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Research article

Predictive modeling and interpretative analysis of risks of instability in patients with Myasthenia Gravis requiring intensive care unit admission

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ABSTRACT

Objective: Myasthenia gravis (MG), a low-prevalence autoimmune disorder characterized by clinical heterogeneity and unpredictable disease fluctuations, presents significant risks of acute exacerbations requiring intensive care. These crises contribute substantially to patient morbidity and mortality. This study aimed to develop and validate machine-learning models for predicting intensive care unit (ICU) admission risk among patients with MG-related disease instability.
Methods: In this retrospective analysis of 314 MG patients hospitalized between 2015 and 2018, we implemented four machine learning algorithms, including logistic regression, support vector machine, extreme gradient boosting (XGBoost), and random forest, to predict ICU admission risk. The models incorporated fourteen clinical parameters as predictive features. The SHapley Additive exPlanations method was utilized to assess the importance of factors associated with ICU admission.
Results: Through 10-fold cross-validation, the XGBoost model demonstrated superior predictive performance (area under the receiver operating characteristic curve: 0.8943, accuracy: 0.8603, sensitivity: 0.7222, and specificity: 0.9125). Among the analyzed features, MG severity, as classified by the Myasthenia Gravis Foundation of America clinical classification, was identified as the most significant factor influencing ICU admission. Additionally, disease duration, a key continuous variable, was inversely correlated with the risk of ICU admission.
Conclusion: MG severity is the primary determinant of ICU admission, with shorter disease duration increasing the risk, possibly due to greater susceptibility to exacerbations. The XGBoost

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model exhibited excellent performance and accuracy, effectively identifying critical clinical factors for predicting ICU admission risk in MG patients. This novel, personalized approach to risk stratification elucidates crucial risk factors and has the potential to enhance clinical decision-making, optimize resource allocation, and ultimately improve patient outcomes.

1. Introduction

Myasthenia gravis (MG) is a low-prevalence autoimmune disease primarily characterized by autoantibodies that interfere with neuromuscular junction signaling, leading to impaired muscle contraction [1,2]. The estimated global prevalence ranges from 150 to 250 cases per million population, with an annual incidence of 8–10 cases per million persons [1]. Among the autoantibodies implicated in MG, anti-acetylcholine receptor (AChR) antibodies are present in approximately 85% of patients, whereas anti-muscle-specific kinase (MuSK) antibodies are found in 1%–10% of patients. Approximately 10% of MG patients exhibit seronegativity for both AChR and MuSK antibodies [1,3]. Furthermore, thymoma occurs in 10%–15% of MG patients [1,2].

MG affects patients of all ages and sexes, with fluctuating symptoms that have the potential for exacerbation, depending on the circumstances [4]. The underlying autoimmune dysfunction in MG patients can lead to altered immune responses, making them more susceptible to infections [1,2,5]. Currently, glucocorticoids and immunomodulatory drugs are commonly used for MG; however, these medications may further suppress immune system function, thereby increasing the risk of infection [4].

MG adversely affects the respiratory muscles, leading to breathing difficulties. Severe respiratory muscle weakness may result in respiratory failure, a fatal condition known as myasthenic crisis, which requires prompt medical intervention, such as mechanical ventilation, and may necessitate admission to the intensive care unit (ICU) for close monitoring and treatment. Specialized critical care and advanced ventilation management techniques can significantly reduce mortality associated with MG crises [1,4]. Early identification of the need for ICU admission is essential for close monitoring, timely treatment, and improved outcomes in hospitalized MG patients.

MG is characterized by high variability, dynamicity, and complexity, with its progression influenced by patient characteristics, treatment approaches, and environmental factors. Consequently, predicting MG progression remains increasingly challenging. This study aimed to utilize advanced machine-learning techniques to analyze the complex nonlinear data of MG patients, focusing on those hospitalized due to disease exacerbation or instability. The primary objectives of this study were to identify the risk factors for MG progression in patients requiring ICU care and to develop an efficient and accurate predictive model for assessing the risk of ICU admission. This model integrates traditional clinical indicators and disease characteristics with treatment protocols and provides comprehensive and individualized risk assessment. Additionally, the SHapley Additive exPlanations (SHAP) method was used to evaluate feature contributions to the model and assess the feasibility of personalized predictions based on individual patient characteristics.

2. Materials and methods

2.1. Data set

This study was approved by the Research Ethics Review Committee of the Shin Kong Wu Ho-Su Memorial Hospital (approval number: 20190109R). The requirement for informed consent was waived because of the retrospective study design and the use of anonymized clinical data.

This retrospective study analyzed data from patients with MG admitted to Shin Kong Wu Ho-Su Memorial Hospital (Taipei, Taiwan) between December 2015 and October 2018. The institution, a medical center with an established MG specialty center, provides comprehensive care for MG patients. The research team identified eligible patients from the hospital's electronic medical records system using the established diagnostic criteria for MG. Data extraction encompassed patients' demographic characteristics, comprehensive medical histories, MG disease trajectories, pharmacological interventions, and hospitalization records. All patient data underwent anonymization before analysis in accordance with institutional ethical guidelines. The inclusion criteria for this study were as follows: (1) patients admitted for worsening MG symptoms, including those admitted to general wards and the ICU, and (2) patients admitted for MG-related treatments, including thymectomy or immunotherapy. Patients with incomplete data and those hospitalized for reasons unrelated to MG were excluded. Initially, 322 patients were identified; after excluding patients with missing data, 314 were included in this study.

The following 14 characteristics were incorporated into the predictive models: age, sex, disease duration, maximum daily dose of prednisolone, immunosuppressant usage, MG severity upon admission (according to the Myasthenia Gravis Foundation of America [MGFA] clinical classification system), autoantibody status, thymoma, hyperplasia, thymectomy history, intravenous immunoglobulin (IVIG) administration, rituximab use, plasmapheresis, and corticosteroid pulse therapy. The maximum daily dose of prednisolone was determined based on the recorded oral steroid prescription at an outpatient visit within 1 month before the index admission. This study focused on ICU admission as a key indicator of clinical instability, comprehensively analyzed the factors influencing the risk of ICU hospitalization, and explored their associations with clinical characteristics. Given the hospital's standard protocol of 1-day post-operative ICU observation for MG patients undergoing thymectomy, patients requiring ICU admission for more than 24 h were classified as the ICU cohort. Conversely, patients with ICU stays of less than 24 h and those admitted to general wards were classified as

the non-ICU cohort, indicating that they did experience severe or unstable clinical manifestations requiring prolonged intensive care.

2.2. Statistical analyses

Baseline characteristics were compared between patients requiring ICU admission and those not requiring ICU admission. The Shapiro–Wilk and Kolmogorov–Smirnov tests were used to assess the normality of the included variables. Continuous variables with a normal distribution were summarized as means with standard deviations, whereas non-normally distributed continuous variables were expressed as medians with interquartile ranges. Categorical variables were presented as frequencies and percentages. Comparisons between groups were conducted using the Mann–Whitney *U* test for non-normally distributed continuous variables and the chi-square test for categorical variables, as appropriate. Statistical significance was defined as a p-value <0.05 for two-tailed tests. All statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA) and Python (version 3.7.11). The scikit-learn package (version 1.2.2) was used to construct the predictive models, and the SHAP package (version 0.44.1) was employed to calculate the SHAP values to interpret the model predictions.

2.3. Development and validation of machine-learning models

Machine-learning models demonstrate exceptional capabilities for processing and analyzing large data volumes, allowing them to identify patterns, trends, and correlations, even with numerous variables and features in high-dimensional datasets, making them ideal for performing predictive tasks in various fields [6–11]. In this study, the following four algorithms, logistic regression [12], support vector machine (SVM) [11,13,14], extreme gradient boosting (XGBoost) [9,15], and random forest (RF) [16,17], were used to construct models for predicting the risk of ICU admission in MG patients.

We performed a 10-fold cross-validation to assess the predictive performance of each model, reducing the risk of overestimating predictive accuracy [18–20]. The dataset was randomly shuffled to mitigate potential biases introduced by data order. Subsequently, the data were then partitioned into 10 equal-sized subsets. Each iteration used one subset as the validation set, and the remaining nine subsets were used for training. This process was repeated 10 times, ensuring each subset served as the validation set exactly once.

2.4. Evaluation measures

Four measures, accuracy, sensitivity, specificity, and area under the receiver operating characteristic (ROC) curve (AUC), were used to evaluate the predictive performance of each model. The AUC, a crucial indicator of the performance of machine-learning models [21], reflects the performance of machine-learning algorithms under all possible conditions [22]. Therefore, we estimated AUC values to select the best prediction model.

2.5. Calibration

A calibration plot was used to investigate whether the predicted probabilities aligned with the actual probability distributions for each class [23]. In an ideal scenario, when the predicted probabilities are equal to the actual probability distribution, the plot should closely follow the diagonal line [24].

Calibration efficiency can be evaluated by assessing the slope and intercept of the calibration curve. In a well-calibrated model, the slope is approximately 1, and the intercept is approximately 0 across individuals or subgroups [25]. The slope indicates the distribution of estimated risks. A slope significantly < 1 suggests that the model systematically underestimates risks, potentially assigning excessively low risks to patients with an actual high risk or excessively high risks to patients with an actual low risk, indicating a lack of calibration. A slope significantly > 1 suggests that the model systematically overestimates the risks for low-risk individuals and underestimates the risks for high-risk individuals, potentially leading to a narrower range of predicted probabilities and difficulty differentiating between risk levels. The intercept was used to evaluate large-scale calibration and assess the model's overall calibration across different subgroups or risk levels. An intercept of significantly < 0 indicates overestimation, whereas an intercept of significantly > 0 indicates underestimation [25,26].

The Brier score, which was proposed by Brier in 1950, is an indicator for assessing the discrepancy between an actual outcome and the predicted probability of the outcome for each observation based on the Euclidean distance. A lower Brier score indicates better performance [27]. The Brier scores were calculated using the following formula:

$$\text{Brier score} = \frac{1}{N}\sum_{i=1}^{N}(r_i - Y_i)^2$$

where N represents the total number of patients or observations, Y_i is the actual outcome for the i-th patient, and r_i is the predicted probability for the i-th patient [28].

2.6. SHAP

SHAP, proposed by Lundberg and Lee [29], integrates Shapley values [30] from coalitional game theory with local interpretable model-agnostic explanations [31] and evaluates the contribution of each feature to model prediction [32]. Moreover, SHAP can

ascertain feature importance, identify correlations, and interpret individual predictions based on the model. The SHAP approach can be explained as follows:

$$f(x) = g(z') = \varnothing_0 + \sum_{i=1}^{M} \varnothing_i z_i'$$

where $z_i' \in \{0,1\}^M$ is the coalition vector, 1 indicates "presence," and 0 indicates "absence." M is the number of simplified inputs, and $\varnothing_i \in \mathbb{R}$; $\varnothing_0$ is the average of marginal contributions, and f is the original prediction model explained by g when $x = h_x(x')$ [29].

Shapley values attribute changes in output.

$$\varnothing_j(val) = \sum_{S \subseteq \{x_1,\ldots x_p\}\{x_j\}} \frac{|S|!(p-|S|-1)!}{p!}\left(val(S \cup \{x_j\}) - val(S)\right)$$

where p is the dataset comprising all features, and S is a subset of features that excludes the feature x_j.

We used the SHAP approach to elucidate the influence of each variable in the prediction model on the outcome of interest, thereby analyzing the feature importance and interaction effects. SHAP provided local and global explanations for our dataset, describing the contribution of each variable and illustrating individual predictions, including the base values and each characteristic attribute of the model. In our study, we estimated SHAP values to compute the feature importance of the variables and constructed summary plots, partial dependence plots, and waterfall plots to interpret the correlation between each variable and the risk of ICU admission.

3. Results

3.1. Baseline demographic characteristics of the MG cohort

Fig. 1 shows the analytical flowchart of this study. Initially, 322 patients were identified; after data preprocessing, 314 (mean age, 44.24 ± 7.22 years; 63.4 % were women) were included in the final analysis. Descriptive statistics for the included patients are presented in Table 1. Approximately 90.4 % of patients had generalized MG (MGFA classification II–V). The mean duration of the

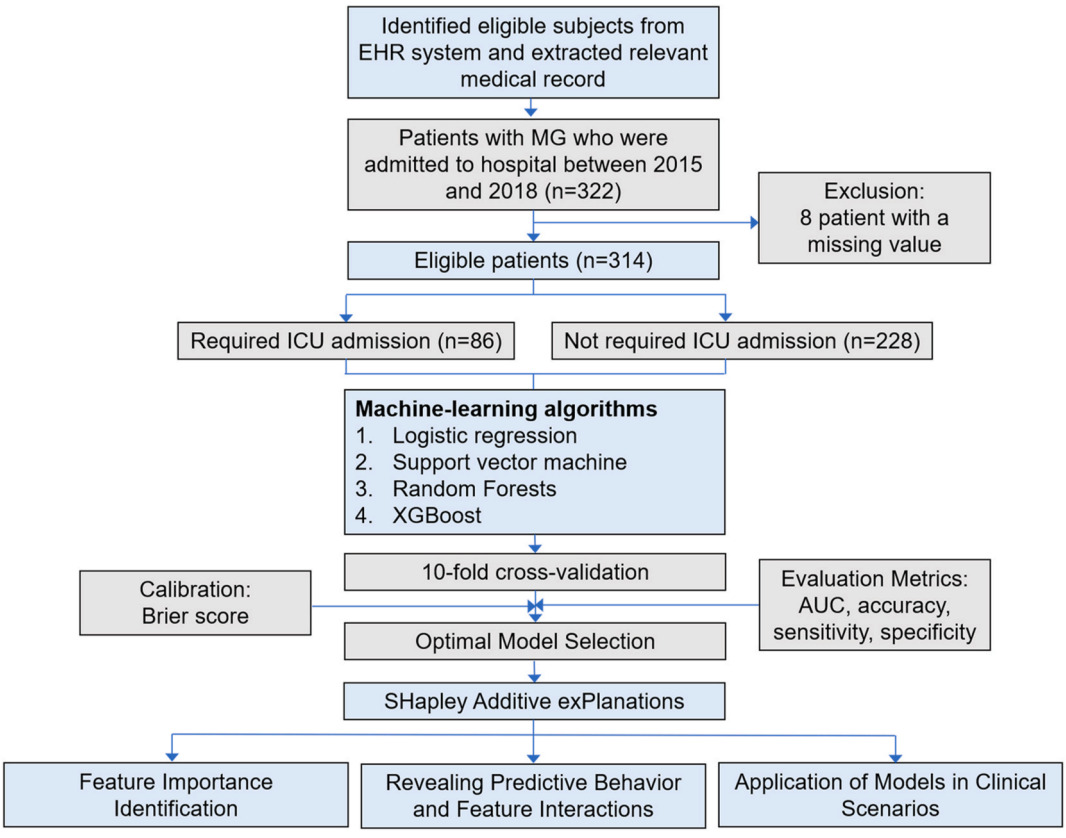

Fig. 1. Analytical flowchart of the present study.
Abbreviations: AUC, area under the curve; EHR, electronic medical record. ICU, intensive care unit; MG, myasthenia gravis; XGBoost, extreme gradient boosting.

disease in the entire cohort was 6.1 ± 7.6 years. AChR and MuSK antibodies were detected in 86.3 % and 5.7 % of the patients, respectively; however, 8.0 % of the included patients exhibited seronegativity for MG-related antibodies. Among the hospitalized MG patients, 86 (27.39 %) required ICU admission.

In our cohort, age, disease duration, and maximum daily dose of prednisolone did not follow a normal distribution based on the Shapiro–Wilk and Kolmogorov–Smirnov normality tests (**Supplementary Table**). A significant difference in disease duration was observed between patients who required ICU admission and those who did not (Table 1). Additionally, for categorical variables, significant differences in MGFA clinical classification, thymoma, types of autoantibodies, use of immunosuppressants, thymectomy, and rituximab treatment were observed between the two groups.

3.2. Comparative analysis of clinical and immunological profiles of patients with and without thymectomy

Table 2 shows the significant demographic and clinical differences between patients who underwent thymectomy and those who did not. A considerable proportion of patients who underwent thymectomy were women, with a longer disease duration and a higher prevalence of thymoma. Furthermore, this cohort demonstrated a higher incidence of anti-AChR antibodies along with a concomitant decrease in anti-MuSK antibodies and seronegative cases.

Regarding treatment modalities for MG, except for corticosteroid pulse therapy, no statistically significant differences were observed between the two groups in the use of immunosuppressants, plasmapheresis, rituximab, or IVIG. Although the severity of MG was comparable between the groups, the proportion of patients who required ICU admission was significantly higher among patients who had undergone thymectomy than in those who had not (40 % vs. 8.73 %).

Table 1
Descriptive statistics of variables stratified by ICU admission status.

	ICU admission		
	Yes (n = 86)	No (n = 228)	
Continuous Variables	Median (IQR)	Median (IQR)	***p*-value**
Age (year)	45 (35–61)	52 (39–63.5)	0.0640
Disease duration (year)	2 (0.33–5)	4 (1–10)	0.0044[b]
Prednisolone maximum daily dose(mg)	5 (0–20)	12.5 (0–22.5)	0.0887
Categorical Variables, n (%)			
Plasmapheresis			0.0044[b]
None	36 (11.46)	78 (24.84)	
1 course	46 (14.65)	150 (47.77)	
2 courses	2 (0.64)	0 (0.00)	
3 courses	2 (0.64)	0 (0.00)	
Corticosteroid pulse therapy			0.0026[b]
None	81 (25.8)	186 (59.24)	
1 course	4 (1.27)	42 (13.38)	
2 courses	1 (0.32)	0 (0.00)	
Sex, female	55 (17.52)	144 (45.86)	0.8962
MGFA clinical classification			<0.0001[c]
I	17 (5.41)	13 (4.14)	
II	38 (12.1)	81 (25.8)	
III	7 (2.23)	96 (30.57)	
IV	6 (1.91)	34 (10.83)	
V	18 (5.73)	4 (1.27)	
Thymoma	56 (17.83)	94 (29.94)	0.0002[c]
Hyperplasia	23 (7.32)	59 (18.79)	0.8761
Autoantibody			0.0013[b]
Anti-AChR Ab	84 (26.75)	187 (59.55)	
Anti-MuSK Ab	0 (0)	18 (5.73)	
Seronegative	2 (0.64)	23 (7.32)	
Immunosuppressant			0.0089[b]
Azathioprine	33 (10.51)	69 (21.97)	
Calcineurin	0 (0.00)	7 (2.23)	
Mycophenolate	0 (0.00)	20 (6.37)	
None	53 (16.88)	132 (42.04)	
Thymectomy	75 (23.89)	113 (35.99)	<0.0001[c]
Rituximab	0 (0.00)	12 (3.82)	0.0301[a]
IVIG	2 (0.64)	12 (3.82)	0.2607

The percentage for each categorical variable reflects its proportion within the entire cohort.
Abbreviation: Ab, antibody; AChR, Acetylcholine receptor; ICU, intensive care unit; IVIG, Intravenous immunoglobulin; MGFA, Myasthenia Gravis Foundation of America; MuSK, muscle-specific tyrosine kinase; SD, standard deviation.
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.

Table 2
Descriptive statistics of variables stratified by thymectomy status.

	Thymectomy		
	Yes (n = 188)	No (n = 126)	
Continuous Variables	Median (IQR)	Median (IQR)	***p*-value**
Age (year)	48 (37–60.75)	54 (39–68.25)	0.0640
Disease duration (year)	4 (0.6–8)	2.25 (0.58–9)	0.0044[b]
Prednisolone maximum daily dose(mg)	10 (0–20)	7.5 (0–25)	0.0887
Categorical Variables n (%)			
Plasmapheresis			0.0044[b]
None	70 (22.29)	44 (14.01)	
1 course	114 (36.31)	82 (26.11)	
2 courses	2 (0.64)	0 (0.00)	
3 courses	2 (0.64)	0 (0.00)	
Corticosteroid pulse therapy			0.0026[b]
None	167 (25.8)	100 (31.85)	
1 course	20 (1.27)	26 (8.28)	
2 courses	1 (0.53)	0 (0.00)	
Sex, female	131 (41.72)	68 (21.66)	0.8962
MGFA clinical classification			<0.0001[c]
I	14 (4.46)	8 (2.55)	
II	17 (5.41)	13 (4.14)	
III	69 (21.97)	50 (15.92)	
IV	61 (19.43)	42 (13.38)	
V	27 (8.60)	13 (4.14)	
Hyperplasia	46 (14.65)	36 (11.46)	0.8761
Autoantibody			0.0013[b]
Anti-AChR Ab	178 (56.69)	93 (29.62)	
Anti-MuSK Ab	1 (0.32)	17 (5.41)	
Seronegative	9 (2.87)	16 (5.10)	
Immunosuppressant			0.0089[b]
Azathioprine	66 (21.02)	36 (11.46)	
Calcineurin	7 (2.23)	0 (0.00)	
Mycophenolate	11 (3.50)	9 (2.87)	
None	104 (33.12)	81 (25.80)	
Thymectomy	139 (44.27)	11 (3.50)	<0.0001[c]
Rituximab	9 (2.87)	3 (0.96)	0.0301[a]
IVIG	8 (2.55)	6 (1.91)	0.2607

The percentage for each categorical variable reflects its proportion within the entire cohort.
Abbreviation: Ab, antibody; AChR, Acetylcholine receptor; ICU, intensive care unit; IVIG, Intravenous immunoglobulin; MGFA, Myasthenia Gravis Foundation of America; MuSK, muscle-specific tyrosine kinase; SD, standard deviation.
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.

3.3. Predictive performance of machine-learning models

Fig. 2 displays the ROC curves for each model following 10-fold cross-validation. Table 3 summarizes the predictive performance metrics of the four machine-learning models after 10-fold cross-validation. XGBoost outperformed the other three algorithms in terms of accuracy, sensitivity, and AUC. The distribution of the performance measures is presented as box plots in Supplementary Figs. S1–S4.

After using calibration plots to assess whether the predicted probabilities aligned with the actual probability distribution, the original XGBoost model demonstrated the lowest Brier score of 0.0057 than those of the XGBoost models calibrated using the isotonic and sigmoid methods (Table 4). The results indicated that the original XGBoost model exhibited a minor deviation between the predicted and actual outcomes. Furthermore, the calibration curve of the original XGBoost model closely approximates the reference line (Supplementary Fig. S5), indicating that the model provides more accurate risk predictions. Therefore, the original XGBoost model was selected as the final model. These calibration methods confirmed that the model exhibited a good fit and that the baseline differences did not introduce bias into its predictive performance. These results suggest that the predictive ability of the model remains robust and reliable after evaluating the calibration methods.

3.4. Importance of model features

Fig. 3a illustrates the importance of each variable based on their corresponding SHAP value, highlighting their predictive value in differentiating between patients who require ICU admission and those who do not. MGFA clinical classification and thymectomy were the two most crucial categorical variables. Among the continuous variables, disease duration, age, and maximum daily dose of prednisolone were the most critical.

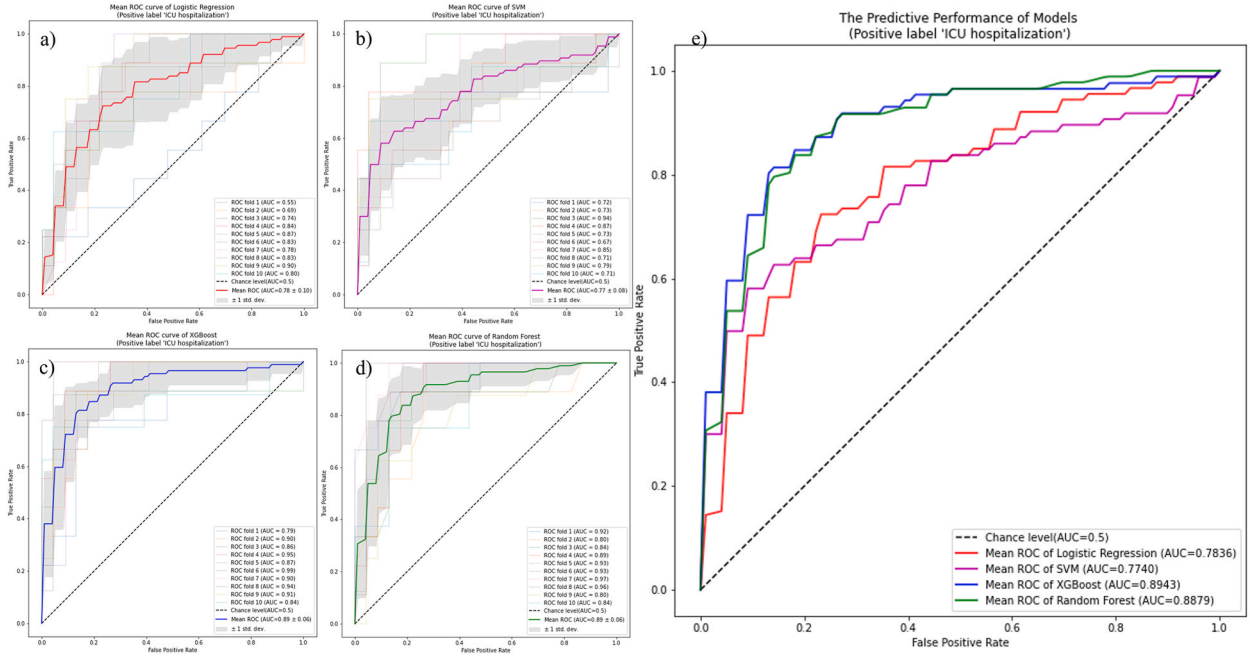

Fig. 2. Receiver operating characteristic curves were constructed using a 10-fold cross-validation for the **(a)** logistic regression model, **(b)** support vector machine model, **(c)** extreme gradient boosting model, and **(d)** random forest model. **(e)** Comparison of the four models.
Abbreviations: AUC, area under the curve; ICU, intensive care unit; ROC, receiver operating characteristic curve; SVM, support vector machine; XGBoost, extreme gradient boosting.

Table 3
Predictive performance of ICU hospitalization using machine learning models.

	Accuracy	Sensitivity	Specificity	AUC
Logistic Regression	0.7742 ± 0.0442	0.4431 ± 0.1518	0.8986 ± 0.0532	0.7836 ± 0.0965
Support Vector Machine	0.7958 ± 0.0532	0.4861 ± 0.1755	0.9115 ± 0.0964	0.7740 ± 0.0827
XGBoost	**0.8603 ± 0.0558**	**0.7222 ± 0.1582**	0.9125 ± 0.0433	**0.8943 ± 0.0551**
Random Forests	0.8315 ± 0.0506	0.6042 ± 0.1386	**0.9168 ± 0.0409**	0.8879 ± 0.0612

The highest value among the four models is shown in bold.
Abbreviation: AUC, area under the curve; ICU, intensive care unit; XGBoost, extreme gradient boosting.

Table 4
Performance metrics for XGBoost and calibrated XGBoost models.

Method	Intercept (95 % CI.)	Slope (95 % CI.)	Brier score
XGBoost	**−0.1525 (-0.3940–0.0890)**	**1.2948 (0.8903–1.6994)**	**0.0057**
Isotonic Calibrated XGBoost	−0.1537 (−0.5027–0.1953)	1.4226 (0.8382–2.0071)	0.0214
Sigmoid Calibrated XGBoost	−0.3253 (−0.6762–0.0257)	2.0098 (1.2947–2.7250)	0.0427

Abbreviation: CI, confidence interval; XGBoost, extreme gradient boosting.
Values for the intercept, slope, and Brier Score of the original XGBoost model are highlighted in bold to emphasize its superior calibration and predictive performance compared to the calibrated models.
Intercept: Assess whether the systematically predicted probabilities are too high or too low. A value closer to 0 indicates better calibration.
Slope: Evaluate the extremeness of the predicted probabilities. A slope of 1 suggests perfect calibration.
Brier Score: Measures the accuracy of probabilistic predictions. Lower scores indicate better model performance.

Fig. 3b illustrates the effect of each variable on the predictive performance of the selected XGBoost model. The figure shows the correlation between each model feature and its corresponding SHAP value. Higher variable values are indicated in red, while lower values are in blue. The *x*-axis represents the effects of different variables on the SHAP values.

Additionally, we constructed a partial dependence plot to demonstrate the relationship between the outcome of interest and each variable (Fig. 4). We focus on the four most significant variables. In these plots, the x- and y-axes represent the variable values and the SHAP values, respectively.

As shown in Fig. 4a, MGFA clinical classification was the most crucial variable for predicting the risk of ICU admission. Patients

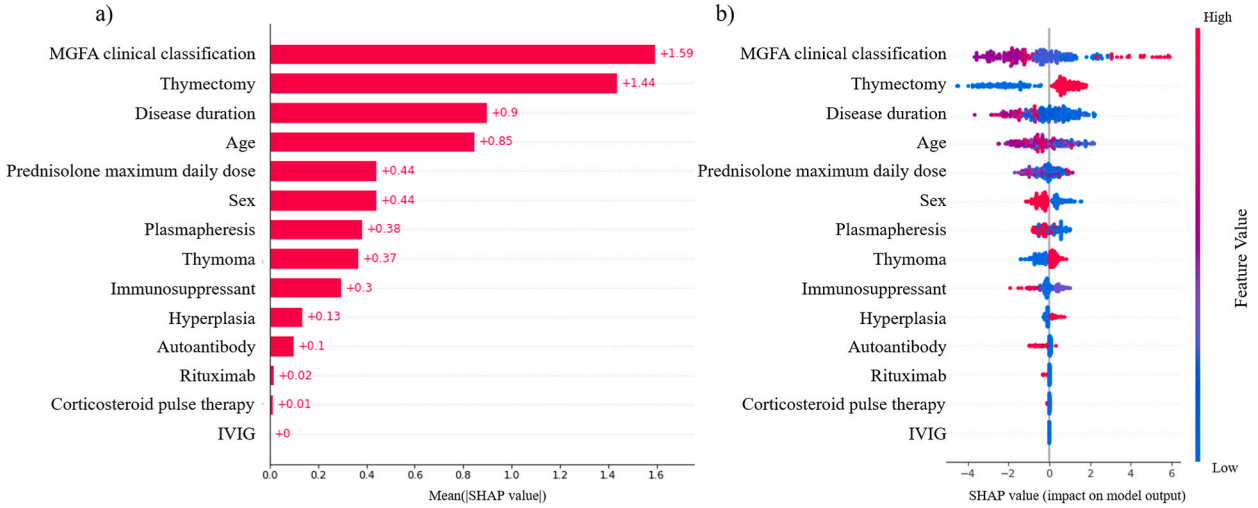

Fig. 3. **(a)** Importance of each feature ranked by the mean SHAP value. **(b)** Effect of each variable on the predictive performance of the XGBoost model.
Abbreviations: IVIG, intravenous immunoglobulin; MGFA, Myasthenia Gravis Foundation of America; SHAP, SHapley Additive exPlanations; XGBoost, extreme gradient boosting.

with an MGFA clinical classification of V had a higher risk of ICU admission than those with other classifications. Patients who underwent thymectomy had a higher risk of ICU admission (Fig. 4b). The duration of MG was negatively correlated with ICU admission risk (Fig. 4c). Longer disease duration was associated with a lower risk of ICU admission. The risk of ICU admission was high in patients aged <40 years and >60 years, but low in those aged 40–60 years (Fig. 4d).

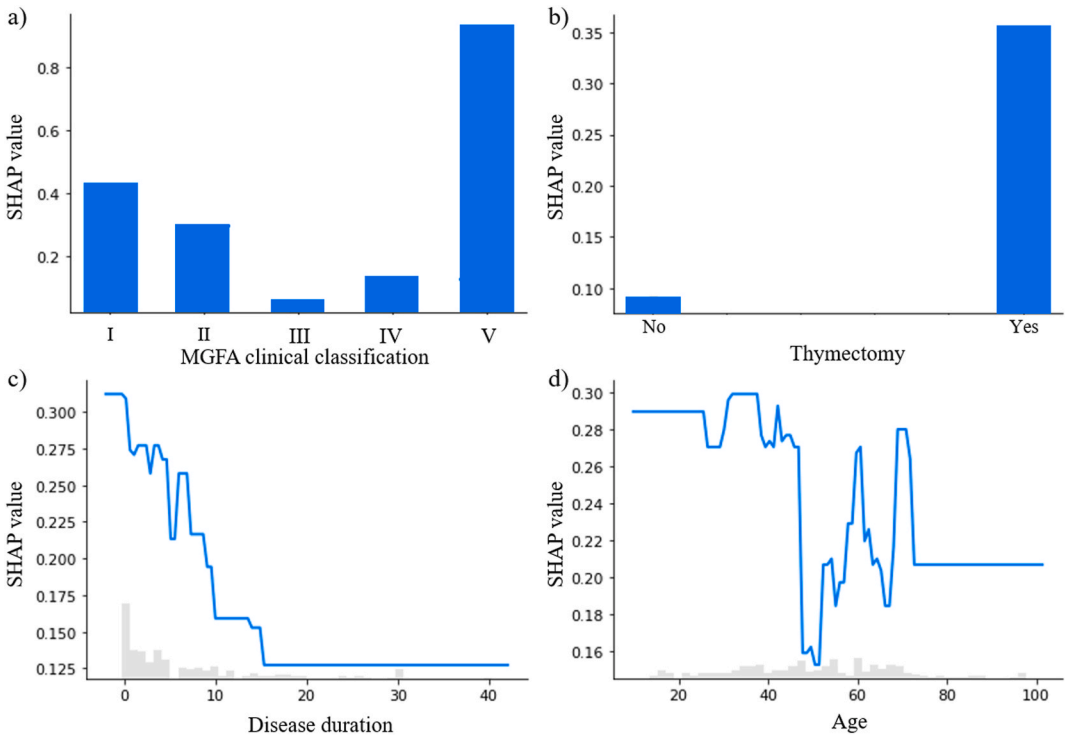

Fig. 4. Partial dependence plots illustrate the relationships between the outcome of interest and the top four important variables: **(a)** MGFA clinical classification, **(b)** thymectomy, **(c)** disease duration, and **(d)** age. The x-axis represents the values of each variable, and the y-axis shows the SHAP values.
Abbreviations: MGFA, Myasthenia Gravis Foundation of America; SHAP, SHapley Additive exPlanations.

3.5. Application of the XGBoost model in clinical scenarios

To further examine the XGBoost model, we retrospectively analyzed its application in two clinical scenarios. Patient 1: A 40-year-old man with a history of MG lasting less than one year. Upon admission, the patient was classified as having class II MG, according to the MGFA classification. The patient was diagnosed with thymoma and subsequently underwent thymectomy, with no pertinent history of steroids or immunosuppressant use before hospitalization. The patient underwent plasmapheresis during the index hospitalization. Patient 2: A 38-year-old woman with a one-year history of MG, classified as having class II MG at admission. The patient underwent a thymectomy for non-thymoma abnormalities (thymic hyperplasia). Anti-AChR and anti-MuSK antibodies were not detected in this patient, and she had not received oral corticosteroids or immunosuppressants for disease management at any previous visit.

Fig. 5 depicts the risk-prediction process for each patient. Waterfall and force plots were constructed to visualize the contribution of each variable to the risk of ICU admission. The waterfall plot indicated the rank of each variable based on its effects. The red arrow indicates that each variable contributes to the prediction of ICU admission risk. E[f(x)] refers to the base value and average prediction outcome of the model in the training set.

Furthermore, the predicted value f(x) represents the sum of the SHAP and base values. A positive f(x) value indicates ICU admission is required. As shown in Fig. 5a, the value of f(x) was positive (4.704); therefore, the model predicted that Patient 1 required ICU admission. As shown in Fig. 5b, the value of f(x) was negative; therefore, the model predicted that Patient 2 did not require ICU admission.

4. Discussion

The marked reduction in myasthenia crisis mortality rates from over 40% in the 1960s to current estimates of 12.0–18.6% underscores the impact of advancements in critical care technologies [5,33,34]. However, myasthenia crisis remains a fatal condition that requires vigilant management. Our predictive model aimed to assist clinicians in the early identification of high-risk patients, potentially enabling preemptive interventions to mitigate severe outcomes. In this context, our predictive model aims to assist clinicians in the early identification of high-risk patients, enabling preemptive interventions to mitigate severe outcomes. By adopting an explainable artificial intelligence approach, we contribute to addressing the complex and heterogeneous nature of MG, which poses significant challenges in predicting disease progression and complications. Given that approximately 15%–20% of MG patients experience myasthenic crises [2,4] and require ICU admission, accurate prediction remains a critical unmet need.

In this study, we evaluated four machine-learning algorithms to develop models for predicting the risk of ICU admission in MG patients. The high AUC achieved by the model demonstrates its robust discriminative ability to identify patients who require ICU admission and those who do not, offering valuable insights for timely clinical interventions. Notably, the XGBoost model outperformed the other algorithms, achieving an AUC of 0.8943, an accuracy of 0.8603, a sensitivity of 0.7222, and a specificity of 0.9125. The original XGBoost model exhibited the lowest Brier score compared with its calibrated counterparts, suggesting greater reliability in predicting ICU admission risk in MG patients and demonstrating its robustness in managing the complexities of our dataset. SHAP analysis further elucidated global and local features contributing to ICU admission risk, highlighting MG severity based on the MGFA clinical classification system as the most significant predictor. This finding underscores the significance of disease severity in influencing ICU admission. Additionally, disease duration was identified as a critical factor in ICU admission risk, highlighting its relevance in patient management.

Machine learning has demonstrated potential across various aspects of MG management, including thymoma classification, invasion prediction, and MG diagnosis in thymoma patients [15,35–38]. Building on these advancements, this research addresses the

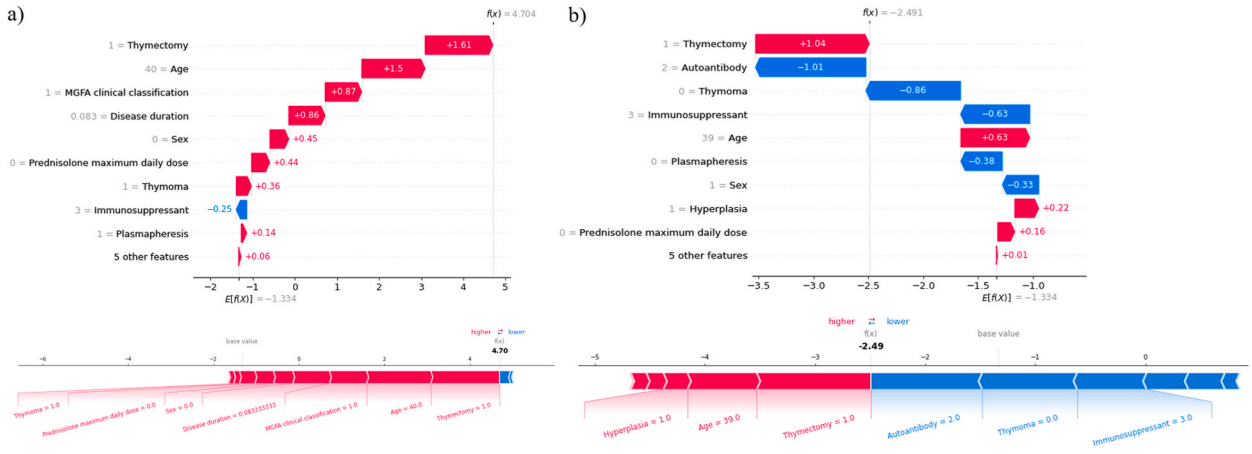

Fig. 5. Waterfall and force plots for **(a)** a patients requiring ICU admission and **(b)** a patient not requiring ICU admission
Abbreviations: ICU, intensive care unit; MGFA, Myasthenia Gravis Foundation of America.

critical need for accurate prediction of ICU admission risk. Compared with prior study employing decision tree algorithms with AUCs ranging from 0.810 to 0.814 [38], the XGBoost model demonstrated improved predictive performance with an AUC of 0.8943. Furthermore, incorporating a more comprehensive array of predictive factors and utilizing advanced algorithmic approaches has refined the predictive tool for ICU admission risk stratification in MG patients. These results reinforce the feasibility of accurately predicting ICU admission risk and set the stage for future investigations to improve MG management further.

Integrating SHAP analysis, this research represents a significant advancement in MG management. By quantifying feature importance and constructing personalized, interpretable machine-learning models, the model enables precise risk assessments tailored to individual patient characteristics and MG severity, potentially revolutionizing clinical decision-making and patient care strategies. The model identified several critical predictors of ICU admission risk in MG patients, with MGFA classification as the predominant predictor [38,39], corroborating the findings of previous studies. Higher MG severity upon admission was strongly associated with an increased risk of myasthenic crisis [34,40], a fatal condition often requiring intensive care. Additionally, patients with severe MG are at higher risk of experiencing comorbidities and complications, underscoring the need for proactive management. These patients often require more intensive therapeutic interventions, including higher doses of immunosuppressants and corticosteroids, which can increase infection risks and further complicate their clinical course [34]. Therefore, integrating MG severity into risk prediction models can provide valuable insights for developing individualized treatment plans. Such tailored approaches can help balance the need for aggressive therapy with potential complications, ultimately improving patient outcomes by informing clinical decision-making.

The analysis identified thymectomy as a critical factor influencing the risk of ICU admission in MG patients. Notably, a substantial proportion of patients in our cohort who had undergone thymectomy (23.9% of the whole cohort, $n = 75$) required ICU admission. This finding emphasizes the complexities involved in post-operative care in this population, indicating that complications or exacerbations of MG symptoms can occur following surgery. The relationship between thymectomy and ICU admission risk likely reflects individual patient variability, disease severity, and post-operative monitoring requirements. These findings suggest that although thymectomy is a valuable treatment option, it is associated with short-term risks that require careful consideration [1,2].

The model also demonstrated an inverse correlation between disease duration and ICU admission risk, with patients having less than five years of MG history showing higher vulnerability. This pattern aligns with previous observations that myasthenic crises frequently occur within the first 2–3 years after disease onset [4,41]. The elevated risk in early-stage patients may be attributed to disease instability and suboptimal treatment responses. Furthermore, these patients may experience increased susceptibility to infections and complications due to the side effects of corticosteroids and immunotherapy. These instabilities can result in sudden or severe exacerbations, which increase the likelihood of ICU admission for intensive monitoring and treatment. These insights emphasize the importance of implementing early risk assessments and timely therapeutic interventions, particularly during the initial years of disease progression.

The analysis revealed a bimodal age distribution in ICU admission risk, with elevated risks observed in patients aged <40 or >60 years, reflecting the characteristic pattern of MG episodes [1,2]. This age-related risk pattern is attributable to distinct factors across different age groups. In younger patients, particularly women, ICU admission often stems from the necessary discontinuation of immunosuppressive therapy during pregnancy, with labor-related stress potentially exacerbating MG symptoms. Conversely, older patients typically require intensive care due to cardiovascular complications or other chronic conditions demanding close monitoring [4,34]. This finding underscores the need for developing age-specific management strategies that consider factors such as pregnancy in younger women and comorbidities in older patients.

Early identification of high-risk patients with MG facilitates timely intervention, prevents symptom exacerbation, and reduces complications, ultimately enhancing clinical outcomes and disease prognosis. Our study highlights the effectiveness of machine-learning models in identifying patterns and correlations within clinical data, thereby enhancing prediction accuracy. We employed a multi-algorithm integration approach to compare the performance of XGBoost with other machine-learning algorithms, including SVM, RF, and logistic regression, in predicting the ICU admission risk in MG patients. Additionally, by focusing on the specific features and clinical characteristics of MG patients, our study provides a model that is accurate and tailored to the clinical context of MG. These models are particularly valuable because they can be continuously updated and optimized based on real-time data, ensuring that their predictive capabilities evolve alongside advancements in clinical practice. In medical data, the challenge of obtaining large-scale patient datasets while maintaining privacy underscores the need to develop reproducible and reliable models, even when using smaller datasets. Traditional linear causality approaches may fail to capture the complexities of the nonlinear and non-modifiable biological phenomena that characterize MG. Therefore, integrating disease mechanisms with nonlinear machine-learning models is crucial.

To enhance the interpretability of our model, we employed the SHAP algorithm for risk prediction and visualization of the results. This approach ensures that healthcare decisions are objective and scientifically grounded, thereby enhancing their credibility and consistency [20,29,31]. Given the inherently volatile and complex developmental patterns and risk factors of MG, integrating medical knowledge with machine-learning models can assist healthcare professionals in accurately identifying high-risk patients. This integration enables the proactive delivery of appropriate care, ultimately improving disease prognosis and treatment outcomes.

Our predictive model represents a significant advancement in comprehensive MG management. Through accurate identification of patients at elevated risk for ICU admission, the model enables healthcare providers to implement targeted preventive strategies, including enhanced respiratory function monitoring and individualized patient education on crisis management. The SHAP analysis-derived quantification of risk factors provides clinicians with actionable insights for developing personalized intervention strategies, aligning with the emerging paradigm of precision medicine in autoimmune disorders. Beyond its primary function of ICU admission risk prediction, the model establishes a framework for early detection of acute exacerbations, including respiratory crises. This proactive approach extends to resource management, enabling strategic allocation of medical equipment and personnel, which is

particularly valuable in settings with limited ICU capacity in the challenging landscape of MG care.

4.1. Study limitations

Despite demonstrating robust internal validation metrics, several methodological limitations merit consideration.

First, the single-center, retrospective design with a defined cohort size inherently constrains external validity. The lack of stratified sampling and patient heterogeneity limits the model's generalizability across different MG subtypes, severity levels, and treatment modalities. Second, the intricate pathophysiology of MG, characterized by dynamic progression and multifactorial determinants—including physiological parameters, environmental factors, and therapeutic interventions—presents significant analytical challenges. The cross-sectional methodology utilizing hospitalization-derived data may inadequately capture disease trajectories and antecedent precipitating factors. Third, the current model's reliance on static clinical parameters and dichotomous ICU admission endpoints potentially underrepresent the full spectrum of disease fluctuations. While ICU admission represents a critical endpoint, typically indicating severe exacerbations or significant comorbidities as extreme manifestations of the disease course, the model remains limited in its ability to reflect the dynamic nature of MG. Fourth, this study's preliminary and exploratory nature limits definitive conclusions on the model's stability and clinical applicability. The retrospective design lacks the temporal depth to evaluate long-term performance or consistency across clinical scenarios, necessitating cautious interpretation of the model's predictive performance within the context of this dataset.

5. Conclusions

This study identified MG severity and disease duration as the most influential variables for predicting ICU admission risk in the studied patient cohort. Patients with more severe MG, as classified by MGFA, exhibited an increased likelihood of requiring intensive care. Those in earlier disease stages, particularly during the initial post-diagnosis period, appeared to experience elevated risks of ICU admission associated with acute exacerbations. These findings suggest the potential value of vigilant monitoring and prompt intervention strategies in this patient population. The implemented XGBoost-based predictive model, incorporating clinical parameters and intervention data with SHAP value analysis, may offer analytical insights for risk stratification. This methodology could serve as an adjunctive tool in clinical assessment, potentially assisting healthcare providers in identifying patients who may benefit from early therapeutic intervention or intensive care monitoring.

CRediT authorship contribution statement

Chao-Yang Kuo: Writing – original draft, Methodology, Formal analysis. **Emily Chia-Yu Su:** Writing – original draft, Methodology. **Hsu-Ling Yeh:** Writing – original draft, Resources, Methodology, Data curation. **Jiann-Horng Yeh:** Writing – review & editing, Supervision, Resources, Conceptualization. **Hou-Chang Chiu:** Writing – review & editing, Supervision, Resources, Conceptualization. **Chen-Chih Chung:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization.

Ethical approval statement

This study was approved by the Research Ethics Review Committee of the Shin Kong Wu Ho-Su Memorial Hospital (approval number: 20190109R). The requirement for informed consent was waived because of the retrospective study design and the use of anonymized clinical data. All procedures were performed in compliance with the applicable guidelines and regulations.

Data availability statement

We are unable to publicly share the raw data used in this study for ethical and privacy reasons, as mandated by the Research Ethics Review Committee of Shin Kong Wu Ho-Su Memorial Hospital. A de-identified and aggregated summary of the data that supports the findings presented in this research can be made available upon reasonable request to the corresponding author, subject to approval by the Research Ethics Review Committee.

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Declaration of competing interest

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e41084.

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