

Clinical and Psychological Factors Affecting Distress Among Chronic Warfarin Patients with Uncontrolled International Normalized Ratio - Findings and Implications

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Abstract

Aim: This study aimed to evaluate the clinical and psychological factors of distress among patients on warfarin therapy with uncontrolled International Normalized Ratio (INR) in Pakistan. **Materials and Methods:** This study used a convenience sampling method to achieve the target size. Perceived distress was measured using a short version of the Cohen Perceived Stress Scale 10. The responses were recorded and statistical analysis was conducted. **Results and Discussion:** Among the participants, a maximum of the participants were male ($n = 280$, 68.5%) compared to the females ($n = 129$, 31.5%). A maximum of the participants were in the above 65 years category. Among all the participants, 347 patients showed the presence of low distress and 62 showed the presence of high distress. This result indicates that there is a positive correlation between the age ($P = 0.005$) and duration of warfarin ($P = 0.011$) with distress in included patients. Associated comorbidities and history of hospitalization showed no association with distress in the study population. **Conclusion:** This study reported that warfarin patients in Pakistan experienced a lower level of distress despite their uncontrolled INR. However, few of the factors, such as age and duration of warfarin, were shown to be associated with the higher level of distress in the study participants.

Key words: Distress, perceived stress scale 10, uncontrolled international normalized ratio, vitamin K, warfarin therapy

INTRODUCTION

Warfarin (Coumadin) which is a Vitamin K antagonist is an anti-coagulant, prescribed to patients suffering from atrial fibrillation (AF), ischemic stroke, and myocardial infarction (MI).^[1-3] In 1920, its first anticoagulant activity (prothrombin inhibitor) was observed in cattle. At that time, to prevent bleeding in cattle, moldy silage (obtained from sweet clover) was used, and the bleeding stopped. In 1940, Karl Link and Harold Campbell discovered that the anticoagulant activity in the sweet clover (*Melilotus alba* and *Melilotus officinalis*) was due to the presence of —3, 3 methylene bis, or 4-hydroxy coumarin. In 1948, Link synthesized

warfarin and at that time it was used to kill rodents (1952), later it got approval for humans in 1954.^[3-5]

Mental well-being is an integral part of the overall health of an individual and is closely associated with physical health, cognitive, behavioral, and emotional patterns of the individual in the sociocultural context. Distress is the amalgamation

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of several events that can happen due to perturbation in normal physiological processes (e.g., thromboembolic disorder), changes in environmental stimulus, development of negative thoughts such as depression, and anxiety (due to socio-economic pressure, behavioral changes, and personal problems).^[3-5] The prothrombotic distress response (controlled by the autonomic and neuroendocrine system) gets aggravated during prothrombotic conditions; hence, patients suffering from thromboembolic disorders such as venous thromboembolism, AF, stroke, MI are often found to be associated with distress, anxiety, and depression.^[2-9]

Warfarin decreases the Vitamin K level; this may stimulate distress signaling pathways, and become a problem of major concern in warfarin patients. Vitamin K and Vitamin K-dependent proteins (VKDP) play a critical role in the normal functioning of the brain.^[7-10] These days, mental distress is part of everyone's life, and individuals experience a higher level of distress in their life, especially in acute and chronic diseases.^[11,12] Patients under distress usually develop psychiatric disorders and even sometimes psychological trauma and distress-related disorders (DRDs).^[11,12] DRDs are a group of mental problems or diseases that are usually diagnosed or established after the presence of a preceding stressful event.^[13,14] Depending on the type of a trigger, its signs and symptoms, and the total duration of an event, the DRDs are categorized as acute stress disorders and chronic distress disorders.^[14,15] Over the past decade, it was reported that various risk factors regarding DRDs were directly or indirectly linked with warfarin therapy.^[11,12] Several studies suggested that psychological traumas and DRDs usually aggravate potential risks of acquiring various chronic and life-threatening diseases, such as cardiovascular disorders with comorbidities, autoimmune diseases, and even mortalities.^[12-14] Furthermore, few studies have advocated the hypothetical relationship between warfarin therapy with psychological unrest and DRDs.^[10] Usually, MI and stroke are caused due to clot formation, whereby warfarin therapy is vital in disease progression and prevention.^[16,17] However, in warfarin therapy, the fear of excessive bleeding can refrain the patients from daily life activities and social gatherings.^[18] This fear often results in anxiety, depression, and distress among warfarin patients. Therefore, this study aims to determine distress levels and the clinical and psychological factors of distress among warfarin patients with uncontrolled International Normalized Ratio (INR) in Pakistan.

MATERIALS AND METHODS

Study design and duration

In this cross-sectional descriptive study, the patients who are above 18 years of age and are on warfarin therapy for at least 2 months because of any clinical indication were included in the study. The study protocol was approved by the institutional review committee. At the very beginning of the study, the

patients were informed about the complete study guidelines. The informed consent was signed and they were assured that all the information shared in this study would be kept confidential and would be used for research purposes only. Patients who were on warfarin therapy for at least 2 months and came for follow-up were included in the study.

Study inclusion and exclusion criteria

Patients who participated in the study willingly and signed in informed consent were only included. Patients who are lower than 18 years of age, not willing to participate, are pregnant or are planning for conception were excluded from the study. As it is reported previously in all trimesters of pregnancy, warfarin is associated with negative outcomes including fetal anomalies, miscarriages, and even in the advanced stage of pregnancy it can cross the placenta and cause intracranial hemorrhage. Patients with abnormal bleeding disorders and INR values were also excluded. The patients with warfarin therapy who were visiting the hospital for the follow-up studies were identified from the hospital records. Patients were identified and briefed about the study pro forma. Written informed consent was provided to the patients after the inclusion and they were briefed about the study procedure. Those who showed their willingness were provided with the questionnaire and their responses were recorded.

Sampling technique

This study used a convenience sampling method to achieve the target size.

Sample size

The sample size was calculated based on a previous study conducted among warfarin patients at the same site but measuring a different outcome. With a 5% marginal error and 95% confidence interval, the total sample after adding a 30% dropout was 311. This was the minimum number based on the formula and we obtained a total of 409 participants to be included in the study.

Distress measurement

Distress among warfarin patients was measured using a short version of the Cohen Perceived Stress Scale (PSS) called PSS 10.^[19] The PSS 10 used to evaluate individuals' feelings, their confidence, the frequency of participant's difficulty, and confidence to handle distress 1 month before the start of the study.

Statistical analyses

The data obtained from the questionnaire were entered in Excel and used using Statistical Package for the Social

Sciences (SPSS) ver. 25 (SPSS Inc., Chicago, IL, USA). Evaluation of demographic and disease characteristics was done using descriptive statistics. The mean and the standard deviation were calculated for variables. For demographic variables percentages were calculated. Independent samples t-test was used to determine the mean distress score among categorical variables. The Chi-square test was used to observe the significance level and to obtain crude odds ratio for the variables. A $P < 0.05$ was considered statistically significant. The variables that had a $P < 0.05$ in the univariate analysis were further analyzed using multivariate analysis. For multivariate analysis, a binary logistic regression model with the Wald statistical criteria was used to obtain the pure clinical and psychological factors (without confounders) with an adjusted odds ratio. The Hosmer-Lemeshow goodness-of-fit test was used to validate the overall model fit.

RESULTS

In this study, a total of 409 participants filled out the questionnaire. The details of the demographic variables are presented in Table 1. Table 1 describes the demographic parameters used in this study. Among the participants, a maximum of the participants were male ($n = 280$, 68.5%) compared to the females ($n = 129$, 31.5%). Among 409 participants 200 were below 65 years of age (48.9%) and 209 participants were more than 65 years age group (51.1%). 59.4% of the participants were married and 40.6% were unmarried. 59.7% of the participants had lower than secondary-level education, and 66.5% of them were unemployed. A maximum of the participants had associated comorbidities ($n = 294$, 71.9%). AF/valvular heart disease was reported in 233 participants (57%) compared to the pulmonary embolisms (PEs)/deep vein thrombosis (DVTs)/Others ($n = 176$, 43%). Around 43.5% of the participants were on warfarin for <12 years and 56.5% were on warfarin for more than 12 years. Self-reported bleeding was reported in 35.5% of the participants and 64.5% reported no such instances. Around 77% of the participants reported no cases of hospitalization in the past 6 months and 23% reported instances of hospitalization. Further, statistical analysis of all the variables showed no statistically significant association between the demographic parameters and distress except for the frequency of hospitalization, co-morbidities, INR value, indication, and duration of warfarin.

Table 2 describes the clinical and psychological factors of distress among warfarin patients by univariate analysis. In univariate analysis, the 347 patients showed the presence of low distress and 62 showed the presence of high distress. On further analysis, maximum male patients showed a low level of distress compared with females ($P = 0.106$). The maximum of the patients who had an age <65 years showed higher distress ($n = 42$) compared with the patients with an age higher than 65 years ($n = 20$). This association was shown to be statistically significant ($P = 0.004$). On univariate

analysis, no association is reported between employment, education, marital status, INR value, self-reported bleeding instances, hospitalization frequency, and warfarin indication. Among the patients with comorbidities, a higher level of distress was reported ($P = 0.009$). Warfarin duration <12 months had a higher distress level ($P = 0.012$). Patients who reported no hospitalization in the past 6 months also had a lower distress level ($n = 277$), compared to the patients with a hospitalization history in the past 6 months ($n = 70$). History of hospitalization in the past 6 months also showed a statistically significant association with distress ($P = 0.001$).

Table 3 describes the results of multivariate analysis. This result indicates that there is a positive correlation between the age ($P = 0.005$) and duration of warfarin ($P = 0.011$) with distress in included patients. Associated comorbidities and history of hospitalization showed no association with distress in the study population.

DISCUSSION

Warfarin is used in thromboembolic diseases such as PE, DVT, AF, MI. Warfarin is an anticoagulant and helps in preventing thromboembolic stroke in AF and stroke patients.^[20,21] It is necessary to constantly monitor the dose of warfarin in patients suffering from thromboembolic diseases.^[22] There is a fixed range to administer oral anticoagulant therapy. The therapeutic range is recommended to maintain an INR.^[23] Recently, studies have started addressing the issue of health-related quality of life in patients who are treated with anticoagulation therapy. However, there is very least information available in research where the distress and its clinical and psychological factors have been investigated in patients on warfarin therapy.^[24] In Pakistan, there was not a single study available that investigated the clinical and psychological factors of distress in patients with warfarin therapy and uncontrolled INR.

Mental distress is a strong condition that can damage the well-being, happiness, and normal life of an individual and can be detrimental and fatal for vulnerable persons. The sensitivity, empathy, emotional quotient, and resilience of people positively contribute to overcoming the crisis and distress in life. The more is the defense system, such as resilience and positive psychology, the less the possibility of suffering from depression and distress affecting mental well-being.^[25] Warfarin therapy is challenging as it is associated with several comorbidities such as bleeding, hypertension, MI, diabetes mellitus, ischemic heart disease, congestive heart failure, peripheral vascular disease, transient ischemic attack, platelet or coagulation disorder renal failure, liver failure, chronic obstructive pulmonary disease/emphysema, cancer, osteoporosis, and mental illnesses i.e., distress, anxiety, depression, etc.^[18-25] Past studies have reported several comorbidities associated with warfarin therapy. Vitamin K was discovered in 1953 as a hemorrhagic factor in

Table 1: Demographic and clinical characteristics of the study participants (n=409)

Variables	n	%	Mean	SD	P-value
Gender					
Male	280	68.5	13.15	6.07	0.045
Female	129	31.5	14.49	6.69	
Age					
<65 years	200	48.9	12.90	6.20	0.035
>65 years	209	51.1	14.21	6.33	
Marital status					
Unmarried	166	40.6	13.59	6.60	0.954
Married	243	59.4	13.55	6.09	
Education					
<Secondary	244	59.7	13.24	5.93	0.194
Post-secondary	165	40.3	14.06	6.79	
Employment					
Employed	137	33.5	13.12	7.33	0.305
Unemployed	272	66.5	13.80	5.70	
Comorbidities					
Yes	294	71.9	12.84	6.09	<0.001
No	115	28.1	15.44	6.46	
Warfarin indication					
AF/VHD	233	57.0	13.09	6.05	0.076
PEs/DVTs/Others	176	43.0	14.21	6.56	
Warfarin duration					
<12 months	178	43.5	14.55	7.16	0.006
>12 months	231	56.5	12.81	5.43	
INR value (past 6 months)					
In range	173	42.3	12.72	6.35	0.019
Not in range	236	57.7	14.19	6.19	
Self-reported bleeding (past 6 months)					
Yes	145	35.5	13.90	7.11	0.435
No	264	64.5	13.39	5.81	
Hospitalization (past 6 months)					
Yes	94	23.0	16.03	6.78	<0.001
No	315	77.0	12.84	5.96	

INR: International Normalized Ratio, AF: Atrial fibrillation, VHD: Valvular heart disease, DVT: Deep vein thrombosis, PE: Pulmonary embolism

chick (cholesterol-free and low-fat diet). It was also observed that vitamin K plays a critical role in homeostasis. It was found that vitamin K is a cofactor for prothrombin, along with factors II, VII, IX, and X, it is involved in the conversion of Glu-Gla residues in VKDPs.^[23-25]

Among 409 patients 347 patients showed the presence of low distress on a perceived distress scale of 10. Only 62 participants showed the presence of higher distress. Based on the age of the patients, they were divided into two groups below 65 years of age and age more than 65 years. It was observed that age is positively associated with the incidences of distress

in warfarin patients. Even the duration of anticoagulation therapy was shown to be associated with distress in these patients. In a previous study by Baumgartner *et al.*, it was reported that in patients with anticoagulation therapy with warfarin the risk of ischemic stroke increases with diagnosed anxiety.^[25] However, there was no significant reason behind this association was reported in any of these studies.

In warfarin patients, Vitamin K and other clotting factors get suppressed, hence, they generally suffer from distress, anxiety, and depression. A closed circuitry loop is created- either distress leads to thromboembolic disorders or thromboembolic disorders

Table 2: Clinical and psychological factors of distress among warfarin patients (univariate analysis)

Variables	Low	High	COR (95% CI)	P-value
Gender				
Male	243	37	1	
Female	104	25	1.579 (0.90–2.75)	0.106
Age				
<65 years	167	42	1	
>65 years	180	20	2.263 (1.27–4.01)	0.004
Marital status				
Single	140	26	1	
Married	207	36	0.936 (0.54–1.62)	0.814
Education				
<Secondary	210	34	1	
Post-secondary	137	28	1.262 (0.73–2.17)	0.401
Employment				
Employed	115	22	1	
Unemployed	232	40	0.901 (0.51–1.58)	0.719
Comorbidities				
Yes	258	36	1	
No	89	26	2.094 (1.19–3.66)	0.009
Warfarin indication				
AF/VHD	203	30	1	
DVTs/PEs	144	32	1.504 (0.87–2.58)	0.138
Warfarin duration				
<12 months	142	36	1	
>12 months	205	26	0.500 (0.28–0.86)	0.012
INR value (past 6 months)				
In range	149	24	1	
Not in range	198	38	1.191 (0.68–2.07)	0.535
Self-reported bleeding (past 6 months)				
Yes	122	23	1	
No	225	39	0.919 (0.52–1.61)	0.769
Hospitalization (past 6 months)				
Yes	70	24	1	
No	277	38	0.400 (0.22–0.71)	0.001

INR: International Normalized Ratio, AF: Atrial fibrillation, VHD: Valvular heart disease, DVT: Deep vein thrombosis, PE: Pulmonary embolism, COR: Crude odds ratio, CI: Confidence interval

lead to distress.^[27] However, no studies have discussed the clinical and psychological factors of distress among patients on anticoagulation therapy. In the past, researchers have reported different aspects of health-related quality of life in patients on anticoagulation therapy.^[28-30] The bleeding incidences in patients with warfarin therapy cause a decrease in the overall health status.^[26-27] Studies have shown that distressful events in patients on warfarin therapy can significantly alter the INR.^[25-27]

The logistic regression analysis found age as a significant predictor of distress among warfarin patients in the present study. These results further determined that any change in age

(years) from <65 years to >65 years, resulted in decreased distress of 0.426 ($P < 0.05$) when adjusted for other studied variables among warfarin patients. A higher distress was noted among <65 years' patients than >65 years. Our study results corroborate with many previous findings in terms of raised INR which may be due to a reduction in the metabolism of warfarin during distress.^[9,31,32] Another study also reported similarly that age was significantly related to distress levels among warfarin patients.^[30] Psychological distress may also result in compromised sleep or complete sleep deprivation among warfarin patients.^[33,34] In multiple regression analysis, warfarin duration had also appeared as a significant predictor of distress

Table 3: Clinical and psychological factors of distress among warfarin patients (multivariate analysis)

Variables	β	S.E.	AOR	95% CI		P-value
				Lower	Upper	
Age						
<65 years	R	R	R	R	R	R
>65 years	0.852	0.301	0.426	0.236	0.769	0.005
Comorbidities						
Yes	R	R	R	R	R	R
No	0.291	0.425	0.747	0.325	1.720	0.493
Warfarin duration						
<12 months	R	R	R	R	R	R
>12 months	0.739	0.291	2.095	1.183	3.709	0.011
Hospitalization (past 6 months)						
Yes	R	R	R	R	R	R
No	0.579	0.436	1.785	0.759	4.198	0.184

AOR: Adjusted odds ratio, CI: Confidence interval, R: Referent group

and confirmed that any change in warfarin taking duration from <12 months to >12 months decreased the distress almost 2-fold ($P < 0.05$) when adjusted for other variables.

The strength of the present study is that it has included a large number of patients on warfarin therapy. All the patients were from diverse sociodemographic backgrounds and patients who were treated only with warfarin were included. This study result reflects real-life clinical outcomes that allowed us to evaluate the potential impact of anticoagulation therapy in these patients. The potential limitation of the study is that in the case of illiterate people, the questionnaire was filled up by the caregivers, nurses, or assistants and thus may result in some reporting bias. These factors also might have influenced the result of this study. Moreover, in the present study, no control group was employed and hence applicable comparative study was not possible. Being a cross-sectional study, this study also has the potential selection bias.

CONCLUSION

This study reported that warfarin patients in Pakistan experienced a lower level of distress despite their uncontrolled INR. However, few of the factors, such as age and duration of warfarin were shown to be associated with the higher level of distress in the study participants. The finding of the present study is the first of its kind conducted in Pakistan and even globally very few studies were done that evaluated clinical and psychological factors of distress among warfarin patients.

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