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Investigation of poor prognostic markers in covid-19 patients hospitalized from emergency department

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Abstract

On March 11. 2020, the World Health Organization declared the coronavirus disease-2019 (COVID-19) outbreak a pandemic. The surge in the number of infected patients has strained healthcare systems globally. The insufficient number of hospital and intensive care unit (ICU) beds has caused a serious problem in patient care and follow-up worldwide. We determined patients who were admitted to the emergency department and hospitalized with a preliminary diagnosis of COVID-19 between March 11, 2020 and November 15, 2020. We recorded all subjects' admission vital signs, anamnesis, physical examination notes, laboratory tests and notes describing the hospital stay from the hospital information system. Patients discharged without requiring ICU admission were included in the good clinical prognosis (GCP) group. Patients who were admitted to the ICU or died in hospital were included in the poor clinical prognosis (PCP) group. When hematological and biochemical parameters were compared, white cell, neutrophil, platelet counts, glucose, urea, creatinine and bilirubin levels were significantly higher and lymphocyte count, hemoglobin, hematocrit, sodium and chlorine levels were lower in the PCP group. Moreover, sedimentation, C Reactive Protein (CRP), ferritin, High Sensitive Troponin I, D-dimer and lactate levels were significantly higher among patients with a poor prognosis. We assessed and identified the more important potential early indicators of prognosis mentioned in the literature that are applicable in the emergency setting. In light of this information, we aimed to establish a basis for the development of future scoring systems.

Keywords: Covid-19, intensive care unit, emergenct unit, poor prognostic markers

1. Introduction

On March 11, 2020, the World Health Organization declared the COVID-19 outbreak a pandemic. As of March 11, 2021, over 117 million cases of COVID-19 and over 2.6 million related deaths worldwide have been reported (1). The disease has caused significant concern among healthcare providers due to its being a previously unknown disease, rapid person-toperson transmission, a poor understanding of transmission routes, the unpredictable clinical course, lack of knowledge about treatment and management, and its life-threatening nature. The surge in the number of infected patients has strained healthcare systems globally. The insufficient number of hospital and ICU beds have caused a serious problem in patient care and follow-up worldwide. One lesson taught by the COVID-19 pandemic is the importance of early recognition and isolation. Uncertainties surrounding the spread and management of the disease mean diligent monitoring is required. Garcia-Castrilla et al. argue that “the most important actions should focus on limiting the spread of infection, identifying all cases and estimating disease severity” (2). Therefore, early indicators of prognosis will have a significant impact on patient management. Accordingly, we examined the parameters that have been potentially associated in the literature with a poor prognosis. We investigated the predictive value of laboratory parameters, demographic characteristics, and comorbidities deemed significant by previous research for prognosis. It is well established that even the smallest research can prove useful guidelines to the clinicians during epidemics.

2. Materials and Methods

2.1. Study desing and setting

The study was conducted in the İzmir Odemis State Hospital, which receives an average of 100,000 patients annually. We chose patients who were admitted to the emergency department and hospitalized with a preliminary diagnosis of COVID-19 between March 11, 2020 and November 15, 2020. The exclusion criteria were as follows: being aged below 18 years, being hospitalized for the purpose of isolation (no chance of isolation at home, living alone and thus having no caregivers, mentally unequipped to care for themselves, etc.), referral to a different department, and a negative PCR test.

2.2. Study population

We screened the files of 96760 patients admitted to the emergency department between March 11, 2020 and November 15, 2020. Among these, 4421 had been hospitalized, 650 of which had suspected or confirmed COVID-19. PCR tests confirmed the COVID-19 diagnosis in 170 patients. Twenty-nine patients were excluded due to meeting the

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exclusion criteria: being aged <18 years (n = 4), incomplete data (n = 1), and hospitalized for the purpose of isolation (n = 24). The remaining 141 patients were recruited.

2.3. Data source and variables

We recorded all subjects' admission vital signs, anamnesis, physical examination notes, laboratory tests, and notes describing the hospital stay from the hospital information system in case files. Patients discharged without requiring ICU admission were included in the good clinical prognosis (GCP) group. Patients who were admitted to the ICU or died in hospital were included in the poor clinical prognosis (PCP) group. We compared demographic characteristics, laboratory results, and comorbidities between the two groups. We prepared ROC curves for all parameters. According to the Republic of Turkey Ministry of Health adult COVID-19 treatment guidelines, ICU admission criteria are as follows: dyspnea, respiratory distress, respiratory rate ≥30/min, PaO_2/FiO_2 <300, increased oxygen requirement, SpO_2 <90% or PaO_2 <70 mmHg despite 5 L/min oxygen therapy, hypotension (systolic blood pressure <90 mmHg and >40 mmHg drop from baseline SBP and mean arterial pressure <65 mmHg), tachycardia (>100 bpm), acute kidney injury, acute liver dysfunction, confusion, immune suppression, acute organ dysfunction (such as acute bleeding or diathesis), elevated troponin and arrhythmia, lactate >2 mmol, and skin disorders such as abnormal capillary refill and cutis marmorata (3).

2.4. Statistical Analysis

Cochran's formula was used to calculate sample size. For this calculation, we used the COVID-19 ICU admission rate (9.1%) reported by the Ministry of Health on October 19, 2020. Accordingly (d=0.5), 125 subjects were required for a Type 1 error of 5%. After the sample size was calculated and power analysis was conducted, the data were analyzed using SPSS v25.5 (IBM, NY, USA). The Shapiro–Wilk and Kolmogorov–Smirnov normality tests were used to determine whether the variables were normally distributed. The Mann–Whitney U test and Student's t-test were used for the comparison of continuous variables, and the chi-square and Fisher's exact test were used for the comparison of categorical data. The results were presented as median (minimum-maximum), mean ± SD, and numbers and percentages (%). The optimal cut-off value, sensitivity, specificity, and odds ratios for the prediction of prognosis were calculated using ROC analysis, area under the curve, and the Youden index. The results were presented with 95% confidence intervals. In all analyses, a P value <0.05 was considered statistically significant.

2.5. Ethics statement

The study protocol was reviewed and approved by the Dr. Suat Seren Training and Research Hospital Izmir-Turkey (approval number and date; 25-17.12.2020), and the requirement for informed consent was waived due to the retrospective nature of this study.

3. Results

We screened the files of 96760 patients admitted to the emergency department between March 11, 2020 and November 15, 2020. Among these, 4421 had been hospitalized, 650 of which had suspected or confirmed COVID-19. PCR tests confirmed the COVID-19 diagnosis in 170 patients. Twenty-nine patients were excluded due to meeting the exclusion criteria: being aged <18 years (n = 4), incomplete data (n = 1), and hospitalized for the purpose of isolation (n = 24). The remaining 141 patients were recruited. The mean age of the participants was 63.3±15.00 ~~years~~ (range 18-94) and 67 (47.51%) were women. Admission complaints included respiratory distress (n = 78, 55.32%), cough (n = 53, 37.59%), and fever (n = 40, 28.37%) and 101 patients (71.63%) had a history of chronic illness. There were 95 patients (67.38%) in the GCP group and 46 patients (32.62%) in the PCP group. A poor clinical prognosis was significantly associated with the older age and male sex. In terms of admission complaints, respiratory distress was significantly more common in the PCP group. Among the comorbidities, hypertension (HT) and chronic obstructive pulmonary disease (COPD) were significantly more common in the PCP group. The demographic characteristics, comorbidities, admission complaints, and vital signs of the two groups are compared in Table 1.

Table 1. Demographic characteristics, additional diseases, complaints and vital signs at the time of application of the patients

	GCPG (n=95)	PCPG (n=46)	P
Demographics			
Age	59.50±14.29	71.10±13.6	**<0.001**
Sex Female Male	 53 (55.79%) 42 (44.22%)	 14 (30.43%) 32 (69.57%)	**0.005**
Comorbidity	58 (61.05%)	43 (93.48%)	**<0.001**
HT	35 (36.84%)	25 (54.35%)	**0.049**
DM	24 (25.26%)	19 (41.30%)	0.052
COPD	6 (6.31%)	10 (21.73%)	**0.007**
Asthma	11 (11.57%)	2 (4.34%)	0.164
CVD	6 (6.31%)	8 (17.39%)	0.067
Complaints			
Dispnea	42 (44.21%)	36 (78.26%)	**<0.001**
Fever	26 (27.36%)	14 (30.43%)	0.705
Cough	39 (41.05%)	14 (30.43%)	0.222
Weakness	38 (40.00%)	15 (32.60%)	0.396
Vital Signs			
Fever	36.60 (36.00-40.00)	36.80(36.00-40.00)	0.475
SBP DBP	124.00 (90.00-166.00) 77.00 (44.00-120.00)	130.00 (93.00-210.00) 75.00 (54.00-110.00)	0.099 0.664
HR	86.00 (56.00-124.00)	89.50 (58.00-166.00)	0.050
RR	20.00 (16.00-28.00)	21.00 (16.00-44.00)	**0.032**
Sat. O_2	96.00 (78.00-100.00)	88.00 (63.00-99.00)	**<0.001**

Abbreviations: HT, hypertension; DM, Diabetes Mellitus; COPD, Cronic Obstructive Pulmoner Disease; CVD, Cardiovasculer Disease; SBP, Sistolic Blood Pressure; DBP, Diastolic Blood Pressure; HR, Heart Rate; RR, Respiratory Rate; Sat O2, Pulse Oxygen Saturation Percent

When hematological parameters were compared, white cell, neutrophil, and platelet counts were significantly higher, and lymphocyte count and hemoglobin and hematocrit lower in the PCP group. In terms of biochemical parameters, glucose, urea, creatinine, AST, LDH and total and direct bilirubin levels were significantly higher and sodium and chlorine levels were significantly lower in the PCP group. Moreover, sedimentation, CRP, ferritin, HS troponin I, CK, CK-MB, D-dimer, PT, INR, and lactate levels were significantly higher among patients with a poor prognosis. The studied laboratory parameters of the PCP and GCP groups are presented and compared in Table 2. We evaluated the value of each parameter in predicting poor prognosis. The resulting ROC curves are plotted in Fig. 1. Sensitivity, specificity, and cut-off values are shown in Table 3.

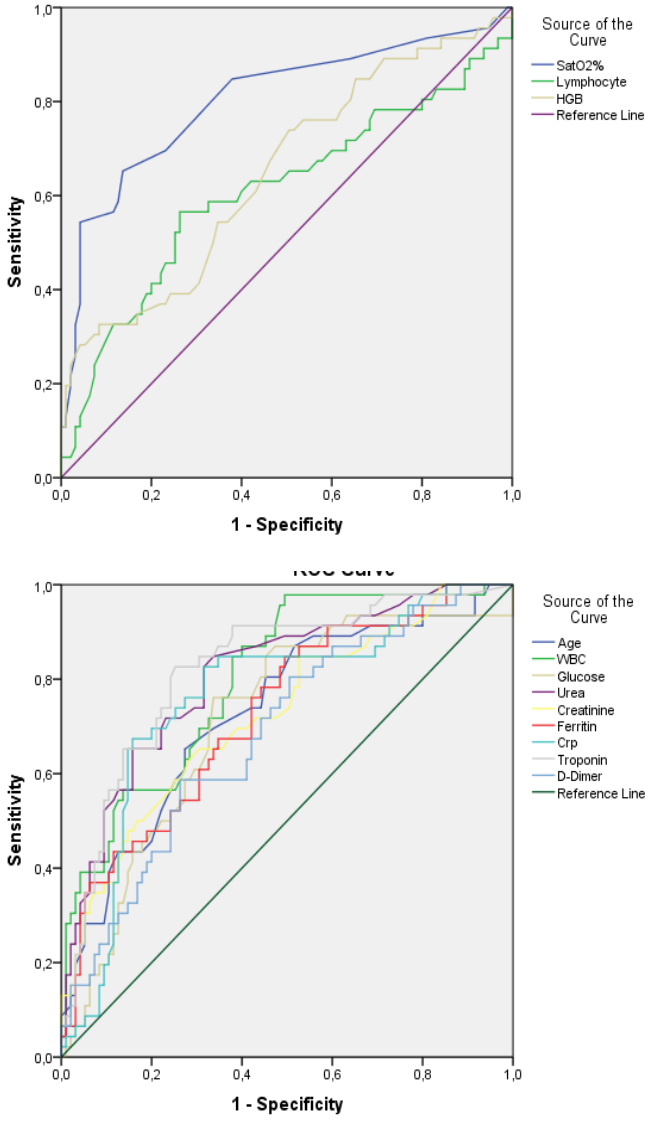

Fig. 1. ROC curves of decreasing and increasing parameters as indicators of poor prognosis

Table 2. The laboratory parameters; the averages and statistical meanings of these parameters in the GCPG and PCPG groups

Laboratory parameters	GCPG (n=95)	PCPG (n=46)	P
WBC (10^3/µL)	5.38 (2.32-14.22)	8.33 (3.08-17.56)	**<0.001**
Neutrophil (10^3/µL)	3.83 (0.87-11.77)	6.29 (1.98-15.25)	**<0.001**
Lymphocyte (10^3/µL)	1.14 (0.37-2.94)	0.84 (0.23-5.64)	**0.035**
Hmg (g/dL)	13.40±1.41	12.38±2.02	**0.003**
Hct (%)	39.17±3.85	36.69±5.28	**0.006**
MCV (fL)	84.21±4.67	85.22±11.02	0.565
MCH (pg)	28.90 (21.40-34.00)	29.70 (19.4-38.2)	0.487
MCHC (g/dL)	34.71±1.24	33.74±1.56	0.068
M (fL)	10.65 (9.0-13.90)	10.95 (9.1-13.6)	0.379
Platelet (10Λ3/µL)	184.00 (101-385)	221.0 (40-353)	**0.030**
Glukoz (mg/dL)	113.00 (82-596)	146.50 (56-486)	**<0.001**
Urea (mg/dL)	32.00 (12-121)	58.00 (22-187)	**<0.001**
Creatinin (mg/dL)	0.95 (0.45-1.71)	1.16 (0.73-3.24)	**<0.001**
AST (U/L)	29.00 (10.00-93.00)	44.50 (16-260)	**0.001**
ALT (U/L)	22.00 (6.00-82.00)	24.50 (8-95.)	0.587
ALP (U/L)	65.00 (24-174)	62.00 (20-175)	0.569
LDH (U/L)	314.00 (134-788)	411 (214-1207)	**<0.001**
Bilirubin totaly (mg/dL)	0.49 (0.14-1.73)	0.66 (0.20-2.00)	**<0.001**
Bilirubin direct (mg/dL)	0.12 (0.01-0.37)	0.18 (0.01-0.78)	**<0.001**
GGT (UL)	26.00 (6.00-233.00)	33.00 (8-255)	0.071
Sodium (mmol/L)	135.00 (124-143)	133.00 (124-158)	**0.049**
Clor (mmol/L)	101.00 (91-109)	99.00 (91-121)	**0.023**
Calcium (mmol/L)	1.11 (0.62-1.35)	1.12 (1.00-1.42)	0.393
Potassium (mmol/L)	4.10 (3.30-5.60)	4.20 (2.70-6.40)	0.886
Magnesium (mmol/L)	1.93 (1.30-3.20)	2.00 (1.52-2.69)	0.221
CRP (mg/L)	34.35 (0.20-159.30)	103.20 (2.7-160)	**<0.001**
CK (U/L)	94.50 (16-1246)	188.50 (20-5565)	**0.001**
CK-MB (U/L)	20.60 (9.00-126.90)	28.00 (11-168)	**0.010**
Hs Troponin I (ng/L)	5.20 (0.00-304.40)	25.40 (0.00-1419.60)	**<0.001**
D-dimer (ng/ml(FEU))	135.20 (3-3143)	258.3 (52-4765)	**<0.001**
Ferritin (ug/L)	128.00 (7-1437.1)	339.8 (50.6-1344.6)	**<0.001**
Sedimentation (mm/hour)	46.00 (10-105)	64.5 (9-133)	**0.004**
APTT (sn)	31.30 (23.70-46.20)	31.90 (20.20-76.20)	0.084
INR	1.04 (0.85-2.47)	1.11 (0.94-15.05)	**<0.001**
PT (sn)	12.05 (10.20-25.50)	13.00 (11-131.7)	**<0.001**
pH	7.42±0.05	7.40±0.07	0.144
pO_2 (mmHg)	35.00 (15-112)	31.50 (11-127)	0.992
pCO_2 (mmHg)	38.00 (27.00-58.00)	37.50 (23-66)	0.441
SO_2 (%)	70.60 (20.60-99.60)	62 (14.6-99.3)	0.751
Lactate (mmol/L)	1.50 (0.60-3.40)	2.10 (1.00-14.50)	**<0.001**

Abbreviations: WBC; White Blood Cell, Hmg; Hemoglobin, Hct; Hemotocrit, MCV; Mean Corpuscular Volume, MCH; mean corpusculer Hemoglobin, MCHC; mean corpusculer hemoglobin concentration, MPV; mean platelet volume, ALT; alanine aminotransferase, ALP; alkaline Phosphatase, APTT; activated partial thromboplastin time, AST; aspartate aminotransferase, LDH; Lactate Dehydrogenase, GGT; gamma-glutamyl transferase, CRP; c-reactive Protein, CK; creatine Kinase, CK-MB; creatine kinase isoenzymes, HS Troponin; High Sensitive Troponin, APTT; activated partial thromboplastin time, INR; international normalization ratio, PT; Prothrombin Time, sO2 (%); Oxygen Saturation percent

Table 3. Prediction and cut-off values of parameters for poor prognosis (ROC Analysis)

	AUC	95%CI	P value	Sensitivity	Specificity	Cut off Value
Age	0.731	0.641-0.820	<0.001	65.2%	72.6%	67.50
Sat.O_2	0.804	0.719-0.889	<0.001	65.2%	86.3%	92.50
WBC	0.801	0.727-0.876	<0.001	84.8%	62.1%	6.175
Lymphocyte	0.610	0.502-0.718	0.035	58.7%	67.4%	0.99
Hmg	0.649	0.551-0.748	0.004	54.3%	65.3%	12.85
Glucose	0.714	0.624-0.805	<0.001	76.1%	66.3%	126.5
Ürea	0.810	0.734-0.886	<0.001	82.6%	68.4%	35.50
Creatinin	0.724	0.634-0.814	<0.001	65.2%	69.5%	1.05
Ferritin	0.728	0.640-0.816	<0.001	67.4%	65.3%	246.85
CRP	0.762	0.675-0.848	<0.001	84.8%	65.3%	50.45
Troponin	0.823	0.749-0.898	<0.001	82.6%	74.7%	8.90
D-Dimer	0.685	0.593-0.777	<0.001	58.7%	73.7%	223.90

4. Discussion

We found that mean age was significantly higher in the PCP group. Duan et al. demonstrated a significant association between age and a severe prognosis during hospitalization for COVID-19 (4). Similarly, Moradi et al. found that increased age was associated with increased COVID-19-related mortality (5). Multivariate logistic regression analysis by Zang JJ et al. identified advanced age as an independent risk factor for death among severely ill patients (6). Our study is consistent with the literature in that advanced age is a significant risk factor for mortality and severe COVID-19 disease.

We also found that poor prognosis was significantly associated with the male sex. Similarly, Li et al. demonstrated that male sex was significantly (p=0.006) associated with a severe prognosis (7). In our study, comorbidities were significantly more common in the PCP group than in the GCP group (93.48% vs. 61.05%, p<0.001). In particular, the prevalence of HT and COPD was significantly different between the two groups. Pan et al. also showed that patients with HT had significantly poorer prognoses compared to those without it (8). A systematic review and meta-analysis by Zhao et al. suggested that concomitant COPD is associated with a 4-fold increase in the risk of developing severe COVID-19 disease (9).

Respiratory distress at admission was significantly associated with a poor prognosis (p=0.001). Consistently, Varol et al. emphasized dyspnea in their COVID-19 mortality index (CoLACD) (10). Admission oxygen saturation, as measured by pulse oximetry, was significantly lower in the PCP group compared to the GCP group (88.00% vs. 9600%, p <0.001).

Bahl et al. showed that admission oxygen saturation was significantly higher among patients who survived versus those who died (92% vs. 88%, p <0.001) (11). We found that the mean WBC count was significantly higher in the PCP group (8.33 vs. 5.38 × 10^3/μL, p<0.001). Huang et al. reported that the WBC count of patients admitted to the ICU was 11.30 × 10^3/μL compared to 5.70 × 10^3/μL in patients who did not require intensive care (p=0.011) (12). Peiró et al. reported that leukocyte count was higher in patients who survived versus those who died, albeit not significantly higher (p=0.065) (13). The discrepancy between our results and those reported by Peiró et al. may be because they included patients who were admitted to the ICU and survived in the good prognosis group. In our study, the mean neutrophil count was significantly higher in the PCP group (6.29 vs. 3.83 × 10^3/μL, p<0.001). Varol et al. compared the neutrophil counts of COVID-19 patients who recovered and those who died and reported a significantly higher neutrophil count in those who died (6.90 vs. 4.35 × 10^3/μL, p<0.001) (10). Numerous studies suggest an association between a low lymphocyte count and poor prognosis. Like our study, Wang et al. reported significantly reduced lymphocytes in patients with a poor prognosis (0.84 vs. 1.14× 10^3/μL, p=0.035) (14).

In a meta-analysis of 19 studies, Hariyanto et al. demonstrated a significant relationship between severe COVID-19 disease and CRP levels (15). We similarly found that CRP was significantly higher in the poor clinical prognosis group. Studies on cardiac markers report that troponin I and troponin T elevation in COVID-19 were associated with acute myocardial injury, ICU admission, hospital deaths, and severe inflammation (16-19). In our study, cardiac markers were significantly higher in the PCP group. CK-MB elevation in COVID-19 was associated with acute myocardial injury, ICU admission, and hospital deaths (14, 16, 20, 21). In our study, CK-MB was significantly higher in the PCP group. Huang C. et al. reported that D-dimer was higher in COVID-19 patients who required intensive care (12). We similarly found that D-dimer levels were higher among PCP patients. Zhou et al. reported that LDH and ferritin were significantly higher in patients who died (20). A meta-analysis of studies from December 25, 2019 and June 1, 2020 by Cheng et al. indicated that ferritin was significantly higher in severe COVID-19. These findings are consistent with our results (22).

Xiaochen Li et al. noted that approximately 50% of all COVID-19 patients were classified as severe and severe disease was associated with advanced age, HT, and elevated

cytokine and LDH levels. Again, that study associated male sex, advanced age, leukocytosis, elevated lactate dehydrogenase, cardiac injury, hyperglycemia, and high-dose corticosteroid use with death among severe COVID-19 patients (23). Eboni G et al. reported that hospital mortality was significantly associated with increased age; increased respiratory rate at admission; elevated lactate, creatinine, or procalcitonin; and low platelet or lymphocyte count (24). The major limitations of our study involved its retrospective nature. Our analysis relied on the accuracy of patient records. The retrospective nature of our study precluded us from making interim assessments during transfer to intensive care.

We assessed and identified the more important potential early indicators of prognosis mentioned in the literature that are applicable in the emergency setting. In light of this information, we aimed to establish a basis for the development of future scoring systems. Further studies are needed to overcome the problems faced by the health system and to improve patient management during the COVID-19 pandemic.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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