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Original article

Complete blood count to evaluate major depressive disorder and/or generalized anxiety disorder: A case-control study

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Abstract. *Purpose:* The aim of this study was to evaluate the clinical diagnostic significance and ratios of complete blood count parameters in patients diagnosed with either or both disorders. *Patients and methods:* This case-control study included 153 drug-naive patients who were diagnosed with either or both disorders and a matched control group comprised of 163 healthy individuals. The complete blood count parameters with their differentials were calculated and analyzed for all the patients. Moreover, logistic regression analysis was performed using binary logistic analysis. *Results:* The cases showed a relatively higher basophil count (0.05 ± 0.09, P = 0.013) and basophil percentage (0.98 ± 1.21, P = 0.019) but a significantly lower lymphocyte count (2.17 ± 0.64, P = 0.035), eosinophil count (0.13 ± 0.14, P = 0.003), and eosinophil percentage (2.1 ± 1.82, P = 0.016). In addition, the odds of being a case is lower with a high lymphocyte count (OR = 0.69; P = 0.04), higher with a high basophil count (OR = 203.91; P = 0.01) and after adjusted logistic regression analysis, odds of being a case was lower with a higher red cell distribution width (odds ratio = 0.63; P < 0.001).*Conclusion*: Several parameters were significantly associated with both major depressive and generalized anxiety disorders. However, larger, multicenter, prospective studies are needed to increase the representation of the data as well as to generalize the results. (www.actabiomedica.it)

Key words: major depressive disorder, generalized anxiety disorder, complete blood count, inflammatory marker

Introduction

Major depressive disorder (MDD) and generalized anxiety disorder (GAD) are common psychiatric diagnoses worldwide that pose a huge burden on the healthcare system. US statistics demonstrated that MDD and GAD affect 8.4% and 2.7% of adults, respectively.

(1,2). These disorders are usually diagnosed on the basis of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), in which patients with additional physical manifestations are included as a diagnostic criterion (ie, sleep disturbances, appetite change, and energy levels in MDD and muscle tension, fatigue, and irritability in GAD) (3). However, the subjectivity of the interpretations of these criteria reflects the lack of consensus regarding objective criteria.

Recent studies have hypothesized the usefulness of physical indicators as supportive tools to aid in the diagnosis of MDD and GAD, in which the complete blood count (CBC) test was used because

it is cheap, quick, and widely available. The usefulness of the CBC test is evident from the derived ratios (eg, neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio), which reflect an inflammatory status that is increased at baseline in patients with MDD and GAD (4–6). The inflammatory status reflected by the CBC (eg, decreased platelets count) was correlated with MDD and GAD severity and suicidal risk, reflecting a subtle pathogenic relation that suggests an added stratum to the complex multifactorial etiopathology of these disorders (7–10). Therefore, the aim of this study was to evaluate the clinical significance and ratios of the CBC parameters in a case-control study among patients in Saudi Arabia diagnosed with MDD, GAD, or both disorders.

Material and Methods

Subject

This retrospective case-control study was conducted collaboratively between the psychiatry and family medicine departments of King Fahad Hospital of the University (KFHU), Dammam, Saudi Arabia. Local institutional review board (IRB) approval was obtained (IRB number: IRB-UGS-2022-01-471) and followed under the ethical regulations of the center.

The sample size of the control group was calculated using the formula ($n = (Z\alpha/2 + Z\beta)2 \times 2 \times \sigma2/d2$), with a σ value of 0.0500 at a power of 0.9000. Accordingly, the minimum sample size required was 120 individuals (120 cases and 120 controls). In addition, the control group included patients aged between 18 and 65 years who had no prior medications (drug-naive), had no known psychiatric disorders, and had medical records containing their CBC results. On the other hand, the cases were patients aged between 18 and 65 years who had no prior medications (drug-naive); were diagnosed with MDD, GAD, or both; and had medical records containing their CBC results. In both groups, patients who had an active chronic condition (eg, endocrine, metabolic disorders, anemia, and malignancy), had an active acute condition (eg, infection, intoxication, trauma, and burns), were currently receiving medications, were smokers, or were alcohol users were excluded.

Data collection

A retrospective analysis and collection of data from patients who met the inclusion criteria were performed between 2021 and 2022 using the electronic medical records system of KFHU. The records used for the secondary data were selected by systematic random sampling. The departments maintained electronic and hand-written records, and the patients' information was verified for reliability and to prevent missing data. In addition, the data were collected over 5 months and inputted into an Excel compilation sheet, including the patients' age, sex, diagnosis, and CBC components (ie, white blood cell count [WBC], red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, platelets, mean corpuscular hemoglobin [MCH], MCH concentration [MCHC], red cell diameter width, and mean platelet volume [MPV]). In addition, the WBC differentials were also included (lymphocytes, monocytes, eosinophils, basophils, and neutrophils) as reference points for the patients' inflammatory statuses.

Diagnosis and definition

MDD was diagnosed on the basis of the DSM-5 criteria, namely low mood or loss of interest for the past 2 weeks or more, with ≥5 physical symptoms (ie, sleep disturbance, guilt, low energy, executive dysfunction, psychomotor agitation, appetite changes, and suicidality), in the absence of any general medical condition affecting social functionality (eg, poor academic performance) (3). Similarly, GAD was diagnosed on the basis of the DSM-5 criteria, namely a constant, non-specific (ie, involving different aspects of the patient's life), and uncontrollable worrying for the past 6 months or more, with ≥3 physical symptoms (ie, muscle tension, sleep disturbance, restlessness, irritability, fatigue, and difficulty concentrating) affecting social functioning, without any general medical condition (eg, iron deficiency anemia) (3). Lastly, the presence of both disorders in patients is common, with

varying severity (ie, a patient might have severe MDD and moderate GAD) depending on their scores; hence, they were subcategorized into a mixed group and analyzed as separate entities.

Data analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 27. The descriptive statistics were in the form of frequency and percentages representing the categorical variables (eg, sex and presenting complaints), and the mean and standard deviation were calculated for the numerical variables (eg, age and CBC parameters). Nonetheless, the data were tested for normal distribution using the Shapiro-Wilk test, in which normally distributed variables were compared using an independent two-samples t test, and the non-normally distributed variables were compared using the Mann-Whitney U test to check for statistically significant differences. The logistic regression (non-adjusted) analysis was performed using binary logistic analysis to assess the association between the CBC parameters and the differential counts in the cases and controls. The variables were then controlled (adjusted), and the results of the binary logistic regression analysis were reported as odds ratios (OR), P values (statistically significant if ≤0.05), and confidence intervals. Furthermore, the reference points were calculated as ratios (ratios of neutrophils, monocytes, platelets, basophils, eosinophils, and WBC to lymphocytes) to increase the sensitivity of the findings.

Results

Characteristics of the case and control groups

The total number of enrolled cases was 153, all of whom were diagnosed with MDD (56.2%), GAD (18.3%), or mixed (25.5%). The mean age of the cases was 27.9 years (SD, ±9.56), and 60.1% of the cases were females. On the other hand, the total number of the enrolled healthy controls was 163, with a mean age of 27.08 years (SD, ±10.3), and females represented 57.1% of them. However, no statistically significant differences were found between the case and control groups in relation to age (P = 0.11) and sex (P = 0.58).

Differences in CBC and its differentials between the case and the control groups

Statistically significant differences were found between the cases and control groups in terms of CBC (Table 1), in which the lymphocyte count, eosinophil count, eosinophil percentage, and eosinophil-to-lymphocyte ratio (ELR) were significantly lower in the cases than in the controls (2.17 ± 0.64 K/uL vs 2.33 ± 0.67 K/uL; 0.13 ± 0.14 K/uL vs 0.17 ± 0.26 K/uL; 2.1% ± 1.82% vs 2.46% ± 1.76%; and 0.06 ± 0.05 vs 0.07 ± 0.05, respectively). On the other hand, the basophil count, basophil percentage, and basophil-to-lymphocyte percentage ratio (BLR) were significantly higher in the cases than in the controls (0.05 ± 0.09 K/uL vs 0.03 ± 0.05 K/uL; 0.98% ± 1.21% vs 0.64% ± 0.5%; and 0.03 ± 0.05 vs 0.02 ± 0.01, respectively).

Differences in CBC and its differentials between the cases with MDD and the control group

Table 2 shows that the lymphocyte count, lymphocyte percentage, eosinophil count, eosinophil percentage, and BLR percentage were significantly lower in the MDD group (n = 86) than in the control group (n = 163; 2.17 ± 0.69 K/uL vs 2.33 ± 0.67 K/uL; 35.77% ± 9.9% vs 38.50% ± 9.15%; 0.13 ± 0.14 K/uL vs 0.17 ± 0.26 K/uL; 1.98% ± 1.71% vs 2.46% ± 1.76%; and 0.03 ± 0.06 vs 0.0 ± 0.01, respectively. However, the neutrophil percentage, white blood cell-to-lymphocyte ratio (WLR), and neutrophil-to-lymphocyte ratio (NLR) were significantly higher in the cases than in the controls (53.28% ± 11.52% vs 50.11% ± 10.32%; 3.04 ± 0.96 vs 2.80 ± 0.74; and 1.71 ± 0.91 vs 1.50 ± 0.70, respectively).

Differences in CBC and its differentials between the cases with GAD and the control group

The lymphocyte count, eosinophil count, BLR percentage, and ELR percentage were significantly lower in the GAD group (n = 28) than in the control group (n = 163; 2.14 ± 0.47 K/uL vs 2.33 ± 0.67 K/uL; 0.15 ± 0.11 K/

Table 1. Differences in case and control groups in relation to CBC and Differential Count.

Variables	Case (n=153)	Control (n=163)	Test of significance
WBC (K/uL)	6.22 ± 2.29 (2.7 - 17.2)	6.28 ± 1.99 (3 - 13.4)	(P=0.579)^
RBC (Mil/uL)	4.91 ± 0.56 (3.73 - 6.42)	4.92 ± 0.57 (3.83 - 6.47)	(P=0.991)^
Hemoglobin (g/dL)	13.72 ± 1.46 (10.1 - 16.9)	13.63 ± 1.32 (10.3 - 17.4)	(P=0.576)^^
Hematocrit (%)	41.7 ± 4.19 (32.6 - 52.3)	41.39 ± 3.78 (33.5 - 51)	(P=0.548)^
MCV (fL)	85.42 ± 6.45 (69 - 100)	83.62 ± 9.18 (26.4 - 102)	(P=0.261)^
Platelets (K/uL)	273.48 ± 75.95 (118 - 547)	273.18 ± 69.87 (126 - 460)	(P=0.855)^
MCH (pg)	28.1 ± 2.6 (21.5 - 34)	27.87 ± 2.59 (18.9 - 32.6)	(P=0.526)^
MCHC (g/dL)	32.92 ± 1.26 (30.2 - 36.4)	33.04 ± 1.24 (30.5 - 36.4)	(P=0.423)^
RDW (%)	13.21 ± 1.44 (10.9 - 18.4)	12.95 ± 1.08 (10 - 16.7)	(P=0.385)^
MPV (fL)	8.75 ± 1.11 (6.1 - 12.9)	8.8 ± 1.22 (6.5 - 12)	(P=0.952)^
Neutrophils count (K/uL)	3.37 ± 1.77 (0.76 - 10.49)	3.27 ± 1.53 (1 - 9.1)	(P=0.747)^
Neutrophils percentage (%)	52.2 ± 11.97 (25.6 - 98.3)	50.11 ± 10.32 (24.7 - 77.5)	(P=0.481)^^
Lymphocyte count (K/uL)	2.17 ± 0.64 (0.9 - 4.8)	2.33 ± 0.67 (1.1 - 4.7)	**(P=0.035*)^**
Lymphocyte percentage (%)	37.04 ± 10.29 (15 - 67.7)	38.5 ± 9.15 (16.9 - 64.9)	(P=0.183)^^
Monocyte count (K/uL)	0.48 ± 0.17 (0.2 - 1.3)	0.49 ± 0.17 (0.1 - 1.2)	(P=0.274)^
Monocyte percentage (%)	7.91 ± 2.05 (3.3 - 12.8)	8.13 ± 2.14 (4 - 14.3)	(P=0.356)^
Basophil count (K/uL)	0.05 ± 0.09 (0 - 0.62)	0.03 ± 0.05 (0 - 0.3)	**(P=0.013*)^**
Basophil percentage (%)	0.98 ± 1.21 (0 - 9.2)	0.64 ± 0.5 (0 - 4.8)	**(P=0.019*)^**
Eosinophil count (K/uL)	0.13 ± 0.14 (0 - 0.9)	0.17 ± 0.26 (0 - 3.1)	**(P=0.003*)^**
Eosinophil percentage (%)	2.1 ± 1.82 (0 - 9.2)	2.46 ± 1.76 (0.1 - 9.2)	**(P=0.016*)^**
NLR	1.61 ± 0.86 (0.33 - 4.56)	1.46 ± 0.7 (0.39 - 4.55)	(P=0.13)^
MLR	0.23 ± 0.08 (0.09 - 0.56)	0.22 ± 0.07 (0.06 - 0.47)	(P=0.46)^
PLR	135.57 ± 55.82 (44.07 - 420.77)	125.08 ± 42.78 (49.33 - 325.38)	(P=0.12)^
WLR	2.94 ± 0.92 (1.52 - 6.44)	2.77 ± 0.74 (1.57 - 5.85)	(P=0.14)^
BLR ratio	0.03 ± 0.05 (0 - 0.46)	0.02 ± 0.01 (0 - 0.13)	**(P<0.001*)^**
ELR ratio	0.06 ± 0.05 (0 - 0.3)	0.07 ± 0.05 (0 - 0.25)	**(P=0.03*)^**

* P value ≤ 0.05 (statistically significant); ^ Mann-Whitney U-test; ^^ independent two samples t-test.

uL vs 0.17 ± 0.26 K/uL; 0.02 ± 0.04 vs 0.00 ± 0.01; and 0.07 ± 0.05 vs 0.1 ± 0.05, respectively; Table 3). On the other hand, the basophil count, basophil percentage, and eosinophil percentage were significantly higher in the cases with GAD than in the controls (0.03 ± 0.07 K/uL vs 0.03 ± 0.05 K/uL; 0.76% ± 0.71% vs 0.64% ± 0.50%; and 2.8% ± 1.63% vs 2.46% ± 1.76%, respectively).

Differences in CBC and its differentials between the cases with both disorders and the control group

The results represented in Table 4 demonstrate that the lymphocyte count, eosinophil count, eosinophil percentage, BLR percentage, and ELR percentage were significantly lower in the case group (n = 39) than in the control group (n = 163; 2.2 ± 0.66 K/uL vs 2.33 ± 0.67 K/uL; 0.1 ± 0.17 K/uL vs 0.17 ± 0.26 K/uL; 1.84% ± 2.1% vs 2.46% ± 1.76%; 0.03 ± 0.04 vs 0.00 ± 0.01; and 0.05 ± 0.06 vs 0.1 ± 0.06, respectively). However, the basophil count and percentage were significantly higher in the case group than in the control group (0.07 ± 0.08 K/uL vs 0.03 ± 0.05 K/uL and 1.19% ± 1.21% vs 0.64% ± 0.50%, respectively).

Logistic regression analysis

The unadjusted model of logistic regression in Table 5. shows that the only predictors of cases were

Table 2. Differences of GAD and Control groups in relation to CBC with differential.

Variables	Case MDD (n=86)	Control (n=163)	Test of significance
Neutrophils percentage (%)	53.28 ± 11.52 (27 - 76.8)	50.11 ± 10.32 (24.7 - 77.5)	**(P=0.03*)^^**
Lymphocyte count (K/uL)	2.17 ± 0.69 (0.9 - 4.8)	2.33 ± 0.67 (1.1 - 4.7)	**(P=0.05*)^**
Lymphocyte percentage (%)	35.77 ± 9.9 (15 - 56.4)	38.5 ± 9.15 (16.9 - 64.9)	**(P=0.03*)^^**
Eosinophil count (K/uL)	0.13 ± 0.14 (0 - 0.8)	0.17 ± 0.26 (0 - 3.1)	**(P=0.01*)^**
Eosinophil percentage (%)	1.98 ± 1.71 (0 - 8.5)	2.46 ± 1.76 (0.1 - 9.2)	**(P=0.02*)^**
NLR	1.71 ± 0.91 (0.33 - 4.56)	1.46 ± 0.7 (0.39 - 4.55)	**(P=0.04*)^**
WLR	3.04 ± 0.96(1.71 - 6.44)	2.77 ± 0.74 (1.57 - 5.85)	**(P=0.03*)^**
BLR percentage	0.03 ± 0.06 (0 - 0.46)	0.02 ± 0.01 (0 - 0.13)	**(P=0.01*)^**

* P value ≤ 0.05 (statistically significant); ^ Mann-Whitney U-test; ^^ independent two samples t-test.

Table 3. Differences of GAD and Control groups in relation to CBC with differential.

Variables	Case GAD (n=28)	Control (n=163)	Test of significance
Lymphocyte count (K/uL)	2.14 ± 0.47 (1.3 – 3.3)	2.33 ± 0.67 (1.1 – 4.7)	**(P=0.035*)^**
Basophil count (K/uL)	0.03 ± 0.07 (0 – 0.3)	0.03 ± 0.05 (0 – 0.3)	**(P=0.013*)^**
Basophil percentage (%)	0.76 ± 0.71 (0 – 3.5)	0.64 ± 0.5 (0 – 4.8)	**(P=0.019*)^**
Eosinophil count (K/uL)	0.15 ± 0.11 (0 – 0.5)	0.17 ± 0.26 (0 – 3.1)	**(P=0.003*)^**
Eosinophil percentage (%)	2.8 ± 1.63 (0.4 – 6)	2.46 ± 1.76 (0.1 – 9.2)	**(P=0.016*)^**
BLR percentage	0.02 ± 0.04 (0 – 0.22)	0.02 ± 0.01 (0 - 0.13)	**(P<0.001*)^**
ELR percentage	0.07 ± 0.05 (0.01 – 0.22)	0.07 ± 0.05 (0 - 0.25)	**(P=0.03*)^**

* P value ≤ 0.05 (statistically significant); ^ Mann-Whitney U-test.

Table 4. Differences of Mixed and Control groups in relation to CBC with differential.

Variables	Case Mixed (n=39)	Control (n=163)	Test of significance
Lymphocyte count (K/uL)	2.2 ± 0.66 (1.05 - 4)	2.33 ± 0.67 (1.1 - 4.7)	**(P=0.035*)^**
Basophil count (K/uL)	0.07 ± 0.08 (0 - 0.3)	0.03 ± 0.05 (0 - 0.3)	**(P=0.013*)^**
Basophil percentage (%)	1.19 ± 1.21 (0.1 - 5.5)	0.64 ± 0.5 (0 - 4.8)	**(P=0.019*)^**
Eosinophil count (K/uL)	0.1 ± 0.17 (0 - 0.9)	0.17 ± 0.26 (0 - 3.1)	**(P=0.003*)^**
Eosinophil percentage (%)	1.84 ± 2.1 (0 - 9.2)	2.46 ± 1.76 (0.1 - 9.2)	**(P=0.016*)^**
BLR percentage	0.03 ± 0.04 (0 - 0.2)	0.02 ± 0.01 (0 - 0.13)	**(P<0.001*)^**
ELR percentage	0.05 ± 0.06 (0 - 0.29)	0.07 ± 0.05 (0 - 0.25)	**(P=0.03*)^**

* P value ≤ 0.05 (statistically significant); ^ Mann-Whitney U-test.

the lymphocyte and basophil counts. The odds of being a case is lower when the lymphocyte count is high (OR = 0.69; P = 0.04) and higher when the basophil count is high (OR = 203.91; P = 0.01). With an increase in lymphocyte count, patients are 0.69 times more likely to develop the conditions. Similarly, an increase in basophil count was significantly associated with the disorders, yielding a 203.91 times likelihood of being a case. In addition, after controlling for all variables in the multivariate regression analysis, the odds of being a case was lower with higher the red cell distribution width (RDW; OR = 0.63; P < 0.001).

Table 5. Adjusted and unadjusted logistic regression analysis of CBC with differential.

Variables	Unadjusted Logistic Regression			Adjusted Logistic Regression		
	P value	Odd ratio	95% CI (Lower – Upper)	P value	Odd ratio	95% CI (Lower – Upper)
WBC	0.81	0.99	(0.89 - 1.1)	0.15	0.22	(0.03 - 1.72)
RBC	0.97	0.99	(0.67 - 1.47)	0.45	0.26	(0.01 - 8.61)
Hemoglobin	0.58	1.05	(0.89 - 1.23)	0.72	0.72	(0.13 - 4.18)
Hematocrit	0.48	1.02	(0.97 - 1.08)	0.42	1.25	(0.73 - 2.14)
MCV	0.05	1.03	(1 - 1.06)	0.11	0.84	(0.69 - 1.04)
Platelets	0.97	1	(1 - 1)	0.93	1	(0.996 - 1)
MCH	0.43	1.04	(0.95 - 1.13)	0.89	1.05	(0.54 - 2.03)
MCHC	0.4	0.93	(0.78 - 1.11)	0.46	1.3	(0.65 - 2.58)
RDW	0.08	1.17	(0.98 - 1.4)	**<0.001***	**0.63**	(0.49 - 0.82)
MPV	0.74	0.97	(0.8 - 1.17)	0.65	1.06	(0.83 - 1.34)
Neutrophils count	0.57	1.04	(0.91 - 1.19)	0.19	3.97	(0.5 - 31.52)
Neutrophils percentage	0.1	1.02	(1 - 1.04)	0.24	0.9	(0.76 - 1.07)
Lymphocyte count	**0.04***	**0.69**	(0.49 - 0.98)	0.06	11.67	(0.94 - 145.05)
Lymphocyte percentage	0.18	0.99	(0.96 - 1.01)	0.14	0.88	(0.73 - 1.05)
Monocyte count	0.34	0.54	(0.15 - 1.93)	0.75	1.99	(0.03 - 138.26)
Monocyte percentage	0.35	0.95	(0.86 - 1.06)	0.86	1.03	(0.75 - 1.42)
Basophil count	**0.01***	**203.91**	(4.84 - 8589.26)	0.26	0.03	(0 - 13.81)
Basophil percentage	0	1.81	(1.22 - 2.7)	0.1	0.59	(0.31 - 1.11)
Eosinophil count	0.08	0.21	(0.04 - 1.19)	0.67	1.52	(0.23 - 10.31)
Eosinophil percentage	0.07	0.89	(0.79 - 1.01)	0.74	1.04	(0.81 - 1.35)

* P value ≤ 0.05 (statistically significant).

Discussion

Recent studies have placed more emphasis on finding specific indicators that can be used to identify the causes and potential risks of mental illnesses, diagnose, predict outcomes, and create effective treatment plans (11). Thus, various studies have been conducted on CBC parameters and their differentials (ie, lymphocytes, monocytes, eosinophils, basophils, and neutrophils) in individuals with mental health disorders. These parameters are utilized in the initial psychiatric evaluation to rule out organic causes (eg, Iron deficiency anemia) as they can be easily measured and are cost-effective, making them ideal for use in regular evaluations. In addition, the review of current literature revealed that this is the first study to compare CBC parameters in patients with MDD, GAD, or both as one group. These disorders were combined in a group on the basis of their shared etiopathological neuropsychiatric theories (eg, deficits in serotonin-receptor function) (12). Therefore, after applying the adjusted logistic regression analysis, a statistically significant increase in RDW was found in the cases, which is in concordance with the results of other descriptive studies, reflecting a subclinical inflammatory background affecting hematopoiesis as a manifestation of the disorder severity (10,13).

CBC parameters in relation to MDD

The relationship between MDD and the CBC parameters is complex and not yet fully understood, as MDD is a multifactorial disorder with a wide range of predisposing causes (eg, genetic, biological, and

neuroimmunological factors), and CBC parameters are influenced by various factors (eg, age, sex, and race) (14,15). Previous studies have discussed this relationship and the derived ratios, in which the monocyte count and MPV were described as statistically significant parameters, with no consensus in the results about whether it increases or decreases in response to MDD (13,16,17). Furthermore, the NLR and WBC count were increased in response to MDD, while the MCHC was consistently reduced (10,13,17,18). Moreover, increases in neutrophil count, platelet count, mean corpuscular volume (MCV), and MCH, and decreases in lymphocyte percentage and red blood cell (RBC) count have been reported (13,17,18). In our study, we found significant increases in neutrophil percentage, WLR, and NLR, and significant decreases in lymphocyte count, lymphocyte percentage, eosinophil count, eosinophil percentage, and BLR percentage, consistent with the findings of some previous studies (13,17,18). The ratios and counts reflect either pathological (eg, chronic inflammation secondary to stress) or physiological factors (ie, increase in catecholamines or Cortisol) affecting the patients' innate immunity deeming them susceptible to other diseases (eg, ischemic heart diseases and autoimmune disorders) (17). Hence, associated with MDD activity and severity leading to a possible mechanism of MDD-related comorbidities (eg, sleep disorders, diabetes mellitus).

CBC parameters in relation to GAD

GAD is a common mental health disorder with a complex origin that is yet to be comprehensively grasped. Several contributing factors have been identified (eg, genetic, environmental, and biological factors), although the exact factors that induce the onset of the disorder are not fully understood (19). Recent studies have been conducted to identify a supporting diagnostic tool for GAD, and CBC parameters were found to have potential usefulness by an increasing number of studies that examined the role of these parameters in the pathophysiology of mental disorders (20,21).

A limited number of studies have examined the relationship of GAD with CBC parameters, resulting in conflicting findings (ie, RDW was reported as a positive significant predictor in GAD, while another study found it insignificantly related to GAD, similar to our results) (10,22). Furthermore, the NLR is an inflammatory indicator that has been found to be significantly higher in GAD in some studies but not in others, as in our study (23–25). Nonetheless, many studies have concurred that specific CBC parameters may indicate the presence of the disorder by being either abnormally decreased or increased (eg, MPV and WBC count), as studies have shown conflicting results (20,24–28).

From the present study results, we found significant decreases in lymphocyte count, eosinophil count, BLR percentage, and ELR percentage and significantly lower basophil count, basophil percentage, and eosinophil percentage in the patients with GAD. However, no previous study has reported any significant findings in these parameters (25–29). Our findings indicate that the inflammatory response is heightened in individuals with GAD, as the increased emotional and physiological responses and stress levels in these patients may contribute to their high inflammatory response compared with their healthy peers (30,31). This could be attributed to alterations in the hypothalamic-pituitary-adrenal (HPA) axis function triggered by stressful experiences in patients with anxiety disorders (32). Therefore, entangling the necessity of cognitive behavioral therapy and practices (eg, emotional regulation, dialectical therapy) in controlling the altered HPA axis's physical sequelae (eg, muscle tension, headache).

CBC parameters in relation to the co-occurring disorders

Comorbid MDD with an anxiety disorder (GAD) or severe anxiety-related symptoms (eg, muscle tension, restlessness, and constant worrying) is a neuropsychiatric entity that is not fairly studied and is labeled anxious depression (AD). Although it increases the severity of depressive symptoms and patients' suicidality and reduces patient quality of life, understanding of its multifactorial etiopathology, clinical course, and management is currently lacking (33–35). In addition, several studies have calculated the prevalence of this phenomenon, with results ranging from 46% to 72% among MDD patients with a co-occurring anxiety disorder (mainly GAD) (36,37).

Several studies have considered the correlation between AD and CBC markers and found that patients with elevated monocyte and neutrophil counts had decreased basophil counts (38,39). Moreover, RBC, RDW, platelet count, and platelet diameter width (PDW) were found to be predictive of AD, as they reflect the structural serotonergic neuro-pathophysiological mechanisms of the brain, although their clinical significance has not yet been proven (40–42).

In our study, 25.5% of the cases had AD, most of whom were females (66.7%) in their mid-twenties (22–24 years old), which is in concordance with the literature (43). Evidently, a statistically significant correlation existed between the cases and elevated basophil count, BLR percentage, and ELR percentage and decreased lymphocyte and eosinophil counts, which could reflect dysfunctional immunity, the inflammatory etiopathology hypothesis, the severity of the disorder, or a predictive sign of AD (44–46). However, it also appears to reflect a transient dysfunctional inflammatory status that can be reversibly normalized with proper management (eg, antidepressants) (42,47).

Limitation and recommendations

This study is the first to be conducted in the Middle East to address CBC changes in a group of psychiatric patients, including drug-naïve patients with MDD and GAD, compared with disease-free controls. However, the following limitations should be considered when analyzing the findings of this study. First, the study was conducted retrospectively, in Saudi Arabia (i.e., affecting the results generalizability and clinical applicability in a different ethnically diverse population) and had a limited number of participants. Second, some data were not available in the patients' records (eg, severity of the disorders), which prevented us from examining the possible connection between the parameters and the severity of the disorders. Third, other laboratory tests (eg, renal function test, liver function test, C-reactive protein, and inflammatory cytokines) were not included in the analysis. Although the study groups were similar in terms of age and sex, uncontrollable factors (eg, lifestyle, body mass index, and diet) could not be assessed. Therefore, we recommend further holistic evaluation of the clinical significance of our results through a prospective study design (to eliminate the previously discussed cofounders), a recently extracted blood sample (to check for current subclinical disorders and perform further investigations such as liver function test), and a larger, multicenter sample to increase the generalizability and representation of the Saudi Arabian population. Moreover, we urge researchers to investigate the potential usefulness of routine examination and laboratory investigations in the diagnostic process of mental health disorders, as mental health is reflected in the physical body.

Conclusion

In conclusion, studies have hypothesized the relationship between CBC parameters and patients with MDD, GAD, or both, which has been confirmed in this study. The total descriptive analysis resulted in a higher level of basophil count and percentage, with significantly lower lymphocyte count, eosinophil count, and eosinophil percentage in the cases than in the controls. In addition, the odds ratio of the cases was lower with the increase in RDW, which was the only significant parameter after the adjusted logistic regression analysis. Therefore, compared with the findings of other studies, our findings show the associations of different CBC parameters with MDD and GAD, which suggests that the inflammatory process underlying MDD and GAD is more complex than currently understood. Accordingly, we encourage the conduction of a prospective study to evaluate the potential usefulness of CBC parameters to facilitate the diagnosis of MDD, GAD, or mixed disorders.

Abbreviations: CBC, Complete blood cell count; MDD, Major depressive disorder; GAD, Generalized anxiety disorder; DSM-5, Diagnostic and statistical manual of mental disorders; KFHU, King Fahad hospital of the university; IRB, Institutional review board; WBC, White blood cell count; PHQ-9, Patient health questionnaire-9; GAD-7, Generalized anxiety disorder scale; SPSS, Statistical package for social sciences; SD, Standard deviation; RBC, Red blood cell count; MCV, Mean corpuscular volume; MCH, Mean corpuscular hemoglobin; MCHC, Mean corpuscular hemoglobin concentration; RDW, Red cell distribution width; MPV, Mean platelet volume; NLR, Neutrophil to lymphocyte ratio; MLR, Monocyte to lymphocyte ratio; PLR, Platelet to lymphocyte

ratio); WLR, White blood cells to lymphocyte ratio; BLR, Basophil to lymphocyte ratio; ELR, Eosinophil to lymphocyte ratio; OR, Odd ratio; CI, confidence interval; HPA, hypothalamic-pituitary-adrenal; AD, anxious depression; IL-6, Iinterleukin-6; TNF, Tissue necrosis factor; CRP, C-reactive protein; CD4+/CD8+, Cluster differentiation 4 and 8 T-cell ratio; LFT, Liver function test.

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