Original Article

Hematological parameters in recent and past dengue infections in Jazan Province, Saudi Arabia

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ABSTRACT

الأهداف: تحليل المعايير الدموية للكشف عن مؤشرات تنبؤية محتملة لحمى الضنك.

المنهجية: جُمعت عينات دم من 146 شخصًا يُشتبه بإصابتهم بحمى الضنك في مستشفيين في جازان، المملكة العربية السعودية. جُمعت عينات التحكم بالتزامن مع بالغين أصحاء (عددهم 59). فُحصت العينات للكشف عن الأجسام المضادة لحمى الضنك باستخدام اختبار الممتز المناعي المرتبط بالإنزيم. حُددت المعايير الدموية، مثل الهيموغلوبين (HGB)، وخلايا الدم البيضاء، والهيماتوكريت (HCT)، وعدد الصفائح الدموية، ومستويات خلايا الدم الحمراء، للعينات الإيجابية لحمى الضنك وجميع العينات الضبطية.

النتائج: من بين المرضى الذين فُحصوا، كانت نسبة الغلوبولين المناعي M لحمى الضنك 15%، بينما كانت نسبة الغلوبولين المناعي G 25%. أظهر مرضى حمى الضنك قيمًا أقل للمعايير الدموية المختبرة مقارنةً بالضوابط، ولوحظت قيم أقل بكثير لخلايا الدم الحمراء (p=0.0022) و الهيموجلوبين (p=0.0002) والهيماتوكريت (p<0.0001). كان متوسط قيم HGB (12.47 جم / ديسيلتر) والهيماتوكريت (39.03%) لمرضى حمى الضنك منخفضًا بشكل غير طبيعي. كان متوسط مستويات HCT أقل بكثير لدى المرضى الذين أصيبوا بعدوى حمى الضنك مؤخرًا (41.41% مقابل 45.91%، p=0.0230) وعدوى حمى الضنك السابقة (38.63% مقابل 45.91%، p<0.0001) مقارنةً بمجموعة التحكم. ومع ذلك، كانت مستويات خلايا الدم الحمراء وHGB أقل بكثير فقط لدى المرضى الذين أصيبوا بعدوى سابقة وليست حديثة.

الخلاصة: تشير نتائج هذه الدراسة إلى أن عدوى حمى الضنك السابقة يمكن أن تؤدي إلى قيم دموية غير طبيعية، على الرغم من الحاجة إلى مزيد من البحث.

Objectives: To analyze hematological parameters for potential predictive markers of dengue.

Methods: Blood samples were obtained from 146 individuals suspected of having dengue at 2 hospitals in Jazan, Saudi Arabia. Control samples were concurrently collected from healthy adults (n=59). Samples were screened for anti-dengue antibodies by employing enzyme-linked immunosorbent assay. Hematological parameters, such as hemoglobin (HGB), white blood cells, hematocrit (HCT), platelets count, and red blood cells (RBCs) levels were determined for the dengue positive samples and all the controls.

Results: Of the patients examined, 15% were dengue immunoglobulin M positive and 25% were immunoglobulin G positive. Dengue-infected patients showed lower values of the tested hematological parameters than controls, and significantly lower values were observed for RBCs (p=0.0022), HGB (p=0.0002), and HCT (p<0.0001). Average HGB (12.47g/dl) and HCT (39.03%) values of dengue patients were abnormally low. The average HCT levels were significantly lower in patients with recent dengue infection (41.41% vs. 45.91%, p=0.0230) and past dengue infection (38.63% vs. 45.91%, p<0.0001) compared to controls. However, RBCs and HGB levels were only significantly lower in patients with past and not recent infections.

Conclusion: The results of this study suggest that prior dengue infections could result in abnormal hematological values, although further research is needed.

Keywords: dengue, hematology, infection, diagnosis, abnormality

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Dengue is a viral disease caused by the dengue virus (DENV), which encompasses 4 distinct serotypes (DENV-1, DENV-2, DENV-3, and DENV-4). It belongs to the *Flavivirus genus* within the *Flaviviridae* family and is a disease of significant global health concern.[1] The virus' mature particle has a spherical shape which is 50 nm in diameter and includes numerous copies of structural proteins, a host-derived membrane bilayer, and a positive-sense single-stranded RNA genome.[2] The viral genome undergoes cleavage by the proteases of the virus and the host, resulting in the formation of 3 structural proteins, which include the capsid (C), the precursor of the membrane (prM, which eventually becomes the membrane protein, M), and envelope (E). In addition, 7 non-structural proteins are made.[2]

Despite the difference in the DENV serotypes, they manifest similar clinical symptoms. Primary infection by one serotype confers lifelong immunity against that particular serotype, but subsequent infections by other serotypes tend to result in more severe forms of the disease. Transmission primarily occurs through female Aedes mosquitoes, particularly *Aedes aegypti* and *Aedes albopictus*, which are predominantly found in subtropical and tropical zones. More than 100 countries of the World Health Organization (WHO)-designated regions suffer widespread dengue, including Southeast Asia, Africa, the Americas, the Western Pacific, and the Eastern Mediterranean.[3] Particularly hard-hit are the Western Pacific, the Americas, and Southeast Asia, with Asia bearing approximately 70% of the worldwide disease load.[3]

The clinical symptoms of dengue closely resemble those of many other febrile illnesses, making differentiation difficult. In 2009, the WHO introduced a clinical classification system for dengue based on observed signs, symptoms, and severity level. This suggested system categorizes cases of dengue into non-severe and severe groups. The non-severe group makes up a large portion of the cases and is subdivided into dengue having no warning signs and dengue with warning signs (including symptoms like fluid accumulation, persistent vomiting abdominal pain, bleeding from mucous membranes, lethargy, enlarged liver, increased hematocrit [HCT], and rapid decrease in platelet count). On the other hand, severe dengue encompasses significant bleeding, serious plasma leakage, and critical organ involvement.[4,5] While most dengue infections either show no symptoms or present as a mild illness, only approximately 10% progress to severe disease. In cases left untreated or inadequately managed, the fatality rate for severe dengue can be as high as 20%.[6] Nevertheless, with proper medical care and treatment, mortality rates can be significantly reduced.

Diagnosing dengue infection involves a combination of clinical observations and laboratory assessments. Laboratory tests encompass both nonspecific assessments, including hematological indices, liver function evaluations, and serum protein levels, as well as specific tests such as viral antigen detection which mainly targets the non-structural protein-1, genomic sequencing, and serological assays for antibody identification.[2,7] Enzyme-linked immunosorbent assay (ELISA) remains the most widely used serological approach to dengue diagnosis, particularly in detecting recent and past infections.[2] Molecular techniques such as reverse transcription polymerase chain reaction are also increasingly being used in routine diagnosis for detection and serotyping of DENV.

In response to dengue infection, the immune system generates antibodies to neutralize the virus while also activating the complement system to aid in the elimination of viral particles by antibodies and white blood cells (WBCs).[8] Additionally, the immune response involves the deployment of CD8+ T-cells (cytotoxic lymphocytes), which identify and eliminate infected cells. The DENV infection is linked to various hematological alterations, including reductions in WBCs count (leukopenia), decreased lymphocyte count or increased lymphocyte levels (lymphopenia or lymphocytosis), low platelet count (thrombocytopenia), and elevated HCT levels.[5] These shifts are typically immune-mediated and may differ across regions or ethnicities due to variances in population characteristics and previous disease exposures. However, there is a lack of comprehensive data detailing these abnormalities among patients in Saudi Arabia. More understanding of the early hematological parameters in local DENV cases might enhance early diagnosis and proper treatment, and reduce mortality significantly. Thus, this research aimed to study hematological parameters in recent and past dengue infections to identify potential biomarkers.

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Methods. Samples for this study were collected from December 2022 to April 2023 at 2 locations within Jazan, Saudi Arabia, a region in the far southwest of

Saudi Arabia where mosquitoes thrive. Inclusion criteria included abnormal complete blood count (CBC) results, arthritis, or hemorrhage. Patients (n=46) who were admitted at Baysh General Hospital and Abu Arish General Hospital (n=100), Jazan, were chosen based on the inclusion criteria to test for DENV (Figure 1). Sample collection was carried out anonymously. Additionally, control samples (n=59), referred to healthy adult individuals with normal CBC and without symptoms, were concurrently collected (46 from Abu Arish General Hospital and 13 from Baysh General Hospital, Jazan, Saudi Arabia).

Ethical approval was obtained from the ethics committee of King Khalid University, Abha, Saudi Arabia, (HAPO-06-B-001; ECM#2023-102) prior to the commencement of this study. The study was carried out in agreement with Helsinki declaration.

Due to the hemorrhagic manifestations associated with dengue infections, hematological tests are beneficial for dengue cases.[9] Because we were unable to retrieve the CBC results of the study participants from Baysh General Hospital, the association of recent and past dengue infection with abnormalities of red blood cells (RBCs) count, WBCs, platelets, hemoglobin (HBG), and HCT was studied on Abu Arish city samples. Consequently, only control samples (n=46) from Abu Arish city were used in the association study.

Before the experiment, the FLOUstar Omega microplate reader was checked for reproducibility. After checking the coefficient of variation, all samples collected from both locations were subjected to immunoglobulin M (IgM) and G (IgG) antibody tests. Tests were carried out by employing the Vircell ELISA kit (product number M1018 for IgM; and G1018 for IgG). The reactivity of samples was determined according to the cut-off values.

Statistical analysis. GraphPad Prism software (version 8.0) was used to analyze the data obtained in this study. In the assessment of hematological parameters, comparisons between the patient and control groups were carried out using either an unpaired t-test or the Mann-Whitney test depending on the Gaussian distribution. One-way ANOVA was employed for comparisons involving more than 2 categories. A *p*-value of less than 0.05 was regarded as statistically significant in all tests.

Results. The assay precision was tested within assay (intra-assay) and between assay (inter-assay variability) for validation purposes. Imprecision was acceptable, and the coefficient of variability was less than 2%. Figure 2 shows that all controls (negative control, positive control, and cut-off value) were within their expected reference range.

A total of 146 patient samples were screened for both IgM and IgG antibodies against DENV. In this study, 15% were found to be DENV IgM positive and 25% were IgG positive. The positivity of anti-DENV antibodies was slightly higher in samples obtained from Abu Arish General Hospital compared to Baysh General Hospital (Table 1). Additionally, control samples (n=59) tested negative for both antibodies.

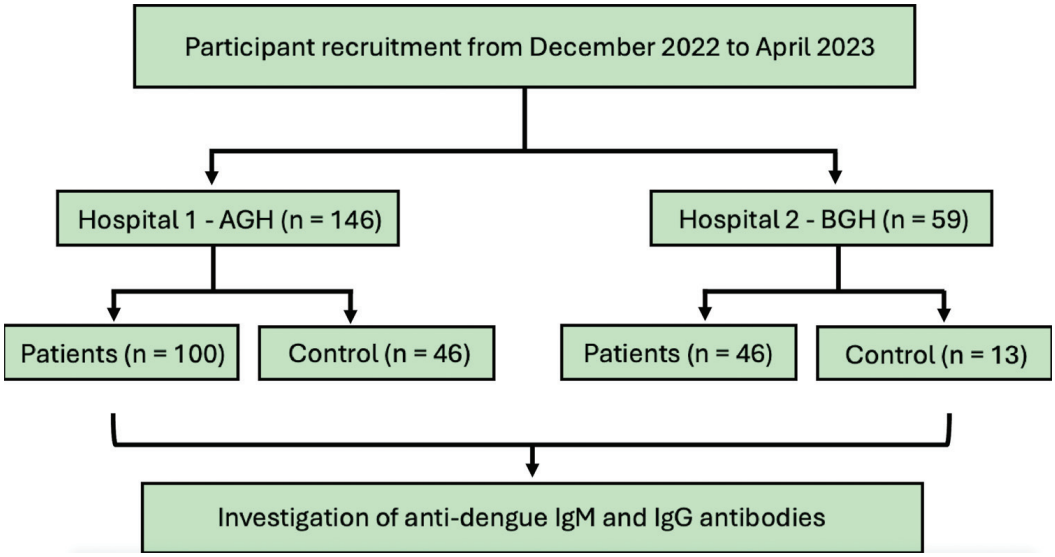

Figure 1 - A flowchart illustrating the study design. AGH: Abu Arish General Hospital, BCH: Baysh General Hospital, IgM: immunoglobulin M, IgG: immunoglobulin G

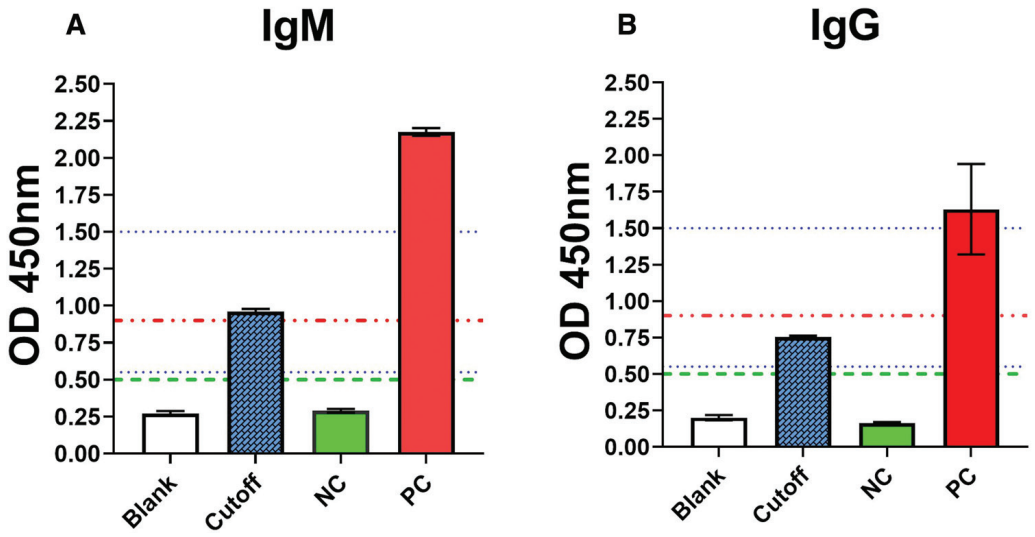

Figure 2 - Positive controls, negative controls and cut-off values of: **A**) immunoglobulin M and **B**) immunoglobulin G. The red dotted line indicates the threshold the positive control should exceed. The green dotted line indicates the threshold the negative control should not exceed. The blue dotted lines indicate the range within which the cut-off value should be. IgM: immunoglobulin M, IgG: immunoglobulin G, OD: optical density, NC: negative control, PC: positive control

Table 1 - Seroprevalence of anti-dengue virus antibodies.

Samples	IgM positive	IgG positive
Abu Arish General Hospital (n=100)	16 (16.0)	27 (27.0)
Baysh General Hospital (n=46)	6 (13.0)	10 (21.7)
Overall (n=146)	22 (15.1)	37 (25.3)

Values are presented as numbers and percentages (%). IgM: immunoglobulin M, IgG: immunoglobulin G

The hematological parameters were assessed in both DENV-infected patients and control samples using 5 different tests. The findings revealed notable differences between the 2 groups. The DENV-infected patients exhibited significantly lower values for these hematological parameters than the control individuals. Specifically, 3 tests, namely RBCs, HGB, and HCT, displayed statistically significant differences (Figure 3). The average values of HGB and HCT were abnormally low among dengue patients. Conversely, all control samples fell within the expected reference range. These results highlight the impact of dengue infection on hematological parameters and emphasize the significance of monitoring these parameters during the disease.

Following the previous data regarding hematological parameters and their statistical significance, 3 tests (with statistical significance) were selected to study their results with anti-DENV antibodies and compare between recent and past infections. In all 3 tests, values were lower than the controls (n=46) in IgG-positive patients, and these differences were statistically significant (Figure 4). For IgM-positive patients, only HCT showed a statistically significant difference (Figure 4). For RBCs and HGB, although not statistically significant, the results of IgM-positive patients were lower than the control.

Discussion. Dengue fever (DF) presents a significant a diagnostic challenge due to the absence of distinctive markers, making it difficult to differentiate from other prevalent viral infections in the region. Until the mid-1990s, Saudi Arabia was considered free from DENV infection.[10] However, there have been multiple outbreaks since 1994, with a growing incidence in recent years. For example, in 2013, the reported cases peaked at 6512, while 2375 cases were documented in the year 2020 and 3647 cases were documented in the year 2022.[10-12] According to a recent report, most DF cases were concentrated in the Jeddah region (74%), followed by the Jazan and Makkah regions (10.5% each) and Riyadh (3.2%), Saudi Arabia.[11] Given DENV's potential for severe outcomes, including fatality, this study aims to analyze hematological parameters to identify predictive biomarkers of disease severity.

In our study, 15% of the subjects were DENV IgM-positive, while 25% were DENV IgG-positive. Studies carried out across different regions of Saudi Arabia have reported varying rates of IgM and IgG seroprevalence for DENV. A previous meta-analysis was carried out to

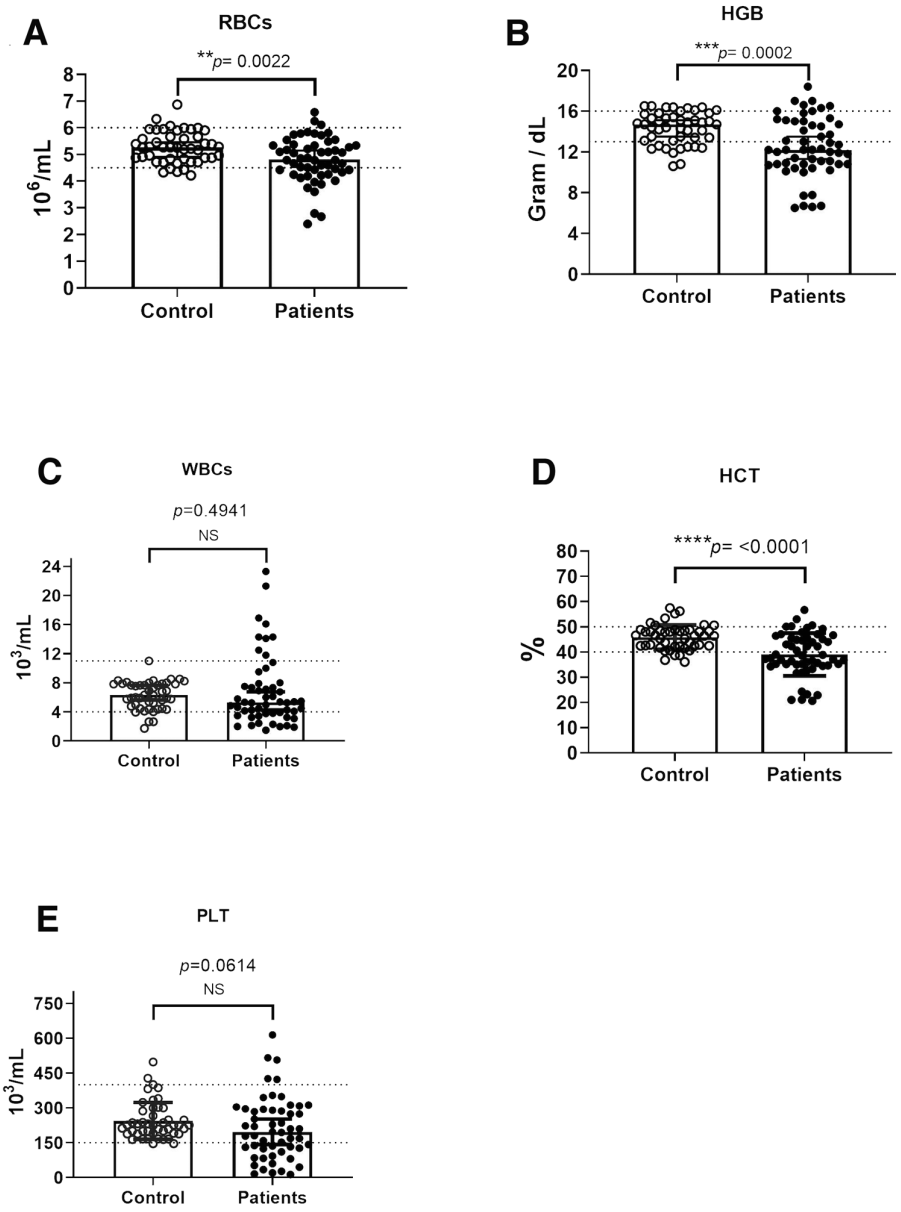

Figure 3 - Comparison of 5 hematological markers in dengue virus infected patients and controls. **A**) Results of red blood cells; **B**) hemoglobin; **C**) white blood cells; **D**) hematocrit; and **E**) platelets.The range between the 2 dotted lines indicates the normal values ($^{****}p<0.0001$, $^{***}p<0.001$, $^{**}p<0.01$). RBCs: red blood cells, HGB: hemoglobin, WBCs: white blood cells, HCT: hematocrit, PLT: platelets

determine the overall seroprevalence of DENV infection in Saudi Arabia from 2003-2023.[13] The pooled analysis showed IgM seroprevalence rate of 17.7% and IgG seroprevalence rate of 26.6%, which aligns with the estimates obtained in the present study.[13] The differences in seroprevalence across the studies examined may be attributed to variations in study duration and location, which could impact the observed rates. In our study, DENV-infected patients exhibited lower levels of the evaluated hematological parameters than the control group.

Thrombocytopenia, which is marked by a low platelet count, is a common clinical feature observed in both mild and severe cases of DENV infections. The development of thrombocytopenia may occur due to reduced production of platelets in the bone marrow

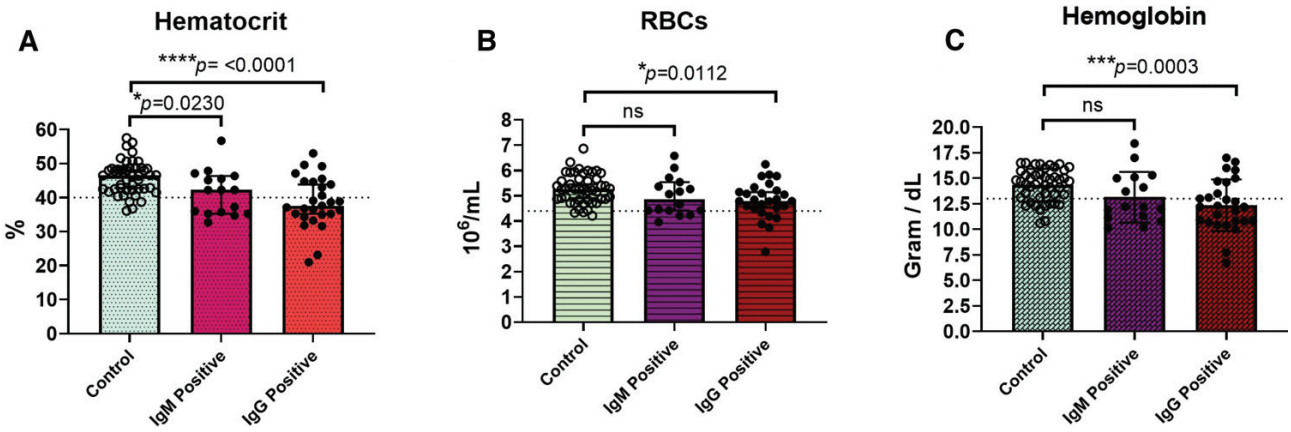

Figure 4 - Comparison of hematological markers between recent and past infection. **A**) hematocrit; **B**) red blood cells; and **C**) hemoglobin. The dotted lines indicate the lower normal value. RBCs: red blood cells, IgM: immunoglobulin M, IgG: immunoglobulin G

and increased destruction and removal of platelets from circulation.[14,15] This reduction in platelets is a significant contributor to bleeding in affected individuals. Platelet levels typically fall below the normal reference range (150,000-450,000 platelets/µL) and can drop as low as <40,000 platelets/µL between the third and seventh day of fever in many patients.[16] In some cases, platelet transfusions are required to restore normal hemostatic function.[17,18] In our study, although DENV-infected patients had lower platelet levels than the controls, the difference was insignificant. A study carried out in Pakistan also found thrombocytopenia to be a common hematological abnormality.[19]

Leukopenia, characterized by a low WBC count, is another hematological feature observed in dengue.[20] Compared to controls, our study found lower, though non-significant WBC levels in dengue patients, suggesting that WBC count alone is not a relaible biomarker for DENV infection. However, previous studies have shown that, compared to other febrile illnesses, leukopenia is often more pronounced in dengue.[21,22]

Notably, our study found significant differences in RBCs, HGB, and HCT levels between the DENV-infected patients and controls. Both HGB and HCT levels were abnormally low in dengue patients. In a previous study, lower HGB levels were observed among DENV-infected patients.[23] Furthermore, our findings align with studies carried out in Sri Lanka and Nepal, where lower levels of HGB and HCT were observed in dengue patients compared to controls, although these differences were not statistically significant.[7,9] Investigating the clinical significance of these hematological parameters is essential, as they may not only aid in diagnosis but also help inform treatment decisions. Moreover, a previous study highlighted a strong correlation between HCT levels and the severity of dengue, emphasizing the importance of monitoring these parameters in assessing disease progression and determining appropriate clinical interventions.[24] According to WHO, HCT and thrombocytopenia are critical laboratory markers in DENV infection. However, a previous study did not find a notable correlation between HCT levels and DENV serological outcomes.[9] This may be because the study focused on patients with mild primary active dengue infections, where the likelihood of plasma leakage - a condition indicative of abnormal HCT results - is considerably lower.

Further, we found that HCT levels were significantly lower in recent and past DENV-infected patients compared to the control group. However, RBCs and HGB levels were only significantly lower in patients with past and not recent infections. These findings calls for further research to understand the mechanisms behind these abnormalities, particularly the long-term impact of DENV on blood health. Future studies should explore the potential for persistent hematological changes post-infection, assess the clinical significance of these alterations, and investigate whether they contribute to other health complications. Additionally, research should consider the role of immune responses in causing these abnormalities.

Study limitations. We did not analyze our data according to the days since infection or onset of fever in patients, particularly the IgM-positive population. This could have provided extra details on the hematological associations to improve our understanding. Further, we did not identify any positive DENV RNA in our

molecular assessment despite detecting some IgM-positive samples using serology. Thus, we could not provide extra information regarding specific DENV serotypes within our study population.

In conclusion, given the potential for severe outcomes in dengue, including fatality, this study investigated hematological parameters to identify predictive biomarkers of DENV infection in the region of Jazan, which has been impacted by numerous DENV outbreaks. The DENV-infected patients displayed lower levels of evaluated hematological parameters than controls, and RBCs, HBG, and HCT levels were notably lower in DENV patients. Additionally, significantly lower HCT, RBC, and HBG levels were evident in patients with past DENV infections than those with recent infections. However, additional studies are warranted to elucidate the findings and explore their clinical relevance. Overall, this study highligths the significance of hematological parameters in assessing DENV and emphasizes the need for continued vigilance in regions experiencing DENV outbreaks, as disease progression could be severe.

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