African Journal of Emergency Medicine 13 (2023) 8–14

Contents lists available at ScienceDirect

African Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/afjem

ORIGINAL ARTICLE

Comparison of the effects of different treatment protocols on mortality in patients presenting with an INR≥10 due to warfarin-associated over-anticoagulation ☆

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ARTICLE INFO

Keywords:
Warfarin
Supratherapeutic INR
Treatment
Vitamin K
Mortality

ABSTRACT

Aim: One of the most anticipated adverse effects of warfarin is over-anticoagulation. There is little to no evidence on the treatment that should be administered in patients with an international normalized ratio (INR)≥10. The primary outcome of this study is to analyze the effects of various treatments on 30-day mortality in patients with INR≥10 and without major bleeding on 30-day all-cause mortality. The secondary outcome is to propose a model that predicts 30-day all-cause mortality in the same patient group.

Methods: Patients older than 18 years of age using warfarin and who had an INR≥10 were included in this retrospective cohort study. Patients with major bleeding on admission were excluded. Patients treated with only cessation of warfarin were named as "Group-1", patients who were treated with vitamin-K in addition to cessation of warfarin were named as "Group-2", and patients who were treated with cessation of warfarin and vitamin-K and fresh frozen plasma or prothrombin complex concentrate were named as "Group-3".

Results: 190 patients were included in the analysis. Seven (38.9%) patients in the first group, 3 (8.6%) in the second group, and 21 (15.3%) in the third group died within 30-days**(p=0.015)**. In the post-hoc analysis, the difference between Group-1 and Group-2 was found to be significant(**p=0.036, OR:0.147, 95%CI=0.032 to 0.671).**

The performance of the model in predicting 30-day all-cause mortality was high (AUC=0.818 (95%CI = 0.716 to 0.920) and found to be compatible with the validation dataset 0.806 (95%CI = 0.631 to 0.981). Administration of vitamin K in addition to the cessation of warfarin was found to be a strong contributor to the model and an independent predictor of survival within 30 days(**p=0.006**).

Conclusions: Until randomized controlled studies are conducted, it may be reasonable to administer vitamin-K in addition to cessation of warfarin in non-bleeding patients with INR≥10.

African relevance

- Lack of monitoring of serum concentration, for drugs that require long-term follow-up, constitutes an important health problem, especially in low-income countries.
- High-quality INR monitoring is critical in middle-low or low-income countries such as Turkey, or African countries because patients with poorly controlled INR have been shown to have a high risk of mortality.
- We think that our study will provide critical information to the literature about the potential treatment strategies in patients with INR≥10 due to warfarin-associated over-anticoagulation, which is frequently seen in low-middle-income countries.

Introduction

One of the most anticipated adverse effects of warfarin, a vitamin K antagonist (VKA), is supratherapeutic INR because of over-anticoagulation. The incidence of warfarin-associated major bleeding is estimated to be approximately 11-13%, with a case-fatality rate of

☆ This article has not been previously presented at any event (congress, symposium, etc.) Institutional Review Board Approval Name: Ümraniye Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu **Approval number and date**: 54132726-000-28930, 12/08/2021

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https://doi.org/10.1016/j.afjem.2022.12.001
Received 4 August 2022; Received in revised form 7 December 2022; Accepted 14 December 2022

2.3-3.0% per year [1]. Since the patients using warfarin are generally in the high-risk group, it is vital to correct the elevated INR to the desired threshold rapidly and safely.

Lack of monitoring of serum concentration, for drugs that require long-term follow-up, constitutes an important health problem, especially when cardiovascular diseases are considered [2]. Although this issue has been briefly addressed in European and American guidelines which originate from high-income countries, studies show that INR control becomes more difficult as the income level decreases and is an actual topic in low-income countries [3]. Therefore, the importance of high-quality INR control is increasing in middle-low or low-income countries such as Turkey or the African countries, because in patients with poorly controlled INR, the risk of mortality increases [4].

Over the years, various guidelines have tried to offer evidence-based recommendations on this issue. The Australasian Society of Thrombosis and Haemostasis guideline, in its 2013 update, recommends only temporary cessation of warfarin in patients with an INR between 4.5 and 10 and with no major bleeding, noting that 1-2mg oral Vitamin K, or 0.5-1mg IV Vitamin K can be administered in patients with high bleeding risk. In the same guideline, 3-5mg oral vitamin K is recommended in addition to the temporary cessation of warfarin with a low level of evidence, for the patients presenting with an INR≥10 and without major bleeding. It is stated that additional prothrombin complex concentrate (PCC) can be applied in patients with high bleeding risk. The use of fresh frozen plasma (FFP) has been recommended only in the absence of PCC [5].

Similarly, in the American College of Chest Physicians (ACCP) guideline published in 2012, oral vitamin K administration was recommended for patients presenting with an INR≥10 and without major bleeding. However, the recommendation in this guideline has a low class of recommendation and a low level of evidence. Although the guideline has been updated twice to date, no new recommendation or evidence has been included on this issue [6].

The most up-to-date guideline on the subject; "Guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy" which was published in 2018 by the American Society of Hematology, did not comment on the treatment that should be administered to the patients presenting with an INR≥10 and without major bleeding [7]. The panel identified a research question about the topic and emphasized the lack of evidence like the other guidelines [5-7].

Regarding this gap of evidence, we aimed to compare the effect of the following treatment protocols on 30-day all-cause mortality in the patients presenting with no major bleeding and INR≥10; i) temporary cessation of warfarin, ii) administration of vitamin-K in addition to temporary cessation of warfarin and iii) administration of vitamin-K and PCC or FFP in addition to temporary cessation of warfarin. We think that this study, which was conducted in a low-income country where the monitoring of serum concentrations and drug compliance is relatively difficult, has critical importance.

Methods

Setting

This retrospective cohort study was conducted in the emergency medicine department (ED) of Umraniye Training and Research Hospital, with an annual capacity of 600,000 patients, following local ethics committee approval (Umraniye Training and Research Hospital ethics committee , number 54132726-000-28930 and date 12/08/2021).

The treatment protocol for the patients presenting to our ED with INR 4.5 to 10 and with no major bleeding is only temporary cessation of warfarin. If the attending physician decides there is a risk of bleeding, IV vitamin K is administered. For the patients presenting with an INR≥10 and without major bleeding, because of the lack of evidence, the treatment protocol to be applied is left to the physician's gestalt and no specific algorithm is implemented.

Although the guidelines suggest that PCC can be administered as the first choice of additional treatment in patients with INR≥10 when high risk of bleeding is present, FFP is frequently used in our hospital for the reasons of cost-effectiveness. PCC is mainly used in a selected group such as patients with congestive heart failure.

Since there is no available oral form of vitamin K in our hospital, an IV form of 10mg (Konakion ®, vitamin K1) is used. The PCC available in our hospital is a 4 factor PCC (Cofact ®), and it is used according to the manufacturer's recommended dosing chart [8]. The dose of FFP that should be used for INR reversal in our hospital is a predetermined standard dose of 15 ml/kg. These treatments were administered in the ED setting within 12 hours after the index INR test.

Selection of the study population and acquisition of data

All the data were extracted from the hospital database after the ethics committee's approval. Patients above 18 years of age who were admitted to the ED between January 1, 2015, and December 31, 2019, using warfarin and had an INR≥10 were included in the study. Patients presented with major bleeding, and patients with missing treatment or outcome data were excluded. Only the data of the first application of the patients who have multiple admissions were considered and recorded. Other applications were excluded.

Patient groups and definitions

Patients were grouped according to the treatment they received. Patients treated with only temporary cessation of warfarin were named as "Treatment Group 1", patients who were treated with vitamin K in addition to temporary cessation of warfarin were named as "Treatment Group 2", and patients who were treated with administration of vitamin-K, and PCC or FFP in addition to temporary cessation of warfarin were named as "Treatment Group 3".

The term "major bleeding" was defined as the presence of any of the following: fatal bleeding, symptomatic bleeding in significant organs (intracranial, intraabdominal, intrathoracic, intra-articular), or bleeding requires at least two erythrocyte suspension transfusion or a decrease in hemoglobin concentrations of at least 20g/L [9].

Outcome measures

The primary outcome of the study is to compare the effects of the treatment protocols on 30-day all-cause mortality in patients presenting with an INR≥10 and without major bleeding.

The secondary outcome of the study was to propose a model that would predict 30-day all-cause mortality effectively and identify the strongest predictors.

Statistical analysis

For the statistical analysis, SPSS 29 (IBM Corp. 2019. IBM SPSS Statistics for Windows, Version 26.0) was used. For the test of normality, the Shapiro-Wilk test was preferred, and all of the continuous data were distributed non-normally. For this reason, the Mann-Whitney U test was used for pairwise group comparisons and Kruskal Wallis for multiple group comparisons of the continuous data. For the comparison of categorical data, the Pearson Chi-Square test was used, and Fisher Exact test was chosen when necessary. Bonferroni correction was applied after post-hoc analysis where necessary.

For the multivariate analysis of the patients with INR≥10, binary logistic regression and forced entry method was used. Variables with a univariate analysis result of $p<0.2$ without missing values were included in the model as potential predictors. Although the p values were adequate for inclusion in the model, the following variables were excluded

due to missing data; systolic blood pressure, diastolic blood pressure, heart rate and oxygen saturation.

In the literature, it has been stated that the number of predictors that should be included in the logistic regression model, especially for sensitivity studies, can be calculated according to the "5-9 events per predictor" formula. According to this reference, we determined the number of predictors to be included in our model as six [10].

The data set was randomly divided into two categories as training set and validation set at a 6 to 4 ratio (training set N=114, validation set N=76). For the training dataset, multicollinearity was checked. The Hosmer-Lemeshow test was performed for the goodness of fit. The diagnostic value of the predicted logits in predicting 30-day all-cause mortality was analyzed with the Receiver Operating Characteristic (ROC). Then, the predicted logit values of the validation set were calculated with the beta-coefficient and intercept values obtained from the training set, and its performance in predicting 30-day all-cause mortality was analyzed with ROC. The statistical significance level was determined as $p<0.05$.

Results

Baseline characteristics

A total of 253 patients with an INR≥10 was found in the database over a 5-year period. Of these patients, 32 were excluded from the study because they were duplicates, 10 due to lack of outcome data, and 21 due to major bleeding on admission to the ED. A total of 190 patients were included in the statistical analysis. The patient flow chart is summarized in Fig. 1.

The median age of the total study population was 74 (65 to 80), and 72 (37.9%) of these patients were male. There were 18 (9.5%) patients in treatment group 1, 35 (18.4%) patients in treatment group 2, and 137 (72.1%) patients in treatment group 3. The groups were well-matched and found to be comparable. A significant difference was observed between the treatment groups only in the medians of systolic blood pressure at admission. It was accepted that this minor difference would not disturb the balance between the groups. The baseline characteristics of the patients and the comparison of the patient groups in terms of these baseline characteristics are summarized in Table 1.

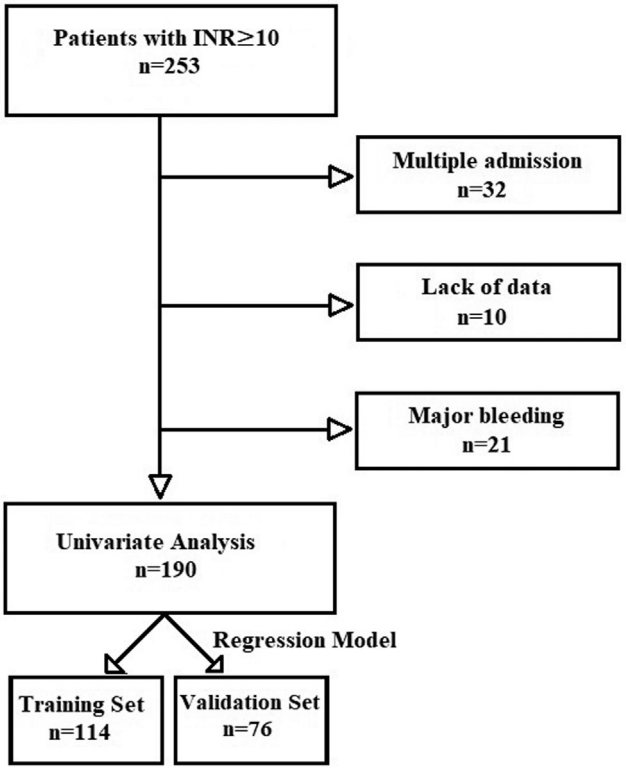

Fig. 1. Patient flow chart.

Outcome measures

In our study, vitamin K was administered intravenously and at a dose of 10mg to group-2 and group-3 patients. Seven (38.9%) patients in the first treatment group, 3 (8.6%) in the second treatment group, and 21 (15.3%) in the third treatment group died within 30 days. The difference between the groups was significant (**p=0.015**, Pearson Chi-Square). In the post-hoc analysis, it was observed that the difference

Table 1
Baseline characteristics of the study population and the comparison of the baseline characteristics of the groups of primary outcome.

	All patients **Median (%25-75 IQR) / N (%)**	Treatment Group 1 **Median (%25-75 IQR) / N (%)**	Treatment Group 2 **Median (%25-75 IQR) / N (%)**	Treatment Group 3 **Median (%25-75 IQR) / N (%)**	p-value
Age	74 (65 to 80)	74 (59 to 79)	75 (66 to 82)	74 (65 to 80)	0.784
Sex (Male)	72 (37.9)	6 (33.3)	12 (34.4)	54 (39.4)	0.784
INR	13.3 (11.5 to 20)	12.8 (11.2 to 14.6)	12.6 (11.3 to 20)	13.9 (11.8 to 20)	0.125
Systolic TA (mmHg)	125 (110 to 148)	130 (120 to 141)	141 (124 to 160)	121 (110 to 143)	**0.019**
Diastolic TA (mmHg)	73 (63 to 80)	80 (70 to 88)	78 (63 to 89)	70 (62 to 80)	0.110
Pulse rate (beat/min)	86 (78 to 99)	93 (83 to 128)	85 (80 to 92)	87 (77 to 100)	0.181
SpO2 (%)	96 (92 to 98)	96 (90 to 99)	95 (95 to 97)	96 (90 to 99)	0.666
GCS	15 (15 to 15)	15 (15 to 15)	15 (15 to 15)	15 (15 to 15)	0.557
Diabetes Mellitus	62 (32.6)	4 (22.2)	10 (28.6)	48 (35.8)	0.421
Hypertension	135 (71.1)	13 (72.2)	26 (74.3)	96 (71.6)	0.953
CAD	77 (40.5)	4 (22.2)	14 (40)	59 (44)	0.208
COPD	37 (19.5)	6 (33.3)	3 (8.6)	28 (20.9)	0.084
CRF	18 (9.5)	0 (0)	2 (5.7)	16 (11.9)	0.187
Ischemic Stroke	46 (24.2)	3 (16.7)	8 (22.9)	35 (25.9)	0.671
A.Fib	107 (56.3)	11 (61.1)	26 (74.3)	70 (51.9)	0.054
VR	43 (22.6)	3 (16.7)	8 (22.9)	32 (23.7)	0.800
Treatment	-	18 (9.5)	35 (18.4)	137 (72.1)	
Thrombotic event in 30 days	2 (1.1)	1 (8.3)	1(3.4)	0(0)	NA*
Major bleeding in 30 days	3 (1.6)	0 (0)	0 (0)	3(2.9)	NA*
Mortality in 30 days	31 (16.3)	7 (38.9)	3 (8.6)	21 (15.3)	**0.015**

A.Fib: Atrial fibrillation, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal failure, FFP: Fresh frozen plasma, GCS: Glasgow coma scale, INR: International normalized ratio, PCC: Prothrombin complex concentration, SpO2: oxygen saturation, TA: arterial tension, VR: Valve replacement. Treatment Group 1: temporary cessation of warfarin only, Treatment Group 2: vitamin K in addition to temporary cessation of warfarin, Treatment Group 3: vitamin-K, and PCC or FFP in addition to temporary cessation of warfarin.

Table 2
Comparison of 30-day all-cause mortality rates of the treatment groups admitted with INR≥10.

		30-day mortality (-) N (%)	30-day mortality (+) N (%)	p-value	Odds ratio	95%CI
Vitamin K group		148 (93.1)	24 (77.4%)	**0.014**	**0.255**	**0.090 to 0.722**
PCC or FFP		116 (73)	21 (67.7)	0.554	0.778	0.339 to 1.786
Omnibus test	**Group 1**	11 (61.1)	7 (38.9)	**0.015**	-	-
	Group 2	32 (91.4)	3 (8.6)			
	Group 3	116 (84.7)	21 (15.3)			
Pairwise comparisons	**Group 1**	11 (61.1)	7 (38.9)	**0.036***	**0.147**	**0.032 to 0.671**
	Group 2	32 (91.4)	3 (8.6)			
	Group 1	11 (61.1)	7 (38.9)	0.069*	0.284	0.099 to 0.817
	Group 3	116 (84.7)	21 (15.3)			
	Group 2	32 (91.4)	3 (8.6)	0.693*	1.931	0.541 to 6.886
	Group 3	116 (84.7)	21 (15.3)			

* Bonferroni correction was applied. **Group 1**: temporary cessation of warfarin only, **Group 2**: vitamin K in addition to temporary cessation of warfarin, **Group 3**: vitamin-K, and PCC or FFP in addition to temporary cessation of warfarin. INR: International Normalized Ratio. FFP: Fresh Frozen Plasma, PCC: Prothrombin Complex Concentrate.

Table 3
Univariate analysis of the predictors of 30-day all-cause mortality in patients with INR≥10.

	Survivors Median (%25-75 IQR) / N (%)	Non-survivors Median (%25-75 IQR) / N (%)	p value
Age	73 (63 to 78)	77 (74 to 81)	**0.025**
Age≥65	117 (73.6)	28 (90.3)	**0.045**
Gender (Male)	57 (35.8% of survivors)	15 (48.4% of non-survivors)	0.188
Systolic blood pressure	130 (115 to 150)	115 (88 to 126)	**<0.001**
Diastolic blood pressure	74 (66 to 80)	67 (48 to 78)	**0.005**
Pulse rate	85 (78 to 96)	97 (79 to 115)	**0.025**
SpO2	96 (94 to 98)	95 (88 to 97)	0.054
Glasgow Coma Scale	15 (15 to 15)	15 (11 to 15)	**<0.001**
GCS<15	4 (2.5)	12 (38.7)	**<0.001**
Diabetes mellitus	52 (33.3)	10 (32.3)	0.908
Hypertension	115 (73.7)	20 (64.5)	0.296
Coronary artery disease	66 (42)	11 (36.7)	0.584
COPD	32 (20.5)	5(16.1)	0.576
Chronic renal failure	14 (9)	4 (12.9)	0.346*
History of ischemic stroke	38 (24.2)	8 (25.8)	0.850
Atrial fibrillation	95 (60.1)	12 (40)	**0.041**
Valve Replacement	32 (20.4)	11 (35.5)	0.067
Alzheimer	8 (5.1)	3 (9.7)	0.210

* Fisher Exact test was used. COPD: Chronic obstructive pulmonary disease, GCS: Glasgow Coma Scale.

between the groups was due to the comparison between treatment group 1 and treatment group 2 (**p=0.036, OR:0.147, 95%CI=0.032 to 0.671,** Fisher Exact, Bonferroni correction applied). When the effects of the treatments on mortality were examined individually, 144 (93.1%) of the patients who were administered vitamin K survived for 30 days, 24 (77.4%) of the patients who were administered vitamin K had 30-day mortality, and the difference between the groups was statistically significant (**p=0.014, OR=0.255, 95%CI=0.090 to 0.722).** However, 116 (73%) of patients administered PCC or FFP survived for 30 days, 21 (67.7%) had 30-day mortality, and the difference between the groups was not statistically significant (p=0.554, OR=0.778 95%CI=0.339 to 1.786). The results were summarized in Table 2.

When the predictors of 30-day all-cause mortality of the patients with INR≥10 were analyzed, advanced age, decreased systolic and diastolic blood pressure, increased pulse rate, GCS<15, and the presence of atrial fibrillation were found to be significant **(p=0.025, p<0.001, p=0.005, p=0.025, p<0.001, and p=0.041 respectively)**. The results of the univariant analysis were summarized in Table 3.

The results of the univariant analysis were used to select the optimal predictors of 30-day all-cause mortality for the model. Age, gender, Glasgow Coma Scale, and presence of valve replacement had p<0.2 without missing values (**p=0.025**, p=0.188, **p<0.001**, p=0.067 respectively). Potential predictors were included in the regression model by using the forced-entry method. For predicting the 30-day all-cause mortality in the patients who presented with INR≥10, binary logistics was used. The preliminary analysis showed that in the training set, the assumption of multicollinearity was met (tolerance>0.1 for all predictors). Standardized residual values showed that there were four outlier patients, and they were not excluded from the model since their effect to the model were limited (standard residuals = 4.023, 5.043, 5.203, -3.931, Cook's Distances = 0.17465, 0.24490, 0.46930, 0.13083). For determining the goodness-of-fit, Hosmer–Lemeshow test was used which yielded a $\chi 2(8)$ of 6.73 and was statistically insignificant (p=0.566). Our model could significantly predict 30-day all-cause mortality (N=114, **p<0.001**). It was able to explain 19.6% (Cox & Snell R square) to 33.2% (Nagelkerke R Square) of the variance in 30-day all-cause mortality and it was able to classify 87.9% of the cases correctly.

GCS, presence of valve replacement, vitamin K administration in addition to cessation of warfarin (group 2 treatment), vitamin K administration, and FFP/PCC administration in addition to cessation of warfarin (group 3 treatment) and age were found to be independent predictors of 30-day all-cause mortality (**p<0.001, p=0.005, p=0.006, p=0.008, and p=0.010** respectively). Decreased GCS was found to be the strongest factor contributing to mortality in our model (Wald=13.933). Coefficients, Wald statistics, p values, and odds ratios for all predictors were summarized in Table 4.

When the diagnostic performance of the model in predicting 30-day all-cause mortality was analyzed with ROC analysis, the area under the

Table 4
The binary logistic regression analysis for 30-day all-cause mortality in patients with INR≥10.

	Coefficient	Wald	p	Odds Ratio (95%CI)
Intercept	-1.900	0.766	0.382	0.150 (-)
Treatment Group 2*	-1.823	7.633	**0.006**	0.161 (0.044 to 0.589)
Treatment Group 3*	-2.415	7.091	**0.008**	0.089 (0.015 to 0.529)
Age	0.065	6.720	**0.010**	1.067 (1.016 to 1.120)
Gender (Male)	0.906	3.710	0.054	2.476 (0.984 to 6.227)
Glasgow coma scale	-0.323	13.933	**<0.001**	0.724 (0.611 to 0.858)
Presence of Valve Replacement	1.454	8.031	**0.005**	4.279 (1.566 to 11.694)

FFP: Fresh frozen plasma, GCS, PCC: Prothrombin complex concentrate. Treatment Group 2: vitamin K in addition to temporary cessation of warfarin, Treatment Group 3: vitamin-K, and PCC or FFP in addition to temporary cessation of warfarin. * Group-1 is not included in the model to avoid the "Dummy Variable Trap".

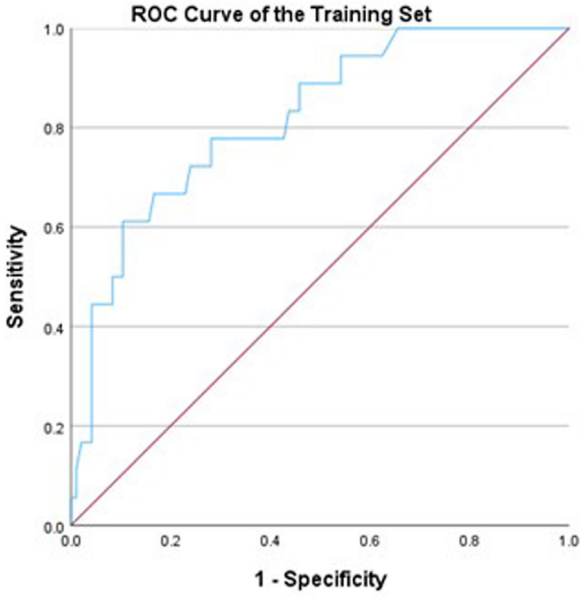

Fig. 2. The receiver operating characteristics curve of the regression model predicted logits of the training set in predicting 30-day all-cause mortality.

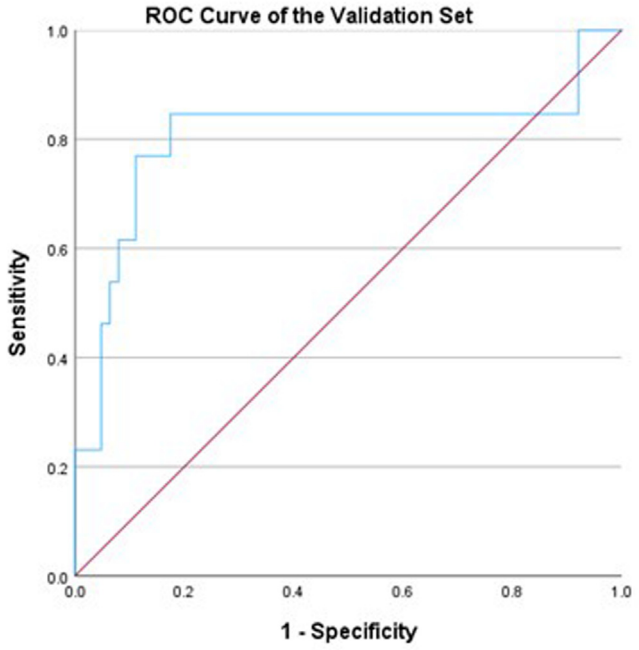

Fig. 3. The receiver operating characteristics curve of the regression model predicted logits of the validation set in predicting 30-day all-cause mortality.

curve (AUC) for the training set (N=114) was 0.818 (95%CI = 0.716 to 0.920). The AUC value of the validation set (N=76) was calculated as 0.806 (95%CI = 0.631 to 0.981) and this value was found to be compatible with the training set. The ROC curves are shown in Figs. 2 and 3.

Discussion

According to the results of our study, administration of vitamin-K in addition to cessation of warfarin caused a significant reduction in 30-day all-cause mortality in patients with INR≥10 and no major bleeding. However, the use of PCC or FFP in addition to vitamin K in the same patient population did not cause any significant difference between the treatment groups. In addition, the administration of vitamin K therapy in addition to the cessation of warfarin was found to be an independent predictor of survival within 30 days. These results indicate that vitamin-K significantly reduced the 30-day all-cause mortality in our study.

The number of studies conducted specifically on patients with INR≥10 is quite limited. In a retrospective study that was published in 2020, 809 patients with INR ≥10 and without major bleeding were included. The two groups that were treated with cessation of warfarin and with vitamin K in addition to cessation of warfarin were compared in terms of 30-day mortality and, different results were obtained in different subgroup analyses. When all patients were analyzed in the study, there was a significant increase in 30-day mortality in the vitamin K group (p=0.032). When propensity score matching was applied, no significant difference was detected (p>0.05) [11].

There may be several reasons why we obtained different results from this study. The mean dose of vitamin K administered in this study was reported as 3.1mg and was given orally to 95.4% of the patients. In addition, vitamin K was administered in different timeframes such as immediately, within 24 hours, or more than 24 hours. In our study, 10mg IV vitamin K was administered to all of the patients in the vitamin K group, in the ED on the same day. Warfarin affects vitamin K-mediated coagulation factors, and the elimination half-life of the drug can be up to 35 hours [12]. Considering that especially elderly and comorbid patients are using warfarin, it is obvious that cessation of warfarin alone, in patients with very high INR values will put these patients at risk for an extended period of time. Intravenous administration of vitamin K has been shown to be associated with faster INR correction [13]. The reason why the 30-day mortality was significantly lower in the vitamin-K group in our study may be due to the difference in the dose, route, and time of vitamin K administration.

It is possible that vitamin K could be a safe exit for patients taking warfarin. A recent debate questions whether low-dose vitamin K administration to patients on warfarin may be a factor that facilitates warfarin titration and stabilization of serum concentrations, meaning that there may be a potential benefit of administering vitamin K even to the pa-

tients whose INR is in the therapeutic range. [14, 15]. In addition, the authors of the only prospective study on the topic, which examined 107 patients with an INR≥10 who were given vitamin K in addition to cessation of warfarin, reported that only 1 patient died in their study within 7 days of initial admission, and they concluded that vitamin K could be a safe and effective treatment option [16].

In a systematic review published in 2016, it was indicated that administering PCC for rapid correction of INR was superior compared to FFP in terms of mortality, INR normalization, and time of INR normalization in patients with major bleeding [1]. Published guidelines also make recommendations that correlate with this result [5]. Besides, blood group compatibility is required in patients who will be administered FFP. This requirement, which takes time for a treatment that is indicated urgently, can be considered a serious limitation. In addition, this treatment has serious potential side effects such as anaphylaxis, transfusion-related acute lung injury (TRALI), transfusion-related infectious diseases, and fluid overload in patients with congestive heart failure [1]. Although relatively rare especially compared to FFP, TRALI and overload still remain as side effects of using PCC. In addition, the use of these treatments can cause a rapid over-correction in the INR value. The reason why the addition of FFP or PCC did not cause a significant decrease in mortality in our study may be these side effects or over-correction of the INR. Considering this information and the results of our study, it does not seem reasonable to administer FFP for INR correction in patients with INR≥10 and no major bleeding. However, it should be kept in mind that due to financial and logistical difficulties in low-middle-income countries, it may be an obligation to choose FFP over PCC in patients with high bleeding risk.

The regression model, which was the secondary outcome of our study, was significant in predicting 30-day all-cause mortality in patients with INR≥10, and its performance in both the training set and the validation set was quite high and consistent. Also, the relatively high Wald statistics value of vitamin-K administration in addition to the cessation of warfarin (group 2) in the treatment gives us the opportunity to make a stronger statement about the effectiveness of this treatment. With this model, precautions can be taken by calculating the risk of mortality in patients who applied with supratherapeutic INR, especially in low-income countries where regular monitoring and drug compliance is an actual problem.

Considering the lack of evidence in the current guidelines for the treatment of patients with no major bleeding and INR≥10, we think that the administration of Vitamin K in these patients may be a reasonable recommendation as it has the potential to reduce mortality.

The retrospective nature of our study prevents us from emphasizing our results strongly. However, we think that our results may be useful in the clinical decision-making process until randomized controlled studies are conducted in patients with INR≥10.

Although propensity score matching was not performed in our study, it is seen in the Table-1 that the groups are similar in terms of basic characteristics. Therefore, we think that the groups are comparable, and the reliability of the data was not compromised.

The fact that we could not include some variables in the regression model due to missing data may have caused us to overlook the effect of these variables on mortality and may have reduced the power of our model. Despite this limitation, our model has been quite successful in predicting 30-day all-cause mortality.

Although the analysis of the variables such as intensive care unit hospitalization, hospital length of stay, the requirement for mechanical ventilation, and median duration to mortality after admission would add value to the study, these variables could not be included in the study because our permission to access these data was expired.

Conclusion

When the results of the primary outcome of our study are considered together with the results of our regression model, it is safe to suggest that administering vitamin K in addition to cessation of warfarin, in patients presenting with INR≥10 and no major bleeding seems reasonable, especially in the lower income countries where the regular monitoring and treatment compliance is more problematic. But the evidence remains insufficient for the treatment of supratherapeutic INR associated with warfarin use in this patient group and there is a need for high-quality studies. Until these studies are conducted, it may be beneficial to administer vitamin K in addition to cessation of warfarin in nonbleeding patients with INR≥10.

Dissemination of results

We shared our results with the emergency medicine specialists and residents in our department. Based on the lack of evidence in the literature, we started to exchange ideas about conducting a randomized controlled study on the subject.

Authors' contributions

Authors contributed as follows to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; and drafting of the work or revising it critically for important intellectual content: MMI contributed 50%, EA 15%, CU 10%, MD 5%, MOS 5%, GA 5%, SEE 5%, SÖ 5%. All authors approved the version to be published and agreed to be accountable for all aspects of the work.

Declaration of Competing Interest

The authors declared no conflicts of interest.

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Acknowledgements

None to declare.

Funding

None to declare.

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