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REVIEW

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Inflammatory and cardiovascular diseases biomarkers in chronic hepatitis C virus infection: A review

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Abstract

Hepatitis C virus (HCV) infects 180 million people worldwide and over 4 million people in the United States. HCV infection is a major cause of chronic liver disease and is recognized as a risk factor for clinical cardiovascular disease (CVD). Many studies have shown increased prevalence of cardiac and inflammatory biomarkers in patients with chronic HCV infection (CHC), and though these markers may be used to risk stratify people for cardiac disease in the general population their role in the HCV population is unknown. Patients with CHC have elevated cardiac and inflammatory biomarkers compared to noninfected controls which may play a role in CVD risk stratification. We undertook a systematic review of inflammatory and cardiac biomarkers in people with HCV infection with a focus on the effect of CHC on serum levels of these markers and their utility as predictors of CVD in this population. Medline, EMBASE, and Cochrane databases were searched for relevant articles until June 2019. A total of 2430 results were reviewed with 115 studies included. Our review revealed that HCV infection significantly alters serum levels of markers of inflammation, endothelial function, and cardiac dysfunction prior to HCV treatment, and some of which may change in response to HCV therapy. Current risk stratification tools for development of CVD in the general population may not account for the increased inflammatory markers that appear to be elevated among HCV-infected patients contributing to increased CVD risk.

KEYWORDS

biomarkers, cardiac biomarkers, chronic hepatitis C infection, hepatitis C, inflammatory biomarkers

ABBREVIATIONS: ALD, alcoholic liver diseases; ART, antiretroviral therapy; ASC HCV, asymptomatic HCV; BMI, body mass index; BNP, brain natriuretic peptide; CAD, coronary artery disease; CFR, coronary flow reserve; CHC, chronic hepatitis C; CHF, congestive Heart Failure; CLD, chronic liver disease; CRF, chronic renal failure; CRP, C-reactive protein; cTn-I, cardiac troponin I; cTn-T, cardiac troponin T; CVA, cerebrovascular accident; CVD, cardiovascular disease; DAAs, directly acting antiviral agents; DM, diabetes mellitus; ESRD, end-stage renal disease; GIB, gastrointestinal bleeding; gp, glycoprotein; HAI, hepatic activity index; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HD, hemodialysis; HDV, hepatitis D virus; HIV, human immunodeficiency virus; hsCRP, high-sensitivity CRP; HTN, hypertension; IDU, injection drug use; IL, interleukin; INF- α, interferon alpha; LPS, lipoprotein polysaccharide; NR, nonresponders; NT-proBNP, N-terminal pro b-type natriuretic peptide; OIs, opportunistic infections; sCD, soluble cellular differentiation; sE-selectin, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1; SLE, systemic lupus erythematosus; sP-selectin, soluble P-selectin; sTWEAK, soluble Tumor necrosis factor like weak inducer of apoptosis; sVCAM-1, soluble vascular cell adhesion molecule-1; SVR, sustained virologic response; TNF- alpha (or TNF-α), tumor necrosis factor-alpha; TNFR, TNF-α receptors; TnI, troponin I; TnT, troponin T; TWEAK, TNF like weak inducer of apoptosis,; VL, viral load..

Mohamed Hassan and Safwan Muhammed contributed equally to this work.

1 | INTRODUCTION

Hepatitis C virus (HCV) is a single stranded RNA virus belonging to the Flaviviridae family. HCV has a global prevalence of 2.5% and infects 180 million people worldwide.[1] In the United States, it is the most common blood borne infection affecting 0.8 persons in every 100 000 and causing significant morbidity and mortality.[2] In 2016, over 2 million Americans had an opioid use disorder with 10% to 20% of those escalating to injection drug use.[3] In this setting the prevalence of HCV has dramatically increased, especially in younger patients, with injection drug use (IDU) now being the primary mode of transmission in the US and a 2-fold increase in the incidence rate of acute HCV infection.[4]

Chronic viral diseases, in particular human immunodeficiency virus (HIV), have been strongly linked to the development of clinical cardiac diseases.[5,6] Chronic HCV infection (CHC) has been linked to subclinical and clinical cardiovascular diseases (CVD), such as myocardial infarctions, congestive heart failure, cerebrovascular accident (CVA), and peripheral arterial disease,[7] and proposed mechanisms include chronic inflammation and immune activation driven by HCV infection as well as direct endothelial invasion and dysfunction. Studies have shown increased prevalence of certain cardiac biomarkers associated with increased CVD risk in patients with CHC compared to age-matched uninfected patients.[8] Some of these biomarkers are combined with traditional risk factors to risk stratify persons for cardiac disease in the general population,[9] but their utility in setting of HCV infection is unknown. Therefore, we aim to review the current literature on inflammatory and cardiac biomarkers in patients with HCV infection with a focus on the effect of CHC on serum levels of these markers and their utility as predictors of CVD in this population.

2 | MATERIALS AND METHODS

We conducted a search based on PRISMA guidelines[10] on Medline, EMBASE, and Cochrane for English language articles published through 14 June, 2019 using the following keywords and mesh terms: Hepatitis C, HCV, hepacivirus, chronic hepatitis C, inflammatory biomarkers, biomarkers and inflammation, biomarkers and inflammation mediators, cardiac biomarker, C-reactive protein, CRP, high sensitivity C-reactive protein, hsCRP, interluekin-6, tumor necrosis factor-alpha, troponin T, troponin I, brain natriuretic peptide, BNP, pro B-type natriuretic peptide, N-terminal pro b-type natriuretic peptide, NT-proBNP cardiovascular diseases, coronary disease, heart failure. All abstracts with the following inclusion criteria were reviewed: human studies in adults with CHC investigating serum levels of biomarkers of interest that included a HCV negative control group, and had full articles available for review. Study designs included randomized clinical trials, prospective, and retrospective observational cohorts, case-control studies, cross-sectional studies, and systemic reviews. Studies of acute hepatitis C and studies in children were excluded. Full-length articles were reviewed by three independent reviewers (A.B., S.M., and M.H.), and any differences in reviewed data from articles were discussed and resolved by these reviewers and S.B. who reviewed these selected articles.

Cardiac biomarkers were categorized into three main groups: biomarkers of inflammation, biomarkers of endothelial function, and biomarkers of cardiac dysfunction.

3 | RESULTS

The search performed in June 2019 yielded 1255 results on Medline, 1100 results on EMBASE, and 75 results on Cochrane giving a total of 2430 results. After duplicates were removed, 2394 references remained for review. Twenty-four additional articles were added after performing ancestry and bibliography searches of all relevant articles, meta-analyses, and systematic reviews. On review of titles and abstracts, 2156 were removed as they were found to be not relevant to our review. Of the remaining 262, 147 were removed because they did not meet eligibility criteria: 66 lacked a seronegative control group, 39 did not examine biomarkers of interest, 27 described only expression of and not serum levels of biomarkers, eight had relevant data missing, four were in a pediatric population, and three described levels of biomarkers following stimulation. Ultimately, 115 studies were included in our review (Figure S1).

3.1 | Biomarkers of inflammation

Biomarkers of inflammation are commonly used to assess CVD risk in the general population. Fifty-six studies evaluating the effect of HCV infection on inflammatory biomarkers were reviewed (Table 1 and Table S1) Biomarkers reviewed included interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-α), TNF-α receptors (TNFR), soluble CD163 (sCD163), and soluble CD14 (sCD14).

IL-10 is an anti-inflammatory cytokine that regulates the production of proinflammatory cytokines[11] and down regulates the expression of adhesion molecules,[12] and through these mechanisms may have anti-atherosclerotic properties.[13] The imbalance between anti- and pro-inflammatory cytokines is thought to be critical in the pathogenesis of plaque formation and destabilization, though the results of clinical studies in angina patients remain inconclusive.[14,15] The same imbalance resulting in increased IL-10 levels may be central to the persistence of HCV infection in CHC.[16] IL-6 is a proinflammatory cytokine that promotes activation and proliferation of lymphocytes and induction of hepatic acute phase proteins.[17] Like IL-10, IL-6 has been linked to the development of atherosclerosis and serum levels have been correlated with cardiovascular disease and mortality.[18]

TNF-α is a proinflammatory cytokine secreted by activated monocytes and macrophages in response to various infections. TNF-α stimulates the release of acute phase proteins in the liver leading to lymphocyte and endothelial activation,[19] and exerts its action through the binding of cellular TNF-α receptor-1 (TNFR-1) and TNF-R2.[20] In

TABLE 1 Biomarkers of inflammation

Biomarker evaluated	Increased level in HCV vs controls		Similar levels in HCV vs controls	Decreased levels in HCV vs controls
IL-6	Oliveira et al[31] Falasca et al[32] Helaly et al[33] Khan et al[34] Migita et al[36] Zekri et al[37] Malaguarnera et al[38] Costantini et al[39] Capone et al[40] Oyanagi et al[41] Lapinski et al[42] Lecube et al[43]	Sandler et al[44a] Grungreiff et al[46a] Cotler et al[48a] Hung et al[49] Antonelli et al[50] Shive et al[52] Cua et al[53] Grungreiff et al[54] Lee et al[84] Mishra et al[87] Sousa et al[91]	Tsui et al[35] Zuwała-Jagiełło et al[57] Mourtzikou et al[58] Han et al[85] Müller et al[92]	
IL-6R	Migita et al[36]	Zekri et al[37]		
TNF-α	Larrea et al[22 a] Oliveira *et al*.[31] Falasca et al[32] Helaly et al[33] Khan et al[34] Tsui et al[35] Zekri et al[37] Lecube et al[43] Hung et al[49] Cua et al[53] Zuwała-Jagiełło et al[57] Mourtzikou et al[58] Akcam et al[59] Talaat et al[60] Abdel-Latif *et al*[61] Kallinowski et al[62a] Al-Jiffri[63]	Kaplanski et al[64] Jia et al[65a] El-Bassiouni et al[66] Antonelli et al[67] Sayed-Ahmed et al[69] Toyoda et al[70a] Kishihara et al[71a] Raghuraman et al[72] Valenti L et al[73] Nelson et al[75] Glowacki et al[76] Riordan et al[77] Zylberberg et al[78a] Mishra et al[87] Zografos et al[96a] Zuwala-Jagiello et al[103]	Cotler et al[48a] Jia et al[65a]	
TNF-RI/RII	Zekri et al[37] Lecube et al[43]	Nelson et al[75]		
TNFR-p55/p75	Kallinowski et al[62a] Valenti et al[73] Zylberberg et al[78a] Itoh et al[79a]	Kakumu et al[80a] Verma et al[81] Farag et al[82]		
IL-10	Falasca et al[32] Khan et al[34] Capone et al[40] Hung et al[49] Mourtzikou et al[58] Akcam et al[59] Jia et al[65a]	Kakumu et al[80a] Verma et al[81] Han et al[85] Priimägi et al[86] Mishra et al[87] Fan et al[88] Marín-Serrano et al[89a]	Zekri et al[37] Jia et al[65a] Bruno et al[93]	Oliveira et al[31]
CRP/hsCRP	Roed et al[8] Khan et al[34] Zuwała-Jagiełło et al[57] Adinolfi et al[100] Yilmaz et al[101]	Alyan et al[102] Zuwala-Jagiello et al[103] Huang et al[104a] Che et al[99]	Oguz et al[105a]	Tsui et al[35] Moura et al[97] Ufearo et al[98]
sCD14	Sandler et al[44a]	Markowtiz et al[83]	Farag et al[82]	
sCD163	Shive et al[52]			
Sgp130			Migita et al[36]	

[a]Assessed HCV therapy.

healthy subjects, increased serum levels of TNF-alpha have predicted CVD risk,[21] and represented an independent risk factor for reduced event-free survival.[21] TNF-dependent processes are up regulated and activated in CHC, and TNF-α mRNA is ubiquitously expressed in hepatocytes, Kupffer cells, and infiltrating mononuclear cells at higher levels in CHC patients than in healthy controls.[22,23]

C-reactive protein (CRP) is an acute phase protein produced predominantly by hepatocytes, and influenced by IL-6 and TNF-α.[24] Studies have shown significant association between increased CRP levels and underlying atherosclerosis, the risk of recurrent cardiovascular events among patients with established disease, and the incidence of first cardiovascular events among individuals at risk for atherosclerosis. CRP has been validated as one of the tools for assessment of CVD risk in the general population,[25] and shown to correlate with survival and mortality in both non-CHC[26] and cirrhotic patients.[27]

Furthermore, monocyte/macrophage activation markers of immune activation such as soluble CD163 (sCD163)[28] and soluble CD14 (sCD14)[29] have been found to be associated with the burden of atherosclerosis and may predict mortality in HCV and HIV-infected patients.[30]

Numerous studies have demonstrated increased expression of and serum levels of IL-6,[31-56] TNF- α,[22,31,33,35,43,45,49,53,56-74] sTNFR,[37,43,59,61,62,72,73,75-82] sCD163,[52] and sCD14[44,52,83] among CHC patients compared to healthy controls (Table 1) and those with other hepatic diseases such as alcoholic liver disease.[84] In addition, increased serum levels of IL-10,[32,34,45,47,49,56,58,59,80,81,85-90] or disturbances in the ratios of proinflammatory/anti-inflammatory cytokines TNF-α/IL-10 and IL-6/IL-10 have been noted among CHC patients compared to healthy controls.[31] A few studies have demonstrated correlations between HCV viral load and cytokine levels.[34,38,80,87,91]

In a cohort of 981 patients with coronary heart disease enrolled in the Heart and Soul study, HCV seropositivity was associated with changes in levels of CRP, TNF-α, IL-6 increased Framingham risk scores,[31] and hospitalizations due to clinical cardiac failure and death.[35]

However, other studies have reported different findings. These studies were smaller in size,[92] and though unable to demonstrate differences between HCV groups and healthy controls they demonstrated increased serum levels of inflammatory markers with advanced HCV liver disease,[91,93] suggesting an evolution of inflammatory changes and cytokine imbalance in CHC as liver disease progresses.[94] Other studies have also demonstrated increased hepatic expression and serum levels of IL-10,[80,81,89] IL-6,[36-39,42,91,95] TNF-α,[23,59,60,62] and sTNFR[62,79-81] with increasing hepatic inflammation, steatosis, fibrosis, cirrhosis,[39,78,80,96] and the development of hepatocellular carcinoma (HCC).[40]

Studies have been mixed about the association between CRP levels and CHC infection. Some studies have demonstrated decreased CRP levels in CHC infection, which was postulated to be due to decreased production of CRP.[35,97-99] Ufearo et al found that CRP levels decreased as transferrin levels (also produced by hepatocytes) increased among HCV patients compared to controls, highlighting mechanisms other than poorly functioning hepatocytes.[98]

In contrast, other studies have shown elevated CRP levels in CHC infection.[8,34,57,100-103] In a study of patients with angiographically documented CAD, CRP, and fibrinogen levels were significantly elevated in HCV-infected patients compared to controls and HCV seropositivity was associated with increased severity of CAD.[103] Similar results were reported with elevated high-sensitivity CRP (hsCRP) levels and CVD in some studies,[103,104] whereas others found no differences in CRP levels among HCV patients and controls.[105]

Among the reported studies, few have linked altered levels of biomarkers with subclinical and clinical CVD in CHC. Tsui et al demonstrated increased levels of CRP, TNF-α, IL-6, and hospitalizations due to clinical cardiac failure among HCV positive patients compared to controls.[35] Adinolfi et al demonstrated increased pro-inflammatory cytokines levels were associated with a significantly higher prevalence of carotid atherosclerosis in HCV-infected patients compared to controls.[100] Similarly, Alyan et al found coronary artery disease (CAD) severity scores were significantly higher among CHC patients than among HCV negative controls. In the study, both HCV, CRP, and fibrinogen were significantly correlated to severity of CAD.[102]

Finally, many studies investigated the effect of HCV therapy on inflammatory markers and the majority demonstrated that HCV therapy significantly altered levels of inflammatory levels and/or predicted treatment success.[22,46-48,62,65,70,71,78-80,89,96,105]

Taken the together, the preponderance of data shows a clear modulation of the immune system, an imbalance of pro-and anti-inflammatory biomarkers with a shift towards a proinflammatory state, and increased serum inflammatory levels among CHC-infected patients. However, possibly due to blunted hepatocyte response and decreased production of CRP, CHC patients may score lower on CVD risk assessment models which rely heavily on CRP values.

3.2 | Biomarkers of endothelial function

One of the early sentinel events in the development of atherosclerosis is endothelial dysfunction which results in an increased interaction between circulating leukocytes and the endothelium.[106] This increased interaction and recruitment of circulating leukocytes is mediated by cellular adhesion molecules, and circulating forms of these molecules such as vascular cell adhesion molecule-1 (VCAM-1), endothelial-leukocyte adhesion molecule-1 (E-selectin), intercellular adhesion molecule-1 (ICAM-1), and soluble selectin (sP-selectin, sE-selectin) have been found to predict endothelial dysfunction variably.[107]

Elevated levels of these markers have been correlated with increased risk of cardiovascular mortality in numerous studies in the general population.[8,107-113] In CHC patients, these adhesion molecules are expressed on sinusoidal cells and may be under the regulatory control of TNF-alpha.[63,114]

Six studies investigated the serum levels of markers of endothelial function among HCV patients (Table 2 and Table S2) Elevated levels of sICAM-1,[8,47,63,64,66] sVCAM-1,[8,63,64,66,90] sE-selectin,[8,63] and sP-selectin[47] were uniformly increased across studies in CHC patients compared to controls.

In a study of 60 patients with CHC infection and age-matched controls, higher levels of hsCRP, sICAM-1, sVCAM-1, and s-E-selectin were found among CHC patients compared to controls and increased biomarker levels correlated with carotid intima thickness.[8] These

TABLE 2 Biomarkers of endothelial function

Biomarker evaluated	Increased level in HCV vs controls	Similar levels in HCV vs controls	Decreased levels in HCV vs controls
sICAM-1	Roed et al[8] Panasiuk et al[47a] Al-Jiffri[63] Kaplanski et al[64] El-Bassiouni et al[66]		
sVCAM-1	Roed et al[8] Al-Jiffri[63] Kaplanski et al[64] El-Bassiouni et al[66] Micheloud et al[90]		
sE-selectin	Roed et al[8] Al-Jiffri[63] El-Bassiouni et al[66]		
sP-selectin	Panasiuk et al[47a]		

[a]Assessed HCV therapy.

markers of endothelial function have also been associated with liver disease progression, with higher levels associated with greater severity of liver disease,[44,66] and treatment response in CHC patients with levels decreasing after HCV therapy.[47] More data is needed to determine whether these markers may be useful in the CVD risk assessment in the HCV patient population, as they are in the general population.

3.3 | Biomarkers of cardiac dysfunction

Brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are natriuretic hormones that are primarily released by the ventricles of the heart. Plasma BNP provides prognostic information in patients with chronic heart failure and in those with asymptomatic or symptomatic left ventricular dysfunction.[115,116] Plasma NT-proBNP has been shown to independently predict long-term risk of death due to congestive heart failure.[117,118] Both markers have been established as reliable diagnostic and prognostic cardiac biomarkers that correlate with both symptoms of CHF and the severity of systolic and diastolic CHF in the general population.[119,120] In addition, these markers have been found to correlate with the degree of circulatory dysfunction in cirrhotic patients.[121]

Troponin T (TnT) and Troponin I (TnI) are cardiac proteins which regulate the calcium mediated interactions between actin and myosin[122] released into the serum after myocardial injury. They have demonstrated prognostic value in a wide array of CVD, especially those associated with ischemic myocardial injury.[123,124]

Nine studies evaluated serum levels of these biomarkers in CHC-infected patients. (Table 3 and Table S3) Among CHC patients, elevated levels of BNP, NT-proBNP,[50,51,67,99,125-129] TnT, and TnI[103,128] have been observed compared to healthy controls.

TABLE 3 Biomarkers of cardiac dysfunction

Biomarker evaluated	Increased level in HCV vs controls	Similar levels in HCV vs controls	Decreased levels in HCV vs controls
NT-proBNP	Antonelli et al[50] Antonelli et al[67] Che et al[99] Antonelli et al[125] Okada et al[126] Wang et al[127] Matsumori et al[128] Che et al[129]		
cTn-I/cTn-T	Matsumori et al[128]		

Che et al found higher levels of NT- proBNP levels and a greater proportion of patients with impaired diastolic filling among HCV-infected patients compared to controls, and the NT-proBNP levels correlated with impaired diastolic filling.[129] Okada et al found that CHC infection independently correlated with elevated levels of NT-proBNP levels, and that patients with higher NT-proBNP (>125 pg/mL) had significantly higher serum HCV RNA levels.[126]

The data above linking HCV infection with elevated biomarker levels and echocardiographic evidence of diastolic dysfunction suggest that HCV infection influences cardiac function asymptomatically and that testing with NT-proBNP may have a role in identifying patients with low-grade cardiac dysfunction and increased CVD mortality risk. There were no studies evaluating the change of these markers with HCV therapy.

4 | SPECIAL POPULATIONS

4.1 | HCV/HIV co-infection

HIV infection has been strongly associated with increased risk of CVD through immune activation, exposure to antiretroviral therapy (ART) and disproportionately increased traditional risk factors for CVD among the HIV population.[130,131] HCV and HIV co-infection have become increasingly common due to shared modes of transmission and become substantial in the current US opioid epidemic. HCV co-infection among HIV patients has been shown to further increase the rate of CVD independent of other risk factors.[132] Hence, monitoring CVD risk in the HIV/HCV co-infected population may be especially important.

Sixteen studies have evaluated the effect of both HIV mono-infection and HIV/HCV co-infection on inflammatory biomarkers. (Table 4 and Table S4) The majority of studies have found that HCV co-infection further increases the serum levels of IL-6,[133-138] IL-10,[139] and sTNFRI[138] but decreases levels of CRP or hsCRP[133,134,136,140-142] irrespective of liver function.[133] Shah et al found that CRP levels fell with increasing IL-6 levels suggesting attenuation of the CRP-related IL-6 response.[134] Similar to HCV mono-infected populations, these markers have been found to increase with progression of HCV liver

TABLE 4 Inflammatory and cardiovascular biomarkers in HCV/HIV co-infection

Biomarker evaluated	Increase level in HCV vs controls	Similar levels in HCV vs controls	Decrease levels in HCV vs controls
IL-6	Salter et al[133] Shah et al[134] Kohli et al[136] Medrano et al[137] de Oca Arjona et al[138]		
IL-10	Garcia-Broncano et al[139]		
TNF-α	Garcia-Broncano et al[139] Dong et al[140]	Garcia-Broncano et al[139]	
sTNFR-1	Medrano et al[137] Guzmán-Fulgencio et al[147a]		
TNFR-p55	de Oca Arjona et al[138]		
CRP/hsCRP	Dong et al[140]	Kohli et al[136] Reingold et al[141] Forrester et al[144]	Salter et al[133] Shah et al[134] Reingold et al[141] Floris-Morre et al[142]
sCD14	Medrano et al[137] de Oca Arjona et al[138] Shaked et al[148]		
sCD163	Beltran et al[149] Mascia et al[150]		
sICAM-1	Medrano et al[137] De Castro et al[145a] Masiá et al[146] Guzmán-Fulgencio et al[147a]		
sVCAM-1	Medrano et al[137] de Castro et al[145a] Masiá et al[146] de Larranaga et al[151]		
sE-selectin	Guzmán-Fulgencio et al[147a]		
sP-selectin	de Larranaga et al[151]		
BNP	Dabrowska et al[152]		

[a]Assessed HCV therapy.

disease[135] and to correlate with mortality[143] in co-infected patients. However, there were no studies that evaluated the change in these inflammatory markers with HCV therapy among co-infected patients. Forrester et al assessed lipid profiles and CRP levels in HCV mono-infected, HIV/HCV co-infected, and healthy controls and found no significant differences in CRP or lipid levels among the different groups.[144] Their results conflicted with previous studies that found decreased lipid levels in co-infected patients.[142] No studies evaluated the change in these inflammatory markers with subclinical and/or clinical CVD among HIV/HCV co-infected patients.

Studies of markers of endothelial function in HIV/HCV co-infected patients have reported similar results to studies in HCV mono-infected patients (Table 4 and Table S4) Studies have demonstrated elevated levels of sVCAM-1,[137,145] sICAM-1,[137,145-147] sCD14,[138,148] sCD163,[148-150] sP-selectin, and sE-selectin[147,151] among co-infected patients, which correlated with disease progression[145] and treatment response,[145] decreased with therapy,[145,147] predicted liver related mortality[143] and were significantly associated with subclinical cardiovascular disease.[148] Finally, one study reported significantly elevated BNP elevated levels among HIV/HCV co-infected patients compared to HIV mono-infected patients.[152]

Therefore, the totality of the data suggests that while HIV mono-infection has a significant influence on serum cardiovascular biomarkers, HCV co-infection may amplify this effect and further increase CVD risk. In addition, it may be possible to identify this increased risk in the HIV/HCV co-infected population through measurement of select inflammatory and endothelial biomarkers.

4.2 | CHC patients with other inflammatory comorbidities

The additive effect of comorbidities such as diabetes mellitus[153] and end-stage renal disease (ESRD) on the levels of inflammatory biomarkers may be important as well, since these markers may be elevated de novo in these specific patient populations.[154] CHC infection is known to interfere with glucose and lipid metabolism, resulting in insulin resistance and DM[43,155] through interference of insulin

TABLE 5 Inflammatory biomarkers in CHC patients with other inflammatory comorbidities

Biomarker evaluated	Increased level in HCV vs controls	Similar levels in HCV vs controls	Decreased l evels in HCV vs controls
IL-6	Pimentel et al[45] Antonelli et al[51] Caliskan et al[55] Cielecka-Kuszyk et al[56] Falasca et al[164] Siloşi et al[166] Ramos-Casals et al[167] Riccio et al[169]	Nascimento et al[162] Afzal et al[163] el-Din et al[165]	
IL-10	Pimentel et al[45] Cielecka-Kuszyk et al[56] Ramos-Casals et al[167]		
TNF- α	Pimentel et al[45] Caliskan et al[55] Cielecka-Kuszyk et al[56] Mezher et al[68] Elsammak et al[74] Pawlak et al[160] Siloşi et al[166] Ramos-Casals et al[167] Antonelli et al[168]		
sTNFRI/II	el-Din et al[165] Realdon et al[170]		
CRP/hsCRP	Caliskan et al[55] Yelken et al[158] Chennu et al[159] Pawlak et al[160]	Caliskan et al[161] Nascimento et al[162] Afzal et al[163]	Skowronski et al[157]
NT-proBNP	Antonelli et al[51]		

signaling pathways related to increased TNF-α[74,156] and higher HCV VL.[69] HCV infection was associated with increased levels of TNF-α and decreased levels of CRP in diabetic HCV-infected patients compared to HCV uninfected diabetics, indicating modulation of HCV infection on the chronic inflammatory state in DM and underscoring the need to account for this co-morbidity when assessing CVD through standard risk scoring.[68,74,157] (Table 5 and Table S5).

TNF-α and IL-6 have been elevated in ESRD patients with and without HCV compared to healthy controls.[55] In contrast, studies among ESRD patients evaluating CRP levels in the CHC population have shown mixed results, with studies demonstrating increased levels,[55,158-160] similar levels,[161-163] and lower levels[163] of serum hsCRP among ESRD patients with HCV infection compared to uninfected controls. In one study, authors found similar levels of serum hsCRP and IL-6 levels in the HCV-infected patients compared to the uninfected patients with mean IL-6/hsCRP ratio significantly lower in the HCV positive group, leading the authors to hypothesize that the liver may have a blunted response to IL-6 in the presence of HCV infection.[162]

The immune activation associated with CHC infection can lead to the development of immune related complications, which may further influence the levels of inflammatory markers associated with CVD. Increased levels of IL-6, IL-10, TNF-α, and sTNFR in HCV-infected patients with complications such as cryoglobulinemia, Sjogren syndrome, lymphoproliferative diseases, hemophilia, and HCV related arthritis have been reported compared to CHC-infected patients without such complications or to healthy controls.[45,51,56,164-170]

Therefore, special consideration may be needed when interpreting serum inflammatory markers in HCV populations who have DM, ESRD, and/or concomitant immune complications. In these populations with HCV infection and inflammatory conditions, there we no studies evaluating the change of these markers with HCV treatment, and none evaluated the association of these markers to subclinical and/or clinical CVD.

5 | DISCUSSION

We found that the preponderance of data suggested that HCV infection significantly alters serum levels of markers of inflammation, endothelial function, and cardiac dysfunction prior to HCV treatment, and some of which may change in response to HCV therapy. The majority of studies demonstrate an imbalance of pro-and anti-inflammatory biomarkers with a shift towards a proinflammatory state among CHC-infected patients.

Clinical presentations of CVD are preceded by an asymptomatic period, which can be long and insidious, but during this period biomarkers can be critical in identifying pathological developments that may lead to clinical cardiac events. Biomarkers are useful tools to risk stratify patients for development of disease and to monitor disease outcomes in response to therapies. Cardiac biomarkers used for these purposes in the general population may be useful in the HCV population too. Since the majority of studies consistently found increased levels of the pro-inflammatory markers IL-6 and TNF-α and markers of endothelial function and cardiac dysfunction among HCV-infected compared to uninfected patients, incorporating these biomarkers into risk stratification tools may improve the ability to discern an individual's risk for developing CVD among HCV-infected patients who were determined to be at intermediate risk based on standard CVD assessment tools using traditional markers such as CRP only.[171]

Traditional risk stratification tools for CVD have been established and widely adopted in routine practice. Risk scoring tools such as the atherosclerotic CVD (ASCVD) risk score incorporate traditional risk factors such as smoking, hypertension and DM, and though these risk factors certainly contribute to an individual's CVD risk they do not fully account for the increased atherosclerosis and CVD events among certain high-risk groups such as the HCV-infected patient population.[25] CVD risk assessment tools have been shown to perform sub optimally in HIV-infected patients[172] likely due to increased systemic inflammation, endothelial dysfunction, and metabolic derangements, which may disproportionately drive the atherosclerotic process in these patients and are not well accounted for in most tools currently. In addition, lipid levels, which are a component of many CVD risk stratification tools are known to be decreased in CHC patients,[173] and therefore may underestimate CVD risk in these patients. Inflammation is recognized as a major component of atherosclerosis among both

HCV-infected and HCV uninfected patients,[100,174] and there is a growing concern that CVD risk assessment using current risk scoring tools may be suboptimal for patients with heightened inflammatory states leading to an underestimation of risk in these patients.[175]

CRP is an established cardiac biomarker for increased CVD risk and has been included in traditional risk assessment algorithms. Treatment strategies based on hsCRP levels have resulted in reduced CVD events,[176] and hsCRP levels are used to re-classify patients with intermediate ASCVD risk currently.[25] However, CRP levels were decreased in HCV patients compared to uninfected patients in many[35,98,99,157,163] but not all studies.[34,102,158,159,163] Inconsistencies in results may be due to differences in patient populations, study designs and types of assay used. For example, CRP levels appear to be higher among HCV-infected patients with ESRD who may have higher CRP levels at baseline. Reduced CRP levels may be due to reduced hepatic synthesis of CRP or direct inhibition during HCV replication regardless of liver function,[133,136,151] and the use of CRP may underestimate the CVD risk in these patients.

Another advantage of some nontraditional biomarkers is their relationship to CHC disease stage,[36-39,42,91,95] response to HCV treatment and achievement of SVR.[46-48] Numerous studies have reported decreased CVD clinical endpoints and mortality with HCV therapy.[7] There were conflicting results about the change of these biomarkers in response to HCV treatment, and these differing results may have been due to heterogeneous study designs, variable study populations, and different treatment regimens among studies.[47,104,105,147] Despite this variability, it was clear that eradication of HCV does have an effect on the HCV driven inflammatory and immune responses with a general trend towards return to normal levels of these markers. Nonetheless, there were a few studies that assessed the changes in inflammatory and cardiac markers with HCV therapy, and in these studies changes in biomarkers with HCV treatment was associated with CVD.[46,47,65,79,80,89,145,147] This finding has especially significant implications in the current era of directly acting antiviral agent (DAA) therapy, since large numbers of patients can be cured of HCV infection offering hope that HCV therapy could potentially mitigate CVD risk. The ability to refine CVD risk further using select cardiac biomarkers based on HCV stage of disease and to recalculate risk in response to DAAs and achievement of HCV cure would provide a powerful tool in selecting the highest-risk patients in whom to target CVD preventive and management strategies in the HCV patient population.

Ours is one of the first comprehensive reviews of the literature reporting on the associations between HCV and a wide array of nontraditional potential CVD biomarkers such as endothelial markers. Strengths of our review included an extensive, systematic review of the topic and inclusion of various study designs, thereby allowing us to include many studies with pertinent, valuable findings. Furthermore, it is the first review to examine the possible additive influence of common comorbidities such as HIV co-infection, DM, and ESRD on CHC and their effects on serum cardiac biomarkers. In addition, our review reported on the effect of antiviral therapy on these cardiac markers, which is of particular interest in the DAA era. Only one other similar systemic review by Osibogun et al included HIV/HCV co-infected patients but it included 28 studies only.[177] Finally, we chose only to investigate the association between CHC and cardiac biomarkers already known to correlate with cardiac disease and mortality in the general population. Limitations of the review included heterogeneous study designs, but this was purposeful because we felt that excluding too many relevant studies in the pursuit of a meta-analysis would compromise the focus of reporting comprehensive data on a heterogeneous group of biomarkers. In addition, the studies included heterogeneous study populations, variable inclusion and exclusion criteria, and outcomes with differing definitions of similar endpoints. Also, there was inconsistent and incomplete capturing of traditional CVD risk factors among studies, which may have affected the associations found between HCV infection and the index cardiac biomarkers. In some studies, patients were on therapy (ART or HCV therapy) which may attenuate the expression of and serum levels of biomarkers investigated. Such differences among studies made it challenging to reconcile differences in results and limited our ability to make firm conclusions about the predictive value of these biomarkers. Importantly, only some studies reported on the association of the change in inflammatory and cardiac biomarkers with subclinical or clinical cardiovascular disease, thereby limiting our ability to conclude on the association of the change of these biomarkers with cardiac disease in the HCV population compared to the general population. However, the markers selected in this review have been associated with subclinical and clinical cardiovascular disease in the general population already, and CHC has been associated with subclinical and clinical cardiac disease in previous studies.[6,7] Furthermore, the scope of our review did not account for the possible contribution of genetic variations leading to genetic predisposition of different ethnic groups and different HCV genotypes to CVD outcomes. In particular polymorphisms in cytokine genes or promoter regions may affect expression of inflammatory mediators and hence may affect CVD risk.[178] Studies investigating genetic associations with inflammatory markers have been inconclusive and were not considered in the scope of this review. Finally, non-English studies were not reviewed which may have excluded some significant findings.

In conclusion, inflammatory pathways are fundamental to the pathogenesis of atherosclerosis and the development of cardiac events, and CHC infection has been shown to heighten the state of inflammation in these patients. Current risk stratification tools for development of CVD in the general population do not account for many of the inflammatory markers that appear to be elevated among HCV-infected patients, and therefore there is concern that the CVD risk in these patients may be underestimated. Given the burden of HCV infection both nationally and internationally, there is an urgent need to evaluate additional cardiac biomarkers that may potentially identify or better discriminate CVD risk among HCV-infected patients more accurately than those in the current standard risk assessment tools. Further prospective studies are needed to confirm the predictive value of these biomarkers of interest in this patient population.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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