Research Brief

Development of an interview-based warfarin nomogram predicting the time spent in the therapeutic INR range: A cost-effective, and non-invasive strategy building from a cross sectional study in a low resource setting

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ABSTRACT

A cross-sectional study was conducted to predict time in therapeutic range (TTR) using clinical history, examination, and socioeconomic data. Study included warfarin-receiving patients from outpatient-clinic. In 203 patients studied, mean warfarin start-dose was 2.55 mg/day and maintenance-dose/week was 30.79 mg. Body mass index (BMI) ($p = 0.03$), warfarin maintenance dose/day ($p = 0.02$), and comorbidity presence ($p = 0.04$) were significantly associated with TTR. Occupation ($p = 0.53$), income ($p = 0.83$), education ($p = 0.55$), and socioeconomic score ($p = 0.73$) showed non-significant association with TTR. A TTR predicting nomogram was built from clinical history and examination findings.

1. Introduction

Atrial fibrillation (AF), prosthetic heart valve disease, and deep venous thrombosis (DVT) increase the risk of stroke and systemic embolism.[1] Thromboembolism risk was significantly reduced in atrial fibrillation patients with warfarin anticoagulation.[2] India records stroke incidence ranging from one to two million new patients annually. However, the management costs ranges initially around 1–10 lakh rupees/year.[3]

Although various novel oral anticoagulants (NOACs) are available, warfarin remains a frequently used oral anticoagulant due to its low cost.[4] NOACs are not recommended for patients with concomitant renal compromise, children, patients with severe mitral stenosis, mechanical heart prosthesis, etc.[4] To maximize the gain, warfarin therapy needs to be assessed on the international normalized ratio (INR), time to reach therapeutic INR (TRT) and total time in therapeutic range (TTR).[5] Quality of warfarin therapy is assessed with the TTR. Studies have shown that more than 70% of TTR showed maximum benefit from warfarin.[6]

Besides diversity in warfarin initiation practices in India, the socioeconomic differences may be responsible for TTR and the overall prognosis, as suggested by Chebrolu et al study.[3] In nearly 50 countries participating in the ROCKET-AF trial showed the worst figure of 35.9% TTR of Indian patients receiving warfarin. Indian rural population was not represented in the same trial.[7] Our hospital is one of the premier tertiary care hospitals in North India, receiving urban as well as rural patients. The present study assessed warfarin anticoagulation quality, prescribing, and monitoring pattern to understand the important factors deciding the percent TTR.

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2. Methods

2.1. Type of study and setting

The cross-sectional study was conducted at outpatient clinics of the tertiary care referral hospital.

2.2. Inclusion criteria

Patients aged 18—75 years, diagnosed with valvular/non-valvular atrial fibrillation, prosthetic heart valve replacement surgery, deep venous thrombosis (DVT), pulmonary embolism (PE) — with ≥60 days on warfarin, and having ≥2 INRs were recruited.

2.3. Exclusion criteria

Patients with renal and hepatic insufficiency, receiving other anticoagulants, and unwilling to participate, including pregnant and lactating women, were excluded.

2.4. Patient interview and examination method

A written informed consent form was obtained from each participant. Sociodemographic details, addiction history, warfarin therapy details, clinical history and examination findings were noted on the case record form (Supplementary file 1). Level of warfarin drug interaction was analyzed using Holbrook et al study.[8] Rosendaal method[9] was used to calculate TRT and percent TTR. Percent TTR of each patient was classified as good (>70%), intermediate (≥50—70%), and poor (<50%) control as per Gallego et al[10] recommendations.

3. Results

Two hundred and three warfarin receiving patients participated in the study from July to October 2021 study period. Male to female ratio was almost equal. Participants' average age was 47.51 ± 12.15 years, and 23.65% of the patients had a BMI of ≥25 (Table 1).

Average warfarin start-dose and maintenance doses were 2.55 ± 0.97 and 4.39 ± 1.31 mg/day, respectively. Warfarin start-dose did not bear any association with patients' socioeconomic status ($p = 0.5$) (Table 2). The median duration of warfarin treatment was 280 days (IQR = 479), while the median TTR was 38.3% (IQR = 42%). Study observed 24 (11.8%) participants belonged to good TTR group (i.e. TTR >70%), 39 (19.2%) patients in intermediate TTR group (i.e. TTR >50% and <70%), and 140 (68%) patients in poor group (i.e. TTR <50%). Another subgroup of 20 (9.85%) patients was yet to reach their target therapeutic INR range. The median TRT was 96 days (IQR = 191) for the rest of the 183 patients observed to have attained the therapeutic range.

1893 INR readings were noted, and the mean INR frequency was 6.87 ± 4.42/participant. INR frequency/participant showed a non-significant association with education, occupation, income, and total socioeconomic score ($p > 0.05$).

Most patients required warfarin for valvular AF (41.4%), followed by prosthetic heart valve (39.4%) and Non-valvular AF (15.3%); 3% of patients with DVT and PTE were analyzed together and formed separate patient pools.

Participants' sociodemographic characteristics, clinical history and examination findings were statistically evaluated against TTR (Table 1). BMI, warfarin maintenance dose/day, and comorbidity presence showed a significant association with percent TTR on univariate logistic regression ($p < 0.05$). A multivariate logistic regression model was built predicting percent TTR using all three variables ($p = 0.01$) (Supplementary file 2 Table S1). The derived equation was:- Percent TTR = 74.54 − (0.876 x BMI) − (3.423 x comorbidity present or not) − (3.570 x warfarin maintenance dose/day).

Occupation, education, income, total socioeconomic score, socioeconomic status, and concomitant prescription of interacting medications showed a non-significant association with Percent TTR ($p > 0.05$) (Supplementary file 2 Table S2).

Hypertension, diabetes, thyroid dysfunction and peptic ulcer disease were the common comorbidies observed in the participants. Most common concomitant medications were metoprolol (66%), followed by spironolactone (60.1%), furosemide (51.23%), pantoprazole (38.42%), torsemide (17.24%), and diltiazem (11.33%).

3.1. Discussion

Warfarin is a zero-order kinetic drug economically suitable anticoagulant option to many patients in India. Efforts have been made in the past to strike a balance between anticoagulant efficacy versus bleeding-clotting risk. The western side of the globe prepared dosing nomograms using pharmacogenetic biomarkers.[4,11] These Lab-based nomograms are rarely practiced in India as it requires monetary expenditure, validation, and a head-to-head comparison of pharmacologically guided warfarin dosing versus standard of care warfarin dosing.[12,13] On the other hand, clinical history, examination, and socioeconomic assessment require no extra price but help understand the patient's capacity for INR monitoring and medication compliance.[14] Present study attempted to find out the important covariates from clinical history, physical examination, and socioeconomic details that may play a role in personalizing warfarin therapy in a low-resource setting.

It becomes pertinent, if the physician can predict percent TTR and thus the complications and overall prognosis.[7,15] Studies on maintenance warfarin dose evaluation have reported BMI, age, and concomitant medications as important covariates for personalizing warfarin therapy.[4,7] The novelty of the present study lies in the identification of a new covariate, i.e., comorbid diagnosis bearing significant association with percent TTR in addition to confirming earlier reports of BMI and warfarin daily maintenance dose.

The study observed almost two-thirds of patients in the poor TTR control group, i.e., TTR <50%. A similar observation was reported earlier in India.[3,11] The average TTR of warfarin receivers in the US is 55%, followed by 46% in the African belt and 37% in Iran.[3,7] Present study tried to dissect and identify if the socioeconomic factors played any role in explaining warfarin dose, actions relationship. The current study saw a statistically non-significant association between income, education, occupation, total socioeconomic score, and TTR. Such an assessment from a low-middle-income country becomes highly important while selecting oral anticoagulant alternatives depending on the patient's reach for INR monitoring, physician consultation fees, and wages lost in caregiving.[3] Median TRT in the present study was 96 days. The reluctance of 10 mg warfarin initiation dose in the present study is supported by a systematic review by Garcia et al reporting benefit uncertainty in the background of heterogeneity of warfarin initiation studies.[5]

3.2. Limitation

The study findings need to be validated in another resource constrained setting with a larger sample size.

3.3. Conclusion

A simple non-invasive nomogram was developed based on clinical history and examination findings. Pharmacogenetic

Table 1
Patient characteristics receiving warfarin and its association with time spent in therapeutic INR (TTR).

Demographic Details	TTR Control			P Value
	Good control	Intermediate Control	Poor Control	
Age (in years)				
18–29	3 (15.79)	4 (21.05)	12 (63.16)	0.59
30–39	6 (14.63)	6 (14.63)	29 (70.73)	
40–49	5 (10.64)	9 (19.15)	33 (70.21)	
50–59	8 (12.7)	14 (22.22)	41 (65.08)	
60–65	2 (6.06)	6 (18.18)	25 (75.76)	
Gender				
Male	24 (25.8)	60 (64.5)	9 (9.7)	0.367
Female	15 (13.6)	80 (72.8)	15 (13.6)	
BMI				
Obesity Class II	0 (0)	0 (0)	2 (100)	0.036*
Obesity Class I	0 (0)	0 (0)	8 (100)	
Pre-obese (overweight)	4 (10.5)	8 (21.1)	26 (68.4)	
Normal Weight	14 (11.6)	24 (19.8)	83 (68.6)	
Underweight	8 (23.5)	7 (20.6)	19 (55.9)	
Final Diagnosis				
DVT/PTE	1 (12.5)	1 (12.5)	6 (75)	0.663
Prosthetic heart valve pts.	7 (8.7)	14 (17.5)	59 (73.8)	
Valvular AF	12 (14.3)	19 (22.6)	53 (63.1)	
Non-valvular AF	4 (12.9)	5 (16.1)	22 (71)	
Comorbid diagnosis				
Yes	6 (7.7)	12 (15.4)	60 (76.9)	0.05*
No	20 (14.5)	26 (21)	78 (64.5)	
Blood pressure				
Controlled	19 (13.19)	27 (18.75)	98 (68.06)	0.56
Uncontrolled	5 (8.47)	12 (20.34)	42 (71.19)	
Interacting drug prescribed				
Yes	16 (11.35)	29 (20.57)	96 (68.08)	0.77
No	8 (12.9)	10 (16.13)	44 (70.97)	
Level of interaction				
Highly Probable	4 (10)	8 (20)	28 (70)	0.87
Probable	3 (17.64)	4 (23.53)	10 (58.82)	
Possible	1 (6.67)	3 (20)	11 (73.33)	
Highly Improbable	8 (11.43)	14 (20)	48 (68.57)	
Not Possible	8 (13.11)	10 (16.39)	43 (70.49)	
History of alcoholism				
Present	3 (6.98)	10 (23.25)	30 (69.77)	0.73
Absent	21 (13.12)	29 (18.13)	110 (68.75)	
Currently consuming alcohol				
Present	0 (0)	0 (0)	4 (100)	0.184
Absent	24 (12.06)	39 (19.6)	136 (68.34)	
History of smoking				
Present	2 (11.76)	5 (29.41)	10 (58.82)	0.41
Absent	22 (11.83)	34 (18.28)	130 (69.89)	
Currently smoking				
Present	0 (0)	1 (100)	0 (0)	0.22
Absent	24 (11.88)	38 (18.81)	140 (69.31)	
History of poor medication compliance				
Present	0 (0)	4 (20)	16 (80)	0.18
Absent	24 (13.11)	35 (19.12)	124 (67.76)	
INR range				
2.5–3.5	9 (11.25)	14 (17.5)	57 (71.25)	0.28
2.0–3.0	19 (15.44)	25 (20.32)	79 (64.22)	
Kuppuswamy's total score and socioeconomic class				
26-29 (Upper class)	0(0)	3 (42.86)	4 (57.14)	0.73
16-25(Upper middle class)	17(14.53)	20 (17.09)	80 (68.38)	
11-15 (Lower middle class)	4(5.97)	13 (19.4)	50 (74.63)	
5-10 (Upper lower class)	3(25)	3 (25)	6 (50)	
<5 (Lower class)	0	0 (0)	0 (0)	

*p value ≤ 0.05 was assumed significant.
TTR- Time spent in therapeutic INR, BMI- Body Mass Index, DVT- Deep vein thrombosis, PTE- Pulmonary thromboembolism, AF- Atrial Fibrillation.
Number outside bracket represent absolute number of patients whereas inside represent percentage of patients. **Kuppuswamy total score is sum of occupation, education and income variables.**

Table 2
Prescription pattern on warfarin start dose.

Start warfarin dose range	Socioeconomic class as per Kuppuswamy socioeconomic scale, 2021					P value
	Upper Class	Upper middle	Lower Middle	Upper lower		
<2.5	6 (5.83)	58 (56.31)	32 (31.07)	7 (6.8)	103	0.51
≥2.5—5	1 (1.02)	58 (59.18)	35 (35.71)	4 (4.08)	98	
>5-10	0 (0)	1 (50)	0 (0)	1 (50)	2	

p value ≤ 0.05 was assumed significant.

algorithms can consider comorbid diagnosis as a significant co-variate, increasing the precision of warfarin dosing algorithms further.

Author statement

AA: data collection and compilation, manuscript writing; RK, AG, SM, RV, DL, PB: provided patients under their care, for study participation along with study conduct inputs; SS: Literature review, data cleaning; ANP: Formal analysis, writing - Review & Editing. AA and RK contributed equally to the manuscript.

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Data availability

The raw data can be accessed from the corresponding author on a reasonable request.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2022.03.008.

References

1. Shafeeq H, Tran TH. New oral anticoagulants for atrial fibrillation. *Pharm Ther.* 2014 Jan;39(1):54—64.
2. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American heart association/American stroke association, 2021 Jul *Stroke.* 2021;52(7):e364—e467.
3. Chebrolu P, Patil S, Laux TS, Al-Hammadi N, Jain Y, Gage B. Quality of anticoagulation with warfarin in rural Chhattisgarh, India. *Indian J Med Res.* 2020 Sep;152(3):303—307.
4. Kaur N, Pandey A, Shafiq N, et al. Genetic and nongenetic determinants of variable warfarin dose requirements: a report from North India. *Public Health Genomics.* 2021 Oct 21:1—9.
5. Garcia P, Ruiz W, Loza Munarriz C. Warfarin initiation nomograms for venous thromboembolism. *Cochrane Database Syst Rev.* 2013 Jul 10;(7):CD007699.
6. Farsad B-F, Abbasinazari M, Dabagh A, Bakshandeh H. Evaluation of time in therapeutic range (TTR) in patients with non-valvular atrial fibrillation receiving treatment with warfarin in tehran, Iran: a cross-sectional study. *J Clin Diagn Res.* 2016 Sep;10(9):FC04—FC6.
7. Singer DE, Hellkamp AS, Piccini JP, et al. Impact of global geographic region on time in therapeutic range on warfarin anticoagulant therapy: data from the ROCKET AF clinical trial. *J Am Heart Assoc.* 2013 Feb 19;2(1), e000067.
8. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions, 10.1001/archinte.165.10.1095. PMID: 15911722 *Arch Intern Med.* 2005 May 23;165(10):1095—1106.
9. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemostasis.* 1993;69(3):236—239.
10. Gallego P, Vilchez JA, Lane DA. Apixaban compared with warfarin for stroke prevention in atrial fibrillation: implications of time in therapeutic range. *Circulation.* 2013 Jun 4;127(22):2163—2165.
11. Johnson JA, Caudle KE, Gong L, et al. Clinical pharmacogenetics implementation consortium (CPIC) guideline for pharmacogenetics-guided warfarin dosing: 2017 update. *Clin Pharmacol Ther.* 2017 Sep;102(3):397—404.
12. Lee MTM, Klein TE. Pharmacogenetics of warfarin: challenges and opportunities. *J Hum Genet.* 2013 Jun;58(6):334—338.
13. Kaye JB, Schultz LE, Steiner HE, Kittles RA, Cavallari LH, Karnes JH. Warfarin pharmacogenomics IN diverse populations. *Pharmacotherapy.* 2017 Sep;37(9): 1150—1163.
14. Tideman PA, Tirimacco R, St John A, Roberts GW. How to manage warfarin therapy. *Aust Prescr.* 2015 Apr;38(2):44—48.
15. Kuruvilla M, Gurk-Turner C. A review of warfarin dosing and monitoring. *Proc - Bayl Univ Med Cent.* 2001 Jul;14(3):305—306.