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Investigation of warfarin overdose and related factors in the emergency department

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ABSTRACT

Objectives: This study aims to analyze the clinical features, symptoms, laboratory findings, and treatment approaches of patients presenting to the emergency department with elevated INR due to warfarin overdose.

Methods: The study was conducted retrospectively from August 1, 2023, to June 1, 2024, in the emergency department of a tertiary hospital in a city with a population of 5 million. Patients aged 18 and over with an INR value of 3.5 or above were included. Data were obtained from electronic health records and patient files. Statistical analyses were performed using IBM SPSS Statistics.

Results: A total of 121 patients were included in the study. The mean age was 71.85±12.28 years, with 53.7% female and 46.3% male. The most common diagnoses were atrial fibrillation (33.1%) and valve replacement (31.4%). The main reasons for emergency admission included general condition disorder (22.3%) and abdominal pain (16.5%). The bleeding rate was 47.9%, with the gastrointestinal system being the most common bleeding site (49.2%). The mean INR value was 9.27±5.45. Vitamin K was administered to 47.1% of patients and fresh frozen plasma to 28.1%. The discharge rate was 38.8%, and the mortality rate was 2.5%.

Conclusions: Patients presenting to the emergency department with warfarin overdose are at significant risk of severe bleeding, requiring careful management. Close monitoring and accurate dose adjustments are essential, especially in elderly and comorbid patients. Antidotes such as vitamin K, fresh frozen plasma, and prothrombin complex are effective in managing bleeding complications. Future studies should aim to standardize and enhance the effectiveness of these treatment protocols.

Keywords: Warfarin, overdose, emergency department

Warfarin is an anticoagulant drug commonly used to prevent thromboembolic events and inhibit blood clotting [1]. It is frequently preferred in the treatment of cardiovascular diseases such as heart disease, atrial fibrillation, mechanical heart valves, deep vein thrombosis, and stroke prophylaxis [2]. The pharmacological activity of warfarin is achieved by inhibiting the synthesis of vitamin K-dependent clotting factors through the inhibition of the vitamin K epoxide reductase enzyme [3]. However, it has a narrow therapeutic index, making it difficult to effectively determine the correct dose in patients and control blood clots [4].

The International Normalized Ratio (INR) is es-

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sential in controlling the treatment of patients using oral anticoagulants and is used to monitor the appropriate dose [5].

Warfarin treatment is warfarin deficiency, which occurs as a result of incorrect dosing or drug interactions [6]. Overdose can lead to excessive dilution of blood and undesirable bleeding complications [7].

Warfarin admission to the emergency department in the literature Comprehensive studies on the analysis of overdosed patients appear to be limited [8]. Such analyses are of great importance to understanding the clinical characteristics, symptoms, laboratory findings, and treatment approaches of patients presenting to the emergency department. Additionally, such studies can serve as an important reference source for future clinical applications, with the aim of providing patients with more effective and safe treatment.

This study aims to add new data to the literature by presenting the analysis of patients with elevated INR due to warfarin overdose who presented to the emergency department and to provide medical personnel in emergency departments with a better understanding of how to deal with such emergencies. The study aims to provide important information about the etiology, clinical course, complications, and treatment approaches of overdose in patients receiving warfarin treatment. The results indicate that emergency department medical personnel are aware of warfarin. It may contribute to decision-making processes in providing more effective and safe treatment for overdose patients.

METHODS

This retrospective study was conducted in the emergency department of a tertiary hospital in a city with a population of 5 million. The non-invasive research ethics committee of the university with which the hospital is affiliated approved the research on 20.07.2023 and numbered 0389.

Study Population

The research covers August 1, 2023, and June 1, 2024.

Inclusion Criteria

Patients aged 18 years and over whose INR value was determined to be 3.5 or above due to warfarin overdose in the emergency department were included in the study.

Exclusion Criteria

Pregnant women, Patients under 18 years of age were excluded due to developmental differences and the presence of factors that may affect INR values in this age group. We also excluded patients with comorbidities such as severe liver diseases, malignancies, coagulopathy and other bleeding tendencies that may cause elevated INR values, in order to be able to attribute the increase in INR to warfarin use alone.

We also included in the exclusion criteria patients taking medications such as antiplatelet or NSAIDs that may alter INR levels in combination with warfarin. Finally, we excluded patients with missing demographic and laboratory data to maintain the accuracy and reliability of the analyses.

Although the upper limit value of INR is 25, higher values are labelled as ‘High’ in the result section. Therefore, we considered patients with INR values above 25 as missing data and excluded them from the study for the sake of clear statistical analysis.

Data Collection

Data were collected through electronic hospital health records and patient files. The data collected includes sociodemographic characteristics of the patients, such as age, gender, and existing diseases. In addition, clinical data such as the patient's complaint at the emergency department, bleeding status, treatment given, and outcome were also noted. Warfarin Hemogram, coagulation tests, and biochemistry tests were used in the evaluation of patients with overdose. In addition, the patients were examined to determine whether they were given vitamin K, fresh frozen plasma (FFP), or prothrombin complex. Discharge, hospitalization, and mortality were also analyzed. The collected data were subjected to statistical analysis and warfarin. The etiology, clinical course, complications, and treatment approaches of overdose were examined.

Statistical Analysis

Data IBM SPSS Statistics standard It was evaluated in the statistical package program Concurrent User V 26 (IBM Corp., Armonk, New York, USA). Descriptive statistics were given as number of units

(n), percentage (%), mean ± standard deviation, median (M), minimum (min) and maximum (max) values. Normal distribution of data of numerical variables Shapiro The homogeneity of variances was evaluated with the Wilk normality test and the Levene test. The characteristics of the patients in the three groups were compared with One-Way Analysis of Variance when the data met the normal distribution conditions and with the Kruskal Wallis H test when the data did not meet the normal distribution conditions. When significant results were obtained in groups according to One-Way Analysis of Variance results, post hoc comparisons were evaluated with the Tukey test, and when significant results were obtained in groups according to Kruskal Wallis H results, post hoc comparisons were evaluated with the Bonferroni-Dunn test. Pearson and Fisher's exact tests were used to compare categorical variables with each other. In Cofact evaluations, INR values were evaluated using ROC analysis. A P-value of <0.05 was considered statistically significant.

RESULTS

The average age of the patients is 71.85±12.28 years; the median age is 72, the minimum is 23, and the maximum is 100. Regarding gender distribution, 53.7% are females and 46.3% are males. According to the diagnosis distribution, 33.1% of the patients presented with atrial fibrillation, 31.4% with valve replacement, 14.0% with coronary artery disease, 11.6% with cerebrovascular disease, and 9.9% with other diagnoses. (Table 1). Among the reasons for emergency admission: dyspnea at 11.6%, poor general condition at 22.3%, hematochezia at 7.4%, hematuria at 7.4%, INR control at 13.2%, abdominal pain at 16.5%, Melena is 9.1%, and other causes are 12.4%. While the rate of patients without bleeding detected in the emergency department was 52.1%, bleeding was detected in 47.9%. Bleeding sites were reported as a gastrointestinal system at 49.2%, genitourinary system at 16.9%, intracranial bleeding at 13.6%, and hematoma at 20.3% (Table 1).

The average hemoglobin value is 9.70±2.82 g/dL; the median value is 10.2 g dL, minimum 3.4, maximum 16.9. The mean hematocrit was 29.39±8.15%, the median value was 30.8%, the minimum was

Table 1. Descriptive characteristics of patients (n=121)

Variables	Data
Age (years)	71.85±12.28 72 (23-100)
Gender, n (%)	
Female	65 (53.7)
Male	56 (46.3)
Diagnosis, n (%)	
Atrial fibrillation	40 (33.1)
Valve replacement	38 (31.4)
Coronary artery disease	17 (14.0)
Cerebrovascular diseases	14 (11.6)
Other	12 (9.9)
Emergency application, n (%)	
Dyspnea	14 (11.6)
General condition disorder	27 (22.3)
Hematochezia	9 (7.4)
Hematuria	9 (7.4)
INR control	16 (13.2)
Stomach ache	20 (16.5)
Melena	11 (9.1)
Other	15 (12.4)
Bleeding in the emergency department, n (%)	
Not Detected	63 (52.1)
Detected	58 (47.9)
Bleeding site, n (%)	
Gastrointestinal system	29 (49.2)
Genitourinary system	10 (16.9)
Intracranial hemorrhage	8 (13.6)
Hematoma	12 (20.3)
Hemoglobin (g/dL)	9.70±2.82 10.2 (3.4-16.9)
Hematocrit (%)	29.39±8.15 30.8 (10.7-48.4)
Platelets ($\times 10^9$/L)	254.23±102.89 245 (16.3-575)
INR	9.27±5.45 7.62 (1.08-24.73)
Prothrombin time (seconds)	106.98±64.57 89.3 (12.7-299.1)
Vitamin K, n (%)	
Not given	64 (52.9)
Granted	57 (47.1)
Contact, n (%)	
Not given	97 (80.2)
Granted	24 (19.8)
TDP, n (%)	
Not given	87 (71.9)
Granted	34 (28.1)
Unit, n (%)	
Discharge	47 (38.8)
Service	37 (30.6)
Intensive care	37 (30.6)
Outcome, n (%)	
Alive	118 (97.5)
Ex	3 (2.5)

Data are shown as mean±standard deviation and median (minimum-maximum or n (%)

Table 2. Comparison of patient identifier values by groups

Variables	Group			Test Statistics	
	Discharge	Service	Intensive care	Test value	P value
Age (years)	72.34±12.34 74 (34-92)	70.08±9.66 70 (45-87)	73.0±13.44 74 (23-100)	H=2.311	0.315
Gender, n (%)					
Female	23 (48.9)	18 (48.6)	24 (64.9)	χ^2=2.664	0.264
Male	24 (51.1)	19 (51.4)	13 (35.1)		
Diagnosis, n (%)					
Atrial fibrillation	14 (29.8)	13 (35.1)	13 (35.1)	χ^2=12.071	0.137*
Valve replacement	19 (40.4)	9 (24.3)	10 (27.0)		
Coronary artery disease	3 (6.4)	4 (10.8)	10 (27.0)		
Cerebrovascular disease.	7 (14.9)	5 (13.5)	2 (5.4)		
Other	4 (8.5)	6 (16.2)	2 (5.4)		
Emergency application, n (%)					
Dyspnea	7 (14.9)	3 (8.1)	4 (10.8)	χ^2=21.579	0.072*
General condition is bad	5 (10.6)	10 (27.0)	12 (32.4)		
Hematochezia	2 (4,3)	2 (5.4)	5 (13.5)		
Hematuria	5 (10.6)	2 (5.4)	2 (5.4)		
INR control	11 (23.4)	3 (8.1)	2 (5.4)		
Stomach ache	8 (17.0)	9 (24.3)	3 (8.1)		
Melena	2 (4.3)	3 (8.1)	6 (16.2)		
Other	7 (14.9)	5 (13.5)	3 (8.1)		
Bleeding, n (%)					
Not Detected	36 (76.6)[a]	16 (43.2)[b]	11 (29.7)[b]	χ^2=19.882	**<0.001**
Detected	11 (23.4)[a]	21 (56.8)[b]	26 (70.3)[b]		
Bleeding site, n (%)					
Gastrointestinal system	2 (18,2)[a]	12 (54.5)[a]	15 (57.7)	χ^2=15.386	**0.017***
Genitourinary system	5 (45.5)[a]	3 (13, 6)[ab]	2 (7.7)[b]		
Intracranial hemorrhage	0 (0,0)[a]	2 (9.1)[a]	6 (23.1)[a]		
Hematoma	4 (36.4)[a]	5 (22.7)[a]	3 (11.5)[a]		
Hemoglobin (g/dL)	10.45± 2.37 [a] 10.8 (4.3-15.6)	10.14± 2.52 [a] 10.9 (5.3-16.2)	8.30± [3.14b] 7.4 (3.4-16.9)	F = 7.441	**<0.001**
Hematocrit (%)	31.50± 6.58[a] 32.1 (13.3-44.1)	30.71± 7.42[b] 32.3 (16.3-45.2)	25.38± 9.32[b] 22.6 (10.7-37.7)	F = 7.203	**0.001**
Neutrophil (×10^9/L)	8.25±6.88 7.08 (0.71-42.7)	9.07±5.25 7.61 (2.6-24.4)	9.54±5.48 8.41 (1.8-24.65)	H =2.759	0.252
Lymphocyte (×10^9/L)	1.30±0.71 1.14 (0.29-3.98)	1.45±0.71 1.38 (0.28-2.8)	1.37±0.65 1.3 (0.43-3.48)	H =1.328	0.515
Platelets (×10^9/L)	254.93±107.14 229 (45-548)	261.84±86.77 257 (16.3-494)	245.72±113.84 248 (34-575)	F =0.226	0.798
WBC (×10^9/L)	10.47±7.63 9.26 (2.0-50.19)	11.62±5.41 10.33 (5.2-27)	11.81±5.66 10.98 (3.7-27.6)	H =3.533	0.171
INR	7.97±5.18 7 (1.08-24.73)	9.39±5.15 8.23 (1.1-21.7)	10.81±5.79 9.5 (1.2-23.1)	H=5.921	0.052
Prothrombin time (seconds)	94.57±62.66 82.9 (12.8-299)	109.67±58.82 98.4 (13-227)	120.06±70.98 99.5 (14-252.8)	H=3.494	0.174
Vitamin K, n (%)					
Not given	25 (53.2)	19 (51.4)	20 (54.1)	χ^2=0.057	0.972
Granted	22 (46.8)	18 (48.6)	17 (45.9)		
Contact, n (%)					
Not given	41 (87.2)	29 (78.4)	27 (73.0)	χ^2=2.755	0.295
Granted	6 (12.8)	8 (21.6)	10 (27.0)		
TDP, n (%)					
Not given	38 (80.9)	29 (78.4)[E.U.]	20 (54.1)[b]	χ^2 =8.465	**0.015**
Granted	9 (19.1) [a]	8 (21.6) [ab]	17 (45, 9) [b]		
Outcome, n (%)					
Alive	47 (100.0)	37 (100.0)	34 (91.9)	χ^2=4.718	0.054*
Ex	0 (0.0)	0 (0.0)	3 (8.1)		

Data are shown as mean±standard deviation and median (minimum-maximum or n (%).
χ^2=Chi-square test, F=One-way analysis of variance, H=Kruskal Wallis test,
*Significance value obtained by Exact method

Table 3. ROC analysis by INR value cofact categories

	Area Under the Curve (AUC)	if	P value	Area Under the Curve (AUC) 95% Confidence Limits		Sensitivity	Selectivity	Limits
				lower limit	upper limit			
INR	0.632	0.071	**0.046**	0.539	0.718	41.67	86.60	>14.84

SE=standard error

10.7%, and the maximum was 48.4%. The mean neutrophil is 8.90±5.98 $\times 10^9$/L, the median value is 7.73 $\times 10^9$/L, minimum 0.71, maximum 42.67. The lymphocyte mean was 1.37±0.69 $\times 10^9$/L, and the median value was 1.28 $\times 10^9$/L, minimum 0.28, maximum 3.98. The mean platelet count is 254.23±102.89 $\times 10^9$/L, and the median value is 245 $\times 10^9$/L, minimum 16.3, maximum 575. White blood cell mean 11.23±6.41 $\times 10^9$/L, the median value is 10.15 $\times 10^9$/L, minimum 2, maximum 50.19. The mean INR is 9.27±5.45, the median value is 7.62, the minimum is 1.08, the maximum is 24.73. The mean prothrombin time was 106.98±64.57 seconds, the median value was 89.3 seconds, minimum 12.7, maximum 299.1. Vitamin K treatment was not applied in 52.9% and was applied in 47.1%. Cofact treatment was not applied to 80.2%, but was applied to 19.8%. Fresh frozen plasma was not applied to 71.9% but was applied to 28.1%. The discharge rate of patients was reported as 38.8%, ward admission as 30.6%, and intensive care admission as 30.6%. According to outcome status, 97.5% of the patients survived, and 2.5% died (Table 1).

Table 2 shows the comparison of patient identifier values by groups. The average age was 72.34±12.34 in the discharged group, 70.08±9.66 in the ward group, and 73.0±13.44 in the intensive care group (P=0.315).

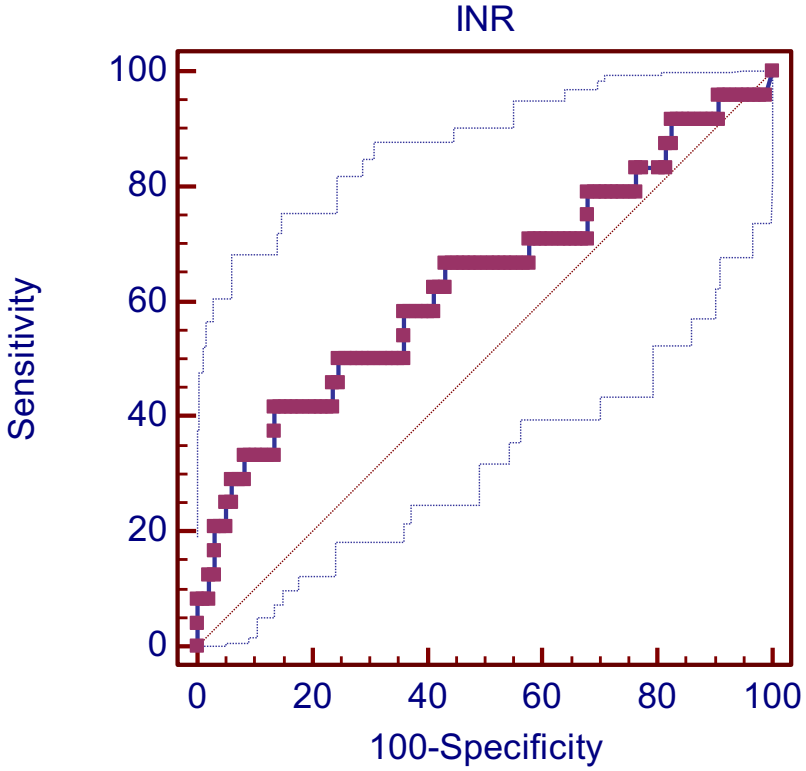

Fig. 1. ROC chart according to INR value cofact categories.

Gender distribution was 48.9% female and 51.1% male in the discharge group, 48.6% female and 51.4% male in the ward group, and 64.9% female and 35.1% male in the intensive care group (P=0.264). There is no significant difference in the diagnosis distribution (P=0.137), and the reasons for emergency admission do not show a similarly significant difference (P=0.072). The presence of bleeding was observed at 23.4% in the discharge group, 56.8% in the ward group, and 70.3% in the intensive care group (P<0.001). Regarding bleeding site distribution, gastrointestinal bleeding was seen as 18.2% in the discharge group, 54.5% in the ward group, and 57.7% in the intensive care group (P=0.017). The mean hemoglobin was 10.45±2.37 in the discharge group, 10.14±2.52 in the ward group, and 8.30±3.14 in the intensive care group (P<0.001). Hematocrit values were recorded as 31.50±6.58 in the discharge group, 30.71±7.42 in the ward group, and 25.38±9.32 in the intensive care group (P=0.001). Neutrophil, lymphocyte, platelet, white blood cell (WBC), INR, and Prothrombin times values do not show any significant difference between the groups. Vitamin K and Cofact administration rates are similar but do not show a significant difference. The FFP administration rate was 19.1% in the discharge group, 21.6% in the ward group, and 45.9% in the intensive care group (P=0.015). In the outcome data, no deaths were observed in the discharge and service groups, but a death rate of 8.1% was observed in the intensive care group (P=0.054).

The Cofact variable, the area under the curve value at INR value, is statistically significant (P=0.046) (0.632 (0.539-0.718)). The differential diagnosis value for INR is over 14.84. In the area under the curve analysis we conducted for Cofact, it was statistically determined that the INR value is a differential diagnosis. In addition, this value, being over 14.84, is an important indicator in the selection of patients. (Table 3, Fig. 1.)

DISCUSSION

This study aimed to examine the clinical features, symptoms, laboratory findings, and treatment approaches of patients with elevated INR due to warfarin overdose who presented to the emergency department.

The average age of the patients in the study was 71.85±12.28 years. This age group generally consists of individuals with chronic diseases requiring multidisciplinary treatment, which increases the difficulties and risks of complications of warfarin treatment [9]. Elderly patients are at higher risk of warfarin therapy, often due to polypharmacy and comorbidities [10].

Among the reasons for patients' admission to the emergency department, general condition disorder (22.3%) stands out. This finding suggests the possibility of the general deterioration of the sections due to warfarin overdose, and the possibility that patients who come to the emergency department with general condition disorder and who are on warfarin should also be evaluated in terms of overdose [11].

The reasons for admission of the patients included in the study included symptoms such as hematochezia (7.4%), hematuria (7.4%), melena (9.1%), and abdominal pain (16.5%), indicating that warfarin overdose may affect various organ systems. Moreover, it may present with different clinical presentations [12]. Similarly, in a study by Fihn *et al*. [13], warfarin administration in elderly patients is associated with a reduced likelihood of experiencing bleeding complications compared to younger patients, with no notable disparity in the severity of such complications between the two age groups.

The rate of patients with bleeding was 47.9%, and the gastrointestinal system (49.2%) has an essential place among the bleeding sites. Both the widespread use of NSAIDs in society and the frequent occurrence of gastroenterological disorders due to eating habits may have paved the way for this situation. In a study of Zapata *et al*. [14], concomitant use of warfarin and an NSAID or COX-2 inhibitor significantly augments the risk of bleeding, underscoring the importance of exercising caution when combining these drugs.

The fact that the average hemoglobin of the patients was 9.70±2.82 g/dL and the average hematocrit was 29.39±8.15% suggests severe bleeding that may develop due to warfarin overdose. These low values may indicate patients experiencing acute blood loss and developing anemia. This situation requires close monitoring and rapid intervention. Regular monitoring of hemoglobin and hematocrit levels may be necessary in these patients. Depending on the clinical course, blood transfusion and hematological support treatments may be applied in a study by Leonard *et al*.

[15]. Within the group of individuals receiving warfarin treatment, the utilization of fibrates raises the likelihood of being admitted to the hospital due to gastrointestinal bleeding or intracranial hemorrhage. On the other hand, there is no connection between the use of statins and these adverse events [16].

Antidotes such as vitamin K, fresh frozen plasma (TDP), and prothrombin complex (Cofact) are used to treat patients with warfarin overdose. In this study, 47.1% of patients were treated with vitamin K, 19.8% with COFACT (4% coagulation factor concentrate), and 28.1% with TDP. These treatment approaches are important for rapidly decreasing INR values and controlling bleeding complications. However, differences in the application rates of these treatment modalities may indicate a need for more standardization in clinical decision-making processes [17, 18].

Demographic, clinical, and laboratory characteristics of the patients participating in the study were compared according to different clinical outcome groups such as discharge, ward admission, and intensive care admission. The rate of patients who applied to the emergency department and were found to have bleeding was 23.4% in the discharge group, 56.8% in the service group, and 70.3% in the intensive care group (P<0.001). This finding highlights the significant impact of bleeding complications due to warfarin overdose on clinical outcomes, similar to the Güven *et al*. [18] study. The fact that most patients with bleeding require intensive care admission reveals the seriousness of this situation and the need for urgent intervention.

Gastrointestinal system (GIS) bleeding was observed at 18.2% in the discharge group, 54.5% in the service group, and 57.7% in the intensive care group. The rate of intracranial bleeding was 0% in the discharge group, 9.1% in the service group, and 23.1% in the intensive care group. These findings show that gastrointestinal and intracranial bleeding are essential factors that increase the need for intensive care and affect patient mortality [19].

The mean hemoglobin of patients in the discharge group was determined as 10.45±2.37 g/dL, 10.14±2.52 g/ dL in patients in the ward group, and 8.30±3.14 g/dL in patients in the intensive care group (P<0.001). These low hemoglobin levels reveal that patients in the intensive care group experienced profound blood loss. Anemia and severe blood loss indicate that these patients require further hematological support therapy and close monitoring. These results are in line with other studies [20].

FFP was given at 19.1% of patients in the discharge group, 21.6% in the ward group, and 45.9% in the intensive care group (P=0.015). This finding shows that patients in the intensive care group need more FFP in cases of severe bleeding. Of TDP, It is clear that warfarin plays a critical role in the management of bleeding complications due to overdose. On the other hand, no significant difference was observed in patients given PCC and vitamin K. The scope and sample size of the study prevented the emergence of a statistically significant difference in patients given prothrombin complex concentrates (PCC) and vitamin K. Studies that are larger and include different patient groups may provide more precise results about the effectiveness of these treatments [21, 22].

Mortality was observed in 8.1% of the patient group admitted to intensive care in the study. No mortality was observed in patients admitted to the ward (P=0.054). This finding indicates that severe complications due to warfarin overdose carry a high risk of mortality, especially in patients requiring intensive care. This highlights the need for careful management of warfarin therapy and tighter follow-up and monitoring to prevent overdose. These results are in line with the literature [23, 24].

Limitations

This study has a retrospective design. The fact that the study was conducted in a single center may limit the generalizability of the findings. Additionally, the limited sample size reduced statistical power in some subgroup analyses.

CONCLUSION

This study shows that patients presenting to the emergency department with warfarin overdose are at risk of severe bleeding and require careful management. It is essential to closely monitor warfarin treatment and make accurate dose adjustments, especially in elderly and comorbid patients. The use of vitamin K, fresh frozen plasma, and prothrombin complex offers a practical treatment approach in the management of complications related to warfarin overdose. Future

studies require more extensive studies to increase the standardization and effectiveness of these treatment protocols.

Authors' Contribution

Study Conception: OSÇ; Study Design: MŞ, SMC; Supervision: DÇ, ESB; Funding: DÇ, SMC; Materials: MŞ, ESB; Data Collection and/or Processing: OSÇ; Statistical Analysis and/or Data Interpretation: MŞ, MSC; Literature Review: ESB, DÇ; Manuscript Preparation: OSÇ and Critical Review: DÇ, MŞ.

Ethics Approval

This study was approved by the Izmir Katip Çelebi University Non-Interventional Clinical Research Ethics Committee (Decision no.: 0337, Date: 20.07.2023).

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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