

## Demographic Analysis of Complications of Warfarin Treatment and Factors Affecting Mortality

Varfarin Kullanan Hastalarda Meydana Gelen Komplikasyonların Demografik Analizi ve Mortalite Üzerine Etkili Faktörler

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### Abstract

**Objective:** This study investigated the demographic analysis of complications of warfarin therapy and the factors affecting mortality.

**Material and Methods:** The digital medical records of patients who applied to our Emergency Clinic with warfarin overdose between September 2007 and September 2010 were retrieved and patient files were assessed retrospectively. Cases were classified into two groups in terms of INR level and hemorrhagic complications; patients with an INR level greater than 3.5 and a hemorrhagic complication, and patients with an INR level greater than 3.5 and no hemorrhagic complication. Furthermore, cases with a hemorrhagic complication were divided into two subgroups as those who died and those who survived.

**Results:** The study enrolled 151 cases presenting to our emergency clinic with warfarin overdose. Among these, 50.3% (n=76) were males and 49.7% (n=75) were females. Mean age was 60.80±16.11 years. There was no significant difference between the groups in terms of sex and age. Hemorrhagic complication was present in 66.89% (n=101) while absent in 33.11% (n=50). PT and INR levels were significantly higher in patients with hemorrhage compared to those without (for PT 90.98±26.52 vs. 55.51±12.70, respectively; p<0.001; for INR 8.97±11.29 vs. 4.63±0.68, respectively; p=0.042). In patients with a hemorrhagic complication who died, the PT level was significantly higher, and hematocrit and platelet levels were significantly lower than those of patients who survived a hemorrhagic complication (p<0.001, p=0.033, and p=0.009, respectively).

**Conclusion:** Education in warfarin use, regular follow-ups, self-monitorization, and increased distribution of home-type coagulometry devices will decrease the frequency of complications. (*JAEM 2013; 12: 139-44*)

**Key words:** Warfarin overdose, complication, emergency department

### Özet

**Amaç:** Bu çalışmada varfarin kullanan hastalarda meydana gelen komplikasyonların demografik analizi ve mortalite üzerine etkili faktörler araştırılmıştır.

**Gereç ve Yöntemler:** Acil servisimize Eylül 2007-Eylül 2010 tarihleri arasında varfarin yüksek dozu nedeni ile başvuran hastalar bilgisayar kayıtlarından tespit edildi ve bu hastaların dosyaları arşivimizden bulunarak geriye dönük olarak incelendi. Çalışmaya dahil edilen olgular varfarin kullanımına bağlı INR değeri 3,5'in üstü olup kanama komplikasyonu gelişenler ve varfarin kullanımına bağlı INR değeri 3,5'in üstü olup herhangi bir kanama komplikasyonu gelişmeyenler olarak iki gruba ayrıldı. Ayrıca kanama komplikasyonu gelişen olgular kendi içinde ölenler ve sağ kalanlar olarak ikiye ayrılarak karşılaştırıldı.

**Bulgular:** Çalışmaya, hastanemiz acil servisine Eylül 2007 ile Eylül 2010 tarihleri arasında varfarin overdozu nedeniyle başvuran 151 olgu dahil edildi. Bunların %50,3'ü (n=76) erkek ve %49,7'si (n=75) kadındı. Ortalama yaş tüm hastalar için 60,80±16,11 idi. İstatistiksel olarak gruplar arasında cinsiyet ve yaş açısından anlamlı bir fark yoktu. Hastaların %66,89'u (n=101) kanama komplikasyonu gelişen, %33,11'i (n=50) ise kanama komplikasyonu gelişmeyen olgular idi. Kanama komplikasyonu gelişen hastalarımızda gelişmeyenlere göre PT ve INR değeri anlamlı derecede daha yüksekti (sırasıyla PT için 90,98±26,52 ve 55,51±12,70 p<0,001 iken; INR için 8,97±11,29 ve 4,63±0,68 p=0,042 idi). Kanama komplikasyonu gelişen hastalarımızdan ölenlerde sağ kalanlara göre PT değeri daha yüksek iken (p<0,001) hematokrit ve platelet değerleri anlamlı derecede düşük idi (sırasıyla p=0,033 ve p=0,009).

**Sonuç:** Varfarin kullanımı ile ilgili eğitim verilmesi, düzenli kontrollerin yapılması, self monitorizasyon ve ev tipi koagulometrenin yaygınlaştırılması komplikasyonların görülme sıklığını azaltacaktır. (*JAEM 2013; 12: 139-44*)

**Anahtar kelimeler:** Varfarin yüksek doz, komplikasyon, acil servis

### Introduction

Warfarin is an anticoagulant agent used for prophylaxis and treatment purposes in clinical conditions with thromboembolism or increased thromboembolism risk (1). Its use is complicated by interaction with other agents, periodic monitoring of International

Normalized Ratio level (INR), dosage requirement, and the potential for major bleeding (2).

Most commonly used among oral anticoagulants, warfarin was introduced in the 1950s. It exerts its effect through factors 2, 7, 9 and 10. These agents are synthesized in inactive form and need to have their glutamic acid residues carboxylated. Vitamin K is the cofactor of

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this reaction. Epoxide reductase converts vitamin K to the "reduced" form (3). Warfarin, which has been shown to have antithrombotic effect, exerts its effect through inhibition of epoxide reductase (4).

Serious complications arise in overdose of warfarin. This study investigated the demographic analysis of complications of warfarin therapy and the factors affecting mortality.

## Material and Methods

The digital medical records of patients who applied to our emergency clinic with warfarin overdose between September 2007 and September 2010 were retrieved and patient files were assessed retrospectively. Patients over the age of 18 years, using warfarin and presenting with an INR level of  $>3.5$  were included. Age, sex, complaint, time of presentation, season of presentation, reason for warfarin use, accompanying diseases, educational level, laboratory tests, admittance to the clinic, duration of hospital stay, medications used, and results of investigations were recorded in pre-designed standard study forms.

Cases were classified into two groups in terms of INR level and hemorrhagic complications; patients with an INR level greater than 3.5 and a hemorrhagic complication and patients with an INR level greater than 3.5 and no hemorrhagic complication. Furthermore, cases with a hemorrhagic complication were divided into two subgroups as those who died and those who survived.

### Statistical analysis

In univariate analysis, chi-square test ( $\chi^2$ ) was used for categorical variables and student t test for continuous variables. Mean values were calculated as mean  $\pm$  standard deviation (SD). A p value  $<0.05$  was considered statistically significant. Statistical analyses were performed using SPSS 11.5 software package.

## Results

The study enrolled 151 cases presenting to our emergency clinic with warfarin overdose between September 2007 and September 2010. Among these, 50.3% ( $n=76$ ) were males and 49.7% ( $n=75$ ) were females. Mean age was  $60.80 \pm 16.11$  years. Hemorrhagic complication was present in 66.89% ( $n=101$ ) while absent in 33.11% ( $n=50$ ). Those with a hemorrhagic complication had a mean age of  $59.97 \pm 16.13$  years, and 47.5% ( $n=48$ ) were males and 52.5% ( $n=53$ ) were females. The mean age of those without a hemorrhagic complication was  $62.50 \pm 16.07$  years, and 56% ( $n=28$ ) were males and 44% ( $n=22$ ) were females. There was no significant difference between the groups in terms of sex and age. The mean presenting time was  $11.75 \pm 5.34$  hours. This number was measured to be  $11.70 \pm 5.71$  hours for those with a hemorrhagic complication and  $11.88 \pm 4.61$  hours for those without. The presenting hours of the two groups were not significantly different.

The medical indication for warfarin use was heart valve replacement in 35.09% ( $n=53$ ), atrial fibrillation in 28.48% ( $n=43$ ), and pulmonary thromboembolism in 19.87% ( $n=30$ ). The most common comorbid disease was ischemic heart disease followed in descending order by, hypertension, chronic obstructive pulmonary disease (COPD), and diabetes mellitus. Ratios of illiterate and literate patients were 60.93% ( $n=92$ ) and 19.87% ( $n=30$ ), respectively, with only 19.20% ( $n=29$ ) being primary-high school graduate. In descending

order, patients with a hemorrhagic complication were mostly treated and monitored at emergency, cardiology, and internal medicine departments, whereas patients having no hemorrhagic complications were all monitored at the emergency department. Clinical and demographic characteristics of patients with and without hemorrhagic complication are given in Table 1.

Prothrombin time (PT) and INR levels were significantly higher in patients with hemorrhage compared to those without (for PT  $90.98 \pm 26.52$  vs.  $55.51 \pm 12.70$ , respectively;  $p < 0.001$ ; for INR  $8.97 \pm 11.29$  vs.  $4.63 \pm 0.68$ , respectively;  $p = 0.042$ ). The laboratory test results of patients with and without hemorrhagic complications are shown in Table 2.

The presenting season was winter in 36.5% ( $n=55$ ) and spring in 29.8% ( $n=45$ ), while summer and fall presentations were relatively rare. The seasonal distribution of cases is given in Figure 1.

Five (4.95%) patients with hemorrhagic complications died. The patients surviving from a hemorrhagic complication most commonly had ischemic heart disease as the comorbid disease followed, in descending order, by hypertension, COPD, and diabetes mellitus. On the other hand, patients who died most commonly had hypertension and chronic renal failure. Chronic renal failure as the comorbid condition increased mortality ( $p = 0.027$ ). The most common presenting symptoms in patients with a hemorrhagic complication, in descending order, were subcutaneous hematoma, GIS bleeding, hematuria, and epistaxis. In addition, 4 of 5 patients who died presented with intracranial hemorrhage and 1 with hemoptysis. Among those with a hemorrhagic complication, 59.4% ( $n=57$ ) of surviving patients were illiterate while 100% of patients who died were illiterate. While treatment and follow-up of patients surviving a hemorrhagic complication were done, in descending order, at emergency, internal medicine, and cardiology clinics, the clinics at which patients who died were treated and monitored were, in descending order, neurology, neurosurgery, and cardiology clinics. Among patients with a hemorrhagic complication, clinical and demographic features of those who survived and those who died are given in Table 3.

In patients with a hemorrhagic complication who died, PT level was significantly higher, and hematocrit and platelet levels were significantly lower than those of patients who survived a hemorrhagic complication ( $p < 0.001$ ,  $p = 0.033$ , and  $p = 0.009$ , respectively). Laboratory values of those who survived and who died are given in Table 4.

## Discussion

Commonly used in treatment and prophylaxis of many diseases, warfarin may pose a serious threat when inappropriately used. Thus, in addition to risks of no warfarin usage, risks of warfarin usage should also be considered. The most important side effect is bleeding (5).

Although overdose of warfarin may cause hemorrhage at any age, it is more common after 50 years of age. Fanikos et al. (6) reported a mean age of 59.7 and Baydin et al. (7) 59. Furthermore, there are studies in the literature suggesting that hemorrhagic complications increase and mortality doubles over the age of 75 (8-13). Similar to the literature, our study found an overall mean age of  $60.80 \pm 16.11$  with a greater mean age in the group of patients who died.

For patients presenting with hemorrhagic complications due to warfarin overdose, there are scales to pick up and more closely

**Table 1.** Clinical and demographic characteristics of patients with and without hemorrhagic complication

Clinical and demographic characteristics	Hemorrhage n=101	No hemorrhage n=50	Total n=151	p value
Age (years;mean±SD)	59.97±16.13	62.50±16.07	60.80±16.11	0.803
<b>Sex</b>				
Male	48	28	76	0.210
Female	53	22	75	
Presenting time (hour;mean±SD)	11.70±5.71	11.88±4.61	11.75±5,34	0.073
<b>Comorbidity</b>				
Ischemic heart disease	42	22	64	0.861
COPD	16	11	27	0.373
Hypertension	23	14	37	0.548
Diabetes Mellitus	9	5	14	0.980
Cerebrovascular Accident	2	--	2	0.554
Liver Cirrhosis	1	--	1	0.521
Chronic Renal Failure	6	2	8	0.471
Malignancy	2	1	3	0.704
No disease	21	7	28	0.378
<b>Indication for warfarin</b>				
Valvular replacement	37	16	53	0.354
Pulmonary Thromboembolism	17	13	30	0.134
Deep Venous Thrombosis	17	7	24	0.423
Cerebrovascular Accident	3	2	5	0.537
Atrial Fibrillation	30	13	43	0.392
<b>Educational Level</b>				
Illiterate	62	30	92	0.503
Literate	20	10	30	0.569
Primary school	15	9	24	0.390
High school	4	1	5	0.463
<b>Hospital clinic of stay</b>				
Emergency	38	50	88	<0.001
Cardiology	24	-	24	0.018
Internal Medicine	24	-	24	0.018
Neurosurgery	2	-	2	0.550
Neurology	2	-	2	0.550
Chest Diseases	4	-	4	0.305
Otorhinolaryngology	2	-	2	0.550
Gynecology	3	-	3	0.401
General Surgery	2	-	2	0.550
<b>Outcome</b>				
Cure	96	50	146	0.171
Died	5	-	5	

monitor groups at risk. The presence of comorbid diseases are an indispensable part of these scales. The most common comorbidity reported has been ischemic heart disease (8, 14-16). Similarly, our study also detected ischemic heart disease as the most common comorbid disease. Increased use of medications for treatment of

comorbid diseases and interaction of these medications with warfarin increase the risk of hemorrhagic complications.

There are many indications for warfarin use. Fanikos et al. (6) reported the most common etiologies, in descending order, as atrial fibrillation (%30), venous thromboembolic disease (%28), and valvu-

**Table 2.** Laboratory results of patients with and without hemorrhagic complication

Laboratory Result	Hemorrhage n=101	No hemorrhage n=50	p value
PT (sec; mean±SD)	90.98±26.52	55.51±12.70	<0.001
INR (INR; mean±SD)	8.97±11.29	4.63±0.68	0.042
WBC (K/UL; mean±SD)	11.41±4.38	10.43±3.98	0.478
HB (g/dL; mean±SD)	10.59±3.30	11.96±3.79	0.238
HTC (%; mean±SD)	32.49±8.35	35.68±7.85	0.837
PLT (K/UL; mean±SD)	285.56±125.18	279.69±116.99	0.962
ALT (U/L; mean±SD)	39.04±95.89	35.74±39.24	0.435
AST (U/L; mean±SD)	38.49±91.80	31.98±16.51	0.232
LDH (U/L; mean±SD)	317.71±142.92	329.94±148.70	0.709
Glucose (mg/dL; mean±SD)	119.03±49.59	114.56±38.28	0.208

PT: Prothrombin time, INR: International Normalized Ratio, WBC: White Blood Cell, HB: Hemoglobin, HTC: Hematocrit, PLT: Platelet, ALT: Alanine transaminase, AST: Aspartate transaminase, LDH: Lactate dehydrogenase

lar heart disease (%15). Baydin et al. (7) reported more common warfarin use in valve replacement. We also detected that valve replacement is the most common reason for warfarin use in both groups.

Patients with hemorrhage due to warfarin may present to the emergency department with GIS hemorrhage, subcutaneous hematoma, hemoptysis, intraabdominal hemorrhage, hematuria, vaginal bleeding, gingival bleeding, and intracranial hemorrhage. Many previous studies reported GIS bleeding as the most common form of hemorrhage, whereas we detected subcutaneous hematoma as the most common form, followed by GIS hemorrhage (5, 7, 17). Another important, albeit rare, complication is intracranial bleeding. Although not common, its mortality is high. Although some studies reported a rate as high as 14-38%, the number in most studies ranges from 1% to 6% (18-23). We also found it to be 2.6%.

We did not find any study in literature regarding the presentation with warfarin overdose and the presenting season. However, we found that the majority of patients presented in winter and spring, whereas patients presenting in autumn were low.

Previous studies reported fewer complications and more compliance to the treatment in patients given education (24, 25). Thus, anticoagulation clinics or units have been established in developed countries like America (26). Warfarin self-monitorization has been introduced in some countries, Germany and Holland being the first. This practice uses home-type coagulometers and it has been shown to be as successful as anticoagulation clinics (27, 28). When we consider Turkey, it is apparent that it is not sufficient to hand over brochures about anticoagulation by a number of universities. Lower literacy rates, particularly in Southeastern Anatolia and Eastern Anatolia, suggests that educational clinics or units should be established. The study by Baydin et al. (7) showed that 41% of cases are illiterate, and 51% were primary school graduates. Our study had a study population the majority of which were illiterates, a state that indicates the significance of education in patients using warfarin.

Previous studies showed that treatment and monitoring of the majority of patients presenting with warfarin overdose were done in emergency departments (5, 29). Similarly, our cases were largely

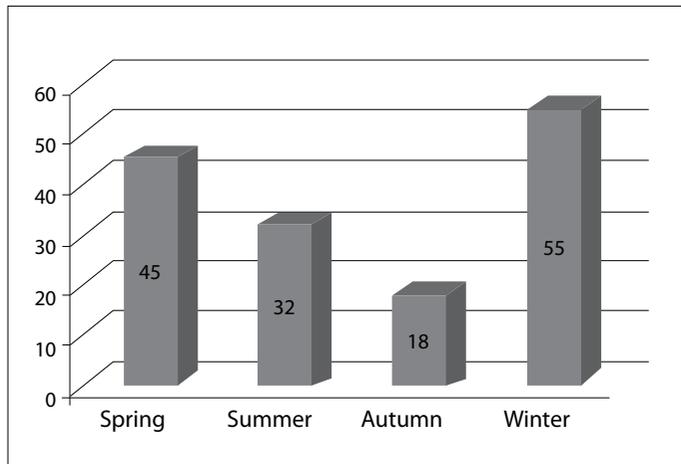
**Table 3.** Clinical and demographic characteristics of patients with a hemorrhagic complication who survived and died

Clinical and demographic characteristics	Survived n=96	Died n=5	p value
Age (years; mean±SD)	59.65±16.28	66.20±12.63	0.386
<b>Sex</b>			
Male	46	2	0.547
Female	50	3	
Presenting Time (hour; mean±SD)	11.75±5.83	10.80±2.68	0.472
<b>Comorbidity</b>			
Ischemic heart disease	41	1	0.305
COPD	16	--	0.414
Hypertension	21	2	0.319
Diabetes Mellitus	8	1	0.379
Cerebrovascular Accident	1	1	0.097
Liver Cirrhosis	1	--	0.950
Chronic Renal Failure	4	2	0.027
Malignancy	2	--	0.903
No disease	21	--	0.304
<b>Presenting symptom</b>			
Subcutaneous hematoma	35	--	0.113
GIS bleeding	24	--	0.249
Hemoptysis	5	1	0.269
Epistaxis	10	--	0.587
Intracranial hemorrhage	--	4	<0.001
Vaginal hemorrhage	2	--	0.903
Intraabdominal hematoma	3	--	0.857
Gingival bleeding	6	--	0.731
Hematuria	11	--	0.555
<b>Indication for warfarin</b>			
Valvular replacement	34	3	0.257
Pulmonary Thromboembolism	17	--	0.390
Deep Venous Thrombosis	16	1	0.610
Cerebrovascular Accident	3	--	0.857
Atrial Fibrillation	29	1	0.532
<b>Educational Level</b>			
Illiterate	57	5	0.082
Literate	20	--	0.323
Primary School	15	--	0.440
High School	4	--	0.814
<b>Hospital Clinic of Stay</b>			
Emergency	38	-	0.096
Cardiology	23	1	0.681
Internal Medicine	24	-	0.267
Neurosurgery	--	2	0.002
Neurology	--	2	0.002
Chest Diseases	4	-	0.814
Otorhinolaryngology	2	-	0.903
Gynecology	3	-	0.903
General Surgery	2	-	0.903
Duration of hospital stay	1.90±0.84	1.80±0.83	0.222

**Table 4.** Laboratory results of patients with a hemorrhagic complication who survived and died

Laboratory Result	Survived n=96	Died n=5	p value
PT (sec; mean±SD)	89.36±26.20	122.00±4.06	<0.001
INR (INR; mean±SD)	7.69±2.63	33.62±2.63	0.270
WBC (K/UL; mean±SD)	11.21±4.35	15.20±3.47	0.051
HB (g/dL; mean±SD)	10.58±3.39	10.76±0.88	0.560
HTC (%; mean±SD)	32.58±8.55	30.80±2.04	0.033
PLT (K/UL; mean±SD)	288.21±127.74	234.60±27.73	0.009
ALT (U/L; mean±SD)	29.73±32.04	217.80±32.04	0.362
AST (U/L; mean±SD)	29.33±26.77	214.40±391.11	0.352
LDH (U/L; mean±SD)	315.45±142.08	361.00±169.45	0.624
Glucose (mg/dL; mean±SD)	119.09±50.22	118.00±39.73	0.981

PT: Prothrombin time, INR: International Normalized Ratio, WBC: White Blood Cell, HB: Hemoglobin, HTC: Hematocrit, PLT: Platelet, ALT: Alanine transaminase, AST: Aspartate transaminase, LDH: Lactate dehydrogenase

**Figure 1.** Seasonal distribution of cases

treated in the emergency service. These results show the importance of the emergency department in monitorization of patients using warfarin and suffering a complication.

Previous studies showed that an INR level equal to or greater than 6 increases the bleeding risk (30, 31). Our study also found that patients with a hemorrhagic complication had a higher INR level. Regular testing and proper education of patients are important in maintaining the INR level at the desired level. Previous studies demonstrated that strict INR follow-ups decrease hemorrhagic risk (32, 33). A higher INR level may be considered as an early predictor of bleeding (7).

Palareti et al. (34) reported 153 hemorrhagic complications in 2011 patients, 5 of which were intracranial hemorrhage. Five patients died. Four of 151 patients in our study had intracranial hemorrhage and all died. Chan et al. (35) found a higher mortality rate in patients with serious comorbidities and malignancy among patients with complications of warfarin overdose. We also found that all patients who died had had comorbid diseases.

## Conclusion

Hemorrhage due to warfarin overdose takes place in advanced age, in the presence of comorbid diseases, in those with low educational level, and in those with a high INR level, while intracranial hemorrhage, illiteracy, low Htc and thrombocyte count, and a high PT increase mortality. Education in warfarin use, regular follow-ups, self-monitorization, and increased availability of home-type coagulometry devices will decrease the frequency of complications.

## Conflict of Interest

No conflict of interest was declared by the authors.

**Peer-review:** Externally peer-reviewed.

## Author Contributions

Concept - M.O.; Design - M.O., M.Ü.; Supervision - M.O., C.G.; Funding - M.O., R.D.; Materials - M.O., R.D.; Data Collection and/or Processing - R.D., A.Ö., H.M.D.; Analysis and/or Interpretation - M.O., M.Ü., C.G.; Literature Review - R.D., A.Ö., H.M.D.; Writer - M.O.; Critical Review - M.O., M.Ü., A.Ö.

## Çıkar Çatışması

Yazarlar herhangi bir çıkar çatışması bildirmemişlerdir.

**Hakem değerlendirmesi:** Dış bağımsız.

## Yazar Katkıları

Fikir - M.O.; Tasarım - M.O., M.Ü.; Denetleme - M.O., C.G.; Kaynaklar - M.O., R.D.; Malzemeler - M.O., R.D.; Veri toplanması ve/veya işleme - R.D., A.Ö., H.M.D.; Analiz ve/veya yorum - M.O., M.Ü., C.G.; Literatür taraması - R.D., A.Ö., H.M.D.; Yazıyı yazan - M.O.; Eleştirel İnceleme - M.O., M.Ü., A.Ö.

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