Lymphocyte-C reactive protein ratio is a promising indicator for predicting intestinal necrosis in neonates with portal venous gas

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Research Article

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Abstract

Purpose: Portal venous gas (PVG) in neonates is a special abdominal imaging, which often indicates the occurrence of intestinal ischemia and necrosis, and is also an indicator to evaluate the severity and surgical timing of neonatal necrotizing enterocolitis. The timely identification and intervention of intestinal necrosis in neonates with PVG is particularly important, but it is still difficult at present. Various inflammatory factors in predicting prognosis and surgery timing have been described in adult literature, but rarely in neonatal literature. Therefore, we investigate the value of inflammatory factors in predicting intestinal necrosis in neonates with PVG.

Methods: We retrospectively reviewed the medical records of neonates with PVG detected by ultrasound in a tertiary-level referral hospital from January 2020 to December 2020. During the study period, 168 neonates with ultrasonographically identified PVG were included and were divided into two groups according to the presence of intestinal necrosis: a necrotic group (n=35) and a non-necrotic group(n=133). We evaluated the predictive values of various combination of inflammatory markers in preoperative period laboratory analyses using the receiver operating characteristic (ROC) method.

Results: In the current cohort, a total of 168 patients were identified. Of these, 35 patients (20.8%) underwent intestinal resection due to intestinal necrosis and 5 patients (3.0%) developed intestinal stricture after medical management. The overall survival rate was 164/168 (97.6%). In patients with intestinal necrosis, platelet count ($p<0.001$), lymphocyte count($p<0.001$), Eosinophil count($p<0.001$), CRP (C-reactive protein, $p<0.001$), PLR (platelet–lymphocyte ratio, $p=0.002$), NLR (neutrophil–lymphocyte ratio, $p=0.001$), LCR (lymphocyte–CRP ratio, $p<0.001$) and PCR (platelet- CRP ratio, $p<0.001$) values were significantly different with those in the patients without intestinal necrosis. Receiver operating characteristic (ROC) analysis results showed that the combination of C-reactive protein levels along with lymphocyte count (LCR) had the highest correlation with intestinal necrosis in neonates with portal venous gas [AUC 0.86 (95% CI 0.79–0.94); $p<0.001$], with sensitivity of 0.81(0.73–0.87) and specificity of 0.86(0.69–0.95) for the diagnosis of intestinal necrosis.

Conclusions: The preoperative LCR score is a promising indicator for predicting intestinal necrosis in neonates with PVG, which could be used as an additional criterion to guide surgical management.

1 Introduction

Portal venous gas (PVG), which is defined as the presence of gas in the portal venous system, is a rare radiologic sign first recognized in neonates with necrotizing enterocolitis (NEC) in 1955 by Wolfe[1]. This finding has historically been considered a poor prognosis and life-threatening factor in neonates with NEC for a long time, as it represents a late sign of intestinal ischemia and a relative indicator for surgical intervention[2–4]. With the development of radiology, more and more recent literatures have reported that PVG is not only present in neonates with intestinal ischemia, but also in those with benign condition, such as bowel inflammation, food allergies and so on[5–7]. Moreover, the strategy of PVG alone as an indication for surgery has been questioned and challenged[8–10]. Therefore, considering the life-threatening impact of intestinal necrosis on neonates, it is particularly important to identify new validated predictors for surgical intervention in neonates with PVG. However, few studies have reported about the surgical indications and prognosis in neonates with PVG.

The role of systemic inflammatory markers in predicting surgical outcomes and oncological prognosis has been widely described in adult studies, but rarely in neonatal studies[11–13]. Recently, several studies have shown that the systemic inflammatory markers such as CRP (C-reactive protein), CAR (C-reactive protein-albumin ratio) and LCR (Lymphocyte-C reactive protein ratio) are recognized as the predictors of intestinal necrosis[14–15]. Based on this understood, some systemic inflammatory markers may predict the occurrence of intestinal necrosis in neonates with PVG.

The aim of this study was to describe the characteristics and outcomes of a recent cohort of neonates with PVG at a tertiary-level referral hospital, and to investigate whether the systemic inflammatory markers have the potential to predict intestinal necrosis in neonates with PVG.

2 Materials And Methods

2.1 Study population and design

A retrospective cohort study of all neonates with PVG diagnosed by ultrasonography using a Philips iU 22 or a Aixplorer machine that were consecutively admitted to the specialized neonatal intensive care unit at the Chongqing Children's Hospital (i.e. large, tertiary- level referral hospital) from 1 January 2020 to 31 December 2020 was performed. All ultrasound images of patients were reviewed on the picture archiving and communication systems monitor (PACS) by the experienced attending ultrasound diagnostic physicians and the observations were noted by consensus. Inclusion criteria was ultrasound imaging evidence of PVG which was Confirmed by two experienced ultrasound diagnostic physicians. Exclusion criteria were severe cardiopulmonary malformation resulting in rapid death of the neonate due to cardiopulmonary failure and significant intestinal perforation. Finally, a total of 168 neonates with PVG were included in current study and were divided into two groups according to the presence of intestinal necrosis: a necrotic group and a non-necrotic group. The necrotic group was defined as the group undergoing surgery due to intestinal necrosis. The non-necrotic group was defined as the group that did not undergo surgery. The presence of intestinal necrosis was comprehensively confirmed by pathological reports and surgical findings.

2.2 Data assessment

The demographic characteristics of neonates and mothers were collected from the electronic medical records: gestational age (GA), birth weight (BW), gender, maternal age, mode of delivery and multiple pregnancies. Simultaneously, the principal clinical manifestations, clinical radiographic and complications were collected too. In addition, inflammation associated biomarkers at the time of diagnosis of PVG such as platelets, lymphocytes, neutrophils, eosinophils, CRP, NLR, PLR, LCR, PCR were further measured and analyzed to identify the highest accuracy one for prediction intestinal necrosis in neonates with PVG.

2.3 Statistics

The statistical analyses were performed using software SPSS (Version 22.0, SPSS Inc., Chicago, IL). The continuous data were expressed as the mean ± SD (standard deviation) or the median and interquartile range (IQR) and compared using t-tests or Mann-Whitney U test according to data distribution. The categories variables were expressed as number (%) and analyzed by Chi-squared test or Fisher's exact test, when applicable. A Receiver operating characteristic curve (ROC curve) was generated to value the various parameters for predicting intestinal necrosis through the area under the curve (AUC) calculation and to assess optimal cut-off points for the different parameters. The results with $P < 0.05$ were considered statistically significant.

2.4 Ethics Committee Approval

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 and was registered under number CHMU2021-189.

3 Results

3.1 Patients' baseline characteristics

A total of 168 consecutive neonates with confirmed PVG were identified during the study period and were subjected to final investigation. Of these, 87 patients (51.8%) were diagnosed with necrotizing enterocolitis (NEC), 35 patients (20.8%) with NEC were managed with intestinal resection due to bowel necrosis and 5 patients (3.0%) developed intestinal stricture after medical management. The mortality rate of neonates with PVG in our study was only 0.02% (4/168). The baseline features of the neonates with PVG among two groups were presented in Table 1. As shown in Table 1, the demographic characteristics were comparable, including gestational age, birth weight, mode of delivery. The neonates suffering from bowel necrosis were more likely lower gestational age ($P<0.001$) and lower birth weight ($P<0.001$). In addition, there were more presentations of abdominal distension and vomiting in the neonates with intestinal necrosis ($P<0.001$). No statistic differences were detected in terms of gender and age at diagnosis between the two groups.

Table 1

Baseline characteristic of 168 neonates with PVG

	Necrotic group (n=35)	Non-necrotic group (n=133)	P=
Age at diagnosis（d）	10(7-19)	11(7-16)	P=0.581
Weight at diagnosis（g）	2000（1780-2290）	2830（2375-3440）	P<0.001
Gender			P=0.205
Male	15（42.9%）	73（54.9%）	
Female	20（57.1%）	60（45.1%）	
Gestational age			P<0.001
Term	3（8.6%）	81（60.9%）	
Preterm（≤37 weeks）	30（85.7%）	51（38.3%）	
Very preterm（≤28 weeks）	2（5.7%）	1（0.8%）	
Birth weight			P<0.001
Normal	3（8.6%）	91（68.4%）	
Low birth weight (≤2500g)	23（65.7%）	36（27.1%）	
Very low birth weight（≤1500g）	9（25.7%）	6（4.5%）	
Pregnancy			P<0.001
Single	16（45.7%）	110（82.7%）	
Twin	19（54.3%）	23（17.3%）	
Mode of delivery			P=0.02
Normal delivery	2（5.7%）	43（32.3%）	
Cesarean delivery	33（94.3%）	90（67.7%）	
Clinical symptoms			
Fever	8（22.9%）	20（15%）	P=0.269
Diarrhea	3（8.6%）	40（30.1%）	P=0.009
Abdominal distension	31（88.6%）	46（34.6%）	P<0.001
Vomiting	28（80%）	48（36.1%）	P<0.001
Blood stool	29（82.9%）	106（79.7%）	P=0.676

Values are presented as median (IQR) or *n* (%)

Abbreviations: IQR=interquartile range.

3.2 Patients' laboratory parameters

To identify the potential of laboratory parameters for predicting intestinal necrosis, we detected several hematologic parameters that may reflect intestinal inflammatory conditions, such as WBC (white blood cells), platelets, lymphocytes, neutrophils, eosinophils, and CRP (C-reactive protein). Further, we explored some combinations of above indicators, especially the up and down regulation combinations, including PLR (platelet–lymphocyte ratio), LCR (lymphocyte–CRP ratio), NLR (neutrophil–lymphocyte ratio), PCR (platelet- CRP ratio). The hematologic parameters of the neonates with PVG among two groups were presented in Table 2. As shown in Table 2, the intestinal necrosis was associated with the higher CRP(P<0.001), PLR(P=0.002) and NLR(P=0.002), but with the lower WBC(P=0.005), platelets(P<0.001), lymphocytes(P<0.001), eosinophils(P<0.001), PCR(P<0.001) and LCR(P<0.001). Moreover, the

hemoglobin level in group with intestinal necrosis was significantly lower than that in group without intestinal necrosis(P=0.011). No statistic difference was detected in neutrophil count between the two groups.

Table 2

Comparison of the hematologic parameters of the groups

	Necrotic group (n=35)	Non-necrotic group (n=133)	P=
WBC(10/L)	6.79(4.48-13.28)	10.6(8.595-13.28)	P=0.005
Hb level(g/dL)	138.06±33.85	152.19±27.53	P=0.011
Platelets(10^9/L)	228.00(185.00-299.00)	338.00(267.50-432.50)	P<0.001
Lymphocytes(10/L)	1.75(1.19-3.33)	4.42(3.00-5.61)	P<0.001
Neutrophils(10/L)	4.91(1.95-8.04)	5.17(3.42-6.55)	P=0.459
Eosinophils(10/L)	0.00(0.00-0.10)	0.28(0.11-0.51)	P<0.001
CRP(g/L)	18.00(5.00-38.00)	5.00(3.00-7.00)	P<0.001
PLR	127.22(70.24-230.21)	80.66(59.35-113.36)	P=0.002
NLR	2.44(1.04-4.59)	1.10(0.76-1.80)	P=0.001
LCR	0.12(0.05-0.23)	0.55(0.35-0.70)	P<0.001
PCR	12.50(7.14-25.00)	33.33(25.00-50.00)	P<0.001

Values are presented as median (IQR) or *M*±*SD* or *n* (%)

Abbreviations: IQR=interquartile range; WBC=White blood cells; Hb=hemoglobin; CRP=C-reactive protein; PLR=platelet–lymphocyte ratio; NLR=neutrophil–lymphocyte ratio; LCR=lymphocyte–CRP ratio; PCR= platelet- CRP ratio.

3.3 Predictive Effects of hematologic parameters

A ROC curve analysis was performed to value all these hematologic parameters for predicting intestinal necrosis. The results are shown in Table 3. As shown in Table 3, the areas under the curve of eosinophils, PCR and LCR were more significant (AUC=0.82, P<0.001; AUC=0.84, P<0.001; AUC=0.86, P<0.001). A serum LCR of ≤0.27 at the time of diagnosis of PVG had the highest predictive ability at sensitivity of 81% (95% CI 73.3–87.2) and specificity of 86% (95% CI 69.0–94.6) in predicting intestinal necrosis in neonates with PVG (Table 3, Fig.1).

Table 3

ROC curve results and sensitivity, specificity values

	WBC	Hb level	Platelets	Lymphocytes	Eosinophils	CRP	PLR	LCR	NLR	PCR
AUC	0.65	0.63	0.73	0.78	0.82	0.77	0.67	0.86	0.68	0.84
(95% CI)	(0.52–0.78)	(0.51–0.74)	(0.64–0.83)	(0.68–0.89)	(0.73–0.90)	(0.67–0.88)	(0.56–0.79)	(0.79–0.94)	(0.58–0.79)	(0.76–0.92)
p values	0.005	0.022	<0.001	<0.001	<0.001	<0.001	0.002	<0.001	0.001	<0.001
Cut-off	<6.87	<117.50	<272.50	<3.42	<0.06	>8.5	>124.59	<0.27	>1.37	<17.51
Sensitivity	0.93	0.90	0.75	0.69	0.89	0.63	0.54	0.81	0.74	0.93
(95% CI)	(0.86–0.96)	(0.84–0.94)	(0.67–0.82)	(0.60–0.76)	(0.81–0.93)	(0.45–0.78)	(0.37–0.71)	(0.73–0.87)	(0.53-0.85)	(0.87–0.97)
Specificity	0.51	0.37	0.66	0.83	0.71	0.90	0.83	0.86	0.63	0.63
(95% CI)	(0.34–0.68)	(0.22–0.55)	(0.48–0.80)	(0.66–0.93)	(0.53–0.85)	(0.83–0.94)	(0.75–0.89)	(0.69–0.95)	(0.54–0.71)	(0.45–0.78)

Abbreviations: WBC=White blood cells; Hb=hemoglobin; CRP=C-reactive protein; PLR=platelet–lymphocyte ratio; NLR=neutrophil–lymphocyte ratio; LCR=lymphocyte–CRP ratio; PCR= platelet- CRP ratio.

4 Discussion

In our study, the mean gestational age and birth weight of neonates with PVG in necrotic group were significantly lower than those in non-intestinal necrosis group, which might reflect the correlation between surgery, gestational age and birth weight. This finding was consistent with the characteristics of neonates with NEC [16,17], which might be due to the distribution of disease in this study that most of patients (51.8%) were diagnosed with NEC. In addition, the surgical rate was 20.8% and the mortality rate was 0.02%, which might reflect the findings of several previous adult studies showing that most of the patients with PVG were in benign conditions that did not require emergency surgery[8,18].

In spite of this, considering the life-threatening impact of intestinal necrosis on neonates, timely recognition and intervention of intestinal necrosis in neonates with PVG is particularly important for the management of this disease. Previous studies have shown that the magnitude of systemic inflammation is correlated with the severity of intestinal ischemia. Yildirim M and Zhou H et al reported that combinations of inflammatory factors such as lymphocytes, neutrophils and CRP released by the ischemic intestinal wall could predict the occurrence of intestinal ischemia [14,19]. Amir T. Mohd Amin et al mentioned that CRP combined with albumin could predict surgical intervention and mortality in neonates with necrotizing enterocolitis[15]. Mengnan Yu et al demonstrated that white blood cell count and platelet count were closely related to surgery and death in neonates with necrotizing enterocolitis[20]. So, in the current study, we explored the value of different inflammatory factors in predicting intestinal necrosis in neonates with PVG. To our knowledge, no study has been reported about this in neonates with PVG before.

In present study, we found that leukocyte, platelet, lymphocyte, eosinophil, CRP values in necrotic group were significantly different from those in non-necrotic group. The surrogate marker of the severity of the inflammatory response were significantly higher for CRP value but lower for leukocyte, platelet, lymphocyte counts in the patients with intestinal necrosis. This result implies that higher concentration of CRP and lower plasma concentrations of leukocyte, platelet, lymphocyte are closely related to intestinal necrosis. However, the ability to predict intestinal necrosis in neonates with PVG by the single use of WBC or PLT was not great, so we further explored the predictive potential of combinations of inflammatory factors, including PLR, NLR, PCR LCR.

The significance of the PLR, NLR and LCR has previously been reported in a variety of adult conditions. It has been shown that NLR, PLR and LCR are useful markers in predicting the prognosis of patients with lung cancer[21], hepatocellular Carcinoma[22], colorectal Cancer[23], kidney disease [24] and COVID-19[25]. The higher LCR value has also been identified to be an independent predictor of intestinal ischemia in the patients with hernia strangulation[14]. To date, no studies have analyzed the combinations of inflammatory factors in neonates with PVG, especially the PCR (platelet- CRP ratio) firstly introduced in our study. Our result with ROC analysis showed among all these parameters, eosinophils, PCR and LCR were good inflammatory parameter, strongly related with intestinal necrosis. Compared with eosinophils and PCR, LCR is a more reliable indicator of intestinal resection in neonates with PVG. The cut-off value of LCR is 0.27, which means if the probability is less than or equal to 0.27, surgery should be considered.

We acknowledge that our study has limitations. First, it was a single-center retrospective study with a relatively limited number of patients. Second, the surgical decision for intestinal necrosis depended on the opinion of the individual pediatric surgeon, which was subjective and therefore variable. Therefore, a further multicenter prospective study with more patients is needed to validate the role of preoperative LCR in neonates with PVG. Finally, inflammatory biomarkers should only be used as an additional criterion to guide surgical management. The final decision of surgery should be made in conjunction with the clinical manifestations of the patients.

5 Conclusion

The current research suggests that preoperative LCR of ≤0.27 is a promising predictive factor for intestinal necrosis in neonates with PVG, which can be used as an additional criterion to guide surgical management. To date, no other studies have specifically addressed this issue specifically in neonates with PVG.

Declarations

Ethics approval and consent to participate

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. The current study protocol was performed following the expedited ethical committee approval by the Institutional Review Board of the Children's Hospital of Chongqing Medical University under the protection of personal information and was registered under number CHMU2021-189. The Institutional Review Board of the Children's Hospital of Chongqing Medical University approved informed consent waiver.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated during and analyzed during the current study are not publicly available due to ongoing analysis in other directions but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors’ Contributions

Jian Cao designed and analyzed the data and wrote the paper. Xinyin Zhang, Jinfeng Hou, Mengying Cui, Pengfei Chen and Qingshuang Liu collected the data and performed the statistical calculations. Chunbao Guo, Zhenhua Guo, Yi Wang, Wei Liu evaluated and modified the manuscript.

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