Blood Count, Markers of Inflammation and Coagulation factors in COVID-19 versus non COVID-19 patients having Medical Emergency in Qena University Hospital

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Abstract

Background: Inflammation play a key role for COVID-19 infection and its adverse outcomes.

Objectives: The study aimed to evaluate different systemic inflammatory indices as a predictor of COVID-19 infection.

Patients and Methods: A cross-sectional study conducted on patients suspected of having COVID-19. PCR was done and laboratory tests including CBC, coagulation profile, D-dimer, CRP, and diverse of established systemic inflammatory ratios were evaluated on admission [Neutrophil/lymphocyte ratio(NLR), platelet/lymphocyte ratio(PLR), lymphocyte/monocyte ratio(LMR), systemic immune-inflammation index(SII), lymphocyte-to-CRP ratio (LCR), prognostic index (PI), Neutrophil platelet score (NPS), systemic inflammatory response syndrome (SIRS), and platelet/monocyte Neutrophil ratio.

Results: We included 128 patients, 56 males (43.75%) and 72 females (56.25%), 48 (37.5%) had positive PCR, and 80 (62.5%) had negative PCR. PCR (+) patients had significantly higher NLR (median: 7.37, range: 0.5:158), MLR (median: 0.56, range: 0.03:4.7), and PLR (median: 274.15, range: 13.2:1475) compared to PCR (-) patients (median: 3.46, range: 0.2:24), (median: 0.333, range: 0.03:3.5), (median: 116.7, range: 50.8:878.1) respectively, (P=0.001). PCR (+) patients had a significantly higher PI (p< 0.00001) and NPS (P=0,004). D-Dimer had the highest Area Under Curve (0.979), followed by CRP (0.950), INR (0.919), PC (0.920), PT (0.831), Neutrophil % (0.710), and inflammatory indices PLR (0.748), SII (0.724), NLR (0.698), SIRS (0.674), LMR (0.668), LCR (0.651), and P2/MS (0.605).

Conclusion: The calculated inflammatory indices, and the prognostic index can be used to estimate the degree of COVID-19 disease, and combined assessments for multiple inflammatory scores are more accurate in predicting disease severity and offer clinical benefits.

Keywords: Lymphocyte to C-reactive protein ratio; NLR; PLR; Prognostic index; Systemic inflammation-based prognostic scores **.**

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Introduction

The Chinese Center for Disease Control and Prevention recognized a novel Coronavirus in throat swabs from pneumonia cases with dry cough, dyspnea, and fever in December 2019 (**Lu et al., 2020**).

Due to its similarity to the SARS Coronavirus 1 that resulted in high morbidity and mortality in 2002–2003, the newly-identified virus has been given the name SARS-CoV-2. World Health Organization (WHO) declared a global pandemic in March 2020 and named the disease Coronavirus disease 2019 (COVID-19) (**Sohrabi et al., 2020**).

Lymphopenia is a hallmark of COVID-19, with over 80% of patients having low lymphocyte counts (**Guan et al., 2020**).

Several studies suggested using the Neutrophil-to-lymphocyte ratio (NLR), indicating overall inflammatory status, as surrogate markers for COVID-19 disease severity (**Forget et al., 2019; Lagunas-Rangel, 2020**).

At the site of inflammation, local production of cytokines and growth factors such as GM-CSF, G-CSF, and M-CSF triggers granulopoiesis, which leads to increased production of Neutrophils and monocytes **(Peñaloza et al., 2019).** During infection, Neutrophils play a variety of roles; apart from phagocytosis, they can produce and release profuse amounts of cytokines to restrict virus replication **(Costa et al., 2019; Giacalone et al., 2020).**

Hypercoagulability is one of the symptoms of COVID-19 (**Becker, 2020**). According to (**Eljilany and Elzouki, 2020; Yao et al., 2020**), changes in coagulation tests, such as increased D-dimers (3.7–68%) and fibrinogen (5.7% in mild cases and 19.1% in severe instances), are accurate predictors of unfavorable outcomes in hospitalized COVID-19 adult patients.

This study aims to assess the changes in blood count, inflammatory markers and indices, and coagulation factors in patients with COVID-19, and to correlate laboratory findings with clinical symptoms of COVID-19 infection.

Patients and Methods

A cross-sectional study was conducted in the Clinical and Chemical Pathology Department and emergency clinic at Qena University Hospital during the six months between December 2021 and June 2022.

Inclusion criteria: all symptomatic mild to moderate disease adult patients (age > 18 years old) of both sexes suspected to have COVID-19 infection. Patients were diagnosed based on the WHO (2021), mild disease patients have a fever, cough, lethargy, upper respiratory symptoms, and/or less common symptoms (headache, loss of taste or smell, etc.), moderate disease patients have lower respiratory symptoms. They may have infiltrates on the chest X-ray. These patients can maintain oxygenation saturation on atmospheric air.

Exclusion criteria: All asymptomatic, or patients with severe or critical COVID-19 disease as difficulty of breathing, confusion, hypoxia, organ failure, Children, on anticoagulants, associated comorbidities e.g. chronic liver or kidney disease, diabetes mellitus, hypertension, coagulation disorder, immune disorders, malignancy, pregnancy, and previous hematologic disease.

Ethical Consideration: The study was approved by the Ethics Committee of the Faculty of Medicine, South Valley

University, Qena, Egypt, and the ethical approval number is SVU-MED-CCP031-12111275.

All patients underwent detailed medical history taking which highlighted the sex, age, family history, and history of associated comorbidities. Nasopharyngeal swabs were taken for SARS-CoV-2 RT-PCR and chest CT scans that were performed for all enrolled subjects.

Laboratory assessment: were evaluated on admission using the standard operating procedures, including PCR for COVID-19 diagnosis using posterior nasopharyngeal (PNP).

Blood samples: 5 ml venous blood samples were collected and divided into 3 tubes: 2 ml blood in an EDTA tube for complete blood count (CBC), 1.8 ml blood in a citrate tube for clotting and fibrinolysis assay, and a plain tube that left to clot. Citrated and plain tubes were centrifuged at 3000 x g for 15 minutes at room temperature to obtain plasma for PT and D-Dimer and serum for CRP estimation.

All patients were subjected to complete blood count (CBC), Prothrombin time (PT), concentration (PC), and international normalized ratio (INR), D-Dimer, and CRP, as well as calculation of inflammatory indices have been established as a useful scoring system in inflammation. Nine systemic inflammatory ratios were calculated as previously described [Neutrophil/lymphocyte ratio (NLR) (**Keizman et al., 2011**), platelet/lymphocyte ratio (PLR) (**Aliustaoglu et al., 2010**), lymphocyte/monocyte ratio (LMR) (**Wang et al., 2015**), lymphocyte-to-CRP ratio (LCR) (**Abensur Vuillaume et al., 2023**), platelet to monocyte Neutrophil ratio (P2/MS) and (**Kim et al., 2012**), prognostic index (PI) based on CRP and white blood cell (WBC) values (**Kasymjanova et al., 2010**), Neutrophil platelet score (NPS) (**Sreeramkumar et al., 2014**), systemic immune-inflammation index (SII) (**Hu et al., 2014**), and systemic inflammatory response syndrome (SIRS) (**Zhang et al., 2021**).

CBC: was analyzed within 2 hours after sampling, using Cell Dyne-Ruby automated cell counter (Abbott Diagnostics-Santa Clara-Ca-USA). The absolute values were retrieved for the calculation of inflammatory indices.

CRP: using Beckman Coulter AU 480-CA-USA for quantitative immuno-turbidimetric assay of CRP, Cat No. OSR6147. In healthy adults, CRP level ranges from 0 to 8 mg/L.

Prothrombin time (PT/PC/INR) clotting test using light scattering method and D-Dimer: using particle-enhanced immune-turbidimetric assay on automated coagulation analyzer CS-1600. Sysmex Corporation Dade Behring. CA analyzers Kobe, Japan. A normal D-Dimer is less than 0.5 µ/mL. A normal PT range of 10-13.6 sec, normal PC of 80.3- 102.3%, and normal INR of 0.92-1.16.

Real-time polymerase chain reaction (RT-PCR): To detect SARS-CoV-2 nucleic acid from PNP patients' samples, fully automated sample was prepared using QIAamp DSP spin mini Elute-column viral RNA nucleic acid kit extraction and purification protocol on QIACUBE Connect (QIAGEN GmbH, Hilden, Germany). Reaction, amplification conditions, and result interpretation were performed according to the manufacturer's instructions.

Statistical analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS)

program (version 24) software for Windows; (IBM Corporation, Armonk, NY, USA). According to the data results, qualitative variables were recorded as frequencies and percentages and compared by the chi-square test. Quantitative measures were presented as means ± standard deviation (SD) and were compared by student t-test.

To assess the performance of the selected biomarkers, the receiver operating characteristics (ROC) curves, the area under the curve (AUC) for the optimal cutoff level, sensitivity, and specificity values were calculated and the p-value was reported.

A (two-tailed) p-value of less than 0.05 was considered statistically significant for all tests.

Results

This study included 128 COVID-19 patients with mild to moderate disease attending the emergency clinic at Qena University Hospital were included in this study. There were 56 males (43.75%) with an average age of (43.43 ± 11.2 years), and 72 females (56.25%) with an average age of (41.46 ±10.6 years).

All the patients (100%) had a fever, with a mean body temperature of 38.31 ± 0.37 °C, 92 (70.8%) patients had a cough, 80 (61.5%) patients had mild shortness of breath, and 71 (54.6%) patients had bone aches. The mean, SD, and range of different laboratory parameters for the studied patients, (**Table.1**).

Table 1. Laboratory values in the studied patients

Variables	Mean	SD	Range	Reference Range
Age (years)	42	10.9	22-71	-
PT (sec)	14	2	11.5-22	10-13.6
PC (%)	85	20	35-103.5	70-120
INR	1	0.2	1-1.9	1-1.3
Hb (gm/dl)	12	1.7	8-16	11.5-17
RBCs (*10^6/ul)	4.3	0.7	2.8-6	3.8-6
RDW (%)	16.6	2.3	11-22	11-17
Platelet Count (*10^3/ul)	269	132	71-849	150-400
MPV (fl)	11	1.5	7.3-16	8-11
Platelet Mass index (fL/mL)	281	126	76-692	75-115
MPV/Platelet Count	5.1	3	0.9-15.1	4-6
WBCs/MPV	1093	872	131-7203	-
PCT (%)	0.28	0.12	0.08-0.69	0.15-0.4
PDW (%)	12.2	3	2.5-22.5	11-22
P-LCR (%)	26	8.5	16-55	18-50
RDW to Platelet Count	0.001	0.0005	0.0002-0.0014	0.02-0.08
WBCs (*10^3/µl)	11.5	9.4	1.4-81.4	3.5-10
Monocyte (%)	7.4%	4.4%	0.4%-33%	4-12
Monocyte count (*10^3/µl)	0.7	0.5	0.03-3	0.2-0.8
Neutrophil (%)	70%	17.4%	20%-95.2%	40-73
Lymphocyte (%)	20.4%	14.3%	1.9%-70.4%	18-45
Lymphocyte Count (*10^3/µl)	1.8	1.3	0.2-9.3	1-3
Platelet Lymphocyte Ratio	218	199	13-1280	<150
RDW to WBCs count	0.002	0.0016	0-0.01	<1.2

	Median	Range	Reference Range
D-dimer (u/ml)	0.3	0.1-3.5	Up to 0.5
Neutrophil count (*10^3/µl)	7.1	0.74-127.8	1.5-8
Neutrophil Lymphocyte Ratio	4.177	0.24-158	<3
Monocyte Lymphocyte Ratio	0.389	0.03-4.7	0.1-0.5
Lymphocyte Monocyte Ratio	2.57	0.2-30	7-14
SII (*10^9/L)	0.001	0.0008-0.07	0.001-0.003
SIRS	2684.75	10-220889	-
P2/MS	5.9	0.19-185	40-591
Lymphocyte/CRP Ratio (LCR)	230.45	2.9-22000	428-2263
CRP (mg/L)	8	0.2-90	<5

Hb: Hemoglobin; PT: Prothrombin Time; INR: International Normalized Ratio; MPV: mean platelet volume; PC: Prothrombin Time; PLT: platelet count; PMI: platelet mass index; RDW: red cell distribution width; WBCs: White Blood Cells; CRP: C-Reactive Protein; SII: Systemic Immune-Inflammation Index; SIRS: Systemic Inflammatory Response Syndrome; SD: Standard Deviation

In this study, 48 (37.5%) patients had positive PCR results for COVID-19, and 80 (62.5%) patients had negative PCR.

Compared to PCR (-) patients, the PCR (+) patient's significantly higher mean D-Dimer, significantly prolonged PT, significantly lower PC, and high INR (P= 0.001) (Table 2).

PCR (+) patients had significantly lower RBC count (3.9 ± 0.6 ×10^6/ul) and Hb (11 ± 1.3 g/dl) compared to PCR (-) patients (4.5 ± 0.67 ×10^6/ul) and (12.5 ± 1.6 g/dl) respectively, (P = 0.001). However, the RDW was significantly higher in PCR (+) patients (17.7 ± 2.2 %), compared to PCR (-) patients (16 ± 2 %), (P= 0.001) (**Table.2**).

PCR (+) patients had significantly higher platelet count compared to PCR (-) patients, (P= 0.001) (Table 2).

The PCR (+) patients had a significantly higher Neutrophil percentage (77.4 ± 14.2 %) compared to PCR (-) patients (65.4 ± 17.7 %), (p= 0.001). However, PCR (+) patients had a significantly lower lymphocyte percentage (14.5 ± 12%) and lymphocyte count (median: 0.895 and range of 0.2-9.3) × 10^3/µl compared to PCR (-) patients (median: 1.8 and range of 0.3-5.2) × 10^3/µl (p= 0.001). Meanwhile, PCR (+) patients had a significantly higher NLR (median: 7.37 and range of 0.5-158) compared to PCR (-) patients (median: 3.46 and range of 0.2-24), (P=0.001). Moreover, PCR (+) patients had a significantly higher mean PLR (342.5 ± 291.6) compared to PCR (-) patients (154 ± 127), (P=0.001) (**Table.2**).

The PCR (+) patients had a significantly higher MLR (median: 0.56 and range of 0.03-4.7) compared to PCR (-) patients (median: 0.333 and range of 0.03-3.5), (P=0.001) (**Table.2**).

The PCR (+) patients had a significantly higher SII (median: 0.0019 and range of 0.0001-0.07) ×10^9/L compared to PCR (-) patients (median: 0.0008 and range of 0.0008-0.004) ×10^9/L, (P=0.01), significantly higher SIRS (median: 4634 and range of 105-220889) compared to PCR (-) patients (median: 2020 and range of 95-73172), (P=0.05), significantly higher mean P2/MS (median: 8.01 and range of 0.53-185) compared to PCR (-) patients (median: 5.13 and range of 0.19-64.39), (P= 0.001), and significantly higher CRP (median: 43 and range of 8-90)

compared to PCR (-) patients (median: 4 and range of 0.2-54), (P=0.001), but significantly lower LCR (median: 24.31 and range of 2.9-252.5) compared to PCR (-) patients (median: 505 and range of 19.54-22,000), (P =0.01) (**Table.2**).

Table 2.Different laboratory values concerning PCR results

Variables	PCR-Positive (+) No 48 (37.5%)			PCR-Negative (-) No 80 (62.5%)			P-value
	Mean	SD	Range	Mean	SD	Range	
Age (year)	41.8	24.1	23-71	42.6	10.5	22:64	0.668
D-dimer (mg/l)	1.5	0.8	0.2-3.5	0.24	0.12	0.1-0.5	0.001*
PT (sec)	15.5	2.5	11.5-22	12.9	0.42	11.6-14	0.001*
PC (%)#	65.9	19.5	35-103.5	97.8	5.8	71-103.5	0.001*
INR	1.3	0.24	1-1.9	1	0.05	1-1.25	0.001*
Hb (gm/dl)	11	1.3	8-14	12.5	1.6	8-16	0.001*
RBCs (* 10^{12}/ul)	3.9	0.6	2.8-5.1	4.5	0.67	2.8-6	0.001*
RDW (%)#	17.7	2.2	11.3:22.4	16	2	11.4-22	0.001*
Monocyte (%)#	6.9%	4.2%	0.7%-24.7%	7.7%	4.5%	0.4-33	0.12
Monocyte (*10^3/µl)	0.7	0.5	0.03-2.3	0.7	0.5	0.03-3	0.98
Neutrophil (%)#	77.4%	14.2%	28.5%-95.2%	65.4%	17.7%	20%-94.6%	0.001*
Lymphocyte (%)#	14.5%	12%	1.9%-58.8%	24%	14.4%	4.1%-70.4%	0.001*
	Median		**Range**	**Median**		**Range**	
PLT count (*10^3/ul	311		73-849	251		71-503	0.001*
WBCs count (/µl)	10.5		2.9-81.4	9.7		1.4-49.6	0.24
Neutrophil (*10^3/µl)	7.915		1.28-127.8	5.8		0.7-46.5	0.1
Lymphocyte (*10^3/µl	0.895		0.2-9.3	1.8		0.3-5.2	0.04*
NLR	7.37		0.5-158	3.46		0.2-24	0.001*
MLR	0.56		0.03:4.7	0.333		0.03-3.5	0.001*
LMR	1.79		0.21-29.7	3		0.28-16.7	0.41
PLR	274.15		13.2-1475	116.7		50.8-878.1	0.001*
SII (*10^9/L)	0.0019		0.0001-0.07	0.0008		0.0008-0.004	0.01*
SIRS	4634		105-220889	2020		95-73172	0.05*
P2/MS	8.01		0.53- 185	5.13		0.19-64.39	0.001*
LCR	24.31		2.9-252.5	505		19.54-22,000	0.01*
CRP (mg/L)	43		8:90	4		0.2:54	0.001*

Student's t-test; # chi-Square; *Significant; SD = Standard Deviation; PT: Prothrombin Time; PC: Prothrombin concentration; INR: International Normalized Ratio; Hb: Hemoglobin; PLT: platelet count; RDW: red cell distribution width; WBCs: White Blood Cells; NLR: neutrophil-lymphocyte ratio; LMR: lymphocyte-monocyte Ratio; PLR: platelet-lymphocyte ratio, MLR: monocyte-lymphocyte ratio.

PCR (+) patients had a significantly higher prognostic index (PI) ($p < 0.001$) compared to PCR (-) patients. The [CRP value ≤ 10 and WBC ≤ 11.000/µl= score zero], were found in 3(5.8%), PCR (+) patients, and 44 (55.7%) PCR (-) patients, While the [CRP ≤ 10 and WBC > 11.000/µl = score 1] found in 22 (27.8%) PCR (-) patients. The [CRP > 10 and WBC ≤ 11.000/µl or CRP > 10 and WBC > 11.000/µl = score 2], was found in 48 (94.1%) PCR (+) patients, and 12 (15.2%) PCR (-) patients, (**Table.3**).

Table 3. CRP, WBCs and NPS values for all patients, PCR (+) and PCR (-) cases

No (%)		Total Patients (n = 128)	PCR-Positive (no = 48)	PCR-Negative (no = 80)	p-value
Prognostic index (PI)	CRP ≤ 10 and WBC ≤ 11.000/µl	45 (35.16%)	2(4.2%)	43(53.75%)	< 0.00001*
	CRP ≤ 10 and WBC > 11.000/µl	23 (17.97%)	0 (0%)	23 (28.75%)	
	CRP > 10 and WBC ≤11.000/µl	30 (23.43%)	23 (47.9%)	7 (8.75%)	
	CRP > 10 and WBC > 11.000/µl	30 (23.43%)	23 (47.9%)	7 (8.75%)	
Neutrophil Platelet Score (NPS)	Neutrophils ≤ $7.5*10^3$/µl and platelets ≤ $400*10^3$/µl	64 (44.6%)	16 (33.33%)	48 (60%)	0.004*
	Neutrophils > $7.5*10^3$/µl Or platelets > $400*10^3$/µl	56 (50%)	26 (54.17%)	30 (37.5%)	
	Neutrophils > $7.5*10^3$/µl and platelets > $400*10^3$/µl	8(5.4%)	6 (12.5%)	2 (2.5%)	

Chi-square -test; *: Significant; CRP = C Reactive Protein, WBC = White Blood Cells.

Moreover, Neutrophil platelet score (NPS), can distinguish between PCR (+) and (-) cases (P = 0.004), [Neutrophils ≤ 7.500/µl and platelets ≤ 400×10^3 /µl= score 0] were found in 16 (33.33%) PCR (+) patients, and 48 (60%) PCR (-) patients. While NPS [Neutrophils > 7.500/µl or platelets > 400×10^3 /µl = score 1] were found in 26 (54.17%) PCR (+) patients, and 30 (37.5%) PCR (-) patients, and NPS [Neutrophils > 7.500/µl and platelets > 400×10^3 /µl = score 2] found in 6 (12.5%) PCR (+) patients, and 2 (2.5%) PCR (-) patients, (**Table.3**).

In the Receiver Operating Characteristics (ROC) curves, the area under the curve (AUC) was statistically significant for the following laboratory parameters (**Table.4**, **Fig.1**), and the insignificant values are demonstrated in (**Fig. 2**).

Table 4. ROC Curve of Different Laboratory Values

Lab parameters	Area under curve	Sensitivity	Specificity	Cut-Off Value	P-value
D-dimer	0.979	92%	100%	0.55	0.0001*
PT	0.831	78%	95%	13.45	0.0001*
PC	0.092	2%	99%	101.75	0.0001*
INR	0.919	84%	88%	1.08	0.0001*
Hemoglobin	0.216	68%	13%	10.35	0.0001*
RBCs	0.228	42%	23%	3.95	0.0001*
Hematocrit	0.236	26%	44%	35.85	0.0001*
MCV	0.546	66%	48%	80.5	0.386
MCH	0.554	56%	65%	28.15	0.303
MCHC	0.516	56%	53%	34.25	0.766
RDW	0.736	78%	73%	16.45	0.0001*

PLT	0.601	58%	82%	292500	0.054
MPV	0.479	48%	63%	10.85	0.694
Platelet Mass	0.595	50%	85%	3243550	0.071
WBC/MPV	0.544	58%	62%	1005.16	0.405
PCT	0.605	44%	92%	0.35	0.045*
PDW	0.467	42%	64%	12.65	0.535
P/LCR	0.491	22%	91%	33.5	0.858
WBCs	0.543	48%	66%	11.27	0.415
Monocyte %	0.432	10%	93%	11.85	0.196
Monocyte Cells	0.467	12%	94%	1350	0.527
Neutrophil %	0.71	90%	39%	61.5	0.0001*
Neutrophil Count	0.603	68%	53%	6200	0.051
Lymphocyte %	0.287	4%	97%	52.9	0.0001*
Lymphocyte Count	0.258	6%	100%	5250	0.0001*
NLR	0.698	52%	82%	6.91	0.0001*
MLR	0.668	46%	83%	0.66	0.001*
LMR	0.332	4%	98%	16.8	0.001*
PLR	0.748	58%	93%	240.25	0.0001*
SII	0.724	66%	80%	1607250	0.0001*
SIRS	0.674	48%	85%	5209.1	0.001*
P2/MS	0.605	44%	85%	1329038939150	0.045*
LCR	0.051	26%	13%	61.86	0.0001*
CRP	0.95	96%	87%	13	0.0001*

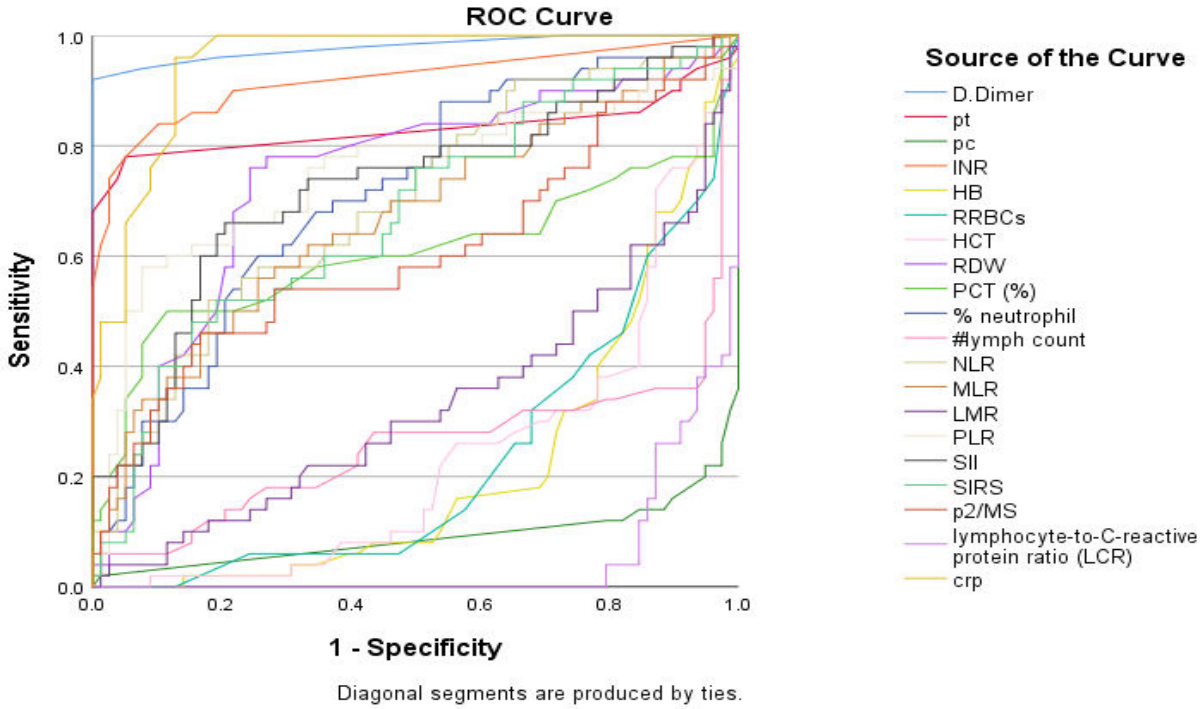

Fig.1. ROC curve for Significant Lab Values

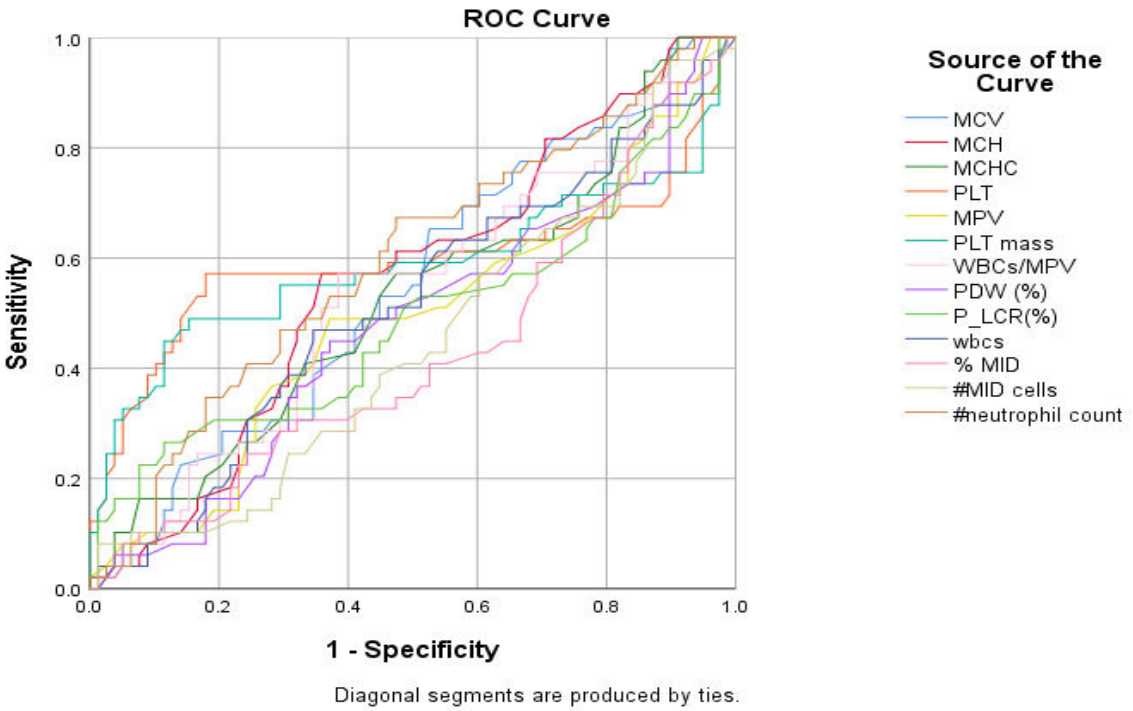

Fig. 2. ROC curve for Insignificant Lab Values

Discussion

There were 56 males (43.75%) with an average age of (43.43 ± 11.2 years), and 72 females (56.25%) with an average age of (41.46 ±10.6 years) (Figure 1).

This study included 128 patients with mild to moderate attending the emergency clinic at Qena University Hospital, the diagnosis of COVID-19 was made based on examination of the nasopharyngeal swabs for SARS-CoV-2 RT-PCR and chest computed tomography (CT) scans that were performed for all enrolled subjects, with a mean age ± SD of 42 ± 10.9 years. There were 56 males (43.75%), and 72 females (56.25%). All the patients (100%) had a fever, 92 (71.8%) patients had a cough, 80 (62.5%) patients had mild shortness of breath, and 71 (55.4%) patients had bone aches. On their chest CT, 100% of patients had a ground glass appearance. 50 (39.06%) patients reported positive COVID-19 PCR results, while 79 (61.7%) patients had negative PCR results.

This study reported the results of blood count, coagulation function, and infection-related biomarkers of adult patients with COVID-19.

In our study, The ROC curve of D-dimer has a sensitivity (92%) and specificity (100%) with an AUC of 0.979 (p = 0.0001) so it has an excellent predictive value and can be used in predicting the COVID-19 infection severity.

Studies have reported an increase in D-dimer and fibrinogen concentrations in the early stages of COVID-19 disease a 3 to 4-fold rise in D-dimer levels is linked to poor prognosis.

In addition, underlying diseases such as diabetes, cancer, stroke, and pregnancy may trigger an increase in D-dimer levels in COVID-19 patients (**Rostami and Mansouritorghabeh,**

2020). **Huang et al. (2020)** reported in a meta-analysis that an elevated serum CRP, PCT, D-dimer, and ferritin were associated with a poor outcome in COVID-19.

In our study, we found that the PT value for all patients was 14 ± 2 sec, The PT was significantly prolonged in PCR (+) patients, compared to PCR (-) patients (P= 0.001). The ROC curve for PT at a cutoff > 13.45 sec had a good sensitivity of 78%, and high specificity of 95%, and an AUC of 0.831 (p = 0.0001), so it can be used as an independent factor in predicting the COVID-19 severity. The PC was significantly lower in PCR (+) patients, compared to PCR (-) patients (P= 0.001) with a high specificity of 99% but is extremely poor sensitivity of 2% (p = 0.0001). **Tang et al. (2020)** reported that on average, PT is 1.9 s longer in fatal COVID-19 cases compared to non-fatal cases. Additionally, approximately 48% of fatal cases develop marked and progressive prolongation of PT by more than 6 s later in the disease course.

The mean INR was significantly higher in PCR (+) patients, compared to PCR (-) patients (P= 0.001). The ROC curve for INR at a cutoff > 1.08 has a high both sensitivity (84%) and specificity (88%) with an AUC of 0.919 (p = 0.0001). So, it can be used as an independent factor in predicting the severity of COVID-19. A meta-analysis of Thirty-eight studies of 9771 COVID-19 patients showed that prolonged INR values were significantly associated with COVID-19 severity and mortality. Both INR prolongation and D-dimer elevations can be useful in diagnosing COVID-19-associated coagulopathy and predicting clinical outcomes (**Zinellu et al., 2021**).

In our study, we found that the RBCs count for all patients was 4.3 ± $0.7*10^6$/ul. PCR (+) patients had significantly lower RBC count (3.9 ± 0.6 $*10^6$/ ul), compared to PCR (-) patients (4.5 ± 0.67 $*10^6$/ul), (P =0.001). The ROC curve for RBCs at a count < $3.95*10^6$/ul had a poor both sensitivity of 42%, a specificity of 23%, and an AUC of 0.228 (p = 0.0001). The mean Hb value for all patients was 12 ±1.7 gm/ dl. PCR (+) patients had significantly lower Hb (11 ± 1.3 mg/dl) compared to PCR (-) patients (12.5 ± 1.6 mg/dl), (P =0.001). The ROC curve for Hb with a cutoff < 10.35 gm/dl had a sensitivity of 68%, a specificity of 13%, and an AUC of 0.216 (p = 0.0001). **Yang et al., 2020** performed a small meta-analysis that found a significant correlation between COVID-19 severity and decreasing Hb concentrations. This could be explained by the fact that inflammatory cytokines reduce erythropoiesis (anemia of inflammation) (**Forget et al., 2019**).

In our study, PCR (+) patients had significantly higher RDW, compared to PCR (-) patients (P= 0.001). The ROC curve for RDW at a cutoff >16.45% had a sensitivity of 78%, a specificity of 73%, and an AUC of 0.736 (p = 0.0001). So RDW can be used as an independent factor in predicting COVID-19 severity. **Lippi et al., 2019** found that higher RDW levels have been linked to more serious illnesses and are assumed to reflect a proinflammatory condition. **Weiss et al., 2019** found that RDW progressively and significantly increased with the severity of the disease. Patients with COVID-19 have a higher mortality risk as RDW increases.

In our study, PCR (+) patients had significantly higher platelet count compared to PCR (-) patients (P=

0.001). The ROC curve for platelet counts at a cutoff > 292.500 *10^3/µl had a low sensitivity (58%) and good specificity (82%). PCR (+) patients had an insignificant difference in the MPV, compared to PCR (-) patients (P = 0.93). PCR (+) patients had significantly higher PCT compared to PCR (-) patients (P= 0.01). However, a meta-analysis involving 3433 COVID-19 patients reported that the MPV is often increased in patients with severe illness, especially in those at higher risk of dying **(Lippi et al., 2021**).

The Neutrophil platelet score (NPS), [Neutrophils ≤ 7.500/µl and platelets ≤ 400] were found in 58 (44.6%) of total patients, 16 (33.3%) PCR (+) patients, and 48 (60%) PCR (-) patients (p = 0.09). While NPS [Neutrophils > 7.500/µl or platelets > 400] were found in 56 (50%) of total patients, 26 (54.17%) PCR (+) patients, and 30 (37.5%) PCR (-) patients (p =0.05). But concerning NPS [Neutrophils > 7.500/µl and platelets > 400] were found in 8 (5.4%) total patients, 6 (12.5%) PCR (+) patients, and 2 (2.5%) PCR (-) patients (p = 0.09). However, NPS cannot differentiate between PCR (+) and PCR (-) cases.

In our study, we found that the mean Neutrophil percentage (%) for all patients was 70 ± 17.4%. The PCR (+) patients had a significantly higher Neutrophil % (77.4 ±14.2%) compared to PCR (-) patients (65.4±17.7%), (p= 0.001). The ROC curve for the Neutrophil % at a cutoff > 61.5% had an excellent sensitivity of 90% but a low specificity of 39% with an AUC of 0.71 (p = 0.0001).

In our study, we found that the PCR (+) patients had a significantly lower mean lymphocyte count compared to PCR (-) patients, (P=0.04). The ROC curve for lymphocyte count at a cutoff value of 5250 ×10^3/µl had a very poor sensitivity of 6% but with a high specificity (100%) with an AUC of 0.258 (p = 0.0001). The lymphocyte % for all patients was 20.4±14.3%. The PCR (+) patients had a significantly lower lymphocyte % (14.5± 12%) compared to PCR (-) patients (24±14.4 %), (p= 0.001). The ROC curve for the lymphocyte % < 52.9% count had a very poor sensitivity of 4% but a high specificity of 97% with an AUC of 0.287 (p = 0.0001).

In our study, Neutrophils up-regulation is accompanying with lymphopenia in patients with COVID-19 this was in line with **(Chen et al., 2019; Liu et al., 2020a**; **Wagner et al., 2020; Erdogan et al., 2021; Li et al., 2021; Peñaloza et al., 2021;Ben Jemaa et al., 2022)**

Liu et al. (2020b) settled that COVID-19-positive group had considerably higher lymphocyte counts than either the critical COVID-19-positive or admitted COVID-19-positive groups, indicating that lymphocyte levels were adversely correlated with the severity of the disease. Moreover, **Hachim et al. (2021)** stated that the presence of lymphopenia and lower absolute lymphocyte count (ALC) at the time of admission were associated with severe to critical COVID-19 illness.

Yao et al., 2020b reported that the lymphopenia, higher Neutrophil counts, and rates of Neutrophilia seen in individuals with severe COVID-19 were also seen in SARS-CoV 1 and MERS-CoV infections. The mechanism behind lymphopenia in ICU patients might be due to the direct attack by the virus on the lymphocytes or immune-mediated apoptosis of lymphocytes (**Stegeman et al., 2020**).

In our study, we hypothesized that inflammatory-based indices and prognostic scores correlate with disease severity.

In our study, The PCR (+) patients had a significantly higher NLR compared to PCR (-) patients (P=0.001). The ROC curve for NLR at a cutoff > 6.91 had a moderate sensitivity of 52% and a high specificity of 82% with an AUC of 0.698 (p = 0.0001).

In our study, The PCR (+) patients had a significantly higher mean MLR compared to PCR (-) patients (P=0.001). The ROC curve of MLR at cutoff > 0.66 had a low sensitivity of 46% but a high specificity of 83% with an AUC of 0.668 (p = 0.001).

In our study, we found that the PLR value for all patients was 218±199. The PCR (+) patients had a significantly higher mean PLR (342.5 ± 291.6) compared to PCR (-) patients (154 ± 127), (P=0.001). The ROC curve of PLR at a cutoff > 240.25 had a low sensitivity of 58% but a high specificity of 93% with an AUC of 0.748 (p = 0.0001).

In our study, The PCR (+) patients had a significantly higher mean SII compared to PCR (-) patients, (p=0.01). It had a moderate sensitivity of 66% and a high specificity of 80% with an AUC of 0.724 (p = 0.0001).

In our study, The PCR (+) patients had a significantly higher mean SIRS compared to PCR (-) patients (P=0.05). The ROC curve for SIRS at cutoff > 5209.1 had a low sensitivity of 48% and a high specificity of 85% with an AUC of 0.674 (p = 0.001).

In this study, we found that many inflammatory markers such as D-Dimer, CRP, platelets count, platelet mass index, MPV, PCT, MLR, INR, Neutrophile %, PLR, SII, NLR, P2/MS, SIRS, and prognostic index (CRP and WBCs count) were positively correlated with the disease, while others had significant negative correlations with the disease such as Hb, lymphocyte count, and percentage, LCR, LMR.

The prognostic index (PI) which entails the combination of CRP and white blood cell (WBC) count, categorizes patients into 3 levels of severity, in our study, PCR (+) patients had a significantly higher PI (p < 0.001) compared to PCR (-) patients. We found that 48 (94.1%) PCR (+) patients had a score of 2, and a score of 1 in 3(5.8%), while PCR (-) cases had a score of zero in 44 (55.7%) cases, a score of 1 in 22 (27.8%) cases, and a score of 2 in 12 (15.2%) cases.

In our study, the Neutrophil platelet score (NPS), cannot significantly differ between PCR (+) patients, and PCR (-) patients (p = 0.09).

The area under the curves (AUCs) for each marker signifies its performance, and D-Dimer had the highest AUC (0.979), followed by CRP (0.950), INR (0.919), PC (0.920), PT (0.831), Neutrophile% (0.710), and the calculated inflammatory indices PLR (0.748), SII (0724), NLR (0.698), SIRS (0.674), LMR (0.668), LCR (0.651), and P2/MS (0.605).

The current study has got some limitations, First, inflammation-based prognostic scores single determination only at baseline; a time-averaged score may be a more proper method for predicting clinical outcomes than a single determinant. Second is the small-sample size population.

Conclusion

several fundamental tests, including D-Dimer, CRP, INR, PC, PT, Neutrophil %, alongside various derived inflammatory indices such as PLR, SII, NLR, SIRS, LMR, LCR, P2/MS, and

prognostic index, exhibit noteworthy elevation in cases tested positive for Polymerase Chain Reaction (PCR) for COVID-19 in comparison to those tested negative for the virus. Combined assessments for multiple inflammatory scores are more accurate in predicting disease severity and offer extra clinical benefit.

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