ORIGINAL RESEARCH

Developing a Nomogram-Based Prediction Model for Malnutrition Risk in Preoperative Elderly Patients with Hip Fracture

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Objective: To evaluate the risk factors contributing to preoperative malnutrition in elderly patients with hip fractures.

Methods: The study retrospectively analysed clinical data from 182 elderly patients aged 60 years or older with hip fractures. Nutritional status was assessed according to the Global Leadership Initiative on Malnutrition diagnostic criteria, and risk factors associated with malnutrition were identified through univariate and logistic regression analyses. Based on the findings, a nomogram was developed, and a calibration curve model was constructed. The predictive performance of the model was evaluated using the receiver operating characteristic (ROC) curve. Finally, the model was validated using an independent cohort of 78 patients.

Results: Data analysis revealed that among the 182 elderly patients with hip fractures, 76 were men and 106 were women, with a mean age of 75.77 ± 8.66 years. The fractures included 135 femoral neck fractures and 47 intertrochanteric fractures. Malnutrition was identified in 39.01% (71/182) of the patients. Independent risk factors for malnutrition included age, body mass index, the number of comorbidities, haemoglobin level and serum albumin level. A nomogram model incorporating these indicators was developed, demonstrating robust predictive performance, with an area under the ROC curve of 0.886 (95% confidence interval: 0.809–0.962). **Conclusion:** It is anticipated that the proposed model will serve as a valuable tool for the timely and accurate clinical identification of

malnutrition risk in elderly patients with hip fractures.

Keywords: malnutrition, older adults, hip fracture, prediction model

Introduction

Hip fractures in the elderly pose a common and serious health concern, with high rates of disability and mortality. Xia et al¹ projected that by 2050, there will be approximately 6.26 million hip fracture cases worldwide. In China alone, around 1 million individuals experience hip fractures annually, predominantly affecting the elderly group.² This issue has escalated into a public health challenge on a global scale. Malnutrition is a common issue among elderly patients with hip fracture, with prevalence ranging from 7% to 70%, depending on the assessment tool used.^{3–6} Malnutrition can result in prolonged hospital stays, increased postoperative complications and elevated mortality rates, significantly impacting the health outcomes and quality of life of the elderly.⁷ Therefore, it is crucial to evaluate and address the nutritional status of patients with hip fracture.

Malnutrition remains a critical concern in clinical settings, particularly in elderly populations. However, despite its significant impact on patient outcomes, there is no universally agreed-upon definition of malnutrition. The Global Leadership Initiative on Malnutrition (GLIM) criteria, which provide a comprehensive and standardised definition, require a range of complex assessments that may not always be feasible in routine clinical practice. This study aims to bridge this gap by developing a simple, easily collected data-driven nomogram to predict malnutrition risk based on the more complex GLIM criteria. By utilising readily available clinical parameters, our model provides a practical tool

for predicting malnutrition risk in preoperative elderly patients with hip fractures, facilitating early intervention and improving patient outcomes.

Previous studies have identified factors such as age, body mass index (BMI), haemoglobin levels and albumin levels as potential risk factors for malnutrition. Timely and effective interventions targeting these factors can significantly improve nutritional status and clinical outcomes.^{4,8} However, despite these insights, no comprehensive predictive model has been developed to assess the risk of preoperative malnutrition specifically in elderly patients with hip fractures.

In this work, a column-line graphical model is developed to forecast preoperative malnutrition in elderly hip fracture patients by analysing age, BMI, haemoglobin, and albumin levels retrospectively. The model underwent internal validation and exhibited a strong predictive capability (consistency [C]-index: 0.886). The study reveals that key risk factors for malnutrition are advanced age, low BMI and low haemoglobin and albumin levels.

This model offers clinicians a simple and dependable tool for identifying high-risk patients before surgery, thus enabling tailored nutritional interventions. Furthermore, it is an essential tool for further studies. The validation and optimisation of this approach will be conducted through multicentre, large-sample studies before being implemented in a wider clinical context. The findings from this research could potentially influence healthcare policies to prioritise the nutritional well-being of elderly patients with hip fractures, leading to enhanced standardisation and effectiveness of nutritional evaluation and treatment.

Materials and Methods

Study Population

The study included patients admitted to the orthopaedic ward of a tertiary Grade A hospital in Ningbo for hip fractures between January 2022 and June 2023. The inclusion criteria were as follows: (1) patients aged 60 years or older; (2) confirmed hip fracture through imaging diagnosis, such as femoral neck fracture or intertrochanteric fracture of the femur;⁹ (3) fracture resulting from low impact injuries (eg falls, minor collisions), defined as an applied force below the threshold causing healthy bone to fracture;¹⁰ (4) patients with an underlying disease diagnosed by a hospital in the stable phase, which means no episodes or drastic changes in the state of illness within the last 3 months;¹¹ and (5) patients with clear consciousness, stable vital signs and the ability to communicate and cooperate until all assessments were completed. The exclusion criteria included (1) pathological fractures due to tumours or multiple fractures complicated with injuries to other body parts; (2) the presence of malignant tumours, tuberculosis or other chronic wasting diseases; (3) loss of activity of daily living before the occurrence of the fracture or in the terminal stage of the disease; and (4) the presence of cognitive impairment.

These criteria were intended to minimise potential confounders and to focus the model on predicting malnutrition risk in a patient population where the five key predictors – age, BMI, comorbidities, albumin and haemoglobin – could be the most relevant. Approval for this study was granted by the ethics committee of the hospital, and all participants provided informed consent.

After reviewing the literature and consulting with experts, key factors contributing to malnutrition in elderly patients with hip fractures were identified. The research findings, aligned with prior studies, indicated that the prevalence of malnutrition among this population was 35.19%. A total of eight variables were incorporated into the predictive model. The sample size was calculated using the logistic events per variable method.¹² Considering a 10%–20% loss to follow-up, a sample size of 138 cases ([$8 \times 5 (1 + 0.2)$] / 0.35) was required for the analysis. Ultimately, 182 cases were included in the modelling group, with an additional 78 cases between July 2023 and January 2024 included for the model validation at a ratio of 7:3.

Research Methods

Nutrition Risk Screening and Malnutrition Diagnosis

Based on the GLIM criteria,^{13,14} the nutritional status of each participant was assessed within 48 hours of hospital admission. The GLIM framework involves a two-step process: nutritional risk screening followed by diagnostic assessment. In the diagnostic stage, individuals identified as being at risk of malnutrition were further classified as malnourished within 48 hours if they exhibited at least one clinical criterion (eg unintentional weight loss, BMI \leq

18.5 kg/m² or reduced muscle mass) and one etiological criterion (eg reduced food intake, impaired nutrient absorption, disease burden or inflammation). While the GLIM criteria involve comprehensive clinical assessments, our approach leverages easily obtainable data, making it a practical alternative for clinical environments with limited resources.

Data Collection

General clinical data, including age, gender, fracture type, BMI, comorbidities and frailty assessment, were collected from the electronic medical record system of the tertiary Grade A hospital in Ningbo. Laboratory test results from the patients' first early-morning fasting venous blood samples were recorded. These tests included ultrasensitive C-reactive protein, haemoglobin, serum albumin and prealbumin levels. Frailty was assessed based on the criteria defined by Fried et al,¹⁵ which classify frailty as the presence of three or more of the following: unintentional weight loss, decreased grip strength, fatigue, slowed walking speed and reduced activity level.

Statistical Methods

Statistical analysis of the data was conducted using SPSS 29.0. The measurement data were subjected to normality testing using the Shapiro–Wilk test. The data following the normal distribution were expressed as mean \pm standard deviation($\bar{x} \pm s$), and inter-group comparisons were conducted using the *t*-test for independent samples. Data not conforming to the normal distribution were expressed in terms of median and quartile (M; P25, P75) and were compared using the Mann–Whitney rank sum test. Count data were presented as frequency and percentage (n [%]), and inter-group comparisons were performed using the chi-square (χ^2) test. The risk factors of preoperative malnutrition in elderly patients with hip fracture were analysed using the binary logistic regression analysis. The effectiveness of the model was evaluated using the area under the receiver operating characteristic curve (AUC), and the C-index value was calculated. Additionally, a calibration curve was plotted using R software to establish a column chart. A P-value of <0.05 was regarded as indicating statistical significance.

Results

General Data of Elderly Patients with Hip Fractures and Univariate Analysis of Preoperative Malnutrition

For this study, a total of 182 medical records of elderly patients with hip fractures were reviewed. The patients ranged in age from 60 to 89 years, with a mean age of 75.77 ± 8.66 years. Among them, 76 patients (41.76%) were men and 106 (58.24%) were women. The types of hip fractures included 135 cases (74.18%) of femoral neck fractures and 47 cases (25.82%) of intertrochanteric fractures. Additionally, 26 patients (14.29%) had five or more underlying comorbidities, with hypertension (64.29%), osteoporosis (52.20%), diabetes mellitus (28.02%), chronic obstructive pulmonary disease (24.73%) and coronary heart disease (20.33%) being the most prevalent. The mean preoperative serum albumin level was 34.66 ± 4.81 g/L, with 35 patients (19.23%) presenting levels below 30 g/L. Based on the GLIM diagnostic criteria, the prevalence of malnutrition was determined to be 39.01% (71/182), as summarised in Table 1.

Multivariate Analysis of Preoperative Malnutrition in Elderly Patients with Hip Fracture Univariate analysis revealed significant correlations between preoperative malnutrition and several factors, including age (P < 0.001), BMI (P < 0.001), number of comorbid underlying diseases (P < 0.001), frailty (P < 0.001), ultrasensitive C-reactive protein (P = 0.017), haemoglobin levels (P < 0.001) and serum albumin levels (P < 0.001) (Table 1). Variable assignments were as follows: categorical variables such as comorbid underlying diseases, frailty, ultrasensitive C-reactive protein and haemoglobin were analysed as dichotomous variables, whereas continuous variables such as age, BMI, serum albumin and prealbumin – were recorded at their original values, as outlined in Table 2. The count data – age, BMI, serum albumin and prealbumin – were recorded at their original values. The findings indicated that age (odds ratio [OR] = 1.135, 95% confidence interval [CI]: 1.025–1.257, P = 0.015), BMI (OR = 0.193, 95% CI: 0.101–0.370, P < 0.001), number of comorbid underlying diseases (OR = 9.489, 95% CI: 1.319–68.267, P = 0.025), haemoglobin level (OR = 10.562, 95% CI: 1.971–56.613, P = 0.006) and serum albumin level (OR = 0.819, 95% CI: 0.767–0.992, P = 0.041) were the independent risk factors for preoperative malnutrition in elderly patients with hip fracture (P < 0.05), as detailed in Table 3.

| ltem | Malnutrition | Normal Nutrition | t (χ ²) | Р |
|--|--------------|------------------|---------------------|--------|
| | Group (n=71) | Group (n=III) | | |
| Age | 80.68±8.53 | 72.64±7.19 | -6.83 | <0.001 |
| BMI (kg/m ²) | 18.76±1.61 | 23.34±2.42 | 15.341 | <0.001 |
| Sex[n (%)] | | | 0.040 | 0.842 |
| Male | 29 (40.85) | 47 (42.34) | | |
| Female | 42 (59. 15) | 64 (57.66) | | |
| Fracture types [n(%)] | | | 0.053 | 0.817 |
| Femoral neck fracture | 52 (73.24) | 83 (74.77) | | |
| Intertrochanteric fracture | 19 (26.76) | 28 (25.23) | | |
| Number of comorbidities [n (%)] | | | | |
| ≤3 | 43 (60.56) | 99 (89. 19) | 20.693 | <0.001 |
| >3 | 28 (39.44) | 12 (10.81) | | |
| Frailty [n (%)] | | | 34.552 | <0.001 |
| No | 15 (21. 13) | 73 (65.77) | | |
| Yes | 56 (78.87) | 38 (34.23) | | |
| hs-CRP (mg/L) | | | 5.733 | 0.017 |
| <5 | 16 (22.54) | 44 (39.64) | | |
| ≥5 | 55 (77.46) | 67 (60.36) | | |
| Hemoglobin (g/L) | | | 41.572 | <0.001 |
| ≥120 (male cases), ≥110 (female cases) | 20 (28. 17) | 85 (76.58) | | |
| <120 (male cases), <110 (female cases) | 51 (71.83) | 26 (23.42) | | |
| Albumin (g/L) | 31.98±4.34 | 36.38±4.30 | 0.607 | <0.001 |
| Prealbumin (g/dl) | 15.74±5.69 | 18.95±5.54 | 3.773 | <0.001 |

 Table I Univariate Analysis of Preoperative Malnutrition in Elderly Patients with Hip Fracture [N;

 Percentage (%)]

Table 2 Independent Variable Assignment

| Factors | Assignments | | |
|------------------|---|--|--|
| Comorbidities | Assigned as 0 if \leq 3, assigned as 1 if $>$ 3 | | |
| Frailty | No=0, Yes=1 | | |
| hs-CRP (mg/L) | Assigned as 0 if <5, assigned as 1 if \geq 5 | | |
| Hemoglobin (g/L) | Assigned as 0 if \geq 120 (male cases) and \geq 110 (female cases); | | |
| | assigned as = 1 if <120 (male cases) and <110 (female cases) | | |

Table 3 Results of Binomial Logistic Regression Analysis of PreoperativeMalnutrition in Elderly Patients with Hip Fracture

| | В | SE | Wald ₂ 2 | Р | OR | 95% CI |
|---------------|--------|-------|---------------------|--------|--------|--------------|
| Age | 0.127 | 0.052 | 2.43 | 0.015 | 1.135 | 1.025~1.257 |
| BMI | -1.646 | 0.332 | -4.95 | <0.001 | 0.193 | 0. 101~0.370 |
| Comorbidities | 2.250 | 1.007 | 2.23 | 0.025 | 9.489 | 1.319~68.267 |
| Frailty | -1.019 | 0.877 | -1.16 | 0.245 | 0.361 | 0.065~2.013 |
| hs-CRP | 0.202 | 0.931 | 0.22 | 0.828 | 1.224 | 0. 198~7.581 |
| Hemoglobin | 2.357 | 0.857 | 2.75 | 0.006 | 10.562 | 1.971~56.613 |
| Albumin | -0.200 | 0.099 | -2.04 | 0.041 | 0.819 | 0.767~0.992 |
| Prealbumin | 0.031 | 0.079 | 0.40 | 0.690 | 1.032 | 0.885~1.204 |
| Constant | 29.044 | 8.971 | 3.24 | 0.001 | 4.107 | - |

Construction and Validation of a Nomogram-Based Prediction Model for Preoperative Malnutrition in Elderly Patients with Hip Fracture

Based on the logistic regression analysis findings, a nomogram-based predictive model was developed to forecast preoperative malnutrition in elderly patients with hip fractures. The model incorporates age, BMI, number of comorbidities, haemoglobin level and serum albumin level as predictors, with the occurrence of malnutrition as the clinical outcome (see Figure 1).

For example, consider a 78-year-old patient with a femoral neck fracture, a BMI of 22, comorbidities including hypertension, diabetes and osteoporosis, a haemoglobin level of 100 g/L and a serum albumin level of 28 g/L. Using the nomogram, the patient's total score would be calculated as follows: 7.5 (age) + 55.5 (BMI) + 7.5 (number of comorbidities) + 8.5 (haemoglobin) + 11 (albumin), resulting in a total score of 90 points. This score corresponds to a predicted malnutrition risk of 80%.

The model's performance was evaluated using the Bootstrap method with 1000 iterations, yielding an AUC of 0.886 (95% CI: 0.809–0.962) (Figure 2). The calibration curve demonstrated a strong agreement between the predicted probabilities and the actual probabilities of malnutrition (Figure 3), indicating the model's reliability and accuracy.

To evaluate the clinical utility of the constructed nomogram, a Decision Curve Analysis (DCA) was performed. The results demonstrated that across a range of threshold probabilities (0.1-0.9), the nomogram exhibited a consistently higher net benefit in both the modeling and validation cohorts compared to the "no intervention" strategy (Figure 4). The model provides significant added value for clinical decision-making within this range.

Discussion

Accurate assessment is fundamental to the implementation of effective nutritional support therapy. Elderly patients with hip fractures frequently exhibit a high prevalence of preoperative malnutrition, emphasising the critical need for precise nutritional evaluation prior to surgery. In this study, the GLIM diagnostic criteria, introduced in 2018, were utilised. These criteria are increasingly acknowledged as a reliable tool for assessing malnutrition in older adults and have gained widespread adoption in various regions due to their robust predictive accuracy.^{16–19} The results indicated that 39.01% of the 182 elderly patients with hip fracture examined were malnourished, agreeing with previous findings from both local and international studies.^{19,20} The multivariate logistic regression analysis revealed that age, BMI, comorbid underlying diseases and haemoglobin and albumin levels are independent risk factors for preoperative malnutrition in elderly patients with hip fractures.



Figure I Prediction nomogram of preoperative malnutrition risk in elderly patients with hip fracture.



Figure 2 ROC of the prediction model for preoperative malnutrition risk in elderly patients with hip fracture (ROC is the abbreviated term for receiver operation characteristic curve).



Figure 3 Correction curves of the prediction model the preoperative malnutrition risk in elderly patients with hip fracture (Number of repeat samples B=1000, Mean absolute error = 0.040, n=78).

The study found that the average age of the patients was significantly higher in the malnourished group than in the normal nutrition group (80.68 ± 8.53 vs 72.64 ± 7.19 ; P < 0.001). Age was positively correlated with the incidence of malnutrition in elderly patients with hip fractures. Previous research has suggested that older adults are more susceptible to malnutrition due to reduced energy and protein intake. Age-related physiological changes, such as diminished dental function and loss of appetite, further exacerbate the risk and severity of malnutrition in this population.²¹ These results

Decision Curve Analysis (DCA)



Figure 4 Decision Curve Analysis (DCA) for the nomogram in the modeling and validation cohorts. The nomogram demonstrates higher net benefit compared to the "no intervention" strategy, particularly within the 0.2–0.8 threshold range, indicating its clinical applicability.

underscore the importance of evaluating the nutritional status of elderly patients pre-surgery to improve postoperative recovery with tailored nutritional support.

Body mass index serves as a practical and easily accessible tool widely used in nutritional screening and assessment. According to the "2023 Guidelines on Appropriate Range of Body Mass Index and Weight Management for Older Adults in China", the recommended BMI range for individuals aged 80 years and above is $22 \text{ kg/m}^2 \leq \text{BMI} < 26.9 \text{ kg/m}^{2.22}$ For elderly patients under 80 years old, low BMI is defined as BMI $\leq 18.5 \text{ kg/m}^2$, whereas for those 80 years and older, it is defined as BMI $\leq 22 \text{ kg/m}^2$. The findings reveal a strong correlation between low BMI and an increased risk of malnutrition. This relationship may be attributed to the impaired nutrient absorption associated with lower BMI. Malnutrition, in turn, exacerbates muscle mass loss, perpetuating a detrimental cycle that further compromises the patient's nutritional and physical status.^{23,24} The findings highlight a significant correlation between low BMI and an elevated risk of malnutrition.

Elderly patients with hip fractures often present with chronic conditions such as cardiovascular, cerebrovascular, respiratory and endocrine diseases. These comorbidities accelerate the decline of organ system functions and impair the body's ability to withstand external stressors, thereby increasing the risks faced by these patients during the perioperative period.²⁵ Out of the 182 elderly patients with hip fracture involved in the present study, the most common five underlying diseases were, in descending order, hypertension (64.29%) (117/182), osteoporosis (52.20%) (95/182), diabetes mellitus (28.02%) (51/182), chronic obstructive pulmonary disease (24.73%) (45/182) and coronary artery disease (20.33%) (37/182). These findings were generally consistent with prior works.^{26,27} Medical care providers specialising in orthopaedics are advised to assess comorbidities and medications in elderly patients, duly collaborate with other multidisciplinary professionals and make informed clinical decisions to optimise therapeutic care, prevent complications and actively enhance prognosis. Additionally, emphasis should be placed on health education to foster healthy dietary habits, stable blood glucose levels and adequate intakes of calcium and vitamin D, and to enhance the adherence level to osteoporosis screening and treatment.

Haematological nutritional parameters are crucial for the nutritional assessment of patients with fracture. According to Lu Panpan et al,²⁸ low haemoglobin level has been identified as a risk factor for preoperative malnutrition in elderly patients with hip fracture. Additionally, Ya LK et al²⁹ discovered that patients with preoperative haemoglobin levels of 80–100 g/L had a significantly higher 1-year postoperative mortality rate of up to 49.2%. Lu et al³⁰ found that haemoglobin level is associated with changes in muscle and fat mass, and that anaemia affects body functions through reduced tissue oxygenation. These

findings have identified low haemoglobin level as an independent risk factor for preoperative malnutrition in elderly patients with hip fracture.

The mean haemoglobin level of the 182 patients involved in this study was (114.38 ± 18.72) g/L, and 42.31% of the patients (39 men and 38 women) had their haemoglobin levels below the normal range. Previous reports^{31,32} indicated that for elderly patients with hip fracture, the indication for blood transfusion should be appropriately eased, and a relatively high haemoglobin level (<100g/L) as the indication for blood transfusion would more effectively address the anaemia symptoms of patients, such that they can successfully complete the surgery and recover faster. Albumin is synthesised by the liver and accounts for more than 50% of the total protein. It has a long half-life (approx. 19 days) and serves as an important indicator for the assessment and monitoring of nutritional status, and has been widely used in the assessment of the nutritional status of patients with bone fractures.²⁶ Several studies have revealed that decreased serum albumin suggests high nutritional consumption and poor tolerance and is a critical risk factor for the occurrence of infections and poor prognosis of patients.^{33–35} The findings of this study also demonstrate that low serum albumin level is an independent risk factor for malnutrition. Therefore, early preoperative screening of patients complicated with hypoproteinaemia and timely supplementation can be considered as significant for improving the nutritional status and prognosis of elderly patients with hip fracture.

The nomogram developed in this study provides a practical tool for predicting malnutrition risk in preoperative elderly patients with hip fractures. By using simple, easily obtainable clinical parameters, such as age, BMI, albumin, haemoglobin and comorbidities, clinicians can assess the likelihood of malnutrition in these patients.

By way of example, a positive result (high predicted risk of malnutrition) would suggest that the patient may benefit from early nutritional interventions, such as referral to a dietitian, provision of nutritional supplements or closer monitoring of nutritional status. This would be crucial in preventing complications associated with malnutrition, particularly in elderly patients undergoing hip fracture surgery. A negative result (low predicted risk of malnutrition) would indicate that no immediate nutritional intervention is necessary, although the patient should still be monitored for any changes in nutritional status as part of routine preoperative care.

The degree of certainty of the predictions is reflected in the C-statistic and CIs. A higher C-statistic indicates that the nomogram has good discriminative ability, which allows clinicians to have greater confidence in the tool's predictions. The CIs provide a sense of the reliability of the predictions for individual patients, helping clinicians understand the level of certainty when making clinical decisions.

DCA is a valuable tool for assessing the clinical utility of predictive models by considering both true positives and false positives in the context of varying threshold probabilities. In this study, the DCA results confirmed that the proposed nomogram offers substantial net benefit across a wide range of threshold probabilities, particularly between 0.2 and 0.8. This demonstrates its potential for effectively identifying elderly patients with hip fractures who are at high risk of malnutrition and may benefit from early nutritional interventions. Compared to a "no intervention" strategy, the nomogram provides a quantifiable basis for clinical decision-making, allowing for more targeted and timely interventions.

The study involves some limitations, including the small sample size and the single-centre trial design, which may have resulted in some bias. Further research should include multi-centre, large-sample studies to validate the findings and provide more extensive data for predicting malnutrition in elderly patients with hip fracture. Future study for further validation should also include larger, more diverse patient cohorts and multiple healthcare settings, and should explore aspects such as physical activity, cognitive function and socioeconomic factors. This would provide a more holistic assessment of malnutrition risk in elderly patients.

Conclusion

In conclusion, this study developed and validated a simple, data-driven nomogram for predicting malnutrition risk in preoperative elderly patients with hip fractures. The model, based on easily obtainable clinical parameters, such as age, BMI, albumin, haemoglobin and comorbidities, demonstrates strong predictive ability, as indicated by its high C-statistic. The nomogram offers a practical tool for clinicians to identify patients at risk of malnutrition, enabling early intervention and potentially improving surgical outcomes.

While the model shows promise, its validation was performed in a specific, homogenous patient population, and further validation in a broader cohort is needed to assess its generalisability. Future studies should aim to refine and test the model in diverse patient groups to ensure its applicability in routine clinical practice.

Data Sharing Statement

Data will be made available on request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of First Affiliated Hospital of Ningbo University, and written informed consent was obtained from all participants. All methods were carried out in accordance with relevant guidelines and regulations.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare.

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