Original Article

Assessment of factors affecting mortality in geriatric patients with warfarin overdose

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Abstract:

OBJECTIVES: The aim of the present study was to perform a demographic analysis of complications and to determine the factors affecting in-hospital mortality in geriatric patients with warfarin overdose.

MATERIALS AND METHODS: All patients aged 65 years or older using warfarin with an international normalized ratio (INR) level above 3.5 IU between 01.01.2014 and 01.01.2018 were included in the study. Characteristics of patients with in-hospital mortality and surviving patients were compared. Multivariate regression analysis was used to assess the predictors for in-hospital mortality.

RESULTS: A total of 302 geriatric patients included in the study for statistical analyses. Bleeding rate was 14.2%. A comparison of patient characteristics for in-hospital mortality (survivor vs. nonsurvivor) revealed significant differences for age, gender, chronic renal failure history, creatinine, aspartate aminotransferase (AST), and alanine aminotransferase levels ($P < 0.05$). A multivariate logistic regression analysis was performed. It was found that elevated AST ($P = 0.029$, odds ratio [OR]: 1.004, 95% confidence intervals [CIs]; 1.001–1.007) and creatinine ($P = 0.045$, OR: 2.36, 95% CIs; 1.02–5.48) levels as well as advanced age ($P = 0.031$, OR: 1.11, 95% CIs; 1.01–1.22) and male gender ($P = 0.017$, OR: 5.48, 95% CIs; 1.35–22.1) had a negative impact on survival.

CONCLUSION: Our study results revealed that male gender, advanced age, and hepatic and renal dysfunctions were the predictors of in-hospital mortality in the elderly with warfarin overdose. In order to avoid serious warfarin-related complications in the older age groups, particularly when there is renal or hepatic dysfunction, patients should be informed about minor warning side effects of warfarin, INR levels should be more frequently checked, and patients should have more strict follow-up schedules.

Keywords:

Ageing, anticoagulant, geriatrics, mortality, warfarin

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Introduction

Warfarin continues to be the most commonly used oral anticoagulant worldwide. Its use in a variety of indications at an increasing rate increases warfarin-associated adverse effects in addition to its benefits.[1] Although the majority of bleedings resulting from warfarin toxicity does not cause severe

clinical problems, major and life-threatening bleedings may also be observed. Studies have shown that bleeding risk grows exponentially when the international normalized ratio (INR), used to assess anticoagulant efficacy, is elevated above the therapeutic range (INR: 2.0–3.0).[2,3] In addition to possible complications, many factors including a fairly narrow therapeutic range, unpredictable and patient-specific dose–response, delayed onset and offset of action, slow reversal of anticoagulant effect when necessary, and interaction with diet and many medications limit warfarin use.[1]

Box-ED section

What is already known on the study topic?

As thromboembolic risk increases with aging, geriatric age group is the one that needs anticoagulation the most for therapeutic and prophylactic purposes

However, the therapeutic range of warfarin could be attained in only half of time in geriatric patients.

What is the conflict on the issue?

There is a general concern of increased warfarin-induced bleeding complications in the geriatric population. Moreover, the available bleeding risk scores have limited clinical benefit in this age group

These reasons can make clinicians abstain from prescribing warfarin to geriatric patients.

How is this study structured?

This was a single-center, retrospective study including data from 302 patients aged 65 years or older using warfarin.

What does this study tell us?

Male gender, advanced age, and hepatic and renal dysfunction were the predictors of in-hospital mortality in the elderly with warfarin overdose.

As thromboembolic risk increases with aging, geriatric age group is the one that needs anticoagulation the most for therapeutic and prophylactic purposes.[1,4] Nevertheless, advanced age also brings about multimorbidity and polypharmacy. It has been reported that in geriatric population, the therapeutic range of warfarin could be attained in only half of time, and that the treatment is abandoned in less than a year in at least 25% of patients newly started on warfarin.[5] At the same time, the concern of an increased rate of bleeding complications among the elderly makes clinicians abstain from prescribing warfarin.[6] Moreover, it has been reported that the available bleeding risk scores have limited clinical benefit in geriatric population.[7] For all these reasons, studies focusing on this particular age group about warfarin-induced bleeding risk are needed.

This study aimed to perform a demographic analysis of complications and to determine the factors affecting in-hospital mortality in geriatric patients with warfarin overdose.

Materials and Methods

Study design and setting

This retrospective study was conducted in a tertiary emergency department (ED) with 250,000 admissions per year after being approved by the local ethics committee. All patients aged 65 years or older using warfarin with an INR level above 3.5 IU who presented to ED between 01.01.2014 and 01.01.2018 were included in the study. Because of the retrospective nature of the present study, written informed consent was not obtained. First, demographic data of the study population were obtained from the hospital information system with a software created. Then, the patients' comorbidities, the first laboratory results at first admission to ED, presence and site of bleeding, presence of trauma, treatments, and in-hospital mortality were recorded by 2 authors responsible for the "data collection and processing" on the preformed form by examining the patients' data from the hospital information system and the patient files taken from the hospital archive one by one. Patients with missing data were excluded.

Laboratory parameters

Venous blood gas analysis was performed with Gestat 1825 (Japan) device; complete blood count was carried out using Abbott Cell Dyn 3700 (USA) device; INR measurement was carried out using Sysmex CS-2100i (Japan) device; and the biochemical parameters were studied using Beckman Coulter AU5800 (USA) device.

Statistical analysis

Study data were analyzed using IBM SPSS16.0 (Chicago, IL, USA) statistical software. Dichotomous and continuous variables were checked for normal distribution using Kolmogorov–Smirnov test. As they did not meet the normality criteria, they were expressed as median values and interquartile range (IQR, 25%–75%); categorical variables were expressed as number and percentage (%). Categorical variables were compared using Chi-square test and continuous variables using Mann–Whitney U-test. A univariate logistic regression analysis was performed to predict in-hospital mortality. After testing each independent variable in the univariate model, those having statistical significance ($P < 0.2$) were included in multivariate logistic regression model. The fitness of the multivariate regression model was tested using the Hosmer–Lemeshow test. In the regression analysis, "Enter" method was used. $P < 0.05$ was considered statistically significant for all tests.

Results

In the study period, the total number of patients aged 65 years and older admitted to the ED was 159,359. It was determined that 328 of them had been using warfarin and had an INR level above 3.5 IU. Twenty-six patients were excluded due to missing data; hence, a total of 302 geriatric patients included in the study for statistical analyses. One hundred and ninety-five patients were male (64.6%) and the median age of the all patients was 78.5 (IQR 25%-75%: 73-84.2).

The most common comorbidity was hypertension (62.9%). Nineteen patients had been using an antiplatelet drug

in addition to warfarin. There was bleeding in 14.2% of all patients. Bleedings were due to trauma in 5% of all patients. The most common type of bleeding was gastrointestinal bleeding. Fourteen (4.6%) of patients died at the ED or intensive care unit. The causes of mortality were intracerebral hemorrhage ($n = 5$), multitrauma ($n = 4$), gastrointestinal bleeding ($n = 3$), and other metabolic reasons ($n = 2$). None of these had been using both warfarin and antiplatelet drug together. Demographics and some laboratory results of all patients are shown in Table 1.

A comparison of patient characteristics for in-hospital mortality (survivor vs. nonsurvivor) revealed significant

Table 1: Demographics and clinical characteristics of patients

Gender male, *n* (%)	195 (64.6)
Age median (IQR 25-75%)	78.5 (73-84.2)
Age group, *n* (%)	
Young old (65-79 years)	168 (55.6)
old old (80 years and older)	134 (44.4)
Comorbidity, *n* (%)	
Hypertension	190 (62.9)
Diabetes mellitus	64 (21.2)
CAD	114 (37.7)
COPD	20 (6.6)
CRF	33 (10.9)
Others	112 (18.7)
Antiplatelet drug use, *n* (%)	19 (6.2)
Presence of bleeding, *n* (%)	43 (14.2)
Traumatic	15 (5)
Bleeding sites, *n* (%)	
Cerebral	5 (1.7)
GIS	20 (6.6)
Hematuria	5 (1.7)
Epistaxis	11 (3.6)
Vaginal bleeding	2 (0.7)
Laboratory parameters median (IQR 25-75%)	
Hematocrit	35 (29.7-39.2)
Platelet count	241.5 (197-303.7)
Creatinine	1.12 (0.87-1.45)
AST	23.5 (18-35)
ALT	17 (12-28.7)
INR	8.78 (7.4-11.3)
PT	96 (80.6-123.5)
Treatment, *n* (%)	
Vitamin K	64 (21.2)
FFP	52 (17.2)
PRBCs	8 (2.6)
Outcome, *n* (%)	
Survivor	288 (95.4)
Nonsurvivor	14 (4.6)

CAD=Coronary artery disease, COPD=Chronic obstructive pulmonary disease, CRF=Chronic renal failure, GIS=Gastrointestinal system, AST=Aspartate aminotransferase, ALT=Alanine aminotransferase, INR=International normalized ratio, PT=Prothrombin time, FFP=Fresh frozen plasma, PRBCs=Packed red blood cells, IQR=Interquartile range

differences for age, gender, chronic renal failure (CRF) history, creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels ($P < 0.05$ for all) [Table 2].

A multivariate logistic regression analysis was performed to assess the effects of the variables presented in Table 2 on mortality. The variables with $P < 0.2$, CRF, trauma, hematocrit, creatinine, platelet, AST, and INR values, as well as age (as a continuous variable) and gender were included. After confirming the fitness of the model with the Hosmer–Lemeshow test ($P = 0.98$), it was found that elevated AST and creatinine levels as well as age and male gender had a negative impact on survival [Table 3].

Discussion

In the present study, which we investigated the complications and in-hospital mortality in geriatric warfarin users, we reached two important conclusions. First of them was that hepatic and renal dysfunction were the predictors of in-hospital mortality as well as advanced age and male gender in geriatric patients with warfarin overdose. It is known that with aging, physiological reserves of all systems are known to decrease. As age and the number of comorbidities increase, failure of compensatory mechanisms may become even more pronounced. We believe that dysfunction of the eliminatory organs (liver and kidneys), in particular, not only lead to the development of the complications associated with warfarin overdose, but also increase mortality by affecting the severity and course of such complications. Second, we determined that bleeding complication due to warfarin overdose rather occurred as spontaneous bleedings unrelated to trauma in the elderly. The elderly tend to be exposed to an increased rate of trauma, falls in particular, due to a variety of physiological and pathological processes. As a result of that, a greater incidence of traumatic bleeding may be expected in the elderly using anticoagulants. Contrary to this expectation, our results may be due to the fact that older age with many comorbid diseases have more effect on the tendency of spontaneous bleeding as a result of systemic effects.

Aging brings about a series of pharmacokinetic and pharmacodynamic changes in human body. Albumin level is reduced with aging, significantly affecting protein binding rates and drug distribution.[8] In addition, changes in drug absorption and metabolism may affect the incidence of overdose and complications in the elderly. Depending on pharmacodynamic alterations, the chance of having labile INR values and overdose episodes increase in parallel to age.[4] However, we determined that the predicted apparent effect of age factor, which led to a significant difference between the

Table 2: Patients characteristics according to mortality

	Survivor (*n*=288)	Nonsurvivor (*n*=14)	*P*
Age median (IQR 25-75%)	78 (73-84)	83 (78.7-90.5)	0.015
Gender, *n* (%)*			
Female	191 (66.3)	4 (28.6)	0.07
Male	97 (33.7)	10 (71.4)	
Comorbidity, *n* (%)			
Hypertension	182 (63.2)	8 (57.1)	0.77
Diabetes mellitus*	63 (21.9)	1 (7.1)	0.31
CAD*	109 (37.8)	5 (35.7)	0.99
CRF*	29 (10.1)	4 (28.6)	0.05
COPD*	19 (6.6)	1 (7.1)	0.99
Trauma, *n* (%)*	13 (4.5)	2 (14.3)	0.14
Bleeding, *n* (%)*	40 (13.9)	3 (21.4)	0.43
Laboratory parameters, median (IQR 25-75%)			
Hematocrit	35.1 (29.7-39.2)	34.5 (25.1-38)	0.51
Platelet count	242 (199-302.2)	222.5 (131.7-232.5)	0.19
Creatinine	1.1 (0.87-1.4)	1.65 (1.08-2.67)	0.04
AST	23 (18-34)	50 (21.7-113)	0.012
ALT	17 (12-28)	33 (16.7-63)	0.022
INR	8.7 (7.4-11.8)	11 (7.7-13.9)	0.16
PT	95.4 (80.6-122.5)	119 (80-146.3)	0.19

*Fisher exact test was used. CAD=Coronary artery disease, COPD=Chronic obstructive pulmonary disease, CRF=Chronic renal failure, AST=*Aspartate aminotransferase*, ALT=*Alanine aminotransferase*, INR=International normalized ratio, PT=Prothrombin time, IQR=Interquartile range

Table 3: Multivariate regression model to predict in-hospital mortality

	Wald	*P*	OR (95% CIs)
Age	4.64	0.031	1.11 (1.01-1.22)
Gender	5.70	0.017	5.48 (1.35-22.1)
CRF	0.02	0.87	0.84 (0.10-6.77)
Trauma	3.51	0.06	5.67 (0.92-34.79)
Hematocrit	0.15	0.69	1.01 (0.93-1.10)
Platelet count	0.05	0.81	0.99 (0.99-1.007)
Creatinine	4.02	0.045	2.36 (1.02-5.48)
AST	4.76	0.029	1.004 (1.001-1.007)
INR	0.25	0.61	1.04 (0.89-1.21)

CRF=Chronic renal failure, AST=Aspartate aminotransferase, INR=International normalized ratio, CIs=Confidence intervals

adult and geriatric population, was suppressed in our study population consisting of only geriatric patients. Furthermore, we found a greater rate of overdose in younger elderly (55.6%) than the older ones (44.4%). This might be caused by a more cautious approach of physicians to warfarin initiation and use as age increases. Furthermore, heterogeneous distribution of comorbidities, drug usage, and level of age-related pharmacodynamic/pharmacokinetic effects in our study population, may be other possible causes of this result.

In the literature the rates of hemorrhagic complications range between 0% and 16% in warfarin users.[9,10] In the geriatric population, on the other hand, vascular biological changes appearing as connective tissue losses and small-vessel fragility in addition to pharmacokinetic/pharmacodynamic changes, and increased trauma exposure create a bleeding tendency as aging.[4] We

observed a bleeding incidence of 14.2% in our geriatric population, which was similar to those reported for normal age groups. Traumatic bleedings, on the other hand, affected 5% of our patients. Although older persons are expected to be more susceptible to the anticoagulant effects of warfarin, the wide spectrum of warfarin effect, both in an individual and between different individuals, due to genetic, dietary, and pharmacological factors, is the most possible reason of the lack of the finding of increased bleeding rates in our geriatric population. Similarly, increased prevalence of traumatic injuries due to cognitive and anatomic disturbances occurring with aging is regarded as one of the most important causes of warfarin-related bleedings in older patients.[11] However, the majority of bleeding in geriatric patients on warfarin had nontraumatic bleedings in our study. This may be caused by a possible greater effect of advanced age, multiple comorbidities and variable drug combinations on spontaneous bleeding tendency due to general systemic alterations in the elderly.

The functions of all organs are expected to decline with aging. Glomerular filtration rate drops by 10% in each decade; liver size shrinks by a third, and hepatic blood flow markedly decreases with aging.[12,13] In our study population, those who died had a significantly higher age, rate of renal disorders, and hepatic and renal dysfunction markers. Constantly increasing deficits in the metabolism and excretion in older people are the most possible cause of this outcome by increasing lethal complications through affecting the process of warfarin in the body. Also, a significant proportion of the patients

with mortality in our study was male. Literature data suggest that females are more susceptible to warfarin effect independently of gene polymorphism.[14,15] This was explained partly by intergender differences of gastric emptying, intestinal transit time, organ blood flow, body fat/water/muscle ratio, and enzymatic differences.[16] Being susceptible to warfarin effect may cause minor complications occurring more frequently and at an earlier stage among women. Therefore, clinicians may cause less warfarin-induced lethal complications in female patients by using lower doses and more strictly follow-up schedules.

In our study, INR level was not found to be associated with in-hospital mortality. In the literature, it has been reported a relation between supratherapeutic INR and risk of bleeding. However, no direct correlation could have been drawn between any specific value of INR and bleeding episodes. Also, it is stated that even when the INR is excessively prolonged, the absolute daily risk of bleeding is low.[17] In the management guidelines of warfarin overdose, it has been mentioned about patient groups who had INR >10 without bleeding.[18] In addition, even if the bleeding occurs, there are many factors that can affect whether the bleeding is minor or major. All of these may explain why INR level was not determined as a mortality predictor in our study.

In the literature, various models for predicting the risk of major bleeding in patients on warfarin therapy have been developed: HEMORR2HAGES score (prior bleeding, hepatic or renal disease, alcohol abuse, malignancy, age >75, reduced platelet function, uncontrolled hypertension, anemia, genetic factors, excessive fall risk, stroke), HAS-BLED score (hypertension, abnormal liver or renal function, stroke, bleeding tendency, labile INR, age >65, drugs or alcohol), ATRIA score (anemia, severe renal disease, age >75, prior bleeding, hypertension), etc.[19-21] Although the most important common parameter of all these models is advanced age, it has been reported that all have limited clinical benefit in geriatric population.[7] In our model, we determined that advanced age, male gender, and hepatic and renal dysfunction were significant predictors of in-hospital mortality in geriatric patients with warfarin overdose. We believe that reduced systemic reserves, dysfunction of elimination organs, and inadequate compensation mechanisms increase mortality rate by increasing the severity of warfarin complications in the elderly.

Limitations

Our study has some limitations. First, it was a retrospective single-center study. Therefore, our results cannot be generalized to all centers and erroneous/missing data may have affected our findings. Second, our population included only patients with an INR level above 3.5 IU.

Literature data suggest that warfarin-associated bleeding may occur even with the therapeutic INR levels.[22,23] However, as no fatal bleeding is expected with such INR levels, we believe that this condition did not have any significant effect on our results. Additionally, we could not able to evaluate the parameters that could change the effectiveness of warfarin, such as the presence of multiple drug use, the types of drugs (except antiplatelets) and dietary factors. Since these data can also be potential predictors for mortality, it can be another limitation of our study.

Conclusion

Our study results revealed that male gender, advanced age, hepatic and renal dysfunction were the predictors of in-hospital mortality in the elderly with warfarin overdose. Therefore, we believe that in order to avoid serious warfarin-related complications in the older people particularly when there is renal or hepatic dysfunction, patients should be informed about minor warning side effects of warfarin, INR levels should be more frequently checked, and patients should have more strict follow-up schedules.

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