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The prognostic value of biomarker levels and chest imaging in patients with COVID-19 presenting to the emergency department

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ABSTRACT

Introduction: We aimed to compare the prognostic value of a quantitative CT severity score with several laboratory parameters, particularly C-reactive protein, Procalcitonin, Neutrophil to lymphocyte ratio, D-dimer, ferritin, lactate dehydrogenase, lactate, troponin and B-type Natriuretic Peptide in predicting in-hospital mortality.
Methods: This was a retrospective chart review study of COVID-19 patients who presented to the Emergency Department of a tertiary care center between February and December 2020. All patients ≥18 years old who tested positive for the COVID-19 real-time reverse transcriptase polymerase chain reaction and underwent CT imaging at presentation were included. The primary outcome was the prognostic ability of CT severity score versus biomarkers in predicting in-hospital mortality.
Results: The AUCs were: D-dimer (AUC: 0.67 95% CI = 0.57–0.77), CT severity score (0.66, 95% CI = 0.55–0.77), LDH (0.66, 95% CI = 0.55–0.77), Pro-BNP (0.65, 95% CI = 0.55–0.76), NLR (0.64, 95% CI = 0.53–0.75) and troponin (0.64, 95% CI = 0.52–0.75). In the stepwise logistic regression, age (OR = 1.07 95% CI = 1.05–1.09), obesity (OR = 2.02 95% CI = 1.25–3.26), neutrophil/lymphocyte ratio (OR = 1.02 95% CI = 1.01–1.04), CRP (OR = 1.01 95% CI = 1.004–1.01), lactate dehydrogenase (OR = 1.003 95% CI = 1.001–1.004) and CT severity score (OR = 1.17 95% CI = 1.12–1.23) were significantly associated with in-hospital mortality.
Conclusion: In summary, CT severity score outperformed several biomarkers as a prognostic tool for covid related mortality. In COVID-19 patients requiring lung imaging, such as patients requiring ICU admission, patients with abnormal vital signs and those requiring mechanical ventilation, the results suggest obtaining and calculating the CT severity score to use it as a prognostic tool. If a CT was not performed, the results suggest using LDH, CRP or NLR if already done as prognostic tools in COVID-19 as these biomarkers were also found to be prognostic in COVID-19 patients.

1. Introduction

1.1. Background

Coronavirus disease 2019 (COVID-19) emerged in Wuhan City, Hubei Province, China in December 2019. Since then, it has spread across every continent, becoming a global health problem, and causing tremendous burden on the healthcare system. As of October 2021, it is estimated that 241 million people have been infected and 4.9 million have died from the novel coronavirus (1). It mainly manifests with nonspecific symptoms such as fever, cough, shortness of breath, and fatigue (2). However, in more severe cases it can lead to acute respiratory distress syndrome (ARDS), increased risk of venous thromboembolism (VTE), intensive care (ICU) admissions, superimposed bacterial infections, cardiac injury and death (3,4). The current medical literature suggests that a variety of patient factors could prove useful in predicting disease severity and patient outcomes of COVID-19. Marin et al. highlighted several demographic, biochemical, radiographic, clinical, hematologic, and immunologic factors that could be used to assess the severity of COVID-19 and predict mortality among Covid-19

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patients (5). Laboratory parameters such as neutrophil to lymphocyte ratio (NLR), procalcitonin (PCT), C-reactive protein (CRP), D-dimer, ferritin, lactate dehydrogenase (LDH), lactate, troponin and B-type Natriuretic Peptide (Pro-BNP) have been studied in COVID-19 patients (6-14). They have been shown to be associated with disease severity, mortality and hospital complications (ARDS, need for invasive and noninvasive mechanical ventilation, venous thromboembolism and acute kidney injury) (6-14). Similarly, the prognostic utility of chest computed tomography (CT) has been studied in COVID-19 patients. In April 2020, a multinational committee advised that chest CT is a more sensitive imaging modality than chest x-ray (CXR) for early detection of and assessment of COVID-19 disease severity (15). Ground glass opacities or bilateral consolidations in the lower lung field are the most common CT features among COVID-19 patients (16,17). Studies have reported scoring systems, findings and quantitative analyses of CT images that correlate with disease severity and predict outcomes of COVID-19 (16-21).

1.2. Importance

This study may help identify tools that can be used to risk stratify patients presenting to the emergency department with Covid-19 and guide patient management.

1.3. Goal of the investigation

In this study, we aimed to compare the prognostic value of a quantitative CT severity score with several laboratory parameters, particularly C-reactive protein (CRP), Procalcitonin (PCT), Neutrophil to lymphocyte ratio (NLR), D-dimer, ferritin, lactate dehydrogenase (LDH), lactate, troponin and B-type Natriuretic Peptide (Pro-BNP) in predicting in-hospital mortality.

2. Methods

2.1. Study design and setting

This was a retrospective chart review study of patients who presented to the Emergency Department (ED) of a tertiary care center between February 2020 and December 22, 2020 and were diagnosed with COVID-19.

2.2. Selection of participants

All patients ≥18 years old who tested positive for the COVID-19 real-time reverse transcriptase polymerase chain reaction (RT-PCR) and underwent CT imaging at presentation were included. Patients below 18 years old, pregnant women, trauma patients and cardiac arrest patients were excluded. Patients who did not undergo Computer tomography (CT) chest imaging were also excluded. The included patients were divided into 2 groups: survivors and non-survivors. This study was conducted during a time where the COVID-19 vaccine was not available. It was approved by the hospital's Institutional Review Board (IRB): BIO-2020-0548.

2.3. Data abstraction

Three research fellows were responsible for data abstraction. They completed training for data abstraction before the start of the study using practice medical records as well as having several meeting with the principal investigator for quality control. A list of patients with both a positive COVID-19 PCR and a chest CT was obtained from the hospital electronic health record system (EPIC©). The research fellows screened the obtained list based on the inclusion and exclusion criteria by reviewing their medical charts. Relevant patient characteristics, vital signs, and lab parameters at baseline, in addition to diagnostic and therapeutic interventions and outcomes of the included patients were extracted from the hospital electronic health record system (EPIC©). Standardized abstraction forms were used during data collection (Research Electronic Data Capture- Redcap). The performance of the data abstractors was monitored frequently by the principal investigators of the study and the department's research coordinator. The data abstractors were not blinded to the hypothesis and objectives of the study because they were involved in the writing of the manuscript. In addition, each medical chart was reviewed by a single research fellow for data abstraction.

2.4. Variables and definitions

The variables of interest that were extracted were: age, gender, height, weight, body mass index (BMI), medical comorbidities, smoking status, vital signs, patients' presenting symptoms, complete blood count, electrolytes, biomarkers (lactate, albumin, C-reactive protein, procalcitonin, ferritin, lactate dehydrogenase, D-dimer, Bilirubin, pro-BNP, cardiac troponin), coagulation studies(PT, PTT, INR), liver enzymes(AST, ALT, Alkaline phosphatase, Gamma-glutamyl transferase). CT severity score was calculated for all included patients. Other variables of interest were: ED disposition (discharged, regular hospital floor admission or ICU admission), therapeutic interventions in the ED and during hospital admission (the need for noninvasive or invasive ventilation, hospital and ICU lengths of stay, the presence of pulmonary bacterial co-infection, development of complications such as sepsis, acute respiratory distress syndrome (ARDS), cardiovascular complications, thromboembolic events and death). The Berlin definition of ARDS was used to diagnose patients with ARDS (22). Sepsis was defined based on the Sepsis-3 criteria (23). A patient was considered to have a pulmonary bacterial co-infection if the infectious disease team treated them with antibiotics based on clinical, radiographic and laboratory findings.

2.5. CT severity score

The CT images of COVID-19 patients were reviewed at presentation by board certified radiologists at our institution. The radiologists responsible for reviewing the CT images were blinded to the clinical and laboratory data of the patients. The findings were reported according to the "Radiological Society of North America Expert Consensus Document on Reporting Chest CT Findings Related to COVID-19" (24).

The semi-quantitative CT scoring system used was the same as the one used by Pan et al., whereby the degree of each lung lobe involvement translates to a raw score of 0–5. 0 = no involvement; 1 < 5% involvement; 2 = 25% involvement; 3 = 26%–49% involvement; 4 = 50%–75% involvement; 5 ≥ 75% involvement (25). Thus, the total CT score was the sum of the individual lobar scores i.e. a total score of 0 means no lung involvement, and a 25 indicates maximum lung involvement (25). Examples of CT chest images with their corresponding COVID-19 lung involvement and CT severity scores are provided in Fig. 1.

2.6. Outcome of interest

The primary outcome was the prognostic ability of CT severity score versus biomarkers in predicting in-hospital mortality.

2.7. Statistical analysis

In the univariate analysis, continuous variables were presented in the form of mean ± standard deviation, and categorical variables were presented as frequency with percentage. In the bivariate analysis, Student's *t*-test and Pearson's Chi-square test were used to assess the significance of the statistical association between the independent variables in the different groups.

In the multivariate analysis, logistic regression was used to assess the association between biomarkers and CT severity score with

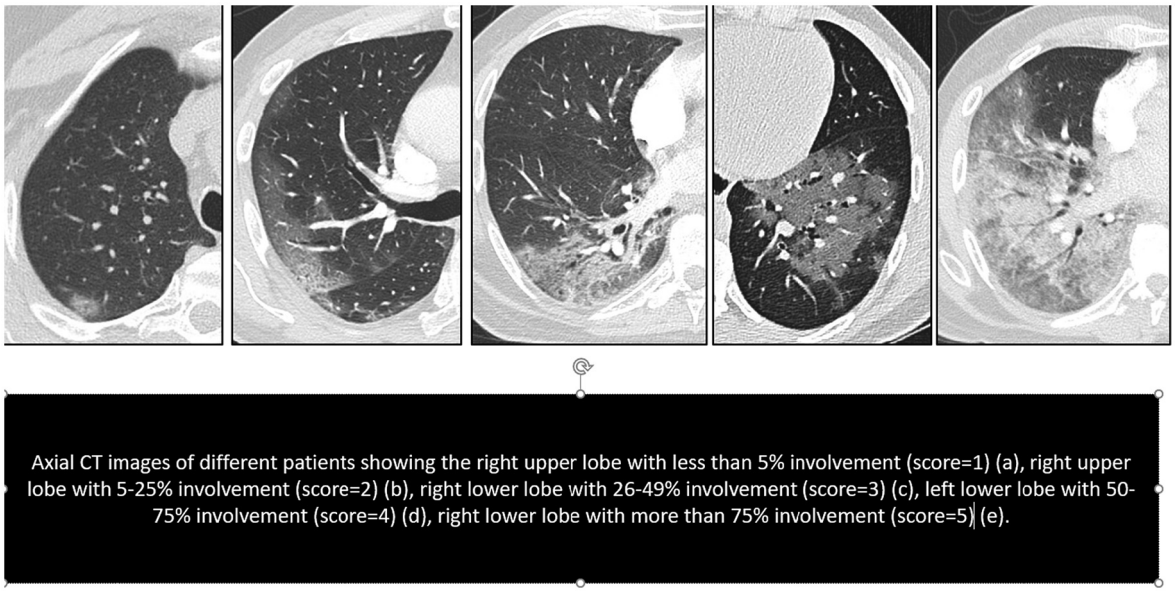


Fig. 1. Axial CT images showing lobar lung involvement and the assigned score.

mortality. The following variables were included in the logistic regression: Age, gender, BMI, smoking, obesity, Hypertension, Dyslipidemia, Atrial fibrillation, Coronary Artery Disease, Congestive Heart Failure, Malignancy, Diabetes Mellitus, Chronic Obstructive Pulmonary Disease, Neutrophil/lymphocyte ratio, Troponin, CRP, Procalcitonin, Lactate dehydrogenase, Ferritin, D-dimer, IL-6, Pro-BNP, CT severity score.

Receiver operating characteristic (ROC) curves were plotted (with regards to mortality) to calculate the area under the curve (AUC) for the relevant biomarkers and CT severity score. Multiple imputations for missing data were not performed because the percentage of missing values for all included variables was <5%. All tests were assessed for significance using 95% CI (Confidence Intervals) and alpha of 0.05. All statistical analyses were performed using SPSS 24 (Statistical Package for Social Sciences.)

3. Results

3.1. Baseline characteristics of presenting patients

During the study period a total of 1043 COVID-19 patients were identified, of whom 761 met the inclusion criteria and 282 were excluded (220 with no CT scan of the chest; 30 were pregnant; 32 were below the age of 18) (Fig. 2)0.119 patients (15.6%) died during their hospital stay (Table 1).

The mean age of the study population was 60.81 ± 16.93 years, of whom 68.1% ($N = 518$) were male. The average BMI of the sample population was 28.90 ± 5.21. 21.7% of the total patient population were current smokers. The four most prevalent comorbidities were hypertension (47.7%), dyslipidemia (37.2%), obesity (30.7%) and diabetes mellitus (27.3%). (Table 1). Non-survivors were older (72.94 ± 12.07 years vs. 58.56 ± 16.76 years, $p < 0.0005$) and had a higher percentage of hypertension (67.2% vs. 44.1%, $p < 0.005$), atrial fibrillation (15.1% vs 6.1%, $p = 0.001$), coronary artery disease (30.3% vs. 15.7%, $p < 0.005$), malignancy (24.4% vs 12.8%, $p = 0.001$) and diabetes mellitus (38.7% vs. 25.2%, $p = 0.003$), (Table 1).

3.2. Initial vital signs, presenting symptoms and lab parameters

Non-survivors had higher respiratory rates (22 breaths/min ± 5.79 vs 20 ± 3.29 breaths/min, $p < 0.0005$) and lower oxygen saturation (95% ± 6.71 vs 86% ± 12.03, $p < 0.0005$) than survivors at presentation.

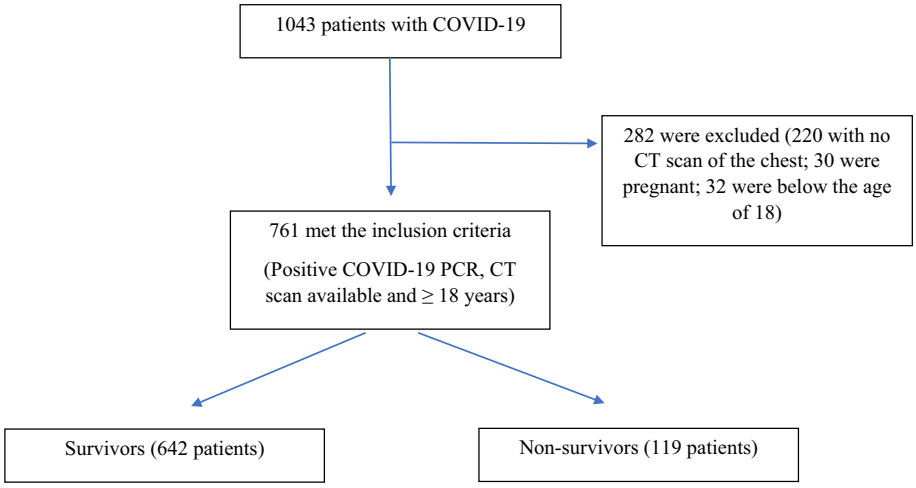


Fig. 2. Flow diagram.

Table 1
Baseline Characteristics of the COVID-19 patients presenting to the Emergency Department of a tertiary care center.

	Total	Survivors	Non survivors	*P* value
	N = 761	*N* = 642	*N* = 119	
	Mean ± SD	Mean ± SD	Mean ± SD	
	N (%)	N (%)	N (%)	
Age (years)	60.81 ± 16.93	58.56 ± 16.76	72.94 ± 12.07	<0.0005
Male	518 (68.1)	439 (68.4)	79 (66.4)	0.67
Height (m)	1.69 ± 0.10	1.69 ± 0.10	1.68 ± 0.10	0.26
Weight (kg)	82.35 ± 17.71	82.27 ± 17.60	83.02 ± 18.15	0.67
BMI	28.90 ± 5.21	28.81 ± 5.06	29.33 ± 5.80	0.34
Obesity	234 (30.7)	188 (29.3%)	46 (38.7)	
Smoking				
Current	165 (21.7)	150 (23.4)	15 (12.6)	<0.0005
Previous	122 (16)	88 (13.7)	34 (28.6)	
None	474 (62.3)	404 (62.9)	70 (58.8)	
Chronic kidney disease	56 (7.4)	41 (6.4)	15 (12.6)	0.017
End stage renal disease	5 (0.7)	4 (0.6)	1 (0.8)	0.57
Hypertension	363 (47.7)	283 (44.1)	80 (67.2)	<0.0005
Dyslipidemia	283 (37.2)	227 (35.4)	56 (47.1)	0.015
Atrial fibrillation	57 (7.5)	39 (6.1)	18 (15.1)	0.001
Coronary Artery Disease	137 (18.0)	101 (15.7)	36 (30.3)	<0.0005
Congestive Heart Failure	38 (5.0)	26 (4.0)	12 (10.1)	0.006
Malignancy	111 (14.6)	82 (12.8)	29 (24.4)	0.001
History of thrombo-embolic disease	60 (7.9)	45 (7.0)	15 (12.6)	0.037
Diabetes Mellitus	208 (27.3)	162 (25.2)	46 (38.7)	0.003
Chronic Obstructive Pulmonary Disease	48 (6.3)	35 (5.5)	13 (10.9)	0.024

With regards to laboratory parameters, non-survivors had higher WBC counts (9968cu.mm ± 8491 vs. 7157cu.mm ± 4758, p = 0.001), neutrophil to lymphocyte ratio (18.92 ± 22.65 vs. 8.5 ± 10.05, $p < 0.0005$), creatinine (1.3 mg/dL ± 1.24 vs. 1.06 mg/dL ± 0.73, $p = 0.04$), lactate (2.3 mmol/L ± 1.41 vs. 1.89 mmol/L ± 1.56, $p = 0.03$), CRP (143 mg/L ± 96 vs. 80 mg/L ± 77.75, $p < 0.0005$), procalcitonin (1.18 ng/mL ± 3.02 vs. 0.48 ng/mL ± 2.54, $p = 0.02$), D-dimer (1363 ng/mL ± 2856.94 vs. 730 ng/mL ± 1122.68, p = 0.03) and Pro-BNP (5822 ng/L ± 6836.06 vs. 1470 ng/L ± 3398.87, p = 0.02). Finally non-survivors had a higher semi-quantitative CT severity score (16.02 ± 5.89 vs 10.84 ± 6.11, $p < 0.0005$) than survivors (Table 2).

3.3. Oxygen therapy requirements

The percentages of patients who received non-invasive ventilation during the first 24 and 48 h of hospitalization were significantly higher in the non-survivor group (79% vs. 33.2% within the first 24 h and 73.1% vs. 32.4% within 24–48 h $p < 0.0005$). Moreover, the percentages of patients requiring intubation within the first 24 or 24–48 h of hospitalization were significantly higher in the non-survivor group (10.9% vs 1.7% within 24 h and 16.8% vs. 0.9% within 24–48 h, both $p < 0.0005$)0.13.9% received mechanical ventilation during their hospital stay (Table 3).

3.4. Outcomes of COVID-19 patients

During their hospital stay, 14.5% of patients were directly admitted to the ICU from the ED, 13.5% developed septic shockand 12.2% developed ARDS (Table 4).

Non-survivors had a significantly higher rate of ICU admission (52.9% vs 7.3%), septic shock (69.7% vs 3.1%) and ARDS (62.2% vs 3%) than survivors (Table 4). Non-survivors also had a significantly higher hospital length of stay and ICU length of stay: (130.39 ± 123.21 days vs 26.64 ± 51.23 days and 20.25 ± 4.57 days vs 10.45 ± 9.25 days respectively) (Table 4).

3.5. ROC curves and AUCs with regards to mortality

The variables that had the highest AUCs were: D-dimer (AUC: 0.67 95% CI = 0.57–0.77, $p = 0.003$), CT severity score (0.66, 95% CI = 0.55–0.77 $p = 0.005$), LDH (0.66, 95% CI = 0.54–0.77, $p = 0.007$), Pro-BNP (0.65, 95% CI = 0.55–0.76, $p = 0.009$), NLR (0.64, 95% CI = 0.53–0.75 $p = 0.02$) and troponin (0.64, 95% CI = 0.53–0.75, $p = 0.02$) (Fig. 3).

3.6. Multivariate logistic regression analysis for in-hospital mortality

In the stepwise logistic regression, age (OR = 1.07 95% CI = 1.05–1.09, $p < 0.0001$), obesity (OR = 2.02 95% CI = 1.25–3.26, $p = 0.004$), neutrophil/lymphocyte ratio (OR = 1.02 95% CI = 1.01–1.04, $p = 0.003$), CRP (OR = 1.01 95% CI = 1.004–1.009, $p < 0.0001$), lactate dehydrogenase (OR = 1.003 95% CI = 1.001–1.004, $p < 0.0001$) and CT severity score (OR = 1.17 95% CI = 1.12–1.23, $p < 0.0001$) were significantly associated with in-hospital mortality (Table 5).

4. Discussion

In this retrospective chart review, our main aim was to identify and compare the prognostic utility of a semi-quantitative CT severity score with several biomarkers. Out of the total patient population, 119 patients (15.6%) died during their hospital stay. The AUCs for predicting mortality from highest to lowest were CT severity score (0.66), LDH (0.66) and NLR (0.64). The variables that were found to be associated with in-hospital mortality were NLR, CRP, LDH and CT severity score, with the CT severity score outperforming all other biomarkers as a prognostic tool. Our results are in line with the existing literature, where several studies have demonstrated that certain baseline patient characteristics, laboratory parameters and imaging findings are associated with adverse complications in COVID-19.

Age and obesity have been reported to play a major role in predicting mortality and assessing severity of COVID-19 (26-29). Gao et al. and Marin et al. reported that age was an independent predictor of in-hospital mortality (5,9). Moreover, COVID-19 patients above 59 years were 5.1 times more likely to die after developing symptoms than those aged between 30 and 59 years (9). According to the Center for Disease control (CDC), a BMI >30 (obesity) increases the risk of severe COVID-19 disease (30). Obesity was also shown to be an independent risk factor associated with hospitalization and death, particularly

Table 2
Initial vital signs, presenting symptoms and lab parameters of the COVID-19 patients presenting to the Emergency Department of a tertiary care center.

	Total	Survivors	Non survivors	P value
	N = 761	N = 642	N = 119	
	Mean ± SD	Mean ± SD	Mean ± SD	
	N (%)	N (%)	N (%)	
Systolic blood pressure (mmHg)	129.12 ± 18.62	129.03 ± 18.53	129.60 ± 19.17	0.8
Diastolic blood pressure (mmHg)	73.28 ± 11.8	73.29 ± 11.66	73.29 ± 12.59	0.9
Heart rate (beats/min)	92.03 ± 17.4	91.29 ± 16.93	96.95 ± 19.37	0.015
O2 saturation (%)	93 ± 8.34	95 ± 6.71	86 ± 12.03	<0.0005
Temperature (C)	37.19 ± 0.84	37.18 ± 0.83	37.25 ± 0.92	0.415
Respiratory rate (Breaths/min)	20 ± 3.89	20 ± 3.29	22 ± 5.79	<0.0005
Presenting symptoms:				
Fever	483 (63.5)	405 (63.1)	78 (65.5)	0.61
Cough	432 (56.8)	366 (57.0)	66 (55.5)	0.75
Shortness of Breath	472 (62.0)	378 (58.9)	94 (79.0)	<0.0005
Fatigue	372 (48.9)	312 (48.6)	60 (50.4)	0.76
Myalgias	179 (23.5)	164 (25.5)	15 (12.6)	0.002
Diarrhea	139 (18.3)	123 (19.2)	16 (13.4)	0.138
Vomiting	59 (7.8)	52 (8.1)	7 (5.9)	0.41
Headaches	54 (7.1)	53 (8.3)	1 (0.8)	0.004
Altered mental status	42 (5.5)	28 (4.4)	14 (11.8)	0.001
Loss of taste	18 (2.4)	18 (2.8)	0 (0.0)	0.093
Loss of smell	18 (2.4)	18 (2.8)	0(0.0)	0.093
Congestion	23 (3.0)	22 (3.4)	1 (0.8)	0.24
Chest pain	139 (18.3)	127 (19.8)	12 (10.1)	0.012
Abdominal pain	71 (9.3)	65 (10.1)	6 (5.0)	0.08
Sore throat	53 (7.0)	49 (7.6)	4 (3.4)	0.093
Rhinorrhea	43 (5.7)	38 (5.9)	5 (4.2)	0.46
White blood cell count (cu.mm)	7600 ± 5603	7157 ± 4758	9968 ± 8491	0.001
Neutrophil count (cu.mm)	5886 ± 3829	5470 ± 3274	8135 ± 5490	<0.0005
Lymphocyte count (cu.mm)	1194 ± 3952	1167 ± 3212	1338 ± 6666	0.7
Neutrophil/lymphocyte ratio	10.14 ± 10.13	8.50 ± 10.05	18.92 ± 22.65	<0.0005
Hematocrit (%)	12.92 ± 1.83	13.04 ± 1.72	12.29 ± 2.25	0.004
Hemoglobin (g/dL)	38.72 ± 5.28	39.00 ± 4.97	37.18 ± 6.49	0.001
Platelets (cu.mm)	214,346 ± 87,886	211,988 ± 82,086	226,966 ± 113,635	0.2
Glucose (mg/dL)	136.77 ± 62.38	133.54 ± 60.08	154.18 ± 71.33	0.006
BUN (mg/dL)	20.79 ± 15.27	18.93 ± 13.07	30.78 ± 21.28	<0.0005
Creatinine (mg/dL)	1.10 ± 0.84	1.06 ± 0.73	1.30 ± 1.24	0.04
Bicarbonate (mmol/L)	23.68 ± 3.32	23.88 ± 3.06	22.62 ± 4.33	0.003
AST	60.59 ± 68.05	54.75 ± 63.30	84.37 ± 100.61	0.06
ALT	48.49 ± 47.29	45.63 ± 51.82	60.18 ± 66.84	0.3
Alkaline phosphatase	78.17 ± 74.74	78.00 ± 67.98	78.85 ± 49.89	0.9
GGT	83.58 ± 51.84	85.69 ± 63.79	75.04 ± 89.35	0.7
Troponin ng/mL	0.024 ± 0.0556	0.019 ± 0.039	0.051 ± 0.099	0.002
PH	7.43 ± 0.07	7.43 ± 0.06	7.42 ± 0.09	0.4
pCO2	32.41 ± 7.20	33.21 ± 7.13	31.28 ± 7.19	0.07
pO2	81.7397 ± 33.70	82.39 ± 35.60	80.84 ± 30.43	0.8
INR	1.27 ± 0.54	1.25 ± 0.52	1.35 ± 0.60	0.09
Lactate (mmol/L)	2.01 ± 1.53	1.89 ± 1.56	2.30 ± 1.41	0.03
Albumin (g/L)	36.08 ± 5.22	36.95 ± 4.85	33.02 ± 5.39	<0.0005
Lactate/albumin ratio	0.065 ± 0.055	0.061 ± 0.054	0.073 ± 0.057	0.1
CRP (mg/L)	91 ± 84.66	80 ± 77.75	143 ± 96.00	<0.0005
Procalcitonin (ng/mL)	0.605 ± 2.64	0.48 ± 2.54	1.18 ± 3.02	0.02
Lactate dehydrogenase (IU/mL)	375 ± 395	356 ± 178	527 ± 381	<0.0005
Ferritin (ng/mL)	941 ± 2009	755 ± 844	1604 ± 3932	0.07
D-dimer (ng/mL)	841 ± 1587	730 ± 1122	1362 ± 2856	0.03
IL-6 (pg/mL)	152 ± 424	137 ± 468	182 ± 317	0.4
Pro-BNP (ng/L)	3610 ± 1956	1470 ± 3398	5822 ± 6836	0.02
CT severity score	11.67 ± 6.35	10.84 ± 6.11	16.02 ± 5.89	<0.0005

Table 3
Oxygen therapy required by the COVID-19 patients during their hospital stay.

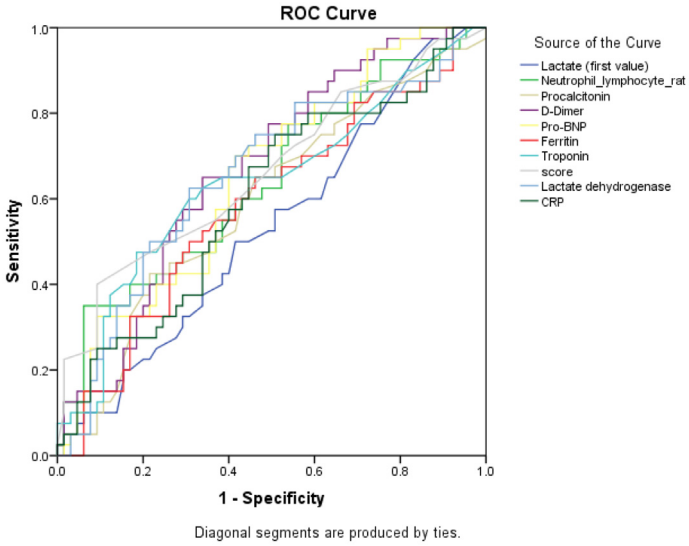
	Total	Survivors	Non survivors	P value
	N = 761	N = 642	N = 119	
	Mean ± SD	Mean ± SD	Mean ± SD	
	N (%)	N (%)	N (%)	
Noninvasive ventilation within the first 24 h	307 (40.3)	213 (33.2)	94 (79.0)	<0.0005
Noninvasive ventilation within 24–48 h	295 (38.8)	208 (32.4)	87 (73.1)	<0.0005
Intubation within the first 24 h	24 (3.2)	11 (1.7)	13 (10.9)	<0.0005
Intubation within 24–48 h	26 (3.4)	6 (0.9)	20 (16.8)	<0.0005
Mechanical ventilation anytime throughout the hospital stay	106 (13.9)	21 (3.3)	85 (71.4)	<0.0005

Table 4
Outcomes of patients with COVID-19.

	Total	Survivors	Non survivors	P value
	N = 761	N = 642	N = 119	
	Mean ± SD	Mean ± SD	Mean ± SD	
	N (%)	N (%)	N (%)	
ED discharge disposition				
Home	290 (38.1)	290 (45.2)	0 (0.0)	
Covid regular floor	361 (47.4)	305 (47.5)	56 (47.1)	<0.0005
Covid ICU	110 (14.5)	47 (7.3)	63 (52.9)	
Length of hospital stay (days)	42.42 ± 76.85	26.64 ± 51.23	130.39 ± 123.21	<0.0005
ICU length of stay (days)	11.27 ± 9.33	10.45 ± 9.25	20.25 ± 4.57	0.01
Presence of bacterial pulmonary superimposed infection	279(36.7)	169 (26.3)	110 (92.4)	<0.0005
Did the patient develop septic shock?	103 (13.5)	20 (3.1)	83 (69.7)	<0.0005
Acute respiratory distress syndrome	93 (12.2)	19 (3.0)	74 (62.2)	<0.0005
Pulmonary Embolism	35 (4.6)	21 (3.3)	14 (11.8)	<0.0005
Stroke	5 (0.7)	4 (0.6)	1 (0.8)	0.6
Myocardial infarction	9 (1.2)	4 (0.6)	5 (4.2)	0.006
Deep vein thrombosis	12 (1.6)	7 (1.1)	5 (4.2)	0.03

among adults younger than 65 years (31). This is most likely multifactorial and could be due to the impairment of immune function in obese patients (32-35). The above studies are in line with the results of this study where age and obesity were found to be independent risk factors of mortality in COVID-19.

Liu et al. reported an 8% increase in in-hospital mortality for each unit increase in NLR (OR = 1.08; 95% CI = [1.01 to 1.14], $p = 0.0147$) (36). A meta-analysis by Li et al. demonstrated an association between NLR and mortality with a pooled sensitivity of 0.83 (95% CI [0.75–0.89]), a pooled specificity of 0.83 (95% CI [0.74–0.89]) and a



Test Result Variable(s)	AUC	Asymptotic 95% Confidence Interval		P-value
		Lower Bound	Upper Bound	
Lactate	0.53	0.42	0.65	0.56
Neutrophil_lymphocyte_ratio	0.64	0.53	0.75	0.02
Procalcitonin	0.60	0.48	0.71	0.10
D-Dimer	0.67	0.57	0.77	0.003
Pro-BNP	0.65	0.55	0.76	0.009
Ferritin	0.59	0.47	0.70	0.13
Troponin	0.64	0.53	0.75	0.02
CT severity score	0.66	0.55	0.77	0.005
Lactate dehydrogenase	0.66	0.55	0.77	0.007
CRP	0.60	0.49	0.71	0.08

Fig. 3. ROC curves for the different biomarkers with the primary outcome being in-hospital mortality among COVID-19 patients (with their respective AUCs).

Table 5
Stepwise logistic regression with the primary outcome being in-hospital mortality.

	OR	95% C.I.		*P*-value
		Lower	Upper	
Age	1.07	1.05	1.09	<0.0001
Obesity	2.02	1.25	3.26	0.004
Neutrophil/lymphocyte ratio	1.02	1.01	1.04	0.003
CRP	1.01	1.004	1.01	<0.0001
Lactate dehydrogenase	1.003	1.001	1.004	<0.0001
CT severity score	1.17	1.12	1.23	<0.0001

Variables included in the model: Age, gender (reference: female); BMI; smoking (reference: none); obesity (reference: no); Hypertension; Dyslipidemia; Atrial fibrillation; Coronary Artery Disease; Congestive Heart Failure; Malignancy; Diabetes Mellitus; Chronic Obstructive Pulmonary Disease; Neutrophil/lymphocyte ratio; Troponin; CRP; Procalcitonin (ng/mL); Lactate dehydrogenase; Ferritin; D-dimer; IL-6; Pro-BNP; CT severity score.

pooled AUC of 0.90 (95% CI [0.87–0.92]) (37). This is also in line with the results of our study where NLR was slightly associated with mortality in COVID-19 and had an OR of 1.02 with an AUC of 0.64, $p = 0.02$.

Another extensively studied biomarker was CRP. It is a widely used inflammatory biomarker that was shown to correlate with disease severity (38-40) and adverse outcomes and in-hospital mortality in COVID-19 patients (40-44). Among hospitalized COVID-19 patients, Smilowitz et al. reported that elevated CRP concentrations above the median value predicted in-hospital mortality (OR 2.59, 95% CI 2.11–3.18) (8). Izcovich et al. showed than an elevated CRP increases the mortality risk by 7.9% (10). In our study, CRP was found to be marginally associated with mortality in patients with COVID-19 with an OR of 1.01. This was similar to what was found in 2 other studies where CRP had an OR of 1.007 (95% CI = 1.004–1.010, $p = 0.0001$ and 95% CI = 1.005–1.009, $p < 0.001$) (45,46).

LDH is a cytoplasmic enzyme involved in glycolysis, and has been linked to tissue damage and inflammation (47-49). Izcovich et al. reported that an LDH (>240–250 U/L) correlates to a 10.4% increased mortality risk (10). Furthermore, Dong et al. showed that a cutoff value of 353.5 U/L had a high AUC of 0.949 (sensitivity and specificity of 94.4% and 89.2%, respectively) for predicting in-hospital mortality, and a pooled analysis confirmed that elevated LDH was an independent risk factor associated with 16-fold increased odds of mortality (50). Although it did not perform as well as in the other studies, LDH was found to be slightly associated with mortality (OR = 1.003 with an AUC = 0.66, $p = 0.007$).

Chest CT is a well-established imaging modality for the assessment of COVID-19, and its prognostic utility has been investigated (15). Colombi et al. reported that a < 73% degree of lung aeration correlates with ICU admission and death (OR 5.4, $p < 0.001$) (51). Yu et al. demonstrated that upper lobe consolidations are associated with ICU admission, acute respiratory failure occurrence and shock during COVID-19 hospitalization (52). Zhang et al. have also reported that the number of affected lobes on chest CT are associated with death (OR, 1.71; 95% CI, 1.06–2.78) (53). In addition, Lieveld et al. reported that a CT severity score ≥ 17 had a ≥ 90% specificity for predicting 30-day mortality, and a score ≤ 5 excluded 30-day mortality with a sensitivity of ≥90% (54). This is similar to our study where chest CT findings were associated with mortality in COVID-19 (AUC = 0.66, $p = 0.005$ and an OR of 1.17).

In summary, in this retrospective chart review, CT severity score outperformed several biomarkers as a prognostic tool for covid related mortality. The authors suggest obtaining a CT chest in COVID-19 patients requiring lung imaging, such as patients requiring ICU admission, patients with abnormal vital signs and those requiring mechanical ventilation and to calculate the CT severity score and use it as a prognostic tool. If a CT was not performed, we suggest using LDH, CRP or NLR if already done as prognostic tools in COVID-19 as these biomarkers were also found to be prognostic in COVID-19 patients.

4.1. Limitations

Our study has several limitations. It was a retrospective single-center study which can limit the generalizability of the results and lead to selection bias. The study only included COVID-19 patients who underwent a CT chest. This would lead to a selection bias of sicker COVID-19 patients since a CT chest would me more likely ordered for this patient population. A CT chest would not be ordered for COVID-19 patients with a milder presentation. The individuals involved in data abstraction were not blinded to the hypothesis and outcomes of the study since they were involved in the writing of the manuscript (however they were not involved in the analysis of the data). In addition, interrater reliability was not tested since each medical chart was reviewed by a single data abstractor and each CT image and CT severity score were reviewed by a single radiologist. All the included patients were not vaccinated as the vaccine was not available at the time. Vaccine status might have an influence on biomarker levels, CT findings and hospital outcomes. Also, the study was conducted before the emergence and testing of the different COVID-19 variants. Despite the previous limitations, a large proportion of the world population remains unvaccinated. In addition, in the setting of the emergence of new COVID-19 variants breakthrough cases still occur in fully vaccinated patients. Thus, our results remain relevant to date. Moreover, we only included patients with a positive RT-PCR. We are well aware of the false negative rate of the PCR and that some patients would have had the clinical and radiographic presentations COVID during the study period and were not included. However, we are not sure of the number of those patients.

We did not trend biomarker levels and did not obtain a second semi-quantitative CT score. This could have provided further information on their prognostic utility. The next step would be to conduct a prospective multi-center study to validate our results.

Ethics approval and consent to participate

The design of this study ensured that it strongly abided by all ethical considerations according to the hospital's Institutional Review Board (IRB), and consent for participation was waived as this was a retrospective chart review. Reference number: BIO-2020-0548.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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CRediT authorship contribution statement

Gilbert Abou Dagher: Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization. **Alain Abi Ghanem:** Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization. **Saadeddine Haidar:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Nadim Kattouf:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Mohamad Assaf:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Mihran Khdhir:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Reve Chahine:** Writing – review &

editing, Writing – original draft, Data curation, Conceptualization. **Jennifer Rizk:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Maha Makki:** Formal analysis. **Hani Tamim:** Formal analysis. **Ralph Bou Chebl:** Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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