Development and implementation of a mathematical model for inpatient warfarin dosing: rationale and methods

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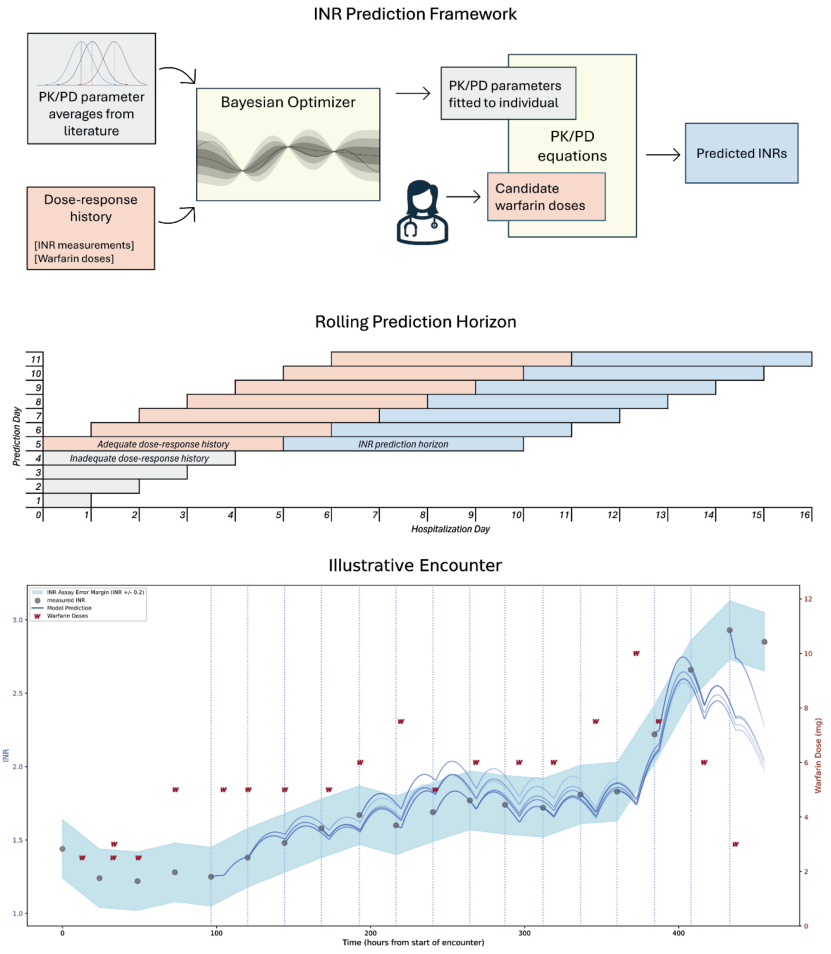
GRAPHICAL ABSTRACT



ABSTRACT

Despite a narrow therapeutic range, need for frequent monitoring, and continuous dosing adjustment, vitamin K antagonists like warfarin remain widely prescribed worldwide owing to superiority over newer anticoagulants in key patient populations and low cost. Several models exist to guide warfarin dosing in stable outpatients, but none validated for inpatient warfarin dosing. Instead, clinicians use blanket pre-specified warfarin initiation strategies, and adjust the dose based on clinical gestalt. There is a need for warfarin dosing guidance during the inpatient period to improve time to achieve the therapeutic effect, potentially decrease adverse events related to over- or under-anticoagulation, and reduce hospitalization times. Warfarin response is characterized by inter-individual and inter-temporal variability. At the same time, modern electronic health record infrastructure has made relevant data easily accessible. A simplified pharmacokinetic/pharmacodynamic (PK/PD) model for inpatient warfarin dosing has been previously described, but no implementation has been disseminated. This methods paper is intended to introduce a stepwise derivation and an open-source implementation of this previously described simplified PK/PD model designed for warfarin dosing in the inpatient setting that can be used for subsequent large-scale validation. The model has the potential, after extensive validation and extension, to serve as the core of a clinical decision support system that can accurately provide dosing recommendations to clinicians.

Key words: warfarin inpatient dosing; pharmacokinetic/pharmacodynamic model; open science.

Introduction

Vitamin K antagonists such as warfarin are used for the prevention and treatment of thromboembolic disease through the inhibition of vitamin K-dependent clotting factors.[1] Despite decades of clinical experience, warfarin therapy remains challenging due to its narrow therapeutic range, typically defined as an International Normalized Ratio (INR) of 2.0-3.0, and a J-shaped risk curve where INR values below 2.0 increase thrombotic risk, while values above 3.0 and especially above 5.0 elevate bleeding risk significantly.[2] Response variability and dosing challenges are attributed to genetic factors (*e.g.* CYP2C9, VKORC1 polymorphisms in White populations),[3] environmental factors (sleep, alcohol, diet, medication interactions), physiological and disease factors (age, body weight, liver function), as well as the lack of response data in key populations.[4]

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Availability of data and materials: the core model python code, along with the sample deidentified dataset analyzed in this study can be found in the Supplementary files.

Conflict of interest: the authors declare that they have no competing interests.

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While validated warfarin dosing nomograms exist for stable outpatients,[5–8] hospitalized patients experience acute medical conditions, and medication and dietary adjustments that can dramatically alter warfarin response throughout the hospitalization. Our previous study showed that 11% of elderly patients on chronic warfarin experienced INRs above 3.0 at admission, and the percentage increased to 33% within just 48 hours of hospitalization,[9] suggesting that even chronic stable warfarin patients enter into a highly unstable anticoagulation milieu immediately prior to and during hospitalization. In previous assessments of attempts to prevent INR overshoots, the Kimmel and Dawson, and High Dose warfarin dosing algorithms for inpatients[10] recommended doses higher than what clinicians prescribed for the most sensitive patients. We observed that rapid increases in INR values over 24-48 hours often preceded significant overshoots, with the rate of change (delta-INR) proving more predictive than absolute INR values.[11]

Predicting the INR of a patient on warfarin is an important intermediate step towards the goal of accurate individualized dosing, as the predictions are immediately actionable and can be used to simulate patient response to different warfarin doses. The prediction device would be integrated into the electronic health record infrastructure and provide specific warfarin dosing recommendations to clinicians. A previous mathematical model using an inpatient's recent warfarin dosing history and 5 INR values revealed reasonable predictive ability in the inpatient setting.[12] While the model has been previously described, no implementation had been made available. This methods paper describes the rationale and methodological considerations of implementing this simplified rolling-horizon pharmacokinetic/pharmacodynamic (PK/PD) model for inpatient warfarin dosing for further large-scale validation.

Materials and Methods

Mathematical model definitions

We used the simplified PK/PD model by Zhao *et al.*[12] The model describes a simplified mechanistic understanding of warfarin kinetics and contains five parameters that, when "fit" to the patient's previous warfarin and INR history provide an approximation of that patient's actual warfarin kinetics.

The five patient-specific parameters that require estimation are the following: warfarin elimination rate k_{el}^{w}, warfarin sensitivity (s), clotting factor elimination rate k_{el}^{c}, and two INR-related parameters (a, A) that define the dynamic bounds between which INR will theoretically range. The parameter a represents a theoretical lower bound for INR, while A is an offset, larger numerically than the lower bound, meaning $A>a$. Prior to fitting to each individual patient, the set of 5 parameters is initially set to population averages from studies that have measured them in real patients partaking in warfarin PK/PD studies.[12–15] A Bayesian minimization approach is then used to find the optimal set of parameters, optimizing for the smallest deviation of the predicted from the actual INR, while penalizing for solutions with parameters that deviate from the population average. This second component ensures parameter values are informed by population knowledge.

The model was implemented following the original paper's methodology on a rolling-horizon of the 5 most recent INR measurements, an admittedly *ad-hoc* timeframe that aligns with warfarin's pharmacokinetic properties (onset of action in 24-72 hours, peak effect 5-7 days after initiation),[1] This ensures the model retains its clinical flexibility and recency relative to the patient's condition, given there is significant inter-patient, temporal variability in warfarin response.[12]

Pharmacokinetic model

The pharmacokinetic (PK) model uses a single-compartment approach with the following assumptions: instant absorption of warfarin, 100% bioavailability and first-order elimination kinetics. Given these, the rate of change of the concentration of warfarin W (t) in the system at time t is described by the following equation.

$$\frac{dW(t)}{dt} = -k_{el}^{w} \times W(t)$$

Here W (t) is warfarin concentration at time t and k_{el}^{w} is the warfarin elimination rate constant. This parameter relates to warfarin's half-life and represents the fraction of drug eliminated per unit time. The warfarin concentration at any time point is calculated by summing the contributions of all previous doses up to 7 days with reference to the window's first known INR, with each dose being represented by its contribution at the timepoint of interest according to warfarin's exponential decay curve.

Pharmacodynamic model

The pharmacodynamic (PD) model describes how warfarin concentration affects clotting factor synthesis and INR, and it consists of three equations. We define warfarin's effects as follows:

$$E(W(t)) = 1 - \tanh(s \times W(t))$$

where $E(W(t))$ represents the effect of warfarin on clotting factor synthesis rates compared to baseline (ranging from 1 when no warfarin is in the system, to lower values with higher warfarin amounts), and s is a patient-specific warfarin sensitivity parameter to be estimated during fitting.

Clotting factor synthesis and elimination model

The physiological model for clotting factor concentration, $\frac{dC(t)}{dt}$ is the difference between the synthesis and the elimination rate:

$$\frac{dC(t)}{dt} = Rate\ of\ Synthesis - Rate\ of\ Elimination$$

In a baseline state, without warfarin, the model is:

$$\frac{dC(t)}{dt} = R_0 - k_{el}^{c} \times C(t)$$

Where C(t) is the current concentration of coagulation factors at time t, R_0 is the rate of synthesis without warfarin, and k_{el}^{c} is the first-order elimination rate constant for all clotting factors. Elimination is proportional to the concentration at each timepoint, and the relationship is defined by this elimination rate constant.

In a steady state without warfarin, the coagulation factor concentration is stable, meaning that $\frac{dC(t)}{dt}$, and we have the following relationship for the constant, baseline steady state concentration (C_{ss}) (eq. 1):

$$R_0 = k_{el}^{c} \times C_{ss} \quad \text{(eq. 1)}$$

None of these parameters are variable and dynamic. They are all stable physiological traits of the patient, and there is a fixed relationship between them. The introduction of warfarin has a modulating effect on the baseline rate of synthesis, causing an equivalent reduction in steady state concentration, scaled by k_{el}^{c}.

Regarding the synthesis rate after introducing warfarin, the synthesis of coagulation factors is inhibited in a manner consistent with $E(W(t))$, as defined previously. Therefore, the equation

$$\frac{dC(t)}{dt} = E(W(t)) \times R_0 - k_{el}^{c} \times C(t) \quad \text{(eq. 2)}$$

Normalization around baseline state

To make the model general, we normalize the clotting factor concentration by using its value relative to the patient's baseline without warfarin. We define the normalized clotting factor concentration $C_{norm}(t)$, as (eq. 3):

$$C_{norm}(t) = \frac{C(t)}{C_{ss}} \quad \text{(eq. 3)}$$

- $C_{norm}(t) = 1$ represents a patient at their normal, pre-warfarin baseline.
- $C_{norm}(t) < 1$ represents a patient with clotting factor levels suppressed by warfarin.

Thus, we can modify eq. 2, given eq. 1 and eq. 3 as follows, after multiplying both sides by C_{SS} (a patient-specific constant, as defined previously):

$$C_{ss}\frac{dC_{norm}(t)}{dt} = (k_{el}^{c} \times C_{ss}) \times E(W(t)) - k_{el}^{c} \times (C_{ss} \times C_{norm}(t)) \Leftrightarrow$$
$$\frac{dC_{norm}(t)}{dt} = k_{el}^{c} \times [E(W(t)) - C_{norm}(t)]$$

This way, we rewrite the equation without the baseline rate of synthesis (R_0). The elimination rate k_{el}^{c} accounts for the necessary scaling, implicitly absorbing the relationship between the baseline rate of synthesis, R_0, and the baseline coagulation factor concentration, C_{SS}.

International normalized ratio model and parameter linking through normalization

The relationship between clotting factor concentration and INR is modeled using an inverse function as seen below. The parameters a and A are introduced, representing the theoretical lower bound of INR for the patient and the baseline steady-state INR without warfarin, respectively ($a < A$). C_{SS} is the coagulation factor concentration at steady state.

$$INR(t) = a + \frac{A-a}{C(t)/C_{ss}} = a + \frac{A-a}{C_{norm}(t)}$$

Per this conception, the INR at each time has two components. The first is a theoretical lower bound represented by a, the theoretical minimum INR if clotting factor concentrations were infinitely high: $\lim_{C(t)\to\infty} INR = a$.

It is a mathematical asymptote, and it helps define the shape and steepness of the INR curve.

The second term, A, helps us define the *increase* of INR from this lower bound a, represented by $(A - a)$, relative to the ratio of coagulation factor activity compared to baseline ($C(t)$ / C_{SS}), or in our case simply the normalized coagulation factor concentration $C_{norm}(t)$. It models how responsive the INR is to changes in coagulation factor concentrations from the baseline steady state.

Model implementation and parameter estimation

The model was implemented in Python using accelerated linear algebra computing libraries.[16–19] Parameter estimation is performed through bounded optimization with the L-BFGS-B method, minimizing the objective function as it was described in the original paper[12] (see Supplementary Material for model implementation).

In the context of optimization, the *objective function* is a mathematical formulation that quantifies the performance associated with a set of choices (parameter values). The objective function defines a criterion that should be reduced to its lowest achievable value to optimize the fit of the model to the observed data. In this case, the first term of the objective function sum accounts for prediction errors (how far the predicted INR is from the observed INR during fitting), while the second term measures parameter deviation from population means, creating a Bayesian framework that adapts population priors to the patient with individualized and time-specific data. The data is time-specific because the model is implemented on a 5-INR measurement rolling-horizon, taking into account only the latest 5 known INRs. Warfarin concentration is predicted by summing the concentrations resulting from all doses administered over the preceding 7-day period since the last known INR, if available, each decayed according to the first-order elimination rate constant (k_{el}^{w}).

Results

The code provided can be used to run the model with individual patient data in a Python notebook. Results are presented for three illustrative examples with data availability for 15 prediction windows (Figure 1, Supplementary Table S1).

Discussion

The simplified PK/PD model for dosing hospitalized patients on warfarin offers several potential benefits for warfarin management in the inpatient setting, including potentially decreasing the time to achieve a therapeutic INR thus reducing the time to hospital discharge, reducing over- and under-anticoagulation rates, and potentially reducing adverse clinical outcomes related to warfarin. The rolling-horizon approach allows for updates to the parameters as new data becomes available, continuously improving model prediction and warfarin dosing. This aspect of the model is particularly valuable in the inpatient setting where clinical conditions change rapidly.

The model's performance varies by individual and prediction window (Figure 2), with better performance for patient 1 compared to 2 and 3 (Table 1).

Other warfarin dosing models have not been shown to improve warfarin management in the inpatient setting. Genetic analysis-informed algorithms can provide actionable insights for warfarin dosing,[20] but there has been no recommendation to pursue this type of testing outside of research settings. Previous attempts to use prespecified warfarin dose initiation strategies, or changes in warfarin dosing based on International Normalized Ratio (INR) dose responses have had limited success or have not been validated outside a narrowly defined population.[10,21–23] Though the dosing requirements for our model are 5 days, which can be considered a long hospital stay, having fewer than 3 INR measurements (*i.e.* fewer than 3 days of INR data) may not be enough to guide dose adjustments with any known method, given the kinetics of the medication.[10] It appears that a need for 4-5 days of data would be realistic with mathematical models, potentially 3-4 with machine learning methods, especially if they still require INR response data as is expected.

The sensitivity parameter (s) can also potentially provide quantifiable and clinically relevant information, if the model fit is acceptable for a sizable cohort of inpatients. It could represent an objective anticoagulation datapoint, aiding future dosing without the need for clinicians to estimate warfarin sensitivity on their own.[24] Patients with high s values would require lower doses to achieve therapeutic anticoagulation compared to what is now considered the population average and may be at higher risk for over-anticoagulation with standard dosing protocols.

Limitations

The current methods paper does not constitute clinical validation of the model or methodology. The randomly selected cases included are only for demonstration purposes and to aid the reader's understanding of the model's function. For it to be applicable in the clinical setting, the model would require extensive validation on large and varied retrospective and prospective datasets.

Future directions

A retrospective validation dataset will be sourced from 21 hospitals in the New York, NY, USA metropolitan area as part of a large health system, of which 5 hospitals are tertiary, 11 hospitals are community hospitals, and 5 hospitals are specialty care hospitals. We will include all inpatients that received

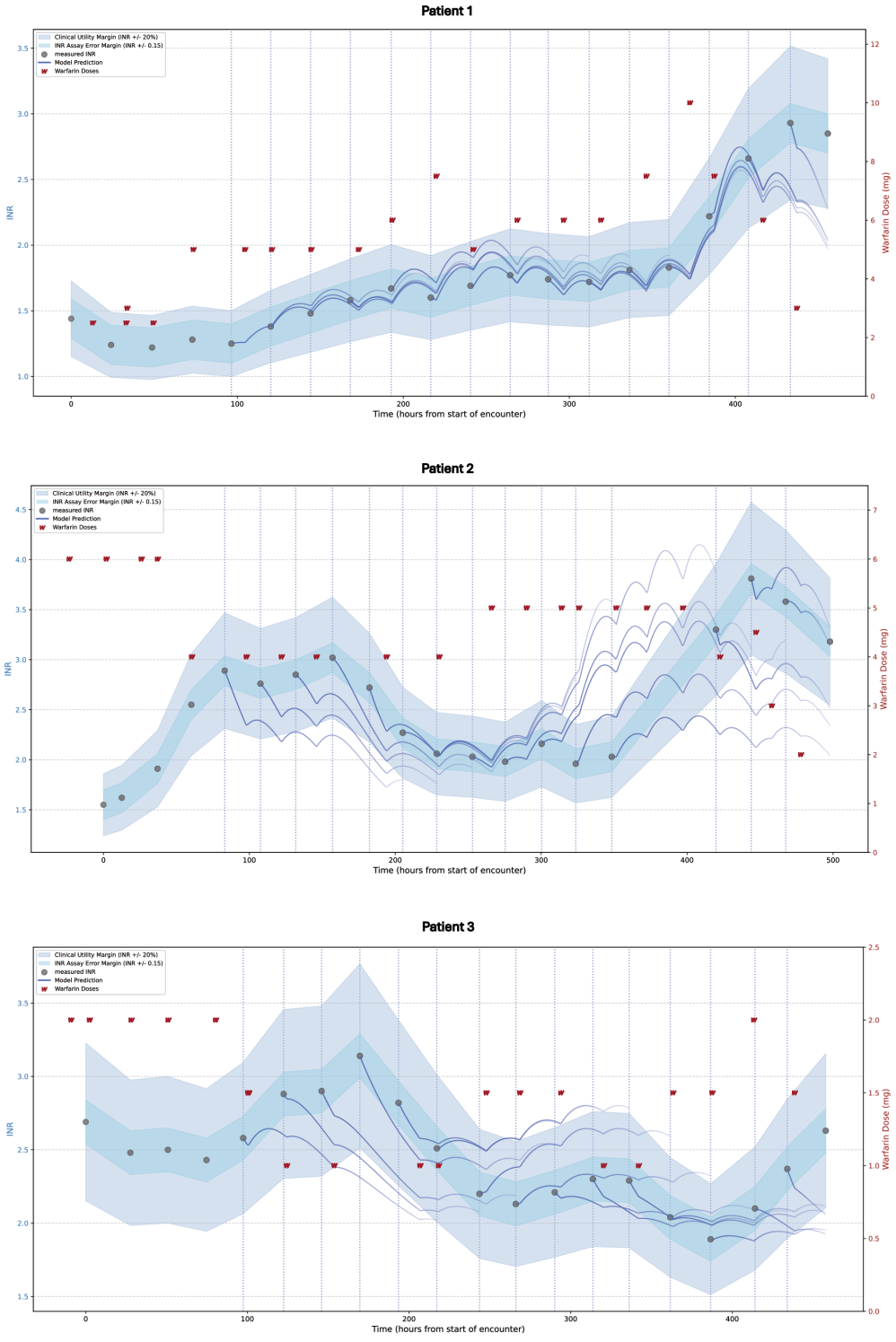

Figure 1. Prediction windows and respective modeled International Normalized Ratio (INR, trajectory lines) for 3 randomly selected real-world patients with 15 windows worth of data available. Each vertical dashed line represents the start of the prediction horizon for the new window, incorporating the 5 latest available INR measurements. The inner blue band represents the accepted INR assay error margin. The outer, lighter blue band represents the prespecified clinical utility cutoff of 20% Mean Absolute Percentage Error (MAPE). Trajectory lines represent continuous INR predictions up to 5-days out, based on previous and upcoming warfarin dosing. Patient 1: good model fit throughout. Patient 2: 1 and 2-day out predictions remain acceptable, despite a disruption due to the lack of INR data for 3 days towards the end of hospitalization. Patient 3: 1 and 2-day out predictions remain clinically useful throughout, but prediction accuracy is generally lower than for the first patient.

warfarin and had at least 6 contiguous INR measurements, admitted in the medical and surgical wards between Jan. 1st, 2018, and Dec. 31st, 2023, excluding Intensive Care Unit (ICU) and pediatrics admissions. Patients admitted between Jan 1st, 2024, and Dec 31st, 2024, will be held out as an internal, temporal validation dataset.

The simplified PK/PD model for dosing hospitalized patients on warfarin could be useful as a standalone or through integration with modern machine learning methods. Its incorporation in machine learning frameworks along with clinical and demographic characteristics represents the logical next step to improve prediction. The question whether a hybrid model of this type would perform better than a standalone causal machine learning model remains to be explored.

Ultimately, the PK/PD model can serve as the core of a clinical decision support framework to guide warfarin dosing. By predicting the patient's response to candidate warfarin doses, the framework could identify the best suggested dose based on the information available. The goal would be to decrease adverse outcomes and discharge delays related to warfarin therapy.[25]

Conclusions

The simplified PK/PD model for warfarin dosing in inpatients in transient clinical states may offer a promising approach to individualizing warfarin prediction in hospitalized settings. This implementation can be used to validate and extend or adapt the model in subpopulations of interest by adjusting the model itself, or the starting points for parameter predictions.

Table 1. Quantitative summary of Model's performance across the three presented cases and overall. A lower MAPE indicates a better fit. The low median MAE and IQR for patient 1 demonstrates consistently accurate predictions, but predictive performance varies across patients.

Patient	Mean MAPE±SD (%)	Median MAE (IQR)
1	8.49±6.55	0.10 (0.18)
2	17.43±9.30	0.46 (0.27)
3	12.67±5.30	0.28 (0.20)
Overall	12.86±7.99	0.28 (0.37)

SD, standard deviation; MAPE, mean absolute percentage error; MAE, mean absolute error; IQR, interquartile range.

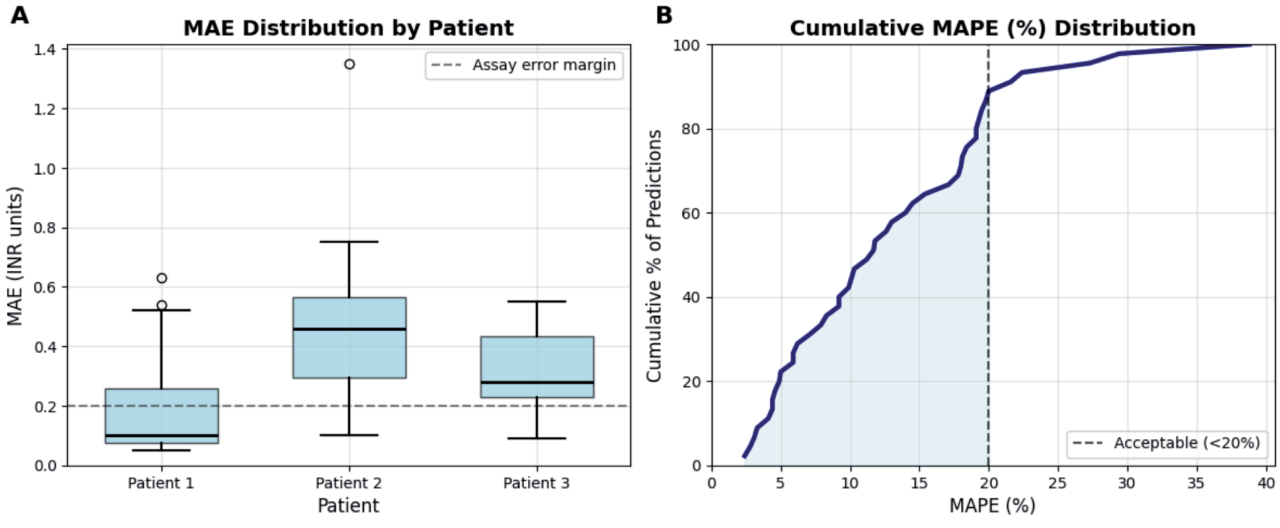

Figure 2. Aggregate performance graphs for the three cases presented. A) Mean Absolute Error (MAE) in International Normalized Ratio (INR) units by patient. INR assay error margin of 0.2 points represented by horizontal dashed line. B) Cumulative Mean Absolute Percentage Error (MAPE) for all predictions. Clinical relevance/acceptability threshold set at 20% of the actual INR value.

References

1. Patel S, Singh R, Preuss CV, et al. Warfarin. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Apr 21]. Available from: http://www.ncbi.nlm.nih.gov/ books/NBK470313/
2. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: executive summary. J Am Coll Cardiol 2006;48:854-906.
3. Kaye JB, Schultz LE, Steiner HE, et al. Warfarin pharmacogenomics in diverse populations. Pharmacotherapy 2017;37:1150-63.
4. Cross B, Turner RM, Zhang JE, et al. Being precise with anticoagulation to reduce adverse drug reactions: are we there yet? Pharmacogenomics J 2024;24:1-23.
5. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2008;133:381S-453S.
6. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141:e419S-e496S
7. Kim YK, Nieuwlaat R, Connolly SJ, et al. Effect of a simple two-step warfarin dosing algorithm on anticoagulant control as measured by time in therapeutic range: a pilot study. J Thromb Haemost 2010;8:101-6.
8. Van Spall HGC, Wallentin L, Yusuf S, et al. Variation in warfarin dose adjustment practice is responsible for differences in anticoagulation control between centers and countries. Circulation 2012;126:2309-16.
9. Cohen J, Sinvani L, Wang JJ, et al. Warfarin quality metrics for hospitalized older adults. TH Open 2018;2:e242-9.
10. Cohen J, Thompson E, Sinvani L, et al. Assessment of warfarin algorithms for hospitalized adults: searching for a safe dosing strategy. J Thromb Thrombolysis 2019;48:570-9.
11. Metersky M, Eldridge N, Wang Y, et al. Predictors of warfarin-associated adverse events in hospitalized patients: opportunities to prevent patient harm. J Hosp Med 2016;11:276-82.
12. Zhao Y, Liu N, Wang Y, et al. A rolling-horizon pharmacokinetic pharmacodynamic model for warfarin inpatients in transient clinical states. Pers Med 2016;13:21-32.
13. Holford NHG. Clinical pharmacokinetics and pharmacodynamics of warfarin: understanding the dose-effect relationship. Clin Pharmacokinet 1986.
14. Vadher B, Patterson DLH, Leaning M. Prediction of the international normalized ratio and maintenance dose during the initiation of warfarin therapy. Br J Clin Pharmacol 1999;48:63-70.
15. Carter BL, Taylor JW, Becker A. Evaluation of three dosage-prediction methods for initial in-hospital stabilization of warfarin therapy. Clin Pharm 1987;6:37-45.
16. Bradbury J, Frostig R, Hawkins P, et al. JAX: composable transformations of python+numpy programs [Internet]. Google; 2018. Available from: https://github.com/google/jax
17. Kidger P. On neural differential equations. Oxford: University of Oxford; 2021.
18. Blondel M, Berthet Q, Cuturi M, et al. Efficient and modular implicit differentiation [Internet]. arXiv; 2022 [cited 2025 Apr 24]. Available from: http://arxiv.org/abs/2105.15183
19. Google. Flax [Internet]. Google; 2025 [cited 2025 Apr 24]. Available from: https://github.com/google/flax
20. Gage BF, Eby CS, Johnson JA, et al. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. Clin Pharmacol Ther 2008;84:326-31.
21. Mahtani KR, Heneghan CJ, Nunan D, et al. Optimal loading dose of warfarin for the initiation of oral anticoagulation. Cochrane Database Syst Rev 2012;12:CD008685
22. Siguret V, Gouin I, Debray M, et al. Initiation of warfarin therapy in elderly medical inpatients: a safe and accurate regimen. Am J Med 2005;118:137-42.
23. Garcia P, Ruiz W, Loza Munárriz C. Warfarin initiation nomograms for venous thromboembolism. Cochrane Database Syst Rev 2016;2016:CD007699.
24. Kovacs MJ, Rodger M, Anderson DR, et al. Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism: a randomized controlled trial. Ann Intern Med 2003;138:714-9.
25. Lawrence JE, Fountain DM, Cundall-Curry DJ, et al. Do patients taking warfarin experience delays to theatre, longer hospital stay, and poorer survival after hip fracture? Clin Orthop Relat Res 2017;475:273-9.

Online supplementary material:

Supplementary Table S1. Mean Absolute Error (MAE), Mean Absolute Percentage Error (MAPE), Root Mean Squared Error (RMSE) and Relative Root Mean Squared Error (RRMSE) for each prediction window, for each patient.