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PAD-4 Elevation Distinguishes Acute from Past CMV Infection in Medical Students

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Abstract

General Background: Cytomegalovirus (CMV) is a persistent herpesvirus with complex interactions between humoral and innate immunity. **Specific Background:** Neutrophil extracellular trap formation (NETosis), mediated by peptidylarginine deiminase-4 (PAD-4), is increasingly recognized in antiviral defense, yet its relation to CMV serological phases remains unclear. **Knowledge Gap:** The association between CMV IgM/IgG serostatus and PAD-4 activity as a surrogate marker of innate immune activation has not been well characterized in healthcare-exposed student populations. **Aims:** This cross-sectional study assessed CMV seroprevalence across three medical departments and examined PAD-4 levels according to CMV serology. **Results:** Among 300 students, overall CMV seroprevalence was 16.33%, highest in nursing (21%) and lowest in medical laboratory students (11%). PAD-4 levels were significantly higher in IgM-positive individuals than IgG-positive and seronegative peers (p=0.003), while no sex-based difference was observed. **Novelty:** The study links CMV serological phase to differential PAD-4 activity, indicating heightened innate activation during recent infection and relative immune quiescence in past exposure. **Implications:** PAD-4 may serve as a biomarker of acute CMV-related innate responses and supports targeted infection-control awareness in healthcare training environments.

Highlights:

- CMV seroprevalence differed across healthcare training departments.
- PAD-4 levels peaked in IgM-positive (recent infection) students.
- PAD-4 showed no significant variation by sex.

Keywords: Cytomegalovirus, PAD-4, NETosis, IgM/IgG Serostatus, Medical Students

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Introduction

Human cytomegalovirus (CMV) is a ubiquitous, double-stranded DNA virus and a member of the family Herpesviridae, and one of the most common, persistent viral infections in the world[1]. Primary infection of CMV often is asymptomatic in immunecompetent patients; however the virus gets into a latent state with recurring reactivation especially during periods of immune stress or dysregulation[2]. CMV infection has remained to be a huge public health issue due to its high seroprevalence rates, its amazing ability to induce subclinical transmission and its potential to affect the immune homeostasis particularly in populations subjected to the healthcare environment[3]. Both innate and adaptive immunity interact in a complex manner to characterize the host immune response against CMV. During the initial infection processes, the innate immune system is rapidly triggered and functions to suppress viral infection and propagation. Neutrophils, which are the central effector cells of innate immunity, are one of the first responders to viral attack and they are central in the containment of pathogens. One of the specialized antimicrobial modalities used by neutrophils is neutrophil extracellular traps (NETs) generation a process known as NETosis. NETs are strands of decondensed chromatin which is decorated with granular antimicrobial proteins and these enzymes can trap and neutralize pathogens[4].

The enzyme peptidylarginine deiminase 4 (PAD -4) is a key mediator of classical NETosis. PAD-4 is found in the nucleus and is an enzyme that catalyzes histone decondensation (citrullination of histone residues) to allow release of NET. High PAD -4 activity has been linked to increased neutrophil activation in a range of infectious and inflammatory diseases, which places PAD -4 as a potential biomarker of NETosis-related innate immune reactions [5-8]. Despite the wide range of studies on NETosis in bacterial infections, there is a growing body of evidence that much like viral pathogens, PAD-4-dependent NETosis can be induced also in antiviral defence, and therefore, can potentially lead to immune-mediated pathology as well [9]. The humoral response evoked by cytomegalovirus infection is typical: IgM antibodies specify new or active infection and IgG antibodies point to exposure in the past or latent infection [6,7]. Although the CMV-specific antibody profiles are highly characterised, the relationship between CMV serological phase and innate activation of immune system and especially NETosis is not clearly understood. The study of biomarkers, like PAD-4, in connection to CMV IgG and CMV IgM positive or negative status can, therefore, provide significant informational support on the dynamics of innate immune activation during specific stages of CMV infection [10]. A unique group of CMV epidemiology and immune response studies can be considered medical students because of their fluctuating exposures to community and clinical settings in training. Curricular, patient, and environmental differences in healthcare related departments could adjust the risk of CMV transmission [11]. Knowledge of CMV seroprevalence among medical students has epidemiological as well as educational implications in its application to infection-control education, as well as preventive outcomes in academic health care environments [11-14].

Against this backdrop, this study made an attempt to estimate seroprevalence of cytomegalovirus (CMV) in students pursuing courses in Community Health Techniques, Nursing Techniques, and Medical Laboratory Techniques streams. Additionally, it aimed at examining the relationship of CMV serostatus and plasma concentrations of peptidylarginine deiminase 4 (PAD-4), a hypothetical surrogate endpoint of innate immunological activation and a potential analog of neutrophil extracellular trap formation (NETosis). Through the combination of serological measurements and immunological biomarkers, it is hoped that this study will not only enhance our understanding of CMV-made innate immunity but also define the future applicability of PAD-4 as an acute-phase biomarker within healthcare exposed student cohort..

Methods

A. Study Design and Setting

An analysis study was conducted across the three cross-sectional healthcare-related academic departments among the medical students who were enrolled to the Community Health Techniques, Nursing Techniques and Medical Laboratory Techniques. The experiment was aimed to measure the relationship of cytomegalovirus (CMV) serostatus and innate immune activation, which is accessed through serum levels of PAD-4.

Inclusion Criteria :

-Studying at one of the chosen departments.

- No overtly ill when analyzed.

- Gave informed consent to attend.

Exclusion Criteria :

-Characteristics of autoimmune disease or chronic inflammatory attacks are known a history of autoimmune disease or chronic inflammatory conditions.

-Recurrent acute bacterial infection not associated with CMV.

- Immunosuppressive or under any anti-inflammatory drugs.

B. Data Collection and Laboratory Analysis :

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Participants' demographic information were collected , including age and sex, was collected through a structured questionnaire. Blood samples were collected from each participant to test for CMV infection using serological assays. Serum samples were analyzed for the presence of CMV-specific antibodies using enzyme-linked immunosorbent assay (elabscience ELISA kit).

PAD-4 were tested for sero- positive Participants and random group of participants with sero-negative tests. So participants were classified into two groups based on serological results: CMV-positive or CMV-negative.

C. Data Analysis:

Descriptive statistics were used to summarize demographic data, and the prevalence of CMV infection was calculated for each department. Chi-squared tests were employed to assess the association between CMV prevalence and demographic variables. Continuous variables (PAD-4 levels) were expressed as mean ± standard deviation (SD) and median with interquartile range (IQR) as appropriate . Welch's independent samples t-test was used to compare PAD-4 levels betweenMales and females,CMV IgM-positive and CMV IgG-positive groups. A p-value < 0.05 was considered statistically significant.

Results

Demographics: The study included 300 medical field students from three different departments: Medical Lab Techniques, Community Health Techniques, and Nursing Techniques. **Table (1).**The participants' ages ranged from 18 to 30 years, and the sex distribution was approximately equal. As the medical field institute has only two college levels :freshman and sophomore the **Figure (1)** shows the distribution of the students according to their stage .

Department	Male No.	%	Female No.	%
Community Health department	45	45%	55	**55%**
Nursing techniques Department	40	40%	60	**60%**
Medical Laboratory techniques	35	35%	65	**65%**
Total	120		180	**300**

Figure 1. **Table (1) :**Distribution of the study population according to sex and departments

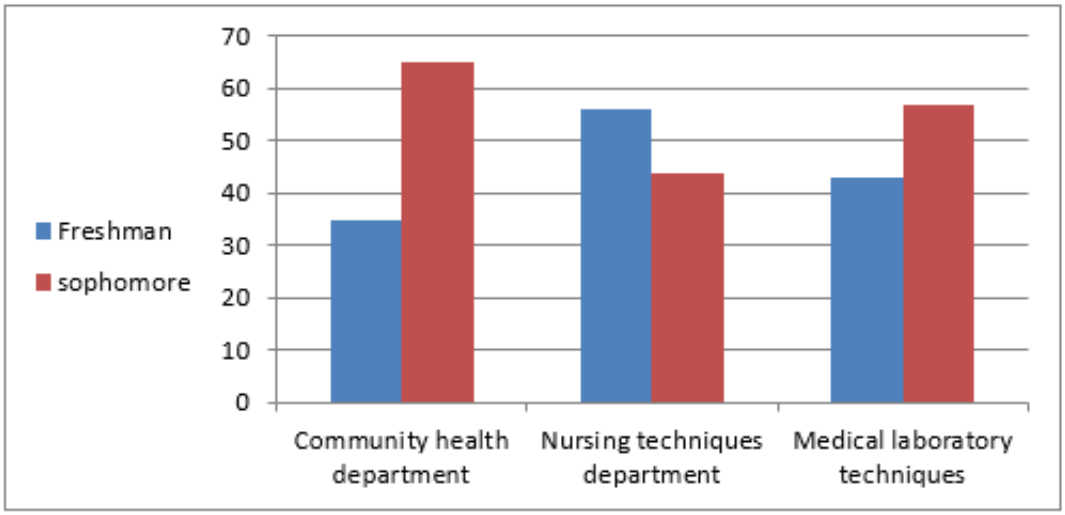

Figure 2. **Figure (1):** shows the distribution of the students according to their stage.

Prevalence of CMV Infection: The prevalence of CMV infection varied among the three departments. Among nursing students, 21% tested positive for CMV. Community Health Techniques department, 17% were CMV-positive. In the Medical Lab Techniques department, 11% were CMV-positive. The total students that showed sero positive IgG/IgM for CMV infections were 49 students which show a prevalence of 16.33 % of the total study population. Of those only 4 students

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showed sero positive for both IgG and IgM accounting for 8.16% of the total positive cases **Table (2).**

Department	IgG	IgM	IgG/IgM	Total
Community Health department	14	2	1	**17**
Nursing techniques Department	15	4	2	**21**
Medical Laboratory techniques	7	3	1	**11**
Grand total	36	9	4	**49**

Figure 3. **Table (2):** Sero positive according to the reactive Immunoglobulins and departments

X^2 (df =4 , N =49) 1.39 , p=0.85

No significant association was found between the reactive Igs and the departments ,college levels or sex in regard to the Igs (p> 0.05). **Figure (2,3).**

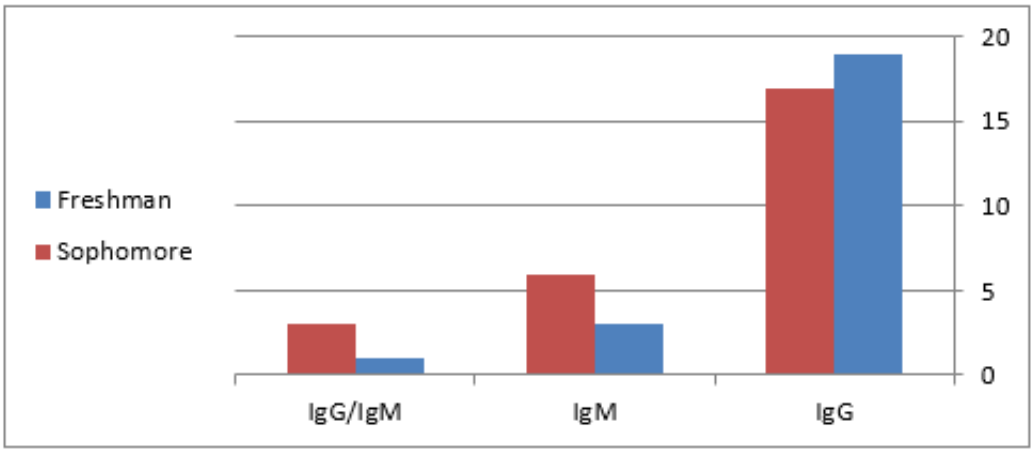

Figure 4. **Figure (2):** Freshman and sophomore students and their positive Igs.

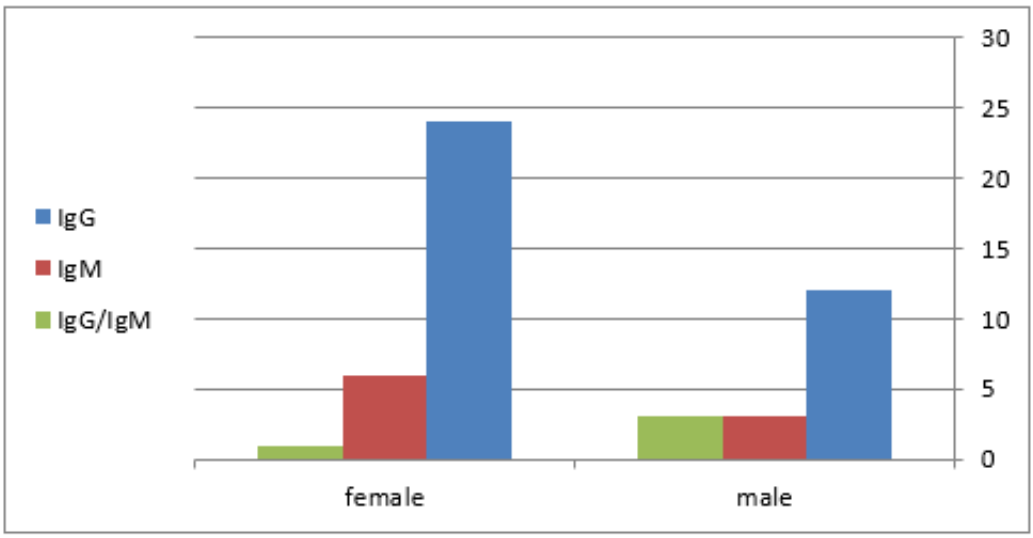

Figure 5. **Figure (3):** Correlation of Igs and sex.

The age were analyzed for correlation with the infection with CMV , the results were assessed and showed no significant

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correlation between the risk of contracting CMV and the age of the person (p>0.05).In order to estimate PAD 4 levels using the ELISA approach, 52 sero-negative participants and 49 sero-positive participants were included.The final analysis includes 91 participants in total. Serum PAD-4 concentrations and CMV-specific antibodies (IgG and/or IgM) were effectively identified for all samples. To assess variations in PAD-4 levels, an indication of cell apoptosis and increased cellular stress and NETosis in response to CMV infection, participants were stratified based on sex and CMV serological status.

PAD-4 concentrations varied significantly between individuals, ranging from low basal levels to considerably higher values. Enzyme levels were markedly higher in a subset of individuals, which is linked to increased immune activation or inflammatory conditions. A non-normal trend was shown by the right-skewed distribution of PAD-4.The median PAD-4 levels of female participants were greater than those of male participants when stratified by sex; however, there was significant heterogeneity in both groups.Statistical comparison using Welch's independent samples t-test revealed no statistically significant difference in PAD-4 concentrations between males and females ($t = -1.56$, $p = 0.12$).These findings indicate that sex alone does not significantly influence PAD-4 levels in this cohort, suggesting that observed PAD-4 elevations are more closely linked to immunological factors rather than biological sex. **Figure (4).**

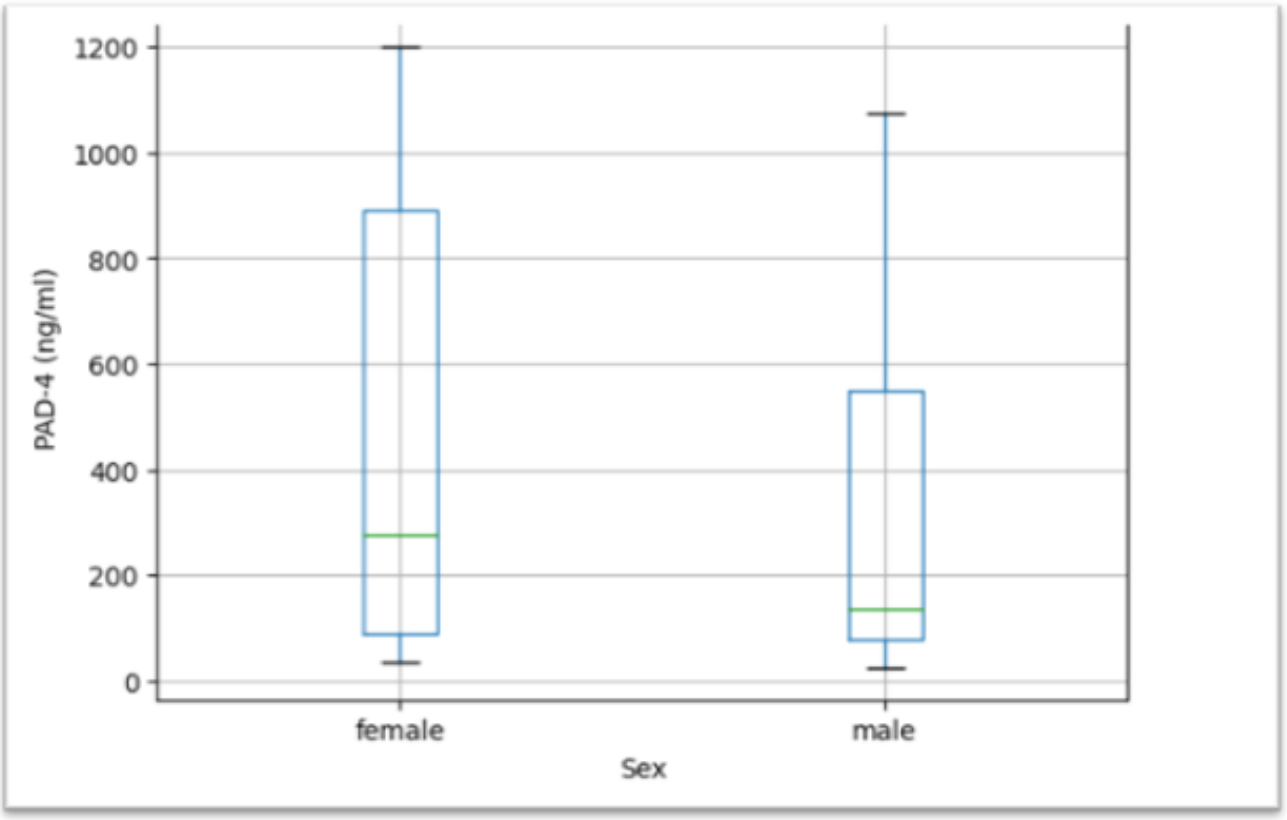

Figure 6. **Figure (4): PAD -4 levels according to sex**

CMV serology was then used to categorize the participants. PAD-4 concentrations were significantly greater in CMV IgM positive persons than in CMV IgG positive individuals, while PAD-4 levels were consistently lowest in seronegative individuals.PAD-4 levels differed statistically significantly between CMV IgM-positive and CMV IgG-positive groups, according to a Welch's t-test ($t = -3.50$, $p = 0.003$).Significantly higher PAD-4 levels were linked to CMV IgM positive, which is a marker of recent or active CMV infection and suggests increased NETosis during the acute phase of the CMV immune response. Conversely, IgG positive, which indicates latent infection or prior exposure, was linked to significantly lower PAD-4 concentrations. Figure (5).

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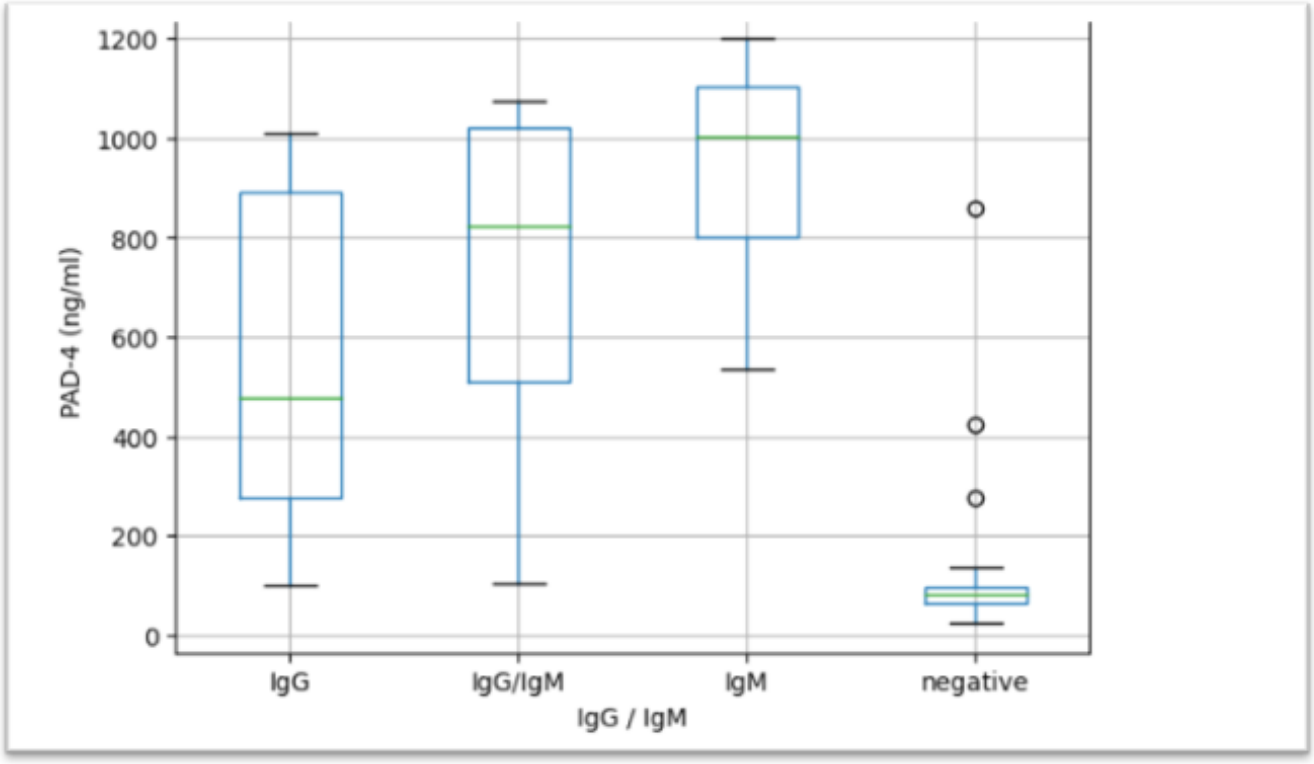

Figure 7. **Figure(5) : PAD-4 according to Antibody reaction**

Increased PAD-4 medians and higher quartiles in CMV IgM-positive participants.More steady and lower PAD-4 levels in seronegative and CMV IgG-positive individuals.Extreme PAD-4 elevations are typically found in IgM-positive participants.These trends provide more evidence that acute CMV infection is associated with increased neutrophil activation and cellular damage. Figure

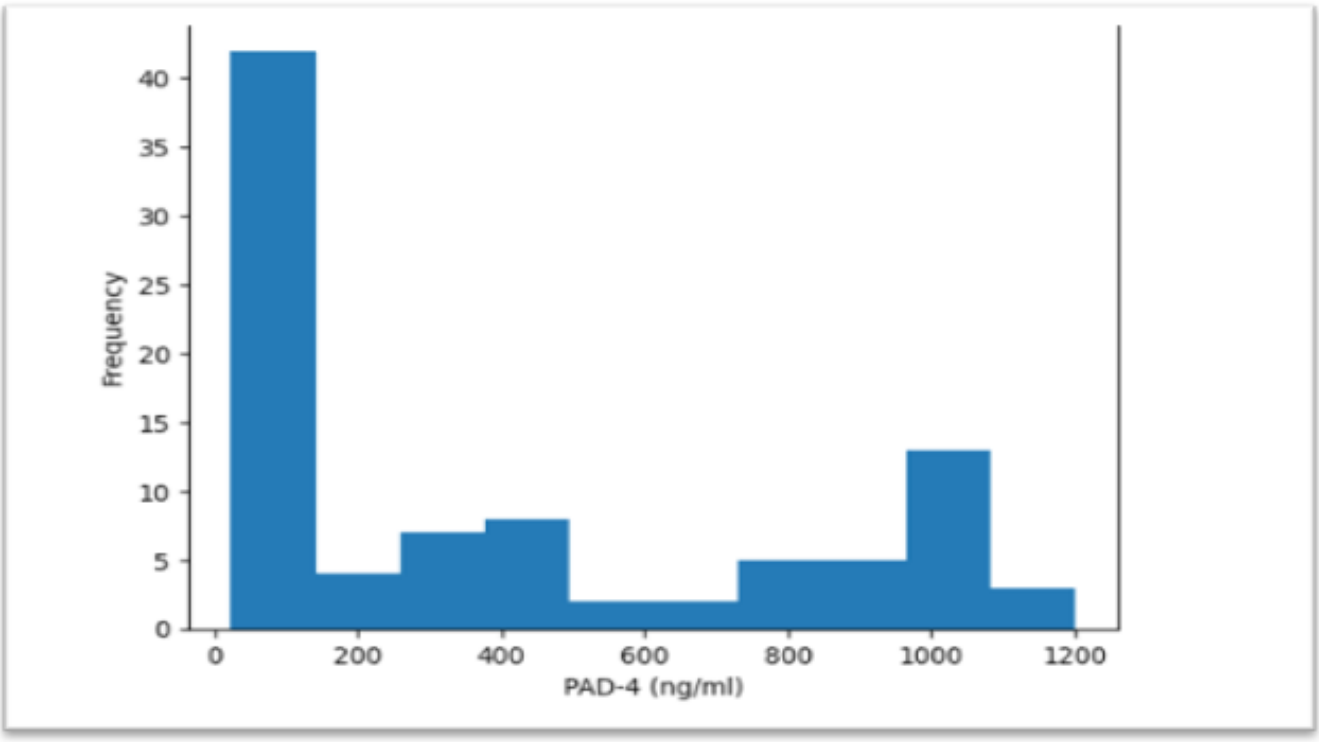

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Figure 8. **Figure (6): PAD-4 distribution in the study population**

The CMV serological status of the participants was used to further stratify them. PAD-4 concentrations were significantly greater in CMV IgM-positive persons than in CMV IgG-positive individuals, and PAD-4 levels were consistently lowest in seronegative individuals.PAD-4 levels differed statistically significantly between CMV IgM-positive and CMV IgG-positive individuals, according to Welch's t-test ($t = -3.50$, $p = 0.003$).**Table (3).**

CMV Serostatus	PAD-4 Trend
IgM-positive	Highest PAD-4 levels
IgG/IgM	Elevated
IgG-positive	Moderate
Seronegative	Lowest

Figure 9. **Table (3): PAD-4 levels according to CMV serology**

Discussion

The research showed a significant department-specific CMV seroprevalence and variations in PAD-4 concentration linked to CMV antibody status in this study of 300 medical students from three healthcare-related departments. In particular, students studying Community Health Techniques had the highest seropositivity (21%), followed by those studying Nursing Techniques (17%) and Medical Laboratory Techniques (11%). This suggests that exposure may vary depending on the training setting. This result could be explained by differences in social behaviors, clinical exposure during training, and community interaction that affect the spread of human cytomegalovirus (CMV), a common herpesvirus with intricate humoral and innate immune responses.An essential component of the NETosis pathway, PAD-4 catalyzes the citrullination of histones and promotes chromatin decondensation, both of which are necessary for the creation of neutrophil extracellular traps (NETs). Proteolytic proteins embedded in extracellular DNA networks, or NETs, have the ability to immobilize pathogens and modify immune responses. It is becoming more well acknowledged that innate immune responses to viruses and other pathogens include the activation of PAD-4 and NET release, which have been thoroughly documented in a variety of infectious situations. Reactive oxygen species (ROS) cause neutrophil activation, granule protein release (such as neutrophil elastase and myeloperoxidase), and PAD-4-mediated chromatin decondensation, which results in the creation of NETs in typical NETosis. These pathways have been reported in viral infection models such as influenza, SARS-CoV-2, and respiratory syncytial virus, where host defense and immunopathology are aided by virus-induced NETosis [11,12,15].Viruses in general can cause NET formation, and these extracellular traps may both contain viral spread and exacerbate inflammatory responses. However, the antiviral function of NETs has been most clearly shown in infections like HIV, where NETs can trap and inactivate virions[13,14,16].These larger models of infection-associated NETosis are consistent with our main finding that CMV IgM-positive participants (indicative of recent or current infection) had significantly greater PAD-4 levels than CMV IgG-positive subjects. In typical adaptive humoral responses, IgM rises before IgG during primary or recent viral exposure. In IgM-positive people, elevated PAD-4 indicates that early CMV immune activation activates innate mechanisms such as neutrophil recruitment and NET release.This finding is consistent with research demonstrating that NET formation and neutrophil activation are triggered by acute viral assaults.

As an example, neutrophils that are subjected to respiratory viruses e.g. respiratory syncytial virus display a strong PAD-4-dependent NETosis thus supporting the postulation that the pathway is a component of virus-associated innate responses[17]. On the wider range of viral models, PAD-4-dependent NET formation has also been linked to the antiviral activity together with immunopathology, thereby highlighting the dualistic nature of NETosis in infectious situations[18]. However, the specific effect of the NETs namely positive or negative might depend on the host-pathogen interaction. Some paradigms show that increased NETosis may amplify immunopathology especially in severe disease conditions, and that other studies theorize that PAD-4 deficiency restrains the release of NET and therefore may have an effect on infections[1921]. Since there is a statistically insignificant difference between sex compatible concentrations of PAD-4 in this cohort, our results show sex does not provide a highly significant influence to a marker of NETosis relative to CMV serostatus, the findings that have to be likely reflective of the complex nature of the control of NET watchful its dam being more dependent on infection and natural immunestatus versus sex or otherwise. The seroprevalence gradients across the departments further amplify this importance of contextual factors of epidemiology in CMV exposure on the health sciences students.. Community health students often engage extensively with community populations, potentially increasing contact with CMV-seropositive individuals in the environment. Nursing students may encounter clinical or patient-care exposures earlier in their training, while medical laboratory students may have comparatively more controlled laboratory environments

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with fewer direct infectious exposures. These variations warrant further investigation, as differential seroprevalence may impact training programs and infection control strategies in academic healthcare settings.

Our study did not include direct measures of NET structures (e.g., DNA–protein complexes or citrullinated histones), which would more definitively link PAD-4 activity to NETosis in CMV infection. Future work incorporating specific NET markers (e.g., neutrophil elastase–DNA complexes) alongside PAD-4 would strengthen mechanistic inferences. Additionally, longitudinal sampling could clarify whether elevated PAD-4 in IgM-positive individuals diminishes with seroconversion to IgG or persists in specific subgroups.

Conclusion

This study shows that acute CMV infection (IgM positive) is characterized by highly elevated levels of PAD-4, suggesting hyperactivation of innate immunity and potential NETosis during the course of infection and IgG CMV is associated with lower PAD-4 expression consistent with immune quiescence. These results indicate that PAD-4 could be a candidate biomarker of the acute CMV-related innate immune response and stress the importance of NETosis in viral infection, although they further raise thequestion of targeted infection-control education in healthcare training settings based on variable risk for CMV acquisition.

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