

Clinical characteristics and machine learning-based prediction of postoperative enterocolitis in intestinal neuronal dysplasia: A 20-year retrospective study

Qingxuan Hu

Department of Pediatric Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

Zongye Yang

Department of Pediatric Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

Lei Xiang

Department of Pediatric Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

Qinxue Lu

Department of Pediatric Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

Xufei Duan

Department of General Surgery, Wuhan Children's Hospital, Tongji Medical College, Huazhong University of Science and Technology

Hongqiang Bian

Department of General Surgery, Wuhan Children's Hospital, Tongji Medical College, Huazhong University of Science and Technology

Jiexiong Feng

Department of Pediatric Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

Jun Xiao

Department of Pediatric Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

Xuyong Chen

Xuyong.Chen@tjh.tjmu.edu.cn

Department of Pediatric Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

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Abstract

Purpose

Intestinal neuronal dysplasia (IND) is a congenital enteric neuropathy characterized by abnormalities of the enteric nervous system, most commonly involving hyperplasia of the submucosal plexus and the presence of giant ganglia. This study aimed to characterize the clinical features of IND, evaluate postoperative enterocolitis (POEC), and develop a machine learning (ML)-based model for POEC prediction.

Methods

Patients diagnosed with IND who underwent pull-through surgery at our institution between 2005 and 2025 were retrospectively reviewed. Clinical characteristics and postoperative outcomes were analyzed. Five feature selection strategies and five machine learning algorithms were combined to construct and evaluate 101 predictive models using out-of-fold area under the receiver operating characteristic curve (AUC).

Results

A total of 84 patients were included in the study. Male patients predominated (57.1%), and 44.0% were underweight. Constipation was the most common presenting symptom (67.9%). Pathological comorbidities identified 30 (35.7%) patients with pure IND and 54 (64.3%) with mixed IND. Statistical analysis demonstrated that lower BMIZ values were associated with mixed IND and female sex in our cohort, whereas the interval from symptom onset to surgery was inversely associated with initial symptom severity. A machine learning model for predicting postoperative enterocolitis (POEC) was subsequently developed, in which BMIZ consistently emerged as a key predictive feature, suggesting its potential value for individualized postoperative risk assessment.

Conclusion

In this study, we characterized the clinical and pathological features of children with isolated intestinal neuronal dysplasia over a 20-year period. Patients were predominantly male, frequently presented with constipation, and most exhibited mixed IND rather than pure IND. Nutritional impairment was common, with female patients and those with mixed IND showing lower BMIZ values. Machine learning analyses consistently identified BMIZ as a potential predictive feature associated with postoperative enterocolitis, highlighting the potential role of nutritional status in postoperative risk stratification.

Introduction

Intestinal neuronal dysplasia (IND) is a congenital enteric neuropathy and one of the allied disorders of Hirschsprung disease (ADHD). It is characterized by developmental abnormalities of the enteric nervous system, histologically manifested as hyperplasia of the submucosal plexus and giant ganglia[1–3]. Clinically, patients with IND may present with chronic constipation, abdominal distension, enterocolitis, intestinal obstruction, or severe gastrointestinal dysmotility[2].

The pathogenesis of IND remains incompletely understood. Abnormal development of enteric neural crest cells is considered a major mechanism[4], and findings from *Ednrb* mutant rats and *Ncx/Hox11L1*-deficient mice further support a genetic basis for the disease[5–7]. Besides, pathological comorbidities, particularly immature ganglia (IMG) and hypoganglionosis (HG), are common in IND and increase the complexity of clinical management [1, 4, 8–10].

Currently, the diagnosis of IND relies almost entirely on histopathological examination of surgical specimens[11]. Despite decades of investigation, IND remains a poorly understood disorder, with no clear consensus regarding its epidemiology, clinical diagnostic criteria, optimal treatment strategies, or prognostic determinants, unlike many more common diseases[12–16]. Therefore, there is a pressing need for additional studies focusing on the description and characterization of the clinical features of IND.

Postoperative enterocolitis (POEC) is the most common complication following pull-through surgery for ADHD and represents an important determinant of long-term quality of life[9, 17, 18]. Although previous studies have explored potential risk factors for POEC[19–21], the determinants of POEC in patients with IND remain incompletely understood. Machine learning (ML) has become an increasingly important approach for developing predictive models in medicine by capturing complex relationships among multiple clinical variables[22]. Compared with conventional statistical methods, ML algorithms are capable of improving risk stratification and individualized outcome prediction[23]. Consequently, ML-based models have been increasingly applied to predict postoperative complications and long-term prognosis, providing valuable support for personalized clinical management[24]. However, their application in IND, particularly for predicting POEC, remains largely unexplored.

In the present study, we performed a comprehensive analysis of the clinical characteristics, pathological findings, nutritional status, and follow-up outcomes of patients with IND treated at our center over a 20-year period. By characterizing the demographic and disease-specific features of this cohort and constructing machine learning models to predict POEC, we sought to identify potential prognostic factors and provide evidence to facilitate the diagnosis, risk stratification, and clinical management of IND.

Methods

Study design and patient selection

A retrospective analysis was conducted on the clinical characteristics and pathological findings of patients with IND who underwent surgical treatment at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology between 2005 and 2025. Statistical analyses were performed based on the collected clinical and pathological data.

Inclusion criteria

Patients were included if they met all of the following criteria: Received a postoperative pathological diagnosis of IND at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology between 2005 and 2025; Underwent laparoscopic or open radical pull-through surgery for Hirschsprung disease or allied disorders at Tongji Hospital; The pathological diagnosis was independently reviewed and confirmed by three experienced pathologists to ensure that the pathological findings met internationally accepted diagnostic criteria for IND, namely the presence of giant ganglia, defined as submucosal ganglia containing ≥ 8 ganglion cells, together with hyperplasia of the submucosal plexus. At least 25 consecutive submucosal ganglia were evaluated, and IND was diagnosed when giant ganglia accounted for $\geq 20\%$ of the examined ganglia [1, 3, 4].

Because pull-through surgery provides an opportunity to obtain a complete specimen of the affected intestinal segment for comprehensive pathological assessment, thereby facilitating a more accurate diagnosis of IND, this study included only surgically treated patients with IND who underwent pull-through procedures. During the study period (2005–2025), no universally accepted surgical criteria for IND were available; therefore, surgical decisions were individualized by the treating pediatric surgeons based on persistent bowel dysfunction despite conservative management (including bowel management, laxatives, and/or enemas) or severe complications such as intestinal obstruction or intestinal perforation.

Exclusion criteria

Patients were excluded under the following conditions: Hirschsprung's disease (HSCR) associated IND; Incomplete pathological records or missing key clinical data; Loss to follow-up resulting in unavailable prognostic outcomes.

Because IND may coexist with HSCR or represent secondary pathological changes within the transition zone of HSCR[11, 25], patients with HSCR-associated IND were excluded to specifically investigate the clinical characteristics of isolated IND.

Data collection

Demographic, clinical, surgical, pathological, and follow-up data were extracted from the electronic medical record system. Variables collected included sex, age at surgery, gestational age, birth history,

blood type, body weight, height, Date of surgery, chief complaint, present illness, past medical history, examination data, surgical approach, pathological data, postoperative complications, and follow-up outcomes.

Pathological diagnosis review

All pathological data, including histopathological images and original pathological diagnoses, were independently reviewed by three experienced pathologists. For cases with diagnostic uncertainty, archived tissue sections were retrieved and re-examined. The final diagnosis was established through consensus discussion based on currently accepted diagnostic criteria of IND, IMG and HG[1, 3, 4, 26–28].

BMI and BMIZ calculation

BMI was calculated as weight (kg) divided by height squared (m^2). To allow comparisons across patients of different ages and sexes, BMI-for-age Z-scores (BMIZ) were calculated according to age- and sex-specific reference standards[29]. Patients were further categorized as underweight, normal weight, overweight, or obese according to standardized pediatric BMI criteria.

Initial symptom severity score

To quantify the severity of initial clinical presentation, a symptom severity score was assigned according to the most severe presenting symptom. Constipation was scored as 1, abdominal distension and abdominal pain as 2, vomiting as 3, overflow fecal incontinence as 4, and intestinal perforation as 5. Higher scores represented more severe clinical presentation.

Follow-up and definition of postoperative enterocolitis

Patients were routinely followed after surgery. Postoperative enterocolitis (POEC) was defined as clinically diagnosed enterocolitis occurring after pull-through surgery during the follow-up period, based on symptoms including abdominal distension, fever, diarrhea, and/or imaging findings, as assessed by pediatric surgeons. Follow-up was continued for up to 5 years to capture late postoperative events. For patients who had undergone surgery less than 5 years before the end of the study period, follow-up data were collected until the most recent available visit. The occurrence time and recurrence of POEC episodes were documented.

Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation (SD), while categorical variables are presented as frequencies and percentages. Comparisons between two groups were performed using the

unpaired two-tailed Student's t-test for normally distributed continuous variables and the Mann–Whitney U test for non-normally distributed variables. Comparisons among multiple groups were performed using the Kruskal–Wallis test. Associations between categorical variables were evaluated using the chi-square test or Fisher's exact test as appropriate. Correlations between symptom severity score and continuous variables were assessed using Spearman correlation analysis. All statistical analyses were conducted using GraphPad Prism (version 10.1.2) and R software. A two-sided P value < 0.05 was considered statistically significant.

Machine learning analysis

To explore predictors of POEC, several machine learning algorithms were constructed, including LASSO Cox regression, Random Survival Forest, XGBoost Cox, XGBoost Binary, and Support Vector Machine (SVM). Model performance was evaluated using the area under the receiver operating characteristic curve (AUC) and concordance index (C-index). Variable importance analyses were performed to identify major contributors to model prediction.

To further improve predictive performance, combined models integrating different feature-selection strategies and machine learning algorithms were generated. A total of 100 model combinations were evaluated using four feature-selection methods (AUC, correlation, t-test, and variance) and five machine learning algorithms. Model performance was compared based on AUC values.

Ethical approval

This study was approved by the Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (Ethics Approval Number: TJ-IRB20230739, TJ-IRB202606007). Due to the retrospective nature of the study, the requirement for informed consent was waived. All procedures were conducted in accordance with the Declaration of Helsinki.

Results

Baseline Characteristics of the Study Cohort

After applying the predefined inclusion and exclusion criteria to patients with IND treated at our center between 2005 and 2025, a total of 84 patients were enrolled in the study cohort (Fig.1). The mean age at surgery was 5.11 ± 4.22 years. Of the 84 patients, 58 (69.0%) were older than 2 years at the time of surgery, while 26 (31.0%) were 2 years old or younger. Among the 84 patients included in the study, 48 (57.1%) were male and 36 (42.9%) were female (Fig.2a). The male proportion in our cohort (57.1%) was higher than that reported in the general newborn population in China during the same period (~52–53%) [30]. Among the 84 patients, 37 (44.0%) were underweight, 38 (45.2%) had normal weight, 5 (6.0%) were overweight, and 4 (4.8%) were obese (Fig.2b). Compared with the general pediatric population in China, patients in our cohort showed a markedly higher prevalence of underweight status (33.3% vs. approximately 7%) and a lower prevalence of overweight/obesity [31].

Among the 84 patients, 12 (14.3%) were born prematurely and 72 (85.7%) were born at full term (Fig.2c). Previous population-based studies in China reported a preterm birth rate of approximately 5%, whereas 14.3% of patients in our cohort were born prematurely[32]. Among the 84 patients, blood type A was observed in 40 (47.6%) patients, followed by blood type B in 20 (23.8%), blood type O in 17 (20.2%), and blood type AB in 7 (8.3%) (Fig.2d). While in the general Chinese population, the distribution of ABO blood groups has been reported as approximately 30.5% for type A, 29.4% for type B, 29.4% for type O, and 10.7% for type AB[33].

Compared with the general population, the IND cohort showed a significantly higher prevalence of underweight status and premature birth, together with an increased frequency of blood type A and a decreased frequency of blood type O (all $P < 0.05$).

Besides 65 (77.4%) underwent laparoscopic surgery, while 19 (22.6%) underwent open surgery. Delayed meconium passage was observed in 29 of the 84 patients (34.5%). After independent review by three experienced pathologists, 30 (35.7%) patients were diagnosed with pure IND, 11 (13.1%) with IND combined with HG, 35 (41.7%) with IND combined with IMG, and 8 (9.5%) with concomitant HG and IMG(Fig.2f). Postoperative enterocolitis during follow-up occurred in 10 of the 84 patients (11.9%) (Fig.2e). The earliest episode of POEC occurred on postoperative day 3, whereas the latest episode was observed 426 days after surgery. In addition, two patients experienced a second episode of POEC during the follow-up period. The interval between the initial onset of related symptoms and pull-through surgery was 2.54 ± 2.39 years among the 84 patients. The initial presenting symptoms included constipation in 57 patients (67.9%), abdominal distension and abdominal pain in 15 (17.9%), vomiting in 7 (8.3%), overflow fecal incontinence in 3 (3.6%), and intestinal perforation in 2 (2.4%).

To enable a more accurate comparison of BMI across children of different ages and sexes, BMI Z-score (BMIZ) were calculated for each patient based on age- and sex-specific reference standards. Analysis of the BMIZ distribution revealed that both male and female patients exhibited a leftward shift relative to the population mean (BMIZ = 0), indicating lower BMI values compared with those of the general pediatric population (Fig.2g). Furthermore, this shift was more pronounced among female patients, suggesting a greater degree of undernutrition in female patients than in male patients.

Pathological comorbidities and postoperative enterocolitis

Among the 84 patients, 30 (35.7%) were classified as pure IND, whereas 54 (64.3%) exhibited pathological comorbidities, including IMG, HG, or both. No significant differences were observed among the four pathological comorbidities subgroups with respect to sex distribution ($P = 0.071$), age at surgery ($P = 0.974$), surgical approach ($P = 0.931$), or postoperative enterocolitis (POEC) occurrence ($P = 0.875$) (Tab 1).

Tab.1 Clinical characteristics according to pathological comorbidities

Categorization	Pure IND	Mixed IND			Fisher–Freeman–Halton exact test
		Only with IMG	Only with HG	IND with both	<i>P</i> value
Total	30	35	11	8	
Gender					0.071
Male	20	21	3	4	
Female	10	14	8	4	
Age–Months–					0.974
≤24	9	11	3	3	
>24	21	24	8	5	
Surgical approach					0.931
Laparotomy	7	8	3	1	
Laparoscopy	23	27	8	7	
Postoperative enteritis					0.875
Yes	4	5	0	1	
No	26	30	11	7	

Among the 84 patients, postoperative enterocolitis (POEC) developed in 10 (11.9%) patients, whereas 74 (88.1%) patients did not develop POEC during follow-up. POEC occurred in 4 patients with pure IND, 5 with IMG-associated IND, and 1 with concomitant IMG and HG, while no cases were observed in the HG-associated group. Male patients accounted for the majority of POEC cases (7/10, 70.0%). Most POEC cases occurred in patients older than 24 months at the time of surgery (6/10, 60.0%). In addition, POEC was more frequently observed in patients who underwent laparoscopic surgery (9/10, 90.0%) than in those who underwent laparotomy (1/10, 10.0%) (Table 2). Although conventional statistical analyses did not identify statistically significant individual predictors of POEC, these methods evaluate variables mainly based on isolated associations and may not fully capture complex interactions among multiple clinical features. Therefore, machine learning approaches were subsequently applied to explore potential predictive patterns.

Tab.2 Clinical Characteristics According to the Presence or Absence of Postoperative Enterocolitis

Categorization	Postoperative enteritis Yes	Postoperative enteritis NO	Fisher's exact test <i>P</i> value
Total	10	74	
Pathological comorbidities			0.897
Pure IND	4	26	
Only with IMG	5	30	
Only with HG	0	11	
IND with both	1	7	
Gender			0.470
Male	7	41	
Female	3	33	
Age (Months)			0.717
≤24	4	22	
>24	6	52	
Surgical approach			0.667
Laparotomy	1	18	
Laparoscopy	9	56	

Differences in BMIZ Among Clinical and Pathological Comorbidities

In our previous analyses, we observed that patients with IND exhibited lower BMI-for-age Z-scores (BMIZ) than the general pediatric population. To further investigate whether the degree of BMIZ reduction differed among patient subgroups, additional statistical analyses were performed. Using the classical two-tailed unpaired *t*-test, we found that female patients had significantly lower BMIZ values than male patients ($P < 0.05$; Fig. 3a). Furthermore, patients with Mixed IND exhibited significantly lower BMIZ values compared with those with Pure IND ($P < 0.005$; Fig. 3b). In contrast, no significant difference in BMIZ was observed between patients who developed postoperative enterocolitis (POEC) and those who did not (Fig. 3c).

Association Between Initial Symptom Severity and Clinical Characteristics

To enable quantitative comparisons of initial clinical presentations, a symptom severity score was assigned to each patient according to the severity of the presenting symptom. Constipation was scored as 1, abdominal distension and abdominal pain as 2, vomiting as 3, overflow fecal incontinence as 4, and intestinal perforation as 5. Correlation analyses were subsequently performed between the symptom severity score and other clinical and pathological characteristics.

The symptom severity score was found to be significantly negatively correlated with the interval from symptom onset to surgery ($P = 0.0006$, $r = -0.365$), indicating that patients with more severe initial symptoms tended to undergo surgical intervention earlier (Fig.3d). In contrast, no significant associations were observed between symptom severity score and age at surgery, BMIZ, pathological comorbidities, sex, or the occurrence of POEC(Fig.3e-i).

To ensure appropriate statistical evaluation, Spearman correlation analysis was used to assess the relationships between symptom severity score and continuous variables, including the interval from symptom onset to surgery, age, and BMIZ. Kruskal–Wallis tests were applied to compare symptom severity scores among different pathological comorbidities and according to POEC status, whereas the Mann–Whitney U test was used to compare symptom severity scores between male and female patients.

Machine Learning-Based Prediction of Postoperative Enterocolitis

To identify potential predictors of postoperative enterocolitis (POEC), several machine learning models were constructed and evaluated, including LASSO Cox regression, Random Survival Forest, XGBoost Cox, XGBoost Binary, and Support Vector Machine (SVM). As shown in Fig. 4a, the XGBoost-based models demonstrated the best predictive performance, achieving the highest AUC values (0.696) and C-index values (0.694), whereas SVM showed substantially poorer discrimination ($AUC = 0.217$).

ROC curve analysis further confirmed the superior performance of the XGBoost models and Random Survival Forest compared with LASSO Cox and SVM (Fig. 4b). Time-dependent AUC analysis demonstrated that XGBoost Cox maintained the highest predictive accuracy across different postoperative time points, while Random Survival Forest showed relatively stable performance over time (Fig. 4c).

Variable importance analyses were subsequently performed for the best-performing models. In the XGBoost Binary model, BMI and BMIZ were identified as the most influential predictors, followed by age at first visit, weight, and height (Fig. 4d). Similar results were observed in the XGBoost Cox model, in which BMI and BMIZ remained the dominant contributors to model performance (Fig. 4e). In the Random Survival Forest model, BMI, weight, height, and BMIZ were among the variables with the greatest importance, whereas comorbidity status and the interval from symptom onset to surgery also contributed substantially to risk stratification (Fig. 4f).

To further investigate prognostic factors associated with POEC, LASSO Cox regression was performed. The coefficient trajectories gradually stabilized as the regularization parameter increased and reached convergence after approximately 19 iterations (Fig. 4g). The final LASSO Cox model identified prematurity, initial symptom severity, pathological comorbidities, blood type, surgical approach, BMI, and BMIZ as the major variables contributing to POEC prediction (Fig. 4h).

Overall, across multiple machine learning approaches, nutritional indicators, particularly BMI and BMIZ, consistently emerged as the most important predictors of postoperative outcomes.

Development and Performance of the Combined Machine Learning Model

To further improve predictive performance, combined machine learning models integrating different feature selection strategies and classification algorithms were constructed and evaluated. A total of 100 model combinations were generated using four feature selection methods (AUC, correlation, *t*-test, and variance) and five machine learning algorithms (LASSO, ElasticNet, Random Forest, SVM, and XGBoost).

As shown in Fig. 5a, XGBoost-based models consistently achieved higher predictive performance than the other algorithms across most feature-selection strategies. The heatmap of out-of-fold AUC values demonstrated that the best-performing models were predominantly concentrated within the XGBoost group. Ranking of all model combinations according to AUC further confirmed this finding, with the top-performing model being the combination of *t*-test-based feature selection (top 15 features) and XGBoost, achieving an AUC of 0.635 (Fig. 5b). Notably, most of the top 30 ranked models were XGBoost-based.

Comparison of AUC distributions among different algorithms revealed that XGBoost exhibited the highest median AUC and the most favorable overall performance, whereas SVM showed the greatest variability and the lowest predictive accuracy (Fig. 5c). When stratified according to feature selection strategy, the four methods demonstrated broadly comparable performance, although variance-based selection exhibited a wider distribution of AUC values (Fig. 5d).

Receiver operating characteristic (ROC) analysis of the five best-performing combined models demonstrated consistent discrimination ability, with AUC values ranging from 0.607 to 0.635 (Fig. 5e). Despite the modest predictive performance, all top-ranked models outperformed random classification and were predominantly based on XGBoost, indicating that this algorithm provided the most effective framework for POEC prediction in the present cohort.

However, despite the integration of multiple feature-selection strategies and machine learning algorithms, the combined models did not demonstrate superior predictive performance compared with the best-performing single-model approaches.

Discussion

This study provides a comprehensive characterization of the clinical features, pathological comorbidities, and postoperative outcomes of children with isolated IND over a 20-year period. Our findings revealed several distinctive characteristics of this population, including frequent nutritional impairment and a high prevalence of mixed pathological features. Furthermore, we systematically evaluated BMIZ patterns and explored potential predictors of POEC using machine learning approaches, which consistently identified BMIZ as a potential predictive feature for postoperative risk stratification.

IND may occur as an isolated entity or coexist with HSCR, with the latter reported to be even more common[11, 25]. This overlap has long complicated the investigation of the clinical characteristics of IND as an independent disease[13, 14]. Therefore, to better define the clinical profile of IND itself, patients with concomitant HSCR were excluded from the present study.

Consistent with previous reports[13, 14], our cohort demonstrated a modest male predominance. Only 35.7% of our patients were classified as pure IND, whereas nearly two-thirds exhibited concomitant IMG, HG, or both, supporting previous observations[34, 35] that pathological comorbidities are common rather than exceptional in IND.

Previous studies have reported impaired growth, poor weight gain, and nutritional deficits in children with HSCR[18, 36-38]; however, corresponding evidence in IND, an allied disorder of Hirschsprung disease, remains limited[11]. By systematically evaluating BMIZ, which are independent of age and sex, our study identified an overall downward trend in BMIZ among children with IND and further revealed significantly lower BMIZ values in female patients and those with mixed IND. One possible explanation is the chronic intestinal dysmotility that commonly manifests as constipation and other gastrointestinal symptoms in IND, which may adversely affect nutritional status and growth[11]. Nevertheless, the mechanisms linking enteric neuropathy to nutritional impairment, as well as the potential contribution of other biological pathways, remain unclear and warrant further experimental investigation.

We also observed considerable heterogeneity in the initial clinical presentation of patients with IND. While some patients presented with only mild constipation, others developed life-threatening complications such as intestinal perforation requiring emergency surgical intervention. To further investigate the factors underlying this variation, we developed a simple symptom severity scoring system based on the initial presenting symptoms and examined its associations with several potentially relevant clinical variables, including the interval from symptom onset to surgery, age, sex, BMIZ, and pathological comorbidities. Interestingly, our analyses demonstrated that the interval from symptom onset to surgery was the only factor significantly associated with symptom severity, showing a clear negative correlation. In contrast, no significant associations were identified with age, sex, BMIZ, or pathological comorbidities. This finding may reflect differences in healthcare-seeking behavior, diagnostic delay, and clinical decision-making, whereby patients with severe manifestations are more likely to undergo earlier evaluation and surgical intervention.

As pediatric surgeons, patient prognosis remains one of our primary concerns. POEC is the most common complication following pull-through surgery and it can substantially impair postoperative

quality of life[9, 17, 18]. Therefore, POEC represents an important prognostic outcome in patients with IND. In the present study, we initially explored potential factors associated with the occurrence of POEC using classical statistical approaches. However, no significant associations were identified.

To further explore potential predictors of POEC, we applied several machine learning approaches using clinical and pathological variables. Unlike conventional regression analyses, which primarily evaluate predefined associations, machine learning models can capture complex nonlinear relationships and interactions among multiple variables and may identify predictive patterns that are not readily detected by traditional methods. Among the evaluated models, LASSO Cox regression, Random Survival Forest, XGBoost Cox, and XGBoost Binary demonstrated relatively favorable performance, with AUC and C-index values exceeding 0.6. BMIZ consistently ranked among the most important predictive features across different algorithms, with higher BMIZ values associated with a lower risk of POEC. Although ensemble models integrating different feature-selection strategies and algorithms did not further improve predictive performance, likely because of the limited sample size and number of POEC events, these findings suggest that nutritional status may contribute to postoperative risk stratification in patients with IND. Importantly, the current models should be considered exploratory rather than clinical decision-making tools, and further validation in larger multicenter cohorts is required.

In conclusion, BMIZ, or more broadly the nutritional status it reflects, appears to represent an important clinical characteristic associated with IND and may contribute to postoperative risk stratification. Our findings suggest that nutritional impairment is common among patients with IND and may be associated with disease severity, pathological comorbidities, and postoperative outcomes. These observations highlight the importance of routinely monitoring height, weight, BMIZ, and other nutritional indicators throughout the clinical course of IND. Early nutritional assessment and appropriate nutritional management may therefore represent important components of comprehensive care for children with IND.

Several limitations of this study should be acknowledged. First, as a single-center retrospective study, the sample size was relatively limited, which may have reduced the statistical power of some analyses, particularly those involving POEC. Although machine learning models were developed in this study, their predictive performance remained modest, with AUC values below the level generally considered excellent (>0.90). This limitation may be partly attributable to the relatively small cohort size and the limited number of POEC events available for model training and validation. Larger multicenter studies are required to validate our findings and provide more robust estimates of the observed associations. Second, our cohort represents children with isolated IND who required surgical intervention and may not fully reflect the broader clinical spectrum of IND, particularly those managed conservatively. If accurate diagnostic approaches that do not rely on surgical specimens become available in the future, the study population could be further expanded to include a wider range of patients with IND. Third, although several interesting associations among nutritional status, pathological characteristics, and clinical outcomes were identified, the underlying biological mechanisms remain unclear. Further experimental

and translational studies are needed to elucidate the complex interactions among these factors and to better understand the pathogenesis and progression of IND.

Conclusion

In this study, we characterized the clinical and pathological features of children with isolated intestinal neuronal dysplasia over a 20-year period. Patients were predominantly male, frequently presented with constipation, and most exhibited mixed IND rather than pure IND. Nutritional impairment was common, with female patients and those with mixed IND showing lower BMIZ values. Machine learning analyses consistently identified BMIZ as a potential predictive feature associated with postoperative enterocolitis, highlighting the potential role of nutritional status in postoperative risk stratification.

Declarations

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Conflict of interest disclosure

The authors declare no competing interests.

Ethics approval statement

This study was approved by the Ethics Committee of Tongji Hospital (Number: TJ-IRB20230739, TJ-IRB202606007).

Author Contribution

All authors read and approved the final manuscript. J. Xiao, J. Feng and X. Chen designed research; Q. Hu, Y. Duan and H. Bian performed research; Z. Yang and Q. Lu. analyzed data; L. Xiang, J. Feng, X. Chen, and J. Xiao provided pathology review; Q. Hu wrote the paper.

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Figures

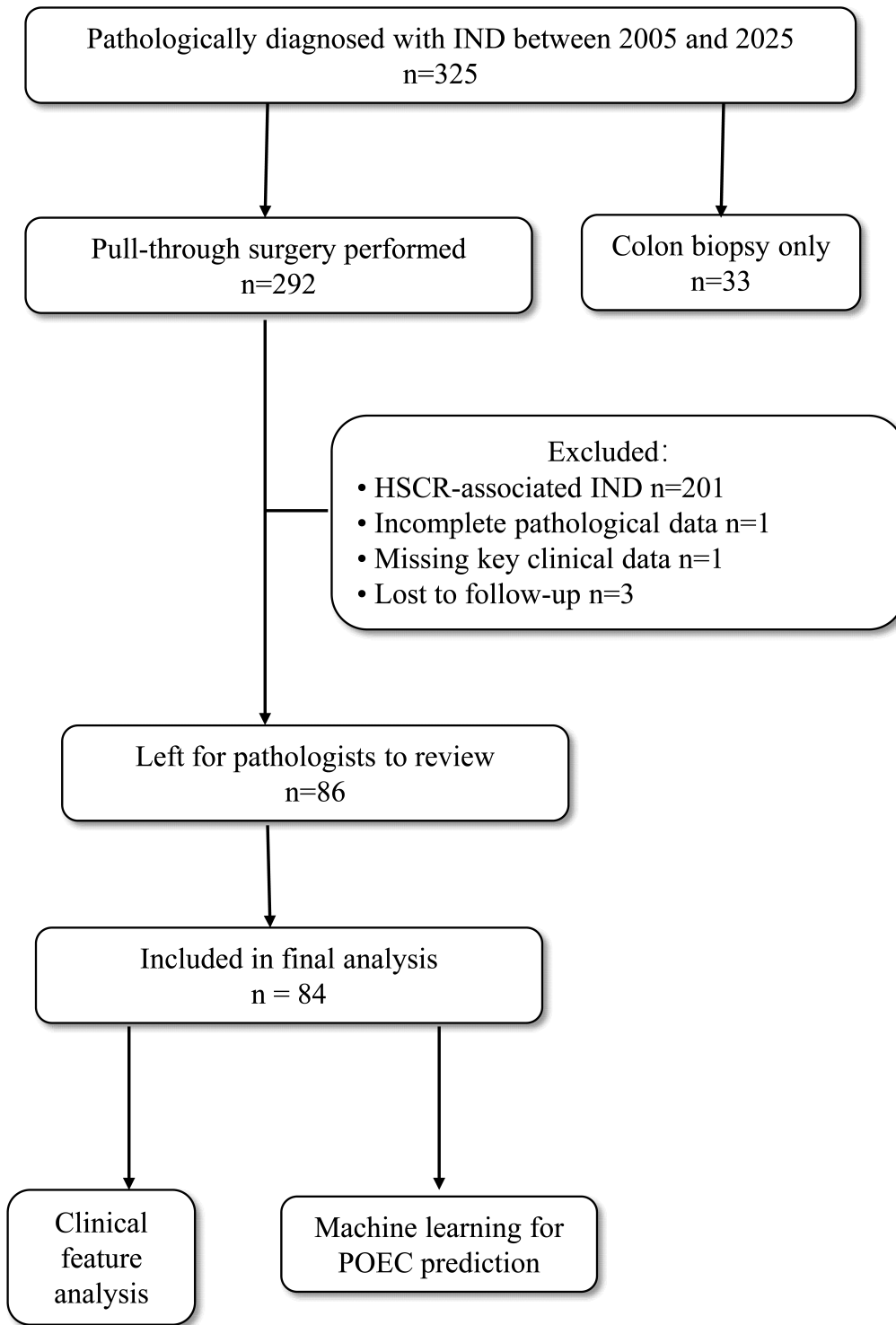


Figure 1

Flow chart patient selection

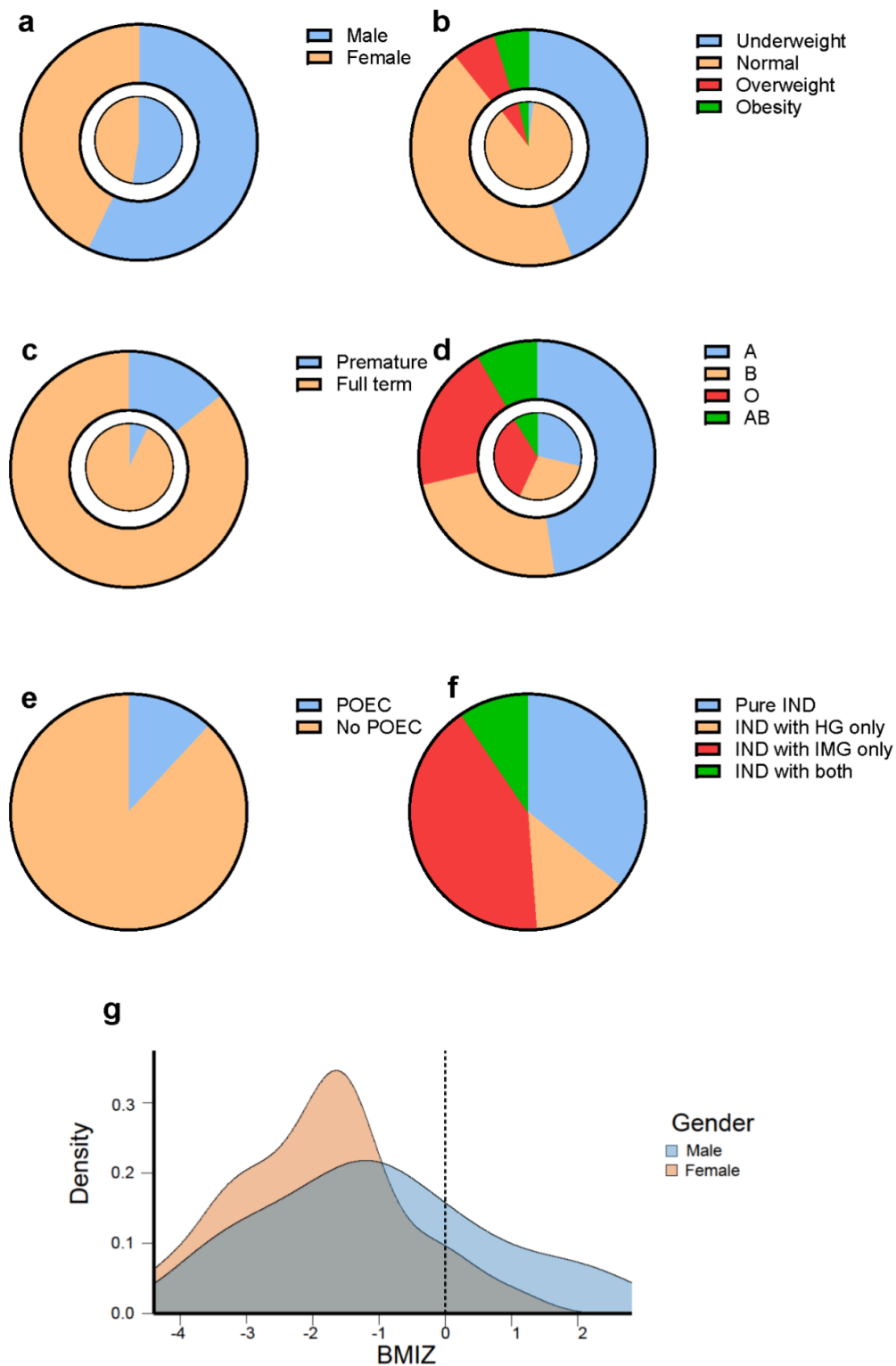


Figure 2

Clinical characteristics of the 84 patients included in this study.

(a–d) The distribution of clinical characteristics among the study cohort. The outer ring represents the proportion of each characteristic observed in the study population, whereas the inner circle indicates the corresponding reference proportion in the general population.

- (e) The distribution of postoperative enterocolitis among patients in the study cohort.
- (f) The distribution of pathological combinations in the study cohort.
- (g) The distribution of BMI-for-age Z-scores (BMIZ) stratified by gender.

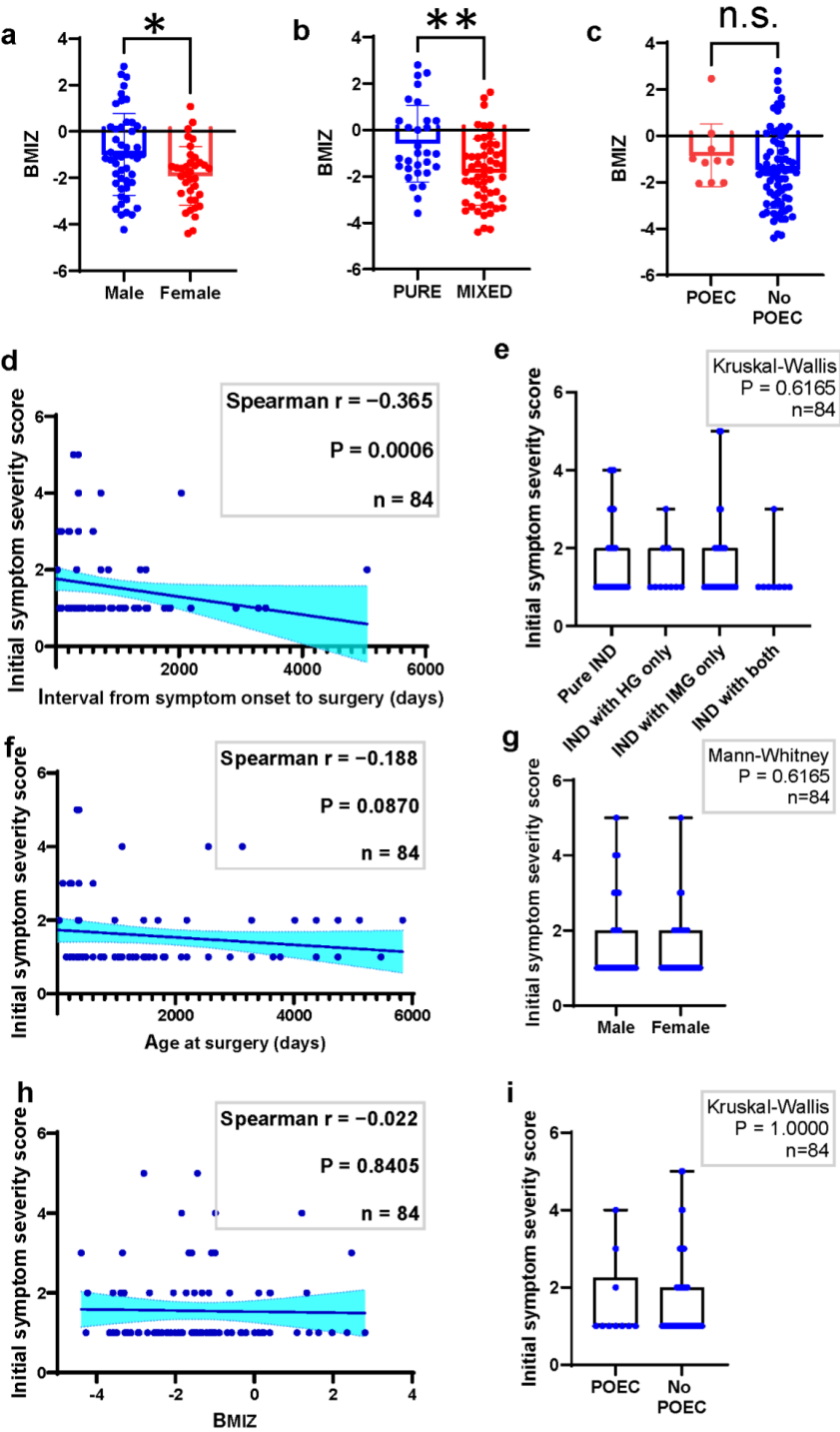


Figure 3

Association of BMIZ and initial symptom severity with clinical characteristics in patients with IND.

(a–c) Comparisons of BMI Z-scores (BMIZ) among patients stratified by sex **(a)**, pathological comorbidities (pure IND vs. mixed IND) **(b)**, and the occurrence of postoperative enterocolitis (POEC) **(c)**. Two-tailed unpaired t-tests were performed for group comparisons. Significant differences in BMIZ were observed between male and female patients and between pure and mixed IND groups, whereas no significant difference was found between patients with and without POEC.

(d–i) Correlation analyses between initial symptom severity score and clinical variables, including the interval from symptom onset to surgery **(d)**, pathological comorbidities **(e)**, age at surgery **(f)**, gender **(g)**, BMIZ **(h)**, and postoperative enterocolitis **(i)**. A significant association was identified between initial symptom severity score and the interval from symptom onset to surgery, whereas no significant associations were observed with pathological comorbidities, age, gender, BMIZ, or postoperative enterocolitis. The statistical methods used for each analysis are indicated within the corresponding panels.

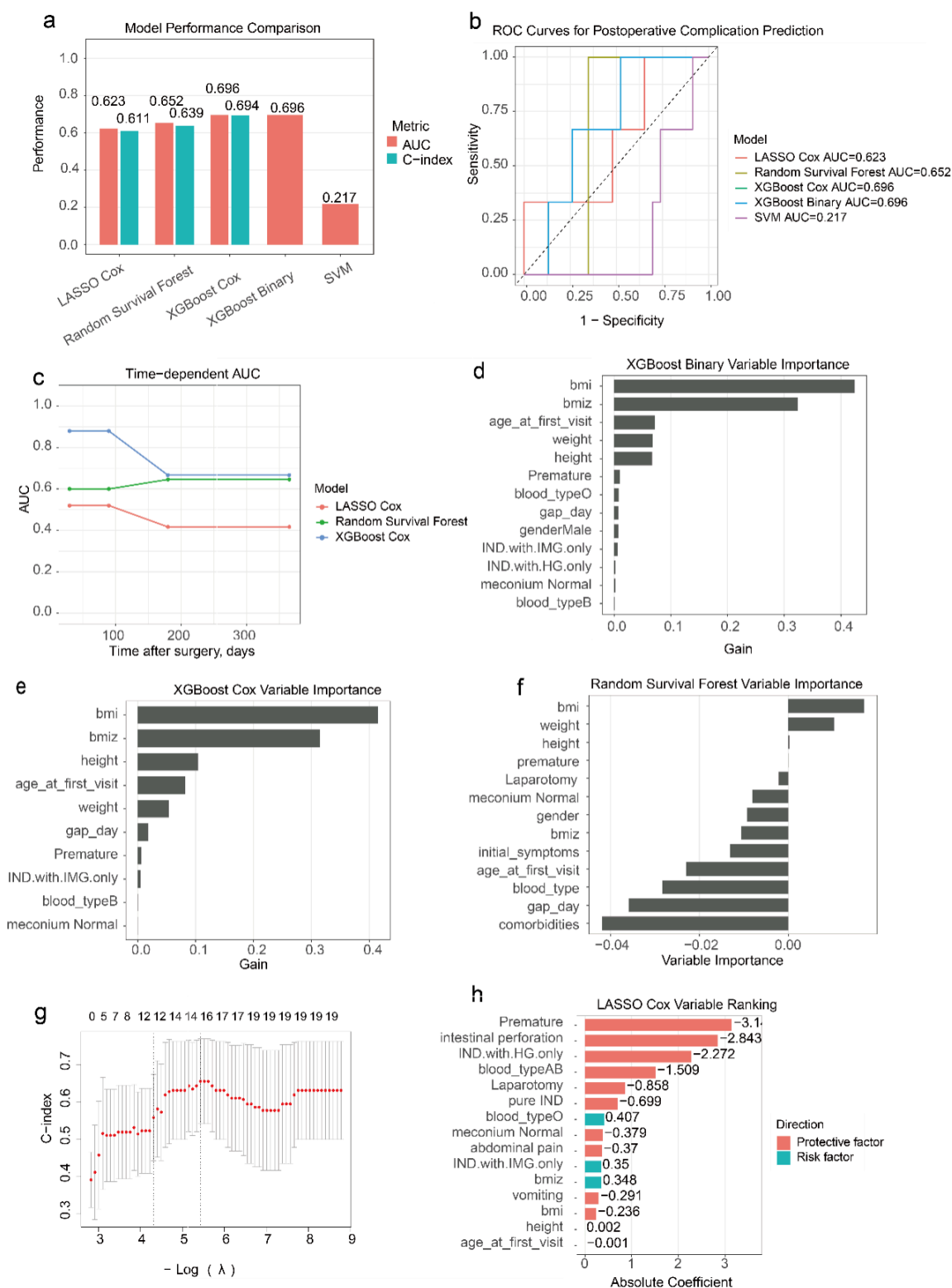


Figure 4

Machine learning-based prediction models for postoperative enterocolitis (POEC)

(a–c) Performance evaluation of different machine learning models for predicting the occurrence of POEC. **(a)** The predictive performance of the models using the area under the receiver operating characteristic curve (AUC) and concordance index (C-index). **(b)** The ROC curves of the evaluated

models, including LASSO Cox, Random Survival Forest, XGBoost Cox, XGBoost Binary, and Support Vector Machine (SVM). **(c)** The time-dependent AUC values of the survival models at different postoperative time points. Among the five commonly used machine learning algorithms, all models except SVM demonstrated satisfactory predictive performance, with XGBoost-based models showing the best overall performance.

(d–f) Variable importance analyses for the XGBoost Binary **(d)**, XGBoost Cox **(e)**, and Random Survival Forest **(f)** models. In all three models, BMI and BMIZ were identified as the most influential predictors of POEC, followed by age at first visit, weight, height, and several clinical characteristics.

(g) Regularization path of the LASSO Cox regression model. As the penalty parameter increased, the regression coefficients gradually converged and became stable after approximately 19 iterations, indicating adequate variable selection and model convergence.

(h) Variable ranking of the final LASSO Cox model after convergence. Variables were ranked according to the absolute values of their regression coefficients. Positive coefficients were considered risk factors, whereas negative coefficients were considered protective factors for POEC occurrence. Prematurity, initial symptom severity, and specific pathological comorbidities contributed most strongly to the prediction model.

Mime-style Machine Learning Model Evaluation

101 machine learning combinations for postoperative complication prediction

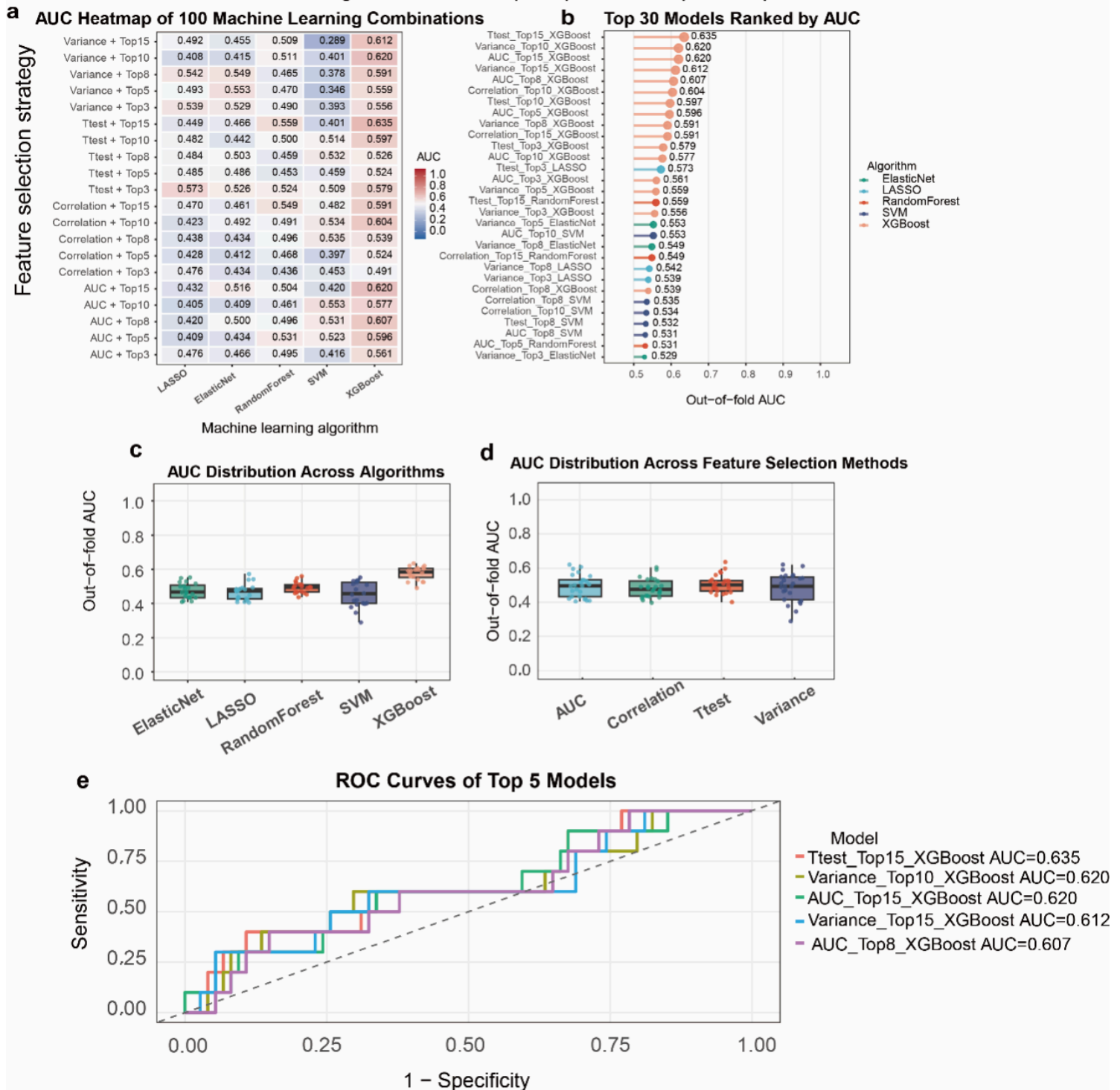


Figure 5

Performance of Feature Selection–Algorithm Combinations for POEC Prediction

(a) Heatmap of the out-of-fold AUC values for 101 machine learning model combinations generated by integrating multiple feature selection strategies (AUC, correlation, t-test, variance, and embedded

methods) with five machine learning algorithms (LASSO, ElasticNet, Random Forest, SVM, and XGBoost). Warmer colors indicate better predictive performance.

(b) Top 30 machine learning model combinations ranked by out-of-fold AUC. The best-performing model combined t-test feature selection with the top 15 selected features and XGBoost classification, achieving an AUC of 0.635. Most of the highest-ranked models were XGBoost-based, highlighting its superior predictive performance within the current dataset.

(c) Distribution of out-of-fold AUC values across the five machine learning algorithms. All algorithms except SVM demonstrated satisfactory predictive performance, while XGBoost-based models consistently exhibited the highest median AUC and the best overall performance.

(d) Distribution of out-of-fold AUC values across different feature selection strategies. Variance-based feature selection showed the widest performance distribution, whereas AUC-, correlation-, and t-test-based methods yielded broadly comparable predictive performance.

(e) Receiver operating characteristic (ROC) curves of the five best-performing machine learning model combinations. All top-performing models demonstrated modest discriminative ability, with AUC values ranging from 0.607 to 0.635.