Research Article

The role of laboratory markers as predictors of severity in Covid 19 patients

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Abstract

Background: The pandemic due to novel coronavirus 19 has spread at a tremendous rate to more than 93 countries around the world. Many studies evaluated the role of laboratory markers in the diagnosis of the disease. However, their role in predicting non severe, severe, and post covid 19 cases is being explored. **Aim of the study:** To evaluate the role of laboratory markers in predicting the prognosis of covid 19 cases and in predicting the evolution of post covid 19 sequalae. **Subjects and methods:** This retrospective study included 650 Covid 19 patients; furtherly classified as 386 non severe patients; 200 severe patients, and 64 post covid patients. Complete blood count (CBC), C-reactive protein (CRP), serum ferritin, D dimer, and Alanine Aminotransferase (ALT) were measured in all patients. **Results:** Higher CRP, ferritin, D dimer, ALT, total leucocytic count (TLC), absolute neutrophil and monocytic counts, neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were significantly found in severe covid 19 cases when compared to non severe and post covid recovered cases, together with lower absolute lymphocytic and eosinophil counts, hemoglobin (Hb), and lymphocyte to monocyte ratio (LMR). Moreover, post covid spontaneous recovery showed a decline in all laboratory markers together with a rise in lymphocytic and eosinophil counts, Hb level, platelet (PLT) count, and LMR upon convalescence. The multivariate regression analysis showed that ICU admission, dyspnea, low absolute lymphocyte count, high TLC, and high absolute monocyte counts are independent risk factors for the severity of covid 19. **Conclusion:** Laboratory markers are fast, simple, cost effective tools to stratify covid cases into non severe and severe and to predict the course of post covid cases. Hence, allowing the proper early intervention to each case.

Keywords: Covid 19, non severe, severe, post covid, laboratory markers, prognosis**.**

Introduction

The novel coronavirus has hit many countries in the world since it started in December 2019. This rapidly evolving virus has produced threats to all mankind and WHO converted COVID 19 risk to "very high" at global level. [1] Covid cases are classified according to the World Health Organization (WHO) into: Non severe patients who have the following conditions: (a) history of exposure to a confirmed SARS-CoV-2 patient, (b) fever or other respiratory symptoms, and (c) typical chest computed tomography (CT) image abnormities compatible with viral pneumonia, and Severe patients who have additionally at least one of the following conditions: (a) Shortness of breath, respiration rate 30 times/min, (b) oxygen saturation (resting state) 93%.[2]

The early detection of severely and critically ill patients remains the basic strategy to improve the outcome of the disease. So far, age, oxygen supply, lymphocyte count and pulmonary radiographic infiltrations are independent factors to classify corona patients.[1] Although laboratory blood tests are fast, easy, and cost effective yet none of them is used in the classification criteria. [3]

This study aims at evaluating the role of laboratory markers in predicting the prognosis of covid 19 cases and in predicting the evolution of post covid 19 sequalae. This will facilitate the early choice for ICU admission, and the selection of the appropriate therapeutic strategies to limit the disease.

Subjects and methods

This retrospective study included 650 patients diagnosed with acute respiratory syndrome coronavirus 2 (SARS-CoV-2), furtherly classified as 386 non severe patients; 200 severe patients, and 64 post covid patients. Non severe patients were selected as patients who had history of exposure to a confirmed SARS-CoV-2 patient, fever or other respiratory symptoms, and typical chest computed tomography (CT) image abnormities compa-tible with viral pneumonia. Severe patients had in addition one or more of these conditions; shortness of breath, or respiration rate 30 times/min, or oxygen saturation (resting state) 93%. Whereas post covid convalescent cases were selected as cases showing spontaneous recovery after infection and PCR turning negative for covid 19 virus.

Patients were recruited from Ain-Shams University Hospital. An informed consent was obtained from each patient before participation. The procedures applied in this study were approved by the Ethical Committee of Human Experimentation of Ain Shams University and are in accordance with the Helsinki Declaration of 1975.

All included patients were subjected to:

1- Detailed medical history, thorough clinical examination, and CT chest
2- Laboratory investigations including:

- Real time reverse transcriptase PCR assay (rRT-PCR, NAAT) for SARS-Co-V-2 RNA using Viasure SARS-COV2 detection kit (Cer Test, Biotec, Spain) after viral RNA extraction form nasopharyngeal swabs using magnetic beads on Chemagic 360 (PerkinElmer, Germany).
- Complete blood count (CBC): Using automated haematology cell counters (Siemens, Advia 560, Germany).
- Blood chemistry: CRP, ferritin, and ALT were analysed by (Biolis-24i, Tokyo Boeki Medisys Inc. Japan).
- D-dimer was measured by (Immunoassay, VIDAS PC, Biomerieux, France. Serial number; IVD3002806).
- Neutrophil to lymphocyte ratio (NLR), PLT to lymphocyte ratio (PLR), and lymphocyte to monocyte ratio (LMR) were calculated.
- The oxygen saturation (SO_2) was retrospectively collected from the patient records.

Sampling and analytical procedures were done according to the standard procedures for each analyte. Approximately 6 ml of venous blood were drawn from each patient and divided into 3 aliquots; the first aliquot was 2 ml blood transferred to a plain tube for serum ferritin, CRP, and ALT. The second aliquot was 2 ml blood transferred into an EDTA tube for CBC. The third aliquot was transferred into citrate tube for D dimer measurement. As for the nasopharyngeal swab, each patient was seated with the head tilted slightly backward and sustained by the headrest, and the swab was gently inserted along the nasal floor to reach the nasopharynx, then rotated for 10 seconds to ensure optimal absorption of pharyngeal secretions and viral RNA.

3- Statistical analysis:

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when parametric and median with inter-quartile range (IQR) when non parametric. The comparison between groups regarding qualitative data was done by using Chi-square test. The comparison between two independent groups with quantitative data was done using Kruskall-Wallis test with more than two groups. The Statistical differences among the means of two or more independent groups was done by One way ANOVA test. The estimation of the relation between dependent variable (outcome), and one or more independent variables (predictors) was done by regression analysis. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant at the level of < 0.05.

Results

1- The descriptive data of the studied patients are shown in Table 1.

Table 1: The descriptive data of the studied patients

		Total no. = 650
Sex	Male	300 (46.2%)
	Female	350 (53.8%)
Age	Mean ± SD	47.02 ± 16.00
	Range	17 – 86
Severity	Non severe	386 (59.4%)
	Severe cases	200 (30.8%)
	Post COVID convalescent	64 (9.8%)
Mechanical ventilation	No	628 (96.6%)
	Yes	22 (3.4%)
ICU admission	No	410 (63.1%)
	Yes	240 (36.9%)
Symptoms	Asymptomatic	98 (15.1%)
	Fever	362 (55.7%)
	Cough	228 (35.1%)
	Diarrehea	34 (5.2%)
	Dyspnea	252 (38.8%)
CT chest	Free	226 (34.8%)
	Unilateral ground glass opacities	84 (12.9%)
	Bilateral ground glass opacities	296 (45.5%)
	Extensive bilateral opacities plus pneumonia	44 (6.8%)
Oxygen saturation (SO2%)	Mean ± SD	95.09 ± 3.86
	Range	70 – 99

2- Demographic and clinical data of the studied patients are shown in Table 2:

Table 2: Demographic and clinical data of the studied patients

		Severity			Test value	P1	P2	P3
		Non severe	Severe cases	Post COVID convalescent				
		No. = 386	No. = 200	No. = 64				
Sex	Male	174 (45.1%)	112 (56.0%)	14 (21.9%)	23.162*	0.012	0.001	0.000
	Female	212 (54.9%)	88 (44.0%)	50 (78.1%)				
Age	Mean ± SD	45.99 ± 16.42	51.24 ± 15.61	40.03±10.40	14.436•	0.000	0.005	0.000
	Range	21 – 85	17 – 86	24 – 60				
Mechanical ventilation	No	382 (99.0%)	182 (91.0%)	64 (100.0%)	28.037*	0.000	0.413	0.013
	Yes	4 (1.0%)	18 (9.0%)	0 (0.0%)				
ICU admission	No	340 (88.1%)	10 (5.0%)	64 (100.0%)	419.136*	0.000	0.182	0.000
	Yes	46 (11.9%)	190 (95.0%)	0 (0.0%)				
Symptoms	Asymptomatic	48 (12.4%)	2 (1.0%)	48 (75.0%)	212.543*	0.000	0.000	0.000
	Fever	242 (62.7%)	108 (54.0%)	12 (18.8%)	43.297*	0.042	0.000	0.000
	Cough	120 (31.1%)	106 (53.0%)	2 (3.1%)	59.600*	0.000	0.000	0.000
	Diarrehea	30 (7.8%)	2 (1.0%)	2 (3.1%)	12.823*	0.001	0.180	0.226
	Dyspnea	70 (18.1%)	182 (91.0%)	0 (0.0%)	339.597*	0.000	0.000	0.000
CT chest	Free	180 (46.6%)	8 (4.0%)	38 (59.4%)	264.918*	0.000	0.001	0.000
	Unilateral ground glass opacities	62 (16.1%)	4 (2.0%)	18 (28.1%)				
	Bilateral ground glass opacities	144 (37.3%)	144 (72.0%)	8 (12.5%)				
	Extensive bilateral opacities plus pneumonia	0 (0.0%)	44 (22.0%)	0 (0.0%)				
SO2%	Mean ± SD	96.19 ± 2.77	91.88 ± 4.17	98.44 ± 0.50	163.165•	0.000	0.000	0.000
	Range	70 – 99	75 – 98	98 – 99				

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test; •: One Way ANOVA test , P1: Non severe Vs severe, P2: Non severe Vs Post COVID convalescent, P3: Severe Vs Post COVID convalescent

3- Comparison between the studied patient groups regarding the laboratory data:

CRP showed a highly significant difference between the studied patients. CRP median (IQR) was 11.4 (6-31) mg/L, 61.15 (16.7-140.5) mg/L, and 6 (5.9-8) mg/L in non severe, severe, and post covid cases respectively. Ferritin as well showed a highly significant difference between the studied patients. Its median (IQR) was 134 (41.1-443) ng/ml, 574 (263.5-1200) ng/ml, and 158 (90.25-217.5) ng/ml in non severe, severe, and post covid cases respectively (Table 3).

In addition, D-dimer showed a highly significant difference between non severe cases (median (IQR): 301 (165-1100) ng/ml FEU), and severe cases (median IQR: 1200 (493-2488) ng/ml FEU). And between severe and post covid cases (median IQR: 400 (300-550) ng/ml FEU) (Table 3).

Other biochemical markers like ALT also showed a highly significant difference between the studied patients. ALT median (IQR) was 28 (22-43) U/L, 40 (19.5-56) U/L, and 22 (21-23) U/L in non severe, severe, and post covid cases respectively. While creatinine showed no significant difference between the patients (Table 3).

By performing CBC for the patients, the following was observed. The TLC showed a highly significant difference when compared between non severe cases (median (IQR): 6.2 (4.8-7.9) $x10^9$/L), and severe cases (median

IQR: 8.66 (6-13.45) $x10^9$/L). And also, between severe cases and post covid cases (median IQR: 6.55 (5.4-9.1) $x10^9$/L). As for the absolute neutrophil count, it showed a highly significant difference between the patient groups. Neutrophil median (IQR) was 3.9 (3.06-5.5) $x10^9$/L, 6.8 (4-11.45) $x10^9$/L, and 3.74 (2.6-6.03) $x10^9$/L in non severe, severe, and post covid cases respectively. Lymphocytic median (IQR) was 1.6(1-2.3) $x10^9$/L, 1(0.62-1.4) $x10^9$/L, and 2 (1.59-2.35) $x10^9$/L in non severe, severe, and post covid cases respectively (Table 3) (figures 1, 2).

The absolute eosinophil count showed a highly significant difference when compared between non severe cases (median (IQR): 0.1 (0.09-0.3) $x10^9$/L), and severe cases (median IQR: 0.1 (0 - 0.1) $x10^9$/L). And also, when compared between severe cases and post covid cases (median IQR: 0.2 (0.1-0.52) $x10^9$/L). While the absolute monocytic count showed a highly significant difference between the patients. Monocytic median (IQR) was 0.07 (0-0.2) $x10^9$/L, 0.15 (0-0.5) $x10^9$/L, and 0.01 (0-0.07) $x10^9$/L in non severe, severe, and post covid cases respectively (Table 3) (figure 3).

Haemoglobin level showed a highly significant difference when compared between non severe cases (mean and SD: 12.93 ± 1.95 gm/dl), and severe cases (mean and SD: 11.59 ± 2.31 gm/dl). And also, when compared between severe cases and post covid cases (mean and SD: 11.59 ± 2.31 gm/dl). Platelets showed no significant difference when compared between severe and non severe cases (P: > 0.05) (Table 3).

By calculating the neutrophil to lymphocyte ratio (NLR), a highly significant difference between the three groups of patients was detected. The NLR median (IQR) was 2.38 (1.54- 4.06), 6.93 (2.54-14.94), and 2.11 (1.1-2.73) in non severe, severe, and post covid cases respectively. A highly significant difference between the patients was detected on calculating the lymphocyte to monocyte ratio (LMR), its median (IQR) was 10 (5.56- 23.57), 4.27 (1.75-12.33), and 19.61 (11.33-50) in non severe, severe, and post covid cases respectively. Moreover, the calculation of the platelet to lymphocyte ratio (PLR) revealed a highly significant difference on comparing non severe cases (median (IQR): 136.67 (94.29-233.33)), to severe cases (median IQR: 236.41 (124.08-392.5)). And also, on comparing severe cases to post covid cases (median IQR: 141.05 (104.72-174.39)) (Table 3) (figures 4,5,6).

Table 3: Comparison between the studied patient groups regarding the laboratory data

		Severity			Test value	P1	P2	P3
		Non severe	Severe cases	Post COVID convalescent				
		No. = 386	No. = 200	No. = 64				
CRP (mg/L)	Median (IQR) Range	11.4 (6 – 31) 2 – 164	61.15 (16.7 – 140.5) 1 – 170	6 (5.9 – 8) 0.58 – 21	143.316≠	0.000	0.000	0.000
Ferritin (ng/ml)	Median (IQR) Range	134 (41.1 – 443) 1 – 1200	574 (263.5 – 1200) 14.8 – 2200	158 (90.25 – 217.5) 29.4 – 587	129.101≠	0.000	0.849	0.000
D-dimer ng/ml (FEU)	Median (IQR) Range	301 (165 – 1100) 0.26 – 10000	1200 (493 – 2488) 2.7 – 10000	400 (300 – 550) 100 – 4800	85.682≠	0.000	0.142	0.000
ALT (U/L)	Median (IQR) Range	28 (22 – 43) 2 – 116	40 (19.5 – 56) 6 – 171	22 (21 – 23) 20 – 26	42.255≠	0.002	0.000	0.000
Creatinine (mg/dl)	Median (IQR) Range	0.8 (0.7 – 0.9) 0.4 – 12.3	0.8 (0.7 – 1) 0.5 – 9.2	0.75 (0.7 – 0.85) 0.5 – 1.2	5.301≠	–	–	–
TLC (x109/L)	Median (IQR) Range	6.2 (4.8 – 7.9) 1.99 – 59	8.66 (6 – 13.45) 0.8 – 29.85	6.55 (5.4 – 9.1) 3.04 – 16.9	55.493≠	0.000	0.112	0.001
Absolute Neutrophil count (x109/L)	Median (IQR) Range	3.9 (3.06 – 5.5) 0.95 – 27.3	6.8 (4 – 11.45) 0.5 – 28.9	3.74 (2.6 – 6.03) 1 – 11.24	66.591≠	0.000	0.455	0.000
Absolute lymphocytic count(x109/L)	Median (IQR) Range	1.6 (1 – 2.3) 0.12 – 10	1 (0.62 – 1.4) 0.2 – 4.6	2 (1.59 – 2.35) 0.7 – 8.5	67.251≠	0.000	0.002	0.000
Absolute eosinophil count(x109/L)	Median (IQR) Range	0.1 (0.09 – 0.3) 0 – 1.28	0.1 (0 – 0.1) 0 – 0.4	0.2 (0.1 – 0.52) 0 – 1.28	78.981≠	0.000	0.140	0.000
Absolute monocytic count(x109/L)	Median (IQR) Range	0.07 (0 – 0.2) 0 – 4	0.15 (0 – 0.5) 0 – 1.4	0.01 (0 – 0.07) 0 – 0.5	30.017≠	0.001	0.000	0.000
PLT (x109/L)	Median (IQR) Range	231 (181 – 278) 8 – 722	234 (157 – 332.5) 15 – 628	249 (215.5– 312) 166 – 371	6.909≠	0.402	0.005	0.135
Hgb (gm/dl)	Mean±SD Range	12.93 ± 1.95 7.5 – 17.1	11.59 ± 2.31 6.9 – 17.2	12.52 ± 1.18 10.4 – 15.2	29.131•	0.000	0.130	0.001
Neutrophil to lymphocyte ratio	Median (IQR) Range	2.38 (1.54 – 4.06) 0.5 – 136.5	6.93 (2.54 – 14.94) 0.64 – 135	2.11 (1.1 – 2.73) 0.31 – 13.54	103.655≠	0.000	0.002	0.000
Lymphocyte to monocyte ratio	Median (IQR) Range	10 (5.56 – 23.57) 0.9 – 280	4.27 (1.75 – 12.33) 0.14 – 160	19.61 (11.33 – 50) 4.2 – 285	61.950≠	0.000	0.001	0.000
Platelet to lymphocyte ratio	Median (IQR) Range	36.67(94.29–233.33) 8.08 – 1733.33	36.41 (124.08 – 392. 18.75 – 2185	41.05(104.72– 174.39 19.53 – 308.75	42.099≠	0.000	0.489	0.000

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test; •: One Way ANOVA test; ≠: Kruskal-Wallis test
P1: Non severe Vs severe, P2: Non severe Vs Post COVID convalescent, P3: Severe Vs Post COVID convalescent

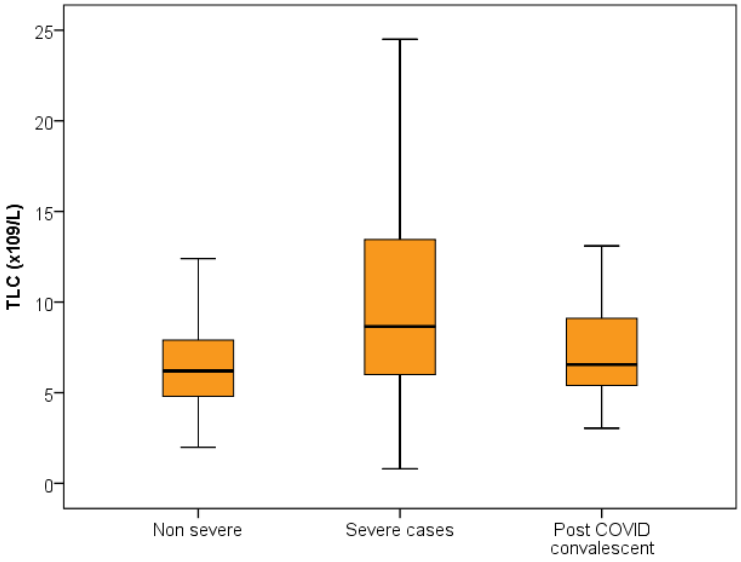

Figure 1: boxplot showing higher TLC in severe covid

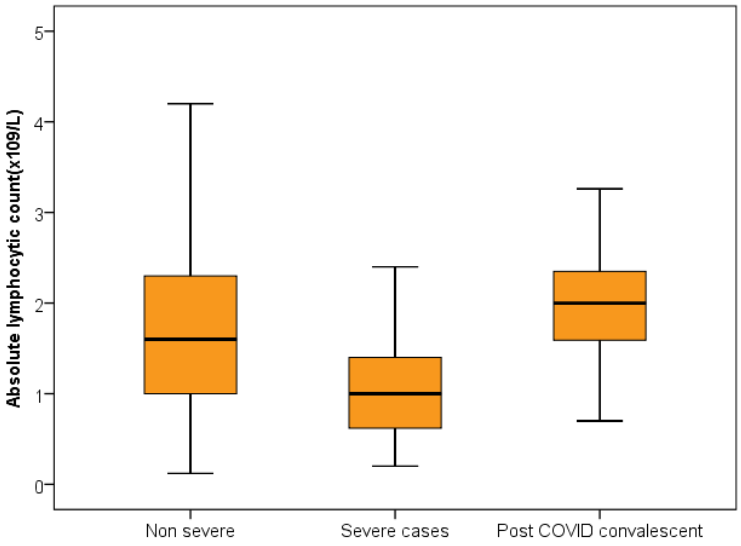

Figure 2: boxplot showing lower lymphocytes in severe covid

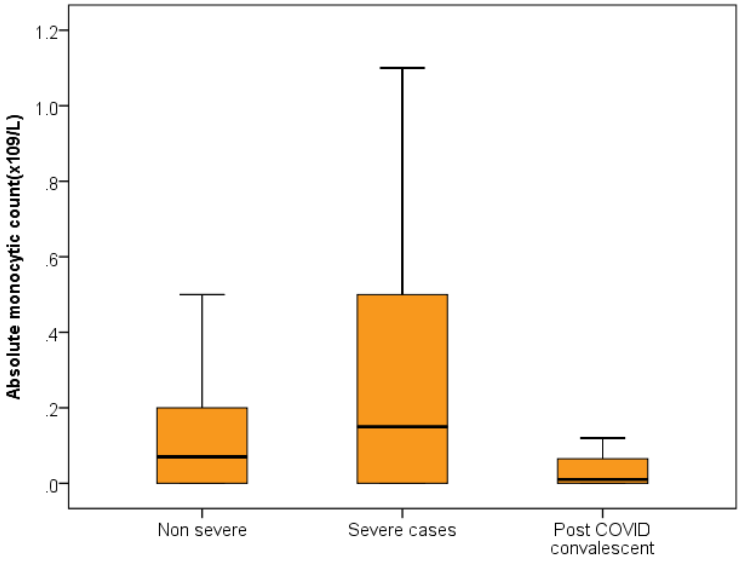

Figure 3: boxplot showing higher monocytes in severe covid

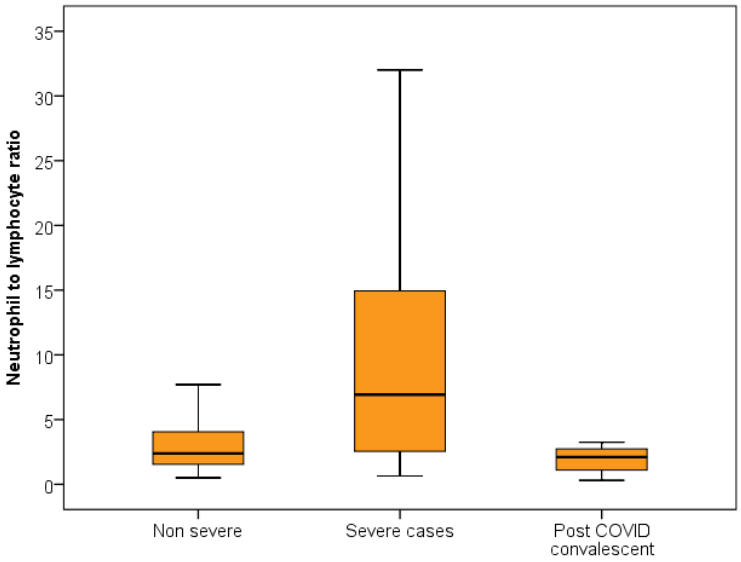

Figure 4: boxplot showing higher NLR in severe covid

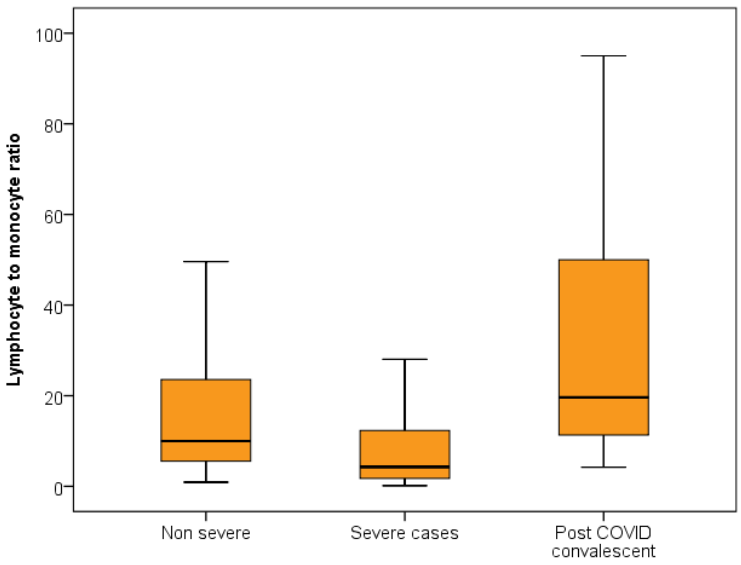

Figure 5: boxplot showing lower LMR in severe covid

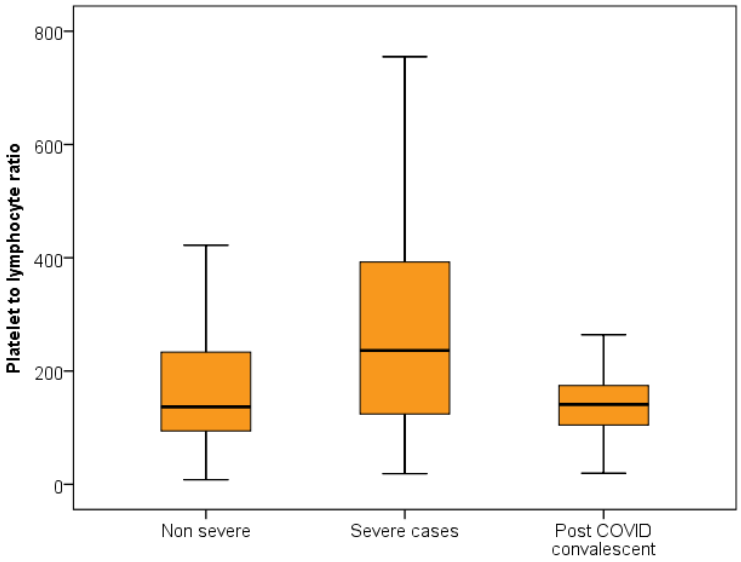

Figure 6: boxplot showing higher PLR in severe covid

4- The multivariate logistic regression analysis for factors associated with severity among the studied patients:

The multivariate analysis showed that the most important factors associated with severity were ICU admission; dyspnea; absolute lymphocyte count ≤ 1.4; TLC > 7.76 and lastly absolute monocyte count >0.19. So, these factors are identified as independent risk factors for the severity and disease progression of covid 19.

Table 4: Multivariate logistic regression analysis for factors associated with severity among the studied patients

	Multivariate			
	P-value	Odds ratio (OR)	95% C.I. for OR	
			Lower	Upper
Sex	–	–	–	–
Age >41	–	–	–	–
Mechanical ventilation	–	–	–	–
ICU admission	**0.000**	2057.833	128.071	33065.193
Asymptomatic	–	–	–	–
Fever	–	–	–	–
Cough	–	–	–	–
Diarrehea	–	–	–	–
Dyspnea	**0.000**	157.748	18.380	1353.884
CT chest	–	–	–	–
SO2% ≤94	–	–	–	–
CRPmg/L >31	–	–	–	–
Ferritin ng/ml >253	–	–	–	–
D-dimer ng/ml (FEU) >561	–	–	–	–
ALT (U/L) >44	–	–	–	–
Creatinine mg/dl >0.6	–	–	–	–
TLC (x109/L) >7.76	**0.010**	9.523	1.715	52.878
Absolute Neutrophil count(x109/L) >8.1	–	–	–	–
Absolute lymphocytic count(x109/L) ≤ 1.4	**0.012**	15.022	1.817	124.165
Absolute eosinophil count(x109/L) ≤ 0.1	–	–	–	–
Absolute monocytic count(x109/L) >0.19	**0.019**	5.937	1.334	26.418
Hgb (gm/dl) ≤ 11.9	–	–	–	–
Neutrophil to lymphocyte ratio >3.75	–	–	–	–
Lymphocyte to monocyte ratio ≤ 6	–	–	–	–
Platelet to lymphocyte ratio >208.33	–	–	–	–

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

Discussion

This study has aimed at emphasising the effectiveness of laboratory markers, not only in the diagnosis of covid 19 infection, but to predict the disease progression, to stratify the cases into severe and non severe, and to speculate the post covid sequalae, in order to give a chance for the early and appropriate therapeutic strategy and the choice for ICU admission before exacerbation of the disease.

This study correlated severity with older age, male sex, symptomatic cases, and extensive CT findings which led to the need for ICU admission and mechanical ventilation in some cases. In accordance Jin et al.,[4] have also deduced that older age and male sex were associated with worse outcome. They expected this could be due to the associated comorbidities with older age. Moreover, Ghweil et al.,[5] explained that older age is accompanied with decline in cell mediated immunity and humoral immunity. Like this study, they also added that respiratory symptoms were more frequently presented and more related to severity rather than GIT symptoms especially dyspnea. They suggested the GIT symptoms presented in milder cases due to weakening of the virus after swallowing by the digestive enzymes.

This study showed that CRP is associated with the severity of the disease, in accordance with Chen et al.,[6] They associated plasma CRP with the chest CT performance and the inpatient duration. They explained that upon stimulation by inflammation, CRP is rapidly synthesized by hepatocytes, then binds to the pathogens, leading to complement activation via classical pathway, lymphocyte infiltration and inflamematory burst.

This study agreed with Lin et al., [7] who recognised serum ferritin as an independent risk factor for the disease severity. They explained that hyperferritinemia associated with COVID-19 is due to the released proinflammatory cytokines such as IL-6, interleukin-Iβ (IL-lβ), tumour necrosis factor-a (TNF-α). Moreover, the cellular damage resulting from inflamemation leads to leakage of intracellular ferritin. In addition, acidosis enhances the excessive production of reactive oxygen species (ROS) which in turn liberates iron from ferritin. This unliganded iron shares in Haber-Weiss and Fenton reactions, releasing hydroxyl radicals, causing more and more cellular damage which leads to a vicious cycle of inflammation.

This study found an association between D-dimer and the severity of the disease, like Vidali et al.,[8] who deduced its importance as a prognostic marker in Covid 19 severe infection and pointed its role in deciding to start the therapeutic administration of low molecular weight heparin (LMWH) and in monitoring the patients' response especially in cases of early and continuous prothrombotic activity of SARS-CoV-2. They mentioned that the coagulation process in covid 19 is triggered by many factors. First, the released proinflammatory cytokines upregulate plasminogen activator inhibitor (PAI)-1 which impairs fibrinolysis, and they also cause proinflammatory changes of the endothelial cells which lead to the expression of chemo attractants necessary for mononucleate cell activation and the production of tissue factor which in turn triggers coagulative extrinsic cascades.

Additionally, cytokines such as IL-8 and IL-6, together with platelets, stimulate platelet activation to maintain the coagulation cascade. Also, hypoxia stimulates many cellular and molecular pathways which release hypoxia inducible factors (HIFs) that stimulate the transcription of genes coding for coagulative proteins such as PAI-1. Moreover, the pathogen itself causes cellular damage and enhances immune responses producing pathogen-associated molecular patterns (PAMPs). PAMPs promote more inflammation and coagulation. SARS-CoV-2 virus also binds with its envelope glycoprotein to angiotensin converting enzyme2 (ACE2) which is present on alveolar epithelial and vascular endothelial cells. This binding leads to consequent damage and activation of coagulation pathways. D-dimer is in released upon fibrinolysis of the formed systemic microthrombi by plasmin enzyme. Thus, it represents a mirror of endovascular thrombosis.[8]

This study detected higher ALT in severe covid patients. Same was found by Afra et al.,[9] who reported evident increase in liver function tests in severe patients at early stages of the infection. Causes include direct liver damage by SARS-CoV-2 binding to cholangiocytes through ACE2 receptors, or indirect damage due to the widespread inflammation and the cytokine storm, or due to hypoxia from pneumonia, or due to drug toxicity.

Severe cases in this study showed higher TLC and lower Hb than non severe cases, whereas PLT showed no significant difference. Unlike this study, a study by Yousif et al.,[10] detected increased mortality with lower TLC, Hb, and platelets. Regarding TLC, although they found lower levels in severe cases, but they also reported that US Centers for Disease Control and Prevention (CDC) stated that leukocytosis and lymphopenia were the most common observations among severe cases and that neutrophils counted for the increased counts. As for PLTs, they explained that thrombocytopenia is induced by direct viral cytotoxicity to bone marrow cells, or by the destruction of progenitors by the cytokine storm, or by inhibition of platelet synthesis by lung injury, or by peripheral platelet destruction by the immune system, or by platelet aggregation in the lungs with subsequent micro thrombi formation and platelet consumption.

In accordance with this study, Lippi and Mattiuzzi [11] reported that Hb is decreased in patients with severe coronavirus disease. Cavezzi et al.,[12] showed that this could be due to the viral direct interaction with the Hb molecule by binding to ACE2, CD147 and CD26 on RBCs or its precursors or due to the viral spike protein which produces hepcidin like action and blocks ferroportin.

Regarding lymphopenia, Tan L. et al.,[3] concluded that lymphopenia is a good predictor of disease severity in COVID19 like this study. They suggested the lymphopenia is caused by direct lymphocytic viral infection via ACE2 receptor, or viral destruction to thymus and spleen, or lymphocytic dysfunction, or lymphocytic apoptosis by inflammatory cyto-kines, or inhibition of lymphocytic proliferation by hyperlactic acidemia.

This study showed lower eosinophil counts with severe cases, concomitantly Lindsley et al.,[13] reported that eosinopenia has been observed in severe patients at the time of admission, and has improved before discharge. The pathophysiology includes blockage of the eosinophil egress from the bone marrow, inhibition of eosinophilopoiesis, and eosinophil apoptosis enhanced by interferons.

As for monocytes, this study showed higher monocytic levels with severe cases. Merad and Martin [14] have also detected a significant expansion of $CD14^{+}CD16^{+}$ monocytic populations in covid 19 patients who needed ICU hospitalization. They assumed that ACE2 on macrophages can be stimulated by inflamematory cytokines like type I interferon or that CD147 receptors may be involved in virus entry.

The NLR is significantly increased in severe covid patients in this work. In agreement, Liu et al.,[15] stated that increased NLR indicated poor clinical prognosis. High NLR is attributed to viral damage to T lymphocytes together with superadded bacterial infections leading to a falling lymphocyte count and a rising neutrophil count.

On the other hand, there is a significantly lower LMR in severe covid patients in this work. Coincidingly, Lissoni et al.,[16] reported the same finding and suggested that that lymphocytopenia may be due to lymphocytic exit from blood to infiltrate the lung tissue together with a concomitant increase in monocytes. Therefore, LMR can be a more adequate, simple, and cost-effective biomarker to monitor the prognosis of infection.

The PLR in this study was increased in severe cases, which agrees with Qu et al.,[17]. They clarify that in severe cases, the inflammatory cytokines may promote megakaryocytic generation and differentiation. IL-6 also stimulates the increase of thrombopoietin. The resulting increase in platelet count with the

decrease in the lymphocytic count will increase PLR. PLR has the advantage of reflecting systemic inflammation.

Concerning post covid cases, this work included cases which showed spontaneous recovery after infection and PCR turning negative for covid 19 virus. All their laboratory markers declined except the lymphocytic count, eosinophil count, Hb level, PLT count, and LMR which raised upon convalescence. If post covid laboratory markers show otherwise, it can be used as an alarming sign for a worse course known as Post covid 19 syndrome or long covid. Greenhalgh et al.,[18] defined post acute covid 19 syndrome as symptoms extending more than three weeks from the onset of first symptoms and chronic covid 19 as symptoms extending beyond 12 weeks. The symptoms vary from thrombotic sequalae to dominating fatigue. PCR testing can be falsely negative, so it is not a prerequisite for diagnosis. They assume the causes are due to persistent viraemia if the antibody response is weak or absent, relapse or even reinfection, continuous release of inflammatory mediators, and post traumatic stress. They agreed with this study, that persistent lymphopenia and increased CRP, TLC, ferritin, and D-dimer may predict this syndrome.

Conclusion

Low absolute lymphocyte count, high TLC, and high absolute monocyte counts are independent risk factors for severe covid 19 cases. The dynamic changes in the laboratory markers can predict the disease severity during acute infection and during the post covid stage. Thus, allowing the early proper management.

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