Immunological Impact of Calprotectin and Interleukin-34 in Immunocompromised Patients with Chronic Cytomegalovirus Infection

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Abstract—**Cytomegalovirus (CMV) causes the most prevalent and severe opportunistic infection in immunocompromised patients following solid organ or hematopoietic stem cell transplantation, with the highest morbidity and mortality rates among herpesviruses. The study objective was to compare and determine the CMV chronic infection and related hematological and immunological markers in immunodeficient and immunocompetent participants. A prospective case–control study among 85 participants was designed to measure CMV-immunoglobulin G (IgG) and to evaluate interleukin-34 and serum calprotectin as biomarkers; total leukocyte, granulocyte, lymphocyte, and platelet counts were also measured following blood collection. A high CMV IgG positivity was observed across all groups in this investigation, indicating widespread chronic infection. CMV IgG, interleukin-34 (IL-34), and calprotectin levels did not differ significantly between immunocompetent and immunocompromised individuals. There was no significant association between CMV IgG and IL-34 or serum calprotectin. Furthermore, IL-34 showed a significantly higher mean in males compared to females ($p = 0.002$). An exploratory observation was that IL-34 had a moderate positive correlation with serum calprotectin ($\rho = 0.609$, 95% confidence interval: 0.450–0.731, $p < 0.001$) across all study participants. The study findings call for more research to elucidate the clinical roles of calprotectin and IL-34 in immunocompromised patients.**

***Index Terms*— Biomarker, Calprotectin, Cytomegalovirus, Immunocompromised, Interleukin-34, Sulaimani**

I. Introduction

Human cytomegalovirus (HCMV) is a member of the beta-herpesviridae subfamily of the Herpesviridae (Liu, et al., 2024). HCMV can infect fibroblasts, epithelial cells, endothelial cells, and immune cells (Vasiljevic, et al., 2024). In healthy individuals, the initial infection is often asymptomatic, leading the virus to remain dormant in bone marrow myeloid lineage cells and hematopoietic progenitor cells (such as CD14+ monocytes) for the individual's lifetime, and under certain conditions, the virus may reactivate (Griffiths and Reeves, 2021; Vasiljevic, et al., 2024). The percentage of adults with specific cytomegalovirus (CMV) immunoglobulin G (IgG) antibodies is over 60% in developed countries, whereas in many developing nations, it is above 90% (Griffiths and Reeves, 2021).

Besides the fact that HCMV infection typically has no symptoms, CMV is also capable of producing a broad spectrum of serious diseases, such as encephalitis, pneumonitis, hepatitis, uveitis, retinitis, and gastrointestinal problems in immunocompromised individuals (Vasiljevic, et al., 2024). Immunocompromised patients have a weakened immune system due to a particular health condition, medication, or treatment that suppresses the immune system, such as hematologic malignancy (with or without hematopoietic stem cell transplantation [HSCT] for any reason), receiving chemotherapy, solid organ transplantation (SOT), intensive care unit patients, or drug-induced immunosuppression (Chaemsupaphan, et al., 2020; Fernández, et al., 2024). In addition, HCMV is the most prevalent and severe opportunistic infection following SOT or HSCT (Atabani, et al., 2012; Griffiths and Reeves, 2021).

Interleukin-34 (IL-34) is a cytokine produced by monocytes, macrophages, neurons, endothelial cells, fibroblasts, epithelial cells, and hepatocytes (Monteleone, et al., 2022). IL-34 plays a crucial role in the development, homeostasis, and function of myeloid-lineage cells, such as monocytes and macrophages, by regulating their survival, proliferation, and differentiation (Shang, et al., 2023). HCMV reactivation is a differentiation-dependent process (Sinclair, 2008). The transition can be triggered by extrinsic ligands such as IL-34 (Kuhara, et al., 2008), which bind to the colony-stimulated factor-1 receptor (CSF-1R) and activate the mitogen-activated protein kinase/extracellular signal-regulated kinase and phosphoinositide 3-kinase/protein kinase pathways. These pathways promote the nuclear translocation of nuclear factor kappa-light-chain-enhancer of activated B cells and cAMP response element-binding protein, which coordinately remodel the epigenetic landscape of the viral major immediate-early promoter, switching the virus from transcriptional silence to active lytic

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replication (Kew, et al., 2014). Moreover, elevated IL-34 levels have been observed in several viral infections, such as hepatitis B, reflecting ongoing immune activation or tissue inflammation, suggesting that viral pathogens may directly modulate its expression (Yu, et al., 2015; Franzè, et al., 2020). IL-34 emerges as a plausible mediator and potential biomarker of HCMV latency and reactivation dynamics. Therefore, understanding how IL-34 influences HCMV reactivation is essential for identifying new prognostic markers and therapeutic targets, particularly in immunocompromised patients at high risk of HCMV disease.

S100A8 and S100A9 subunits from the S100 protein family form the calcium and zinc-binding heterodimer calprotectin (Kopi, et al., 2019). The cytoplasm of neutrophils, monocytes, macrophages, and dendritic cells all exhibit high levels of its expression (Kopi, et al., 2019; Bayrakci, et al., 2022). During the early immune-cell differentiation, calprotectin is rapidly upregulated, especially in response to pathogen- or damage-associated molecular patterns (PAMPs) (Kopi, et al., 2019). In recent studies, serum and fecal calprotectin levels are valuable indicators of inflammation in viral infections, such as COVID-19 (Kopi, et al., 2019; Bayrakci, et al., 2022; Toma, et al., 2022). HCMV infection activates NF-κB-dependent inflammatory pathways and promotes myeloid cell activation, both of which are known to induce calprotectin expression (Chen, et al., 2025). Therefore, calprotectin may reflect CMV-related immune activation rather than non-specific inflammation alone, especially in immunocompromised patients. However, despite these biologically plausible links, the role of calprotectin as a CMV-specific biomarker in immunocompromised patients has not been systematically characterized, and its ability to distinguish CMV-related inflammation from other infectious or non-infectious causes remains unclear.

This study aimed to evaluate the immunological impact of calprotectin and interleukin-34 in immunocompromised patients with chronic CMV infection by comparing HCMV seropositivity and associated immunological and hematological parameters between immunocompromised patients and immunocompetent individuals. The study hypothesis is to determine whether these markers are associated with CMV-related immune alterations in immunocompromised hosts.

II. Materials and Methods

A. Study Design and Setting

This study was conducted as a prospective case–control investigation to assess immunological characteristics among HCMV-IgG-positive individuals with different immune statuses. The study population consisted of (1) a study group of CMV IgG-positive immunocompromised patients (including kidney transplant [KT] recipients, individuals who had undergone bone marrow transplantation, and patients with hematological malignancies [HMs]). (2) A control group of CMV IgG-positive immunocompetent individuals was included to provide a baseline for comparison. All participants were recruited between October 2024 and February 2025 at Hiwa Hospital, the bone marrow transplant (BMT) center, and a private health clinic specializing in kidney transplantation monitoring in Sulaimani, Iraq.

B. Sampling and Data Collection

Sampling and data collection were initiated following validation of the questionnaire by six subject-matter specialists and approval from the research ethics committee (22nd of October, 2024, reference number 37). Before participation, all individuals were provided with patient information sheets and verbal consent forms, which were completed to ensure informed participation. Sociodemographic and clinical data were collected from 106 individuals using a validated questionnaire, and each participant was assigned a unique code. The collected descriptive sociodemographic variables included age, body mass index (BMI), smoking status, and gender, whereas the clinical data included the presence of chronic diseases. Following questionnaire completion, venous blood samples were collected from each participant using two separate tubes: One ethylenediaminetetraacetic acid (EDTA) tube for hematological analysis and one gel tube for serological testing. Hematological assessments were performed on the same day as sample collection. Serum samples were centrifuged at 3000 rpm for 5 min, then aliquoted into multiple 0.5 mL portions, and stored at −20°C for subsequent immunological investigations.

C. Participant Selection Criteria

Participants were chosen based on their immune status. Individuals considered immunocompromised (those who had undergone bone marrow or KTs or had received chemotherapy for HM) were assigned to the study group. In contrast, immunocompetent healthy individuals were assigned to the control group. Among the participants, further filtering was performed based on inclusion criteria: (1) Immunocompromised transplant patients should have undergone transplantation within 1–3 months, (2) immunocompromised cancer patients must have received three to six doses of chemotherapy, (3) the lymphocyte count in a complete blood count (CBC) test had to be below $1.5 * 10^9$/L for immunocompromised patients, and (4) all participants must be CMV-IgG seropositive. Those who did not meet these criteria were excluded from the study group, leaving 85 participants out of the initial 106 for further investigation. The final participant breakdown included 25 immunocompetent control individuals (C) and 60 immunocompromised patients (20 KT recipients, 20 BMT recipients, and 20 patients with HMs).

D. CBC

A CBC was performed on the same day as blood collection for all participants to evaluate essential hematological parameters. EDTA anticoagulated blood samples were analyzed to determine total white blood cell (WBC) count, lymphocyte count, and granulocyte count using the Coulter counter (Swelab Alfa, Boule Diagnostics AB, Sweden), following standardized laboratory protocols. These immune cell counts were used not only to profile participants' immunological status but also as inclusion criteria to ensure hematological consistency across study groups. Only individuals who's their CBC values fell within clinically acceptable ranges relative to their health status were included in the final analysis, to ensure the validity and comparability of results between the immunocompromised groups and the immunocompetent control group.

E. Detection of CMV IgG

Before sample analysis, both the instrument and the reagent kits were validated using the manufacturer-provided calibrators and quality control materials to ensure accuracy and reliability. Then, CMV-specific immunoglobulin G (CMV IgG) level was measured using the Chorus CMV-IgG specific kit (CMV IgG quantitative Enzyme Immunoassay, DIESSE, Italy) on the Chorus Trio instrument (Diesse Diagnostica Senese, Italy), a fully automated, single-test format enzyme-linked immunosorbent assay (ELISA)-based system. All procedures were performed in strict accordance with the manufacturer's instructions.

F. Immunological Markers

Serum calprotectin and IL-34 were quantified using ELISA kits (BT-LAB, Korea), a microplate reader (BioTek 800TS, Merck, USA), and a serum aliquot for each sample, according to the manufacturer's instructions. The optical density values for both IL-34 and calprotectin were measured and converted to concentrations using a standard curve generated in GraphPad Prism (version 9.0, GraphPad, La Jolla, CA, USA) with the standards provided by the kit manufacturer.

G. Data Analysis

Research data were analyzed using IBM SPSS Statistics for Windows (version 27.0; IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests, along with skewness and kurtosis values. Most variables, including age, interleukin-34, serum calprotectin, granulocyte count, lymphocyte count, and HCMV IgM, were not normally distributed (Shapiro–Wilk $p \leq 0.05$), whereas BMI and platelet count were approximately normally distributed (Shapiro–Wilk $p > 0.05$). Considering the non-normal distribution of primary variables, statistical tests were selected, which include the Chi-square test for examining associations or independence between two categorical variables, Spearman's rank correlation test for evaluating the strength and direction of association between two continuous or ordinal variables, and the Mann–Whitney U test for differentiation between continuous and categorical variables when comparing two independent groups. Multi-quantile regression analysis used to adjust cofounders. A $p \leq 0.05$ is considered significant.

III. Results

A. Participant Characteristics

The sociodemographic data were analyzed for all participants, and the results for the 85 participants indicated that 33 (38.8%) were female and 52 (61.2%) were male. Regarding BMI, the median value was 24.4 (8.8) kg/m^2. Clinical data analysis showed that 38 (44.7%) of all participants had a chronic disease, while 47 (55.3%) did not. Among the 38 participants with chronic disease, 6 cases (15.7%) had comorbidity. Further details about the study participants' sociodemographic data are presented in Table I.

Two patient groups (hematological cancer and KT) were studied separately compared to the immunocompetent control group concerning smoking and clinical outcomes; all BMT

TABLE I
Sociodemographic and Clinical Data of the Study Groups

Variables	T (n=85)	KT (n=20)	BMT (n=20)	HM (n=20)	C (n=25)
Numerical variables			Median (IQR)		
Age, years	39.5 (33)	40.5 (27)	25 (42)	51 (29)	36 (36)
BMI, kg/m^2	24.4 (8.8)	24.5 (8.3)	20.2 (12.8)	25.9 (7.8)	24.9 (10.3)
Categorical variables			Frequency (%)		
Gender					
Female	33 (38.8)	3 (15)	9 (45)	11 (55)	10 (40)
Male	52 (61.2)	17 (85)	11 (55)	9 (45)	15 (60)
Immune status					
Immunocompromised CMV IgG+Ve	60 (70.6)	20 (100)	20 (100)	20 (100)	0
Immunocompetent CMV IgG+Ve	25 (29.4)	0	0	0	25 (100)
Smoking status					
Yes	14 (16.5)	8 (40)	0	4 (20)	2 (8)
No	71 (83.5)	12 (60)	20 (100)	16 (80)	23 (92)
Chronic disease*					
Chronic kidney disease	20 (52.6)	20 (100)	0	0	0
Hypertension	20 (52.6)	12 (60)	1 (5)	7 (35)	0
Diabetes	13 (34.2)	8 (40)	1 (5)	4 (20)	0
Thalassemia	4 (10.5)	0	4 (20)	0	0

All the sociodemographic data regarding the study participants are presented in this table. n: Case frequency, and %: Percentage for categorical variables, while median and IQR: Interquartile range used for present non-parametric numerical variables. T: Total participants, KT: Kidney transplant, BMT: Bone marrow transplant, HM: Hematological malignancy, and C: control group (immunocompetent). Reported zero values reflect true zero counts rather than missing observations. *Out of 85 participants, 38 had chronic diseases, and 6 of them had more than one. The percentages for each disease represent the rate of each chronic disease among these 38 participants

participants were non-smokers. The hematological cancer group exhibited an odds ratio of 2.500 (95% confidence interval [CI]: 0.509–12.287) and a Pearson's Chi-Square value of 1.385 (p = 0.239), indicating that the connection was not statistically significant. This statistic suggests a potential trend, although the CI is wide and includes 1. The KT group, on the other hand, had a statistically significant correlation between transplant status and smoking. Smokers had considerably higher odds of being in the KT group, according to the Chi-Square test, which produced a value of 6.583 (p = 0.010), a strong odds ratio of 5.000 (95% CI: 1.192–20.969), and supporting significance in Fisher's exact test (p = 0.014) (data not shown).

B. Immunological Parameters

The statistical analysis for differentiating immunological variables between study groups is shown in Fig. 1. In addition to fluctuations in CMV-IgG, IL-34, and serum calprotectin levels between study groups, the Mann–Whitney U test (U) with two-tailed Monte Carlo simulation (10,000 permutations) showed no statistically significant differences in these parameters between the C group and the other groups.

Total WBC in HM had a significantly lower median (2.2) than C group (7.3) (U = 68, p = 0.001, r = 0.62, very large effect), followed by the BMT group (5.7), which in compare to C group had U = 138, p = 0.01, r = 0.38, moderate effect). The median granulocyte count was the lowest in the HM group (1.75) and the highest in the KT group (5.5). Their differences were significant (U = 125.5, p = 0.005, r = 0.42, moderate effect for HM and U= 161.5, p = 0.04, r = 0.3 for KT) compared to the C group (4.4). The lymphocyte median was 3 in the C group, the highest among the groups. Then, BMT had 2, which is lower than the C group but higher than KT, which was 0.95. The lymphocyte median was lowest for HM 0.35. Their differences compared to the C group were significant (p < 0.001; effect size moderate to very large). Platelet levels were at their peak in the control group, then in KT, BMT, and HM, at 261, 201, 131, and 88.5, respectively. Platelets showed significant differences across all groups compared to the C group (p < 0.05 in KT, p < 0.001 in both BMT and HM).

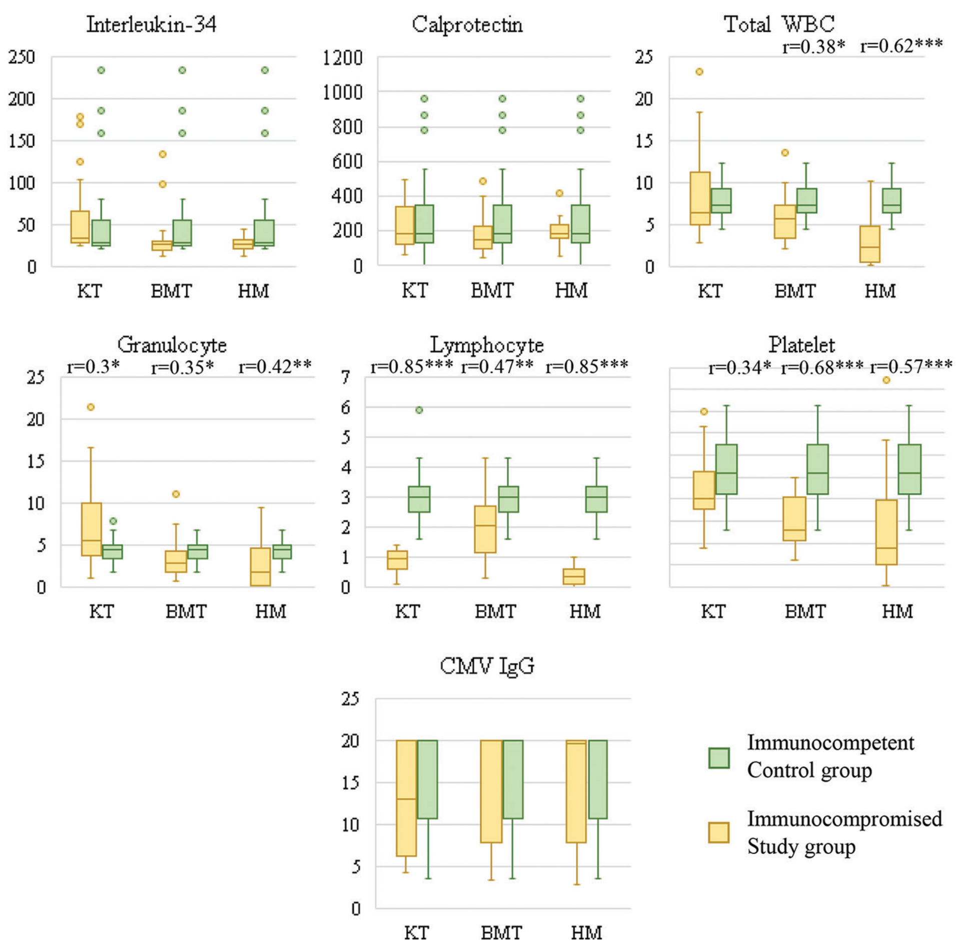

Fig. 1: Cluster boxplot difference of immunological parameter between study groups. This boxplot figure shows the median, interquartile range, and whiskers for each immunological and hematological parameter across study groups. Group differences were assessed using the Mann–Whitney U test with Monte Carlo two-tailed estimation (10,000 permutations). *Indicates statistical significance (p < 0.05), **(p < 0.01), ***(p ≤ 0.001). Effect size is reported as rank-biserial correlation (r), only for significant differences. No asterisk means no significance. T.WBC: Total white blood cells, CMV IgG: Cytomegalovirus immunoglobulin G, BMT: Bone marrow transplant group, KT: Kidney transplant group, HM: Hematological malignancy group.

C. Comparisons

The non-parametric distributions of IL-34, serum calprotectin, and CMV IgG were investigated in this study in relation to several clinical and sociodemographic factors, as shown in Table II. Gender differences in IL-34 were statistically significant ($p = 0.002$), with males exhibiting higher levels (mean rank = 49.5) than females (mean rank = 32.8) across all study groups. In addition, patients with chronic kidney disease (CKD) had considerably higher IL-34 levels ($p = 0.001$), with a significantly higher mean rank (58.9) than those without CKD (38.1). Although IL-34 measurements were generally higher in smokers (mean rank = 53.1) than in non-smokers (41), this difference was not statistically significant ($p > 0.05$). Other chronic diseases and continuous variables had no substantial connection with IL-34. However, multi-quantile regression analysis evaluating the independent effects of age, sex, and CKD on IL-34 concentrations revealed that gender was the only predictor consistently associated with IL-34 levels in the 0.25 ($\beta = 6.102$, 95% CI: 3.215–8.989, $p < 0.001$) and 0.50 quantiles ($\beta = 7.397$, 95% CI: 1.089–13.705, $p = 0.022$), whereas CKD demonstrated a statistically significant predictive effect restricted to the 0.25 quantile ($\beta = 8.482$, 95% CI: 4.718–12.246, $p < 0.001$) (data not shown).

Calprotectin and CMV IgG levels did not significantly vary across any of the categorical and numerical variables studied, in contrast to IL-34, as indicated in Table II.

This table illustrates the effects of certain sociodemographic and clinical variables on IL-34, serum calprotectin, and CMV IgG levels, as determined by p-values, which indicate correlation for numerical variables and difference for categorical variables. A $p \leq 0.05$ is considered significant.

D. Correlations of IL-34 with Immunological Parameters

The Spearman's Rank Correlation coefficients (r) between IL-34 levels and other immunological markers for each study group are displayed in the annotated correlation heatmap in Fig. 2. None of the correlation results between IL-34 and other immunological parameters were significant in either study group ($p > 0.05$).

E. Correlations of Serum Calprotectin with Immunological Parameters

The Spearman's Rank Correlation coefficients (r) between calprotectin and several immune-related parameters for all study groups are displayed in the annotated correlation heatmap in Figure III. The most noteworthy result was that IL-34 and calprotectin showed a statistically significant, moderate-to-strong positive correlation across all groups, except HM ($\rho = 0.34$, 95% CI: - 0.14–0.67, $p > 0.05$). The C group had the strongest correlation ($\rho = 0.77$, 95% CI: 0.53–0.89, $p < 0.001$), followed by KT ($\rho = 0.65$, 95% CI: 0.28–0.85, $p = 0.002$), T ($\rho = 0.609$, 95% CI: 0.450–0.731, $p < 0.001$), and BMT had a moderate positive correlation ($\rho = 0.65$, 95% CI: 0.29–0.85, $p = 0.002$).

On the other hand, there were typically weak or no significant relationships between calprotectin and CMV IgG levels or other immune cell populations.

IV. Discussion

All patients in the current study were CMV-specific IgG seropositive, confirming latent infection or universal past exposure. This result is consistent with several studies that have been carried out in Iraq and have found consistently

TABLE II
Sociodemographic and Clinical Data Association With IL-34, Calprotectin, and+Ve CMV-IgG Level

Variables	Interleukin-34		Serum calprotectin		CMV-IgG	
	Mean rank	p-value	Mean rank	p-value	Mean rank	p-value
Age	37.1	0.095	37.1	0.219	37.1	0.155
BMI	23.9	0.227	23.9	0.127	23.9	0.494
Gender						
Female	32.8	0.002	39.9	0.348	41.8	0.71
Male	49.5		45		43.7	
Smoking						
Yes	53.1	0.095	41.6	0.817	44.4	0.809
No	41		43.3		42.7	
Thalassemia						
Yes	58.5	0.198	48	0.678	41.8	0.911
No	42.2		42.8		43.1	
Hypertension						
Yes	45.7	0.576	43.3	0.95	42	0.82
No	42.2		42.9		43.3	
Diabetes						
Yes	51.6	0.171	42.5	0.937	53.4	0.076
No	41.4		43.1		41.1	
Chronic kidney disease						
Yes	58.9	0.001	43.3	0.955	36	0.121
No	38.1		42.9		45.2	

This table illustrates the effects of certain sociodemographic and clinical variables on IL-34, serum calprotectin, and CMV IgG levels, as determined by p-values, which indicate correlation for numerical variables and difference for categorical variables. A $p \leq 0.05$ is considered significant

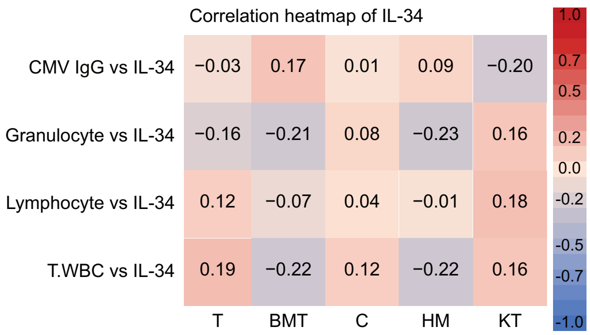

Fig. 2. Correlation heatmap of interleukin-34 with other immunological parameters by groups. This correlation heatmap illustrates the correlations between interleukin-34 and other immunological variables, including total white blood cells, lymphocyte, and granulocyte counts, and CMV IgG levels, separately within each group and collectively across all study groups. The intensity and direction of the correlation are indicated by each cell; warmer colors denote positive correlations, whereas cooler colors denote negative ones. T: Total participants, BMT: Bone marrow transplant, C: control, HM: Hematological malignancy, KT: Kidney transplant.

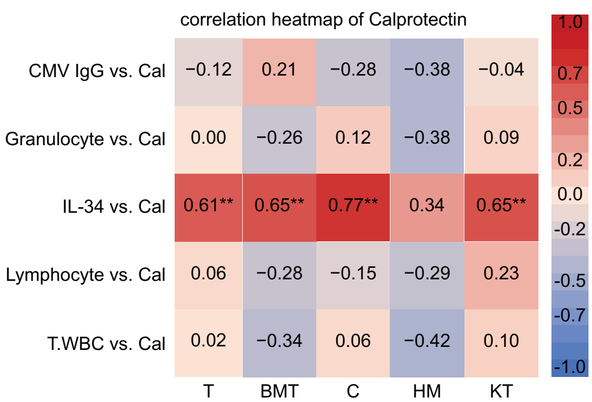

Fig. 3. Correlation heatmap of calprotectin with other immunological parameters by groups. Spearman's rank correlation coefficients between calprotectin and specific immunological characteristics across various study groups are shown in an annotated correlation heatmap. The intensity and direction of the correlation are indicated by each cell; warmer colors denote positive correlations, whereas cooler colors denote negative ones. Asterisks indicate statistically significant relationships (*$p < 0.05$, **$p < 0.01$). CAL: Calprotectin, T: Total participants, BMT: Bone marrow transplant, C: Control, HM: Hematological malignancy, KT: Kidney transplant.

high rates of CMV IgG seropositivity, especially among immunocompromised patients. A survey in Baghdad reported a 97.7% seroprevalence of CMV IgG among KT recipients (Al-Alousy, et al., 2011). HCMV IgG seropositivity rates of 98.3%, 95–96%, and 95%, respectively, were reported in research conducted among women with poor obstetric history in Kirkuk, pregnant women in Diwaniyah and Zakho, indicating that CMV latency is common in Iraq's general and reproductive-age populations (Aljumaili, Alsamarai and Najem, 2014; Abdulqader Naqid, et al., 2019; Al-Zubaidi, et al., 2025).

In the details of statistical analysis, an exploratory result showed that smoking was significantly more common among KT CMV IgG seropositive patients. Smokers had considerably higher odds of being in the KT group, highlighting how smoking history may affect the kidney dysfunction and clinical course that leads to transplantation. This result is compatible with other research showing that smoking has a negative impact on the progression of chronic renal disease, as well as the results of KTs (Ritz, Zeier and Orth, 2000). Furthermore, according to Lee, et al., research, the degree of smoking exposure may have detrimental impacts on the development of CKD (Lee, et al., 2021).

Regarding the hematological parameters, the current study's findings align with earlier research demonstrating that leukopenia, lymphopenia, and thrombocytopenia are commonly observed in individuals with HMs, resulting from either marrow infiltration or chemotherapy-induced suppression (Colombo, Gallipoli and Castelli, 2014). A study reported that early post-transplant pancytopenia is common in BMT patients, and engraftment protocols are necessary to support delayed immune reconstitution (Castillo, et al., 2017). Although KT patients may have relatively stable WBC counts despite immunosuppression, thrombocytopenia and lymphocytopenia remain frequent adverse effects of immunosuppressive medications, particularly with tacrolimus and mycophenolate mofetil (Hurst, et al., 2011; Yu, et al., 2018).

The CMV IgG findings revealed no significant difference between immunocompromised patients and immunocompetent participants. In contrast, a study claims that a specific immunosuppressant decreases immunoglobulin G levels (Dalvand, et al., 2025). This may be due to the immunosuppressant rituximab used in Dalvand's study, but the participants in this study have not used it.

The IL-34 findings revealed no significant difference between immunocompromised and immunocompetent participants in this study. To the best of the researcher's knowledge, there is no clinical research directly evaluating the IL-34 level in relation to immunodeficiency. However, there are several studies on the role of IL-34 in immune-dysregulated disease. A survey among liver transplant patients recorded that after transplantation, IL-34 levels stay high and rise even more in response to rejection. IL-34 may suppress the immune system during transplantation (San Segundo, et al., 2016). These differences may be due to variations in study populations. Thus, these findings should be evaluated cautiously and confirmed in larger, multicenter populations.

The KT and C groups had numerically higher IL-34 levels than the BMT and HM groups, but the differences were not statistically significant. These results suggest that, at least in stable clinical settings, IL-34 may not distinguish between immunocompromised states and those of healthy individuals at the systemic level. Similarly, previous studies suggest that IL-34 expression is frequently context-dependent and mainly localized rather than systemic. While individuals with stable conditions may have blood levels comparable to those of healthy controls, IL-34 has been associated with immune modulation in transplant settings, particularly during acute rejection events and active disease (San Segundo, et al., 2016; Freuchet, et al., 2021). In addition, IL-34 expression in the bone marrow fluctuates and may not always be detectable in serum measures in HMs, such as multiple myeloma (Baghdadi, et al., 2019).

Across all positive CMV IgG groups, males had higher mean ranks for IL-34 than females, and there was a statistically significant difference in IL-34 levels between the genders. This difference suggests that sex-related factors, such as male sex hormones, may influence IL-34 expression. These results may indicate immunological regulation, in which sex-specific hormonal or genetic factors could influence IL-34. Sex-based variation in IL-34 expression has not received much attention to date. Direct comparisons between the sexes in healthy individuals or in illnesses associated with immunodeficiency are still rare, despite studies reporting higher IL-34 levels in female populations with autoimmune and endocrine disorders, such as polycystic ovary syndrome (Cai, et al., 2022).

Despite variations in serum calprotectin levels among study groups, the differences were not statistically significant. To the best of the researcher's knowledge, this is the first study to assess and compare serum calprotectin levels in these specific clinical groups, namely CMV-IgG-positive patients. Relatively, elevated fecal calprotectin has been noted in graft-versus-host disease and gastrointestinal inflammation in hematopoietic stem cell transplant recipients, making it a valuable tool for the early detection and follow-up of intestinal complications following transplantation (Weber, et al., 2017; Imhann, et al., 2018). However, rather than in post-transplant or cancer-related situations, serum calprotectin has been more often examined in chronic renal disease or dialysis settings, where elevated levels were observed in these groups (Kanki, et al., 2020; Lee, et al., 2025). The lack of significant variation in this study may be due to the individuals' stable clinical condition, the localized expression of calprotectin, or individual variations in systemic inflammatory activity.

Another exploratory result was that IL-34 and calprotectin showed a consistently high, statistically significant, moderate-to-strong positive correlation across all groups, except HM. This is a new observation, since no prior research has documented this relationship, to the best of the researcher's knowledge. IL-34, which promotes monocyte/macrophage survival through CSF-1R signaling, may regulate neutrophil-mediated inflammation, as evidenced by the release of calprotectin (Xing and Lo, 2017). This interaction might be a compensatory reaction to inflammation in the transplant environment or a common innate immune pathway.

Study limitations include small subgroup sizes, which may limit the ability to detect small effect sizes. In addition, the study was conducted in Sulaimani city, Iraq, which may limit the generalizability of the findings. Future studies with larger, longitudinal cohorts and CMV viral load assessments are warranted to further elucidate the roles of IL-34 and calprotectin in CMV infection among immunocompromised patients.

V. Conclusion

This study highlights key immunological and inflammatory features of CMV-IgG-seropositive individuals across clinical groups, confirming that CMV remains a common latent infection. Smoking was also identified as a contributing risk factor for CKD and post-transplant complications. Notably, IL-34 could be gender-based associated. This study found no association between immune state and IL-34 nor calprotectin. Furthermore, there was no significant association between CMV IgG and IL-34 or serum calprotectin. A novel finding is the positive correlation between IL-34 and serum calprotectin. Further longitudinal and mechanistic studies are needed to clarify the clinical value of these biomarkers and to guide care for immunocompromised patients and improve transplant outcomes.

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