The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90, Page 2716-2727

Clinical Characteristics, Risk Factors and Short-Term Outcomes of Severe Cases of COVID-19: A Retrospective Analytic Single Center Study

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ABSTRACT

Background & objectives: About 26% of hospitalised patients with COVID-19 have high mortality rates and up to 17% will require ventilatory support and critical care. We aimed to evaluate the clinical characteristics of patients with severe COVID-19, short- term outcomes (discharge, ventilator free, mechanical ventilation, dead) & their predictive values.

Methods: This retrospective analytic single center study included 80 hospitalized patients with severe COVID-19. Clinical data, complications and outcomes including admission to an ICU, use of non-invasive ventilation, and death, were analysed. The in-hospital complications were ARDS, pneumonia, hyperglycemia, shock, acute kidney injury. Levels of D-dimer, ferritin and lactate were measured. ROC analysis was used & p- value≤ 0.05 was considered statistically significant.

Results: The mean age was 53.45± 13.17years (range 18-77 years) and 46 (51%) were males. ARDS was the most common complication followed by hyperglycemia. Out of 80 patients; 52(65%) patients used CPAP and 25(31.25%) used non-invasive ventilator; 59 patients died with mortality rate (73.75%). There was a statistically significant association between lymphocyte count, neutrophil count and neutrophil- lymphocyte ratio (NLR), D- dimer, S. Ferritin and lactate with the development of ARDS. As predictors for mortality; the AUC for lactate, ferritin& D-dimer was [(0.902, 95%CI= 0.830-0.973, **p<0.001**), (0.800, 95%CI= 0.678-0.923, **p<0.001**), (0.757, 95%CI= 0.637-0.877, **p=0.001**)] respectively.

Conclusions: High levels of (S. Ferritin, D-dimer and NLR) are correlated with increased mortality in cases of severe Covid-19, and that the development of ARDS was associated with neutrophil& lymphocyte count, S. Ferritin, D-dimer and NLR.

Keywords: COVID-19; Complications; Outcomes; Severe.

INTRODUCTION

About 26% of widely used biomarker for evaluating the prognosis of many health-related problems. Recently, a study showed that NLR is elevated in patients with severe COVID-19, and its performance in the prognosis of severe disease should be further evaluated [(13)]. We aimed to evaluate the demographic, clinical, laboratory findings, treatment, the distribution of short-term outcomes (discharge, ventilator free, mechanical ventilation, dead), the distribution of complications (ARDS, AKI, acute liver injury, and septic shock) and to study the predictive value of different variables in prediction of different complications and outcome.

PATIENTS & METHODS

Study design& sample

From October 1, 2020, to December 31, 2020; this retrospective analytic single center study included 80 patients with confirmed COVID-19 pneumonia hospitalized at Al- Kindy hospital in Baghdad, Iraq. Diagnosis was based on interim guidance provided by the WHO (defined as a positive result on real-time reverse-transcriptase polymerase-chain-reaction assay of nasal or pharyngeal swab specimens). Reasons for admission were severe COVID-19 patients with other severe concomitant acute or chronic diseases. Demographic, epidemiologic, clinical, laboratory findings, complications, imaging studies, treatment, complications, and outcomes, including admissions to an intensive care unit (ICU), the use of non-invasive ventilation, and death, were analysed. The study was retrospective in nature and therefore patient consent was deemed not necessary.

Inclusion criteria

Based on the Diagnosis and Treatment Scheme for SARS- CoV-2 of Chinese (The Seven Edition), severe patients were diagnosed if one or more of following criteria were met: Dyspnea with respiratory rate (RR) ≥30 times/min, resting finger oxygen saturation ≤93%, and artery PaO2/FiO2 ≤300 mm Hg (1 mm Hg = 0.133 kPa). Regarding management, all patients received the same treatment according to the [The WHO Therapeutics and COVID-19: living guidelinese First version, published in 2nd of September 2020] [(14)].

Complications

The primary outcome of this study was the incidence of in-hospital complications, defined as organ-specific diagnoses occurring alone or in addition to any hallmarks of COVID-19 illness. All

Received: 03/09/2022
Accepted: 06/11/2022

complications were recorded so that total morbidity could be described, not just those directly attributable to COVID-19. Although COVID-19 is a multisystem disease, severe respiratory infection was considered characteristic of COVID-19 and was not regarded as a complication. Organ-specific complications were ARDS, pneumonia, hyperglycemia, sepsis, shock, AKI, pulmonary embolism, and pneumothorax. The occurrence of complications was determined from routine clinical records by local investigators with the exceptions of bloodstream infection and microbiologically confirmed bacterial pneumonia. These were defined based on recorded results from sputum, deep respiratory, or blood cultures and restricted to instances where clinically significant organisms were detected in the sample.

Definitions

- **Blood stream infection** was defined as growth of clinically significant bacteria (excluding coagulase-negative Staphylococci) or fungus recorded from blood culture or PCR of the blood. Results considered to represent contamination or colonisation were excluded [(15)].
- **ARDS** was described clinically or defined by being nursed in prone position and receiving noninvasive ventilation with a ratio of partial pressure of arterial oxygen to fraction of inspired air of 300 mm Hg or less, and should be suspected in those with progressive symptoms of dyspnea, an increasing requirement for oxygen, and alveolar infiltrates on chest imaging within 6 to 72 hours (and up to one week) of an inciting event [(16)].
- **AKI** was defined as a creatinine rise which corresponded to the Kidney Disease Improving Global Outcomes stage 1 or above (creatinine rise ≥1·5×baseline value or by ≥26·5 μmol/L). We did not incorporate urine output into this definition as this parameter is not universally recorded for all patients, particularly without critical care [(17)].
- **Hypertension** is considered if the recorded systolic blood pressure ≥ 140 mmHg and or diastolic blood pressure ≥ 90 mmHg, or if the patient was on current antihypertensive therapy [18].
- **Diabetes mellitus** is defined as the use of insulin or glucose-lowering medication on admission, or a diet for diabetes documented in medical history. The diagnosis of ‘‘undiagnosed DM’’ was made if patients with fasting glucose >7.0 mmol/L or random glucose >11.1 mmol/L together with an admission HbA1c >6.5% according to the latest American Diabetes Association (ADA) recommendations [(19)].
- **Coronary artery disease** is defined as the presence of angiographically proven coronary artery stenosis, history of myocardial infarction or coronary artery bypass grafting operation and presence of current myocardial ischemia by ischemic changes indicated electrocardiography [(20)].
- **Obesity** is defined as body mass index [BMI] over 30 [(21)].
- **CVA** is defines as a neurological deficit attributed to an acute focal injury of the central nervous system (CNS) by a vascular cause, including cerebral infarction, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage [SAH] [(22)].

Measurements

We also collected laboratory test results, including complete blood count (CBC), blood glucose levels, D-dimer levels, renal and liver function tests, serum ferritin and lactate. Blood samples were collected from each participant in plain tubes, and CBCs were measured on [CELL-DYN Emerald 22 Hematology Analyzer].

D-dimer level, renal and liver function tests and S. ferritin were measured using [Automatic clinical chemistry analyzer Yumizen C1200], and blood lactate was measured using [ABL800 FLEX blood gas analyzer].

- **Normal values (**used as references in this study):
- **Leukocyte count:** 4.5 to 11 x 10^9/L (SI)
- **Absolute neutrophil count (ANC):** 2 to 8.25 x 10^9/L (SI)
- **Lymphocyte count:** 1.5-4.0 x 10^9/L (SI)
- **Glucose, plasma (fasting):** 70 to 99 mg/dL
- **D-dimer, plasma=** <0.5 mg/L
- **Blood urea=** 15-40 mg/dl
- **Serum creatinine=** 0.72-1.26 mg/dl
- **Serum ferritin=** 24 to 336 ng/mL
- **Lactate, arterial blood=** less than 1.3 mmol/L

Ethical consent:

Informed consent was taken from the patient’s relatives or the patient himself when he was still conscious with keeping the patients ` records confidential in all stages of the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

Statistical analyses were performed by using SPSS software version 25.0 (SPSS, Chicago). Continuous data were presented as mean and standard deviation, and analysed with Student t-test.

Categorical variables were expressed as number and percentage and analysed with Chi-square test. Receiver operating characteristic curve (ROC) was used to evaluate the predictive value of different markers in prediction of different complications and outcome.

A p- value less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

Demographic and clinical characteristics of the patients

This study included 80 patients as cases with severe COVID-19. The mean age of the patients was 53.45± 13.17years (range 18-77 years), about half of them 46 (51%) were males. Hypertension and DM were common comorbidities accounting for 40 (50%) and 30 (37.5%) of the patients, respectively (Table I).

Table I: Demographic and clinical characteristics of the patients (n=80)

Variables	Values
Age, years	
Mean± SD*	53.45±13.17
Range	18-77
Gender	
Male	46 (51%)
Female	34 (49%)
Comorbidity	
None	21(26.25%)
Hypertension	40 (50%)
DM∞	30 (37.5%)
Obesity	19 (23.75%)
CAD**	9 (11.25%)
CVA§	5 (6.25%)
Others⸸	8 (10%)

*: Standard deviation; ∞: Diabetes mellitus; **: Coronary artery disease; §: Cerebrovascular accident; ⸸: Including 3 cases of malignancy, and one case of each of cerebral palsy, renal failure, heart failure, asthma, hypothyroidism.

Laboratory findings

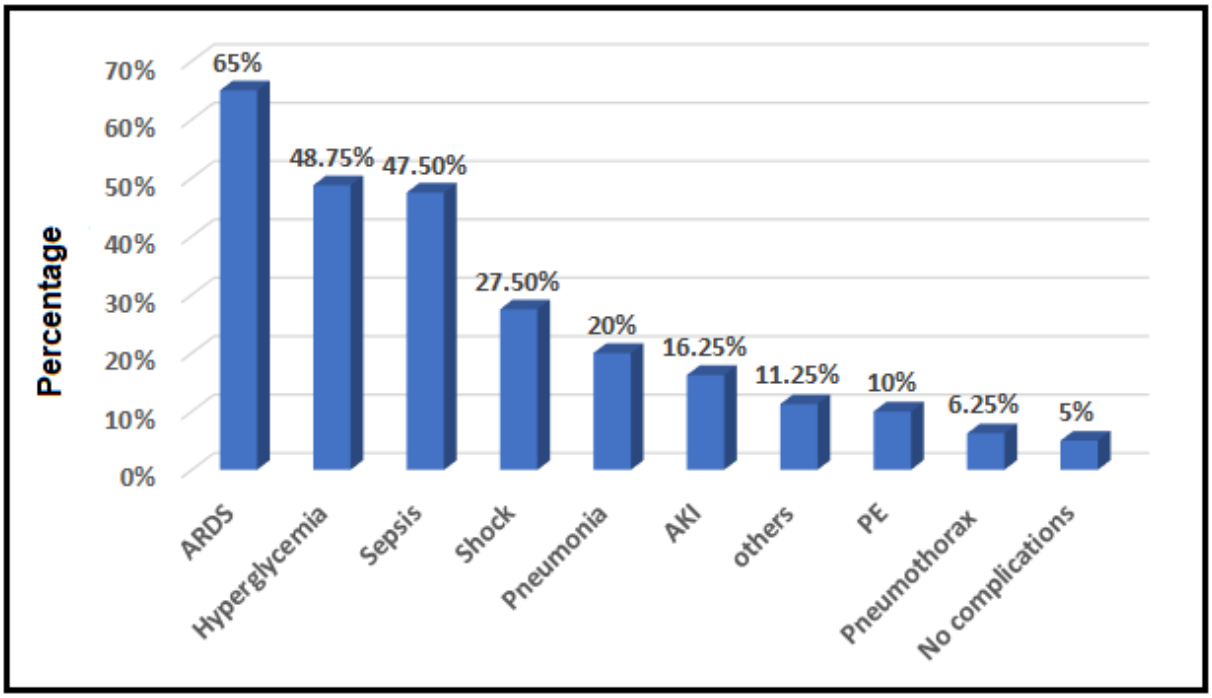
Table II: Laboratory findings of the patients (n=80)

Variables	Mean± SD*
WBC×10^3/ml	12.62± 2.46
Neutrophil×10^3/ml	12.22± 2.29
Lymphocyte×10^3/ml	0.77±0.16
NLR**	25.56± 2.23
PLT×10^3/ml∞	255.39± 12.84
D-dimer, µg/ml	0.15.6± 0.06
Serum ferritin, ng/ml	578.39± 99.18
Serum lactate, mmol/L	2.21± 0.28

*: Standard deviation; **: Neutrophil- lymphocyte ratio; ∞: Platelets count

Complications

As illustrated in graph I, ARDS was the most common complication in in the study sample found in 52 (65%) patients, followed by hyperglycemia in 39 (48.75%) patients and the those with no complications were 4 (5%).



Graph I: Complications developed in patients with severe COVID-19

Table III: Association demographic, and clinical factors with development of shock in patients with severe COVID-19

Variables	Without shock (n=58)	With shock (n=22)	P-value †
Age, years	60(18-8)	66(45-80)	**0.034**
Gender:			
Male	32(55.17%)	14(63.64%)	0.494
Female	36(62.09%)	8(36.36%)	
Comorbidity:			
None	16(27.59%)	5(22.73%)	0.659
Hypertension	27(46.55%)	13(59.09%)	0.317
DM*	21(36.21%)	9(40.91%)	0.698
Obesity	14(21.14%)	5(22.73%)	0.895
CAD★	3(5.17%)	6(27.27%)	**0.005**
CVA❖	2(3.45%)	3(13.64%)	0.093
Others	4(6.9%)	4(18.18%)	0.133
WBC×10^3/ml	13.3(4.37-26.6)	12.94(6.12-25.2)	0.829
Lymphocyte×10^3/ml	0.62(0.15-3.71)	0.6(0.16-2.16)	0.974
Neutrophil×10^3/ml	11.72(3.72-25.4)	11.73(5.52-23.25)	0.970
NLR∔	18.75(2.43-107.8)	19.2(4.0-81.25)	0.838
PLT×10^3/ml∞	241.35(44.4-586)	232.7(68-544)	0.635
D-dimer, µg/ml	2.96(0.22-8.41)	4.35(0.4-8.74)	0.647
S. Ferritin, ng/ml	673.5(39-916)	592.64(235.26-856.2)	0.594
S. Lactate, mmol/L	1.8(0.7-5.2)	2.35(0.6-6.5)	0.122

*: Diabetes mellitus; ★: Coronary artery disease; ❖: Cerebrovascular accident; ∔: Neutrophil- lymphocyte ratio; ∞: Platelet count; †: P-value ≤ 0.05 is statistically significant.

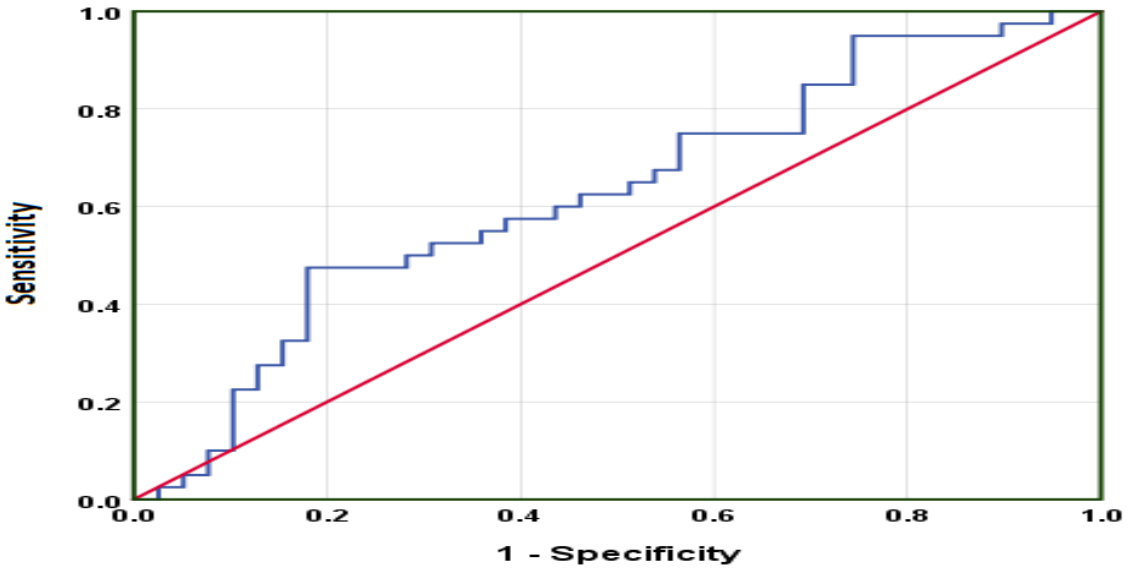
Table IV: Association between demographic, and clinical variables with development of hyperglycemia in patients with severe COVID-19.

Variables	Without hyperglycemia (n=41)	With hyperglycemia (n=39)	P-value †
Age, years	60 (18-80)	63 (43-80)	0.198
Gender:			
Male	24 (58.54%)	22 (56.41%)	0.848
Female	17 (41.46%)	17 (43.59%)	
Comorbidity:			
None	16 (39.02%)	5 (12.82%)	**0.008**
Hypertension	16 (39.02%)	24 (61.54%)	**0.044**
DM*	5 (12.2%)	25 (64.1%)	**<0.001**
Obesity	9 (21.95%)	10 (25.64%)	0.698
CAD★	5 (12.2%)	4 (10.26%)	0.784
CVA❖	3 (7.32%)	2 (5.13%)	0.686
Others	4 (9.76%)	4 (10.26%)	0.941
WBC×10^3/ml	13.47 (6.12-24.7)	12.87 (4.37-26.6)	0.503
Lymphocyte×10^3/ml	0.59 (0.15-1.76)	0.64 (0.16-3.71)	0.593
Neutrophil×10^3/ml	11.95 (4.86-23.25)	11.1(3.72-25.4)	0.410
NLR∞	20.0 (4.05-107.8)	17.21 (2.43-87.56)	0.597
PLT×10^3/ml❖	230 (44.4-544)	240 (63.4-586)	0.510
D-dimer, µg/ml	2.85 (0.22-8.74)	4.2 (0.29-8.05)	0.294
S. Ferritin, ng/ml	679.4 (97-856.2)	623.3 (39.916)	**0.05**
S. Lactate, mmol/L	2.0 (0.6-4.8)	1.7 (0.7-6.5)	0.992

*: Diabetes mellitus; ★: Coronary artery disease; ❖: Cerebrovascular accident; ∞: Neutrophil- lymphocyte ratio; ❖: Platelet count; †: P-value ≤ 0.05 is statistically significant.

Predictors for complications

For serum ferritin as a predictor for the development of hyperglycemia, the area under the curve (AUC) was (0.626, 95%CI= 0.502-0.750, **p=0.050**). The sensitivity and specificity of the test at cut off value of S. Ferritin= 675.85 ng/ml were 58% and 61%, respectively as shown in graph II.



Graph II Receiver operating characteristic (ROC) curve for S. ferritin as predictor for hyperglycemia in patients with severe COVID-19.

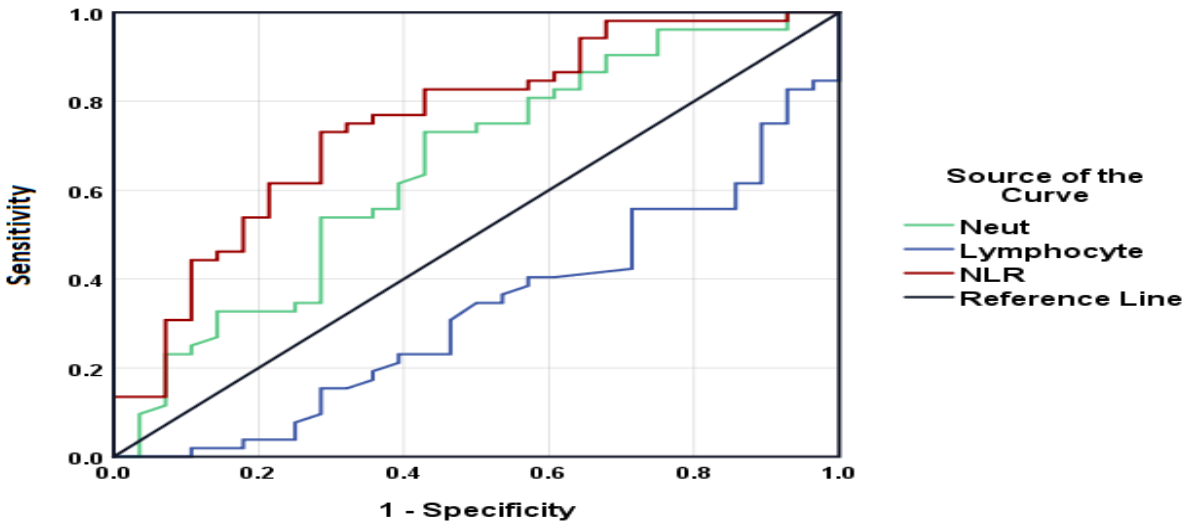
Table V: Association between demographic, and clinical variables with development of adult respiratory distress syndrome in patients with severe COVID-19.

Variables	**Without ARDS*** **(n= 28)**	**With ARDS (n=62)**	**P-value †**
Age, years	62 (35-80)	63(18-80)	0.705
Gender			
Male	14 (50%)	32(51.61%)	0.319
Female	14 (50%)	20(32.36%)	
Comorbidity			
None	18 (64.29%)	41 (66.13%)	0.158
Hypertension	13 (46.51%)	27 (43.55%)	0.639
DM★	13 (46.51%)	17 (27.42%)	0.226
Obesity	6 (21.43%)	13 (20.97%)	0.720
CAD❖	2 (7.14%)	7 (11.29%)	0.394
CVA❖	1 (3.57%)	4 (6.45%)	0.468
Others	3 (10.71%)	5 (8.06%)	0.876
WBC×10^3/ml	12.34 (4.37-26.6)	13.53 (6.12-25.2)	0.178
Lymphocyte×10^3/ml	0.68 (0.26-3.71)	0.54 (0.15-2.16)	**0.011**
Neutrophil×10^3/ml	10.32 (3.72-25.4)	12.42 (5.27-23.25)	**0.025**
NLR∞	11.92 (2.43-50.87)	23.0 (4.04-107.8)	**<0.001**
PLT×10^3/ml‡	262 (125-455)	221.2 (44.4-586)	0.065
D-dimer, µg/ml	1.62 (0.28-8.05)	4.4 (0.22-8.74)	**0.023**
S. Ferritin, ng/ml	454.1 (39-810.3)	676.7 (235.3-916)	**<0.001**
S. Lactate, mmol/L	1.0 (0.7-6.5)	2.4 (0.6-5.6)	**<0.001**

*: Adult respiratory distress syndrome; ★: Diabetes mellitus; ❖: Coronary artery disease; ❖: Cerebrovascular accident; ∞: Neutrophil- lymphocyte ratio; ‡: Platelet count; †, P-value ≤ 0.05 is statistically significant.

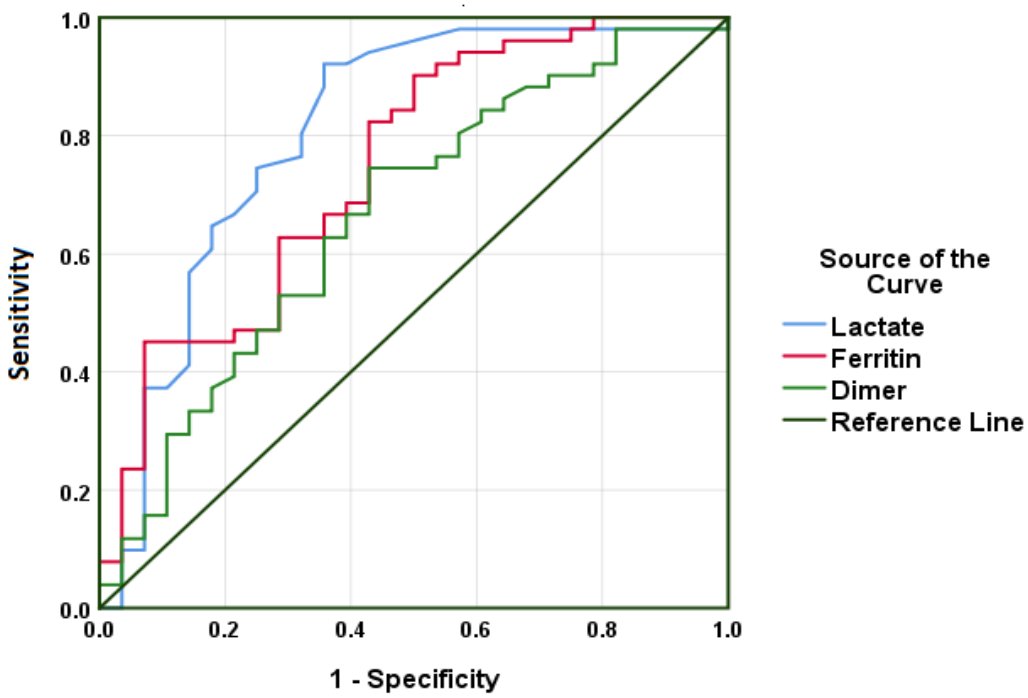
As predictors for the development of ARDS, the AUC of neutrophil count was (0.651, 95%CI= 0.521-0.781, **p=0.009**). The sensitivity and specificity of the test at cut off value of neutrophil= 10.51 $\times 10^3$/ml were 73% and 67%, respectively.

For lymphocyte count, the AUC was (0.678, 95%CI= 0.556-0.799, **p<0.001**). The sensitivity and specificity of the test at cut off value of lymphocyte= 0.6 $\times 10^3$/ml were 71% and 58%, respectively. For NLR, the AUC was (0.754, 95%CI= 0.641-0.867, **p<0.001**). The sensitivity and specificity of the test at cut off value of NLR= 14.66 were 77% and 64%, respectively as shown in graph III.



Graph III: Receiver operating characteristic (ROC) curve for neutrophil and lymphocyte count and neutrophil-lymphocyte ratio as predictors of adult respiratory distress syndrome in patients with severe COVID-19.

For serum lactate level, the AUC was (0.807, 95%CI= 0.696-0.919, **p<0.001**). The sensitivity and specificity of the test at cut off value of lactate= 1.65 mmol/L were 75% for both. For serum ferritin level, the AUC was (0.746, 95%CI= 0.631-0.862, **p< 0.001**). The sensitivity and specificity of the test at cut off value of ferritin= 613.5 ng/ml were 68% and 61%, respectively. For D-dimer level, the AUC was (0.665, 95%CI= 0.538-0.792, **p=0.016**). The sensitivity and specificity of the test at cut off value of D-dimer= µg/ml were 75% and 57%, respectively as shown in graph IV.



Graph IV: Receiver operating characteristic (ROC) curve for serum level of lactate, ferritin and D-dimer as predictors of adult respiratory distress syndrome in patients with severe COVID-19.

Table VI: Association between demographic, and clinical variables with development of acute kidney injury in patients with severe COVID-19.

Variables	Without AKI* (n=67)	With AKI (n=13)	P-value †
Age, years	63 (35-80)	65 (18-78)	0.938
Gender:			
Male	38 (56.72%)	8 (61.54%)	0.748
Female	29 (43.28%)	5 (38.46%)	
Comorbidity:			
None	51 (76.12%)	8 (61.54%)	0.274
Hypertension	34 (50.75%)	6 (46.15%)	0.762
Diabetes mellitus	27 (40.3%)	3 (23.08%)	0.240
Obesity	17 (25.37%)	2 (15.38%)	0.439
CAD★	8 (11.94%)	1 (7.69%)	0.657
CVA❖	2 (3.0%)	3 (23.08%)	**0.006**
Others	6 (8.96%)	2 (15.38%)	0.479
WBC×10^3/ml	13.2 (4.37-26.6)	12.2 (6.15-24.7)	0.809
Lymphocyte×10^3/ml	0.6 (0.15-3.71)	0.54 (0.16-1.69)	0.181
Neutrophil×10^3/ml	11.8 (3.72-25.4)	10.7 (5.62-23.25)	0.990
NLR∞	18.48 (2.43-107.8)	21.75 (8.69-101.8)	0.208
PLT×10^3/ml‡	231.7 (44.4-586)	280.5 (61.4-464.8)	0.584
D-dimer, µg/ml	3.1(0.22-8.41)	5.23 (1.13-8.74)	0.086
Ferritin, ng/ml	649.7 (39-916)	672.9 (444.7-856.2)	0.088
Lactate, mmol/L	1.9 (0.7-6.5)	2.2 (0.6-3.9)	0.567

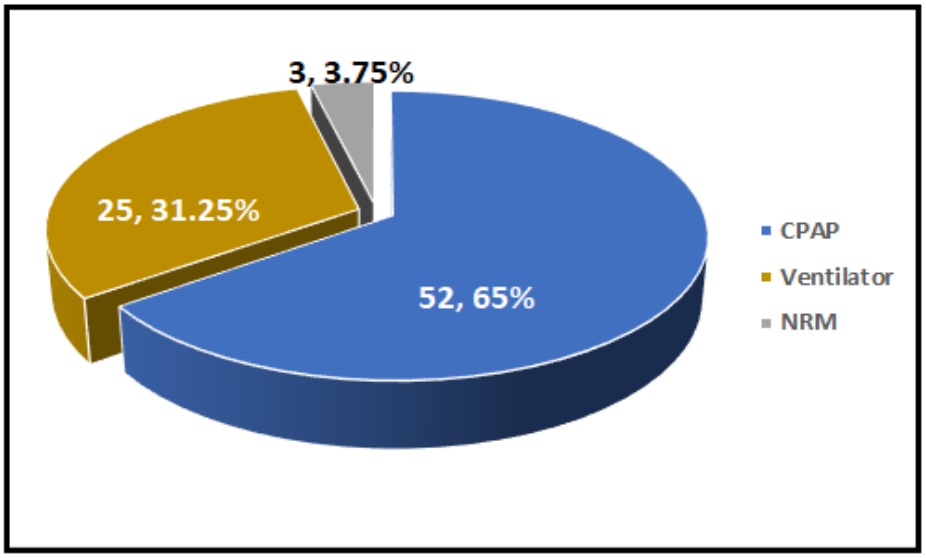
*: Acute kidney injury; ★: Coronary artery disease; ❖: Cerebrovascular accident; ∞: Neutrophil- lymphocyte ratio; ‡: Platelet count; †: P-value ≤ 0.05 is statistically significant.

Table VII: Association between demographic, and clinical variables with development of sepsis in patients with severe COVID-19.

Variables	Without sepsis (n=42)	With sepsis (n=38)	P-value †
Age, years	60 (31-80)	65 (18-80)	0.116
Gender:			
Male	25 (59.52%)	21 (55.26%)	0.700
Female	17 (40.48%)	17(44.74%)	
Comorbidity:			
None	13 (30.95%)	8 (21.05%)	0.315
Hypertension	21 (50%)	19 (50%)	1.0
DM*	17 (40.48%)	13 (34.2%)	0.563
Obesity	8 (19.05%)	11 (28.95%)	0.299
CAD★	3 (7.14%)	6 (15.79%)	0.222
CVA∞	0 (0%)	5 (13.16%)	**0.015**
Others	4 (9.52%)	4 (10.53%)	0.881
WBC×10^3/ml	12.73 (4.37-26.6)	14.2 (6.26-24.7)	0.111
Lymphocyte×10^3/ml	0.62 (0.16-3.71)	0.6 (0.15-2.16)	0.791
Neutrophil×10^3/ml	10.9 (3.72-25.4)	12.72 (5.27-23.25)	0.056
NLR❖	15.16 (2.43-87.56)	20.26 (4.04-107.8)	0.138
PLT×10^3/ml‡	242.35(63.4-464.8)	230.5 (44.4-586)	0.870
D-dimer, µg/ml	2.97 (0.28-8.05)	4.15 (0.22-8.74)	0.441
Ferritin, ng/ml	607.97 (39-843.5)	685.3 (235.3-916)	**0.02**
Lactate, mmol/L	1.8 (0.6-5.2)	2.25 (0.8-6.5)	**0.05**

*: Diabetes mellitus; ★: Coronary artery disease; ∞: Cerebrovascular accident; ❖: Neutrophil- lymphocyte ratio; ‡: Platelet count; †: P-value ≤ 0.05 is statistically significant.

As illustrated in graph V, out of 80 patients with severe COVID-19, there was 52(65%) patients used Continuous Positive Airway Pressure (CPAP) during admission, and 25(31.25%) used non-invasive ventilator, while only 3(3.75%) used non- rebreather mask (NRM) during admission.



Graph V Mode of ventilation.

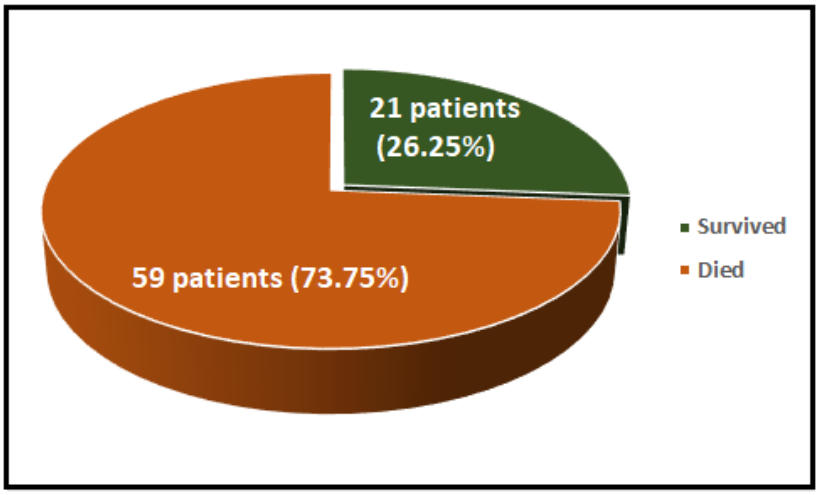
Table VIII: Association between demographic, and clinical variables with the mode of ventilations in patients with severe COVID-19

Variables	**CPAP*** **(n=52)**	**Ventilator (n= 25)**	**NRM**** **(n=3)**	**P-value †**
Age, years	64.5(31-8)	59(18-78)	53(35-70)	0.346
Gender:				0.316
Male	29(55.77%)	14(56%)	3(100%)	
Female	23(44.23%)	11(44%)	0(0%)	
Comorbidity:				
None	12(23.31%)	7(28%)	2(66.67%)	0.242
Hypertension	3(5.77%)	9(36%)	1(33.33%)	0.172
Diabetes mellitus	24(46.15%)	6(24%)	0(0%)	0.067
Obesity	11(21.15%)	8(32%)	0(0%)	0.356
CAD★	6(11.54%)	3(12%)	0(0%)	0.819
CVA∞	3(5.77%)	2(8%)	0(0%)	0.839
Others	7(13.46%)	1(4%)	0(0%)	0.363
WBC×10^3/ml	13.14(4.37-25.2)	13.2(6.12-24.7)	13.1(10.2-26.6)	0.862
Lymphocyte×10^3/ml	0.65(0.16-3.71)	0.54(0.15-1.76)	1.03(0.5-2.5)	0.273
Neutrophil××10^3/ml	11.72(3.72-23.1)	11.95(5.27-23.25)	10.24(8.34-25.4)	0.737
NLR❖	17(2.43-107.8)	20.63(8.81-63.47)	8.1(4.11-50.8)	0.299
PLT×10^3/ml‡	248.9(61.4-586)	202(44.4-544)	176(125-331)	0.061
D-dimer, µg/ml	3.43(0.22-8.05)	4.6(0.4-8.74)	1.1(0.29-4.11)	0.204
S. Ferritin, ng/ml	651.6(39-834)	676.7(336-916)	513.4(166.9-680.8)	0.219
S. Lactate, mmol/L	1.7(0.6-6.5)	2.2(0.8-5.2)	1.6(0.8-1.9)	0.210

*: Continuous positive airway pressure; **: Non-rebreather mask; ★: Coronary artery disease; ∞: Cerebrovascular accident; ❖: Neutrophil- lymphocyte ratio; ‡: platelet count; †: P-value ≤ 0.05 is statistically significant.

3.5 Outcomes

As illustrated in Graph VI, out of 80 patients with severe COVID-19, 59 patients died with mortality rate (73.75%), and 21 patients survived which represents (26.25%).



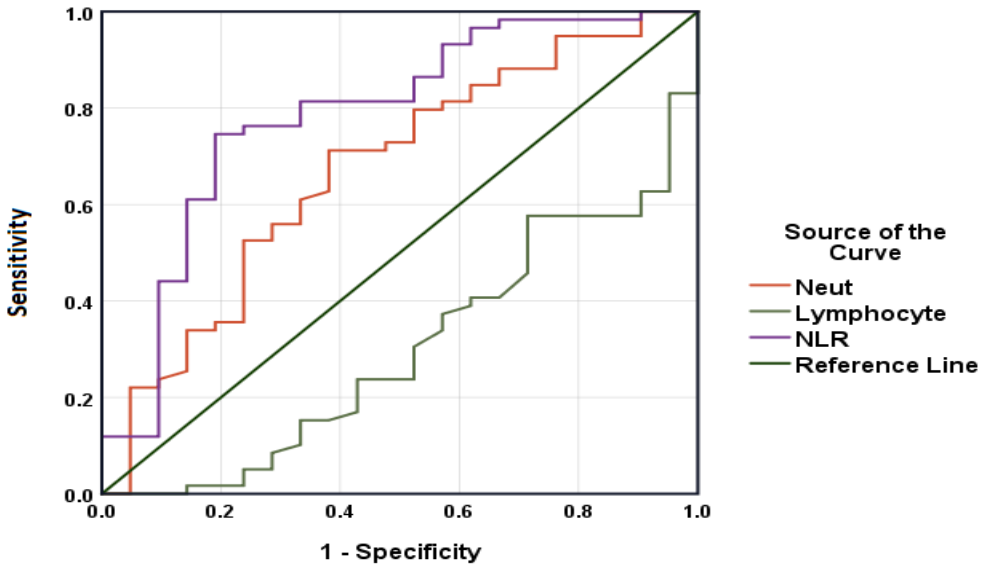
Graph VI: Outcomes of patients with severe COVID-19

Table VIIII: Association between demographic, and clinical variables with outcome in patients with severe COVID-19.

Variables	**Died (n=59)**	**Survived (n=21)**	**P-value †**
Age, years	63(18-80)	57(35-80)	0.665
Gender:			
Male	37(62.71%)	9(42.86%)	0.114
Female	22(37.29%)	12(57.14%)	
Comorbidity:			
None	13(22.03%)	8(38.1%)	0.151
Hypertension	32(54.24%)	8(38.1%)	0.204
Diabetes mellitus	22(37.29%)	8(38.1%)	0.948
Obesity	16(27.12%)	3(14.29%)	0.235
CAD*	9(15.25%)	0(0%)	0.057
CVA★	5(8.47%)	2(9.52%)	0.168
Others	6(10.17%)	8(38.1%)	0.932
WBC×10^3/ml	13.51(6.12-25.2)	12.0(4.37-26.6)	0.147
Lymphocyte×10^3/ml	0.55(0.15-2.16)	0.82(0.29-3.71)	**0.006**
Neutrophil×10^3/ml	12.27(5.27-23.25)	10.24(3.72-25.4)	**0.021**
NLR∞	21.75(4.0-107.8)	11.4(2.43-50.87)	**<0.001**
PLT×10^3/ml❖	230(44.4-586)	262(125-455)	0.233
D-dimer, µg/ml	4.6(0.22-8.74)	1.3(0.28-8.05)	**0.001**
Serum ferritin, ng/ml	675.6(235.3-916)	367(39-810.3)	**<0.001**
Serum lactate, mmol/L	2.4(0.6-6.5)	0.9(0.7-2.2)	**<0.001**

*: Coronary artery disease; ★: Cerebrovascular accident; ❖: Platelet count; ∞: Neutrophil- lymphocyte ratio; †: P-value <0.05 is statistically significant.

As predictors for mortality, the AUC of neutrophil count was (0.671, 95%CI= 0.532-0.809, **p=0.021**). The sensitivity and specificity of the test at cut off value of neutrophil= 10.61 ×10^3/ml were 71% and 62%, respectively.
For NLR, the AUC was (0.785, 95%CI= 0.663-0.908, **p<0.001**). The sensitivity and specificity of the test at cut off value of NLR= 13.65 were 81% and 67%, respectively.
For lymphocyte count, the AUC was (0.701, 95%CI= 0.574-0.828, **p=0.006**). The sensitivity and specificity of the test at cut off value of lymphocyte= 0.62 ×10^3/ml were 67% and 59%, respectively as shown in graph VII.

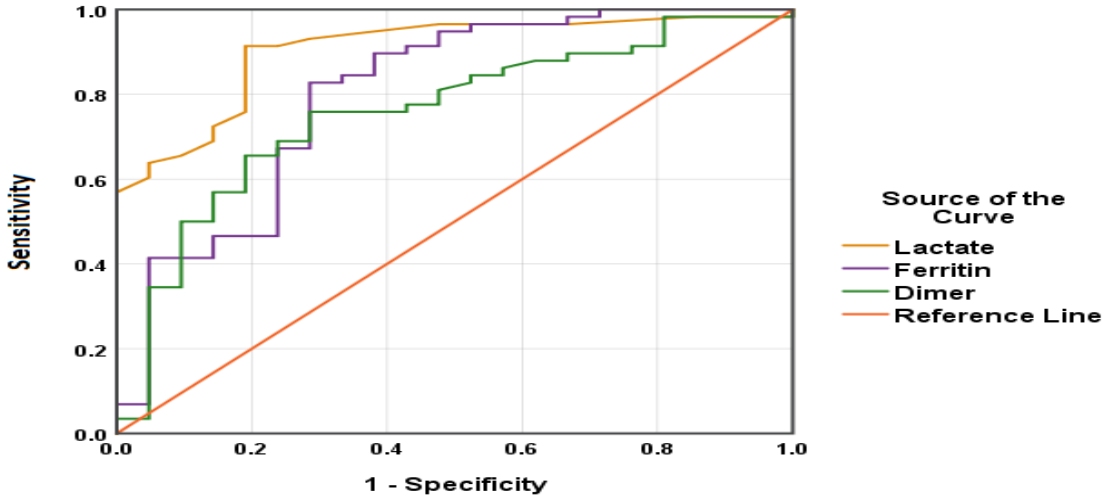


Graph VII Receiver operating characteristic (ROC) curve for neutrophil and lymphocyte count and neutrophil-lymphocyte ratio (NLR) as predictors for mortality in patients with severe COVID-19.

For S. Lactate level, the AUC was (0.902, 95%CI= 0.830-0.973, **p<0.001**). The sensitivity and specificity of the test at cut off value of lactate= 1.25 mmol/L were 90% and 81%, respectively.

For S. Ferritin level, the AUC was (0.800, 95%CI= 0.678-0.923, **p<0.001**). The sensitivity and specificity of the test at cut off value of ferritin= 526 ng/ml were 83% and 71%, respectively.

For serum D-dimer level, the AUC was (0.757, 95%CI= 0.637-0.877, **p=0.001**). The sensitivity and specificity of the test at cut off value of D-dimer = 1.76 µg/ml were 76% and 71%, respectively as shown in graph VIII.



Graph VIII: Receiver operating characteristic (ROC) curve for serum level of lactate, ferritin and D-dimer as predictors for mortality in patients with severe COVID-19.

DISCUSSION

In this single center study; we have evaluated 80 hospitalized patients with severe COVID-19 and studied their related risk factors and laboratory investigations. The mean age of the patients was 53.45± 13.17years (range 18-77 years), about half of them 46 (51%) were males. Hypertension and DM were common comorbidities accounting for 40 (50%) and 30 (37.5%) of the patients, respectively.

In our study, the most common complication was ARDS (65%), followed by hyperglycemia (48.75%), while only (5%) survived without complications. In another single canter experience, (Nowak B, et al. 2020) in Poland, it showed that ppneumonia was diagnosed in (51.5%), while ARDS was found in (24.3%), acute kidney injury in (10.1%), and septic shock in (10.1%) [(23)].

In another study published in (THE LANCET 2020) in Wuhan/ China, the common complications were ARDS [29%], followed by anemia [15%], acute cardiac injury [12%], and secondary infection [10%] [3]. In another study done by (Yang X, et al. 2020) in Wuhan, China, ARDS was encountered in 65% of patients [(4)].

In our study, 39 (48.75%) patients had hyperglycemia during admission, only 5 of them (12.82%) had no previous history of DM, and 25 patients (64.1%) had history of DM. This can be attributed to the effect of COVID-19 itself or due to the use of steroid during admission. In a single center study done in Pisa, Italy, from 271 patients, 122 (45%) had hyperglycemia during admission, 56 patients (20.7%) had history of diabetes and 66 patients (24.3%) had no history of DM before admission [(24)].

In another study done in the United States, out of 1122 patients admitted with severe Covid-19 in 88 US hospitals, 451 patients (40%) had hyperglycemia during admission, 194 patients (17.3%) of total population had pervious history of DM and 257 patients (23%) of total population had no history of DM before admission [(25)].

In our study, there was a statistically significant association between development of ARDS in patients with severe COVID-19 and neutrophil and lymphocyte count, and with both ferritin and d-dimer levels. Similar results were found in a study done in Wuhan, China [(26)].

In our study, NLR was found to be statistically associated with the development of ARDS in patients with severe COVID-19. Similar results were found in study by (Ma A, et al. 2020) [(27)].

In our study, AKI was found in 16.25% of patients with severe COVID-19, while in another study done in Wuhan, China, AKI was found in 29% of patients [(4)]. In our study, among the patients who developed AKI, (46.15%) of patients had history of hypertension, and (23.08%) of patients had history of DM, while only (7.69%) of patients with hx of CAD developed AKI during admission.

In a study done by (Hirsch JS, et al. 2020) who found that (36.6%) developed AKI during their hospitalization, and that (64.8%) had hx of hypertension, and (41.6%) had hx of DM, and (14.5%) had hx of CAD [(28)].

In another systematic review and meta-analysis done by (Robbins-Juarez S, et al.) from December 1, 2019 to May 24, 2020, the Prevalence of AKI was 17%, and the the prevalence of diabetes was 17% (range, 6%–33.3%) and of hypertension was 33% (range, 11.5%–64.7%) [(29)].

In our study, 65% of patients used portable CPAP during admission, and 31% of patients used non-invasive ventilator, while only 3.7% used NRM during admission. In another study done in Wuhan/ China; 66% of patients used nasal cannula during admission, 24% used Non-invasive ventilation or high-flow nasal cannula, while 5% used Invasive mechanical ventilation and 5% of patients were put on Invasive mechanical ventilation and ECMO [(3)].

While in another study; it was found that 63.5% of patients used high flow nasal cannula during admission, 71% of patients were put on mechanical ventilation, 56% of them used the non-invasive mode of ventilation while 42% used needed invasive mechanical ventilation, and 11.5% were treated with prone position ventilation, while 11.5% were put on ECMO [(4)].

Our study included only patients hospitalized with severe COVID-19, which may explain why other modalities of ventilation (like simple-face mask and non-rebreather mask) was not used in our patients.

In our study, the mortality rate was (73.75%), which is higher than a study done in Poland, in which the overall mortality was 26.3% (n = 46), and Seventeen out of 29 patients admitted to the intensive care unit died (mortality, 58.6%) [(23)].

In another study established in UK which included more than 20000 patients; 41% (8199/20 133) of patients were discharged alive, 26% (5165/20 133) died, and 34% (6769/20 133) continued to receive care at the reporting date.17% (3001/18 183) required admission to high dependency or intensive care units; of these, 28% (826/3001) were discharged alive, 32% (958/3001) died, and 41% (1217/3001) continued to receive care at the reporting date. The difference in mortality between our study and other studies can be attributed to the fact that; until the period of our study; our hospitals lack some advanced modalities of ventilation like high-flow nasal cannula and ECMO which can put an impact on survival beside the fact that early in the pandemic, endotracheal intubation was not an option for patients with severe COVID-19 and respiratory failure.

In our study, (54.24%) of non-survived patients had history of hypertension, (37.29%) of them had history of DM, and (27.12%) were obese.

While in another study done by (Zhou F, et al. 2020) in Wuhan/ China, 48% of non-survived patients had history of hypertension, and 31% had history of DM, while 24% had history of DM (obesity was not considered risk factor in this study) [(11)]. Another study done by (Williamson EJ, et al. 2020), 34.3% of non-survived patients had history of hypertension, 9.9% had history of DM which was further classified according to HbA1c to (6% to those with HbA1c <58 mmol, 2.8% those with HbA1c >58 mmol, and 1.1% with no recent HbA1c). 21.8% of non-survived patients in this study were classified as obese [(8)].

In our study, higher levels of D-dimer, ferritin and NLR were associated with increase mortality in patients with severe Covid-19, and there was a statistically significant association between neutrophil count, lymphocyte count and NLR with mortality in patients with severe covid-19. Similar results were found in a study by (Kermali A, et al. 2020) [(13)].

In this single center study; we concluded that high levels of inflammatory markers (ferritin, d-dimer and NLR) are correlated with increased mortality in patients with severe Covid-19, and that the development of ARDS (which is the most common complication encountered in our study) was associated with other immune-inflammatory parameters such as neutrophil count, lymphocyte count, ferritin, D-dimer and NLR.

CONCLUSION: in this study concluded that high levels of (S. Ferritin, D-dimer and NLR) are correlated with increased mortality in cases of severe Covid-19, and that the development of ARDS was associated with neutrophil& lymphocyte count, S. Ferritin, D-dimer and NLR.

Sources of funding: This research did not receive funding.

Conflict of interest: The authors declare no conflict of interest.

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