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Original article

Assessment of Quality of Life, Anxiety, and Depression via WHOQOL-BREF, And HADS among Egyptian Patients on Warfarin Therapy: A Cross-Sectional Study.

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ABSTRACT

Background: Being not fully explored, This study aimed to assess the impact of anticoagulation management on the Health-Related Quality of Life (HRQoL) and Psychological Distress (PD) of cardiac patients on warfarin therapy in Egypt. **Methods**: Using Arabic versions of the World Health Organization Quality of Life Assessment Brief Form (WHOQOL-BREF) and Hospital Anxiety and Depression Scale (HADS), patients on warfarin were evaluated across four WHOQOL-BREF domains: social, psychological, environmental, and physical. PD, differentiating between anxiety and depression, was assessed through HADS.

Results: We assessed 302 patients (57% of participants were males). The social domain had the highest mean score (56.05±16.899), followed by psychological (48.89±18.83), environmental (46.26±13.809), and physical domains (36.23±18.575). Depression mean score (9±8.401) exceeded anxiety (6.83±7.939), with 51% experiencing depression and 40.4% anxiety. Positive correlations were found among WHOQOL-BREF domains, with a strong negative correlation between anxiety and depression ($r = -0.93$, $p < 0.001$). Significant associations were noted between comorbidities, employment status, marital status, and HRQoL/PD indicators. Comorbidities other than cardiovascular diseases (CVD) and employment status significantly correlated with physical and social domains ($p < 0.001$ each). Marital status correlated significantly with psychological and social domains ($p < 0.001$ each), and depression and anxiety were significantly correlated with marital status ($p = 0.031$ and $p = 0.049$, respectively).

Conclusion: participants reported higher HRQoL scores in the social domain, with depression prevalence exceeding anxiety. Socio-demographic and clinical factors significantly influenced HRQoL and PD, providing insights into factors affecting CVD patients' well-being during anticoagulation therapy in a sector of Egyptian population.

Keywords
WHOQOL-BREF; HADS; warfarin patients; QoL; anxiety; depression; psychological distress; HRQoL; quality of life.

INTRODUCTION

Patients with a variety of cardiovascular diseases (CVD) including deep venous thrombosis, acute pulmonary embolism, atrial fibrillation, and intra-cardiac thrombosis, and patients with prosthetic heart valves are frequently prescribed warfarin treatment [1–3]. It is well-documented that CVD represents a significant public health concern and ranks among the leading causes of premature mortality worldwide [4–9]. Additionally, CVD can

have a profound impact on an individual's Health-Related Quality of Life (HRQoL), leading to substantial impairments in mental well-being and physiological processes [9–11]. Egypt, like many countries, faces serious healthcare challenges related to CVD. Egypt accounts for 15% of total CVD mortality in the Middle East and North Africa region, with CVD being responsible for approximately 40% of annual fatalities in the country [12–14].

According to the World Health Organization (WHO) [15], an individual's quality of life (QoL) is defined as their perception of their position in life within the context of their goals, expectations, standards, and concerns, situated within their culture and value systems. A subset of this, HRQoL [16], specifically reflects an individual's satisfaction with various aspects of life that are influenced by their overall health status. HRQoL is a subjective outcome, reported by individuals to identify unique challenges posed by illness [9,11]. Particularly in chronic illness patients, HRQoL assessments focus on the individual's perception of their overall health and how their disease impacts various facets of their lives, such as environmental, psychological, social, and physical dimensions. These assessments are vital for monitoring treatment effectiveness and guiding the development of healthcare policies aimed at improving the general health of populations [17–19].

In the context of CVD, several conditions require prolonged treatment with oral anticoagulants (OACs) and their use as a prophylactic measure against thromboembolic disorders [20,21]. However, warfarin treatment poses its own set of challenges, including considerable intra- and inter-individual variability and a restricted therapeutic index. Warfarin regimens are complicated due to the unpredictability of physiological responses, potential for bleeding incidents, and interactions with food and other drugs [20]. Unlike other direct OACs, warfarin demands rigorous and consistent laboratory monitoring to maintain appropriate international normalized ratio (INR) values, alongside strict adherence to the prescribed treatment plans and medication durations. This is necessary to effectively manage bleeding risks and achieve optimal therapeutic outcomes [22, 23], but these factors can adversely affect the overall HRQoL and mental status of patients [9], increasing the risk of psychological distress (PD) [24]. Adverse medication reactions to warfarin can lead to emergency hospitalizations in severe cases, and failure to effectively manage these issues may result in increased morbidity and mortality [25, 26]. Lengthy hospitalizations, costly treatments, and the associated fear of dying can negatively impact patients' daily lives and health [27,28], further increasing the risk of PD [23,24]. Additionally, long-term use of warfarin often leads to lifestyle changes due to concerns about compromised exercise, dietary restrictions related to vitamin K, and alterations in daily routines, treatment plans, and outcomes. These changes, along with socio-economic and socio-demographic shifts, can negatively influence patients' perceptions of their HRQoL, mental status, and health condition [20, 29–32], raising the risk of PD [23]. Warfarin is also linked to low self-esteem, anxiety, depression, work performance issues, and emotional problems, which contribute to diminished HRQoL [11, 33]. Perceived reductions in HRQoL among warfarin patients may affect their medication use and adherence [34], and can influence healthcare professionals' decisions regarding warfarin prescription [9,21 ,35].

While there is a global interest in researching HRQoL and PD among patients receiving OAC treatments like warfarin in different countries [9,11,20,23,36–41], no studies to our knowledge have specifically assessed HRQoL and PD among warfarin patients in Egypt using World Health Organization Quality of Life Assessment Brief Form (WHOQOL-BREF) and Hospital Anxiety and Depression Scale (HADS). This study, therefore, aims to investigate these aspects in Egyptian warfarin patients and examine the correlations of HRQoL and PD with various socio-demographic and clinical factors, such as gender, smoking status, marital status, educational level, age, work environment, history of cardiac surgery, underlying CVD, comorbidities other than CVD, duration of warfarin treatment, and use of other chronic medications besides warfarin.

METHODS

Participants, study design, and setting

This observational cross-sectional study was conducted on 320 patients attending the cardiology outpatient clinic in Zagazig University Hospital, Zagazig, Egypt. The study was carried out following the Declaration of Helsinki [42] and was approved by the Institutional Review Board (IRB) of Zagazig University Hospital under approval number (ZU-IRB#11270-5/11-2023). Participation in this study was entirely voluntary, with strict confidentiality maintained regarding patients'

identities and private information. Participants were fully informed about the purpose and nature of the study and their right to withdraw at any time. Oral consent was obtained from all participants at the beginning of the study. The study targeted patients aged 18 to 70 years who had been taking warfarin for at least two months, a duration necessary for adjusting the therapeutic dose of warfarin [43]. Exclusion criteria included being under 18 years of age, refusal to sign the consent form, pre-existing mental disorders before warfarin treatment, undergoing other major medical treatments, and inability to give informed consent, especially due to cognitive disorders. Additionally, pregnant women, or those planning to conceive, were excluded due to the risks associated with warfarin during pregnancy, such as teratogenicity, fetal abnormalities, miscarriage, low birth weight, and premature birth in the first and second trimesters, and the increased risk of cerebral hemorrhages and maternal bleeding in the third trimester [44–46].

A structured questionnaire was used to gather socio-demographic and clinical data from the patients, including gender, smoking status, employment status, marital status, educational level, age, history of cardiac surgery, underlying CVD, and comorbidities other than CVD (such as gastrointestinal diseases, pulmonary disorders, musculoskeletal disorders, respiratory diseases, and diabetes). The questionnaire also covered the length of time on warfarin treatment and other chronic medications besides warfarin.

The primary method of data collection was a structured sociodemographic interview, supplemented by the pre-validated Arabic version of the WHOQOL-BREF to evaluate health-related quality of life (HRQoL) [47]. The WHOQOL-BREF questionnaire includes 24 questions across four domains: physical, psychological, social, and environmental. These domains provide insights into various aspects of the respondents' lives, assessing how problematic or satisfactory they are in relation to their overall HRQoL [11,48]. Domain scores for the WHOQOL-BREF were calculated by summing the scores of individual questions and then linearly transforming them according to WHOQOL-BREF guidelines on a 0-100 scale [49]. A higher score in any WHOQOL-BREF domain indicates a higher level of HRQoL, and vice versa.

In addition to the WHOQOL-BREF, the assessment of psychological distress (PD) levels among warfarin patients was conducted using a pre-validated Arabic version of the Hospital Anxiety and Depression Scale (HADS) [50]. HADS is specifically designed to measure levels of anxiety and depression in hospital settings, making it particularly useful for patients undergoing therapies with potential psychological side effects. The scale comprises two subscales, one for anxiety and the other for depression, each covering the patient's experiences over the previous month. Each subscale contains seven items, scored from 0 to 3, where higher scores indicate more severe symptoms. The total score for each subscale ranges from 0 to 21. A score between 8 and 10 is considered indicative of a mild disorder (borderline case), while a score of 11 or higher suggests a more serious problem, such as significant anxiety or depression [51,52].

Statistical analysis

The questionnaire data were analyzed using SPSS Inc. version 26 (IBM Corp., Armonk, NY, USA). Descriptive statistics were employed to assess the patients' socio-demographic and clinical factors. Percentages and frequencies were used for categorical variables, while means and standard deviations were computed for continuous variables. To verify the normality of the distribution of results, Q-Q plots and the Shapiro-Wilk test were utilized. The variable of other chronic medications besides warfarin was not included in the analysis as it was identical across all participants. Chi-square tests were used to compare categorical data, and independent samples t-tests were applied for continuous data analysis. Additionally, Pearson's correlation coefficient was used to evaluate the correlations between socio-demographic, clinical factors, and scores from the HADS and WHOQOL-BREF domains. The relationships between the investigated variables and WHOQOL-BREF domains and HADS scores were examined using linear regression models. Furthermore, random forest classification graphs were created using the R package random Forest [53].

RESULTS

Out of 320 patients who completed the study's questionnaire, 18 were excluded due to having more than 20% missing data, resulting in a final count of 302 respondents for data analysis. The socio-demographic and clinical characteristics of these 302 participants are detailed in Table 1. Of these, a higher number of participants were male (n=172; 57%) compared to female (n=130; 43%). The age distribution showed that 222 participants (73.5%) were over forty years old, while 80 (26.5%) were

under forty. Regarding education, 160 participants (53%) had secondary education, and 142 (47%) had an advanced degree. A majority, 252 participants (83.4%), had a diagnosis of underlying cardiovascular diseases (CVD), and 134 (44.4%) had comorbidities other than CVD. In terms of warfarin treatment duration, 190 participants (62.9%) had been on warfarin for more than one year, while 112 (37.1%) for less than one year. Notably, all respondents were taking chronic medications in addition to warfarin.

The mean scores and standard deviations of the WHOQOL-BREF domains and HADS for the research participants are presented in Table 2. Among the WHOQOL-BREF's four domains, the social domain scored highest with a mean of 56.05 (±16.899), while the physical domain had the lowest mean score of 36.23 (±18.575). In terms of the HADS results, depression had a higher mean score (9±8.401) compared to anxiety (6.83±7.939). According to the HADS, 154 patients (51%) were classified as having depression with a score above 11, and 14 patients (4.6%) were considered borderline for depression. Additionally, 122 patients (40.4%) had anxiety with a score above 11, and 12 patients (4%) were borderline for anxiety.

The correlations between the four WHOQOL-BREF domains and HADS scores are detailed in Table 3. A statistically significant positive association was observed between the physical domain and the psychological, social, and environmental domains of WHOQOL-BREF ($r = 0.318$, 0.202, and 0.287, respectively), with p-values less than 0.05 indicating significance. Similarly, the psychological domain showed a significant positive association with the other three WHOQOL-BREF domains (physical, social, and environmental) ($r = 0.318$, 0.338, and 0.206, respectively), also with p-values less than 0.05. The strongest significant positive association was between the psychological and social domains of WHOQOL-BREF ($r = 0.338$), followed by the psychological and physical domains ($r = 0.318$). The physical and social domains exhibited the weakest, yet still significant, positive association ($r = 0.202$). Conversely, a strong negative correlation was found between anxiety and depression ($r = -0.93$), with a p-value less than 0.001 indicating a high level of statistical significance.

The bivariate relationships between WHOQOL-BREF domains, HADS scores, and socio-demographic and clinical factors are presented in supplement table 1. Participants under 40 years showed significantly higher HRQoL ratings in the social domain (60.78±18.866) compared to those aged 40 years and above (54.34±15.879), with a p-value of 0.039. Respondents with an advanced degree of education had significantly higher HRQoL ratings in the psychological and environmental domains (52.85±21.259 and 50.26±12.285, respectively) than those with secondary education (45.08±15.352 and 42.43±14.176, respectively), with p-values less than 0.05. Significant variations were observed in the scores of marital status versus the psychological and social domains, depression, and anxiety ($p = 0.00$ for all). Employment status showed considerable significant variations with the physical and social domains, and depression ($p = 0.00$, 0.00, and 0.026, respectively).

Patients with an underlying CVD diagnosis reported significantly lower HRQoL ratings in the social and environmental domains (54.21±16.148 and 45.13±13.425, respectively) compared to those without such a diagnosis (65.28±17.897 and 51.96±14.582, respectively). Patients with comorbidities other than CVD exhibited significantly lower HRQoL ratings in the physical and social domains (30.34±15.857 and 49.52±14.446, respectively) than those without such comorbidities (41.1±19.28 and 61.25±16.982, respectively), with a p-value of 0.00. Notably, there was no significant variation ($p < 0.05$) in anxiety scores across all investigated socio-demographic and clinical factors, except for marital status ($p= 0.049$). Additionally, no significant variations ($p < 0.05$) were found among the scores of gender, duration of warfarin therapy, smoking status, and history of cardiac surgery versus all WHOQOL-BREF domains and HADS scores.

The correlations between the various WHOQOL-BREF domains, HADS scores, and socio-demographic and clinical factors are detailed in Table 4. Our findings indicate that the four WHOQOL-BREF domains and HADS scores show statistically significant positive and negative associations with socio-demographic and clinical factors, with p-values less than 0.05 indicating significance. Specifically, depression scores were significantly associated with employment and marital status, with positive ($r = 0.181$) and negative ($r = -0.176$) correlations, respectively. Anxiety scores also showed a significant positive correlation with marital status ($r = 0.16$, $p = 0.049$). Furthermore, education level was significantly correlated with HRQoL ratings in the psychological

and environmental domains, showing negative (r = -0.207) and positive (r = 0.284) correlations, respectively. Additionally, employment status, age group, marital status, underlying CVD diagnosis, and comorbidities other than CVD demonstrated significant low to moderate negative correlations with various WHOQOL-BREF domains, with Pearson's correlation coefficients (r) ranging from -0.169 to -0.453.

Figure 1 , figure S1A and S1B depict the importance of various variables based on the mean decrease in accuracy in the random forest classification for WHOQOL-BREF domains and HADS. In the physical and social domains of WHOQOL-BREF, the most significant variable, as indicated by the highest mean decrease in accuracy, was employment status. This suggests that employment status has the most substantial impact in these domains. Additionally, the variables with the greatest impact in the psychological and environmental domains were the underlying CVD diagnosis and history of cardiac surgery, respectively. For HADS, the most significant variable affecting both depression and anxiety scores was the education level.

The results of the linear regression analysis for WHOQOL-BREF domains are presented in Table 5. The analysis revealed that an increase in education level from secondary to higher education was associated with a 0.248 increase in the environmental domain score (p = 0.002), keeping other variables constant. A change in employment status from full-time employment to unemployment was linked to decreases of 0.221 and 0.217 in the physical and social domain scores, respectively (p = 0.02 and 0.008). A change in marital status from married to single/separated was associated with decreases of 0.307 and 0.431 in the psychological and social domain scores, respectively (p = 0.00 for both). Furthermore, having no underlying CVD diagnosis was linked to a decrease of 0.21 in the environmental domain score (p = 0.015), and having comorbidities other than CVD was associated with decreases of 0.222 and 0.193 in the physical and social domain scores, respectively (p = 0.033 and 0.031). Age group, gender, duration of warfarin therapy, smoking status, and history of cardiac surgery were not found to be significant variables (p > 0.05) in any of the four WHOQOL-BREF domains.

The linear regression model for HADS is presented in Table 6. The analysis indicated that a change in marital status from married to single/separated was associated with a significant decrease in the depression score by 0.224 (p = 0.007) and a significant increase in the anxiety score by 0.204 (p = 0.016), when adjusted for other participant variables. Similarly, a change in the history of cardiac surgery from having no history to having one was linked to a significant increase in the depression score by 0.325 (p = 0.005) and a significant decrease in the anxiety score by 0.262 (p = 0.026), with other investigated variables held constant. Notably, education level, employment status, age group, gender, smoking status, duration of warfarin therapy, underlying CVD diagnosis, and comorbidities other than CVD were not significant variables (p > 0.05) in relation to the HADS scores.

Table 1: Socio-demographic, and clinical factors characteristics of the study participants

Variables		**Frequency (%) (n= 302)**
Gender	Male	172 (57)
	Female	130 (43)
Age group (25-70)	<40 Years	80 (26.5)
	≥ 40 Years	222 (73.5)
Education level	Secondary	160 (53)
	Higher secondary or above	142 (47)
Marital Status	Single/Separated	140 (46.4)
	Married	162 (53.6)
Employment	Employed full time	232 (76.8)
	Unemployed	70 (23.2)
Underlying cardiovascular disease diagnosis		252 (83.4)
Length of time on warfarin	<1 Year	112 (37.1)
	≥1 Year	190 (62.9)

Variables	Frequency (%) (n= 302)
Comorbidities other than cardiovascular diseases	134 (44.4)
Smoking	102 (33.8)
History of cardiac surgery	50 (16.6)
Other chronic medications besides warfarin	302 (100)

Table 2: Mean scores of WHOQOL-BREF domains and HADS in cardiac patients on warfarin therapy

Variable		Scores n = 302
WHOQOL-BREF Domains	Physical	36.23± 18.575 (4-75)
	Psychological	48.89± 18.83 (13-88)
	Social	56.05± 16.899 (25-83)
	Environmental	46.26± 13.809 (13-69)
HADS	Depression	9± 8.401 (0-21)
	Anxiety	6.83± 7.939 (0-21)

WHOQOL-BREF: World Health Organization Quality of Life Assessment Brief Form; HADS: Hospital Anxiety and Depression Scale

Table 3 : Correlation coefficients in domains of WHOQOL-BREF and HADS in cardiac patients on warfarin therapy.

		WHOQOL-BREF				HADS
		Physical domain	Psychological domain	Social domain	Environmental domain	Depression
Psychological domain	R	0.318				
	P	0.000				
Social domain	R	0.202	0.338			
	P	0.013	0.000			
Environmental domain	R	0.287	0.206	0.103		
	P	0.000	0.011	0.207		
Depression	R	0.093	0.077	0.036	0.019	
	P	0.250	0.347	0.665	0.816	
Anxiety	R	-0.065	-0.066	-0.027	0.000	-0.930
	P	0.431	0.419	0.746	0.999	0.000

WHOQOL-BREF: World Health Organization Quality of Life Assessment Brief Form; HADS: Hospital Anxiety and Depression Scale; R: correlation coefficient; P: P value

Table 4: Correlations between socio-demographic, and clinical factors variables and different domains of WHOQOL-BREF and HADS.

Variables		WHOQOL-BREF				HADS	
		Physical domain	Psychological domain	Social domain	Environmental domain	Depression	Anxiety
Education level	r	0.149	-0.207*	-0.015	0.284	0.07	0.043
	p-value	0.068	0.011	0.851	0.000	0.395	0.599
Employment	r	-0.314	-0.133	-0.368	-0.005	0.181	-0.143
	p-value	0.000	0.103	0.000	0.953	0.026	0.079
Age group	r	-0.079	0.021	-0.169	-0.069	-0.057	-0.064
	p-value	0.332	0.796	0.039	0.398	0.491	0.437
Gender	r	-0.071	-0.076	0.06	-0.053	0.027	-0.013

	***p*-value**	0.378	0.355	0.467	0.516	0.743	0.873
Marital status	**r**	-0.047	-0.345	-0.453	-0.077	-0.176	0.16
	***p*-value**	0.565	0.000	0.000	0.349	0.031	0.049
History of cardiac surgery	**r**	0.022	-0.081	0.048	-0.087	0.092	-0.06
	***p*-value**	0.791	0.321	0.556	0.286	0.259	0.467
Comorbidities other than CVD	**r**	-0.289	-0.132	-0.346	-0.062	.104	-0.06
	***p*-value**	0.000	0.105	0.000	0.451	0.205	0.461
Smoking	**r**	-0.05	-0.008	0.004	0.077	-0.028	0.02
	***p*-value**	0.545	0.918	0.963	0.349	0.734	0.805
Duration of warfarin	**r**	0.054	0.011	0.137	-0.055	-0.001	0.051
	***p*-value**	0.511	0.896	0.093	0.505	0.988	0.536
Underlying CVD diagnosis	**r**	-0.089	-0.147	-0.244	-0.184	0.12	-0.14
	***p*-value**	0.275	0.072	0.003	0.023	0.143	0.087

CVD: Cardiovascular diseases; WHOQOL-BREF: World Health Organization Quality of Life Assessment Brief Form; HADS: Hospital Anxiety and Depression Scale; R: correlation coefficient; P: P value

Table 5: Linear regression model of WHOQOL-BREF

Variable	WHOQOL-BREF Domain											
	Physical			Psychological			Social			Environmental		
	(β)	*p*-value	VIF	(β)	*p*-value	VIF	(β)	*p*-value	VIF	(β)	*p*-value	VIF
Education level (Secondary vs higher secondary or above)	0.139	0.086	1.067	0.146	0.065	1.067	-0.061	0.373	1.067	0.248	0.002	1.067
Employment (Employed full-time vs unemployed)	-0.221	0.02*	1.46	-0.064	0.486	1.46	-0.217	0.008	1.46	0.045	0.63	1.46
Age group (< 40 years vs ≥ 40 years)	-0.023	0.855	2.574	-0.019	0.875	2.574	0.027	0.801	2.574	0.153	0.224	2.574
Gender (Female vs Male)	-0.073	0.396	1.216	-0.087	0.301	1.216	0.038	0.6	1.216	-0.065	0.454	1.216
Marital status (Married vs Single/separated)	0.01	0.898	1.075	-0.307	0.000	1.075	-0.431	0.000	1.075	-0.049	0.544	1.075
Smoking (No/quit vs Yes)	-0.064	0.471	1.32	0.032	0.719	1.32	0.00	0.995	1.32	0.142	0.114	1.32
Duration on warfarin (< 1 Year vs ≥1 Year)	-0.017	0.826	1.041	0.061	0.437	1.041	-0.074	0.28	1.041	0.098	0.217	1.041

Underlying CVD diagnosis (No vs Yes)	0.023	0.787	1.19	-0.109	0.191	1.19	-0.147	0.044	1.19	-0.21	0.015	1.19
History of cardiac surgery (No vs Yes)	-0.109	0.333	2.103	-0.098	0.377	2.103	-0.045	0.644	2.103	-0.003	0.976	2.103
Comorbidities other than CVD (None vs Present)	-0.222	0.033	1.776	-0.1	0.326	1.776	-0.193	0.031	1.776	-0.109	0.297	1.776

CVD: Cardiovascular diseases; WHOQOL-BREF: World Health Organization Quality of Life Assessment Brief Form

Model fitness for different domain: **Physical** = [ANOVA (F = 2.676, p = 0.005); R^2 = 0.16 and adjusted R^2 = 0.1]; **Psychological** = [ANOVA (F = 3.269, p = 0.001); R^2 = 0.189 and adjusted R^2 = 0.131]; **Social** [ANOVA (F = 8.676, p = 0.00); R^2 = 0.383 and adjusted R^2 = 0.339], and **Environmental** [ANOVA (F = 2.472, p = 0.009); R^2 = 0.15 and adjusted R^2 = 0.089].

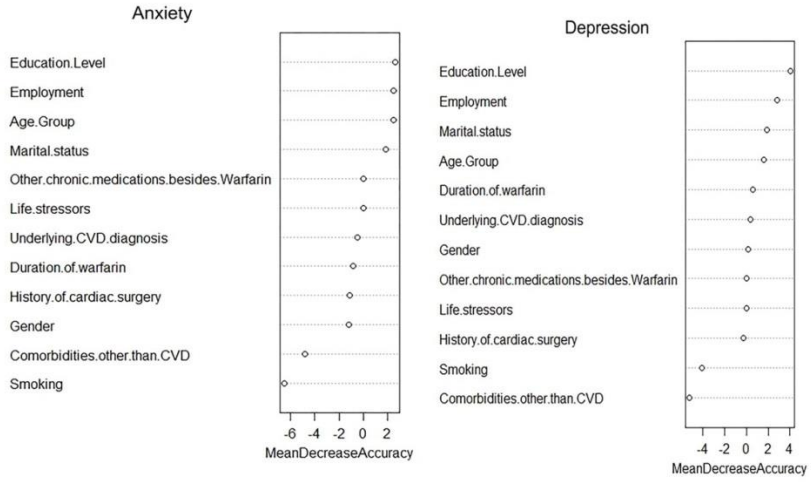
Table 6 : Linear regression model of HADS.

Variable	Depression			Anxiety		
	(β)	*p*-value	VIF	(β)	*p*-value	VIF
Education level (Secondary vs higher secondary or above)	0.068	0.405	1.067	-0.04	0.627	1.067
Employment (Employed full-time vs unemployed)	0.186	0.052	1.46	-0.156	0.109	1.46
Age group (< 40 years vs ≥ 40 years)	0.182	0.152	2.574	-0.178	0.169	2.574
Gender (Female vs Male)	0.054	0.534	1.216	-0.026	0.771	1.216
Marital status (Married vs Single/separated)	-0.224	0.007**	1.075	0.204	0.016*	1.075
Smoking (No/quit vs Yes)	0.018	0.839	1.32	-0.024	0.795	1.32
Duration on warfarin (< 1 Year vs ≥1 Year)	0.002	0.979	1.041	-0.048	0.561	1.041
Underlying CVD diagnosis (No vs Yes)	0.091	0.29	1.19	-0.116	0.185	1.19
History of cardiac surgery (No vs Yes)	0.325	0.005**	2.103	-0.262	0.026*	2.103
Comorbidities other than CVD (None vs Present)	0.02	0.849	1.776	0.041	0.702	1.776

CVD: cardiovascular diseases

Model fitness for **Depression** = [ANOVA (F = 2.13, p = 0.026); R^2 = 0.132 and adjusted R^2 = 0.07]; and **Anxiety** [ANOVA (F = 1.552, p = 0.127); R^2 = 0.1, and adjusted R^2 = 0.035].

Figure 1: Variables importance in terms of mean decrease in accuracy in random forest classification for anxiety and depression in Hospital Anxiety and Depression Scale.



DISCUSSION

Recently, HRQoL has emerged as a critical concept and a measure for evaluating an individual's overall health, the effectiveness of their treatments, and overall disease control [54]. Additionally, PD can significantly influence treatment effectiveness, particularly if it affects treatment adherence or induces further physiological stress reactions [55–57]. Given the severity of chronic illnesses, primary healthcare practitioners should focus on patients' HRQoL and mental status. Researchers worldwide have investigated PD and different aspects of HRQoL in individuals on OAC and warfarin treatment [9,11 ,23,36,40,41,43,52]. However, to our knowledge, no studies have assessed HRQoL and PD among warfarin patients in Egypt using WHOQOL-BREF and HADS. Therefore, this study aimed to evaluate HRQoL and PD in Egyptian warfarin patients using these tools, in addition to assessing correlations with various socio-demographic and clinical factors.

Patients on warfarin treatment often need to make significant adjustments to their daily activities and lifestyle, especially in managing bleeding complications [29]. Warfarin patients' diets are typically affected, leading to changes in eating habits, medication adherence, physical activity, alcohol consumption, and increased stress. These precautions often reduce patients' HRQoL and increase the risk of developing PD [23, 30]. Previous studies indicate that psychological effects, disease burden, medication availability, and the incidence of bleeding events are major concerns affecting warfarin patients' HRQoL [9, 33,36 ,43]. An earlier study found that HRQoL in individuals using OAC treatment was significantly correlated with clinical and socio-demographic characteristics [33]. Factors like treatment duration, INR levels, age, comorbidities, drug interactions, and bleeding severity directly affected HRQoL [36, 58].

In this study, the social domain of WHOQOL-BREF had the highest mean score (56.05±16.899), indicating satisfaction with social aspects like religion, support from friends, and personal relationships [11]. In contrast, the physical domain had the lowest mean score (36.23±18.575), suggesting limitations in daily activities, reduced work capacity, fatigue, medication reliance, and mobility issues, aligning with findings from Malaysia [9], and Pakistan [11]. Additionally, the study noted appropriate mean scores for satisfaction levels in the psychological and environmental domains, recorded as 48.89±18.83 and 46.26±13.809, respectively. These scores reflect satisfaction derived from various factors. In the psychological domain, this includes healthcare facilities, personal convictions, religious applicability, a high degree of confidence, and predominantly positive emotions. In the environmental domain, factors contributing to satisfaction include good physical appearance, active religious participation, opportunities for learning, high-quality healthcare, adequate security and safety, and regular access to affordable and

practical transportation. [11,36]. In the current study, we observed statistically significant positive associations within the WHOQOL-BREF instrument. Specifically, there was a notable association between the physical domain and the other three domains, as well as between the psychological domain and the remaining three domains. This finding is in line with previous studies, which have also reported statistically significant positive associations across all four domains of the WHOQOL-BREF in patients taking warfarin [9,11].

Regarding HADS results, depression had a higher mean score (9± 8.401) than anxiety (6.83± 7.939). This contrasts with the findings of a previous study conducted on oral anticoagulant (OAC) patients in Turkey, where anxiety had a higher HADS mean score (5.96±2.10) compared to depression (4.44±1.73) [52]. Additionally, our results were higher than those of previous work carried out on CVD patients in Malaysia, where HADS mean scores for anxiety and depression were 4.25±4.271, and 4.71±4.493, respectively. The present study HADS findings showed that, 154 (51%) and 122 (40.4%) patients had depression and anxiety, respectively. These findings were partially similar to those of earlier works conducted in Turkey [41] and Uganda [23], where 48% and 32% of the warfarin patients suffered from depression [41], and PD [23], respectively. These variations could be linked to the various study populations, and different tools utilized for measuring PD.

In the initial trial, the majority of warfarin patients attending the study locations were over 40 years old, with few exceptions. Consequently, we set 40 years as the age cutoff, dividing participants into two primary age groups: those under 40 years and those 40 years or older. Our findings revealed that younger participants (<40 years) generally had a higher HRQoL than their older counterparts (≥40 years) in the social, physical, and psychological domains. Interestingly, in the environmental domain, the older patients demonstrated better HRQoL compared to the younger ones. These observations are consistent with previous studies, which have also reported higher HRQoL in younger patients compared to elderly participants [32,59]. These outcomes may be attributed to the tendency of younger individuals to perceive their illnesses as a natural, less daunting aspect of life, potentially viewing them as temporary rather than permanent challenges. Consequently, this perspective could lead to a more contented and self-assured approach to life, particularly in the social, physical, and psychological domains [32,60]. Contrary to our findings, previous studies have indicated that older warfarin patients generally experienced higher HRQoL than younger ones in the environmental, social, and psychological domains. However, these studies also noted that in the physical domain, younger participants exhibited higher HRQoL compared to their elderly counterparts [9,11]. These results lend support to the theory that older individuals, even when on warfarin therapy, may have a better understanding and acceptance of the social, psychological, and environmental aspects of life. This acceptance of their illnesses as a challenge could lead to greater life satisfaction [36].

Our investigation revealed that participants with advanced educational degrees exhibited statistically significantly higher HRQoL scores in the psychological and environmental domains. Although not statistically significant, these participants also showed better HRQoL scores in the physical and social domains compared to those with secondary education. This difference could be attributed to factors often linked with higher education levels, such as excellent treatment adherence and regulation, enhanced understanding of dosage, and greater self-interest [61]. In line with our findings, patients with higher levels of education exhibited significantly superior HRQoL scores compared to patients with only primary education. This difference was observed not only in overall health satisfaction levels but also across all four domains of the WHOQOL-BREF [32,62]. On the contrary, two previous studies [37, 40] found no significant variation in HRQoL scores when comparing different levels of education [54,63].

Herein, married warfarin patients demonstrated significantly better HRQoL across the psychological, social, physical, and environmental domains compared to single or separated patients. These findings partially align with those of a previous study, where married individuals on warfarin therapy showed significantly better HRQoL in overall health satisfaction and the physical domain. However, that study did not record significant differences in HRQoL based on marital status in the other WHOQOL-BREF domains [9]. These outcomes could be linked to the fact that marriage is frequently associated with receiving support in some cultures. Additionally, earlier studies stated that marital status did not have any significant impact on HRQoL [54,59]. On the contrary, an earlier study conducted in Pakistan

indicated that married warfarin patients had significantly higher HRQoL in the physical domain of WHOQOL-BREF [11], which may be attributed to Pakistan's strong family ties, which provide unmarried patients with sufficient material and emotional support from their parents and relatives.

In our study, HADS findings indicated a significant correlation between marital status and scores for anxiety and depression. Specifically, married warfarin patients exhibited higher depression scores but lower anxiety scores compared to single or separated patients. These findings are in complete agreement with an earlier study conducted in Iran, which also reported that married patients experienced significantly higher depression and lower anxiety prevalence compared to single patients. [64]. Similarly, patients with chronic diseases often face marital disturbances, as long-term illness can create stress due to changes in responsibilities within the marriage [65]. On the contrary, a previous study showed that unmarried CVD patients had higher total HADS scores than married patients [66]. These variations may be attributed to differences in individuals' socioeconomic backgrounds, ethnicities, religions, and beliefs. [67].

In the current study, warfarin patients who were employed full-time exhibited statistically significantly higher HRQoL scores in the physical and social domains. Additionally, these employed patients showed comparatively better HRQoL scores in the psychological and environmental domains of the WHOQOL-BREF than their unemployed counterparts. Corroborating our results, previous studies have also reported that employed patients had better HRQoL scores across all four domains of the WHOQOL-BREF compared to unemployed patients [54,68]. These findings might be attributed to employed patients having better access to high-quality healthcare facilities, higher income, and opportunities to stay informed about the latest research on warfarin. Notably, higher income appears to be a particularly strong predictor of improved HRQoL [54]. Likewise, better income was substantially correlated with higher psychological and environmental domain scores of WHOQOL-BREF [3,68]. These results are not surprising, as patients with higher incomes are typically better positioned to select superior treatment options that align more closely with their healthcare needs, compared to those who are unemployed [32,36].

Additionally, our HADS results indicated that unemployed patients had statistically significantly higher depression scores compared to employed patients. Similarly, previous studies have reported that unemployed patients experience higher rates of developing depression than employed patients [23,69,70]. The relationship between unemployment and PD could be attributed to challenges in obtaining medical care, reflecting the financial stress often experienced by many unemployed patients [71]. The limited healthcare facilities available to CVD patients in developing countries exacerbate the difficulty of accessing medical care. Consequently, patients often face the burden of paying out of pocket for their medical treatments [72,73].

In our study, warfarin patients without any comorbidities exhibited statistically significantly higher HRQoL scores in the physical and social domains. Additionally, they showed comparable, non-statistically significant, better scores in the psychological and environmental domains compared to patients with various comorbidities, excluding CVD. These results are consistent with those of a previous study conducted on oral OAC patients in the Netherlands. [74]. Herein, the duration of warfarin treatment had no significant impact on the four domains of WHOQOL-BREF. This contrasts with the findings of a previous study, which reported that the duration of oral anticoagulant (OAC) treatment utilization had a statistically significant impact on Health-Related Quality of Life (HRQoL) scores in the WHOQOL-BREF. [74]. Lastly, we assessed HRQoL among warfarin patients using the WHOQOL-BREF, and our linear regression model analysis identified education levels, employment status, marital status, underlying CVD diagnosis, and comorbidities other than CVD as significant predictors (after adjusting for confounders) across various domains of the WHOQOL-BREF. Similarly, a previous study conducted in Pakistan employed the WHOQOL-BREF to measure HRQoL among warfarin patients. Their linear regression model also confirmed that variables such as comorbidities other than CVD, education level, and marital status were significant predictors in various domains of the WHOQOL-BREF [11].

CONCLUSIONS

Our study makes a significant contribution to understanding the impact of warfarin on HRQoL and PD among patients in a sector of Egyptian population, providing important insights for the first

time. Our results indicate that while warfarin patients in Egypt generally have good HRQoL across all WHOQOL-BREF domains, there are indications of moderate to low HRQoL in some areas. Additionally, there is a notable proportion of patients, 51% with depression and 40.4% with anxiety, experience psychological distress. This distress and the lower HRQoL scores could stem from factors such as patients' reluctance to adhere to their treatment regimen, high direct and indirect healthcare costs, inadequate treatment plans, the financial burden of living expenses, and the inability to work.

The findings of this study are crucial for healthcare providers, including doctors, pharmacists, and healthcare workers, as well as patients' families. They offer a deeper understanding of the range of environmental, social, psychological, and physical challenges that patients often face while undergoing warfarin therapy. Additionally, there is a clear need for tertiary healthcare centers to implement routine PD screening for warfarin patients and to provide them with focused attention. It is essential to support warfarin patients adequately to reduce the likelihood of PD, improving their overall quality of life and treatment outcomes.

Limitations

The study faced several limitations, one of which was its focus on a limited number of participants from a single geographic location in Zagazig, Egypt. This specificity may affect the generalizability of the results to warfarin patients in different regions or countries, especially considering diverse cultural and healthcare backgrounds. Additionally, being a cross-sectional study, it was only able to capture data at a single point in time, which limits our ability to infer causality and directionality in the relationships between warfarin use, HRQoL, and PD. The reliance on self-reported questionnaires, WHOQOL-BREF and HADS, could also introduce response bias, as patients might underreport or overreport their symptoms or quality of life due to various personal factors. The exclusion criteria, such as omitting pregnant women and patients with pre-existing mental disorders, might limit the applicability of the findings to these specific populations. Furthermore, the absence of a control group, such as patients with CVD not on warfarin treatment, restricts the ability to compare and contrast the specific impacts of warfarin treatment. The study also had to contend with potential confounding factors, including lifestyle choices and the severity of comorbid conditions, which might not have been fully accounted for. There's also a possibility of selection bias due to the voluntary nature of participation and the specific setting of the cardiac care unit in Zagazig University Hospital, possibly enrolling patients with more pronounced symptoms or concerns. Lastly, the study's focus was primarily on depression and anxiety, potentially overlooking other relevant psychological aspects or disorders that could be impacted by warfarin treatment. To enhance our understanding of the impacts of warfarin on HRQoL and PD, future research should aim to address these limitations by incorporating larger and more diverse populations, employing longitudinal designs, utilizing objective clinical measures, broadening the scope of psychological assessments, and including comparison groups.

Abbreviations

QoL: Quality of Life
HRQoL: Health-Related Quality of Life
CVD: Cardiovascular diseases
PD: Psychological distress
OAC: Oral anticoagulant
WHOQOL-BREF: World Health Organization Quality of Life Assessment Brief Form
HADS: Hospital Anxiety and Depression Scale

Declarations

Ethics approval and consent to participate

The study received approval from the Institutional Review Board (IRB) of Zagazig University Hospital, under approval number ZU-IRB#11270-5/11-2023. Informed oral consent was obtained from all participants at the beginning of the study. This process involved clearly explaining all the steps of the study and affirming the participants' right to withdraw at any time.

Availability of data and materials

Data are available from the corresponding author upon reasonable request.

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Authors' contributions

All authors made substantial contributions to the study and have given their approval for the final version of the manuscript.

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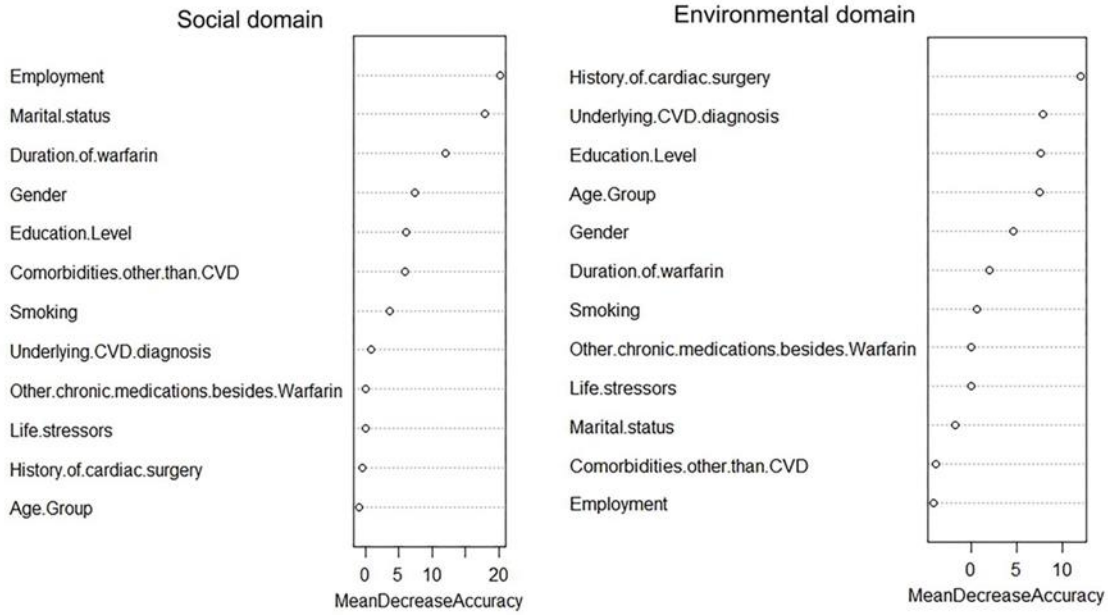
Table S1: subgroup analysis of WHOQOL-BREF domains and HADS mean scores based on sociodemographic, and clinical factors of the study population.

Variable	WHOQOL-BREF domain				HADS	
	Physical	Psychological	Social	Environmental	Depression	Anxiety
Gender						
Male	35.16±19.134	47.65±16.566	56.92±16.38	45.63±11.878	9.21±8.206	6.74±8.221
Female	37.86±17.839	50.52±21.489	54.89±17.623	47.11±16.071	8.75±8.709	6.95±7.613
***p*-value**	0.374	0.355	0.472	0.516	0.745	0.872
Age group (25-70)						
<40 Years	38.78±21.451	49.55±17.666	60.78±18.866	44.68±12.263	8.23±8.648	7.68±8.166
≥ 40 Years	35.44±17.447	48.65±19.304	54.34±15.879	46.84±14.334	9.3±8.331	6.53±7.871
***p*-value**	0.332	0.788	0.039*	0.364	0.5	0.446
Education level						
Secondary	33.62±17.514	45.08±15.352	55.79±16.55	42.43±14.176	8.44±8.287	7.17±7.979
Higher secondary or above	39.14±19.337	52.85±21.259	56.31±17.363	50.26±12.285	9.61±8.533	6.49±7.937
***p*-value**	0.069	0.011	0.851	0.000	0.396	0.599
Marital Status						
Single/Separated	35.39±18.442	41.93±16.726	47.84±14.94	45.13±14.608	7.43±8.455	8.2±7.853
Married	37.14±18.765	54.9±18.562	63.14±15.269	47.25±13.092	10.38±8.159	5.65±7.871
***p*-value**	0.565	0.000	0.000	0.353	0.031	0.049
Employment						
Employed full time	39.52±17.773	50.26±18.208	59.45±16.728	46.3±13.271	8.18±8.281	7.46±8.047
Unemployed	25.74±17.429	44.34±20.379	44.77±11.958	46.14±15.672	11.77±8.321	4.77±7.305
***p*-value**	0.000	0.129	0.000	0.957	0.029	0.079
Underlying CVD diagnosis						
Yes	35.59±17.854	47.66±18.399	54.21±16.148	45.13±13.425	9.46±8.32	6.34±7.846
No	40.04±21.885	55.08±20.127	65.28±17.897	51.96±14.582	6.76±8.613	9.32±8.102

***p*-value**	0.275	0.097	0.007	0.038	0.159	0.101
Length of time on warfarin						
<1 Year	37.63±19.277	48.63±19.254	59.05±18.085	45.29±14.581	9±8.774	7.36±8.236
≥1 Year	35.56±18.208	49.04±18.677	54.27±15.992	46.84±13.379	9.02±8.22	6.53±7.787
***p*-value**	0.517	0.897	0.105	0.515	0.988	0.543
Comorbidities other than CVD						
Present	30.34±15.857	46.1±19.324	49.52±14.446	45.31±14.348	9.99±8.497	6.3±7.945
None	41.1±19.28	51.11±18.237	61.25±16.982	47.02±13.402	8.24±8.292	7.26±7.956
***p*-value**	0.000	0.107	0.000	0.455	0.207	0.461
Smoking						
Yes	35.04±20.711	48.67±17.409	56.14±18.327	47.75±10.753	8.69±8.279	7.06±8.179
No/quit	36.98±17.46	49±19.599	56±16.218	45.51±15.127	9.18±8.499	6.72±7.854
***p*-value**	0.568	0.915	0.964	0.297	0.732	0.808
History of cardiac surgery						
Yes	37.25±20.341	45.38±16.111	57.92±17.673	43.5±13.878	10.79±8.807	5.75±7.691
No	36.51±18.304	49.55±19.286	55.69±16.797	46.79±13.788	8.68±8.315	7.04±7.998
***p*-value**	0.807	0.267	0.573	0.295	0.285	0.460

CVD: cardiovascular diseases; WHOQOL-BREF: World Health Organization Quality of Life Assessment Brief Form; HADS: Hospital Anxiety and Depression scale

Supplement Figure S1: Variables importance in terms of mean decrease in accuracy in random forest classification for World Health Organization Quality of Life Assessment Brief Form domains; S1A: physical and psychological domains and S1B: social and environmental domains



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