Original Article

Prognostic Significance of Hematological Parameters in Hospitalized Elderly with COVID-19

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ABSTRACT

Background/Aim: COVID-19 is a global pandemic; it caused more than 256 million cases, early detection of patients at high risk of mortality is of great importance in saving lives of COVID-19 patients. "In our study" we aimed to utilize the hematological parameters in predicting prognosis and mortality among elderly patients diagnosed with COVID19 infection admitted at Geriatric isolation hospital, Ain Shams University during the period from 26/12/2020 to 20/6/2021.

Methods: This is a retrospective cohort study involving elderly patients admitted at Geriatric isolation hospital, Ain Shams University during the period from 26/12/2020 to 20/6/2021.Retrospective evaluation of medical records was used to collect data. The study included patients older than 60 years with proof of SAR-CoV2 by nasopharyngeal swab. Serial complete blood count parameters were reported during admission: hemoglobin (Hb), Total leukocytic count (TLC), Neutrophils (N), lymphocytes (L), platelets (PLT), Red Cell Distribution Width (RDW), Neutrophil/lymphocyte(NLR), platelet/lymphocyte(PLR) ratios were calculated, other hematological parameters as C-reactive protein (CRP) and ferritin were reported.

Results: Among 50 hospitalized COVID 19 patients with mean age of 68.5 years, 54% were males. Mortality of those patients has statistically significant association with presence of high NLR, CRP, Ferritin and lymphopenia on admission and the likelihood of patients' mortality will rise with presence of NLR>12.4, CRP>120mg/L, FERRITIN>493.6mcg/L and Lymphocytes≤0.88 $*10^{9/}$ L on admission, however, presence of CRP>120mg/L is an independent factor for mortality in hospitalized elderly with COVID 19.

Conclusion: Hematological parameters as (NLR, CRP, Ferritin and lymphopenia) are predictor markers for mortality in hospitalized elderly with COVID-19.

Key words: COVID 19, mortality, neutrophil/lymphocyte ratio (NLR), C-reactive protein (CRP), Ferritin.

INTRODUCTION

By the end of 2019, many cases of pneumonia with unknown etiology emerged in Wuhan, Hubei Province, China. The pneumonia spread rapidly. Then, more patients had similar symptoms. On 7 January 2020, the ovel corona virus was detected in the throat swab sample of one patient by the

Chinese Center for Disease Control and Prevention (CDC). As the situation became worse, WHO announced the pandemic disease as corona virus disease 2019 (COVID-19). [1] the most reported symptoms of COVID-19 are fever, dry cough, dyspnea and fatigue. There are various reported non-respiratory symptoms (e.g. diarrhea, nausea, vomiting, headache, and muscle pain). [2] It has been reported that COVID-19 may progress to acute respiratory distress syndrome, followed by septic shock, refractory metabolic acidosis, coagulation dysfunction, multiple organ failure and death. [3] These adverse events represent 50% to 75% of deaths. They are more common in elderly patients and in those with previous comorbidities, especially diabetes, cardio and cerebrovascular diseases, obesity; cancer, digestive, endocrine, nervous, and respiratory systems pathologies.[4] severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) like many other known viruses can cause hematological changes that can predict the severity of infection. The occurrence of hematological manifestations was able in discriminating the severe and non-severe patients with COVID-19. A blood workup as well as continuous tracking of hematological changes could reveal risks of disease progression.[5] The most common hematological changes related to COVID-19 were lymphocytopenia, neutrophilia, mild thrombocytopenia, eosinopenia, and less common, thrombocytosis. Occasionally, reactive lymphocytes have been reported. However, leukocytic count may remain normal, become reduced or increased in response to SARS-COV2 infection. Many reports suggested that leukocytosis, lymphopenia and thrombocytopenia were related to disease severity and even fatality in COVID-19 cases. [6]

Moreover, multiple observational studies have suggested that the neutrophil to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) considered
as inflammatory markers of immune-mediated, metabolic, and neoplastic diseases.

They were commonly investigated as useful predictors for the prognosis in multiple diseases. Recent research of COVID-19 indicated patients with severe infection tended to have higher NLR. [7]

Earlier reports have also indicated that C-reactive protein (CRP) levels at admission and before discharge or death are markers of bad prognosis in patients with COVID-19. Higher (CRP) values during the early stages of the disease were associated with extensive lung involvement; Higher (CRP) values have been correlated with increased mortality in COVID-19 patients. [8]

Also, High serum ferritin prior to the terminal event (which is, survival or death) were more significantly associated with death as the final outcome and high serum ferritin values at time of admission have been independently associated with a severe disease course. [9]

OBJECTIVE:

In our study, we aimed to utilize the hematological parameters in predicting the prognosis and mortality among elderly patients diagnosed with COVID19 infection admitted at Geriatric isolation hospital, Ain Shams University during the period from 26/12/2020 to 20/6/2021.

METHODS:

A retrospective cohort study was done using the medical records from Ain Shams Geriatrics University hospital from 26/12/2020 to 20/6/2021. A sample of 50 elderly patients older than 60 years both males and females with proof of SAR-CoV2 by nasopharyngeal swab were included.

Sample size was suggested as 50 cases with expected 17 severe and 12 deaths achieves a power of 80% to detect an AUC of the ROC curve of at least 0.80 against the null value of 0.50 with level of significance of 0.05.

While cases below 60 years old, those with preexisting hematological disorders, and those with end organ disease affecting CBC parameters e.g. chronic liver disease (CLD), chronic renal failure (CRF) were excluded. Demographic and clinical characteristics, co morbidities, laboratory findings, and outcome data of each patient were obtained from medical records. Serial complete blood count parameters were reported during their admission: hemoglobin (Hb), Total leukocytic count (TLC), Neutrophils (N), lymphocytes (L), platelets (PLT), Red Cell Distribution Width (RDW), Neutrophil/lymphocyte, platelet/lymphocyte ratios were calculated and other hematological parameters as C-reactive protein (CRP) and ferritin were also reported.

Study tools and ethical considerations:

Data was obtained by retrospective reviews of medical records of 50 elderly patients diagnosed with COVID-19 admitted at Geriatric isolation hospital, Ain shams university, the study methodology reviewed and approved by the Research Review Board of the Geriatric medicine department, Faculty of medicine, Ain Shams University, faculty of medicine Ain shams Research Institute (MASRI) and Research Ethics Committee (REC) No.FWA 000017585.Confidentiality and anonymity of participants were ensured.

Data entry and statistical analysis:

Data were tabulated and statistically analyzed using Statistical Package for Social Science (SPSS) (version 26) Quantitative variables were presented in the form of means and standard deviation. Qualitative variables were presented in the form of frequency tables (number and percent). A comparison between quantitative variables was carried out using student T test for parametric data and Mann Whitney test for non-parametric data. A comparison between qualitative variables was carried out using Pearson's $\chi 2$ test. Correlation between two quantitative variables was carried out using the Spearman correlation coefficient. The statistical differences were accepted when $P < 0.05$ and $P< 0.001$ were considered highly significant, logistic regression and ROC curve was also used to detect predictors of mortality and their cut off value.

RESULTS:

A sample of 50 elderly patients diagnosed with COVID-19 admitted at Geriatric isolation hospital from 26/12/2020 to 20/6/2021 was taken. Among those patients, the mean age was 68.5 years, 54% were males (table 1).

The mean of hematological parameters of all studied patients on admission: TLC 10.29 $*10^9/L$, HB 11.89 g/dL, PLT 243.56 $*10^9/L$, Neutrophils 8.8 $*10^9/L$, lymphocytes 0.98 $*10^9/L$, NLR 15.35, PLR 345.7, RDW 16.25, CRP 121.42 mg/L, ferritin 872.61 mcg/L (table 2)

The outcome among studied patients was 38% recovered and discharged to home,

36% mortality and 26% referred to other care facility with complications (table 3)

Our study showed that mortality of hospitalized patients with COVID 19 has statistically significant association with presence of high NLR, CRP, Ferritin; and lymphopenia on admission (table 4)

The likelihood of patients' mortality will rise with presence high NLR>12.4, CRP>120 mg/L, FERRITIN>493.6 mcg/L and Lymphocytes≤0.88 $*10^{9/}$ L on admission so they can be used as predictors for mortality when present on admission, however, presence of CRP>120mg/L is an independent factor for mortality in hospitalized elderly with COVID 19. (Table 5).

Through follow up of hematological parameters across length of hospital stay(day0,7-10 days after admission, at mortality), there is statistically significant difference in CRP between on admission and at mortality While there is statistically significant difference in Ferritin across the time and between on admission and at mortality (table 6).

Table (1) Description of demographic data of the studied patients:

		Mean ± SD (min – max)	Median (IQR)
Age		68.5 ± 7.2 (60-85)	67 (62-75)
		N	**%**
Sex	**Female**	23	46.0%
	Male	27	54.0%

Table (2) Description of hematological parameters of studied patients on admission:

	Mean ± SD (min – max)	Median (IQR)
TLC	10.29 ± 5.42 (2-26)	10 (6.1-14.1)
HB	11.89 ± 2.7 (1.5-17.2)	12.25 (10.8-13.5)
PLT	243.56 ± 92.77 (50-446)	219 (186-327)
Neutrophils	8.8 ± 5.37 (1-25.06)	7.86 (4.66-11.8)
Lymphocytes	0.98 ± 0.69 (0.1-3.95)	0.81 (0.6-1.2)
NLR	15.35 ± 34.37 (1.19-248)	9.8 (5.5-13.3)
PLR	345.7 ± 312.63 (62.2-2110)	262.75 (198.7-405)
RDW	16.25 ± 4.13 (11.9-28.1)	14.95 (13.3-18)
CRP	121.42 ± 83.75 (11.7-392)	87.5 (65-150)
Ferritin	872.61 ± 878.1 (120-3883)	552.5 (320-1200)

Total leukocytic count (TLC), hemoglobin (HB), platelet count (PLT), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ration (PLR), red cell distribution width (RDW), C–reactive protein (CRP).

Table (3) Description of the outcome of the studied patients:

	N	%
Discharge	19	38.0%
Death	18	36.0%
Transferal to other care facility	13	26.0%

Table (4) Relation of hematological parameters on admission among survival and mortality in studied patients:

On admission		Survival	Mortality	Test value	P-value	Sig.
TLC	Mean ± SD Median (IQR) Range	9.35 ± 4.22 8.75 (5.95 – 12) 3 – 17.1	11.96 ± 6.91 11.55 (6.4 – 15) 2 – 26	-1.662•	0.103	NS
HB	Mean ± SD Median (IQR) Range	12.01 ± 2.28 12.55 (10.9 – 13.15) 6.5 – 15.6	11.67 ± 3.38 12 (10.4 – 13.6) 1.5 – 17.2	0.420•	0.676	NS
PLT	Mean ± SD Median (IQR) Range	261.41 ± 93.84 254 (189 – 340.5) 69 – 446	211.83 ± 84.15 197.5 (182 – 266) 50 – 387	-1.637‡	0.102	NS
Neutrophils	Mean ± SD Median (IQR) Range	7.68 ± 4.00 6.47 (4.6 – 10.72) 1.81 – 15.5	10.81 ± 6.88 10.48 (5.44 – 13.3) 1 – 25.06	-1.657‡	0.097	NS
Lymphocytes	Mean ± SD Median (IQR) Range	1.15 ± 0.78 0.94 (0.68 – 1.3) 0.5 – 3.95	0.69 ± 0.34 0.74 (0.43 – 0.84) 0.1 – 1.36	-2.498‡	0.012*	**S**
NLR	Mean ± SD Median (IQR) Range	8.40 ± 5.47 8.06 (4.55 – 10.97) 1.2 – 27.4	27.72 ± 55.65 13.1 (10 – 16.25) 1.19 – 248	-3.234‡	0.001*	**HS**
PLR	Mean ± SD Median (IQR) Range	300.55 ± 206.79 221.15 (193.9 – 397.85) 62.2 – 892	425.97 ± 439.41 331.2 (223.5 – 465.1) 64.7 – 2110	-1.718‡	0.086	NS
RDW	Mean ± SD Median (IQR) Range	16.22 ± 3.81 15.05 (13.6 – 18.15) 12.1 – 28.1	16.29 ± 4.76 14.65 (13.2 – 16.6) 11.9 – 27.8	-0.057•	0.955	NS
CRP	Mean ± SD Median (IQR) Range	88.35 ± 52.08 72.5 (55 – 112.5) 11.7 – 241	180.22 ± 97.74 180 (93 – 230) 64 – 392	-3.479‡	0.001*	**HS**
FERRITIN	Mean ± SD Median (IQR) Range	666.64 ± 742.96 365 (288.5 – 734.4) 120 – 3455	1238.78 ± 997.02 1116 (550 – 1320) 310 – 3883	-2.932‡	0.003*	**HS**

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)

•: Independent t-test; ‡: Mann Whitney test

Table (5) Logistic regression analysis for predictors of mortality in haematological parameters on admission:

	Uni-variety				Multi-variety			
	P-value	Odds ratio (OR)	95% C.I. for OR		P-value	Odds ratio (OR)	95% C.I. for OR	
			Lower	Upper			Lower	Upper
On admission								
Lymphocytes≤0.88	**0.006**	**7.308**	**1.755**	**30.423**	0.290	2.823	0.414	19.257
NLR>12.4	**0.001**	**10.800**	**2.750**	**42.409**	0.097	4.174	0.774	22.519

CRP>120	**0.000**	**18.200**	**4.184**	**79.168**	**0.013***	**9.794**	**1.610**	**59.585**
FERRITIN>493.6	**0.004**	**8.333**	**1.992**	**34.870**	0.996	1.005	0.122	8.245

P-value ≤ 0.05 is considered statistically significant P-value< 0.01: highly significant

Table (6) Comparison of changes in Hematological parameters overtime among the studied patients at mortality:

	On admission (T1)		7 – 10 days after admission (T2)		At mortality (T3)		P (all)	P (T1&T3)
	Mean ± SD (min – max)	Median (IQR)	Mean ± SD (min – max)	Median (IQR)	Mean ± SD (min – max)	Median (IQR)		
TLC	11.96 ± 6.91 (2-26)	11.55 (6.4-15)	14.7 ± 7.82 (2.6-31.2)	13.2 (8.9-21.7)	15 ± 8.78 (2.3-27.1)	13.95 (7.3-22)	.262	.169
HB	11.67 ± 3.38 (1.5-17.2)	12 (10.4-13.6)	11.92 ± 2.23 (9.4-17)	11.45 (9.8-13)	11.33 ± 1.89 (7.5-15)	11.55 (10-12.6)	.522	.568
PLT	211.83 ± 84.15 (50-387)	197.5 (182-266)	210.5 ± 104.62 (43-412)	179.5 (146-294)	155.5 ± 110.59 (51-405)	105.5 (69-229)	.120	.096
Neutrophils	10.81 ± 6.88 (1-25.06)	10.48 (5.44-13.3)	13.28 ± 7.65 (1.2-29.64)	11.4 (7.8-20.3)	13.9 ± 7.93 (1.3-25.7)	13.4 (7.3-20.3)	.222	.120
Lymphocytes	0.69 ± 0.34 (0.1-1.36)	0.74 (0.43-0.84)	0.86 ± 0.42 (0.11-1.72)	0.86 (0.64-1.1)	0.88 ± 0.61 (0.07-2.54)	0.8 (0.48-1.1)	.332	.229
NLR	27.72 ± 55.65 (1.19-248)	13.1 (10-16.25)	20.05 ± 15.89 (1.2-62)	16.7 (9.1-25.4)	22.46 ± 16.77 (1.4-51)	17.5 (8.8-32)	.655	.714
PLR	425.97 ± 439.41 (64.7-2110)	331.2 (223.5-465.1)	352.07 ± 311.93 (37.4-1291)	256.4 (144.5-393.5)	268.51 ± 284.03 (20.5-1286)	218.35 (88.9-362.5)	.337	.174
RDW	16.29 ± 4.76 (11.9-27.8)	14.65 (13.2-16.6)	15.91 ± 3.23 (12.8-23.9)	15.05 (13.3-16.8)	23.56 ± 30.21 (13-144)	15.9 (14-19.6)	.320	.338
CRP	180.22 ± 97.74 (64-392)	180 (93-230)	189.33 ± 87.2 (40-348)	174.5 (134-250)	227.67 ± 102.88 (47-420)	225 (170-310)	.151	.046*
Ferritin	1238.78 ± 997.02 (310-3883)	1116 (550-1320)	1596.67 ± 1012.67 (300-3800)	1525 (860-2200)	1993.44 ± 1599.16 (310-5479)	1560 (800-2600)	.014*	.007**

Repeated measure ANOVA test was used, P-value ≤ 0.05 is considered statistically significant (*) P-value< 0.01: highly significant (**)

DISCUSSION

The COVID-19 pandemic disproportionally impacted older adults and they were the most at-risk for severe COVID-19 clinical forms, complications and death, showing the highest mortality rates worldwide. **(10)**

Globally, more than 157 million confirmed cases of COVID-19, including more than 3 million deaths, were reported to the World Health Organization (WHO). In Egypt, from January 3, 2020, to May 16, 2021, a total of 244,520 confirmed cases and 14,269 deaths were reported. **(11)**

In the current study, the mean age of the participants was 68.5 ± 7.2 years. In ***Yang et al. (2020)*** study which included 52 critically ill with COVID-19, they observed that non-survivors were older than survivors, so older adult patients should be prioritized in the implementation of preventive measures. **(12)**

Our study included 50 elderly patients The mean of hematological parameters of them on admission: TLC 10.29 $*10^9/L$, HB 11.89 g/dL, PLT 243.56 $*10^9/L$, Neutrophils 8.8 $*10^9/L$, lymphocytes 0.98 $*10^9/L$, NLR 15.35, PLR 345.7, RDW 16.25%, CRP 121.42 mg/L, ferritin 872.61 mcg/L and that was partially supported by retrospective study done by **Sharma et al., 2021** About Prognostic relevance of hematological parameters and ratios in COVID-19 patients in New Delhi, India, in the emergency (Pathology) department from March 2020 to May 2020. At which 829 COVID-19

positive patients were included in the study, and showed that COVID 19 had minimal effects on the baseline CBC values. [13] And consistent with study done by **Pourbagheri-Sigaroodi et al., 2020** About "Laboratory findings in COVID-19 diagnosis and prognosis," that showed the total leukocyte count differs amongst individuals, which may reflect the dominance of either lymphopenia or neutrophilia. Taken together and C-reactive protein (CRP)and ferritin level are elevated in COVID-19 patients as a whole so it is important to discuss the diagnostic use of CRP as well as the potential diagnostic value of high ferritin levels.[14]

That was in partial contrast to the study done by **Lippi, et al.,2020** From the journal Clinical Chemistry and Laboratory Medicine (CCLM) about "Laboratory abnormalities in patients with COVID-2019 infection" who reported leukocytosis, neutrophilia, and lymphopenia in Covid-19 patients [15] and that is may be explained as Lippi, et al was focusing on severe cases of COVID 19 also The results of a study done by **Usul et al., 2020** on "The role of hematological parameters in COVID-19 patients in the emergency room," which included 282 patients who visited the emergency room of the Etimesgut State Hospital in Ankara between March 15 and April 15, 2020 and were suspected of having COVID-19, revealed that PLTs and low absolute neutrophil and lymphocyte counts may have diagnostic value for COVID-19 that is may be explained as studied patients by **Usul, et al** was middle aged patients and with early stage of disease and low incidence of bacterial infections on top.[16]

The outcome among our studied patients was 38% recovered and discharged to home, 36% mortality and 26% referred to other care facility with complications so 36% as non survivors and 64% as survivors that was similar to a study done by **Bellan, et al., 2021** at the "Maggiore della Carità" University Hospital in Novara, Northern Italy between 1st March 2020 and 28th April 2020. About CBC Parameters value in Prediction of In-Hospital Mortality in COVID-19 at which retrieved all consecutive patients older than 18 years of age, admitted to the hospital following emergency room evaluation, with a confirmed diagnosis of SARS-CoV-2 infection. This included 664 patients, with a median age of 70 (56-81) years. 453/664 patients (66.7%) had been discharged, while 221/664 patients (33.3%) had died. [17] And a retrospective study done by **Rahman,et al., 2021** between 12 April and 31 August 2020 at Dhaka Medical College Hospital, Bangladesh which is approved by the Hospital Ethical Committee at which outcomes were collected for 103 patients Survived (59.22%), Death (40.78%).[18] And that was in contrast with **Sharma, et al., 2021** that included 829 patients among them 67 (8.1%) patients died whereas the rest were discharged after recovery that was explained by limited number of patients in our study and variable age groups in Sharma, et al study. [13]

Our study showed that Mortality of hospitalized patients with COVID 19 has statistically significant association with presence of high NLR, CRP, Ferritin; and lymphopenia on admission and with logistic regression The likelihood of patients' mortality will rise with presence high NLR>12.4, CRP>120 mg/L, FERRITIN>493.6 mcg/L and Lymphocytes≤0.88 $*10^{9/}$ L on admission so they can be used as predictors for mortality when present on admission, however, presence of CRP>120 mg/dL is

an independent factor, **Citu, et al., 2022** in "The predictive role of NLR, d-NLR, MLR (monocyte/lymphocyte ratio), and the systemic inflammatory response index (SIRI) which calculated as (monocyte × neutrophil / lymphocyte ratio) in COVID-19 mortality" with a sample of 108 patients diagnosed with COVID-19 and followed up during hospitalization suggested cut off points for NLR 9.1 showed a superior prognostic possibility for mortality with the highest sensitivity and NLR is also included as a variable in a risk score to predict the occurrence of critical illness in patients with COVID-19.[19]

But in contrast, **Bellan et al., 2021** in "Simple Parameters from Complete Blood Count Predict In-Hospital Mortality in COVID-19" showed that Hemoglobin levels were not associated with mortality and the best cut-off for mortality prediction is A NLR > 4.86 and RDW > 13.7 and PLT count > 166,000 was, conversely, protective that is may be explained as in **Bellan, et al** study length of hospital stay is less than 7 days and in include larger number of patients. [17]

In our study CRP value is obvious in prediction of mortality and it can be used as independent factor for mortality when it is more than 120 mg/dL **which is supported by Ruan, et al., 2020** about predictors of mortality in COVID-19 based on an analysis of data of 150 patients from Wuhan, China" with a retrospective study of 68 death cases and 82 discharged cases reported higher levels of C-reactive protein (126.6 in fatal cases vs. 34.1 in discharged cases)

Furthermore, the induction of acute kidney damage and the extent of the cardiac injury has been directly linked with the CRP concentrations.[20]

Through follow up of hematological parameters across length of hospital stay patients at mortality, there is statistically significant difference in CRP between on admission and at mortality While there is statistically significant difference in Ferritin across the time and between on admission and at mortality that was supported by a retrospective study done by **Chen et al.,2020** at which 548 patients with COVID-19 with different outcome (discharged or deceased) serial hematological parameters across 3 times period were recorded and showed that in non-survivor group there is upward trend or maintained higher levels of CRP and ferritin during hospitalization.[21]

Also in retrospective study done by **Mueller et al.,2020** at which 100 patients were included for evaluation and showed that rising CRP predicts subsequent respiratory deterioration and progressive respiratory failure later during their hospital course and subsequent mortality.[22]

That was in partial contrast with **Chen et al., 2021** study at which serial laboratory parameters were collected retrospectively and patients were divided into two groups survived and non-survived and showed that CRP showed gradually increasing differences on prior to death.

Unexpectedly, ferritin remained relatively elevated in both two groups throughout hospitalization as in **Chen et al., 2021** study patients with malignancies and immunosuppression weren't excluded and that may affect inflammatory markers not only COVID19 infection effect.[23]

CONCLUSION

Hematological parameters as (NLR, CRP, Ferritin and lymphopenia) are predictor markers for mortality in hospitalized elderly with COVID-19.

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