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An easy nomogram to predict 30-day mortality in warfarin overdose patients undergoing endoscopy for gastrointestinal bleeding

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ABSTRACT

Introduction: Gastrointestinal bleeding (GIB) is a crucial medical issue in patients receiving oral anticoagulant therapy. Thus, the management of these patients is important in daily clinical practice. In this study, first, we sought to show the predictors of mortality and, second, provide a nomogram for clinicians to evaluate the risk of mortality in patients undergoing endoscopic therapy with warfarin overdose.

Materials and Methods: Patients who underwent endoscopic treatment with warfarin overdose and GIB between February 15, 2019, and March 20, 2021, were retrospectively evaluated. Clinical, demographic, and laboratory parameters of patients were recorded. The primary outcome was 30-day all-cause mortality after the procedure.

Results: A total of 359 patients admitted with warfarin overdose and GIB who underwent endoscopic treatment were included in the study. All-cause death was observed in 50 (14%) patients in the 30-day period after the procedure. According to univariate and multivariate logistic regression analysis, age (OR=1.019; 95% CI=1.000–1.039; p=0.008), hypertension (OR=1.909; 95% CI=1.051–3.468; p=0.004), alcohol history (OR=1.618; 95% CI=1.196–2.954; p=0.018), and albumin value (OR=0.318; 95% CI=0.214–0.471; p=0.001) were determined as independent predictors for 30-day all-cause mortality. The areas under the curves of the nomogram were 0.73 (95% CI: 0.70–0.76) may have clinical usefulness.

Conclusion: This study provides a nomogram containing age, hypertension, alcohol, and albumin that can be conveniently used to predict individual mortality in warfarin overdose patients undergoing endoscopy for GIB.

Keywords: Gastrointestinal bleeding, mortality, overdose, warfarin

Introduction

Oral anticoagulant (OAC) treatment is a vital treatment method for the prophylaxis and treatment of thromboembolic diseases, which constitute a wide spectrum in terms of localization and clinic.[1] However, the maintenance dose required for the therapeutic target, the International Normalized Ratio (INR) value, varies between individuals. Warfarin overdose is relatively rare, but it is associated with significant morbidity potential.[2] Bleeding is a common complication and is the most important reason

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limiting the widespread use of warfarin.[3] Therefore, it is important to achieve an effective INR with a low risk of bleeding. Gastrointestinal bleeding (GIB) due to warfarin overdose is a common complication with a rate of 4.5%/year.[4] For patients with unknown gastric lesions, even therapeutic INR values may cause GIB. Studies have shown that besides environmental factors, genetic factors may play a role in bleeding complications.[5] Data to guide the optimal warfarin management after admission with GIB are limited.[6,7]

Identifying clinical factors and laboratory parameters affecting mortality in patients presenting with GIB after warfarin overdose may be an important way to improve clinical results.[9,10] Determining the current risk with the scales determined in patients using warfarin is an important parameter that can affect the duration and management of treatment in patients with GIB and can predict the risk of mortality. In patients with high-risk scores, closer INR follow-up can be planned.

In the light of the above information, we, therefore, aimed to determine the predictors of mortality in patients who undergo endoscopic treatment with warfarin overdose and GIB and to develop a nomogram that can be used as a mortality predictor in these patients.

Materials and Methods

Patients who underwent endoscopic treatment with warfarin overdose and GIB between February 15, 2019, and March 20, 2021, were retrospectively evaluated. Patients who received antiplatelet therapy other than warfarin, which may affect the risk of bleeding and the clinical results of the patient, and patients who experienced procedural complications during endoscopy were excluded from the study. The clinical and demographic data of the patients and laboratory parameters on admission to the hospital were recorded. Age, gender, hypertension, diabetes mellitus, coronary artery disease, previous cerebrovascular disease, chronic renal failure, cancer history of smoking and alcohol use, admission INR, and serum albumin values of the patients were recorded. The primary outcome was 30-day mortality after the endoscopy date which defined from hospital records and the database of the Republic of Turkey Ministry of Health. The patients clinical and laboratory data were presented according to two groups as survivors and non-survivors. The study was approved by the Ankara City Hospital Ethics Committee (Date: 04/07/2021, Decision no: E2-21-424).

Statistical Analysis

All statistical analyses were done using by Stata (version 16.0 MP; StataCorp). The distribution of continuous variables was determined using the Kolmogorov–Smirnov test. Continuous data were defined as mean±SD for normal distributions and as median (range) for skewed distributions. Categorical data were defined as the number of cases. Statistical analysis differences in variables showing normal distribution were compared between the two groups using Student's t-test, Mann–Whitney U-test was used for non-normally distributed data. Categorical variables were compared using Pearson's Chi-square test. To show significant predictors of 30-day all-cause of mortality, a univariate logistic regression model was created for each variable, and then those which had <0.1 P-values were tested in the multivariable logistic regression model. Odds ratios (ORs) and their 95% Confidence intervals (CIs) for mortality were presented. Receiver operating characteristic (ROC) analysis was used to show the discrimination of the final model. Finally, a nomogram including significant predictors was graphed. P<0.05 was considered significant in all statistical analyzes.

Results

A total of 359 patients admitted with warfarin overdose and GIB who underwent endoscopic treatment were included in the study. The number of female patients was 194 (54.0%). Hypertension in 211 (59.8%) patients, diabetes in 72 (20.4%), coronary artery disease in 136 (38.7%), cerebrovascular event in 92 (26.1%), chronic renal failure in 21 (5.9%), and 17 (4.8%) had a history of cancer. The number of smoking patients was 183 (51.0%), and the number of patients using alcohol was 56 (15.6%).

All-cause death was observed in 50 (14%) patients in the 30-day period after the procedure. Between the survivors and non-survivors groups, the mean age was significantly higher in the non-survivors group (p=0.007). Hypertension was significantly higher in the non-survivors group (p=0.003). Although alcohol use was more common in the non-survivors group, the difference was not significant (p=0.078). There were no statistically significant differences between survivors and non-survivors groups for gender (p=0.76), diabetes mellitus (p=0.76), coronary artery disease (p=0.90), cerebrovascular disease (p=0.44), chronic renal failure (p=0.57), history of cancer (p=0.62), and smoking (p=0.29).

Most patients (45.0% n=159) had dysrhythmia for the in-

dication of anticoagulation. Subsequently, 87 (24.6%) patients had valvular heart disease, 45 (12.7%) patients had cerebrovascular disease, 44 (12.5%) patients had pulmonary thromboembolism, and 18 (5.1%) patients had venous thromboembolism for anticoagulation indications. There was no significant difference between the survivors and non-survivors groups in terms of warfarin indications (p=0.39). All demographic and clinical characteristics of the patients according to survivors and non-survivors groups are shown in Table 1.

The mean INR value at admission was 9.612±5.287 for all patients, 9.442±5.178 in the survivors group, 10.660±5.867 in the non-survivors group, and there was no significant difference between the groups (p=0.13). Serum albumin levels were on average 3.61±0.62 for all patients, 3.66±0.57 in the survivors group, and 3.34±0.81 in the non-survivors group, the difference was significant (p=0.002), (Fig. 1). Upper GIB was found in 220 (61.2%) of the patients, and lower GIB in 139 (38.3%). Upper GIB was significantly higher in the non-survivors group (p=0.001). The baseline clinical characteristics of the patients according to survival status are summarized in Table 2.

Univariate and multivariate logistic regression analysis were used to identify factors predicting 30-day mortality. Age (OR=1.019; 95% CI=1.000–1.039; p=0.008), hypertension (OR=1.909; 95% CI=1.051–3.468; p=0.004), alcohol (OR=1.618; 95% Cl=1.196–2.954; p=0.018), and

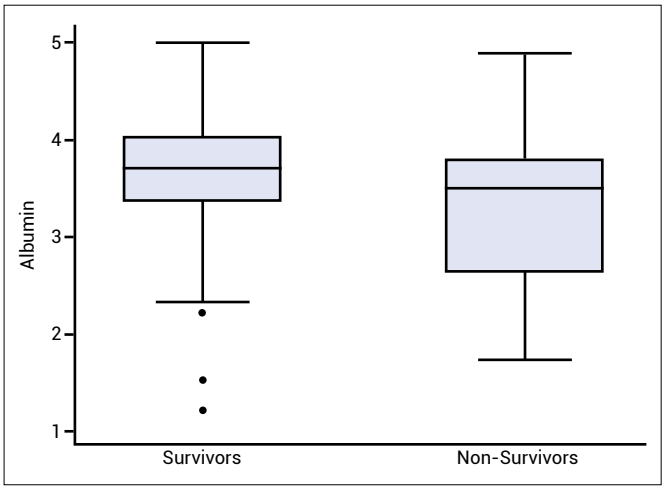

Figure 1. The box plot for serum albumin levels according to the survivors and non-survivors groups.

serum albumin value (OR=0.318; 95% Cl=0.214–0.471; p=0.001) were determined as independent predictors for 30-day all-cause mortality. Univariate and multivariate logistic regression analysis data are presented in Table 3.

The accuracy of predicting mortality was assessed by the area under the ROC curve which was = 0.73 (an acceptable discrimination) as shown in Figure 2. A novel nomogram has been developed with significant predictors (age, hypertension, alcohol, and serum albumin) for the primary outcome and was graphed in Figure 3.

Table 1. Baseline demographic of patients according to the survivor status

	Total n=359		Survivors n=309		Non-survivors n=50		p
	n	%	n	%	n	%	
Age, mean (SD)	70 (13)		69 (14)		75 (11)		0.007*
Gender							
Female	194	54.0	166	53.7	28	56.0	0.76
Male	165	46.0	143	46.3	22	44.0	
History of disease							
Hypertension	211	59.8	173	56.7	38	79.2	0.003*
Diabetes mellitus	72	20.4	63	20.7	9	18.8	0.76
Coronary artery disease	136	38.7	117	38.6	19	39.6	0.90
Cerebrovascular disease	92	26.1	76	24.9	16	33.3	0.44
Chronic renal failure	21	5.9	19	6.2	2	4.2	0.57
Cancer	17	4.8	14	4.6	3	6.3	0.62
Smoking	183	51.0	161	52.1	22	44.0	0.29
Alcohol	56	15.6	44	14.2	12	24.0	0.078

Table 2. Baseline clinical characteristics of patients according to the survivor status

	Total n=359		Survivors n=309		Non-Survivors n=50		p
	n	%	n	%	n	%	
Indication for warfarin							
Pulmonary thromboembolism	44	12.5	39	12.8	5	10.4	0.39
Valvular heart disease	87	24.6	76	24.9	11	22.9	
Cerebrovascular disease	45	12.7	39	12.8	6	12.5	
Dysrhythmia	159	45.0	133	43.6	26	54.2	
Venous thromboembolism	18	5.1	18	5.9	0	0.0	
Bleeding localization							
Upper gastrointestinal	220	61.2	182	58.9	38	76.0	0.001*
Lower gastrointestinal	139	38.3	127	41.1	12	24.0	
Laboratory							
International normalized ratio, mean (SD)	9.612 (5.287)		9.442 (5.178)		10.660 (5.867)		0.13
Albumin, g/dL, mean (SD)	3.61 (0.62)		3.66 (0.57)		3.34 (0.81)		0.002*

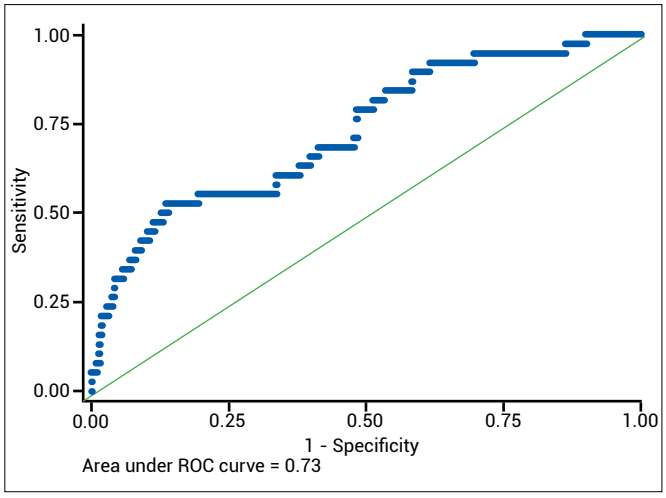

Figure 2. The area of under the curve for significant predictors of 30-day all-cause mortality.

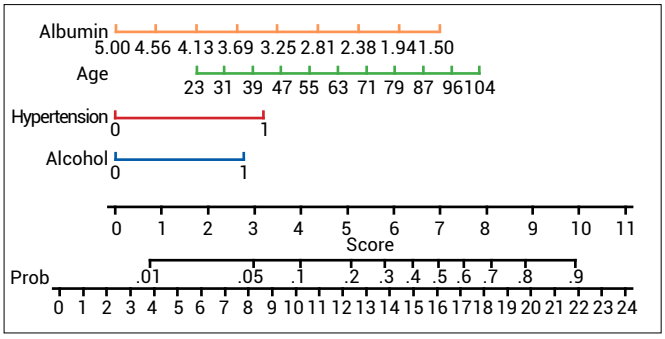

Figure 3. The nomogram for 30-day all-cause mortality.

Discussion

In the current study, we found that advanced age, hypertension, serum albumin level, and alcohol use were significantly associated with 30-day all-cause mortality in patients admitted with warfarin overdose and GIB. We created a novel nomogram that includes 4 variables with an AUC of 0.73 (acceptable discrimination). As defining predictors for mortality is important in terms of affecting patient follow-up, length of hospital stay, and treatment protocols, our nomogram can be conveniently used to predict individual 30-day all-cause mortality in warfarin overdose patients undergoing endoscopy for GIB.

Various scoring systems have been developed to predict the risk of bleeding in patients receiving warfarin therapy: Anticoagulation and risk factors in atrial fibrillation, Outcome Record for Better Informed Treatment scores, HAS-BLED score (hypertension, abnormal liver or kidney function, stroke, bleeding tendency, and variable INR, age> 65, drugs, or alcohol) are some of these.[11,12] However, these models are not specifically developed for mortality in GIS bleeding patients. In our model, the discrimination (as assessed by c-index) of the risk score determined according to the nomogram was found to be 0.73. It is thought that it may be beneficial in clinical practice as it had moderate accuracy.

In our study, the short-term 30-day mortality rate was 14% in patients who underwent endoscopy with the diagnosis

Table 3. Univariate and multivariate logistic regression results for predicting 30-day mortality

	Univariate logistic regression				Multivariate logistic regression			
	Odds ratio	Confidence intervals		p	Odds ratio	Confidence intervals		p
		Lower	Upper			Lower	Upper	
Age	1.043	1.005	1.105	0.008*	1.019	1.000	1.039	0.049*
Female	0.608	0.199	1.855	0.764				
Hypertension	3.075	1.627	6.869	0.004*	1.909	1.051	3.468	0.034*
Diabetes mellitus	0.333	0.0404	2.744	0.761				
Coronary artery disease	1.803	0.556	5.838	0.898				
Cerebrovascular disease	0.975	0.244	3.891	0.345				
Chronic renal failure	3.681	0.602	22.507	0.577				
Cancer	0.160	0.089	0.288	0.619				
Smoking	0.836	0.279	2.504	0.289				
Alcohol	1.636	0.461	5.804	0.081	1.618	1.196	2.954	0.018*
Indication for warfarin	0.859	0.540	1.365	0.764				
Upper bleeding localization	1.319	1.085	1.621	0.041*	1.166	0.985	1.347	0.155
International normalized ratio	1.060	0.955	1.176	0.133				
Albumin	0.118	0.027	0.508	0.003*	0.318	0.214	0.471	<0.001*

of warfarin overdose and GIB. In another study, mortality was observed in 8.7% of 172 patients who presented with GIB treated with warfarin during 1-month follow-up.[13] The high mortality rate in our study was thought to be related to the evaluation of a specific group undergoing endoscopic treatment with GIB, and the fact that the selected group included high-risk patients with higher bleeding findings that would require endoscopic treatment.

In a meta-analysis, it was shown that re-initiation of warfarin following discontinuation due to GIB was associated with a decrease in thromboembolic events and mortality without a statistically significant increase in recurrent GIB.[14] In our study, after the bleeding control was achieved, an appropriate anticoagulant regimen was initiated for the patients.

According to our study data, advanced age, hypertension, alcohol use, and serum albumin levels are associated with 30-day mortality in patients who underwent endoscopic treatment with GIB after warfarin overdose. Unlike the HAS-BLED scoring, which is a guide in terms of bleeding risk in the OAC treatment plan, serum albumin level was associated with mortality in our study, while there was no difference between survivors and non-survivors groups in terms of cerebrovascular event history, presence of chronic renal failure, and smoking. It may be considered to be improved by adding serum albumin level parameter to HAS-BLED scoring. In the study of Zhang et al., male gender, coronary heart disease, hypertension, stroke, systolic blood pressure, hematocrit, plasma albumin, and alanine amino transferase levels are associated with GIB in patients applying to cardiology.[15] In a study aimed at assessing the risks

of re-bleeding and thromboembolism in anticoagulated patients with acute GIB, re-bleeding was associated with low platelet count and albumin level and low dose aspirin use, but the HAS-BLED score, no endoscopic result, heparin bridge, or INR 2.5.[16] Based on these studies and our study data, it should be considered to develop new risk score models including serum albumin level.

Similar studies with new generation OACs and developing mortality determinant nomograms may be a guide in the management of follow-up and treatment of patients with bleeding complications. This article shows the factors predicting 30-day mortality in patients undergoing endoscopic therapy with warfarin overdose and GIB, and provides a practical algorithm to support clinicians in the management of these patients.

There are several limitations of our study. First, because the study was designed retrospectively, parameters affecting long-term mortality could not be evaluated. Second, we were not able to include some other clinical and laboratory parameters due to lack of information. Finally, we were not able to test our model in an external validation cohort which might have strengthened our findings.

Conclusion

Advanced age, hypertension, serum albumin level, and alcohol use are associated with 30-day all-cause mortality in patients undergoing warfarin overdose and endoscopic treatment with GIB. An easily applicable and relatively cheap nomogram that includes age, hypertension, serum albumin level, and alcohol can be used to define high-risk warfarin overdose patients admitting with GIB.

Disclosures

Ethichs Committee Approval: The study was approved by the Ankara City Hospital Ethics Committee (date: 04/07/2021, decision no: E2-21-424).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – H.T., A.A.S.; Design – H.T., A.A.S.; Supervision – H.T., A.A.S.; Materials – H.T., A.A.S.; Data collection and/or processing – H.T., A.A.S.; Analysis and/ or interpretation – H.T.; Literature search – H.T.; Writing – H.T.; Critical review – H.T., A.A.S.

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