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Predictors of hospital mortality and serious complications in patients admitted with excessive warfarin anticoagulation

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ABSTRACT

Introduction: Warfarin is the most commonly used oral anticoagulant and serious bleeding remains the most feared complication. Excessive warfarin anticoagulation (EWA) can be associated with adverse outcome. We aimed to identify the predictors of adverse clinical outcomes in patients admitted with EWA.
Methods and Materials: Medical records of patients admitted with EWA from March-2004 through Feb-2015 were reviewed. EWA was defined as international normalized ratio (INR) > 3.5 in patients who have been receiving warfarin. Primary outcome was death within hospital and secondary outcome was major composite complications (MCC) defined as intracranial hemorrhage (ICH), a need for transfusing ≥4 units packed red blood cell (PRBC), a need for surgical intervention for hemostasis or death within hospital.
Results: 267 patients (153 females and 114 male) were enrolled. 25 patients (9.4%) died during hospitalization. ICH, upper gastrointestinal bleeding and hemoptysis were more common in patients who did not survive (P-value: <0.001, 0.033 and 0.028; respectively). There was no correlation between indication for anticoagulation and death within hospital or development of MCC. In multivariate analysis, O blood group, ICH and the number of transfused PRBC and fresh frozen plasma units were identified as independent predictors of death within hospital. Lower hemoglobin concentrations and higher pulmonary pressures on admission were independent predictors of MCC, which occurred in 47 patients (17.6%).
Conclusion: Hospital mortality correlated with the severity of bleeding (requiring ≥4 units PRBC), intracranial hemorrhage and O blood group, while MCC associated with lower hemoglobin and pulmonary hypertension at the time of admission.

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1. Introduction

Warfarin is used in a relatively large population of patients prone to thromboembolic events. Atrial fibrillation (AF) and mechanical valve implants continue to be the most common reasons for warfarin anticoagulation [1]. Warfarin has unpredictable dose–response relationship [2], narrow therapeutic margins and need for frequent monitoring and dose adjustments [3].

The most feared side effect of warfarin treatment is bleeding [4]. The incidence of major bleeding is estimated at 1% to 3% per year [5]. The reported number is even higher for community-based studies enrolling elderly with comorbidities [6]. Concerns about major bleeding prevent many patients from receiving warfarin as physicians constantly struggle to weigh the risks and benefits [7]. The risk factors associated with bleeding have been examined to define clinical prediction scoring systems though none has been validated yet [8–12]. A few studies have evaluated the clinical impact of bleeding associated with anticoagulation [7,13].

In this study we examined the predictors of major complications and hospital mortality in patients admitted with excessive warfarin anticoagulation (EWA). We hypothesized that a multivariate logistic regression model could be constructed to predict the occurrence of unfavorable outcomes.

2. Methods and materials

This is a retrospective cross-sectional study conducted through evaluation of medical records of patients admitted during 2004–2015 with excessive warfarin anticoagulation (EWA) to two teaching university hospitals. Study protocol was reviewed and approved by the ethics committee of Tabriz University of Medical Sciences. This study was exempted from the informed consent process due to the retrospective design of the study, but all patient data were handled carefully to assure that patient confidentiality was maintained.

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2.1. Study Population

Patient records were examined for "warfarin overdose", "warfarin toxicity" or "supra-therapeutic INR" using admission diagnosis codes. Patients were enrolled if they were receiving warfarin and got admitted with a supratherapeutic INR of >3.5. Exclusion criteria included: 1- accidental or intentional (i.e. suicide attempt) ingestion of warfarin, 2- high INR unrelated to warfarin therapy, and 3- incomplete records.

2.2. Independent variables

Medical records were examined, and demographic data including age, gender, level of education, and living place were recorded. Indication for warfarin treatment (non-valvular AF valvular AF, prosthetic heart valve, deep vein thrombosis, pulmonary thromboembolism, cerebrovascular thromboembolism, dosage (mg), duration of treatment and the status of INR testing) were reported. Medication history and concomitant use of platelet inhibitors antibiotics or amiodarone were also recorded. The presence of comorbid conditions (diabetes mellitus, hypertension smoking, ischemia, congestive heart failure, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD; eGFR < 60 mL/min), cerebrovascular accident (CVA), peptic ulcer, or neoplastic disease were collected. Polypharmacy was defined as concomitant use of ≥5 medications.

Clinical manifestation of bleeding such as petechia/ecchymosis, hematoma, gastrointestinal (GI) and intracranial bleeding (ICH) was recorded. CHA2DS2-VASc score was calculated for patients with AF. Electrocardiographic, echocardiographic and laboratory findings were also documented at the time of admission. Laboratory data, included a complete coagulation profile (prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), and platelet count), Complete blood cell count, ABO and Rh blood group, and renal function tests (blood urea nitrogen (BUN) and creatinine) at the time of admission. Hemoglobin and coagulation profile were also measured daily until the patients were deceased or discharged from the hospital.

Patients were treated at the discretion of the treating internist and generally included observation, vitamin K, and/or transfusion of packed red blood cells (PRBC), fresh frozen plasma (FFP), as indicated. The therapeutic information was also documented. Hospital length of stay (HLOS) was collected.

2.3. Statistical analysis

The primary outcome variable was death within hospital and the secondary outcome variable was the occurrence of a major composite complication (MCC). MCC was defined as an occurrence of ICH; need for transfusion of ≥4 unit PRBC, a need for surgical intervention or death within hospital. Data were collected into an Excel worksheet and then were exported to SPSS ver. 22.0 (Chicago, IL, USA) for statistical analysis. Nominal variables were analyzed using chi-square test and reported as numbers and percentages. Odds ratios were calculated and reported along with 95% confidence intervals (CI). Continuous variables were analyzed with t-tests if they followed a normal distribution and were reported as mean ± standard deviation. Mann–Whitney U tests were used if the normality was rejected for the numerical variables and data were expressed as median with interquartile range. Multivariate regression models were constructed for hospital mortality and MCC and hazard risks and 95% CI were depicted by forest plots. P-value < 0.05 was regarded as statistically significant.

3. Results

Medical records for 302 patients were examined, and after excluding 12 cases of intentional/accidental toxicity and 23 cases for incomplete data, 267 patients (153 female and 114 male patients) were enrolled. They were 217 patients from the Heart Center and 50 cases from the General Hospital. The most common indication for anticoagulation was mechanical heart valve in 98 (37.5%) followed by non-valvular AF in 89(33.3%). Hypertension (40.8%), congestive heart failure (31.1%) and diabetes (15.0%) were among the most common comorbidities.

A total of 209 (78%) patients presented with symptomatic bleeding and 58(22%) were purely admitted based on incidental finding of supratherapeutic INR/PT values. Ecchymosis, hematuria and upper GI bleeding were among common manifestations and constituted 31.6%, 24.9% and 19.1% of the clinical presentation, respectively (Table 1). Polypharmacy was noted in 113 (42.3%) of the patients at the time of admission. Patients were concomitantly using aspirin (27.7%), amiodarone (5.4%) and clopidogrel (2.2%).

3.1. Hospital mortality

Total of 25(9.36%) patients died within hospital (9 male and 16 female patients). This included 22 patients who presented with bleeding on admission. Twenty one of these patients died from bleeding complications and only one patient developed recurrent pulmonary embolism during hospitalization and died of right-sided heart failure. Three patients who didn't have bleeding on admission, later developed fatal bleeding including two ICH and one upper GI bleeding and died of bleeding complications. The frequency of ICH was higher among non-survivors than the survivors (9/25 vs. 6/242; $P < 0.001$). Similarly, there were more patients with upper GI bleeding in non-survivor group (32%) than in survivors (13.2%; $P = 0.031$). Hemoptysis was more common in patients in non-survivors (20%) compared to survivors (6.6%; $P = 0.028$). Hematuria also shows a trend of being more common in patients who didn't survived ($P = 0.059$). However epistaxis, petechia, purpura, ecchymosis, lower GI bleeding, vaginal bleeding and gingival bleeding were equally seen among the survivors and non-survivors (Table 2).

Survivors did not differ from non-survivors in terms of age, gender, or living place. However, the non-survivors more frequently had no official education compared to those who survived ($P = 0.031$). From 81 patients with mechanical valve 7 (8.6%) died within hospital, similar to 18 (9.7%) who died from 186 patients with no mechanical valve implants. Among comorbidities, only CKD was relatively more common among non-survivors compared to survivors (24.0% vs. 7.4%; $P = 0.015$). The concomitant use of antiplatelet drugs, amiodarone or polypharmacy was similar between survivors and non-survivors. While there was a strong trend of higher hospital mortality in those with lower LV ejection fraction (LVEF) on admission ($P = 0.079$), RV systolic pressure (RVSP) was lower (38 ± 12 mm Hg) in survivors than non-survivors (49 ± 17 mm Hg; $P = 0.003$).

PT, INR, PTT, platelet count, mean corpuscular volume, serum creatinine and hemoglobin were not significantly different between the two groups (Table 3). Admission counts of white blood cells (WBCs) were significantly higher in those who did not survive compared with survivors (15.5 ± 8.0 vs. 10.2 ± 10.7 × 1000 cells/μL; $P = 0.021$). Comparatively, BUN on admission was significantly higher among non-survivors than survivors (38.5 ± 31.4 vs. 24.2 ± 15.7 mg/dL; $P < 0.001$). Expectedly,

Table 1
The frequency of clinical manifestations of symptomatic patients.

	Non-survivors (N = 25)	Survivors (N = 242)	Symptomatic (N = 209)
Ecchymosis	6	60	66 (31.6%)
Hematuria	1	51	52 (24.9%)
Upper gastrointestinal bleeding	8	32	40 (19.1%)
Gingival bleeding	1	19	20 (9.6%)
Hemoptysis	5	15	20 (9.6%)
Hematoma	2	15	17 (8.1%)
Intracranial hemorrhage	9	6	15 (7.2%)
Lower gastrointestinal bleeding	1	10	11 (5.3%)
Vaginal bleeding	0	8	8 (3.8%)
Petechia or purpura	0	3	3 (1.4%)

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