Orjinal Araştırma Makalesi/ Original Paper

COVID-19: Risk factors, Drugs Used in Treatment and Mortality Rate

COVID-19: Risk faktörleri, Tedavide Kullanılan İlaçlar ve Ölüm Oranı

Ersoy ÖKSÜZ[1]*, Muhammet Serdar BUĞRA[2], Leman Acun DELEN[3], Özlem ÇAĞAŞAR[4],
Bilgehan DEMİR[5], İbrahim AKTAŞ[6], Muhammet Selçuk SİNANOĞLU[7], Ayşegül Altıntop GEÇGİL[8],
Rabia Aydoğan BAYKARA[9], Hülya ALADAĞ[10], Erdal AKTÜRK[6], İrem PEMBEGÜL[12].

[1] Department of Medical Pharmacology, Malatya Turgut Özal Universty, Malatya, TURKEY.
[2] Department of Urology, Malatya Turgut Özal Universty, Malatya, TURKEY.
[3] Department of Anesthesia and Reanimation, Malatya Training and Research Hospital, Malatya, Turkey
[4] Department of Infectious Diseases, Malatya Training and Research Hospital, Malatya, Turkey
[5] Department of Emergency Medicine, Malatya Turgut Özal Universty, Malatya, Turkey
[6] Department of Cardiology, Malatya Turgut Özal Universty, Malatya, Turkey
[7] Department of pediatric, Malatya Turgut Özal Universty Malatya, Turkey
[8] Department of Thoracic medicine, Malatya Turgut Özal Universty, Malatya, Turkey
[9] Department of Physiotherapy and Rehabilitation, Malatya Turgut Özal Universty, Malatya, Turkey
[10] Department of Obstetrics and Gynecology, Malatya Turgut Özal Universty, Malatya, Turkey
[11] Department of Hematology, Malatya Training and Research Hospital, Malatya, Turkey
[12] Department of Nephrology, Malatya Turgut Özal Universty, Malatya, Turkey
* Corresponding Author: Ersoy ÖKSÜZ;.E-mail: drugoksuz@hotmail.com.

ÖZET

 Amaç: Corona Virüs 19'un neden olduğu hastalık, 2019 yılının sonunda ortaya çıkan halen Dünya genelinde yaygın olarak görülen pandemik hastalıktır. Hafif vakalarda klasik bir üst solunum enfeksiyonu şeklinde seyretse de ağır vakalarda pnömoni ve solumun sıkıntısına yol açarak ölüme neden olur. Günümüzde halan spesifik bir ilaç tedavisi bulunmamakta ve çeşitli ilaçlar tedavi için denenmektedir. Bu çalışmada, Corona Virüs 19'a yakalanan hastaların demografik özellikleri, risk faktörleri, kullanılan ilaçlar ve bu ilaçların mortalite üzerine etkilerinin araştırılması amaçlandı.

Materyal ve Metot: Malatya Eğitim ve Araştırma Hastanesi'nde 2020 yılı Mart-Mayıs ayları arasında Covid 19 tanısı ile yatan ve test sonucu pozitif olan toplam 71 hasta, hastanenin veri tabanından ve Halk Sağlığı Yönetim Sisteminden retrospektif olarak taranarak kaydedildi. Bu hastaların, demografik özellikleri, yattıkları servis, yatış süreleri, ek hastalıkları, sağ kalım durumları, kullandıkları ilaçlar tespit edildi. İstatiksel analiz için SPSS (IBM SPSS for Windows, ver.24) ve Minitab (Statistical Software for Windows, ver.17) istatistik paket programları kullanılmıştır.

Bulgular: Erkek hastaların sayısı kadınlara göre istatiksel anlamlı olarak yüksekti (p: 0.001). Ölüm oranı erkeklerde kadınlara göre daha yüksekti (p:0,001). Hastaların %73'ünde en az bir ek hastalık vardı. En fazla görülen ek hastalık hipertansiyondu (%48). Ek hastalığı olan hastaların ölüm oranı olmayanlara göre istatiksel anlamlı olarak yüksekti (p: 0.001). Hastanemizde Covid 19'a karşı rutin olarak hidroksiklorokin, oseltamivir, azitromisin, favipiravir, ritonavir ve lopinavir olmak üzere beş ilaç grubu kullanılmıştır. Bu ilaçlar içerisinden en fazla kullanılan hidroksiklorokin'di (%77). Kullanılan ilaçların mortalite üzerine herhangi bir etkisi yoktu (p: 0.582).

Sonuç: Çalışmamızın sonuçları, Covid 19 hastalığına yakalananların çoğunluğunun erkek olduğunu, yaşın önemli bir risk faktörü olduğunu, ek hastalıkların mortalite riskini artırdığını, kullanılan bütün ilaçların mortalite üzerinde herhangi bir etkisinin olmadığını göstermektedir.

Anahtar Kelimeler: COVID 19, Favipiravir, Hidroksiklorokin

ABSTRACT
Objective: The disease caused by Coronavirus 19 is a pandemic disease that emerged at the end of 2019 and has spread worldwide. Although it progresses as a classical upper respiratory tract infection in mild cases, it causes death by causing pneumonia and respiratory distress in severe cases. Although various drugs have been tried, there is still no specific drug treatment. The aim of this study is to investigate the demographic characteristics, risk factors, drugs used and the effects of these drugs on mortality of patients who were infected with Coronavirus 19.

Materials and Methods: A total of 71 patients hospitalized in Malatya Training and Research Hospital with the diagnosis of COVID-19 due to positive test results between March 2020 and May 2020 were retrospectively reviewed and recorded from the hospital's database and the Public Health Management System. The demographic characteristics of these patients, the service they were hospitalized, the duration of hospitalization, ad-

ditional diseases, survival status, and the drugs they used were recorded. statistical analyses were performed by using SPSS (IBM SPSS for Windows, ver.24) and Minitab (Statistical Software for Windows, ver.17) statistical package programs.

Results: The number of male patients was statistically significantly higher than female patients (p: 0.001). Mortality rate was higher in males than females (p: 0.001). 73% of the patients had at least one additional disease. The most common additional disease was hypertension (48%). The mortality rate of patients with comorbidities was statistically significantly higher than those without (p: 0.001). In our institution 5 drug groups, including hydroxychloroquine, oseltamivir, azithromycin, favipiravir, ritonavir and lopinavir have been were routinely used against COVID-19. The most frequently used drug was hydroxychloroquine (77%). The drugs used had no effect on mortality (p: 0.582).

Conclusion: The results of our study indicate that the majority of those who get COVID 19 are men, age is an important risk factor, additional diseases increase the risk of mortality, and all the drugs used have no effect on mortality.

Keywords: COVID 19, Favipiravir, Hydroxychloroquine

INTRODUCTION

COVID 19 is a current pandemic disease characterized by severe acute respiratory syndrome caused by the RNA virus. Although it is highly contagious, its mortality rate varies between 1-5%. The presence of additional diseases, including heart and lung diseases, hypertension (HT) and diabetes mellitus, significantly increases the rate of mortality (Ankit, 2020). In various epidemiological studies, it has been determined that especially HT increases the mortality and morbidity risk compared to other chronic diseases (Wuand et al., 2020)

Methods including quarantine, isolation, and other infection control measures have been widely used, in order to prevent the COVID19 outbreak, worldwide. Supportive treatments constitute the basis of the treatment. However, although it has been claimed that antivirals such as lopinavir, ritonavir, favipiravir, oseltamivir, chloroquine, azithromycin, and vitamin C increase the success of the treatment, there is no definite information about the effectiveness of these drugs. Although the basis of treatment is mostly clinical experience, there are various studies evaluating the effectiveness of these drugs. For example, in a study comparing the clinical results of lopinavir and ritonavir, in China, it was shown that neither of drugs provided a clinical improvement in patients. However, in the same study, it was found that the mortality rate was lower in patients using these drugs (Lindsey et al., 2020). Again, in another study conducted in China, it was found that favipiravir provided more clinical improvement in patients, compared to lopinavir and ritonavir (Qingxian et al., 2020). Another drug which has been commonly used in the treatment of COVID 19 is chloroquine, which was effective against malaria.

In vitro studies was shown that low concentrations of chloroquine stopped the proliferation of corona virus (Jianjun et al., 2020). In a study conducted on more than 100 patients, in China, it has been shown that the progression of pneumonia decreased, lung images improved, virus tests become negative faster and duration of the disease decreased after chloroquine treatment (Jianjun et al., 2020). It is very important to conduct research to determine the effectiveness of all these drugs in the treatment of COVID 19 and to implement new treatment options.

The aim of this study is to investigate the risk factors, drugs used and the effects of these drugs on mortality in patients hospitalized with the diagnosis of COVID 19 in Malatya Training and Research Hospital, retrospectively.

MATERIALS and METHODS

Approval for the study was obtained from the Ministry of Health and the Scientific Research Board of Malatya Training and Research Hospital. The data of 71 patients hospitalized in Malatya Training and Research Hospital between March and May 2020 with a diagnosis of COVID 19 were scanned retrospectively from the hospital's database and the Public Health Management System. The demographic

characteristics of the patients, the service they were hospitalized, length of stay, additional diseases, survival status, and medications they used were recorded.

Statistical Analysis

SPSS (IBM SPSS for Windows, ver.24) and Minitab (Statistical Software for Windows, ver.17) statistical package programs were used for statistical analyses. In calculating the sample size of the study, for each variable the Power (Power of Test) was determined to be at least 0.80 and the 1st Type Error was accepted to be 0.05. Chi-square test or Z-ratio (Fisher's exact test) was used to determine the relationship between categorical variables. Statistical significance level (α) was taken as 5% in calculations.

RESULTS

The demographic characteristics of the patients are given in table 1. The number of male patients was statistically significantly higher than female patients (p: 0.001). Mortality rate was statistically significantly higher in males than females (p: 0.001). Most patients were under 65 years of age (51%). There was no statistical difference between the patients who died in terms of age (p> 0.05). The majority of male patients were under 65 and female patients were over 65 years of age (59%, 60%, respectively).

Table 1. Demographic characteristics of the patients

Gender	Female (n/%)	Male (n/%)	Total (n/%)	*p.
Total	25/35	46/65	71/100	0,001
Age				
<65	9/36	27/59	36/51	0,059
65-85	15/60	13/28	28/39	0,007
≥85	¼	6/13	7/10	0,153
***p.**			0,001	
Discharge	22/88	31/67	53/76	0,030
Total death	3/12	15/33	18/25	0,001
***p.**			,001	
Death age				
<65	0/0	3/20	3/17	0,053
≥65-85	2/67	7/47	9/50	0,507
≥85	1/33	5/33	6/33	0,990
***p.**			,319	
Hospitalization				
Reanimation	5/20	11/24	16/23	0,303
Routine Ward	20/80	35/76	55/77	0,701
***p.**			0,001	

73% of the patients had at least one comorbidity. The frequency of comorbidity was higher in females than males (72%, 57%, respectively). The most common additional disease was HT (48%). HT was present in 56% of females and 46% of males. The mortality rate was statistically significantly higher in patients with comorbidities compared to those without comorbidity (p: 0.001) (Table 2).

Table 2. Comorbidities in total and in dead patients

Comorbidity	Female (n/%)	Male (n/%)	Total (n/%)
HT	3/12	4/9	7/10
DM	2/8	1/2	3/4
COPD	0/0	2/4	2/3
HT+CAD	6/24	10/22	16/22
HT+DM	5/20	4/9	9/13
HT+COPD	0/0	2/4	2/3
Other	2/8	3/7	5/7
None	7/28	20/43	27/38
Dead	**Female (n/%)**	**Male (n/%)**	**Total (n/%)**
HT	1/33	2/13	3/17
COPD	0/0	1/7	1/5
HT+CAD	0/0	5/33	5/28
HT+DM	1/33	2/13	3/17
HT+COPD	0/0	2/13	2/11
Other	0/0	2/13	2/11
None	1/33	1/7	2/11
Dead with a comorbidity	2/66	14/93	16/89
***p**			0,001

*Significance levels according to Z-ratio (Fisher'sexact) test

In our hospital, 5 drug groups, including hydroxychloroquine, oseltamivir, azithromycin, favipiravir, ritonavir and lopinavir, were used routinely in the treatment of COVID 19. Other drugs used against chronic diseases of the patients included enoxparin, vitamin C, and antihypertensive drugs. The most commonly used drug was hydroxychloroquine (77%). Favipiravir was used in 35% of the patients. We found that drugs had no effect on mortality (p: 0.582) (Table 3).

Table 3. Used drugs in total and in dead patients

Patient	HK (n/%)	OT (n/%)	AZT (n/%)	FP (n/%)	RN/N (n/%)	Other (n/%)	
Female	18/72	13/52	10/30	8/32	4/16	15/60	
Male	37/80	21/46	22/48	17/37	3/7	39/85	
Total	55/77	34/48	32/45	25/35	7/10	54/76	
Dead							
Female	1/33	1/33	0/0	0/0	0/0	2/67	
Male	13/87	9/60	4/26	9/60	2/13	9/60	
Total	14/78	10/55	4/22	9/100	2/11	11/61	
***p.**	14/55	10/34	4/32	9/25	2/7		0,582

* Significance levels according to the results of the chi-square test. HK: hydroxychloroquine OT: oseltamivir, AZT: azithromycin, FP: favipiravir, RN / LN: Ritonavir / Lopinavir

DISCUSSION

An increase in the number of patients with pneumonia of unknown cause began to be seen in Wuhan, China, at the end of 2019, and the Chinese Center for Disease Control and Prevention announced that they detected a new type of corona virus in these patients, in January 2020. Later, the World Health Organization (WHO) named this virus as Novel COVID 19 (Chakraborty et al., 2020). As soon as COVID 19 was detected in China, it spread rapidly to the whole world and eventually WHO declared COVID 19 as a pandemic (Chakraborty et al., 2020). According to the data of the end of March, a total of 693,224 cases were reported worldwide and 33,106 of them died (Francesco et al., 2020). The incubation period of the disease is approximately 4 days. Symptoms generally begin to manifest within 1 week. The symptoms of COVID 19, including fever (98%), cough (76%), dyspnea (76%), myalgia-fatigue (44%), sputum (28%), and headache (8%), are generally seen in upper respiratory tract infections. In very few cases, symptoms such as runny nose, diarrhea, and hemoptysis have been reported (Mary, 2020). However, the course of COVID 19 is severe in many patients. These patients develop acute respiratory distress syndrome (ARDS) or pneumonia and are treated in the intensive care unit (ICU). In a study, it was found that the rate of patients who were treated in the ICU due to ARDS and needed respiratory support was 32% (Chaolin et al., 2020). In our study, 23% of the patients were hospitalized in the ICU. The rate of hospitalization in the ICU was higher in male patients compared to females, however, the difference was not statistically significant (24%, 20%, respectively, p> 0.05).

Gender, age and the presence of comorbidity are the most important risk factors for getting COVID 19 disease. In a study, it was found that 50-75% of patients infected with COVID 19 were males (Huipeng et al., 2020). Again, as the age increases, the risk of getting COVID 19 also increases. In a study, it was shown that the average age of patients with COVID 19 ranged between 41 and 57 years, and the most of the patients were in the 50-75 age range (Wang et al., 2020; Xu et al., 2020). The mortality rate of COVID 19 disease is relatively lower (2%) than other viral diseases such as SARS (Jiang et al., 2020). In another study, it was reported that this rate was found to be 3.4% (Huipeng et al., 2020). However, when hospitalized patients were evaluated exclusively, the mortality rate increases considerably (11-15%) (Harapan et al., 2020). In some studies, it was reported that the mortality rate of hospitalized patients increased up to 23% (Nanshan et al., 2020). The results of our study were similar to the previous studies. The rate of male patients was statistically higher (65% p = 0.001). The average age of the patients was 57.4. Again, our findings supported the literature claiming that the incidence of the disease increases as the age increases, and 73% of the patients were over the 45 years of age. In our study, the mortality rate was 25% and this rate was higher in males compared to females (p: 0.001). This rate may be due to the general condition of the patients, the presence of comorbidities that may cause a change in the course of the disease, the duration of the intervention, or the low number of patients in our study.

The most important risk factor for COVID 19 is the presence of chronic diseases in patients. These diseases increase the rate of contamination and change the course of the disease by reducing the immune response. In a study, it was found that 30% of patients with COVID 19 had comorbidities and the vast majority of them had HT, diabetes, and cardiovascular diseases (CVD) (Chaolin et al., 2020). In another study, it has been shown that the presence of comorbidities varies between 25.2% and 50.5% (Harapan et al., 2020). In our study the most common comorbidity was HT (62%) and DM, COPD were other common comorbidities. In our study the rate of comorbidities was higher compared to other studies. However, our study was similar to other studies in terms of higher rate of HT among other comorbidities, higher frequency in men, and in-

creased risk of death in those with comorbid diseases.

The basis of the treatment of COVID 19 is symptomatic treatments, including oxygen supplementation, supporting respiration and hemodynamic parameters (Wang et al., 2020). Currently, there is no specific antiviral drug used in COVID 19 treatment. However, drugs that had been used in different viral diseases have been tried in the treatment of COVID 19. For example, there are many studies suggesting that drugs such as lopinavir and ritonavir, which had been used in the treatment of HIV, known as protease inhibitors, and act by inhibiting viral aspartate polymerase, were used in the initial stage of the disease, but these drugs have little or no effect (Francesco et al., 2020). Similarly, in another study involving 199 patients, it was reported that there was no improvement and no reduction in mortality in patients using lopinavir and ritonavir, twice a day for 14 days (Cao et al., 2020). Another antiviral drug used in COVID 19 is oseltamivir, which is currently used in influenza treatment. Oseltamivir strongly and selectively inhibits the neuraminidase enzyme of influenza virus. In various studies conducted with this drug, it has been found that it has very little efficacy similar to lopinavir and ritonavir (Huipeng et al., 2020). Another antiviral drug used in the treatment of COVID 19 is favipiravir, which selectively and potently inhibits the RNA polymerase of influenza virus (Furuta et al., 2005; Yousuke et al., 2017). In another study, it has been shown that the administration of favipiravir on the first day at two doses of 1600 mg a day, then two doses of 600 mg for 5 days increased the recovery in patients, provided clinical improvement and improved the radiological findings (Qingxian et al., 2020). Similarly, in various in vitro and human studies, favipiravir has been shown to be effective in the treatment of Covid19 (Şimşek-Yavuz et al., 2020). However, contrary to the above studies, there are different studies indicating that it has no effect (Şimşek-Yavuz et al., 2020).

One of the most commonly used drugs in the treatment of COVID 19 is chloroquine, which is used in the treatment of various autoimmune diseases such as systemic lupus and rheumatoid arthritis due to its anti-inflammatory properties as well as malaria (Jianjun et al., 2020). Chloroquine has been shown to be highly effective and safe in the treatment of pneumonia caused by COVID 19, especially in clinical trials conducted in China (Jianjun et al., 2020). Similarly, in other studies, it has been reported that chloroquine improved the symptoms and shortened the duration of recovery (Awadhesh et al., 2020; Şimşek-Yavuz et al., 2020). It has been reported to be more effective especially when used in combination with azithromycin (Cortegiani et al., 2020). However, there are other studies claiming that chloroquine has no effect on COVID 19 (Nicholas, 2020). In our study we found that the drugs used in the treatment of COVID 19 have no effect on mortality (p> 0.05). This result supports the studies that have shown that favipiravir and chloroquine have no effect. However, in our study, we only evaluated the effects of drugs on mortality, so it is not possible to suggest that these drugs have no effect on improving the symptoms and recovery. In addition, the small number of patients in our study may have affected the results. There is need for more comprehensive studies conducted on larger samples.

Conclusion

In our study we found that the majority COVID 19 patients are males, age is an important risk factor, comorbidities increase the risk of both being infected and mortality, and the drugs used have no effect on mortality.

Conflict of interest: There is no conflict of interest.

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