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HEALTH LITERACY AND MEDICATION ADHERENCE AMONG PATIENTS TAKING WARFARIN

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ABSTRACT

Aim: The aim of this study was to examine the relationship between health literacy (HL) and medication adherence (MA) of patients who presented at the INR outpatient clinic with a history of warfarin usage.

Methods: In the study, 173 patients over the age of 18 years who were being followed up at the INR outpatient clinic of Bursa Yuksek Ihtisas Training and Research Hospital between October 2022 and April 2023 and were using warfarin were evaluated. All the cases were evaluated with the Newest Vital Sign (NVS) Scale, and an MA scale.

Results: It was found that only 43.4% of the cases using warfarin had an adequate HL level. Only 11.6% of the cases using warfarin showed high compliance with the use of the drug. There was a significant positive relationship between the NVS scores and MA scores of the patients ($r=0.555$, $p<0.001$). Cases with a bleeding history had statistically significantly lower mean scores of NVS ($p<0.001$) and MA ($p<0.001$). In addition, the mean INR scores in patients with a bleeding history was also statistically significantly higher ($p<0.001$). MA ($p<0.001$), INR values ($p=0.009$), and education ($p=0.012$) were variables with an effect on an increased risk of bleeding.

Conclusion: There is a relationship between HL and MA in cases using warfarin. It was observed that cases with a history of bleeding were patients with high INR values, worse HL, and low MA. It may be valuable for physicians to evaluate the HL and MA in patients using warfarin in order to identify patients at high risk of bleeding.

Keywords: Warfarin, INR, health literacy, medication adherence

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Introiduction

Warfarin is a drug from the anticoagulant group and is among the most frequently used drugs in the world (1). It is frequently used to prevent blood clots as in pulmonary embolism and deep vein thrombosis, and to prevent stroke development in patients with atrial fibrillation or heart disease (2, 3). Warfarin inhibits the production of vitamin K-dependent clotting factors and thus reduces blood clotting (4). It inhibits the synthesis of vitamin K-dependent clotting factors and prevents their synthesis by inhibiting epoxy-reductase.

Warfarin dosage depends on factors such as the patient's age, diet, and genetic predisposition, and the drug's interactions with other drugs and it is often used following a detailed clinical evaluation by the physician. Warfarin doses are determined according to the INR result and it is recommended to start the treatment at a dose of 2 to 3 mg/day and then adjust it (5). Initial dose adjustment and maintenance treatment are continued by evaluating any additional diseases and the interactions between the drugs used. Most patients can be satisfactorily maintained at doses of 2 to 10 mg/day.

It is known that the INR value varies according to the demographic and clinical characteristics of the patients. Clinical evidence suggests that an INR of 2.0–3.0 is sufficient to prevent venous thromboembolism and minimizes the risk of bleeding associated with a higher INR (6). It has been found that an INR value of 2.4 is sufficient to prevent thromboembolic events in patients with atrial fibrillation, and may be lower in cases using combined aspirin; in addition, the risk of cerebral hemorrhage increases significantly when the INR value increases to 4 (7). It has been stated that the target INR value should be in the range of 2.0–2.5 in cases of myocardial infarction, and that the INR values in these cases may be reduced slightly depending on the use of aspirin or the risk of bleeding (8).

Health literacy is defined as a person's ability to obtain, understand, and use health information to make correct health decisions and follow instructions for their own or their dependents' treatment (9). Health literacy (HL) changes with the person's education, cultural characteristics, and the design of the health system by which they are provided service, and it helps people to receive more informed health care (10).

Increasing HL can increase medication adherence (MA) of elderly people with chronic diseases (11). Therefore, the development, implementation, and evaluation of HL interventions for older people with chronic conditions are important to increase MA and potentially improve patient outcomes.

In a study examining the relationship of HL with warfarin knowledge, MA, and warfarin control, it was reported that low HL was associated with incorrect answers to questions about warfarin's mechanism of action, side effects, and drug interactions, whereas it was not associated with self-reported adherence to the INR control (12). It has been found that limited HL is

associated with poor anticoagulation control in patients receiving warfarin therapy, and lack of medication understanding may hinder the safe and effective use of this drug with a narrow therapeutic index (13). When the literature is reviewed, only a limited number of studies evaluating the relationship between warfarin use and HL are found from Turkey. Therefore, the aim of this study was to examine the relationship between compliance with warfarin use and HL in cases being monitored in the INR outpatient clinic.

Methods

The research was conducted at the INR monitoring polyclinic of the Bursa Yüksek İhtisas Training and Research Hospital between 01.11.2022 and 30.04.2023. Ethics committee approval for the research was received from the ethics committee of the Bursa Yüksek İhtisas Training and Research Hospital. A total of 173 patients over the age of 18 years who presented at the INR clinic volunteered for the study. The sociodemographic characteristics of the volunteers were recorded after obtaining consent. Additionally, the patients were asked about their warfarin treatment and how long they had been taking the medication, the types of bleeding they had experienced, and the number of hospital emergency admissions and hospitalizations in the last year were recorded. In addition, the volunteers were asked questions from the Newest Vital Sign (NVS) scale and the Morisky Medication Adherence-8 scale.

NVS Scale

The Newest Vital Sign scale is a health literacy-related measurement tool that measures both reading and comprehension with 6 questions taking 3 minutes to administer (14). In the NVS, the patients are given a nutritional label and their reading and comprehension capacity is evaluated through the questions. While 4 of the questions require calculation and numerical skills, 2 are related to finding the appropriate answer. Getting a score of 0-1 from the NVS defines possibly limited HL, 2-3 defines limited HL and 4 or above defines adequate HL. The validation of NVS for the Turkish language has been conducted by Çiftçi et al. (15).

Morisky Medication Adherence-8 Scale

The Morisky Medication Adherence scale is a measurement tool that consists of eight questions and measures the subject's compliance with the treatment received (16). The questions in the MA section are answered as yes/no, and the last question (8th question) is in the Likert type. In the first step, the MA scale was developed as a seven-question measurement tool, and one more question was added in order to increase validity and reliability and to obtain a measurement tool that better measures MA. Getting a score below 6 represents low compliance, scores between 6-8 represents moderate compliance, and a score of 8 represents high compliance. The Turkish adaptation of the MA scale was realized by Sayiner (17).

Statistical Analysis

The demographic and clinical characteristics of the cases evaluated in the study were evaluated with descriptive statistical analyzes (number, percentage, mean, standard deviation, etc.). Comparison of the INR, and the NVS and MA scores according to the demographic characteristics, reason for using warfarin, duration of warfarin use, comorbidity status, bleeding status, and comparison of median values and averages of the INR and MA scale results according to the INR groups; the Independent Groups t-test and the Mann-Whitney U-test were used for groups of two while the Kruskal-Wallis H test was used for groups of three or more. The relationship between demographic and clinical characteristics and the INR, NVS, and MA values and the relationship between these values were evaluated using Spearman and Pearson Correlation Analysis. The factors associated with increasing bleeding risk were assessed by Multivariate Binary Logistic Regression Analysis. The significance level for all analyses was determined as $p<0.05$. The suitability of the data for a normal distribution was checked with kurtosis and skewness values (±1.5). The IBM SPSS 22.0 program was used in the analysis.

RESULTS

The average age of the cases evaluated in the study was 63.48±11.51 years and 77 of them (44.5%) were male. The average INR of the cases evaluated in the study was2.68±1.15.

The INR group values was 1-1.9 in 45 cases (26%), 2-2.9 in 76 cases (43.9%), 3-3.9 in 41 cases (23.7%), and over 4 in 11 cases (6.4%).

The HL level was inadequate in 26 cases (15%), limited in 72 cases (41.6%), and adequate in 75 cases (43.4%) while the MA was low in 86 cases (49.7%), medium in 67 cases (38.7%), and high in 20 cases (11.6%).

According to the Kruskal-Wallis H-test, it was found that the median NVS values of the cases evaluated in the study showed statistically significant differences regarding the education ($p < 0.001$) and occupation ($p < 0.001$) groups and the smoking ($p = 0.005$) groups (Table1).

According to the Mann-Whitney U-test, the median NVS score of the alcohol-consuming cases was statistically significantly higher than the median NVS score of the cases that did not use alcohol ($p=0.007$) (Table1).

The Independent Groups t-test showed that the NVS score averages of the single cases evaluated in the study were statistically significantly higher ($p=0.010$) than the NVS score averages of the married cases (Table1).

According to the Kruskal-Wallis H test, the median MA values of the cases evaluated in the study showed a statistically significant difference ($p <0.001$) between the education groups (Table1).

The Independent Groups t test showed that the MA score averages of the single cases evaluated in the study were statistically significantly higher ($p = 0.003$) than the MA score averages of the married cases (Table1).

Table1. Comparison of INR, NVS, and MA scores according to the demographic characteristics

		INR						NVS						MA					
		Mean	SD	Med.	%25	%75	p	Mean	SD	Med.	%25	%75	p	Mean	SD	Med.	%25	%75	p
Gender	Female (n=96)	2.75	1.29	2.58	1.97	3.10	0.438a	3.49	1.58	3.00	2.00	5.00	0.102a	5.52	1.61	6.00	4.00	7.00	0.924a
	Male (n=77)	2.62	1.03	2.55	1.94	3.17		3.09	1.60	3.00	2.00	4.50		5.54	1.44	5.50	4.00	7.00	
Education	Illiterate (n=29)	2.59	1.07	2.52	2.20	2.75	0.676b	1.86	1.22	**2.00**	1.00	3.00	**<0.001b**	4.45	1.30	**4.00**	4.00	5.00	**<0.001b**
	Literate (n=33)	2.92	1.77	2.51	1.84	3.25		2.33	1.05	**2.00**	2.00	3.00		5.00	1.15	**5.00**	4.00	6.00	
	Primary (n=75)	2.60	1.00	2.59	1.88	3.02		3.36	1.27	**3.00**	3.00	4.00		5.67	1.46	**6.00**	4.00	7.00	
	Secondary (n=29)	2.78	.71	2.66	2.27	3.35		5.00	1.10	**5.00**	5.00	6.00		6.48	1.15	**6.00**	6.00	7.00	
	University (n=7)	2.37	.88	2.59	1.18	3.18		5.43	.53	**5.00**	5.00	6.00		7.14	1.86	**8.00**	7.00	8.00	
Occupation	Unemployed (n=90)	2.59	.95	2.52	1.96	3.15	0.635b	2.90	1.46	**3.00**	2.00	4.00	**<0.001b**	5.43	1.38	5.00	4.00	6.00	0.315b
	Officer/retired (n=62)	2.86	1.50	2.64	1.84	3.21		3.34	1.63	**3.00**	2.00	5.00		5.53	1.71	5.50	4.00	7.00	
	Worker/others (n=21)	2.52	.65	2.46	2.20	2.66		4.67	1.28	**5.00**	4.00	6.00		5.95	1.47	6.00	5.00	7.00	
Marital Status	Single (n=35)	2.61	.97	2.55	1.96	3.10	0.112a	3.43	1.55	**3.00**	2.00	5.00	**0.010a**	5.70	1.47	**6.00**	5.00	7.00	**0.003a**
	Married (n=138)	2.95	1.70	2.59	2.02	3.35		2.66	1.64	**3.00**	1.00	4.00		4.86	1.52	**4.00**	4.00	6.00	
Smoking	No (n=107)	2.57	.99	2.51	1.84	3.11	0.377b	3.03	1.52	**3.00**	2.00	4.00	**0.005b**	5.47	1.46	5.00	4.00	7.00	0.733b
	Quitted (n=42)	2.97	1.60	2.64	2.03	3.34		3.33	1.63	**3.00**	2.00	5.00		5.60	1.71	6.00	4.00	7.00	
	Active smoker (n=24)	2.64	.78	2.57	2.29	2.94		4.25	1.54	**4.50**	3.00	6.00		5.71	1.46	5.50	5.00	7.00	
Alcohol	No (n=161)	2.68	1.19	2.55	1.91	3.15	0.793c	3.18	1.58	**3.00**	2.00	5.00	**0.007c**	5.50	1.52	6.00	4.00	7.00	0.424c
	Yes (n=12)	2.62	.58	2.62	2.29	2.90		4.50	1.38	**4.50**	3.50	6.00		5.92	1.51	5.50	5.00	7.50	

SD=Standard Deviation, Med.=Median, a=Independent Groups t test, b=Kruskal-Wallis H test, c=Mann-Whitney U-test. NVS=Newest Vital Sign, MA=Medication Adherence

Of the cases evaluated in the study, 50 (28.9%) were using warfarin due to arterial fibrillation, 94 (54.3%) due to prosthetic valve replacement, 9 (5.2%) due to cerebrovascular disease, and 4 (2%) due to cerebrovascular disease were warfarin. It was observed that 88 (50.9%) of the cases had been using warfarin for <3 years, 28 (16.2%) for 3-6 years, and 57 (32.9%)for >6 years. Additionally, 8 (4.6%) were 1 medication, 44 (25.4%) were using 2 medications, 44 (25.4%) were using 3, 16 (9.2%) were using 4, 33 (19.1%) were using 5, 20 (11.6%) were using 6, 6 (3.5%) were using 7, and 2 (1.2%) were using 8 medications (Table2).

There was bleeding in 40 (23.1%) of the cases. Of these 22 (12.7%) were dental, 16 (9.2%) were nasal, 5 (2.9%) were on the skin, 2 (1.2%) because of a cut, 8 (4.6%) in the stool, 2 (1.2%) in the vomit, 5 (2.9%) as hematuria, and 1 (0.6%) in another form (Table3).

Table2. Treatment characteristics of the cases evaluated in the study

		n	%
Reason for using warfarin	Atrial fibrillation	50	28.9
	Prosthetic valve replacement	94	54.3
	Cerebrovascular disease	9	5.2
	Pulmonary embolism	4	2.3
	Venous thromboembolism	8	4.6
	Other	8	4.6
Duration of warfarin use	<3 years	88	50.9
	3-6 years	28	16.2
	>6 years	57	32.9
Number of drugs used by the patient	1	8	4.6
	2	44	25.4
	3	44	25.4
	4	16	9.2
	5	33	19.1
	6	20	11.6
	7	6	3.5
	8	2	1.2

Table3. Bleeding characteristics of the cases evaluated in the study

		n	%
Bleeding	No	133	76.9
	Yes	40	23.1
Dental	No	151	87.3
	Yes	22	12.7
Nose	No	157	90.8
	Yes	16	9.2
Skin	No	168	97.1
	Yes	5	2.9
Because of a cut	No	171	98.8
	Yes	2	1.2
In the stool	No	165	95.4
	Yes	8	4.6
In the vomit	No	171	98.8
	Yes	2	1.2
Hematuria	No	168	97.1
	Yes	5	2.9
Other	No	172	99.4
	Yes	1	0.6

According to the Independent Groups t-test, it was found that the NVS and MA score averages of the cases without bleeding evaluated in the study were statistically significantly higher than the NVS ($p<0.001$) and MA ($p<0.001$) score averages of the cases with bleeding. In addition, it was found that the INR score averages of the cases with bleeding were statistically significantly higher ($p <0.001$) than the INR score averages of the cases without bleeding.

Table4.Comparison of the INR values and the NVS and MA scores according to bleeding history

		INR			NVS			MA		
		Mean	SD	p	Ort.	SS.	p	Ort.	SS.	p
Bleeding history	No	2.47	0.74	**<0.001**	3.53	1.50	**<0.001**	5.90	1.41	**<0.001**
	Yes	3.36	1.84		2.42	1.65		4.30	1.16	

SD=Standard Deviation, Independent Groups t test, NVS=Newest Vital Sign, MA=Medication Adherence

According to Multivariate Binary Logistic Regression Analysis, the MA scores were found to reduce the risk of bleeding at a statistically significant level (OR=0.346, p<0.001, CI:0.218 - 0.548).

Multivariate Binary Logistic Regression Analysis revealed that education (primary school and below) reduced the risk of bleeding at a statistically significant level (p = 0.012, CI; 0.023 - 0.629).

Multivariate Binary Logistic Regression Analysis also revealed that the INR scores increased the risk of bleeding at a statistically significant level by 1.865 times (p = 0.009, CI; 1.170 - 2.974).

Table5. Factors that increase the risk of a history of bleeding

	B	SE	Wald	df	p-value	Odds Ratio	95% CI	
							LL	UL
Age	0.048	0.033	2.131	1	0.144	1.049	0.984	1.118
Gender (women)	-0.517	0.534	.936	1	0.333	0.596	0.209	1.699
Education (Primary school)	-2.122	0.846	6.295	1	**0.012**	**0.120**	0.023	0.629
Marital Status (Single)	0.646	0.614	1.106	1	0.293	1.908	0.572	6.362
Smoking (No)	-1.074	0.707	2.307	1	0.129	0.342	0.085	1.366
INR	0.623	0.238	6.855	1	**0.009**	**1.865**	1.170	2.974
Number of drugs	-0.275	0.208	1.747	1	0.186	0.760	0.506	1.142
Comorbid Disease (No)	-1.015	0.792	1.641	1	0.200	0.362	0.077	1.712
Health Literacy	-0.269	0.239	1.271	1	0.260	0.764	0.478	1.220
Medication Adherence	-1.061	0.235	20.440	1	**<0.001**	**0.346**	0.218	0.548

Standard Error=SE, Confidence Interval=CI, Lower Limit=LL, Upper Limit=UL, Multivariate Binary Logistic Regression Analysis, NagelkerkeR2=0.46, X2=62.79, p<0.001.

According to the Pearson Correlation Analysis, there was a statistically significant positive correlation between the NVS values and the MA values of the cases (r=-0.555, p<0.001).

DISCUSSION

Only 43.4% of the cases using warfarin had an adequate level of HL in this study. In addition, only 11.6% of the cases using warfarin showed high compliance with the use of the drug. There was a significant positive relationship between the NVS scores and MA scores of the patients. Cases without bleeding had statistically significantly higher mean scores of NVS and MA. In addition, the mean INR score of cases with bleeding was also statistically significantly higher. MA, INR values, and education were variables with an effect on an increased risk of bleeding.

The average age of the cases was 63.48 years. It is known that comorbidities increase with advancing age, and that the use of warfarin reduces the risk of mortality and the risk of developing new comorbidities as age progresses (23-25). For these reasons, the high average age of the participants evaluated in the study can be considered an expected situation.

Females made up 55.5% of the cases in the study. It is known that the rates of comorbidities differ between men and women, and that health problems such as metabolic syndrome and obesity are more common among women (21, 22). The higher proportion of women in the study may be related to such factors. In addition, it should be kept in mind that the study was conducted in cardiology outpatient clinics and men may tend to benefit less from health services.

It was found that 16.8% of the cases evaluated in the study were uneducated and 19.1% were literate. Therefore 35.9% of the cases evaluated in the study had an education level below primary school. According to the TUIK 2022 statistics, it is known that 92.5% of the population in Turkey is at least a primary school graduate, and in addition, the education level is lower in the older population (23). In addition, it should be kept in mind that the hospital where the research was conducted is located in the Yildirim district of Bursa province, and this region has a population that receives intense immigration from the eastern provinces and has a lower level of education.

We found that 13.9% of the cases in the study were smokers. 24.3% of the cases stated that they had quitted smoking. Smoking is one of the important health problems that causes various additional diseases. According to the 2022 health survey of TUIK, the rate of people using tobacco every day is 28.3% in the population over the age of 15 years (24). For this reason, it can be said that the smoking rate in the cases evaluated in the study was low and a significant number of them had quitted smoking. In addition, cases using warfarin are at risk for health problems. It would be beneficial for public health to encourage warfarin users who smoke to quit smoking.

The average INR of the cases in the study was 2.68. It can be said that sufficient INR values were reached in the cases evaluated in the study. Researchers have reported that the risk of cerebral hemorrhage increases significantly when the INR value increases to 4, and in addition, a standard INR value in the range of 2.0-3.0 is more effective and safer in reducing the thromboembolic risk in patients over 65 years of age (12, 25). The research showed that 23.7% of the cases evaluated had an INR value of 3-3.9 and 6.4% had an INR value of 4 or more. Therefore, the risk of bleeding should be taken into consideration in these cases.

The study found that 54.3% of the cases were treated with warfarin in the INR outpatient clinic due to prosthetic valve replacement. In a study evaluating the satisfaction of people receiving warfarin treatment, it was found that the most common reason for warfarin use was mechanical valve prosthesis with 45% (26). It has

been stated that lifelong anticoagulant use is required to prevent thromboembolic problems in patients with mechanical heart valves, and the INR value in these people should be 2-3.5 (27). Therefore, in line with the literature, more than half of the cases treated in the INR clinic used warfarin due to valve problems in the current study.

The study found that 28.9% of cases were treated with warfarin for arterial fibrillation. Atrial fibrillation is a disease with a high risk of stroke and is one of the diseases for which warfarin is prescribed (2,3). It has been found that a low dose (INR 1.5 to 2.0) is effective in warfarin treatment in cases of atrial fibrillation and a standard or high dose (INR 2.0 to 3.0) is effective in reducing thromboembolic risk in elderly patients (25). The cases followed in the INR polyclinic are followed by physicians who are experts in their field. Therefore, the physicians in charge of the INR polyclinic are more experienced than family physicians in the use of warfarin in cases with prosthetic valve replacement or arterial fibrillation. For this reason, it may be more beneficial for patient health for family physicians to provide the necessary information to their patients, to increase their patients' adherence to medication, and to refer cases in which they have difficulty in terms of treatment to specialist physicians in INR polyclinics.

An adequate level of HL was found in only 43.5% of the cases evaluated in the study. It is known that low HL is common in people with low education levels and that education is the primary criterion in the improvement of HL (19, 20). Cases followed in the INR clinic and using warfarin often consist of people with serious physical diseases. Therefore, low HL in these people may lead to various health problems. Increasing the HL of cases followed in INR polyclinics may be beneficial for public health. In addition, it should be kept in mind that there was no control group in this study, so it would not be correct to say that HL in cases using warfarin is lower than in the general population.

The MA was low in 49.7% of the cases evaluated in the study. Warfarin is one of the most widely used drugs in the world (1). It is a very important drug to prevent the development of stroke, especially in people with atrial fibrillation and heart disease (2, 3). One of the main goals of physicians prescribing warfarin is to ensure that patients reach adequate INR values. On the other hand, nearly half of the cases treated in the INR clinic appear to have low MA. Therefore, in these cases, it is necessary to consider factors that reduce MA as MA is the key to the success of the treatment process. It may be very beneficial for public health for family physicians and INR polyclinic physicians to plan activities that will increase MA in cases using warfarin.

The study found that HL and MA varied according to demographic characteristics (education, marital status, etc.), but the INR values did not change. HL is defined as a person's ability to obtain, understand, and use health information to make correct health decisions and follow instructions for their own and their

dependents' treatment (9). HL changes with the person's education, cultural characteristics, and the design of the health system from which they receive service, and it helps people to receive more informed health care (10). Therefore, as a result of this research, it can be said that HL and MA are related to demographic characteristics in cases using warfarin, as in the literature, but the INR value is not related to demographic characteristics.

Bleeding had occurred in 23% of cases in the last year in the current study. In addition, the average INR value in cases with bleeding was 3.36, and these people had lower HL and MA. In the logistic regression analysis, primary school education or lower reduced the risk of bleeding, a one-unit increase in the INR value increased the risk of bleeding by1.87 times, and MA significantly reduced the risk of bleeding. These results show that keeping the INR value at a certain level and using the drug regularly reduces the risk of bleeding. Researchers have recommended that the INR value should not exceed 4 to avoid the risk of bleeding (4). The fact that primary school education or lower is a positive demographic feature in reducing the risk of bleeding can be interpreted as an unexpected situation. In logistic regression analysis controlling the effects of variables such as age, gender, marital status, smoking, comorbid disease, number of medications, HL, and MA, it was shown that low education may have a protective effect. The fact that low-educated people are more susceptible to suggestions or that the patient's relatives monitor their medications may be related to the emergence of such a result. Evaluation of the bleeding history according to the patient's statement seems to be a limitation in reaching a final conclusion. Conducting prospective studies on this subject will contribute to the literature.

In recent years, the use of new generation oral anticoagulants has become increasingly common in order to prevent the disadvantages of vitamin K antagonists (28). However, it is known that these drugs, which have a lower risk of bleeding, are less commonly preferred because treatment costs are higher than drugs such as warfarin (29). Therefore, it may be beneficial for public health for physicians to consider new treatment options in cases using warfarin and at risk of bleeding, and to ensure that patients with this condition benefit from new treatments.

One of the limitations of the research is the limited number of participants. Another limitation of the study is that the data obtained in the study consists only of the hospital INR clinic. The HL and MA of patients who do not come to the INR clinic may differ from the results of this study. Recording the bleeding history according to the patient's declaration can be considered as another limitation.

In conclusion, there is a relationship between HL and MA in cases using warfarin. It was observed that cases with a history of bleeding were patients with high INR values, low HL, and low MA. It may be valuable for physicians to evaluate HL and MA in patients using warfarin in

order to identify patients at high risk of bleeding in advance.

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