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Pre-hospital antithrombotic drug use status of died COVID-19 patients

Fatih Güneysu, Ensar Durmuş
Sakarya University, Training and Research Hospital, Clinic of Emergency Medicine, Sakarya, Turkey

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ABSTRACT

Objectives: In this study, we determine the prehospital antithrombotic drug use rates of patients in COVID-19 mortality to reveal the differences between patients using antithrombotic drugs and those who did not to show whether antithrombotic drugs impact the duration of stay in intensive care.

Material and Method: This retrospective study was conducted with 291 patients admitted to the Sakarya University Training and Research Hospital emergency department between March 13 and December 1, 2020. Patients whose PCR test was positive and who died in our hospital were included in the study.

Results: The median number of days in the intensive care unit of patients using acetylsalicylic acid (7; 3-11) was longer than patients who were not using acetylsalicylic acid (5; 1-10) (p=0.041). Also, the median days in the intensive care unit of patients who were not using any antithrombotic drug (5; 1-10) was shorter than patients who were using an antithrombotic drug (7;3-11) (p=0.032). There was no difference in patients using or not using other antithrombotic drugs (p=0.640) or acetylsalicylic acid and other antithrombotic drugs (p=0.979).

Conclusion: This study shows that the prehospital use of aspirin has a positive effect on survival as it prolongs the length of stay in the intensive care unit. Since it is known that one of the most important causes of death in COVID-19 is hypercoagulopathy and considering the irreversible antiplatelet activity of aspirin and since this activity lasts for up to 10 days, the result seems reasonable.

Keywords: COVID-19, acetylsalicylic acid, prehospital, antithrombotic

INTRODUCTION

Coronavirus disease 2019 (COVID-19), the severe acute respiratory syndrome, is an infectious condition originated by coronavirus 2 (SARS-CoV-2) (1). COVID-19 can affect multiple organ systems, and in particular, its impact on the respiratory tract has led to an increase in morbidity and mortality worldwide (1). While mortality in COVID-19 is primarily attributed to hypoxemia due to acute respiratory distress syndrome (ARDS) (2), hypercoagulopathy is also defined among the causes in recent studies (3,4).

Thrombotic complications are common in COVID-19 patients (2). Available data on thrombotic complications in COVID-19 cases intimate that the rates of venous thromboembolic situations can occur as leading as 25% to 30%, especially in critically ill inmates and mechanically ventilated cases (3,4). Platelets have an essential function in the pathogenesis of sepsis and thrombosis and are a potential target to limit complications (5).

The most commonly applied parenteral anticoagulants are low molecular weight heparins (LMWH) and unfractionated heparin (6). Furthermore, they have antithrombotic activities, are inferred to have anti-inflammatory and antiviral features (7). Heparin therapy is shown to reduce the binding of the SARS-CoV-2 spike protein to heparan sulfate proteoglycan on the cell surface, thus inhibiting initial infection (8).

Previous studies designate that aspirin is beneficial in preventing ARDS and reducing severe lung damage in animals and human observational researches (9,10). Aspirin is reported to reduce mortality in prehospital use and intensive care use (9). The anti-thrombus effect of aspirin lasts up to 10 days after the last use (11).

Corresponding Author: Fatih Güneysu, fatihguneysu55@hotmail.com
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In this study, we determine the prehospital antithrombotic drug use rates of patients in COVID-19 mortality to reveal the differences between patients using antithrombotic drugs and those who did not and to show whether antithrombotic drugs impact the duration of stay in intensive care.

MATERIAL AND METHOD

This retrospective study was conducted with 291 patients admitted to the Sakarya University Training and Research Hospital emergency department between March 13 and December 1, 2020. The patients were diagnosed with PCR-confirmed COVID-19, were hospitalized, and subsequently died. Study protocol Sakarya University Faculty of Medicine Local Ethics Committee (Date: 28.12.2020, Decision No: 71522473/050.01.04/644).

Patients and Study Plan

The necessary data for this retrospective research were collected from the patients' electronic medical documents in the hospital's information system. Patients whose PCR test was positive and who died in our hospital were included in the study. Within the scope of the study, patients' demographic features, length of stay in the hospital, RT-PCR test results, antithrombotic drugs used before hospital admission, and mortality states were recorded.

According to the Ministry of Health Guide, intensive care specialists decided to admit the cases to the intensive care unit (12).

Inclusion and exclusion criteria for the study are as follows:

- **Inclusion criteria:** 18 years and over patients who died with a positive RT-PCR test.
- **Exclusion criteria:** Younger than 18 years patients and whose records could not be reached.

Statistical Analysis

To summarize data from the study, descriptive statistics were given as the mean±standard deviation or median, first quartile, and third quartile according to the distribution of the data. Categorical variables were summarized as number and frequency. The normal distribution of numerical variables was evaluated by histogram, q-q graphs, the Kolmogorov-Smirnov test, and the homogeneity of variance controlled with the Levene test. Independent Samples t-test was used to compare mean age values according to sex, and the Mann-Whitney U test was used to compare median intensive care unit stay according to sex. One-Way ANOVA was used to compare mean ages according to drug type being used, and the Kruskal-Wallis test was used to compare median intensive care unit stay according to drug type being used. Spearman's Rho correlation coefficient was used to evaluate the relationship between age and the duration of intensive care unit stay. The statistical analyses were performed using "Jamovi project (2020), Jamovi (Version 1.6.8) [Computer Software] (Retrieved from https://www.jamovi.org) and JASP (Version 0.14) (Retrieved from https://jasp-stats.org) software and the significance value was $p < 0.05$.

RESULTS

Between 15.03.2020-31.12.2020, 291 patients died due to COVID-19. Among them, 190 (65.3%) were males, and 101 (34.7%) were females. Their mean age was 72.2±12.0. The median intensive care unit stay was 6.0 days. Among the patients, 83 (28.5%) were using acetylsalicylic acid, 12 (4.1%) were using acetylsalicylic acid and other antithrombotic drugs, 36 (12.4%) were using other antithrombotic drugs, and 160 (55.0%) were not using any antithrombotic drug (**Table 1**).

Table 1. Sex, age, and antithrombotic drug use of patients died due to COVID-19

	Overall
Gender (%)	
Male	190 (65.3)
Female	101 (34.7)
Age	72.2±12.0
Days in intensive care unit (median [IQR])	6.0 [2.0-11.0]
Acetylsalicylic acid (%)	
Yes	95 (32.6)
No	196 (67.4)
Drug type (%)	
Acetylsalicylic acid	83 (28.5)
No antithrombotic drug	160 (55.0)
Other antithrombotic drugs	36 (12.4)
Acetylsalicylic acid and other antithrombotic drugs	12 (4.1)
Use of any antithrombotic drugs (%)	
Yes	131 (45.0)
No	160 (55.0)

IQR: Interquartile range

Although the mean age of females (74.1±14.0) was higher than males (71.2±10.7), the difference was not statistically significant (p=0.075). The median duration of intensive care unit stay was not different according to sex (p=0.825) (**Table 2**).

Table 2. Comparison of age and days in intensive care unit according to sex

	Sex		p value
	Male (n=190)	Female (n=101)	
Age	71.2±10.7	74.1±14.0	0.075*
Days in intensive care unit (median [IQR])	7.0 [2.0-11.0]	6.0 [2.0-11.0]	0.825†

* Independent Samples t-test, †Mann Whitney U test, IQR: Interquartile range

The patients were classified into four groups according to the used antithrombotic drug as acetylsalicylic acid, other antithrombotic drugs, acetylsalicylic acid, and other antithrombotic drugs, and no antithrombotic drug groups. No significant difference could be detected among these groups according to age and days in the intensive care unit (p=0.376, p=0.155; respectively) (**Figure 1** and **Table 3**).

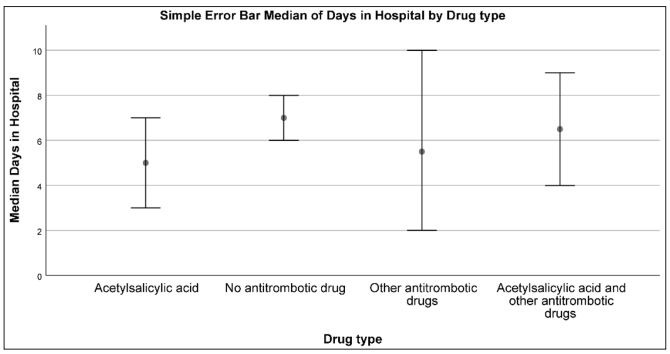

Figure 1. Median days in hospital according to the used antithrombotic drug

Table 3. Comparison of age and days in intensive care unit according to the used antithrombotic drug group

	Age	p value	Days in intensive care unit	p value
Drug type		0.376*		0.155†
Acetylsalicylic acid	71.9±9.82		5 [1-10]	
No antithrombotic drug	71.68±13.67		7 [3-11]	
Other antithrombotic drugs	75.53±8.7		5.5 [2-10.5]	
Acetylsalicylic acid and other antithrombotic drugs	72.17±10.17		6.5 [4.5-8.5]	

*One-Way ANOVA, †Kruskal Wallis

The median number of days in the intensive care unit of patients using acetylsalicylic acid (7; 3-11) was longer than patients who were not using acetylsalicylic acid (5; 1-10) (p=0.041). Also, the median days in the intensive care unit of patients who were not using any antithrombotic drug (5; 1-10) was shorter than patients who were using an antithrombotic drug (7;3-11) (p=0.032). There was no difference in patients using or not using other antithrombotic drugs (p=0.640) or acetylsalicylic acid and other antithrombotic drugs (p=0.979) (**Table 4**).

Table 4. The evaluation of the effect of each drug group on days in the intensive care unit

		Days in intensive care unit	p value*
Acetylsalicylic acid (median [IQR])	No	7 [3-11]	0.041
	Yes	5 [1-10]	
No antitrombotic drug (median [IQR])	No	5 [1-10]	0.032
	Yes	7 [3-11]	
Other antitrombotic drugs (median [IQR])	No	6 [2-11]	0.640
	Yes	5.5 [2-10.5]	
Acetylsalicylic acid and other antithrombotic drugs (median [IQR])	No	6 [2-11]	0.979
	Yes	6.5 [4.5-8.5]	

*Mann Whitney U test

The correlation between age and days in the intensive care unit was not statistically significant (r=-0.049; p=0.407).

DISCUSSION

Hypercoagulation occurs due to excessive thrombin formation and inability to perform fibrinolysis due to endothelial dysfunction due to COVID-19 infection (13). At the same time, hypoxia that occurs in severe COVID-19 can induce thrombosis by increasing blood viscosity and signaling a hypoxia-inducible transcription factor (14). In severe cases, the autopsy conducted on individuals who did not survive revealed that most had microthrombi in pulmonary circulation (15,16). The use of prophylactic antithrombotic drugs is widely recommended in patients diagnosed with COVID-19 (17); however, there are a limited number of studies on prehospital antithrombotic use and effects in COVID-19 patients.

The exact mechanism of sex differences in COVID-19 has not been revealed, but literature indicates the possible mechanisms and the high incidence and deaths in men (18). Studies show that women are more resistant and less susceptible to viral infections than men (19,20). Estrogen has also been reported to increase the activity and proliferation of T cells (19). Similar to the literature, male patients (65.3%) were the majority in our study.

COVID-19 has been reported in all age groups but more severe in elderly patients (21,22). With advanced age, the production of defense cells T and B decreases, which prevents a proper immune response in the presence of infection, with an irregular immune response causing a cytokine storm (23). In addition, it is believed that subclinical inflammation, also called inflammaging in the elderly, contributes to poor prognosis (24). In our study, mortality was higher in the elderly population, and the average age of patients was 72.

COVID-19 pneumonia has significantly amplified the burden on intensive care units. Due to the rising number of cases since the beginning of the pandemic, the number of intensive care beds in xxx increased rapidly. In our study, the time from admission to the intensive care unit until death was determined six days. In a similar study, this period was reported as 12.5 days (25). The late-arriving of patients to intensive care due to occupancy in intensive care units or the differences in intensive care hospitalization indications can cause differences.

Thrombosis prophylaxis plays a vital role in preventing mortality and morbidity due to the hypercoagulation seen in COVID-19 infection (26). In a study of 412 COVID-19 cases, aspirin treatment was correlated with lower mechanical ventilation needs, ICU admission, and fatality risk (26). Aspirin, an irreversible antiplatelet

agent, has been proved to inhibit platelets produced from megakaryocytes from aggregating, also forming microthrombus (27). Aspirin is considered beneficial in lung injury due to decreased platelet-neutrophil clusters in the lungs, reduced inflammation, and raised lipoxin formation, which repairs pulmonary endothelial cell role (26). In a study comparing the effectiveness of aspirin and placebo in 390 patients diagnosed with ARDS, it was found that prehospital drug use decreased intensive care mortality (9). Our study found that the number of days spent in intensive care increased in COVID-19 patients using aspirin before hospital admission, thus extending their life span. This result suggests that prehospital aspirin use may prevent thrombus formation in the early period compared with post-diagnosis use, considering the incubation period, hospital admission time, and PCR result times at the COVID-19 diagnosis stage.

ARDS is one of the common causes of mortality in COVID-19 cases, but the inclusion of all COVID-19 patients confirmed with an RT-PCR in our study may pose a limitation at this point.

CONCLUSION

This study shows that the prehospital use of aspirin has a positive effect on survival as it prolongs the length of stay in the intensive care unit. Since it is known that one of the most important causes of death in COVID-19 is hypercoagulopathy and considering the irreversible antiplatelet activity of aspirin and since this activity lasts for up to 10 days, the result seems reasonable. Our study also provides data for more comprehensive studies to be carried out later.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Sakarya University Faculty of Medicine Local Ethics Committee (Date: 28.12.2020, Decision No: 71522473/050.01.04/644).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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