

A Promising New Predictive Factor for Detecting Bowel Resection in Childhood Intussusception: Lymphocyte-C Reactive Protein Ratio

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Abstract

Background: The most critical concern for management of childhood intussusception is the bowel resection due to the intestinal ischemia and necrosis. It is of great importance for early prediction of this problem. We investigate the value of various combinations of inflammatory factors to predict the intestinal necrosis and resection.

Methods: We retrospectively reviewed the medical records of pediatric patients with intussusception, which undergone surgical management. During the research period, 47 patients undergone intestinal resection due to intestinal necrosis and 68 patients without intestinal resection were enrolled. We evaluated the diagnostic values of various combination of inflammatory markers from preoperative period laboratory analyses using the receiver operating characteristic (ROC) method.

Results: In the current cohort, 115 patients were operated for intussusception, among them, 47 patients (40.9%) undergone intestinal resections. In patients with intestinal resections, neutrophil count($p=0.013$), CRP($p=0.002$), platelet–lymphocyte ratio(PLR, $p=0.008$), NLR(neutrophil–lymphocyte ratio, $p=0.026$), and LCR(lymphocyte–CRP ratio, $p<0.001$) values were significantly higher than those in the patients without any resections. Receiver operating characteristic (ROC) analysis results showed that the combination of lymphocytic count along with C-reactive protein levels (LCR) demonstrated the highest correlation with intestinal resection due to intussusception compared with other parameters in patients, with sensitivity of 0.82(0.73–0.86) and specificity of 0.80(0.57–0.94) for the diagnosis of strangulation.

Conclusion: The preoperative LCR level is a useful marker to predict the need for intestinal resection due to intestinal necrosis in patients with intussusception.

Introduction

Childhood intussusception is a serious emergent diseases, present with classic triad of abdominal pain, vomiting and red currant jelly stool[1, 2]. Most of the intussusception could be managed with non-operative reduction through fluoroscopic guided barium enema and pneumatic reduction, emergency surgery still should be performed in the cases with the non-operative reduction failed[3]. In terms of surgical planning and patient management, it is of great importance to early detect the potential complications as any delay may result into impairment of intestinal circulation, which can cause intestinal necrosis, perforation or life-threatening secondary peritonitis, resulting in bowel resection and mortality[4].

Based on this understood, the potential of biomarkers that can help identify patients with intestinal necrosis should be urgent need to develop. Systemic inflammation is currently recognized as the hallmark of intestinal necrosis, perforation or secondary peritonitis[5, 6]. Several systemic inflammatory markers, including neutrophil, CRP, albumin, platelets, lymphocytes, and also biomarker combination ratios, have been suggested for the early predict the various inflammatory conditions, like pancreatitis, acute appendicitis, cancer or mesenteric ischemia[7, 8, 9, 10]. Lymphopenia reflects acute inflammation

under stress conditions in addition to leukocyte counts and neutrophil ratio increase, which often used as hematological inflammatory markers.

In particular, the combination of inflammatory factors, like PLR (platelet-lymphocyte ratio), NLR (neutrophil-lymphocyte ratio), and CAR(CRP albumin ratio) have been suggested as valuable inflammatory biomarkers[7]. In the clinical practice for intussusception patients undergoing surgery, we should address what is the best combination of these factors in predicting intestinal necrosis in intussusception patients. Furthermore, the cut-off thresholds for this inflammatory markers should be investigated to estimate strangulation in the preoperative period.

In the current research, we performed the receiver operating characteristic (ROC) curve analysis to explore the predictive value of different combinations of biomarkers, involving the need for bowel resection.

Materials And Methods

Patient cohort

A retrospective review for a cohort of patients with the diagnosis of intussusception managed with procedure was performed in a collaborative multidisciplinary program from July 1, 2017 to June 30, 2019. The collaborative institutes included 4 pediatric general surgical dept. at Qingdao Maternity and Child Care Hospital, Yongchuan Hospital of Chongqing Medical University, Jinan Maternity and Child Care Hospital and Chongqing Children's Hospital. All of them provide tertiary care in their districts with a capacity of over 1500 beds. The patients should also meet the following inclusion criteria: age>0.5 year and <5 years; enema reduction failure, preoperative atropine administration. The subjects were excluded if they were managed directly with operation. Additionally, we only enrolled the patients undergone the open operation to achieve a more homogenous cohort of patients. The current study protocol was performed following the expedited ethical committee approval by the Institutional Review Board of the Chongqing Medical University under the protection of personal information.

In the clinical practice, this following standard protocol was followed with management the patients with intussusception, enema reduction was firstly attempted under the pressure of 12 kPa, and if patients were still not reduced, the procedures were stopped and the patients were taken to operation room immediately for surgical manual reduction or resection with bowel anastomosis. A total of 125 patients undergone laparotomy was enrolled during the research period, and the patients were divided into two groups according to the intestinal resection or not: with resection group compared with no resection group. Intestinal necrosis is comprehensively evaluated based on the usual practice to get the blood flow back, which decided the resect for the bowel segment.

Data assessment

The laboratory data on admission collected from the medical records which were obtained within 2 days prior to the surgical administration were reviewed. The following inflammation associated biomarkers

were routinely measured during the operation, including neutrophil, platelet, CRP, lymphocyte and albumin. We further investigated several combination of inflammatory markers to identify the highest accuracy one for prediction intestinal resection in patients with intussusception, including NLR, PLR, LCR and CAR.

Statistics

The statistical software SPSS (Version 22.0, SPSS Inc., Chicago, IL) was conducted for the data statistical analysis. The continuous data are presented with means \pm standard deviations and medians (interquartile ranges) according to data distribution and compared using the Mann-Whitney U test, the Shapiro–Wilk test or the Wilcoxon rank-sum test, when applicable. Categorical variables are expressed as frequencies (percentages) and tested using Fisher's exact test or chi-squared test.

Receiver operating characteristic (ROC) analysis was conducted to value the various parameters for detecting bowel resection through the area under the curve (AUC) calculation. The Youden index in the ROC analysis was carried out to identify the best cut-off points of the different parameters. Statistical significance was set at $p < 0.05$.

Results

A total of 115 patients within the study period meet the previously mentioned inclusion criteria and were subjected to final investigation, of which, 47 patients (40.9%) were managed with the intestinal resection. The baseline features based on intestinal resection or not were presented in Table 1. As shown in the Table 1, the distribution of demographic were comparable, including age, gender distribution, duration of symptoms. There were statistical differences between the two groups regarding the features of severity covariates, including diameter of lesion at admission ($p = 0.006$). There was more presentation of red currant jelly stool in the patients with intestinal resection, suggesting severe strangulation condition ($p = 0.007$). No statistic differences were detected in terms of lesion location between the two groups.

Table 1
Baseline characteristic of eligible population

	Total Population		
	without intestinal resection(68)	With intestinal resection(47)	p Values
Age (yrs), mean \pm SD	1.87 \pm 0.92	1.79 \pm 0.88	0.21
Female: Male	183(37.5)	191(39.9)	0.31
Weight (kg), mean \pm SD	9.34 \pm 2.57	9.22 \pm 2.61	0.22
Duration of symptoms on admission(hours), Means \pm SDs	15.21 \pm 11.54	14.76 \pm 11.38	0.19
The time to operation after admission(hours), Means \pm SDs	5.87 \pm 2.65	5.38 \pm 2.84	0.26
Clinical symptoms, N (%)			
Abdominal pain	35	26	0.42
vomiting	62	46	0.14
red currant jelly stool	31	33	0.007
Location of lesion			
ascending colon	19	11	0.37
hepatic flexure of colon	35	21	0.30
Splenic Flexure of Colon	14	13	0.20
sigmoid colon	0	2	0.17
Diameter of lesion(mm), median (range)	24.6 (20.9–32.8)	28.7 (22.5–39.7)	0.006

To identify the potential of biomarkers for intestinal necrosis, we explore several parameters, that might acutely reflected the strangulation condition, including neutrophils, platelets, CRP, lymphocytes and albumin. Moreover, we identified few combinations of above factors, especially the up and down regulation combinations, that might offer the more accuracy in predicting intestinal resection in intussusception patients.

As shown in Table 2, the intestinal resection was associated with the higher neutrophil count($p=0.013$), CRP($p=0.002$). Similar trend was detected in the combinations of above parameters, like PLR($p=0.008$), NLR($p=0.026$). Moreover, the anemia was more critical in the patients with intestinal resection ($p=0.087$), in concert with a higher proportion of patients needing intreoperation transfusion (data not shown), although statistic significance were not attained.

Table 2
Comparison of the preoperative hematologic and biochemical parameters of the two groups

	without intestinal resection(68)	With intestinal resection(47)	P
Preoperative Hb level(g/dL), Mean ± SD	11.37±2.66	12.81±3.16	0.087
Albumin(g/L), mean ± SD	39.52±5.68	34.67±6.26	0.102
Lymphocyte(10 ⁹ /L), mean ± SD	1.47±1.1	1.16±0.89	0.064
Neutrophil(10 ⁹ /L), mean ± SD	6.59±3.87	8.78±5.47	0.013
CRP(g/L), mean ± SD	9.42±4.26	12.87±6.83	0.002
Platelet(10 ⁹ /L), mean ± SD	238.3±102.8	276.33±130.15	0.056
PLR, mean ± SD	152.9±127.8	216±184.2	0.008
NLR, mean ± SD	4.64±3.39	6.97±5.11	0.026
LCR, mean ± SD	0.1498±0.0841	0.0963±0.0521	<0.001
CAR, mean ± SD	0.2561±0.1923	0.3218±0.2123	0.083
Abbreviations: CAR=CRP-albumin ratio; CRP=C-reactiveprotein; LCR=lymphocyte–CRP ratio; NLR=neutrophil–lymphocyte ratio; PLR=platelet–lymphocyte ratio			

The ROC results for all these parameters are shown in Table 3. The area under the curve was found to be statistically significant for CRP(p=0.011), PLR(p=0.008), LCR(p<0.001), and NLR(p=0.028)(Table3), which could significantly indicate intestinal resection with a relatively high accuracy. The highest degree of accuracy was observed for the preoperative LCR at the cut off value of 0.121 in patients with intussusception, with sensitivity of 0.82(0.73–0.86), specificity of 0.80(0.57–0.94), and AUC of 0.81(0.67–0.93).

Table 3
ROC curve results and sensitivity, specificity values

	CRP	albumin	PLR	LCR	NLR	CAR
AUC (95% CI)	0.71(0.59–0.84)	0.764(0.67–0.83)	0.69(0.48–0.71)	0.81(0.67–0.93)	0.74(0.63–0.89)	0.69(0.51–0.84)
p values	0.011	0.083	0.008	<0.001	0.028	0.064
Cut-off	>11.26	>29.4	>188.5	<0.121	>5.72	0.286
Sensitivity (95% CI)	0.68 (0.52–0.81)	0.52(0.38–0.71)	0.80(0.57–0.92)	0.82(0.73–0.86)	0.72(0.61–0.82)	0.51(0.36–0.68)
Specificity (95% CI)	0.81(0.72–0.93)	0.83 (0.71–0.88)	0.69(0.53–0.82)	0.80(0.57–0.94)	0.83(0.71–0.96)	0.77(0.57–0.89)

Discussion

In the current study, we explored the distinguishing power of combinations of various factors especially the up and down combinations, detected with the preoperative routine laboratory work, and delineate several findings. The major finding in this research was that LCR defined as the combination of lymphocyte counts along with CRP levels, was found significantly lower in the patients underwent intestinal resection compared with the patients without resection. Compared with other parameters, like neutrophil count, CRP level and NLR level, LCR is a more reliable indicator of intestinal resection in patients with intussusception.

The intussusception can become strangulated, which can cause bowel ischemia and necrosis due to the blood flow blocking. The operation is highly important to avoid the intestinal ischemia and necrosis in intussusception, because a delayed response might cause unnecessary bowel resection, sepsis, and even death [11, 12], all these were serious complications following bowel ischemia and necrosis due to intussusception. The primary rationale for early operative intervention is to avoid bowel resection due to ischemia[13]. Previous studies have suggested that approximately one-half of children admitted with intussusception required an surgical intervention[14], although conservative management was first attempted for a interval of 5.5 hours.

To determine the presence of ischemia, there are accumulating studies indicating various factors involve in systemic inflammatory condition. In peripheral blood, as a result of strangulation, a measurable inflammatory factors could be detected, which were response and released from the local ischemic intestinal wall [15]. In many disease conditions, various inflammatory indicators have been suggested valuable in diagnosis and treatment monitoring [16]. However, the best parameters for predicting the bowel ischemia and necrosis using peripheral blood systemic inflammatory factors examination in intussusception patients remains unclear.

In present study, we found that the surrogate marker of the severity of the inflammatory response were significantly higher for CRP and leukocyte count values and lower for albumin and lymphocyte in the patients who underwent intestinal resection, compared the patients without intestinal resections, indicating the inflammatory response for the intestinal ischemia and necrosis. ROC analysis was further conducted to investigate the optimal accuracy for the involved surrogate markers. In previous research involved the inguinal hernia, LCR was indicated to be higher in the patients with strangulation and could be a predictor to indicate bowel resections[5]. In another multivariate analysis, NLR was also found to be significantly related to hernia strangulation with obvious bowel ischemia[18]. It was concluded that certain surrogate markers can be used to predict intestinal necrosis and had clinical correlations. Furthermore, LCR has been associated with the prognosis of specific cancer patients, like stomach cancer and colorectal cancer[7, 16, 19]. similarly, Our result with ROC analysis showed that among all these parameters, LCR was alone a good inflammatory parameter, strongly related with intestinal resection. Although LCR has been researched in many inflammatory conditions, to our knowledge, the use of LCR in the prediction of intestinal resection was firstly reported here in the current study.

In various clinical settings, including the present intestinal resection in our patients, the LCR value, was found the most rapid respond indicator reflecting systemic inflammatory responses[7]. Here the LCR value represent the combination of the immunological and inflammatory response with the intestinal ischemia due to strangulation during the preoperative period. the negative predictive value was come from the contribution of lymphocyte[21, 23]. because peripheral lymphocytes should contribute to the host cytotoxic immune response to intestinal microflora and CRP is alone a good factor as an inflammatory marker[20]. As indicated in the current study, low LCR value means an enhancement of systemic inflammatory response or impaired immunological response in patients with intussusception and could be used to assess the intestinal ischemia.

A retrospective analysis reported that the CRP and NLR levels were increase in acute pancreatitis patients[23]. Another research suggested that NLR levels were significantly associated with patients with acute mesenteric ischemia, and underwent intestinal resection[24, 25]. In the current research, NLR, CRP, neutrophil count were found significantly increased in the patient with intestinal resection. Among them, the LCR represented the most valuable indicative marker, which, is simple and easy to calculate using routine laboratory data without an additional technique or cost.

We acknowledged that the present results must be considered in the context of its limitations, which should be interpreted cautiously. The samples size collected in the current research was still somewhat smaller. Although the study was a single center investigation, the diagnosis of intestinal necrosis and decision on the resection depended on the opinion of individual surgeon, which should be subjective, with the possibility of over or under-classification of the degree of intestinal necrosis. In order to conduct a powerful study that specifically aimed at intestinal necrosis in intussusception, further investigation with more patients would need to be recruited to validate the role of preoperative LCR with consistent cut-off value in patients undergoing intestinal resection.

In conclusion, the current research suggested that preoperative LCR from routine hematologic parameters was a promising predictive factor for bowel resection in patients with intussusception, which should also be effective for perioperative management. To date, no other study has addressed this issue specifically in pediatric with appendicitis.

Declarations

Compliance with Ethical Standards:

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Authors' contributions: BC, JC and CG designed the study and analyzed the data. CY, CZ and JC evaluated the manuscript. CG and CY performed the statistical measurements and analyzed the data. CG analyzed the data and wrote the paper. All authors have read and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest: The authors declare that they have no competing interests.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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