OLDER ADULTS WITH CORONAVIRUS DISEASE 2019; A NATIONWIDE STUDY IN TURKEY

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Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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ABSTRACT

Background: A novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) occurred in China in December 2019 and has spread globally. In this study we aimed to describe the clinical characteristics and outcomes of hospitalized older adults with coronavirus disease 2019 (COVID-19) in Turkey.

Methods: We retrospectively analyzed the clinical data of hospitalized patients aged ≥ 60 years with confirmed COVID-19 from March 11, 2020, to May 27, 2020 using nationwide health database.

Results: In this nationwide cohort, a total of 16942 hospitalized older adults with COVID-19 were enrolled, of whom 8635 (51%) were women. Mean age was 71.2 ± 8.5 years, ranging from 60 to 113 years. Mortality rate before and after curfew was statistically different (32.2% vs 17.9%; p < 0.001, respectively). Through multivariate analysis of the causes of death in older patients, we found that male gender, diabetes mellitus, heart failure, chronic kidney disease, dementia, cancer, admission to intensive care unit, computed tomography finding compatible with COVID-19 were all significantly associated with mortality in entire cohort. In addition to abovementioned risk factors, in patients aged between 60-79 years, coronary artery disease, oxygen support need, total number of drugs, and cerebrovascular disease during hospitalization, and in patients 80 years of age and older acute coronary syndrome during hospitalization were also associated with increased risk of mortality.

Conclusions: In addition to the results of previous studies with smaller sample size, our results confirmed the age-related relationship between specific comorbidities and COVID-19 related mortality.

Key	Words:	Nationwide,	COVID-19,	Infection,	Risk	Factors
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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) infection which is caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has recently emerged and spread rapidly causing a pandemic (1). As of May 28, 2020, there were 5,593,631 confirmed cases of COVID-19 with 353,334 deaths globally (2). The Centers for Disease Control and Prevention (CDC) reported that individuals older than age 65 comprise 17% of the total population in the United States, though they are responsible for 31% of COVID-19 infections, 45% of hospitalizations, 53% of intensive care unit (ICU) admissions and 80% of deaths caused by COVID-19 (3). In a study with 44,672 confirmed cases, the case fatality rate (CFR) is 2.3 %, however 70–80-year-old age group patients have a CFR of 8.0%, and patients above age 80 have a CFR of 14.8% (4). This suggests that older adults are more susceptible to COVID-19 and are at significantly increased risk for morbidity and mortality compared with the general population (5). Physiologic changes of aging, multiple age-related comorbid conditions such as heart and lung disease, diabetes, dementia, and polypharmacy are associated with poor outcomes in older patients (6).

The first case in Turkey was detected on March 11, 2020. As of May 28, 2020, there were 159,797 confirmed COVID-19 cases and 4431 deaths (2). In addition to the several measures taken to prevent the spread, a curfew imposed for whom aged \geq 65, on March 21, 2020, intending to lower the mortality among geriatric individuals (7).

This study aims to describe the clinical characteristics and to evaluate the outcomes of the geriatric patients with COVID-19 in a nationwide basis, which might provide evidence for the risk stratification and help to improve the clinical practice.

MATERIAL AND METHODS

Study population and Data collection

Every patient aged 60 years and over with confirmed COVID-19 by positive real-time reverse transcriptase polymerase chain reaction (RT-PCR) test in Turkey between March 11 and May 27, 2020 were screened retrospectively. Epidemiological, clinical, and radiological characteristics along with treatment and outcome data were obtained from Turkish Ministry of Health National COVID-19 Database. Presentation symptoms such as fever, cough, and shortness of breath were also recorded however they were excluded from the analysis because of the great number of missing data. The presence of underlying comorbidities and the complications of COVID-19 after admission were identified based on the International Classification of Diseases and Injuries-10 diagnostic codes on the database.

This study was carried out in accordance with the permission of the Ministry of Health issue numbered 95741342-020.

Statistical Analysis

SPSS for Windows v.23.0 (SPSS Inc., Chicago, IL) was used for the statistical analyses. Variables were examined using visual and analytical methods to determine whether they were normally distributed. Categorical variables were shown as numbers and frequencies, with differences being analyzed by the Chi-square test or Fisher's exact test, where appropriate. Continuous data that followed a normal distribution was described with mean and standard deviation and between-group comparisons were performed by independent samples t-test. When distributions were not normal, the data were described with median (min-max) and group comparisons were done using the Mann – Whitney U test. The unadjusted logistic regression model was used to assess the significant predictors of mortality. Multivariate models were also generated by adjusting gender, presence of hypertension (HT), diabetes

mellitus (DM), chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), atrial fibrillation (AF), chronic kidney disease (CKD), dementia, depression, malnutrition, and hyperlipidemia (HL) in model. Patients were categorized into two groups based on their age (60-79 and 80-133) while performing multivariable logistic regression. Hosmer–Lemeshow goodness-of-fit statistics were used to assess model fit. A 5% type I error level was used to infer statistical significance.

RESULTS

The total number of the ≥ 60 years-of-age patients infected with SARS-CoV-2 until date of May 27 was 24510 of whom 16942 (69.1%) hospitalized and 7568 (30.9%) were treated as outpatients. While the mean age of all patients was 71.2 ± 8.5, it was 70.6 ± 8.2 and 71.8 ± 8.8 for the males and females, respectively. Number of hospitalized and non-hospitalized patients, sex distribution and mortality rates by age groups are shown in Table 1.

On admission, 1663 people (9.8%) were taken to ICU directly and 15279 patients (90.2%) were hospitalized in normal wards of whom 21.1% (n=3224) were transferred to ICU during follow-up. While the rate of hospitalization in the 60-64 age group on admission was 5.5%, 18.9% of the patients in this age group required intensive care during hospitalizations. In the 80+ age group, 17.4% were directly hospitalized in ICU, whereas 43.1% of the patients who were hospitalized in normal wards firstly were required intensive care eventually. Median durations of ICU stay were statistically similar among the age groups and approximately 6 days. However, there was a significant difference between the age groups in the total length of hospital stay which increased with age. Similarly, rates of need for oxygen support and requirement for intubation were increasing with the age. The distribution of patients' service admissions, ICU follow-ups and intubation rates by age groups are shown in Table 1.

During hospitalization, 57.6% of people who had a history of ICU stay and 2.7% of whom without a history of ICU stay died. Mortality rates for the patients who were intubated and without intubation were 71.4% and 5.2%, respectively. Mortality rates increased with advancing age for both ICU patients and intubated patients. The details of these rates according to age groups is shown in Table 2.

To evaluate the effectivity of the partial curfew which was imposed for the individuals \geq 65years-of-age starting on March 21st,2020 considering the 14-day incubation time of the virus, the patients were divided into two, which were diagnosed before and after April 5, 2020 after exclusion of the patients of age group 60-64 from the study sample. Of the 3355 patients aged \geq 65 who were diagnosed with COVID-19 before April 5, 1081 (32.2%) died. Whereas it was 1623 (17.9%) who died among the 9050 patients who were diagnosed after April 5, 2020 as of May 27, 2020. The difference between the fatality rates of these two groups was statistically significant (p <0.001). In Table 3, the effects of curfew on the rates of mortality, ICU hospitalizations and intubations are shown.

Computed tomography (CT) of the chest was performed at least once in 79.5% of the patients of which 61.9% were found to be compatible with COVID-19 radiological findings. In the CT examination, in which bacterial, viral, and mixed infection findings, which are frequently confused with the COVID-19 clinically, were also differentiated, and 1.1% was found to be compatible with bacterial and 42% with viral pneumonia.

In Turkey, 34.5% of the patients infected with SARS-CoV-2 over the age of 60 and 40.8% of the age group \geq 80 were given favipiravir for treatment. Hydroxychloroquine, which was commonly used as well as favipiravir, was given to 79.3% of the patients. Other agents tried in treatment regimens other than hydroxychloroquine and favipiravir were lopinavir /

ritonavir, high-dose vitamin C, azithromycin and other macrolide antibiotics, quinolone group antibiotics, tocilizumab and steroids.

Studies till now showed that some comorbidities may constitute risk factors for poor prognosis. Among these, DM, HT, COPD, CAD, HL, heart failure (HF), AF, CKD, dementia, depression, malnutrition, osteoporosis, urinary incontinence, and malignancy in older patients were examined in our study. The table related to the frequencies of these comorbidities according to age groups can be accessed from the supplementary appendix in Table S1.

Complications that develop during hospitalization such as ACS, deep vein thrombosis (DVT), CVE, seizures, falls and fractures were examined and the most striking among these was the frequency of DVT which was developed in 534 patients (3.2%).

In univariate regression analysis, ACS was observed to increase the mortality risk by 3.42 times (Confidence Interval (CI): 2.0-5.83; p <0.001). Similarly, CVE and seizures during hospitalization, increased the mortality risk by 3.88 (CI: 2.89-5.21; p <0.001) and 2.45 (CI: 1.30-4.60; p: 0.006) times, respectively. The rates of all complications by age groups and the results of univariate regression analysis are accessible in supplementary appendix (Table S2).

The factors associated with COVID-19-related mortality were examined, firstly with univariate regression model which included age and the comorbidities. Considering that the prevalence of certain chronic diseases that might affect the vulnerability of the patient increases with advancing age, the analyses was carried out for the whole group, 60-79 years old and \geq 80 age group, separately. Age and male sex increased the risk of mortality. Need for oxygen support seemed to be a poor prognostic factor in terms of mortality. Polypharmacy which is a common problem and an indirect indicator of frailty for older patients, caused an increased risk of mortality per drug added. DM, HT, COPD, CAD, HL, HF, AF and CKD, which are common comorbidities in the older patients, were shown to increase mortality for

whole sample and DM, CAD, AF, COPD, HF, and CKD were common risk factors for mortality in separate age groups. Dementia, depression, and malnutrition are geriatric syndromes that cause frailty in older patients and increase morbidity and mortality. In univariate regression, these geriatric syndromes increase mortality risk in COVID-19 patients. Odds ratios for dementia and malnutrition were 2.33 (CI: 2.08-2.60) and 2.73 (CI: 2.01-3.7), respectively (both p<0.001). Other factors affecting mortality are accessible in supplementary appendix (Table S3).

Multivariate regression analysis was conducted after dividing the whole sample into two agegroups, as 60-79 and \geq 80 with the aim of obtaining more homogeneous groups by reducing the known effect of advancing age on mortality. Variables such as gender, HT, DM, COPD, CAD, AF, CKD, dementia, depression, malnutrition, and HL were included in the model. In the 60-79 age group, male sex, HT, DM, HF, CKD, dementia, and cancer diagnosis; in the age group of \geq 80, male sex, DM, HF, dementia, and malnutrition were shown to increase mortality risk significantly (Table 4).

DISCUSSION

COVID-19 has caused an ongoing pandemic that affected people of all ages. However, it was recognized as more like a geriatric health disaster (8), with a high mortality rate in older adults with multimorbidities. Despite this, existing data yielded from studies included particularly older patients is scarce. The present study was conducted to investigate the clinical characteristics and outcomes of COVID-19, specifically for older adults on a nationwide scale. Data on patients aged 60 and over who were infected with SARS-CoV-2 in Turkey, were obtained from the national registry system of the ministry of health. Thus, it is estimated that this study will contribute significantly to the literature owing to its large sample size and scope.

The first COVID-19 case in Turkey was detected on March 11, 2020 which was the date WHO declared the outbreak a global pandemic (9). The first COVID-related death occurred on March 15, 2020 and then the disease had spread across the country with a trend similar to rest of the world. To reduce the spread of this highly contagious infection, Turkey responded by taking precautions quite rapidly. The Scientific Advisory Board established within the Ministry of Health gave recommendations on the management and treatment of the disease and published a guideline that were being updated according to current scientific data. In addition to the general preventive measures like prohibitions of gatherings and closure of all schools, mosques and public places, weekend curfews and a partial lockdown for the citizens aged ≥ 65 and ≤ 20 were imposed. In Turkey, universal health insurance system enables for all registered individuals to reach healthcare services free of charge. During the outbreak, The Turkish Ministry of Health expanded its coverage to provide testing and treatment for all residents free of charge. As of May 27, 2020, the crude CFR was 2.7% for all cases in Turkey. The main factor that kept the CFR lower compared to many countries is probably that individuals aged 60 and older make up 13.3% of the population. The percentage of individuals aged 80 and over is only 1.8% (10). Older patients (≥60 years of age) accounted for approximately 15% of all cases and 81% of nonsurvivors. CFR was 14.7% for the older patients including both hospitalized cases and outpatients and was 18.5% for hospitalized patients. Proportion of deceased cases increased with age, it was 32.8% and highest for the age group 80 and over. Besides all the preventive measures taken with the onset of the outbreak in Turkey, the imposition of a partial curfew for older individuals has been shown to significantly reduce the mortality rate in this group in addition to reductions in proportions of requirement for intubation and intensive care.

The fact that advanced age is among the important risk factors for COVID-19 related mortality has been almost certainly demonstrated by the evolving evidence on this subject (11, 12). However, the varying rates in different countries might have occurred due to multiple factors such as the proportion of older adults in the populations, how widespread the testing strategy that countries adopted, timing of the measures taken for risk groups as well as for general population, health centers' preparedness for the pandemic, and sufficiency of the resources in relation to the magnitude of the case surge. Latter two may also explain how mortality rates differ from region to region in a country. The sample size and sampling time during the course of the outbreak, and whether the study was a single-center experience, or multi-centered also might have resulted in changes in calculated CFRs (11, 13).

In the very first reports from Wuhan, the epicenter of the outbreak, fatality rate of the disease was frighteningly high for older adults. For instance, Chen et al (14) reported the mortality rate of the older patients from a university hospital located in Wuhan as 34.5% whereas it was 4.7% for younger patients. In our study sample, CFR of the hospitalized patients was 18.5% and reached to 32.8% for the age group ≥ 80 . It was higher than the rate for the same age group reported by Wu et al. (4), and in line with the results of a study from United States (US) (15), and based on data from the Pacific coast of US, lower than the rates which was calculated as 37.3% for the hospitalized patients aged 80 years and older (16). In New York City, the epicenter for US, CFRs reported as even higher: 21% for the whole sample and, 32% for the patients 60 years and older and 53% for the age group ≥ 80 (17). It is largely known that older individuals more commonly suffer from critical illness, namely requirement for hospitalization, intensive care and intubation are more frequent related to COVID-19 (12, 18). Thus, the high mortality rates shown in these studies can be partially explained by the relative shortage of healthcare resources due to the higher proportion of older individuals compared to our study. This could probably be the case in Italy where latest update reports declared that 53.2% of all cases were aged 60 years and over whose fatality rate approximately 25% (19)(20).

It is demonstrated that the total lockdown in Wuhan, provided slowing down of the spread of the infection and a significant increase in doubling time of the cases (21). In Turkey, in addition to closures of all public places and prohibition of social gatherings, a partial lockdown which included mainly seniors (≥ 65 years) and children was imposed on March 21, 2020. The results of the present study showed that, the lockdown measure had a significant impact on the decrease in frequencies of requirements for intensive care and intubation, and fatality rates of the patients aged 65 and older (32.2% vs 17.9%). Sanchez-Caballero et al. reported that partial and total lockdowns are equally effective at slowing the spread of COVID-19 (22). Furthermore, Bonardi et al. claimed that partial lockdowns were as effective as total lockdowns in slowing down the growth of number of deaths (23). Epidemiologic analysis of first 7755 cases of the Republic of Korea revealed that the spread of the disease start with younger population and proceed with older population surge (24). The partial lockdown measure in Turkey might have prevented further transmission of the disease by minimization of contact between older and younger individuals. Moreover, with the help of partial lockdown the viral load to be exposed by older patientsmight have decreased. In other words, since the older adults do not have intense contact with the external environment, they were introduced with relatively lower viral load even they were infected.. As a result of the decrease in the viral load, we think that the related disease course may have been observed milder as discussed in a few articles in the literature (25, 26).

Our results indicated that advancing age was also associated with more serious illness. It was 9.8% of older adults who had required intensive care on admission, and it increased with age and reached 17.4% for the age group \geq 80. Similarly, ICU requirements during the follow-up of the patients rise with increasing age which was 18.9% for the age group 60-64 and as high as 43.1% for the patients aged \geq 80. Length of ICU stay did not differ between age groups. Comparison with other studies in the literature may be misleading, as the criteria for ICU

admission may vary across countries and health-centers, depending on the availability of intensive care settings of different levels. However, several studies underscored increasing age among the main predictors of critical or severe illness (12, 14, 18). Correspondingly, proportions of the patients who required oxygen support and invasive mechanical ventilation (IMV) were higher with increasing age. Admission to ICU and requirement for IMV were both associated with higher rates of mortality: 57.6% and 71.4%, respectively. One of the earliest studies from China (27)and the study conducted by Richardson et al. (17) reported a worrying mortality rate of 97% for the patients who required IMV. According to the study conducted in New York City by Petrilli et al., 60.4% of the patients who required mechanical ventilation deceased (12). Mortality rates of patients might have varied according to whether early or late intubation strategies was adopted across different centers.

Male sex is another significant risk factor for mortality (14, 28) and is associated with a higher risk for a more severe clinical course (12, 29-31) that result in increased frequency of hospitalizations (32), increased probability of ICU admission (16) and death for all age groups (33). The present study revealed that, in univariate analysis male sex associated with 1.7-fold increased risk for death for older population. In multivariate analysis, this association revealed to be stronger for the "younger" geriatric population with an OR of 2.0 for the age group of 60-79 whereas it was calculated to be 1.5 for the patients aged 80 and older. This result is consistent with the findings reported in a review: results of pooled data from four countries of Europe showed the ratio of male-to-female case fatality to be most prominent for the age group of 50-59 and followed a decreasing trend through increasing age (32). Hence, it could be concluded that the age and sex interaction in COVID-19 fatality had been confirmed with the results of our study.

Underlying multiple chronic diseases constitute another important risk factor for severe illness and COVID-related mortality (14, 34, 35). Determined frequencies of several comorbidities and geriatric syndromes of the study sample revealed that HT, CAD, and DM were the three most common coexisting diseases. Proportions of the comorbidities were consistent with the results of the previous prevalence studies representing all population of geriatric age group in Turkey (36, 37), however, far more higher than other similar studies including older patients with COVID-19 (14, 18, 38). Rates of all investigated common comorbidities and geriatric syndromes were significantly higher for the deceased patients with an only exception of osteoporosis. Moreover, DM, HF, CKD, cancer diagnosis and dementia were the comorbidities which were independently associated with mortality in multivariable regression. Taking all these into account, it could be suggested that the relatively high CFR of our sample was partially due to the fact that the population described in this study composed of more or less 'frailer' individuals having multiple comorbidities (39-41). In a recent editorial, authors coined a term as "COVID Spiraling Frailty Syndrome" to explain the special vulnerability of older adults with DM and HT to COVID-19 related death (39). Further, in SARS-RAS study, Iaccarino et al emphasized that in addition to advanced age, the most important factor determining mortality was 'physical frailty' caused by disease burden measured with Charlson Comorbidity Index (42).

Along with other comorbidities, HL was more prevalent among the deceased patients. Notwithstanding this, multivariate regression revealed HL as an independent factor for lower mortality risk for the patients aged \geq 80. Considering the results that malnutrition was independently associated with higher mortality risk and observed with relatively higher frequency in this age group of patients, it may be suggested that the protective effect of HL against mortality could be originated from the inverse relationship with malnutrition (43). Moreover, about lipids and COVID-19, few studies are available some of which suggest that cholesterol levels decrease in relation to the severity of the COVID-19 and have prognostic value (44, 45) while others investigate the possible importance of lipid metabolism for viral

replication and effects of lipid-lowering drugs on COVID-19 treatment (46). In the current state, insufficient number of studies on this subject, as well as missing data on the treatment status of the patients diagnosed with HL and lipid level measurements during disease course avoid us to understand the underlying mechanism.

Among the mentioned chronic diseases, dementia deserves special emphasis for the scope of present study. Ten percent of the study sample had diagnosed with dementia and its frequency increase with age from 1.3% for the age group of 60-65 to 28.2% for the age group of \geq 80. The results that it was seen more frequently in patients who deceased and an independent risk factor for mortality in regression analyses, were in line with the results reported by Bianchetti et al (47).

With growing evidence and experience on management of COVID-19, CT gained more importance for the diagnosis. Its sensitivity was reported between 60%-98% in different studies (48, 49). Lian et al. reported that, older patients were more commonly and severely presented with multiple mottling and ground-glass opacity which are among the typical findings for COVID-19 (18). Further, Ai et al. found the positive predictive value and accuracy of CT imaging higher for the patients 60 years and older in comparison with that for younger (48). In the present study, 79.5% of the patients were evaluated with chest CT and most of them (61.9%) classified to be consistent with typical COVID-19 findings.

There are some limitations of the present study. First, since the data extracted from medical records retrospectively, data related to symptomatology of the patients, physical examination findings, comprehensive geriatric assessment, frailty, and malnutrition evaluations were missing or incomplete. Second, patients were not classified according to severity of clinical status. Third, it includes only RT-PCR confirmed cases.

To the best our knowledge, this study is the largest sample nationwide study to examine the clinical features and outcomes of older individuals diagnosed with COVID-19 so far. In addition to supporting the results of the previous studies with smaller sample sizes which had put forward the association of the factors like older age, male gender, and excessive comorbidity with the severity and mortality of the disease, our work confirmed the age-related relationship between specific comorbidities (DM, HF, CKD and cancer) and mortality, which have contradictory results in the available literature. Furthermore, as far as we know, for the first time, geriatric syndromes such as dementia, malnutrition, depression, and urinary incontinence were also included in the analysis investigating the factors associated with mortality.

CONCLUSION

In conclusion, SARS-CoV-2 in Turkey as well as all over the world has led to an ongoing epidemic that affected older individuals disproportionately. Patients aged 60 and older constituted more than 80% of the deceased patients. Timely preventive measures and lockdowns seemed to be contributed to the reduction of mortality at least for geriatric population. Except for osteoporosis, all the mentioned comorbidities and geriatric syndromes were more common among the nonsurvivors. Multivariate logistic regression revealed male sex, DM, HF, CKD, cancer, and dementia as the independent risk factors for mortality. Besides, for the "older old" patients (age group \geq 80) malnutrition was an additional independent risk factors and HL was related to lower mortality risk.

Declaration of interests

We declare no competing interests.

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REFERENCES

1. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;**579**:270-273. doi:10.1038/s41586-020-2012-7.

2. World Health Organization, Coronavirus Disease 2019 – Situation report-129. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200528-covid-19sitrep-129.pdf?sfvrsn=5b154880_2 (Accessed June 01,2020)

3. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) -United States, February 12-March 16, 2020. MMWR Morb Mortal Wkly Rep. 2020;**69**:343-346. doi:10.15585/mmwr.mm6912e2.

4. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. Jama. 2020;**323**:1239-1242. doi:10.1001/jama.2020.2648.

5. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al.* Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. Jama. 2020;**323**:1061-1069. doi:10.1001/jama.2020.1585.

6. Nikolich-Zugich J, Knox KS, Rios CT, Natt B, Bhattacharya D, Fain MJ. SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes. Geroscience. 2020;**42**:505-514. doi:10.1007/s11357-020-00186-0.

7. Demirbilek Y, Pehlivantürk G, Özgüler ZÖ, MEŞE EA. COVID-19 outbreak control, example of ministry of health of Turkey. Turkish journal of medical sciences. 2020;**50**:489-494. doi:10.3906/sag-2004-187.

8. Salimi S, Hamlyn JM. COVID-19 and Crosstalk With the Hallmarks of Aging. J Gerontol A Biol Sci Med Sci. 2020. doi:10.1093/gerona/glaa149.

9. WHO Timeline - COVID-19. <u>https://www.who.int/news-room/detail/27-04-2020-</u> who-timeline---covid-19. Accessed: June 6, 2020.

Türkiye İstatistik Kurumu (TÜİK) (Turkish Statistical Institute), Elderly Statistics,
 <u>http://www.turkstat.gov.tr/PreHaberBultenleri.do?id=33712</u>. Published: March 18,
 Accessed: June 6, 2020

11. Deng X, Yang J, Wang W, Wang X, Zhou J, Chen Z, *et al.* Case fatality risk of the first pandemic wave of novel coronavirus disease 2019 (COVID-19) in China. *C*lin Infect Dis. 2020. doi:10.1093/cid/ciaa578.

12. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, *et al.* Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ*. 2020;3**69:**m1966. doi:10.1136/bmj.m1966.

13. Wang W, Tang J, Wei F. Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. Journal of Medical Virology. 2020;92:441-447. doi:10.1002/jmv.25689.

14. Chen T, Dai Z, Mo P, Li X, Ma Z, Song S, *et al.* Clinical characteristics and outcomes of older patients with coronavirus disease 2019 (COVID-19) in Wuhan, China (2019): a single-centered, retrospective study. *J* Gerontol A Biol Sci Med Sci. 2020. doi:10.1093/gerona/glaa089.

15. Centers for Disease Control and Prevention. Severe Outcomes Among Patients with
Coronavirus Disease 2019 (COVID-19) — United States, February 12–March 16, 2020.
MMWR Morb Mortal Wkly Rep 2020;69:343-346. DOI: http://dx.doi.org/10.15585/mmwr.mm6912e2. Accessed June 6,2020.

16. Lewnard JA, Liu VX, Jackson ML, Schmidt MA, Jewell BL, Flores JP, *et al.* Incidence, clinical outcomes, and transmission dynamics of severe coronavirus disease 2019 in California and Washington: prospective cohort study. *B*mj. 2020;3**69:**m1923. doi:10.1136/bmj.m1923.

17. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, *et al.* Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *Jama.* 2020;323:2052-2059. doi:10.1001/jama.2020.6775.

18. Lian J, Jin X, Hao S, Cai H, Zhang S, Zheng L, *et al.* Analysis of Epidemiological and Clinical features in older patients with Corona Virus Disease 2019 (COVID-19) out of Wuhan. *C*lin Infect Dis. 2020. doi:10.1093/cid/ciaa242.

19. Italian SARS-CoV-2 Surveillance Group. Epidemia COVID-19, Aggiornamentonazionale,3giugno2020–ore15:00.https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-193-giugno-2020.pdfPublished: June 5, 2020, Accessed June 15, 2020.

20. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *Jama.* 2020;323:1775-1776. doi:10.1001/jama.2020.4683.

21. Lau H, Khosrawipour V, Kocbach P, Mikolajczyk A, Schubert J, Bania J, *et al.* The positive impact of lockdown in Wuhan on containing the COVID-19 outbreak in China. *Journal of Travel Medicine*. 2020;27. doi:10.1093/jtm/taaa037.

22. Sanchez-Caballero S, Selles MA, Peydro MA, Perez-Bernabeu E. An Efficient COVID-19 Prediction Model Validated with the Cases of China, Italy and Spain: Total or Partial Lockdowns? *J*ournal of clinical medicine. 2020;9. doi:10.3390/jcm9051547.

23. Bonardi J-P, Gallea Q, Kalanoski D, Lalive R. Fast and local: lockdown policies affect the spread and severity of covid-19. *C*ovid Economics 325. 2020;2**51.** doi.

24. Coronavirus Disease-19: The First 7,755 Cases in the Republic of Korea. *O*song Public Health Res Perspect. 2020;11:85-90. doi:10.24171/j.phrp.2020.11.2.05.

25. Liu Y, Yan LM, Wan L, Xiang TX, Le A, Liu JM, *et al.* Viral dynamics in mild and severe cases of COVID-19. *L*ancet Infect Dis. 2020;20:656-657. doi:10.1016/s1473-3099(20)30232-2.

26. Pujadas E, Chaudhry F, McBride R, Richter F, Zhao S, Wajnberg A, *et al.* SARS-CoV-2 viral load predicts COVID-19 mortality. *L*ancet Respir Med. 2020. doi:10.1016/s2213-2600(20)30354-4.

27. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *L*ancet. 2020;3**95**:1054-1062. doi:10.1016/s0140-6736(20)30566-3.

28. Promislow DEL. A Geroscience Perspective on COVID-19 Mortality. *The Journals of* Gerontology: Series A. 2020. doi:10.1093/gerona/glaa094.

29. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, *et al.* Clinical Characteristics of Coronavirus Disease 2019 in China. *N*ew England Journal of Medicine. 2020;3**82:**1708-1720. doi:10.1056/NEJMoa2002032.

30. Zhao S, Cao P, Chong M, Gao D, Lou Y, Ran J, *et al.* The time-varying serial interval of the coronavirus disease (COVID-19) and its gender-specific difference: A data-driven analysis using public surveillance data in Hong Kong and Shenzhen, China from January 10 to February 15, 2020. *Infect* Control Hosp Epidemiol. 2020:1-8. doi:10.1017/ice.2020.64.

31. Mo P, Xing Y, Xiao Y, Deng L, Zhao Q, Wang H, *et al.* Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *C*linical Infectious Diseases. 2020. doi:10.1093/cid/ciaa270.

32. Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL. Impact of sex and gender on COVID-19 outcomes in Europe. *B*iol Sex Differ. 2020;11:29. doi:10.1186/s13293-020-00304-9.

33. Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, *et al.* Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. *Front* Public Health. 2020;8:152. doi:10.3389/fpubh.2020.00152.

34. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, *et al.* Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *International* Journal of Infectious Diseases. 2020;94:91-95. doi:https://doi.org/10.1016/j.ijid.2020.03.017.

35. McMichael TM, Currie DW, Clark S, Pogosjans S, Kay M, Schwartz NG, *et al.* Epidemiology of Covid-19 in a Long-Term Care Facility in King County, Washington. *New* England Journal of Medicine. 2020;3**82:**2005-2011. doi:10.1056/NEJMoa2005412.

36. Satman I, Omer B, Tutuncu Y, Kalaca S, Gedik S, Dinccag N, *et al.* Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. *European Journal of Epidemiology*. 2013;28:169-180. doi:10.1007/s10654-013-9771-5.

37. Sengul S, Akpolat T, Erdem Y, Derici U, Arici M, Sindel S, *et al.* Changes in hypertension prevalence, awareness, treatment, and control rates in Turkey from 2003 to 2012. *Journal of hypertension.* 2016;3**4**:1208. doi:10.1097/HJH.00000000000000901.

38. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, *et al.* Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *Jama.* 2020;323:1574-1581. doi:10.1001/jama.2020.5394.

39. Abbatecola A, Antonelli-Incalzi R. COVID-19 spiraling of frailty in older Italian patients. *J* Nutr Health Aging. 2020:1-3. doi:10.1007/s12603-020-1357-9.

40. Bellelli G, Rebora P, Valsecchi MG, Bonfanti P, Citerio G, Galimberti S, *et al.* Frailty index predicts poor outcome in COVID-19 patients. *Intensive Care Medicine*. 2020. doi:10.1007/s00134-020-06087-2.

41. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the Concepts of Disability, Frailty, and Comorbidity: Implications for Improved Targeting and Care. *The Journals of Gerontology: Series A. 2004;59:M255-M263. doi:10.1093/gerona/59.3.M255.*

42. Iaccarino G, Grassi G, Borghi C, Ferri C, Salvetti M, Volpe M. Age and Multimorbidity Predict Death Among COVID-19 Patients: Results of the SARS-RAS Study of the Italian Society of Hypertension. *Hypertension*. 2020:Hypertensionaha12015324.

43. Hrnciarikova D, Hyspler R, Vyroubal P, Klemera P, Hronek M, Zadak Z. Serum lipids and neopterin in urine as new biomarkers of malnutrition and inflammation in the elderly. *Nutrition* (Burbank, Los Angeles County, Calif). 2009;2**5:**303-308. doi:<u>https://doi.org/10.1016/j.nut.2008.09.009</u>.

44. Fan J, Wang H, Ye G, Cao X, Xu X, Tan W, *et al.* Letter to the Editor: Low-density lipoprotein is a potential predictor of poor prognosis in patients with coronavirus disease 2019. *M*etabolism. 2020;107:154243. doi:10.1016/j.metabol.2020.154243.

45. Wei X, Zeng W, Su J, Wan H, Yu X, Cao X, *et al.* Hypolipidemia is associated with the severity of COVID-19. *J* Clin Lipidol. 2020;14:297-304. doi:10.1016/j.jacl.2020.04.008.
46. Abu-Farha M, Thanaraj TA, Qaddoumi MG, Hashem A, Abubaker J, Al-Mulla F. The Role of Lipid Metabolism in COVID-19 Virus Infection and as a Drug Target. *Int J Mol Sci.* 2020;21. doi:10.3390/ijms21103544.

47. Bianchetti A, Rozzini R, Guerini F, Boffelli S, Ranieri P, Minelli G, *et al.* Clinical Presentation of COVID19 in Dementia Patients. *The journal of nutrition, health & aging.* 2020;24:560-562. doi:10.1007/s12603-020-1389-1.

48. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, *et al.* Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *R*adiology. 2020:200642. doi:10.1148/radiol.2020200642.

49. Inui S, Fujikawa A, Jitsu M, Kunishima N, Watanabe S, Suzuki Y, *et al.* Chest CT Findings in Cases from the Cruise Ship "Diamond Princess" with Coronavirus Disease 2019 (COVID-19). *R*adiology: Cardiothoracic Imaging. 2020;2:e200110. doi:10.1148/ryct.2020200110.

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Table 1. Characteristics of hospitalized and non-hospitalized patients and service follow-up

				HOSPI	TALIZED	PATIENTS				NON- HO PAT	SPITALI FIENTS	ZED
Age	Number of	Gender (male)	Death	Type of	Intensive care	Duration of	The day of	Need for	Number of	Number of patients	Gender (male)	Death
	patients	.0	0	wards*	needs	intensive care	stay in hospital	oxygen support	patients intubated			
60-64	4537	2412 53.2%	437 9.6%	251 ICU 5.5%	860 ICU 18.9%	6 (0-56)	8 (1-55)	1421 31.3%	588 %13	2782 36.8%	1398 50.3%	61 2.2%
65-69	3739	1857 49.7%	498 13.3%	259 ICU 6.9%	873 ICU 23.3%	6 (0-58)	9(1-58)	1235 33%	608 %16.3	1855 24.5%	857 46.2%	76 4.1%
70-74	3234	1565 48.4%	592 18.3%	293 ICU 9.1%	940 ICU 29%	6 (0-56)	9 (1-56)	1124 34.8%	642 %19.9	1248 16.5%	574 46%	79 6.3%

						i	8					
75-79	2260	1114	572	307	844 ICU	7 (0-53)	10 (1-	834	623	756	350	68
		49.3%	25.3%	ICU	37.3%	0	61)	36.9%	%27.6	10%	46.3%	9%
				13.6%	\sim							
80 +	3172	1359	1042	553	1370	6 (0-55)	10(1-	1278	950	927	356	171
		42.8%	32.8%	ICU	ICU		60)	40.3%	%29.9	12.2%	38.4%	18.4%
				17.4%	43.1%							
TOTAL	16942	8307	3141	16942	4887	6 (0-58)	9 (1-61)	5892	3411	7568	3535	455
		49%	18.5%			р : 0.06	p:	34.8%	20.1%		46.7%	%6
	0	D					0.0001					
	.Co											
* Туре	of	service	tha	ıt pa	tients	are re	ceived	first,	ICU:	Intensive	Care	Unit

Table 2. Mortality	rates in ICU	and mortality	rates of intubated	patients according to
the age group				

	Mortality	y rates of pa	tients with	Mortality rates of intubated patients					
	IC	U hospitaliz	ation						
Age	Number	Death	P value	Number of	Death Rate	P			
	of	Rate		patients	×	value			
	patients								
60-64	860	402		588	357 (60.7%)				
		(46.7%)		C	\mathbf{S}^{*}				
65-69	873	456		608	407 (66.9%)				
		(52.2%)							
70-74	940	535		642	480 (74.8%)				
		(56.9%)							
75-79	844	519		623	456 (73.2%)				
		(61.5%)							
80 +	1370	902		950	734 (77.3%)				
	0	(65.8%)							
			0.0001			0.0001			
P	5		1	1	1	1			

	D	eath rates		Int	ensive care	9	Intu	bation rate	es
				hospit	alization r	ates			
Age	Before	After	Р	Before	After	Р	Before	After	Р
	curfew	curfew	value	curfew	curfew	value	curfew	curfew	value
65-	239/114	259/259	<0.0	355/114	518/259	<0.0	279/114	329/259	<0.0
69	3	6	01	3	6	01	3	6	01
	20.9%	10%		31.1%	20%	\mathbf{O}	24.4%	12.7%	
70-	249/892	343/234	<0.0	327/892	613/234	<0.0	259/892	383/234	<0.0
74	27.9%	2	01	36.7%	2	01	29%	2	01
		14.6%		>	26.2%			16.4%	
75-	242/623	330/163	<0.0	302/623	542/163	<0.0	251/623	372/163	<0.0
79	38.8%	7	01	48.5%	7	01	40.3%	7	01
		20.2%			33.1%			22.7	
80+	351/697	691/247	<0.0	385/697	985/247	<0.0	305/697	645/247	<0.0
	50.4%	5	01	55.2%	5	01	43.8%	5	01
7		27.9%			39.8%			26.1%	
Tot	1081/33	1623/90	<0.0	1369/33	2658/90	<0.0	1094/33	1729/90	<0.0
al	55	50	01	55	50	01	55	50	01
	32.2%	17.9%		40.8%	29.4%		32.6%	19.1%	

Table 3. Comparison of death rates, intensive care hospitalization rates and intubationrates by age groups before and after curfew

* The curfew was imposed on March 21, 2020. Including the 14-day incubation period, the

date April 5 was taken as the term

	Odds Ratio	95% CI	P value
60-79 age			
Gender (Male)	2.1	1.91-2.34	< 0.001
Hypertension	1.17	1.03-1.32	0.013
Diabetes Mellitus	1.18	1.06-1.30	0.001
Heart Failure	1.79	1.57-2.05	<0.001
CKD	2.08	1.81-2.40	<0.001
Dementia	1.63	1.36-1.94	<0.001
Cancer	1.65	1.44-1.89	<0.001
80+ age		0	
Gender (Male)	1.5	1.29-1.75	< 0.001
Diabetes Mellitus	1.26	1.07-1.49	0.006
Heart Failure	1.38	1.15-1.65	0.001
Dementia	1.47	1.24-1.73	< 0.001
Malnutrition	1.52	1.01-2.29	0.004
Hyperlipidemia	0.77	0.64-0.93	0.007
N			
* Variables such as gene	ler, hypertension, diab	etes mellitus, COPD, CA	D, AF, CKD,

Table 4. Factors affecting mortality in multivariate regression analysis