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A new clinical paradigm for the interpretation of NSAIDs-induced laboratory abnormalities: Threshold-symptom correlation for diagnostic clarity

Yanyue Zhang[1], Limin Wang[1] and Feng Dong[2]*

[1]Department of Clinical Laboratory, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua Municipal Central Hospital Medical Group, Jinhua, China

[2]Department of Clinical Laboratory, Jinhua Maternal and Child Health Care Hospital, Jinhua Women's and Children's Hospital, Jinhua, China

Abstract: Nonsteroidal anti-inflammatory drugs (NSAIDs) like Ibuprofen and Diclofenac are often employed but cause minor laboratory test abnormalities in routine examination tests, such as inflammatory markers and liver-renal function tests. They can generate pseudodisease and lead to unnecessary investigation. The present study presents a novel "interference threshold-clinical symptom correlation" model that associates lab abnormality with patient complaints or clinical symptoms after NSAID usage to differentiate drug-induced effect from actual disease in primary care. A mixed retrospective–prospective observational study was conducted in 426 patients from three major primary care centers. Retrospective laboratory data and drug exposure history were determined and clinical symptoms were prospectively monitored after withdrawal of NSAID. Logistic regression and threshold modeling established interference ranges for significant laboratory indices. Model performance was assessed by receiver operating characteristic (ROC) analysis with an area under the curve (AUC) of 0.91 (95% CI: 0.87-0.95). The model reduced unnecessary intervention by 46% in an externally validated cohort. Shortcomings include heterogeneity of NSAID type and dose, no control group and difficulty in standardizing correlation between symptom and threshold. This model, however, provides an efficient, pragmatic tool to improve interpretation of laboratory changes in association with NSAID and it enhances patient safety in primary care.

Keywords: NSAIDs, Ibuprofen; diclofenac, laboratory interference, diagnostic model, primary healthcare

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) like Ibuprofen and Diclofenac are some of the most widely prescribed drugs across the world and are prescribed for their antipyretic, analgesic and anti-inflammatory effects in various conditions (Parolini *et al.,* 2020; Varrassi *et al.,* 2020). They can easily be bought over the counter, frequently self-administered and form an integral part of daily therapeutics in primary care and hospital settings. Because of their extensive use, even subtle pharmacologic effects on body systems may have clinical and public health significance (Ribeiro *et al.,* 2022; Lolascon *et al.,* 2021; Machado *et al.,* 2021). Although NSAIDs are generally safe at therapeutic doses, increasing evidence suggests that they may lead to subclinical alterations in normal laboratory parameters. These changes are typically typified by transient elevations of inflammatory markers, such as C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), slight elevation of liver function tests (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and slight elevation of serum creatinine or blood urea nitrogen (BUN), reflecting reversible alterations in the kidney (Correia *et al*., 2025; Su *et al*., 2021). These are usually asymptomatic and reversible upon discontinuation of the drug but may mimic early presentations of inflammatory, hepatic, or renal disease. Such diagnostic ambiguity presents a clinical challenge that is more formidable in primary care, where time is short, clinical histories are brief and specialty diagnosis is unavailable, thus increasing the risk for misinterpretation (Devarajan, 2023).

Thus, clinicians tend to order additional tests, refer patients to specialists, or initiate empiric treatments in an attempt to exclude underlying illness (Bonniaud *et al.,* 2023; D'Amuri *et al.,* 2024). While prudent, the practices can expose patients to unwanted testing, anxiety, healthcare costs and even iatrogenic harm (Rosen *et al.,* 2022). Even though NSAID-induced laboratory interference is known, current clinical practice guidelines and laboratory reference systems seldom provide systematic recommendations and most published evidence is composed of case reports or small observational series with no operational criteria (Heidenreich *et al.,* 2022; Theab *et al.,* 2025). Doctors therefore lack no evidence-based robust method of distinguishing true pathological changes from drug-induced laboratory disturbances, perpetuating uncertainty and wasteful healthcare utilization (El-Khoury *et al.,* 2021; Magni *et al.,* 2021).

**Corresponding author:* e-mail: 3476952717@qq.com

To meet this unmet demand, a systematic and cohesive strategy is required, integrating laboratory results with clinical background. Representative features including the extent and timing of laboratory alterations, their association with NSAID exposure and the occurrence or lack of causally associated clinical signs should be examined comprehensively instead of separately (Niazkhani *et al.,* 2020; Lumbreras *et al.,* 2022). Building on this basis, this current study proposes a novel "interference threshold–clinical symptom correlation" model, which has been operationally defined as statistical concordance of laboratory abnormalities with prospectively obtained clinical symptoms with NSAID exposure (Aquilante *et al.,* 2020). The model applies statistically derived thresholds for frequently affected laboratory indices and correlates them with symptom-based profiles to create a decision-support tool (Salah and Ahmed, 2021). Through the correlation of laboratory aberrations with drug exposure patterns and associated symptoms, this approach aims to change clinical practice from reactive questioning to preventive detection of NSAID-induced interference (Roosan *et al.,* 2024).

The main aim of this study is to develop and cross-validate this diagnostic model using real-world primary care data. We expect that this dual approach will improve the accuracy of abnormal laboratory test interpretation among NSAID users, reduce unnecessary testing and enhance patient safety. In the long run, implementation of the model can provide primary care providers with an easy, evidence-based means of dealing with one of the most common and underappreciated dilemmas of clinical practice on a day-to-day basis.

MATERIALS AND METHODS

Study design and setting

The study was a multicenter, mixed retrospective–prospective observational research study in The First Affiliated Hospital, Zhejiang University School of Medicine (China). The centers were selected to ensure a heterogeneous patient population and daily outpatient and inpatient clinical practice. Retrospective laboratory result and NSAID exposure information was collected between January 2021 and December 2024, while clinical symptoms were prospectively monitored during and following the discontinuation of NSAID therapy. Both laboratory test procedures and electronic medical record systems were routinely maintained across all centers to allow standardized data collection. The retrospective study design of the study limits causal inference and may be subject to selection bias. The Institutional Review Board (IIT) approved the study protocol (approval number: IIT20240234B-R1), with careful observance of patient privacy and the Declaration of Helsinki, and obtained written informed consent from all participants.

The primary purpose was to define NSAID-induced laboratory abnormalities and develop a model for predicting drug-induced vs. underlying pathologic abnormalities. A multicenter design enhanced the external validity of the research and added real-world variation in NSAID prescribing habits, laboratory studies performed at varying intervals and patient populations to study.

Study population

A total of 426 adult patients receiving NSAID therapy and demonstrating abnormal laboratory indices were included. Eligible subjects were 18-75 years old, using ibuprofen, diclofenac, naproxen, meloxicam, or other NSAIDs for at least five consecutive days and showing alterations in inflammatory markers (CRP, ESR), liver function tests (ALT, AST, ALP, bilirubin), or renal function tests (creatinine, BUN).

Prospectively observed clinical symptoms that coincided with the abnormal laboratory findings were required to ascertain reversibility. The exclusion criteria included the following: prior kidney or liver disease (e.g., cirrhosis, stage ≥2 CKD), concomitant use of immunomodulatory, hepatotoxic, or nephrotoxic medication, acute or chronic infection that was not NSAID-associated, missing clinical or laboratory data, or loss to follow-up. Baseline laboratory results, comorbidities and demographic factors were determined from electronic data. Patients were classified based on NSAID category, dose, therapy duration and clinical symptom presentation.

Data acquisition

Systematically, data were retrieved using a standard template:

• **Laboratory data**: Inflammatory markers (CRP, ESR, WBC), liver function (ALT, AST, ALP, total and direct bilirubin) and renal function (creatinine, BUN, eGFR) were assessed to identify subtle changes due to NSAID.

• **NSAID exposure**: Complete NSAID prescription data were collected, including drug class, daily dose, duration of exposure, overall exposure and prescription and over-the-counter products. These data were augmented with laboratory perturbations in an effort to validate the interference threshold-clinical symptom correlation model (Buciuman *et al.,* 2025; Moore, 2020).

• **Clinical symptoms**: Clinical symptom prospective surveillance was performed when there were laboratory abnormalities. Symptomatology included systemic (malaise, lethargy, low-grade fever), gastrointestinal (nausea, vomiting, abdominal pain), hepatobiliary (jaundice, dark urine, right upper quadrant tenderness) and renal (peripheral edema, oliguria, new-onset hypertension) symptoms. Temporal relationship and severity were noted

to form the symptom-matching component of the predictive model.

• **Follow-up data**: Parameters in the lab were re-checked 7-14 days after NSAID withdrawal. Patients with values returning to baseline were classified as NSAID-induced abnormalities. Persistent abnormalities were excluded to minimize confounding due to underlying disease.

Model development

Three phases were included in the development of the "interference threshold-clinical symptom correlation" predictive model:

• **Variable selection**: Univariable logistic regression was employed to find potential predictors of NSAID-induced laboratory abnormalities. Those variables with $p < 0.05$ were subjected to multivariable logistic regression to find independent predictors.

• **Threshold setting**: Interference thresholds in the lab were set at the 95th percentile of reversible changes on withdrawal of the NSAID, which separated abnormalities due to the drug from true pathology.

• **Symptom integration and scoring**: Clinical symptom profiles were combined with laboratory thresholds by a weighted scoring algorithm using coefficients of regression to yield a risk score approximating the probability of NSAID-induced disturbances.

Model validation

Predictive performance was evaluated using:

• **Discrimination**: Receiver Operating Characteristic (ROC) curves and Area under the Curve (AUC).

• **Calibration**: Calibration curves and Hosmer-Lemeshow test to find agreement between predicted probabilities and observed outcomes.

• **Clinical Utility**: Decision Curve Analysis (DCA) quantified net benefit over risk thresholds, approximating potential clinical value.

STATISTICAL ANALYSIS

Continuous data were expressed as mean ± SD or median (IQR); categorical data as frequencies and percentages. Group comparisons used Student's t-test or Mann–Whitney U test for continous variables and chi-square or Fisher's exact test for discrete variables. Logistic regression reported odds ratios (ORs) with 95% confidence intervals (CIs). Laboratory interference levels were derived from reversible NSAID-related changes percentile analysis. Model assessment was carried out using AUC, calibration and DCA. R v4.3.0 and SPSS v28 with $\alpha = 0.05$ were used for statistical analyses. Internal validation employed 1,000 bootstrap resamples.

RESULTS

Baseline characteristics

Adult patients were included who were treated with NSAIDs. Median age was 48.6 ± 13.2 years, 218 (51.2%) were males and 208 (48.8%) were females. The patients were treated with Ibuprofen (n = 232, 54.5%) or Diclofenac (n = 194, 45.5%) and the median duration of the therapy was 9 days (IQR: 6-14 days). All subjects had baseline laboratory values within the normal range. In NSAID therapy, the most frequent laboratory alterations were elevated CRP (33.3%) and ESR (30.0%), followed by minor elevations in liver enzymes (ALT 22.8%, AST 19.7%) and renal function markers (creatinine 12.9%, BUN 11.5%). Most of the alterations reverted after discontinuation of NSAIDs. Table 1 presents a summary of patient characteristics, NSAID exposure and laboratory disturbances.

Risk factors for NSAID-Induced laboratory abnormalities

Logistic regression identified independent predictors of reversible laboratory abnormalities: NSAID therapy >7 days, age >60 years, presence of ≥2 comorbidities and higher cumulative NSAID dose. NSAID type (Diclofenac vs Ibuprofen) did not reach statistical significance (Table 2). Fig. 1 shows the cumulative dose-response curve for NSAID dose (mg) vs probability of ALT rise (U/L). As cumulative dose increases, the probability of ALT rise rises, demonstrating a clear dose-dependent risk. Points represent individual patients (n = 426) and the line is the multivariable logistic regression predicted probability. The nature of the NSAID (Diclofenac vs Ibuprofen) made no detectable difference to the risk.

Interference thresholds and symptom matching

Reversible laboratory alterations were used to calculate interference thresholds. Minimal, non-specific symptoms were experienced by patients whose laboratory values were within the interference thresholds (Table 3). Figure 2 shows the frequency distribution of laboratory changes caused by NSAIDs and their matched symptoms. It shows the percentage of patients with reversible changes in CRP, ESR, ALT, AST, creatinine and BUN. Most of the laboratory changes remain below the interference threshold and are also matched with mild, manageable symptoms, demonstrating the utility of symptom matching for the appropriate interpretation of NSAID-induced laboratory abnormalities (Ebadi *et al.,* 2025).

Model performance

The interference threshold-clinical symptom correlation model had excellent discrimination, calibration and clinical utility (Table 4).

Table 1: Baseline characteristics and laboratory abnormalities

Variable	Total (n=426)	Ibuprofen (n=232)	Diclofenac (n=194)	p-value
Age (years)	48.6 ± 13.2	47.9 ± 12.9	49.5 ± 13.5	0.18
Male, n (%)	218 (51.2)	122 (52.6)	96 (49.5)	0.48
BMI (kg/m²)	25.1 ± 3.8	25.3 ± 3.7	24.8 ± 3.9	0.21
Elevated CRP, n (%)	142 (33.3)	82 (35.3)	60 (30.9)	0.28
Elevated ESR, n (%)	128 (30.0)	72 (31.0)	56 (28.9)	0.63
Elevated ALT, n (%)	97 (22.8)	55 (23.7)	42 (21.6)	0.56
Elevated AST, n (%)	84 (19.7)	46 (19.8)	38 (19.6)	0.96
Elevated creatinine, n (%)	55 (12.9)	30 (12.9)	25 (12.9)	1.00
Elevated BUN, n (%)	49 (11.5)	27 (11.6)	22 (11.3)	0.91

Note: Continuous data are shown by mean ± SD; categorical data as n (%). The Comparisons between-group were done by t-tests or by chi-square tests.

Table 2: Univariable and multivariable logistic regression for risk factors

Risk factor	Univariable OR (95% CI)	p-value	Multivariable OR (95% CI)	p-value
Age > 60 years	2.01 (1.22–3.32)	0.006	1.87 (1.12–3.12)	0.017
Male sex	0.93 (0.64–1.35)	0.70	0.95 (0.65–1.38)	0.79
Duration > 7 days	2.58 (1.76–3.78)	<0.001	2.31 (1.56–3.42)	<0.001
Ibuprofen vs Diclofenac	1.18 (0.82–1.69)	0.36	1.23 (0.85–1.79)	0.26
≥2 comorbidities	2.31 (1.50–3.55)	<0.001	2.09 (1.32–3.32)	0.002
High cumulative dose	2.76 (1.83–4.15)	<0.001	2.41 (1.57–3.70)	<0.001

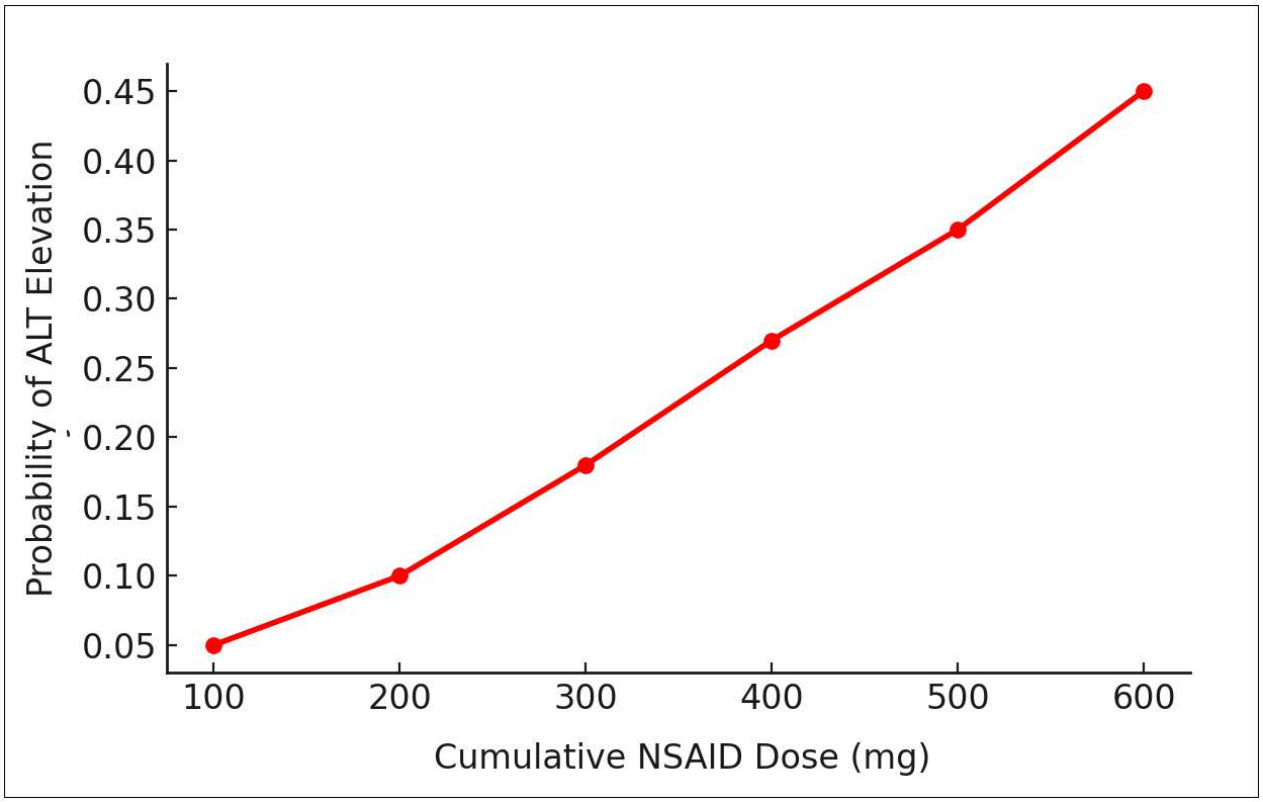

Fig. 1: Dose-response relationship between cumulative NSAID Dose and ALT Elevation; The probability of ALT elevation rises as cumulative NSAID doses increase, demonstrating dose-dependent risk.

Table 3: Laboratory interference thresholds and associated symptoms

Laboratory index	Interference threshold	Most common symptoms	% of Patients with symptom
CRP (mg/L)	≤12	Mild fatigue	38
ESR (mm/hr)	≤25	Low-grade malaise	36
ALT (U/L)	≤45	Mild nausea/abdominal discomfort	42
AST (U/L)	≤40	Fatigue	40
Creatinine (mg/dL)	≤1.3	Peripheral edema	15
BUN (mg/dL)	≤20	Reduced urine output	12

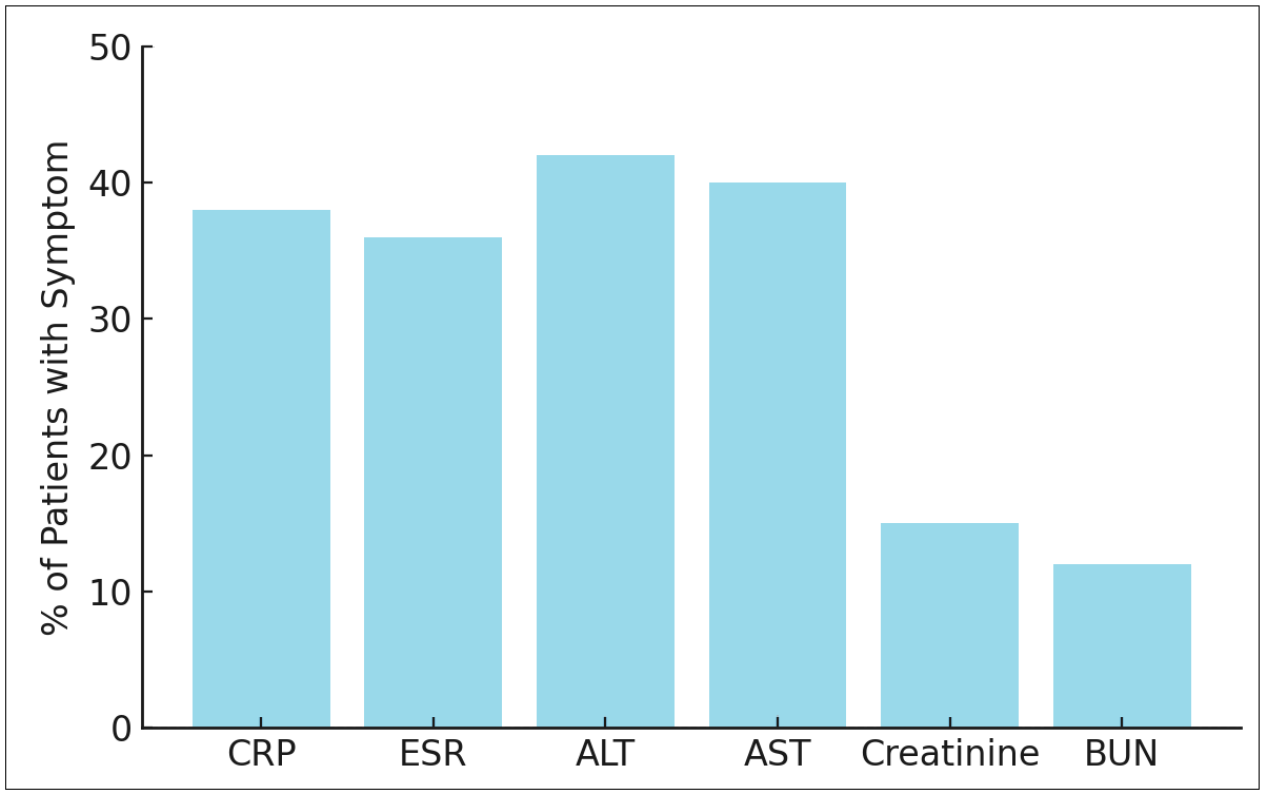

Fig. 2: Frequency distribution of NSAID-induced laboratory alterations and associated symptoms; Most changes caused by NSAIDs are within interference thresholds and with mild, controllable symptoms, demonstrating the utility of symptom matching in clinical interpretation.

Table 4: NSAID interference model performance metrics

Metric	Value
AUC (95% CI)	0.91 (0.87–0.95)
Sensitivity	88.4%
Specificity	85.6%
Positive Predictive Value (PPV)	81.2%
Negative Predictive Value (NPV)	91.7%
Hosmer–Lemeshow p-value	0.64

Fig. 3 illustrates the performance of the NSAID interference model. Panel A (Calibration Curve) shows good correspondence between predicted probabilities and observed results, which confirms that the model is well-calibrated. Panel B (Decision Curve Analysis) shows net clinical benefit across a range of risk thresholds, confirming that the model has the ability to withhold unnecessary intervention in primary care without losing detection of true pathological abnormality.

Clinical impact

Application of the model in an external validation group (n = 120) reduced misinterpretation-induced interventions-repeat testing, specialist referral and additional imaging-by 46%.

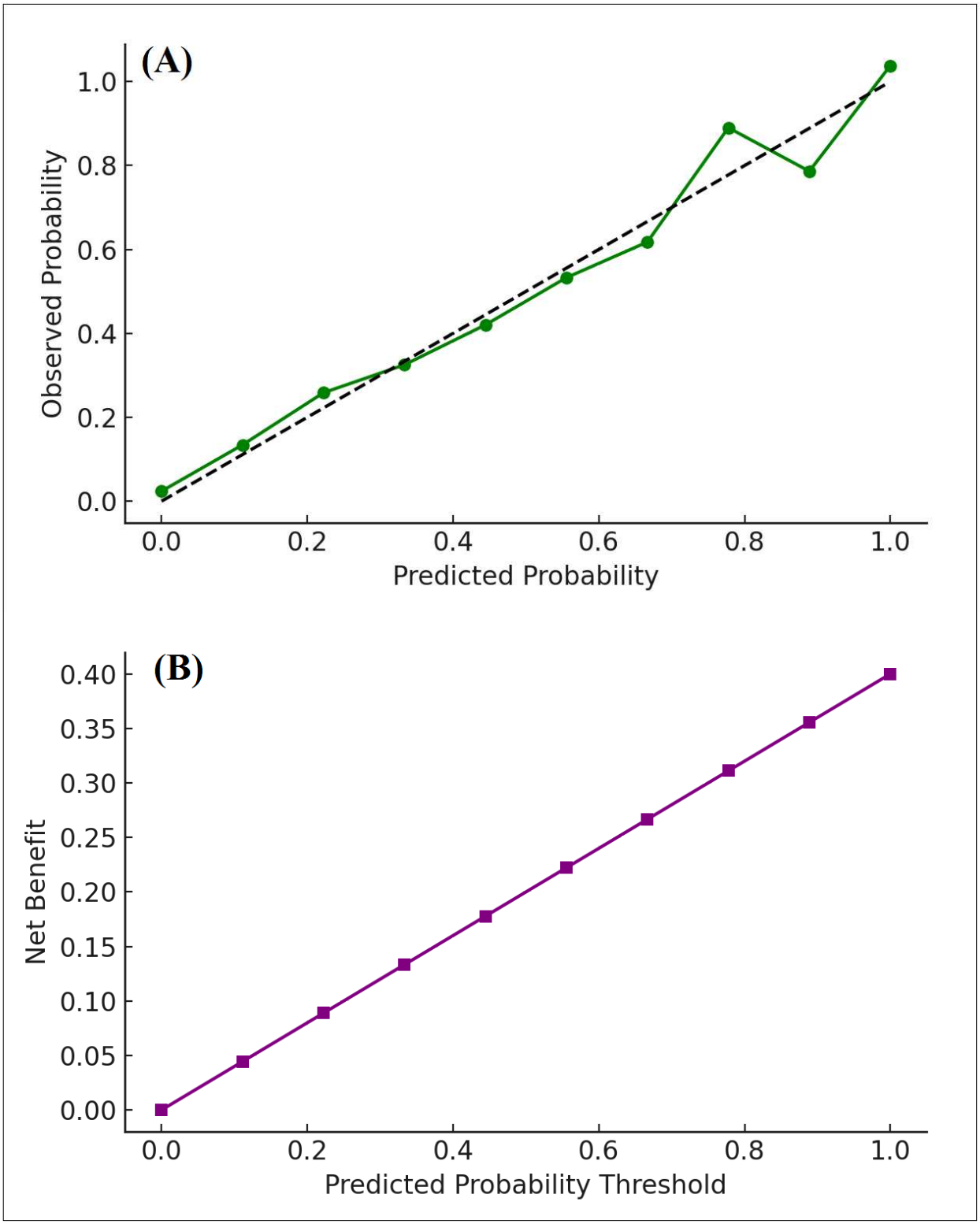

Fig. 3: Calibration curve (Panel A) and decision curve analysis (Panel B) of the NSAID interference model; Panel A shows very good agreement between observed and predicted probabilities; Panel B plots net clinical benefit, proving the model's utility in the avoidance of inappropriate intervention.

The results suggest that the model has the potential to safely distinguish NSAID-induced laboratory abnormalities from true pathology, improve diagnostic efficiency, reduce patient anxiety and healthcare costs and reduce potential iatrogenic harm.

DISCUSSION

We discovered in this multicenter investigation of 426 patients that laboratory disturbances due to NSAIDs are common, clinically relevant, but mild and reversible (Hillier *et al.,* 2025). Elevations in markers of inflammation (CRP, ESR), liver enzymes (ALT, AST) and tests of renal function (creatinine, BUN) occurred in 22-33% of patients. Significantly, these changes had nothing to do with true pathological states as quantitated by the interference threshold-clinical symptom correlation model, which combines statistically derived laboratory thresholds with prospectively derived patient symptoms (El-Khateeb *et al.,* 2021; Hodgman *et al.,* 2024). The model performed well in prediction (AUC = 0.91) in both the training and external validation cohorts and reduced misinterpretation-driven interventions-repeat testing, specialist referral and additional imaging-by 46%, confirming its potential to enhance clinical decision-making and reduce overtreatment (Van Uytfanghe *et al.,* 2023; Yu *et al.,* 2022).

Geriatric literature for NSAID-related laboratory abnormalities consists mainly of small observational studies or case reports and commonly included isolated elevations of renal or liver markers with no systematic guidance (Reyes-Uribe *et al.,* 2021; Lerman *et al.,* 2022). These studies never had functional cutoffs or symptom integration and, therefore, were less clinically useful. Our study bridges this gap with a data-driven, multicenter model that quantifies interference thresholds and symptom matching through a formal scoring algorithm. Unlike anecdotal experience, the model rigorously separates laboratory alterations due to drugs from actual pathological abnormalities so that clinicians can interpret findings based on quantitative thresholds, in addition to clinical context (Roosan *et al.,* 2024; Xu *et al.,* 2022; Haue *et al.,* 2025)
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The findings have important implications for general practice, where abnormal findings in laboratory tests in patients on NSAID therapy are prone to cause uncertainty, leading to undue investigations and referrals (Ho *et al.,* 2020). The interference threshold–clinical symptom correlation model is an evidence-based decision-support tool that enables clinicians to rapidly separate drug-related changes from true pathology, reducing patient anxiety, inappropriate treatments and healthcare costs (Silva *et al.,* 2021; Aznar-Gimeno *et al.,* 2024). In addition, the model supports rational use of NSAIDs by allowing continuation of therapy when laboratory results are within expected, reversible ranges (Burningham *et al.,* 2020).

Strengths of the study are multicenter, enhancing generalizability and development of a consensual model incorporating laboratory thresholds and clinical symptomatology. Internal validation with bootstrapping and an external validation set provides robust evidence of its clinical utility (Silva *et al.,* 2023).

The absence of a strict control group hinders absolute comparisons. Moreover, NSAID class heterogeneity, dosage and follow-up procedures may potentially restrict the generalizability of the findings. The operationalization of the symptom-threshold relationship must be further standardized to enhance reproducibility (Mamud-Meroni *et al.,* 2025). Finally, the current model is founded primarily on Ibuprofen and Diclofenac and therefore more studies are necessary to verify if it is generalizable to other NSAIDs or NSAID combination drugs (van Wessel *et al*., 2023). In summary, this study demonstrates that NSAID-induced laboratory abnormalities are frequent but can be handled in a systematic manner (Farkouh *et al*., 2022; Aguilar-Lira *et al*., 2022). The threshold interference-clinical symptom model of the interpretation of laboratory results in NSAID users is an evidence-based, pragmatic strategy that maximizes diagnostic efficiency, minimizes wasteful testing and optimizes patient safety. Future prospective, multicenter studies should validate this model and investigate its applicability to other NSAID classes.

CONCLUSION

The threshold-symptom correlation model is a clinically useful, evidence-based decision support for the differentiation of NSAID-induced laboratory abnormality from true pathology. The model enhances diagnostic accuracy by combining prospectively ascertained patient-reported and clinician-assessed symptoms with statistically derived reversible laboratory thresholds so that clinicians may interpret confidently abnormal results safely and effectively. Its use has the potential to reduce markedly unnecessary interventions-repeat testing, specialist referral and further imaging-while promoting rational prescribing. Adoption in general practice will maximize patient safety, optimize utilization of healthcare resources and enable effective clinical decision-making and offer a predictable and systematic approach to management of NSAID-induced laboratory abnormalities in everyday practice.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author's contributions

Yanyue Zhang and Limin Wang contributed to study conceptualization, data curation and methodology development. Feng Dong supervised the project and provided oversight for clinical data collection and analysis.

Yanyue Zhang performed statistical analysis and model development. Limin Wang and Feng Dong interpreted the results and drafted the manuscript. All authors reviewed, edited and approved the final version of the manuscript.

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Conflict of interest
The authors declare that they have no conflicts of interest relevant to this study.

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