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ARTICLE

The Predictive Value of Serum miR-141-3p, Fibrinogen, and Prostate-Specific Antigen Levels for Bone Metastasis in Prostate Cancer

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Abstract

Aims/Background Prostate cancer is a prevalent malignancy among men that frequently progresses to bone metastasis, significantly affecting prognosis and quality of life. Serum biomarkers such as miR-141-3p, fibrinogen (FIB), and prostate-specific antigen (PSA) are emerging as promising tools for early detection and personalised interventions for bone metastasis. This study investigated their predictive value for bone metastasis in prostate cancer.

Methods Conducted from March 2018 to March 2023, this study included 100 prostate cancer patients monitored over time. All participants underwent radionuclide bone imaging combined with positron emission tomography-computed tomography (PET-CT). Patients who developed bone metastasis (32 cases) were classified as the metastasis group, while those without (68 cases) were categorised as the non-metastasis group. Additionally, a control group of 50 healthy volunteers was established for comparison. A retrospective analysis assessed serum miR-141-3p, FIB, and PSA levels across the three groups. Clinical data were analysed to identify factors influencing bone metastasis using univariate and multivariate analyses, after which a prediction model was created to evaluate its prognostic value.

Results Serum levels of miR-141-3p, FIB, and PSA were significantly different among the three groups, with the highest levels in the metastasis group, followed by the non-metastasis group, and the lowest in the control group ($p < 0.05$). Both univariate and multivariate analyses confirmed that these serum biomarkers significantly influenced the occurrence of bone metastasis. The combined predictive model demonstrated high clinical value for assessing the risk of bone metastasis in prostate cancer, with an area under the curve (AUC) of 0.923 (95% confidence interval [CI]: 0.868–0.979, $p < 0.05$).

Conclusion Serum levels of miR-141-3p, FIB, and PSA are elevated in prostate cancer patients, particularly those with bone metastasis. The predictive model utilising these biomarkers effectively forecasts the likelihood of bone metastasis.

Key words: miR-141-3p; fibrinogen; prostate-specific antigen; prostate cancer; bone metastasis

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Introduction

Prostate cancer is a malignant tumour that originates in the epithelial cells of the prostate, with prostate adenocarcinoma accounting for over 95% of cases (Sekhoacha et al, 2022; Tong et al, 2023). Its incidence increases with age, particularly in men over 55, making it the sixth most common malignancy among men and posing a significant health risk. Often asymptomatic in its early stages, prostate

cancer is frequently diagnosed after the occurrence of bone metastasis, which is a common reason for clinical consultations (Desai et al, 2021). When prostate cancer metastasises to the bones, it can lead to severe bone pain, spinal cord compression, and pathological fractures, all of which severely affect the patient's well-being and prognosis (Nishimura, 2023). Therefore, early diagnosis of bone metastasis in prostate cancer is crucial.

Prostate-specific antigen (PSA) is the primary biomarker used for prostate cancer screening. However, its diagnostic efficacy is limited for individuals presenting with PSA levels between 4 and 10 ng/mL, often referred to as the "diagnostic grey zone". This ambiguity necessitates a more comprehensive evaluation, typically involving prostate biopsy and supplementary diagnostic techniques to ascertain the presence of cancer (Kachuri et al, 2023). Fibrinogen (FIB), a glycoprotein produced by liver cells, plays a critical role in blood coagulation and thrombus formation. Research has shown that patients with malignant tumours often exhibit elevated plasma FIB levels, which contribute to coagulation abnormalities and increase the risks of both bleeding and thrombosis (Wang et al, 2023). Additionally, microRNAs (miRNAs) with abnormal expression patterns are significantly associated with tumour development and progression. For instance, miR-141-3p has been shown to inhibit the proliferation and metastasis of prostate cancer cells (Li et al, 2023). This suggests that serum concentrations of miR-141-3p may be linked to bone metastasis in prostate cancer patients.

In light of the above, this study aims to investigate the relationship between these biomarkers and bone metastasis by retrospectively analysing clinical data and biomarker levels in 100 prostate cancer patients. The objective is to develop a risk prediction model for bone metastasis, thereby providing a stronger scientific basis for personalised management and early intervention in individuals with prostate cancer.

Methods

General Information

This study, conducted from March 2018 to March 2023, included a total of 150 participants, comprising 100 prostate cancer patients and 50 healthy volunteers as the control group. Among the prostate cancer patients, 32 were diagnosed with bone metastasis, included as the metastasis group, and 68 without bone metastasis, categorised as the non-metastasis group. This retrospective study included prostate cancer patients diagnosed and treated at the Department of Urology, The Fourth Affiliated Hospital of Soochow University, Suzhou, China. The healthy control group consisted of individuals who attended the same hospital for routine health check-ups and were confirmed to have no history of prostate disease or cancer. To ensure comparability, the control group was age- and sex-matched with the patient groups. This matching was crucial to minimise the confounding effects of demographic variables on serum biomarker levels.

Baseline characteristics, including age, body mass index (BMI), hypertension, diabetes, and other relevant clinical parameters, were collected and analysed to as-

sess the similarity between groups. The patients were followed up and underwent radionuclide bone imaging. The next morning after hospital admission, 6 mL of peripheral venous blood was drawn from each fasting patient. This research received approval from the Institutional Review Board of The Fourth Affiliated Hospital of Soochow University (Approval No.: 2024-240835) and was conducted in compliance with the ethical principles established by the Declaration of Helsinki. Prior to data collection, informed written consent was obtained from all participants.

Inclusion and Exclusion Criteria

The inclusion criteria of this study are as follows: (1) patients meeting the diagnostic standards for early prostate cancer as specified by the Chinese expert consensus; (2) patients were divided into two groups based on radionuclide bone imaging combined with positron emission tomography-computed tomography (PET-CT): the bone metastasis group included patients with confirmed bone metastasis, and the non-metastasis group included those without bone metastasis; (3) patients treated at our hospital, with no systemic inflammatory response (fulfilling two or more of the following criteria is considered diagnostic of systemic inflammatory response: body temperature >38 °C or <36 °C; heart rate >90 beats/min; respiratory rate >20 breaths/min or partial pressure of arterial carbon dioxide ($PaCO_2$) <32 mmHg; and peripheral blood leukocyte count $>12 \times 10^9$/L or $<4 \times 10^9$/L); and (4) first-time treatment receivers with no history of cancer treatment.

Individuals fulfilling the following criteria were excluded from this study: (1) concurrent blood system diseases or autoimmune diseases, (2) concurrent treatment with anticoagulant drugs or other related medications, and (3) severe impairment of liver or kidney function.

Serum Biomarker Assay

The next morning after hospital admission, 6 mL of peripheral venous blood was drawn from each fasting patient. The blood was centrifuged at 3000 rpm for 15 minutes using a centrifuge (TDZ4, Eppendorf, Hamburg, Germany). The serum collected was divided into two separate tubes, which were then kept at –80 °C for future analysis. Enzyme-linked immunosorbent assay (ELISA) was employed to measure serum PSA levels using commercial kits (batch number DKK300; R&D Systems, Minneapolis, MN, USA), in accordance with the protocol specified by the manufacturer. FIB levels were determined using a CA7000 fully automatic blood coagulation analyser from Sysmex, Kobe, Japan.

Serum collected in a separate tube was used for the determination of the expression level of miR-141-3p using real-time quantitative polymerase chain reaction (qPCR). Serum total RNA was isolated utilising the TRIzol reagent (15596026CN, Thermo Fisher Scientific, Shanghai, China), and its concentration and purity were assessed with a UV5 spectrophotometer (Mettler-Toledo International Inc., Zurich, Switzerland). The isolated total RNA was subsequently converted into cDNA using a reverse transcription kit (batch number 150204; Invitrogen, Carlsbad, CA, USA) and stored at –20 °C. Each qPCR reaction comprised 20 µL of SYBR Green I reagent (SY1020, Solarbio, Beijing, China), 4.0 µL of cDNA, 0.5 µL each of for-

ward and reverse primers, and 5.0 μL of enzyme-free RNA water. After mixing and brief centrifugation, the mixture was amplified in a 9700 PCR system (ABI, Waltham, MA, USA). The amplification procedure started with pre-denaturation at 95 °C for 30 seconds, then continued with 40 cycles consisting of a 5-second denaturation at 95 °C and a 34-second annealing at 60 °C. The experiment was performed in triplicate, and the mean values were calculated. *U6* was used as the reference gene, and the relative expression levels of miR-141-3p in serum were determined using the $2^{-\Delta\Delta Ct}$ method. Primers and reagents were provided by Takara Bio Inc., Shiga, Japan. Primer sequences used for the analysis of miR-141-3p and U6 RNA are shown in **Supplementary Table 1**.

Given the inherent variability in biomarker levels, it was crucial to standardise the PSA, FIB, and miR-141-3p values to ensure accurate comparisons among different study groups. PSA and FIB levels were log-transformed to achieve normal distribution and minimise the impact of extreme values. miR-141-3p expression levels were normalised to the reference gene *U6* and further standardised using z-scores to account for inter-individual variability. These normalisation steps were essential to minimise bias and enhance the robustness of the subsequent analyses.

Observation Indicators

Baseline data collected included patient demographics (age, BMI), medical history (hypertension, diabetes, smoking, alcohol consumption, family history), laboratory indices (such as D-dimer, Cystatin C [CysC], white blood cell count [WBC], creatinine and neutrophil count [N]), and tumour characteristics including clinical T stage, Gleason score, tumour size, and lymph node status for both the non-metastasis and metastasis groups of prostate cancer patients. Clinical data were analysed through univariate and multivariate analyses to explore factors influencing bone metastasis occurrence. Based on the results of multivariate analysis, a prognostic model for bone metastasis in prostate cancer patients was established using Logistic regression analysis. The prognostic model was evaluated through receiver operating characteristic (ROC) curve analysis, and the area under the curve (AUC) with 95% confidence intervals was calculated.

Data Analysis

All biomarker data (PSA, FIB, and miR-141-3p) were standardised to account for variability and ensure comparability across groups. Statistical analyses were conducted using SPSS software (version 25.0, IBM Corp., Armonk, NY, USA). The normality of data distribution was tested using the Shapiro-Wilk test. Continuous variables are presented as means ± standard deviation for normally distributed data, while categorical variables are reported as frequencies and percentages.

For categorical variables, the Chi-square test was employed. For continuous data that met the assumptions of normal distribution and equal variances, independent sample *t*-tests were used to compare two groups, while one-way analysis of variance (ANOVA)—F-test was utilised for comparisons involving more than two groups. Following ANOVA, post hoc comparisons following ANOVA were per-

Table 1. Baseline characteristics of control, non-metastasis, and metastasis groups.

Characteristic	Control group (n = 50)	Non-metastatic group (n = 68)	Metastatic group (n = 32)	p-value	F/χ^2
Age (years)	60.5 ± 8.2	61.0 ± 7.9	60.8 ± 8.1	0.872	12.61
BMI (kg/m^2)	22.5 ± 2.3	22.3 ± 2.5	22.6 ± 2.4	0.756	7.64
Hypertension (%)	20 (40%)	18 (26.5%)	14 (43.8%)	0.149	3.81
Diabetes (%)	10 (20%)	12 (17.6%)	8 (25.0%)	0.692	0.74
Smoking (%)	15 (30%)	20 (29.4%)	10 (31.3%)	0.983	0.04
Alcohol consumption (%)	12 (24%)	15 (22.1%)	7 (21.9%)	0.962	0.08
Family history (%)	5 (10%)	7 (10.3%)	3 (9.4%)	0.990	0.02

Note: BMI, body mass index.

Table 2. Comparative serum levels of miR-141-3p, FIB, and PSA.

Group	miR-141-3p	FIB (g/L)	PSA (ng/mL)
Control group (n = 50)	4.16 ± 1.02	3.36 ± 0.41	3.11 ± 0.45
Non-metastatic group (n = 68)	25.15 ± 2.13*	3.98 ± 0.35*	14.11 ± 4.10*
Metastatic group (n = 32)	33.96 ± 1.56*$^+$	4.25 ± 0.36*$^+$	23.67 ± 5.46*$^+$
F	3515.358	65.446	305.987
p-value	<0.001	<0.001	<0.001

Note: *A significant difference compared to the control group ($p < 0.05$); $^+$A significant difference compared to the non-metastatic group ($p < 0.05$). FIB, fibrinogen; PSA, prostate-specific antigen.

formed using Tukey's Honestly Significant Difference (HSD) test to identify pairwise differences. A significance threshold of $p < 0.05$ was set to determine statistical significance.

Results

Baseline Characteristics of Study Groups

To evaluate the comparability of the study groups, baseline characteristics were analysed and are presented in Table 1. There were no significant differences among the control, non-metastasis, and metastasis groups, indicating successful matching.

Analysis of Serum miR-141-3p, FIB, and PSA Levels Across Three Groups

Notable variations were observed in the serum concentrations of miR-141-3p, FIB, and PSA across the control group, non-metastasis group, and metastasis group. To account for inter-individual variability, PSA and FIB levels were log-transformed, and miR-141-3p expression levels were standardised using z-scores. The metastasis group exhibited the highest levels, followed by the non-metastasis group and the control group, with all differences being statistically significant ($p < 0.05$). These findings were detailed in Table 2.

Table 3. Clinical data analysis between non-metastatic and metastatic groups.

Parameter	Non-metastatic group (n = 68)		Metastatic group (n = 32)		χ^2	p-value
	Number of cases	Percentage (%)	Number of cases	Percentage (%)		
Age (years)						
≤35	35	51.47	15	46.88	0.184	0.668
>35	33	48.53	17	53.13		
Clinical T stage						
≤T2a	45	66.18	13	40.63	5.832	0.016
≥T2b	23	33.82	19	59.38		
Gleason score						
≤6	33	48.53	6	18.75	8.111	0.004
≥7	35	51.47	26	81.25		
Lymph node metastasis						
Yes	12	17.65	9	28.13	1.440	0.230
No	56	82.35	23	71.88		
Hypertension						
Yes	13	19.12	8	25.00	0.454	0.501
No	55	80.88	24	75.00		
Diabetes						
Yes	15	22.06	9	28.13	0.439	0.508
No	53	77.94	23	71.88		
Alcohol consumption						
Yes	12	17.65	6	18.75	0.018	0.893
No	56	82.35	26	81.25		
Family history						
Yes	4	5.88	2	6.25	0.144	0.705
No	64	94.12	30	93.75		

Univariate Analysis of the Influences on Bone Metastasis in Prostate Cancer Patients

The univariate analysis revealed that the metastasis group had a significantly higher percentage of patients with a clinical T stage of T2b or greater, a Gleason score of 7 or above, and elevated levels of D-dimer and CysC ($p < 0.05$). As shown in Tables 3,4, there were no notable distinctions among the groups in terms of age, lymph node metastasis, hypertension, diabetes, alcohol abuse, family history, tumour size, BMI, creatinine levels, WBC, and neutrophil levels ($p > 0.05$).

Multivariate Regression Analysis of Factors Affecting Bone Metastasis in Patients With Prostate Cancer

In multivariate analysis, the presence of bone metastasis in patients (1 = occurred, 0 = did not occur) was taken as the dependent variable. Factors such as PSA, FIB, miR-141-3p levels, clinical T stage, Gleason score, D-dimer, and CysC were explored for their impact on the development of bone metastasis. The findings demonstrated that the levels of PSA, FIB, and miR-141-3p, along with the

Table 4. Comparison of clinical data between non-metastatic and metastatic groups.

Parameter	Non-metastatic group (n = 68)	Metastatic group (n = 32)	t	p-value
Tumour size (cm)	5.33 ± 1.02	5.38 ± 1.12	–0.222	0.825
BMI (kg/m^2)	22.13 ± 2.65	22.36 ± 2.48	–0.413	0.680
D-dimer (mg/L)	0.39 ± 0.11	0.66 ± 0.12	–11.120	<0.001
CysC (mg/L)	0.91 ± 0.12	1.31 ± 0.25	–10.843	<0.001
WBC ($\times 10^9$ /L)	7.44 ± 1.12	7.65 ± 1.36	0.818	0.415
Creatinine (μmol/L)	70.45 ± 15.26	74.25 ± 15.68	–1.151	0.252
N ($\times 10^9$/L)	4.48 ± 1.02	4.78 ± 0.68	–1.511	0.134

Note: BMI, body mass index; CysC, Cystatin C; N, neutrophil count; WBC, white blood cell count.

Table 5. Assignment of parameters in analyses.

Parameter	Assignment
PSA	Actual values
FIB	Actual values
miR-141-3p	Actual values
Clinical T stage	≤T2a = 0, ≥T2b = 1
Gleason score	≤6 = 0, ≥7 = 1
D-dimer	Actual values
CysC	Actual values

Notes: CysC, Cystatin C; FIB, fibrinogen; PSA, prostate-specific antigen.

clinical T stage, Gleason score, D-dimer, and CysC levels, significantly impacted the incidence of bone metastasis in patients with prostate cancer, as presented in Tables 5,6.

Development of a Predictive Model for Bone Metastasis in Prostate Cancer Patients

A logistic regression model was developed from the multivariate analysis results to predict bone metastasis in individuals with prostate cancer. The outcome variable was the occurrence status of bone metastasis (1 for occurrence, 0 for non-occurrence), and the model incorporated variables that had a significant effect on bone metastases in the multifactorial analysis. The equation of the model is as follows: logit(P) = 2.860 × clinical T stage + 4.086 × Gleason score + 4.884 × D-dimer + 5.419 × CysC + 8.602 × miR-141-3p + 5.610 × FIB + 1.587 × PSA – 71.000.

Analysis of the Predictive Value of the Bone Metastasis Risk Prediction Model for Prostate Cancer Patients

The employed predictive model evaluated a cohort of 100 prostate cancer patients within the study, aiming to confirm its predictive accuracy. ROC curve analysis indicated that the model achieved an AUC of 0.923 for predicting bone metas-

Table 6. Multivariate analysis of factors affecting patient bone metastasis.

Factor	β	SE	Wald	*p*-value	OR	95% CI	
						Lower	Upper
Clinical T stage (≥T2b)	1.051	0.442	5.654	0.017	2.860	1.203	6.799
Gleason score (≥7)	1.407	0.514	7.493	0.006	4.086	1.492	11.185
D-dimer	1.586	0.421	14.192	<0.001	4.884	2.140	11.147
CysC	1.690	0.503	11.289	<0.001	5.419	2.022	14.525
miR-141-3p	2.152	0.383	31.571	<0.001	8.602	4.061	18.223
FIB	1.725	0.604	8.157	0.004	5.610	1.717	18.329
PSA	0.462	0.096	23.160	<0.001	1.587	1.316	1.914

Note: CI, confidence interval; CysC, Cystatin C; FIB, fibrinogen; OR, odds ratio; PSA, prostate-specific antigen; SE, standard error.

tasis, with a 95% CI spanning 0.868 to 0.979. The model exhibited a sensitivity of 0.969 and a specificity of 0.544, with the optimal threshold value identified as 123.164 ($p < 0.05$, Fig. 1).

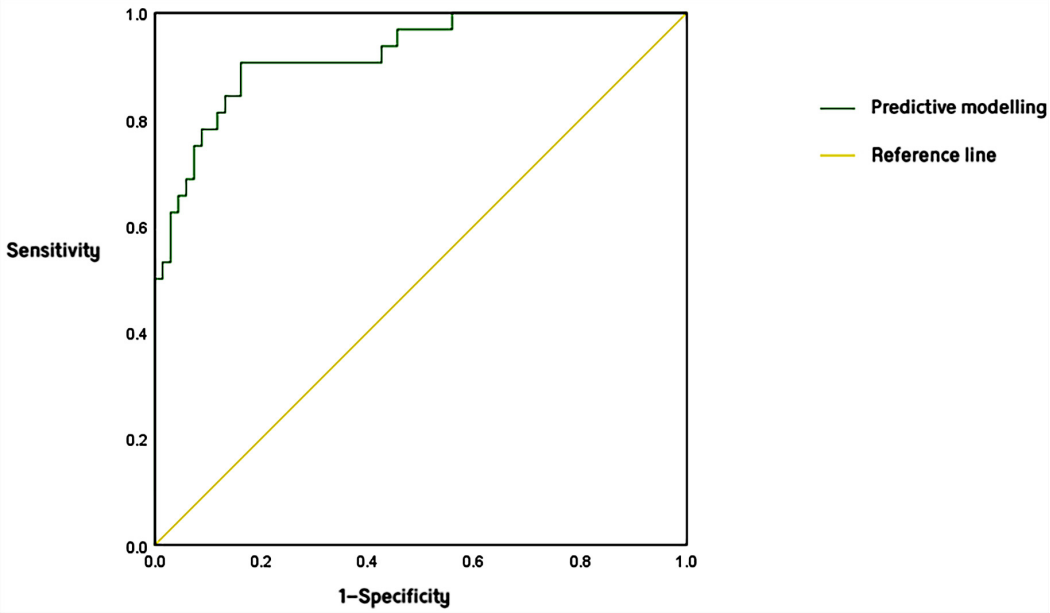

Fig. 1. Receiver operating characteristic (ROC) curve of the risk model for predicting bone metastasis in prostate cancer patients.

Discussion

Globally, prostate cancer remains a leading cause of morbidity and mortality among men, with approximately 1.6 million new cases diagnosed annually (Ali et al, 2021; Kang et al, 2022). The progression to bone metastasis is particularly concerning, as it severely impacts quality of life and overall survival. Current diagnostic methods primarily rely on imaging techniques, which, while effective, can

be costly and invasive (Mohseninia et al, 2024; Chao et al, 2021). In this context, the identification of non-invasive biomarkers such as miR-141-3p, FIB, and PSA could revolutionise the management of prostate cancer by facilitating earlier interventions (Yu et al, 2023; Lei et al, 2023).

The predictive model constructed in this study, which achieved an AUC of 0.923 and demonstrated a sensitivity of 0.969. This suggests that the combined use of miR-141-3p, FIB, and PSA could provide a more reliable method for predicting bone metastasis, thereby enhancing clinical decision-making. The integration of these biomarkers into routine clinical practice could allow for timely monitoring and personalised treatment strategies, ultimately improving patient outcomes.

When comparing our results with existing literature, we found that elevated levels of miR-141-3p have been associated with tumour progression and metastasis in various studies (Castro et al, 2013; Deek and Tran, 2020). For instance, prior research indicates that miR-141-3p can enhance tumour cell proliferation and migration, facilitating the transition to metastatic disease. This aligns with our findings, which suggest a strong correlation between elevated miR-141-3p levels and the presence of bone metastasis (Skok et al, 2020; Breznik et al, 2019).

Additionally, our analysis revealed that FIB levels are significantly associated with tumour progression (Leto and Sepporta, 2020; Liu et al, 2024). Previous studies have shown that FIB can create a supportive microenvironment for tumour growth and metastasis, acting as a carrier for growth factors that promote angiogenesis (Atallah et al, 2021; Boehm et al, 2023). This reinforces the notion that FIB is not merely a marker of coagulation but also a critical player in cancer biology (Hupe and Merseburger, 2021).

However, it is essential to acknowledge the limitations of our study. The sample size of 100 prostate cancer patients, while sufficient for preliminary findings, may limit the generalizability of our results. Future studies with larger, more diverse cohorts are necessary to validate our predictive model. Moreover, the retrospective design of our study may introduce biases, and the reliance on serum biomarkers alone may not capture the full complexity of tumour biology. Thus, prospective studies are warranted to validate the clinical applicability of our model.

We also recognise the need to discuss the limitations of our predictive model. While it demonstrates high accuracy, external validation in different populations and settings is crucial to confirm its applicability. Furthermore, exploring additional biomarkers and integrating imaging techniques could enhance the model's predictive power.

Conclusion

This study highlights the significant association of serum miR-141-3p, FIB, and PSA levels with bone metastasis in prostate cancer patients. The predictive model developed offers a cost-effective, non-invasive method for assessing metastasis risk. These findings can inform clinical strategies, enabling early interventions to improve patient outcomes.

Key Points

- Laboratory parameters such as D-dimer and CysC are risk factors for bone metastasis in prostate cancer patients.
- Tumour indices such as clinical T stage and Gleason score might be useful as predictors of bone metastasis in patients with prostate cancer.
- Serum biomarkers including miR-141-3p, fibrinogen and prostate-specific antigen collectively have potential in predicting of bone metastasis in prostate cancer patients.
- The predictive model developed demonstrates high sensitivity and specificity, making it a valuable tool for clinical decision-making in the context of detecting bone metastasis in prostate cancer.

Availability of Data and Materials

All data included in this study are available from the corresponding author upon reasonable request.

Author Contributions

JL: Conceptualization, Methodology, Data Analysis, Writing – Original Draft, Data Collection, Validation, Review & Editing, Supervision, Project Administration, Funding Acquisition. WW: Statistical Analysis, Software, Visualization. Both authors contributed to the important editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This research received approval from the Institutional Review Board of The Fourth Affiliated Hospital of Soochow University (Approval No.: 2024-240835) and was conducted in compliance with the ethical principles established by the Declaration of Helsinki. Prior to data collection, informed written consent was obtained from all participants.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0881.

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