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A prognostic nomogram for all frequencies sudden sensorineural hearing loss based on the commixed index of inflammatory-immune-hemostasis-nutrition

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Abstract

Background: All-frequencies sudden sensorineural hearing loss (AF-SSNHL) is a common otology emergency that greatly impacts patient's quality of life. Given that inflammatory-immune-hemostasis-nutrition-related parameters are commonly reported prognostic factors, this study aimed to compare and evaluate the clinical value of such parameters to develop a prognostic nomogram.

Methods: The analysis prospectively enrolled 245 patients with AF-SSNHL patients from August 2018 to May 2022. Patients were divided into training and validation cohorts randomly. The predictive values of the hematological indexes were calculated by receiver operating characteristic analysis, and predictive abilities were evaluated using logistic regression. A predictive prognostic model was developed using logistic regression and internally/external validated using calibration curves, decision curve analysis, and ROC analysis; a nomogram was constructed as its graphical representation.

Results: The prognostic nutritional index (PNI) and neutrophil lymphocyte D-dimer albumin score (NLDA) were superior to other hematological indexes in predicting the outcome of AF-SSNHL. The predictive prognostic model revealed that a high value of NLDA [odds ratio (OR), 4.363; 95% confidence interval (CI), 0.828-10.416; $P < 0.05$] and a low level of PNI (OR, 2.439; 95% CI, 1.188-5.006; $P < 0.05$) were independent risk factors for ineffective AF-SSNHL treatment. The concordance indexes for internal and external validation of the predictive model were 0.815 (95% CI, 0.754–0.875, $P = 0.770$) and 0.788 (95% CI, 0.663–0.913, $P = 0.348$), respectively. The areas under the curves of the nomogram-based predicted probabilities (nomogram scores) were 0.815 (95%CI, 0.754 - 0.875; $P < 0.05$) and 0.849 (95%CI, 0.737 - 0.961; $P < 0.05$), respectively.

Conclusions: PNI and NLDA were superior hematological parameters and independent predictors of AF-SSNHL prognosis. Our predictive model, visualized as a nomogram based on vertigo, hearing level onset, PNI, and NLDA, may facilitate individualized prediction of treatment outcome of AF-SSNHL.

Trial registration: ChiCTR1800017072, https://www.chictr.org.cn/showprojen.aspx?proj=29023, **Registration Date**: 07/10/2018

Keywords: all frequencies sudden sensorineural hearing loss; inflammatory-immune-hemostasis-nutrition index; nomogram; prognosis.

Background

Sudden sensorineural hearing loss (SSNHL) is defined as a rapid onset of hearing impairment ≥30 dB in at least 3 consecutive frequencies within 3 days, with its cause currently unknown [1]. The morbidity rate of SSNHL has been increasing in recent years reaching 5 to 27 people per 100,000 people and about 66,000 new cases in the United States each year [2-4]. SSNHL usually occurs unilaterally, sometimes accompanied by tinnitus, vertigo, and ear fullness. The communicative and psychological impairments experienced during acute SSNHL episodes, as well as during potentially irreversible hearing loss and persistent tinnitus, create a strong desire for treatment [5, 6]. Although the cause of SSNHL is not clear, its pathogenesis has been proven to be related to the viral infection, autoimmune disease, and microcirculation disorder [1, 7].In this context, AF-SSNHL is considered a multifactorial condition in which inflammation, immune dysregulation, and microcirculatory impairment are closely interconnected rather than independent mechanisms. Systemic inflammatory activation may induce endothelial dysfunction and oxidative stress, thereby promoting a hypercoagulable state and impairing cochlear microcirculation. Given that the cochlea is supplied by a terminal artery with minimal collateral circulation, even subtle reductions in blood flow may result in ischemic injury to sensory hair cells [7,12]. Meanwhile, inflammatory activation has been shown to correlate with disease onset and poor prognosis in SSNHL [31], and increasing evidence indicates that the cochlea is not an immunologically privileged site, with local immune and inflammatory responses detectable within the inner ear microenvironment [10]. These interacting processes may form a pathological cascade that ultimately contributes to irreversible hearing loss and poor prognosis in AF-SSNHL.

In addition, clinical factors such as the frequency and extent of hearing loss, age, presence of vertigo, and the initial duration of treatment have been shown to influence the prognosis of SSNHL [7]. Among these factors, the frequency involvement and severity of hearing loss are considered the most critical determinants of outcome [8]. Accordingly, all-frequencies SSNHL (AF-SSNHL), defined as hearing impairment across the entire audiometric spectrum, represents the subtype with the poorest prognosis and often results in substantial and irreversible impairment of quality of life [7].

Experimental and clinical trials for the treatment of SSNHL are difficult to perform due to the difficulty in determining control groups and the many factors affecting patient outcomes. However, through extensive studies investigating potential biomarkers, hope is on the horizon for better SSNHL prognosis and targeted treatment. While experimental and clinical studies have certified that inner ear microenvironment concerning the inflammatory, immune, hemostasis-coagulation, and nutrition metabolism [9-13] are closely associated with treatment outcomes, the comprehensive hematological indexes including the above four aspects are scarcely studied in clinic, and thus there is a lack of high specificity biomarker available. Along the same lines, other predictive methods such as otoacoustic emission, auditory brainstem response [14], three-dimensional fluid

attenuation inversion recovery magnetic resonance imaging (MRI) [15], 3-dimensional inversion recovery sequence with real reconstruction MRI [16], synthetic MRI [17], and laser-doppler flowmetry [18] also lack specificity are quiet costly for patients. To address these issues, the present study aims to comprehensively review the hematological indexes and discover a novel, comprehensive, and economic index for predicting AF-SSNHL prognosis.

Methods

Study population

This was a single-center prospective study. The aim was to establish a predictive prognostic model and calculate a new hematological index as an independent prognostic factor of AF-SSNHL by incorporating a prospective cohort of patients hospitalized at Shanghai Jiao Tong University Affiliated Sixth People's Hospital between August 2018 and May 2022. Written informed consent was obtained for all participants for the use of their clinical data for research, and the study protocol was approved by the Institutional Ethics Committee of the Shanghai Jiao Tong University Affiliated Sixth People’s Hospital [2018-KY-036(K)]. This study was conducted in conformity with the principles of the Declaration of Helsinki. All patients who visited our hospital within 2 weeks after SSNHL onset were included. All included patients satisfy the criteria outlined in the American guideline of SSNHL, experiencing hearing loss at all frequencies and ≥ 30 dBHL decrease in mean pure tone average (PTA) across 0.25 to 8 kHz [1]. Patients were excluded from the study if they had any other otologic disease that may interfere with SSNHL diagnoses such as chronic otitis media, acoustic trauma or otologic surgery history, conductive hearing loss, and Meniere's disease. Those with previous history of malignant disease, psychiatric conditions, dementia, or other major comorbidities (heart failure; stroke; and severe hepatic, pulmonary, or renal dysfunction) were also excluded. The flow chart of this study is shown in Figure 1. A total of 245 patients were finally included in this study. Subjects with complete information were randomly assigned at a 4:1 ratio to the training cohort (n=196) and the validation cohort (n=49) for nomogram construction and validation.

Data collection

Data collected for analysis include baseline characteristics [included age, gender, height, weight, body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP) on admission], and clinical characteristics [included affected side, accompanying symptoms (like tinnitus, vertigo, ear fullness), time to treatment, and hearing level on admission]. Hearing assessments were carried out according to standard laboratory procedures in standard shielding rooms and pure tone audiometry was performed by measuring air conduction and bone conduction at 0.125, 0.25, 0.5, 1, 2, 4, and 8 kHz before and after 2 weeks of systemic treatment. Hearing levels were calculated as the average of all impaired frequencies after onset while the extent of hearing recovery is calculated using PTA after onset minus PTA after treatment. Temporal bone computed tomography

or inner ear MRI was performed to rule out ear structural abnormality and tumors in all patients.

Upon admission, three categories of hematological indexes were recorded by analyzing blood samples obtained from the antecubital veins of all patients between 6 and 7 a.m. after an overnight fast. The hematological indexes include: (1) the inflammatory-immune reaction including the absolute value of white blood cell (WBC), neutrophil (N), and lymphocyte (L); (2) the routine hemostasis indexes such as platelet (PLT), D-dimer (D), and fibrinogen (Fg); (3) the nutrition indexes containing red blood cell (RBC), hemoglobin (Hb), and albumin (ALB). The normal reference ranges of the parameters in our hospital are as follows: WBC, 3.50-9.50*10^9/L; N, 1.80-6.30*10^9/L; L, 1.10-3.20*10^9/L; P, 125.00-350.00*10^9/L; D, 0.00-0.50 mg/L; Fg, 2.00-4.00 g/L; RBC, 3.80-5.10*10^{12}/L; Hb, 115.00-150.00 g/L; ALB, 35.00-55.00 g/L. Based on these original hematological indexes, we calculated the following commixed hematological indexes: neutrophil-to-lymphocyte ratio (NLR) (NLR = N / L) [30,31], platelet-to-lymphocyte ratio (PLR) (PLR = P / L) [32]; systemic immune inflammation index (SII) (SII = P × N / L) [32], prognostic nutritional index (PNI) (PNI = ALB + 5 × L) [51], neutrophil lymphocyte D-dimer albumin score (NLDA) [NLDA = N × D/(L × ALB)] [13], and neutrophil lymphocyte fibrinogen albumin score (NLFgA) [NLFgA = N × Fg/(L × ALB)] [22,23]. The above data were collectively described as inflammatory-immune-hemostasis-nutrition indexes in this study.

Treatment and evaluation

Each patient underwent comprehensive treatment, including treatment with steroids and batroxobin according to the Chinese guideline of SSHNL [7]. All patients received a 7-day course of systemic glucocorticoid therapy (Prednisone 1mg/kg/day for 3-5 days, followed by dose reduction in the remaining days according to the hearing improvement) and intravenous batroxobin (10U batroxobin was used for the first time, and then reduced to 5U batroxobin, once every other day, for a total of 1-3 times according to the level of fibrinogen) as described previously [13, 19]. According to the hearing recovery observed during the 2 weeks follow-up, patients were classified into two groups: the effective group (PTA of impaired frequency improvement greater than or equal to 15 dB, or returned to normal / unaffected ears) and the ineffective group (PTA of impaired frequency improvement less than 15 dB) [7].

Statistical analysis

All statistical analyses were performed with SPSS for Windows version 24.0 (IBM Corp., Armonk, NY, USA). Data were investigated using Kolmogorov-Smirnov test to determine the distribution pattern. Descriptive variables are expressed as mean ± standard deviation, median (interquartile range), or a percentage, as appropriate. Continuous variables were assessed by the t-test or the Mann-Whitney U test according to normality for variables while categorical variables were assessed by Chi-squared test. The area under the curve (AUC) was calculated

using the receiver operating characteristic (ROC) curve analysis to detect the predictive values of the hematological indexes related to the outcome of AF-SSNHL. The related parameters, including sensitivity, specificity, and optimal cut-off points of the hematological indexes, were calculated using receiver operating characteristic (ROC) curve analysis in MedCalc 20.022 for Windows (MedCalc Software Ltd., Ostend, Belgium). The optimal cut-off values were determined based on the Youden index, defined as the maximum value of sensitivity + specificity − 1. Backward conditional logistic regression was performed using a backward elimination procedure, and the final model retained variables that met the predefined significance criterion. Nomograms, calibration curves, and decision curve analysis (DCA) were created using RStudio 3.0.1 for windows (RStudio Inc., Boston, MA, USA) to conduct the internal and external validation of the established predictive prognostic model, and the results were evaluated using the concordance index (C-index). The C-index is an index that indicates the concordance level between the observed value and the value of expectation, and it is calculated to illustrate the predictive accuracy of the independent variables in the adjusted model. The packages in R used in this study were “rms” and “rmda”. P values < 0.05 were considered statistically significant for all tests.

Results

Baseline and clinical characteristics of participants

245 AF-SSNHL patients met the inclusion criteria and were enrolled in this study. Interval validation was performed by drawing a random sample of 20% patients from the original study population, using the Caret package in R 3.0.1. The baseline characteristics of 196 and 49 patients were included in the training and validation cohorts, respectively. About half of the patients (n = 85, 43.37%) were male in the training cohort and 20 (40.82%) in the validation cohort. The median age of the training cohort was 54.00 (38.00-65.75) years old and that of the validation cohort was 49.00 (44.50-60.50) years old. There were no differences in baseline characteristics (included age, gender, height, weight, BMI, SBP, DBP), and clinical characteristics [affected side, accompanying symptoms (like tinnitus, vertigo, ear fullness), time to treatment, and hearing level on admission] between the two groups. The hematological indexes of these two groups had no significant difference (all P > 0.05) except for the D level being significantly higher in the validation cohort than that of the training cohort (P < 0.05). A detailed analysis of the 245 patients is shown in Table 1.

Prognostic significance of the inflammation-immune-hemostasis-nutrition indexes in the training cohort

To identify potential prognostic factors, we first evaluated the association between hematological indices and clinical outcomes using univariate logistic regression analysis (Table 3). Based on the identified associations, we subsequently performed ROC curve analysis to assess the discriminative ability and determine optimal cut-off values for these significant predictors. The prognostic abilities of

hematological indexes were evaluated using the ROC analysis. Supplement Figure 1 shows the ROC curve analysis for the outcome of AF-SSNHL. As listed in Supplement Table 1, the hematological parameters of L, D, ALB, PLR, SII, PNI, NLDA, NLFgA may be prognostic predictors of AF-SSNHL. Among these parameters, the value of NLDA was identified as the poorest prognostic factor in the training cohort with an AUC of 0.715 (95%CI, 0.642-0.788, $P < 0.05$). ROC for optimal cut off point of these hematological parameters predicts AF-SSNHL effective outcome to be WBC ≤ $9.60*10^9$/L; N ≤ $4.00*10^9$/L; L > $1.40*10^9$/L; P > $207.00*10^9$/L; D ≤ 0.21 mg/L; Fg ≤ 2.23 g/L; RBC > $5.00*10^{12}$/L; Hb > 137.00 g/L; ALB > 45.90 g/L; NLR ≤ 5.28; PLR ≤ 178.82; SII ≤ 1174.83; PNI > 52; NLDA ≤ 0.0258; and NLFgA ≤ 0.2214.

Inflammation-immune-hemostasis-nutrition indexes in the training cohort

AF-SSNHL patients were divided into the effective group (n=74) and the ineffective group (n=122) according to different levels of hearing recovery as shown in Table 3. The ages of ineffective group were higher than that in effective group ($P < 0.05$). A higher number of patients with vertigo symptom were in the ineffective group than effective group ($P < 0.05$). The hearing level onset was significantly higher in the ineffective group than effective group ($P < 0.05$). Comparing the hematological indexes of these two groups, we found that the number of patients with low levels of N, D, Fg, NLR, PLR, SII, NLDA, and NLFgA in the effective group were higher than those in the ineffective group, while the number of patients with a high level of L, P, RBC, Hb, ALB, and PNI in the effective group were higher than those in the ineffective group (all $P < 0.05$).

Logistic regression models based on inflammation-immune-hemostasis-nutrition indexes and other parameters including age, gender, BMI, body pressure, affected side, tinnitus, vertigo, ear fullness, time to treatment, and hearing level onset are presented in Table 3. The parameters of height, weight, and original hematological indexes were eliminated by collinearity of all continuous variables using the variance inflation factor. With unadjusted ORs of 3.456 (95% CI, 1.342-8.897, $P < 0.05$), 0.972 (95% CI, 0.953-0.991, $P < 0.05$), and 4.363 (95% CI, 1.828-10.416, $P < 0.05$), vertigo, the hearing level onset, and NLDA level showed strong association with treatment outcome. After adjusting for all other significant outcome predictors, the four factors of vertigo, the hearing level onset, PNI level and NLDA level were deemed independent outcome predictors with adjusted ORs of 3.268 (95% CI, 1.340-7.965, $P < 0.05$), 0.970 (95% CI, 0.952-0.988, $P < 0.05$), 2.439 (95% CI, 1.188-5.006, $P < 0.05$), and 4.363 (95% CI, 1.828-10.416, $P < 0.05$), respectively. These results suggest that presence of vertigo, worse hearing level onset, lower PNI level, and higher NLDA level correlate to worse AF-SSNHL functional outcomes. It is noteworthy that established biomarkers, including NLR and PLR, failed to show statistical significance in the univariate analysis ($P > 0.05$). Conversely, the NLDA score was identified as a significant predictor ($P = 0.001$), indicating its superior prognostic value in this cohort.

Development and internal validation of a nomogram of the predictive prognostic model in the training cohort

Logistic regression analysis identified vertigo, hearing level onset, PNI level, and NLDA level as independent predictors of the prognosis of SSNHL. The model that incorporated the above independent parameters is presented as a nomogram (Figure 2A). The consequence of the internal validation depends on the parameter of the calibration curve and DCA of the training cohort. The C-index of the predictive prognostic model was 0.815 (95% CI, 0.754–0.875). The result of the calibration curve demonstrated that the predictive probability of an effective outcome was close to the actual effective outcomes (Hosmer-Lemeshow P = 0.770) (Figure 2B). A DCA for nomogram was performed to determine its clinical validity by quantifying the net benefit at different threshold probabilities in the validation cohort (Figures 2C). The decision curve showed that the nomogram could provide a greater net benefit than the models combining conventional components (vertigo + hearing level onset + PNI +NLDA) when the threshold probability ranged from 1 to 82%. As shown in Figure 3A, the AUC of the nomogram score for the prediction of outcome of AF-SSNHL in the training cohort was 0.815 (95% CI, 0.754 - 0.875; P < 0.05). At the optimal cut-off threshold, the prognostic model demonstrated a Positive Predictive Value (PPV) of 59.7% and a Negative Predictive Value (NPV) of 88.4% in the training cohort. Similarly, in the validation cohort, the PPV and NPV were 74.5% and 83.7%, respectively. This model has good clinical value for evaluating the outcome of patients with AF-SSNHL.

External validation of the predictive prognostic model in the validation cohort

The demographics and laboratory variables in the validation cohort with different outcomes are shown in Table 4. Age in the effective group was lower than that in the ineffective group (P < 0.05). The ineffective group had a worse hearing level onset than the effective group (P < 0.05). Comparing the hematological indexes of these two groups, we found that the number of patients with low levels of SII and NLDA in the effective group was higher than those in the ineffective group (P < 0.05). As shown in Figure 3B, The AUC of the nomogram score for prediction of the outcome of AF-SSNHL in validation cohort was 0.849 (95% CI, 0.737 - 0.961; P < 0.05). The C-index was 0.788 (95% CI, 0.663-0.913) in the validation cohort and the calibrated curve testified that the predictive model applied in the validation cohort was well-calibrated for clinical settings (Hosmer-Lemeshow P = 0.348) (Figure 4A). DCA was performed to investigate the net benefit of this predictive model in the validation cohort (Figure 4B). The results suggested that the nomogram is beneficial in predicting the effective probability of AF-SSNHL outcome in the validation cohort. External validation yielded results similar to those of the training cohort.

Discussion

We explored the prognostic value of the novel inflammatory-immune-hemostasis-nutrition index in patients with AF-SSNHL and designed a prognostic nomogram

in this prospective cohort study. This study found that the effective rate was generally higher in the subgroup with normal hematological indexes than that in the subgroup with abnormal hematological indexes, which was in accordance with many other studies [13, 20-24]. PNI and NLDA which were established using pretreatment values of N, L, D, and ALB reflects the different characteristics of the inner ear microenvironment. Our results show that PNI and NLDA were the superior hematological indexes for predicting prognosis of AF-SSNHL. Moreover, we found that presence of vertigo, severe hearing loss at onset, lower PNI value and higher NLDA value were independent predictors of prognosis. According to the score of each clinical variable, our nomogram model accurately predicted the effective possibility of patients with AF-SSNHL by internal and external validation. Therefore, this nomogram can be used as a reference for patient stratification and clinical decision-making.

Inflammatory-immune indexes in AF-SSNHL

SSNHL is said to be associated with inflammation, since inflammation increases the risk of microvascular damage and ischemia, leading to atherosclerosis [25]. The blood labyrinth barrier was thought to separate the inner ear from systemic cellular and humoral immunity. Recently, however, local immune responses have been observed in the inner ear presenting as increased movement of immunocompetent cells in the inner ear bloodstream [26]. Therefore, the inner ear is no longer regarded as a privileged immunological site, suggesting that inflammatory-immune mediated mechanisms may be involved in the pathogenesis and of prognosis SSNHL [27]. Circulating inflammatory molecules have harmful effects on vascular tissue in the cochlea. The ability of inflammatory-immune response associated factors to serve as developmental and prognostic markers of SSNHL has been analyzed. N with thrombotic characteristics serves as a risk factor and prognostic factor for stroke and myocardial infarction. Since the pattern of AF-SSNHL is the same as that of myocardial infarction and cerebral infarction, thrombotic characteristics of N may be associated with AF-SSNHL [28]. L plays a critical role in the elimination and repair of inflammation, and lower L counts are associated with worsening neurological function and poor prognosis after ischemic stroke [29]. NLR is the most researched factor, with over 10 papers assessing its relationship with the diagnosis of SSNHL by comparing its prognostic ability to other inflammation-related factors, including WBC, CRP, and PLR. A meta-analysis of these studies involving 1029 patients with SSNHL and 1020 healthy control subjects showed that the NLR levels in patients with SSNHL were significantly higher NLR than controls. In addition, the level of NLR was significantly higher in ineffective patients than in effective patients. Taken together, these studies suggest that NLR may be a useful biomarker for the pathogenesis and prognosis of SSNHL [30, 31], and also the roles of inflammatory-immune mechanism. Another study comparing blood cell populations in SSNHL patients showed that L, monocyte, NLR, PLR, and glucose values were increased significantly in the ineffective group than effective group [32], and our results are

in agreement. We found the value of L, NLR, PLR, and SII show a good prediction of AF-SSNHL. When comparing these two groups, the number of patients with high levels of N, NLR, PLR, and SII in the ineffective group was higher than those in the effective group, while the number of patients with low levels of L and P in the ineffective group was higher than those in the effective group.

Hemostasis indexes in AF-SSNHL

The guidelines of SSNHL in China and German showed that different types of SSNHL may correlate to different causes, with hemodynamic disorder being a potential cause of AF-SSNHL [7, 33], manifesting as a sudden reduction of blood flow in the labyrinthine arteries. This hints that hematological indexes reflecting risks of thrombosis may serve as biomarkers for SSNHL. Platelets participate in the pathophysiology of inflammation, coagulation, thrombosis, and vascular atherosclerosis [34]. PLR was used to assess the extent of systemic inflammation and endothelial damage in the peripheral vascular system. The increase in PLR was related to the increased adhesion of platelets to recently damaged vessels, which was recognized as an independent prognostic factor of cardiovascular disease [35]. Sun Y et al. [20] reported that L, MPV, and PLR were associated with SSNHL, low lymphocyte count and elevated MPV and PLR were associated with poor prognosis in patients with high-frequency SSNHL.

Fg is ultimately participates in clot formation. Cochlear microcirculation is closely related to hearing levels. A previous study reported that a high Fg level in guinea pigs was associated with cochlear blood flow reduction and that the use of defibrinogen drug enhances cochlear blood flow [36]. This was particularly effective in SSNHL patients with severe hearing loss and high initial plasma Fg levels [22]. Although a meta-analysis reported there is no difference in Fg concentrations between the control and SSNHL groups, serum Fg concentrations in SSNHL patients with effective outcomes were significantly lower than those with ineffective outcomes. This suggested that high Fg levels were associated with poor prognosis of SSNHL patients [23]. Nevertheless, the mechanism by which hyperfibrinogen affects the incidence rate of SSNHL is still unclear although these findings suggest that defibrinogen treatment should be administered according to the pathophysiology of SSNHL. D is a stable end product of fibrin degradation. High concentrations of D are associated with a variety of diseases, including deep venous thrombosis, pulmonary thromboembolism, atrial fibrillation, stroke, and coronary artery disease [37-39]. However, the study of congenital thrombophilic risk factors in a population of consecutive Italian patients affected by SSNHL found no association between SSNHL and abnormal levels of D [40]. In the present study, we found that the level of D, Fg, and commixed indexes (NLDA and NLFgA) in effective group were lower than that in ineffective group (Table 2).

Nutrition indexes in AF-SSNHL

Nutritional status was shown to be associated with prognosis in many diseases. Serum ALB is considered an indicator of nutritional status and can be easily

measured in clinical use. As a strong marker in diseases related to infection and inflammation, the concentration of ALB is usually reduced under conditions of acute and chronic inflammation and malnutrition [41, 42]. Some studies have also shown that ALB can reflect the severity of inflammation in acute diseases [43]. Recent studies indicated that ALB plays an active role in the pathophysiology of coagulation, thrombosis, and atherosclerosis [44-46]. Zhong Z et al. [13] investigated the occurrence and hearing outcome in AF-SSNHL patients in relation to serum liver function levels and found that the ALB levels of the effective group were significantly higher than that in the ineffective group, and ALB may be a strong marker for a favorable outcome of AF-SSNHL. The possible biologic mechanisms are that ALB binds to a variety of ligands, such as nitric oxide, and interacts with free fatty acids to inhibit its role in promoting vascular tone, platelet aggregation and thrombosis [47, 48], greatly relieving the inner ear microcirculation disturbance of AF-SSNHL. Moreover, ALB can inhibit the production of peroxidase and free radicals [49] which are involved in the pathogenesis of AF-SSNHL. Finally, ALB can increase serum osmotic pressure, thereby attracting interstitial fluid and improving organ perfusion [42].

In this study, we found the older the patient, the worse the prognosis (Table 2 and Table 4). It was reported that hypoalbuminemia and lower serum ALB were independently associated with older age [50]. Older patients have lower serum ALB levels, so they are less able to repair the damage than younger patients, which may lead to a worse prognosis of AF-SSNHL. PNI is a comprehensive nutritional evaluation method, which has been proved to be related to the efficacy and prognosis of a variety of diseases such as cancer [51], cardiovascular diseases [52], and acute injury [53]. This study found that the lower the PNI, the worse the prognosis of AF-SSNHL patients, indicating that the nutritional status of the body can affect the prognosis of AF-SSNHL patients. Clinically, the prognosis can be preliminarily judged according to PNI and appropriate nutritional support treatment can be given to patients in time to improve the prognosis of AF-SSNHL.

Inflammatory-immune-hemostasis-nutrition in AF-SSNHL

Compared with other hematological indexes, NLDA combines more hematological parameters to provide a more comprehensive assessment of disease. Here, we show that a high NLDA value significantly correlated with a poor prognostic outcome, which was further associated with low ALB and a significantly higher NLR and D levels. Combined with the logistic regression results, we showed here that the combination of these factors serves as an independent predictor of AF-SSNHL prognosis and that NLDA is superior for this purpose than each alone. Moreover, high NLDA predicted poor prognosis of patients with AF-SSNHL based on possible complications of systemic inflammation, thrombosis, hemostasis, and malnutrition. It is a cost-effective, simple parameter to easily assess the inflammatory-immune-hemostasis-nutritional status.

Compared with the previous studies, our research that added more clinical factors significantly improved the accuracy and discriminative power of prediction.

Our nomogram, which combined vertigo, hearing loss, PNI, and NLDA, achieved significant value for predicting the outcome of AF-SSNHL. This prognostic model may have important clinical use in patient management, risk stratification, and therapeutic intervention. In addition, it can enhance risk communication between clinicians and patients. The significant predictive values of PNI and NLDA indicate that more attention should be preoperatively directed to assessing inflammation, hemostasis, and malnutrition of AF-SSNHL patients. Moreover, early intervention will likely ameliorate these symptoms to improve the outcome of patients with AF-SSNHL.

This study has some limitations. First, this was a single-center study, and all hematological indices were obtained using the inspection equipment and testing protocols of our institution. As a result, the study population may not fully represent the heterogeneity of patients with AF-SSNHL across different regions or healthcare settings, which may limit the generalizability of the findings. In addition, inter-institutional variability in laboratory equipment and testing protocols may influence the absolute values of hematological indices. Second, hematological indices were measured only once upon admission, without longitudinal monitoring during treatment. Therefore, the proposed model primarily reflects the prognostic value of baseline systemic inflammatory, immune, hemostatic, and nutritional status at disease onset, rather than dynamic treatment-related changes. Longitudinal monitoring of these parameters may further improve prognostic accuracy and should be explored in future studies. Third, we only focused on clinical indexes of AF-SSNHL, the potential underlying mechanisms of AF-SSNHL remain to be determined. Therefore, prospective, multi-centered, large-scale studies are warranted to validate our results and more basic research needs to be done to clarify the mechanism.

Conclusions

The PNI and NLDA levels were significantly associated with the outcomes of AF-SSNHL, suggesting that these indices may serve as convenient and cost-effective tools for prognostic assessment in clinical practice. By integrating routinely available laboratory parameters at admission, the proposed model can be applied for early risk stratification, helping clinicians identify patients at higher risk of poor hearing recovery and potentially guiding the intensity of follow-up and treatment strategies. Further large, well-designed prospective multicenter studies are warranted to validate these findings, and future research should explore whether longitudinal changes in these hematological indices during treatment could further improve prognostic accuracy.

Abbreviations

SSNHL, sudden sensorineural hearing loss; AF-SSNHL, all-frequencies sudden sensorineural hearing loss; MRI, magnetic resonance imaging; PTA, pure tone average; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; N, neutrophil; L, lymphocyte; PLT, platelet; D, D-dimer; Fg, fibrinogen; RBC, red blood cell; Hb, hemoglobin; ALB, albumin; NLR

neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune inflammation index; PNI, prognostic nutritional index; NLDA, neutrophil lymphocyte D-dimer albumin score; NLFgA, neutrophil lymphocyte fibrinogen albumin score; AUC, area under the curve; ROC, receiver operating characteristic; OR, odds ratio; CI, confidence interval; DCA, decision curve analysis; C-index, concordance index.

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Authors' contributions:
conceptualization: Zhong Zheng, Liang Xia, Xiaoyan Chen, Yanmei Feng; methodology: Fuquan Chen, and Yanmei Feng; software: Yi chen and Niannian Li; validation: Zhong Zheng and Xiaoyan Chen; formal analysis: Hui Li and Lili Xiao ; investigation: Zhong Zheng, Xiaoyan Chen, Kexin Song, Niannian Li, and Lili Xiao; data curation: Yanmei Feng; original draft preparation: Zhong Zheng, Hui Li, review and editing: Fuquan Chen andYanmei Feng.

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Availability of data and materials
The data used to support the findings of this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved and implemented according to the ethical standards of the Shanghai Jiaotong University Affiliated Sixth People’s s Hospital ethics committee. Information of patients was anonymized and de-identified before analysis. The progress was conducted in accordance with the spirit of the Helsinki Declaration. All participants provided written informed consent for their inclusion in the database and the use of their data for research purposes.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Tables and Figures

Figure 1. Flow chart of inclusion and exclusion process of patients admitted with AF-SSNHL. SSNHL, sudden sensorineural hearing loss; PTA, pure tone average; ROC, receiver operating characteristic; C-index, concordance index; DCA, decision curve analysis.

Table 1. Demographics and laboratory variables in the primary and validation cohorts.

	Training cohort (n=196)	Validation cohort (n=49)	P value
Baseline characteristics			
Age (years) [a]	54.00 (38.00-65.75)	49.00 (44.50-60.50)	0.606
Gender (male, %) [b]	85 (43.37%)	20 (40.82%)	0.747
Height (m) [a]	1.65 (1.60-1.73)	1.65 (1.60-1.70)	0.989
Weight (kg) [a]	65.00 (57.25-73.00)	62.00 (52.50-72.00)	0.521
BMI (kg/m2) [c]	23.49±3.24	23.12±3.50	0.485
SBP (mmHg) [c]	123.19±18.41	121.18±16.27	0.486
DBP (mmHg) [c]	77.09±10.52	75.71±10.55	0.455
Clinical characteristics			
Affected side (left, %) [b]	108 (55.10%)	29 (59.18%)	0.607
Tinnitus (%) [b]	135 (68.88%)	38 (77.55%)	0.233
Vertigo (%) [b]	57 (29.08%)	15 (30.61%)	0.833
Ear fullness (%) [b]	52 (26.53%)	17 (34.69%)	0.256
Time to treatment (days) [a]	4.00 (2.00-7.00)	4.00 (2.00-7.00)	0.832
Hearing level (dBHL) [c]	76.52±19.95	73.83±16.29	0.384
Original hematological indexes			
WBC (*10^9/L) [a]	8.45 (6.60-10.63)	8.20 (7.00-9.65)	0.524
N (*10^9/L) [a]	6.20 (4.30-8.70)	6.40 (4.80-7.60)	0.823
L (*10^9/L) [a]	1.50 (1.20-2.10)	1.70 (1.05-2.50)	0.560
P (*10^9/L) [a]	219.00 (184.50-266.00)	246.00 (181.50-281.00)	0.434
D (mg/L) [a]	0.25 (0.13-0.36)	0.30 (0.23-0.34)	0.017*
Fg (g/L) [a]	2.21 (2.09-2.49)	2.23 (2.12-2.68)	0.393
RBC (*10^{12}/L) [a]	4.57 (4.22-4.99)	4.52 (4.23-4.88)	0.384
Hb (g/L) [a]	138.00 (126.00-152.00)	137.00 (126.00-148.50)	0.529
ALB (g/L) [a]	44.00 (41.00-47.00)	44.00 (41.40-47.50)	0.467
Commixed hematological indexes			
NLR [a]	4.09 (2.24-6.25)	3.24 (2.28-5.86)	0.741
PLR [a]	140.36 (97.90-196.25)	135.45 (96.32-193.73)	0.890
SII [a]	838.89 (545.01-1353.72)	776.95 (545.46-1313.59)	0.840
PNI [a]	52.25 (48.50-55.58)	52.00 (49.20-58.75)	0.302
NLDA [a]	0.0207 (0.0109-0.0385)	0.0237 (0.0146-0.0362)	0.325
NLFgA [a]	0.2066 (0.1226-0.3234)	0.1878 (0.1280-0.3120)	0.669

[a] The values were given as median with its interquartile range (25th - 75th) in parentheses; [b] The values were given as the number of cases and the percentage in parentheses; [c] The values were given as mean ± standard deviation. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; N, neutrophil; L, lymphocyte; P, platelet; D, D-dimer; Fg, fibrinogen; RBC, red blood cell; Hb, haemoglobin; ALB, albumin; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune inflammation index; PNI, prognostic nutritional index; NLDA, neutrophil lymphocyte D-dimer albumin score; NLFgA, neutrophil lymphocyte fibrinogen albumin score; * The correlation was significant at the 0.05 level ($P < 0.05$).

Table 2. Demographics and laboratory variables in the training cohort with different outcomes.

	Effective (n=74)	Ineffective (n=122)	P value
Baseline characteristics			
Age (years) [a]	47.00 (32.75-62.00)	59.00 (43.00-65.00)	<0.001*
Gender (male, %) [b]	36 (48.65%)	49 (40.16%)	0.245
Height (m) [a]	1.66 (1.60-1.74)	1.64 (1.60-1.71)	0.376
Weight (kg) [a]	65.00 (55.75-70.25)	64.50 (58.00-75.00)	0.765
BMI (kg/m2) [c]	23.16±3.11	23.69±3.32	0.270
SBP (mmHg) [c]	120.26±16.87	124.97±19.13	0.082
DBP (mmHg) [c]	77.36±9.86	76.92±10.94	0.778
Clinical characteristics			
Affected side (left, %) [b]	40 (54.05%)	68 (55.74%)	0.818
Tinnitus (%) [b]	54 (72.97%)	81 (66.39%)	0.335
Vertigo (%) [b]	9 (12.16%)	48 (39.34%)	<0.001*
Ear fullness (%) [b]	21 (28.38%)	31 (25.41%)	0.648
Time to treatment (days) [a]	4.00 (2.00-7.00)	4.00 (2.00-7.00)	0.439
Hearing level (dBHL) [c]	68.02±18.76	81.67±18.93	<0.001*
Original hematological indexes			
WBC (≤9.60*109/L) [b]	53 (71.62%)	71 (58.20%)	0.059
N (≤4.00*109/L) [b]	21 (28.38%)	18 (14.75%)	0.021*
L (>1.40*109/L) [b]	49 (66.22%)	57 (46.72%)	0.008*
P (>207.00*109/L) [b]	49 (66.22%)	60 (49.18%)	0.020*
D (≤0.21 mg/L) [b]	47 (63.51%)	43 (35.25%)	<0.001*
Fg (≤2.23 g/L) [b]	48 (64.86%)	56 (45.90%)	0.010*
RBC (>5.00*1012/L) [b]	26 (35.14%)	21 (17.21%)	0.004*
Hb (>137.00 g/L) [b]	47 (63.51%)	53 (43.44%)	0.006*
ALB (>45.90 g/L) [b]	38 (51.35%)	31 (25.41%)	<0.001*
Commixed hematological indexes			
NLR (≤5.28) [b]	58 (78.38%)	70 (57.38%)	0.003*
PLR (≤178.82) [b]	60 (81.08%)	77 (63.11%)	0.008*
SII (≤1174.83) [b]	60 (81.08%)	75 (61.48%)	0.004*
PNI (>52) [b]	50 (67.57%)	48 (39.34%)	<0.001*
NLDA (≤0.0258) [b]	61 (82.43%)	54 (44.26%)	<0.001*
NLFgA (≤0.2214) [b]	49 (66.22%)	54 (44.26%)	0.003*

[a] The values were given as median with its interquartile range (25th - 75th) in parentheses; [b] The values were given as the number of cases and the percentage in parentheses; [c] The values were given as mean ± standard deviation. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC,

white blood cell; N, neutrophil; L, lymphocyte; P, platelet; D, D-dimer; Fg, fibrinogen; RBC, red blood cell; Hb, haemoglobin; ALB, albumin; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune inflammation index; PNI, prognostic nutritional index; NLDA, neutrophil lymphocyte D-dimer albumin score; NLFgA, neutrophil lymphocyte fibrinogen albumin score; * The correlation was significant at the 0.05 level ($P < 0.05$).

Table 3. Univariate and multivariate logistic regression analysis of the clinicopathological characteristics and commixed hematological indexes in training cohort

Parameter	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Predictor: outcome of disease						
Age	0.989	0.961-1.017	0.419			
Gender (male)	1.199	0.544-2.639	0.653			
BMI	1.003	0.883-1.139	0.965			
SBP	0.978	0.948-1.009	0.161	0.984	0.966-1.002	0.073
DBP	1.016	0.960-1.075	0.592			
Affected side (left)	1.196	0.567-2.526	0.638			
Tinnitus	0.635	0.279-1.447	0.280			
Vertigo	3.456	1.342-8.897	0.010*	3.268	1.340-7.965	0.009*
Ear fullness	1.431	0.600-3.415	0.420			
Time to treatment	0.978	0.860-1.112	0.735			
Hearing level	0.972	0.953-0.991	0.004*	0.970	0.952-0.988	0.001*
NLR (≤5.28)	1.217	0.294-5.044	0.787			
PLR (≤178.82)	0.874	0.303-2.516	0.802			
SII (≤1174.83)	1.906	0.469-7.747	0.367			
PNI (>52)	2.105	0.948-4.675	0.068	2.439	1.188-5.006	0.015*
NLDA (≤0.0258)	4.363	1.828-10.416	0.001*	5.066	2.333-11.003	<0.001*
NLFgA (≤0.2214)	0.776	0.268-2.242	0.639			

OR, odds ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood

pressure; DBP, diastolic blood pressure; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune inflammation index; PNI, prognostic nutritional index; NLDA, neutrophil lymphocyte D-dimer albumin score; NLFgA, neutrophil lymphocyte fibrinogen albumin score; * The correlation was significant at the 0.05 level ($P < 0.05$).

Figure 2. Nomogram presentation and performance evaluation of the predictive model in the training cohort. PNI, prognostic nutritional index; NLDA, neutrophil lymphocyte D-dimer albumin score. (A) The predictive prognostic model, incorporating vertigo, hearing level at onset, PNI, and NLDA, was developed using logistic regression and presented as a nomogram. (B) Calibration curves of the predictive model, based on nomogram-derived predicted probabilities, in the training cohort. The x-axis represents the predicted the effective probability of AF-SSNHL outcome. The y-axis represents the actual effective probability of AF-SSNHL outcome. The diagonal dotted line represents a perfect prediction by an ideal model. The solid line represents the performance of the nomogram, of which a closer fit to the diagonal dotted line represents a better prediction. (C) Decision curve analysis of the predictive model in the training cohort. The y-axis measures the net benefit. The dotted line represents the effective probability of AF-SSNHL outcome nomogram. The thin solid line represents the assumption that all patients have effective outcome. The thick solid line represents the assumption that no patients have effective outcome.

Figure 3. Receiver operating characteristic curve analysis of the predictive model for AF-SSNHL outcome. (A) Receiver operating characteristic curve in training cohort. (B) Receiver operating characteristic curve in validation cohort.

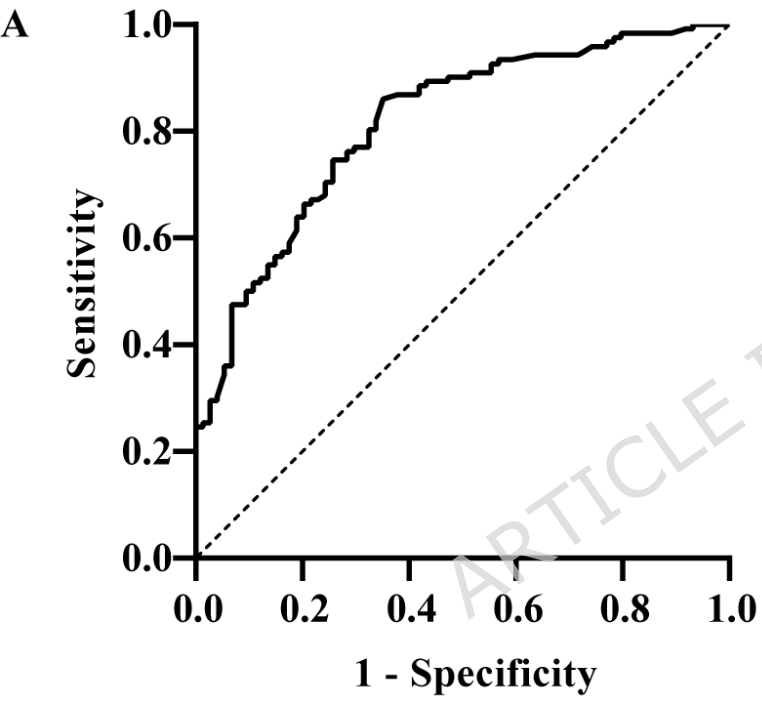
Table 4. Demographics and laboratory variables in the validation cohort with different outcomes.

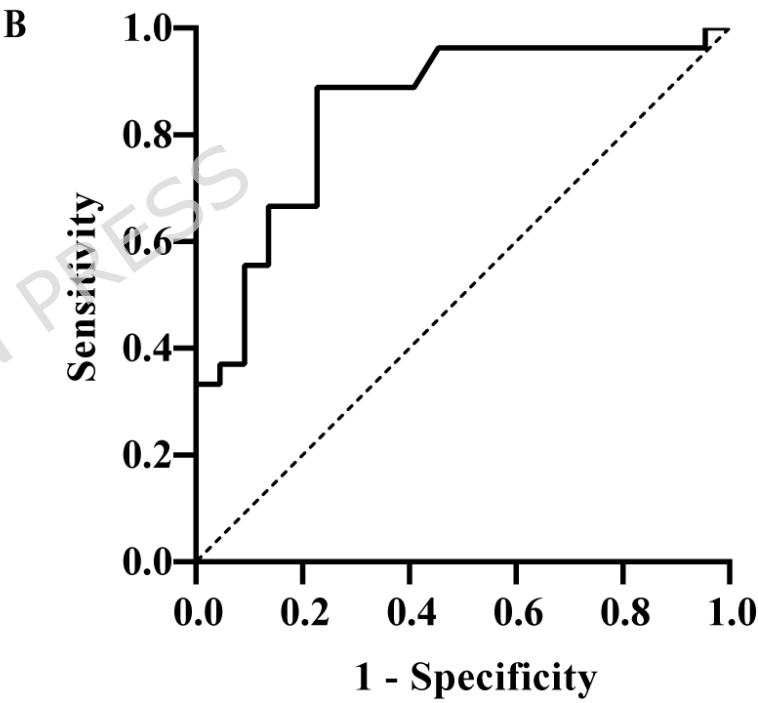
	Effective (n=22)	Ineffective (n=27)	P value
Baseline characteristics			
Age (years) [a]	47.00 (44.00-54.00)	54.00 (47.00-63.00)	0.033*
Gender (male, %) [b]	8 (36.36%)	12 (44.44%)	0.567
Height (m) [a]	1.64 (1.59-1.70)	1.66 (1.60-1.74)	0.268
Weight (kg) [a]	62.50 (52.75-72.75)	61.00 (52.00-72.00)	0.936
BMI (kg/m2) [c]	23.58±3.78	22.74±3.28	0.413
SBP (mmHg) [c]	119.59±12.98	122.48±18.67	0.542
DBP (mmHg) [c]	74.14±11.19	77.00±10.02	0.350
Clinical characteristics			
Affected side (left, %) [b]	13 (59.09%)	16 (59.26%)	0.990
Tinnitus (%) [b]	17 (77.27%)	21 (77.78%)	0.966
Vertigo (%) [b]	4 (18.18%)	11 (40.74%)	0.088
Ear fullness (%) [b]	10 (45.45%)	7 (25.93%)	0.153
Time to treatment (days) [a]	4.00 (2.00-7.00)	4.00 (2.00-7.00)	0.846
Hearing level (dBHL) [c]	63.79±13.32	82.01±13.85	<0.001*
Original hematological indexes			
WBC (≤9.60*109/L) [b]	17 (77.27%)	20 (74.07%)	0.796
N (≤4.00*109/L) [b]	5 (22.73%)	4 (14.81%)	0.477
L (>1.40*109/L) [b]	16 (72.73%)	13 (48.15%)	0.082
P (>207.00*109/L) [b]	14 (63.64%)	15 (55.56%)	0.567
D (≤0.21 mg/L) [b]	6 (27.27%)	5 (18.52%)	0.465
Fg (≤2.23 g/L) [b]	9 (40.91%)	16 (59.26%)	0.201
RBC (>5.00*1012/L) [b]	4 (18.18%)	6 (22.22%)	0.727
Hb (>137.00 g/L) [b]	11 (50.00%)	12 (44.44%)	0.698
ALB (>45.90 g/L) [b]	9 (40.91%)	9 (33.33%)	0.584
Commixed hematological indexes			
NLR (≤5.28) [b]	20 (90.91%)	17 (62.96%)	0.024
PLR (≤178.82) [b]	18 (81.82%)	17 (62.96%)	0.146
SII (≤1174.83) [b]	19 (86.36%)	16 (59.26%)	0.037*
PNI (>52) [b]	13 (59.09%)	11 (40.74%)	0.201
NLDA (≤0.0258) [b]	16 (72.73%)	11 (40.74%)	0.025*
NLFgA (≤0.2214) [b]	14 (63.64%)	14 (51.85%)	0.407

[a] The values were given as median with its interquartile range (25th - 75th) in parentheses; [b] The values were given as the number of cases and the percentage in parentheses; [c] The values were given as mean ± standard deviation. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; N, neutrophil; L, lymphocyte; P, platelet; D, D-dimer; Fg,

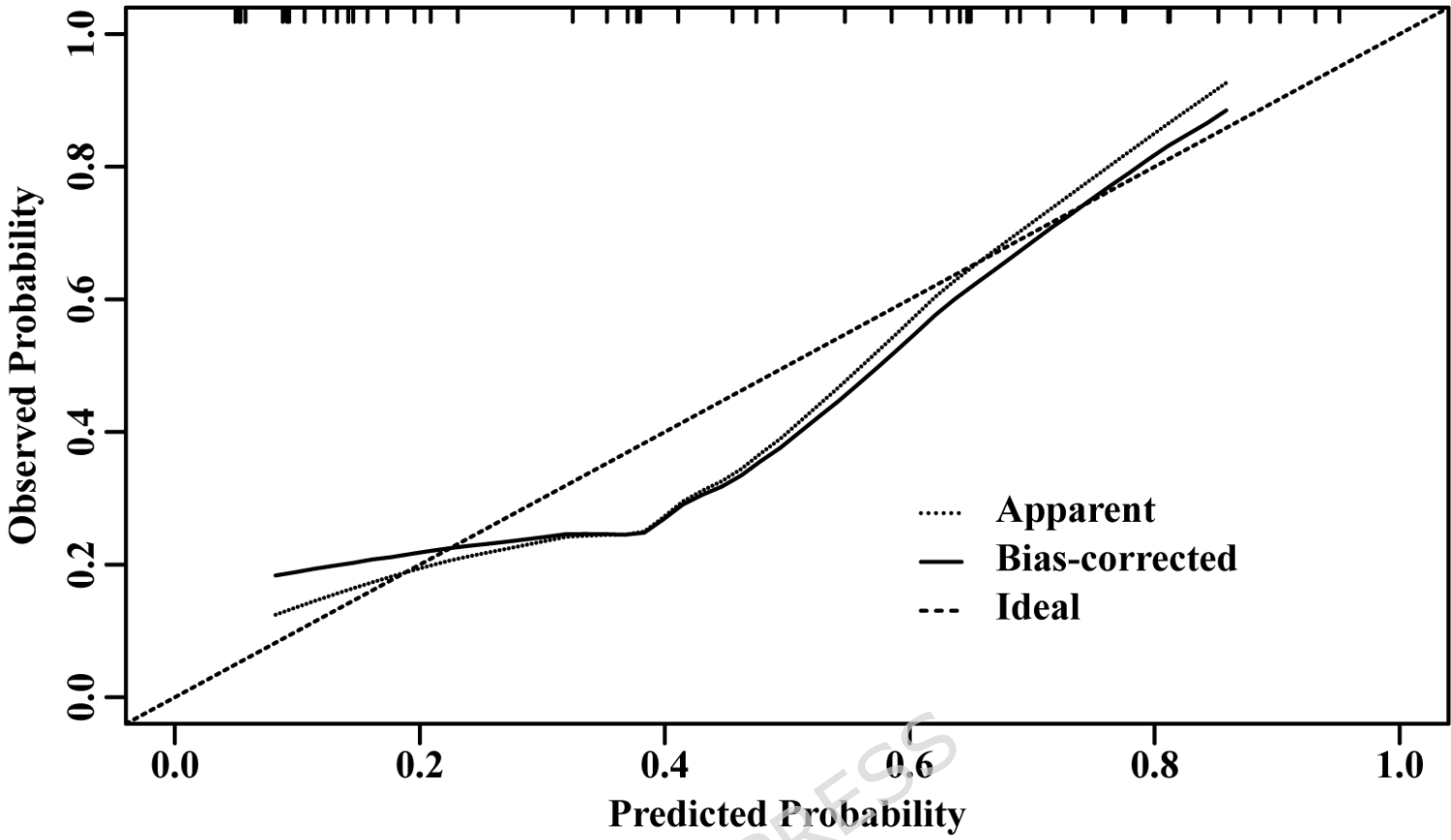
fibrinogen; RBC, red blood cell; Hb, haemoglobin; ALB, albumin; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune inflammation index; PNI, prognostic nutritional index; NLDA, neutrophil lymphocyte D-dimer albumin score; NLFgA, neutrophil lymphocyte fibrinogen albumin score; * The correlation was significant at the 0.05 level ($P < 0.05$).

Figure 4. External validation of the predictive model in the validation cohort. (A) Calibration curves of the predictive model, based on nomogram-derived predicted probabilities, in the validation cohort. The x-axis represents the predicted effective probability of AF-SSNHL outcome. The y-axis represents the actual effective probability of AF-SSNHL outcome. The diagonal dotted line represents a perfect prediction by an ideal model. The solid line represents the performance of the nomogram, of which a closer fit to the diagonal dotted line represents a better prediction. (B) Decision curve analysis of the predictive model in the validation cohort. The y-axis measures the net benefit. The dotted line represents the effective probability of AF-SSNHL outcome nomogram. The thin solid line represents the assumption that all patients achieved effective outcomes. The thick solid line represents the assumption that no patients achieved effective outcomes.

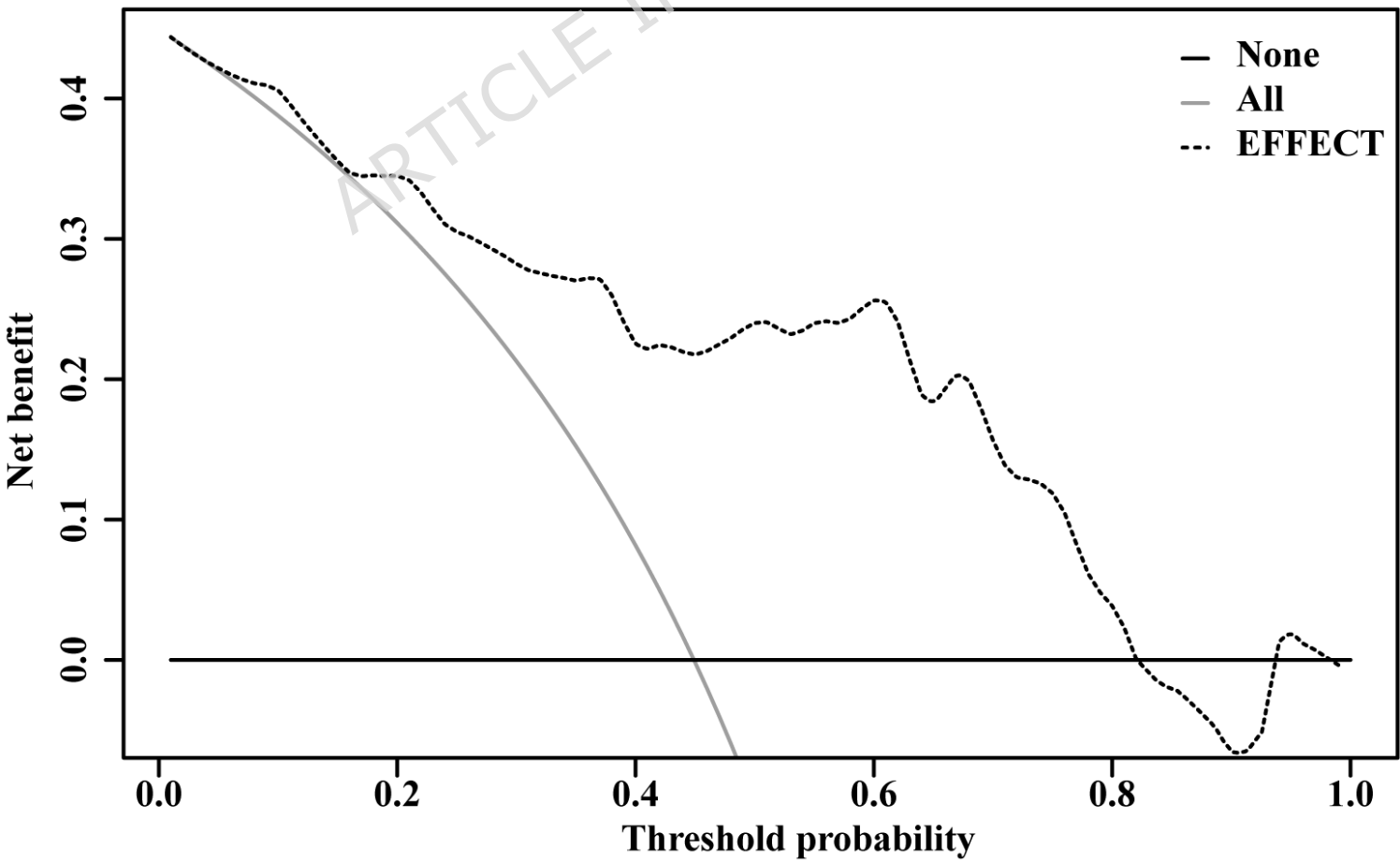


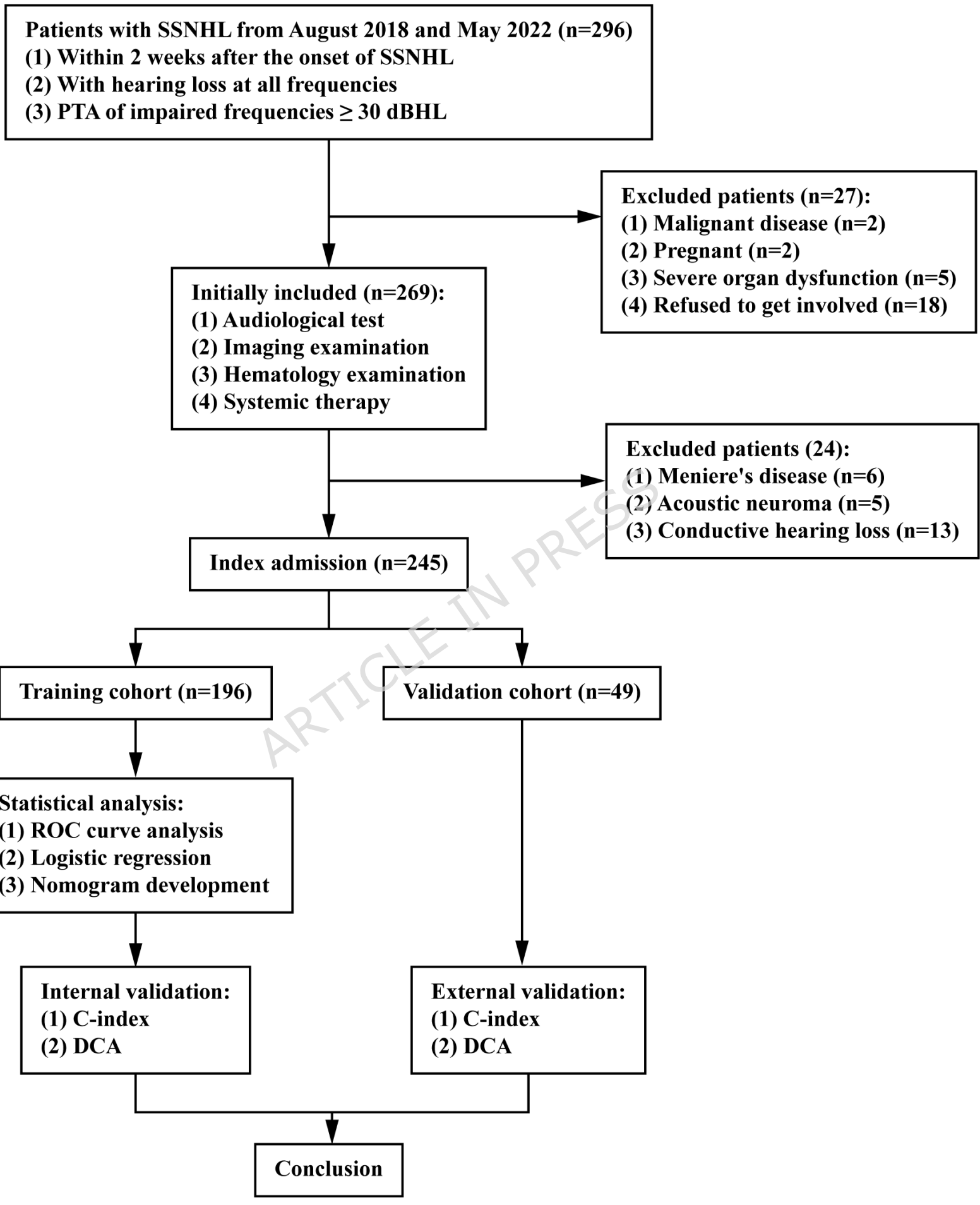


A



B





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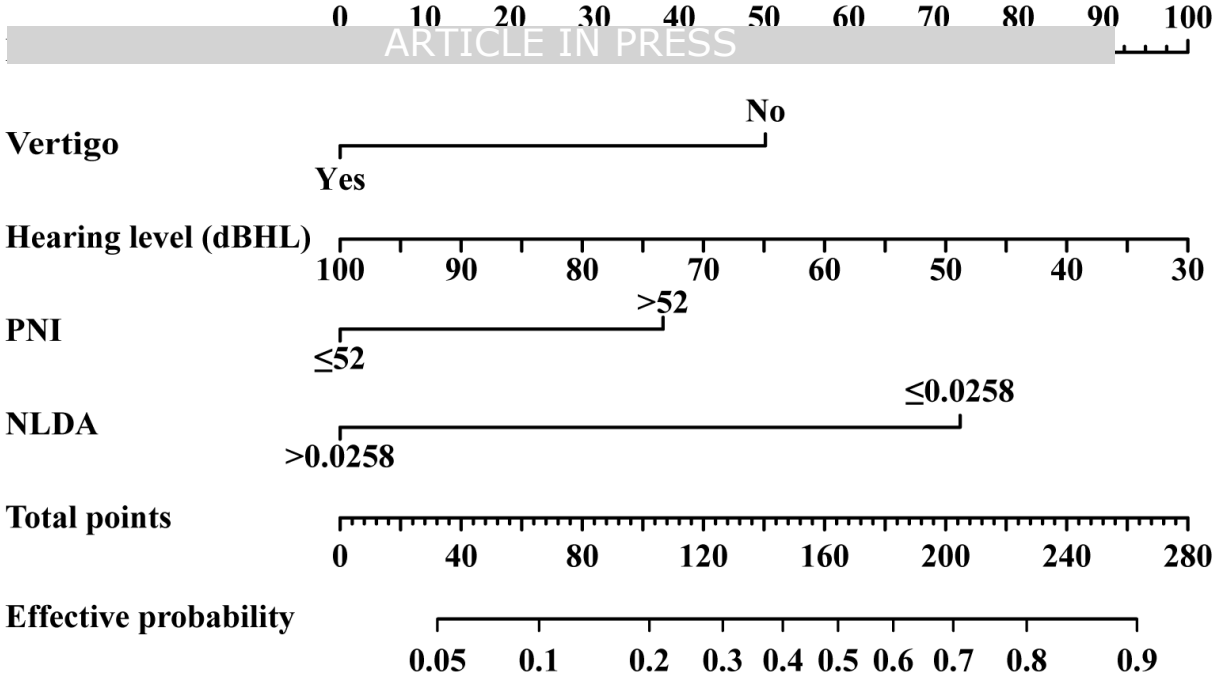

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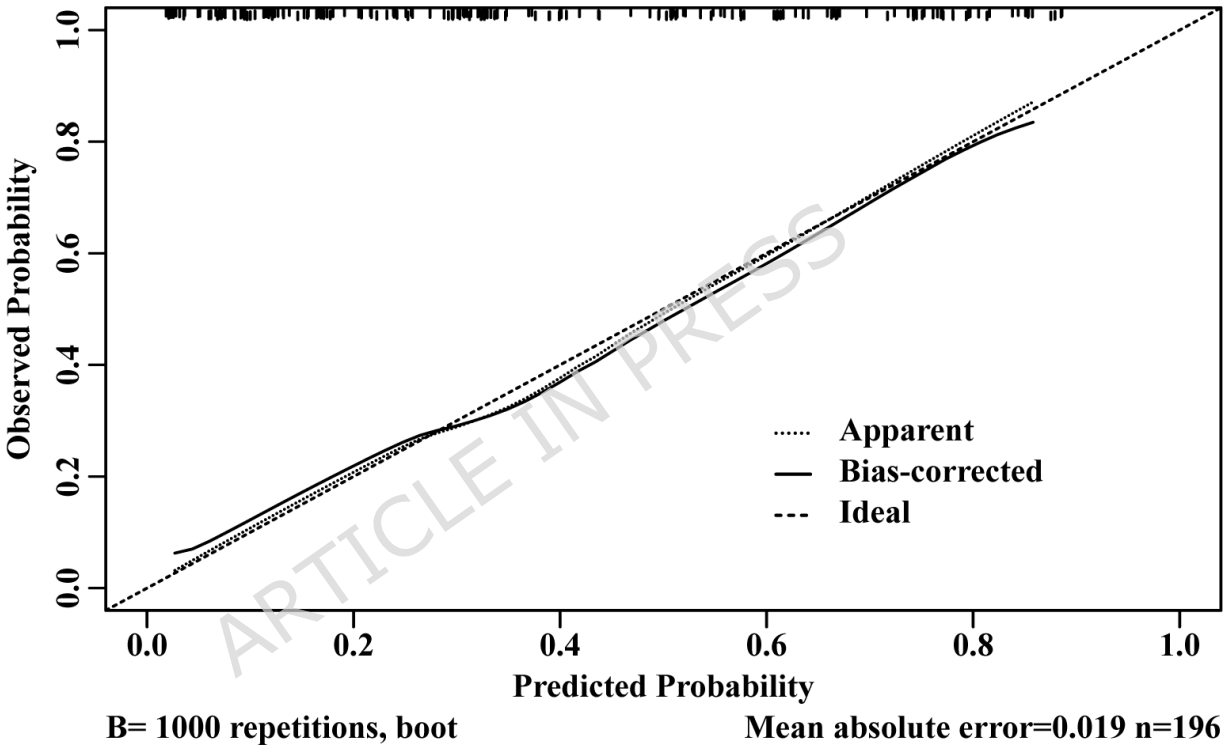

C