

Peer Review File

Article information: <https://dx.doi.org/10.21037/tp-23-56>

Reviewer A

This is a retrospective single center study evaluating the measures of multiple possible biomarkers for inflammation in preterm infants who are diagnosed with medical or surgical NEC. The authors conclude that the sensitivity and specificity of combined markers can help separate out those who need surgery from those who don't. They indicated that "Serum samples were collected before operation in the operation group and on the day of diagnosis in the nonoperation group". This may suggest that timing of sampling was possibly different in the two groups. If so then the utility of these tests may be underwhelming as those that reach peak surgical intervention are going to be inherently sicker and thus would have higher levels of inflammatory markers. It would be beneficial to have more data on the initial timing of the diagnosis and when samples were drawn. It was not clear if some infants had more than one measurement done. If available this information would be helpful. More clinical detail on how an infant was deemed a surgical candidate would have been important too. For example how was hemodynamic stability, change in hematologic values, persistent metabolic acidosis, change in abdominal exam, etc. factored into deciding who went for surgery. This would be above the presence of perforation.

Minor:

The manuscript should be edited by an English editor to ensure accuracy.

Reply: Thanks for your suggestion, the manuscript edited by an English editor to ensure accuracy

Line 57: Congestion is not an ideal term for the abdomen. Tenderness, swelling/edema, discoloration are findings with NEC.

Reply: Thanks for your suggestion. We revised it into "Neonatal necrotizing enterocolitis (NEC) is a common gastrointestinal emergency in newborns with abdominal distension tenderness, swelling/edema and discoloration as the main clinical manifestations."

Changes in the text: see Page 3, line 59-60.

Reviewer B

The paper titled "Predictive value of serum markers in the operation evaluation of neonatal necrotizing enterocolitis" is interesting. The serum markers CRP, PCT, IL-6, I-FABP, and SAA have certain guiding value in the choice of operation opportunity for pediatric patients with NEC. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) The abstract is not sufficient and needs further modification. The research background did not indicate the clinical needs of the research focus.

Reply: Thanks for your suggestion. Background: Neonatal necrotizing enterocolitis (NEC) is a common gastrointestinal emergency in newborns. Currently, the pathogenesis of the disease remains unknown, serum markers may have a certain reference value for the choice of NEC

surgery opportunity.

Changes in the text: see Page 2, line 27-30.

2) The description of some methods and results in this study is too simplistic, please describe in detail.

Reply: Thanks for your suggestion. We describe in detail. However, due to different detection indicators, there are some differences in the relevant details, but we have attached the product batch number, so it can be used as a reference.

Changes in the text: see Page 5-6, line 152-157.

3) In addition to the markers in this study, what other serum markers have predictive value in NEC? How to translate the discovery of markers into clinical applications? It is recommended to add relevant content.

Reply: Thanks for your suggestion. The analysis of a study showed that various serum markers have some significance in guiding the diagnosis and treatment, disease progression and prognosis of NEC (30). I-FABP, SAA, intestinal trefoil factor (ITF) have good sensitivity and specificity in predicting the diagnosis and severity of NEC. The sensitivity and specificity of CRP are good (31); increased CRP is a high-risk factor in children with NEC requiring surgical treatment (32). Procalcitonin (PCT) is a diagnostic marker for detecting bacterial infections (33); a severe decrease in serum protein and platelet (PLT) indicates a deterioration of NEC and even the possibility of perforation (34). The timeliness and validity of these serological indices have irreplaceable advantages and facilitate repeated monitoring, so they have good application prospects. However, based on the small sample size of this study and the fact that it is a retrospective analysis, some bias in the results may be caused, so it is necessary to further confirm the findings of this study through multicenter clinical trials while expanding the sample size in the future.

Changes in the text: see Page 10, line 292-304.

4) In the introduction of the manuscript, it is necessary to clearly indicate the pathogenesis of NEC.

Reply: Thanks for your suggestion. In addition, immaturity of the digestive system, mucosal barrier, gastrointestinal dynamics and intestinal bacterial translocation in preterm infants are also major causes of necrotizing small bowel colitis in newborns.

Changes in the text: see Page 3, line 64-67.

5) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “The protective effect and mechanism of epidermal growth factor on necrotizing enterocolitis in a neonatal rat model, *Transl Pediatr*, PMID: 34012839”. It is recommended to quote the article.

Reply: Thanks for your suggestion. This study is a clinical study, but this article is a basic study and the citation is somewhat inappropriate.

Changes in the text: NA.

6) This study is a retrospective analysis, which is likely to cause some deviations in the results. It needs to be further confirmed by multi-center clinical trials.

Reply: Thanks for your suggestion. We have already analyzed it in the discussion section

Changes in the text: see Page 10, line 298-301.

Editorial Comments (Please do not delete this section. Editorial comments should also be replied point by point.)

1. Since Dr. Qian Wang have no conflicts of interest to declare, we helped to fill the COI form. Please confirm whether you are ok with the attached COI form.

Reply: Thanks for your suggestion. We are satisfied

2. Correspondence

According to our new journal policy, please also indicate the **academic degrees** and **affiliation** of the corresponding author.

Here is an example:

Anthony Lemaire, **MD**, Division of Cardiothoracic Surgery, Department of Surgery, RUTGERS-Robert Wood Johnson Medical School, 125 Paterson Street, New Brunswick, NJ 08903, USA. Email: Anthony.lemaire@rwjms.rutgers.edu.

1
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5 ✉
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9 Tongji Medical College, Huazhong University of Science and Technology, Wuhan,
10 China ✉
11 ✉
12 Running title: Serum markers in necrotizing enterocolitis.✉
13 ✉
14 Contributions: (I) Conception and design: J Liu; (II) Administrative support: J Liu; (III)
15 Provision of study materials or patients: Q Wang; (IV) Collection and assembly of data:
16 Q Wang; (V) Data analysis and interpretation: K Jin, X Su; (VI) Manuscript writing: All
17 authors; (VII) Final approval of manuscript: All authors.✉
18 ✉
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Reply: Thanks for your suggestion. We are provided it.

Changes in the text: see Page 1, line 19-22

3. Abstract should be structured as: **Background, Methods, Results, Conclusions**. The objective sentence should be indicated in the Background. Please also revise it as a complete sentence.

30 **Abstract**[✉]
31 **Background:** At present, serum markers may have a certain reference value for the
32 choice of NEC surgery opportunity.[✉]
33 **Objective:** To determine the application value of serum markers in the selection of
34 operation opportunity for necrotizing enterocolitis (NEC).[✉]
35 **Methods:** This study consisted of a retrospective analysis of the clinical data of 150

Reply: Thanks for your suggestion. We revised it. **Background:** Neonatal necrotizing enterocolitis (NEC) is a common gastrointestinal emergency in newborns. Currently, the pathogenesis of the disease remains unknown, this study aims to determine the application value of serum markers in the selection of operation opportunity for NEC.

Changes in the text: see Page 2, line 27-30

4. Below pointed one in the ethics approval file is the ethics approval number. This one (V1.0,2022.6) is not the ethics arrival number. Please edit the ethical statement:

The study was approved by the ethics committee of Maternal and Child Health Hospital of Hubei Province (Approve number: *****).

湖北省妇幼保健院医学伦理委员会
伦理审查批件

[2023] IEC (017) 号

The value of serum markers in selecting the operation opportunity of

49 from the newborns' guardians. The study was approved by the Hubei Maternal and
50 Child Health Hospital ethics committee (Approve number: V1.0,2022.6).

Reply: Thanks for your suggestion. The study was approved by the ethics committee of Maternal and Child Health Hospital of Hubei Province (Approve number: 2023IEC017).

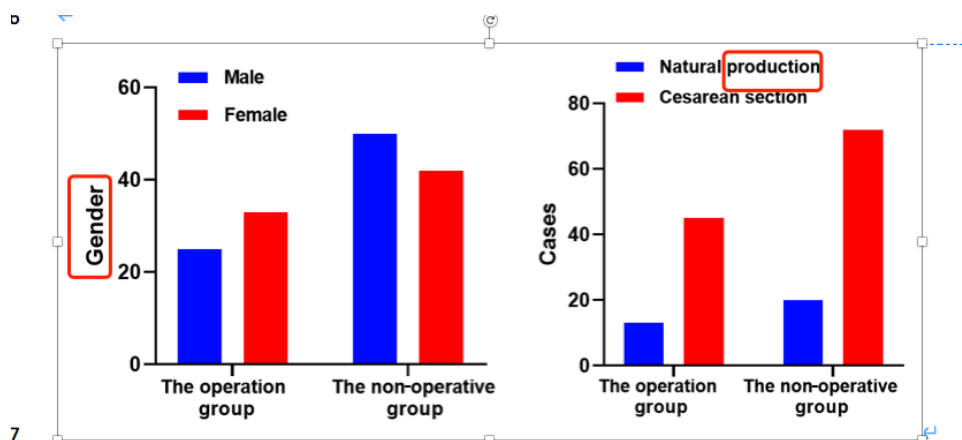
Changes in the text: see Page 5, line 141-145.

5. Figure 1

a. it seems that "Gender" is not appropriate as the description of Y-axis. Please revise.

b. please revise "natural production" to "natural birth".

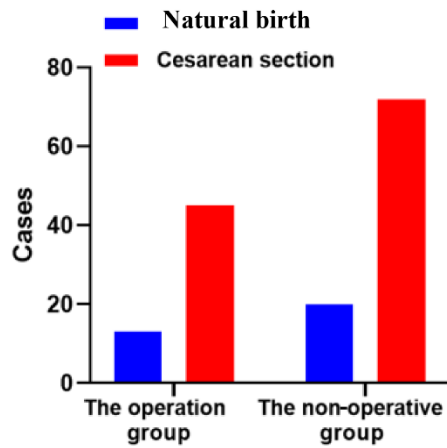
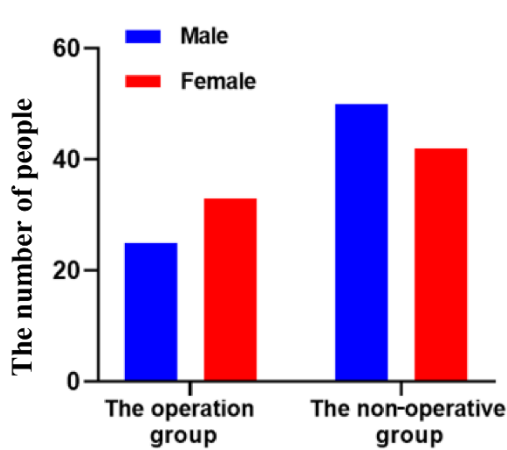
After revision, please send the revised figure 1 back to us as a separate file in jpg or tiff format.



8 Figure 1 Gender, natural birth, and cesarean section in the 2 groups.

9

Reply: Thanks for your suggestion.



Changes in the text: see Page 16, line 455.

6. You have resent us the tables. However, tables 1-2 are different from the one in the main text. Please confirm which version is correct. If the versions in the main text is correct, there is no need to resend us the separate file of tables.

For example:

406 [Ⓔ]

407 **Table 1** Comparison of basic data between the 2 groups [Ⓔ]

Grouping [Ⓔ]	n [Ⓔ]	Gender (male/female, n) [Ⓔ]	Gestational age (weeks) [Ⓔ]	Natural production/cesarean section (n) [Ⓔ]	Start of feeding time (days) [Ⓔ]	Birth weight (g) [Ⓔ]	Age (days) [Ⓔ]
Operation group [Ⓔ]	58 [Ⓔ]	25/33 [Ⓔ]	32.5±3.5 [Ⓔ]	13/45 [Ⓔ]	3.5±1.2 [Ⓔ]	1,580.5±440.2 [Ⓔ]	15.2±2.8 [Ⓔ]
Nonoperative group [Ⓔ]	92 [Ⓔ]	50/42 [Ⓔ]	32.1±3.6 [Ⓔ]	20/72 [Ⓔ]	3.3±1.0 [Ⓔ]	1,602.1±435.4 [Ⓔ]	14.8±2.5 [Ⓔ]
χ ² /t value [Ⓔ]	[Ⓔ]	1.799* [Ⓔ]	0.670 [Ⓔ]	0.009* [Ⓔ]	1.103 [Ⓔ]	0.295 [Ⓔ]	0.911 [Ⓔ]
P value [Ⓔ]	[Ⓔ]	0.180 [Ⓔ]	0.504 [Ⓔ]	0.923 [Ⓔ]	0.272 [Ⓔ]	0.769 [Ⓔ]	0.364 [Ⓔ]

408 Data are presented as mean ± standard deviation if not otherwise specified. * in

409 χ² value.[Ⓔ]

Ⓔ Table 1 Basic data between the two groups was compared[Ⓔ]

Grouping [Ⓔ]	n [Ⓔ]	Gender (male/female, n) [Ⓔ]	Gestational age (weeks) [Ⓔ]	Natural production/cesarean section (n) [Ⓔ]	Start feeding time (d) [Ⓔ]	Birth weight (g) [Ⓔ]	Diagnosis age (d) [Ⓔ]
The operation group [Ⓔ]	58 [Ⓔ]	25/33 [Ⓔ]	32.5±3.5 [Ⓔ]	13/45 [Ⓔ]	3.5±1.2 [Ⓔ]	1580.5±440.2 [Ⓔ]	15.2±2.8 [Ⓔ]
The nonoperative group [Ⓔ]	92 [Ⓔ]	50/42 [Ⓔ]	32.1±3.6 [Ⓔ]	20/72 [Ⓔ]	3.3±1.0 [Ⓔ]	1602.1±435.4 [Ⓔ]	14.8±2.5 [Ⓔ]
χ ² /t value [Ⓔ]	[Ⓔ]	1.799* [Ⓔ]	0.670 [Ⓔ]	0.009* [Ⓔ]	1.103 [Ⓔ]	0.295 [Ⓔ]	0.911 [Ⓔ]
P value [Ⓔ]	[Ⓔ]	0.180 [Ⓔ]	0.504 [Ⓔ]	0.923 [Ⓔ]	0.272 [Ⓔ]	0.769 [Ⓔ]	0.364 [Ⓔ]

Note: * was marked as χ² value.[Ⓔ]

Reply: Thanks for your suggestion. The versions in the main text is correct
Changes in the text: NA.