

# Comparative Predictive Value of Pre-hospital and In-hospital Delays for Acute Gangrenous or Perforated Appendicitis: Analysis Using LASSO Regression and Restricted Cubic Splines

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## Research Article

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## Abstract

## Background

Gangrenous or perforated appendicitis represents the most severe pathological form of acute appendicitis. The predictive value of pre-hospital and in-hospital delays for gangrene/perforation remains uncertain, and the functional forms of their associations with this outcome have rarely been examined.

## Objective

To compare the independent predictive value of pre-hospital and in-hospital delays for gangrenous/perforated appendicitis within the same model and to explore the underlying shapes of their associations with the outcome.

## Methods

This multicentre retrospective cohort study included 640 surgically treated acute appendicitis patients (88, 13.8%, with gangrene/perforation). LASSO was applied for covariate selection, with the two time variables forced into the model; a multivariable logistic regression was then built to compare their independent predictive values. Linear, quadratic, and RCS models were compared via AIC and likelihood-ratio tests to identify the optimal fit for each time variable.

## Results

pre-hospital delay (PHD) was significantly longer in the gangrenous/perforated group, whereas no significant between-group difference was observed for in-hospital delay (IHD). LASSO selected the neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP) and PHD from the 10 candidate covariates. In multivariable regression, both PHD (OR 1.029, 95% CI 1.013–1.044;  $P < 0.001$ ) and IHD (OR 1.042, 95% CI 1.005–1.080;  $P = 0.024$ ) were independent predictors of gangrenous/perforated appendicitis. Model comparison showed that PHD was best fitted by a nonlinear RCS model (AIC 460.4;  $P$  for nonlinearity = 0.007). The risk of gangrene/perforation increased more rapidly after approximately 24 h of abdominal pain and reached a peak at approximately 41 h (OR 1.499). IHD was best fitted by a linear model (AIC 476.1;  $P$  for nonlinearity = 0.956) and no threshold effect was observed. Replacing linear PHD with its RCS form in the multivariable model improved model fit and discrimination (AIC 457.9 vs. 464.7; AUC 0.774 vs. 0.746). The standardised effect size was greater for PHD ( $\beta = 0.463$ ) than for IHD ( $\beta = 0.244$ ). NRI/IDI analysis showed that replacing IHD with PHD yielded a continuous NRI of 0.327 and an IDI of 0.022.

## Conclusion

PHD, along with sex, CRP and NLR, emerged as an independent predictor of gangrenous/perforated appendicitis and demonstrated superior predictive performance over IHD. Patients presenting beyond 24 h of symptom onset carried a substantially elevated risk of gangrene/perforation—a finding that may inform clinical risk stratification and guide triage decisions.

## Introduction

Acute appendicitis is one of the most common surgical emergencies worldwide, with an estimated lifetime risk of 7–8%[1]. In 2021, the global age-standardised incidence was approximately 214 cases per 100,000 population, corresponding to about 17 million new cases annually[2]. During the course of acute appendicitis, gangrene and perforation represent critical pathological transitions from localised to diffuse inflammation. Once present, they may lead to severe complications such as diffuse peritonitis, intra-abdominal abscesses and sepsis, along with prolonged hospitalization and increased mortality[3, 4]. Despite advances in diagnosis and treatment, the reported incidence of gangrenous or perforated appendicitis remains as high as 20–40% in some regions and populations[5, 6]. Early identification of patients at high risk of gangrene or perforation, followed by timely surgical management, is therefore central to improving outcomes.

Conventional thinking holds that the longer the total interval from symptom onset to appendicectomy, the greater the risk that appendicitis will progress to gangrene or perforation[7]. However, this interval comprises two distinct phases: pre-hospital delay, from

symptom onset to presentation, and in-hospital delay, from arrival at hospital to surgery[8, 9]. Most previous studies have focused on the prognostic effect of in-hospital delay, but their conclusions have been inconsistent[10, 11]. Some have suggested that delaying appendectomy for up to 24 h after admission does not increase the risk of complicated appendicitis or postoperative complications[12, 13]. A meta-analysis of 11 non-randomised studies likewise found no association between a 12–24-h in-hospital delay and complicated appendicitis (OR 0.97;  $P = 0.750$ )[14]. However, other studies have reported that, among patients with established complicated appendicitis, an in-hospital delay of more than 8 h is associated with a higher risk of postoperative complications[15]. A meta-analysis of 28 studies involving more than 510,000 patients showed that an in-hospital delay exceeding 24 h significantly increased the risks of postoperative complications (OR 1.51) and mortality (OR 1.81)[16]. Compared with in-hospital delay, the association between pre-hospital delay and adverse outcomes has been more consistent. Several studies have shown that perforation rates and postoperative complications increase with longer pre-hospital delays, whereas similar associations have not been observed for in-hospital delay[17, 18]. A prospective study similarly revealed a strong association between prehospital delay and complicated appendicitis (median 47.8 h vs. 20.1 h;  $P < 0.001$ ), whereas in-hospital delay did not reach statistical significance (11.3 h vs. 13.3 h;  $P = 0.960$ )[19]. However, most of these studies either entered pre-hospital and in-hospital delays into separate models or examined them only in univariable analyses. Their independent predictive value therefore has not been directly compared within the same multivariable framework, leaving their relative contributions to the outcome uncertain. More importantly, nearly all existing studies of the relationship between time delays and appendicitis severity have prespecified a linear association, assuming that each additional hour produces a constant proportional increase in risk. Evidence regarding specific treatment windows also remains inconsistent, and the 2024 SAGES guideline gives only a conditional recommendation supported by limited evidence[20].

Accordingly, using multicentre retrospective cohort data, we sought to use LASSO regression to select covariates objectively, construct a multivariable logistic regression model, and use restricted cubic splines (RCS) to compare the independent predictive value of pre-hospital and in-hospital delays for gangrenous/perforated appendicitis and to identify the best-fitting functional form for each delay. The results were intended to inform patient education and more targeted emergency triage strategies.

## Methods

### Patients

This multicentre retrospective cohort study consecutively included patients who underwent emergency appendectomy at two hospitals between January 2018 and December 2025. Inclusion criteria were: (1) no conservative treatment before admission; (2) postoperative pathological confirmation of acute appendicitis; and (3) complete clinical data and records of the relevant time points. Patients were excluded if they (1) had another acute abdominal condition or (2) had an interval of more than 7 days from symptom onset to treatment.

#### Ethics approval and consent to participate

This retrospective study was approved by the Medical Ethics Committee of Zhangzhou Municipal Hospital. The need for written informed consent was waived by the ethics committee due to the retrospective use of anonymized clinical data.

### Surgical and Perioperative Management

All operations were performed by senior surgeons. Laparoscopic or open appendectomy was selected according to the patient's condition, the extent of intra-abdominal infection, and the operating surgeon's judgment. The indication for surgery was a preoperative diagnosis of acute appendicitis in the absence of an absolute contraindication. If purulent exudate or gangrene/perforation was identified intraoperatively, the pus was thoroughly aspirated, and an intra-abdominal drain was placed at the surgeon's discretion. Postoperative antibiotic regimens were determined by the operating surgeon according to the patient's condition and intraoperative findings.

### Definitions

Gangrenous/perforated appendicitis was defined as intraoperative evidence of appendiceal gangrene or perforation together with a postoperative pathological diagnosis of gangrenous or perforated appendicitis. Pathological criteria included transmural necrosis of the appendix, disruption of the appendiceal wall, or purulent exudate adherent to the serosal surface with a defect in the wall.

Simple/suppurative appendicitis was defined as intraoperative evidence of acute simple or suppurative appendicitis and a postoperative pathological diagnosis of acute simple or suppurative appendicitis, including phlegmonous appendicitis, without meeting any of the above criteria for gangrene or perforation (eFigure 1). Pathological specimens were independently reviewed by two pathologists at each centre, each with an intermediate or higher professional rank; disagreements were adjudicated by a senior consultant pathologist. To distinguish the sources of delay, total delay was decomposed into two independent exposure variables. Pre-hospital delay (PHD) was defined as the interval from the onset of abdominal pain to arrival at and registration in the emergency department, in hours. In-hospital delay (IHD) was defined as the interval from presentation to the emergency department to the start of surgery, in hours. The neutrophil-to-lymphocyte ratio (NLR) was calculated as the absolute neutrophil count divided by the absolute lymphocyte count in peripheral blood. Its cut-off value was determined by receiver operating characteristic (ROC) curve analysis using the maximum Youden index.

## Statistical Analysis

All statistical analyses were performed using SPSS version 27.0 and R version 4.6.1. Two-sided tests were used, and a P-value < 0.05 was considered statistically significant. Continuous variables were presented as mean  $\pm$  standard deviation or median (interquartile range) depending on the results of normality testing, and were compared between groups using the \*t\*-test or Mann–Whitney U test, as appropriate. Categorical variables were presented as counts (percentages) and compared using the chi-square test or Fisher's exact test. LASSO regression was applied to preselect from 10 preoperative candidate variables, with the optimal model determined via 10-fold cross-validation and the  $\lambda_{1se}$  criterion. PHD and IHD, as the primary exposure variables, were forced into the final multivariable model alongside age and sex, irrespective of the LASSO selection results. A multivariable logistic regression model was then constructed incorporating both the LASSO-selected variables with non-zero coefficients and the forced-retained variables. Prior to model entry, collinearity was assessed using the variance inflation factor (VIF), with a VIF > 5 indicating significant collinearity. Internal validation was performed using Bootstrap resampling with 500 replicates, from which the bias-corrected area under the curve (AUC) and calibration slope were calculated. Model calibration was evaluated using the Hosmer–Lemeshow test. To compare the relative effect sizes of PHD and IHD, both variables were standardised as z-scores and entered into the multivariable model, with standardised regression coefficients ( $\beta$ ) compared. To explore the optimal functional form for each time variable, linear, quadratic-term, and restricted cubic spline (RCS) models were constructed separately, and their model fit was compared using AIC, likelihood-ratio tests, and AUC. For the RCS models, knots were placed at the 5th, 35th, 65th, and 95th percentiles, with the reference point set at 1 hour (the clinically achievable minimum delay). Continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated to quantify the incremental predictive value of each time variable.

## Results

### Clinical Characteristics

Of the patients meeting the inclusion and exclusion criteria, 640 with acute appendicitis were included in the final analysis (Figure 1). The simple/suppurative group comprised 552 patients (86.2%), and the gangrenous/perforated group comprised 88 patients (13.8%). Baseline and perioperative characteristics are presented in Table 1. Age distributions did not differ significantly between groups (P = 0.245). Sex distribution differed between groups (P = 0.011), with a greater proportion of men in the gangrenous/perforated group (64.8% vs. 50.2%). A history of cardiovascular disease (P = 0.201) and previous abdominal surgery (P = 0.554) did not differ significantly between groups. Median IHD was 3.5 h and 3.0 h in the two groups, respectively, with no significant difference (P = 0.683); by contrast, PHD was longer in the gangrenous/perforated group (median 24.0 h vs. 16.0 h, P < 0.001). Preoperative laboratory findings showed that the gangrenous/perforated group had higher white blood cell counts (median  $14.86 \times 10^9/L$  vs.  $13.48 \times 10^9/L$ , P = 0.031) and neutrophil counts ( $12.53 \times 10^9/L$  vs.  $11.02 \times 10^9/L$ , P = 0.011) than the simple/suppurative group. The proportion of patients with NLR  $\geq 6$  was also higher in the gangrenous/perforated group (83.0% vs. 63.2%, P < 0.001). Preoperative C-reactive protein (CRP) levels were higher in the gangrenous/perforated group (median 40.9 mg/L vs. 12.8 mg/L, P < 0.001). Preoperative haemoglobin levels did not differ significantly between groups ( $136.7 \pm 16.0$  g/L vs.  $134.9 \pm 15.8$  g/L, P = 0.158).

Intraoperative findings and perioperative management are summarised in Table 2. The proportion undergoing open appendicectomy was higher in the gangrenous/perforated group than in the simple/suppurative group (28.4% vs. 16.1%, P = 0.005). Purulent exudate was observed more frequently in the gangrenous/perforated group (86.4% vs. 68.1%, P < 0.001), and estimated blood loss was greater (10.0 mL vs. 5.0 mL, P < 0.001). Operation time (median 90.0 min vs. 70.0 min), time to resumption of oral intake (2.00 d [2.00, 4.00] vs. 2.00 d [1.00, 2.00]) and postoperative hospital stay (7.0 d vs. 4.0 d) were all longer in the gangrenous/perforated group (all P < 0.001). Drain placement was more common in this group (48.9% vs. 11.6%, P < 0.001), as was postoperative dual-agent antibiotic therapy (47.7% vs.

18.8%,  $P < 0.001$ ). Postoperative laboratory testing showed higher white blood cell counts ( $7.39 \times 10^9/L$  vs.  $6.38 \times 10^9/L$ ,  $P = 0.003$ ), neutrophil counts ( $4.77 \times 10^9/L$  vs.  $3.80 \times 10^9/L$ ,  $P = 0.001$ ), and CRP levels (20.0 mg/L vs. 14.0 mg/L,  $P < 0.001$ ) in the gangrenous/perforated group. The proportion with postoperative NLR  $\geq 6$  did not differ significantly between groups (5.7% vs. 4.2%,  $P$  value not statistically significant), and postoperative haemoglobin levels were also comparable ( $126.94 \pm 15.55$  g/L vs.  $128.07 \pm 15.81$  g/L,  $P = 0.756$ ).

## LASSO Variable Selection and Multivariable Analysis

LASSO regression using the  $\lambda_{1se}$  criterion selected three preoperative variables with non-zero coefficients from the 10 candidate covariates: NLR, CRP, and PHD. The coefficients for age, sex, white blood cell count, neutrophil count, history of cardiovascular disease, history of abdominal surgery, and IHD were shrunk to zero (eFigure 2). After the two time variables and the LASSO-selected covariates were included, and age and sex were adjusted for, a multivariable logistic regression model was constructed (eTable 1). PHD was independently and positively associated with gangrenous/perforated appendicitis (OR 1.029, 95% CI 1.013–1.044;  $P < 0.001$ ), as was IHD (OR 1.042, 95% CI 1.005–1.080;  $P = 0.024$ ). NLR  $\geq 6.0$  (OR 3.703, 95% CI 1.957–7.005;  $P < 0.001$ ), CRP (OR 1.010, 95% CI 1.004–1.016;  $P < 0.001$ ), and male sex (OR 1.896, 95% CI 1.154–3.115;  $P = 0.012$ ) were also identified as independent predictors of gangrenous/perforated appendicitis. Age  $\geq 60$  years was not statistically significant (OR 1.039, 95% CI 0.496–2.177;  $P = 0.918$ ). The model's apparent AUC was 0.746 (95% CI 0.689–0.803). After internal validation with 500 bootstrap resamples, the optimism-corrected AUC was 0.731, the calibration slope was 0.918, and the Hosmer–Lemeshow test yielded  $P = 0.190$ .

To remove the effect of differences in scale on effect-size comparisons, PHD and IHD were standardised to z-scores before the multivariable model was refitted (eTable 2). The standardised regression coefficient for PHD was  $\beta = 0.463$  (OR 1.589, 95% CI 1.244–2.029;  $P < 0.001$ ), compared with  $\beta = 0.244$  for IHD (OR 1.277, 95% CI 1.032–1.579;  $P = 0.024$ ).

## Comparison of Model Forms

To determine whether PHD and IHD had nonlinear associations with gangrenous/perforated appendicitis, linear, quadratic-term, and RCS logistic regression models were fitted separately. Model fit and predictive performance were compared using the AIC, likelihood-ratio tests, and AUC (Table 3). For PHD, the RCS model had the lowest AIC (460.4) and the highest AUC (0.748). Compared with the linear model, both the quadratic-term model (LRT  $P = 0.005$ ) and the RCS model (LRT  $P = 0.004$ ) significantly improved model fit. For IHD, the linear model had the lowest AIC (476.1) and the highest AUC (0.716). The quadratic-term model did not significantly improve fit compared with the linear model (LRT  $P = 0.308$ ). Although the RCS model improved fit (LRT  $P = 0.031$ ), its AIC was higher than that of the linear model (480.0), and no improvement in AUC was observed (0.716 vs. 0.716). In the overall model comparison, replacing IHD with its RCS form did not improve model fit or AUC (LRT  $P = 0.893$ ; AIC 468.5 vs. 464.7; AUC 0.747 vs. 0.746). By contrast, replacing PHD with its RCS form significantly improved model fit and discrimination (LRT  $P = 0.004$ ; AIC 457.9 vs. 464.7; AUC 0.774 vs. 0.746).

RCS analysis showed no nonlinear relationship between IHD and acute gangrenous/perforated appendicitis ( $P$  for nonlinearity = 0.956). The curve was nearly flat, with no clear threshold or accelerating upward trend (Figure 2A). By contrast, PHD demonstrated a significant nonlinear relationship with the outcome ( $P$  for nonlinearity = 0.007; Figure 2B). The odds ratio first exceeded 1.2 at approximately 21 h of PHD; the slope was steepest at approximately 24 h, and the peak odds ratio was observed at approximately 41 h (OR 1.499).

### Evaluation of Incremental Predictive Value

Incremental predictive value analysis (eTable 3) showed different contributions from PHD and IHD. Using the conventional covariate model as the reference, adding PHD alone yielded a continuous NRI of 0.548 and an IDI of 0.026. Adding IHD alone yielded a continuous NRI of 0.124 and an IDI of 0.004. When PHD was added to a model that already included IHD, the continuous NRI was 0.521 and the IDI was 0.028. When PHD replaced IHD, the continuous NRI was 0.327 and the IDI was 0.022.

## Discussion

The predictive value of pre-hospital and in-hospital delays for gangrenous/perforated appendicitis remains unsettled, and the underlying forms of their associations with the outcome have rarely been examined. In this multicentre retrospective cohort, PHD was longer in the gangrenous/perforated group, whereas IHD did not differ significantly between groups. Both PHD and IHD were independently associated with gangrenous/perforated appendicitis, but the standardised effect size was greater for PHD than for IHD. RCS

comparison showed that the best-fitting model for PHD was nonlinear, with risk accelerating after approximately 24 h of abdominal pain and reaching a peak at approximately 41 h. Modelling PHD nonlinearly improved overall model fit and discrimination, and NRI and IDI analyses further supported its incremental predictive value.

PHD was significantly longer in the gangrenous/perforated group, whereas IHD did not differ significantly. This pattern suggests that the interval from symptom onset to presentation, rather than the post-admission wait for surgery, may be the key modifiable factor associated with progression to gangrene or perforation. The present analysis placed PHD and IHD in the same multivariable model and directly compared their relative contributions using standardised effect sizes and incremental predictive analyses. After standardisation, the  $\beta$  coefficient for PHD was 0.463 (OR 1.589, 95% CI 1.244–2.029;  $P < 0.001$ ), compared with 0.244 for IHD (OR 1.277, 95% CI 1.032–1.579;  $P = 0.024$ ). Replacing IHD with PHD yielded a continuous NRI of 0.327 and an IDI of 0.022. These results indicate that, between the two time variables, disease severity was more strongly related to the duration of symptoms before presentation than to the time spent waiting for surgery after admission.

The present study also found a higher proportion of men in the gangrenous/perforated group (64.8% vs. 50.2%), whereas age did not differ between groups. Preoperative white blood cell count, neutrophil count, and CRP levels were all higher in this group, as was the proportion with  $\text{NLR} \geq 6$  (83.0% vs. 63.2%). These markers may therefore serve as rapid preoperative screening signals for complicated appendicitis. Intraoperative and postoperative measures showed higher rates of open surgery, more purulent exudate, and greater blood loss in the gangrenous/perforated group. Operation time, time to resumption of oral intake, and hospital stay were also longer (all  $P < 0.001$ ), while drain placement (48.9% vs. 11.6%) and dual-agent antibiotic use (47.7% vs. 18.8%) were more common. Together, these findings are consistent with greater intra-abdominal contamination, a more protracted recovery, and greater healthcare resource use.

In this cohort, PHD showed a stronger and more complex conditional predictive signal than IHD. Temple et al. reported in a prospective study that patients who developed perforation had a longer interval between symptom onset and presentation but were assessed and treated more rapidly after arriving at hospital, suggesting that perforation may often occur before patients enter the healthcare system[8]. A meta-analysis of 21 studies by Li et al. found that a pre-hospital delay of 24–48 h was associated with a higher risk of complicated appendicitis (OR 1.99), whereas a short in-hospital delay was not associated with a comparable increase in risk[21]. A similar pattern was reported in another prospective observational study of 421 adults in south-western China: patients with complicated appendicitis had a longer PHD than those without complicated disease (27 h vs. 25 h), while IHD was similar between groups (5 h vs. 5 h), suggesting that the between-group difference in total delay arose mainly before hospital arrival[22]. In addition, a prospective cohort study of 804 patients by Agnesi et al. found no clear association between IHD and disease severity or postoperative complications; symptom duration before admission was the more consistent predictor[23]. Progression from simple inflammation to gangrene or perforation is a continuous process centred on local tissue ischemia and transmural necrosis, with the course of disease driven mainly by the duration of luminal obstruction and the accumulation of intraluminal pressure[24]. These changes may already have occurred before the patient reaches the hospital[25]. Although patients receive antibiotics, fluid resuscitation, and other medical interventions after admission, these measures cannot reverse established luminal obstruction or ischemic necrosis. Consequently, the length of IHD may have limited influence on an already established gangrenous process, producing a weaker predictive signal, whereas PHD more directly reflects the extent of disease progression and may be the dominant determinant of gangrene or perforation risk. Clinically, PHD may therefore be more useful than IHD for risk stratification in the emergency setting, although IHD remains a modifiable process variable.

To characterise the risk functions for gangrenous/perforated appendicitis, RCS analyses and model comparisons were performed for PHD and IHD. PHD showed a nonlinear association with the outcome ( $P$  for nonlinearity = 0.007), whereas no nonlinear association was observed for IHD ( $P$  for nonlinearity = 0.956). Introducing PHD as an RCS term improved overall model fit and discrimination, whereas the corresponding IHD model provided no clear benefit. The PHD curve showed an accelerated change in risk at approximately 20–24 h and reached its highest estimated level relative to the reference point at approximately 41 h. These results indicate that the association between longer PHD and gangrenous/perforated appendicitis was not simply linear; the probability of gangrene or perforation rose more sharply after a higher-risk time window was reached. By contrast, the association between IHD and gangrenous/perforated appendicitis showed no clear nonlinear pattern. Jiang et al. observed in a study of 255 patients that the risk of perforation began to increase significantly after related symptoms had persisted for 48 h[26]. Another prospective study of 658 patients also suggested that perforation risk did not increase linearly but followed a quantifiable time gradient[27]. These findings, consistent with our work, suggest that the association between prehospital delay and gangrene/perforation is graded in nature rather than simply linear. Clinical risk assessment may therefore benefit from high-risk PHD thresholds rather than relying solely on the incremental increase in elapsed time.

Raised NLR and CRP and male sex were also strongly associated with gangrenous/perforated appendicitis, indicating that time exposure was not the only source of preoperative risk information. Existing systematic reviews and pathological subgroup studies generally support the discriminatory value of NLR and CRP for complicated appendicitis, and the association between male sex and perforation risk has been observed in prospective cohorts and large multicentre studies[28–30]. However, study populations, outcome definitions, and cut-off values for NLR and CRP have differed and some studies did not find stable discriminatory performance[31–33]. Accordingly,  $\text{NLR} \geq 6$ , raised CRP, and male sex should be regarded as supplementary signals for preoperative risk stratification alongside PHD, rather than as universal independent risk factors.

This study has several limitations. First, although the  $\lambda_{1se}$  criterion was used for LASSO selection and RCS models were compared to avoid imposing a prespecified linear form on the time variables, the retrospective design cannot fully exclude selection bias and residual confounding inherent to real-world data. Second, although PHD and IHD were compared within the same model and model discrimination and incremental predictive value were assessed from several perspectives, the results do not establish a stronger causal effect of PHD on pathological outcome. Finally, although bootstrap validation supported model stability, the model has not yet been validated in an independent external cohort. NRI and IDI reflect model-level reclassification and discrimination changes and cannot replace calibration assessment, decision-curve analysis, or evaluation of real-world clinical impact.

## Conclusion

In conclusion, PHD, together with sex, CRP, and NLR, independently predicted gangrenous/perforated appendicitis and showed better predictive performance than IHD. The risk of gangrene or perforation was higher among patients presenting after 24 h of abdominal pain, supporting the use of pre-hospital symptom duration in clinical risk stratification and emergency triage.

## Declarations

### Consent for publication

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal.

### Conflict of Interest declaration

All authors have no conflict of interest and no potential benefits.

### Clinical trial number

Not applicable.

### Consent for publication

Not applicable.

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### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### Authors' contributions

Concept and design: HYL, CZB, SJ, SYQ, CLS and CQX. Acquisition, analysis, or interpretation of data: ZLP, ZJM, YKP and YJY. Drafting of the manuscript: HYL, CZB, SJ and SYQ. Statistical analysis: HYL, CZB, SJ and ZLP. Administrative, technical, or material support: HYL, CZB, SJ, ZLP and ZJM. Supervision: HYL, CZB, CLS and SYQ.

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# Tables

**Table 1. Baseline characteristics of patients.**

| Variable                                        | Total<br>(N=640)     | Simple/Suppurative<br>type<br>(N=552) | Gangrenous/Perforated<br>type<br>(N=88) | P      |
|-------------------------------------------------|----------------------|---------------------------------------|-----------------------------------------|--------|
| <b>Demographic and Clinical Characteristics</b> |                      |                                       |                                         |        |
| <b>Age, years [n (%)]</b>                       |                      |                                       |                                         | 0.245  |
| < 60                                            | 575 (89.84)          | 499 (90.40)                           | 76 (86.36)                              |        |
| ≥ 60                                            | 65 (10.16)           | 53 (9.60)                             | 12 (13.64)                              |        |
| <b>Sex [n (%)]</b>                              |                      |                                       |                                         | 0.011  |
| Female                                          | 306 (47.81)          | 275 (49.82)                           | 31 (35.23)                              |        |
| Male                                            | 334 (52.19)          | 277 (50.18)                           | 57 (64.77)                              |        |
| <b>Cardiovascular disease [n (%)]</b>           |                      |                                       |                                         | 0.201  |
| No                                              | 607 (94.84)          | 526 (95.29)                           | 81 (92.05)                              |        |
| Yes                                             | 33 (5.16)            | 26 (4.71)                             | 7 (7.95)                                |        |
| <b>History of abdominal surgery [n (%)]</b>     |                      |                                       |                                         | 0.554  |
| No                                              | 578 (90.31)          | 497 (90.04)                           | 81 (92.05)                              |        |
| Yes                                             | 62 (9.69)            | 55 (9.96)                             | 7 (7.95)                                |        |
| <b>In-hospital delay, h [median (IQR)]</b>      | 3.50 (2.00, 8.00)    | 3.50 (2.00, 8.00)                     | 3.00 (2.00, 8.75)                       | 0.683  |
| <b>Pre-hospital delay, h [median (IQR)]</b>     | 24.00 (9.25, 24.00)  | 16.00 (8.00, 24.00)                   | 24.00 (24.00, 28.00)                    | <0.001 |
| <b>Preoperative Laboratory Findings</b>         |                      |                                       |                                         |        |
| <b>WBC, ×10<sup>9</sup>/L [median (IQR)]</b>    | 13.66 (11.28, 16.49) | 13.48 (11.08, 16.30)                  | 14.86 (11.39, 17.88)                    | 0.031  |
| <b>NEUT, ×10<sup>9</sup>/L [median (IQR)]</b>   | 11.27 (8.94, 14.15)  | 11.02 (8.74, 13.88)                   | 12.53 (9.54, 15.03)                     | 0.011  |
| <b>NLR</b>                                      |                      |                                       |                                         | <0.001 |
| < 6                                             | 218 (34.06)          | 203 (36.78)                           | 15 (17.05)                              |        |
| ≥ 6                                             | 422 (65.94)          | 349 (63.22)                           | 73 (82.95)                              |        |
| <b>CRP, mg/L [median (IQR)]</b>                 | 15.50 (6.90, 50.40)  | 12.80 (5.00, 39.50)                   | 40.90 (12.37, 73.30)                    | <0.001 |
| <b>Hemoglobin (g/L) [mean ± SD]</b>             | 135.18 ± 15.79       | 134.94 ± 15.76                        | 136.69 ± 16.01                          | 0.158  |

Abbreviations: WBC, White blood cell; NEU, Neutrophil; NLR, Neutrophil-to-lymphocyte ratio; CRP, C-reactive protein.

**Table 2. Postoperative Clinical Outcomes and Laboratory Parameters.**

| Variable                                             | Total<br>(N=640)     | Simple/Suppurative<br>type<br>(N=552) | Gangrenous/Perforated<br>type<br>(N=88) | P      |
|------------------------------------------------------|----------------------|---------------------------------------|-----------------------------------------|--------|
| <b>Purulent discharge [n (%)]</b>                    |                      |                                       |                                         | <0.001 |
| No                                                   | 188 (29.38)          | 176 (31.88)                           | 12 (13.64)                              |        |
| Yes                                                  | 452 (70.63)          | 376 (68.12)                           | 76 (86.36)                              |        |
| <b>Operative time, min [median (IQR)]</b>            | 75.00 (55.00, 95.00) | 70.00 (55.00, 90.00)                  | 90.00 (61.25, 120.00)                   | <0.001 |
| <b>Intraoperative blood loss, mL [median (IQR)]</b>  | 5.00 (5.00, 10.00)   | 5.00 (5.00, 10.00)                    | 10.00 (5.00, 20.00)                     | <0.001 |
| <b>Time to oral intake, d [median (IQR)]</b>         | 2.00 (1.00, 2.00)    | 2.00 (1.00, 2.00)                     | 2.00 (2.00, 4.00)                       | <0.001 |
| <b>Postoperative hospital stay, d [median (IQR)]</b> | 5.00 (4.00, 6.00)    | 4.00 (4.00, 6.00)                     | 7.00 (6.00, 9.00)                       | <0.001 |
| <b>Drainage placement [n (%)]</b>                    |                      |                                       |                                         | <0.001 |
| No                                                   | 533 (83.28)          | 488 (88.41)                           | 45 (51.14)                              |        |
| Yes                                                  | 107 (16.72)          | 64 (11.59)                            | 43 (48.86)                              |        |
| <b>Number of antibiotics used [n (%)]</b>            |                      |                                       |                                         | <0.001 |
| One type                                             | 494 (77.19)          | 448 (81.16)                           | 46 (52.27)                              |        |
| Two types                                            | 146 (22.81)          | 104 (18.84)                           | 42 (47.73)                              |        |
| <b>Surgical approaches [n (%)]</b>                   |                      |                                       |                                         | 0.005  |
| Open approach                                        | 114 (17.81)          | 89 (16.12)                            | 25 (28.41)                              |        |
| Laparoscopic approach                                | 526 (82.19)          | 463 (83.88)                           | 63 (71.59)                              |        |
| <b>Operative Laboratory Findings</b>                 |                      |                                       |                                         |        |
| <b>WBC, ×10<sup>9</sup>/L [median (IQR)]</b>         | 6.49 (5.40, 7.86)    | 6.38 (5.40, 7.73)                     | 7.39 (5.70, 8.75)                       | 0.003  |
| <b>NEU, ×10<sup>9</sup>/L [median (IQR)]</b>         | 3.94 (3.00, 5.05)    | 3.80 (3.00, 4.83)                     | 4.77 (3.24, 6.02)                       | 0.001  |
| <b>NLR</b>                                           |                      |                                       |                                         | 0.571  |
| < 6                                                  | 612 (95.63)          | 529 (95.83)                           | 83 (94.32)                              |        |
| ≥ 6                                                  | 28 (4.38)            | 23 (4.17)                             | 5 (5.68)                                |        |
| <b>CRP, mg/L [median (IQR)]</b>                      | 14.99 (7.23, 27.98)  | 14.00 (6.69, 25.99)                   | 20.00 (11.09, 40.62)                    | <0.001 |
| <b>Hemoglobin (g/L) [mean ± SD]</b>                  | 127.91 ± 15.77       | 128.07 ± 15.81                        | 126.94 ± 15.55                          | 0.756  |

Abbreviations: WBC, White blood cell; NEU, Neutrophil; NLR, Neutrophil-to-lymphocyte ratio; CRP, C-reactive protein.

**Table 3. Comparison of model performance between in-hospital and pre-hospital delays.**

| Model | Delay type              | Variable treatment | df | AIC   | LRT P (vs linear) | AUC   |
|-------|-------------------------|--------------------|----|-------|-------------------|-------|
| A1    | In-hospital delay       | Linear             | 6  | 480.5 | —                 | 0.716 |
| A2    | In-hospital delay       | Quadratic          | 7  | 482.0 | 0.308             | 0.717 |
| A3    | In-hospital delay       | RCS                | 8  | 484.3 | 0.031             | 0.716 |
| B1    | Pre-hospital delay      | Linear             | 6  | 473.7 | —                 | 0.718 |
| B2    | Pre-hospital delay      | Quadratic          | 7  | 466.8 | 0.005             | 0.740 |
| B3    | Pre-hospital delay      | RCS                | 8  | 460.4 | 0.004             | 0.748 |
| C1    | Full model              | Linear             | 7  | 464.7 | —                 | 0.746 |
| C2    | Full model with IHD-RCS | RCS                | 9  | 468.5 | 0.893             | 0.747 |
| C3    | Full model with PHD-RCS | RCS                | 9  | 457.9 | 0.004             | 0.774 |

Abbreviations: Full model includes NLR ( $\geq 6.0$  vs  $< 6.0$ ), CRP, sex, age ( $\geq 60$  years vs  $< 60$  years), IHD, and PHD; IHD, In-hospital delay; PHD, Pre-hospital delay; RCS, Restricted cubic spline; df, Degrees of freedom; AIC, Akaike information criterion; LRT, Likelihood ratio test.

## Figures

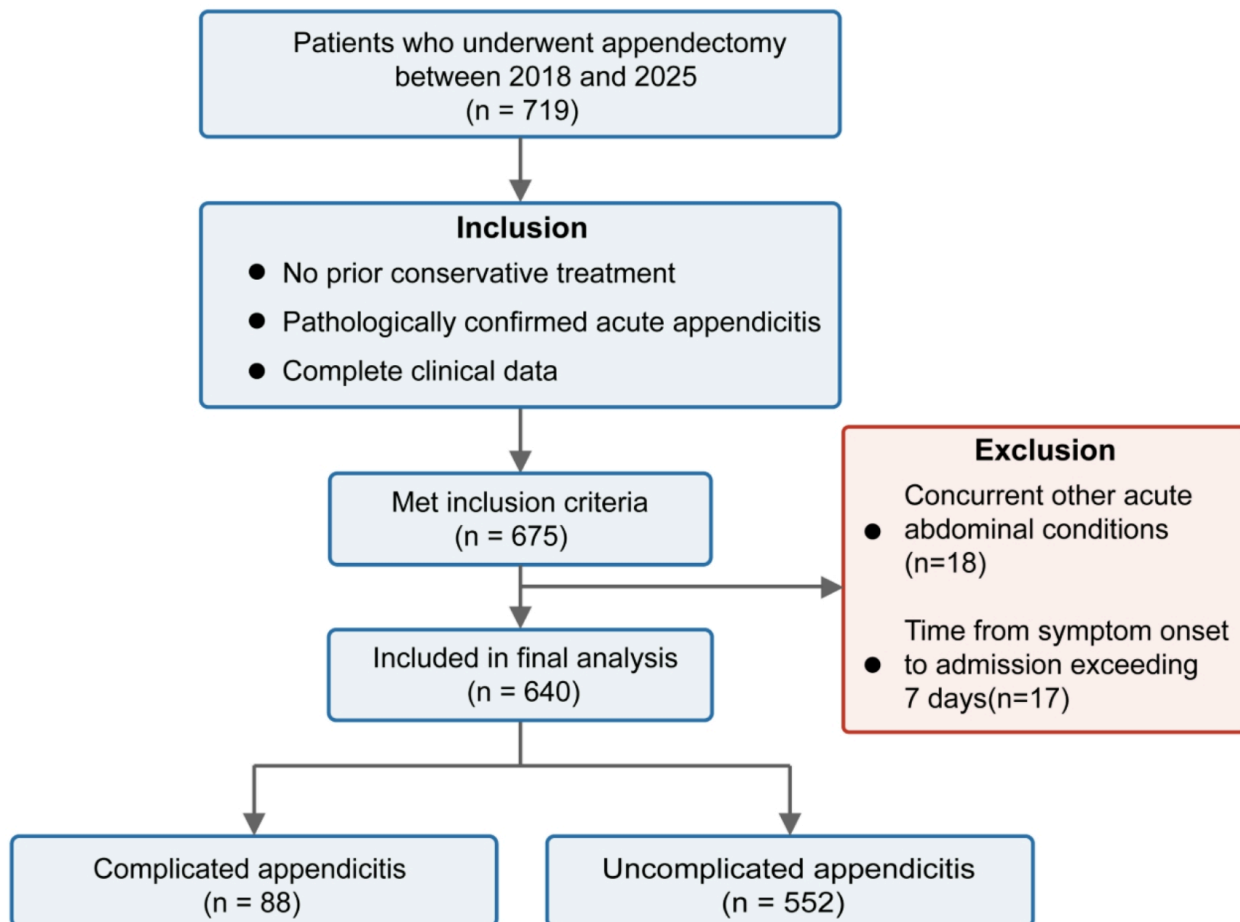


Figure 1

Flow chart of patient enrollment.

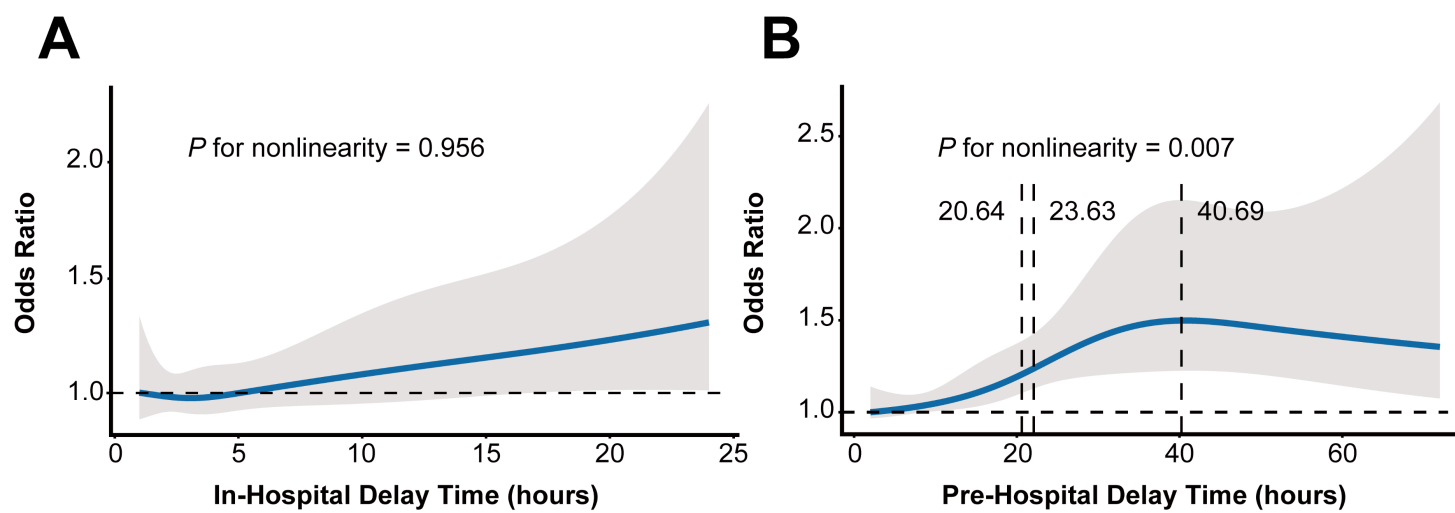


Figure 2

Restricted cubic spline (RCS) curves for the association between each time variable and the log odds of gangrenous/perforated appendicitis. (A) RCS curve for in-hospital delay. (B) RCS curve for pre-hospital delay.

Supplementary Files

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