The Association of Hematological Inflammatory Markers and Psychological Function Among in COVID-19 Patients: a Cross Sectional Study

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Abstract

Background: Due to high inflammation and mental health disorders in Covid-19 patients, we aimed to investigate the relationship between blood inflammatory markers such as WBC, RDW, NLR and PLR and psychological function in COVID-19 patients.

Method: The current cross-sectional study and psychological function and a complete blood count (CBC) were measured on 120 COVID-19 patients aged >30 years from the Imam Reza hospital in Mashhad, Iran. Depression, anxiety and stress of participants were evaluated using DASS questionnaire. Also Quality of life, insomnia and sleep quality were measured via SF-36, Insomnia Severity Index and Pittsburgh Sleep Quality Index questionnaire, respectively.

Result: No blood parameters were significantly associated with depression, sleep disorders and quality of life ($P>0.05$), but in MCHC, WBC and PLR anxiety showed a significant relationship ($p<0.05$). In the stress subgroup, only RPR was associated with stress ($p<0.05$). In linear regression between hematological parameters and psychological score indicated that RDW and PLR were significantly associated with depression ($p=0.045$ and 0.016 respectively) and anxiety scores ($p=0.038$ and 0.010 respectively). PLR was also associated with stress ($p=0.012$).

Conclusion: This study showed a positive association between depression/anxiety/stress symptoms and levels of hematological inflammatory markers including PLR and RDW.

Background

The 2019 coronavirus COVID-19 pandemic, has affected more than 170 million individuals resulting in 3.5 million deaths globally by May 2021[1, 2]. In addition to the impact on physical health, has had taken a toll on mental health as a result of fear of illness and hospitalization and social distancing efforts may have a unique and significant influence on mental health. Given the significance of stress in the etiology of anxiety and depressive disorders, the prevalence of these diseases may rise due to intensified stress related to COVID-19. Preliminary research also suggests that these symptoms and disorders may be linked to more severe COVID-19 progression [3]. Mental health of COVID-19 hospitalized patients during the epidemic has been reported in previous studies. In this context, patients who were diagnosed with COVID-19 were more likely to have psychological concerns such as fear of disease progression, disability, or higher mortality. It is essential to investigate the prevalence and severity of anxiety and depression in COVID-19 infected patients [4]. In addition to COVID-19 situations, perceived stress related to COVID-19- expected to have a significant increasing prevalence in poorer mental health outcomes.

When early response pro-inflammatory cytokines are overproduced, it may result in a cytokines storm, which increases the risk of vascular hyper permeability, multi organ failure and mortality if the cytokine concentration are not decreased [5]. The inflammatory response is mediated by phagocytic cells such as monocytes (MON) and neutrophils (NEU), as well as cytokines, which are important components of the immune system. In anxiety and related disorders, central and peripheral immune system cells release cytokines and cause inflammation in response to increased stress [6]. Inflammation and anxiety disorders are linked, which hematological parameters are also thought to be a useful marker in the follow-up of patients with anxiety disorders [7]. Systemic inflammation has been linked to depression and anxiety, two common mood disorders [8]Several studies have found a link between depression and higher levels of pro-inflammatory cytokines, and there is some correlation between anxiety and inflammation [9, 10].

The white blood cell count (WBC) is a non-specific inflammatory marker that is usually measured as part of a complete blood count (CBC) panel. A high WBC count has been linked to a variety of diseases, including hypertension, diabetes, and atherosclerotic cardiovascular disease [11]Moreover, numerous studies reported that having a higher WBC count is associated with an increased risk of all-cause cardiac disease and cancer mortality [12]. The quantitative measure of anisocytosis, red cell distribution width (RDW), is a simple, low-cost parameter that is routinely reported as part of the CBC test [13]. Previous research has found a significant association between RDW and inflammatory markers such as hs-CRP and erythrocyte sedimentation rate, indicating that increased RDW may be the result of an underlying inflammatory state that is associated with negative outcomes [14]. The findings of one study suggested that RDW should be included in routine laboratory monitoring and assessment of COVID-19 [15].

In COVID-19 confirmed cases, reported that lymphopenia, eosinopenia, neutrophilia, leucocytosis and decline of hemoglobin. When compared to the control group, these parameters demonstrated a significant deterioration in critically acute ICU patients [16]. Increased NLR has been reported as a significant risk factor for clinical complications. Despite the fact PLR did not show a

significant difference [16]. Previous research has found that personal experiences with COVID-19 diagnosis, mortality in acquaintances, and COVID-19-related stress are related to a significantly increased risk of emotional disorder symptomatology, and that the COVID-19 pandemic may result in an increase in demand for mental health services [17].

In contrast to measuring peripheral cytokine levels, studies on this topic have found that measuring peripheral blood cells, which are the source of some of these cytokines, by complete blood count is a cheap, easy, and rapid procedure. Leukocytes, which are counted as part of a complete blood count, play an important role in inflammation. By secreting cytokines, NEU and MON play an important role in the inflammatory response [18]. The neutrophil/lymphocyte ratio (NLR), which is determined by the ratio of these two key cells participating in the inflammatory response, has been accepted as a measure of systemic inflammatory response [18]. NLR is recognized as an inflammatory response and prognostic factor in a variety of chronic diseases, including autoimmune, cardiovascular, and respiratory diseases [19, 20]. NLR has been reported to be higher in several psychiatric diseases, such as mood disorders, anxiety disorders, and schizophrenia, than in healthy adults, and has already been considered as a biomarker of increased inflammatory response [21, 22]. Platelets are another essential cell type that is counted in a complete blood count (PLT). Active PLT, in collaboration with MON and leukocytes, play a key role in implementing and sustaining inflammation by facilitating the release of inflammatory cytokines [23]. Platelet/lymphocyte ratio (PLR) is a biomarker used as a diagnostic of chronic inflammation, similar to NLR, and is useful in a number of disease groups, especially autoimmune illnesses and cancer [19, 24]. And is often used to diagnose psychiatric diseases [25].

In the present study, due to high inflammation and mental health disorders in Covid-19 patients, we aimed to investigate the relationship between blood inflammatory markers such as WBC, RDW, NLR and PLR and depression, anxiety, stress, and quality of life in COVID-19 patients. Our study hypothesized that there was a relationship between psychiatric disorders in Covid-19 patients and inflammation using blood parameters, which is a cheap, fast, and easy method.

Methods And Materials

Study design

The current cross-sectional study was carried out during 2021 within a sample of COVID-19 patients from the Imam Reza hospital in Mashhad, Iran. The total subjects included 120 covid-19 patients aged >30 years. The exclusion criteria were: cancer, autoimmune diseases, hepatic or renal failure, metabolic bone disease and without anti-depressant drug treatment during the previous 6 months.

General and clinical characteristics

Demographics and clinical characteristic including age, smoking status, comorbidity data were collected from each participant at the baseline by trained interviewers.

Blood Collection and Biochemical Measurements

A CBC including red blood cell (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC), platelet (PLT), platelet distribution width (PDW), mean platelet volume (MPV), RDW, and WBC was measured by using an auto hematology analyzer (Sysmex K-800) for each individual.

Depression anxiety stress scales (DASS)

Depression anxiety stress scales (DASS) is an accurate and valid tool to evaluate mood status [26]. This tool is a questionnaire that consists of three subscales includes 7 questions, generally consists 21 items. Each question is ranged on a four point (0-3) Likert scale to identify the severity of mood disorder including depression, anxiety and stress. Score of each item must be doubled because of DASS 21 is a brief version of DASS 42. In this tool a higher score shows higher degree of negative mood status and lower score indicates lower degree of negative emotion. The reliability and validity of DASS has been previously reported in Iranian population [27]. The scores for depression, anxiety and stress were divided into 2 classifications: No or minimal scores, some degree of mood disorder. Based on the scores obtain from each item determined as follows: (≤ 9 , No), (> 9 , some degree of depression), (≤ 7 , No), (> 7 , some degree of anxiety), (≤ 14 , No), (> 14 some degree of stress).

Insomnia Severity Index (ISI)

The ISI is a seven-item self-report tool for determine of the insomnia symptom and its consequences. The dimensions measured are: severity of sleep onset, sleep preservation, early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others and distress caused by the sleep difficulties [28]. Each item according to severity scored on 0–4 scale. The total scale ranging from 0 to 28 and explained as follows: no insomnia (0–7), sub-threshold insomnia (8–14), mild insomnia (15–21) and severe insomnia (22–28). The validity and reliability of Persian version of this questionnaire have been confirmed in the Iranian population (Cronbach's $\alpha > 0.8$ and intra-class correlation coefficient > 0.7) [29].

Pittsburgh Sleep Quality Index (PSQI)

Sleep quality was evaluated using 19-item self-reported PSQI questionnaire that assesses sleep quality over the last 30 days duration [30]. It consisting of 19 items combined for 7 component scores, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The responses are scored on a 3-point scale, ranging from 0 to 3. The overall score for sleep quality can be calculated by combination of the 7 component scores, which ranges from 0 to 21. Patients were classified into two groups based on their PSQI score: poor-sleeper group (PSQI > 5) and good-sleeper group (PSQI ≤ 5). The Persian version of PSQI has also been validated in a previous study by Farrahi Moghaddam et al in 2012 [31].

Quality of Life Questionnaire

The Short Form Health Survey (SF-36) validated questionnaire was used for evaluating general quality of life. SF-36 categorized into eight subscales: Role Physical, Physical Functioning, General Health, Bodily Pain Social Functioning, Vitality, Role Emotional and Mental Health. Scores of this questionnaire range from 0 to 100. The Persian version of SF-36 was assessed in previous study and indicated good reliability and construct validity [32].

Statistical analysis

SPSS Statistics for Windows v20 (SPSS, Inc., Chicago, IL) was used for statistical analysis. The normality of variables were analyzed using the Kolmogorov–Smirnov test. Descriptive statistics including mean and standard deviation (SD) were determined for all variables and expressed as mean $\pm$ SD for normally distributed variables and as median and interquartile range (IQR) for non-normally distributed variables. Also categorical indices were demonstrated by number (%). Chi-square tests were used to compare the qualitative variables. Two independent sample t-test and Man-Witney test was used to evaluate the significant difference in normal and non-normal variables between two groups, respectively. Finally, multivariate linear regression was performed between hematological parameters and psychological scores. All analyses were considered bilateral, and a p-value of < 0.05 was considered to be significant.

Results

The demographic data of the patients are reported in Table 1, which shows the mean age, sex, smoking conditions and underlying diseases of the participants. The number of patients participating in all three subgroups of depression, anxiety, stress, sleep disorders and quality of life questionnaire are listed separately.

Table 1
General characteristics of study participants.

variable	Depression	Anxiety	Stress	Sleep		Quality of Life
	Some degree depression	Some degree anxiety	Some degree stress	Mild to Sever Insomnia	Poor Sleep Quality	(score<55)
	n=78	n=90	n=93	n= 28	n=85	n=58
Gender						
Male	44 (57.8%)	49 (55.8%)	51(55.7%)	13 (45.5%)	42 (49.4%)	31 (53.4%)
Female	34 (42.2%)	41 (44.2%)	42(44.3%)	15 (54.5%)	43 (50.6%)	27 (46.6%)
Age (year)	60.42±14.85	59.71±14.33	60.41±14.30	57.59±14.18	61.42±13.56	60.77±15.56
Current smoking	18 (28.5%)	20 (26.3%)*	21 (27%)*	7 (25.0%)	16 (18.8%)	15 (25.8%)
Comorbidity						
Cardiovascular disease	14 (22.2%)	17 (22.4%)	17 (21.8%)	4 (14.2%)	14 (16.4%)	9 (15.5%)
Hypertension	25 (39.7%)	31 (40.8%)	32 (41.0%)	10 (35.7%)	30 (35.2%)	20 (34.4%)
Diabetes	25 (39.7%)	33 (43.4%)	35 (44.9%)	10 (35.7%)	32 (37.6%)	19 (32.7%)
Data presented as Mean ± SD or n (%)						
Obtained from <i>t</i> test for continuous variables and χ^2 test for categorical variables.						
* <i>p</i> < 0.05						

Table 2 shows the relationship between hematological parameters and variables of depression, anxiety, stress, sleep disorders and quality of life. No blood parameters were significantly associated with depression, sleep disorders and quality of life, but in MCHC, WBC and PLR anxiety showed a significant relationship. In the stress subgroup, only RPR was associated with stress.

Table 2
Hematological parameters in groups of depression, anxiety, Stress, sleep disorders and quality of life.

variable	Depression	Anxiety	Stress	Sleep		
	Some degree depression n=78	Some degree anxiety n=90	Some degree stress n=93	Mild to Sever Insomnia n= 28	Poor Sleep Quality n=85	Quality of Life (score<55) n=58
RBC (10 ¹² /L)	4.58±0.86	4.60±0.84	4.60±0.82	4.52±0.78	4.69±0.78	4.61±0.79
Hemoglobin (g/dl)	12.81±2.58	12.95±2.43	12.94±2.41	12.39±2.37	13.13±2.30	12.85±2.38
Haematocrit	39.35±6.59	39.92±6.59	39.92±6.51	38.09±6.61	40.23±6.16	39.59±6.52
MCV (fl)	86.46±6.77	87.06±6.55	87.06±6.56	87.13±7.40	86.69±6.43	87.06±7.01
MCH (pg)	28.53±2.68	28.68±2.52	28.96±2.49	28.30±2.98	28.58±2.51	28.54±2.67
MCHC (g/dl)	32.83±1.89	32.71±1.68*	32.71±1.65	32.54±1.67	33.42±6.72	33.54±7.46
RDW (%)	14.75±2.32	14.59±1.99	14.67±1.99	14.89±2.05	14.48±1.79	14.57±1.82
PDW (fl)	14.02±2.47	13.89±2.41	13.88±2.40	13.47±2.80	13.83±2.64	13.86±2.48
WBC (10 ³ /μL)	9.83±4.72	12.23±5.43*	11.25±5.34	8.58±3.55	9.26±4.39	9.77±4.76
MPV (fl)	9.70±3.09	9.71±2.77	9.72±2.74	10.33±0.87	9.78±2.82	9.59±3.41
NLR	8.15 (4.05-13.82)	7.64 (4.39-13.65)	7.86 (4.41-13.87)	7.47 (3.78-12.94)	7.75 (4.22-14.43)	7.35 (3.85-13.61)
RPR	0.07 (0.05-0.11)	0.07 (0.06-0.11)	0.07 (0.05-0.11)*	0.06 (0.05-0.09)	0.07 (0.05-0.10)	0.07 (0.05-0.13)
PLR	17.93 (13.34-31.73)	28.72 (15.88-41.31)*	23.25 (14.06-36.67)	17.20 (11.20-27.83)	16.1 (9.92-30.36)	13.57 (8.98-26.42)
Data presented as Mean ± SD or Median (IQR)						
WBC: white blood cell; RBC: red blood cell; HGB: hemoglobin; HCT: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width; NLR: Neutrophil to lymphocyte ratio; RPR: RDW to platelet count ratio; PLR: Platelet lymphocyte ratio.						
*P<0.05; **P<0.01						
Obtained from independent sample t- test for normal variable and Man-Witney test for nonparametric variable.						

Table 3 shows the linear regression between hematological parameters and psychological score. RDW and PLR were significantly associated with depression and anxiety scores. PLR was also associated with stress. This table shows the age, gender and smoking conditions. Other hematological parameters were not significantly associated with depression, anxiety, stress, sleep disorders and quality of life.

Table 3
Multivariate linear regression between hematological parameters and psychological scores

Haematological parameters	Depression		Anxiety		Stress		Insomnia		Sleep Quality		Quality of Life	
	β	p	β	p	β	p	β	p	β	p	β	p
RBC ($10^{12}/L$)	-0.001	0.957	-0.011	0.562	0.003	0.846	-0.224	0.245	0.150	0.498	0.009	0.951
Hemoglobin (g/dl)	-0.082	0.134	-0.079	0.165	-0.070	0.133	-0.742	0.198	0.083	0.900	0.356	0.440
Haematocrit	-0.136	0.355	-0.154	0.315	-0.105	0.397	-2.066	0.192	0.481	0.786	0.607	0.632
MCV (fl)	-0.197	0.147	-0.114	0.421	-0.207	0.070	0.646	0.658	-1.246	0.463	0.241	0.836
MCH (pg)	-0.100	0.051	-0.092	0.086	-0.104	0.016	-0.096	0.867	-0.264	0.687	0.198	0.664
MCHC (g/dl)	-0.037	0.764	-0.106	0.408	-0.074	0.480	-0.788	0.529	1.408	0.393	-0.734	0.462
RDW (%)	0.086	0.045	0.100	0.038	0.064	0.103	0.374	0.454	0.500	0.331	-0.144	0.717
PDW (fl)	0.084	0.121	0.014	0.798	0.046	0.299	-0.311	0.594	-0.118	0.873	-0.193	0.682
WBC ($10^3/\mu L$)	0.021	0.841	-0.158	0.143	-0.093	0.296	-1.414	0.204	-0.865	0.475	-0.398	0.657
MPV (fl)	0.097	0.207	0.007	0.926	0.006	0.923	0.739	0.269	0.079	0.926	0.344	0.542
NLR	-0.375	0.058	-0.242	0.207	-0.219	0.168	-1.156	0.553	1.282	0.601	1.133	0.472
RPR	0.003	0.241	0.004	0.107	0.003	0.185	-0.017	0.535	-0.005	0.892	0.010	0.649
PLR	1.326	0.016	1.356	0.010	1.102	0.012	4.146	0.445	1.078	0.876	-3.372	0.440
WBC: white blood cell; RBC: red blood cell; HGB: hemoglobin; HCT: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width; NLR: Neutrophil to lymphocyte ratio; RPR: RDW to platelet count ratio; PLR: Platelet lymphocyte ratio.												
Adjusted for age, gender and smoking status.												

Discussion

Our results suggest that higher depression and anxiety scores in COVID-19 patients are associated with an enhanced inflammatory state, as assessed by higher hematological inflammatory markers including RDW and PLR. However, PLR was also associated with stress in participants.

There are several theoretically viable hypotheses that can be used to justify the potential prognostic role of anisocytosis in COVID-19, including direct cytopathic injury disease associated of circulating erythrocytes or their bone marrow precursors, indirect erythrocyte damage caused by hemolytic anemia or intravascular coagulopathy, and profound iron metabolism disruption caused by the sustained inflammatory response [15]. All of these factors would eventually lead to deranged erythrocyte biology and explain the wide range of erythrocyte sizes in circulation. The dramatic derangement of erythrocyte biology in patients with SARS-CoV-2 infection could also be explained by a coexisting indirect injury. First, cases of autoimmune hemolytic anemia have been linked to SARS-CoV-2 infection [33] a phenomenon that has been attributed to the high molecular similarity between the SARS-CoV-2 spike protein and the protein ankyrin 1 found on RBC surfaces [34]. In COVID-19 patients who develop severe or critical illness, intravascular coagulopathy, either localized to the lung parenchyma or disseminated, is also common [35]. The formation of micro- and macrothrombi in various blood veins is a well-known cause of erythrocyte injury, which would contribute to the existence of RBCs with numerous morphological defects high size heterogeneity in the circulation [36].

Coronavirus infection is associated with alterations in the white blood cell count. Alteration in the white blood cell count are linked to Coronavirus infection. A Wuhan study found no significant change in WBC counts, a reduction in the severity of symptoms, and a complete recovery, especially in individuals with no co-morbidities. So, when comparing severe and non-severe patients, total leukocyte counts have a wide range of findings in the literature. The mechanism behind this phenomenon is unknown, while some

researchers believe it is linked to the worsening of cytokine storm syndrome, a clinical state of hyper inflammation caused by the production of pro-inflammatory cytokines and inflammatory cytokines. Multi organ failure, which can be dangerous, can occur as a result of cytokine storm syndrome [16].

A higher WBC count has been identified in depressed and anxious people in several investigations [10, 37]. After 5 years of follow-up, the participants with recurring depressive symptoms have higher WBC counts [10]. In one study results showed that after adjusting for age and cigarette smoking, there is still a link between major depressive illness and leukocyte counts for males but not for women [38]. Furthermore, Pitsavos et al. discovered that anxiety score is positively connected with WBC count in women, but not in men [39]. Another study found that WBC count and related indicators are associated with depressed symptoms, particularly in women [40]. In depressed patients, Darko and colleagues discovered relative lymphopenia, absolute neutrophilia, and leukocytosis. However, the authors speculated that leukocytosis and neutrophilia could be a side effect of taking specific medications [41]. Similarly, when compared to control subjects, newly diagnosed antidepressant-naïve patients had a decreased lymphocyte count [42]. A number of studies have demonstrated a link between depression and inflammation, and some have even suggested that depression is an inflammatory disease. Since WBC count is an independent predictor of atherosclerosis and cardiovascular disease, it's possible that higher WBC counts or the related inflammatory state could explain some of the elevated cardiac events shown in depressed people [43, 44].

NLR was considerably higher in ICU patients than in non-ICU patients, indicating that it is a useful severity indicator. NLR was also proven to be an effective predictor of critical disease risk in other trials [45]. Another study indicated that patients with NLR >3 were more likely to have severe illness in the population under 50 years old. All of these investigations concluded that the NLR was the most important prognostic factor for patients with serious illnesses [46].

Another study found that patients with major depressive disorder had significantly higher RDW and Neutrophil/Lymphocyte ratio (NLR) levels than the control group [47, 48]. May and colleagues also discovered a link between rising RDW levels and a prospective depression diagnosis, which remained after controlling for risk factors, medications, and indicators of other disease states [49]. MCV, MCH, MCHC, and RDW were not significantly different between major depressed subjects and normal controls in another study [50]. RDW has received a lot of attention in the last decade because of its ability to successfully predict the risk of death in the general population [51], patients with non-cardiovascular critical illness, sepsis, pneumonia, and other respiratory tract infections [52, 53]. It is not surprising that our findings show RDW to be a significant and independent predictor of disease severity and kidney injury in patients infected with SARS-CoV-2. Remarkably, after managing for confounding variables, an increased value of this laboratory variable was associated with a 9.2- and 16.0-fold higher risk of estimating severe illness and AKI, respectively, with predictive precision as high as 73 percent and 80 percent and suggested that RDW should be part of routine laboratory assessment and monitoring of COVID-19 [15]. Wang et al. measured RDW in 45 COVID-19 patients with moderate to severe illness over a nearly 20-day period in this latter study. Patients with severe COVID-19 had significantly higher RDW values than those with a milder form of the disease. Furthermore, both RDWs were found to be significant predictors of severe illness, with diagnostic accuracy ranging from 65 to 76 percent [54].

Many other research, however, reveal that thrombocytopenia is a common characteristic in severe COVID-19 patients. Although, few investigations found no variations in platelet count between patients with severe disease and those with mild disease. Regarding the authors' conflicting observations, new research suggests that coagulopathy is a known hazard of COVID-19 [55]. The PLR, a general inflammatory marker, represents a concurrent interaction of platelet count and lymphocyte count, and it indicates aggregation as well as inflammatory pathways. It has been reported to be increased in response to a variety of acute and chronic proinflammatory conditions, and it has been linked to a poor prognosis in individuals with COPD and carcinomas [19, 55–57]. A previous study has found a relationship between elevated PLR and a poor prognosis of sepsis-induced acute renal injury and mortality [58]. In COVID19 patients, the change in PLR from baseline appears to be linearly associated with severity of illness and length of hospital stay [59]. PLR appeared as an independent predictive factor for prolonged hospitalization in one study's multivariate analysis. A high PLR may indicated a more intense cytokine storm as a result of increased platelet activation [60]. No major differences in PLR were seen in Tiwari's investigative process, as was observed in the current study. However, because platelets are a dynamic variable, the validity of PLR can only be determined by collecting follow-up samples at different time points [16].

Conclusion

In conclusion, this study showed a positive association between depression/anxiety/stress symptoms and levels of hematological inflammatory markers including PLR and RDW, which persisted despite adjustment by potential confounders.

Abbreviations

Complete blood count: CBC

Depression anxiety stress scales: DASS

Hematocrit: HCT

Hemoglobin: HGB

Insomnia Severity Index: ISI

Mean corpuscular hemoglobin concentration: MCHC

Mean corpuscular hemoglobin: MCH

Mean corpuscular volume: MCV

Mean platelet volume: MPV

Neutrophil to Lymphocyte Ratio: NLR

Pittsburgh Sleep Quality Index: PSQI

Platelet distribution width: PDW

Platelet to Lymphocyte Ratio: PLR

Platelet: PLT

Red blood cell: RBC

Red cell distribution width: RDW

White blood cell: WBC

Declarations

Ethics declarations

The authors confirm that all procedures contributing to this work was based on the ethical standards laid down in the 1964 Declaration of Helsinki, as revised in 2008.

Ethics approval and consent to participate

The Ethics Committee of MUMS (Mashhad University of Medical Sciences), Mashhad, Iran, approved the trial (Ethic no: IR.MUMS.REC.1399.237). Informed written consent was obtained from all participants included in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interests

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Authors' contributions

MGH initially conceptualized and designed the study, ZKH, MR, EH and MA upgraded the design. The manuscript was written by RR. PA and PSH were responsible for the design optimizing and statistical analysis. NA, NV and SR contribute sampling. GF performed English editing. All authors read and approved the final manuscript.

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