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Haematological Alterations Associated with Panic Disorder among Sri Lankan University Students: A Case-Control Study

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Short Report

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Abstract

Panic Disorder (PD) is a significant mental health concern in Sri Lanka, with a prevalence of 14% that exceeds global averages. Despite its prevalence, the pathophysiology of PD remains unexplored locally. This case-control study assessed the haematological alterations and panic severity associated with PD employing 60 university students (30 PD patients and 30 healthy controls). PD patients showed significantly higher scores across all panic measures (*p < 0.001). Results reveled that RBC (*p = 0.002) and platelet (*p = 0.003) counts of the PD group were significantly higher than those of the HC group and differential WBC count profiles also differed between the two groups. These parameters could potentially act as cost-effective means of disease confirmation. The NLR of the PD group was found to be significantly elevated (*p = 0.002) in the PD group suggesting chronic inflammation. Thus, these findings contribute significantly to understanding PD within South Asian populations providing a strong foundation for similar future research.

1.0 Introduction

Panic disorder (PD) is a prevalent, chronic and incapacitating anxiety disorder, affecting 3–5% globally. Being twice as common among females, it typically sprouts in early adulthood, recording highest incidence among those in their early twenties (Gottschalk et al., 2016; Na et al., 2011; Roy-Byrne et al., 2006). Due to its extreme disease burden, acute symptomology, and profoundly incapacitating nature, is considered as the most burdensome anxiety disorder (Bandelow & Michaelis, 2015; Schumacher et al., 2011).

It is characterized by recurrent, unexpected panic attacks; abrupt episodes of intense fear accompanied by physical manifestations such as dizziness, dyspnea, palpitations, pounding heart, tachycardia, sweating, tremors, nausea, and syncope, alongside cognitive and emotional symptoms like derealization, depersonalization, and intense fears of dying, losing control, or going crazy (American Psychiatric Association, 2022; Gottschalk et al., 2016).

Diagnosis is often complicated and involving symptom evaluation via questionnaire analysis. Currently, PD diagnosis is conducted as per the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition); one or more attacks with 4 or more symptoms followed by avoidance, maladaptive behavioral changes and the persistent fear of future attacks spanning at least a month. However, misdiagnosis is common, as 89% of patients initially complain of intense physical symptoms (Gottschalk et al., 2016). Untreated PD increases the risk of cardiovascular disease, self-harm, and suicide (Coryell, 1988).

Emerging research indicates that PD is associated with subtle changes in haematological parameters, such as elevated erythrocyte sedimentation rate (ESR) and altered red blood cell (RBC), white blood cell (WBC), and platelet counts though findings are often inconsistent and may reflect ethnic variation (Orum, 2021; Ransing et al., 2020) implying the requirement of similar research in difference ethnic contexts (Ersoy et al., 2008; Roy-Byrne et al., 1988).

The findings are expected to contribute to the understanding of PD within Asian populations which are often underrepresented in the literature, providing a foundation for developing culturally appropriate diagnostic strategies that will benefit university students and society.

2.0 Methodology

2.1 Study Design

The study employed a case-control design, with ethical approval from the Ethics Review Committee of The Open University of Sri Lanka (ERC-OUSL).

2.2 Sample Size and Power Consideration

The sample size for this study was informed by the reported prevalence of PD among Sri Lankan undergraduates (14%) (Wijesekara, 2022). Using standard formulas for sample size assessment studies, 185 participants would be required to achieve 95% confidence with a 5% margin of error (Taherdoost, 2017). This preliminary study was conducted with 60 participants, which provided adequate power to detect moderate-to-large effect sizes in haematological, biochemical, and genetic parameters.

2.3 Participant Screening and enrollment

The study was conducted at the OUSL and enrolled undergraduate and postgraduate students aged 20–35 years. Prior to participation, all participants were briefed on the study and provided with an information sheet detailing the study objectives and procedures. Participation was entirely voluntary, and written informed consent was obtained prior to any assessment pertaining to the study or collection of any personal information or biological samples. Demographic data were recorded for all participants.

All volunteers were subjected to a thorough psychological evaluation by a consultant psychiatrist associated with the Department of Psychology. They were screened for PD via a screening tool (see Additional file 01-Tool 01) with structured in-person interviews to confirm diagnoses. Additionally, the psychological evaluation included the assessment of other major psychiatric conditions. Individuals suffering from severe psychiatric conditions that could influence results (Major Depressive Disorder, Post Traumatic Stress Disorder, schizophrenia, psychosis) were not recruited as participants for the study.

Other exclusion criteria included chronic illnesses, neurological issues, extreme BMI values (< 18.5 and > 29.9), menstruation, current psychiatric treatment, substance abuse and infectious diseases at the time of biological sample collection.

A preliminary sample of 60 participants was recruited, including 30 individuals diagnosed with panic disorder (PD) according to DSM-5 criteria (test group) and 30 age- and sex-matched healthy controls (HC).

The Panic Assessment Questionnaire (PAQ) was used to assess panic severity in the study population (see Additional file 01-Tool 02). The questionnaire was pilot-tested among 40 undergraduate students for reliability and validity prior to the main study; they demonstrated strong psychometric integrity, with an internal consistency value of α = .934. Comprehensive statistical analyses, factor loadings, and validity metrics are detailed in Additional file 02.

The screening tool and questionnaire were available only in English language since the research population consisted exclusively of university students whose curriculum was in English. Given the simplicity of the material and the proficiency in English of the study population, the material provided was considered entirely legible by all participants. To protect confidentiality and minimise participant discomfort, all questionnaires were completed using a unique study ID. Data were de-identified and stored securely in password-protected electronic files accessible only to the research team.

2.4 Panic Assessment Questionnaire (PAQ)

The Panic Assessment Questionnaire (PAQ) comprised binary, checklist, and Likert-scale items designed to capture panic symptoms, severity, behavioural changes, and extreme coping behaviours. A total panic score was derived by summing sub-scores across domains, with higher scores indicating greater severity.

Content validity was supported through expert review by a consultant psychiatrist, who confirmed the clinical appropriateness and comprehensiveness of the items.

Details of scoring procedures are provided in Additional file 02.

2.5 Haematological Parameters

Blood samples were collected into K_2EDTA tubes as biological samples for the haematological, biochemical and genetic analyses.

A volume of blood was aliquoted for the haematological parameter assessment and the genetic analysis. The remaining blood was processed to yield plasma. For plasma separation, the EDTA blood samples were centrifuged at 3500 rpm and 4°C for 15 minutes within 30 minutes of sample collection (Hudson and Hay, 1989). The supernatant was extracted, aliquoted and stored at -20°C until biochemical analyses were followed.

Red blood cell (RBC), white blood cell (WBC), and platelet counts were determined manually according to Hudson and Hay (1989). Cell counts were expressed as $\times 10^6/\mu L$ for RBC, and $\times 10^3/\mu L$ for WBC and platelets.

Differential WBC counts were obtained by preparing a Giemsa-stained thin blood smear as described by Owen et al. (2013). The Neutrophil-Lymphocyte Ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count obtained during the differential WBC count (Bisgaard et al., 2017).

2.6 Statistical Analysis

All analyses were performed using SPSS v20 (IBM, USA). Continuous variables are presented as mean ± SD, and categorical variables as frequencies (%). Normality was assessed with the Shapiro-Wilk test. Comparisons were performed using independent samples *t*-tests or Mann-Whitney *U* tests for normally and non-normally distributed variables, respectively. Categorical variables, were compared using chi-square or Fisher's exact tests. Spearman's correlation coefficients were used to assess associations between continuous variables. Statistical significance was set at $p < 0.05$.

3.0 Results

3.1 Demographic Data

The mean age of participants in the HC group was significantly higher than in the PD group (*t*-test; *p = 0.035). Although the PD group had slightly more females, the sex distribution was well-matched between groups (chi-square test; $\chi^2=1.736$; $p = 0.112$). Participants were distributed across various academic years, with undergraduates comprising 65% of participants while 35% were postgraduates. However, no significant differences in academic level distribution were observed between groups (Table 01). Participants were matched by geographic location to minimise the effect of environmental confounding factors (Fig. 01).

HC-Healthy Controls, PD-Panic Disorder

Table 01
Demographic data of the study population

Categories	HC	PD	Statistical Test	p-value
Number	30	30		
Ages	26.97 ± 2.66 years	25.53 ± 2.49 years	*t*-tests	*p = 0.035
Sex				
Males	50%	30%	χ^2 test	χ^2=1.736, p = 0.112
Females	50%	70%		
Academic Level				
1st year UG	10%	7%	χ^2 test	χ^2=6.370, p = 0.272
2nd year UG	3%	10%		
3rd year UG	14%	10%		
4th year UG	13%	3%		
Final year UG	37%	23%		
Postgraduates	23%	47%		
HC-Healthy Controls, PD-Panic Disorder, UG-Undergraduates				

3.2 Clinical History

3.2.1 Control Group

Among the 30 HCs, 12 (40%) reported a history of panic attacks, but none met diagnostic criteria for PD (Fig. 02A).

3.2.2 Test Group

A severity assessment of the test group (PD) showed that most cases of PD were moderate (70%), followed by severe (20%) and mild (10%) (Figure 02B).

3.3 Clinical Panic Measures

The PD group also had significantly higher total panic scores (39.27 ± 12.35) compared to HCs (16.53 ± 13.32) (Mann-Whitney *U* test; *p = 0.000).

Other panic severity comparisons between study groups are detailed in Additional file 02.

3.4 Haematological Parameters

RBC counts were significantly higher in the PD group (5.199 ± 0.527 mil/μL) compared to HCs (4.747 ± 0.648 mil/μL) (Mann-Whitney *U* test; *p = 0.002). Sex-based analysis showed this effect was restricted to females, while no significant difference was observed in males (Mann-Whitney *U* tests; females *p = 0.005, males p = 0.096) (Fig. 03A,B).

WBC counts did not differ significantly between groups overall (HC 11.260 ± 3.063 thousand/μL, PD 11.988 ± 2.740 thousand/μL) or when stratified by sex (Mann-Whitney *U* tests; all p > 0.05) (Fig. 03C,D).

PD group significantly higher platelet counts (371 ± 70.169 thousand/μL) had than the HC group (312 ± 81.638 thousand/μL) (Mann-Whitney *U* test; *p = 0.003). Sex-based analysis showed this effect also to be restricted to females, while no significant difference was observed in males (Mann-Whitney *U* tests; females *p = 0.033, males p = 0.096) (Fig. 03E,F).

In the differential WBC count analysis, the PD had higher percentages of neutrophils (NEU) (HC 57.37 ± 5.62%, PD 61.37 ± 5.56%) and monocytes (MON) (HC 6.70 ± 1.86%, PD 8.47 ± 3.17%). Conversely, eosinophil (EOS) (HC 7.43 ± 3.14%, PD 5.53 ± 2.30%) and lymphocyte (LYM) (HC 27.30 ± 6.02%, PD 23.47 ± 5.15%) percentages were higher in the HC group. These differences were significant between groups (Mann-Whitney *U* tests; NEU *p = 0.014, MON *p = 0.033, EOS *p = 0.011, LYM *p = 0.004). The basophil (BAS) counts, however, remained similar between groups (HC 1.20 ± 0.76%, PD 1.17 ± 0.83%) and no significant associations were observed (Mann-Whitney *U* test; p = 0.813) (Fig. 03G).

The PD group (2.753 ± 0.697) had significantly higher NLR values than the HC group (2.229 ± 0.647) (Mann-Whitney *U* test; *p = 0.002) (Fig. 03H).

RBC-Red Blood Cell, WBC-White Blood Cell, NLR-Neutrophil-Lymphocyte Ratio, HC-Healthy Control, PD-Panic Disorder

3.5 Correlations between Panic Scores and Haematological Parameters

Spearman's rho correlation analyses confirmed that total RBC counts were positively correlated with panic scores (rs = 0.306, *p = 0.018), while no significant correlations were observed for WBC counts (rs = 0.139, p = 0.289) or platelet counts (rs = 0.147, p = 0.263) (Fig. 04A-C).

For differential WBC counts, panic scores were positively correlated with neutrophil counts (rs = 0.330, *p = 0.010), but negatively correlated with eosinophil (rs=-0.413, *p = 0.001) and lymphocyte (rs=-0.326, *p = 0.011) counts. No significant correlations were observed for monocytes (rs = 0.206, p = 0.115) or basophils (rs=-0.008, p = 0.952) (Fig. 04D-G).

The panic scores were also positively correlated with the NLR values (rs = 0.351, *p = 0.006) (Fig. 04H).

Summary of correlation statistics are provided in Additional file 03.

RBC-Red Blood Cell, WBC-White Blood Cell, NLR-Neutrophil-Lymphocyte Ratio

4.0 Discussion

This study investigated the haematological alterations associated with PD in Sri Lankan university students. Significant associations were observed between PD and haematological markers supporting investigations of PD in this population.

The study employed a cohort of 60 university students where, the test group consisted 30 students with clinical PD and the control group consisted 30 HCs of which, 40% had a history of panic attacks which was essential for providing insights into the factors that define and contribute to clinical PD, beyond the mere presence of panic attacks.

The PD group demonstrated a significantly higher total panic score compared to HCs, aligning with the diagnostic distinction between context-specific subclinical panic attacks and clinical PD. This finding underscores the chronic, debilitating nature of PD, marked by elevated panic symptomatology, distress, and impairment beyond isolated panic episodes in healthy individuals.

The current study revealed a significant elevation in RBC counts within the PD group, predominantly among females, with significant positive correlations to panic scores. These findings complement the findings of Ransing et al. (2017, 2020). However, certain studies reported no differences (Gurok et al., 2019; Kulogu et al., 2002; Orum 2021) or lower counts (Hamzekolaei et al., 2020).

Elevated RBC counts likely reflect a profound physiological response to the chronic stress associated with PD. Erythropoiesis mediates RBC count elevation by the release of erythropoietin (EPO), mediated by stress-induced hypoxia or activation of the HPA axis induced by catecholamines and cortisol, which are typically elevated in PD patients (Bandelow et al., 2000; Fernández-Serrano et al., 2022; Roy-Byrne et al., 1986; Schreiber et al., 1996; Stones et al., 1999; Wedekind et al., 2000). Studies also report that catecholamines increase RBC counts by stimulating the release of reticulocytes from the bone marrow (Mairbäurl, 2013). Catecholamines also mediate splenic contraction to enhance the blood's oxygen transport during stress, influencing higher RBC counts in chronic stress conditions such as PD (Baković et al., 2005).

Despite splenic contraction also influencing leukocytosis, WBC counts did not differ significantly between PD and controls, aligning with Gurok et al. (2019) and Ransing et al. (2017), though Orum (2021) reported elevations. However, given the sample size, this analysis may have been underpowered to detect subtle group differences.

Differential counts showed clear alterations: the PD group exhibited higher NEU and MON percentages, and lower EOS and LYM. NEU positively correlated with panic scores, whereas EOS and LYM were negatively correlated. While Gurok et al. (2019) reported elevated LYM and reduced NEU and EOS, Orum (2021) found increased NEU and reduced LYM, more consistent with the present study, which also highlighted higher MON and lower EOS. These differences underscore the need for further investigation.

The elevations in NEU and MON may reflect inflammatory processes (Prame Kumar et al., 2018), as supported by prior work on PD showing increased CRP, homocysteine, and pro-inflammatory cytokines (Brambilla et al., 1994; Choi et al., 2021; Herrán et al., 2005; Hoge et al., 2009; Yang et al., 2023). Conversely, reduced LYM and EOS may indicate suppressed adaptive immunity or a compensatory shift driven by neutrophilia.

Platelet counts were also significantly elevated in the PD group, mainly among females, though not correlated with panic severity. This may be linked to the increased thrombopoietin (TPO) levels resulting in platelet overproduction induced by elevated IL-6 levels in PD (Choi et al., 2021; Hoge et al., 2009; Kaser et al., 2001; Kim et al., 2019; Zou et al., 2020). Our findings complemeted those of Ransing et al. (2017, 2020) while contradicting studies reporting no changes (Gurok et al., 2019, Orum 2021) or even significantly lower counts (Hamzekolaei et al., 2020).

Our findings also detected significantly higher NLR values in the PD group, with positive correlations to panic scores. indicating that PD is associated with higher rates of inflammation. This suggests both systemic inflammation and stress severity contribute to NLR elevations, supporting Orum (2021).

These findings, particularly the increased RBCs, platelets, and NLR may contribute to the heightened cardiovascular risk, a frequently observed comorbidity in individuals with PD (Coryell, 1988; Yapislar et al., 2012).

5.0 Limitations

Despite employing a relatively substantial sample size with 50% PD patients, the limited overall number may still restrict generalizability to broader populations and thus, future research should involve larger and more diverse cohorts.

6.0 Conclusions

Thus, the study identified significant haematological alterations associated with PD improving the knowledge of PD in South Asia. Elevated RBC counts, platelet counts, and NLRs were recorded alongside altered differential WBC counts. These findings suggest that PD is associated with measurable haematological changes that may reflect underlying physiological stress and inflammatory processes. Thus, following future studies with larger cohorts, routine haematological assessments could be utilized as potential cost-effective biomarkers to complement the clinical diagnosis of PD.

Abbreviations

BAS: Basophils; BMI: Body Mass Index; CRP: C-Reactive Protein; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; EOS: Eosinophils; EPO: Erythropoietin; ERC-OUSL: Ethics Review Committee of The Open University of Sri Lanka; ESR: Erythrocyte Sedimentation Rate; HC: Healthy Controls; HPA: Hypothalamic-Pituitary-Adrenal (axis); IL-6: Interleukins; K_2EDTA: Dipotassium

Ethylenediaminetetraacetic acid; LYM: Lymphocytes; MON: Monocytes; NEU: Neutrophils; NLR: Neutrophil-Lymphocyte Ratio; OUSL: The Open University of Sri Lanka; PAQ: Panic Assessment Questionnaire; PD: Panic Disorder; RBC: Red Blood Cell; rpm: Revolutions per minute; SD: Standard Deviation; TPO: Thrombopoietin; UG: Undergraduate; WBC: White Blood Cell.

Declarations

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Author Contributions

R G A Fernando: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Software, Visualization, Writing – Original Draft, Writing – Review and Editing

C D Jayasinghe: Conceptualization, Funding Acquisition, Methodology, Resources, Project Administration, Supervision, Validation, Writing – Review and Editing

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Availability of Data

The data supporting the findings of this study are not publicly available due to participant confidentiality but are available from the corresponding author upon reasonable request.

Ethical Approval

The study was approved by the Ethics Review Committee of the Open University of Sri Lanka on the 06th of June 2025 (reference number – ER/2025/069).

Consent to Participate

All participants provided written informed consent at enrolment. A copy of the consent form can be provided upon request.

Consent for Publication

Not Applicable.

Competing Interests

The authors declare no competing interests.

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Figures

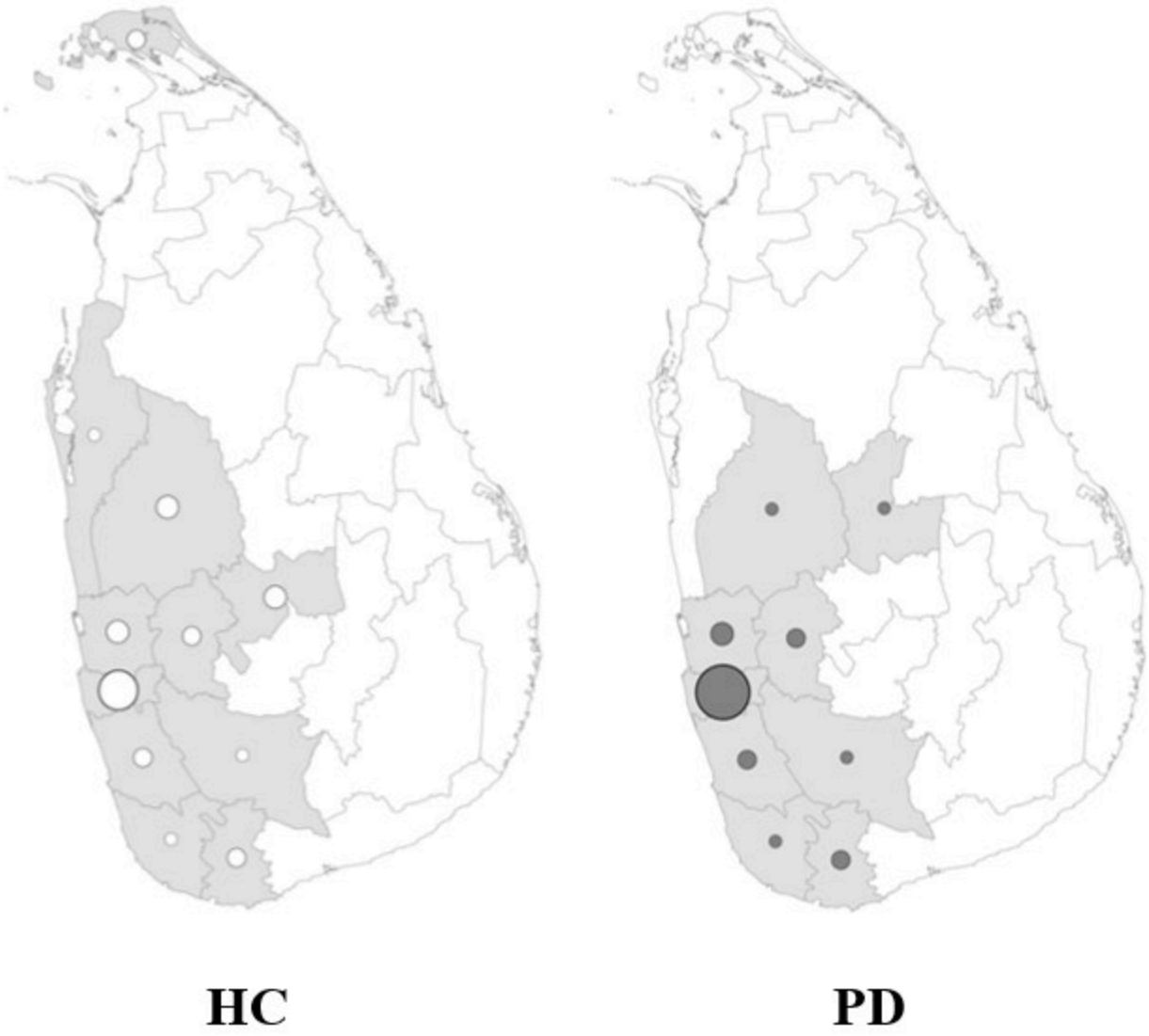


Figure 1

Comparison between Geographic Distribution of participants of the HC group and PD group.

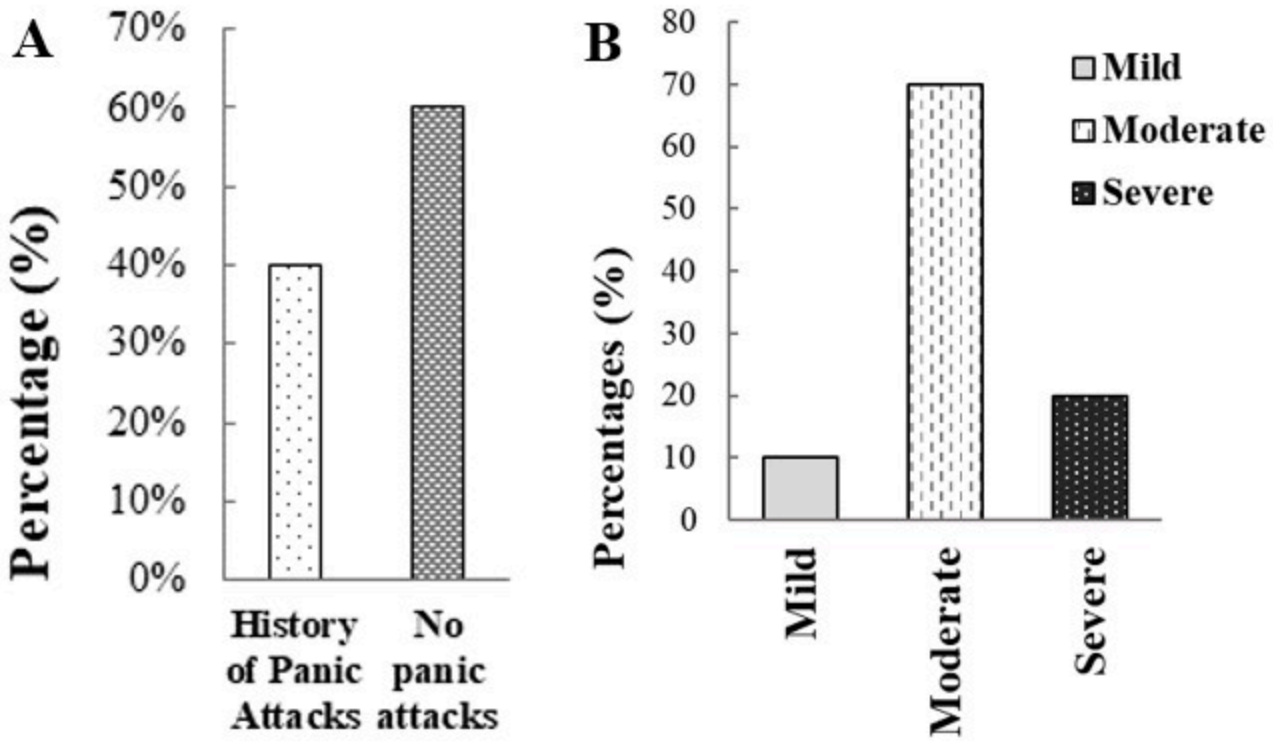


Figure 2

Clinical history of the study groups.

(A) History of Panic Attacks in the HC Group, (B) Panic Disorder Severity within the PD Group

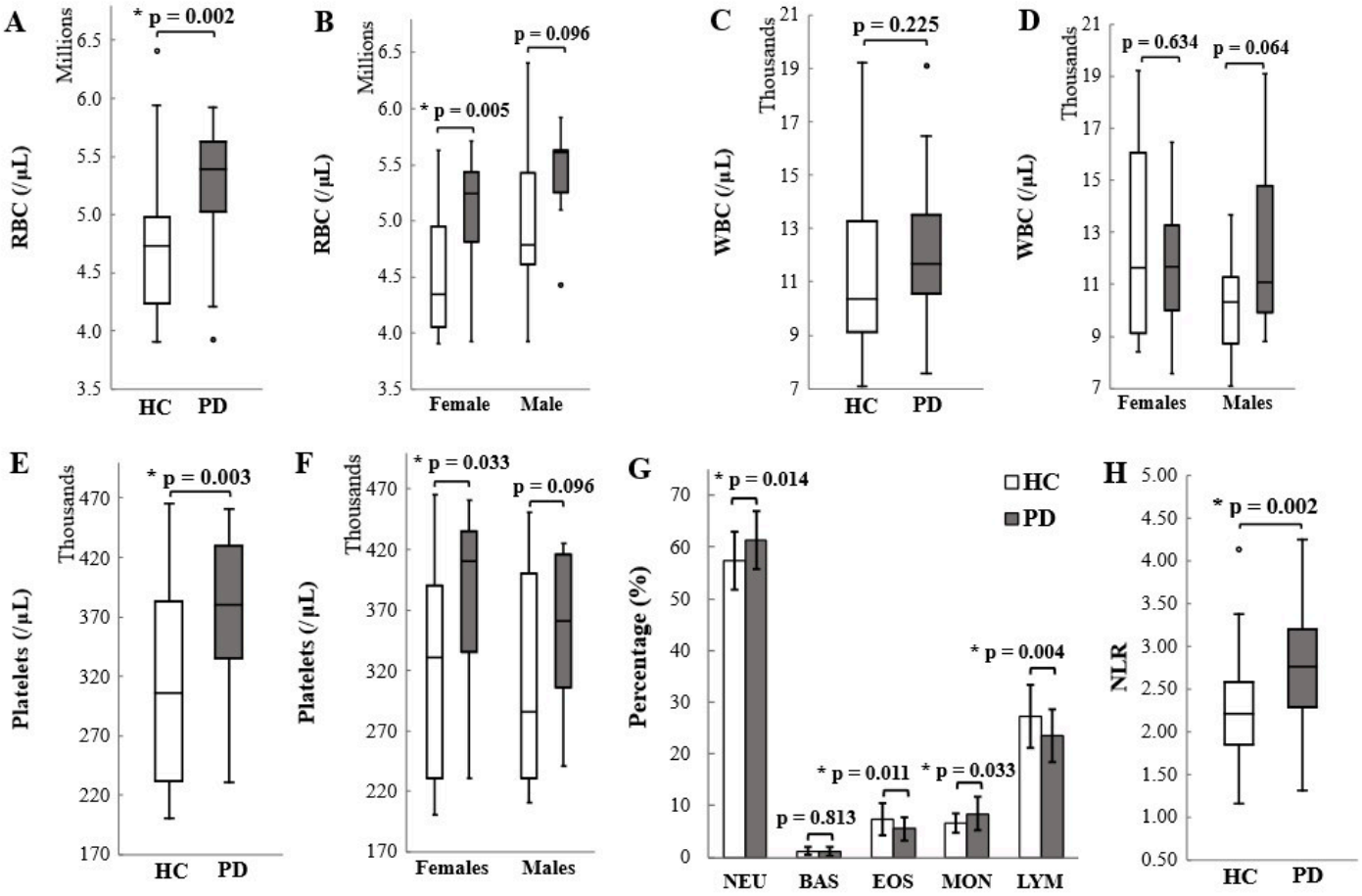


Figure 3

Comparison of Haematological Parameters between Study Groups.

(A) RBC counts, (B) Sex-based RBC count variation, (C) WBC counts, (D) Sex-based WBC count variation. (E) Platelet counts, (F) Sex-based platelet count variation, (G) Differential WBC Counts. Presented as mean ± SD, (H) NLR, (Mann-Whitney *U* tests; *p<0.05)

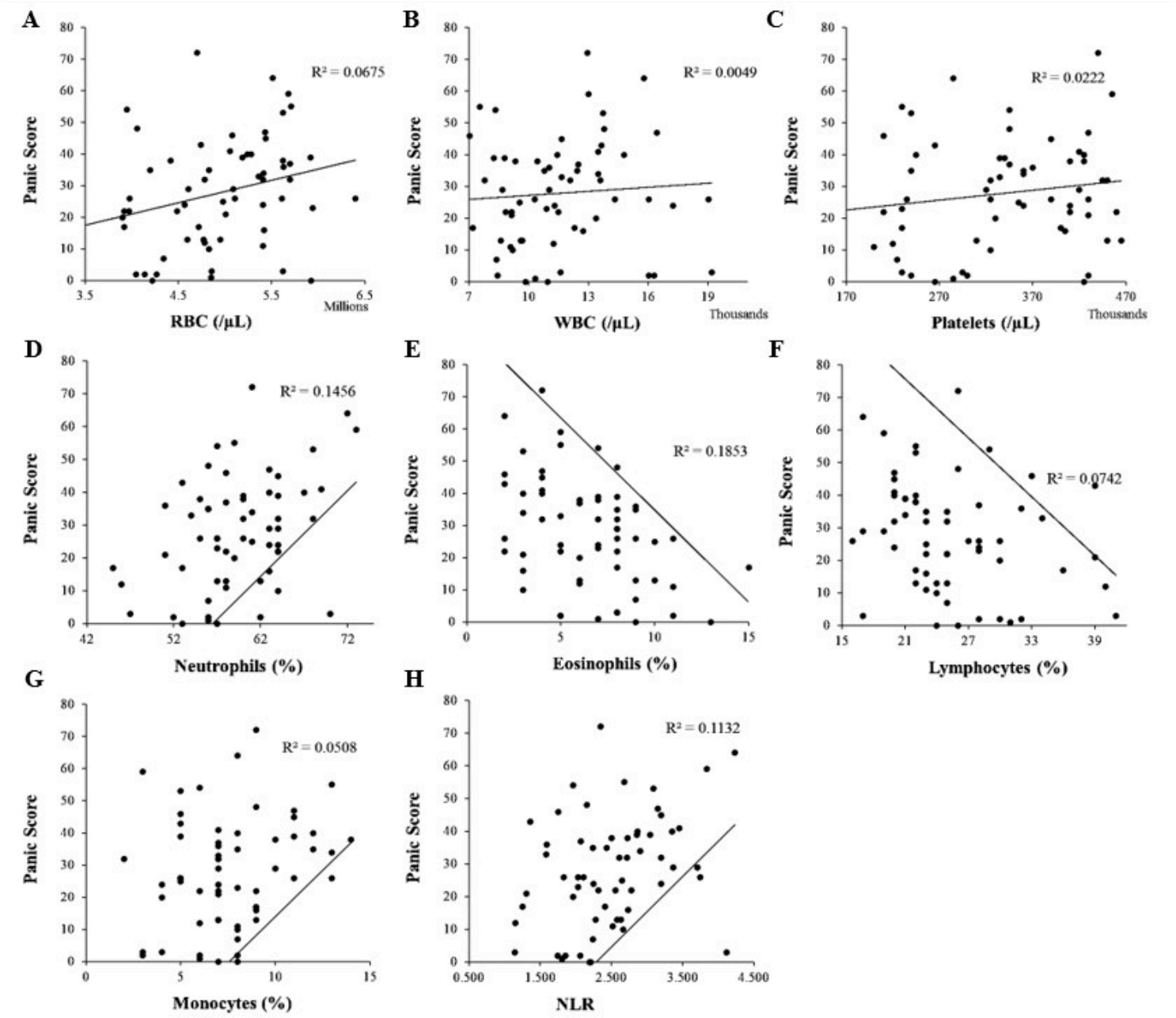


Figure 4

Parameters showing correlation with Panic Scores.

(A) RBC count, (B) WBC count, (C) Platelet count (D) Neutrophil (%), (E) Eosinophil (%), (F) Lymphocyte (%), (G) Monocyte (%), (H) NLR (Spearman's Rho Correlation).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AdditionalFile01ToolsInstrumentsUsedintheStudy.pdf

- AdditionalFile02PanicAssessmentQuestionnaireAnalysis.pdf
- AdditionalFile03SummaryofCorrelationStatistics.pdf