# Progress in evaluating the status of hepatitis C infection based on the functional changes of hepatic stellate cells (Review)

WEI WANG, XUELIAN HUANG, XUZHOU FAN, JINGMEI YAN and JIANFENG LUAN

Department of Blood Transfusion Medicine, School of Medicine, Jinling Hospital, Nanjing University, Nanjing, Jiangsu 210002, P.R. China

Received April 7, 2020; Accepted August 18, 2020

DOI: 10.3892/mmr.2020.11516

**Abstract.** Hepatitis C virus (HCV) infection is a global public health problem. Cirrhosis and hepatocellular carcinoma are the main causes of death in patients with chronic hepatitis C (CHC) infection. Liver fibrosis is an important cause of cirrhosis and end-stage liver disease after CHC infection. Along with the course of infection, liver fibrosis exhibits a progressive exacerbation. Hepatic stellate cells (HSCs) are involved in both physiological and pathological processes of the liver. During the chronic liver injury process, the activated HSCs transform into myofibroblasts, which are important cells in the development of liver fibrosis. At present, HCV infection still lacks specific markers for the accurate detection of the disease condition and progression. Therefore, the present review focused on HSCs, which are closely related to HCV-infected liver fibrosis, and analyzed the changes in the HSCs, including their surface-specific markers, cytokine production, activation, cell function and morphological structure. The present review aimed to propose novel diagnostic markers, at both the cellular and molecular level, which would be of great significance for the timely diagnosis of the disease. According to this aim, the characteristic changes of HSCs during HCV infection were reviewed in the present article.

**Contents**



*Correspondence to:* Professor Jianfeng Luan, Department of Blood Transfusion Medicine, School of Medicine, Jinling Hospital, Nanjing University, 305 Zhongshan East Road, Nanjing, Jiangsu 210002, P.R. China
Email: dbzqblood@163.com

*Key words:* hepatic stellate cells, hepatitis C virus, state assessment, fibrosis, detection

## 1. Introduction

Hepatitis C virus (HCV) is an infectious disease of global concern. The World Health Organization suggests that there are >71 million individuals infected with HCV worldwide and ~475,000 deaths are caused by HCV infections annually (1,2). The prevalence and incidence of HCV infections are the highest in low- and middle-income countries (3,4). The HCV can cause chronic liver disease, which is long-lasting and can progress to fibrosis, cirrhosis and hepatocellular carcinoma (HCC) if it is not treated in a timely manner (5-7). The dormant period of the HCV is long, sometimes up to 20-30 years, and the clinical symptoms are not obvious, thus they are easy to ignore once infected (8,9).

During the early course of HCV infection, the activation and proliferation of hepatic stellate cells (HSCs) is the central link in the development of liver fibrosis (10,11). When the HCV infection causes damage to the liver, cytokines and reactive oxygen species released by the tissues activate HSCs to develop into myofibroblasts (MFBs), which undergo considerable proliferation, and secrete collagen and metalloproteinase inhibitors (12-14), the secretion of which notably increases extracellular matrix deposition and decreases its degradation, respectively (15). The excessive deposition of the extracellular matrix results in the destruction of the structure of the liver, eventually leading to the development of liver fibrosis (16).

At present, several serological makers and viral antigens in the serum, such as HCV antibody (Ab), HCV core antigen (cAg) and HCV-RNA, are routinely assessed for to diagnose the status of the HCV infection and liver disease associated with the HCV (17-19). Nevertheless, given the complexity and variability in HCV infections, the levels of serological markers do not sufficiently reflect the status of HCV infection and disease progression (20,21). Therefore, it is necessary to identify additional indices that may be used to differentiate varying degrees of HCV progression. The changes in the function and status of HSCs was discovered to be closely associated with the course of HCV infection (22). Therefore, in the present review, the functional changes of important cell populations, such as HSCs, during alterations to liver immune function following the infection with HCV are described, with the aim of highlighting avenues for the identification of complementary laboratory indices that may be used for the diagnosis of HCV infection.

## 2. Functional characteristics of HSCs

*Activation of HSCs*. As early as the 19th century, German scientist von Kuffer first discovered the presence of stellate cells in the hepatic sinus space (23). In 1996, international standardization stipulated that such stellate cells were named HSCs (24). In addition to the known functions of storing lipid droplets and participating in fibrosis, HSCs also possess several other important functions, such as their role in mediating the immune response of the liver (25-27). Previous studies have reported that HSCs were heterogeneous and plastic in the liver, and different subsets of HSC phenotypes exist, which all have various functions (28-30). In the physiological liver, HSCs exist in a quiescent non-proliferative state, termed quiescent (q)HSCs (31). qHSCs were discovered to serve a role in the storage and transport of retinoids (vitamin A compounds), and the quantity of vitamin A lipid droplets in the cytoplasm of qHSCs in the liver may account for up to 45-72% of the total content in the human body (32). Nervous system markers, such as glial fibril acidic protein and neurotensin, nerve growth factor receptor and desmin were also discovered to be expressed in qHSCs (33,34). qHSCs can also secrete extracellular matrix protein and protein substances, such as laminin, polysaccharide protein and type IV collagen, which are required for the formation of the basement membrane (35-37).

Following chronic liver damage as a result of alcoholic steatohepatitis, non-alcoholic fatty liver disease, hepatitis B or HCV infection, or cholestatic liver injury, several external stimuli and cell types converge upon HSCs to promote their activation and development into MFB cells (38-40). The other cell types involved in the activation of HSCs include liver macrophages, hepatic sinusoidal endothelial cells, natural killer (NK) cells, B cells and hepatocytes (41). These cells secrete various components, including oxidative stress products, cytokines and apoptotic bodies, amongst others, to activate the HSCs (42-44). MFBs possess a potent ability to contract and migrate through the upregulation of fibrosis markers, such as type I collagen, α-smooth muscle actin (SMA), matrix metalloproteinases and tissue inhibitor of matrix metalloproteinases (45-47). α-SMA is present in vascular smooth muscle cells and fibroblasts, and is a widely recognized marker of HSC activation (48,49). In addition, previous studies have identified that cytokine receptor-like factor 1, secreted phosphoprotein 1, lysyl oxidase, lysyl oxidase-like 2 and IL-17 receptor A are also recognized markers associated with the activated phenotype of qHSCs, and are upregulated following activation (50-54).

HSCs also secrete chemokines to recruit cells and regulate the local immune microenvironment (55). Current studies have reported that HSCs expressed chemokine receptors, such as C-C chemokine receptor type (CCR)5, CCR7 and C-X-C motif chemokine receptor (CXCR)3, and secreted the chemokines C-C motif chemokine (CCL)5, CCL3, CCL2, C-X-C motif chemokine ligand (CXCL)10, CXCL9 and CXCL8 (56,57).

*Immune function of HSCs*. HSCs serve an important role in regulating the immune environment in the liver (58). The liver is rich in macrophages, which are an important innate immune system response cell group physiologically (59,60). The interactions between macrophages and HSCs were discovered to serve vital roles in the development of liver diseases; for example, a previous study revealed that HSCs induced monocytes to differentiate into specific $CD14^+$/human leukocyte $antigen^-$-$DR^-$ phenotypes when activated HSCs were co-cultured with mature peripheral blood mononuclear cells (61). HSCs are activated via pattern recognition receptor pathways, such as Toll-like receptors (TLR)4 and TLR2, inflammatory markers produced by hepatic macrophages (TNF-α, NLR family pyrin domain containing 3, IL-1β, IL-6 and CCL5) and chemokines (CCL2, CCL8 and CX3 chemokine receptor 1) that directly influence HSC activation (62). A previous study illustrated that NK cells served an important role in inhibiting liver fibrosis by producing the antifibrotic cytokine IFN-γ to selectively kill or age the early-activated HSCs (63). After the activation of early HSCs, vitamin A is metabolized to retinoic acid, and the expression of retinoic acid early inducible gene 1 is upregulated, which in-turn promotes the killing ability of NK cells (64). Increased retinoic acid metabolism in late-activated HSCs was discovered to inhibit the IFN-γ/STAT1 signaling pathway, increase the secretion of TGF-β, inhibit the activity of NK cells and reduce the antifibrotic function of NK cells (43,65). It was reported that activated HSCs functioned as antigen presenting cells, which triggered T cell proliferation (27). HSCs were also discovered to express the immunomodulatory programmed cell death receptor 1, which binds to programmed death-ligand 1 presented on the T cell surface to induce T cell apoptosis (44,66). In summary, HSCs possess a diverse and complex array of functions, serve an important role in the liver microenvironment, participate in a variety of physiological and pathological reactions and are closely associated with changes in immune function.

## 3. Role of HSCs in the process of HCV infection

Chronic HCV infection can cause liver damage and result in a range of mild to more severe diseases, such as chronic hepatitis C (CHC), fibrosis and cirrhosis (67). The activation of HSCs was identified as an important signal in the control of extracellular matrix synthesis and degradation in HCV-induced liver fibrosis (68). At the cellular level, the activatory properties on HSCs are considered to be associated with the amino domain of HCV core protein (69). Furthermore, HCV infection was discovered to stimulate the innate immune response, and changes in the functions of HSCs were also affected by other important immune cells, such as NK cells, natural killer T (NKT) cells and macrophages (70,71). At the molecular level, during HCV infection, two types of cytokines that are closely associated with the activation of HSCs were discovered to serve different roles; one type of chemokine primarily promoted fibrosis, such as CXCL9, CXCL10, CXCL11, IL-4, IL-13, IL-17 and TGF-β, while the other type of cytokine contributed to the inflammatory response, such as IL-5, IL-20, IL-22, IFN-γ, TNF-α and CCL5 (72). At the mRNA level, previous studies have illustrated that several different microRNAs (miRNAs/miRs) were abnormally expressed in HCV-induced liver fibrosis, such as miR-16, miR-21, miR-122, miR-150, miR-214 and miR-221, where they were involved in the activation of HSCs (Fig. 1) (73-75).

*Properties of immune cells in CHC infection*. HSCs can express several HCV co-receptors that interact with the HCV proteins

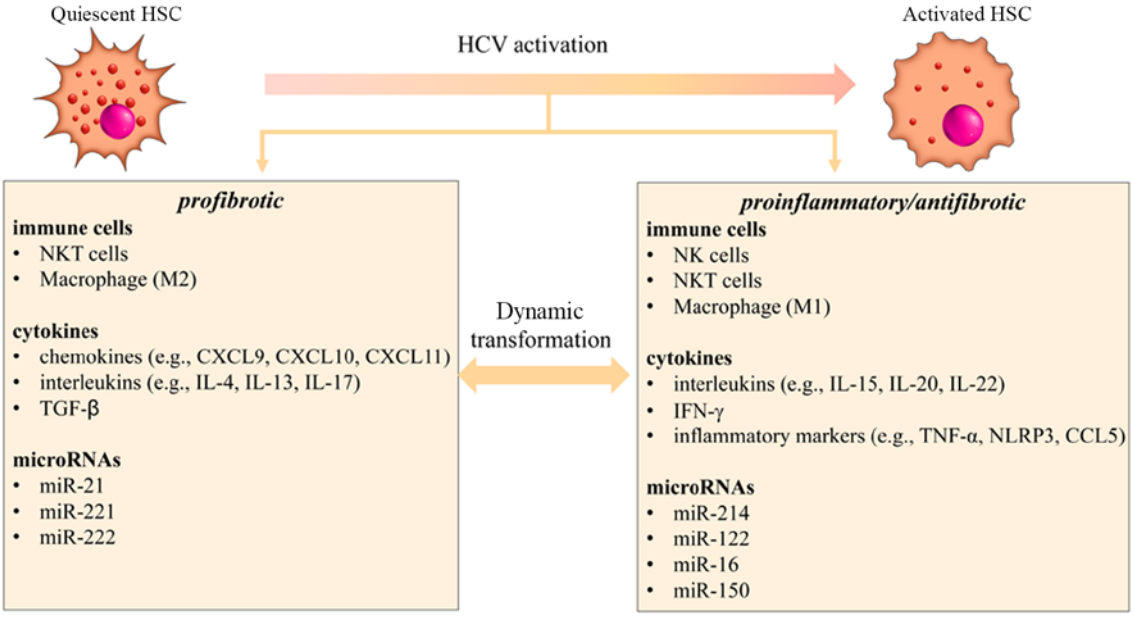


Figure 1. Indicators associated with HSCs in patients with CHC infection. In HCV-related liver fibrosis, the activation of HSCs is a dynamic process. On the one hand, NK cells generally help clear senescent-activated HSCs, including via directly killing of activated HSCs and by producing IFN-γ. M1 macrophages promote antifibrotic differentiation of HSCs and are associated with proinflammatory response, which involves proinflammatory and antifibrotic cytokines, such as IL-5, IL-20, IL-22, IFN-γ, TNF-α, NLRP3 and CCL5. Antifibrotic miRNAs include miR-214, miR-16, miR-122 and miR-150. On the other hand, NKT cells and M2 macrophages exert profibrotic effects by producing CXCL9, CXCL10, CXCL11, IL-4, IL-13, IL-17 and TGF-β. Profibrogenic miRNAs include miR-21, miR-221 and miR-222. HSC, hepatic stellate cell; HCV, hepatitis C virus; CHC, chronic hepatitis C; NK, natural killer; NKT, natural killer T; CXCL, C-X-C motif chemokine ligand; miR, microRNA; CCL5, C-C motif chemokine ligand 5; NLRP3, NLR family pyrin domain containing 3; M1, classically activated; M2, alternatively activated.

to promote liver fibrosis (76). For example, the binding of the HCV E2 protein and CD81 on the surface of HSCs may result in an increase in the fibrogenic effects occur to HSCs (77,78). In addition, the expression of HCV core and NS3-NS5 proteins was suggested to promote HSC proliferation and induce the secretion of proinflammatory cytokines in HSCs, such as IL-8 and monocyte-chemotactic protein-1 (79,80).

Exosomes are small extracellular vesicles that are secreted by the majority of cells through the endocytic pathway; however, there is no direct contact between the different cells. Exosomes carry different biomolecules and are therefore an important vehicle for intracellular and intercellular communication (81). Notably, previous studies have confirmed the existence of exosome-mediated communications between HCV-infected hepatocytes and HSCs (82,83). Exosomes secreted from HCV-infected hepatocytes (HCV-exo) were discovered to possess the potential to activate HSCs (84). A high expression of miR-19a in exosomes was observed from HCV-exo, which in turn enhances fibrosis marker genes and activates the STAT3-mediated TGF-β signaling pathway (85). In a previous study on the activation and function of NK cells in the pathogenesis of HCV infection, hepatocytes were reported to produce a host of cytokines, including IFN-α/β, which activated NK cells and enhanced NK cell-mediated cell cytotoxicity (86). NK cells generally display antifibrotic properties, including the inhibition of liver fibrosis by selectively expressing death receptor ligands for the receptors on activated HSCs and by producing the antifibrotic cytokine IFN-γ (87). In addition, NKT cells were revealed to perform similar antifibrotic functions as NK cells by killing HSCs and producing IFN-γ (88). However, NKT cells also produce profibrotic cytokines to promote liver fibrogenesis; for example, the secretion of IL-4 and IL-13 from NKT cells were significantly increased in patients with HCV with cirrhosis (89). Macrophages are divided into two phenotypically and functionally distinct subsets, classically and alternatively (M2) activated macrophages (90). M2 macrophages are considered to possess anti-inflammatory and profibrotic effects by producing profibrotic cytokines (CCL3, CCL5, TGF-β and TNF-α) (91). Clinically, it has also been reported that the expression levels of CCL5 are upregulated in the serum and liver of patients with HCV (56).

*Effect of chemokines and ILs in CHC infection*. Chemokines are divided into four groups: CC, CXC, CX3C and C families (92). HSCs primarily express receptors, such as CXCR4 and CXCR3, and can secrete chemokines, such as CXCL10, CXCL9 and CXCL8, which participate in the induction process of liver fibrosis by recruiting inflammatory immune cells and inhibiting the secretion of collagen I by HSCs, all of which exhibit immunomodulatory functions in the liver (93-95). Following HCV infection in the liver, CXCR4 expression levels were revealed to be upregulated, which subsequently activated HSCs (96). CXCR4 was found to bind to its ligand CXCL12 to stimulate the activation of HSCs, increasing the secretion of CXCL12 and leading to further proliferation and activation (97). Following the initial HCV infection, TLR3 and retinoic acid-inducible gene I were identified to activate CXCR3 ligands, such as CXCL10, in infected hepatocytes, thereby increasing their activity and stimulating the production of IFN-γ (98). During acute HCV infection, the presence of CXCR3-related ligands, such as CXCL9, CXCL10, CXCL11

Table I. Comparison of different methods for detecting HCV.

| Diagnostic marker | Technology | Advantages | Disadvantages | (Refs.) |
|---|---|---|---|---|
| HCV antibodies, HCV core antigen | ELISA, chemilumine scence immunoassays, gold immunochro matographic assay, recombinant immunoblot assay | Sensitive and specific. | Easily susceptible to interference and produces false positive and false negative results. | (140-143) |
| HCV-RNA | Reverse transcription-quantitative PCR, transcription mediated amplification | Higher specificity and often used as a confirmatory experiment. | Inaccurate quantification due to numerous sources of variation. | (17) |
| HCV genetic | PCR-sequence specific primers, line probe assay, PCR-restriction fragment length polymorphism | Helps to determine the establishment of different treatment methods. | Troublesome operation and expensive equipment and reagents. | (2,144,146) |
| Fibrosis | APRI, FIB-4 score | Improve prediction of advanced fibrosis and cirrhosis in patients with chronic hepatitis C infection. | Low sensitivity of APRI and FIB-4 in gauging improvements in liver fibrosis following therapy. | (23,154) |
| Other indicators | hematoxylin and eosin staining, immunohisto chemical staining, abdominal ultrasound examination, CT, magnetic resonance imaging | More intuitive observation. | Invasive and only provides an auxiliary diagnosis. | (150,153) |

HCV, hepatitis C virus; APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis-4.

and other chemokines, increases rapidly within a few weeks of viral infection (99). For instance, Zeremski *et al* (100) demonstrated that CXCL9-11 induction began at 38-53 days and peaked at 72-83 days after viral infection. In the process of HCV infection, the upregulation of CXCL12, CXCL9, CXCL10, CXCL11 and other chemokines significantly accelerates the process of fibrosis, which gradually advances to cirrhosis and potentially even liver cancer, both of which are considerably harder to treat (101-103). Therefore, studies have proposed that chemokines, such as CXCL9, CXCL10 and CXCL11, related to CXCR3 in the peripheral blood of patients with CHC infection may be used as markers of fibrosis, and changes in their secretion may be useful to evaluate the degree of fibrosis for more targeted and effective treatment options (104-106).

IL-15 and its high-affinity receptor IL-15 receptor (R)α are widely expressed in immune cells and liver cells (107,108). NK cells, NKT cells and $CD8^+$ T cells generate IL-15 to maintain system homeostasis and promote liver regeneration (109). A previous study confirmed that IL-15 and IFN-γ exhibited protective effects against HCV via the ERK signaling pathway *in vitro* (110). Jiao *et al* (108) reported that increased fibrosis was observed in IL-15Rα knockout (KO) mice. Furthermore, the study demonstrated that collagen production was increased in HSCs isolated from IL-15RαKO mice. Therefore, IL-15 and IL-15Rα may serve a protective role in the development of liver fibrosis by regulating the expression levels of fibrotic molecules and collagen in HSCs and maintaining the balance of NK cells *in vivo*.

IL-17 was discovered to be important in the development of liver fibrosis in mice (111). It was reported that IL-17 was strongly associated with an improved prognosis in patients with CHC (112). Thus, IL-17 may be a therapeutic target for the treatment of fibrosis. IL-17 regulates fibrosis through two separate mechanisms. First, IL-17 stimulates macrophages to express the inflammatory cytokines IL-6, IL-1β and TNF-α, as well as the major fibrogenic cytokine, TGF-β1 (113). Additionally, IL-17 directly stimulates HSCs to express type I collagen and promotes their activation, and MFBs were discovered to be formed through the STAT3 signaling pathway during the fibrosis of HSCs (114-116).

IL-20, a proinflammatory cytokine in the IL-10 cytokine family, reportedly activates qHSCs and upregulates TGF-β expression levels (117,118). In a mouse model of cell injury induced by CCL4, the use of antibodies to neutralize IL-20 or IL-20 receptors inhibited HSC activation and liver fibrosis, and downregulated TGF-β production (119).

IL-22 is also a member of the IL-10 cytokine family that activates the STAT3 signaling pathway in hepatocytes, which has been illustrated to promote the development of HCC (120). IL-22 simultaneously expresses IL-10 receptor 2 and IL-22

receptor 1, both of which were identified to induce the senescence of HSCs, thereby improving liver fibrosis (121). Previous studies have revealed that the increase in IL-22 in the liver of mice reduced the expression of fibrosis-associated genes, and accelerated the recovery of the liver damage caused by fibrosis by increasing the number of senescent HSCs and decreasing the expression levels of α-SMA (122-124).

*Role of miRNAs in CHC infection*. miRNAs are small non-coding RNAs of ~22 nucleotides in length that regulate post-transcriptional gene expression by altering mRNA degradation (125). The abnormal expression of different miRNAs, such as miR-122, miR-126, miR-129, miR-199a and miR-155, in HCV-induced liver fibrosis and HCC has been previously reported (126). Activated HSCs were discovered to express a low number of miRNAs (n=259), of which 47 were downregulated and 212 were upregulated upon activation (127). Clinical data also revealed that miR-21 expression levels were associated with the viral load, fibrosis and serum liver transaminase levels (128). It was also identified that miR-221/222 expression levels were upregulated in the human liver, and the upregulation was dependent on the progression of fibrosis (129). In addition, the increased expression levels of miR-221/222 have also been confirmed in a mouse model of liver fibrosis (130). By contrast, antifibrotic miRNAs include miR-19 (85), miR-214 (131), miR-16 (132), miR-122 (133) and miR-150 (134), amongst others. For example, connective tissue growth factor 2 (CCN2) was discovered to drive fibrogenesis in HSCs (135), while in the fibrotic or steatotic liver, the upregulation of CCN2 was associated with the mutual downregulation of miR-214 (131). The expression levels of miR-122 were also discovered to be negatively correlated with fibrosis, liver transaminase levels and patient age in another study (134).

## 4. Indicators for the detection of CHC infection

*Serological test*. At present, the primary markers used to detect the presence of the HCV in the laboratory include HCV-Ab, HCV-cAg, HCV-RNA, and the presence of an HCV genotype and subtype (136,137). For the initial diagnosis, the most commonly used methods for detection are ELISAs and chemiluminescence immunoassays (CLIAs) for analyzing the presence of HCV-Ab in the blood, as they are relatively easy to perform and provide results quickly (138,139). However, the HCV-Ab test often provides false-positive results in patients with a chronic infectious disease (140-142). For example, it was reported that in 477 individuals with an anti-HCV response analyzed using a recombinant immunoblot assay (RIBA), 105 (22%) were confirmed as false positives (143). Thus, if a sample is reactive in the primary screening test, further tests are required to confirm this result. The additional tests usually used are RIBAs or nucleic acid amplification assays (NATs) (2,144). NATs are more specific than ELISAs or CLIAs and have a higher detection accuracy, but a shorter time window for detection (145). In addition, NATs require specific laboratory equipment and trained personnel; thus, it is difficult to perform this assay in conventional laboratories (146).

*Diagnosis of fibrosis*. Liver biopsies to measure liver fibrosis have been almost completely replaced by noninvasive methods, including the detection of biochemical markers, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), as well as scoring systems, such as the AST to platelet ratio index (APRI) score and fibrosis (FIB)-4 score (147,148). The scoring systems of APRI and FIB 4 are generally cheap and simple to use for the evaluation of liver fibrosis; however, FIB-4 and APRI have been shown to have a considerably higher rate of false-negatives or false-positives in the detection of both fibrosis and cirrhosis (20). Thus, the results should be further confirmed using more accurate tests.

*Other diagnostic methods*. Aberrant lymphocyte proliferation is a primary characteristic of CHC, with evidence of focal and bridging necrosis and lobular degeneration in the portal area (149). These lesions can be observed by pathological examination, such as hematoxylin and eosin staining and immunohistochemical staining (150). However, the pathogenesis and mechanism underlying the formation of liver lesions in the process of CHC infection has not been fully determined; therefore, it is difficult to accurately diagnose HCV infection through pathological methods (151). Other diagnostic methods, such as image-based examinations, including abdominal ultrasound examination, CT, magnetic resonance (MR) imaging or MR scans, can be used for the partial screening of liver diseases (152); however, these methods are not without their own problems. For example, regarding specificity, it is difficult to determine whether the presence of lesions was caused by the HCV infection or not and it is hard to accurately detect the course of HCV (153). A breakdown of the markers, methods and their advantages and disadvantages are described in Table I.

## 5. Conclusions

Despite numerous studies investigating the role of HSCs in different models of liver fibrosis caused by various types of disease, there remains a lack of research into the changes in the characteristics and functions of HSCs following HCV infection. At present, routine laboratory serological examinations, pathological examinations and other methods are used for the diagnosis of HCV infection; however, each technique has its limitations. For example, considering that HCV infection is a dynamic process, the serum indicators are unstable and patients with varying degrees of HCV infection and courses have differing serum marker levels. Thus, a new test is required to supplement or replace preliminary screening, particularly in patients who are diagnosed as positive, to assess the extent and status of HCV infection. HSCs are a vital immune cell population activated during HCV infection. Following an HCV infection, the expression of specific molecular markers and chemokines or the secretion of cytokines associated with HSCs are synchronously altered. At present, to the best of our knowledge, there remains a lack of studies investigating the alterations to HSC-related indicators. If the expression of one or several of the markers are discovered to be consistently altered during the course of HCV infection, they may serve as a suitable marker to assess the stage of HCV infection and they may also highlight novel avenues for understanding and eventually treating an HCV infection.

## Acknowledgements

Not applicable.

**Funding**

The present work was supported by the Peoples Liberation Army Major Project (grant no. ANJ13J001).

**Availability of data and materials**

Not applicable.

**Authors' contributions**

WW reviewed the functional characteristics of the HSCs and the role of HSCs in the process of HCV infection; XZF wrote the introduction and the conclusion. XLH and XZF corrected the grammar of the manuscript; JFL reviewed the indicators for the detection of CHC infection section; and JMY edited the figure and table in the manuscript. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**References**

1. Wiktor S: How feasible is the global elimination of HCV infection. Lancet 393: 1265-1267, 2019.
2. Spearman CW, Dusheiko GM, Hellard M and Sonderup M: Hepatitis C. Lancet 394: 1451-1466, 2019.
3. Li Y, Zhao L, Geng N, Zhu W, Liu H and Bai H: Prevalence and characteristics of hepatitis C virus infection in Shenyang City, Northeast China, and prediction of HCV RNA positivity according to serum anti-HCV level: Retrospective review of hospital data. Virol J 17: 36, 2020.
4. Lee MH, Yang HI, Yuan Y, L'Italien G and Chen CJ: Epidemiology and natural history of hepatitis C virus infection. World J Gastroenterol 20: 9270-9280, 2014.
5. Martinello M, Hajarizadeh B, Grebely J, Dore GJ and Matthews GV: Management of acute HCV infection in the era of direct-acting antiviral therapy. Nat Rev Gastroenterol Hepatol 15: 412-424, 2018.
6. Toyoda H, Kumada T, Tada T, Mizuno K, Sone Y, Akita T, Tanaka J and Johnson PJ: The impact of HCV eradication by direct-acting antivirals on the transition of precancerous hepatic nodules to HCC: A prospective observational study. Liver Int 39: 448-454, 2019.
7. Shiffman ML and Benhamou Y: Cure of HCV related liver disease. Liver Int 35 (Suppl 1): S71-S77, 2015.
8. Owusu Sekyere S, Schlevogt B, Mettke F, Kabbani M, Deterding K, Wirth TC, Vogel A, Manns MP, Falk CS, Cornberg M and Wedemeyer H: HCC immune surveillance and antiviral therapy of hepatitis C virus infection. Liver Cancer 8: 41-65, 2019.
9. Lin MV, King LY and Chung RT: Hepatitis C virus-associated cancer. Annu Rev Pathol 10: 345-370, 2015.
10. Wang Y, Li J, Wang X, Sang M and Ho W: Hepatic stellate cells, liver innate immunity, and hepatitis C virus. J Gastroenterol Hepatol 28 (Suppl 1): S112-S115, 2013.
11. Kocabayoglu P, Lade A, Lee YA, Dragomir AC, Sun X, Fiel MI, Thung S, Aloman C, Soriano P, Hoshida Y and Friedman SL: β-PDGF receptor expressed by hepatic stellate cells regulates fibrosis in murine liver injury, but not carcinogenesis. J Hepatol 63: 141-147, 2015.
12. Cheng JC, Tseng CP, Liao MH, Peng CY, Yu JS, Chuang PH, Huang JT and Chen JJW: Activation of hepatic stellate cells by the ubiquitin C-terminal hydrolase 1 protein secreted from hepatitis C virus-infected hepatocytes. Sci Rep 7: 4448, 2017.
13. Gieseler RK, Marquitan G, Schlattjan M, Sowa JP, Bechmann LP, Timm J, Roggendorf M, Gerken G, Friedman SL and Canbay A: Hepatocyte apoptotic bodies encasing nonstructural HCV proteins amplify hepatic stellate cell activation: Implications for chronic hepatitis C. J Viral Hepat 18: 760-767, 2011.
14. Saeed A, Baloch K, Brown RJ, Wallis R, Chen L, Dexter L, McClure CP, Shakesheff K and Thomson BJ: Mannan binding lectin-associated serine protease 1 is induced by hepatitis C virus infection and activates human hepatic stellate cells. Clin Exp Immunol 174: 265-273, 2013.
15. El-Ahwany E, Nagy F, Zoheiry M, Shemis M, Nosseir M, Taleb HA, El Ghannam M, Atta R and Zada S: Circulating miRNAs as predictor markers for activation of hepatic stellate cells and progression of HCV-induced liver fibrosis. Electron Physician 8: 1804-1810, 2016.
16. Munsterman ID, Kendall TJ, Khelil N, Popa M, Lomme R, Drenth JPH and Tjwa ETTL: Extracellular matrix components indicate remodelling activity in different fibrosis stages of human non-alcoholic fatty liver disease. Histopathology 73: 612-621, 2018.
17. Warkad SD, Nimse SB, Song KS and Kim T: HCV detection, discrimination and genotyping technologies. Sensors (Basel) 18: 3423, 2018.
18. Vanhommerig JW, van de Laar TJ, Koot M, van Rooijen MS, Schinkel J, Speksnijder AG, Prins M, de Vries HJ and Bruisten SM: Evaluation of a hepatitis C virus (HCV) antigen assay for routine HCV screening among men who have sex with men infected with HIV. J Virol Methods 213: 147-150, 2015.
19. Laperche S, Le Marrec N, Girault A, Bouchardeau F, Servant-Delmas A, Maniez-Montreuil M, Gallian P, Levayer T, Morel P and Simon N: Simultaneous detection of hepatitis C virus (HCV) core antigen and anti-HCV antibodies improves the early detection of HCV infection. J Clin Microbiol 43: 3877-3883, 2005.
20. Mazzola G, Adamoli L, Calvaruso V, Macaluso FS, Colletti P, Mazzola S, Cervo A, Trizzino M, Di Lorenzo F, Iaria C, *et al*: Suboptimal performance of APRI and FIB-4 in ruling out significant fibrosis and confirming cirrhosis in HIV/HCV co-infected and HCV mono-infected patients. Infection 47: 409-415, 2019.
21. Sakiani S, Koh C and Heller T: Understanding the presence of false-positive antibodies in acute hepatitis. J Infect Dis 210: 1886-1889, 2014.
22. Chida T, Ito M, Nakashima K, Kanegae Y, Aoshima T, Takabayashi S, Kawata K, Nakagawa Y, Yamamoto M, Shimano H, *et al*: Critical role of CREBH-mediated induction of transforming growth factor β 2 by hepatitis C virus infection in fibrogenic responses in hepatic stellate cells. Hepatology 66: 1430-1443, 2017.
23. Wake K: 'Sternzellen' in the liver: Perisinuosoidal cells with special reference to storage of vitamin A. Am J Anat 132: 429-462, 1971.
24. No authors listed: Hepatic stellate cell nomenclature. Hepatology 23: 193, 1996.
25. Zhao W, Zhang L, Yin Z, Su W, Ren G, Zhou C, You J, Fan J and Wang X: Activated hepatic stellate cells promote hepatocellular carcinoma development in immunocompetent mice. Int J Cancer 129: 2651-2661, 2011.
26. Higashi T, Friedman SL and Hoshida Y: Hepatic stellate cells as key target in liver fibrosis. Adv Drug Deliv Rev 121: 27-42, 2017.
27. Zhao W, Zhang L, Xu Y, Zhang Z, Ren G, Tang K, Kuang P, Zhao B, Yin Z and Wang X: Hepatic stellate cells promote tumor progression by enhancement of immunosuppressive cells in an orthotopic liver tumor mouse model. Lab Invest 94: 182-191, 2014.
28. Zhou CL, Kong DL, Liu JF, Lu ZK, Guo HF, Wang W, Qiu JF, Liu XJ and Wang Y: MHC II$^-$, but not MHC II$^+$, hepatic stellate cells contribute to liver fibrosis of mice in infection with schistosoma japonicum. Biochim Biophys Acta Mol Basis Dis 1863: 1848-1857, 2017.
29. Najar M, Fayyad-Kazan H, Faour WH, El Taghdouini A, Raicevic G, van Grunsven LA, Najimi M, Sokal E and Lagneaux L: Immuno-biological comparison of hepatic stellate cells in a reverted and activated state. Biomed Pharmacother 98: 52-62, 2018.
30. Bansal MB: Hepatic stellate cells: Fibrogenic, regenerative or both? Heterogeneity and context are key. Hepatol Int 10: 902-908, 2016.

31. Lee UE and Friedman SL: Mechanisms of hepatic fibrogenesis. Best Pract Res Clin Gastroenterol 25: 195-206, 2011.
32. Li H, Lan J, Han C, Guo K, Wang G, Hu J, Gong J, Luo X and Cao Z: Brg1 promotes liver fibrosis via activation of hepatic stellate cells. Exp Cell Res 364: 191-197, 2018.
33. Senoo H, Mezaki Y and Fujiwara M: The stellate cell system (vitamin A-storing cell system). Anat Sci Int 92: 387-455, 2017.
34. Senoo H, Kojima N and Sato M: Vitamin A-storing cells (stellate cells). Vitam Horm 75: 131-159, 2007.
35. Bi Y, Mukhopadhyay D, Drinane M, Ji B, Li X, Cao S and Shah VH: Endocytosis of collagen by hepatic stellate cells regulates extracellular matrix dynamics. Am J Physiol Cell Physiol 307: C622-C633, 2014.
36. Chen Y, Ou Y, Dong J, Yang G, Zeng Z, Liu Y, Liu B, Li W, He X and Lan T: Osteopontin promotes collagen I synthesis in hepatic stellate cells by miRNA-129-5p inhibition. Exp Cell Res 362: 343-348, 2018.
37. Wang C, Yang S, Huang J, Chen S, Li Y and Li Q: Activation of corticotropin releasing factor receptors up regulates collagen production by hepatic stellate cells via promoting p300 expression. Biol Chem 397: 437-444, 2016.
38. Testino G, Leone S, Fagoonee S and Pellicano R: Alcoholic liver fibrosis: Detection and treatment. Minerva Med 109: 457-471, 2018.
39. Malagnino V, Bottero J, Miailhes P, Lascoux-Combe C, Girard PM, Zoulim F, Lacombe K and Boyd A: Hepatitis B virus genotype G and liver fibrosis progression in chronic hepatitis B and human immunodeficiency virus coinfection. J Med Virol 91: 630-641, 2019.
40. Chung SI, Moon H, Ju HL, Cho KJ, Kim DY, Han KH, Eun JW, Nam SW, Ribback S, Dombrowski F, *et al*: Hepatic expression of sonic hedgehog induces liver fibrosis and promotes hepatocarcinogenesis in a transgenic mouse model. J Hepatol 64: 618-627, 2016.
41. Tsuchida T and Friedman SL: Mechanisms of hepatic stellate cell activation. Nat Rev Gastroenterol Hepatol 14: 397-411, 2017.
42. Pradere JP, Kluwe J, De Minicis S, Jiao JJ, Gwak GY, Dapito DH, Jang MK, Guenther ND, Mederacke I, Friedman R, *et al*: Hepatic macrophages but not dendritic cells contribute to liver fibrosis by promoting the survival of activated hepatic stellate cells in mice. Hepatology 58: 1461-1473, 2013.
43. Jin H, Jia Y, Yao Z, Huang J, Hao M, Yao S, Lian N, Zhang F, Zhang C, Chen X, *et al*: Hepatic stellate cell interferes with NK cell regulation of fibrogenesis via curcumin induced senescence of hepatic stellate cell. Cell Signal 33: 79-85, 2017.
44. Li X, Su Y, Hua X, Xie C, Liu J, Huang Y, Zhou L, Zhang M, Li X and Gao Z: Levels of hepatic Th17 cells and regulatory T cells upregulated by hepatic stellate cells in advanced HBV-related liver fibrosis. J Transl Med 15: 75, 2017.
45. Corpechot C, Barbu V, Wendum D, Kinnman N, Rey C, Poupon R, Housset C and Rosmorduc O: Hypoxia-induced VEGF and collagen I expressions are associated with angiogenesis and fibrogenesis in experimental cirrhosis. Hepatology 35: 1010-1021, 2002.
46. Hong IH, Park SJ, Goo MJ, Lee HR, Park JK, Ki MR, Kim SH, Lee EM, Kim AY and Jeong KS: JNK1 and JNK2 regulate α-SMA in hepatic stellate cells during CCl4-induced fibrosis in the rat liver. Pathol Int 63: 483-491, 2013.
47. Giannandrea M and Parks WC: Diverse functions of matrix metalloproteinases during fibrosis. Dis Model Mech 7: 193-203, 2014.
48. Holm Nielsen S, Willumsen N, Leeming DJ, Daniels SJ, Brix S, Karsdal MA, Genovese F and Nielsen MJ: Serological assessment of activated fibroblasts by alpha-smooth muscle actin (α-SMA): A noninvasive biomarker of activated fibroblasts in lung disorders. Transl Oncol 12: 368-374, 2019.
49. Elzamly S, Agina HA, Elbalshy AE, Abuhashim M, Saad E and Abd Elmageed ZY: Integration of VEGF and α-SMA expression improves the prediction accuracy of fibrosis in chronic hepatitis C liver biopsy. Appl Immunohistochem Mol Morphol 25: 261-270, 2017.
50. Stefanovic L and Stefanovic B: Role of cytokine receptor-like factor 1 in hepatic stellate cells and fibrosis. World J Hepatol 4: 356-364, 2012.
51. Latoche JD, Ufelle AC, Fazzi F, Ganguly K, Leikauf GD and Fattman CL: Secreted phosphoprotein 1 and sex-specific differences in silica-induced pulmonary fibrosis in mice. Environ Health Perspect 124: 1199-1207, 2016.
52. Kumar P, Smith T, Raeman R, Chopyk DM, Brink H, Liu Y, Sulchek T and Anania FA: Periostin promotes liver fibrogenesis by activating lysyl oxidase in hepatic stellate cells. J Biol Chem 293: 12781-12792, 2018.
53. Dongiovanni P, Meroni M, Baselli GA, Bassani GA, Rametta R, Pietrelli A, Maggioni M, Facciotti F, Trunzo V, Badiali S, *et al*: Insulin resistance promotes lysyl oxidase like 2 induction and fibrosis accumulation in non-alcoholic fatty liver disease. Clin Sci (Lond) 131: 1301-1315, 2017.
54. Zhang SC, Zheng YH, Yu PP, Min TH, Yu FX, Ye C, Xie YK and Zhang QY: Lentiviral vector-mediated down-regulation of IL-17A receptor in hepatic stellate cells results in decreased secretion of IL-6. World J Gastroenterol 18: 3696-3704, 2012.
55. Ehling J and Tacke F: Role of chemokine pathways in hepatobiliary cancer. Cancer Lett 379: 173-183, 2016.
56. Kim BM, Abdelfattah AM, Vasan R, Fuchs BC and Choi MY: Hepatic stellate cells secrete Ccl5 to induce hepatocyte steatosis. Sci Rep 8: 7499, 2018.
57. Li Z, Zhang Q, Zhang Q, Xu M, Qu Y, Cai X and Lu L: CXCL6 promotes human hepatocyte proliferation through the CXCR1-NFkB pathway and inhibits collagen I secretion by hepatic stellate cells. Biochem Cell Biol 94: 229-235, 2016.
58. Puche JE, Saiman Y and Friedman SL: Hepatic stellate cells and liver fibrosis. Compr Physiol 3: 1473-1492, 2013.
59. Ma PF, Gao CC, Yi J, Zhao JL, Liang SQ, Zhao Y, Ye YC, Bai J, Zheng QJ, Dou KF, *et al*: Cytotherapy with M1-polarized macrophages ameliorates liver fibrosis by modulating immune microenvironment in mice. J Hepatol 67: 770-779, 2017.
60. Sasaki R, Devhare PB, Steele R, Ray R and Ray RB: Hepatitis C virus-induced CCL5 secretion from macrophages activates hepatic stellate cells. Hepatology 66: 746-757, 2017.
61. Höchst B, Schildberg FA, Sauerborn P, Gäbel YA, Gevensleben H, Goltz D, Heukamp LC, Türler A, Ballmaier M, Gieseke F, *et al*: Activated human hepatic stellate cells induce myeloid derived suppressor cells from peripheral blood monocytes in a CD44-dependent fashion. J Hepatol 59: 528-535, 2013.
62. Wang B, Trippler M, Pei R, Lu M, Broering R, Gerken G and Schlaak JF: Toll-like receptor activated human and murine hepatic stellate cells are potent regulators of hepatitis C virus replication. J Hepatol 51: 1037-1045, 2009.
63. Jeong WI, Park O, Suh YG, Byun JS, Park SY, Choi E, Kim JK, Ko H, Wang H, Miller AM and Gao B: Suppression of innate immunity (natural killer cell/interferon-γ) in the advanced stages of liver fibrosis in mice. Hepatology 53: 1342-1351, 2011.
64. Radaeva S, Wang L, Radaev S, Jeong WI, Park O and Gao B: Retinoic acid signaling sensitizes hepatic stellate cells to NK cell killing via upregulation of NK cell activating ligand RAE1. Am J Physiol Gastrointest Liver Physiol 293: G809-G816, 2007.
65. Langhans B, Alwan AW, Krämer B, Glässner A, Lutz P, Strassburg CP, Nattermann J and Spengler U: Regulatory $CD4^+$T cells modulate the interaction between NK cells and hepatic stellate cells by acting on either cell type. J Hepatol 62: 398-404, 2015.
66. Li Y, Lu L, Qian S, Fung JJ and Lin F: Hepatic stellate cells directly inhibit B cells via programmed death-ligand 1. J Immunol 196: 1617-1625, 2016.
67. Bedossa P and Paradis V: Approaches for treatment of liver fibrosis in chronic hepatitis C. Clin Liver Dis 7: 195-210, 2003.
68. Ignat SR, Dinescu S, Hermenean A and Costache M: Cellular interplay as a consequence of inflammatory signals leading to liver fibrosis development. Cells 9: 461, 2020.
69. Shahin K, Hosseini SY, Jamali H, Karimi MH, Azarpira N and Zeraatian M: The enhancing impact of amino termini of hepatitis C virus core protein on activation of hepatic stellate cells. Gastroenterol Hepatol Bed Bench 13: 57-63, 2020.
70. Wang L, Wang Y and Quan J: Exosomes derived from natural killer cells inhibit hepatic stellate cell activation and liver fibrosis. Hum Cell 33: 582-589, 2020.
71. Cai B, Dongiovanni P, Corey KE, Wang X, Shmarakov IO, Zheng Z, Kasikara C, Davra V, Meroni M, Chung RT, *et al*: Macrophage MerTK promotes liver fibrosis in nonalcoholic steatohepatitis. Cell Metab 31: 406-421, 2020.
72. Tsukamoto H: Cytokine regulation of hepatic stellate cells in liver fibrosis. Alcohol Clin Exp Res 23: 911-916, 1999.
73. Wang S, Li M, Zhao X, Wang H, Zhu J, Wang C, Zhou M, Dong H and Zhou R: Upregulation of KSRP by miR-27b attenuates schistosomiasis-induced hepatic fibrosis by targeting TGF-β1. FASEB J 34: 4120-4133, 2020.
74. Huang JL, Fu YP, Gan W, Liu G, Zhou PY, Zhou C, Sun BY, Guan RY, Zhou J, Fan J, *et al*: Hepatic stellate cells promote the progression of hepatocellular carcinoma through microRNA-1246-RORα-Wnt/β-Catenin axis. Cancer Lett 476: 140-151, 2020.

75. Winkler I, Bitter C, Winkler S, Weichenhan D, Thavamani A, Hengstler JG, Borkham-Kamphorst E, Kohlbacher O, Plass C, Geffers R, *et al*: Identification of Pparγ-modulated miRNA hubs that target the fibrotic tumor microenvironment. Proc Natl Acad Sci USA 117: 454-463, 2020.
76. Dawood RM, El-Meguid MA, Ibrahim MK, Bader El Din NG, Barakat A, El-Wakeel K, Alla MDAA, Wu GY and El Awady MK: Dysregulation of fibrosis related genes in HCV induced liver disease. Gene 664: 58-69, 2018.
77. Chouteau P, Defer N, Florimond A, Caldéraro J, Higgs M, Gaudin A, Mérour E, Dhumeaux D, Lerat H and Pawlotsky JM: Hepatitis C virus (HCV) protein expression enhances hepatic fibrosis in HCV transgenic mice exposed to a fibrogenic agent. J Hepatol 57: 499-507, 2012.
78. Mazzocca A, Sciammetta SC, Carloni V, Cosmi L, Annunziato F, Harada T, Abrignani S and Pinzani M: Binding of hepatitis C virus envelope protein E2 to CD81 up-regulates matrix metalloproteinase-2 in human hepatic stellate cells. J Biol Chem 280: 11329-11339, 2005.
79. Bataller R, Paik YH, Lindquist JN, Lemasters JJ and Brenner DA: Hepatitis C virus core and nonstructural proteins induce fibrogenic effects in hepatic stellate cells. Gastroenterology 126: 529-540, 2004.
80. Coenen M, Nischalke HD, Krämer B, Langhans B, Glässner A, Schulte D, Körner C, Sauerbruch T, Nattermann J and Spengler U: Hepatitis C virus core protein induces fibrogenic actions of hepatic stellate cells via toll-like receptor 2. Lab Invest 91: 1375-1382, 2011.
81. Charrier A, Chen R, Chen L, Kemper S, Hattori T, Takigawa M and Brigstock DR: Exosomes mediate intercellular transfer of pro-fibrogenic connective tissue growth factor (CCN2) between hepatic stellate cells, the principal fibrotic cells in the liver. Surgery 156: 548-555, 2014.
82. Li M, Jiang M, Meng J and Tao L: Exosomes: Carriers of pro-fibrotic signals and therapeutic targets in fibrosis. Curr Pharm Des 25: 4496-4509, 2019.
83. Kim JH, Lee CH and Lee SW: Exosomal transmission of MicroRNA from HCV replicating cells stimulates transdifferentiation in hepatic stellate cells. Mol Ther Nucleic Acids 14: 483-497, 2019.
84. Khatun M and Ray RB: Mechanisms underlying hepatitis C virus-associated hepatic fibrosis. Cells 8: 1249, 2019.
85. Devhare PB, Sasaki R, Shrivastava S, Di Bisceglie AM, Ray R and Ray RB: Exosome-mediated intercellular communication between hepatitis C virus-infected hepatocytes and hepatic stellate cells. J Virol 91: e02225-e02216, 2017.
86. Njiomegnie GF, Read SA, Fewings N, George J, McKay F and Ahlenstiel G: Immunomodulation of the natural killer cell phenotype and response during HCV infection. J Clin Med 9: 1030, 2020.
87. Glässner A, Eisenhardt M, Krämer B, Körner C, Coenen M, Sauerbruch T, Spengler U and Nattermann J: NK cells from HCV-infected patients effectively induce apoptosis of activated primary human hepatic stellate cells in a TRAIL-, FasL- and NKG2D-dependent manner. Lab Invest 92: 967-977, 2012.
88. Wang H and Yin S: Natural killer T cells in liver injury, inflammation and cancer. Expert Rev Gastroenterol Hepatol 9: 1077-1085, 2015.
89. de Lalla C, Galli G, Aldrighetti L, Romeo R, Mariani M, Monno A, Nuti S, Colombo M, Callea F, Porcelli SA, *et al*: Production of profibrotic cytokines by invariant NKT cells characterizes cirrhosis progression in chronic viral hepatitis. J Immunol 173: 1417-1425, 2004.
90. Locati M, Curtale G and Mantovani A: Diversity, mechanisms, and significance of macrophage plasticity. Annu Rev Pathol 15: 123-147, 2020.
91. Suzuki K, Meguro K, Nakagomi D and Nakajima H: Roles of alternatively activated M2 macrophages in allergic contact dermatitis. Allergol Int 66: 392-397, 2017.
92. Brass A and Brenndörfer ED: The role of chemokines in hepatitis C virus-mediated liver disease. Int J Mol Sci 15: 4747-4779, 2014.
93. Wasmuth HE and Weiskirchen R: Pathogenesis of liver fibrosis: Modulation of stellate cells by chemokines. Z Gastroenterol 48: 38-45, 2010 (In German).
94. Liang YJ, Luo J, Lu Q, Zhou Y, Wu HW, Zheng D, Ren YY, Sun KY, Wang Y and Zhang ZS: Gene profile of chemokines on hepatic stellate cells of schistosome-infected mice and antifibrotic roles of CXCL9/10 on liver non-parenchymal cells. PLoS One 7: e42490, 2012.
95. Marra F and Tacke F: Roles for chemokines in liver disease. Gastroenterology 147: 577-594, 2014.
96. Tan HX, Gong WZ, Zhou K, Xiao ZG, Hou FT, Huang T, Zhang L, Dong HY, Zhang WL, Liu Y and Huang ZC: CXCR4/TGF-β1 mediated hepatic stellate cells differentiation into carcinoma-associated fibroblasts and promoted liver metastasis of colon cancer. Cancer Biol Ther 21: 258-268, 2020.
97. Ferrari SM, Fallahi P, Ruffilli I, Elia G, Ragusa F, Paparo SR, Patrizio A, Mazzi V, Colaci M, Giuggioli D, *et al*: Immunomodulation of CXCL10 secretion by hepatitis C virus: Could CXCL10 Be a prognostic marker of chronic hepatitis C? J Immunol Res 2019: 5878960, 2019.
98. Pineda-Tenor D, Berenguer J, Jiménez-Sousa MA, Guzmán-Fulgencio M, Aldámiz-Echevarria T, Carrero A, García-Álvarez M, Diez C, Tejerina F, Briz V and Resino S: CXCL9, CXCL10 and CXCL11 polymorphisms are associated with sustained virologic response in HIV/HCV-coinfected patients. J Clin Virol 61: 423-429, 2014.
99. Liu Y, Chen L, Zou Z, Zhu B, Hu Z, Zeng P, Wu L and Xiong J: Hepatitis C virus infection induces elevation of CXCL10 in human brain microvascular endothelial cells. J Med Virol 88: 1596-1603, 2016.
100. Zeremski M, Dimova R, Astemborski J, Thomas DL and Talal AH: CXCL9 and CXCL10 chemokines as predictors of liver fibrosis in a cohort of primarily African-American injection drug users with chronic hepatitis C. J Infect Dis 204: 832-836, 2011.
101. Sahin H, Borkham-Kamphorst E, Kuppe C, Zaldivar MM, Grouls C, Al-samman M, Nellen A, Schmitz P, Heinrichs D, Berres ML, *et al*: Chemokine Cxcl9 attenuates liver fibrosis-associated angiogenesis in mice. Hepatology 55: 1610-1619, 2012.
102. Joshi D, Carey I, Foxton M, Al-Freah M, Bruce M, Heaton N, Quaglia A, O'Grady J, Aluvihare V and Agarwal K: CXCL10 levels identify individuals with rapid fibrosis at 12 months post-transplant for hepatitis C virus and predict treatment response. Clin Transplant 28: 569-578, 2014.
103. Gorin JB, Malone DFG, Strunz B, Carlsson T, Aleman S, Björkström NK, Falconer K and Sandberg JK: Plasma FABP4 is associated with liver disease recovery during treatment-induced clearance of chronic HCV infection. Sci Rep 10: 2081, 2020.
104. Lu Y, Lin LY, Tan JG, Deng HP, Li XH, Zhang Z, Li Y, Zhou Z, Xu X, Xie X and Mei SJ: A correlation study between gene polymorphism of Th cell expressed chemokine receptor CXCR3 and its ligand levels with HCV infection prognosis. Eur Rev Med Pharmacol Sci 21: 1290-1295, 2017.
105. Berres ML, Asmacher S, Lehmann J, Jansen C, Görtzen J, Klein S, Meyer C, Strunk HM, Fimmers R, Tacke F, *et al*: CXCL9 is a prognostic marker in patients with liver cirrhosis receiving transjugular intrahepatic portosystemic shunt. J Hepatol 62: 332-339, 2015.
106. Chalin A, Lefevre B, Devisme C, Barget N, Amiot L and Samson M: Circulating levels of CXCL11 and CXCL12 are biomarkers of cirrhosis in patients with chronic hepatitis C infection. Cytokine 117: 72-78, 2019.
107. Patidar M, Yadav N and Dalai SK: Interleukin 15: A key cytokine for immunotherapy. Cytokine Growth Factor Rev 31: 49-59, 2016.
108. Jiao J, Ooka K, Fey H, Fiel MI, Rahmman AH, Kojima K, Hoshida Y, Chen X, de Paula T, Vetter D, *et al*: Interleukin-15 receptor α on hepatic stellate cells regulates hepatic fibrogenesis in mice. J Hepatol 65: 344-353, 2016.
109. Golden-Mason L, Kelly AM, Doherty DG, Traynor O, McEntee G, Kelly J, Hegarty JE and O'Farrelly C: Hepatic interleuklin 15 (IL-15) expression: Implications for local NK/NKT cell homeostasis and development. Clin Exp Immunol 138: 94-101, 2004.
110. Vahedi F, Lee AJ, Collins SE, Chew MV, Lusty E, Chen B, Dubey A, Richards CD, Feld JJ, Russell RS, *et al*: IL-15 and IFN-γ signal through the ERK pathway to inhibit HCV replication, independent of type I IFN signaling. Cytokine 124: 154439, 2019.
111. Isailovic N, Daigo K, Mantovani A and Selmi C: Interleukin-17 and innate immunity in infections and chronic inflammation. J Autoimmun 60: 1-11, 2015.
112. Abou El-Khier NT, Elhammady D, Arafa MM, Shahin D, Eladl E, Abousamra NK, Sharaf-Eldeen O, Shaker G and Esmael ME: Th17 and IL-17 as predictors of hepatic inflammation in patients with chronic hepatitis C virus infection and treated with direct antiviral therapy. Egypt J Immunol 25: 61-74, 2018.
113. Gu Y, Hu X, Liu C, Qv X and Xu C: Interleukin (IL)-17 promotes macrophages to produce IL-8, IL-6 and tumour necrosis factor-alpha in aplastic anaemia. Br J Haematol 142: 109-114, 2008.

114. Zhang Y, Huang D, Gao W, Yan J, Zhou W, Hou X, Liu M, Ren C, Wang S and Shen J: Lack of IL-17 signaling decreases liver fibrosis in murine schistosomiasis japonica. Int Immunol 27: 317-325, 2015.
115. Amara S, Lopez K, Banan B, Brown SK, Whalen M, Myles E, Ivy MT, Johnson T, Schey KL and Tiriveedhi V: Synergistic effect of pro-inflammatory TNFα and IL-17 in periostin mediated collagen deposition: Potential role in liver fibrosis. Mol Immunol 64: 26-35, 2015.
116. Elkhawaga AA, Hosni A, Zaky DZ, Kamel AA, Mohamed NA, Abozaid MA and El-Masry MA: Association of treg and TH17 cytokines with HCV pathogenesis and liver pathology. Egypt J Immunol 26: 55-63, 2019.
117. Zhang LJ, Yu JP, Li D, Huang YH, Chen ZX and Wang XZ: Effects of cytokines on carbon tetrachloride-induced hepatic fibrogenesis in rats. World J Gastroenterol 10: 77-81, 2004.
118. Niess JH and Francés R: Editorial: The IL-20 cytokines and related family members in immunity and diseases. Front Immunol 10: 1976, 2019.
119. Chiu YS, Wei CC, Lin YJ, Hsu YH and Chang MS: IL-20 and IL-20R1 antibodies protect against liver fibrosis. Hepatology 60: 1003-1014, 2014.
120. Rutz S, Eidenschenk C and Ouyang W: IL-22, not simply a Th17 cytokine. Immunol Rev 252: 116-132, 2013.
121. Kronenberger B, Rudloff I, Bachmann M, Brunner F, Kapper L, Filmann N, Waidmann O, Herrmann E, Pfeilschifter J, Zeuzem S, *et al*: Interleukin-22 predicts severity and death in advanced liver cirrhosis: A prospective cohort study. BMC Med 10: 102, 2012.
122. Sertorio M, Hou X, Carmo RF, Dessein H, Cabantous S, Abdelwahed M, Romano A, Albuquerque F, Vasconcelos L, Carmo T, *et al*: IL-22 and IL-22 binding protein (IL-22BP) regulate fibrosis and cirrhosis in hepatitis C virus and schistosome infections. Hepatology 61: 1321-1331, 2015.
123. Kong X, Feng D, Wang H, Hong F, Bertola A, Wang FS and Gao B: Interleukin-22 induces hepatic stellate cell senescence and restricts liver fibrosis in mice. Hepatology 56: 1150-1159, 2012.
124. Lu DH, Guo XY, Qin SY, Luo W, Huang XL, Chen M, Wang JX, Ma SJ, Yang XW and Jiang HX: Interleukin-22 ameliorates liver fibrogenesis by attenuating hepatic stellate cell activation and downregulating the levels of inflammatory cytokines. World J Gastroenterol 21: 1531-1545, 2015.
125. Zhao Z, Lin CY and Cheng K: siRNA- and miRNA-based therapeutics for liver fibrosis. Transl Res 214: 17-29, 2019.
126. Shaker OG and Senousy MA: Serum microRNAs as predictors for liver fibrosis staging in hepatitis C virus-associated chronic liver disease patients. J Viral Hepat 24: 636-644, 2017.
127. Coll M, El Taghdouini A, Perea L, Mannaerts I, Vila-Casadesús M, Blaya D, Rodrigo-Torres D, Affò S, Morales-Ibanez O, Graupera I, *et al*: Integrative miRNA and gene expression profiling analysis of human quiescent hepatic stellate cells. Sci Rep 5: 11549, 2015.
128. Marquez RT, Bandyopadhyay S, Wendlandt EB, Keck K, Hoffer BA, Icardi MS, Christensen RN, Schmidt WN and McCaffrey AP: Correlation between microRNA expression levels and clinical parameters associated with chronic hepatitis C viral infection in humans. Lab Invest 90: 1727-1736, 2010.
129. Appourchaux K, Dokmak S, Resche-Rigon M, Treton X, Lapalus M, Gattolliat CH, Porchet E, Martinot-Peignoux M, Boyer N, Vidaud M, *et al*: MicroRNA-based diagnostic tools for advanced fibrosis and cirrhosis in patients with chronic hepatitis B and C. Sci Rep 6: 34935, 2016.
130. Ogawa T, Enomoto M, Fujii H, Sekiya Y, Yoshizato K, Ikeda K and Kawada N: MicroRNA-221/222 upregulation indicates the activation of stellate cells and the progression of liver fibrosis. Gut 61: 1600-1609, 2012.
131. Chen L, Charrier A, Zhou Y, Chen R, Yu B, Agarwal K, Tsukamoto H, Lee LJ, Paulaitis ME and Brigstock DR: Epigenetic regulation of connective tissue growth factor by MicroRNA-214 delivery in exosomes from mouse or human hepatic stellate cells. Hepatology 59: 1118-1129, 2014.
132. Guo CJ, Pan Q, Li DG, Sun H and Liu BW: miR-15b and miR-16 are implicated in activation of the rat hepatic stellate cell: An essential role for apoptosis. J Hepatol 50: 766-778, 2009.
133. Li J, Ghazwani M, Zhang Y, Lu J, Li J, Fan J, Gandhi CR and Li S: miR-122 regulates collagen production via targeting hepatic stellate cells and suppressing P4HA1 expression. J Hepatol 58: 522-528, 2013.
134. Zheng J, Lin Z, Dong P, Lu Z, Gao S, Chen X, Wu C and Yu F: Activation of hepatic stellate cells is suppressed by microRNA-150. Int J Mol Med 32: 17-24, 2013.
135. Leask A: CCN2/decorin interactions: A novel approach to combating fibrosis? J Cell Commun Signal 5: 249-250, 2011.
136. Yue ZH, Xia CS and Wang H: Performance evaluation of the mindray anti-HCV assay for the detection of hepatitis C virus infection. J Clin Lab Anal 32: e22600, 2018.
137. Wasitthankasem R, Vongpunsawad S, Siripon N, Suya C, Chulothok P, Chaiear K, Rujirojindakul P, Kanjana S, Theamboonlers A, Tangkijvanich P and Poovorawan Y: Genotypic distribution of hepatitis C virus in Thailand and Southeast Asia. PLoS One 10: e0126764, 2015.
138. He J, Xiu B, Wang G, Chen K, Feng X, Song X, Zhu C, Ling S and Zhang H: Double-antigen sandwich ELISA for the detection of anti-hepatitis C virus antibodies. J Virol Methods 171: 163-168, 2011.
139. Kim S, Kim JH, Yoon S, Park YH and Kim HS: Clinical performance evaluation of four automated chemiluminescence immunoassays for hepatitis C virus antibody detection. J Clin Microbiol 46: 3919-3923, 2008.
140. Heinrichs A, Antoine M, Steensels D, Montesinos I and Delforge ML: HCV false positive immunoassays in patients with LVAD: A potential trap! J Clin Virol 78: 44-46, 2016.
141. Ali A and Lal A: False positivity of serological tests for hepatitis C virus. J Ayub Med Coll Abbottabad 22: 43-45, 2010.
142. Vo MT, Bruhn R, Kaidarova Z, Custer BS, Murphy EL and Bloch EM: A retrospective analysis of false-positive infectious screening results in blood donors. Transfusion 56: 457-465, 2016.
143. Moorman AC, Drobenuic J and Kamili S: Prevalence of false-positive hepatitis C antibody results, national health and nutrition examination study (NHANES) 2007-2012. J Clin Virol 89: 1-4, 2017.
144. Scott JD and Gretch DR: Molecular diagnostics of hepatitis C virus infection: A systematic review. JAMA 297: 724-732, 2007.
145. Safic Stanic H, Babic I, Maslovic M, Dogic V, Bingulac-Popovic J, Miletic M, Jurakovic-Loncar N, Vuk T, Strauss-Patko M and Jukic I: Three-year experience in NAT screening of blood donors for transfusion transmitted viruses in croatia. Transfus Med Hemother 44: 415-420, 2017.
146. Bustin SA: Quantification of mRNA using real-time reverse transcription PCR (RT-PCR): Trends and problems. J Mol Endocrinol 29: 23-39: 2002.
147. Papadopoulos N, Vasileiadi S, Papavdi M, Sveroni E, Antonakaki P, Dellaporta E, Koutli E, Michalea S, Manolakopoulos S, Koskinas J and Deutsch M: Liver fibrosis staging with combination of APRI and FIB-4 scoring systems in chronic hepatitis C as an alternative to transient elastography. Ann Gastroenterol 32: 498-503, 2019.
148. Kim WR, Berg T, Asselah T, Flisiak R, Fung S, Gordon SC, Janssen HL, Lampertico P, Lau D, Bornstein JD, *et al*: Evaluation of APRI and FIB-4 scoring systems for non-invasive assessment of hepatic fibrosis in chronic hepatitis B patients. J Hepatol 64: 773-780, 2016.
149. Sagnelli C, Uberti-Foppa C, Pasquale G, De Pascalis S, Coppola N, Albarello L, Doglioni C, Lazzarin A and Sagnelli E: Factors influencing liver fibrosis and necroinflammation in HIV/HCV coinfection and HCV monoinfection. Infection 41: 959-967, 2013.
150. Bedossa P and Patel K: Biopsy and noninvasive methods to assess progression of nonalcoholic fatty liver disease. Gastroenterology 150: 1811-1822, 2016.
151. Francque SM, De Pauw FF, Van den Steen GH, Van Marck EA, Pelckmans PA and Michielsen PP: Biopsy of focal liver lesions: Guidelines, comparison of techniques and cost-analysis. Acta Gastroenterol Belg 66: 160-165, 2003.
152. Childers RE and Ahn J: Diagnosis of alcoholic liver disease: Key foundations and new developments. Clin Liver Dis 20: 457-471, 2016.
153. Colli A, Fraquelli M, Andreoletti M, Marino B, Zuccoli E and Conte D: Severe liver fibrosis or cirrhosis: Accuracy of US for detection-analysis of 300 cases. Radiology 227: 89-94, 2003.
154. Shiha G, Seif S, Eldesoky A, Elbasiony M, Soliman R, Metwally A, Zalata K and Mikhail N: A simple bedside blood test (Fibrofast; FIB-5) is superior to FIB-4 index for the differentiation between non-significant and significant fibrosis in patients with chronic hepatitis C. Hepatol Int 11: 286-291, 2017.