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Evaluation of *CRP* SNV rs2808630 and acute proinflammatory biomarkers in patients with CKD and PLHIV with CKD: a case-control study

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Abstract

Background The CKD in PLHIV is highly prevalent in Jalisco. Despite its control with ART, HIV is characterized by generating low-grade inflammation events that contribute to the development and progression of CKD. Considering the importance of hs-CRP in the context of CKD, various genetic predisposition studies have been conducted to search for variants of the *CRP* gene, among which the SNV rs2808630 has been associated with serum hs-CRP concentrations and progression of CKD. Due to the above, there is interest in studying this SNV, addressing the limited information available on this topic in Mexico.

Methods The case-control study included 163 patients with CKD, 102 PLHIV with CKD under ART with undetectable viral loads from the Hospital Civil of Guadalajara "Fray Antonio Alcalde" and 115 controls. Clinical assessment and general laboratory studies were carried out. Also, serum quantification of inflammatory biomarkers was performed by ELISA method. The determination of *CRP* SNV rs2808630 by qPCR and the association with inflammatory biomarkers was evaluated. Statistical analysis was carried out considering significant values $p < 0.05$.

Results Lower prevalence of CC genotype was shown in our population. Of the 358 samples, 221 (61.7%) present the wild-type genotype. The results analyzed correspond with what has been reported worldwide in studies of *CRP* SNV rs2808630 in the development of CKD without having a relationship with inflammatory and kidney function biomarkers. However, higher creatinine and IL-6 concentrations were observed in the group with the CC genotype. A significant correlation between IL-6 and eGFR was identified in CKD patients, but not for PLHIV with CKD, highlighting a potential difference in inflammatory dynamics between these groups. Importantly, in PLHIV with CKD, we found a strong correlation between hs-CRP and IL-8, suggesting a possible association with a higher proportion of the inflammatory isoform of hs-CRP, which may have implications for disease progression and cardiovascular risk.

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Conclusions The presence of the *CRP* SNV does not appear to contribute to the development of CKD and has no association with inflammatory biomarkers. Though, genetically independent manner, hs-CRP levels are slightly different between groups and are underrated when related to the CKD stage in PLHIV. Also, high IL-6 concentrations are related to CKD progression, while IL-8 seems to have a better relation to CKD in PLHIV.

Keywords Chronic Kidney Disease (CKD), Human Imunodeficiency Virus (HIV), C-Reactive Protein (CRP), Interleukin 6 (IL-6), Interleukin 8 (IL-8), Interleukin 18 (IL-18)

Background

Chronic kidney disease (CKD) is a significant public health challenge in Mexico, with a prevalence ranging from 3.5 to 9.7% in the general population [1]. In Jalisco, 10% of the population has some form of kidney damage, making it the region with the highest incidence of CKD requiring treatment worldwide [2]. While CKD is commonly associated with type 2 diabetes (T2D), in 40% of cases, the cause remains unknown [3].

The prevalence of CKD among people living with HIV (PLHIV) has been rising [4]. HIV infection induces chronic low-grade inflammation that, even with antiretroviral therapy (ART), can contribute to kidney damage [5, 6]. Certain ART regimens further increase CKD risk, prompting modifications to improve kidney tolerability [7]. Consequently, inPLHIVtheriskof progression to end-stage renal disease (ESRD) increases up to 20 times compared to the general population. Currently, 30% of PLHIV have CKD, which is the fourth leading cause of mortality in this population [8].

A previous study reported that 45% of ART-naive PLHIV had abnormal kidney function before initiating therapy. Of these, 15.8% continued to have abnormalities after 12 months of follow-up while already on ART, considered as patients with CKD. This data was of great interest because the prevalence is higher than the reported worldwide and in other studies in the country. Moreover, it suggests that kidney dysfunction in PLHIV is related to the chronic use of ART and the high inflammatory state derived from the presence of the virus. However, the relation between the HIV infection and CKD development remains under study [9].

Given the significant role of inflammation in CKD, elevated concentrations of Interleukin 6 (IL-6) and high sensitivity C-reactive protein (hs-CRP) have been reported to correlate positively with lower estimated glomerular filtration rate (eGFR) and increased mortality. Therefore, both IL-6 and hs-CRP are highly relevant biomarkers in the study of CKD [10, 11].

Recently, Interleukin 18 (IL-18) has been associated with the inflammatory process in CKD. Elevated IL-18 levels, driven by uremia and monocyte activation, have been reported in patients undergoing kidney replacement therapy (KRT) [12].

In a genetic context, the *CRP* single nucleotide variant (SNV) rs2808630 has been associated with serum concentrations of CRP and CKD progression, highlighting its importance in genetic studies on CKD [13]. This SNV is located in the 3' UTR non-coding region, where it may disrupt microRNA (miRNA) binding sites, potentially affecting mRNA stability and protein translation. These alterations could contribute to the development of various diseases [14]. Based on the above, the primary objective of this study was to evaluate if whether the *CRP* SNV rs2808630 is associated with CKD in the Mexican western population. The secondary objective of the study was to characterize the inflammatory state of CKD in PLHIV and non-HIV and to assess the association of this SNV with the inflammatory state in both groups of interest.

Methods

Study population

The participants included were enrolled from 2021 to 2023 at the HIV Unit and the Nephrology Service of the Antiguo Hospital Civil of Guadalajara "Fray Antonio Alcalde", as well as in the Nephrology Service of the Regional General Hospital No. 46 of the IMSS. The study population was composed of 163 patients with CKD, 102 PLHIV with CKD under ART (for at least 1 year) with undetectable viral loads, and appropriate immune reconstitution ($CD4^+$ T cells > 350 cells/mL), and 115 controls from Western Jalisco. CKD diagnosis was defined according to the KDIGO guidelines, using the CKD-EPI equation for eGFR values below 60 mL/min/1.73m^2 [15].

Sample size

The sample size (n) was calculated using the OpenEpi v3 software, based on the reported frequency (19.5%) of the *CRP* SNV rs2808630 in the Mexican population, as documented by the 1000 Genomes Project. The calculation was performed using Fleiss' formula with continuity correction. The formula estimated a requirement of 190 chromosomes for the case group, corresponding to 95 individuals per group. To account for potential patient loss, the final estimated sample size was 100 individuals per group.

Laboratory assessment

Blood samples were collected from all participants; to obtain serum and plasma, the samples were left to rest at room temperature for 30 min, followed by centrifugation

in 1700 rcf for 10 min. Serum and plasma were separated and aliquoted, then stored at -80ºC until further analysis. Glucose, cholesterol, triglycerides, creatinine, and urea were assayed using routine biochemical methods in the Central Laboratory of Hospital Civil de Guadalajara "Fray Antonio Alcalde", in all participants who had 12-hour fast. Also, participants were asked to provide urine samples in sterile bottles to measure microalbumin and urine albumin to creatinine ratio (uACR) using CLINITEK Microalbumin 2 reagent strips.

Serological diagnostic tests for HIV infection

Viral load was quantified using the Roche AmpliPrep/COBAS® TaqMan® HIV-1 Test platform. The $CD4^+$ T Lymphocyte count was performed in FACS Calibur platform (BD, Indianapolis) validated for clinical diagnostics.

DNA isolation and *CRP* SNV rs2808630 genotyping

For genotyping, blood samples were collected into EDTA tubes, and DNA was extracted according to Miller's salting-out method. After DNA extraction, the determination of *CRP* SNV rs2808630 (C/T) was analyzed by allelic discrimination using TaqMan polymerase chain reaction (PCR) master mix. Primer sequences were generated based on the PubMed RefSeq database with these primers (TaqMan SNV assays, ID: C_177489_10 SNV, ID rs2808630), and the amplification was performed in Thermal Cycler, Quant Studio 5 (All reagents mentioned from Applied Biosystems, California).

hs-CRP, IL-6, IL-8 and IL-18 serum levels quantification

Serum levels of hs-CRP and IL-6 were determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits. Particularly, hs-CRP was quantified with the CRP High Sensitivity ELISA kit (TECAN IBL International, Germany) and IL-6 was measured using the Human IL-6 high sensitivity ELISA kit (ABCAM, Massachusetts). The measurements of IL-8 and IL-18 were quantified by bead-coupled ELISA using LEGENDPlex™ Human Inflammation Panel 1. The samples were analyzed in the BeckmanCoulter® flow cytometer and the data generated were analyzed with the LEGENDplex™ QOGNIT virtual software (BioLegend, California). All determinations were conducted according to the manufacturer´s instructions.

Statistical analysis

Normality was assessed using the Shapiro-Wilk test. Quantitative data with a normal distribution are presented as mean ± standard deviation, while non-normally distributed data are expressed as median and interquartile range. Qualitative data are shown in frequency and percentage. The Chi-square test was used to compare proportions between groups, to assess deviations from Hardy-Weinberg equilibrium in genotype frequencies, and to analyze genotype and allele frequencies. Group comparisons were conducted using the Student's T-test or Mann-Whitney U test, depending on the data distribution. For comparisons across three groups, the Kruskal-Wallis Test was applied. Correlations were evaluated using Spearman´s correlation test. Statistical significance was set at $p < 0.05$. All analyses were conducted using GraphPad Prism (version 10.1.1) and RStudio (version 2023.12.1 + 402).

Results

The demographic and clinical characteristics of the study group are summarized in Table 1. Significant age differences were observed between the groups. Additionally, the PLHIV with CKD group had a higher percentage of men (91.1%), reflecting the predominant demographic risk for this condition. Also, significant differences were found in glucose, creatinine, and urea levels, with higher concentrations observed in the CKD group. Additionally, microalbumin and uACR levels were significantly elevated (> 300 mg/g) in 73.6% of CKD patients and 42.3% of PLHIV with CKD. Furthermore, the CKD group showed a higher prevalence of T2D (52.7%) and HTN (80%) than the other groups.

All PLHIV with CKD were on ART regimens and had undetectable viral loads. At the onset of the infection, they had a median nadir $CD4^+$ T cell count of 112 (30.5-276.5) cells/μL. Currently, their median $CD4^+$ T cell count is 485 (323–707) cells/μL, indicating adequate immune reconstitution following ART initiation. The average time living with HIV infection and ART treatment was 12 ± 8 years. Of these, 67.65% were on Biktarvy (composed of 3 drugs: an integrase inhibitor and two nucleoside reverse transcriptase inhibitors (NRTIs), including tenofovir alafenamide (TAF)), and to a lesser extent, Kivexa (composed of two NRTIs: abacavir and lamivudine) accompanied by Dolutegravir (DTG).

Among all PLHIV with CKD, 70.5% had previously been treated with Movitrem for a median duration of 5 years and 2 months (IQR: 1 year 6 months – 8 years), which contains tenofovir disoproxil fumarate (TDF). Of these, only 2.9% continued with this treatment, while 36.2% changed to other regimens due to nephrotoxicity. A sub-analysis was performed, in which time with HIV infection and ART duration, as well as type of ART regimen had no impact on the inflammatory biomarkers levels.

On the other hand, hs-CRP determination was performed, revealing no significant differences between the CKD and PLHIV with CKD groups; however, differences were observed compared to the control group. Additionally, 52.47% of the CKD group, 40.20% of PLHIV with CKD, and 26.31% of the control group have exhibited

Table 1 Clinical-demographic and laboratory characteristics of all the participants

	PLHIV with CKD (*n* = 102)	CKD (*n* = 163)	Controls (*n* = 115)	*p*-value
Age (years) median (IQR)	51 (40–59)	55 (35–66)	38 (29–52)	*< 0.0001*[a]*
Males, n (%)	90 (88.2%)	111 (68%)	66 (57.4%)	*< 0.0001*[a]*
Females, n (%)	12 (11.8%)	52 (31.9%)	49 (42.6%)	
Creatinine (mg/dL) median (IQR)	1.47 (1.29–1.98)	5.22 (1.83–11.14)	0.79 (0.62–0.91)	*< 0.0001*[b]*
Urea (mg/dL) median (IQR)	49 (41-65.9)	106 (66.35–183.5)	32 (26–38)	*< 0.0001*[b]*
Microalbumin (mg/L) median (IQR)	30 (10–150)	150 (80–150)	-	*< 0.0001*[c]*
uACR (mg/g) median (IQR)	167.7 (47.25–947.0)	1894 (470.8–1894)	-	*< 0.0001*[c]*
eGFR (mL/min/1.73 m^2) median (IQR)	52.24 (38.45–60.77)	10.62 (4.40–37)	108 (97.15–118.2)	*< 0.0001*[b]*
eGFR < 60 mL/min (%)	27.8%	3.1%	-	-
CKD stage 3 (%)	57.7%	29.8%	-	-
CKD stage 4 (%)	9.2%	13.6%	-	-
CKD stage 5 (%)	5.1%	53.4%	-	-
PD, n (%)	-	59 (36.1%)	-	-
HD, n (%)	6 (5.8%)	27 (16.5%)	-	-
Glucose (mg/dL) median (IQR)	94 (87-103.8)	107.5 (88.7-130.3)	81 (76–86)	*< 0.0001*[b]*
BMI (kg/m^2) median (IQR)	25.39 (22.67–28.98)	25.40 (22.77–27.65)	25.27 (23.35–28.26)	*0.9156*[b]
Cholesterol (mg/dL) median (IQR)	163 (138–196)	136 (109–179)	190.5 (153.8-220.5)	*< 0.0001*[b]*
Triglycerides (mg/dL) median (IQR)	133 (98-204.5)	129 (98.6–165)	108 (78.5-151.5)	*0.0028*[b]*
T2D, n (%)	23 (22.6%)	85 (52.7%)	-	*< 0.0001*[a]*
HTN, n (%)	42 (41.2%)	130 (80%)	-	*< 0.0001*[a]*
T $CD4^+$ (cels/ µL) median (IQR)	496 (323–707)	-	-	-
T CD4 nadir (cels/ µL) median (IQR)	112 (30.5-272.3)	-	-	-
Viral loads (copies/mL) median (IQR)	39 (39–39)	-	-	-
Nadir viral load of VIH (copies/mL) median (IQR)	77,519 (15,870 – 257,892)	-	-	-
Current ART treatment				
Biktarvy, n (%)	69 (67.65%)	-	-	-
Movitrem, n (%)	3 (2.94%)	-	-	-
Kivexa, n (%)	7 (6.86%)	-	-	-
DTG/3TC, n (%)	23 (22.55%)	-	-	-
Inflammation biomarkers				
hs-CRP (mg/L) median (IQR)	2.067 (0.824–5.454)	3.386 (0.963–7.023)	1.424 (0.665–3.404)	*0.0023*[b]*
hs-CRP ≥ 3.5 (mg/L), n (%)	41 (40.20%)	85 (52.47%)	25 (26.31%)	*0.0002*[a]*
hs-CRP < 3.5 (mg/L), n (%)	61 (59.80%)	77 (47.53%)	70 (73.68%)	
IL-6 (pg/mL) median (IQR)	3.378 (1.513–6.140)	6.424 (3.403–20.43)	-	*< 0.0001*[c]*
IL-8 (pg/mL) median (IQR)	992.1 (588.7- 1,641)	693.1 (297.9-1,196)	-	*0.0253*[c]*
IL-18 (pg/mL) median (IQR)	2,798 (1,791-4,161)	2,901 (1,184-4,691)	-	*0.8036*[c]

PLHIV: People Living with HIV, CKD: Chronic Kidney Disease, ACR: Urine albumin to creatinine ratio, eGFR: estimated Glomerular Filtration Rate, PD: Peritoneal Dialysis, HD: Hemodialysis, BMI: Body Mass Index, T2D: Type 2 Diabetes, HTN: Hypertension, ART: Antiretroviral Therapy, DTG/3TC: Dolutegravir/Lamivudine, hs-CRP: high sensitivity C Reactive Protein. Qualitative variables expressed as frequencies and percentages, and nonparametric variables as medians and interquartile. IQR: interquartile, [a]: Chi-square, [b]: Kruskal-Wallis's test, [c]: Mann-Whitney test, * Statistical significance

hs-CRP concentrations greater than 3.5 mg/L, indicating increased cardiovascular risk. Also, significant differences were observed between the groups in the concentrations of both interleukins, IL-6 was higher in CKD patients, while IL-8 was elevated in PLHIV with CKD. However, no significant differences were observed in IL-18 concentrations between the groups, though a non-significant trend of higher levels was noted across CKD stages. A sub-analysis by gender revealed no differences in biomarker levels. However, age-based analysis showed statistically significant differences in IL-6 levels only in the CKD male group, specially between adults (35–65 years) and elderly (> 65 years). The elderly group had lower IL-6 levels (4.25, IQR: 2.49–10.93 pg/mL). Additionally, we observed statistically significant differences in hs-CRP levels among males in the PLHIV with CKD, potentially due to a higher proportion of patients in CKD stages 3 and 4 in the < 55-year age group. These findings align with the behavior of hs-CRP across CKD stages, as shown in Fig. 1.

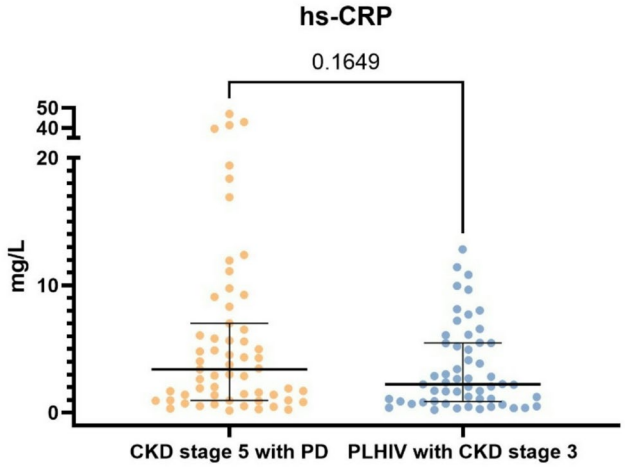

Fig. 1 Comparisons of hs-CRP concentrations between stage 5 CKD on PD and PLHIV with stage 3 CKD. Scatter plot illustrating hs-CRP concentrations in patients with stage 5 CKD undergoing peritoneal dialysis (PD) and PLHIV with stage 3 CKD. hs-CRP: high-sensitivity C-reactive protein; CKD: chronic kidney disease; PLHIV: people living with HIV; PD: peritoneal dialysis. Data are presented as median and interquartile ranges. Statistical analysis was performed using the Mann-Whitney test

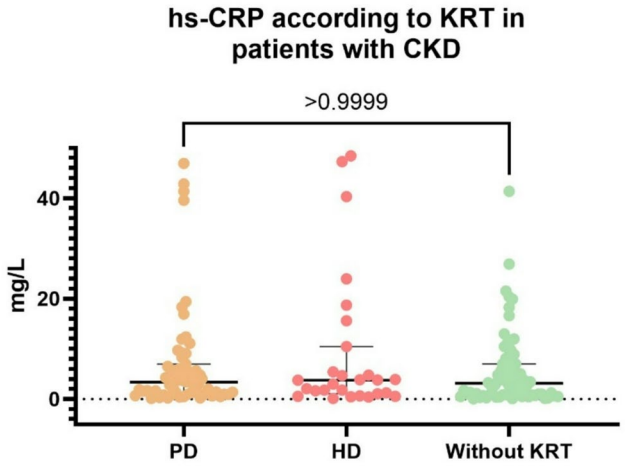

Fig. 2 hs-CRP concentrations according to the type of KRT in the CKD group. Scatter plot showing hs-CRP concentrations in CKD patients based on the type of kidney replacement therapy (KRT), including peritoneal dialysis (PD) and hemodialysis (HD). hs-CRP: high-sensitivity C-reactive protein; CKD: chronic kidney disease; KRT: kidney replacement therapy; PD: peritoneal dialysis; HD: hemodialysis. Data are presented as median and interquartile ranges. Statistical analysis was performed using the Kruskal-Wallis's test

IL-6 showed statistically significant differences across CKD stages in both groups, not being so for the rest of the inflammation biomarkers. Consistent with this result, there is correlation between IL-6 and eGFR in both CKD (r = -0.50, p < 0.001) and PLHIV with CKD groups (r = -0.26, p = 0.001), while no correlation was observed with hs-CRP values. As expected, a positive correlation was found between IL-6 and hs-CRP in PLHIV with CKD (r = 0.54, p < 0.0001), and in the CKD group (r = 0.22, p = 0.011). Also, a low negative correlation (r=-0.37, p = 0.008) between IL-8 and hs-CRP in PLHIV with CKD was found, but not in the CKD group. No correlation was found between IL-8 and IL-6 in both study groups (data not shown).

Regarding hs-CRP concentrations, we observed that PLHIV with stage 3 CKD had similar hs-CPR levels to those of stage 5 CKD patients undergoing peritoneal dialysis (PD). Figure 1 shows a sub-analysis that was performed with hs-CRP serum levels, in which no significant differences were observed between patients with stage 5 on PD (n = 59) (3.40, IQR 0.97-7.00) and PLHIV with stage 3 CKD(n = 55) (2.22, IQR 0.88–5.45).

Also, patients with CKD were further stratified according to their type of KRT (Fig. 2). In the hemodialysis (HD) group (n = 27), the hs-CRP value was 3.76 (IQR 1.07–10.49), while in the PD group (n = 59), it was 3.40 (IQR 0.97-7.0); and in patients without KRT (n = 77), it was 3.18 (IQR 0.85–7.02). No significant differences were observed between the groups.

The genotype and allele frequencies of *CRP* SNV rs2808630 by groups are shown in Table 2. All three groups exhibited a low presence of the CC genotype (< 5%), with the remaining percentage having the wild-type TT genotype, which was the most common genotype in each of the three groups analyzed.

Based on the observed frequencies, it was concluded that there is no significant deviation from Hardy-Weinberg equilibrium in the studied population (X^2= 2.719, p > 0.05), which suggests that the population is in genetic equilibrium at the analyzed locus.

A comparison was made between the *CRP* SNV genotypes and serum levels of hs-CRP and IL-6, with no significant differences observed in either group. Additionally, comparisons were made between the *CRP* SNV genotypes and kidney function biomarkers, including creatinine and eGFR. Differences were found between creatinine and eGFR in the CKD group, but not in the PLHIV with CKD group (Table 3).

On the other hand, an analysis was conducted to evaluate the impact of the C allele on inflammation and kidney function biomarkers, using a dominant model (TT/TC-CC) across our three study groups. However, no significant differences were observed in biomarker levels or across CKD stages, although an intragroup influence was noted.

Discussion

The main objective of this research was to evaluate the role of the *CRP* genetic variant rs2808630 in the development and progression of CKD, as well as to determine whether this genetic factor contributes to CKD development in PLHIV after the introduction of ART.

Table 2 Comparisons of genotype and allelic frequencies between controls, CKD patients and PLHIV with CKD

Genotype/ Allele	Group	Frequency, *n* (%)	Comparison	OR	95% CI	*p*
TT	Control	67 (59.4%)	Control vs. CKD	0.9430	0.5764 to 1.552	*0.8979*[a]
	CKD	90 (61.2%)	Control vs. PLHIV with CKD	0.8017	0.4654 to 1.409	*0.4794*[a]
	PLHIV with CKD	65 (65%)	CKD vs. PLHIV with CKD	0.8502	0.5049 to 1.454	*0.5929*[a]
TC	Control	40 (36%)	Control vs. CKD	0.9293	0.5531 to 1.540	*0.7960*[a]
	CKD	55 (37.4%)	Control vs. PLHIV with CKD	1.181	0.6541 to 2.070	*0.6632*[a]
	PLHIV with CKD	32 (32%)	CKD vs. PLHIV with CKD	1.270	0.7322 to 2.187	*0.4172*[a]
CC	Control	5 (4.5%)	Control vs. CKD	0.2952	0.0580 to 1.414	*0.2447*[a]
	CKD	2 (1.3%)	Control vs. PLHIV with CKD	0.6619	0.1719 to 2.590	*0.7249*[a]
	PLHIV with CKD	3 (3%)	CKD vs. PLHIV with CKD	2.242	0.4495 to 12.78	*0.3971*[a]
T (Allele)	Control	172 (77.4%)	Control vs. CKD	0.8637	0.5666 to 1.329	*0.5149*[a]
	CKD	235 (79.9%)	Control vs. PLHIV with CKD	0.8069	0.4987 to 1.280	*0.4023*[a]
	PLHIV with CKD	162 (81%)	CKD vs. PLHIV with CKD	0.9343	0.5974 to 1.459	*0.8180*[a]
C (Allele)	Control	50 (22.5%)	Control vs. CKD	1.158	0.7524 to 1.765	*0.5149*[a]
	CKD	59 (20%)	Control vs. PLHIV with CKD	1.239	0.7815 to 2.005	*0.4023*[a]
	PLHIV with CKD	38 (19%)	CKD vs. PLHIV with CKD	1.070	0.6852 to 1.674	*0.8180*[a]

PLHIV: People Living with HIV, CKD: Chronic Kidney Disease, CI: Confidence Interval. Qualitative variables expressed as frequencies and percentages. [a]: Chi square

Table 3 Concentrations of hs-CRP, IL-6 and kidney function biomarkers by genotypes

	Groups	TT [me (IQR)]	TC [me (IQR)]	CC [me (IQR)]	*P*
hs-CRP	CKD	4.001 (1.044–9.122)	2.876 (0.943–7.355)	1.752 (0.225–3.278)	*0.2693*[a]
	PLHIV with CKD	2.033 (0.791–5.781)	2.826 (1.611–6.803)	0.730 (0.209–3.848)	*0.2180*[a]
IL-6	CKD	6.409 (3.788–23.91)	6.091 (2.578–14.02)	7.871 (5.392–10.35)	*0.5076*[a]
	PLHIV with CKD	2.772 (1.513–6.334)	3.570 (1.307–5.194)	3.821 (2.744–90.65)	*0.5920*[a]
Creatinine	CKD	16.60 (4.850–35.65)	4.510 (1.620–10.69)	18.17 (9.34-27.00)	*< 0.0001*[a]*
	PLHIV with CKD	1.480 (1.300-2.015)	1.420 (1.210–1.660)	2.420 (1.4203.490)	*0.3262*[a]
eGFR	CKD	4.010 (1.825–10.36)	13.50 (4.710–38.90)	4.055 (2.450–5.660)	*< 0.0001*[a]*
	PLHIV with CKD	53.88 (37.08–61.04)	49 (42.87–60.80)	34.54 (21.10–50.90)	*0.2207*[a]

CKD: Chronic Kidney Disease, PLHIV: People Living with HIV, hs-CRP: high sensitivity C Reactive Protein, eGFR: estimated Glomerular Filtration Rate. Non-parametric variables expressed as medians and interquartile. Kruskall-Wallis's test was used. [me]: median, [IQR]: interquartile, [a]: Kruskall-Walli's test, *: Statistical Significance

Among PLHIV with CKD, based on their $CD4^+$ T cell count and undetectable viral load status, we suggest that CKD per se is not a cause of poor immune reconstitution in this group. Our data is consistent with previous reports, including a study conducted on 417 PLHIV, in which 93.8% achieved viral suppression under the DTG regimen. Of the 391 HIV patients who achieved viral suppression, 50.1% had an undetectable viral load (< 20 copies/mL), while 40.3% of participants had a viral load class of 20–200 copies/mL [16].

The above is important because kidney function biomarkers may increase due to immune activation. In the context of HIV, cystatin C has not proven to be a promising biomarker for the diagnosis and monitoring of CKD. Various studies have shown that PLHIV without ART have a greater state of immune activation mediated mainly by activated $CD4^+$ T and $CD8^+$ T cells, suggesting an increase in cystatin C due to HIV replicative infection [17]. On the other hand, cystatin C levels tend to decrease after viral suppression with ART, because immunomodulatory drugs influence its serum levels. Therefore, kidney function may be underestimated due to the decrease in cystatin C resulting from ART use [18].

Regarding the impact of ART in PLHIV, even though most of our study group was not receiving TDF at the time of evaluation, significant percentage had previous exposure to this drug. In this sense, it has been reported that TDF nephrotoxicity is due to its excretion through the kidney, by glomerular filtratation and to a lesser extent by tubular secretion. Although the exact mechanism of nephrotoxicity has not been established, it is likely that an altered expression of the multidrug resistance protein (MRP-2 and MRP-4) transporters contributes to intracellular TDF accumulation ofin the proximal tubule cells, compromising cellular integrity, and reducing kidney excretion [19]. Also, an increase in the number of cases of kidney failure has been described when TDF is combined with certain antiretrovirals, such as protease inhibitors. This is believed to result from pharmacokinetic interactions that enhance its nephrotoxic potential [20].

It has also been reported that nephrotoxicity associated with TDF treatment is generally low. In a clinical study

involving more than 10,000 patients from India who participated in the TDF expanded access program, only 0.5% of cases developed severe kidney conditions, and 2.2% suffered an increase in creatinine levels greater than 0.5 mg/dL. Risk factors for TDF nephrotoxicity included the presence of previous CKD, concomitant use of other nephrotoxic drugs, low body weight, older age, and a low $CD4^+$ T cell count [21]. Some of these risk factors were prevalent in our population of PLHIV with CKD, which may explain why the observed rate of nephrotoxicity in our cohort is higher than the reported in the previous study.

On the other hand, the genetic results show that the genotype and allele frequencies of the *CRP* SNV are similar to those reported in other studies examining its role in CKD development (Table 2) [13, 22].

In a study that included African American participants from the African American study of kidney (AASK) ($n = 642$) and non-Hispanic black and Mexican American participants from the third national health and nutrition examination survey (NHANES III) ($n = 450$), the objective was the association between *CRP* SNVs and the prevalence of CKD. The frequency of the TT genotype was reported as 74% and 69%, respectively [22]. In another study by the same authors, with NHANES III participants, it was reported that the frequency of the TT genotype was 61% in both populations with CKD, while populations without CKD presented 72% of the TT genotype in non-Hispanic black participants and 62% in Mexican Americans [13].

Similarly, in our study, the presence of the TT genotype was observed in 61.2% of the CKD group, 65% of PLHIV with CKD, and 59.4% of the control group. The results show that the CC genotype was found only in 2.02% of patients with CKD (all, including PLHIV with CKD) and in 4.5% of the control group. These data align with those reported for this SNV in the Mexican American populations with and without CKD (5% and 4%, respectively).

TC genotype has been associated with the presence of CKD in non-Hispanic Black population when compared with controls (36.4% vs. 25.4%). However, this association was not observed in the Mexican American population, where the TC genotype was found in 33% of the population with and without CKD [22]. The results of our study showed a similar pattern.

The secondary objective was to define the inflammatory state of CKD in PLHIV and non-HIV and associate the SNV with the inflammatory state. The presence of the CC genotype was not linked to hs-CRP levels, consistent with the findings reported by Hung et al. However, this contrasts with the NHANES III court, where the minor allele of this SNV was associated with lower hs-CRP levels. Similar associations have been reported between this *CRP* SNVand reduced CRP levels in cancer and cardiovascular disease (CVD) studies involving non-Hispanic Blacks and Mexican Americans [23–25].

The search for a genetic variant of *CRP* that leads to the development of CKD was driven by the importance of hs-CRP as a biomarker of inflammation, mortality, and cardiovascular risk. However, an interesting finding in our study was that hs-CRP values were similar between PLHIV with stage 3 CKD and patients with stage 5 CKD. This suggests that the inflammatory status in PLHIV with CKD in earlier stages may be underrated, indicating that the CKD stage classification in PLVIH is not sufficient to fully reflect the risk of complications related to CKD and chronic inflammation, such as cardiovascular disease. It is well known that hs-CRP concentrations > 3.5 mg/L represent an increased cardiovascular risk. Elevated hs-CRP levels have been observed in PLHIV experiencing their first episode of acute coronary syndrome (ACS) compared to PLHIV without ACS [26]. Similarly, in a study conducted in a South African population of PLHIV and individuals without HIV infection, it was reported that 58% of participants had hypertension (HTN), and 38.4% had hs-CRP concentrations > 3.5 mg/dL, aligning with our findings [27].

Interestingly, there were no differences between hs-CRP concentrations when considering KRT in patients with CKD (Fig. 2). This contrasts with previous studies, in which reported higher concentrations of hs-CRP and IL-6 in HD patients [28]. On the other hand, we observed a correlation of IL-6 with hs-CRP in both groups, consistent withIL-6´s role in stimulating hs-CRP production as an acute phase reactant. Additionally, a negative correlation of IL-6 with eGFR was observed in both study groups. IL-6 is considered a senescence biomarker, in contrast of what we expected, the lowest concentrations of IL-6 were detected in the elderly CKD male group. This might be since most of these patients are under KRT, which impact on IL-6 expected kinetics [29].

Likewise, a correlation between hs-CRP and IL-8 was observed in the PLHIV group, but not in patients with CKD. In this sense, Kibayashi et al. showed that CRP (particularly mCRP isoform) promotes IL-8 production through the activation of the ERK, p38 MAPK, and JNK pathways in human endothelial cells [30]. Conversely, another study indicated that recombinant or tumor-derived IL-8 induces CRP production in hepatocytes, providing a potential feedback loop [31]. However, this pathway has not been confirmed in a different pathogenic model. These findings suggest that the establishment of the inflammatory process between both scenarios in the context of CKD is characterized by specific differences, while IL-6 and hs-CRP present a parallel behavior in CKD, the PLHIV with CKD exhibit a pattern more closely associated with hs-CRP or IL-8. Whether IL-8 high concentrations are associated with the inflammatory

isoform of CRP (mCRP) in the context of HIV and CKD remains to be elucidated.

On the other hand, IL-18 is a pro-inflammatory cytokine that plays a crucial role in immune activation, particularly in chronic inflammatory conditions such as CKD and HIV infection. As a member of the IL-1 cytokine family, it contributes to kidney inflammation, fibrosis, and the progression of kidney disease. Additionally, IL-18 has been identified as a key component of the inflammatory profile of CVD. Elevated IL-18 levels in CKD have been linked to uremia and monocyte activation, as monocytes are among the primary producers of IL-18 [32, 33]. Our observations indicate that IL-18 levels tend to be higher in advanced CKD stages, a trend also reported by Formanowicz, who found that lower IL-18 concentrations were associated with a protective effect against cardiovascular mortality in non-diabetic CKD patients [34].

In the context of CKD, IL-18 is recognized as a biomarker of tubular injury and is strongly associated with disease severity and progression [35]. Elevated IL-18 levels have been reported in patients with reduced kidney function and are linked to worse clinical outcomes [36]. However, in our results, no statistically significant differences were found between groups, nor correlation with eGFR.

For PLHIV, IL-18 is particularly relevant due to its role in persistent immune activation and inflammation, key drivers of comorbidities in individuals with long-term HIV infection. Previous studies have shown that PLHIV have higher IL-18 levels than HIV-negative individuals, with these levels correlating with biomarkers of immune activation and cardiovascular risk [37].

Finally, numerous studies have shown that IL-6, IL-8, and hs-CRP, particularly IL-8, are excellent prognostic biomarkers for predicting mortality associated with cardiovascular events in people with ESRD [38–40]. We suggest that elevated levels of IL-8 and hs-CRP in PLHIV with CKD group, represent great concern related to the higher risk of cardiovascular complications, regardless of CKD stage.

Given the lack of studies addressing the immunopathogenesis of CKD in the context of HIV, these findings contribute to a better understanding of the characteristics of the inflammatory process in PLHIV who have developed CKD.

Conclusions

In conclusion, the inflammatory state associated with CKD appears to be directly related to genetic susceptibility in our study. *CRP* SNV rs2808630 was not a genetic marker for CKD in our population. However, hs-CRP levels showed slightl differences between groups and appeared to be underestimated when related with CKD stage in PLHIV. Also, high IL-6 concentrations were related to the CKD group by eGFR, while IL-8 showed stronger association with CKD in PLHIV, which shows a mild difference in the inflammatory profile of CKD with and without the presence of HIV. Our key findings are listed below in Table 4.

Table 4 Key findings

Key findings
• The SNV rs2808630 of CRP is not associated with CKD in the western Mexican population.
• The presence of this SNV does not appear to influence hs-CRP or IL-6 levels.
• hs-CRP levels in PLHIV remain similar between early and advanced CKD stages.
• Elevated IL-6 concentrations are associated with CKD, as determined by eGFR.
• IL-8 shows a stronger association with CKD in PLHIV.
• IL-18 is not linked to CKD progression in either group; however, follow-up studies may clarify whether IL-18 serves as a prognostic biomarker for cardiovascular protection.

Abbreviations

AASK	African American study of kidney
ACS	Acute coronary syndrome
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
BMI	Body mass index
CKD	Chronic kidney disease
CRP	C-Reactive protein
CVD	Cardiovascular disease
DNA	Desoxyribonucleic acid
DTG	Dolutegravir
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme linked immunosorbent assay
ESRD	End stage renal disease
HD	Hemodialysis
HIV	Human immunodeficiency virus
hs-CRP	High sensitivity C-Reactive protein
HTN	Hypertension
KDIGO	Kidney disease improving global outcomes
KRT	Kidney replacement therapy
mCRP	Monomeric C-Reactive protein
miRNA	Micro ribonucleic acid
mRNA	Messenger ribonucleic acid
MRP	Multidrug resistance protein
NHANES III	Third national health and nutrition examination survey
NNRTIs	Non-Nucleoside reverse transcriptase inhibitors
NRTIs	Nucleoside reverse transcriptase inhibitors
PCR	Polymerase chain reaction
pCRP	Pentameric C-Reactive protein
PD	Peritoneal dialysis
PLHIV	People living with HIV
SNV	Single nucleotide variant
T2D	Type 2 diabetes
TAF	Tenofovir Alafenamide
TDF	Tenofovir disoproxil fumarate
uACR	Urine albumin to creatinine ratio

Supplementary Information

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Supplementary Material 1

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Author contributions
MA, AT, LG, JH and JA conceptualized the idea of the project; LG, JA, AV, VR, PM, JC, JT, PM and AT performed patient recruitment; AT carried out the experimentation; MA, KS and AT reviewed the experimentation; LG, JC, JA, AV, VR, PM, JT, ZR, JH, KS, MA and AT analysis of clinical and experimental data; AT and MA wrote original draft and its preparation; MA took charge of resources; all authors read, review and have agreed the final manuscript.

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Data availability
The datasets generated and/or analyzed during the current study are not publicly available, only available under reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
This research has been approved from the Ethics and Biosafety Committee of the Civil Hospital of Guadalajara "Fray Antonio Alcalde" with registration No. 120/30 and official No. HCG/CEI-1502/20. And a written informed consent was obtained from all participants before inclusion to the study, according to the ethical guidelines of 2013 Declaration of Helsinki for medical research involving human subjects and ensured ethical standards and methodological transparency.

Consent for publication
Participants gave written informed consent for the publication of their clinical data.

Competing interests
The authors declare no competing interests.

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