HCV induced liver cirrhosis. Stem Cell Rev. 2012; **8**:972-981. https://doi.org/10.1007/s12015-011-9322-y
115. *Shi M, Zhang Z, Xu R, et al*. 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. https://doi.org/10.5966/sctm.2012-0034
116. *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-onchronic liver failure treated with plasma exchange and Entecavir: a 24-month prospective study. Stem Cell Rev. 2016; **12**:645-53. https://doi.org/10.1007/s12015-016-9683-3
117. *Zhang Z, Lin H, Shi M, et al*. Human umbilical cord mesenchymal stem cells improve liver function and ascites in decompensated liver cirrhosis patients. J Gastroenterol Hepatol. 2012; **27(2)**:112-120. https://doi.org/10.1111/j.1440-1746.2011.07024.x

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Ураження печінки при гострому респіраторному дистрес-синдромі та перспективи корекції печінкової недостатності за допомогою мезенхімальних стромальних клітин

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РЕЗЮМЕ

Патогенез гострого респіраторного дистрес-синдрому (ГРДС) включає в себе нейтрофільний альвеоліт, ураження альвеолярного епітелію та ендотелію, формування гіалінових мембран та мікроваскулярних тромбів, унаслідок чого виникає гостра гіпоксемічна дихальна недостатність. ГРДС спричиняє значні структурно-клітинні зміни органів та систем. Зокрема він зумовлює дисфункцію печінки у важко хворих пацієнтів шляхом паракринної дії цитокінів та інших запальних медіаторів, гіпоксемії, оксидативного стресу, токсичних сполук і гіпоперфузії.

При COVID-19-асоційованому ГРДС печінка уражається як унаслідок синдрому системної запальної відповіді, гіпоксії, так і унаслідок цитокінового шторму. При цьому у хворих спостерігається підвищення рівнів печінкових трансаміназ та холестатичних печінкових ферментів у плазмі крові.

Терапія з використанням мультипотентних мезенхімальних стромальних клітин (ММСК) є одним із перспективних новітніх методів лікування печінкової недостатності, викликаної ГРДС. У багатьох дослідженнях ММСК були диференційовані у функціонуючі гепатоцитоподібні клітини, що згодом були успішно застосовані для регенерації печінки. Виявлено, що ММСК проявляють антиапоптотичну дію на гепатоцити, володіють антифібротичною та протизапальною активністю, що дозволяє успішно використовувати їх у терапії ГРДС-зумовленого ураження печінки.

***КЛЮЧОВІ СЛОВА**: гострий респіраторний дистрес-синдром; COVID-19; мезенхімальні стромальні клітини; ураження печінки; печінкова недостатність*