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TANAFFOS

Age-Dependent Clinical Features and Prognosis of COVID-19 Patients

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Background: The clinical and paraclinical symptoms of COVID-19 differ across age groups. This study investigated the differences between these parameters and their outcomes in young, middle-aged, and elderly patients admitted to a COVID-19 referral center.

Materials and Methods: This retrospective study encompassed patients with COVID-19 hospitalized at Khorshid Hospital (Isfahan, Iran) during February 23 to April 30, 2020. The patients' predisposing conditions, clinical and paraclinical findings, and outcomes were compared among three young, middle-aged, and elderly groups.

Results: Of the 1185 hospitalized patients with suspected COVID-19, 1065 were discharged or died at the end of the study. Among these 1065 patients, 654 patients with the mean age of 57.7 years had positive PCR results or typical CT scans and were included in the study, of whom 77 (11.8%), 353 (54%), and 234 (34.2%) patients were assigned into the young, middle-aged, and elderly groups, respectively. There was no statistically significant difference among the three groups regarding the prevalence of clinical symptoms. Moreover, CRP, ESR, WBC, BUN, Cr, and lymphocytes were higher in the elderly group. The ground-glass opacity (GGO) (24.1%), GGO-consolidation (27.4%), and consolidation (10.3%) were the most common CT scan findings in the young, middle-aged, and elderly groups, respectively. Fifty-three patients (8.1%) died, and the mortality rates were 10.36%, 7.27%, and 3.8% in the elderly, middle-aged, and young groups, respectively.

Conclusion: COVID 19 symptoms do not depend on age; however, paraclinical findings differ across young, middle-aged, and elderly patients.

Key words: COVID-19; Age; Outcome; Prognosis

INTRODUCTION

The first patient with a definitive diagnosis of COVID-19 was reported in Iran on February 18, 2020 (1). At the beginning of the pandemic, the symptoms were mainly limited to respiratory tract infection; however, other symptoms such as gastrointestinal, cutaneous, and neurological symptoms gradually emerged (2).

Age is an important host factor in response to infections (3). Asymptomatic carriers are mainly observed in the middle-aged group in close contact with the families of the infected (4). Although an acceptable prognosis is provided for most patients, the elderly with underlying chronic diseases have a poor prognosis (5). Several studies have examined the symptoms, clinical course, and outcome of COVID-19 (5); however, few studies have addressed and compared these variables among different age groups.

The present study examined the demographics, clinical symptoms, paraclinical findings, and outcomes of COVID-19 in different age groups. Examining the virus behavior in different age groups, the present study aimed to determine the diagnostic key factors leading to the diagnosis of COVID-19 at different age groups. Furthermore, by detecting the predictor factors for fatality among these patients, it is possible to identify high-risk groups and reduce the fatality rate by focusing on their treatment.

MATERIALS AND METHODS

In this prospective cohort study, the required data were obtained from patients with COVID-19 admitted to Khorshid Hospital (Isfahan, Iran) during February 23 and April 30, 2020 (6). All the patients were included in the study when they were either discharged from the hospital or passed away. All patients aged above 18 years, who were hospitalized with clinical symptoms of COVID-19 for more than a night and had positive RT-PCR test results (7) or typical COVID-19 CT scan findings (according to the benchmarks of Society of Radiology) (8), were included in this study. This study was supported by the Isfahan University of Medical Sciences and approved by the Ethics committee of the university (Code: IR.MUI.MED.REC.1399.351).

The clinical data were extracted from the patients' medical history and then recorded. The collected data encompassed demographic information, comorbidity, home medication, clinical symptoms, initial laboratory, CT scan findings, and outcomes (i.e., intubation, admission to ICU, length of stay in ICU, length of stay in the ward, and fatality rate). In this regard, the patients who died immediately after intubation were classified as non-intubated. The primary objective of this study was to compare the clinical and paraclinical symptoms among three young, middle-aged, and elderly groups, and the secondary objective of the research was to evaluate the outcomes in these three groups.

Statistical analysis

One-way analysis of variance (ANOVA) was applied for continuous variables as means and standard deviations, while categorical variables were compared by chi-squared tests. The Cox proportional hazards model was employed for the classified variables to compare groups of time with event data. The statistically significant hazard ratios were considered in a 95% confidence interval. The linear regression model was adopted for a continuous outcome at $p < 0.05$ was considered a statistically significant beta coefficient. All the statistical data were processed for analysis and visualization using IBM SPSS software version 26.0 and MS-Excel.

RESULTS

Out of the 1185 patients with suspected COVID-19, 1065 patients were discharged or died. Among the 1065 patients, 654 patients had positive PCR results (N=451) and typical CT-scan findings and were thus included in the study (median age: 57.7 years; range: 18-99 years). Table 1 presents the participants' baseline characteristics. As presented in Table 1, 77 (11.8%), 353 (54%), and 234 (34.2%) patients were assigned into the young, middle-aged, and elderly groups, respectively. Above 80% of the young patients self-reported that they had been in close contact with the infected individuals; however, the rates were 65.2% and 18.2% for the middle-aged and elderly groups, respectively (p=0.017). The time interval between symptom onset and hospitalization was significantly shorter in the young group than in the middle-aged and elderly groups (p=0.009).

Table 2 presents the clinical and paraclinical findings. As it can be noticed, there are no statistically significant differences in clinical symptoms among the three age groups. Dry coughing was the most common symptom observed in the elderly and middle-aged groups (76.3% and 77.14%, respectively), while fever was the most common symptom in the young group (77.7%). Among the laboratory findings (Table 3), significant differences were observed in C-reactive protein (CRP) (p=0.023) and ESR (p=0.001); however, not such a difference was noticed among the three groups in terms of ferritin (p=0.094).

Although the severity of involvement in the CT scans of young patients (6±7.67) was less than that of middle-aged (9.6±5.2) and elderly (9.23±5.67) patients, this difference was not statistically significant among the research groups (p=0.142). Ground-glass opacity (GGO), consolidation, and GGO-consolidation were the most common findings in the elderly (p=0.013), young (p=0.024), and middle-aged (p=0.004) groups, respectively (Table 3).

Of the 654 patients, 88 persons (13.5%) were admitted to the ICU, 23 persons (5.1%) were intubated, and 53 individuals (8.1%) died (Table 4). The intubation rates in the young, middle-aged, and elderly groups were 2.3%, 1.38%, and 6.4%, respectively (p≤0.001). In the Cox model, the young group was considered the reference group, and the hazard ratio was estimated in comparison with each of the other categories (Table 5). The first model was a raw model for all the outcomes. Although the estimated hazard ratios were not significant, admission to the ICU and fatality rate in the middle-aged group were 29% and 27% higher than those ratios in the young group, respectively. However, the intubation rate in the middle-aged group was 66% less than that in the young group. The hazard ratio of admission to ICU in the middle-aged to young groups was 0.96%. The outcomes of fatality and intubation in the elderly group increased by 0.06% and 0.82%, respectively, compared to the young group. The effect of gender and main variables (in the groups of contact variables, vital symptoms, comorbidities, and biochemistry parameters) on the desired outcome was eliminated in the second to fourth models. Although the results were not significant in the fourth model, the hazard ratios of the length of stay in the hospital were 1.10 and 3.27 in the elderly and middle-aged groups compared to the young group, respectively.

Moreover, the hazard ratios of fatality rate in the middle-aged and elderly groups were 1.65 and 2.40 times higher than those in the young group, respectively. The hazard ratio of intubation in the middle-aged group decreased by 25% compared to the young group; however, the difference was not statistically significant. In contrast, as a statistically non-significant finding, the hazard ratio of intubation in the elderly group was 4.8 times higher than that in the young group.

The regression coefficients estimated by the linear regression model for the outcomes of the length of stay at hospital and ICU showed that the length of stay at hospital increased by about half a day with aging in each age group at a statistically significant *p*-value. On the other hand, the length of stay in ICU decreased by about two days with increasing age in each age group, at a statistically non-significant value. These results are reported in Table 5 in the form of four fitted models. The first model did not adjust the effect of any of the variables. In the three other models, the effects of gender and significant variables on contact variables, vital symptoms, comorbidities, and biochemistry parameters were adjusted in the three groups, respectively.

Table 1. Demographics and baseline characteristics of patients by age groups

Variables	Young people (<35 years)	Middle age (35-65 years)	Elderly (=<65 years)	P-value
Total number, %	77(11.8%)	353(54%)	224(34.2%)	
Gender (Men), %	39(50.6%)	225(63.7%)	121(54.0%)	0.038
House area, (M^2)	163.1(80.54)	165.4(86.23)	198.1(128.03)	0.001
Close contact, %	61(80%)	229(65.2%)	40(18.2%)	0.017
Travel,%	14(15.2%)	64(18.1%)	23(10.3%)	0.295
Symptom duration (day)	5.4(4.5)	7.6(5.8)	7.6(6.6)	0.009
BMI (kg/m2)	28.0 (5.51)	27.9	27.0	0.018
Co-morbidities (N),%				
Diabetes	3(3.9%)	86(24.3%)	85(37.9%)	<0.001
Hypertension	7(9.1%)	106(30.0%)	120(37.9%)	<0.001
Cardiovascular disease	3(3.9%)	55(15.6%)	80(35.9%)	<0.001
Respiratory disease	10(12.9%)	54(15.29%)	35(15.6%)	0.300
Chronic kidney disease	6(7.8%)	18(5.1%)	14(6.25%)	0.133

Table 2. Signs and symptoms of patients at admission by age groups

Variables on Triage	Young people (<35 years)	Middle age (35-65 years)	Elderly (<65 years)	P-value
Sneeze	8(1.3%)	20(5.6%)	20(8.9%)	0.147
Fever	56(72.7%)	245(69.1%)	139(62.1%)	0.088
Fatigue	37(48.0%)	202(57.4%)	118(52.5%)	0.102
Dry cough	49(63.5%)	265(75.1%)	163(72.2%)	0.552
Headache	25(32.8%)	145(41.5%)	75(33.9%)	0.058
Shortness of breath	47(61.5%)	228(64.8%)	149(66.5%)	0.652
Diarrhea	17(22.9%)	78(22.8%)	56(29.0%)	0.796
Nausea	28(36.8%)	139(39.5%)	73(32.2%)	0.220
Sore throat	14(18.9%)	59(16.3%)	40(17.8%)	0.820
Vomiting	19(24.8%)	93(26.8%)	53(23.2%)	0.778
Abdominal pain	18(23.4%)	57(16.1%)	35(15.6%)	0.395
Decreased appetite	32(41.5%)	155(43.9%)	91(40.6)	0.725
Temperature (**℃**)	37.7 (1.39)	37.3(1.08)	37.2(1.10)	0.004
Temperature ≥38	32(41.6%)	107(30.3%)	58(25.9%)	0.035
Respiratory rate (breath/min)	22.4 (5.16)	21.8 (5.25)	22.4 (5.53)	0.229
Respiratory rate ≥20	49(63.6%)	225(63.7%)	158(70.5%)	0.432
Heart rate (beat/min)	94.1 (15.6)	95.0 (17.45)	95.8 (17.60)	0.618
Systolic blood pressure (mmHg)	125.1 (16.18)	132.7 (19.99)	132.9 (21.30)	<0.001
SaO_2 (%)	89.0 (7.93)	89.2 (7.79)	88.9 (8.07)	0.282
SaO_2 **(≥90%)**	32(41.6%)	107(30.3%)	58(25.9%)	0.414
PH	7.36(0.07)	7.35(0.06)	7.35(0.08)	0.178
HCO_3 (mEq/L)	23.98(3.52)	24.23(4.25)	23.60(4.39)	0.112
PCO_2 (mmHg)	45.54(10.90)	46.57(11.97)	45.62(13.09)	0.418

Table 3. Paraclinical (Laboratory and radiological) findings of patients by age groups

Variables	Young people (<35 years)	Middle age (35-65 years)	Elderly (<65 years)	P-value
Biochemistry Parameters				
White blood cell count (× 10^9 /L)	6835.00 (48883.37)	6654.63 (4469.94)	7767.1 (5850.11)	0.005
Lymphocyte (%)	20.1 (9.84)	19.6 (9.67)	21.00 (11.72)	0.057
Lymphocyte count <1500	52(67.5%)	269(76.2%)	144(64.2%)	0.007
Platelet count (× 10 9 /L)	199.2 (94.81)	196.55 (79.55)	193.8 (76.08)	0.793
HB (g/dl)	13.5(2.0)	13.4(1.8)	12.4(1.9)	<0.001
ALT (U/L)	32.8 (35.89)	43.6 (146.6)	21.00 (11.72)	0.124
AST (U/L)	337.4 (35.89)	50.1 (93.62)	44.8 (38.19)	0.208
Ferritin (micrograms / liter)	545.9 (236.48)	461.8 (285.09)	506.1 (286.6)	0.094
CRP (mg/l)	23.27 (22.16)	29.48 (22.08)	30.1 (23.18)	0.023
ESR (mm/hr)	33.84 (27.86)	43.88 (27.6)	44.95 (28.69)	0.001
Cr (mg/dl)	1.16 (1.18)	1.13 (1.01)	1.24 (1.11)	<0.001
CT scoring	6.0 (7.76)	9.6 (5.26)	9.23(5.67)	0.142
CT scoring ≥7	67(29.9%)	147(41.6%)	20(25.9%)	0.003
GGO	12(15.6%)	80(22.6%)	54(24.1%)	0.013
GGO + consolidation	13(16.9%)	97(27.4%)	29(12.9%)	0.004
Consolidation	8(10.3%)	15(4.2%)	8(3.5%)	0.024
Pleural effusion	1(0.4%)	14(3.9%)	19(8.5%)	0.004
Distribution				0.419
Upper	18(23.3%)	65(18.4%)	50(22.3%)	
Lower	35(45.4%)	148(41.9%)	84(37.5%)	
None	24(31.2%)	139(39.4%)	89(39.7%)	
Transverse				0.346
Peripheral	32(41.5%)	181(51.3%)	104 (46.4%)	
Central	18(23.4%)	60(16.9%)	48 (21.4%)	
None	27(35.1%)	112 (31.7%)	72 (32.1%)	
Region (*Bilateral*)	26 (33.7%)	167(47.3%)	83 (37.1%)	0.439

Table 4. Estimated HRs and betas by Cox proportional hazards regression and linear regression models for different outcomes

		Model 1	Model 2	Model 3	Model 4
Estimated HRs and 95% CIs by Cox proportional hazards regression models					
Admission to ICU	HR_1	1.29 (0.67-2.47)	1.30 (0.68-2.5)	1.10 (0.55-2.1)	1.10 (1.11-11.1)
	HR_2	0.96 (0.67-1.38)	0.96 (0.67-1.37)	0.95 (0.65-1.38)	3.27 (0.70-15.2)
Mortality	HR_1	1.27 (0.53-3.04)	1.28 (0.53-3.09)	1.15 (0.45-2.89)	1.65 (0.2-11.9)
	HR_2	1.06 (0.65-1.72)	1.04 (0.63-1.71)	1.01 (0.62-1.67)	2.40 (0.7-7.2)
Intubation	HR_1	0.66 (0.15-2.85)	0.52 (0.11-2.35)	0.66 (0.12-3.37)	0.25 (0.02-3.12)
	HR_2	1.82 (0.78-4.23)	1.85 (0.79-4.31)	2.28 (0.91-5.73)	4.85 (1.45-16.3)
Estimated B coefficient and standard error by linear regression models					
Hospitalization duration	B coefficient (std. error)	1.35 (0.243)	1.36 (0.243)	1.20 (0.265)	1.36 (0.724)
	p-value	<0.001	<0.001	<0.001	0.061
ICU duration	B coefficient (std. error)	-2.323 (5.49)	-2.357 (1.379)	-1.7 (1.302)	-1.5 (1.462)
	p-value	0.090	0.084	0.215	0.277

HR_1: hazard ratio for young to middle-age group

HR_2: hazard ratio for young to elderly group

Model 1: adjusted for age group

Model 2: adjusted for age group and sex

Model 3: adjusted for age group, sex and comorbidities

Model 4: adjusted for age group, sex, comorbidities and symptom duration with the rest of significant biochemistry parameters

DISCUSSION

This cohort study on 654 patients with COVID-19 investigated the behavior of the virus in terms of clinical and paraclinical manifestations and outcomes at different age groups. The results showed that the risk of COVID-19 infection varies in different age groups. Although no significant differences were observed in clinical manifestations of this disease between the groups, some clinical and paraclinical findings and outcomes were different among them.

In our study, more than half of the patients were in the middle-aged group (65-35 years) with the mean age of 52 years. Like most studies, men constituted most of the infected population in the present study (2, 9-12). The prevalence of SARS and MERS infections was also higher among men (13, 14). The present findings revealed that the clinical symptoms of upper respiratory tract infection (URTI) were fewer than those of the lower respiratory tract infection (LRTI), and that there was no significant difference among the age groups. Dyspnea is the most important symptom of LRTI, the prevalence of which in COVID-19 is reported to vary from 30% to 50% (2, 15). There are different causes of dyspnea in respiratory infections. The different prevalence of dyspnea in different populations seems to be influenced by these factors, and infection cannot justify the degree of dyspnea. Like some other studies, the results of the present study indicated no significant difference in the prevalence of coughing among the age groups (15, 16); however, it was lower in the elderly group than in the other groups.

Fever is a defense response to infection. In this regard, older adults are less likely to develop fever in infection due to their weakened immune systems. According to some relevant studies, 44-75% of patients with COVID-19 had

fever at the time of referral (15-17). Different fever prevalence may be due to differences in the mean ages of the studied population or in the days of fever screening. It can be predicted that the lower prevalence of fever in the elderly due to underlying diseases or weakened immune systems can suppress the infection symptoms and delay the diagnosis of the infection. In other words, fever cannot be an excellent diagnostic predictor of the disease; especially in the elderly as such its use for screening and ruling out the disease may lead to the diagnosis failure in many patients.

Almost half of the patients complained of fatigue and myalgia, and this was more frequent in this study compared to the statistics of other studies (2, 10, 18). However, there was no significant difference among different age groups in this regard. Fatigue-inducing factors such as anemia, depression, comorbidities, nutritional problems, and vitamin deficiencies are more common in the elderly. Lack of difference in the prevalence of fatigue among the age groups indicates that the main causes of fatigue and weakness in patients with COVID-19 probably are the nature of the disease and the excessive secretion of inflammatory cytokines (19).

In this study, some factors providing the grounds for virus transmission were evaluated, which encompassed the house area, being in close contact with the infected, and a history of traveling to areas with a high prevalence of COVID-19. In general, 80% of the young patients reported close contact with infected persons, while only 18% of the elderly had experienced such close contact. Furthermore, the area of the house was larger for the elderly group. These findings suggest that the elderly are much more prone to infection than the young and middle-aged. Coronaviruses are usually transmitted through the air or close contact (20). Although previous studies have all reported higher fatality rates among the elderly, we found no study reporting that the older are more likely to develop COVID-19 compared to other age groups. Our investigation indicated that older individuals, including those observing social distancing, were more likely to be affected by COVID-19 than the other age groups. The time interval between symptom onset and hospitalization in the young group was shorter than in that in the middle-aged and elderly groups (p = 0.006). Given that there was no significant difference in clinical symptoms among the research groups in this study, the hospitalization of young patients could be because this age group was either more concerned about the disease or more afraid of the virus. It also seems that the elderly individuals do not refer to hospitals because of being afraid of contact with COVID-19 in hospitals.

Our study revealed that about one-third and two-thirds of the patients had RR <20 and HR <100 beats/minute at the triage, respectively. This finding is consistent with other studies' findings (9, 21), implying that normal vital signs do not rule out COVID-19-induced pneumonia at any age. Although the prevalence of hypoxia at the triage was higher in the elderly than in the other groups, the difference was not statistically significant. According to the findings of our study, in all three age groups, among the vital signs, RR and sataO2 were the most sensitive criteria for suspected COVID-19 patients with pulmonary involvement.

In our patients, the average number of WBCs was significantly higher in the elderly than in other groups; however, leukocytosis was prevalent in none of the study group. Unlike Liu's et al. study (16), the present study concluded that the prevalence of lymphopenia was higher in the middle-aged and elderly groups. The prevalence of lymphopenia has been 30-80% among the COVID-19 patients (9, 10, 21). Regarding the COVID-19 disease, the release of cytokines by inflammatory cells leads to severe inflammation (22). Moreover, there was no significant difference among different age groups in terms of mean ferritin level; however, the CRP and ESR levels in the elderly group were higher than those in the other two groups. Although an increase in the ESR levels can be justified by increased age, elevated CRP levels in the elderly may indicate more inflammation. Some studies have also documented that the CRP levels were higher in

the elderly than in other groups (16). According to our findings, among the inflammatory factors, increased ferritin levels in all groups and increased CRP in the elderly are acceptable markers to determine the severity of inflammation in patients with COVID-19.

According to our findings, the CT scan involvement in the middle-aged group was more extended than that in the young and elderly groups. Moreover, consolidation and GGO lesions varied across age groups. Since one of the factors leading to lesion densification on the CT scan is the body's response to the virus, consolidation lesions were probably more common in the young patients, and the GGO pattern was more observed in the elderly (23). The higher prevalence of pleural effusion in the elderly can be due to concomitant diseases such as heart failure (Table 4).

In this study, 53 patients died (8%), while other studies have reported different Coronavirus mortality rates (3.8%-28%) (2, 9). Although in our study population, 10.26% of individuals aged above 65 years old and 3.8% of young individuals died, there was no significant difference among the research groups. Most studies have concluded that aging is a mortality predictor in COVID-19 patients (9, 10, 21). Although this finding was also achieved in the present study, the difference was not significant in this regard. This lack of statistical significance can be due to unequal sample sizes.

In our study, the elderly patients were intubated or hospitalized in ICU more frequently than the other groups, and this finding was consistent with other studies (3, 9, 10, 21). Although the length of hospital stay was longer in the elderly group, the mean length of ICU stay in the young group was twice as long as that of the elderly group. Young patients are usually admitted to ICU when they are under critical conditions; however, older individuals are transferred to ICU when their condition is not much severe or critical because of the complications of their disease. In other words, older individuals discharge from ICU sooner.

Limitations

This study had several limitations. First, due to the lack of diagnostic kits for PCR at the beginning of the outbreak in Iran, including all the patients in the study was impossible. As a result, several hospitalized patients with COVID-19 symptoms were not included. Second, since we compared only the three age groups, this analogy cannot be generalized to out-patients. Third, the number of patients was not similar in the research groups. Fourth, although the treatment protocols were the same, the effect of medication on the outcomes was not considered.

CONCLUSION

The present study showed that elderly patients were more likely to develop COVID-19, while they may have no close contact with other patients and may even live in larger houses. Although there was no significant difference in the clinical symptoms and some paraclinical findings among the age groups, an increase in CRP, ESR, WBC, Bun, Cr, and lymphocytes was mainly observed in the elderly. No significant difference was also observed in the involvement on CT scans of the patients in different age groups; however, the type and pattern of involvement differed. Finally, the length of hospital stay was longer in the elderly group; however, the length of ICU stay was more prolonged in the young group.

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