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ORIGINAL ARTICLE

Establishing Mean Normal Prothrombin Time Bias Benchmarks for PT/INR Accuracy: a Patient-Based Simulation Study

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ABSTRACT

Background: **Accurate assessment of prothrombin time (PT)/International Normalized Ratio (INR) is essential for warfarin monitoring. Mean normal prothrombin time (MNPT) is the critical denominator in the INR formula. However, laboratories often adopt manufacturer-assigned MNPTs, tolerating up to 10% deviation from the locally established mean. This study quantitatively evaluated the clinical impact of this variation on dosing reclassification to establish a stringent evidence-based analytical tolerance threshold.**
Methods: **INR variations were simulated using patient data from 120 individuals receiving warfarin (target INR 2.0 - 3.0) at a single institution. The MNPT baseline was defined by the locally derived geometric mean MNPTs following the Clinical and Laboratory Standards Institute H47-A2 guidelines. Analytical biases ranging from ± 2.5 to ± 10.0% were applied to the baseline to calculate the reclassification rates across critical therapeutic boundaries (under-anticoagulation < 2.0, therapeutic 2.0 - 3.0, and over-anticoagulation > 3.0). The simulated results were interpreted alongside current international analytical performance specifications.**
Results: **Applying a ± 10.0% MNPT bias resulted in a clinical reclassification rate of 14.2 to 19.2%. Restricting MNPT bias to ± 2.5% reduced reclassification to 3.3%, with no patients showing an absolute INR difference ≥ 0.2 units relative to baseline.**
Conclusions: **Larger MNPT biases may result in clinically meaningful changes in INR interpretation and therapeutic classification. Patient-based simulation findings support the use of ± 2.5% MNPT verification target as a practical analytical goal that can be interpreted alongside existing international analytical performance specifications.**
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KEYWORDS

prothrombin time, international normalized ratio, mean normal prothrombin time, patient simulation, analytical performance specification

INTRODUCTION

Prothrombin time (PT) and the international normalized ratio (INR) are routine coagulation assays used to monitor patients receiving vitamin K antagonists (VKAs) such as warfarin [1,2]. Given the narrow therapeutic index of VKAs, ensuring the analytical accuracy of the PT/INR results is essential for appropriate clinical management. A key factor affecting INR accuracy is the

mean normal prothrombin time (MNPT), which serves as the denominator in the INR calculation formula: INR = (PT/MNPT) ^{ISI}, where ISI is the International Sensitivity Index [1].

Although the Clinical and Laboratory Standards Institute (CLSI) H47-A2 guideline recommends establishing a local MNPT using the geometric mean of at least 20 healthy donors, many laboratories routinely adopt manufacturer-assigned MNPT values provided in package inserts [3]. This practice implicitly assumes that the manufacturer's global reference population is directly applicable to the local patient demographic. Although manufacturer-assigned MNPT values are commonly used as an initial reference during local verification, such a verification requires a precise and reliable analytical tolerance threshold. Although laboratories commonly compare locally determined MNPT values with manufacturer-assigned values during reagent lot verification, the acceptable degree of agreement is largely based on manufacturer practice rather than on evidence derived from clinical outcome or patient-based analyses. The clinical evidence supporting the magnitude of acceptable agreement between the two values remains limited. The CLSI H47-A2 guideline recommends that the analytical imprecision of PT testing should not exceed a coefficient of variation (CV) of 5.0% for routine coagulation assays [3]. Although this recommendation addresses analytical precision rather than systematic bias, it provides a general benchmark indicating that analytical variability should be maintained within relatively narrow limits.

The clinical significance of MNPT accuracy is particularly important when considering the narrow therapeutic boundaries of INR: under-anticoagulation (< 2.0), the therapeutic range (2.0 - 3.0), and over-anticoagulation (> 3.0) [2]. In real-world clinical practice, to balance the competing risks of bleeding and thrombosis, many patients are tightly managed near these critical thresholds (e.g., maintained near an INR of 2.0 or 3.0) [4]. Therefore, even minor analytical deviations in MNPT can lead to clinical reclassification, prompting clinicians to make unsuitable dosage adjustments that increase the risk of major hemorrhage or thromboembolic events. This study aimed to quantitatively evaluate the impact of analytical variations in MNPT on the clinical reclassification of INR therapeutic categories using a mathematical simulation model based on clinical data. To our knowledge, no previous studies have systematically quantified the potential effects of MNPT on therapeutic classification using real-world clinical datasets. Furthermore, we proposed an evidence-based threshold for local MNPT validation to enhance patient safety and analytical quality in coagulation laboratories.

MATERIALS AND METHODS

Study design and population

In this retrospective simulation study, the clinical data of patients treated at a single institution between January 2025 and March 2026 were used. A total of 120 consecutive outpatients receiving maintenance warfarin therapy were included (Supplementary Table S1). The primary indications for warfarin included atrial fibrillation, valvular heart disease (predominantly mitral stenosis without mechanical prosthesis), venous thromboembolism (pulmonary embolism and other venous thrombosis), and antiphospholipid syndrome, all of which require a standard target INR range of 2.0 to 3.0. Patients requiring alternative target ranges (e.g., those with mechanical heart valves) were excluded to maintain cohort homogeneity. This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of Kyung Hee University Hospital at Gangdong (IRB No. KHNMC 2026-06-035), and the requirement for informed consent was waived due to the retrospective and anonymized nature of the data analysis.

Laboratory setting and baseline establishment

All routine coagulation tests were performed using a Cobas t711 automated coagulation analyzer and PT Rec A reagent (Roche Diagnostics, Mannheim, Germany). During the 15-month study period, four different reagent lots were used in the laboratory. To establish the baseline for our mathematical simulation, the locally derived geometric mean MNPT was calculated for each reagent lot in accordance with the CLSI H47-A2 guidelines [3]. Local MNPT was established for each of the four Cobas PT Rec A reagent lots. For each lot verification, fresh plasma samples were collected from 20 healthy adult donors (10 males and 10 females) with no history of anticoagulant therapy or liver disease. Testing was performed on the cobas t711 analyzer. The local MNPT was calculated as the log-transformed geometric mean of the 20 PT values in seconds (Supplementary Table S2). For the simulation, each patient's raw PT (in seconds) was paired with the specific local MNPT and ISI of the active reagent lot when the blood sample was obtained. This locally derived MNPT served as a reference baseline against which all analytical biases were evaluated.

Mathematical simulation protocol

A mathematical simulation was designed to evaluate the clinical impact of MNPT analytical errors on the INR calculation. Based on the standard equation, INR = (PT/MNPT) ISI, systematic analytical biases were applied to the reference baseline MNPT. Specifically, simulated deviations of ± 2.5%, ± 5.0%, ± 7.5%, and ± 10.0% were sequentially introduced into the baseline MNPT for each patient. Four analytical bias levels (± 2.5%, ± 5.0%, ± 7.5%, and ± 10.0%) were defined a priori to evaluate stepwise bias impacts on INR classification.

Simulated INRs were recalculated for each patient under each bias condition. Subsequently, the clinical reclassification rates were evaluated by analyzing how patients shifted across three critical therapeutic boundaries: under-anticoagulation (< 2.0), therapeutic range (2.0 - 3.0), and over-anticoagulation (> 3.0). The reclassification rate was defined as the percentage of patients whose simulated INR crossed these predefined clinical boundaries compared with their baseline classification.

RESULTS

Baseline characteristics

A total of 120 patients receiving maintenance warfarin therapy were included in this study. The median age of the cohort was 68 years (interquartile range, 62 - 78 years), and 70 patients (58.3%) were male. AF was the most frequent indication for warfarin use (n = 82, 68.3%). The detailed demographic and clinical characteristics are summarized in Table 1. Based on the locally derived baseline MNPT, the initial INR distribution was as follows: 58 patients (48.3%) in the under-anticoagulation category (< 2.0), 44 (36.7%) in the therapeutic range (2.0 - 3.0), and 18 (15.0%) in the over-anticoagulation category (> 3.0).

Impact of progressive MNPT bias on INR reclassification

The mathematical application of progressive MNPT biases to our baseline patient cohort demonstrated a bias-dependent escalation in both therapeutic category reclassification and individual INR discrepancies. The effect of progressive MNPT bias on INR category reclassification is summarized in Figure 1 (Supplementary Table S3). At a restrictive bias of ± 2.5%, only 4 of 120 patients (3.3%, 95% CI: 0.91% - 8.30%) crossed the therapeutic boundary (< 2.0 or > 3.0) in both directions and no patients (0.00%, 95% CI: 0.00% - 3.03%) exhibited an absolute INR deviation of ≥ 0.2 units from their baseline. Increasing the bias to ± 5.0% resulted in clinical reclassification rates of 7.5% at +5.0% bias and 10.0% at -5.0% bias, and individual outliers ≥ 0.2 INR units emerging in 1 (0.8%) and 8 (6.7%) cases, respectively. At ± 7.5% bias, the reclassification rate increased further to 10.8% at +7.5% bias and 16.7% at -7.5% bias, and individual discrepancies ≥ 0.2 INR units increased to 13 (10.8%) and 35 (29.2%) cases, respectively. Applying the conventional ± 10.0% tolerance limit produced reclassification rates of 14.2% at +10.0% bias and 19.2% at -10.0% bias, and the number of patients with an absolute discrepancy ≥ 0.2 INR units increased to 41 (34.2%) and 65 (54.2%) cases, respectively.

Comparison with existing recommendations

To evaluate whether the observed MNPT biases are acceptable in clinical practice, we reviewed the established guidelines for PT/INR testing. Because the ISI of most commercially used thromboplastins is generally close to 1.0, proportional errors in the MNPT translate into nearly equivalent proportional changes in the INR. Therefore, the existing analytical performance specifications for INR can be used to evaluate the clinical acceptability of the simulated MNPT bias. A comparison of these guidelines and their equivalent analytical targets is presented in Table 2.

Evaluation according to the College of American Pathologists (CAP) performance criteria

The CAP proficiency testing program uses a Special INR Evaluation scheme to rigorously monitor the accuracy of the reported INRs. In this evaluation, a laboratory's reported INR is compared against a calculated target INR, which is derived using the laboratory's specific ISI and MNPT. According to CAP grading criteria, acceptable analytical performance is achieved only if at least 80% of the reported INRs fall within a margin of ± 0.2 units of the calculated INR. While this scheme evaluates internal mathematical alignment rather than independent calibration accuracy, it provides a functional benchmark for equation stability under systematic MNPT bias [5].

Using this criterion, all patients remained within ± 0.2 INR acceptable limit under the ± 2.5% bias condition. At ± 5.0% bias, 99.2% and 93.3% of the patients remained within the acceptable range for positive and negative biases, respectively. Agreement decreased further to 89.2% and 70.8% at ± 7.5% bias, and to 65.8% and 45.8% at ± 10.0% bias.

Evaluation according to the International Council for Standardization in Haematology (ICSH) recommendations

The ICSH provides outcome-based quality criteria for evaluating PT/INR test systems using clinical samples specifically within the therapeutic range (INR 2.0 - 3.0). According to the guidelines, the validation of a new or unvalidated test system requires that the relative difference between the mean INRs of the two methods remains within 0.2 INR units. If this condition is not satisfied, the guidelines explicitly indicate that the assigned MNPT or ISI is incorrect. Furthermore, for the verification of an established PT/INR system, acceptable performance is defined as having greater than 85% of samples demonstrating an absolute difference of less than 0.5 INR units between the methods [6]. To contextualize the magnitude of these mathematical shifts against established method-comparison frameworks, we applied the 0.2 INR difference threshold from the ICSH 2021 recommendations as a theoretical reference benchmark. Although the ICSH criteria are originally defined for paired-method evaluations across distinct test systems, using this threshold to assess our single-system simulation demonstrated that in the present simulation, the number of patients showing absolute INR deviations ≥ 0.2 units increased in parallel with increasing MNPT bias. At ± 2.5% bias, no such deviations were observed, whereas progressively larger proportions of patients ex-

Table 1. Baseline demographic and clinical characteristics of the study population.

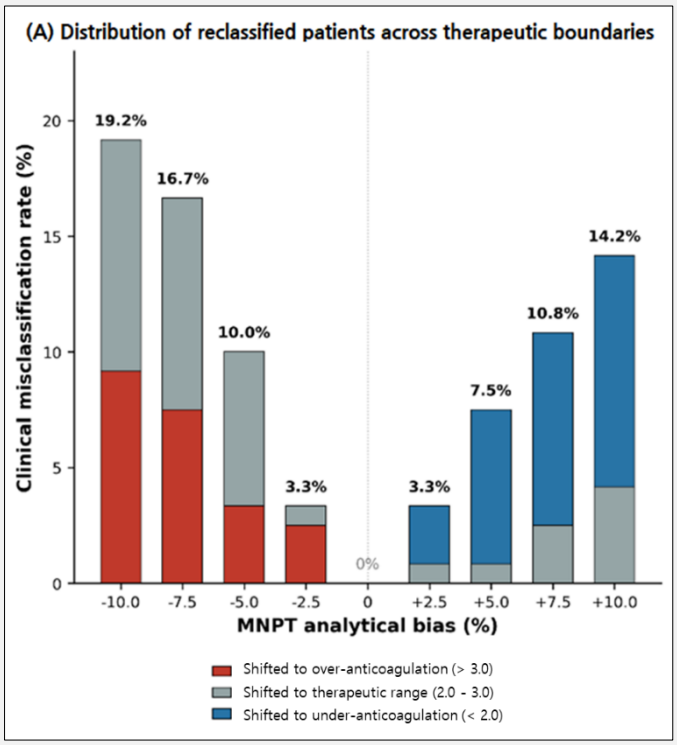
Characteristics	Total (n = 120)
Age, years	
Median (IQR)	68 (62 - 78)
Range (min - max)	30 - 95
Sex, n (%)	
Male	70 (58.3)
Female	50 (41.7)
Primary indication for warfarin, n (%)	
Atrial fibrillation	82 (68.3)
Mitral stenosis	15 (12.5)
Antiphospholipid syndrome	8 (6.7)
Venous thromboembolism *	8 (6.7)
Others †	7 (5.8)
Reagent lot distribution, n (%)	
Lot 1 (MNPT 8.89 seconds, ISI 0.932)	34 (28.3)
Lot 2 (MNPT 8.90 seconds, ISI 0.954)	10 (8.3)
Lot 3 (MNPT 9.00 seconds, ISI 0.987)	31 (25.8)
Lot 4 (MNPT 9.05 seconds, ISI 0.883)	45 (37.5)
Baseline therapeutic category distribution based on INR, n (%)	
Under-anticoagulation (< 2.0)	58 (48.3)
Therapeutic range (2.0 - 3.0)	44 (36.7)
Over-anticoagulation (> 3.0)	18 (15.0)

*** Venous thromboembolism included pulmonary embolism (n = 7) and portal vein thrombosis (n = 1).**
† Others include arterial thromboembolism of the lower extremity (n = 3) and ventricular fibrillation with concomitant anticoagulation indication (n = 4).
IQR: interquartile range, INR: International Normalized Ratio, ISI: International Sensitivity Index, MNPT: mean normal prothrombin time.

Table 2. Comparison of international quality guidelines.

Source	Recommendation	Equivalent analytical target
CAP Special INR Evaluation [5]	≥ 80% of reported INRs within ± 0.2 INR of a target calculated from the laboratory's own ISI, MNPT, and PT	internal mathematical consistency of the ISI/MNPT/PT-to-INR calculation within ± 0.2 INR; not a direct limit on MNPT accuracy
ICSH 2021 (Gardiner et al., part 1) [6]	between-method mean INR difference ≤ 0.2 INR units in the therapeutic range; non-conformity attributed to an incorrect ISI or MNPT	≈ 6.7 - 10% systematic bias across INR 2.0 - 3.0 (fixed 0.2-INR limit)
EFLM Biological Variation Database (model 2, BV-based APS) [7]	minimum bias goal = $0.375 \times \sqrt{(CV_I^2 + CV_G^2)}$; desirable bias goal = $0.250 \times \sqrt{(CV_I^2 + CV_G^2)}$	≈ 2.15% systematic bias (minimum); ≈ 1.43% (desirable)

APS: analytical performance specification, BV: biological variation, CAP: College of American Pathologists, CLSI: Clinical and Laboratory Standards Institute, CV_G: between-subject biological variation, CV_I: within-subject biological variation, EFLM: European Federation of Clinical Chemistry and Laboratory Medicine, ICSH: International Council for Standardization in Hematology, INR; International Normalized Ratio, ISI: International Sensitivity Index, MNPT: mean normal prothrombin time, PT: prothrombin time.



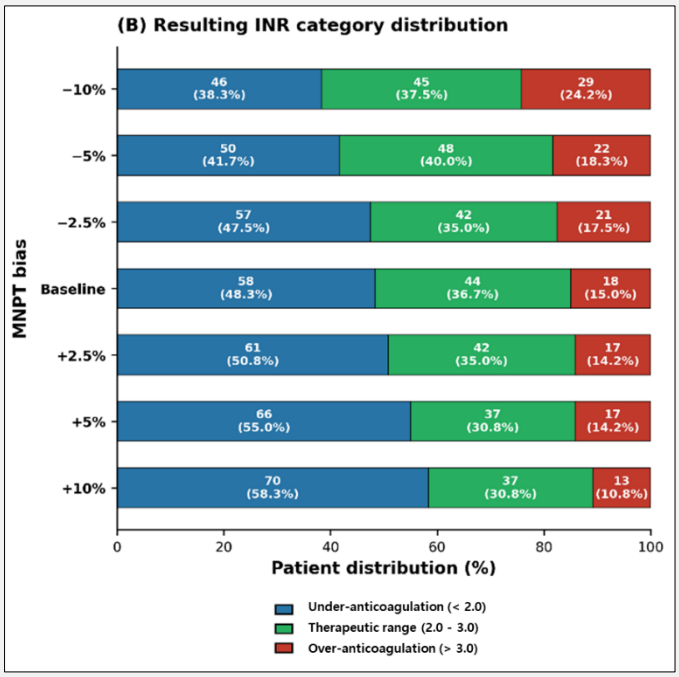


Figure 1. Impact of MNPT analytical bias on clinical INR reclassification.

A: Clinical reclassification rates across simulated MNPT biases ranging from -10.0 to +10.0%. Bars are stacked by the destination category to which patients are reclassified: over-anticoagulation (> 3.0, red), therapeutic range (2.0 - 3.0, gray), and under-anticoagulation (< 2.0, blue). Negative MNPT biases exclusively shift patients upward (toward over-anticoagulation), whereas positive biases exclusively shift patients downward (toward under-anticoagulation). A ± 10.0% bias results in reclassification rates of 14.2% (at + 10.0%) to 19.2% (at -10.0%), while the proposed ± 2.5% analytical tolerance reduces the rate to 3.3% in both directions. B: Resulting distribution of the 120-patient cohort across INR categories under each bias condition. Compared with the locally derived MNPT (baseline), the proportion of patients in the under-anticoagulation category increases from 48.3 to 58.3% at +10.0% bias, while over-anticoagulation increases from 15.0 to 24.2% at -10.0% bias.
INR: International Normalized Ratio, MNPT: mean normal prothrombin time.

ceeded this threshold at ± 5.0%, ± 7.5%, and ± 10.0% bias levels.

Comparison with the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) biological variation specifications

EFLM guidelines use natural biological variation (BV) data to establish quality standards for laboratory tests. According to the EFLM Model 2, a test's maximum allowable error (bias) was calculated using the natural physiological fluctuations found within an individual (CV_I) and between different individuals (CV_G). For PT/INR testing, applying these BV-based formulas provides an objective and theoretical limit to the extent to which the MNPT can deviate without misleading the clinician's interpretation of the patient's true status. According to the updated EFLM Biological Variation Database, the within-subject (CV_I) and between-subject (CV_G) biological variation estimates for PT are 2.6% and 5.1%, respectively [7]. Applying the EFLM Model 2 (biological variation-based) formulas [8,9] to these values, the desirable bias specification is calculated as $Bias_{desirable} = 0.250 \times \sqrt{(CV_I^2 + CV_G^2)}$ is approximately 1.43%. The minimum bias specification, calculated as $Bias_{minimum} = 0.375 \times \sqrt{(CV_I^2 + CV_G^2)}$, is approximately 2.15%. Although PT biological variation specifications cannot be directly extrapolated to lot-specific MNPT assignment, the calculated minimum bias target (2.15%) serves as a supportive reference framework that broadly aligns with the order of magnitude observed in our simulation scenario.

DISCUSSION

This study evaluated the clinical impact of MNPT bias on the interpretation of INR using a simulation model based on real-world warfarin-treated patients. Unlike previous studies that primarily evaluated the analytical verification procedures for MNPT assignment, the present study quantified the clinical consequences of systematic MNPT bias using patient-derived INR data. By integrating the simulation results with international analytical performance specifications (CAP, ICSH, and EFLM), this study provides an evidence-based framework for interpreting the clinical significance of MNPT verification. Our findings demonstrate that even modest deviations in MNPT can lead to clinically meaningful changes in therapeutic classification. While a ± 2.5% MNPT bias resulted in only a 3.3% therapeutic category reclassification rate, application of the conventionally accepted ± 10% tolerance produced reclassification rates of up to 19.2% and caused more than half of the patients to exhibit INR discrepancies exceeding 0.2 units. These findings suggest that inaccuracies in the MNPT assignment may have a potentially greater clinical impact than is frequently appreciated. This simulation indicates that the systematic MNPT bias not only alters the numerical INR values and but also actively shifts patients across critical therapeutic boundaries. Such misclassifications carry significant clinical implications because, to balance the competing risks of hemorrhage and thrombosis, many patients are tightly managed near the lower or upper boundaries of the therapeutic target [4]. A negative MNPT bias overestimates the calculated INR, potentially masking an under-anticoagulated state and exposing patients to hidden thrombotic risks such as ischemic stroke [4,10]. Conversely, a positive MNPT bias induces an underestimation of the true INR value, causing patients originally in the therapeutic range to be misclassified as under-anticoagulated. In real-world clinical practice, this artifactual underestimation could prompt clinicians to escalate the warfarin dose inappropriately, significantly increasing the risk of major hemorrhagic events [2].

The clinical relevance of the present study is supported by an observation made during the routine implementation of a new PT reagent lot (Lot 782325, ISI 0.954). The manufacturer-assigned MNPT (9.78 seconds) differed by approximately -9.3% from the locally derived geometric mean MNPT (8.90 seconds, n = 20). Although this discrepancy remained within the manufacturer-recommended acceptance limit of ± 10%, it resulted in clinically meaningful changes in a subset of patients. Notably, in nationwide external quality assessment programs (Korean Association of External Quality Assessment Service, Scheme HC1-24-04 to 06), although the INR results calculated using the local MNPT (e.g., 3.11 for HC1-24-04 and 2.44 for HC1-24-05) deviated from the manufacturer-MNPT-based peer-group mean (2.80 and 2.23, respectively), they showed closer agreement with the all-method consensus means (4.604 and 3.274) and the results obtained from other major PT testing systems, such as Werfen RecombiPlasTin (4.035 and 2.983) and Sysmex Thromborel-S (4.684 and 3.362). While applying the locally established MNPT successfully restored alignment with external quality assessment (EQA) national consensus means and alternate testing platforms, we explicitly acknowledge that this single-center observation lacks multi-center comparator validation. Because the primary objective of INR standardization is to achieve comparable results across different PT testing systems, this practical challenge directly prompted our systematic investigation to evaluate the acceptable magnitude of MNPT deviation that can be tolerated without introducing clinically meaningful changes in INR interpretation and therapeutic classification.

From an analytical perspective, large MNPT biases induce substantial individual INR deviations that compromise internal calculation consistency. The CAP proficiency testing criteria for special INR evaluation require that ≥ 80% of reported INRs must fall within a strict window of ± 0.2 units of the target value to achieve analytical acceptability [5]. Although the ± 2.5% bias condition achieved 100% compliance, the -10.0% bias condition triggered a systematic failure, with 54.2% of the patients violating the CAP threshold in this study. This

demonstrates how unverified MNPT systematic bias propagates through the INR equation, even though CAP evaluation itself does not serve as an independent clinical outcome threshold.

This analytical risk is further illuminated when theoretical comparison is made with the ICSH 2021 guidelines, which specify that the mean difference between a candidate test system and an established reference method should not exceed 0.2 INR units within the therapeutic range [6]. In our single-system simulation, a -10.0% MNPT bias yielded a mean INR discrepancy of 0.26 units among therapeutic samples. Although our study evaluated single-system mathematical perturbations rather than a true paired-method comparison against a second physical analyzer, this theoretical benchmark highlights that conventionally accepted MNPT tolerances (± 10.0%) can generate mathematical errors that exceed the allowable limits set for inter-system comparability. At a moderate ± 5.0% bias, the mean deviation reached 0.13 INR units.

The EFLM Model 2 defines the minimum and desirable analytical bias specifications based on physiological and biological variations [11,12]. For PT testing, the EFLM biological variation database defines allowable biases of 2.15% (minimum) and 1.43% (desirable) [7]. Although these specifications are derived from biological variation in healthy-subject PT and do not directly define acceptable lot-to-lot differences in MNPT, the numerical proximity between the EFLM minimum bias specification (2.15%) and the ± 2.5% MNPT bias scenario evaluated in our patient-based simulation provides a useful, independent analytical context. We acknowledge that applying PT biological variation-based specifications to MNPT assignment represents an extrapolation across distinct measurement contexts that has not been independently validated. Nevertheless, this comparison illustrates that restricting MNPT bias to 2.5% aligns reasonably with both patient-based reclassification constraints and standard analytical performance expectations.

Establishing a local MNPT not only ensures clinical accuracy but also helps monitor the laboratory's pre-analytical phase. Based on our findings, we propose a practical framework for validating new PT reagent lots. Laboratories should routinely establish their own MNPT instead of relying solely on the manufacturer's value. After calculation, the local MNPT should be compared with the manufacturer's mean. If the difference is within our proposed ± 2.5% limit, the local MNPT can be safely used for routine patient care. However, if the difference exceeds 2.5%, the laboratories should not automatically switch to the manufacturer's value. Instead, this gap should be considered an early warning of potential systematic errors in the laboratory. In such cases, the laboratories can verify the MNPT calculation by testing additional normal donor samples or carefully review local pre-analytical processes to identify and correct potential sources of systematic error. Rather than defining an absolute universal cutoff, this study provides patient-based evidence supporting a practical verification target that can be interpreted alongside existing international analytical performance specifications.

This study had some limitations. First, our results were derived from reagents with ISI values close to 1 (0.883 - 0.987), under which the MNPT bias propagated approximately linearly to the INR. For reagents with higher ISI values, the propagation is exponential, and the proposed ± 2.5% threshold may be conservative; this requires confirmation in laboratories using such reagents. Second, our cohort showed a skewed baseline distribution, with 48.3% of the patients in the under-anticoagulation category (< 2.0), which was higher than that typically reported in well-controlled warfarin populations. Because reclassification rates depend on how densely patients are distributed near the critical INR thresholds of 2.0 and 3.0, the absolute reclassification rates observed in this study may not be directly generalizable to cohorts with different baseline INR distributions. In particular, the zero-exceedance observation (≥ 0.2 INR shift at the 2.5% bias level) applies strictly to the current study cohort and should not be interpreted as a guarantee of zero risk across different clinical settings or larger populations. However, the directional relationship between MNPT bias and clinical reclassification is expected to be preserved. Third, as a single-center retrospective simulation study using a single analyzer (Cobas t711) and a single reagent (PT Rec A), we mathematically assessed the risk of clinical reclassification rather than tracking direct adverse clinical outcomes, such as actual bleeding or thrombotic events. Future prospective multicenter studies linking MNPT variance directly to longitudinal clinical outcomes across diverse reagent-instrument combinations are warranted to validate these findings.

In conclusion, the conventional practice of accepting manufacturer-assigned MNPT values with an approximately ± 10% tolerance has not been supported by patient-based clinical evidence and may contribute to clinically meaningful INR reclassification. In patients with narrow therapeutic indices, particularly those maintained near the critical therapeutic boundaries, tolerance can lead to considerable clinical reclassification. To ensure analytical accuracy and minimize the risk of adverse clinical outcomes, coagulation laboratories should establish locally derived MNPTs in accordance with CLSI guidelines [3]. Furthermore, our findings suggest that approximately 2.5% may be considered a preliminary verification target for locally established MNPT values. This proposal is based on the observed effects of MNPT perturbation in the patient-based simulation and should not be interpreted as an established acceptance criterion derived from international analytical quality frameworks.

Declaration of Generative AI in Scientific Writing:
This manuscript and figures were not drafted and edited using artificial intelligence assisted writing tools.

Declaration of Interest:
The authors declare that they have no conflict of interest.

Additional material can be found online at:
http://supplementary.clin-lab-publications.com/261013/

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