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Predictors of mortality in patients less than 50 years old with coronavirus disease 2019: a multicenter experience in Istanbul

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SUMMARY

OBJECTIVE: The objectives of this study were to identify predictors of mortality in young adult patients with coronavirus disease 2019 and to assess the link between blood type and mortality in those patients.

METHODS: This multicenter retrospective study, which was conducted in seven training and research hospitals in Istanbul, involved young adults who aged ≥18 and <50 years and hospitalized with coronavirus disease 2019.

RESULTS: Among 1,120 patients, confusion at admission (p<0.001) and oxygen saturation (p<0.001) were significantly predictive factors of mortality. Blood type O was significantly associated with mortality compared to those discharged from the hospital (p<0.001). Among co-morbidities, the most reliable predictive factors were cerebral vascular disease (p<0.001) and chronic renal failure (p=0.010). Among laboratory parameters, high C-reactive protein (p<0.001) and low albumin (p<0.001) levels were predictors of mortality in young adult patients with coronavirus disease 2019.

CONCLUSIONS: SpO_2 at admission was the best predictor of mortality in young adult patients with coronavirus disease 2019. The mortality rate was increased by cerebral vascular disease and chronic renal failure. Also, high C-reactive protein and low albumin levels were predictive factors of mortality. Moreover, blood type O was associated with a higher mortality rate than the other types.

KEYWORDS: Adult. COVID-19. Mortality.

INTRODUCTION

Background

Coronavirus disease 2019 (COVID-19), caused by the highly contagious severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was first identified in Wuhan, China, in December 2019, and it has become the pandemic of the last century. SARS-CoV-2 has infected around 100 million people, 2 million of whom have died[1].

In the early stages of the pandemic, it was thought that COVID-19 affected only older adults and killed only geriatric patients. Therefore, most COVID-19 studies involved patients of advanced age. Indeed, the mortality rate is higher in patients with chronic medical conditions, such as diabetes mellitus (DM) and hypertension (HT)[2]. Moreover, high D-dimer and ferritin levels are predictive factors of mortality[3]. During the early days of the pandemic, the relationship between ABO blood type and COVID-19 susceptibility and mortality was much discussed[4]. As the pandemic progressed, COVID-19 deaths occurred in younger patients[5]. However, few studies have examined predictive factors of mortality, including laboratory findings, in younger patients.

In this multicenter study, we examined predictors of mortality in terms of demographics, co-morbidities, and laboratory findings in young adult patients with COVID-19 and evaluated the link between blood type and mortality.

METHODS

Study design and setting

This multicenter, retrospective, observational study was carried out between March 20, 2020 and June 30, 2020. Data were

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collected from seven research and training hospitals in Istanbul, Turkey. This study enrolled young adult patients (aged ≥18 and <50 years) who were admitted to the pandemic ward or pandemic intensive care unit with signs of COVID-19 pneumonia on chest computed tomography (CT) or positive in polymerase chain reaction (PCR) test. Admission decisions were made according to the COVID-19 guidelines[6] of The Coronavirus Scientific Advisory Board of the General Directorate of Public Health, Turkish Ministry of Health. According to these guidelines, patients with mild–moderate pneumonia, those with mild–moderate pneumonia with poor prognostic factors in laboratory tests at admission, or patients with severe pneumonia are hospitalized.

Data collection

The total number of patients admitted to emergency departments of the centers during the study period was 513,168, among whom 34,304 were hospitalized for any diagnosis. We identified 1,629 young adult patients with COVID-19.

Data were collected by searching for U06.0 and U07.3 International Classification of Disease codes in the hospitals' automation systems. We assessed patients' demographics, vital signs at admission, complaints at admission, comorbidities, result of PCR test, blood type, laboratory parameters, hematological findings, and biochemical findings.

This study was approved by the Institutional Review Board of XXX Research and Training Hospital, Istanbul, Turkey (no. 2020-KSSH-1331 and clinicaltrials.gov ID: NCT04479137).

Statistical analysis

Statistical analysis was performed by using MedCalc Statistical Software version 19.4.1. Patient data are expressed as medians for normally distributed variables and as percentages for categorical variables. The normality of the distribution of continuous variables was examined using the Kolmogorov–Smirnov test. Between-group comparisons of normally distributed parameters were conducted using Student's t-test; the Mann–Whitney U-test was applied for non-normally distributed parameters. Categorical variables were analyzed using chi-square test or Fisher's test.

RESULTS

Data from 1,120 patients with COVID-19 were evaluated. Among them, 60.4% (n=677) were males with a median (quartiles) age of 42.0 (35.0–46.0) years. Of the patients, 88.6% were discharged (survivors) and 11.4% (n=128) were died (non-survivors). The distributions of demographic parameters, complaints at admission, and co-morbidities in survivors and non-survivors are shown in Table 1. There were significant differences between non-survivors and survivors in age, SpO_2 at admission, confusion, fatigue, HT, DM, cerebrovascular disease (CVD), and chronic renal failure (CRF) ($p<0.001$). Based on age categories, i.e., 18–29, 30–39, and 40–49 years, 69.5% (n=89) of non-survivors were in the age group of 40–49 years. Of the total deaths, 21.9% (n=28) were in the age group of 30–39 years, and 8.6% (n=11) were in the age group of 18–29 years. Among 489 patients, the frequency of blood type O was significantly higher among non-survivors ($p=0.010$). The distribution of blood groups by age and survival is shown in Figure 1.

Laboratory parameters at admission are listed in Table 1. The lymphocyte, thrombocyte, calcium, and albumin values were lower, and the lactate dehydrogenase (LDH), blood urea nitrogen (BUN), ferritin, D-dimer, and CRP levels were higher in non-survivors than in survivors. Univariate and multivariate regression analyses were performed to identify predictors of mortality (Table 2). Model 1 comprised age, vital signs at admission, and complaints at admission, model 2 added co-morbidities and blood type O, and model 3 added laboratory parameters. A multivariate regression analysis showed that confusion ($p<0.001$) and SpO_2 at admission ($p<0.001$) were reliable predictors of mortality in model 1. In model 2, CVD ($p<0.001$), CRF ($p=0.010$), and blood type O ($p=0.014$); and in model 3, platelet count ($p=0.022$), albumin ($p<0.001$), BUN ($p=0.005$), and CRP ($p<0.001$) were predictive factors of mortality in young adult patients with COVID-19.

DISCUSSION

In this large multicenter study, we evaluated the factors associated with mortality in young adult patients with COVID-19. In this study, instead of PCR, we used chest CT because of its higher sensitivity. All patients included in the study had chest CT findings indicative of COVID-19. The key findings were as follows: (1) age was associated with mortality, and the majority of non-survivors (69.5%) were 40–50 years of age. (2) Confusion at admission, SpO_2 at admission, CVD, and CRF were independently predictive factors of mortality. (3) Non-survivors had a higher rate of blood type O (43.9%) than survivors. (4) The albumin and CRP levels were predictive factors of mortality.

Advanced age is a predictor of mortality in patients with COVID-19[7]. We obtained similar results and the mortality rate increased as patients approached 50 years. In a study of patients with COVID-19 who aged 18–34 years, male sex was a risk

Table 1. Characteristics of the patients and laboratory results.

	Non-survivors (n=128)	Survivors (n=992)	p-value
Male [%(n)]	62.5 (80)	60.2 (597)	0.614
Age (years)	42.5±6.1	39.0±8.4	**<0.001**
Admission systolic blood pressure (mmHg)	125.0 (110.0–140.0)	127.0 (110.0–140.0)	0.295
Admission diastolic blood pressure (mmHg)	70.0 (63.2–80.0)	70.0 (65.0–80.0)	0.350
Admission oxygen saturation (%)	92.0 (88.0–95.0)	97.0 (95.0–98.0)	**<0.001**
Admission heart rate (BPM)	92.0 (78.0–109.0)	87.0 (76.0–92.0)	**0.004**
Admission fever (°C)	37.0 (36.0–37.5)	36.8 (36.5–37.5)	0.349
Cough [%(n)]	50.8 (63)	64.8 (593)	**0.002**
Fever [%(n)]	44.3 (54)	41.6 (364)	0.584
Nausea and vomiting [%(n)]	15.6 (19)	9.5 (85)	**0.038**
Impaired consciousness [%(n)]	70.5 (86)	29.4 (267)	**<0.001**
Sore throat [%(n)]	4.2 (5)	10.3 (92)	**0.032**
Weakness [%(n)]	43.8 (53)	27.4 (244)	**<0.001**
Chest pain [%(n)]	12.1 (15)	6.7 (59)	**0.030**
HT [%(n)]	22.6 (28)	9.4 (83)	**<0.001**
DM [%(n)]	21.8 (27)	10.2 (90)	**<0.001**
CAD [%(n)]	6.5 (8)	2.5 (22)	**0.015**
CVD [%(n)]	9.7 (12)	0.8 (7)	**<0.001**
COPD/Asthma [%(n)]	8.1 (10)	5.1 (45)	0.172
CRF [%(n)]	10.3 (12)	1.9 (15)	**<0.001**
WBC count ($\times 10^3$ per μL)	5.85 (3.3–9.5)	6.25 (4.7–10.4)	0.668
Platelet count ($\times 10^3$ per μL)	160.0 (119.0–204.0)	206.0 (164.0–239.0)	**<0.001**
Neutrophil count ($\times 10^3$ per μL)	4.38 (2.5–6.4)	4.44 (3.3–8.1)	0.092
Lymphocyte count ($\times 10^3$ per μL)	0.85 (0.5–1.1)	1.3 (1.0–1.9)	**<0.001**
BUN (mg/dL)	16.5 (11.2–35.4)	12.1 (9.3–15.4)	**<0.001**
LDH (U/L)	382.5 (280.7–528.2)	312.0 (235.0–366.0)	**<0.001**
Albumin (g/L)	30.0 (24.0–33.0)	36.0 (32.0–40.0)	**<0.001**
CRP (mg/L)	95.6 (55.1–203.6)	51.8 (27.1–83.6)	**<0.001**
Ferritin (ng/mL)	617.6 (371.9–1497.0)	283.3 (120.8–629.0)	**<0.001**
D-Dimer (mg/L)	1.64 (0.7–3.1)	0.78 (0.4–1.4)	**<0.001**
Calcium (mg/dL)	8.3 (7.7–8.4)	8.5 (8.0–8.9)	**<0.001**

Bold indicates significance at p<0.005. Fisher's exact test. Data are means±standard deviation, medians (quartiles), and percentages for categorical variables.

factor for mortality and ventilation[8]. In contrast, we found no significant gender difference between survivors and non-survivors. COVID-19 can cause severe lung pathology and reduce the SpO_2; indeed, SpO_2 at admission and HR were predictors of mortality, as reported by Sands et al[9].

The COVID-19 mortality rate is higher in patients with co-morbidities, such as DM and HT. Here, the mortality rate was significantly higher in patients with HT, DM, [cardiovascular disease (CAD)], CVD, and CRF; the latter two parameters were reliable predictors of mortality in the multivariate regression analysis. It is hypothesized that COVID-19 causes coagulopathy and thrombosis and, therefore, aggravates CVD[10].

Siepmann et al. reported that COVID-19 is more likely to occur and to be more severe in patients with CVD[11]. Together with our results, this shows that COVID-19 and coagulopathy frequently co-occur. In the multivariate regression

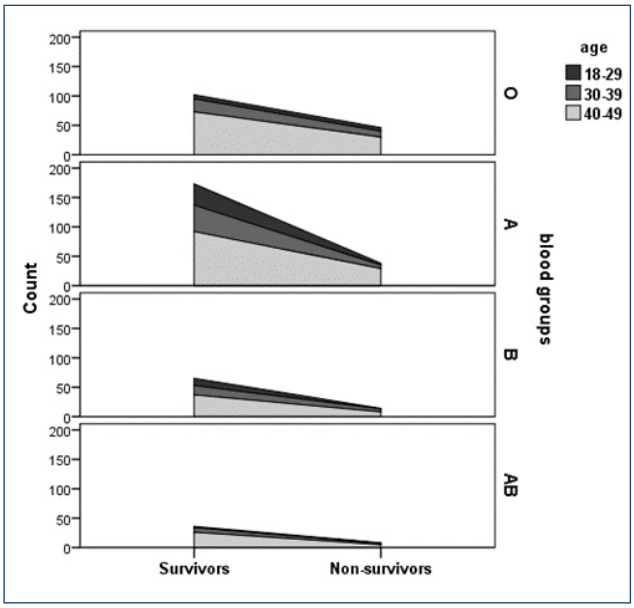

Figure 1. Distribution of blood groups by age and survival.

analysis, CRF was a more predictive factor of mortality than DM and HT. This study included 27 patients with CRF, 44.4% of whom died, suggesting that the mortality rate of COVID-19 is increased by CRF in younger patients. The International Society of Nephrology guidelines recommend that patients with CRF take stringent measures to prevent COVID-19[12].

The effect of ABO blood type and Rh factor on mortality has been debated. Zietz et al. reported that among 112 patients, the infection rate was higher for non-O types, and the mortality rate was higher for types AB and B compared with type O[13]. Similarly, Ray et al. reported that mortality from SARS-CoV-2 was lower among patients with blood type O[14]. Most studies of the relationship between COVID-19 severity and blood type concluded that the risk of severe disease is high for type A and low for type O[15]. Research on the relationship between COVID-19 and blood type is based on the similarity of genetic variants linked to the immune system and blood type[16]. In some studies in the literature, it was determined that there was no relationship between

Table 2. Regression analysis models for identifying predictors of mortality.

Variable	Univariate		Multivariate	
	OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
Model 1				
Age (years)	1.051 (1.023–1.078)	**<0.001**	1.048 (1.011–1.087)	**0.011**
Admission heart rate (BPM)	1.007 (0.997–1.018)	0.170		
Cough	1.783 (1.223–2.600)	**0.003**	1.284 (0.753–2.190)	0.359
Impaired consciousness	36.583 (16.338–81.915)	**<0.001**	36.089 (10.925–119.212)	**<0.001**
Admission oxygen saturation (%)	0.736 (0.691–0.784)	**<0.001**	0.748 (0.697–0.802)	**<0.001**
Model 2				
DM	2.462 (1.525–3.974)	**<0.001**	1.428 (0.716–2.850)	0.312
HT	1.250 (0.348–4.486)	**<0.001**	1.672 (0.858–3.257)	0.131
KAH	2.702 (1.176–6.210)	**0.019**	1.225 (0.360–4.158)	0.745
CVD	13.408 (5.172–34.762)	**<0.001**	7.726 (2.167–27.554)	**<0.001**
CRF	5.862 (2.670–12.867)	**<0.001**	3.199 (1.317–7.771)	**0.010**
O blood group	2.084 (1.335–3.254)	**0.001**	1.847 (1.135–3.005)	**0.014**
Model 3				
Platelet count ($\times 10^3$ per µL)	0.994 (0.991–0.997)	**<0.001**	0.993 (0.986–0.999)	**0.022**
Lymphocyte count ($\times 10^3$ per µL)	0.745 (0.600–0.925)	**0.008**	1.375 (0.770–2.454)	0.281
Albumin (g/L)	0.963 (0.940–0.987)	**0.003**	0.060 (0.160–0.224)	**<0.001**
BUN (mg/dL)	1.015 (1.008–1.022)	**<0.001**	1.055 (1.016–1.094)	**0.005**
LDH (U/L)	1.007 (1.005–1.009)	**<0.001**	1.003 (1.000–1.006)	0.093
Calcium (mg/dL)	0.649 (0.487–0.866)	**0.003**	1.120 (0454–2.766)	0.805
CRP (mg/L)	1.001 (1.013–1.016)	**<0.001**	1.012 (1.006–1.019)	**<0.001**
Ferritin	1.134 (1.061–1.211)	**<0.001**	1.005 (0.926–1.090)	0.913
D-Dimer (mg/L)	1.362 (1.203–1.543)	**<0.001**	0.996 (0.893–1.112)	0.948

Bold indicates significance at p<0.005.

ABO blood group and COVID-19[5,17]. In contrast, Solmaz et al. reported that blood type O protects against COVID-19[18]. In this study, blood type O was associated with mortality among 489 patients and was a predictive factor of mortality in model 2.

Laboratory tests are typically performed to determine the severity of COVID-19. In Turkey, the Ministry of Health guidelines recommend considering the ferritin, lymphocytes, D-dimer, and CRP values when making decisions on hospitalization and treatment. Among middle-aged patients, a high D-dimer (>1 µg/mL) level and low albumin level were risk factors for severe COVID-19[6]. CRP, an acute-phase reactant, is an indicator of COVID-19 severity[19], as well as for other viral respiratory diseases, e.g., severe acute respiratory syndrome and Middle East respiratory syndrome[20,21]. In model 3, a high CRP level, hypoalbuminemia, thrombocytopenia, and a high BUN value were predictive factors of mortality, as well as of the severity of COVID-19 in young adult patients.

CONCLUSIONS

SpO_2 at admission is a reliable predictor of mortality in young adult patients who hospitalized with COVID-19 and so may be useful for triaging such patients at admission. Among co-morbidities, CVD and CRF were more predictive factors of mortality than DM and HT. In addition, blood type O, a high CRP level, and a low albumin level were predictive factors of mortality in young adult patients with COVID-19.

AUTHORS' CONTRIBUTIONS

RG: Conceptualization, Data curation. **ŞÇ:** Formal Analysis, Funding acquisition. **BGY:** Investigation, Methodology. **MÇ:** Project administration, Resources. **EA:** Software. **NMH:** Supervision, Validation. **GE:** Visualization. **İT:** Writing – original draft. **AÇ:** Writing – review & editing.

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