SEROEPIDEMIOLOGICAL AND IMMUNO-VIROLOGICAL CHARACTERISATION OF PARVO B19 IgM AMONG FEBRILE HIV-INFECTED INDIVIDUALS IN CALABAR, NIGERIA

Etoroabasi Okpon Okpon[1], Blessing Jachinma Okonko[2], Edith Nnenna Oketah[1], Ann Onyinyechi Chukwu[1], Tochi Ifeoma Cookey[1] & Iheanyi Omezuruike Okonko[1]

[1]Virus & Genomics Research Unit, Department of Microbiology, University of Port Harcourt,Choba, Rivers State, Nigeria. iheanyi.okonko@uniport.edu.ng; + (234) 7069697309:
[2]Medical Microbiology & Epidemiology Research Unit, Department of Microbiology, Madonna University Nigeria, Elele, Rivers State, Nigeria

Abstract: Human Parvovirus B19 (B19V) is an icosahedral single-stranded DNA virus which causes acute and persistent infections in immunocompromised individuals. Despite its potential impact, limited data is available on the seroepidemiological and immunovirological characterisation of Parvovirus B19 in febrile HIV individuals in Calabar, Nigeria. Therefore, this study is aimed at investigating the seroepidemiological and clinical manifestations of Parvovirus B19 IgM among febrile HIV-infected individuals in Calabar, Nigeria. The socio-demographic characteristics, as well as blood samples of 186 consenting individuals living with HIV presenting with febrile illness, were obtained and labelled accordingly, ruling out error. Following the manufacturer's instructions on ELISA, Plasma was extracted and tested for Parvovirus B19 IgM antibodies. The results showed an overall prevalence of Parvovirus B19, 53.2% for IgM, indicating an ongoing infection. Higher IgM seropositivity was observed among males (61.9%), age group >51 (54.2%), married (53.4%), with primary education (63.6%), and public servants (100.0%). Based on clinical characteristics, a higher IgM prevalence occurred among individuals with viral load of ≥1000 copies/mL (92.9%) and CD4 cells of ≤ 200 cells/µL (68.4%), suggesting a strong association between recent B19V infection and virological failure. In conclusion, the study showed a high prevalence of Parvovirus B19 IgM among the studied population. The outcome of this study contributed to the understanding of the burden and clinical impact of Parvovirus B19 in HIV-positive patients. It informed the development of effective prevention and treatment strategies. These results enhanced knowledge of the variables that put these populations at risk for B19V infection.
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1. INTRODUCTION

Parvovirus B19 was first discovered in 1975 by Yvonne Cossart and her research team in Melbourne, Australia, during their investigation of tests for the Hepatitis B virus surface antigen. The discovery was incidental, as the virus was initially identified while evaluating a serum sample labelled "19" from panel B that produced inconsistent results when tested using counterimmunoelectrophoresis and radioimmunoassay (Sabella et al., 1999). In 1981, people were formally informed that Parvovirus B19 posed a risk to humans (Heegaard et al., 2002; Sabella et al., 1999; Young et al., 2004; Rogo et al., 2014). It was from this specific blood sample number that the name "Parvovirus B19 originated. Initially, it was believed to be a parvovirus-like particle present in blood. The International Committee on Taxonomy of Viruses formally identified it as a member of the genus Erythroparvovirus in the family Parvoviridae in 1985 (Siegl et al., 1985).

Not covered by a coat, Parvovirus B19 is a single-stranded DNA virus. About 5.5 kilobases (KB) long, its genome is composed of individual viral particles, or virions (Summers et al., 1983). Three genotypes abound in the virus: B19V, LaLi-like, and V9-like. In terms of nucleotides (Nguyen et al., 1999; Rogo et al., 2014; Servant et al., 2002; Molar-de Backer et al., 2012), these genotypes differ by 10%. Though there are many different genotypes, they usually react with one another in the same manner. Special primers might be required to differentiate them, though, should they be identified by PCR amplification. This information underscores the complexity of Parvovirus B19's molecular biology and its role as a human pathogen.

Parvovirus B19 infection is widespread and occurs worldwide, affecting individuals regardless of their ethnicity or geographical location. Epidemiologically, Parvovirus B19 infection is primarily transmitted through the respiratory route and causes cyclic outbreaks at 3-5-year intervals. It is endemic, and sporadic in various populations with children, individuals with hemolytic disorders, immunocompromised individuals, and pregnant women being at risk (CDC, 1989). The infection is mostly during childhood and is continuous at slower rates till adulthood, so much so that about 70 -85% of grown-ups manifest serological evidence of previous infection (Cohen & Buckley, 1988; de Jong et al., 2011). In pregnant women, the seropositivity rate is 1.5%, with 13% in endemic and epidemic situations (Chorba et al., 1986). Its prevalence in Central Nigeria is about 13.2 % (Emiasegen et al., 2011) and in Nigeria's South-West, 20% (Abiodun et al., 2013). It is responsible for a range of clinical conditions, including transient aplastic crisis, pure red cell aplasia, glomerulopathy, fifth disease, hydrops fetalis, and anaemia in individuals with end-stage renal disease. Additionally, it may play a role in the development of other infections and medical conditions (Cohen and Buckley, 1988; De Jong et al., 2011).

A short and unremarkable bout of fever was observed in soldiers numbering two in 1980, and B19 was identified in serum with EM (Schneerson et al., 1980). Until 1981, no specific link was established between the virus and the disease, but there was an observed association between the virus and ephemeral bone marrow failure in individuals with sickle cell anaemia. Further investigation revealed that sera of Jamaican children who reside in London contained B19 antigen during aplastic crisis, and subsequent serum samples indicated seroconversion. Some years later, it was confirmed through seroepidemiology that the virus was identified as the trigger for erythema infectiosum in otherwise healthy children. (Rasmussen, 1989). The virus was recognised as the cause of erythema infectiosum in children who are otherwise healthy. (Brown et al., 1984), post-infectious symmetrical peripheral polyarthropathy or arthritis in adults (Reid et al., 1985; White et al., 1985), pure red cell aplastic which could be alleviated with immunoglobulin, was also later identified as a syndrome associated with B19V (Kurtzman et al., 1989).

Human immunodeficiency virus (HIV) is a retrovirus responsible for triggering the long-lasting and life-threatening condition called acquired immunodeficiency syndrome (AIDS). Since its first identification in the 1980s, it has spread around the world and now poses a threat to public health (Eisinger, 2018). According to data, 38 million people worldwide were HIV-positive in 2023 (Bekker et al., 2023). The largest prevalence is found in Sub-Saharan Africa, where around 1.3 million cases are reported from Nigeria. Despite the availability of antiretroviral medication (ART), HIV-positive individuals remain vulnerable to opportunistic infections, hence elevating their risk of mortality and morbidity. The global burden of the malady is estimated at 3.3 million yearly, and the incidence declined rapidly from 1997 to 2005 to about 2.6 million (Wang et al., 2016).

The co-existence of HIV and B19V is harnessed by the effect of an immunocompromised immune system. HIV-infected individuals experience anaemia due to factors such as zidovudine use, malnutrition, infections, and HIV itself. Persistent Parvovirus B19 infestation is a significant trigger of transient red cell aplasia and severe anaemia. The depletion of CD4+ is caused by HIV infections, and this causes a suppression of the immune system, thereby giving room for opportunistic infections which Parvovirus B19. B19V-specific tropism for Erythroid progenitor cells leads to an aplastic war, which is the suppression of red blood cell production in the bone marrow (Mishra et al., 2005; Ideguchi et al., 2007), thereby leading to severe anaemia. B19V infection induces immune activation (a facilitator of HIV progression) by producing pro-inflammatory cytokines, aggravating HIV replication.

In regions like Africa's Sub-Saharan, where the prevalence of HIV is high, the co-infection of HIV and Parvovirus B19 is not an outlier. Previous studies show that about 10% to 25% of Parvovirus B19 prevalence is recorded in HIV-infected individuals. In South Africa and Kenya, the rate is 17% and 20 %, respectively. A case study in Ibadan, Nigeria, revealed the prevalence of co-infection of HIV and Parvovirus to be 5 to 10% in the region (Aleru et al., 2018). The prevalence rates vary according to age and geographical location (Karami et al., 2020; Okojukwo et al., 2018).

Clinical manifestations span from minute symptoms to chronic deadly conditions that may consist of fever, headache, and nausea due to reduced CD4+ T-cell count (Nasir et al., 2018). Anaemia and Aplastic Crisis: B19V renders a severe manifestation of aplastic crisis in HIV-infected individuals, where the manufacture of blood red cells is suspended temporarily in the bone marrow, leading to severe anaemia (Gadwalker et al., 2013). Chronic Anaemia: Persistent anaemia may be experienced in the case of untreated parvovirus B19 infestation, and this leads to persistent fatigue, weakness, and decreased life engagements in affected individuals. 25% of chronic severe anaemia in HIV-positive persons is caused by B19V infestation (Fuller et al., 1996). HIV increased infection: The combined effect of chronic immune activation and suspension of red blood cell production by Parvovirus B19 may hasten the rapid fall in CD4+ T-cell tally and rise in viral load, thereby initiating an increase in HIV proliferation (Mishra et al., 2005).

The evident immunological effect of co-infection is the lower CD4+ T-cell count (He et al., 2012), causing a rapid increase in viral load. HIV and Human Parvovirus B19 (B19V) co-infection is a critical area of study due to the unique immunological interactions between these two viruses. HIV primarily targets CD4+ T lymphocytes, leading to immunosuppression, while B19V selectively infects erythroid progenitor cells in the bone marrow, causing a range of haematological abnormalities. Zhang et al. (2014) provided a meta-analysis of B19V prevalence and its implications in HIV-infected populations. The co-infection exacerbates clinical outcomes, affecting both immune response dynamics and disease progression. Young and Brown (2004) offered a comprehensive review of B19V pathogenesis, immune responses, and its clinical manifestations. HIV infection reduces CD4+ T cells, impairing the adaptive immune response. This creates an environment where B19V infection may persist or re-emerge due to inadequate viral clearance. Young and Brown (2004) offered a comprehensive review of B19V pathogenesis, immune responses, and its clinical manifestations, showing that while B19 infection impairs innate immune response, HIV infection reduces CD4+ T cells, thus impairing the adaptive immune response. HIV-related dysregulation of cytokines, including reduced IFN-γ and increased TNF-α, can enhance B19V replication. B19 affinity for erythroid precursor cells in the bone marrow causes aplastic crises, which lead to chronic anaemia. Zoufaly et al. (2012) explored case studies of B19V-related anaemia in HIV-positive patients in a resource-limited setting, stating that co-infection often results in persistent anaemia due to erythroid suppression, worsened by both direct B19V effects and HIV-associated myelosuppression. Kerr (2000) explored the autoimmune implications of B19V and how it may be exacerbated in conditions like HIV. HIV and B19V co-infection creates a complex immunological interplay, resulting in compounded immunosuppression, chronic anaemia, and potential autoimmune complications. Comprehensive management requires early detection, appropriate therapeutic interventions, and continued research to address the unique challenges of this co-infection.

2. MATERIALS AND METHODS

2.1 Study Area

Dr Lawrence Henshaw Memorial Hospital, also known as the Infectious Disease Hospital (IDH), in Calabar, Cross River State, Nigeria. The hospital serves as a referral centre for HIV management in the region, offering both antiretroviral therapy (ART) and routine laboratory monitoring for people living with HIV (PLHIV).

2.2 Study Design

This is a cross-sectional study which focused on febrile HIV-infected individuals receiving medical care at the Dr Lawrence Henshaw Memorial Hospital, also known as the Infectious Disease Hospital (IDH), in Calabar, Cross River State, Nigeria. Ethical approval was obtained from the University of Port Harcourt Ethics Committee following the cardinal principles of ethics in medical research, and the patient's demographic information and past medical records were obtained through the administration of standardised questionnaires.

2.3 Study Population

A total of 186 confirmed HIV-positive individual serum samples were obtained and tested for Parvo IgM antibodies against B19.

2.4 Sample Size Determination

The sample size for this study was calculated and finalised using a specific mathematical formula.

$$N = \frac{Z^2 pq}{d^2}$$

Where:
N represents the required sample size
P denotes the anticipated prevalence within the target population
q is derived as 1 - P
Z corresponds to 1.96 (the standard error value),
d indicates the chosen level of statistical significance, set at 0.05.
A value of P as 2.0% (for Cross River State) by NAIIS in 2019 (NACA, 2019) will be used to represent maximum uncertainty (Macfarlane, 1997; Awando et al., 2013; Okonko, 2017).

Z is the normal standard distribution, and 1.96 is the 95.0% confidence interval.
$Z^2 = 1.96 \times 1.96 = 3.84$
P = 2.0% = 0.020
q is equal to 1-p. q = 1 - p (1 - 0.020) = 0.980
d = The expected level of accuracy or precision was designated as 0.05.
$d^2 = 0.05 \times 0.05 = 0.0025$

$$n = \frac{3.84 \times 0.020 \times 0.980}{0.0025}$$

Therefore, a sample size of 33 individuals was estimated, with an extra 10.0% to account for potential loss to follow-up (Macfarlane, 1997; Naing et al., 2006; Awando et al., 2013)

2.5 Eligibility Criteria

2.5.1 Inclusion Criteria: All consenting HIV individuals presenting with febrile illness attending the Infectious Disease Hospital, Calabar, Nigeria.

2.5.2 Exclusion Criteria: Non-consenting HIV-infected individuals, children under the age of 2 and HIV seronegative individuals.

2.6 Ethical consideration

The study was conducted after obtaining ethical clearance from the University of Port Harcourt Research Ethics Committee.

2.7 Laboratory Analysis

Plasma was analysed for the presence of Parvo B19 IgM using the ELISA technique following the manufacturer's instructions at the University of Port Harcourt's Virus & Genomics Research Unit of the Department of Microbiology. All plasma samples were analysed for the presence of Parvo B19 IgM using an ELISA kit manufactured by DIA PRO. The serologic test and reading adhered to the kit manufacturer's instructions. The test results were calculated based on a cut-off value established using the following formula: **Cut-Off (Co) = CAL 5/5.** The appropriate formula was applied to calculate the cut-off value, ensuring an accurate interpretation of the results.

2.8. Data analysis

Microsoft Excel version 2021 (Microsoft, USA) was utilised to evaluate the data. The statistical significance of every analysis was determined where appropriate using the Chi-square test or Fisher's exact test at a 5% significance threshold

3. RESULTS AND ANALYSIS

3.1. Socio-demographic Characteristics of the Study Population

The group of individuals enrolled in the study consisted of one hundred and eighty-six (186) HIV-infected individuals who utilised the Infectious Disease Hospital (IDH) in Calabar, Nigeria. The socio-demographics considered in this study were age, sex (gender), marital status, educational status, and occupational status. After the data obtained were analysed, the socio-demographics were further categorised (Table 1). The age distribution ranges from 2 to 66 years, with a median age of 40 years. The age group 31 – 50 ranked highest in population with a 51.6% aggregate, followed by ≥51 with 25.8%, and the least age group was ≤31 with 22.6%.

The sex category was further divided into male and female. Females constituted the highest study population size of 102, with 54.8%, while males were 84, with 45.2% (Table 1). For Marital status, the single population was the highest with 98 individuals and 52.7%, while the married population size was 88 with 47.3% (Table 3.1). For educational status, the highest proportion of participants was recorded among Primary school attendees with 66 in number and 35.4%, followed by Secondary 60 (32.3%), Tertiary 21 (11.3%), and the least individuals with no formal education 39 (21.0%). Based on occupational status, the business group constituted the highest being 63 and 33.9%, followed by traders with 28 (15.1%), students with 24 (12.9%), civil servants with 20 (10.8%), both self-employed and employed with 13 (6.9%), skilled workers with 9 (4.8%), farmers with 7(3.8%), artisans with 5 (2.7%), and the least being public servants with 4 (2.2%) (Table 1).

Table 1: Sociodemographic Characteristics of the Study Population

Variables	**Categories**	**No. Tested (%)**
Age Group (Years)	≤31	42 (22.6)
	31-50	96 (51.6)
	≥51	48 (25.8)
Gender	Males	84 (45.2)
	Females	102 (54.8)
Marital Status	Single	98 (52.7)
	Married	88 (47.3)
Educational Status	Primary	66 (35.4)
	Secondary	60 (32.3)
	Tertiary	21 (11.3)
	No Formal Education	39 (21.0)
Occupational Status	Self- Employed	13 (6.9)
	Civil Servants	20 (10.8)
	Employed	13 (6.9)
	Students	24 (12.9)
	Skilled Workers	9 (4.8)
	Business	63 (33.9)
	Artisans	5 (2.7)
	Farmers	7 (3.8)

	Traders	28 (15.1)
	Public Servants	4 (2.2)
	Total	**186 (100.0)**

3.1.2 Immunological Markers of the study population

Immunological makers (CD4+ cells) of the study population, ranging from ≤ 200 to ≥ 350, were analysed (Table 2). The category of ≤ 200 cells/mm³ recorded the highest proportion of 114 (61.3%), followed by 200-349 cells/mm³ with 40 (21.5%), and ≥350 cells/mm³ being the least with 32 (17.2%).

3.1.3 Virological Markers of the Study Population

The virological data obtained for the study were further categorised into three groups: ≤ 40, 41-999, and ≥ 1000. The viral load proportion was observed to be higher among group 41 – 999 copies/ml comprising 94 (50.5) individuals, followed by ≤ 40 (42.0) and the least ≥ 1000 (7.5%) (Table 2).

Table 2: Immunological and Virological Markers of the HIV-Infected Individuals in Calabar, Nigeria

Markers	**Categories**	**Population Tested (%)**
CD4 count (cells /mm³)		
	≤ 200	114 (61.3)
	200-349	40 (21.5)
	≥ 350	32 (17.2)
Viral Load (copies/ml)	≤ 40	78 (42.0)
	41-999	94 (50.5)
	≥ 1000	14 (7.5)
Total		**186 (100.0)**

3.2. Overall Seroprevalence of Parvovirus B19

Among the 186 HIV-infected participants enrolled in the study at the Infectious Disease Hospital in Calabar, Nigeria, 172 individuals (92.5%) tested positive for IgG antibodies against Parvovirus B19 (as shown in Figure 1).

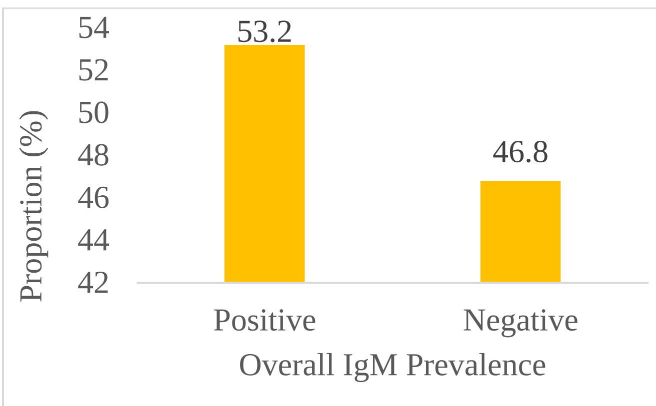

Figure 1: Overall Seroprevalence of Parvovirus B19 IgM

4. DISCUSSION

Human Parvovirus B19 is hyperendemic in sub-Saharan Africa, specifically in Nigeria (Aleru et al., 2018). Presenting both in healthy and immunocompromised individuals who are susceptible to this viral infection and when left untreated results in complications such as anaemia, chronic kidney failure, aplastic crisis and hydrops fetalis, increased viral load among others. Symptoms of B19 which includes joint pains, headache, fatigue, cough, rashes and nausea (Servant-Delmas et al., 2010; Leung et al., 2023) are prone to be misdiagnosed. The overall prevalence rate of B19V IgM antibody revealed by this study was 53.2% which is higher than the 41.8% findings by Akele et al., 2021. This contrasts with the 39.9% findings reported in India (Kishore et al., 2010), higher than the 7.1% findings by Awolesi et al in South-West Nigeria (Awolesi et al., 2020), 7.53% reported by Kumar et al (Kumar et al., 2013) in India, 3.3% reported in South Africa (Mirambo et al., 2017), 13% reported in Central

Nigeria (Emiasegen et al., 2011), 1.3% as documented in Nigeria by Ihaeancho et al., 2014, 1% as documented in America by Doyle et al., 2000, and 0% as documented in Spain by Munoz et al., 1998, and 4% findings in Oyo by Abiodun et al., 2013. This disparity may not be a s a result of variation in seasonal peaks and the epidemiology of B19V. Reports have it that the B19V peak period is usually late winter and spring, with 75% of positive IgM recorded between January and June (Ender et al., 2007; Crowcroft et al., 1999; Bremner et al., 1994). Seropositivity for B19V IgM indicates recent infections, and this study reveals that parvovirus B19V infection is endemic in Calabar, Nigeria.

This study revealed the highest prevalence of B19V IgM concerning age among participating individuals ≥ 51 years at 54.2%, and the lowest being the ≤ 30 years at 52.4%. In contrast to this study, findings in South-West, Nigeria by Awolesi et al., 2020 showed a higher seroprevalence of 36.1% in the age group 27-35 years and the lowest among the 52-60 years at 9.3%. Similar to the findings by Awolesi et al, a high prevalence of 23.7% among 26-35-year-olds was recorded in Ekiti by Akele et al. (2021). This prevalence in this study is lower but similar to that of Abiodun et al. (2013), findings of 67% in individuals over 49 years of age, suggesting continued exposure to B19V (Koch et al., 1989). This study also contrasts the findings of De Paschale et al. (2023 in Northern Benin, which showed a higher prevalence of 61.7% among the 21-30 years. Despite the high seroprevalence rate displayed, there is no statistically significant relationship between age and B19V IgM.

Concerning sex (gender), this study revealed a higher seropositivity for B19V IgM among males than females. This finding is lower but consistent with the findings in South-West, Nigeria, by Awolesi et al. (2020), which reported a higher prevalence in males at 89.6%. The finding in this study also agrees with that of Adelrahman et al. (2021) in Qatar, showing a higher prevalence among males at 96.73%, which was relatively higher than the findings in this study. It is also in line with but lower than 98.0% in a study by Kumar et al. (2013). There is a statistically significant relationship between sex (gender) and B19V IgM prevalence.

Regarding marital status, this study revealed a higher IgM seropositivity against B19V among the married group, which had a slight difference from the prevalence of the single group. This finding is higher than but consistent with the findings of Akele et al. (2021), who stated that a higher prevalence was exhibited among the married, with 36.9% but lower than the findings of De Paschale et al. (2023), which revealed a 71.1% among the married group in Northern Benin. This finding is also lower than 63.5% in South-West, Nigeria by Awolesi et al., 2020. Despite the higher prevalence of marital status, there is no statistically significant relationship with B19V IgM prevalence.

This study revealed the findings concerning educational status, with a higher IgM prevalence against B19V in the primary education group. This contrasts with Awolesi et al. (2020), whose findings stated a higher prevalence among the secondary education group and the lowest among the no formal group. There is no statistically significant relationship between educational status and B19V IgM prevalence.

In terms of occupational status, there was a higher prevalence of B19V IgM among public servants. This finding contrasts with other studies showing it was relatively higher than the findings by Akele et al. (2021) among the self-employed. There was a significant difference concerning occupation, where De Paschale et al. (2023) and Emiasegen et al. (2011) contradict the findings by indicating a higher prevalence among housewives at 61.7% and 40%, respectively. This recorded prevalence among housewives was attributed to the number of children who pose as the main source of infection through non-immune household contacts. Despite the high prevalence of occupational status, there was no statistically significant relationship between B19V IgM prevalence.

The study findings were also based on the clinical characteristics of the participating individuals. In terms of CD4 counts, the highest seroprevalence of B19V IgM was recorded among individuals with ≤ 200 cells/µl. Irrespective of its high prevalence rate, there was no statistically significant relationship between B19V IgM prevalence. Concerning viral load, a higher prevalence was recorded among individuals with ≥ 1000 copies/ml. Unlike CD4 counts, there is a statistically significant relationship and B19V IgM prevalence.

5. CONCLUSION

The study showed a high prevalence of Parvovirus B19 among the studied population. The study revealed an overall high prevalence of Parvovirus B19 among HIV-infected individuals, with 92.5% showing IgG seropositivity. The study identified significant demographic and clinical factors associated with higher Parvovirus B19 IgM seropositivity, was higher among individual aged ≥ 30, male, married, having a primary education, public servant group, CD4≤ 200 cells/µl, and those with viral load of≥ 1000 cells/ml.

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Disclosure of conflict of interest

The authors claim that there are no conflicting interests.

Statement of ethical approval

All authors declare that all experiments have been examined and approved by the University of Port Harcourt Research Ethics Committee. Therefore, the study is performed following the ethical standards

Statement of informed consent

All authors declare that informed consent was obtained from all individual participants included in the study.

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