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Research Article

The CRP/PAB ratio outperforms the LRINEC score in early diagnosis of Fournier's gangrene

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ABSTRACT

Background: Fournier's gangrene (FG) is scarce and potentially fatal disease. Although the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score was established in 2004, its reliability as a diagnostic tool to differentiate between FG and perianal abscess is still debated. The objective of this study was to assess the reliability of the LRINEC score and other relevant inflammatory markers. The diagnostic effectiveness of these inflammatory factors was evaluated and compared.

Methods: Retrospective observational study of patients with FG or with perianal abscess. Fifty-two patients with FG and 39 patients with perianal abscess treated in Shenyang Coloproctology Hospital between January 2019 and December 2023 were enrolled in the study.

Results: The area under the ROC curve (C-statistic) of a LRINEC score $\geq$6 for diagnosing FG was 0.736. Inflammatory markers, including C-reactive protein (CRP), procalcitonin (PCT), prealbumin (PAB), neutrophil-to-lymphocyte ratio (NLR), and systemic immune inflammation index (SII), demonstrated better diagnostic ability compared to the LRINEC score. Particularly, the compound inflammatory factor of CRP-to-PAB (CRP/PAB) ratio exhibited superior diagnostic ability compared to other markers (C-statistic: 0.908; $p < 0.001$).

Conclusions: The LRINEC score demonstrated only modest discriminative performance in this study. Patients with PAB$<$ 91mg/L and a CRP/PAB$\geq$ 1.52 should undergo careful evaluation for the presence of FG. The elevated CRP/PAB ratio is considered an early indicator for FG, particularly in distinguishing it from deep perianal abscesses. Further investigation is warranted in future studies to support these findings.

Background

Fournier's gangrene (FG), also known as necrotizing fasciitis, is an uncommon type of tissue infection that primarily affects the perianal, perineal, or external genital areas. This condition may not be obvious in the early stage, but sometimes their condition deteriorates sharply within a few hours, involves the rapid spread of severe inflammatory and infectious processes along fascial planes, affecting both deep and superficial tissues [1].

The perianal abscesses also exhibit similar sites of onset [2]. In certain cases, the progression of the disease may be delayed and influenced by individual factors, leading to the development of FG. Among perianal abscesses, the ischiorectal abscess is the predominant etiology of FG [3–5]. It is crucial to accurately differentiate between FG and perianal abscesses; however, this initial distinction can pose challenges due to limited or absent early-stage skin manifestations, making it challenging to distinguish them from evolving perianal abscesses.

Based on the latest reports, it has been observed that the fatality rate of FG varies between 8.3% and 22%. This indicates that the prognosis of individuals afflicted with this condition is influenced by multiple factors; however, delayed diagnosis and insufficient treatment remain the primary causes [6,7]. Although Wong et al. introduced the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) scoring system to assess risk and aid in the diagnosis of necrotizing fasciitis from other soft tissue infections [8], its ability to differentiate between perianal abscess and FG has not been verified. This retrospective study aimed to validate the LRINEC score at Shenyang Coloproctology Hospital in China. Additionally, the validation included systemic immune inflammation index (SII) neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), procalcitonin (PCT), prealbumin (PAB), and C-reactive protein (CRP) / prealbumin (PAB) (CRP/PAB) as markers of systemic immune-inflammation.

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Methods

This retrospective case-control study was approved by the ethics committee at our hospital. From January 2019 to December 2023, a total of 52 patients diagnosed with FG were identified through the Medical Records Department. Data were retrospectively extracted from medical record files. The following characteristics observed during surgical exploration were used to establish a definitive diagnosis: 1) Fragile superficial fascia showing gray discoloration or necrosis; 2) Exudate resembling dishwater-gray color; 3) Remarkable absence of pus formation; 4) Absence of bleeding in the fascia and superficial tissues during dissection; and 5) Possible presence of subcutaneous crepitus upon local examination [8–10]. During the same time frame, a control group consisting of 39 patients with perianal deep abscesses or severe cellulitis (such as ischiorectal space abscess, pelvic-rectal space abscess, and high intermuscular abscess) was randomly selected.

Data collection

Demographic information and clinical records of comorbidities were collected and reviewed to extract data (Table 1). In addition, we collected the first biochemical and hematologic tests results at admission. The variables analyzed included total white blood cell count (WCC), hemoglobin level (Hb), platelet count (Plt), serum sodium (Na), potassium (K), glucose level (Glu), creatinine level (Cr), prealbumin level (PAB), neutrophil count (NEUT), lymphocyte count (LYMPH), C-reactive protein level (CRP), and procalcitonin level (PCT) (Table 2).

Assessment of LRINEC, SII, NLR, PLR and CRP/PAB

The initial blood tests conducted upon admission were analyzed to calculate the LRINEC score (Table 3) and other systemic immune-inflammation markers. The SII was defined as follows: SII = platelet count(cells/mm^3) × neutrophil count(cells/mm^3) / lymphocyte count (cells/mm^3). The blood CRP-to-PAB (CRP/PAB) ratio were calculated by dividing the CRP concentration (mg/L) by the PAB concentration (mg/L). The ratios of NLR were calculated by dividing the total neutrophil count (cells/mm^3) by the total lymphocyte count (cells/mm^3). Similarly, the ratios of PLR were obtained by dividing the platelet count (cells/mm^3) by the lymphocyte count (cells/mm^3).

Table 1
Demographic, clinical characteristics, and outcomes of patients in cases and control.

	Cases($n = 42$)	Control($n = 39$)	P
Mean age [a]	56 (43.5–64.0)	37(32–51)	**0.001**
Gender [b]			
Male	36(85.7)	34(87.2)	0.847
Female	6(14.3)	5(12.8)	
Comorbidities [b]			
Diabetes			
Yes	19(45.2)	13(33.3)	0.273
No	23(54.8)	26(66.7)	
Cardiovascular and cerebrovascular diseases			
Yes	11(26.2)	2(5.1)	**0.01**
No	31(73.8)	37(94.9)	
Multiple organ dysfunction			
Yes	7(16.7)	3(7.7)	0.22
No	35(83.3)	36(92.3)	
Hypoproteinemia			
Yes	36(85.7)	9(23.1)	**<0.001**
No	6(14.3)	30(76.9)	
Acid-base disturbance			
Yes	8(19.0)	4(10.3)	0.266
No	34(81.0)	35(89.7)	
Sepsis AND/OR Shock			
Yes	15(35.7)	1(2.6)	**<0.001**
No	27(64.3)	38(97.4)	

[a] Data are presented as mean with range in parentheses;.
[b] Data are presented in terms of patient numbers, with the corresponding percentages indicated within parentheses.

Statistics

The statistical analysis was conducted using IBM SPSS Statistics version 24.0, employing a two-tailed approach and setting the significance level at $p < 0.05$. The cutoff points for analysis were determined based on laboratory diagnostic criteria and previous research findings. Independent *t*-tests were used to compare continuous variables between groups, while Fisher's exact or Chi-squared tests were employed for comparing categorical data. Univariate and multivariate analyses were performed using a backward stepwise logistic regression procedure. The performance of LRINEC score, WCC, CRP, PCT, PAB, SII, NLR, PLR, and CRP/PAB in distinguishing between FG cases and severe perianal abscesses was evaluated by calculating the C-statistic. The Youden method was utilized to calculate the optimal diagnostic cut-off value, along with its corresponding sensitivity and specificity.

Results

The analysis included a total of 52 patients diagnosed with FG (Using 81% of the patients diagnosed with FG ($n = 42$) as the training set and 19% as the validation set ($n = 10$)) and 39 patients with severe perianal abscess between January 2019 and December 2023. Table 1 provides an overview of the demographic and clinical characteristics, as well as the outcomes, for both cases and controls. Common comorbidities observed encompassed diabetes, cardiovascular and cerebrovascular diseases, multiple organ dysfunction, hypoproteinemia, acid-base disturbances, sepsis, and/or shock. It was found that FG cases had a significantly higher average age compared to those with severe perianal abscesses ($p < 0.001$). Furthermore, the incidence of cardiovascular and cerebrovascular disease was notably elevated in the case group when compared to the control group ($p = 0.01$). Additionally, there was a considerably higher occurrence of sepsis and shock in the case group than in the control group ($p < 0.001$).

The laboratory results for our cases and controls, including means, standard deviations (SD), and ranges, are presented in Table 2. The PAB in the cases group showed a significant decrease (67.9 ± 34.09 vs 168.83±70.22) (Cases vs Control), while the inflammatory markers PCT and CRP both obviously increased (PCT: 2.48±4.36 vs 0.46±1.11; CRP: 203.17±50.98 vs 155.54±47.19) (Cases vs Control).

We conducted both univariate and multivariate logistic regression analyses on the potential diagnostic variables. In the univariate analysis (Table 4), we identified WBC, PAB, Age, and PCT as potential diagnostic variables. However, only PAB ($P = 0.002$) and Age ($P = 0.034$) remained significant as candidate diagnostic variables in the multivariate analysis.

To assess the diagnostic power of these inflammatory factors, we initially performed ROC analysis on each individual factor. The area under the ROC curve (C-statistic) indicated that 1/PAB had superior diagnostic performance compared to other factors with a C-statistic of 0.895(95% CI 0.827–0.964; $P < 0.001$) (Fig 1A; Table 5). The ROC analysis was performed on compound inflammatory factors. The C-statistic of the LRINEC score for diagnosing FG was 0.736 (95% CI 0.625–0.846; $P < 0.001$). The diagnostic efficacy of the LRINEC score was not significantly superior to PLR, NLR, and SII. However, the CRP/PAB demonstrated markedly superior diagnostic efficacy with a C-statistic of 0.908 in the training cohort (95% CI 0.843–0.972; $P < 0.001$) (Fig 1B; Table 5). Furthermore, in the validation cohort, the CRP/PAB exhibited comparable diagnostic efficacy, as indicated by a C-statistic of 0.900 (95% CI 0.808–0.992; $P < 0.001$) (Fig 2).

Table 2
The mean, SD, and ranges of laboratory results of patients with FG (cases) and those with severe perianal abscesses (control) upon admission.

Variable (Normal values)/ Units	WCC (3.8–10.0) per mm^3	Hb (120–160) g/L	Plt (100–300) per mm^3	Na (135–145) mmol/L	K (3.5–5.5) mmol/L	Glu (3.9–6.1) mmol/L	Cr (55–150) μmol/L	PAB (80–400) mg/L	NEUT (2–7.7) per mm^3	LYMPH (0.8–4.0) per mm^3	CRP (0–8.2) mg/L	PCT (≤0.25) ng/ml
Cases												
Mean	19.00	137.02	257.57	136.79	4.20	9.65	80.98	67.90	16.04	1.37	203.17	2.48
SD	6.45	18.56	107.27	4.21	0.46	3.94	66.65	34.09	6.26	0.64	50.98	4.36
Min	4.93	88.00	24.00	124.00	3.20	4.76	31.00	8.00	3.62	0.31	110.40	0.13
Max	36.22	169.00	578.00	143.00	5.60	19.80	474.00	169.05	33.54	2.98	300.00	19.40
Control												
Mean	14.85	145.05	240.13	138.85	4.23	7.99	76.38	168.83	11.73	2.04	155.54	0.46
SD	7.11	24.65	84.03	3.50	0.61	3.89	22.76	70.22	7.02	0.92	47.19	1.11
Min	5.65	80.00	113.00	132.00	2.60	4.66	39.00	43.92	4.11	0.51	34.70	0.00
Max	41.11	180.00	563.00	146.00	6.20	18.56	181.00	320.74	37.43	4.28	214.10	3.18

FG, Fournier gangrene; SD, standard deviation; WCC, white blood cell count; Hb, hemoglobin; Plt, platelet count; Na, serum sodium; K, potassium; Glu, glucose; Cr, creatinine; PAB, prealbumin; NEUT, neutrophil count; LYMPH, lymphocyte count; CRP, C-reactive protein; PCT, procalcitonin.

Table 3
The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score.

Variable (units)	Score [a]
C-reactive protein (mg/L)	
<150	0
≥150	4
Total white cell count (per mm3)	
<15	0
15–25	1
>25	2
Hemoglobin (g/dL)	
>13.5	0
11–13.5	1
<11	2
Sodium (mmol/L)	
≥135	0
<135	2
Creatinine (μmol/L)	
≤141	0
>141	2
Glucose (mmol/L)	
≤10	0
>10	1

[a] The score range is between 0 and 13; a score ≤ 5 low risk; 6–7 intermediate risk; ≥ 8 high risk for Fournier's gangrene (FG).

Discussion

The LRINEC score has been proposed as an adjunctive diagnostic tool for necrotizing fasciitis, however, the detecting ability of LRINEC score were not always accurate. Recent meta-analyses have reported that the LRINEC score exhibits poor sensitivity and should not be utilized for ruling out necrotizing soft tissue infection [11]. Cribb et al. [7] suggested that the LRINEC score only have modest discriminative ability for differentiating between cases of necrotizing fasciitis from controls with severe cellulitis. Previous research has indicated a higher prevalence of FG among the elderly, consistent with our own data analysis [12,13]. The research conducted by Zhang et al. [6] revealed that FG patients had an average LRINEC score of 10.1, and a score≥8 indicates a strong likelihood of FG. This score suggests that the LRINEC scoring method is not ideal for early diagnosis of FG. To accurately diagnose FG, it is important to comprehensively consider both the clinical manifestations and the LRINEC score. In our study, we conducted a comprehensive evaluation of the diagnostic efficacy of the LRINEC score, while also comparing the diagnostic efficacy of individual inflammatory factors (such as WCC, CRP, PCT, and PAB) and combinations of inflammatory factors (including SII, NLR, PLR, and CRP/PAB) for diagnosing FG. In individual inflammatory factors analysis group, we found that the diagnostic performance of PAB is significantly better than that of PCT, CRP, and WCC. It expressed the better diagnostic accuracy at differentiating between FG and perianal abscesses with C-statistic of 0.895, followed by PCT (C-statistic=0.760), CRP (C-statistic=0.742) and WCC (C-statistic=0.716). In the compound inflammatory factors analysis group, CRP/PAB was found to be the most effective diagnostic parameter compared to others, with a C-statistic of 0.908 in the training cohort, and this result has also been confirmed in the validation cohort. It was followed by NLR (C-statistic=0.762), SII (C-statistic=0.758), LRINEC (C-statistic=0.736), and PLR (C-statistic=0.733).

Inflammation plays a crucial role in the formation of FG. Many biomarkers are associated with inflammation. The measurement of WCC, CRP, PCT, PAB, and other markers can be used to assess the level of inflammation. However, these factors differ in terms of sensitivity and specificity for judging inflammation. Therefore, it is essential to select appropriate factors to determine the degree of inflammation and disease progression.

PAB are synthesized by the hepatocytes and strongly suppressed in inflammatory or tissue necrosis environments [14–16]. It has been reported that low levels of PAB, associated with vitamin C deficiency and subclinical inflammation, are common in dialysis patients [17]. Perianal abscess progresses to necrotizing fasciitis with acute inflammatory response as its main feature. Therefore, we hypothesized that in patients with perianal abscess progressing to FG, the decrease of PAB may cause rapid depletion of vitamin C. Because vitamin C plays a key role in antioxidant and anti-inflammatory processes [18], deficiency can exacerbate the spread of abscess inflammation until necrotizing fasciitis develops. Additionally, it has been reported that a decreased level of serum PAB is associated with the prognosis of heart failure [19]. PAB serves as an independent influencing factor for heart failure following acute myocardial infarction [20]. All the above research findings highlight that patients exhibiting low PAB levels experience unfavorable clinical outcomes.

PCT as the prohormone of calcitonin, has been used as a biomarker to aid in diagnosis of bacterial infection or sepsis. The previous findings have indicated that PCT exhibits superior diagnostic efficiency compared to CRP and WCC, both in terms of earlier detection and accuracy [21]. In certain studies, researchers have also observed that PCT demonstrates superior sensitivity and specificity compared to CRP in the diagnosis and prediction of sepsis [22]. These findings are consistent with the results obtained from our study. However, Oliveira et al.'s randomized controlled trial comparing CRP and PCT indicates that there is no discernible advantage of using PCT over CRP in terms of the duration of antibiotic administration [23]. Due to the differential timing of release and the limited sensitivity and specificity exhibited by the aforementioned biomarkers, simultaneous measurement of these three parameters is frequently employed in clinical practice for accurately predicting the extent of inflammation. In our studies, the sensitivity of PCT reached its highest value at 0.929; however, the specificity was only

Table 4
Univariate and multivariate logistic regression analysis of potential predictors for the diagnosis of FG.

Variable Name	Univariate Analysis			Multivariate Analysis		
	OR(Unadjusted)	95% CI	p Value	OR(Unadjusted)	95% CI	p Value
CRP, mg/L						
<150	1	–	–			
≥150	3.355	0.821–13.717	0.092			
Hb, g/L						
>135	1	–	–			
110–135	0.769	0.185–3.198	0.718			
<110	0.721	0.259–2.01	0.531			
Na, mmol/L						
≥135	1	–	–			
<135	0.471	0.145–1.527	0.209			
WCC, per mm^3						
<15.0	1	–	–	1	–	–
15.0–25.0	11.250	2.058–61.498	**0.005**	3.465	0.489–24.541	0.213
>25.0	2.348	0.436–12.644	0.320	1.755	0.261–11.808	0.563
Cr,μmol/L						
≤141	1	–	–			
>141	0.342	0.034–3.436	0.362			
Glu, mmol/L						
≤10.0	1	–	–			
>10.0	0.400	0.153–1.048	0.062			
PAB, mg/L						
≥80	1	–	–	1	–	–
<80	13.75	4.588–41.210	**<0.001**	7.876	2.115–25.832	**0.002**
K, mmol/L						
≤5.5	1	–	–			
>5.5	0.927	0.056–15.344	0.958			
Plt, per mm^3						
≥100	1	–	–			
<100	1.081	0.145–8.071	0.939			
PCT, ng/ml						
≤0.5	1			1	–	–
>0.5	5.032	1.948–13.004	**<0.001**	1.911	0.576–6.342	0.147
Age						
<50	1	–	–	1	–	–
≥50	4.712	1.821–12.198	**<0.001**	0.287	0.091–0.909	**0.034**
Gender						
Female	1	–	–			
Male	1.133	0.316–4.060	0.848			

FG, Fournier gangrene; OR, odds ratio; CI, confidence interval; CRP, C-reactive protein; Hb, hemoglobin; Na, serum sodium; WCC, white blood cell count; Cr, creatinine; Glu, glucose; PAB, prealbumin; K, potassium; Plt, platelet count; PCT, procalcitonin.

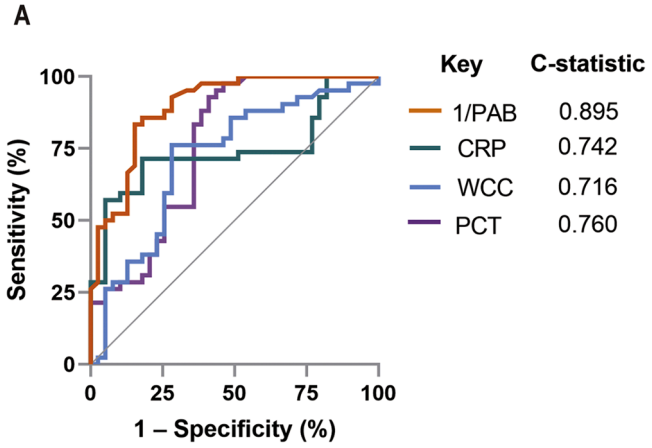

Fig 1A. ROC analysis to assess the diagnostic performance of each individual inflammatory parameter for FG. ROC, receiver operating characteristic; FG, Fournier gangrene; PAB, prealbumin; CRP, C-reactive protein; WCC White blood cell count; PCT, procalcitonin; C-statistic, the area under the ROC curve (AUC).

0.590, indicating suboptimal performance.

CRP are also synthesized by the hepatocytes, which functions as an acute-phase reactant, exhibiting a significant increase in response to

Table 5
Diagnostic performance of the tested markers in individually and compound inflammatory factors.

Variables	Cut-off	Sensitivity	Specificity	Youden index	C-statistic (95% CI)
PAB	<91.007	0.833	0.846	0.679	0.896 (0.828–0.964)
CRP	>177.238	0.714	0.821	0.535	0.742 (0.630–0.855)
WCC	>15.755	0.762	0.718	0.480	0.716 (0.602–0.831)
PCT	>0.235	0.929	0.590	0.518	0.760 (0.652–0.869)
LRINEC	≥6	0.667	0.744	0.410	0.736 (0.625–0.847)
CRP/ PAB	>1.523	0.905	0.795	0.700	0.908 (0.843–0.972)
SII	>1929.92	0.714	0.744	0.458	0.758 (0.651–0.865)
PLR	>123.74	0.810	0.615	0.425	0.733 (0.622–0.844)
NLR	>6.90	0.810	0.667	0.476	0.762 (0.658–0.867)

PAB, prealbumin; CRP, C-reactive protein; WCC White blood cell count; PCT, procalcitonin; LRINEC, laboratory risk indicator for necrotizing fasciitis; CRP/PAB, C-reactive protein-to-prealbumin; SII, systemic immune-inflammation index; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio. C-statistic, the area under the ROC curve (AUC).

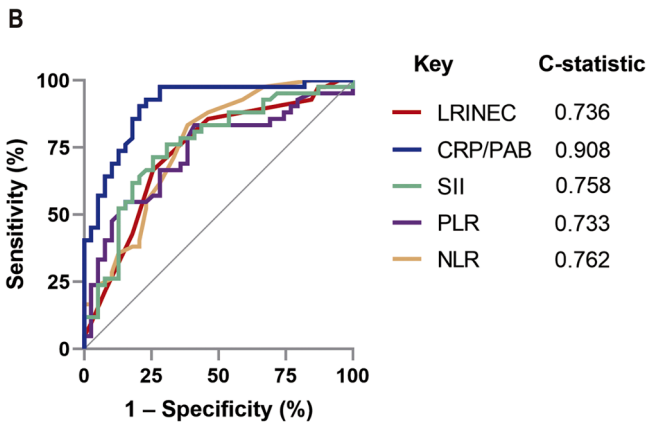

Fig 1B. ROC analysis to assess the diagnostic performance of compound inflammatory parameters for FG. LRINEC, laboratory risk indicator for necrotizing fasciitis; CRP/PAB, C-reactive protein-to-prealbumin; SII, systemic immune-inflammation index; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio.

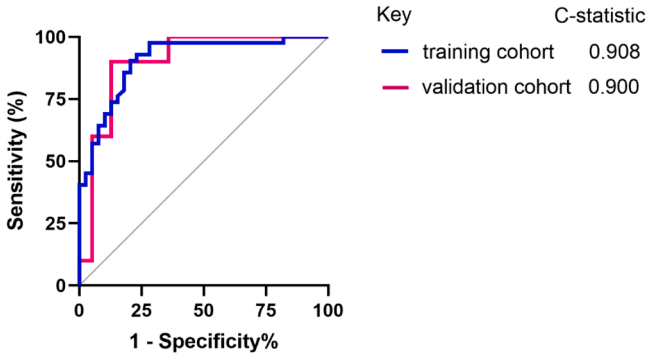

Fig 2. ROC analysis to assess the diagnostic performance for FG in the training cohort and validation cohort.

inflammatory and infectious stimuli, particularly bacterial infections [22,24]. The evaluation of the ratio between CRP and PAB in blood samples has garnered significant attention due to their shared synthesis by hepatocytes. Our research has uncovered a significant positive correlation between an elevated CRP/PAB ratio and an increased prevalence of FG. Notably, the C-statistic values for CRP/PAB reached 0.908 in the training cohort and 0.900 in the validation cohort, respectively, underscoring its exceptional diagnostic performance in comparison to other parameters. Therefore, this parameter can serve as an early diagnostic tool for FG. Previous studies have found that an elevated CRP/PAB ratio was associated with higher mortality rates among patients in the medical intensive care unit (ICU) [25]. Conversely, a low CRP/PAB ratio in surgical patients has been shown to indicate successful closure of gastrointestinal fistulas [26]. These results strongly suggest that the CRP/PAB ratio is intricately linked to disease progression.

Blood biomarkers NLR and PLR have been reported as useful inflammatory and immune markers in various infections and tumor diseases [27–30]. Previous studies have shown that high NLR and high PLR are associated with higher mortality and morbidity rates in patients with FG [31,32]. However, Wirjopranoto [33] reported that only NLR had prognostic predictive value for FG, whereas PLR did not. In our studies, we found that NLR has modest diagnostic efficacy, while the diagnostic efficacy of PLR was lowest among compound inflammation factors. This is roughly consistent with previous research findings. SII is a new predictive marker recently developed [27], calculated as platelet count × neutrophil count / lymphocyte count or as platelet count × NLR ($\times 10^9$) (a modified expression to emphasize NLR). Recently, Ucaner et al. [34] proposed that there were no statistically significant interactions between SII and FG. Our report demonstrated that the diagnostic efficiency of SII was between NLR and PLR. Since changes in Plt are not obvious between FG and severe perianal abscesses, SII is not significant in the differential diagnosis of necrotizing fasciitis and perianal abscess compared to NLR and PLR.

One limitation of this study is the inability to accurately measure the time from disease onset to patient visit, as deep abscesses or FG may have been concealed in some patients, leading to difficulties in recalling discomfort time. Given the significance of timing in disease development [35], future studies should conduct more comprehensive investigations and quantification of patient visit times to mitigate potential interference with research findings. To minimize the impact of time-related factors on study results, we focused on analyzing blood routine and biochemical test results from patients' initial visits.

Conclusion

Compared to the LRINEC score and other inflammatory markers, the CRP/PAB ratio offers a more convenient and rapid clinical application method, facilitating risk stratification of patients at potential risk for developing FG. Early identification of FG and comprehensive surgical treatment will positively impact the prognosis and hospital stay duration for FG patients. Further research is warranted to elucidate these study findings in future investigations.

Funding

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Ethics approval

The present study carried out at Shenyang Coloproctology Hospital (Shenyang, Liaoning province, China). Research involving human subjects complied with all relevant national regulations and institutional policies and is in accordance with the Declaration of Helsinki (as revised in 2013) and has been approved by the Ethics Committee of Shenyang Coloproctology Hospital.

Informed consent

The requirement for obtaining informed consent was waived for all participants enrolled in this study by the Ethics Committee of Shenyang Coloproctology Hospital.

Data availability

Please contact author for data requests.

CRediT authorship contribution statement

Jin-Liang Zhu: Writing – review & editing, Writing – original draft, Data curation. **Hong-Jian Gao:** Writing – review & editing, Supervision. **Zhi-Tao Yin:** Writing – review & editing, Validation, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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