

## ORIGINAL ARTICLE

# The predictive value of laboratory biomarkers in defining COVID-19 severity.

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### ABSTRACT

<p><b>Keywords:</b> COVID-19- Ferritin- NLR- SARSCoV-2- D- dimer</p> <p><b>*Corresponding author:</b> Hassan Abdelrazzak Mohamed Email: ahsn6607@gmail.com Mobile: 01144636078</p>	<p><b>Background:</b> The COVID-19 outbreak poses a serious hazard to human health. We aimed to correlate between the severity of clinical presentation and laboratory results. <b>Material and methods:</b> All COVID-19 positive cases that were admitted to Aswan University Hospitals were prospectively collected and classified into either severe or non-severe COVID-19 cases . All the demographic, clinical characteristics, HRCT results and the basic laboratory biomarkers at time of admission were collected including [WBC, absolute neutrophil count, absolute lymphocyte count, CRP, D-dimer, NLR and ferritin]. <b>Results:</b> The severe case group (n=71) had considerably higher mean levels of WBCs, absolute neutrophils, absolute lymphocytes, CRP, D-dimer, NLR and ferritin than the non-severe case group (n=137) (p &lt;0.0001 considerably). However, CRP and serum ferritin are considered the independent risk factors for COVID-19 severity (p= 0.009 &amp; 0.033 respectively). Moreover, at a cut-off point (5.73), the sensitivity of NLR ratio to predict the case severity was low (43%) but higher specificity (93.2%). Similarly, at a cut-off point of (1.56), the sensitivity and specificity of D-dimer were (60.6% and 78.1% respectively). <b>Conclusions:</b> Increased NLR (&gt; 5.73), and D-dimer level (&gt; 1.56 mg\L), CRP (&gt; 86.5 mg/L and serum Ferritin &gt;256.5 at time of admission can be simple available prognosticators for severe COVID-19 contagion.</p>
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## INTRODUCTION

The COVID-19 outbreak poses a serious risk to human well-being (WHO, 2020). The clinical presentations of COVID-19 vary from asymptomatic cases to mild, moderate, and severe forms rapidly progressing to hospital admission, septicemia, or even decrease in 4–15% of cases (Wang et al, 2020). So, it is critical to classify the COVID-19 illness and its severity as early as possible.

Along with the disease course, COVID-19 cases may be roughly classified into 2 clusters; [asymptomatic or mild cases that usually recover and severe cases that proceed to multi-organ failure, principally respiratory failure, necessitating admission to the intensive care unit (ICU). [(Wang et al, 2020) (Guan et al, 2020)].

Numerous laboratory bio-markers are used primarily for COVID-19 contagion assessment or diagnosis; however, their accuracy to evaluate contagion severity and prognosis along with the levels at which they are alarming results are still to be appraised (**Knight et al, 2020**).

Currently, the usual technique for proving COVID-19 is the real-time polymerase chain reaction (RT-PCR). Other laboratory investigations include leucopenia, lymphopenia, low platelet count, high serum CRP, and ferritin [(**Wu et al, 2020 a**) (**Habibzadeh et al, 2020**)].

We aimed to correlate between the severity of clinical presentation and hematological [CBC including: lymphocyte count, neutrophil to lymphocyte ratio] and immunological (CRP, serum ferritin, D-Dimer) laboratory results of COVID-19 cases and estimate the precise cut-off value for those indicators.

## PATIENTS AND METHODS

### Design:

it is a prospective observational study

### Settings:

**Inclusion criteria:** patients with PCR positive for COVID-19 who were admitted to COVID-19 isolation department and COVID-19 isolation ICU in Aswan University Hospital during the period from January 2021 to January 2022.

**Exclusion criteria:** patients with PCR positive for COVID-19 less than 18 years old, patients who had laboratory and radiological findings suspicious of COVID-19 but negative PCR results and pregnant females.)

### Ethical approval

The study protocol was approved by the ethical committee of the Faculty of Medicine, Aswan University (IRB no: 521/3/21 ).

### All eligible patients had subjected to:

- 1- **Demographic and clinical characteristics:** comprising age, gender, site of admission, presenting complains, the clinical severity of the cases and comorbid disorders. We classified the Clinical severity of COVID-19 illness according to **WHO, (2021)** into: [Asymptomatic or pre-symptomatic contagion, mild, moderate, severe, and critical illness].
- 2- **The outcomes measures of the patients** (ICU admittance, decease, recovery, prerequisite for invasive or non-invasive mechanical ventilation or referral).
- 3- **Laboratory data** comprising [complete blood count (Sysmex XN-1000-Japan), C-reactive protein (CRP) (Beckman Coulter AU480), D dimer, serum ferritin (Vidas–Biomerieux-France)], & kidney functions.
- 4- **High resolution CT chest:**  
HRCT was accomplished on all the study cohort using standard protocol through Toshiba 160- slice CT scanner, aquilion TM prime, Japan. Non-contrast scans *were captured at*

full inspiration from the apex to the base of the lung in supine patients. the following criteria were emphasized: Ground-glass opacities (GGO), and consolidation. For the radiological classification of COVID-19 we used the CORAD score as shown in Figure (2).

<b>CO-RADS*</b>		
<b>Level of suspicion COVID-19 infection</b>		
		<b>CT findings</b>
<b>CO-RADS 1</b>	No	normal or non-infectious abnormalities
<b>CO-RADS 2</b>	Low	abnormalities consistent with infections other than COVID-19
<b>CO-RADS 3</b>	Indeterminate	unclear whether COVID-19 is present
<b>CO-RADS 4</b>	High	abnormalities suspicious for COVID-19
<b>CO-RADS 5</b>	Very high	typical COVID-19
<b>CO-RADS 6</b>	PCR +	

Figure (1): COVID-19 CO-RADS classification (WHO, 2020),

This study included 208 confirmed COVID - 19 cases with positive PCR. **Based on this the clinical severity of the cases as illustrated in Figure (2) (WHO, 2020)**, The study cohort was divided into:

- **Severe cases group:** including severe and critical case COVID-19 (n= 71).
- **Non severe cases group:** including the asymptomatic, mild and moderate cases (n=137).

	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>	<b>Critical</b>
<b>Adult</b>	<ul style="list-style-type: none"> <li>• Symptomatic</li> <li>• Meets case definition</li> <li>• No evidence of pneumonia or hypoxia</li> </ul>	<ul style="list-style-type: none"> <li>• Clinical signs of pneumonia (febrile, cough, dyspnoea, tachypnoea)</li> <li>• Saturations <math>\geq</math> 90% in air</li> </ul>	Signs of pneumonia and any of: <ul style="list-style-type: none"> <li>• respiratory rate <math>&gt;</math> 30 breaths/min</li> <li>• severe respiratory distress</li> <li>• Saturations <math>&lt;</math> 90% in air</li> </ul>	<ul style="list-style-type: none"> <li>• ARDS</li> <li>• Sepsis</li> <li>• Septic shock</li> </ul>
<b>Child</b>			<ul style="list-style-type: none"> <li>• Clinical signs of non-severe pneumonia (cough or dyspnoea + tachypnoea with or without recessions)</li> </ul>	

Figure (2): The clinical severity of COVID-19 (WHO, 2020),

**Statistical analysis**

The data was analyzed by SPSS (statistical package for social science) version 26.0 on IBM compatible computer (SPSS Inc., Chicago, IL, USA).  $P < 0.05$  was considered significant.

## RESULTS

This study included 208 confirmed COVID-19 cases with positive PCR, presenting at the Quarantine section in Aswan University Hospital.

**Table (1): Socio-demographic and baseline clinical characteristics of the studied cohort (N=208).**

		N=208
<b>Age (Y)</b>	Mean $\pm$ SD	58.4 $\pm$ 17.5
<b>Gender N (%)</b>	Male	96 (46.2 %)
	Female	112 (53.8 %)
<b>DM N (%)</b>		51 (24.5 %)
<b>Hypertension N (%)</b>		145 (69.7 %)
<b>Chronic kidney disease N (%)</b>		9 (4.3 %)
<b>Chronic lung disease N (%)</b>		16 (7.7 %)
<b>Chronic cardiac disease N (%)</b>		77 (37 %)
<b>CVD N (%)</b>		13 (6.2 %)
<b>Smoking status N (%)</b>	Non-smoker	144 (69.2 %)
	Mild smoker	8 (3.8%)
	Moderate smoker	11 (5.3 %)
	Heavy smoker	45 (21.6 %)
<b>Symptoms</b>		
<b>Fever N (%)</b>		155 (74.5 %)
<b>Dyspnea N (%)</b>		146 (70.2 %)
<b>Cough N (%)</b>		124 (59.6 %)
<b>Rhinorrhea N (%)</b>		38 (18.3 %)
<b>Diarrhea N (%)</b>		40 (19.2 %)
<b>Headache N (%)</b>		82 (39.4 %)
<b>Fatigue N (%)</b>		81 (38.9 %)
<b>Duration of symptoms (days)</b>	Mean $\pm$ SD	4.4 $\pm$ 2.2

<b>Management</b>	Invasive ventilation	23 (11.1 %)
	Non-invasive ventilation	101 (48.6 %)
	O <sub>2</sub> therapy	84 (40.4 %)
<b>Clinical Severity</b>	Severe	71 (34.1 %)
	Non- severe	137 (65.9 %)
<b>Outcome</b>	Death	82 (39.4 %)
	Recovery	126 (60.6 %)

Socio-demographic and baseline clinical characteristics of the studied cohort were illustrated in Table (1).

**Table (2): Relation between both Laboratory and radiological data and the clinical cases severity of the study population (N=208)**

		COVID-19 Clinical Severity		P value
		Severe (n=71)	Non- severe (n= 137)	
<b>Hemoglobin (g/dl)</b>	Mean ± SD	11.2 ± 2.2	12.9 ± 1.9	<0.0001
<b>WBCs (10<sup>3</sup>/ul)</b>	Mean ± SD	14.0 ± 6.4	10.2 ± 5.4	<0.0001
<b>Absolute neutrophils (10<sup>3</sup>/ul)</b>	Mean ± SD	69.6 ± 27.5	46.9 ± 37.4	0.001
<b>Absolute lymphocytes (10<sup>3</sup>/ul)</b>	Mean ± SD	7.7 ± 4.5	7.3 ± 8.6	0.032
<b>NLR</b>	Mean ± SD	13.2 ± 0.3	4.5 ± 0.5	<0.0001
<b>CRP (mg/dl)</b>	Mean ± SD	75.6 ± 49.7	50.8 ± 29.9	<0.0001
<b>D-dimer (mg/l)</b>	Mean ± SD	4.57 ± 8.371.9	1.81 ± 2.5	<0.0001
<b>Serum ferritin (ng/ml)</b>	Mean ± SD	538.4 ± 338.2	404.6 ± 336.3	<0.0001
<b>Radiological data</b>				
<b>GGO</b>		71 (100 %) 0	132 (96.4 %) 5 (3.6 %)	0.103
<b>Consolidation</b>		23 (32.4 %) 48 (67.6%)	27 (19.7 %) 110 (80.3 %)	0.042

Table (2) disclosed that the severe cases had considerably higher mean levels of WBCs, absolute neutrophils, absolute lymphocytes, CRP, D-dimer, NLR, and ferritin than the non-severe cases ( $p < 0.0001$  considerably).

**Table (3): Binary logistic regression analysis for independent risk elements for the case severity.**

	S.E.	P value	$\beta$	95% CI	
				Lower	Upper
<b>WBCs</b>	0.033	0.115	1.053	0.987	1.124
<b>Absolute neutrophils</b>	0.015	0.078	1.015	0.998	1.031
<b>Absolute lymphocytes</b>	0.038	0.165	0.948	0.879	1.022
<b>NLR</b>	0.396	0.491	1.313	0.605	2.852
<b>CRP</b>	0.005	0.009	1.013	1.003	1.023
<b>D-dimer</b>	00	0.082	1.000	1.000	1.000
<b>Serum ferritin</b>	0.001	0.033	1.001	1.000	1.002
<b>Consolidation</b>	0.391	0.063	0.484	0.225	1.040

*SE = standard error, CI = confidence interval*

CRP and serum ferritin are considered independent risk factors for COVID-19 severity ( $p = 0.009$  &  $0.033$  respectively) as illustrated in Table (3).

**Table (4): Accuracy of the hematological markers to predict the severity of COVID-19 among the studied cases (N= 208)**

	WBCs	Absolute neutrophils	Absolute lymphocytes	NLR
<b>AUC</b>	0.687	0.644	0.591	0.333
<b>SE</b>	0.040	0.040	0.039	0.039
<b>P value</b>	<0.0001	0.001	0.032	<0.0001
<b>95% CI</b>	0.609 – 0.766	0.567 – 0.722	0.514 – 0.668	0.256 – 0.410
<b>Cut-off point</b>	13.7	74.5	1.73	5.73
<b>Sensitivity</b>	52.1%	76.1%	90.1%	43%
<b>Specificity</b>	79.6%	55.5%	27.0%	93.2%

*AUC: area under curve, SE = standard error, CI = confidence interval*

Table (4) displayed the diagnostic accuracy of the hematological markers to predict the severity of COVID-19 among the studied cases where at a cut-off point ( $13.710^3$ /ul), the sensitivity and specificity of WBCs to forecast the clinical severity of COVID-19 were (52.1% and 79.6% respectively). Similarly, at a cut-off point of ( $74.510^3$ /ul), the sensitivity and specificity of absolute neutrophil count to predict severity were (76.1% and 55.5% respectively). However, at a cut-off point ( $1.73 10^3$ /ul), the sensitivity of absolute lymphocyte counts to predict severity was (90.1%) but low specificity (27.0%). Moreover, at a cut-off point (5.73), the sensitivity of the NLR ratio to predict the case severity was low (43%) but higher specificity (93.2%).

**Table (5): Accuracy of the immunological markers to predict the severity of COVID-19 among the studied cases (N= 208)**

	<b>CRP</b>	<b>D-dimer</b>	<b>Serum ferritin</b>
<b>AUC</b>	0.668	0.732	0.656
<b>SE</b>	0.040	0.036	0.038
<b>P value</b>	<0.0001	<0.0001	<0.0001
<b>95% CI</b>	0.590 – 0.747	0.662 – 0.803	0.581 – 0.731
<b>Cut-off point</b>	86.5	1.56	256.5
<b>Sensitivity</b>	39.4%	60.6%	90.1%
<b>Specificity</b>	86.9%	78.1%	38.0%

*AUC: area under curve, SE = standard error, CI = confidence interval*

Table (5) disclosed the diagnostic accuracy of the immunological markers to forecast the severity of COVID-19 among the studied cases where at a cut-off point of (86.5 mg/l), the sensitivity of CRP to predict severity is (39.4%) but high specificity (86.9%). Similarly, at a cut-off point of (1.56 mg/l), the sensitivity and specificity of D-dimer to forecast severity were (60.6% and 78.1% respectively). Furthermore, at a cut-off point of (256.5 ng/ml), the sensitivity of serum ferritin to predict severity was high (90.1%) but low specificity (38.0%).

## DISCUSSION

The COVID-19 outbreak poses a serious risk to human well-being (WHO, 2020). So, it is crucial to identify the COVID-19 illness and its severity as early as possible. This study included 208 confirmed COVID-19 cases with positive PCR, [of them 71 cases (34.1 %) were admitted to ICU presenting at the Quarantine section in Aswan University Hospital during the period from January 2021 to January 2022.

As anticipated, the most common symptom among the studied cohort was fever (74.5%), followed by 70.2% dyspnea, while 59.6% had a cough which is in harmony, with numerous studies [(Chen et al., 2020) (Guan et al., 2020) (Wu et al., 2020) b]. A recent systematic review summarized that fever and cough were the most common complaints in COVID-19 cases under the age of 20 years with other complaints infrequent (Viner et al., 2021).

Complete blood count is one of the essential widely available investigations for COVID-19 infection diagnosis and severity assessment (Cavezzi et al., 2020). In this study, we found



that severe cases had considerably higher levels of WBCs, absolute neutrophils, absolute lymphocyte count, & NLR ( $p < 0.0001$  considerably).

Lymphopenia & leukocytosis were also proposed to be risk elements for severe COVID-19 contagion and worse outcomes [(Yamada et al., 2020) (Huang et al., 2020) a]. A recent meta-analysis summarized that leukocytosis and lymphopenia were allied with severe disease (Huang et al., 2020 b). Lymphopenia was previously used as a predictive biomarker in other communicable disorders such as influenza. Association between lymphopenia and severe illness may be the sequel of direct contamination of the lymphocyte, destruction of the lymphatic tissue, lymphocytic apoptosis owing to inflammation, or some metabolic troubles such as lactic acidosis triggering lymphocytes inhibition (Tan et al., 2020 a). In this study, in harmony with Hashem et al., (2021) in spite of being allied with severe COVID-19 contagion, neither lymphopenia nor leukocytosis was a substantial hazard element by multivariate regression analysis. Furthermore, the optimal WBC cut-off point to predict the clinical severity of COVID-19 was [ $13.7 \times 10^3/\text{ul}$ ] with (79.6%) sensitivity but (52.1%) specificity. Similarly, the optimal cut-off point of absolute neutrophil count to predict severity was [ $74.5 \times 10^3/\text{ul}$ ], with sensitivity (76.1%) nevertheless (55.5%) specificity. Besides, the optimal cut-off point of absolute lymphocyte count to predict severity was [ $1.73 \times 10^3/\text{ul}$ ] with (90.1%) sensitivity but (27.0%) specificity.

The neutrophil-to-lymphocyte ratio (NLR) is an anxiety and immune element. For COVID-19, the increased neutrophil count may specify the degree of the inflammatory feedback, and the reduced lymphocytes estimate the degree of immune disparity. These relations are augmented by the concept of NLR (Zahorec et al., 2020). The normal values of NLR in adults range from 1.0 to 2.3. The cut-off value of NLR that could forecast unfortunate COVID-19 contagion fluctuates widely among studies. It varies between 3.1 and 9 (Wang et al., 2021). In this study, the optimal cut-off point that could predict severe COVID-19 contagion was [5.73]. A previous study found a statistically considerable strong relation of in-hospital decrease with  $\text{NLR} > 3.1$  (Asem et al., 2021). The non-existence of a single general explanation for severe COVID-19 contagion and the fluctuating outcome measures used in diverse studies might clarify this wide range and variances. However, there is accordance about the value of raised baseline NLR in forecasting severe COVID disease.

Regarding inflammatory biomarkers associated with the COVID-19 contagion, in this study, we found that severe cases had considerably higher levels of CRP, D dimer & ferritin. several meta-analysis studies disclosed higher concentrations of C-reactive protein (CRP) among patients with severe COVID-19 infection [(Henry et al., 2020) (Tan et al., 2020 b) (Elshazli et al., 2020)]. In this study, higher levels of CRP were found in severe COVID-19 cases. moreover, by applying multivariate regression analysis, it was established to be a forecaster of severity ( $p = 0.009$ ) in contrast to Hashem et al., (2021).

SARS-CoV-2 virus can affect coagulation and hemostasis by diverse measures involving both abnormal bleeding hazard and thrombo-embolism. Consequently, all main coagulation biomarkers disorders were displayed in COVID-19 cases specifically higher serum D-dimer level, longer prothrombin time (PT), and lower platelet counts (Danwang et al., 2020). Elevated levels of D-dimer may help in competent diversity between mild and severe cases of COVID-19 infection (Zhang et al., 2020) and may be used as a mirror for the documentation of disease evolution toward unfavorable outcomes or even decrease (Bashash et al., 2020). The optimal D-dimer level that could forecast a worse prognosis varies among studies between  $> 1 \text{ mg/L}$  to  $>$



2.14 mg/L (**Zhou et al., 2020 b**). In this study, D-dimer > [1.56 mg\L] found to be a subtle forecaster for severe COVID-19 infection

Serum Ferritin is an acknowledged inflammatory biomarker in COVID-19. A recent meta-analysis summarized that Hyper-ferritinaemia was found to be allied with more severe illness and worse COVID-19 sequel. Consequently, serum ferritin level can aid as a significant prognostic biomarker in the management of COVID-19 cases. However, in the presence of other comorbidities, serum ferritin levels are required to be taken carefully (**Kaushal et al., 2022**). This agreed with our results., Besides, we found that serum ferritin was considered an independent hazard factor for COVID-19 severity ( $p= 0.033$ ). Moreover, the optimal cut-off point of serum ferritin to predict severe COVID-19 infection was [256.5 (ng/ml)] with (90.1%) sensitivity but (38.0%) specificity.

However, this study had numerous limitations including the following: First: the retrospective design of the study. Second: the changing treatment protocol and admission policy during the study period. Third: it's a single-center study with a small number of patients to identify the outcome. Fourth: the follow-up laboratory data and linear changes in association with the clinical condition of the patients were not evaluated and the other bio-markers such as IL-6 level, LDH, CK-MB, troponin, and procalcitonin were not assessed. Finally, the inter-observer bias is presented in the CT interpretation.

## CONCLUSIONS

Increased NLR (> 5.73), D-dimer level (> 1.56 mg\L), CRP (> 86.5 mg/L and serum Ferritin (>256.5 ng/ml) at the time of admission can be simply available prognosticators for severe COVID-19 contagion. Upcoming studies are desired to appraise the linear variation of NLR, CRP, Ferritin, and D-dimer with disease progression.

## Abbreviations

COVID- 19: Corona virus disease 2019

CRP: C-reactive protein

Hb: Hemoglobin

ICU: Intensive care unit

NLR: Neutrophil-to-lymphocyte ratio

SARS CoV-2: Severe acute respiratory syndrome coronavirus 2

WHO: World Health Organization

AUC: Area under curve

SE = Standard error

CI = Confidence interval

HRCT: High resolution CT chest:

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