Determinants of health-related quality of life among warfarin patients in Pakistan

Muhammad Shahid Iqbal1,*, Fares M. S. Muthanna2, Yaman Walid Kassab3, Mohamed Azmi Hassali4, Fahad I. Al-Saikhan1, Muhammad Zahid Iqbal5, Abdul Haseeb6, Muhammad Ahmed7, Salah-Ud-Din Khan8, Atta Abbas Naqvi9, Md. Ashraful Islam9, Majid Ali6

1 Department of Clinical Pharmacy, College of Pharmacy, Prince Sattam bin Abdulaziz University, Al-kharj, Saudi Arabia, 2 Faculty of Pharmacy, University Teknologi MARA (UiTM), Selangor Darul Ehsan, Malaysia, 3 Department of Hospital and Clinical Pharmacy, Faculty of Pharmacy, Cyberjaya University College of Medical Sciences, Selangor, Malaysia, 4 Discipline of Social and Administrative Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia, 5 Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, AIMST University, Kedah Darul Aman, Malaysia, 6 Department of Clinical Pharmacy, College of Pharmacy, Umm Al-Qura University, Al-Abdia Campus, Makkah, Saudi Arabia, 7 Department of Pharmacology and Toxicology, College of Pharmacy, Umm Al-Qura University, Al-Abdia Campus, Makkah, Saudi Arabia, 8 Department of Biochemistry, College of Medicine, Al-Imam Mohammad Ibn Saud University, Riyadh, Saudi Arabia, 9 Department of Pharmacy Practice, College of Clinical Pharmacy, Imam Abdul Rehman Bin Faisal University, Dammam, Saudi Arabia

* drmmsiqbal@gmail.com

Abstract

Introduction

The effect of anticoagulation control on overall Health-Related Quality of Life (HRQoL) in patients taking warfarin in Pakistan has not been explored yet. Therefore, this study aimed to evaluate HRQoL among warfarin patients in Pakistan.

Methods

This cross-sectional study was conducted among patients on warfarin in Pakistan. By purposive sampling, data were collected using demographic data collection form and the World Health Organization Quality of Life: Brief Version (WHOQOL-BREF). The WHOQOL-BREF is comprised of four domains; physical, psychological, social relationships, and environment. Descriptive and inferential statistical analysis was done using SPSS version 22.

Results

Out of 295 warfarin patients, more females than males (<0.001) were observed (n = 184, 62.4%, and n = 111, 37.6% respectively). One hundred and eighteen (40.0%) patients were less than 30-years of age, whereas one hundred and seventy-seven (60.0%) patients were above 30-years of age. Mean scores for the physical (62.44±15.36), psychological (67.84±15.54), social (64.27±26.28) and environment domains (63.45±17.66) were observed.
Conclusion
Patients had overall lower to moderate but satisfactory HRQoL scores in all four domains. Age, gender, employment status, education level, the indication of use and duration of warfarin therapy was associated with one or more domains of HRQoL among warfarin patients. The findings of this study would serve as a primary database for future studies. This study highlights how non-clinical factors could impact HRQoL in studied patients.

Introduction
"WHO defines Quality of Life as an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns’’ [1]. Health-Related Quality of Life (HRQoL) is an important measure that enables healthcare professionals (HCPs) to understand patients’ perceptions of illnesses [1–3]. HRQoL is an individual’s perceived Quality of Life (QoL), demonstrating satisfaction in areas of life that are affected by patients’ general health states [4,5]. Furthermore, HRQoL measurement helps in overseeing interventions and making numerous healthcare strategies to amplify the overall health status of a populace [1,2,6].

Warfarin therapy is often used in patients with various cardiovascular diseases (CVDs) like peripheral vascular disease, stroke, atrial fibrillation, and coronary heart disease [7–9]. Studies reported that these CVDs were among the leading causes of premature deaths worldwide [10–14]. These CVDs are anticipated to affect all aspects of patients’ HRQoL [1,2,15]. Pakistan is also facing serious healthcare issues in CVDs. Various studies show that 1 in 5 of middle-aged adults in Pakistan may develop coronary artery disease, whereas overall CVDs account for approx. 27% of the total deaths [16–18].

In recent decades, the use of oral anticoagulant (OAC) therapy has increased due to its greater efficacy and lesser side effects [4]. Warfarin and heparin have a narrow therapeutic index but high inter and intrapatient variability. Like other anticoagulants, warfarin requires careful and regular laboratory monitoring to help control bleeding complications and achieve superior therapeutic outcomes [19]. In some life-threatening situations, adverse drug reactions caused by warfarin may require immediate hospitalization that if not handled appropriately may lead to morbidity and mortality [20,21]. These prolonged hospital stays expensive therapies and subsequent fear of death negatively affect patients’ daily life activities causing decreased health status [22,23]. Furthermore, warfarin therapy often causes loss of self-esteem, depression, anxiety, failure to perform at the workplace, and emotional problems result in deprived and poor HRQoL [1,2,24].

Similarly, sociodemographic and socioeconomic changes, varied patient care plannings and treatment outcomes also affect HRQoL of patients on warfarin [25–27]. To date, the effect of anticoagulation control on overall HRQoL in patients taking warfarin in Pakistan has not been explored. This study was specially designed to cater to this scarcity and the need for published literature about overall HRQoL of warfarin patients in Pakistan. This study also determined the overall HRQoL of warfarin patients and its relationship with some sociodemographic variables like gender, age, marital and working status, educational level, indication and duration of warfarin use. The study is novel in the aspect that this study first-time documented real-time data of HRQoL among patients on warfarin in Pakistan. Furthermore, as this study is first of its kind and disseminating a primary source of information of
HRQoL among warfarin patients in Pakistan so it will serve as the basis for further investigations in the relevant field.

**Material and methods**

**Study design and setting**

A descriptive and cross-sectional study was conducted among warfarin patients in Pakistan. Though to date, there is no ethical approval requirement for non-clinical and observational studies in Pakistan [28] yet this study was performed following the international clinical guidelines and the principles of the Helsinki Declaration, version 2013 [29]. This study was approved by the Institutional Review Board (IRB) of Clifton Hospital, Karachi Pakistan. All aspects of the study protocol including information on an individual’s background were strictly confidential and used for the research only. Patients were also assured of the confidentiality of their personal information and properly guided about their right to withdraw from the study at any time. All of the participants were ≥18 years and on warfarin from at least 2 months due to any clinical indication and attended the clinic for follow-ups. The period of 2 months is the average time needed to adjust the therapeutic dose of the warfarin [30]. A written consent according to the declaration of Helsinki 1964 and its amendments on comparable ethical standards was taken from all the participants.

Patients who gave written consent and familiar with Urdu (National language of Pakistan) were included in the study. For exclusion criteria, participants who did not give written consent, those from other countries who could not read and understand Urdu, and aged below 18 years were excluded from the study. Pregnant women or those planning to become pregnant were also excluded from the study because, in the first trimester of pregnancy, warfarin therapy can cause fetal anomalies, teratogenicity and fetal miscarriage. In the second trimester, it may lead to premature delivery and low birth weight fetus. In the third trimester, warfarin easily crosses the placenta which may result in fatal maternal bleeding and intracranial hemorrhages [31–33]. The patients having bleeding risks and have uncontrolled INR values i.e. not in the recommended therapeutic range were also excluded.

**Sampling strategy**

Purposive sampling was conducted in the hospital and patients undergoing warfarin therapy were identified from the pharmacy’s record. After identification, patients were approached and briefed about the study. Written informed consent was provided to them to indicate their willingness to participate in the study. Those who participated in the study were provided with the questionnaires and their data was noted.

**Sample size calculation**

The post-hoc power calculation was conducted using the following formula to determine an adequate sample size.

\[
n = \frac{(Z_{1-\beta})^2 \cdot p(1-p)}{d^2}
\]

Where, \(n\) = required sample size; \(Z_{1-\beta}\) = Z value at power 1-\(\beta\) (at power 95% this value is 1.64); \(p\) = referred prevalence, \(d\) = margin of error (ideal value is 0.05). Considering 95% power of the test, 5% marginal error and 74% prevalence of warfarin therapy patients within this patient population, in Pakistan [34], the sample size according to the formula was found to be 206.99. The sample size was adjusted for unintentional error/missing rate [35] using the following
Where, \( n = 206.99 \) and \( d = 20\% \). The formula provided a required sample of 258.73 patients. This was the minimum number we obtained from the calculation and we managed to collect 295 complete responses (samples) in our current study.

HRQoL was assessed using the WHOQOL-BREF research tool. This 26 item HRQoL self-administered tool is cross-culturally sensitive which has shown good to excellent psychometric properties [3]. In the WHOQOL-BREF tool’s 26 questions, 2 questions assess the perception of QoL and overall health satisfaction status whereas the other 24 questions comprise the physical, psychological, social and environmental domains. The WHOQOL-BREF tool’s 26 questions explain how respondents attribute to each aspect of their life and how problematic or satisfactory they perceive them to be for their total HRQoL [3]. Demographic characteristics measured were gender, age, marital status, educational level, employment status, comorbidities other than CVDs (diabetes, respiratory diseases, musculoskeletal disorders, pulmonary disorders, and gastrointestinal diseases) indication, and duration of warfarin use. The score of each question for each domain was used to obtain as summarized domain score and finally, all the scores were transformed linearly according to the provided WHOQOL-BREF questionnaire guidelines (0–100 scale) [3]. Higher scores indicate higher levels of HRQoL and vice versa. The Urdu version of the WHOQOL-BREF questionnaire was kindly provided by the WHO officials. A panel of experts reconfirmed the content and face validity of the research instrument in the present study. This study was novel among its types as there was no study evident so far which measured HRQoL among warfarin patients using WHOQOL-BREF in Pakistan.

**Statistical analysis**

Descriptive statistics were used to evaluate the demographic and disease characteristics of the patients. Percentages and frequencies were used for the categorical variables, while means and standard deviations were calculated for the continuous variables. The reliability of the WHOQOL-BREF tool was determined using Cronbach’s alpha. The Cronbach’s alpha determines how precisely a set of items, variables or attributes measures a single, one-dimensional latent aspect of participants involved in a study. It is usually used to determine internal consistency (all the items measure the same concept or construct) or inter-item correlations, reliability and statistical power of the items of a research tool for accurate measuring potential research outcomes [36]. To confirm the normality distribution of the data Shapiro–Wilk test and Q–Q plots were used. Independent samples t-test and Spearman’s correlation coefficient was used to evaluate correlations (agreements) between demographics and domains, and to know the differences in overall HRQoL and its domains. By using the linear regression model, predictors were identified and confounders were addressed in the regression model. Data from the questionnaire were analyzed using Statistical Package for the Social Sciences (SPSS) version 22.0.

**Results**

In total, 322 respondents filled out the questionnaire in this study. Twenty-seven questionnaires were excluded from the study as they had more than 20% missing data. The remaining 295 respondents were considered for data analysis. The Cronbach’s alpha (reliability) of the WHOQOL-BREF was 0.898. The demographic characteristics of the study participants are presented in Table 1. There was a total of 295 participants with more females than males (n = 184, 62.4%, and n = 111, 37.6%, respectively). One hundred and eighteen (40.0%) were less than 30-years, whereas one hundred and seventy-seven (60.0%) were above 30-years. Ten
(3.4%) had a primary level of education and 285 (96.6%) had a higher level of education. One hundred and three (34.9%) had comorbidities other than CVDs and one hundred and ninety-two had no comorbidity.

Table 2 depicts the individual responses against each item of the questionnaire. Cronbach’s alpha for the whole WHOQOL-BREF was 0.807. The Cronbach’s alpha for four domains i.e. physical, psychological, social and environment were 0.765, 0.700, 0.812 and 0.780 respectively.

Table 3 presents the mean HRQoL scores for all the four domains of WHOQOL-BREF among the study respondents. The mean score for the physical health domain was 62.44 ±15.36. Mean scores for the psychological domain, social relationships domain, and environment domain were 67.84±15.54, 64.27±26.28 and 63.45±17.66, respectively.

Table 4 shows the correlations between four different domains of WHOQOL-BREF. Based on the observed findings, statistically significant positive correlations were noted between all four domains of WHOQOL-BREF. There was also a statistically significant positive correlation between the first two questions of WHOQOL-BREF i.e. QoL and overall health satisfaction status and scores obtained from different domains. The strength of correlation among QoL and overall health status was moderately-strong (Spearman’s r >0.4), whereas four domains showed low, moderate, strongly-moderate and strong correlations (Spearman’s r ranged 0.155 to 0.627).

Table 5 represents correlation coefficients and the bivariate relationship between demographic variables and the domain scores. Statistically, a significant difference was observed
between the scores of various age groups, marital status, education level, comorbidities other than CVDs against the psychological domain (p≤0.05). Patients in the age group of ≥30 years had significantly higher HRQoL scores in their psychological domain (69.48±14.74) than those in <30 years (65.38±16.43). A statistically significant difference was observed between the scores of marital status and the psychological domain (p = 0.045). A significant difference was also observed in education levels and psychological (p = 0.002) and environment domains.

### Table 2. Distribution of WHOQOL-BREF items’ response (n = 295).

| WHOQOL-BREF items                  | Very Poor (1) | Poor (2) | Average (3) | Good (4) | Very Good (5) | Mean ± SD |
|------------------------------------|---------------|----------|-------------|----------|---------------|-----------|
| Overall QoL & Health               |               |          |             |          |               |           |
| QoL Rating                         | 3             | 14       | 86          | 114      | 78            | 3.84±0.90 |
| Health Satisfaction Status         | 6             | 20       | 90          | 124      | 55            | 3.68±0.92 |
| Physical Domain                    |               |          |             |          |               |           |
| Q3 Physical Pain                   | 12            | 39       | 101         | 85       | 58            | 3.46±1.07 |
| Q4 Medication Need                 | 10            | 31       | 70          | 87       | 97            | 3.77±1.11 |
| Q10 Everyday Energy                | 4             | 32       | 83          | 95       | 81            | 3.73±1.02 |
| Q15 Get around Ability             | 1             | 14       | 33          | 90       | 157           | 4.31±0.87 |
| Q16 Sleep Satisfaction             | 11            | 29       | 80          | 121      | 54            | 3.60±1.01 |
| Q17 Daily Activities               | 4             | 29       | 116         | 112      | 34            | 3.48±0.87 |
| Q18 Work Capacity                  | 8             | 11       | 119         | 118      | 39            | 3.57±0.86 |
| Psychological Domain               |               |          |             |          |               |           |
| Q5 Enjoying Life                   | 1             | 42       | 113         | 96       | 43            | 3.46±0.92 |
| Q6 Meaningful Life                 | 5             | 23       | 72          | 104      | 91            | 3.85±1.00 |
| Q7 Ability to Concentrate          | 3             | 37       | 115         | 111      | 29            | 3.42±0.86 |
| Q11 Body Appearance                | 9             | 46       | 81          | 73       | 86            | 3.61±1.14 |
| Q19 Self Satisfaction              | 9             | 13       | 80          | 124      | 69            | 3.78±0.95 |
| Q26 Negative Feelings              | 32            | 77       | 140         | 30       | 16            | 2.73±0.97 |
| Social Domain                      |               |          |             |          |               |           |
| Q20 Relationship Satisfaction      | 16            | 21       | 75          | 94       | 89            | 3.74±1.12 |
| Q21 Sexual Satisfaction            | 36            | 24       | 85          | 62       | 88            | 3.48±1.32 |
| Q22 Social Support                 | 29            | 29       | 82          | 76       | 79            | 3.49±1.25 |
| Environmental Domain               |               |          |             |          |               |           |
| Q8 Life Safety                     | 12            | 18       | 77          | 111      | 77            | 3.75±1.03 |
| Q9 Healthy Environment             | 21            | 40       | 108         | 96       | 30            | 3.25±1.04 |
| Q12 Financial Satisfaction         | 14            | 40       | 105         | 90       | 46            | 3.38±1.05 |
| Q13 Informational Sources          | 6             | 25       | 89          | 129      | 46            | 3.62±0.91 |
| Q14 Leisure Activities             | 36            | 100      | 79          | 57       | 23            | 2.76±1.13 |
| Q23 Living Place                   | 23            | 21       | 59          | 90       | 102           | 3.76±1.21 |
| Q24 Healthcare Satisfaction        | 18            | 43       | 72          | 84       | 78            | 3.54±1.19 |
| Q25 Transport Satisfaction         | 29            | 44       | 52          | 56       | 114           | 3.61±1.37 |

### Table 3. Mean HRQoL scores for four domains of WHOQOL-BREF.

| Domains                         | HRQoL Scores (Mean±SD) |
|---------------------------------|------------------------|
| Physical Domain                 | 62.44±15.36            |
| Psychological Domain            | 67.84±15.54            |
| Social Relationship Domain      | 64.27±26.28            |
| Environmental Domain            | 63.45±17.66            |

https://doi.org/10.1371/journal.pone.0234734.t002

https://doi.org/10.1371/journal.pone.0234734.t003

between the scores of various age groups, marital status, education level, comorbidities other than CVDs against the psychological domain (p≤0.05). Patients in the age group of ≥30 years had significantly higher HRQoL scores in their psychological domain (69.48±14.74) than those in <30 years (65.38±16.43). A statistically significant difference was observed between the scores of marital status and the psychological domain (p = 0.045). A significant difference was also observed in education levels and psychological (p = 0.002) and environment domains.

### Table 3. Mean HRQoL scores for four domains of WHOQOL-BREF.

| Domains                         | HRQoL Scores (Mean±SD) |
|---------------------------------|------------------------|
| Physical Domain                 | 62.44±15.36            |
| Psychological Domain            | 67.84±15.54            |
| Social Relationship Domain      | 64.27±26.28            |
| Environmental Domain            | 63.45±17.66            |

https://doi.org/10.1371/journal.pone.0234734.t003
Table 4. Correlation coefficients in overall health and domains of WHOQOL-BREF.

| QoL                              | Overall Health | Physical Domain | Psychological Domain | Social Domain | Environmental Domain |
|----------------------------------|----------------|-----------------|----------------------|--------------|----------------------|
| Correlation (r)                  | 0.472          | 0.416           | 1                    |              |                      |
| Sig. (2-tailed)                  | <0.001         | <0.001          | <0.001               | <0.001       |                      |
| Physical Domain                  |                |                 |                      |              |                      |
| Correlation (r)                  | 0.348          | 0.391           | 0.530                | 1            |                      |
| Sig. (2-tailed)                  | <0.001         | <0.001          | <0.001               | <0.001       |                      |
| Psychological Domain             |                |                 |                      |              |                      |
| Correlation (r)                  | 0.242          | 0.155           | 0.513                | 0.301        | 1                    |
| Sig. (2-tailed)                  | <0.001         | <0.001          | <0.001               | <0.001       |                      |
| Social Domain                    |                |                 |                      |              |                      |
| Correlation (r)                  | 0.487          | 0.376           | 0.627                | 0.494        | 0.481                |
| Sig. (2-tailed)                  | <0.001         | <0.001          | <0.001               | <0.001       |                      |

Table 5. Comparison of WHOQOL-BREF mean scores, standard deviations, and significance levels based on sociodemographics.

| Variable                          | QoL          | Health Satisfaction | Physical        | Psychological   | Social          | Environmental   |
|-----------------------------------|--------------|---------------------|-----------------|-----------------|----------------|----------------|
| Gender                            |              |                     |                 |                 |                |                |
| Male                              | 3.71±0.97    | 3.62±0.95           | 62.34±15.33     | 68.13±15.36     | 64.68±24.95    | 63.18±17.86    |
| Female                            | 3.92±0.84    | 3.72±0.90           | 62.50±15.42     | 67.66±15.69     | 64.02±27.12    | 63.61±17.59    |
| P Value                           | 0.045        | 0.362               | 0.932           | 0.801           | 0.834          | 0.838          |
| Age                               |              |                     |                 |                 |                |                |
| < 30 Years                        | 3.93±0.90    | 3.72±0.87           | 64.19±15.34     | 65.38±16.43     | 62.60±25.40    | 63.38±18.29    |
| ≥ 30 Years                        | 3.79±0.90    | 3.65±0.95           | 61.27±15.31     | 69.48±14.74     | 65.38±26.87    | 63.49±17.28    |
| P Value                           | 0.189        | 0.503               | 0.110           | **0.026**       | 0.374          | 0.961          |
| Marital Status                    |              |                     |                 |                 |                |                |
| Single/Separated                  | 3.77±0.96    | 3.60±1.03           | 60.46±15.51     | 70.10±14.95     | 65.10±27.91    | 64.62±18.21    |
| Married                           | 3.89±0.86    | 3.73±0.84           | 63.70±15.18     | 66.39±15.78     | 63.73±25.26    | 62.70±17.31    |
| P Value                           | 0.265        | 0.207               | 0.078           | **0.045**       | 0.664          | 0.362          |
| Education Level                   |              |                     |                 |                 |                |                |
| Primary and secondary             | 3.20±1.03    | 3.50±0.52           | 54.00±13.75     | 52.60±7.87      | 63.10±16.55    | 50.20±17.45    |
| Higher secondary and above        | 3.87±0.89    | 3.69±0.93           | 62.73±15.35     | 68.37±15.48     | 64.31±26.58    | 63.91±17.52    |
| P Value                           | 0.021        | 0.520               | 0.077           | **0.002**       | 0.886          | **0.016**      |
| Work Status                       |              |                     |                 |                 |                |                |
| Not working                       | 3.84±0.90    | 3.71±0.90           | 63.56±15.68     | 69.57±15.48     | 65.77±25.02    | 62.64±17.25    |
| Job/Business                      | 3.85±0.90    | 3.66±0.93           | 61.73±15.16     | 66.74±15.52     | 63.32±27.07    | 63.95±17.94    |
| P Value                           | 0.537        | 0.437               | 0.128           | 0.321           | 0.610          | 0.936          |
| Comorbidities other than CVDs     |              |                     |                 |                 |                |                |
| Yes                               | 3.74±1.04    | 3.48±0.99           | 58.18±16.00     | 60.73±17.12     | 57.98±27.15    | 58.79±18.15    |
| No                                | 3.90±0.81    | 3.79±0.86           | 64.72±14.55     | 71.65±13.17     | 67.64±25.24    | 65.94±16.92    |
| P Value                           | 0.165        | **0.006**           | <0.001          | <0.001          | **0.002**      | **0.001**      |
| Warfarin Indication               |              |                     |                 |                 |                |                |
| AF/Valve replacements             | 3.81±0.90    | 3.69±0.91           | 61.54±16.09     | 66.76±15.24     | 64.98±26.26    | 62.76±17.91    |
| DVTs/PEs                          | 3.87±0.90    | 3.67±0.93           | 63.17±14.75     | 68.72±15.78     | 63.68±26.37    | 64.01±17.49    |
| P Value                           | 0.543        | 0.906               | 0.365           | 0.283           | 0.673          | 0.548          |
| Warfarin Duration                 |              |                     |                 |                 |                |                |
| < 1 Year                          | 3.83±0.93    | 3.70±0.96           | 60.87±17.11     | 67.04±16.50     | 60.95±28.53    | 62.85±19.14    |
| ≥ 1 Year                          | 3.85±0.88    | 3.66±0.89           | 63.60±13.85     | 68.43±14.81     | 66.74±24.27    | 63.89±16.51    |
| P Value                           | 0.817        | 0.729               | 0.131           | 0.450           | 0.061          | 0.619          |

https://doi.org/10.1371/journal.pone.0234734.1004

https://doi.org/10.1371/journal.pone.0234734.1005
Patients having primary and secondary education had significantly lower HRQoL in both psychological (54.00 ± 13.75) and environment domain (50.20 ± 17.45) than higher educated patients, respectively. Employed or business-doing patients had significantly higher HRQoL scores in the environmental domain (63.95 ± 17.94) than non-workings (62.64 ± 17.25).

Patients with comorbidities other than CVDs were having compromised HRQoL in all four domains and QoL and overall health satisfaction status than those without any comorbidity (p-value ranged from 0.000 to 0.165).

Table 6 shows correlations between demographic variables vs different domains of WHOQOL-BREF. Based on the observations, statistically significant positive and negative correlations were noted between various demographic variables and four domains of WHOQOL-BREF. Statistically significant (positive and negative) correlation between the first two questions of WHOQOL-BREF i.e. QoL and overall health satisfaction status and demographic variables were noted. The strength of correlation among demographic variables and various domains of WHOQOL-BREF showed low, moderate and strongly-moderate positive and negative correlations (Spearman’s ‘r’ ranged from -0.117 to 0.335).

Table 7 represents the linear regression analysis which revealed that for any change in marital status from single/separated to married, a score of 0.109 is increased for the physical domain (p<0.05) when adjusted for other demographic variables. Similarly, a change in education level from primary to secondary/higher was associated with an increase of 0.089 in the score for the psychological domain (p<0.05) keeping other demographic variables as constant. Furthermore, a change in comorbidity status, i.e., having no cardiovascular disease as comorbidity as opposed to having it, it would increase the scores by 0.153, 0.267, 0.143 and 0.127 in the physical, psychological, social and environmental domains (p<0.05) when adjusted for other patient variables. Furthermore, for a unit increase in the QoL score, it would increase to 0.496, 0.358, 0.280 and 0.487 in scores in the physical, psychological, social and environmental domains (p<0.05) when adjusted for other demographic variables. The variables of age and duration of warfarin therapy were not significant (p>0.05).
In the past decade, HRQoL is an emerging concept and an important treatment outcome parameter to assess patients’ general health state, treatment efficacy, and overall disease management [37]. This study determines the HRQoL of warfarin patients in four different domains of WHOQOL-BREF, together with overall health satisfaction and the factors responsible for such HRQoL outcomes. The severity of the chronic diseases demands healthcare practitioners to pay due attention to the HRQoL of the affected individuals. To the best of our knowledge, to date, this is the first-ever study done in Pakistan regarding HRQoL of warfarin patients using WHOQOL-BREF thus there are no studies evident as a cross-reference to this study.

Researchers from different parts of the world explored different aspects of HRQoL among patients on anticoagulation therapy [38–43]. Limited access to medication use, annoyance, the burden of the CVDs, and both positive and negative psychological impacts are the significant concerns affecting HRQoL among patients on anticoagulation therapy [38–40]. The occurrence of a bleeding episode in patients on warfarin may cause a substantial decrease in their general health and overall health status [44–46]. In a study done by Abubaker et al., the HRQoL of patients on anticoagulant therapy was greatly associated with socio-demographic and clinical variables. They studied patients’ knowledge, satisfaction, and adherence to oral anticoagulant therapy using Oral Anticoagulant Knowledge (OAK) test. They determined that the intensity of bleeding events, the presence of comorbidities, various drug interactions, education level differences, patient’s age factors, and total therapy duration have a direct influence on the HRQoL [38].

The study population was categorized into two main age groups i.e. <30 years and ≥30 years of age because in the pilot study most of the warfarin patients visiting the study sites were ≥30 years of age with fewer exceptions, that’s why the cut-off was set at 30 years of age. This study indicated that younger patients had considerably better HRQoL than elders in the physical domain, whereas in psychological, social, and environmental domains, elderly patients had better HRQoL than youngsters. The results of our study in terms of elder patients having better HRQoL were similar to the earlier two studies that discussed HRQoL among older patients but in different diseases [25, 47]. Our study findings could be endorsed to the

| Variables | Physical | Psychological | Social | Environmental |
|-----------|-----------|---------------|--------|--------------|
| Age (<30 Years vs ≥30 Years) | NA | 0.06 | 0.336 | 1.50 | NA |
| Marital status (Single/Separated vs Married) | 0.109 | 0.032 | 1.04 | 0.052 | 0.408 | 1.48 | NA |
| Education Level (Primary and secondary vs Higher secondary or above) | 0.031 | 0.534 | 1.05 | 0.089 | 0.032 | 1.05 | NA |
| Comorbidities other than CVDs (Yes, vs No) | 0.153 | 0.003 | 1.04 | 0.267 | <0.001 | 1.05 | 0.143 |
| Warfarin Duration (<1 Year vs >1 Year) | NA | 0.103 | 0.065 | 1.00 | NA |
| QoL | 0.496 | <0.001 | 1.03 | 0.358 | <0.001 | 1.03 | 0.280 | <0.001 | 1.00 | 0.487 | <0.001 | 1.01 |

Model fitness for different domain: Physical = ANOVA (F = 30.54, p = <0.001); R² = 0.296 and adjusted R² = 0.286; Psychological = ANOVA (F = 18.96, p = <0.001); R² = 0.248 and adjusted R² = 0.235; Social = ANOVA (F = 12.26, p = <0.001); R² = 0.113 and adjusted R² = 0.103) and Environmental = ANOVA (F = 36.11, p = <0.001); R² = 0.272 and adjusted R² = 0.264.

https://doi.org/10.1371/journal.pone.0234734.t007

### Discussion

In the past decade, HRQoL is an emerging concept and an important treatment outcome parameter to assess patients’ general health state, treatment efficacy, and overall disease management [37]. This study determines the HRQoL of warfarin patients in four different domains of WHOQOL-BREF, together with overall health satisfaction and the factors responsible for such HRQoL outcomes. The severity of the chronic diseases demands healthcare practitioners to pay due attention to the HRQoL of the affected individuals. To the best of our knowledge, to date, this is the first-ever study done in Pakistan regarding HRQoL of warfarin patients using WHOQOL-BREF thus there are no studies evident as a cross-reference to this study.

Researchers from different parts of the world explored different aspects of HRQoL among patients on anticoagulation therapy [38–43]. Limited access to medication use, annoyance, the burden of the CVDs, and both positive and negative psychological impacts are the significant concerns affecting HRQoL among patients on anticoagulation therapy [38–40]. The occurrence of a bleeding episode in patients on warfarin may cause a substantial decrease in their general health and overall health status [44–46]. In a study done by Abubaker et al., the HRQoL of patients on anticoagulant therapy was greatly associated with socio-demographic and clinical variables. They studied patients’ knowledge, satisfaction, and adherence to oral anticoagulant therapy using Oral Anticoagulant Knowledge (OAK) test. They determined that the intensity of bleeding events, the presence of comorbidities, various drug interactions, education level differences, patient’s age factors, and total therapy duration have a direct influence on the HRQoL [38].

The study population was categorized into two main age groups i.e. <30 years and ≥30 years of age because in the pilot study most of the warfarin patients visiting the study sites were ≥30 years of age with fewer exceptions, that’s why the cut-off was set at 30 years of age. This study indicated that younger patients had considerably better HRQoL than elders in the physical domain, whereas in psychological, social, and environmental domains, elderly patients had better HRQoL than youngsters. The results of our study in terms of elder patients having better HRQoL were similar to the earlier two studies that discussed HRQoL among older patients but in different diseases [25, 47]. Our study findings could be endorsed to the...
fact that older people may have a better feeling and understandings of the meanings of social, psychological, and environmental life, so maybe they are more satisfied with their lives despite that they are on warfarin [41]. Furthermore, elders may embrace their diseases as a challenge and started living a more satisfactory life than youngers. Similarly, the youngers may also find their diseases as part of their lives and consider them a less challenging and life-long phenomenon, so they started living more satisfactorily and confidently in terms of the physical domain [25, 47]. However, another previous study on warfarin patients did not describe any significant association between HRQoL scores and their age [48]. Our findings are contrary to Casais et al, where they found out that younger patients had a better satisfaction with their anticoagulant therapy as compared to the older patients [25]. These differences could be due to different research tools used, varied patients’ characteristics, lifestyle changes, and bleeding disorders. Gadisseur et al. reported that different factors like modalities of treatment plans, self-handling of the medicines, and counseling by specialized anticoagulation clinic staff are important influencing parameters affecting patients HRQoL while they are on warfarin [48].

In the current study, among the four domains of WHOQOL-BREF, the highest mean score (satisfaction level) was noted for the psychological domain (67.84±15.54) than the rest of the domains, which may be due to adequate healthcare facilities, body appearance, no negative feelings, more positive feelings, a greater level of self-esteem, high religious activities, spiritual applicability and personal beliefs [41]. Moreover, the lowest mean score (satisfaction level) was observed for the physical domain (62.44±15.36) among all domains, indicating compromised activities of daily living, more dependence on medicinal substances and medical aids, less mobility, and more fatigue, discomfort, and less work capacity. On the other hand, acceptable mean scores were observed for social and environment domains (64.27±26.28 and 63.45 ±17.66 respectively) showing good personal relationships, greater social support, satisfactory sexual activities, freedom in religious activities, and frequent access to cheap and convenient transportation [41–43].

On the contrary to the findings of Saad et al., our study determined a significant association of various sociodemographic factors with HRQoL among patients on warfarin [44]. We observed a significant effect of gender on HRQoL among patients on warfarin. It was interesting to note that females seemed more satisfied in overall health satisfaction states, physical domain, and environmental domain as compared with the males. Similarly, males appeared to be more satisfied in psychological and social domains as compared with females. These results are contrary to another study where investigators observed no difference in HRQoL scores between males and females [45]. These differences are may be due to different populations, different study sites, and different research tools used, i.e., they used SF-36 and Perceived Stress Scale, whereas we used WHOQOL-BREF. Our study results regarding gender differences are in accordance with Sayin et al. that the males had overall less HRQoL than the females [41, 46].

In the past, mixed findings were observed as in some other studies, married patients had higher HRQoL, whereas few studies reported that marital status did not have any effect on HRQoL [10, 37, 49, 50]. Our study also confirmed that married patients had higher HRQoL in QoL, overall health satisfaction states, and the physical domain, whereas unmarried or singles had better HRQoL in other domains. This could be because Pakistan has an extensive family structure where unmarried patients get adequate financial support and emotional backups from their parents and families. This is in contrast to various other countries and cultures, where support is often linked to marriages.

In literature, the association between education levels and HRQoL among chronically ill patients is well studied [37, 41]. According to our study, statistically significant differences were observed between the well and the poorly educated patients. Higher education is often linked with self-interest, better dosage understandings, high treatment compliance and
medication adherence [51]. The findings of our study confirmed that the education level had a significant effect on overall HRQoL among patients on warfarin in Pakistan. In all four domains of HRQoL and overall health satisfactory states, much better scores were observed among highly educated patients than those having a primary level of education [52]. In general, highly educated patients were reported to live longer and enjoy better health status as compared to the less educated patients [41, 52, 53]. Our study results are similar to Casais et al, where study participants with higher education levels had better HRQoL [25]. In contrast, our study results are opposite to two other studies where no significant differences were found among education levels and HRQoL [37, 40].

In this study findings, employed/self-employed individuals scored comparatively better scores in three domains (physical, psychological, and social) of the WHOQOL-BREF than those who were not working, but the results were not statistically significant (p > 0.05). These findings are contrary to the findings of Joshi et al., in terms of environment domain and overall general health satisfaction states [37]. The differences in physical, social and psychological domains are may be due to differences in age groups, gender, educational status, ethnicity, marital status, employment, the environment of the study population, family income and duration of illnesses. Our study findings maybe because of the better access to the financial resources (employment), type of healthcare they received, access to the opportunities for acquiring up-to-date information regarding warfarin. These results were also consistent with that of Yang et al. and Casais et al., who presented significantly better scores for their respondents in the environment domain [25, 54]. Employment or having self-business can significantly improve HRQoL scores in physical, psychological, social, and environmental domains as in the studies conducted by Casais et al. [25] and Sathvik et al. [55]. Our findings in the social domain are contrary to Yang et al findings where they found low scores in the social domain particularly dissatisfaction with sexual life [54]. The reason for both opposite findings may include different disease states, cultural backgrounds, healthcare policies, access to quality transportation, religious matters, and satisfaction with healthcare facilities. Another contributing factor regarding the social domain may be that patients spend more time with their families and friends that may positively affect their personal and social relationships. Undeniably, better income appears to be a unique predictor of improved HRQoL [37]. According to the findings of another study, income was significantly associated with improved psychological and environmental domain scores [9, 55]. These findings are not surprising as high earning patients can easily adopt better treatment options to fulfill their healthcare needs as compared to those who are neither businessmen nor employed [25, 41].

In our study, better HRQoL was observed in patients with no comorbidity than those who were affected by various comorbidities other than CVDs. In all four domains of HRQoL and overall health satisfactory states, much better scores (p < 0.05) were present in the patients without any comorbidity than those who were facing comorbidities. Our results are in agreement with a study done by Gadisseur et al., where they also found similar results [48]. In bivariate analysis, our results illustrate that the duration of warfarin usage had a significant effect on all domains of the WHOQOL-BREF. Patients had greater HRQoL who were on warfarin for more than a year than those who were on less than a year. These results are similar to Gadisseur et al., where they also found statistically significant differences among their respondents regarding the duration of warfarin utilization [48]. The linear regression model confirmed that marital status, education level, comorbidities other than CVDs, and general QoL variables are pure predictors (after adjusting confounders) against different domains the WHOQOL-BREF in determining HRQoL among warfarin patients in Pakistan.

In developing countries like Pakistan, warfarin yet is the drug of choice for various CVDs because of its therapeutic benefits and perceived cost-effectiveness [56, 57]. Conversely,
warfarin’s optimum therapy management poses a greater challenge to the healthcare staff because of its varied dose-response, narrow therapeutic index, multi-factorial drug-food interactions and the need for adequate dose adjustments and monitoring [57, 58]. In developed countries, such challenges are dealt with by devising innovative treatment strategies like advanced anticoagulation clinics, patients’ self-monitoring, and various computer-aided adherence and treatment plans [56–58]. Generally, the total period and the treatment patterns of chronic illnesses like patients on longer warfarin requires longer treatment durations. In countries other than developed, the majority of them are facing a lot of challenges in providing optimum healthcare facilities to their population [1,2]. Though these days in Pakistan, some of the healthcare costs for chronic diseases are borne by the government, but still better treatment plans, adherence to the medications, compliance with the lifestyle modifications, awareness of the drug regimen are greater contributing factors affecting HRQoL of the patients on warfarin.

Though currently, Pakistan is facing some thwarting challenges in terms of economic, social, and political areas, yet lack of these resources does not mean people always die because of poverty or lack of healthcare facilities. Indeed, the quality healthcare in Pakistan has a high price tag, and good quality healthcare facilities are mostly available to the elite class in private healthcare set-ups, yet these days, much better facilities are being offered in public hospitals and clinics where patients are somehow more satisfied than the past. Both federal and provincial governments are trying their level best to overcome healthcare challenges to provide optimal healthcare facilities to the public. Definitely, lack of advanced healthcare facilities and less financial resources do have their impact on the patients’ overall HRQoL but from the results of our study, HRQoL among warfarin patients in Pakistan was not that bad as were the rumors. Moreover, in Pakistan, currently, various policies are also underway for the implementation of Minimum Service Delivery Standards (MSDS) for the provision of safe medicines, better patient care, improving cleanliness and hygiene conditions of the hospitals and clinics, infection control strategies and provision of the required healthcare staff, that will further improve the HRQoL of the patients especially in chronic diseases.

Conclusion
The findings from this study confirm that the WHOQOL-BREF research tool is a reliable instrument to measure HRQoL among warfarin patients in Pakistan (Cronbach Alpha 0.898). From the obtained data, it is evident that warfarin patients in Pakistan enjoy overall satisfactory HRQoL in all domains of the WHOQOL-BREF, although some of the variables showed a relatively moderate or lower HRQoL in some domains. This lower HRQoL is may be due to non-acceptance of treatment pattern by the patients, inappropriate therapeutic plans, non-compliance, increased indirect medical costs, increased direct non-medical costs, inability to work, and increased overall living expenses. The findings of this study are an imperative contribution in literature for the understanding of the effect of warfarin on overall HRQoL among patients on warfarin in Pakistan. This study is also novel and first of its kind because few studies are done in various countries to measure HRQoL of warfarin patients, but none is done in Pakistan using the WHOQOL-BREF. Since most of the information evident in the literature regarding the relationship between HRQoL and anticoagulation control of the warfarin comes from other countries, whose extrapolation for the Pakistani society is limited by cultural, religious, socio-economic differences and the way the healthcare system is developed and managed in Pakistan.

Limitations of the study
As the majority of the HRQoL questionnaires, the WHOQOL-BREF is also a self-reported study tool and in cases of illiterate patients, the tool is filled with the help of patients’
caregivers, nurses or the investigators themselves that may report some biases. In this scenario, data reporting biases may have acted as confounding factors in our study. One of the limitations noted for our study was that there was no control group to make applicable comparisons for the findings obtained. Another limitation of this study was its cross-sectional design as in cross-sectional studies, generalizability is often limited by the sampled population because sample size requirements are often very large. The cross-sectional studies, on the other side, also have the potential for selection bias where they cannot exactly determine the causal relationship between the studied variables and the outcomes obtained. This study also did not discuss the HRQoL of warfarin patients having uncontrolled INRs i.e. bleeding risks, which is another limitation of this study. As this study used purposive sampling technique, which also has some limitations like errors in judgment by the researchers, less reliability and high levels of bias, and research findings can not be too generalized. Despite some limitations, the findings of this study shed significant light on the overall status of HRQoL among warfarin patients in Pakistan. The findings of this study could help physicians, pharmacists, allied healthcare professionals, and the family members of the patients to better understand the physical, psychological, social and environmental problems patients usually face while on warfarin. This, in return, will definitely help and encourage them to provide more physical, psychological, and social support to their patients.

Supporting information

S1 Raw data.

(SAV)

Acknowledgments

The authors would like to thank the Deanship of Scientific Research at Prince Sattam bin Abdulaziz University, Alkharji, Saudi Arabia for the support in the publication of this manuscript. The authors would also like to express their sincere gratitude to all of the participants involved in this study in any capacity.

Author Contributions

Conceptualization: Muhammad Shahid Iqbal, Fares M. S. Muthanna, Fahad I. Al-Saikhan, Muhammad Ahmed, Atta Abbas Naqvi.

Data curation: Yaman Walid Kassab.

Formal analysis: Yaman Walid Kassab, Abdul Haseeb.

Methodology: Muhammad Shahid Iqbal, Fares M. S. Muthanna, Fahad I. Al-Saikhan, Muhammad Zahid Iqbal, Salah-Ud-Din Khan, Md. Ashraful Islam, Majid Ali.

Supervision: Mohamed Azmi Hassali.

Writing – review & editing: Muhammad Shahid Iqbal, Md. Ashraful Islam, Majid Ali.

References

1. The WHOQOL Group. Development of the World Health Organization WHOQOL-BREF Quality of Life Assessment. Psychol Med. 1998; 28(3):551–8. https://doi.org/10.1017/s0033291798006667 PMID: 9626712

2. Saleem F, Hassali MA, Shafie AA. A cross-sectional assessment of health-related quality of life (HRQoL) among hypertensive patients in Pakistan. Health Expect. 2014; 17(3):388–95. https://doi.org/10.1111/1369-7625.2012.00765.x PMID: 22390260
3. Nu Haq, Hassan MA Shafie AA, Saleem F, Farooqui M, Aljadhey H, et al. Association between Hepatitis B-Related Knowledge and Health-Related Quality of Life. Trop J Pharm Res. 2014; 13(7):1163–8. http://dx.doi.org/10.4314/tjpr.v13i7.22

4. Peterson SJ, Bredow TS. (2008) Middle-range theories: Application to nursing research. 2nd ed. Philadelphia: Wolters Kluver Health/Lippincott Williams & Wilkins, c2009.

5. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005; 365(9455):217–23. https://doi.org/10.1016/S0140-6736(05)17741-1 PMID: 15652604

6. Khaw WF, Hassan STS, Latiffah AL. Health-related Quality of Life among Hypertensive Patients Compared with General Population Norms. J Med Sci. 2011; 11(2):84–9. http://dx.doi.org/10.3923/jms.2011.84.89.

7. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet. 2006; 367(9524):1747–57. https://doi.org/10.1016/S0140-6736(06)68770-9 PMID: 16731270

8. Cardiovascular diseases. Geneva: World Health Organization. 2017. http://www.who.int/mediacentre/factsheets/fs317/en. Accessed online 05-10-2019.

9. Haltijema S, de Borst GJ, Vries JP, Moll F, Pasterkamp G, Ruijter H. Health-related quality of life is poor but does not vary with cardiovascular disease burden among patients operated for severe atherosclerotic disease. IJC Heart Vessels. 2014; 4(1):53–8. https://dx.doi.org/10.1016/j.ijcvh.2014.07.001

10. Fukuoka Y, Lindgren TG, Rankin SH, Cooper BA, Carroll DL. (2007). Cluster analysis: a useful technique to identify elderly cardiac patients at risk for poor quality of life. Qual Life Res. 2007; 16(10):1655–63. https://doi.org/10.1007/s11136-007-9272-7 PMID: 17955345

11. Megari K. Quality of Life in Chronic Disease Patients. Health Psychol Res. 2013; 1(3): e27. https://doi.org/10.4081/hpr.2013.e27 PMID: 26973912

12. Harrison MB, Juniper EF, Mitchell-Dicenso A. Quality of life as an outcome measure in nursing research. "May you have a long and healthy life". Can J Nurs Res. 1996; 28(3):49–68. PMID: 8997939

13. Lam ET, Lam CL, Lai CL, Yuen MF, Fong DY. Psychometrics of the chronic liver disease questionnaire for Southern Chinese patients with chronic hepatitis B virus infection. World J Gastroenterol. 2009; 15(26):3288–97. http://dx.doi.org/10.3748/wjg.v15.3288 PMID: 19598306

14. Wang HM, Beyer M, Gensichen J, Gerlach FM. Health-related quality of life among general practice patients with differing chronic diseases in Germany: cross sectional survey. BMC Public Health. 2008; 8:246. https://doi.org/10.1186/1471-2458-8-246 PMID: 18638419

15. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: Part II: variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. Circulation. 2001; 104(23):2855–64. https://doi.org/10.1161/hc4701.099488 PMID: 11733407

16. The World Bank. The World Bank data for world populations. 2016. https://data.worldbank.org/indicator/SP.POP.TOTL?locations=KR Accessed online 05-10-2019.

17. Misra A, Tandon N, Erbhum A, Sattar N, Alam D, Shrivastava U, et al. Diabetes, cardiovascular disease, and chronic kidney disease in South Asia: current status and future directions. BMJ. 2017; 357:j1420. https://doi.org/10.1136/bmj.j1420 PMID: 28400361

18. Jafar TH, Qadri Z, Chaturvedi N. Coronary artery disease epidemic in Pakistan—more electrocardiographic evidence of ischemia in women than in men. Heart. 2007; 94(4):406–13. https://doi.org/10.1136/hrt.2007.120774 PMID: 17646192

19. Kuruvilla M, Gurk-Turner C. A review of warfarin dosing and monitoring. Proc (Bayl Univ Med Cent). 2001; 14(3):305–6. https://doi.org/10.1080/08998280.2001.11927781 PMID: 16369639

20. Kimmel SE. Warfarin therapy: in need of improvement after all these years. Expert Opin Pharmacother. 2008; 9(5):677–86. https://www.tandfonline.com/action/cookieAbsent PMID: 18345947

21. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18820 patients. BMJ. 2004; 329(7456):15–9. https://doi.org/10.1136/bmj.329.7456.15 PMID: 15231615

22. Sobohnaisdusak A, Silpakit C, Kongsaok R, Sattipornkul P, Sripetch C, Khanthavit A. Factors influencing health-related quality of life in chronic liver disease. World J Gastroenterol. 2006; 12(48):7786–91. http://dx.doi.org/10.3748/wjg.v12.i48.7786 PMID: 17293521

23. Svrilith N, Pavic S, Terzic D, Delic D, Simonovic J, Gvozdenovic E, et al. Reduced quality of life in patients with chronic viral liver disease as assessed by SF12 questionnaire. J Gastrointestin Liver Dis. 2008; 17(4):405–6. PMID: 19104701

24. Corbi IS, Dantas RA, Pelegrino FM, Carvalho AR. Health related quality of life of patients undergoing oral anticoagulation therapy. Rev Lat Am Enfermagem. 2011; 19(4):865–73. http://dx.doi.org/10.1590/ S0104-11692011000400005 PMID: 21876937
25. Casais P, Meschengieser SS, Sanchez-Luceros A, Lazzari MA. Patients’ perceptions regarding oral anticoagulation therapy and its effect on quality of life. Curr Med Res Opin. 2005; 21(7):1085–90. http://doi.org/10.1185/030079905X062649 PMID: 16004677

26. Anees M, Malik MR, Abbasi T, Nasir Z, Hussain Y, Ibrahim M. Demographic factors affecting quality of life of hemodialysis patients–Lahore, Pakistan. Pak J Med Sci. 2014; 30(5):1123–1127. https://doi.org/10.12669/pjms.305.5239 PMID: 25225539

27. Barcellona D, Contu P, Sorano GG, Pengo V, Marongiu F. The management of oral anticoagulant therapy: the patient’s point of view. Thromb Haemost. 2000; 83(1):49–53. PMID: 10669154

28. National Bioethics Committee (NBC) Pakistan. 2004. Ethical Research Committee-Guidelines– 2010. Available from http://www.pmcrc.org.pk/erc_guidelines.htm Accessed online 07-10-2019.

29. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects Adopted by the 18th WMA General Assembly, Helsinki, Finland, June, 1964, and amended by the 48th WMA General Assembly, Somerset West, Republic of South Africa, October, 1996. Accessed online 07-10-2019.

30. Eltayeb TYM, Mohamed MS, Elbur AI, Elsayed ASA. Satisfaction with and adherence to warfarin treatment: A cross-sectional study among Sudanese patients. J Saudi Heart Assoc. 2017; 29(3):169–75. http://dx.doi.org/10.1016/j.jsaha.2016.10.007 PMID: 28652670

31. Born D, Martinez EE, Almeida PA, Santos DV, Carvalho AC, Moron AF. Pregnancy in patients with prosthetic heart valves: the effects of anticoagulation on mother, fetus, and neonate. Am Heart J. 1992; 124(2):413–7. https://doi.org/10.1016/0002-8703(92)90606-v PMID: 16365881

32. Meschengieser SS, Fondevila CG, Santarelli MT, Lazzari MA. Anticoagulation in pregnant women with mechanical heart valve prostheses. Heart. 1999; 82(1):23–6. https://doi.org/10.1136/hrt.82.1.23 PMID: 10377303

33. Yurdakök M. Fetal and neonatal effects of anticoagulants used in pregnancy: a review. Turk J Pediatr. 2012; 54(3):207–15. PMID: 23094528

34. Yasmeen F., Ghafoor M. B., Khalid A. W., Latif W., Mohsin S., & Khaliq S. Analysis of CYP2C9 polymorphisms (*2 and *3) in warfarin therapy patients in Pakistan. Association of CYP2C9 polymorphisms (*2 and *3) with warfarin dose, age, PT and INR. Journal of thrombosis and thrombolysis. 2015; 40(2):218–224. https://doi.org/10.1007/s11239-015-1215-5 PMID: 25904339

35. Sakpal Tushar Vijay. Sample size Estimation in Clinical Trial. Perspect Clin Res. 2010; 1(2):67–69. PMID: 21829786

36. Heo M, Kim N, Faith MS. Statistical power as a function of Cronbach alpha of instrument questionnaire items. BMC Med Res Methodol. 2015; 15:86. https://doi.org/10.1186/s12874-015-0070-6 PMID: 26467219

37. Joshi U, Subedi R, Poudel P, Ghimire PR, Panta S, Sigdel MR. Assessment of quality of life in patients undergoing hemodialysis using WHOQOL-BREF questionnaire: a multicenter study. Int J Nephrol Renovasc Dis. 2017; 10:195–203. https://doi.org/10.2147/IJNRD.S136522 PMID: 28790861

38. Abubaker IE, Albarrag AA, Maugrahi MM, Alhaththi SA. Knowledge of, Satisfaction with and Adherence to Oral Anticoagulant Drugs among Patients in King Faisal Hospital; Taif, Kingdom Saudi Arabia. Int J Pharm Sci Rev Res. 2015; 31(2):274–80.

39. Almeida GO, Noblat LA, Passos LC, do Nascimento HF. Quality of life analysis of patients in chronic use of oral anticoagulant: an observational study. Health Qual Life Outcomes. 2011; 9:91–6. https://doi.org/10.1186/1477-7525-9-91 PMID: 22027368

40. Barcellona D, Contu P, Sorano GG, Pengo V, Marongiu F. The management of oral anticoagulant therapy: the patient’s point of view. Thromb Haemost. 2000; 83(1):49–53. PMID: 10669154

41. Almeida G., Noblat L., Passos L.C. Quality of Life analysis of patients in chronic use of oral anticoagulant: an observational study. Health Qual Life Outcomes (2011); 9:91–6. https://doi.org/10.1186/1477-7525-9-91 PMID: 22027368

42. Nedjat S, Montazeri A, Holakouie NK, Mohammad K, Majdzeadeh SR. The World Health Organization quality of life (WHOQOL-BREF) questionnaire: Translation and validation study of the Iranian version. Iran J Health Sch. 2006; 4(4):1–12.

43. Goretti B, Portaccio E, Zipoli V, Razzolini L, Amato MP. Coping strategies, cognitive impairment, psychological variables and their relationship with quality of life in multiple sclerosis. Neurol Sci. 2010; 31(Suppl 2):S227–30. https://doi.org/10.1007/s10072-010-0372-8 PMID: 20640468

44. Saad MM, Eli-Douaihy I, Boumitri C, Rondia C, Mousayl E, Daoud M, et al. Predictors of quality of life in patients with end-stage renal disease on hemodialysis. Int J Nephrol Renovasc Dis. 2015; 8:119–23. https://doi.org/10.2147/IJNRD.S84929 PMID: 26366104

45. Gemmell LA, Terhorst L, Jhamb M, Unruh M, Myaskovsky L, Keester L, et al. Gender and Racial Differences in Stress, Coping, and Health-Related Quality of Life in Chronic Kidney Disease. J Pain Symptom Manage. 2016; 52(6):806–12. https://doi.org/10.1016/j.jpainsymman.2016.05.029 PMID: 27697565
46. Sayin A, Mutluay R, Sindel S. Quality of life in hemodialysis, peritoneal dialysis, and transplantation patients. Transplant Proc. 2007; 39(10):3047–53. https://doi.org/10.1016/j.transproceed.2007.09.030 PMID: 18089319

47. Lemos CF, Rodrigues MP, Veiga JR. Family income is associated with quality of life in patients with chronic kidney disease in the pre-dialysis phase: a cross sectional study. Health Qual Life Outcomes. 2015; 13:202. https://doi.org/10.1186/s12955-015-0390-6 PMID: 26690667

48. Gadisseur AP, Kaptein AA, Breukink-Engbers WG, van der Meer FJ, Rosendaal FR. Patient self-management of oral anticoagulant care vs. management by specialized anticoagulation clinics: positive effects on quality of life. J Thromb Haemost. 2004; 2(4):584–91. https://doi.org/10.1111/j.1538-7836.2004.00659.x PMID: 15102012

49. Ogutmen B, Yildirim A, Sever MS, Bozfakio glu S, Ataman R, Erek E, et al. Health-related quality of life after kidney transplantation in comparison intermittent hemodialysis, peritoneal dialysis, and normal controls. Transplant Proc. 2006; 38(2):419–21. https://doi.org/10.1016/j.transproceed.2006.01.016 PMID: 16549136

50. Bayoumi M, Al-Harbi A, Al Suwaida A, Al Ghonaim M, Al Wakeel J, Mishkiry A. Predictors of quality of life in hemodialysis patients. Saudi J Kidney Dis Transpl. 2013; 24(2):254–9. https://doi.org/10.4103/1319-2442.109566 PMID: 23538347

51. Daher AM, Ibrahim HS, Daher TM, Anbori AK. Health related quality of life among Iraqi immigrants settled in Malaysia. BMC Pub Health. 2011; 11:407. https://doi.org/10.1186/1471-2458-11-407 PMID: 21624118

52. Nedjat S, Montazeri A, Holakouie K, Mohammad K, Majdzadeh R. Psychometric properties of the Iranian interview-administered version of the World Health Organization’s Quality of Life Questionnaire (WHOQOL-BREF): A population-based study. BMC Health Serv Res. 2008; 8:61–6. https://doi.org/10.1186/1472-6963-8-61 PMID: 18366715

53. Gerasimoulia K, Lefkothea L, Maria L, Victoria A, Paraskevi T, Maria P. Quality of life in hemodialysis patients. Mater Sociomed. 2015; 27(5):305–9. https://doi.org/10.5455/msm.2015.27.305-309 PMID: 26622195

54. Yang SC, Kuo PW, Wang JD, Lin MI, Su S. Quality of life and its determinants of hemodialysis patients in Taiwan measured with WHOQOL-BREF (TW). Am J Kidney Dis. 2005; 46(4):635–41. https://doi.org/10.1053/j.ajkd.2005.06.015 PMID: 16183418

55. Sathvik BS, Parthasarathi G, Narahari MG, Gurudev KC. An assessment of the quality of life in hemodialysis patients using the WHOQOL-BREF questionnaire. Indian J Nephrol. 2008; 18(4):141–9. http://dx.doi.org/10.4103/0971-4065-4065.45288 PMID: 20142925

56. Hakem H, Khan AZ, Aziz K, Abbasi A, Haider A, Moiz B. Evaluation of quality of warfarin therapy by assessing patient’s time in therapeutic range at a tertiary care hospital in Pakistan. J Pak Med Assoc. 2018; 68(9):1339–44. http://dx.doi.org/10.7759/cureus.3439 PMID: 30317261

57. Ageno W, Gallus AS, Wittkowski AS, Crowther M, Hyle EM, Palareti G. Oral anticoagulant therapy—Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012; 141(2 Suppl.):e445S–e698S. http://dx.doi.org/10.1378/chest.11-2292 PMID: 22315269

58. Wigle P, Hein B, Bloomfield HE, Tubb M, Doherty M. Updated guidelines on outpatient anticoagulation. Am Fam Physician. 2013; 87(8):556–66. PMID: 23668445