

Association Between Alkaline Phosphatase-to-Albumin Ratio and Post-Stroke Dysphagia: A Retrospective Cohort Study from the MIMIC-IV Database

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Article

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Abstract

Background

Post-stroke dysphagia is a common and serious complication that significantly increases the risk of aspiration pneumonia, malnutrition, and prolonged hospitalization. The alkaline phosphatase-to-albumin ratio (APAR) has been recognized as a potential biomarker reflecting systemic inflammation and nutritional status, yet its association with post-stroke dysphagia remains unclear.

Methods

This retrospective cohort study extracted data from the Medical Information Mart for Intensive Care IV (MIMIC-IV, v3.0) database, involving 1563 ICU patients diagnosed with stroke. The primary outcome was the occurrence of post-stroke dysphagia, identified through bedside swallowing screening records (item ID 225118) in the chartevents table. Multivariable logistic regression models were constructed to evaluate the association between APAR and dysphagia, with restricted cubic spline regression for nonlinearity exploration and subgroup analyses for consistency assessment.

Results

Among the 1,563 included stroke patients, a higher alkaline phosphatase-to-albumin ratio (APAR) was significantly and independently associated with an increased risk of post-stroke dysphagia after adjusting for potential confounders. The restricted cubic spline analysis indicated a nonlinear dose-response relationship between APAR and dysphagia risk. Furthermore, subgroup analyses demonstrated that this positive association was generally consistent across most patient strata.

Conclusions

Elevated APAR is independently associated with an increased risk of post-stroke dysphagia in critically ill patients. The nonlinear relationship and consistent findings across subgroups suggest that APAR may serve as a useful biomarker for identifying stroke patients at heightened risk of dysphagia, facilitating early risk stratification and targeted interventions.

Introduction

Stroke remains a leading cause of death and long-term disability worldwide, with a steadily increasing global incidence driven by population aging and metabolic risk factors[1, 2]. Beyond its high mortality, stroke frequently results in persistent neurological impairments that impose substantial burdens on patients, families, and healthcare systems[3].

Among the various complications affecting stroke survivors, post-stroke dysphagia (PSD) is one of the most common and clinically consequential, with a pooled prevalence of 42% in acute stroke patients [4]. Dysphagia after stroke is consistently associated with significantly increased risks of aspiration pneumonia, malnutrition, dehydration, prolonged hospitalization, and mortality [5, 6]. Early identification of at-risk patients is therefore a clinical priority [7]. However, existing screening methods are either subjective or resource-intensive, limiting their utility in the ICU [8]. Objective and easily obtainable biomarkers are therefore needed to facilitate early identification of patients at risk for PSD.

Alkaline phosphatase (ALP) and albumin (ALB) are readily available laboratory parameters that reflect systemic inflammation and nutritional status, respectively [9, 10]. The alkaline phosphatase-to-albumin ratio (APAR), which integrates these two complementary indicators, has emerged as a novel prognostic biomarker that captures the dual dimensions of inflammation and nutrition in various critical care settings [11, 12]. A recent retrospective study of 1,690 critically ill patients with ischemic stroke from the MIMIC-IV database demonstrated that elevated APAR was significantly associated with increased 28-day, 90-day, and 365-day all-cause mortality, independent of multiple confounding factors [13]. However, the association between APAR and PSD has not yet been investigated..

Given that swallowing is a complex neuromuscular process susceptible to both inflammatory status and nutritional reserve [14, 15], we hypothesized that APAR may help identify stroke patients at risk for dysphagia, and designed this retrospective cohort study using the MIMIC-IV database to test this hypothesis.

Materials and methods

Data collection

This retrospective study utilized data from the Medical Information Mart for Intensive Care IV (MIMIC-IV, v3.0), a publicly available electronic health record database. MIMIC-IV contains comprehensive clinical data from over 65,000 intensive care unit (ICU) admissions and more than 200,000 emergency department visits at Beth Israel Deaconess Medical Center in Boston, Massachusetts, USA, spanning from 2008 to 2022. The database provides detailed information on patient demographics, vital signs, laboratory results, and diagnoses coded according to the International Classification of Diseases, Ninth and Tenth Revisions (ICD-9 and ICD-10). As MIMIC-IV is a de-identified database, the requirement for individual patient informed consent was waived[16].

Study Population

Patients were included in this study if they met all of the following criteria: (1) diagnosed with stroke; (2) had an ICU length of stay ≥ 24 hours; (3) underwent bedside swallowing assessment during ICU admission; (4) aged ≥ 18 years; and (5) for patients with multiple hospitalizations, only the first admission record was included.

Variables

The variables included in this study were categorized as follows:

- (1) Demographic characteristics: age, sex, weight, and race/ethnicity;
- (2) Laboratory parameters: alkaline phosphatase (ALP), albumin (ALB), hemoglobin, hematocrit, white blood cell count, blood urea nitrogen, calcium, chloride, potassium, sodium, and creatinine. The alkaline phosphatase to albumin ratio (APAR) was calculated based on laboratory results obtained during the first ICU admission, using the following formula[13]:

$$\text{APAR} = \text{ALP (U/L)} / [10 \times \text{ALB (g/dL)}] \text{ (U/g)};$$

- (3) Comorbidities: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, peptic ulcer disease, mild liver disease, diabetes without chronic complications, diabetes with chronic complications, paraplegia, renal disease, malignancy, severe liver disease, metastatic solid tumor, and acquired immunodeficiency syndrome (AIDS).

For variables with missing proportions < 20%, multiple imputation was performed using the random forest method implemented in the R package mice (Version 3.16.0), generating five complete datasets with 10 iterations each. Variables with missing proportions $\geq 20\%$ were excluded from the analysis [17].

Outcome

The primary outcome was post-stroke dysphagia, defined as a positive finding on the bedside swallowing screening recorded under item ID 225118 in the chartevents table [18].

Statistical Analysis

All statistical analyses were performed using R software (Version 4.3.3). To minimize the impact of missing data on model development, multiple imputation was performed using the random forest method implemented in the R package mice for variables with missing proportions < 20%, while variables with missing proportions $\geq 20\%$ were excluded from the analysis. A two-sided $P < 0.05$ was considered statistically significant. Model performance was developed in the training set and internally validated in the validation set.

Baseline characteristics and group comparisons. Categorical variables were presented as frequencies (n) and percentages (%). Normality of continuous variables was assessed using the Shapiro-Wilk test combined with Q-Q plots. Normally distributed continuous variables were expressed as mean $\pm$ standard deviation (SD), while non-normally distributed variables were expressed as median with interquartile range (IQR). Comparisons between groups were performed using the chi-square test or Fisher's exact test for categorical variables, the independent samples t-test for normally distributed continuous variables, and the Mann-Whitney U test for non-normally distributed continuous variables.

Logistic regression models and model evaluation. The total sample was randomly divided into a training set and a validation set at a 6:4 ratio using stratified random sampling (R package caret, Version 6.0-94), ensuring that the distribution of the outcome variable remained consistent between the two sets. Two multivariable logistic regression models were constructed to evaluate the association between APAR and dysphagia: Model 1 (unadjusted) included APAR as the sole independent variable; Model 2 (adjusted) included APAR and adjusted for covariates selected based on clinical relevance and prior literature [13, 18–20], including age, sex, weight, myocardial infarction, congestive heart failure, dementia, paraplegia, hemoglobin, hematocrit, white blood cell count, blood urea nitrogen, calcium, chloride, potassium, sodium, and creatinine. APAR was analyzed as a continuous variable. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each variable.

The discriminatory ability of the models was evaluated using receiver operating characteristic (ROC) curves, and the area under the curve (AUC) was calculated using the R package pROC (Version 1.18.5) [21] for both the training and validation sets. A nomogram was constructed based on Model 2 in the training set using the R package rms (Version 6.7.1) to visualize the contribution of each predictor. Model calibration was assessed using calibration curves and the Brier score. Decision curve analysis (DCA) was performed using the R package ggDCA (Version 1.2) [22] to evaluate the clinical net benefit of the model across a range of threshold probabilities.

Nonlinearity assessment. To explore the potential nonlinear relationship between APAR and dysphagia risk, restricted cubic spline (RCS) regression was performed. RCS models were fitted under both unadjusted (Model 1) and fully adjusted (Model 2) conditions. Knot positions were placed at the 5th, 35th, 65th, and 95th percentiles of the APAR distribution, following the recommendations of Harrell[23]. The P value for nonlinearity was calculated by testing the joint significance of all spline terms beyond the first.

Subgroup analyses and interaction testing. Subgroup analyses were conducted to evaluate the consistency of the APAR-dysphagia association across different patient strata. Stratification variables included race/ethnicity (White, Black, and other), peripheral vascular disease (yes/no), cerebrovascular disease (yes/no), chronic pulmonary disease (yes/no), diabetes without chronic complications (yes/no), diabetes with chronic complications (yes/no), and renal disease (yes/no). Logistic regression (Model 2) was repeated within each subgroup. Effect heterogeneity was assessed by including interaction terms between APAR and each stratification variable (P for interaction). As these analyses were exploratory, no adjustment for multiple testing was applied.

Results

3.1 Patient Selection

A total of 8,520 stroke admission records were initially extracted from the MIMIC-IV database. After excluding patients with multiple ICU admissions (retaining only the first admission), those with missing

ALP or albumin data, those without documented bedside swallowing assessment, those with ICU stay < 24 hours, and those aged < 18 years, a final cohort of 1,563 patients was included in the analysis. (Fig. 1)

3.2 Baseline Characteristics

Baseline characteristics of the study population, stratified by APAR quartiles (Q1: ≤ 1.756 , Q2: 1.757–2.353, Q3: 2.354–3.690, Q4: ≥ 3.691), are summarized in Table 1. patients in higher APAR quartiles exhibited significantly lower levels of hematocrit, hemoglobin, and serum calcium, along with significantly higher levels of blood urea nitrogen, white blood cell count, heart rate, respiratory rate, and blood glucose (all $p < 0.001$). The prevalence of comorbidities - including myocardial infarction, congestive heart failure, liver disease, diabetes, renal disease, and malignancy-increased progressively with rising APAR quartiles. In contrast, the proportion of patients with paraplegia was lower in the highest APAR quartile (Q4: 23%) compared to the lowest (Q1: 36%, $p < 0.001$). (Table 1)

Table 1
Baseline characteristics according to APAR quartiles

Characteristic	Overall N = 1,563 ¹	Q1 N = 391 ¹	Q2 N = 392 ¹	Q3 N = 389 ¹	Q4 N = 391 ¹	p- value ²
APAR	2.35 [1.76, 3.69]	1.48 [1.25, 1.61]	2.05 [1.90, 2.18]	2.79 [2.56, 3.14]	6.19 [4.55, 9.46]	< 0.001
Age	68.89 [57.94, 79.86]	67.66 [53.86, 78.84]	70.93 [59.30, 80.95]	70.97 [61.74, 81.92]	66.85 [55.50, 77.66]	< 0.001
Gender						0.172
Female	747 (48%)	176 (45%)	203 (52%)	191 (49%)	177 (45%)	
Male	816 (52%)	215 (55%)	189 (48%)	198 (51%)	214 (55%)	
Weight	76.55 [64.50, 92.15]	77.30 [65.50, 92.00]	75.87 [63.70, 91.20]	76.40 [64.00, 90.60]	76.80 [65.00, 93.00]	0.692
Race_white	1,018 (65%)	265 (68%)	254 (65%)	246 (63%)	253 (65%)	0.597
Race_black	156 (10.0%)	27 (6.9%)	38 (9.7%)	47 (12%)	44 (11%)	0.072
Race_other	336 (21%)	85 (22%)	85 (22%)	84 (22%)	82 (21%)	0.997
Race_asian	53 (3.4%)	14 (3.6%)	15 (3.8%)	12 (3.1%)	12 (3.1%)	0.938
Albumin	3.60 [3.20, 4.00]	4.00 [3.60, 4.20]	3.70 [3.40, 4.00]	3.50 [3.10, 3.80]	3.20 [2.70, 3.60]	< 0.001
¹ Median [Q1, Q3]; n (%)						
² Kruskal-Wallis rank sum test; Pearson's Chi-squared test with simulated p-value (based on 2000 replicates)						
APAR: Alkaline Phosphatase to Albumin Rati; Diabetes_without_cc: Diabetes without Complications; Diabetes_with_cc: Diabetes with Complications; Alp: Alkaline Phosphatase; Min: minimum; Max maximum; Wbc: White Blood Cell; Bun: Blood Urea Nitrogen; Inr: International Normalized Ratio; Pt: Prothrombin Time; Ptt: Partial Thromboplastin Time; Sbp: Systolic Blood Pressure; Dbp: Diastolic Blood Pressure; Mbp: Mean Blood Pressure; Resp: Respiratory;						
Spo2: Peripheral capillary Oxygen Saturation.						

Characteristic	Overall N = 1,563 ¹	Q1 N = 391 ¹	Q2 N = 392 ¹	Q3 N = 389 ¹	Q4 N = 391 ¹	p- value ²
Myocardial_infarct	244 (16%)	47 (12%)	49 (13%)	54 (14%)	94 (24%)	< 0.001
Congestive_heart_failure	395 (25%)	50 (13%)	88 (22%)	115 (30%)	142 (36%)	< 0.001
Peripheral_vascular_disease	165 (11%)	43 (11%)	34 (8.7%)	43 (11%)	45 (12%)	0.575
Cerebrovascular_disease	1,274 (82%)	327 (84%)	346 (88%)	312 (80%)	289 (74%)	< 0.001
Dementia	75 (4.8%)	14 (3.6%)	21 (5.4%)	23 (5.9%)	17 (4.3%)	0.437
Chronic_pulmonary_disease	249 (16%)	43 (11%)	58 (15%)	74 (19%)	74 (19%)	0.007
Rheumatic_disease	56 (3.6%)	14 (3.6%)	16 (4.1%)	8 (2.1%)	18 (4.6%)	0.222
Peptic_ulcer_disease	28 (1.8%)	5 (1.3%)	0 (0%)	12 (3.1%)	11 (2.8%)	0.003
Mild_liver_disease	119 (7.6%)	8 (2.0%)	9 (2.3%)	39 (10%)	63 (16%)	< 0.001
Diabetes_without_cc	387 (25%)	70 (18%)	95 (24%)	110 (28%)	112 (29%)	0.003
Diabetes_with_cc	157 (10%)	19 (4.9%)	39 (9.9%)	40 (10%)	59 (15%)	< 0.001
Paraplegia	534 (34%)	142 (36%)	160 (41%)	141 (36%)	91 (23%)	< 0.001
Renal_disease	288 (18%)	50 (13%)	61 (16%)	74 (19%)	103 (26%)	< 0.001
¹ Median [Q1, Q3]; n (%)						
² Kruskal-Wallis rank sum test; Pearson's Chi-squared test with simulated p-value (based on 2000 replicates)						
APAR: Alkaline Phosphatase to Albumin Rati; Diabetes_without_cc: Diabetes without Complications; Diabetes_with_cc: Diabetes with Complications; Alp: Alkaline Phosphatase; Min: minimum; Max maximum; Wbc: White Blood Cell; Bun: Blood Urea Nitrogen; Inr: International Normalized Ratio; Pt: Prothrombin Time; Ptt: Partial Thromboplastin Time; Sbp: Systolic Blood Pressure; Dbp: Diastolic Blood Pressure; Mbp: Mean Blood Pressure; Resp: Respiratory;						
Spo2: Peripheral capillary Oxygen Saturation.						

Characteristic	Overall N = 1,563 ¹	Q1 N = 391 ¹	Q2 N = 392 ¹	Q3 N = 389 ¹	Q4 N = 391 ¹	p- value ²
Malignant_cancer	179 (11%)	22 (5.6%)	29 (7.4%)	48 (12%)	80 (20%)	< 0.001
Severe_liver_disease	50 (3.2%)	2 (0.5%)	2 (0.5%)	14 (3.6%)	32 (8.2%)	< 0.001
Metastatic_solid_tumor	97 (6.2%)	10 (2.6%)	12 (3.1%)	27 (6.9%)	48 (12%)	< 0.001
Aids	4 (0.3%)	0 (0%)	1 (0.3%)	0 (0%)	3 (0.8%)	0.158
Alp	85.0 [66.0, 124.0]	57.0 [48.0, 64.0]	76.0 [68.5, 83.0]	99.0 [87.0, 110.0]	189.0 [146.0, 295.0]	< 0.001
Hematocrit_min	34.40 [29.00, 38.90]	36.80 [32.40, 40.30]	36.05 [31.80, 39.40]	34.20 [28.90, 38.30]	29.90 [24.40, 35.30]	< 0.001
Hematocrit_max	37.50 [32.60, 41.20]	39.10 [35.20, 42.40]	38.75 [34.70, 42.15]	36.70 [32.00, 40.60]	33.70 [29.10, 38.90]	< 0.001
Hemoglobin_min	11.4 [9.5, 12.9]	12.3 [10.7, 13.5]	11.9 [10.4, 13.2]	11.2 [9.3, 12.7]	9.8 [8.0, 11.7]	< 0.001
Hemoglobin_max	12.4 [10.6, 13.8]	13.1 [11.7, 14.2]	12.7 [11.5, 14.0]	12.3 [10.5, 13.6]	11.1 [9.4, 12.7]	< 0.001
Platelets_min	194.0 [143.0, 250.0]	196.0 [161.0, 239.0]	203.0 [153.0, 253.5]	198.0 [141.0, 268.0]	169.0 [102.0, 245.0]	< 0.001
Platelets_max	217 [166, 280]	215 [177, 266]	222 [173, 279]	223 [166, 295]	201 [134, 285]	0.012
¹ Median [Q1, Q3]; n (%)						
² Kruskal-Wallis rank sum test; Pearson's Chi-squared test with simulated p-value (based on 2000 replicates)						
APAR: Alkaline Phosphatase to Albumin Rati; Diabetes_without_cc: Diabetes without Complications; Diabetes_with_cc: Diabetes with Complications; Alp: Alkaline Phosphatase; Min: minimum; Max maximum; Wbc: White Blood Cell; Bun: Blood Urea Nitrogen; Inr: International Normalized Ratio; Pt: Prothrombin Time; Ptt: Partial Thromboplastin Time; Sbp: Systolic Blood Pressure; Dbp: Diastolic Blood Pressure; Mbp: Mean Blood Pressure; Resp: Respiratory;						
Spo2: Peripheral capillary Oxygen Saturation.						

Characteristic	Overall N = 1,563 ¹	Q1 N = 391 ¹	Q2 N = 392 ¹	Q3 N = 389 ¹	Q4 N = 391 ¹	p- value ²
Wbc_min	8.90 [6.60, 11.90]	8.40 [6.40, 10.50]	8.60 [6.50, 11.15]	9.00 [6.90, 12.20]	9.80 [7.00, 13.80]	< 0.001
Wbc_max	10.90 [8.10, 15.10]	10.00 [7.60, 12.90]	10.20 [7.85, 13.70]	11.40 [8.40, 15.60]	13.00 [8.80, 17.80]	< 0.001
Aniongap_min	13 [11, 15]	13 [11, 15]	13 [11, 15]	13 [12, 15]	13 [11, 15]	0.733
Aniongap_max	15 [13, 18]	15 [13, 17]	15 [13, 18]	15 [14, 18]	16 [13, 19]	0.008
Bicarbonate_min	22 [20, 24]	23 [21, 25]	22 [20, 24]	22 [20, 24]	21 [18, 23]	< 0.001
Bicarbonate_max	24 [22, 26]	24 [23, 26]	24 [22, 26]	24 [22, 26]	23 [21, 26]	< 0.001
Bun_min	16 [12, 24]	15 [11, 20]	15 [11, 21]	17 [12, 26]	19 [13, 31]	< 0.001
Bun_max	19 [14, 28]	17 [13, 22]	18 [13, 25]	20 [15, 30]	24 [16, 39]	< 0.001
Calcium_min	8.60 [8.00, 9.00]	8.70 [8.30, 9.10]	8.70 [8.25, 9.00]	8.50 [8.10, 9.00]	8.10 [7.50, 8.60]	< 0.001
Calcium_max	8.9 [8.4, 9.2]	9.0 [8.6, 9.3]	8.9 [8.6, 9.3]	8.9 [8.4, 9.2]	8.5 [8.0, 9.0]	< 0.001
Chloride_min	102 [99, 105]	103 [100, 106]	102 [99, 105]	102 [99, 105]	102 [98, 105]	0.003
Chloride_max	105 [102,	105 [102,	105 [102,	104 [102,	105 [101,	0.461

¹Median [Q1, Q3]; n (%)

²Kruskal-Wallis rank sum test; Pearson's Chi-squared test with simulated p-value (based on 2000 replicates)

APAR: Alkaline Phosphatase to Albumin Rati; Diabetes_without_cc: Diabetes without Complications; Diabetes_with_cc: Diabetes with Complications; Alp: Alkaline Phosphatase; Min: minimum; Max maximum; Wbc: White Blood Cell; Bun: Blood Urea Nitrogen; Inr: International Normalized Ratio; Pt: Prothrombin Time; Ptt: Partial Thromboplastin Time; Sbp: Systolic Blood Pressure; Dbp: Diastolic Blood Pressure; Mbp: Mean Blood Pressure; Resp: Respiratory;

Spo2: Peripheral capillary Oxygen Saturation.

Characteristic	Overall N = 1,563 ¹	Q1 N = 391 ¹	Q2 N = 392 ¹	Q3 N = 389 ¹	Q4 N = 391 ¹	p- value ²
	108]	108]	108]	108]	109]	
Creatinine_min	0.9 [0.7, 1.2]	0.9 [0.7, 1.0]	0.8 [0.7, 1.1]	0.9 [0.7, 1.2]	1.0 [0.7, 1.5]	< 0.001
Creatinine_max	1.0 [0.8, 1.3]	0.9 [0.8, 1.2]	0.9 [0.7, 1.2]	1.0 [0.8, 1.4]	1.1 [0.8, 1.8]	< 0.001
Sodium_min	138 [135, 140]	138 [136, 141]	138 [136, 140]	137 [134, 140]	137 [134, 140]	< 0.001
Sodium_max	140 [138, 142]	140 [138, 142]	140 [138, 142]	140 [137, 142]	140 [137, 142]	0.007
Potassium_min	3.9 [3.5, 4.2]	3.9 [3.6, 4.2]	3.8 [3.5, 4.1]	3.9 [3.5, 4.2]	3.9 [3.5, 4.2]	0.345
Potassium_max	4.3 [3.9, 4.7]	4.2 [3.9, 4.6]	4.2 [3.9, 4.6]	4.3 [4.0, 4.7]	4.4 [4.0, 4.9]	< 0.001
Inr_min	1.1 [1.0, 1.3]	1.1 [1.0, 1.2]	1.1 [1.0, 1.2]	1.1 [1.1, 1.3]	1.2 [1.1, 1.4]	< 0.001
Inr_max	1.2 [1.1, 1.4]	1.1 [1.1, 1.2]	1.1 [1.1, 1.3]	1.2 [1.1, 1.4]	1.36 [1.2, 1.6]	< 0.001
Pt_min	12.5 [11.5, 14.1]	11.9 [11.1, 13.0]	12.15 [11.3, 13.4]	12.8 [11.6, 14.2]	13.7 [12.3, 15.5]	< 0.001
Pt_max	13.10 [11.90, 15.40]	12.30 [11.50, 13.60]	12.60 [11.80, 14.35]	13.40 [12.10, 15.80]	14.90 [12.90, 17.70]	< 0.001
Ptt_min	28.00 [25.40, 31.30]	27.60 [25.10, 30.70]	27.25 [25.30, 30.55]	28.20 [25.60, 31.70]	28.80 [25.90, 33.10]	< 0.001

¹Median [Q1, Q3]; n (%)

²Kruskal-Wallis rank sum test; Pearson's Chi-squared test with simulated p-value (based on 2000 replicates)

APAR: Alkaline Phosphatase to Albumin Ratio; Diabetes_without_cc: Diabetes without Complications; Diabetes_with_cc: Diabetes with Complications; Alp: Alkaline Phosphatase; Min: minimum; Max maximum; Wbc: White Blood Cell; Bun: Blood Urea Nitrogen; Inr: International Normalized Ratio; Pt: Prothrombin Time; Ptt: Partial Thromboplastin Time; Sbp: Systolic Blood Pressure; Dbp: Diastolic Blood Pressure; Mbp: Mean Blood Pressure; Resp: Respiratory;

Spo2: Peripheral capillary Oxygen Saturation.

Characteristic	Overall N = 1,563 ¹	Q1 N = 391 ¹	Q2 N = 392 ¹	Q3 N = 389 ¹	Q4 N = 391 ¹	p- value ²
Ptt_max	30.60 [27.30, 39.20]	29.60 [26.90, 36.20]	30.00 [27.05, 36.30]	30.80 [27.70, 39.30]	32.20 [27.90, 44.70]	< 0.001
Heart_rate_min	67 [58, 77]	62 [56, 71]	65 [57, 73]	68 [59, 79]	71 [62, 83]	< 0.001
Heart_rate_max	99 [87, 113]	95 [85, 107]	97 [86, 109]	100 [87, 115]	104 [92, 122]	< 0.001
Heart_rate_mean	81.10 [71.29, 92.04]	76.92 [68.44, 85.05]	78.57 [69.33, 87.94]	82.65 [71.18, 93.35]	85.90 [76.38, 98.20]	< 0.001
Sbp_min	100 [88, 112]	104 [94, 116]	102 [91, 114]	100 [87, 115]	92 [82, 104]	< 0.001
Sbp_max	156 [142, 172]	157 [145, 173]	160 [147, 172]	158 [141, 175]	149 [134, 168]	< 0.001
Sbp_mean	127.48 [115.33, 140.06]	130.00 [120.58, 140.16]	129.98 [118.49, 142.35]	129.04 [115.11, 142.06]	119.00 [107.02, 132.61]	< 0.001
Dbp_min	51 [43, 59]	53 [44, 63]	52 [45, 60]	50 [41, 57]	48 [41, 55]	< 0.001
Dbp_max	95 [82, 109]	98 [84, 109]	97 [85, 111]	96 [82, 110]	90 [78, 102]	< 0.001
Dbp_mean	68.11 [59.94, 77.17]	69.91 [62.00, 79.43]	70.28 [62.00, 79.42]	67.42 [60.35, 76.27]	64.79 [57.52, 73.67]	< 0.001
Mbp_min	65 [56, 75]	69 [59, 78]	67 [59, 77]	65 [55, 74]	62 [54, 69]	< 0.001
¹ Median [Q1, Q3]; n (%)						
² Kruskal-Wallis rank sum test; Pearson's Chi-squared test with simulated p-value (based on 2000 replicates)						
APAR: Alkaline Phosphatase to Albumin Rati; Diabetes_without_cc: Diabetes without Complications; Diabetes_with_cc: Diabetes with Complications; Alp: Alkaline Phosphatase; Min: minimum; Max maximum; Wbc: White Blood Cell; Bun: Blood Urea Nitrogen; Inr: International Normalized Ratio; Pt: Prothrombin Time; Ptt: Partial Thromboplastin Time; Sbp: Systolic Blood Pressure; Dbp: Diastolic Blood Pressure; Mbp: Mean Blood Pressure; Resp: Respiratory;						
Spo2: Peripheral capillary Oxygen Saturation.						

Characteristic	Overall N = 1,563 ¹	Q1 N = 391 ¹	Q2 N = 392 ¹	Q3 N = 389 ¹	Q4 N = 391 ¹	p- value ²
Mbp_max	110 [98, 124]	112 [101, 125]	111 [100, 125]	110 [99, 125]	106 [93, 121]	< 0.001
Mbp_mean	84.43 [75.96, 93.86]	86.88 [78.71, 96.00]	87.22 [78.54, 95.83]	84.50 [75.88, 93.80]	79.68 [72.50, 89.31]	< 0.001
Resp_rate_min	12 [10, 14]	12 [10, 14]	12 [10, 14]	13 [10, 15]	13 [11, 15]	< 0.001
Resp_rate_max	27 [24, 31]	25 [23, 29]	26 [24, 30]	27 [24, 32]	28 [25, 33]	< 0.001
Resp_rate_mean	18.65 [16.75, 21.04]	17.88 [16.20, 19.79]	18.38 [16.63, 20.49]	18.96 [17.06, 21.29]	19.69 [17.25, 22.82]	< 0.001
Temperature_min	36.50 [36.33, 36.72]	36.56 [36.39, 36.72]	36.50 [36.33, 36.72]	36.50 [36.33, 36.67]	36.50 [36.17, 36.72]	< 0.001
Temperature_max	37.22 [37.00, 37.61]	37.17 [37.00, 37.56]	37.22 [36.94, 37.50]	37.22 [36.94, 37.67]	37.22 [36.94, 37.83]	0.209
Temperature_mean	36.85 [36.67, 37.10]	36.89 [36.70, 37.09]	36.85 [36.68, 37.07]	36.83 [36.64, 37.12]	36.82 [36.65, 37.18]	0.252
Spo2_min	93 [90, 95]	93 [91, 95]	93 [91, 95]	92 [90, 95]	92 [90, 94]	0.001
Spo2_max	100 [99, 100]	100 [99, 100]	100 [99, 100]	100 [99, 100]	100 [99, 100]	0.015
Spo2_mean	96.72 [95.44, 97.96]	96.81 [95.46, 97.80]	96.62 [95.55, 98.00]	96.70 [95.38, 97.94]	96.71 [95.35, 98.25]	0.946
¹ Median [Q1, Q3]; n (%)						
² Kruskal-Wallis rank sum test; Pearson's Chi-squared test with simulated p-value (based on 2000 replicates)						
APAR: Alkaline Phosphatase to Albumin Rati; Diabetes_without_cc: Diabetes without Complications; Diabetes_with_cc: Diabetes with Complications; Alp: Alkaline Phosphatase; Min: minimum; Max maximum; Wbc: White Blood Cell; Bun: Blood Urea Nitrogen; Inr: International Normalized Ratio; Pt: Prothrombin Time; Ptt: Partial Thromboplastin Time; Sbp: Systolic Blood Pressure; Dbp: Diastolic Blood Pressure; Mbp: Mean Blood Pressure; Resp: Respiratory;						
Spo2: Peripheral capillary Oxygen Saturation.						

Characteristic	Overall N = 1,563 ¹	Q1 N = 391 ¹	Q2 N = 392 ¹	Q3 N = 389 ¹	Q4 N = 391 ¹	p- value ²
Glucose_min	104 [89, 127]	101 [89, 119]	102 [89, 125]	108 [89, 128]	111 [92, 134]	< 0.001
Glucose_max	149 [119, 201]	135 [112, 176]	145 [117, 197]	151 [123, 216]	162 [128, 212]	< 0.001
Glucose_mean	127.63 [106.00, 158.70]	118.00 [101.50, 143.00]	123.10 [105.00, 158.83]	128.67 [108.67, 162.58]	133.90 [112.00, 171.29]	< 0.001
¹ Median [Q1, Q3]; n (%)						
² Kruskal-Wallis rank sum test; Pearson's Chi-squared test with simulated p-value (based on 2000 replicates)						
APAR: Alkaline Phosphatase to Albumin Rati; Diabetes_without_cc: Diabetes without Complications; Diabetes_with_cc: Diabetes with Complications; Alp: Alkaline Phosphatase; Min: minimum; Max maximum; Wbc: White Blood Cell; Bun: Blood Urea Nitrogen; Inr: International Normalized Ratio; Pt: Prothrombin Time; Ptt: Partial Thromboplastin Time; Sbp: Systolic Blood Pressure; Dbp: Diastolic Blood Pressure; Mbp: Mean Blood Pressure; Resp: Respiratory;						
Spo2: Peripheral capillary Oxygen Saturation.						

3.3 Association Between APAR and Dysphagia

Logistic regression analyses revealed a significant positive association between APAR and post-stroke dysphagia in both unadjusted and adjusted models (Table 2). In the unadjusted model (Model 1), each unit increase in APAR was associated with a 4.8% higher odds of dysphagia (OR = 1.048, 95% CI: 1.008–1.088, p = 0.014). After adjustment for demographic factors and clinically relevant comorbidities (Model 2), the association strengthened (OR = 1.088, 95% CI: 1.039–1.140, p < 0.001).

Table 2
Logistic Regression Results of Clinical Indices and Dysphagia

Variable	OR	95% CI	P value	Model
APAR	1.048	1.008, 1.088	0.014	Model 1
APAR	1.088	1.039, 1.140	< 0.001	Model 2
Age	1.026	1.012, 1.042	< 0.001	Model 2
Gender	1.015	0.668, 1.544	0.944	Model 2
Weight	0.994	0.984, 1.004	0.257	Model 2
Myocardial_infarct	1.375	0.807, 2.286	0.229	Model 2
Congestive_heart_failure	0.836	0.511, 1.343	0.468	Model 2
Dementia	1.712	0.818, 3.450	0.141	Model 2
Paraplegia	2.225	1.506, 3.291	< 0.001	Model 2
Hematocrit	0.966	0.856, 1.090	0.58	Model 2
Hemoglobin	1.117	0.789, 1.589	0.536	Model 2
Wbc	0.993	0.966, 1.007	0.488	Model 2
Bun	1.016	1.000, 1.033	0.046	Model 2
Calcium	1.087	0.803, 1.456	0.583	Model 2
Chloride	0.966	0.915, 1.019	0.209	Model 2
Potassium	0.793	0.594, 1.024	0.095	Model 2
Sodium	1.073	1.008, 1.142	0.027	Model 2
Creatinine	0.776	0.541, 1.017	0.122	Model 2
Model 1: Unadjusted. Model 2: Adjusted for age, sex, weight, myocardial infarction, congestive heart failure, dementia, paraplegia, hematocrit, hemoglobin, white blood cell count, blood urea nitrogen, calcium, chloride, potassium, sodium, and creatinine. CI, confidence interval; OR, odds ratio; APAR, alkaline phosphatase to albumin ratio; WBC, white blood cell count; BUN, blood urea nitrogen.				

Among the covariates in Model 2, older age (OR = 1.026, 95% CI: 1.012–1.042, $p < 0.001$), paraplegia (OR = 2.225, 95% CI: 1.506–3.291, $p < 0.001$), higher BUN (OR = 1.016, 95% CI: 1.000–1.033, $p = 0.046$), and higher sodium (OR = 1.073, 95% CI: 1.008–1.142, $p = 0.027$) were independently associated with increased dysphagia risk. Other covariates, including gender, weight, and most laboratory parameters, did not reach statistical significance. (Table 2)

3.4 Model performance

The discriminative ability of the logistic regression models was evaluated using ROC curves (Fig. 2A-B). In the training set, the AUC for Model 1 was 0.554, and for Model 2 was 0.712. In the validation set, the AUC for Model 1 was 0.559, and for Model 2 was 0.619.

The calibration curve for Model 2 (Fig. 2C) showed a calibration slope of 1.000 and an intercept of 0.000 in the training set. Deviation from the ideal diagonal line was observed at higher predicted risk ranges. The Brier score was 0.118, and the model R^2 was 0.135.

The nomogram (Fig. 2D) visualized the contribution of each variable in Model 2. Serum creatinine showed the largest relative contribution, followed by APAR, paraplegia, and age. Sex showed the smallest contribution (OR = 1.015, $p = 0.944$). The total points correspond to an estimated probability of dysphagia.

Decision curve analysis (Fig. 2E) showed that Model 2 yielded a positive net benefit compared with the "treat-all" and "treat-none" strategies across a range of threshold probabilities.

3.5 Restricted Cubic Spline Regression

Restricted cubic spline regression was performed to examine the relationship between APAR and dysphagia risk (Fig. 3A-B). In Model 1 (unadjusted), a linear relationship was observed (p for nonlinearity ≥ 0.05). In Model 2 (adjusted), a nonlinear relationship was observed (p for nonlinearity < 0.05).

3.6 Subgroup Analyses

Subgroup analyses were conducted to evaluate the consistency of the APAR-dysphagia association across different patient strata (Fig. 4). In the fully adjusted model, significant associations were observed in Black patients (OR = 1.35, 95% CI: 1.11–1.67), patients of other races (OR = 1.07, 95% CI: 1.01–1.15), and those without peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, diabetes (with or without complications), or renal disease (all $p < 0.05$).

All tests for interaction were non-significant (all P for interaction > 0.05), although cerebrovascular disease showed a borderline value ($P = 0.057$) that may warrant further investigation.

Discussion

Post-stroke dysphagia (PSD) remains a prevalent and prognostically significant complication among stroke survivors, yet objective and readily available biomarkers for early risk identification remain limited. In this study, we examined whether APAR, a composite marker of inflammation and nutrition, was associated with post-stroke dysphagia in critically ill patients. The results showed that higher APAR was independently associated with increased odds of PSD, supporting our hypothesis. We also observed a nonlinear dose-response relationship and found the association to be generally consistent across most subgroups. These findings suggest that APAR may have potential as an accessible biomarker for early risk awareness, though its predictive performance was only modest.

In this cohort, patients in higher APAR quartiles exhibited a progressively worsening systemic physiological profile, characterized by elevated white blood cell count, blood urea nitrogen, heart rate, respiratory rate, and blood glucose, alongside decreased hematocrit, hemoglobin, and serum calcium levels (all P for trend < 0.001). This clustering of abnormalities suggests that APAR may serve as a composite indicator reflecting systemic physiological derangement in critically ill stroke patients, which aligns with its recently established prognostic value for mortality in this population[13]. These baseline differences underscore the importance of multivariable adjustment when evaluating the independent association between APAR and post-stroke dysphagia.

The central finding of this study is the independent association between APAR and PSD, which persisted after extensive adjustment for potential confounders. This association may be explained by the dual biological pathways captured by APAR.

Elevated ALP is thought to reflect systemic inflammation, while low albumin indicates poor nutritional reserve[24, 25]. In our cohort, higher APAR was associated with a pro-inflammatory and pro-catabolic profile—higher white blood cell count, lower hemoglobin and calcium—which aligns with this dual-pathway framework. One plausible explanation is that inflammation may compromise the cortical and brainstem swallowing networks through neuroinflammatory and vascular mechanisms, while hypoalbuminemia may impair neurorepair and reduce endogenous protection against ischemic injury [26, 27]. Although our observational data cannot establish causality, the consistency of the APAR-PSD association across most subgroups lends some support to this integrative hypothesis.

Our findings extend previous evidence linking APAR to adverse outcomes in stroke populations. While prior studies have focused on mortality, our investigation extends this line of inquiry to post-stroke dysphagia, demonstrating that APAR is associated with not only survival but also a major functional complication after stroke. The consistency across different endpoints suggests that APAR may reflect a fundamental pathophysiological state predisposing stroke patients to multiple adverse outcomes, rather than being specific to a single event.

The modest predictive performance of APAR in this cohort suggests it is unlikely to replace formal instrumental assessments or bedside screening. Rather, its value may lie in providing early risk awareness—particularly in ICU settings where swallowing evaluations are not immediately available—and in complementing existing clinical assessment. In this sense, APAR could serve as an easily obtainable reference that prompts earlier clinical attention, rather than a standalone diagnostic tool.

The RCS analysis revealed a nonlinear relationship between APAR and PSD risk in the fully adjusted model (P for nonlinearity < 0.05), while the unadjusted model showed a linear pattern. Contrary to a saturation effect, the curve demonstrated a gradual increase in risk at lower APAR levels, which accelerated significantly as APAR values rose. Similar nonlinear associations have been reported for APAR with all-cause mortality in the general population [12]. From a clinical standpoint, this pattern suggests that patients with high APAR levels face a disproportionately elevated risk, highlighting the importance of aggressive management for this subgroup.

Subgroup analyses demonstrated that the association between APAR and PSD was generally consistent across most patient strata, as indicated by non-significant interaction tests (all P for interaction > 0.05), except for cerebrovascular disease which showed a borderline interaction ($P = 0.057$). This overall consistency suggests that the APAR-PSD association is robust. The borderline interaction for cerebrovascular disease raises the possibility that pre-existing cerebrovascular pathology may modify the relationship between APAR and PSD, warranting further investigation in larger cohorts with adequate statistical power.

Several limitations should be acknowledged. First, the retrospective design precludes causal inference, and residual confounding from unmeasured variables such as stroke severity, lesion location, and pre-stroke swallowing function cannot be excluded. Second, PSD was identified via bedside screening records rather than instrumental assessments, which may have introduced misclassification bias. Third, APAR was based on a single admission measurement, which cannot capture dynamic changes over time. These findings should therefore be interpreted as hypothesis-generating rather than confirmatory, and require prospective validation.

Conclusion

In conclusion, this retrospective cohort study of 1,563 critically ill stroke patients from the MIMIC-IV database demonstrated that elevated APAR was independently associated with an increased risk of post-stroke dysphagia. The association was nonlinear, with a potential threshold effect suggesting that risk may escalate more steeply beyond certain APAR levels. The APAR-PSD association remained generally consistent across most demographic and comorbidity subgroups, supporting the robustness of this relationship. Although the predictive model showed only moderate discriminative ability, decision curve analysis indicated a positive net benefit, suggesting potential value in risk stratification. These findings suggest that APAR may serve as an accessible laboratory indicator for early risk awareness, although further refinement and external validation are needed before it can be recommended for independent clinical use.

Declarations

Ethics approval and consent to participate

Not applicable.

Clinical trial number

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The data underlying this study are from the MIMIC-IV (v3.0) database, a publicly accessible resource available at <https://physionet.org/content/mimiciv/3.0/> after approved data use agreement. The analysis code is accessible via the MIMIC Code Repository (<https://github.com/MIT-LCP/mimic-code/>) and from the corresponding author upon reasonable request. Processed data are provided in the Supplementary Materials and are also available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LS and JM conceived and designed the study. LS performed the data extraction and statistical analysis, and drafted the initial manuscript. ZS contributed to data processing and statistical analysis, and prepared the tables and figures. YZ and HZ conducted the literature review, participated in data interpretation, and contributed to the discussion section. JM supervised the study, provided methodological guidance, and critically revised the manuscript for important intellectual content. All authors reviewed and approved the final manuscript.

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Figures

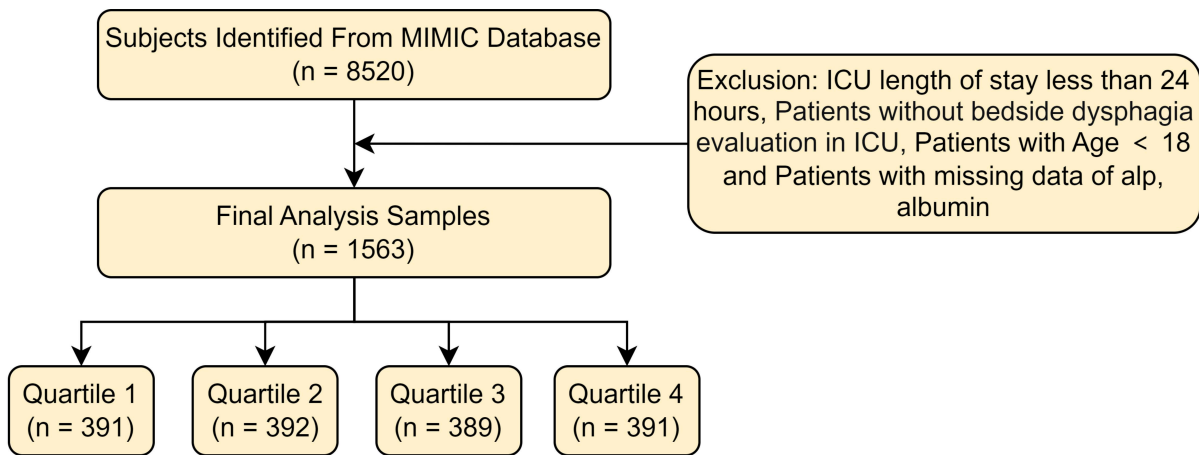


Fig.1 Patient selection process

MIMIC: Medical Information Mart for Intensive Care; N:Numbers; ICU:Intensive Care Unit; ALP:Alkaline Phosphatase

Figure 1

See image above for figure legend.

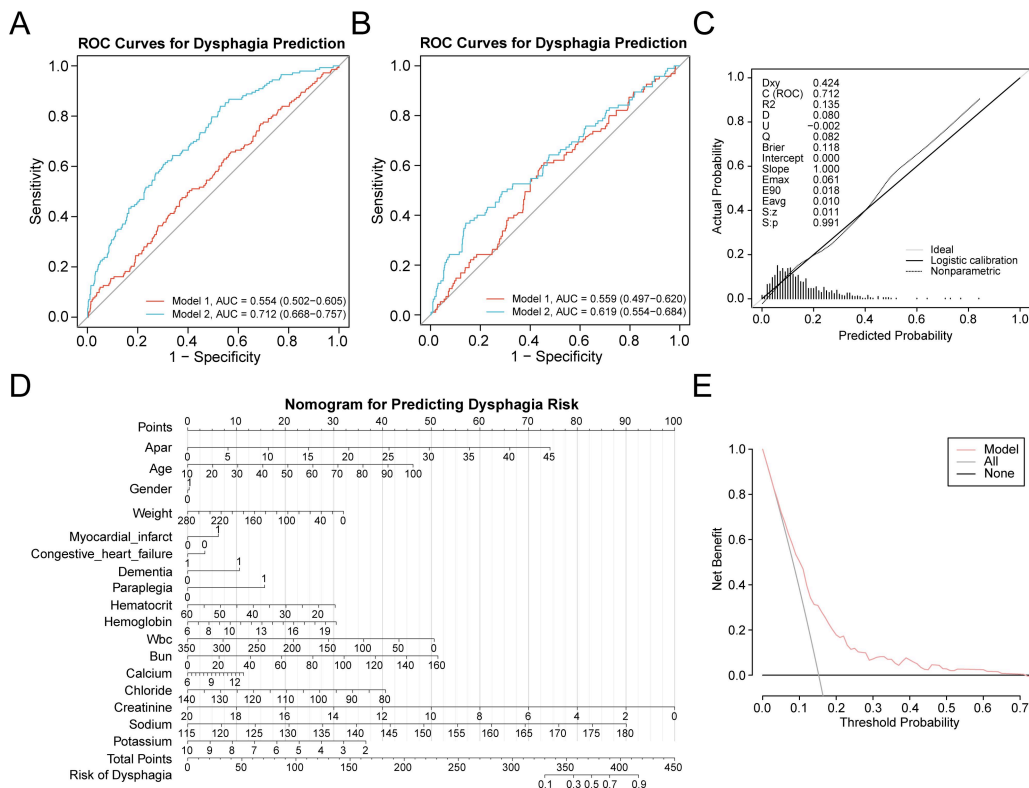


Fig.2 Diagnostic and Validation Analysis

Figure 2

See image above for figure legend.

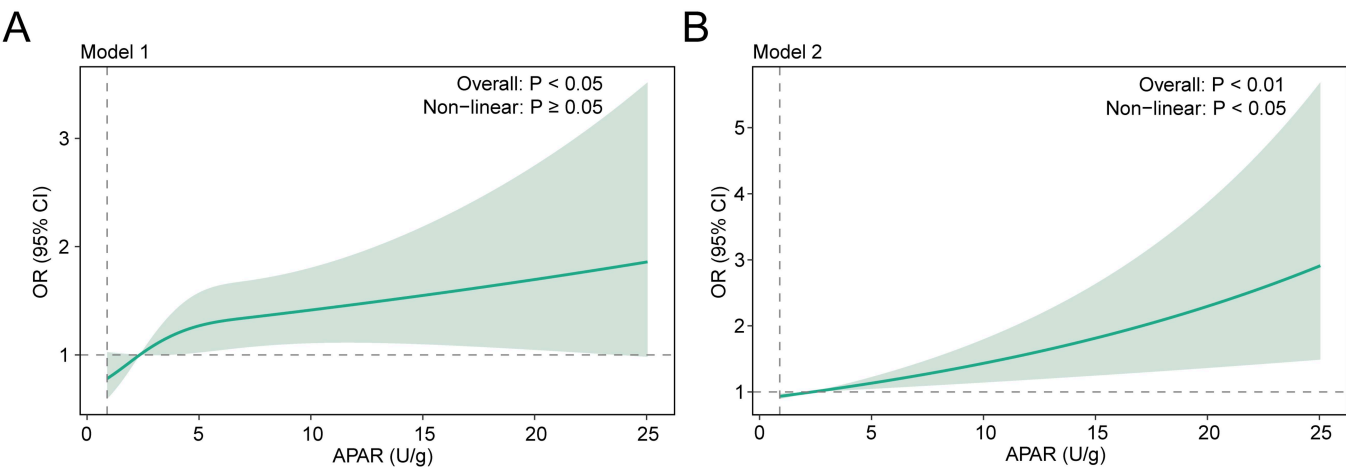


Fig.3 RCS Analysis of APAR with Dysphagia

Figure 3

See image above for figure legend.

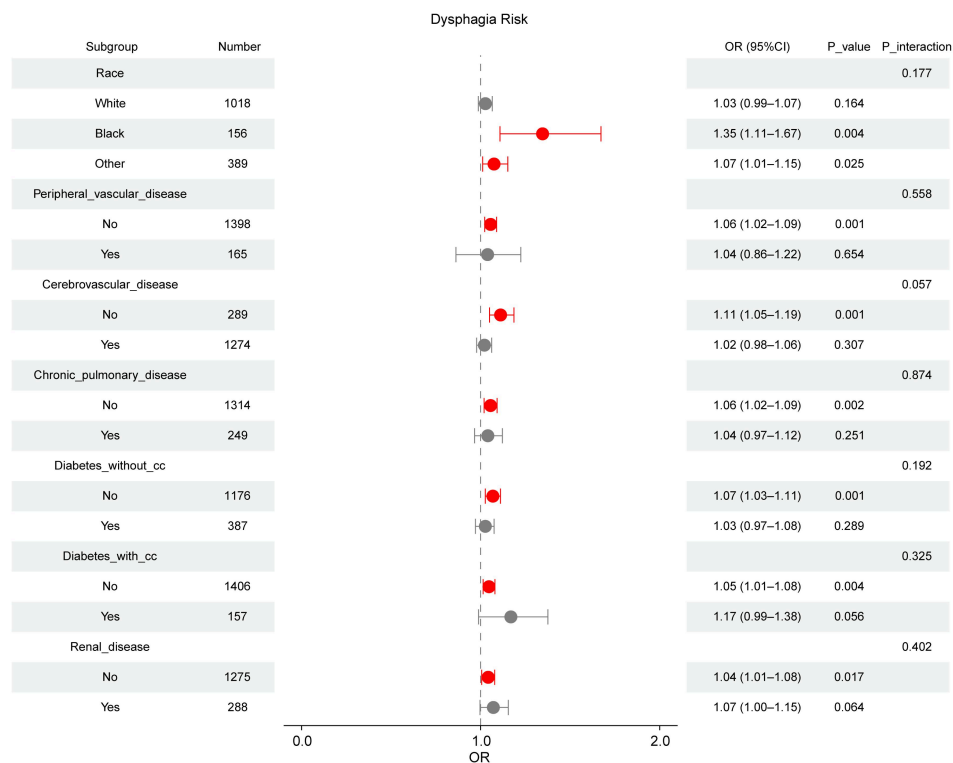


Fig.4 Subgroup Analysis for Dysphagia

Figure 4

See image above for figure legend.

Supplementary Files

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- [TableS1impdataCVA4.csv](#)