Correlations of Long COVID Symptoms and Inflammatory Markers of Complete Blood Count (CBC): A cross-sectional study.

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Abstract

Background: Long-COVID refers to lasting unspecific symptoms like fatigue, decreased concentration and sleep issues after infection which persist for at least three months and cannot be attributed to other causes. Previous studies surveyed the association between inflammatory markers like C - reactive protein (CRP) at hospital admission and long-COVID symptoms in the preceding months. Post-COVID syndrome can affect one-third of patients. Thus early diagnosis can assist in reducing burdens on public health. We attempted to see any correlations between complete blood count (CBC) markers (like red blood cell (RBC), white blood cell (WBC), Neutrophil to lymphocyte ratio (NLR), etc.) at hospital admission and long COVID symptoms at a 6-month follow-up.

Methods: 167 patients (44.9% females, mean age 49 years old) answered semi-structural interviews through telemedicine which focused on the three prominent symptoms: fatigue, loss of concentration and decreased libido.

Results: Two third of patients have symptoms of long COVID and others do not have. NLR in the symptomatic group was statically higher. Patients who underwent decreased libido at a 6-month follow-up had significantly more severe lymphopenia (p = 0.028) and higher NLR values (p-value = 0.007). Poor mental concentration is associated with high WBC in numbers and polymorphonuclear (PMN) count. Other symptoms do not correlate with blood markers.

Conclusion: Utilizing available data like CBC can help predict the upcoming symptoms of previously hospitalized patients and further measures like rehabilitation. Additional investigations should be done on the effect of COVID vaccination on converting long COVID. Different variants of the virus may have different results.

Keywords: Long COVID, Post-COVID-Syndrome, Fatigue, Decreased concentration, Decreased libido, Complete blood count(CBC), Neutrophil to lymphocyte ratio(NLR), Mean platelet volume(MPV), Inflammatory markers

1. Introduction

Severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) as a neoteric infectious agent caused a global pandemic that has endangered public health and safety.[1−5]

Long COVID is an expression utilized to describe the state presented by patients who have recuperated from the acute stage of COVID-19 but still have regular clinical presentations of the disease for more extended amounts of time than expected.[1−11] Corresponding to the World Health Organization

consensus, long COVID is defined as symptoms persisting at least three months after the infection after ruling out other causes.[12] The Centers for Disease Control (CDC) has described long COVID as health issues persisting more than four weeks after acute infection with COVID-19.[13] The prevalence of long COVID varies between 10 and 35% of infected persons and can reach up to 70% in patients post-hospitalization. The pathogenesis of long COVID is generally unknown in some patients. However, prolonged viremia, immune responses, or the patient's mental health may play a part in the pathogenesis of the disease.[7] Muscle pain, fatigue, various mental disorders (including anxiety, depression, and memory disorder), hair loss, anosmia, and sleeping disorders are common complications of long COVID.[10,14−16] Moreover, other organs, including respiratory, cardiovascular, hematological, endocrine, and gastrointestinal systems, may be affected by complications of Long COVID -19.[10] The potentially associated risk factors are old age, female sex, severe clinical status, multiple chronic conditions, and hospital admission.[6]

Several articles analyzed the association of inflammatory and complete blood count (CBC) markers with complications of long COVID-19.[3,4,10,14−24] Hs-CRP and ferritin were correlated with complications of long COVID-19 in patients infected with the Alpha variant. However, the Delta variant revealed a more significant correlation with Hs-CRP, red cell distribution width (RDW), and NLR.[20]

A group of studies suggested that NLR increases in post-COVID-19 patients, which may demonstrate a direct relationship between the amount of NLR and the severity of complications in post-COVID-19 patients. At the same time, no institutions were founded for platelet-to-lymphocyte ratio (PLR).[17,18,20,21,23−27]

This study aimed to investigate the association between inflammatory markers of CBC and long COVID-19 complications.

2. Methods

We established a post-COVID follow-up among two university hospitals in Tehran, Iran. All patients who survived the disease and were discharged between February and April 2022, the sixth peak of COVID in Iran, were included. The COVID diagnosis was based on symptoms plus positive polymerase chain reaction (PCR) and/or evidence of lung involvement on imaging. They were hospitalized in general wards for COVID. None were in the critical care unit (CCU) or other special wards.

Patients with premorbid conditions, including receiving a blood transfusion one week before admission, active cancer, liver cirrhosis, end-stage renal disease (ESRD), pregnancy, breastfeeding, age older than 70, and previous neuro/psychiatric disorders like dementia and addiction, were excluded. Patients with hematological disorders like thalassemia and malignancies which impact blood cells were also excluded.

399 patients have been chosen based on the abovementioned inclusion and exclusion criteria. 232 of them missed the follow-up. The remaining 169 patients were asked to participate in a follow-up study. Data were collected using a self-reported semi-structured questionnaire via telemedicine. The interview evaluates the presence of long COVID symptoms. It has eight qualitative multiple-choice questions (MCQs). The translated interview is located in supplementary materials. Answers contain adverbs of frequency, including usually, often, and never.

Some queries ask about physical or mental tiredness, premature exhaustion at activities, anxiety before initiating activity, and insufficient energy. The questions associated with poor mental health ask about losing concentration while doing things. Losing sexual desire is one of the other questions. We designed the questionnaire based on valid questionnaires from previous studies, and the level of fatigue increased with the higher scores.

3. Results

167 patients filled out the questionnaire for this study. Among those interviewed, 44.9% were women and the median age of 51 (23−70) years old.

Table 1 shows the age and CBC and inflammatory markers on admission.

We have done four sets of bivariate analyses. The mean ± SD of the CBC and inflammatory markers were compared between the groups:

Table 1. WBC: white blood cell, PMN: polymorphonuclear, MPV: mean platelet volume, RDW: red blood cell distribution width, PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio.

Parameters	Mean ± SD	Median (min−max)
Age (years)	48.87 ± 12.15	51 (23−70)
WBC ($\times 10^9$/L)	9.19 ± 4.74	8.2 (2.8−25.5)
Platelet ($\times 10^9$/L)	222.39 ± 90.1	206 (58−625)
PMN ($\times 10^9$/L)	7.5 ± 4.44	6.69 (1.21−23.66)
Lymphocyte ($\times 10^9$/L)	1.26 ± 0.71	1.06 (0.35−4.83)
MPV (fL)	10.43 ± 6.77	9.9 (7.2−96)
RDW (%)	14.09 ± 1.8	13.6 (11.3−21.7)
PLR	225.24 ± 149.19	190.69 (18−873)
NLR	7.14 ± 5.85	5.66 (0.63−43)

First, the study participants were grouped based on the presence of chronic COVID symptoms at a 6-month follow-up into "chronic" (68.26%) and "non-chronic" (31.73%). The resulting p-values showed no significant differences between the two groups, except NLR which shows higher values in patients with chronic COVID symptoms (p-value = 0.023). (Table 2).

Second, based on concentration at work, 58.68% had impaired concentration compared to the others (41.31%), who had normal concentration. Patients with impaired concentration had significantly high WBC and PMN counts and also high NLR compared to the normal group (p = 0.035, p = 0.013, and p = 0.005 respectively). Based on the p-values, other hematological parameters showed no significant difference between groups (Fig. 1, Table 2).

Third, the participants were grouped based on decreased libido. 52.69% experienced decreased libido compared to the others (47.31%). Patients who experienced decreased libido at a 6-month follow-up had significantly more severe lymphopenia (p = 0.028) and higher NLR values (p-value = 0.007). Based on the p-values, other hematological parameters showed no significant difference between groups. Age and gender do not have a significant correlation with any of the results (Fig. 2, Table 2).

Table 2 shows the results of three steps which mentioned above.

Fourth, the first six questions are related to fatigue. There is no correlation between the score of these questions and blood markers except NLR which is higher in patient with greater scores (Table 3).

We have studied nine different factors within each of these three categories. By chance alone, one or more of these comparisons may have a p-value below 0.05. For instance, PMN change is present in two categories: persistent chronic symptoms and impaired concentrations, but not in the decreased libido group. However, the noteworthy aspect is that NLR exhibits the most significant variation for all symptoms since it is the only parameter that consistently increases in all three symptom groups.

4. Discussion

To our knowledge, this is the first study investigating the role of inflammatory biomarkers like NLR, PLR, and MPV on long COVID sequels like fatigue, impaired concentration, or decreased libido in 6-month follow-up after discharge.

Post-acute COVID-19 syndrome (PCS) is a systemic inflammatory syndrome developing during or after an infection consistent with COVID-19, lasting

Table 2. P: P-value, WBC: white blood cell, PMN: polymorphonuclear, MPV: mean platelet volume, RDW: red blood cell distribution width, PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, F: female, M: male.

| Parameters	PRESENCE OF THE CHRONIC SYMPTOMS			Impaired Concentration			Decreased Libido		
	Non-chronic	Chronic	P	Non-impaired	Impaired	P	Non-decreased	Decreased	P
Gender	F: 47.16% M:52.84%	F:43.85% M:56.15%	0.740	F:49.27% M:50.73%	F:41.83% M:58.17%	0.349	F:45.56% M:54.44%	F:44.31% M:55.69%	0.878
	Mean ± SD			Mean ± SD			Mean ± SD		
	Non-chronic	Chronic		Non-impaired	Impaired		Non-decreased	Decreased	
Age	47.41 ± 12.81	49.55 ± 11.83	0.246	47.88 ± 12.12	49.55 ± 12.19	0.288	48.26 ± 12.56	49.42 ± 11.82	0.503
WBC(× 10^9/L)	8.31 ± 4.42	9.6 ± 4.84	0.06	8.24 ± 4.14	9.85 ± 5.03	0.035	8.91 ± 4.96	9.44 ± 4.54	0.256
Platelet(× 10^9/L)	220.89 ± 106.45	222.98 ± 81.92	0.413	217.62 ± 98.09	225.62 ± 84.4	0.317	229.58 ± 98.34	215.8 ± 82.04	0.463
PMN(× 10^9/L)	6.63 ± 4.07	7.9 ± 4.56	0.053	6.51 ± 3.75	8.19 ± 4.76	0.013	7.15 ± 4.72	7.81 ± 4.17	0.124
Lymphocyte(× 10^9/L)	1.32 ± 0.8	1.23 ± 0.67	0.506	1.36 ± 0.84	1.19 ± 0.6	0.28	1.39 ± 0.79	1.15 ± 0.62	0.028
MPV(fL)	11.53 ± 11.99	9.92 ± 0.98	0.857	11.19 ± 10.48	9.9 ± 1.02	0.879	10.87 ± 9.82	10.04 ± 0.96	0.096
RDW (%)	14.08 ± 1.99	14.09 ± 1.72	0.774	14.02 ± 1.94	14.14 ± 1.71	0.527	14.28 ± 1.95	13.92 ± 1.65	0.235
PLR	213.85 ± 163.26	230.54 ± 142.63	0.162	210.43 ± 155.46	235.67 ± 144.51	0.077	213.61 ± 148.27	235.68 ± 150.09	0.189
NLR	5.88 ± 4.66	7.73 ± 6.26	0.023	5.71 ± 4.29	8.15 ± 6.58	0.005	6.22 ± 5.97	7.97 ± 5.65	0.007
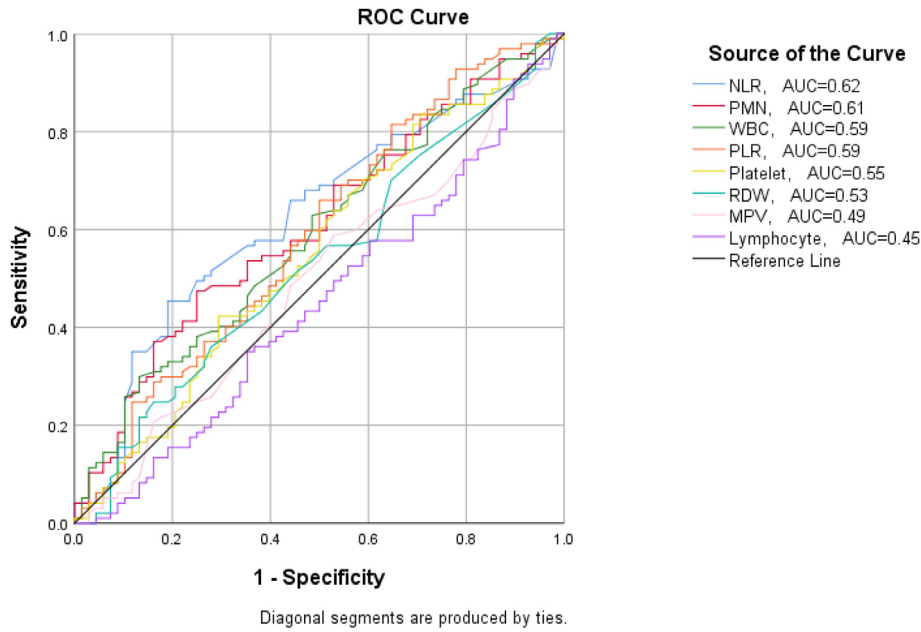
Fig. 1. Receiver Operating Characteristic (ROC) curves for CBC markers in the prediction of impaired concentration.

from 12 weeks to 12 months, and not attributable to any alternative diagnosis.[28] A study suggested that the severity of the acute infection and a history of Chronic obstructive pulmonary disease (COPD), migraine, chronic fatigue syndrome (CFS), or fibromyalgia may be risk factors for long COVID symptoms.[29] Another study claimed that premorbid vulnerability and severity of COVID-19 infection impact the prevalence and severity of long-term neurological manifestations.[30]

4.1. Chronic or non-chronic

Nearly 170 participants were grouped based on chronic COVID symptoms like fatigue, decreased libido, and lack of concentration at a 6-month follow-up into chronic (68.26%) and non-chronic (31.73%). Our study demonstrated that patients with long COVID symptoms like decreased libido or lack of concentration and fatigue had higher NLR in their CBC on the first 2days of admission.
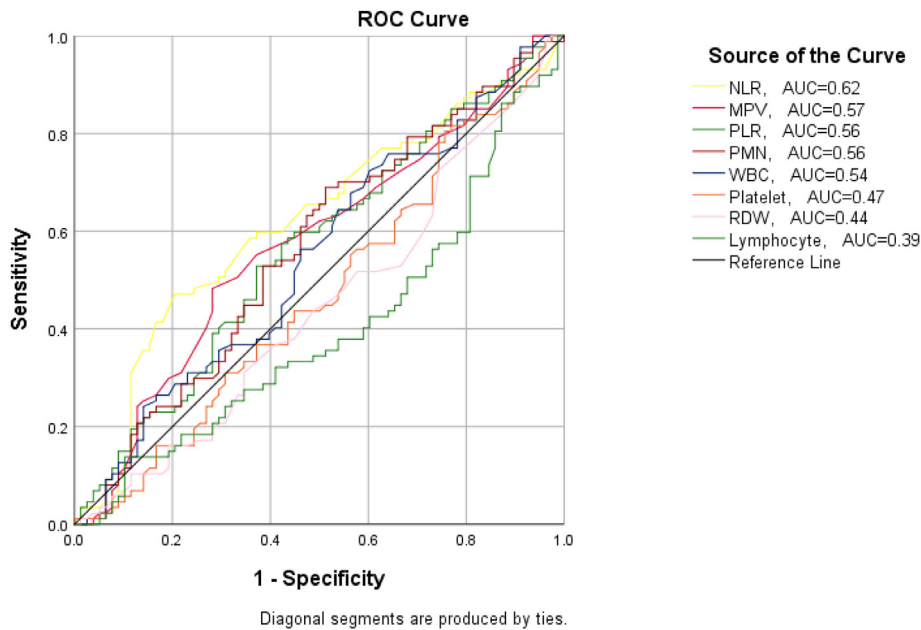

Fig. 2. Receiver Operating Characteristic (ROC) curves for CBC Markers in the prediction of decreased libido.

Table 3. Correlation between blood markers and question scores (Q1-6).

Marker	Correlation coefficient	P value
WBC	−0.207	0.118
PMN	−0.249	0.060
Lymphocyte	0.157	0.240
Platelet	−0.031	0.816
NLR	−0.301	0.021
PLR	−0.138	0.302
RDW	−0.019	0.890
MPV	0.052	0.700

WBC: white blood cell, PMN: polymorphonuclear, MPV: mean platelet volume, RDW: red blood cell distribution width, PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio.

Individuals with confirmed COVID-19 infection are at increased risk of an expansive range of persistent symptoms, including persisting fatigue, neuro-cognitive changes (like impaired concentration), and decreased libido at ≥12 weeks after infection.[31] Persistent symptoms are reported in over 36% of COVID-19 survivors,[32] and up to 25% of patients reported sequelae beyond six months.[33] A study showed that some inflammatory biomarkers measured in COVID-19, including CRP and NLR, are independently correlated with the emergence of sequelae in people at higher risk of developing long COVID-19.[25] Increased NLR is an established marker of the worsening of COVID-19 in the general population.[34] Excess systemic cytokine alters lymphopoiesis, which causes lymphocytopenia alongside abnormal compensatory granulopoiesis.[35] The pro-inflammatory response is a mediator of adverse outcomes in patients with COVID-19. Thus NLR, as an available inflammatory marker, provides helpful information to prioritize patients at higher risk of developing COVID-19 sequelae for follow-up procedures and clinical trials with anti-inflammatory strategies.[36–38]

4.2. Concentration and mental health

Our results suggest that Patients with impaired concentration had significantly higher WBC, PMN counts, and NLR than the normal group.

Several studies reported that impaired concentration was one of the main symptoms of long COVID.[39–41] For instance, a study showed that sustained attention and processing speed were impaired in 56.2% and 41.4% of post-COVID-19 patients, respectively. They found that cognitive impairment in long COVID is similar to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Brain fog in both conditions was characterized by a reduced attention capacity and a slower visual processing speed, but ME/CFS characterizes by greater physical and neuropsychiatric problems.[42]

Another study showed that moderate COVID-19 severity was associated with attention/processing speed impairment.[43]

Stressors like the ambiguous nature of the disease, high infection rate, social isolation, unpredictable future, vast exposure to media, and survivor guilt experienced by patients contribute to the development of psychopathological outcomes following the infection.[44,45]

Another study also showed that being female, diabetic, having oxygen support or mechanical ventilation, and having a high Neutrophil/lymphocyte ratio (NLR) level makes someone more vulnerable to get mental illness in post-COVID-19 syndrome. At the same time, NLR was the only risk factor for post-traumatic stress disorder (PTSD).[46]

4.3. Decreased libido

Patients who experienced decreased libido at a 6-month follow-up had significantly more severe lymphopenia (p = 0.028) and higher NLR values (p = 0.007). There is no significant difference between the two genders (p = 0.878), which is incompatible with some studies showing that women are more likely to describe long-COVID mood changes, including decreased libido.[47,48] Another study declared that the most commonly reported issues during the COVID-19 lockdown were depressive symptoms, including sexual dysfunction with decreased libido and lower sexual frequency.[49] Although a study showed that during COVID-19 pandemic female sexual dysfunction did not differ, depressive symptoms and fear intensified.[50] Most data showed that the COVID-19 pandemic significantly impacted mental and sexual health.[49–51] They stated that the difference in libido during the COVID-19 lockdown might be not feeling well or less interest in sexual intercourse.[52]

4.4. Fatigue

In our study, there is no statistical correlation between fatigue and disruption of blood markers except NLR (p = 0.021).

A study stated that fatigue is the most common symptom in the post-acute phase of COVID infection.[53] On the other hand, the Northwest Spain cohort shows fatigue is the most common symptom after extra-respiratory symptoms and is more common in hospitalized than inpatients.[54] In another study in China, fatigue or muscle weakness was the most common symptom during 6-month fallow-up in patients discharged from hospitals, which was about 63%.[55]

The exact cause of fatigue is not yet known, but the interaction of the virus and angiotensin-converting enzyme 2(ACE 2) may change muscle fibers.[2] As mentioned before, fatigue is one of the significant features of ME/CFS. This syndrome commonly occurs after infection and cause fatigue, cognitive problem, physical intolerance, and emotional stress. Many viruses, such as Epstein bar virus (EBV) and herpes simplex virus (HSV), can cause this. There could be a shared pathology in ME/CFS and post-COVID fatigue, but it is not cleared yet.[56]

An exciting hypothesis states that the virus's direct effect on olfactory neurons can impair cerebrospinal fluid (CSF) flow through the cribriform plate, finally leading to the accumulation of toxins in the brain. Based on this view, the drainage of CSF can help reduce symptoms.[57]

MPV was also measured and compared between groups but the resulting p-values showed no significant difference, but some studies have shown platelet pathology in long COVID patients. For example, a study observed platelet hyperactivation in long COVID patients who reported symptoms including fatigue, brain fog, and loss of concentration. They reported the presence of significant platelet pathology in all cases. Patients were treated with one month of dual antiplatelet therapy (DAPT) and the direct oral anticoagulant (DOAT). All cases reported that their main symptoms were resolved, and fatigue as the major symptom was relieved, which was also reflected in a decrease in platelet pathology scores.[14] Another study shows that passing the time by an average of 4 months may eliminate the severity of fatigue without any treatment.[58]

5. Limitations

While conducting our study, we encountered some limitations. It should be acknowledged that the study was conducted during the peak of the COVID-19 outbreak in Iran, which led to some cases being overlooked. Furthermore, follow-up was not possible for certain patients who may have passed away after discharge. Moreover, it is important to acknowledge that cultural limitations prevented some patients from answering the questionnaire that contained queries about sexual desire and libido.

Telemedicine interviews have been conducted in many studies like ours, and we do not examine patients directly for weakness and lethargy.

Post-COVID fatigue could result from post COVID diabetes, which occurs in the context of corticosteroid use. Furthermore, post-COVID-19 thyroiditis can be significantly associated with symptoms of weakness and fatigue in patients, which has not been evaluated in this regard. Therefore, it is recommended that patients with fatigue and other symptoms related to long-term COVID be tested to rule out other common causes that justify the symptoms.

On the other hand, the vaccination status of patients is also a very important factor because some studies have shown that people who have been vaccinated experienced fewer symptoms associated with long COVID, which was not evaluated in our study. We followed up on the admitted patients between February and April of 2022. Although we did not have any facilities to distinguish COVID variants, it was estimated that most of our patients had been infected with the Omicron variant at that time of COVID peak.

6. Conclusion

This study shows that CBC routine markers like NLR and WBC count can use to estimate the risk of developing long COVID symptoms like decreased libido or concentration and fatigue six months after acute COVID-19. These markers are accessible in many centers and may predict the risk of long COVID sequel in patients for further measures like psychiatric follow-up and rehabilitation.

Disclaimers

This article has not been published or presented anywhere else.

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Conflict of interest

The authors declare that they have no conflict of interest.

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