

Machine Learning–Driven Prediction of Early Enteral Nutrition Intolerance in ICU Patients Using Intra-Abdominal Pressure and Selected Gut Microbial Taxa

KAIHUI ZHENG¹, XUENA ZHANG¹, LISHI QU² and RENSHU WANG^{1*}

¹Department of Critical Care Medicine, Wenzhou Central Hospital, Wenzhou, China

²Department of Neonatology, The 2nd Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, China

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Abstract

To develop and validate a machine learning model integrating intra-abdominal pressure (IAP) and gut microbial characteristics for early identification of enteral nutrition intolerance (EENI) in critically ill ICU patients. This cohort study (January 2023–December 2025) included 300 ICU patients receiving early enteral nutrition. Baseline clinical characteristics, intra-abdominal pressure, laboratory indices, and quantitative gut microbial taxa were collected. Candidate predictors were selected using the least absolute shrinkage and selection operator regression, and independent predictors were incorporated into a multivariable logistic regression model, which was presented as a nomogram. Model performance was assessed using discrimination, calibration, and decision curve analyses. The incidence of EENI was 49.00% (147/300). LASSO selected 16 features: age, analgesic use, serum albumin, glucose, IAP, and the absolute counts of *Enterococcus*, *Bacteroides*, *Escherichia-Shigella*, *Klebsiella*, *Bifidobacterium*, and *Parabacteroides*. The absolute counts of *Enterococcus*, *Bacteroides*, *Escherichia-Shigella*, *Klebsiella*, *Bifidobacterium*, and *Parabacteroides* were significant independent predictors ($P < 0.05$). The model achieved an AUC of 0.900 (95% CI: 0.863–0.936) in the training set and 0.900 (95% CI: 0.859–0.941) in the validation set. Calibration was good (Hosmer-Lemeshow $P = 0.425$ and $P = 0.423$, respectively). DCA demonstrated clinical utility across a wide range of risk thresholds. The developed machine learning model, combining IAP and selected genus-level gut microbial markers, demonstrates strong predictive performance and clinical potential for forecasting and managing early enteral nutrition intolerance in ICU patients.

Key words: intensive care units, enteral nutrition, nutrition disorders, intra-abdominal hypertension, bacteria

Introduction

Patients admitted to intensive care units (ICUs) are typically in critical condition, frequently exhibiting physiological instability and dysfunction across multiple organ systems. This places them at high nutritional risk and necessitates the early initiation of nutritional support. Data from a recent cohort study demonstrated a strong correlation between patients' nutritional status during ICU stay and both the likelihood of requiring mechanical ventilation and in-hospital survival (Mohammadi et al. 2022). In light of these associations, the

American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Clinical Nutrition and Metabolism (ESPEN) have issued recommendations advocating for the initiation of enteral nutrition within 24 to 48 hours of ICU admission, provided that gastrointestinal (GI) function remains intact. This early nutritional support aims to fulfill metabolic requirements, prevent the onset of malnutrition (Singer et al. 2019; Taylor et al. 2016), bolster immune defenses, maintain intestinal mucosal integrity, and facilitate recovery (Shi et al. 2018).

* Corresponding author: R. Wang, Department of Critical Care Medicine, Wenzhou Central Hospital, Wenzhou, China; **e-mail:** Wangrenshu163@163.com

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Nevertheless, due to physiological stress responses and pharmacologic influences, some patients may develop impaired GI motility or mucosal barrier dysfunction, resulting in early enteral feeding intolerance. Reported rates of such intolerance among ICU patients receiving early enteral nutrition vary, ranging from 29.17% to 60.47% (Xu et al. 2024). Clinical indicators of enteral feeding intolerance may include elevated gastric residual volume, loose stools, and bloating or abdominal distension. These symptoms can disrupt enteral feeding schedules and may lead to reduced caloric intake (Salciute-Simene et al. 2021), which, in turn, can adversely affect clinical outcomes. Consequently, being able to recognize, in advance, which patients are more likely to experience intolerance to enteral nutrition is vital. Doing so would enable clinicians to apply personalized preventive strategies, improving prognosis and recovery trajectories.

Intra-abdominal pressure (IAP), the force exerted by abdominal contents against the internal walls of the cavity, plays a crucial role in sustaining organ perfusion, optimizing respiratory dynamics, and regulating systemic circulation. Studies have established an independent association between increased IAP and the onset of enteral feeding intolerance, suggesting that high IAP could be a risk factor for such complications (Murcia-Sáez et al. 2010). Additionally, IAP has emerged as a promising biomarker for predicting intolerance to enteral feeds (Chen et al. 2025). The gut microbiome is essential in preserving gastrointestinal tract integrity, influencing motility and digestion, and shaping immune responses in the host (Clemmensen et al. 2017). Studies have shown that individuals who develop feeding intolerance often exhibit reduced microbial diversity, diminished populations of beneficial microbes, and elevated levels of pathogenic organisms. Furthermore, specific gut microbial patterns have been associated with clinical signs of intolerance (Hu et al. 2021). Evidence from neonatal studies indicates that feeding intolerance may disrupt gut microbial balance, with a relative increase in *Klebsiella* species observed in affected preterm infants (Yuan et al. 2019). Despite these findings, most investigations into the gut microbiota–feeding intolerance relationship have focused on children, leaving a knowledge gap regarding this interaction in critically ill adults.

Although numerous predictive models have been proposed to assess the likelihood of intolerance to enteral nutrition, most rely heavily on clinical param-

eters, which often yield suboptimal predictive performance and are generally inadequate for early-stage risk detection.

Recent studies have increasingly focused on developing clinical prediction models for feeding intolerance in patients receiving enteral nutrition. For example, the NOFI model developed by Wang et al. (2023) incorporated primary diagnosis, acute gastrointestinal injury grade, and APACHE II score to predict enteral feeding intolerance in critically ill patients. Other models have been proposed for specific high-risk populations, including patients with sepsis and neurocritical illness, and have commonly incorporated variables such as age, disease severity scores, mechanical ventilation, feeding route, hyperglycemia, serum albumin, and intra-abdominal pressure. Recent systematic reviews have further highlighted that although these models show promising discriminatory performance, their methodological quality, external validation, and clinical generalizability remain variable. Importantly, most existing models rely primarily on clinical and laboratory variables, whereas few have incorporated gut microbiota features that may reflect early gastrointestinal ecological disruption before overt clinical intolerance develops. Therefore, the present study aimed to develop and validate a predictive model integrating intra-abdominal pressure, gut microbiota profiles, and routinely available clinical variables to enable early identification of enteral nutrition intolerance in ICU patients (Lu et al. 2022).

Although several predictive models have been proposed to estimate the risk of enteral nutrition intolerance, most have relied primarily on clinical, laboratory, and feeding-related variables. Recent models, including the NOFI model and models developed in neurocritical or septic populations, have incorporated variables such as disease severity scores, gastrointestinal injury grade, mechanical ventilation, feeding route, hyperglycemia, serum albumin, and intra-abdominal pressure. However, few models have incorporated specific gut microbial markers that may reflect early ecological disruption in the intestine before overt clinical intolerance develops. Therefore, this retrospective cohort study aimed to develop and validate a predictive model that integrates intra-abdominal pressure, selected genus-level gut microbial markers, and routinely available clinical variables to enable early identification of enteral nutrition intolerance in ICU patients.

Experimental

Materials and Methods

General information. Sample size calculation was conducted using PASS version 15.0. Preliminary pilot data indicated that when intra-abdominal pressure was below the average level, the baseline incidence of feeding intolerance during early enteral nutrition was estimated at $P = 0.192$. With an odds ratio (OR) of 1.639, a determination coefficient (R^2) of 0.078, a significance threshold of $\alpha = 0.05$, and a power of $\beta = 0.90$, the required sample size was determined to be 300. To achieve the study’s objectives, we retrospectively enrolled 300 critically ill individuals admitted to the intensive care unit (ICU) at our hospital between January 2023 and December 2025. Using a hold-out sampling approach, participants were randomly divided into a model development set ($n = 240$) and a validation group ($n = 60$), maintaining a 4-to-1 ratio. Inclusion criteria encompassed: (a) age ≥ 18 years; (b) initiation of enteral feeding within 24 to 48 hours after ICU admission; (c) continuation of enteral nutrition for more than 72 hours; (d) availability of complete clinical datasets, including measurements of intra-abdominal pressure and analysis of selected microbial taxa. Exclusion criteria: (a) death or transfer within 72 hours of admission; (b) pre-existing gastrointestinal diseases; (c) concomitant urinary system diseases; (d) gastrointestinal bleeding; (e) severe organ dysfunction; (f) malignancy; (g) pregnancy or lactation. This investigation was conducted under a waiver of informed consent. An overview of the study protocol and participant flow is shown in Fig. 1.

Data collection. The analytical dataset compiled for this study comprised a broad spectrum of clinical and biochemical parameters. These included demographic characteristics (age, sex), body mass index (BMI), illness severity scores based on the Acute Physiology and Chronic Health Evaluation II (APACHE II), therapeutic interventions (such as mechanical ventilation and therapeutic hypothermia), and administered medications (including sedatives, pain relievers, corticosteroids, and vasopressors). Additional data points related to enteral nutrition included the type of formula used, method of delivery, and feeding rate. Laboratory evaluations encompassed inflammatory and nutritional biomarkers: C-reactive protein (CRP), white blood cell (WBC) count, lymphocyte (Lym) and monocyte (Mon) counts, serum albumin (ALB), blood glucose (GLU), intra-abdominal pressure (IAP), and quanti-

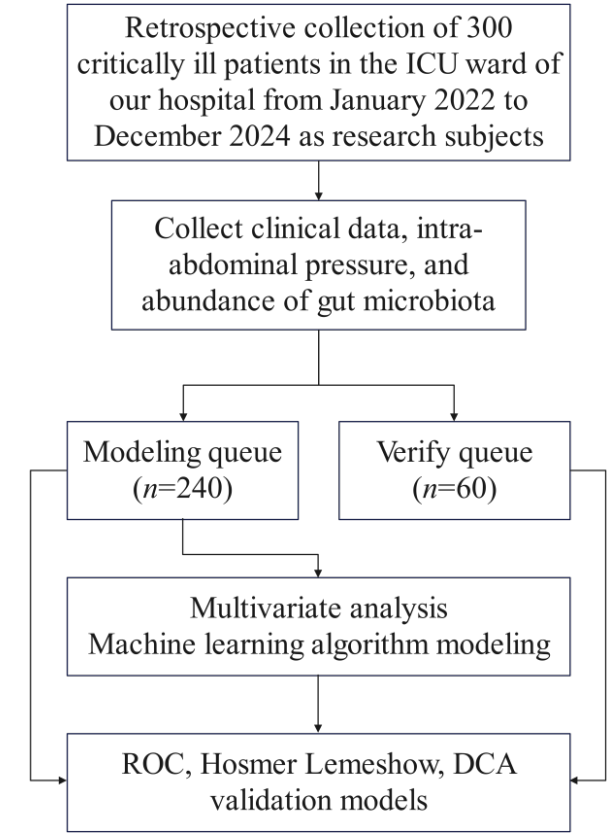


Fig. 1. Patient inclusion flowchart.

fied levels of gut microbial biomass. CRP was collected as a general systemic inflammatory marker and candidate covariate, rather than as a specific biomarker of enteral nutrition intolerance. It was included because systemic inflammation, sepsis, tissue injury, and disease severity may influence gastrointestinal function and feeding tolerance in critically ill patients.

Index detection methods. (a) Serum Biomarker Evaluation: Upon ICU entry, 5 milliliters of fasting venous blood were drawn from the antecubital vein. For sample processing, centrifugation was performed at 3000 rpm for 15 minutes at 4°C, using a rotor with a radius of 8 cm. The resulting supernatant serum was then carefully separated for downstream analysis. A fully automated hematology analyzer (Yumizen H2500, HORIBA ABX SAS) was used to quantify WBC, Lym, and Mon counts. Concentrations of CRP, ALB, and GLU were determined via a fully automated biochemical analyzer (TBA-FX8, Canon Medical Systems Corporation).

(b) Intra-Abdominal Pressure Monitoring: After ICU entry, all patients had a urinary catheter placed. With the patient lying supine, the bladder was emptied, and the catheter was temporarily clamped. A pressure transducer was then attached via the catheter,

and 25 ml of sterile saline (warmed to 37°C) was slowly infused into the bladder over more than one minute. Relaxation of the abdominal wall musculature was carefully maintained during measurement. To ensure measurement consistency, the pressure transducer was calibrated at the level where the midaxillary line intersects the iliac crest. IAP measurements were taken at the end of expiration, after the values had stabilized. This procedure was repeated three times, and the average value was recorded. Aseptic technique was strictly maintained throughout.

(c) Quantification of Gut Microbiota Absolute Abundance: Within 24 hours following ICU admission, each patient provided a 2 g morning stool sample, which was immediately stored at -80°C. All specimens were transported to the testing facility within 1 hour of collection. After thawing, 0.2 g of stool was subjected to DNA extraction using a commercial fecal genomic DNA kit (QIAGEN, Catalog No. 51604), according to the manufacturer's protocol. DNA concentration and purity were determined using a NanoDrop 2000c UV spectrophotometer (Thermo Fisher Scientific), and DNA integrity was evaluated by electrophoresis on a 1% agarose gel. Specific primers targeting selected gut microbial taxa were used for PCR amplification. Plasmid standards were prepared for each targeted taxon, and copy numbers were calculated according to plasmid DNA molecular weight and concentration. Standard curves were established using log-transformed copy numbers and Ct values. The absolute abundance of each targeted microbial taxon was then calculated. To reduce model dimensionality and avoid overfitting, given the available sample size, subsequent modeling was restricted to the 10 most abundant genus-level taxa. These variables should therefore be interpreted as selected genus-level microbial markers rather than a comprehensive assessment of the entire gut microbiome. The combined term *Escherichia-Shigella* was retained because the assay could not reliably distinguish closely related members of these genera at the species level.

Criteria for identifying feeding intolerance during early enteral nutrition. According to the European Society of Intensive Care Medicine guidelines: ESICM Recommendations: Terminology, Definitions, and Management of Gastrointestinal Function in Critically Ill Patients (Reintam Blaser et al. 2012) feeding intolerance during early enteral nutrition is diagnosed when at least one of the following criteria is met: (a) enteral feeding is halted due to gastrointestinal disturbances, including but not limited to vomiting, diarrhea, abdominal distension, constipation, gastroesophageal

reflux, gastrointestinal bleeding, or hypoactive/absent bowel sounds; (b) a single-day gastric residual volume reaches or exceeds 500 ml; (c) the prescribed energy intake of 83.6 kJ/(kg·day) via early enteral feeding is not achieved after 72 hours of nutritional intervention.

Statistical analysis. All statistical analyses were performed using SPSS software version 27.0. To assess the distribution of continuous variables, the Kolmogorov-Smirnov test was applied. When data were normally distributed, results were expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$), and comparisons across groups were made using independent-samples t-tests. If normality assumptions were violated, results were presented as median and interquartile range (M (P25, P75), and group differences were evaluated using the Mann-Whitney U test. For categorical variables, data were summarized as frequency and percentage n (%), and the chi-square test (χ^2) was used for intergroup comparisons. To identify significant predictors, LASSO (least absolute shrinkage and selection operator) regression was employed for feature selection. Subsequently, a nomogram was developed in R version 4.4.3, based on the identified predictors. The model's discrimination performance was assessed using ROC (receiver operating characteristic) curve analysis, while calibration was examined via the Hosmer-Lemeshow goodness-of-fit test and plotted calibration curves. In addition, decision curve analysis (DCA) was conducted to evaluate the model's potential clinical value. A p-value less than 0.05 was considered indicative of statistical significance.

Given the modest size of the validation cohort and the expected heterogeneity of selected microbial taxa in critically ill patients, model performance was interpreted cautiously. The hold-out validation results were considered preliminary internal validation, and the need for further external validation in larger multicenter cohorts was acknowledged as an important limitation.

Results

Clinical characteristic comparison. Out of the 300 ICU patients analyzed, 147 individuals (49.00%) experienced feeding intolerance during the early phase of enteral nutrition. There were no statistically significant differences in baseline characteristics between the model construction group and the validation group ($P > 0.05$), indicating a comparable distribution of clinical variables between the two cohorts. Details of patient characteristics for each group are summarized in Table I.

Table I
Baseline clinical characteristics of the model development and validation cohorts.

Variable	Modeling cohort (n = 240)	Validation cohort (n = 60)	χ^2/t	P
Feeding Intolerance during early enteral nutrition			0.013	0.908
No	122 (50.83)	31 (51.67)		
Yes	118 (49.17)	29 (48.33)		
Sex			0.004	0.952
Male	153 (63.75)	38 (63.33)		
Female	87 (36.25)	22 (36.67)		
Age (years)	62.10 ± 6.18	62.77 ± 6.02	-0.755	0.451
BMI (kg/m ²)	22.49 ± 2.43	22.27 ± 2.66	0.601	0.548
APACHE II score (points)	20.41 ± 5.60	20.72 ± 5.15	-0.382	0.703
Treatment strategies				
Mechanical ventilation	171 (71.25)	43 (71.67)	0.004	0.949
Mild hypothermia therapy	11 (4.58)	2 (3.33)	0.005	0.943
Medication use				
Vasoactive agents	142 (59.17)	35 (58.33)	0.014	0.907
Glucocorticoids	51 (21.25)	13 (21.67)	0.005	0.944
Analgesics	120(50.00)	31(51.67)	0.053	0.817
Sedatives	125(52.08)	32(53.33)	0.030	0.862
Type of early enteral nutrition formula			0.015	0.903
Whole protein	158(65.83)	40(66.67)		
Peptide-based	82(34.17)	20(33.33)		
Early enteral nutrition administration method			0.083	0.773
Intermittent early enteral nutrition	117(48.75)	28(46.67)		
Continuous early enteral nutrition	123(51.25)	32(53.33)		
Feeding rate (ml/h)	40.29 ± 4.99	40.78 ± 5.49	-0.668	0.504
Biochemical indicators				
CRP (mg/l)	30.38 ± 14.07	31.19 ± 14.52	-0.396	0.693
WBC (×10 ⁹ /l)	10.41 ± 3.41	10.76 ± 3.52	-0.701	0.484
Lym (×10 ⁹ /l)	6.88 ± 2.66	6.79 ± 2.41	0.254	0.800
Mon (×10 ⁹ /l)	4.62 ± 1.75	4.39 ± 1.90	0.865	0.388
ALB (g/l)	32.52 ± 4.55	32.85 ± 4.25	-0.507	0.612
GLU (mmol/l)	8.01 ± 1.92	7.83 ± 1.58	0.679	0.498
IAP (mmHg)	15.42 ± 3.56	15.34 ± 3.99	0.161	0.873
Absolute abundance of gut microbiota (×10 ⁹ copies/g)				
<i>Enterococcus</i>	37.55 ± 14.57	37.67 ± 20.26	-0.052	0.959
<i>Bacteroides</i>	23.03 ± 4.78	23.91 ± 4.45	-1.285	0.200
<i>Escherichia-Shigella</i>	6.83 ± 2.40	6.79 ± 2.68	0.122	0.903
<i>Alistipes</i>	4.20 ± 2.24	4.24 ± 2.32	-0.126	0.900
<i>Klebsiella</i>	0.78 ± 0.34	0.82 ± 0.33	-0.779	0.437
<i>Bifidobacterium</i>	5.64 ± 2.39	5.75 ± 2.59	-0.300	0.765
<i>Parabacteroides</i>	6.19 ± 3.04	6.28 ± 2.99	-0.188	0.851
<i>Sphingomonas</i>	0.96 ± 0.64	1.09 ± 0.67	-1.416	0.158
<i>Erysipelatoclostridium</i>	2.16 ± 1.11	2.11 ± 1.12	0.319	0.750
<i>Subdoligranulum</i>	3.60 ± 1.69	3.70 ± 1.61	-0.409	0.683

Data are presented as n (%) for categorical variables and mean ± standard deviation for normally distributed continuous variables. BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II; CRP, C-reactive protein; WBC, white blood cell count; Lym, lymphocyte count; Mon, monocyte count; ALB, albumin; GLU, glucose; IAP, intra-abdominal pressure.

Table II
Comparison of clinical characteristics between non-feeding intolerance and feeding intolerance patients during early enteral nutrition in the modeling cohort [*n* (%), ($\bar{x} \pm s$)].

Variable	Non-feeding intolerance (n = 122)	Feeding intolerance (n = 118)	χ^2/t	<i>P</i>
Sex			0.556	0.456
Male	75(61.48)	78(66.10)		
Female	47(38.52)	40(33.90)		
Age (years)	60.41 $\pm$ 6.26	63.84 $\pm$ 5.62	-4.461	<0.001
BMI (kg/m ²)	22.47 $\pm$ 2.38	22.50 $\pm$ 2.49	-0.102	0.919
APACHE II score (points)	19.83 $\pm$ 5.79	21.02 $\pm$ 5.36	-1.649	0.100
Treatment strategies				
Mechanical ventilation	79(64.75)	92(77.97)	5.111	0.024
Mild hypothermia therapy	5(4.10)	6(5.08)	0.133	0.715
Medication use				
Vasoactive agents	69(56.56)	73(61.86)	0.699	0.403
Glucocorticoids	26(21.31)	25(21.19)	0.001	0.981
Analgesics	52(42.62)	68(57.63)	5.402	0.020
Sedatives	54(44.26)	71(60.17)	6.082	0.014
Type of early enteral nutrition formula			1.626	0.202
Whole protein	85(69.67)	73(61.86)	-	-
Peptide-based	37(30.33)	45(38.14)	-	-
Early enteral nutrition administration method			4.849	0.028
Intermittent early enteral nutrition	68(55.74)	49(41.53)	-	-
Continuous early enteral nutrition	54(44.26)	69(58.47)	-	-
Feeding rate (ml/h)	39.46 $\pm$ 5.37	41.15 $\pm$ 4.43	-2.659	0.008
Biochemical indicators				
CRP (mg/l)	28.66 $\pm$ 14.66	32.16 $\pm$ 13.25	-1.935	0.054
WBC($\times 10^9$ /l)	9.95 $\pm$ 2.61	10.88 $\pm$ 4.04	-2.108	0.036
Lym($\times 10^9$ /l)	6.74 $\pm$ 2.45	7.03 $\pm$ 2.86	-0.850	0.396
Mon($\times 10^9$ /l)	4.46 $\pm$ 1.67	4.77 $\pm$ 1.83	-1.367	0.173
ALB (g/l)	33.11 $\pm$ 4.87	31.91 $\pm$ 4.12	2.054	0.041
Glucose (mmol/l)	7.36 $\pm$ 1.64	8.68 $\pm$ 1.96	-5.658	<0.001
IAP (mmHg)	14.30 $\pm$ 2.67	16.58 $\pm$ 3.97	-5.255	<0.001
Absolute abundance of gut microbiota ($\times 10^9$ copies/g)				
<i>Enterococcus</i>	34.51 $\pm$ 10.64	40.69 $\pm$ 17.24	-3.357	0.001
<i>Bacteroides</i>	24.36 $\pm$ 4.71	21.66 $\pm$ 4.48	4.538	<0.001
<i>Escherichia-Shigella</i>	7.53 $\pm$ 2.86	6.11 $\pm$ 1.51	4.797	<0.001
<i>Alistipes</i>	4.39 $\pm$ 2.48	4.00 $\pm$ 1.95	1.339	0.182
<i>Klebsiella</i>	0.74 $\pm$ 0.19	0.82 $\pm$ 0.44	-1.863	0.064
<i>Bifidobacterium</i>	5.18 $\pm$ 1.92	6.12 $\pm$ 2.73	-3.104	0.002
<i>Parabacteroides</i>	6.51 $\pm$ 3.23	5.87 $\pm$ 2.81	1.637	0.103
<i>Sphingomonas</i>	0.90 $\pm$ 0.54	1.02 $\pm$ 0.73	-1.437	0.152
<i>Erysipelatoclostridium</i>	2.30 $\pm$ 1.16	2.01 $\pm$ 1.05	2.085	0.038
<i>Subdoligranulum</i>	3.64 $\pm$ 1.77	3.55 $\pm$ 1.62	0.404	0.686

Comparison of clinical characteristics between non-feeding intolerance and feeding intolerance patients during early enteral nutrition in the modeling cohort. Univariate analysis was first performed using clinical data obtained from patients in the modeling cohort. The analysis identified statistically significant differences between patients who developed feeding intolerance and those who did not. These differences were observed in variables such as patient age, use of mechanical ventilation, administration of sedatives and analgesics, mode of early enteral nutrition delivery, infusion speed, white blood cell (WBC) count, serum albumin, blood glucose levels, intra-abdominal pressure (IAP), and absolute abundances of several gut microbes, including *Enterococcus*, *Bacteroides*, *Escherichia-Shigella*, *Bifidobacterium*, and *Erysipelatoclostridium*. CRP levels tended to be higher in patients with feeding intolerance than in those without ($P = 0.054$). CRP was not retained by LASSO regression and was therefore not included as an independent predictor in the final multivariable model. Additional details can be found in Table II.

Key variable selection via LASSO regression. Subsequently, the least absolute shrinkage and selection operator (LASSO) regression was applied to screen for variables potentially associated with early-phase enteral feeding intolerance, which was treated as the primary outcome. Thirty clinical indicators were included as independent variables. The analysis identified a minimum penalty value ($\lambda_{\min}$) of 0.017 and a one-standard-error value (λ_{1se}) of 0.043. Based on these thresholds, 22 predictors were retained under $\lambda_{\min}$, while 16 variables were selected using λ_{1se} . To achieve a balance between reducing binomial deviance and preventing overfitting caused by too many covariates, λ_{1se} was chosen as the final criterion for variable selection in this study. Ultimately, 16 variables were retained: age, mechanical ventilation, use of analgesics, early enteral nutrition administration method, feeding rate, white blood cell count (WBC), albumin (ALB), blood glucose (GLU), intra-abdominal pressure, and the absolute abundances of *Enterococcus*, *Bacteroides*, *Escherichia-Shigella*, *Klebsiella*, *Bifidobacterium*, *Parabacteroides*, and *Erysipelatoclostridium*. See Fig. 2 for details.

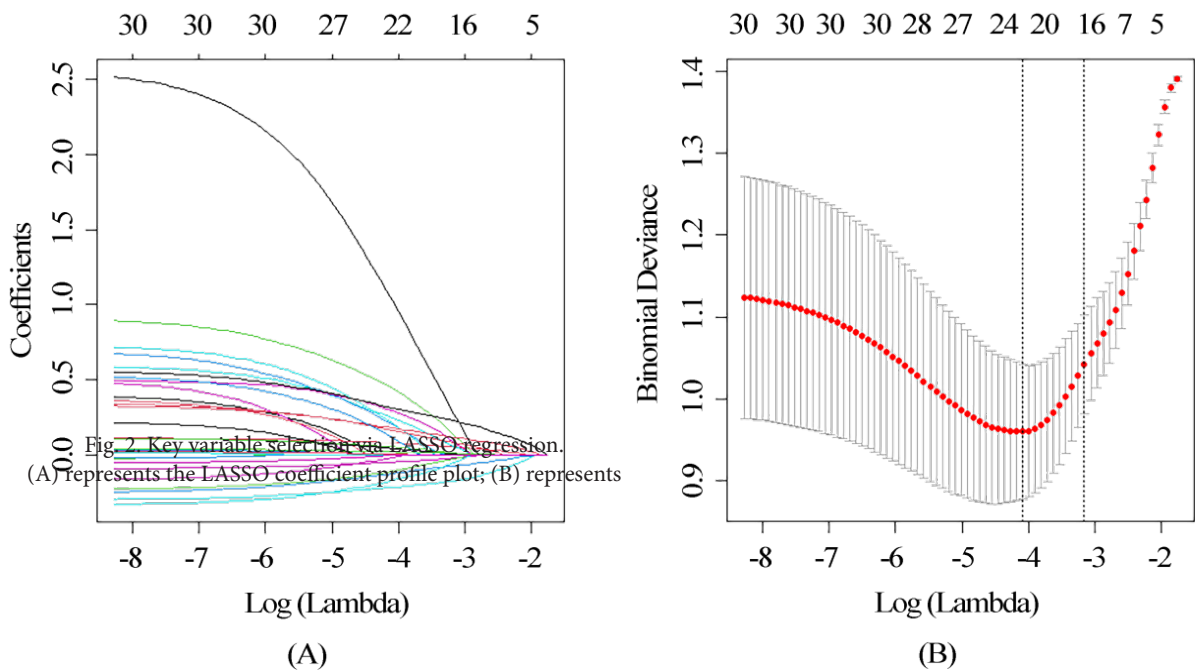


Fig. 2. Key variable selection via LASSO regression. (A) represents the LASSO coefficient profile plot; (B) represents the LASSO cross-validation curve.

Multivariate logistic regression analysis of risk factors for feeding intolerance in ICU patients receiving early enteral nutrition. A multivariate logistic regression model was constructed using clinical and biochemical data collected from the

development cohort. The dependent variable was defined as the occurrence of feeding intolerance during the initial phase of enteral nutrition administration in ICU settings. Sixteen predictors previously shortlisted via LASSO regression were incor-

Table III
Multivariate logistic regression analysis of risk factors for feeding intolerance in ICU patients receiving early enteral nutrition.

Variable	B	S.E.	waldχ ²	P	OR	95%CI	
						Lower limit	Upper limit
Age	0.112	0.037	9.280	0.002	1.118	1.041	1.202
Mechanical ventilation (Yes)	0.512	0.457	1.259	0.262	1.669	0.682	4.084
Analgesics (Yes)	0.880	0.415	4.498	0.034	2.412	1.069	5.440
Early enteral nutrition method (Continuous)	0.646	0.406	2.534	0.111	1.907	0.861	4.224
Feeding rate	0.079	0.043	3.404	0.065	1.082	0.995	1.177
WBC	0.121	0.063	3.614	0.057	1.128	0.996	1.278
ALB	-0.091	0.045	4.116	0.042	0.913	0.837	0.997
GLU	0.470	0.120	15.353	<0.001	1.601	1.265	2.025
IAP	0.282	0.068	17.367	<0.001	1.326	1.161	1.514
Absolute abundance of gut microbiota							
<i>Enterococcus</i>	0.036	0.014	6.707	0.010	1.037	1.009	1.066
<i>Bacteroides</i>	-0.200	0.050	15.881	<0.001	0.819	0.742	0.903
<i>Escherichia-Shigella</i>	-0.320	0.096	11.238	0.001	0.726	0.602	0.875
<i>Klebsiella</i>	1.988	0.676	8.653	0.003	7.304	1.942	27.478
<i>Bifidobacterium</i>	0.301	0.094	10.232	0.001	1.351	1.123	1.624
<i>Parabacteroides</i>	-0.210	0.069	9.229	0.002	0.811	0.708	0.928
<i>Erysipelatoclostridium</i>	-0.361	0.187	3.719	0.054	0.697	0.483	1.006
Constant	-13.459	3.871	12.089	0.001	0		

porated into the model as independent variables to assess their contributions to the risk of feeding intolerance. The results demonstrated that multiple factors showed a statistically significant association with feeding intolerance among ICU patients receiving early enteral support. These included older age, use of analgesic drugs, lower serum albumin (ALB)

concentrations, elevated blood glucose (GLU) levels, higher intra-abdominal pressure (IAP), and absolute abundances of specific gut microbial genera *Enterococcus*, *Bacteroides*, *Escherichia-Shigella*, *Klebsiella*, *Bifidobacterium*, and *Parabacteroides* ($P < 0.05$). A complete summary of these findings is presented in Table III.

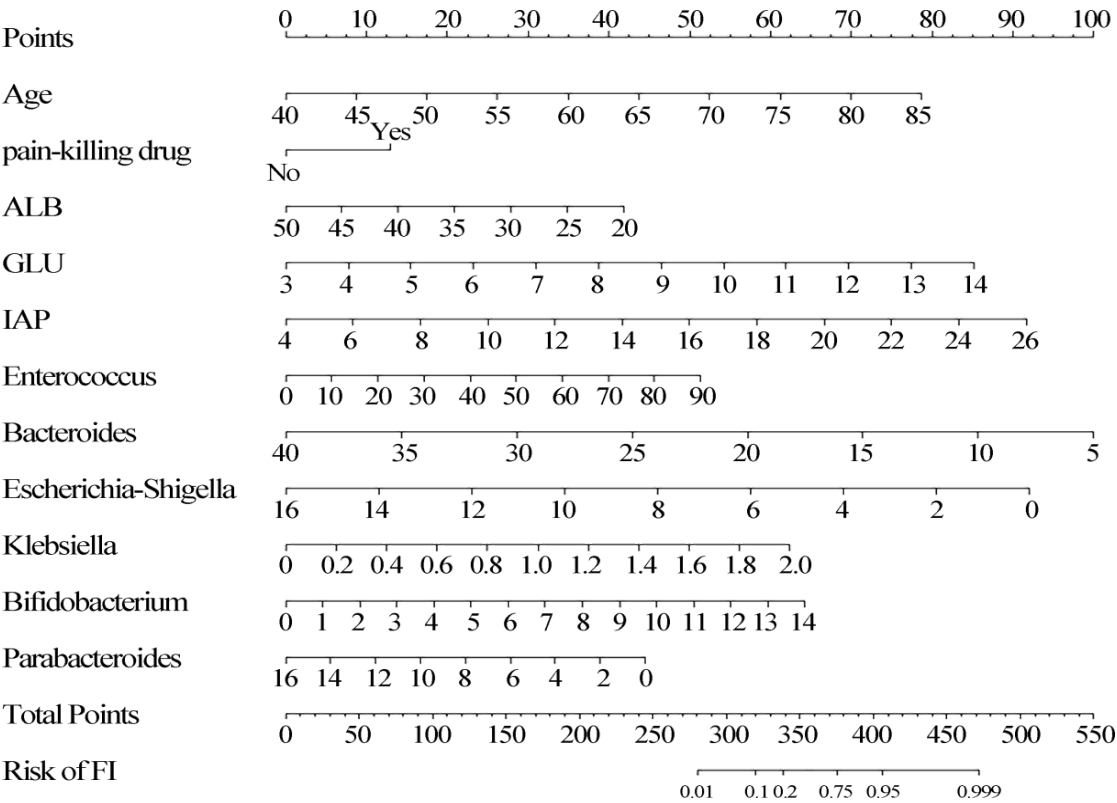


Fig. 3. Development of a predictive nomogram for early enteral feeding intolerance in ICU patients.

Development of a predictive nomogram for early enteral feeding intolerance in ICU patients. A predictive nomogram was developed, incorporating 11 independent predictors of feeding intolerance in critically ill patients receiving early enteral nutrition. The model assigns a cumulative score ranging from 0 to 550, where a higher total score correlates with an increased likelihood of developing intolerance during nutritional therapy. For instance, a patient score of 280 is associated with an estimated 1% risk of intolerance, while a score of 472 predicts a probability of 99.9%. A graphical representation of the nomogram is provided in Fig. 3.

Assessment of predictive performance in the ICU population receiving early enteral nutrition. To evaluate how well the model distinguishes between patients who do and do not develop feeding intolerance, a receiver operating characteristic (ROC) curve analysis was performed. The resulting area under the ROC curve (AUC) was 0.900 (95% confidence interval [CI]: 0.863–0.936) in the training dataset and identically 0.900 (95% CI: 0.859–0.941) in the validation set, indicating outstanding discriminatory capability. The model showed good discrimination in the develop-

ment cohort and maintained comparable performance in the hold-out validation cohort. However, because the validation cohort was relatively small, these results should be interpreted as preliminary internal validation rather than definitive evidence of generalizability. ROC curves are shown in Fig. 4. The Hosmer–Lemeshow goodness-of-fit test showed no statistically significant lack of fit in either the development cohort ($\chi^2 = 8.086$, $P = 0.425$) or the validation cohort ($\chi^2 = 8.089$, $P = 0.423$), indicating acceptable agreement between predicted and observed probabilities. A visual display of the calibration results is shown in Fig. 5.

Clinical utility of the predictive model for early enteral nutrition intolerance in critically ill patients. To evaluate the model’s practical significance, decision curve analysis (DCA) was conducted. Results showed that, over the full range of threshold probabilities (0 to 1.0), applying the nomogram to inform clinical decisions resulted in a higher net clinical benefit in both the development and validation sets compared with default approaches of treating all patients or none. These results indicate that the model possesses considerable value in clinical practice. See Fig. 6 for details.

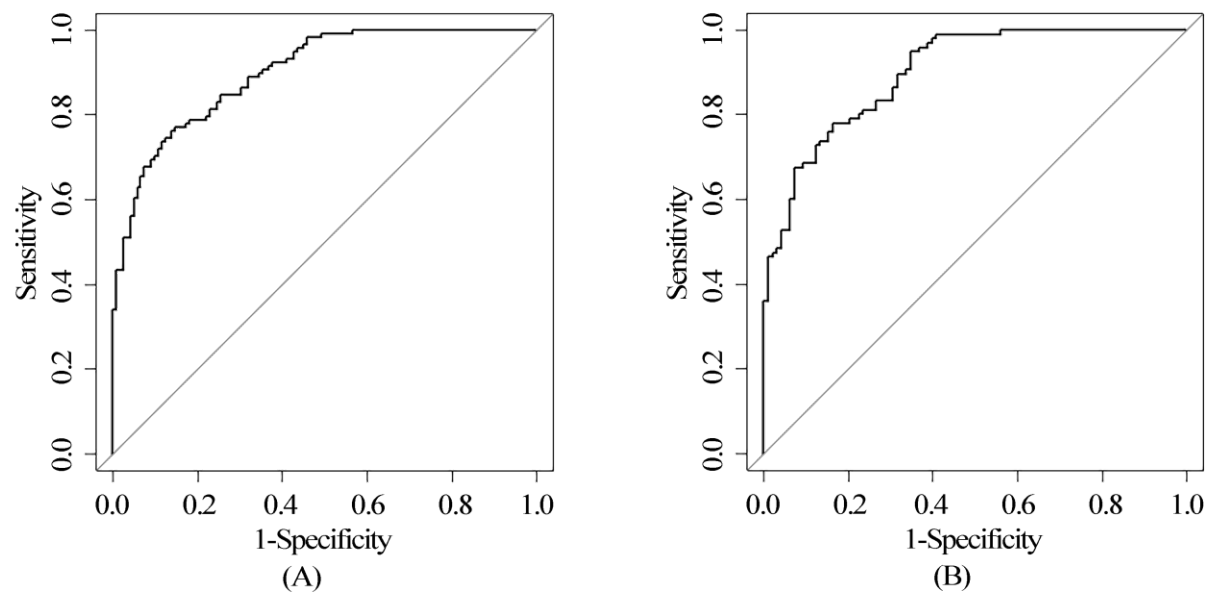


Fig. 4. Receiver operating characteristic (ROC) curves demonstrating the model’s ability to predict feeding intolerance during the early phase of enteral nutrition in patients admitted to the ICU, (A) Modeling cohort; (B) Validation cohort.

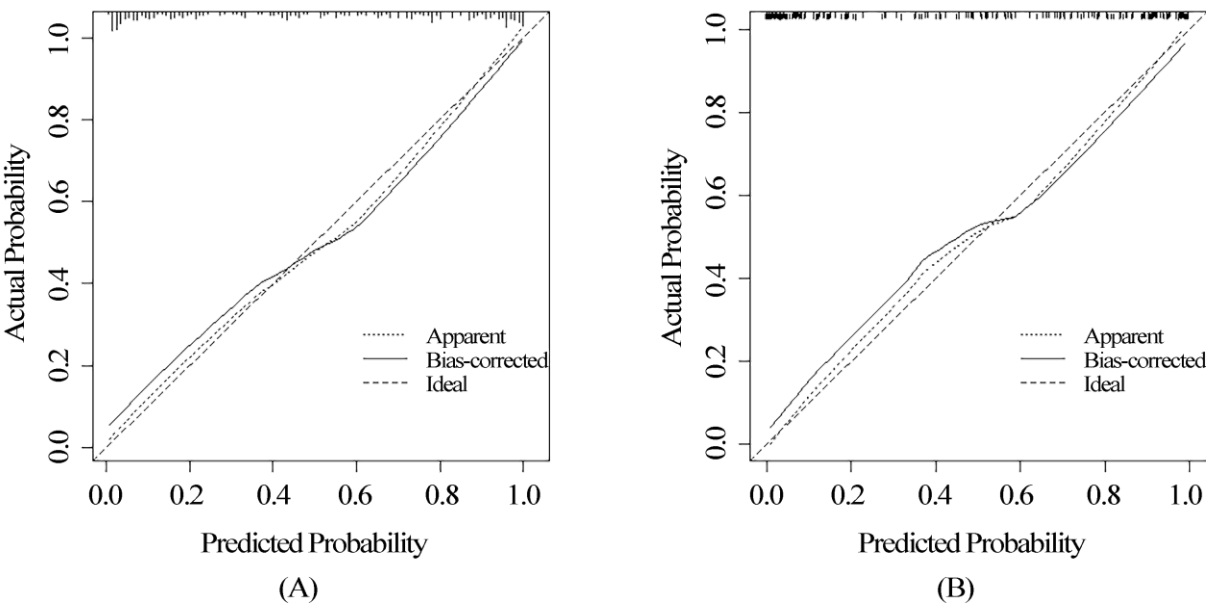


Fig. 5. Calibration charts illustrating the consistency between estimated risk probabilities and actual outcomes for feeding intolerance in ICU patients undergoing early enteral nutrition; (A) Modeling cohort; (B) Validation cohort.

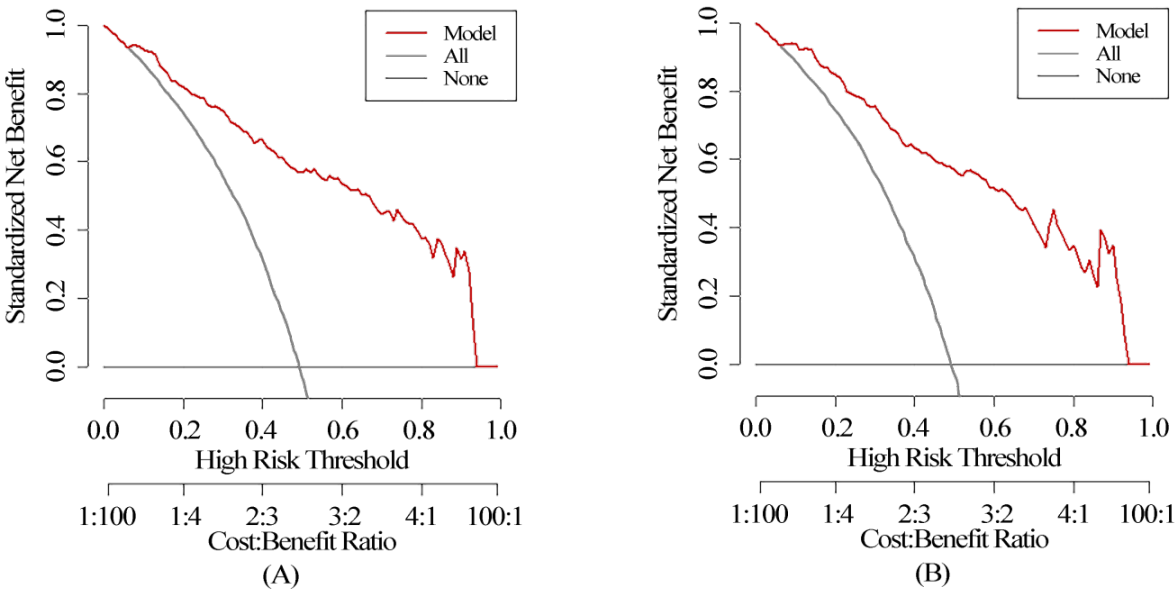


Fig. 6. Decision curve analysis (DCA) evaluating the net clinical benefit of the predictive model across a range of decision thresholds in the ICU population receiving early enteral feeding; (A) Modeling cohort; (B) Validation cohort.

Discussion

Among the 300 ICU patients included in this study, feeding intolerance occurred in 49.00% during the initial phase of enteral nutritional support. This observed rate aligns with previously published data regarding the prevalence of intolerance to early enteral nutrition in critically ill cohorts (Xiao and Xu 2023). Prior studies have indicated that intolerance to early enteral feeding may adversely affect clinical outcomes in intensive care settings. Therefore, identifying relevant risk factors and implementing appropriate preventive measures are essential for reducing the risk of feeding intolerance and improving prognosis in this vulnerable population.

Intra-abdominal pressure has gained widespread clinical application due to its simplicity, noninvasiveness, high measurement accuracy, and minimal susceptibility to operator-dependent variation or interference from underlying disease conditions (Maddison et al. 2016). Studies have shown that elevated intra-abdominal pressure significantly reduces gastrointestinal blood perfusion, causes villous injury and mucosal bleeding, and leads to mesenteric compression with impaired venous return. These changes contribute to intestinal edema and delayed gastric emptying, ultimately resulting in gastrointestinal dysfunction (Cheng et al. 2013). Under such conditions, initiating early enteral nutrition carries a high risk of inducing feeding intolerance.

Moreover, the development of feeding intolerance can further exacerbate dyspepsia and delayed gastric emptying, increasing the volume of intra-abdominal contents and thereby raising intra-abdominal pressure, forming a vicious cycle. The results further confirmed that intra-abdominal pressure (IAP) is an independent risk factor for intolerance to early enteral nutrition in critically ill patients in ICU settings. Notably, patients presenting with elevated IAP at the time of admission exhibited a significantly increased likelihood of developing feeding intolerance—a pattern that aligns with conclusions drawn in previous investigations (Bejarano et al. 2013).

CRP was evaluated as a nonspecific marker of systemic inflammation rather than as a direct indicator of enteral nutrition intolerance. Although systemic inflammation may contribute to gastrointestinal dysfunction through impaired perfusion, mucosal injury, altered motility, and increased metabolic stress, CRP can also be elevated in sepsis, trauma, tissue injury, and organ dysfunction. In our cohort, CRP showed only a borderline difference between patients with and without feeding intolerance and was not retained in the final prediction model. Therefore, our findings do not support CRP as an independent or specific predictor of early enteral nutrition intolerance.

Gastrointestinal functionality and homeostasis are closely associated with gut microbiota diversity. The abundance of fecal microbial populations is consid-

ered an indicator of intestinal health and functional stability; however, in healthy hosts, microbial abundance more accurately reflects ecological succession during gut development rather than the community's resilience (Falony et al. 2018). According to findings from an observational study, patients who developed feeding intolerance during the initial day of enteral nutrition exhibited notably higher relative abundances of *Enterococcus* and *Klebsiella*, along with a reduction in *Parabacteroides*. These microbial shifts may indicate an increased susceptibility to intra-abdominal infection. By the third day of enteral nutrition, patients with feeding intolerance had elevated levels of *Enterococcus* and *Sphingomonas*, and reduced levels of *Bifidobacterium*. Notably, *Sphingomonas* infection is often associated with gastrointestinal symptoms, skin manifestations, and systemic signs, while *Bifidobacterium*, a well-known probiotic, is essential for intestinal homeostasis; its depletion may signal microbial imbalance and contribute to acute or chronic diarrhea and intestinal inflammation (Xu et al. 2022).

In this study, microbial predictors were analyzed and reported primarily at the genus level. Therefore, the findings should be interpreted as associations between selected genus-level microbial markers and early enteral nutrition intolerance, rather than species-level effects. To avoid taxonomic ambiguity, species-level names such as *C. perfringens* were not used interchangeably with genus-level variables such as *Erysipelatoclostridium*. Similarly, *Escherichia-Shigella* was reported as a combined taxonomic group when species-level discrimination was not possible. This standardized nomenclature provides consistency between the text, tables, and predictive model. In this study, five bacterial genera were found to differ markedly in relative abundance between patients who developed feeding intolerance and those who did not. Further multivariate analysis revealed that six microbial genera *Enterococcus*, *Bacteroides*, *Escherichia-Shigella*, *Klebsiella*, *Bifidobacterium*, and *Parabacteroides* served as independent risk indicators for intolerance to early enteral feeding. Among them, *Parabacteroides* has been reported to exert beneficial effects in metabolic diseases (Ojima et al. 2016). Specifically, we observed a marked decline in the absolute abundance of *Parabacteroides* among individuals with feeding intolerance. However, whether this genus exerts a protective influence during the early phase of enteral nutrition remains an open question requiring further investigation.

To reduce the influence of potential confounders, we performed a multivariate regression analysis. The analysis identified multiple independent predictors of feeding intolerance among critically ill patients receiving early enteral nutrition in the ICU. These included older age, analgesic administration, low serum albumin, and elevated blood glucose levels. With aging, the jejunal villi become progressively sparser, shorter, and blunter, accompanied by mucosal atrophy and a decline in digestive and absorptive function (Yuan et al. 2024), which may increase susceptibility to feeding intolerance. In the context of pain management, opioid-based analgesics exert their effects by activating opioid receptors located in the gastrointestinal tract, which leads to increased smooth muscle tone and suppression of intestinal motility. Furthermore, opioid administration is recognized for its role in stimulating the vestibular nuclei and the chemoreceptor trigger zone, which increases vagal nerve sensitivity and contributes to gastrointestinal disturbances such as nausea and emesis (Zhang et al. 2023). Albumin plays a critical role in sustaining colloid osmotic pressure. In the intensive care setting, patients frequently experience a heightened catabolic state and reduced anabolic activity, primarily due to severe physiological stress and inadequate caloric provision, ultimately resulting in protein breakdown. A decline in serum albumin may reduce plasma colloid osmotic pressure, resulting in fluid redistribution and interstitial retention. This can cause mucosal edema in the intestines, further aggravating gastrointestinal symptoms and increasing the risk of feeding intolerance. Furthermore, hyperglycemia has been associated with impaired gastric motility and delayed relaxation of the gastric fundus, both of which can contribute to slowed gastric emptying and elevate the risk of feeding intolerance (Mesotten et al. 2015).

The present model should be interpreted in the context of recently developed prediction tools for feeding intolerance. Previous models have generally relied on demographic variables, disease severity scores, gastrointestinal function indicators, feeding-related variables, and routine laboratory parameters. The NOFI model, for instance, identified primary diagnosis, AGI grade, and APACHE II score as key predictors in critically ill patients, whereas models developed in neurocritical or septic populations have incorporated factors such as GCS score, mechanical ventilation, feeding route, hyperglycemia, and serum albumin. More recent ICU-based nomograms have also includ-

ed intra-abdominal pressure as a clinically relevant predictor, supporting the role of gastrointestinal pressure dynamics in the development of enteral nutrition intolerance (Yuan et al. 2024).

Compared with these prior models, the main contribution of the present study is the integration of gut microbiota absolute abundance data with intra-abdominal pressure and conventional clinical variables. This approach may capture both mechanical and microbial dimensions of gastrointestinal dysfunction. The model achieved an AUC of 0.900 in both the development and validation cohorts, with acceptable calibration and favorable decision curve analysis, suggesting potential value for early risk stratification. Nevertheless, unlike some externally validated models, our model was validated only with an internal hold-out cohort; therefore, multicenter external validation is needed before routine clinical implementation (Cao et al. 2025; Chen et al. 2025).

Machine learning serves as a foundational component of artificial intelligence. Among its various algorithmic approaches, logistic regression is particularly well-suited to clinical prediction tasks. This method enables the integration of multiple risk factors into a nomogram, offering a visual representation of how predictors relate to clinical outcomes. Such visualization aids clinicians in swiftly recognizing key contributors to adverse events. In this study, a logistic regression-based predictive model was constructed incorporating intra-abdominal pressure, gut microbiota characteristics, and other relevant clinical risk variables. Assessment of model performance indicated strong discriminatory capacity, with the area under the ROC curve (AUC) reaching 0.900 in both the training and validation datasets. In addition, the Hosmer–Lemeshow goodness-of-fit test yielded non-significant results in both cohorts, indicating no evidence of poor calibration. Collectively, these findings support the predictive model's ability to accurately identify high-risk patients at risk of feeding intolerance in the ICU and highlight its clinical utility as a diagnostic aid. Furthermore, decision curve analysis (DCA) showed that across a threshold probability range from 0 to 1.0, utilizing the nomogram to guide clinical decision-making resulted in greater standardized net benefit compared to universal or no intervention strategies in both patient cohorts. However, external validation was not performed in this study, and the model's generalizability remains to be confirmed.

Conclusions

This research developed a prediction model designed to evaluate the risk of feeding intolerance among ICU patients receiving early enteral nutrition. This study developed a prediction model incorporating intra-abdominal pressure and selected genus-level gut microbial markers for early identification of enteral nutrition intolerance in ICU patients. Because the microbiota analysis was restricted to selected taxa, future studies using comprehensive microbiome profiling are needed to clarify the broader dysbiotic patterns and functional microbial pathways underlying feeding intolerance. The results demonstrated that the model had strong discriminatory power, reliable predictive accuracy, and meaningful clinical value—highlighting its potential as a useful tool for the early identification of feeding intolerance in critically ill populations. Nonetheless, certain limitations should be acknowledged. Given that the study was retrospective and conducted at a single institution, the generalizability of the findings to broader populations may be limited. Although the sample size was determined a priori, the validation cohort was relatively small, which may limit the precision and stability of the estimated model performance. This limitation is particularly relevant because ICU patients show substantial interindividual variability in gut microbiota composition and clinical biomarkers. Therefore, the validation results should be regarded as preliminary internal validation rather than definitive evidence of generalizability. Future studies should evaluate the model in larger, prospective, multicenter cohorts and assess its transportability across different ICU populations and microbiome profiling platforms.

Furthermore, the relatively uniform characteristics of the patient cohort and the presence of missing data restricted the inclusion of some potentially significant variables in the multivariate analysis, possibly introducing selection bias. To improve the robustness and external validity of these findings, future research should include larger and more heterogeneous patient samples and employ prospective, multicenter methodologies. Future studies employing multicenter designs and prospective methodologies will be essential to confirm the prognostic significance of intra-abdominal pressure further and selected microbial taxa in predicting early enteral nutrition intolerance in the ICU setting.

Ethics approval

The study was approved by the Health Research Ethical Committee of Wenzhou Central Hospital. All experiments were performed in accordance with relevant guidelines and regulations, such as the Declaration of Helsinki and the patients. Informed consent was obtained from each pregnant woman before delivery as the participants of the study and after delivery, as the mother of the infant who participated in the study.

Authors' contributions

KZ, XZ, LQ, and RW conceptualized the study, collected data, developed the methodology, did the analysis, drafted and designed the manuscript, and developed the tables. All authors reviewed and supported the revision of the manuscript and agreed with the final version

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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