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Appropriateness of anticoagulation level in older adult patients on Warfarin: A multicenter retrospective study

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ABSTRACT

Warfarin is favored over newer direct oral anticoagulants (DOACs) for many older adults. However, its use necessitates rigorous monitoring due to the fine line between toxic and therapeutic doses. Few studies have evaluated the anticoagulation quality of warfarin among elderly patients in Saudi Arabia. This study aimed to assess and identify factors affecting the anticoagulation quality of warfarin using the time in the therapeutic range (TTR) among older adults attending two hospitals in Saudi Arabia. Additionally, we aimed to evaluate differences in the anticoagulation quality of warfarin when managed by pharmacists or physicians. This cross-sectional study was conducted at King Abdullah bin Abdulaziz University Hospital (KAAUH) and King Fahad Medical City (KFMC) in Riyadh, Saudi Arabia. After calculating the TTR of each patient, the anticoagulation control level was determined using these values: a) good control: >70 %; b) intermediate control: 50–70 %; c) poor control: <50 %. A total of 132 patients prescribed warfarin therapy for different indications were included. Most patients (45.5 %) had poor control with TTRs < 50 %, while 18.2 % had intermediate control, and 36.4 % had good control.

Our exploratory findings suggest that having three or more comorbidities was a significant factor associated with a poor TTR [odds ratio (OR) = 3.36; (95 % confidence interval 1.28–8.81); $P = 0.014$]. Thus, the anticoagulation quality of warfarin among older adult patients was poor in two Saudi Arabian tertiary hospitals, and the number of comorbidities was a potentially poor TTR predictor.

1. Introduction

Warfarin is one of the most frequently prescribed anticoagulant drugs and has been used as an anticoagulant since the 1950 s (Wen & Lee, 2013). Despite direct oral anticoagulants (DOACs) availability and their proven safety as well as efficacy, warfarin is still used by many patients (Farsad et al., 2016). Warfarin is commonly prescribed to prevent thrombosis in older adult patients at risk of thromboembolism (Albabtain et al., 2020). Unlike DOACs, warfarin initiation is recommended at a lower dose that is 10–20 % below the normal starting dose in older adult patients due to the bleeding risk (Patel et al., 2022). Moreover, warfarin requires careful international normalized ratio (INR) monitoring because there is a narrow margin between toxic and effective doses (Albabtain et al., 2020; Habet, 2021). The warfarin dose is determined based on the INR target range for the treatment indication (Alyousif & Alsaileek, 2016). For example, a therapeutic target INR range of 2–3 is recommended for patients with atrial fibrillation (AF), deep vein thrombosis, pulmonary embolism, valvular heart disease, and myocardial infarction. Furthermore, a higher 2.5–3.5 therapeutic range is recommended for patients with mechanical mitral valve replacement

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or dual aortic and mitral mechanical valve replacement.

Older adults are more likely to experience thromboembolic events and bleeding, even when they are within the therapeutic anticoagulation range. This heightened risk is due to multiple factors, including frailty, multi-comorbidities, and polypharmacy (de Padua Mansur et al. (2012)). Additionally, older adults undergo physiological changes that may cause significant adverse events. These physiological changes include decreased CYP2C19 activity, which is necessary for warfarin metabolism, and decreased liver mass as well as blood flow, resulting in decreased drug clearance. Older adults tend to have a two- to three-fold increase in minor bleeding and cerebral hemorrhage (Laínez-Sánchez & Villalobos-Masis, 2011).

Time in therapeutic range (TTR) assesses anticoagulation warfarin quality and is defined as the percentage of time that the INR of a patient is within the intended treatment range (Hossam et al., 2009). TTR is a crucial tool for weighing warfarin therapy risks as well as benefits and is frequently used to measure the quality of warfarin therapy (Hossam et al., 2009). Because the TTR is a key factor in determining warfarin effectiveness and safety, its measurement enables clinicians to determine the success of warfarin therapy. The maximum benefit occurs when the TTR exceeds 70 % (Hossam et al., 2009).

Few studies have assessed the anticoagulation effects of warfarin among older adults in Saudi Arabia. A retrospective cohort study included 1914 patients receiving warfarin. Most study subjects were adult female patients with non-valvular AF, valvular AF, prosthetic valves, and venous or pulmonary embolisms. Participants in this study had a 52 % median TTR, lower than the recommended value (>60 %) (Albabtain et al., 2020).

Another retrospective cohort study assessed the anticoagulation quality of warfarin in 110 patients with nonvalvular AF. Most participants were female, with a 59 % mean TTR, and 32.7 % had TTR values lower than 50 %, indicative of suboptimal anticoagulation control. The study concluded that patients with high $CHADS_2$ scores were likelier to receive poor anticoagulation (Alyousif & Alsaileek, 2016). These studies included patients receiving warfarin for specific indications. This study aimed to include older adults with broad warfarin anticoagulation indications.

Our study aimed to evaluate the anticoagulation quality of warfarin among older adults in two Saudi Arabian hospitals, identify factors affecting the anticoagulation quality of warfarin, and assess anticoagulation quality differences of warfarin when managed by pharmacists or physicians.

2. Methods

2.1. Study design and study population

This cross-sectional study was conducted at King Abdullah Bin Abdulaziz University Hospital (KAAUH) and King Fahad Medical City (KFMC), Riyadh, Saudi Arabia. Patients meeting the following criteria were included: 1) aged 60 years or older, 2) received warfarin therapy at the outpatient clinic for over three months, and 4) underwent at least two INR readings. Patients who were maintained on another anticoagulant agent or warfarin and had only one INR reading were excluded. Institutional Review Board (IRB) approval was obtained from the KAAUH (IRB #22–0644) and KFMC (IRB #22–518) Scientific Committees. Additionally, all participant data were collected anonymously, and only the research members could access the data.

2.2. Data collection

Study data were collected from the KAAUH and KFMC electronic medical records. Sociodemographic data were collected, including age, sex, warfarin indication, medical history, current medications, latest serum creatinine level, and INR readings. Each TTR of the patients was calculated using the Rosendaal method, defined as follows:

$TTR = \frac{no.ofdaysinrange}{totalmonitoreddays}$(Siddiqui et al., 2018). This calculation was performed using an Excel spreadsheet developed by the INR PRO Reporting Systems. Before calculating the TTR for each patient, the system requires their INR values, testing dates, and target INR levels. The anticoagulation quality of warfarin was determined for each patient after calculating their TTR using the following values: good control: TTR > 70 %; intermediate control: TTR 50–70 %; and poor control: TTR < 50 %. Additionally, HAS-BLED and CHA2DS2-VASc scores were calculated for each patient to predict the stroke as well as bleeding risks, respectively (Zhu et al., 2015; Gažová et al., 2019).

2.3. Statistical analysis

Data was analyzed using the Statistical Package for Social Sciences (SPSS), version 29 (IBM Corp., Armonk, NY, USA). Descriptive statistical data analysis using frequency and percentage (%), mean and standard deviation (±SD), or median and interquartile range (IQR) was reported based on data type and distribution. A chi-square (X^2) test assessed the associations between categorical data.

To determine the factors associated with the anticoagulation quality of warfarin, patients were categorized into two groups according to their TTR, namely poor anticoagulation quality (TTR < 70 %) and good anticoagulation quality (TTR ≥ 70 %). A logistic regression model was used to determine factors associated with the anticoagulation quality of warfarin. All logistic regression model assumptions were checked and met before conducting unadjusted and adjusted variable analyses, including demographic characteristics, comorbidities, warfarin dose, creatinine clearance, clinical pharmacist involvement, polypharmacy, and warfarin indications. An adjusted logistic regression model was constructed after collecting all the variables and verifying the model assumptions. All the variables were tested at a 0.05 significance level.

3. Results

There were 132 patients who met the inclusion criteria. Female participants represented 60.6 % of the study sample. The median age of the study sample was 66, with a 63-year minimum and a 73.5-year maximum. On average, the participants had three comorbidities (±1.2), and 70.5 % were using ≥ five medications. The most common warfarin indications were AF (47 %), mechanical valve replacement (37.87 %), and coronary artery disease (CAD; 11.37 %). Table 1 describes the patient demographics and characteristics.

Approximately 45.5 % participants had poor anticoagulation control, 18.2 % had intermediate control, and 36.4 % had good control as demonstrated in Table 1.

Table 2 presents the unadjusted and adjusted logistic regression model findings. In the unadjusted models, no tested variables were significant, including age, sex, BMI, comorbidities, warfarin dose, creatinine clearance (CrCl), healthcare professional management, polypharmacy, and warfarin indications. However, comorbidities were significant when all other factors were controlled for in the adjusted model. The odds of having a poor quality of warfarin increased 3.36-fold when having ≥ three comorbidities after controlling for other variables [P = 0.014; (1.28 – 8.81)].

Fig. 1 reveals a forest plot of the pre-specified TTR predictor multivariate analyses. Concerning warfarin-related complications, most participants were at a potential risk of experiencing issues related to warfarin. More than half of the participants (55.3 %) had a high bleeding risk, 37.9 % had a moderate risk, and 6.8 % had a low risk. However, as demonstrated in Fig. 2, there was no statistically significant association between bleeding risk and TTR (p = 0.51). CHA2DS2-VASc scores for most participants (90 %) were ≥ two (Table 2). Fig. 3 describes a statistically significant association between the CHA2DS2-VASc score and TTR (p = 0.02). Patients with poor TTR control had higher CHA2DS2-VASc scores than those with intermediate and good TTR control.

Table 1
Study participants' demographic and characteristics.

Variables	Total (n = 132)
Age, years (median, IQR)*	66 (63–73.50)
Female sex, n (%)	80 (60.6)
BMI (mean, ±SD)	30.91 (7.71)
Serum creatinine (umol/L) (median, IQR)	82 (67.5–110.50)
CrCl (ml/min) (mean, ±SD)	69.50 (30.23)
Indication for warfarin, n (%)	
AF	62 (47)
TAPS	4 (3)
CAD	15 (11.36)
VT	12 (9.1)
MVR	50 (37.87)
Warfarin dose (mg/week)	
Continuous (median, IQR range)	28 (15–42)
HAS-Bled score, n (%)	
Low risk (=0)	9 (6.8)
Moderate risk (1–2)	50 (37.9)
High risk (≥3)	73 (55.3)
CHA2DS2-VASc n (%)	
Low to intermediate risk (≤1)	12 (9.1)
High risk (≥2)	120 (90.9)
Comorbidities, (mean, ±SD)	2.87(±1.2)
Comorbidities, n (%)*	
Arthritis	21 (15.9)
Osteoporosis	11 (8.3)
Degenerative disc disease	3 (2.3)
Pulmonary disease	26 (19.7)
Heart diseases	124 (93.9)
Neurological disease	3 (2.3)
Cerebrovascular disease	23 (17.4)
Peripheral vascular disease	9 (6.8)
Diabetes mellitus	71 (53.8)
Obesity	61 (46.2)
GI diseases	8 (6.1)
Depressive disorders	5 (3.8)
Anxiety disorders	3 (2.3)
Visual impairment	4 (3)
Hearing impairment	2 (1.5)
Medication Polypharmacy, n (%)	
<5 medications	39 (29.5)
≥5 medications	93 (70.5)
Medication history, n (%)	
TTR (median, IQR)	56.4 (23.7–78.37)
TTR, n (%)	
Good control (<50 %)	48 (36.4)
Intermediate control (50–70 %)	24 (18.2)
Poor control (>70 %)	60 (45.4)
Who is managing warfarin in KFMC, n (%)	
By physicians	54 (43.5)
By pharmacists	70 (56.5)

IQR = Interquartile Range.
SD = Standard Deviation
n = number.
CrCl – Creatinine Clearance.
BMI = Body Mass Index.
AF = Atrial Fibrillation
TAPS = Thrombotic Antiphospholipid Syndrome.
CAD = coronary artery disease.
VT = Venous Thromboembolism.
MVR = Mechanical Valve Replacement.
HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol) score.
CHA2DS2-VASc score = Congestive Heart Failure, Hypertension, age ≥ 75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65 to 74 and Sex category (Female).
TTR = Time in Therapeutic Range.
* Some participants may have had one or more comorbidities, resulting in the sum of numbers and percentages not equaling the total.

Table 2
Finding of logistic regression models to identify factors affecting the time in therapeutic range (TTR).

Variable	Model1 (unadjusted)		Model 2 (Adjusted)	
	OR (95 % CI)	***P-value***	**OR (95 % CI)**	***P-value***
Age	0.99 (0.94–1.05)	0.85	0.96 (0.90–1.03)	0.32
Female sex	0.70 (0.33–1.50)	0.36	1.84 (0.76–4.44)	0.17
BMI (kg/m2)	0.97 (0.92–1.04)	0.41	0.93 (0.86–1.01)	0.067
Comorbidity (≥3)	1.74 (0.824–3.68)	0.15	3.36 (1.28–8.81)	0.014
Dose of warfarin (mg/week)	0.98 (0.96–1.01)	0.27	0.98 (0.95–1.01)	0.15
CrCL (ml/min)	0.99 (0.98–1.01)	0.66	0.99 (0.97–1.011)	0.52
Managed by pharmacist	0.75 (0.35–1.59)	0.45	0.84 (0.35–2.04)	0.73
Polypharmacy (≥5 medications)	0.77 (0.33–1.76)	0.54	0.51 (0.18–1.39)	0.19
Indication for warfarin				
AF	**1.00**		**1.00**	
CAD	1.25 (0.35–4.47)	0.73	1.36 (0.34–5.45)	0.66
VT	6.35 (0.67–57.89)	0.17	6.95 (0.69–70.14)	0.11
MVR	1.10 (0.48–2.50)	0.82	0.95 (0.37–2.43)	0.91

Model 1 = univariateModel 2 = multivariate

CrCl = Creatinine Clearance.
BMI = Body Mass Index.
AF = Atrial Fibrillation
CAD = coronary artery disease.
VT = Venous Thromboembolism.
MVR = Mechanical Valve Replacement.
TTR = Time in Therapeutic Range.

Although the warfarin doses in KFMC were managed by a pharmacist (56.5 %) or a physician (43.5 %), the warfarin anticoagulation level (TTR) was not significantly different between patients managed by pharmacists or physicians (P = 0.36), as revealed in Fig. 4.

4. Discussion

TTR is a popular method used to measure the warfarin anticoagulation quality, closely related to the therapeutic warfarin efficacy and predicts adverse events (Siddiqui et al., 2018). This study found that older adult patients receiving warfarin at two different hospitals for various indications had lower TTR levels than the recommended optimal anticoagulation control level (>70 %). In this study, the median TTR level was 56.4 %, with a 23.7 % minimum and a 78.37 % maximum. These findings are consistent with previous studies that assessed TTR among younger patients (Albabtain et al., 2020; Alyousif & Alsaileek, 2016; Farsad et al., 2016; Hossam et al., 2009). Various patient factors may have caused inadequate warfarin anticoagulation levels. Previous studies have revealed that warfarin anticoagulation levels measured using the TTR may be affected by various patient factors (Albabtain et al., 2020; Alyousif & Alsaileek, 2016; Farsad et al., 2016; Hossam et al., 2009). In this study, the factor that significantly predicted lower warfarin anticoagulation control levels was the presence of ≥ three comorbidities. However, other factors were significant in other studies. Factors associated with poor anticoagulation control of warfarin among Egyptian patients included female sex, unemployment, illiteracy, and smoking (Hossam et al., 2009). A study conducted in Saudi Arabia found that patients with AF have poor anticoagulation control and high CHADS2 scores (Alyousif & Alsaileek, 2016). Another study conducted in Saudi Arabia revealed that uncontrolled diabetes, high alkaline

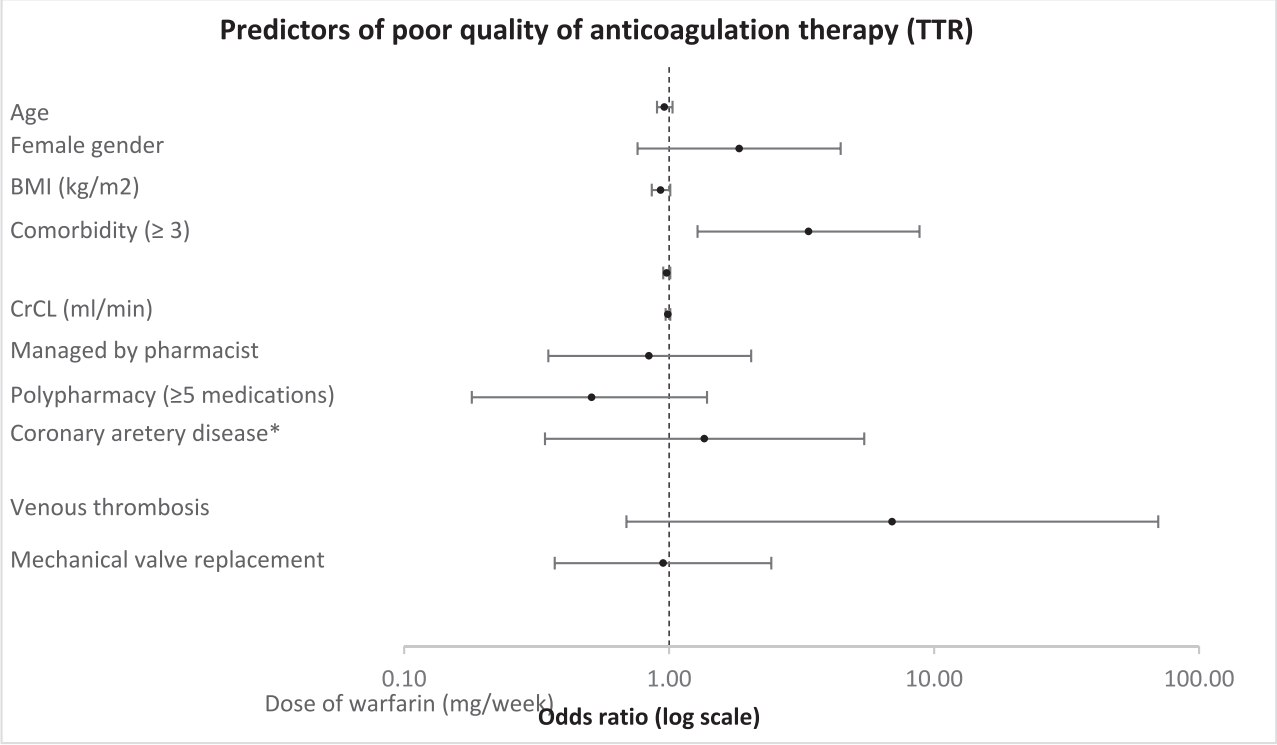

Fig. 1. Forest plot of multivariable logistic regression for predictors of poor TTR.

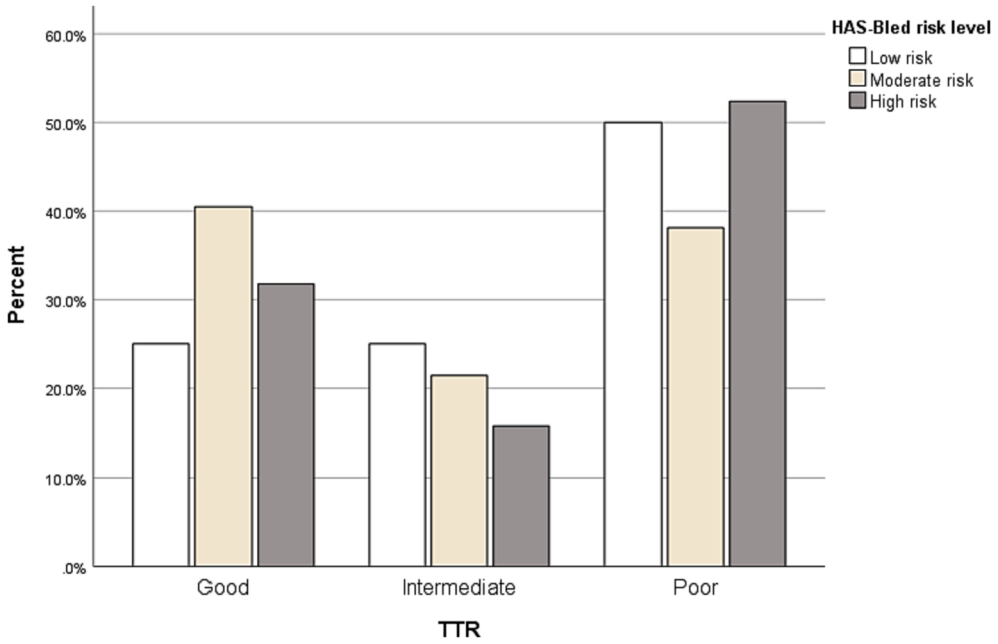

Fig. 2. Differences in the risk of bleeding between participants based on different levels of quality of anticoagulation control (TTR).

phosphatase levels, and venous thromboembolism warfarin indications were associated with low TTR level (Albabtain et al., 2020). Among Iranian patients, polypharmacy was the only significant factor associated with poor TTR level (Farsad et al., 2016). Additionally, in the current study, age was not significantly associated with anticoagulation control levels of warfarin, consistent with results of previous studies. Although factors including female sex, BMI, CrCl level, and venous thromboembolism indication for warfarin were not statistically significant, the trend in p-values for these factors revealed that there might be a significant association. A significant association between these factors and TTR may be found in a larger sample size. Therefore, further studies with larger sample sizes are required.

Pharmacist-led anticoagulation clinics play a significant role in warfarin therapy management (Alghadeeer et al. (2020)). The current study did not find a significant difference in the anticoagulation control warfarin levels between patients managed by a pharmacist or a physician in anticoagulation clinics. The few patients in the physician-led clinics may have affected this finding. Other studies that evaluated

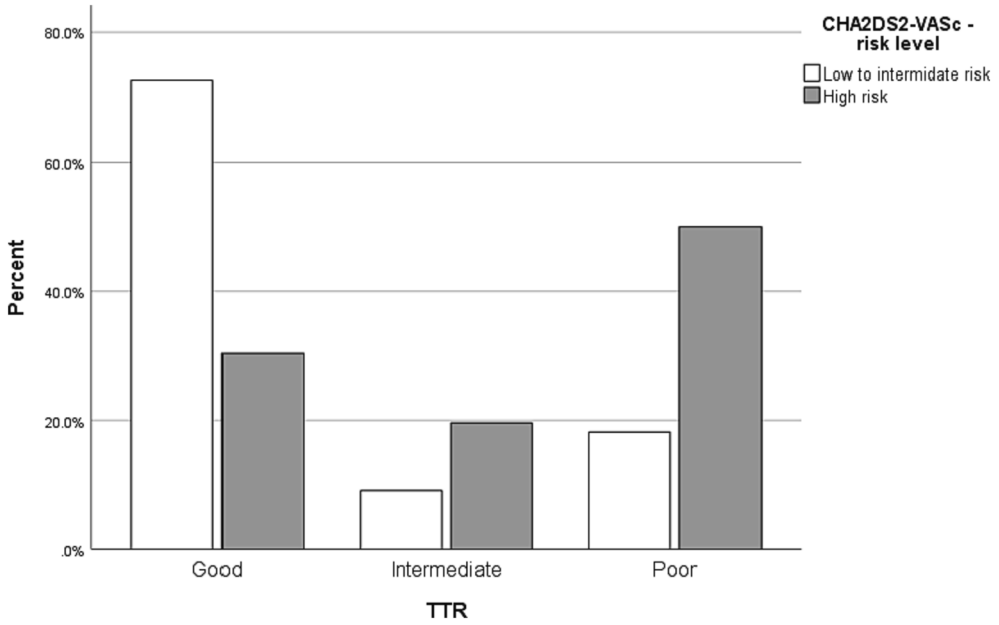

Fig. 3. Differences in CHAD2-VASc between participants based on different levels of quality of anticoagulation control (TTR).

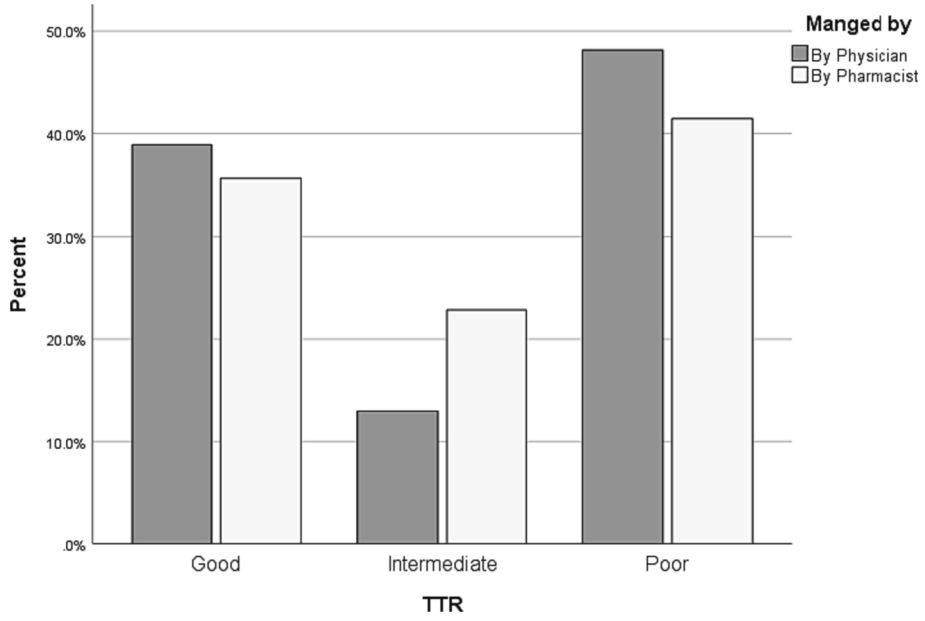

Fig. 4. The difference in anticoagulation level of warfarin (TTR) between participants who were managed by pharmacists and physicians.

physician-versus pharmacist-led anticoagulation management found that patients in pharmacist-led clinics had better TTR. Alghadeer et al. found that a pharmacist-led anticoagulation clinic achieved better TTR than a physician-led anticoagulation clinic (87 % ±3% and 52.5 % ±5.5 %, respectively; $p < 0.001$).

The strengths of this study include the assessment of the anticoagulation control warfarin levels in older adults with a wide indication range. Another strength was the inclusion of populations from two different hospitals.

This study had some limitations. First, it was a cross-sectional study with a small sample size. However, we attempted to overcome this issue by considering the biological definition of older adults as having multiple chronic diseases and functional limitations rather than the chronological 65 years of age definition (Jazwinski & Kim, 2019). Second, several factors that might affect TTR were not recorded, including herbal diet and educational level. Third, nonmedical factors could also be confounding factors contributing to poor TTR. As a tertiary hospital, the KFMC receives patients throughout Saudi Arabia. Due to the vast distance, many patients may have been advised to continue their follow-up at anticoagulation clinics closer to their homes. This follow-up system could have influenced the time interval accuracy between INR readings obtained at KFMC or KAAUH in Riyadh.

5. Conclusion

The anticoagulation control quality among older adult patients receiving warfarin therapy was suboptimal in a cohort of patients from two hospitals in Saudi Arabia. Older adult patients with ≥ three comorbidities are more likely to have inadequate anticoagulation control levels when treated with warfarin than those with fewer

comorbidities. Therefore, close monitoring is recommended for older adult patients with ≥ three comorbidities.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical Consideration.

This study was approved by the Institutional Review Boards (IRB) of King Abdullah bin Abdulaziz University Hospital (KAAUH) (IRB#22-0644) and King Fahad Medical City (KFMC) (IRB#22-518). No informed consent was required from the patients because all patient data were collected from electronic records.

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