Exploring the association between hepatitis C virus infection, and serum platelet factor 4 and RANTES levels in patients with chronic kidney disease

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Abstract. Chronic kidney disease (CKD) and hepatitis C virus (HCV) infection are critical health concerns. Individuals with CKD are more susceptible to HCV infection owing to their weakened immune systems. Chemokines, such as regulated upon activation, normal T-cell expressed and secreted (RANTES) and platelet factor 4 (PF4) play a crucial role in both illnesses, as they indᵭuce long-term inflammation and activate platelets. PF4 and RANTES are known to promote blood vessel inflammation and immune system alterations; however, knowledge regarding their roles in individuals with CKD and concomitant HCV infection is limited. Therefore, the present study aimed to investigate the effects of HCV infection on the levels of PF4 and RANTES in the bloodstream of patients with CKD. For this purpose, a case-control study involving 270 participants (90 healthy individuals, 90 patients with CKD without HCV infection and 90 patients with CKD with HCV infection) was conducted. All patients with CKD had stage 5 disease (end-stage renal disease) and required maintenance hemodialysis. Enzyme-linked immunosorbent assay was employed to determine the serum concentrations of PF4 and RANTES. While patients CKD without HCV infection exhibited significantly higher blood PF4 levels (11.24±12.49 ng/ml), those with HCV infection had even higher values (17.66±13.92 ng/ml) than the healthy controls (7.26±3.84 ng/ml; P<0.001). The highest concentrations were found in patients with CKD and comorbid HCV infection. RANTES levels were also significantly higher in patients with CKD without HCV infection (4,837.48±104.60 pg/ml) and those with HCV infection (4,850.91±23.63 pg/ml) than in the healthy controls (3,181.93±1,461.16 pg/ml; P<0.001). On the whole, these results indicate that patients with CKD have significantly higher levels of PF4 and RANTES than healthy controls, with the highest levels occurring in patients with CKD with HCV infection.

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Introduction

Chronic kidney disease (CKD) is a disorder in which the ability of the kidneys to function slowly deteriorates over the course of >3 months. This complicates the ability of the body to eliminate waste and maintain fluid and electrolyte balance. CKD frequently progresses to end-stage renal disease (ESRD), which requires dialysis or kidney transplantation (1-3).

The increased global prevalence of chronic kidney disease is largely due to the convergence of demographic and epidemiological trends. CKD is growing more prevalent in numerous parts of the world. The primary reasons for this include an increase in the number of elderly individuals, a higher life expectancy and an increase in the incidence of non-communicable diseases, such as diabetes and high blood pressure. More people with heart disease are living longer lives, using kidney-damaging medications, and developing inflammatory and metabolic diseases. This has led to an increase in the number of cases with CKD, particularly in low- and middle-income nations (1-4).

Hepatitis C virus (HCV) infection presents a distinct risk to individuals with CKD, particularly those receiving hemodialysis, due to markedly higher prevalence rates compared to the general population (5). Researchers indicate that CKD and HCV infection are becoming increasingly linked. Patients with CKD are more likely to become infected with HCV as their immune systems are out of balance, they have vascular access created or replaced more than once, and they are often surrounded by healthcare workers, particularly when they undergo hemodialysis. Chronic HCV infection, conversely, may expedite the advancement of CKD and exacerbate cardiovascular outcomes by eliciting prolonged systemic inflammation, endothelial dysfunction and metabolic disturbance (6,7).

Platelets become active and release platelet factor 4 (PF4; also known as CXCL4) from their alpha granules. Regulated upon activation, normal T-cell expressed and secreted (RANTES; also known as CCL5), is a CC chemokine produced by T-cells, platelets and other cells that reside in tissues (8,9). PF4 and RANTES are chemokines that are critical in controlling the movement and activation of immune

cells. PF4 mainly changes how monocytes, macrophages, neutrophils, natural killer cells and T-lymphocytes differentiate, move and become active. Depending on the amount of PF4 present and the type of cell, it can be involved in both pro-inflammatory and anti-inflammatory processes (9). When platelets are stimulated, they produce PF4, which can interact with other chemokines, such as RANTES. This facilitates the movement of white blood cells, such as monocytes, to sites of inflammation (10). RANTES is a strong chemoattractant for memory T-cells, eosinophils, monocytes and other immune cells. It is essential for delivering white blood cells to inflamed regions, enhancing immunological responses, and regulating both innate and adaptive immunity (8). PF4 and RANTES are key chemicals that link platelet activation to immune cell recruitment and the spread of inflammatory responses in both healthy and diseased states (8-10).

Although there is strong evidence linking CKD and HCV infection to systemic inflammation and poor cardiovascular outcomes, the platelet-mediated immuno-inflammatory processes that enhance this connection are not yet fully understood. The majority of prior research has concentrated on conventional inflammatory markers or platelet counts, with insufficient emphasis on platelet-derived chemokines that directly facilitate immune cell recruitment and vascular inflammation (6,7,10,11). Data on the behavior of PF4 and RANTES in patients with CKD co-infected with HCV are limited (12-14), particularly in populations undergoing hemodialysis, where platelet activation and viral infection occur concurrently. Addressing this gap has therapeutic significance, as identifying platelet-associated inflammatory markers may improve risk classification and shed light on the mechanisms driving the increased thrombo-inflammatory load in this vulnerable population. Therefore, the present study aimed to investigate serum PF4 and RANTES levels in patients with CKD with and without HCV infection, highlighting their potential role in the immunopathogenesis of CKD and HCV co-infection.

Patients and methods

Study population. A case control study was conducted on serum samples from 90 patients with CKD and positive for HCV, 90 patients with CKD and negative for HCV and 90 apparently healthy individuals as the control group. Samples were collected from the Dialysis Center Laboratory at Al-Imamain Al-Kadhimain Medical City in Baghdad, Iraq after obtaining official permission from the hospital. The study samples were collected from patients and healthy controls between November, 2024 and May, 2025. Patients with HCV were classified based on the results of tests performed on patients in the dialysis center laboratory. All patients underwent HCV testing as part of routine checkups at dialysis centers. The standard diagnosis for HCV at these centers is the presence of antibodies to the HCV (anti-HCV antibodies) in the serum of patients, which is determined using enzyme linked immunosorbent assay (ELISA) technology. All patients with CKD had stage 5 disease (ESRD) and were undergoing regular hemodialysis. The inclusion criteria for the patients were adult patients (≥18 years) with ESRD on maintenance hemodialysis, while the exclusion criteria included those with acute infections, autoimmune diseases, malignancy and recent blood transfusion.

Detailed information regarding CKD etiology and comorbidities was not uniformly available. The age of the patients with CKD ranged from 30 to 85 years, with a median age of 50 years. PF4 and RANTES levels were measured for all samples using ELISA. The manufacturer of the kits used in the present study was Elabscience (cat. no. E-EL-H6184 for PF4 and cat. no. E-EL-H6179 for RANTES).

The present study was approved by the Ethics Committee of Ibn Sina University of Medical and Pharmaceutical Sciences, Baghdad, Iraq (Approval no. ISU14.10.24). Written informed consent was obtained from all participants prior to sample collection.

Statistical analysis. Data analysis was performed using the Statistical Package for Social Sciences (SPSS) software, version 26 (IBM Corp.) and Microsoft Excel 2019 (Microsoft Corp.). The normality of data distribution was assessed using the Shapiro-Wilk test. Parametric tests, including the one-way ANOVA with the LSD post hoc test were used for normally distributed variables. The Chi-squared test was used to assess associations between categorical variables. A P-value <0.05 was considered to indicate a statistically significant difference.

Results

The sex distribution among three groups (control, CKD without HCV and CKD with HCV) is demonstrated in Table I. There was a statistically significant difference between the groups (P=0.005). The highest proportion of females was found in the control group (43.1%), whereas males were more frequent in the CKD without HCV group and CKD with HCV group (each 37.9%).

As regards age, the results revealed that the control group had a significantly lower mean age (38.17±15.525 years) compared to both the CKD without HCV group and the CKD with HCV group (52.19±11.161 years each). The analysis revealed a highly significant difference among the groups (F=36.104, P=0.0001) (Table II).

The analysis of PF4 levels revealed statistically significant differences between all three groups. PF4 levels were significantly higher in the CKD without HCV group compared to the control group, and were even higher in the CKD with HCV group. Additionally, the PF4 levels were significantly higher in the CKD with HCV group than in CKD without HCV group. A similar was observed for the RANTES levels (Figs. 1 and 2, and Tables III and IV).

Discussion

People with CKD have severe immune dysregulation, which is evidenced by issues with both their innate and adaptive immune responses, ongoing systemic inflammation, and issues with their platelets. Uremia causes immune exhaustion, repeated vascular access and frequent exposure to extracorporeal circulation in hemodialysis settings, all of which render these patients more likely to acquire viral infections and maintain ongoing chronic inflammation. In this case, chemokines that are produced from platelets are a critical, yet not

Table I. Distribution of sex across the study groups.

Sex	Groups			Total (%)	Chi-squared test P-value
	Controls (%)	CKD negative C (%)	CKD positive C (%)		
Male	34 (24.3)	53 (37.9)	53 (37.9)	140 (51.9)	0.005
Female	56 (43.1)	37 (28.5)	37 (28.5)	130 (48.1)	
Total	90 (33.3)	90 (33.3)	90 (33.3)	270 (100.0)	

CKD, chronic kidney disease; Controls, healthy controls; CKD negative C, patients with chronic kidney disease without hepatitis virus C infection; CKD positive C, patients with chronic kidney disease with hepatitis virus C infection.

Table II. Mean age distribution across the study groups.

Groups	Mean ± SD deviation	F (P-value)
Control	38.17±15.525	36.104 (0.0001)
CKD with negative C	52.19±11.161	
CKD with positive C	52.19±11.161	

CKD, chronic kidney disease; Controls, healthy controls; CKD negative C, patients with chronic kidney disease without hepatitis virus C infection; CKD positive C, patients with chronic kidney disease with hepatitis virus C infection.

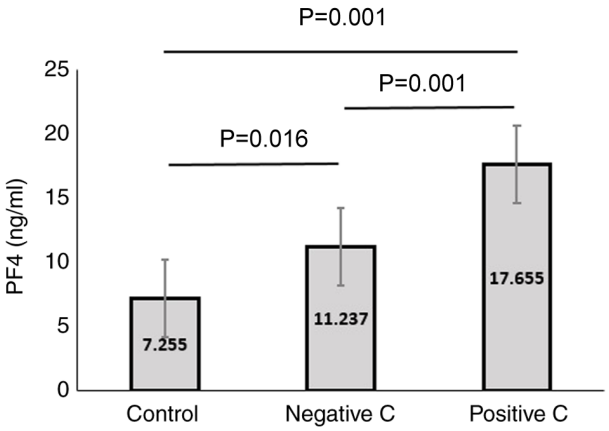

Figure 1. Mean values of PF4 and comparisons between groups. PF4, platelet factor 4; Controls, healthy controls; Negative C, patients with chronic kidney disease without hepatitis virus C infection; Positive C, patients with chronic kidney disease with hepatitis virus C infection.

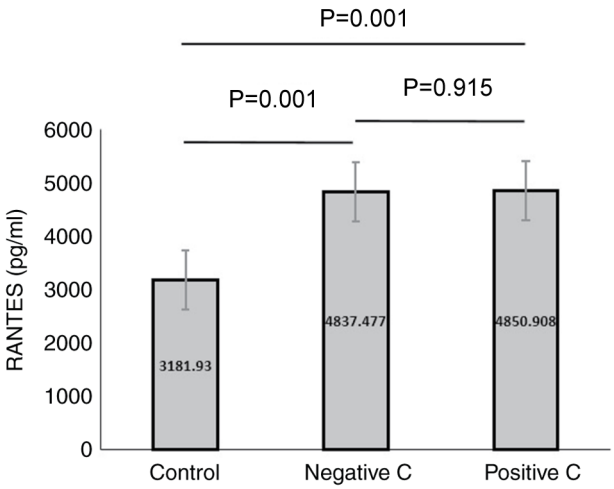

Figure 2. Mean values of RANTES and comparisons between groups. RANTES, regulated upon activation, normal T-cell expressed and secreted; Controls, healthy controls; Negative C, patients with chronic kidney disease without hepatitis virus C infection; Positive C, patients with chronic kidney disease with hepatitis virus C infection.

extensively studied link between immune system issues and increased inflammation. The present study opted to investigate PF4 and RANTES (CCL5), since platelets produce a large quantity of these chemokines when activated. They are also vital for bringing white blood cells into the body, activating immune cells and combating infections. PF4 and RANTES are essential markers for exploring the molecular immunological link between chronic HCV infection and CKD, due to their participation in thrombo-inflammatory processes and viral pathogenesis. PF4 and RANTES are not like other inflammatory markers; they indicate that platelets are engaging the immune system. This is a procedure that is becoming increasingly significant in CKD to treat inflammation and blood vessel issues (4,10,12,15).

Patients with CKD are more prone to become infected with HCV infection, which increases their risk of mortality and illness due to complicated immunological and inflammatory pathways (16,17). Previous studies have found that patients with HCV infection have worse cardiovascular outcomes and are more likely to develop CKD (18,19). Both CKD and viral infections are largely caused by inflammation and immunological responses, which are mediated by the chemokines PF4 and RANTES, which are released upon platelet activation (11,16). Research explicitly examining how HCV infection affects blood levels of these chemokines in patients with CKD is still lacking, despite the known roles of PF4 and RANTES in inflammatory conditions. The majority of the literature to date has either examined inflammatory markers separately in CKD or HCV populations or concentrated on the prevalence and clinical effects of HCV in CKD (11,17,19).

Serum PF4 and RANTES levels in control subjects, patients with CKD without HCV, and patients with CKD with HCV infection have not, to date, to the best of our knowledge, been compared in any previous study. In order to clarify the

Table III. Comparison of mean PF4 and RANTES levels among the groups.

Groups	PF4 (ng/ml)	RANTES (pg/ml)
Control		
Mean	7.255	3181.930
Std. deviation	3.843	1461.163
CKD with negative C		
Mean	11.237	4837.477
Std. deviation	12.489	104.600
CKD with positive C		
Mean	17.655	4850.908
Std. deviation	13.92	23.629
F (p-value)	20.391 (0.0001)	115.860 (0.0001)

CKD, chronic kidney disease; PF4, platelet factor 4; RANTES, regulated upon activation, normal T-cell expressed and secreted; Controls, healthy controls; CKD negative C, patients with chronic kidney disease without hepatitis virus C infection; CKD positive C, patients with chronic kidney disease with hepatitis virus C infection.

combined impact of CKD and HCV on platelet-mediated inflammation and possibly identify novel biomarkers or therapeutic targets in this clinically susceptible population, the present study aimed to fill the gap by assessing these biomarkers across these various groups.

Known epidemiological patterns of CKD and HCV infection can account for the observed sex distribution differences among the three groups in the present study (the control, patients with CKD without HCV, and patients with CKD with HCV); there was a higher proportion of females in the control group and a male predominance in the CKD groups. Males with the prevalence of HCV infection is greater in CKD, according to several studies (12,14,18,20). Male predominance in HCV-positive patients, for instance, has been reported in studies on CKD populations in India and Pakistan. This is attributed to higher rates of underlying CKD risk factors in men, such as diabetes and hypertension, as well as potential increased exposure risk to HCV through behaviors or healthcare-related factors in men (13,20,21). In a similar vein, a sizable population-based study conducted in Taiwan discovered that, in addition to advanced age and other comorbidities, the male sex was a substantial independent risk factor for CKD in patients with HCV (22).

In the present study, the larger percentage of women in the control group may be a result of the demographic makeup of the general population sample, as well as the distinct risk factor profiles for HCV infection and CKD. Notably, while the prevalence of HCV infection tends to be higher in males across CKD populations, some studies have also documented interactions where females with HCV may have worse renal outcomes (such as post-transplant chronic renal failure) (6,23).

Herein, the mean age of the control group (38.17±15.53 years) was significantly lower than that of both CKD groups (52.19±11.16 years), and the difference was highly significant (F=36.104, P=0.0001). This is in line with established epidemiological evidence indicating that the prevalence of HCV infection and CKD increases with age. According to numerous studies, CKD primarily affects middle-aged and older individuals, and its incidence significantly increases beyond the age of 50 years. In elderly CKD populations, HCV infection is also more prevalent and has a larger clinical impact. For instance, HCV-seropositive patients were considerably older than HCV-negative people and had a greater prevalence of CKD, particularly in those >45 years of age, according to a large population-based study conducted in Taiwan (22). The majority of patients with CKD, whether HCV-positive or -negative, were between the ages of 35 and 50 years, according to another Indian study, and the prevalence of HCV was highest in these middle-aged groups (13). Additionally, this age-associated risk is influenced by pathophysiological factors, such cumulative kidney injury, extended exposure to viral infections, or comorbidities (e.g., diabetes and hypertension) (11,14). Therefore, the greater age in CKD groups (independent of HCV status) corresponds with the higher risk and progression of renal disease and chronic infections observed in later life, whereas the younger age in the controls indicates the lack of CKD and HCV-related comorbidities.

A progressive increase in platelet activation and inflammatory chemokine release linked to both CKD and HCV infection is suggested by the finding that PF4 levels were lowest in healthy controls, significantly elevated in patients with CKD without HCV, and highest in the patients with CKD with HCV. These findings are also reflected by the RANTES levels, and all groups exhibited statistically significant differences. Cortical roles in inflammatory and immunological processes are played by the chemokines, PF4 and RANTES, which are held in platelet alpha granules and released upon platelet activation. Chronic inflammation, endothelial dysfunction and an altered hemostasis are known to activate platelets in CKD, which increases PF4 and RANTES levels compared to healthy individuals (7,9). The additional inflammatory and immunological stimulation brought on by HCV infection is probably the cause of the further rise in PF4 and RANTES observed in HCV-infected CKD patients. Chronic inflammation and systemic immunological activation brought on by HCV are known to aggravate kidney damage and promote platelet activation, both of which increase the release of chemokines (11,24). In addition, immune-complex deposition and direct viral effects on kidney tissue aggravate HCV-related kidney disease by promoting the release of inflammatory chemokines such as PF4 and RANTES platelets from immune cells (24). In the present study, the detailed virological characteristics of HCV infection, including genotype, viral load, and antiviral treatment status, were not uniformly available and therefore could not be analyzed. This may exacerbate the course of CKD by increasing vascular inflammation. The levels of these chemokines gradually increased from the controls to those with CKD without HCV and those with CKD with HCV, which is in line with data form a previous study demonstrating that persistent HCV infection causes kidney damage and systemic inflammation, apart from the inflammatory milieu of CKD alone (25). These associations are discussed in the context of biological plausibility and previously published evidence rather than direct statistical testing in the present study. Inflammation and

Table IV. Post hoc multiple comparisons of PF4 and RANTES between the groups.

Dependent variable	Groups	Mean difference	Sig.
PF4	Control vs. Negative C	-3.982556[a]	0.016
	Control vs. Positive C	-10.400478[a]	0.000
	Negative C vs. Positive C	-6.417922[a]	0.000
RANTES	Control vs. Negative C	-1,655.546867[a]	0.000
	Control vs. Positive C	-1,668.978533[a]	0.000
	Negative C vs. Positive C	-13.431667	0.915

[a]Indicates statistically significant differences (P<0.05). CKD, chronic kidney disease; PF4, platelet factor 4; RANTES, regulated upon activation, normal T-cell expressed and secreted; Controls, healthy controls; CKD negative C, patients with chronic kidney disease without hepatitis virus C infection; CKD positive C, patients with chronic kidney disease with hepatitis virus C infection.

platelet activation are central features of both CKD and chronic HCV infection. Previous studies have consistently reported elevated levels of inflammatory markers, such as C-reactive protein, IL-6 and TNF-α in CKD and HCV, reflecting persistent immune activation and endothelial dysfunction. In parallel, platelet-related abnormalities, including increased platelet activation and release of platelet-derived mediators, have been described in these conditions. Within this inflammatory milieu, PF4 and RANTES represent platelet-derived chemokines that link platelet activation with immune cell recruitment. The elevated PF4 and RANTES levels observed in the present study are therefore consistent with the broader pattern of heightened inflammation and platelet involvement reported in CKD and HCV, supporting their potential role as complementary biomarkers of thrombo-inflammatory activity in this population (11,16).

On the whole, the results of the present study are consistent with earlier research demonstrating that inflammation causes platelet-derived chemokines to rise in CKD and that HCV infection intensifies this systemic inflammatory response, leading to additional elevations in PF4 and RANTES levels. This lends credence to the notion that HCV exacerbates inflammatory pathways and platelet activation in patients with CKD.

Even though immune-mediated platelet destruction, bone marrow suppression, the impaired liver production of thrombopoietin and hypersplenism leading to platelet sequestration are some of the mechanisms that cause thrombocytopenia (decreased platelet count) in chronic HCV infection (12,15,26), the serum levels of platelet-derived chemokines, such as PF4 and RANTES can still be increased, despite the lower platelet count and this case can be explained by several factors.

The remaining circulating platelets in chronic inflammatory states tend to be hyperactivated, despite the fact that overall platelet counts decline in HCV infection. Despite thrombocytopenia, activated platelets can increase the serum levels of PF4 and RANTES by releasing these chemokines from their alpha granules into the bloodstream (15,27). HCV infection causes autoimmune reactions and the creation of immune complexes against platelets, which destroys the platelets, but also activates them before they are cleared. Ironically, the immune system's targeting of platelets may temporarily or in subsets of platelets boost the release of chemokines (26,27). Even though chronic HCV infection often causes thrombocytopenia, a decrease in the number of platelets does not always indicate that the platelets are less active. In inflammatory conditions, such as CKD and HCV infection, the residual circulating platelets are frequently hyperreactive and demonstrate increased degranulation capability. When these hyperactivated platelets are activated, they can release numerous platelet-derived chemokines, such as PF4 and RANTES, from their alpha granules. Furthermore, immune-mediated platelet destruction and faster platelet turnover may render younger, more reactive platelets with more secretory potential more likely to respond. In the case of CKD and HCV co-infection, ongoing systemic inflammation and endothelial dysfunction may cause platelets to become even more active, maintaining chemokine levels high even though there are fewer platelets. This observation highlights a critical pathophysiological notion: the functionality of platelets, not just their number, may be a key factor in the thrombo-inflammatory burden in patients with CKD who are also infected with another disease. This provides new information regarding the increased risk of inflammation and heart disease in patients with CKD (12,15).

Even though liver disease and bone marrow suppression decrease platelet production, thrombopoietin levels can occasionally rise in response, encouraging megakaryocytes to create younger, more reactive platelets that release more PF4 and RANTES when activated (12,27). Elevated systemic levels of PF4 and RANTES can be found in serum when platelets in inflammatory vascular beds or organs (such the kidneys in CKD or the liver in HCV) become activated and release these chemicals locally (28).

In summary, thrombocytopenia in chronic HCV is characterized by a lower platelet count mostly as a result of increased destruction and decreased formation; yet, the remaining or newly formed platelets are hyperactivated, which results in increased PF4 and RANTES secretion. This explains why in patients infected with HCV, PF4 and RANTES levels increase even when their platelet counts are low.

The findings of elevated PF4 and RANTES levels in patients with CKD co-infected with HCV raise several important avenues for future research and potential clinical application. Given their close association with platelet activation and inflammation, PF4 and RANTES may serve as candidate biomarkers for identifying CKD-HCV patients at

an increased risk of thrombo-inflammatory complications, including cardiovascular events. Further research is required to determine whether investigating these chemokines over time can help to identify who is at a higher risk more accurately than traditional inflammatory indicators. The role of platelet-derived chemokines suggests that altering the way platelets function or chemokines signal may be beneficial in treating patients. Some of these treatments could include improved anti-platelet procedures, tailored anti-inflammatory medicines, or methods for limiting the number of times platelets and immune cells come into contact. More mechanistic and interventional research are needed to determine whether addressing PF4- and RANTES-mediated pathways can improve the health of this high-risk group by increasing inflammation.

In conclusion, the present study demonstrates that patients with CKD and HCV infection have markedly higher levels of the platelet-derived chemokines, PF4 and RANTES, in their circulation than those with CKD without HCV. This is due to the fact that the virus damages platelets, increasing the likelihood of inflammation. The increased chemokine levels found in the co-infected group suggests that HCV infection may exacerbate the pre-existing inflammatory milieu in CKD. These findings shed light on putative immuno-inflammatory processes that could explain the increased illness risk in patients with CKD and HCV co-infection. They also support previous research on how PF4 and RANTES impact the immune system and produce inflammation via platelets (9,29-32). The present study did not examine platelet numbers; however, the findings support the concept that platelet activation pathways contribute to systemic inflammation in this population. The present study addresses a fundamental gap in the understanding of the interactions between HCV infection, CKD and platelet-derived inflammatory biomarkers. It indicates that further longitudinal and mechanistic studies are necessary to ascertain their potential prognostic and therapeutic effects.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HHL was involved in the conceptualization of the study, as well as in the study methodology, data collection, and in the writing of the original draft of the manuscript. AMJA was involved in data analysis and interpretation, and in the writing, reviewing and editing of the manuscript. Both authors have read and approved the final manuscript. HHL and AMJA confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Ibn Sina University of Medical and Pharmaceutical Sciences, Baghdad, Iraq (Approval no. ISU14.10.24). Written informed consent was obtained from all participants prior to sample collection.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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