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Predictors of disease severity, clinical course, and therapeutic outcome in COVID-19 patients: Our experience with 1700 patients

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Abstract

Objective: To investigate the impacts of demographic, hematological, and biochemical factors on the clinical course and the prognostic outcome in adult COVID-19 patients. Methods: This retrospective study was performed in the internal medicine departments of 2 hospitals and data were extracted from the medical files of 1700 adult COVID-19 patients (836 females, 49.2%; 864 males, 50.8%) with an average age of 48.23 ± 16.68 (range: 18-93). Clinical data included baseline descriptives, prior medical history, admission date, treatment, and hematological and biochemical blood test results. The relationship between the survival, length of hospitalization, hematological, and biochemical parameters was investigated. Results: Advanced age ($p<0.001$), presence of at least 1 comorbid disease ($p=0.045$), increased length of hospitalization ($p=0.006$), elevated white blood cell ($p=0.001$) and neutrophil ($p=0.002$) counts, increased serum levels of glucose ($p=0.027$), blood urea nitrogen ($p<0.001$), AST ($p=0.006$), LDH ($p<0.001$), CRP ($p>0.001$), and D-dimer ($p=0.001$). In contrast, diminution of serum levels of albumin ($p<0.001$), ALT ($p=0.028$), calcium ($p=0.022$), and platelet count ($p=0.010$) were associated with increased mortality. There was a positive and weak relationship between serum D-dimer levels and length of hospitalization. Conclusion: Our data imply that identification and validation of indicators that predict COVID-19 disease progression to improve health outcomes are crucial. Age, comorbidities, immunological response, radiographic abnormalities, laboratory markers, and signs of organ dysfunction may all predict poor outcomes individually or collectively. It is critical to identify characteristics that predict COVID-19 problems to guide clinical management, improve patient outcomes, and allocation of limited resources. Keywords: SARS-Cov-2, COVID-19; severity; prognosis; outcome

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Conclusion: Our data imply that identification and validation of indicators that predict COVID-19 disease progression to improve health outcomes are crucial. Age, comorbidities, immunological response, radiographic abnormalities, laboratory markers, and signs of organ dysfunction may all predict poor outcomes individually or collectively. It is critical to identify characteristics that predict COVID-19 problems to guide clinical management, improve patient outcomes, and allocation of limited resources.

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What is already known about this topic?

There are always new developments in the Covid-19 disease. Over time, we know more about the course of the disease and its clinical and therapeutic consequences. There are many publications and guides on this subject.

What does this article add?

This study was designed using data from a wide range of Covid-19 patients. In this way, it has become possible to present our experience with the Covid-19 disease to a wider patient population. This study presents predictors of Covid-19 disease to clinicians.

Introduction

COVID-19, a coronavirus infection caused by SARS-CoV-2, has put a strain on healthcare systems. The infection spreads quickly, and the lack of universal testing and personal protective equipment have aggravated the situation, as has the prevalence of silent infections. Because of the vast number of COVID 19-infected individuals who present to various hospitals, a thorough understanding of the clinical, radiographic, and laboratory findings connected to higher severity of disease severity and death is required. The identification of potential risk factors for illness progression could be immensely valuable for healthcare personnel in triaging patients, customizing treatment, monitoring clinical progress, and allocating sufficient support at all levels to prevent disease progress and death (1,2).

The SARS-CoV-2 characteristic of primary dormancy signs is another element leading to the fast prevalence and dangerously large number of affected patients. Fever with a quick start, coughing, and dyspnea are the most prevalent symptoms of COVID-19. Pneumonia, renal failure, bacterial superinfections, coagulation problems, and thrombosis are complications. Several clinical and demographic variables, such as advanced age, cardiovascular disease, and diabetes, are associated with poor outcomes and higher risks of mortality. In more vulnerable patients, such as infants, children, the elderly, and pregnant women, this knowledge gap has an impact on infection risk, illness progression, and outcomes. It is critical to understand better the risks of these vulnerable patients to improve and personalize their treatment and prevention techniques (2,3).

In terms of the extent of precautions and limits adopted by countries, COVID-19 mortality and morbidity rates differ substantially. The epidemiology of COVID-19 is substantially variable due to socio-cultural or lifestyle disparities among residents, as well as disparities in-country health policy. As a result, the fundamental causes of the severe pandemic outbreak need to be elucidated and we aimed to investigate the impacts of demographic, hematological, and biochemical factors on the clinical course and the prognostic outcome in adult COVID-19 patients.

Methods

Study design

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Between 01.06.2020 and 01.06.2021 , this retrospective cohort was conducted in the internal medicine departments of two institutions. Before the trial, the local institutional review board gave their approval. Patients or their immediate family signed a written informed consent form. Data were gathered from the hospital databases that include the medical records of a total of 1700 adult patients Our series consisted of 1700 COVID-19 patients (836 females, 49.2%; 864 males, 50.8%) with an average age of 48.23 ± 16.68 (range: 18-93). Clinical were gathered directly from the institutional computerized patient database, including baseline descriptives, prior medical records, date of admission, the treatment process, and results of biochemical and hematological tests.

Patients under the age of eighteen and the presence of comorbidities that could compromise immune functions, such as recent chemotherapy, hematological malignancies, and autoimmune illness, were excluded from the study.

Diagnostic study

Nasal and pharyngeal swabs were analyzed for COVID-19 infection via quantitative real-time reverse transcriptase-polymerase chain reaction (qPCR). COVID-19 was diagnosed and treated based on the World Health Organization (WHO) interim standards and the Turkish Ministry of Health's COVID-19 Diagnosis and Treatment Program (4-6).

The study population was divided into three groups, based on the Turkish Ministry of Health's COVID-19 guide: (1) hospitalized patients with severe clinical conditions such as oxygen saturation below 90% breathing room air, bilateral diffuse pulmonary infiltrates, and tachypnoea (30/min); (2) out-patient follow-up of participants with a mild clinical condition (7).

Patients underwent routine blood testing, chemical, and immunological investigations, and chest CT scanning to establish the COVID-19 severity. A serial chest CT scan was then conducted every other day to track illness progression and therapy success.

Chest computed tomography (CT) scans were accomplished using a particular inspiratory period in a commercial multi-detector CT scanner (Optima CT540, GE Healthcare, USA). Patients were told to hold their breath to reduce artifacts and motion. The following settings were used to create computed tomography images: tube voltage of 100–120 kVp; effective tube current of 110–250 mAs; detector collimation of 0.625 mm; slice thickness of 1 mm; slice interval of 1 mm.

In our hospital's laboratory, blood samples were tested using normal methods. A standard approach was used to evaluate blood samples. Vacuum tubes were used to collect venous blood samples for hematological and biochemical analysis. The sample was centrifuged for 10 minutes at 3000 RPM after the blood had coagulated. The tubes containing K3-EDTA were utilized to investigate the complete blood count (CBC). An automated hematological analyzer was used to determine the quantity of CBC parameters (*XT2000i, Sysmex, Osaka, Japan*). Biochemical and hematological tests were performed on a 15 mL sample of peripheral blood. After centrifugation at 3000 rpm, serum was extracted and kept at -20°C until analysis. The VITROS 5600 Integrated Immunodiagnostic System was used to examine serum biochemistry (*VITROS 5600, Johnson, New Jersey, USA*).

Statistical analysis

The IBM Statistical Package for Social Sciences (SPSS) Statistics v. 21 software (SPSS Inc., Chicago, IL, USA) and the easyROC web tool were used to analyze our data (8). The mean and standard deviation of descriptive data, as well as the median and minimum-maximum values, were used. Numbers and percentages are used to represent categorical variables. The Kolmogorov-Smirnov test was used to test the assumption of normality. The Mann-Whitney U test was used to compare two independent groups. Spearman correlation coefficients were used to analyze the link between quantitative variables. The univariate logistic regression test was used to estimate the factors that influence survival. Finally, the area under the ROC curve was used to estimate the performance of clinical factors in estimating survival. Statistical significance was defined as a p-value of less than 0.05.

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Outcome parameters

Data for the baseline descriptives (such as age and sex), prognostic outcome, comorbidities, medical history, chest computed tomography findings, length of hospitalization, duration of intensive care unit stay, and disease severity were extracted from the hospital records. The complete blood count and serum biochemistry studies included the measurements of mean platelet volume, white blood cell count, platelet count, red cell distribution width, as well as serum levels of glucose, calcium, potassium, sodium, blood urea nitrogen, albumin, alanine aminotransferase (ALT), creatinine, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), D-dimer, ferritin, and C-reactive protein (CRP). The impacts of these variables on the therapeutic outcome in COVID-19 patients were sought.

Results

Our series consisted of 1700 patients (836 females, 49.2%; 864 males, 50.8%) with an average age of 48.23 ± 16.68 (range: 18-93). A total of 479 patients (28.4%) had comorbidities. As for the prognostic outcome, mortality was reported in 32 patients (2.0%), and the length of hospitalization was 5.03 ± 3.60 days (range: 0-32 days) (**Table 1**).

As shown in **Table 2** , the impacts analysis of demographic and clinical variables on survival yielded that advanced age ($p<0.001$), presence of at least 1 comorbid disease ($p=0.045$), increased length of hospitalization ($p=0.006$), elevated white blood cell ($p=0.001$) and neutrophil ($p=0.002$) counts, increased serum levels of glucose ($p=0.027$), blood urea nitrogen ($p<0.001$), AST ($p=0.006$), LDH ($p<0.001$), CRP ($p>0.001$), and D-dimer ($p=0.001$). In contrast, diminution of serum levels of albumin ($p<0.001$), ALT ($p=0.028$), calcium ($p=0.022$), and platelet count ($p=0.010$) were associated with increased mortality (**Table 2**).

Table 3 demonstrates the relationship between clinical variables and length of hospitalization. We noted that there was a positive and weak relationship between serum D-dimer levels and length of hospitalization ($r=0.322$, $p<0.001$; **Table 3**).

The performances of clinical variables for the estimation of prognostic outcomes are shown in **Table 4.** Accordingly, the variables with the highest potential to estimate survival were creatinine (93.7%), D-dimer (88.9%), blood urea nitrogen (87.2%), neutrophil count (80.9%), and LDH (75.9%), respectively. Lower levels of albumin, calcium, salt, and lymphocyte count in the blood were all linked to an increased risk of death (**Table 4**).

Discussion

The current study was performed to investigate whether clinical, hematological, and biochemical variables had significant impacts on the clinical course, therapeutic outcomes, and prognosis in adult COVID-19 patients. Our data yielded that advanced age, presence of at least 1 comorbid disease, increased length of hospitalization, elevated white blood cell and neutrophil counts, increased serum levels of glucose, blood urea nitrogen, AST, LDH, CRP, and D-dimer were associated with increased mortality. On the other hand, decreased serum levels of albumin, ALT, calcium, and platelet count were associated with higher mortality. Remarkably, there was a positive and weak relationship between serum D-dimer levels and length of hospitalization in adult COVID-19 patients.

Some COVID-19 patients did not develop hypoxemia or respiratory stress, suggesting that SARS-CoV-2 infection is a heterogeneous illness. One accurate and practical biomarker is required to prognosticate the COVID-19 pneumonia severity (9). The BCG vaccination has no effect on the COVID-19 pneumonia severity. Low income and age are the primary causes of COVID-19 pneumonia severe (10).

Mousavi et al. looked at the demographics, outcome, hematology-related, and laboratory parameters of COVID-19 patients admitted to a tertiary care hospital (11). They tried to figure out what hematologic factors were linked to death in the 24 percent of our patients who died during their stay. In prior investigations, it was discovered that being male and older increased the risk of in-hospital mortality (12-14).

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The average age of their hospitalized patients was 60 years old, with non-survivors nearly ten years older than survivors. Around 67 percent of non-survivors were over 60 years old. The deceased were mostly male and elderly., according to Yang et al. (15). Despite the fact that male patients were more likely to die, sex did not have a significant impact on mortality (11). An immune response irregularity and a lack of adaptive immunity cause severe inflammatory responses in patients with COVID-19 (16). Thrombocytopenia and decreased nadir platelet counts have been recorded in non-survivors (17).

Serum CRP levels were considerably greater in non-survivors compared to discharged COVID-19 patients, according to Ruan et al. (17). Increased CRP values were a common laboratory abnormality in individuals with COVID-19 infection, according to Pan et al. Levi et al. discovered a raised D-dimer concentration and increased prothrombin time in COVID-19 patients as typical signs of coagulopathy (18,19). Other laboratory irregularities in COVID-19 that might be linked to thrombotic microangiopathy and coagulopathy include ferritin concentrations and high LDH (20).

In COVID-19, Yuan et al. found that a decrease in serum LDH could indicate a good response to treatment (21). A minor increase in white blood cell count was seen in patients with acute illness, but a clinically significant increase was seen in individuals who died. As a result, a considerable increase in WBCs in patients with severe disease could indicate clinical deterioration and a higher risk of poor outcomes. Although an increase in neutrophils may cause WBCs to increase, lymphocytes, monocytes, and eosinophils may decrease. Lymphocytes are thought to be essential for the elimination of virally infected cells in the SARS virüs, and survival may be related to the capacity of reviving lymphocytes destroyed by the virüs (22,23).

Both substantial and catastrophic outcomes are possible. Patients with a positive test of COVID-19 had significant levels of cardiac and muscle injury biomarkers. Non-survived patients showed a significant level of high cardiac troponin at the time of admission, indicating a risk of cardiac injury caused by multiple organ failure progression, viral myocarditis, and secondary cardiac caused by organ-targeted diseases. A significant increase in liver enzymes (ALT and AST) and renal indicators (blood urea nitrogen) reveals a picture of multiple organ failure (24).

Plasma CRP levels were associated with the COVID-19 pneumonia severity. As a result, it could help distinguish between patients with mild COVID-19 pneumonia and those with moderate to severe COVID-19 pneumonia. These findings could help clinicians better stratify patients for transfer to an intensive care unit by serving as an early warning sign of serious disease (25).

The clinical sequence of patients with severe COVID-19 from admission to discharge was reported in this study, with various outcomes. Lymphocyte, CRP, and LDH dynamic monitoring could be useful in predicting the severe patients' prognosis. Furthermore, the fatal aspect of COVID-19 was primarily related to significant systemic inflammation with caused cardiac failure (26). Comorbidities, age, secondary infection, and higher indicators in inflammation were predictors of a fatal result in COVID-19 cases. COVID-19 death could possibly be related to virus-activated "cytokine storm syndrome" or fulminant myocarditis, according to the findings (17).

It is important to note the limitations of our study. Our findings may be influenced by the retrospective design and possibly socioeconomic factors. Given the pandemic's rapid spread, these findings are clinically significant and may aid clinicians in identifying and treating persons with a higher risk of acquiring the severe disease. Therefore, our findings should be regarded as preliminary and exploratory. Because participants who are more likely to die exhibit significant variations in some of these co-variates, the correlations we observe should not be assumed to represent cause and effect.

Conclusion

To conclude, our data imply that identifying and validating indicators for predicting COVID-19 disease progress to improve health outcomes is crucial. Age, immunological response, comorbidities, radiographic abnormalities, signs of organ dysfunction, and laboratory markers could predict poor outcomes individually or collectively. Because SARS-CoV-2 has a tropism for various tissues, such as the brain, endothelium, heart,

kidney, liver, and respiratory system, predicting the COVID-19 severity is much more challenging. It is critical to identify characteristics that predict COVID-19 problems to guide clinical management, improve patient outcomes, and allocate limited resources.

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Tables

Table 1. The demographic and clinical features of our population (n=1700).

Variable		**Statistics**
Age (mean ± std. deviation)	Age (mean ± std. deviation)	48.23 ± 16.68 (range: 18 – 93)
Sex	Female Male	836 (49.2%) 864 (50.8%)
Comorbidity	No Yes	1208 (71.6%) 479 (28.4%)
Survival	Alive Dead	1570 (98.0%) 32 (2.0%)
Length of hospitalization (mean ± std. deviation)	Length of hospitalization (mean ± std. deviation)	5.03 ± 3.60 (range: 0 – 32)

Table 2. The analysis of the impacts of demographic and clinical measurements on survival.

	Survival	**Survival**		**p-value**
	Alive (n=1570)	**Dead (n=32)**	**Odds Ratio (%95 CI)**	
Age (years)	47.38 ± 16.45	74.5 ± 10.50	1.145 (1.105 – 1.186)	**<0.001***
Sex (Female)	808 (51.5)	16 (50.0)	1.060 (0.527 – 2.135)	0.870
Comorbidity	0 [0 - 25]	2 [0 - 9]	1.090 (1.002 – 1.186)	**0.045***
Length of hospitalization (days)	4 [0 - 32]	4.5 [1 - 23]	1.103 (1.029 – 1.182)	**0.006***
White blood cell count (cells/mL)	5.89 [0.89 – 76.2]	8.5 [3.9 – 66.34]	1.123[a] (1.035 – 1.218)	**0.001***
Neutrophil count (cells/mL)	3.8 [0.0 – 69.9]	6.5 [3.4 – 63.6]	1.147[a] (1.051 – 1.253)	**0.002***

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	Survival	**Survival**		**p-value**
Lymphocyte count (cells/mL)	1.42 [0.11 - 136]	0.78 [0.2 – 5.77]	0.656[a] (0.312 – 1.379)	0.266
Platelet count (cells(μL)	207 [11 - 738]	204 [96 - 628]	1.005[a] (1.001 – 1.009)	**0.010***
RDW (%)	13.3 [10.6 – 111.8]	14.45 [12.4 – 23.1]	1.035[a] (0.978 – 1.095)	0.235
MPV (fL)	10.1 [7 - 17]	10.2 [8.4 – 16.4]	1.272[a] (0.946 – 1.710)	0.112
Glucose (mg/dL)	106 [48 - 476]	133 [70 - 532]	1.005[a] (1.001 – 1.010)	**0.027***
Blood urea nitrogen (mg/dL)	27 [1 - 178]	58.35 [23 - 267]	1.039[a] (1.025 – 1.053)	**<0.001***
Creatinine (mg/dL)	0.8 [0.08 - 99]	1.3 [0.69 – 10.21]	1.028[a] (0.974 – 1.084)	0.318
Sodium (mEq/L)	138 [66 - 4137]	136 [129 - 328]	1.00[a] (0.998 – 1.002)	0.988
Potassium (mEq/L)	4 [3 - 43894]	4.35 [3 - 136]	1.000[a] (0.999 – 1.001)	0.845
Calcium (mg/dL)	9 [0 – 12.2]	8.35 [4.2 – 9.1]	0.665[a] (0.469 – 0.943)	**0.022***
Albumin (g/dL)	40 [0 - 47160]	37.5 [7 - 45]	0.856[a] (0.803 – 0.913)	**<0.001***
AST (U/L)	23 [5 - 669]	32.5 [10 - 199]	1.009[a] (1.003 – 1.015)	**0.006***
ALT (U/L)	21 [6 - 228]	17.5 [8 - 187]	1.017[a] (1.002 – 1.032)	**0.028***
LDH (U/L)	233 [0 - 2005]	322.5 [150 - 1317]	1.004[a] (1.002 – 1.006)	**<0.001***
CRP (mg/L)	12.9 [0 - 350]	110.55 [2 - 350]	1.015[a] (1.009 – 1.021)	**<0.001***
D-dimer (ng/mL)	170.5 [0 - 36480]	905.5 [121 - 36000]	1.000[a] (1.0 – 1.0)	**0.001***
Ferritin (μg/L)	150 [1.2 - 3154]	305 [18.8 - 2000]	1.001[a] (1.001 – 1.002)	0.065

(*Hint:* [a] Since age, comorbidity, and length of hospitalization have significant impacts on survival, a correction has been performed to eliminate the effects of these 3 variables on the other parameters during the analysis.)

(*Abbreviations:* *: statistically significant; CI: confidence interval; RDW: red cell distribution width; MPV: mean platelet volume; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; CRP: C-reactive protein)

Table 3. The relationship between clinical variables and length of hospitalization.

Variable	**Length of hospitalization (n=1700)**	**Length of hospitalization (n=1700)**
	r[a]	**p-value**
White blood cell count (cells/mL)	-0.068	0.005*
Neutrophil count (cells/mL)	0.004	0.872
Lymphocyte count (cells/mL)	-0.193	<0.001*
Platelet count (cells/μL)	-0.155	<0.001*

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Variable	Length of hospitalization (n=1700)	Length of hospitalization (n=1700)
Red cell distribution width (%)	0.089	<0.001*
Mean platelet volume (fL)	0.024	0.327
Glucose (mg/dL)	0.133	<0.001*
Blood urea nitrogen (mg/dL)	0.059	0.014*
Creatinine (mg/dL)	0.043	0.078
Sodium (mEq/L)	-0.215	<0.001*
Potassium (mEq/L)	0.024	0.333
Calcium (mg/dL)	-0.261	<0.001*
Albumin (g/dL)	-0.031	0.203
AST (U/L)	0.127	<0.001*
ALT (U/L)	-0.025	0.311
LDH (U/L)	0.143	<0.001*
CRP (mg/L)	0.234	<0.001*
D-dimer (ng/mL)	0.322	<0.001*
Ferritin (µg/L)	0.103	<0.001*

(*Abbreviation:* [a] Spearman correlation coefficient)

(*Hint:* Both p and r values must be considered during analysis of the relationship between a variable and the correlation coefficients must be interpreted as follows: 0.0-0.30: negligible; 0.31-0.50: low; 0.51-0.70: moderate; 0.71-0.90: high; 0.91-1.00: very high)

Table 4. The performances of clinical variables for the estimation of survival.

Variable	AUC	%95 CI	Cut-off value	Sensitivity	Specificity
White blood cell count	0.725	0.63 – 0.82	9.65	0.469	0.874
Neutrophil count	0.809	0.744 – 0.874	5.3	0.719	0.745
Lymphocyte count*	0.743	0.640 – 0.847	0.8	0.562	0.897
RDW	0.719	0.634 – 0.805	13.8	0.688	0.691
Glucose	0.613	0.498 – 0.727	129	0.562	0.765
Blood urea nitrogen	0.872	0.812 – 0.933	50.1	0.656	0.936
Creatinine	0.937	0.760 – 0.913	1	0.781	0.807
Sodium*	0.659	0.540 – 0.778	136	0.625	0.730
Potassium	0.685	0.561 – 0.809	4.1	0.656	0.823
Calcium*	0.695	0.613 – 0.777	8.9	0.75	0.669
Albumin*	0.699	0.602 – 0.796	32	0.375	0.950
AST	0.692	0.593 – 0.791	28	0.719	0.642
LDH	0.759	0.671 – 0.846	252	0.844	0.587
CRP	0.854	0.784 – 0.923	52	0.844	0.800
D-dimer	0.889	0.834 – 0.944	342	0.929	0.785

(*Hint:* * Lower values indicate a higher risk for mortality. The table presents only the variables that yield significant results as for the values in the area under the ROC curve. For each variable, the optimal cut-off values with the highest predictive potential for the estimation of prognostic outcome as well as their sensitivities and specificities have been presented. For e.g. The potential of neutrophil count for estimation of the prognostic outcome is 80.9%. The opitmal cut-off point is 5.3 and the sensitivity and specificity at this point is 0.719 and 0.745, respectively)

(*Abbreviations:* AUC: area under curve; CI: confidence interval; RDW: red cell distribution width; AST:

aspartate aminotransferase; LDH: lactate dehydrogenase; CRP: C-reactive protein)

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