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Identification of the Factors Affecting the Time Interval Between the COVID-19 Diagnosis Date and Death Date in Sivas: A Retrospective Study

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ABSTRACT

The aim of this study was to determine the factors affecting the time interval between the Coronavirus disease 2019 (COVID-19) diagnosis date and death date. In this retrospective observational study, the files of 651 patients who were reported to have died due to COVID-19 in the intensive care unit of XXX Hospital between 11.03.2020 and 31.12.2020 were reviewed. The patients' age, gender, COVID-19 diagnosis date, death date, and chronic disease presence were examined. Of those who died, 601 (92.3%) were aged 60 and over, and 383 (58.8%) were male. 96.8% (630 people) of the deceased had at least one chronic disease. The most common chronic disease accompanying deaths was hypertension (HT) (82.6%). Comorbid chronic diseases had a higher incidence in deaths aged 60 years and over. Coronary artery disease (CAD) was more common in deaths in male and asthma in deaths in female. The median time interval between the COVID-19 diagnosis date and the death date was 10 days and did not differ by age groups, gender, or at least one chronic disease presence. Having female gender (p=0.024) and having Alzheimer's disease (p=0.007) were factors affecting the time interval between the diagnosis and death date. To prevent deaths caused by COVID-19, it may be recommended to closely monitor patients with some characteristics (chronic disease, advanced age, and male gender) and to increase protection measures especially for these patients.

Keywords: COVID-19, Death, Gender, Chronic Disease

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Introduction

On March 11, 2020, the Coronavirus disease 2019 (COVID-19) was identified as a pandemic by World Health Organization (WHO) (World Health Organization., 2020). As of March 30, 2022, more than 483 million confirmed cases and 4.1 million deaths have been seen in the world since the beginning of the pandemic (WHO, n.d.). In Turkey, the first COVID-19 case was seen on March 11, 2020 and as of March 30, 2022, the total number of confirmed cases 14.831.231, and the total number of deaths was 97.924 (WHO, 2022a).

In the first year following the declaration of COVID-19 as a pandemic, the case fatality rate reached 9.6% all over the world (reaching its highest peak) and reached 4.2% in Turkey (WHO, 2022b). The rapid spread of the disease has become a burden for health systems in many countries, as those with underlying metabolic, cardiovascular or respiratory diseases continue to develop severe COVID-19 disease and are at increased risk (Guan et al., 2020). The fact that vaccination rates are not at the desired level causes the disease to continue to maintain its importance today (WHO, 2022c). As a matter of fact, deaths due to COVID-19 still continue all over the world and in our country (WHO, 2022b).

Death rates differed across the world with respect to gender and age groups (Upadhyaya et al., 2022; WHO, 2020). Advanced age and male gender have been shown as risk factors associated with the disease (Cai, 2020). Although less than half of the patients have one or more comorbidities, comorbidities have been found to aggravate deaths from COVID-19 (Biswas et al., 2021). Comorbidities are accepted as a risk factor for death, and the prevalence of comorbidities in fatal cases has been found to increase up to 90% (Korean Society of Infectious Diseases and Korea Centers for Disease Control and Prevention, 2020). Cardiovascular diseases, diabetes mellitus (DM), hypertension (HT), chronic obstructive pulmonary disease (COPD), and hypercholesterolemia are the most common comorbidities known in COVID-19 patients (Asirvatham et al., 2021; Espinosa et al., 2020; Grasselli, Greco, Zanella, Albano, Antonelli, et al., 2020; Yang et al., 2020). On the other hand, the relatively short time interval between hospitalization and death in cases is a concern and possible causes must be evaluated and addressed to reduce preventable deaths (Asirvatham et al., 2021).

There are many studies in the literature evaluating risk factors associated with COVID-19 mortality. However, in this study, it was aimed to examine the distribution of age, gender, and chronic disease in deaths due to COVID-19 and the factors affecting the time interval between COVID-19 diagnosis date and death date. Thus, it was aimed to provide preventive public health recommendations to reduce deaths due to this disease.

Material and Methods

In this retrospective observational study, the files of patients who were reported to have died due to COVID-19 between 11 March 2020 and 31 December 2020 in the intensive care unit of Sivas Numune Hospital, which served as a pandemic hospital, were retrospectively reviewed. Patients who were found to be positive for the COVID-19 Polymerase Chain Reaction (PCR) test and reported to have died by the hospital were included in the study. No exclusion criteria were used. The epicrisis information of these patients was obtained from the hospital and analysed one by one. The time interval between the diagnosis date and death date was taken as the dependent variable. On the other hand, the age, gender, and presence of chronic disease were taken as the independent variables. Since the median time to death value was calculated as 10 days in our study, this value was taken as the cut-off value.

Statistical analysis

The data obtained from our study were evaluated with the SPSS for Windows, version 22.0 (IBM Corp., Armonk, NY, USA) program. Numerical variables were presented with descriptive statistics such as mean, standard deviation, median (Q1-Q3). Categorical variables were reported as number and percentage. The normality of the data was checked with the 1-sample Kolmogorov-Smirnov test ($p<0.05$). Since the data did not show a normal distribution, they were evaluated with Mann Whitney U test and Kruskal Wallis test. Categorical data were evaluated by using chi-square analysis. Binary logistic regression analysis was conducted to estimate factors associated with the time interval between diagnosis date and death date. While conducting the logistic regression analysis, gender, age, presence of chronic disease, and chronic diseases of the patients who died were included in the model as factors that could affect the time interval. Reference categories are listed in Table 4. Hosmer-Lemeshow test results ($P>.05$) revealed that the model-data fit was good enough. $p< 0.05$ was considered significant.

Ethics statement

The study was conducted in accordance with the recommendations of the Declaration of Helsinki and was approved by the Sivas Cumhuriyet University Non-Invasive Clinical Research Ethics Committee (Decision no: 2021-03/12). Institutional permission was obtained for the study (Number: E-76728045-619).

Results

Distribution of chronic disease presence in patients who died due to COVID-19 by age groups and gender is presented in Table 1. The total number of patients who died due to COVID-19 during the study period was 651. Of those who died, 601 (92.3%) were aged 60 and over (mean age = 74.9±10.8, min= 7, max= 99), 383 (58.8%) were male, 630 (96.8%) had at least one chronic disease. The most common chronic disease accompanying deaths was HT (82.6%). Afterwards, coronary artery disease (CAD) (36.6%), COPD (23.0%), DM (16.9%) and cerebrovascular disease (CVD) (16.9%) were the most common accompanying diseases. The incidence of at least one chronic disease ($p<0.001$), HT ($p<0.001$), CAD ($p=0.040$), chronic kidney disease (CKD) ($p=0.042$), and chronic liver disease (CLD) ($p=0.042$) was higher in deaths at 60 years and over compared to younger age groups. DM was more common in deaths between the age of 60-74 years ($p=0.027$). CVD ($p<0.001$) and Alzheimer's ($p=0.003$) comorbidity rates were higher in deaths aged 75 years and over. CAD ($p=0.008$) was more common in deaths in male patients and asthma was more common in deaths in female patients ($p=0.022$) (Table 1).

Table 2 shows the distribution of the time interval between the COVID-19 diagnosis date and the death date of the patients by age groups and gender. The median time interval between the patients' COVID-19 diagnosis date and death date was 10 (IQR: 6-14) days. This time interval did not show any difference according to age groups ($p=0.458$) and gender ($p=0.109$) (Table 2).

The distribution of the time interval between the COVID-19 diagnosis date and the death date of the patients by chronic disease presence is given in Table 3. No difference was observed between the mean time intervals between those with and without any chronic disease ($p=0.133$). This mean duration was significantly higher in patients with CKD comorbidity than those without ($p=0.039$). In patients with Alzheimer's comorbidity, the mean time was significantly lower than those without ($p=0.014$) (Table 3).

Table 4 presents the factors affecting the the time interval between COVID-19 diagnosis date and death date. Female gender (OR=1.44, 95% CI=1.05-1.98, $p=0.024$) and Alzheimer's disease (OR=4.71, 95% CI=1.54-14.39, $p=0.007$) were determined as factors that shortened the time from diagnosis to death (Table 4).

Discussion

In this study, we examined the time interval between COVID-19 diagnosis date and death date recorded in a city in Turkey in the first nine months when death rates peaked during the pandemic process (WHO, 2022b). Therefore, since this study was conducted in the periods when COVID-19 vaccination had not yet started in Turkey, all cases included in the study were unvaccinated, and vaccination is one of the most effective prevention methods in the fight against COVID-19 today. We identified the distribution of age, gender, and chronic disease in deaths and the factors affecting the duration of death. Today, although deaths due to COVID-19 have decreased compared to the beginning of the pandemic with the effect of vaccination and protective measures, it still continues, which shows that the pandemic maintains its importance (WHO, n.d.).

Table 1. Distribution of chronic disease presence in patients who died due to COVID-19 by age groups and gender.

Presence of chronic disease	Total (n, %)	Age groups (n, %)			Gender (n, %)	
		≤59	60-74	≥75	Male	Female
	651(100.0)	50(7.7)	255(39.2)	346(53.1)	383(58.8)	268(41.2)
At least one	630(96.8)	42(84.0)	247(96.9)	341(98.6)	367(95.8)	263(98.1)
		x^2=29.657, p<**0.001**			x^2=2.010, p=0.156	
HT	538(82.6)	28(56.0)	207(81.2)	303(87.6)	308(80.4)	230(85.8)
		x^2=30.985, p<**0.001**			x^2=3.209, p=0.073	
CAD	238(36.6)	10(20.0)	96(37.6)	132(38.2)	156(40.7)	82(30.6)
		x^2=6.419, p=**0.040**			x^2=6.982, p=**0.008**	
COPD	150(23.0)	9(18.0)	53(20.8)	88(25.4)	91(23.8)	59(22.0)
		x^2=2.566, p=0.277			x^2=0.271, p=0.603	
DM	110(16.9)	9(18.0)	55(21.6)	46(13.3)	57(14.9)	53(19.8)
		x^2=7.204, p=**0.027**			x^2=2.689, p=0.101	
CVD	110(16.9)	2(4.0)	27(10.6)	81(23.4)	72(18.8)	38(14.2)
		x^2=23.604, p=**0.001**			x^2=2.397, p=0.122	
CKD	102(15.7)	14(28.0)	36(14.1)	52(15.0)	57(14.9)	45(16.8)
		x^2=6.326, p=**0.042**			x^2=0.435, p=0.510	
Asthma	101(15.5)	11(22.0)	42(16.5)	48(13.9)	49(12.8)	52(19.4)
		x^2=2.494, p=0.287			x^2=5.255, p=**0.022**	
Osteoporosis	40(6.1)	1(2.0)	13(5.1)	26(7.5)	19(5.0)	21(7.8)
		x^2=3.100, p=0.212			x^2=1.789, p=0.181	
Parkinson	22(4.9)	2(4.0)	4(1.6)	16(4.6)	15(3.9)	7(2.6)
		x^2=4.262, p=0.119			x^2=0.471, p=0.493	
Alzheimer	20(3.1)	0(0.0)	2(0.8)	18(5.2)	10(2.6)	10(3.7)
		x^2=11.339, p=**0.003**			x^2=0.342, p=0.559	
CLD	14(2.2)	4(8.0)	2(0.8)	8(2.3)	5(1.3)	9(3.4)
		x^2=10.435, p=**0.005**			x^2=2.557, p=0.133	
Cancer	10(1.5)	2(4.0)	3(1.2)	5(1.4)	6(1.6)	4(1.5)
		x^2=2.244, p=0.298			p=1.000[1]	
Others	52(8.0)	7(14.0)	21(8.2)	24(6.9)	30(7.8)	22(8.2)
		x^2=3.001, p=0.223			x^2=0.001, p=0.978	

n number, *HT* Hypertension, *CAD* Coronary artery disease, *COPD* Chronic obstructive pulmonary disease, *DM* Diabetes mellitus, *CVD* Cerebrovascular disease, *CKD* Chronic kidney disease, *CLD* Chronic liver disease, [1]Fisher's exact test

Table 2. Distribution of the time interval between the COVID-19 diagnosis date and the death date of the patients by age groups and gender (n=651).

Characteristics		Time interval between the COVID-19 diagnosis date and the death date		
		Mean ± SD	Median (Q_1-Q_3)	
Age groups	≤59	11.0±7.6	10 (6-14)	KW=1.563,
	60-74	10.1±6.7	9 (5.5-14)	p=0.458
	≥75	10.6±6.6	10 (6-14)	
Gender	Male	10.8±7.0	10 (6-14)	U=47545.5,
	Female	9.9±6.3	9 (5-13)	p=0.109
Total		10.4±6.7	10 (6-14)	

n Number, *SD* Standard deviation, *KW* Kruskal Wallis H test, *U* Mann Whitney U test

Advanced age has been shown as a risk factor for death cases (Cai, 2020). Indeed, more than 90% of those who died in our study were aged 60 and over, while more than half were aged 75 and over. Previous systematic review and meta-analysis studies also supported this finding (Espinosa et al., 2020; Khan et al., 2020; Noor & Islam, 2020). Studies conducted in Italy, India, and Brazil have also reported that deaths due to COVID-19 occur at an advanced age (Asirvatham et al., 2021; Grasselli, Greco, Zanella, Albano, Antonelli, et al., 2020; Pachiega et al., 2020).

Male gender is another prominent risk factor for deaths due to COVID-19 (The Covid-19 sex-disaggregated data tracker, 2020) and more than half of those who died in our study were male. Espinosa et al. found that men were the most affected among the deaths, similar to our study (Espinosa et al., 2020). In various studies, male sex ratios in death cases were determined as 82%, 71.4%, and 58.6% (Asirvatham et al., 2021; Grasselli, Greco, Zanella, Albano, Antonelli, et al., 2020; Pachiega et al., 2020). In addition, Noor et al. reported in their meta-analysis study that the risk of death in male patients with COVID-19 was 63% higher than in female patients (Noor & Islam, 2020).

In our study, we detected at least one chronic disease in almost all the patients who died due to COVID-19. In a systematic review and meta-analysis study, the overall prevalence of comorbidities was found to be 77% (71% for China, 92% for Korea) (Espinosa et al., 2020). In studies conducted in different parts of the world, the presence of at least one comorbidity has been reported between 74.6% and 85.3% (Asirvatham et al., 2021; Grasselli, Greco, Zanella, Albano, Antonelli, et al., 2020; Pachiega et al., 2020). Although there are differences in the rates that can be described as regional reasons, the presence of additional disease is an important risk factor in death cases (Korean Society of Infectious Diseases and Korea Centers for Disease Control and Prevention, 2020). Thus, the probability of death was found to be 2.4 for a patient with an additional disease when compared to a patient without additional disease (Espinosa et al., 2020).

Table 3. Distribution of the time interval between the COVID-19 diagnosis date and the death date of the patients by chronic disease presence (n=651).

Presence of chronic disease		Time interval between the COVID-19 diagnosis date and the death date		
		Mean ± SD	**Median (Q_1-Q_3)**	**U, p**
At least one	No	8.6±6.8	7 (5-11)	7884.0,
	Yes	10.5±6.7	10 (6-14)	0.133
HT	No	9.9±6.4	9 (5-13)	31775.0,
	Yes	10.5±6.8	10 (6-14)	0.447
CAD	No	10.4±6.8	10 (6-14)	49648.0,
	Yes	10.5±6.6	10 (6-14)	0.828
COPD	No	10.2±6.7	10 (5-14)	40650.5,
	Yes	11.0±6.7	10 (7-14)	0.127
DM	No	10.1±6.4	10 (6-14)	32883.0,
	Yes	11.8±7.8	10 (6-15)	0.081
CVD	No	10.2±6.6	10 (6-14)	31851.0,
	Yes	11.3±7.2	9.5 (7-14)	0.242
CKD	No	10.2±6.6	10 (6-14)	31589.5,
	Yes	11.8±7.4	10.5 (4-15)	**0.039**
Asthma	No	10.4±6.8	10 (6-14)	28592.0,
	Yes	10.5±6.3	10 (7-13)	0.637
Osteoporosis	No	10.3±6.7	10 (6-14)	13229.0,
	Yes	11.6±7.4	9 (7-15)	0.380
Parkinson	No	10.4±6.7	10 (6-14)	7760.5,
	Yes	11.9±7.2	10 (7-14)	0.330
Alzheimer	No	10.5±6.7	10 (6-14)	4273.0,
	Yes	7.6±5.8	5 (4-8)	**0.014**
CLD	No	10.4±6.8	10 (6-14)	4634.5,
	Yes	9.9±3.9	10 (7-14)	0.800
Cancer	No	10.4±6.7	10 (6-14)	4011.5,
	Yes	8.9±4.8	10 (6-12)	0.742

n Number, *SD* Standard deviation, *U* Mann Whitney U test, *HT* Hypertension, *CAD* Coronary artery disease, *COPD* Chronic obstructive pulmonary disease, *DM* Diabetes mellitus, *CVD* Cerebrovascular disease, *CKD* Chronic kidney disease, *CLD* Chronic liver disease

Table 4. Factors affecting the time interval between COVID-19 diagnosis date and death date (n= 651)

Time interval between COVID-19 diagnosis date and death date (<10 days) (Ref C; ≥10 days)		
	OR (95% CI)	**p**
Gender (Ref C; Male)		
Female	1.442 (1.050-1.982)	**0.024**
Age groups (years) (Ref C; ≤59)		
60-74	1.189 (0.643-2.199)	0.581
≥75	0.908 (0.497-1.661)	0.754
Chronic kidney disease (Ref C; No)		
Yes	0.752 (0.487-1.161)	0.198
Alzheimer (Ref C; No)		
Yes	4.707 (1.540-14.385)	**0.007**

OR Odds ratio, *CI* Confidence interval, *Ref C* Reference category

Factors that increase the risk of serious illness in COVID-19 are additional diseases such as heart disease, DM, cancer, COPD, and CKD (Centers for Disease Control and Prevention, 2021). Previous studies have shown that hypertensive patients are at higher risk of developing serious consequences from COVID-19 (Guan et al., 2020; Wang et al., 2020). Thus, in our study, we found that HT accompanied most deaths. As in our study, in a systematic review and meta-analysis study, HT (35%) was the most common additional disease in death cases, followed by DM (19%) and chronic heart disease (17%) (Espinosa et al., 2020). Grasselli et al. observed that the most accompanying disease was HT (Grasselli, Greco, Zanella, Albano, Antonelli, et al., 2020). On the other hand, there are also studies reporting that the disease that most often accompanies deaths was DM alone (Asirvatham et al., 2021; Mantovani et al., 2020) or DM and HT together (Pachiega et al., 2020).

In our study, we found that concomitant diseases (HT, CAD, CVD, CKD, CLD, and Alzheimer) in patients who died were mostly in people aged 60 and over. Asirvatham et al. in their study, they stated that the comorbidities were significantly higher among the elderly compared to the younger age groups, similar to our study (Asirvatham et al., 2021). However, in our study, we found that DM was more common in deaths 60-75. Mantovani et al. in their meta-analysis study, they reported that the prevalence of DM was found to be higher in patients aged 60 years and above compared to those under 60 years of age, similar to our study (Mantovani et al., 2020).

We observed that asthma was significantly higher in deaths in female patients than in males. Indeed, female with asthma have been reported to be a somewhat susceptible subgroup for severe COVID-19 requiring hospitalization (Atkins et al., 2020). In this study and in three additional studies from France and the United States (USA), it was reported that 56-71% of asthmatic patients hospitalized for COVID-19 were female (Beurnier et al., 2020; Chhiba et al., 2020; Lovinsky-Desir et al., 2020). This can be explained by the higher prevalence of asthma in female than in male (Fernando et al., 2021). On the other hand, Asirvatham et al. found that the presence of one or more additional diseases ($p=0.002$) and comorbidity categorized as others ($p<0.001$) were higher in female (Asirvatham et al., 2021).

We found a few study that have evaluated the time interval between the COVID-19 diagnosis date and death date. In our study, the time interval between the COVID-19 diagnosis date and the death date was 10 days on average and did not differ according to age groups and gender. In a study, the researchers estimated the time interval between exposure to infection and death was 13 days and similar to our study, they did not find any difference between the mentioned time intervals and the age groups and gender (Asirvatham et al., 2021). In the study conducted with COVID-19 patients followed in the intensive care unit in Italy, it was reported that the median time from symptom onset to admission to the intensive care unit was 10 (95% CI, 9-10; IQR, 6-14) days; the median length of stay in the ICU was 12 (95% CI, 12-13; IQR, 6-21) days (Grasselli, Greco, Zanella, Albano, Antonelli, et al., 2020). The quality of health service delivery of countries and hospitals where the studies were conducted may be a factor in the differences in the mentioned time.

Although male deaths due to COVID-19 are generally higher than females, there are inconsistencies between countries in the world and it has been reported that this situation can be explained by genetic, epigenetic and innate immune errors (Traish, 2021). In our study, we determined that female gender and Alzheimer's disease shorten the time from diagnosis to death, but we could not find any data about this in the literature. This may be because the presence of at least one chronic disease was higher in female than in male, as we determined in our study, and that most Alzheimer's patients were in the advanced age group.

The limitations of the study may be that deaths occurring in only one hospital were evaluated in a limited time, and therefore possible deaths that occurred at home were not included in the study, the study was conducted retrospectively only from the data in the file records, and therefore other socio-demographic data of the patients could not be evaluated.

Conclusion

In conclusion, having chronic disease, especially HT, advanced age, and male gender (female gender for asthma) were the most common features in deaths. Female gender and Alzheimer's disease were determined as factors that shortened the time from diagnosis to death. To prevent deaths caused by COVID-19, it may be recommended to closely monitor patients with these characteristics and to increase protection measures against COVID-19, especially for these patients. It should not be forgotten that vaccination is one of the most effective prevention methods in the fight against COVID-19 today.

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