Comparison of Clinical Manifestation and Mortality-Related Risk Factors Between Elderly and Middle-Aged COVID-19 Patients

Majid Akrami[1,2], Hadiseh Hosamirudsari[3], Neda Faraji[4], Masoomeh Nataj Majd[5]

[1] *Department of Anesthesiology, Baharloo Hospital, Tehran University of Medical Sciences, Tehran, Iran*

[2] *Anesthesia, Critical Care and Pain Management Research Center, Tehran University of Medical Sciences, Tehran, Iran*

[3] *Department of Infectious Diseases, Baharloo Hospital, Tehran University of Medical Sciences, Tehran, Iran*

[4] *Department of Internal Medicine, Baharloo Hospital, Tehran University of Medical Sciences, Tehran, Iran*

[5] *Department of Anesthesiology, Arash Hospital, Tehran University of Medical Sciences, Tehran, Iran*

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Abstract- Given that the risk factors associated with mortality and morbidity of Coronavirus Disease (COVID-19) vary among age groups, this study aimed to describe the differences in clinical characteristics and mortality-related risk factors between elderly and middle-aged COVID-19 patients. A total of 1061 patients were included in this retrospective cohort study. Patients' radiology reports and laboratory data were extracted from the available data on the Hospital Information System (HIS), and clinical findings were added in special forms. We followed up cases until death or discharge to evaluate patients' outcomes. Chronic obstructive pulmonary disease (COPD) (95% CI, HR 2.73 (0.97-6.62)), need for antibiotics (95% CI, HR 2.26 (1.20-4.26)), and diabetes (95% CI, HR 1.77 (0.97-3.24)) were associated with a higher risk of mortality among middle-aged COVID-19 patients; while, age (95% CI, HR 1.04 (1.01-1.06)) was associated with increased mortality rate in elderly patients. We found that the need for antibiotics was associated with a worse outcome of COVID-19. Additionally, we described the differences between elderly and middle-aged COVID-19 patients regarding their comorbidities, laboratory findings, and clinical manifestation.

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Keywords: COVID-19; Aged; Middle-aged; Mortality; Survivors

Introduction

In late December 2019, a newly discovered coronavirus disease (COVID-19) emerged in Wuhan, China, and spread rapidly across many countries borders (1). The accurate diagnosis and appropriate management of COVID-19 have been a subject of debate among intellectuals and academics (2) Coronaviruses are members of the Coronavirinae subfamily in the family Coronaviridae. Several coronavirus species cause mild to severe respiratory and intestinal infections in humans (3). The average mortality rate of COVID-19 across the globe has not remained constant and has changed throughout the pandemic. The worldwide death rates varied from 1.7% to 39.0% during February to March 2020, and it decreased to less than 0.3% between July and August 2022 (4).

The clinical manifestation of COVID-19 varies; most infected people will be asymptomatic or experience mild to moderate disease that subsides. The common symptoms are fever, tiredness, dry cough, dyspnea, and muscular pain (5,6). Several factors may account for severe disease and death. Most studies have shown that age (older patient) and underlying medical problems such as heart disease, diabetes, chronic respiratory diseases, hypertension, renal failure, and cancer are the risk factors for severe COVID-19 disease and related death (7,8).

A study conducted in China revealed that older patients with severe disease had more highlighted laboratory abnormalities, including lymphocytopenia 83.2% and leukopenia 33.7%, compared to non-severe younger cases by a median of 7 years (9). In another study

Corresponding Author: H. Hosamirudsari
Department of Infectious Diseases, Baharloo Hospital, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 9123142382, E-mail address: h-hosami@sina.tums.ac.ir

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in Italy, lymphocytopenia was found as a risk factor for a negative outcome (10). Also, an abnormal increase in CRP, followed by a decrease in lymphocyte count and an abnormal increase in LDH levels, has high sensitivity in detecting severe or critical COVID-19 patients (11). Given that risk factors associated with mortality and morbidity of COVID-19 vary in age groups; thus, we aimed to describe the differences between elderly and middle-aged COVID-19 patients' clinical manifestations and mortality-related risk factors.

Materials and Methods

The present hospital-based retrospective cohort study was performed on COVID-19 patients admitted to Tehran, Baharloo Hospital, as one of the centers for COVID-19, under the supervision and approval of the Medical Ethics Committee of Baharloo Hospital affiliated to Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1399.148). All 1061 confirmed cases of COVID-19, hospitalized from February 20, 2020, to April 18, 2021, were used in the present analysis. Informed consent was obtained from patients to participate in the study. The primary outcome of the study was mortality, the time from hospital admission to death. The secondary outcome was the time from hospital admission to discharge.

Data collection

From available data on Hospital Information System (HIS), patients' paraclinical and laboratory data were extracted, and clinical findings were added in special forms. We followed up cases until death or discharge to evaluate patients' outcomes. The inclusion criteria for this study were patients aged 40 years and older with diagnosis of COVID-19. The patients with incomplete hospital records were excluded from the study.

Data analysis

Categorical variables were described with frequency(percentage) and for continuous variables, mean and standard deviation have been reported. To show the differences in baseline characteristics and type of treatment and laboratory findings between two groups, t-test for continuous variables and Chi-square test for categorical variables were used. Patients were divided into two groups, middle-aged cases were under 40 to 60 years, and elderly patients were defined as over 60 years old. The Kaplan-Maier method and Log-rank test were used to calculate the survival rate in the groups. Hazard ratios (HRs) of the related risk factors for mortality were calculated by stepwise Cox proportional hazard models. The independent variables were examined in a univariate Cox regression model and variables with a significance level below 0.2 entered the multivariate regression model to find related risk factors. The SPSS software version 25 and STATA software version 14 were used for analyzing the data with a significant level of <0.05.

Results

A total of 1061 patients were enrolled in this study, including 599 middle age and 462 elderly patients. Participants mean age in the elderly category was 72.87±8.27, and in middle age was 43.35±11.02 (P<0.0001).

On average, ICU admission time in elderly patients was 1.3 days higher than in middle-aged patients statistically significant. Also, in elderly patients, the proportion of ischemic heart disease (IHD) (P<0.0001), COPD (P=0.003), chronic kidney disease (P<0.0001), hypertension (P<0.0001), diabetes (P<0.0001), stroke (P<0.0001), and rheumatic disease (P=0.046) were significantly higher than middle-aged patients. However, in elderly patients, most of the initial symptoms such as fever (P=0.044), chills (P=0.001), myalgia (0.047), dyspnea (P<0.0001), and cough (P<0.0001) were significantly lower than in middle-aged patients. Additional information on clinically and statistically different demographic characteristics in survivor and non-survivor patients based on elderly and middle-aged subgroups is shown in Table 1.

Neutrophil (P<0.0001), Neutrophil-Lymphocyte Ratio (NLR) (P<0.0001), CRP (P=0.005), ESR (P=0.003), BUN (P<0.0001), and CR (P<0.0001) of the elderly patients were significantly higher. Moreover, hemoglobin level (P=0.028) and blood oxygen saturation (SpO2) (P<0.0001) of the elderly patients were significantly lower than middle-aged patients. Clinical and statistical differences in survivor and non-survivor patients' major laboratory markers based on elderly and middle-aged subgroups are shown in Table 2.

Table 1. Baseline characteristics of COVID-19 Patients' compression between elderly and middle-aged patients

Variables	Elderly patients (n=462)				Middle-aged patients (n=599)				
	Total (n=462)	Survivor (n=348)	Non-survivor (n=114)	*P*	Total (n=599)	Survivor (n=543)	Non-survivor (n=56)	*P*	*P***
Demographic									
Age (years)	72.87 ±8.27	71.73± 7.97	76.35±8.25	<0.0001	43.35±11.02	42.71±11.06	49.58±8.49	<0.0001	<0.0001
Male	249 (53.9)	181 (52)	68 (59.6)	0.156	342 (57.1)	309 (56.9)	33 (58.9)	0.771	0.298
***BMI kg/m2**	26.94 ± 5.22	27.05 ± 5.73	26.65 ± 3.62	0.556	27.68 ± 4.51	27.48 ± 6.64	29.18 ± 8.93	0.025	0.054
ICU admission (days)	8.14 ± 7.53	7.45 ± 6.54	10.24 ± 9.71	0.005	6.85 ± 7.54	6.64 ± 7.21	8.93 ± 8.45	0.310	0.006
Comorbidity									
Ischemic heart disease	119 (25.8)	87 (25)	32 (28.1)	0.515	36 (6.0)	28 (5.2)	8 (14.3)	0.006	<0.0001
COPD	33 (7.1)	27 (7.8)	6 (5.3)	0.369	19 (3.2)	15 (2.8)	4 (7.1)	0.075	0.003
Chronic kidney disease	23 (5.0)	16 (4.6)	7 (6.1)	0.511	5 (0.8)	3 (0.6)	2 (3.6)	0.018	<0.0001
Hypertension	235 (50.9)	179 (51.4)	56 (49.1)	0.668	93 (15.5)	74 (13.6)	19 (33.9)	<0.0001	<0.0001
Diabetes	173 (37.4)	130 (37.4)	43 (37.7)	0.945	118 (19.7)	101 (18.6)	17 (30.4)	0.035	<0.0001
Stroke	47 (10.2)	34 (9.8)	13 (11.4)	0.617	24 (4.0)	22 (4.1)	2 (3.6)	0.862	<0.0001
Hyper/Hypo Thyroid	13 (2.8)	10 (2.9)	3 (2.6)	0.892	30 (5.0)	25 (4.6)	5 (8.9)	0.158	0.072
Rheumatism	12 (2.6)	7 (2)	5 (4.4)	0.162	6 (1.0)	5 (0.9)	1 (1.8)	0.536	0.046
Anemia	7 (1.5)	7 (2)	0	-	13 (2.2)	11 (2)	2 (3.6)	0.450	0.437
Cancer	3 (0.6)	1 (0.3)	2 (1.8)	0.091	9 (1.5)	8 (1.5)	1 (1.8)	0.855	0.193
Initial symptoms									
Fever	239 (51.7)	176 (50.6)	63 (55.3)	0.385	347 (57.9)	312 (57.5)	35 (62.5)	0.467	0.044
Chill	127 (27.5)	100 (28.7)	27 (23.7)	0.294	222 (37.1)	202 (37.2)	20 (35.7)	0.826	0.001
Myalgia	128 (27.7)	95 (27.3)	33 (28.9)	0.733	200 (33.4)	188 (34.6)	12 (21.4)	0.046	0.047
Dyspnea	277 (60.0)	220 (63.2)	57 (50)	0.012	423 (70.6)	395 (72.7)	28 (50)	0.105	<0.0001
Cough	277 (60.0)	220 (63.2)	57 (50)	0.012	423 (70.6)	395 (72.7)	28 (50)	<0.0001	<0.0001
Anorexia	76 (16.5)	52 (14.9)	24 (21.1)	0.127	77 (12.9)	69 (12.7)	8 (14.3)	0.737	0.098
Nausea	80 (17.3)	62 (17.8)	18 (15.8)	0.620	111 (18.5)	105 (19.3)	6 (10.7)	0.114	0.610
Vomiting	42 (9.1)	29 (8.3)	13 (11.4)	0.322	60 (10.0)	55 (10.1)	5 (8.9)	0.776	0.612
Diarrhea	31 (6.7)	24 (6.9)	7 (6.1)	0.779	53 (8.8)	52 (9.6)	1 (1.8)	0.051	0.201
Antibiotics	250 (53.1)	173 (49.7)	77 (67.5)	0.001	311 (51.9)	268 (49.4)	43 (76.8)	<0.0001	0.478

All data are reported as frequency and percent, except for age and BMI mean±SD
BMI= body mass index, ICU= intensive care unit, IHD= ischemic heart disease COPD=chronic obstructive pulmonary disease,
*BMI for 416 patients was missing
***P* for compassion between elderly and middle-aged patients

Table 2. Laboratory findings in COVID-19 Patients compression between elderly and middle-aged patients

Variables	Elderly patients (n=462)				Middle-aged patients (n-599)				
	Total (n=462)	Survivor (n=348)	Non-survivor (n=114)	*P*	Total (n=599)	Survivor (n=543)	Non-survivor (n=56)	*P*	*P* **
WBC count, 10^9/L	7.67 ± 5.54	7.24±3.76	8.98±8.90	0.003	6.96 ± 4.32	6.71 ± 4.01	9.36± 6.13	<0.0001	0.190
Neutrophil, percent	75.19 ± 10.86	73.87±10.74	79.22±10.25	<0.0001	72.37 ± 10.99	71.73±10.68	78.52±12.08	<0.0001	<0.0001
Lymphocyte, percent	19.53 ± 10.82	20.58±10.46	16.33±11.27	<0.0001	24.01 ± 44.61	24.81± 46.67	16.30±10.36	0.175	0.035
NLR	5.92 ± 5.22	5.23 ±4.51	8.00±6.53	<0.0001	4.49 ± 3.46	4.24± 3.06	6.94± 5.52	<0.0001	<0.0001
Hemoglobin, g/L	12.67 ± 1.82	12.62±1.75	12.77±2.00	0.447	13.63 ± 9.25	13.72± 9.69	12.71±1.88	0.440	0.028
PLT, 10^9/L	206.22 ± 85.40	213.26±87.75	184.71±74.10	0.002	209.60 ± 84.74	209.23± 84.79	213.16±84.92	0.742	0.521
CRP mg/L	48.23 ± 33.63	43.53±32.99	62.56±31.53	<0.0001	41.29 ± 44.17	38.61±44.88	67.29±24.52	<0.0001	0.005
ESR, mm/hr	57.71 ± 29.86	58.66±30.52	54.77±27.68	0.227	52.26 ± 29.25	51.01±29.29	64.34±26.04	0.001	0.003
BS, mg/dl	154.65 ± 70.51	152.99±69.30	159.67±74.13	0.381	148.01 ± 70.15	144.58±67.49	181.21±85.82	<0.0001	0.128
SpO2, percent	89.78 ± 7.35	91.46±3.99	84.63±11.65	<0.0001	91.91 ± 5.21	92.19±4.84	89.17±7.43	<0.0001	<0.0001
BUN mg/dL	53.89 ± 32.88	49.13±25.43	68.39±46.28	<0.0001	36.15 ± 20.60	34.34± 18.31	53.65±31.01	<0.0001	<0.0001
CR, mg/dL	1.38 ± 0.86	1.28±9.67	1.68±1.21	<0.0001	1.15 ± 0.67	1.10±0.52	1.54±1.38	<0.0001	<0.0001
LDH, U/L	585.97 ± 340.61	539.84±320.61	726.78±362.06	<0.0001	564.67 ± 264.01	547.02±249.14	735.72±336.63	<0.0001	0.267

Data are reported as mean±SD

WBC= white blood counts, NLR; Neutrophil to lymphocyte ratio, PLT= platelet count test, CRP= C-reactive protein, ESR= erythrocyte sedimentation rate, BS= blood sugar, BUN= blood urea nitrogen, CR= Creatinine, LDH= Lactate dehydrogenase, SpO2= Blood O2 saturation

Table 3. Related risk factors for mortality in elderly and middle-aged COVID-19 patients by using Cox proportional hazard Model

Middle-aged patients (n- 599)				Elderly patients (n= 462)			
Variables	**HR**	**95% CI**	***P***	**Variable**	**HR**	**95% CI**	***P***
COPD	2.73	0.97-5.62	0.056	Age	1.04	1.01-1.06	0.001
Diabetes	1.77	0.97-3.24	0.059				
Antibiotics	2.26	1.20-4.26	0.012				

COPD=chronic obstructive pulmonary disease

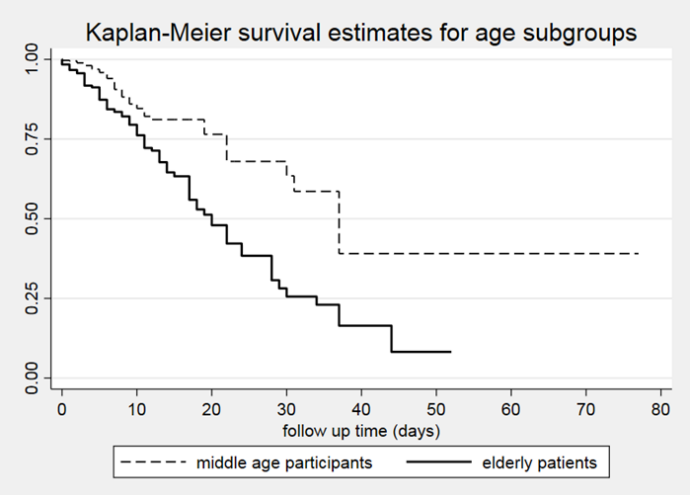

Figure 1. Kaplan-Meier survival function for middle-aged and elderly patients

According to the Cox regression in middle-aged patients, the hazard ratio of death in patients with antibiotic needs was 2.26 (95% CI: 1.20, 4.26, *P*=0.012) compared to middle-aged patients without antibiotics therapy. Also, in this subgroup, the hazard of death in patients with comorbidities with COPD was 2.73 (95%: 097, 6.62, *P*=0.056) and diabetes was 1.77 (955 CI: 0.97, 3.24, *P*=0.059) compared to patients without COPD and diabetes, respectively.

However, in the elderly patients' subgroup, the hazard of death increased by 1.04 (95% CI: 1.01, 1.06, *P*=0.001) times each year, which was statistically significant.

As shown in Figure 1, the survival of patients in the middle-aged group was higher than elderly patients which was statistically significant (*P*<0.0001). Survival was higher in middle-aged patients at all times than in elderly patients.

Discussion

In this study, pre-existing conditions such as hypertension, diabetes, CKD and ischemic heart disease were significantly more frequent among middle-aged non-survivors than middle-aged survivors. Moreover, diabetes and COPD independently were associated with higher mortality among middle-aged COVID-19 patients. In contrast, the prevalence of these comorbidities was nearly similar among elderly survivors and non-survivors. This points out that older age itself may be responsible for the high mortality rate among elderly patients, whereas pre-existing conditions more greatly impact on younger patients' mortality rate.

Previous studies reported that comorbidities and advanced age are risk factors for hospitalization and mortality of COVID-19 patients (12-14). COVID-19 patients finally die because of multi-organ failure, shock, respiratory insufficiency, heart failure, arrhythmias, and renal failure (15). The older age and chronic diseases are associated with inadequate physiologic reserve of the cardiovascular, respiratory, renal, and neurological systems, which can predispose patients to multi-organ failure and in-ICU death. Also, higher age is associated with an impaired immune system response to pathogens and dysregulated release of inflammatory mediators, resulting in organ failure and death (16). A similar immune system dysfunction pattern and abnormal inflammatory response are observed in chronic diseases such as diabetes and cardiovascular (17). Older age and comorbidities can accelerate the burst of inflammation in COVID-19 patients and, with the help of their diminished physiologic reserve, eventually lead to their death (18). By grouping patients based on age, the current study revealed that comorbidities are more critical among middle-aged COVID-19 patients, while older age alone is vigorously responsible for the higher mortality rate among elderly patients. However, comorbidities were more frequent among elderly patients, but these coexisting medical conditions were similarly distributed among the survivors and non-survivors of this group.

A meta-analysis of 24 studies revealed that bacterial co-infection was identified in 3.5% of hospitalized COVID-19 patients, and secondary bacterial infection was diagnosed in 14.3% of hospitalized COVID-19 patients. Additionally, it was shown that bacterial infection was more common among critically ill patients (19). The presence of bacterial co-infection or secondary infection can increase the COVID-19 mortality rate (20). Administration of antibiotics during COVID-19 infection can lead to changes in the gut microbiome, dysregulation of the immune system response, and increased morbidity. Similarly, the present study revealed that the need for antibiotics could predict a higher risk of mortality.

Numerous studies evaluated the prevalence of different signs and symptoms among COVID-19 patients, but few studies discuss the distribution of signs and symptoms within age categories (21-23). Interestingly, our data showed that fever, chills, myalgia, and respiratory signs and symptoms such as dyspnea and cough were significantly more frequent among middle-aged patients. In contrast, digestive signs and symptoms such as anorexia, nausea, vomiting, and diarrhea were similar among middle-aged and elderly patients. A Spanish study divided COVID-19 patients into six age categories and compared their characteristics. The study uncovered that the specific symptoms of COVID-19 are less common among elderly patients than young patients. Furthermore, the study revealed that atypical symptoms are more frequent among elderly COVID-19 patients (24). The atypical presentation of COVID-19 in older individuals may be attributed to thymic aging, leading to the dysregulation of the T cell response against pathogens. Furthermore, the presence of various concomitant comorbidities in elderly patients can result in a nonspecific manifestation of COVID-19.

Most previous studies attempted to define a single cut-off level for laboratory findings of all patients with COVID-19, regardless of their age (25,26). According to our results, there is a noticeable difference between laboratory findings of elderly and middle-aged patients. Further, the survivors of elderly patients and middle-aged

patients showed a different range of laboratory findings from their non-survivors. This suggests that using an age-dependent cut-off for laboratory findings of COVID-19 patients may contribute to determining the prognosis of the disease.

Limitations

Our study has several limitations: it is a single-centered, retrospective study design, and there are some missing data.

Also, the included cases were only hospitalized patients, so we could not study many outpatient cases. Finally, defining middle or old age presents a challenge due to the lack of an exact definition in the existing literature.

This study revealed that comorbidities are more critical among middle-aged patients compared with elderly patients. It seems middle age cases with comorbidity need more aggressive care, compared with older patients. It was also shown that laboratory findings and clinical presentations of COVID-19 are different between middle-aged and elderly COVID-19 patients. This suggests that using an age-dependent cut-off for laboratory findings of COVID-19 patients improves the diagnosis of COVID-19 and contributes to determining the prognosis of the disease.

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