Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.339842.3706 Volume 31, Issue 3, March. 2025
Manuscript ID: ZUMJ-2411-3706
DOI: 10.21608/ZUMJ.2024.339842.3706
ORIGINAL ARTICLE

The Role of Plasma Receptor Interacting Protein3 in Early Detection of Neonatal Sepsis

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Submit Date: 27-11-2024
Accept Date: 22-12-2024

ABSTRACT:

Background: In neonatal sepsis, the purpose of this study is to investigate the possible diagnostic and prognostic utility of receptor interacting protein 3 (RIP3). **Methods:** This case control study included 70 participants divided into 2 groups, 35 sepsis cases and 35 controls. Plasma level of Receptor Interacting Protein (RIP3) before and after antibiotic treatment was assessed to all subjected participants. **Results:** There was highly statistical significant difference between the two groups as regards RIP3 levels. Regarding RIP3 (pg/mL), AUC was 0.848, Cutoff value was 16375.5, Sensitivity was 74.3% and Specificity was 97.1%. Regarding RIP3 + hs-CRP combination, AUC was 0.848, Cutoff value was 16378.75, Sensitivity was 74.3% and Specificity was 97.1%. Regarding RIP3 + PLT combination, AUC was 0.851, Cutoff value was 16557.5, Sensitivity was 74.3% and Specificity was 97.1%. Regarding RIP3 + hs-CRP + PLT combination, AUC was 0.851, Cutoff value was 16560.75, Sensitivity was 74.3% and Specificity was 97.1%. **Conclusion:** The early detection and comprehension of the therapeutic impact of newborn sepsis may be attributed to RIP3. When diagnosing neonatal sepsis, the simultaneous detection of RIP3, CRP, and PLT may be more useful than their separate detection.

Keywords: Sepsis, Receptor Interacting Protein 3, Platelets, C-reactive protein.

INTRODUCTION

In neonatal populations, the primary cause of morbidity and death is newborn sepsis [1–3]. Due to its very varied clinical characteristics and potential for confusion with non-infectious illnesses, newborn sepsis is difficult to diagnose early [4, 5]. Multiple organ dysfunctions can quickly result from improper diagnosis and postponed therapy [6-8].

Additionally, behavioral and neurocognitive dysfunction, mood disorders, and other issues substantially burden society and the medical system, and poor quality of life that some neonatal sepsis survivors may have [2, 9]. To enhance outcomes and prognosis, newborn sepsis must be diagnosed as soon as possible. Nevertheless, despite significant efforts, early detection of newborn sepsis continues to be a major worldwide concern.

Blood culture remains a gold standard for diagnosing neonatal sepsis, though its sensitivity is limited due to small blood volumes and prior antibiotic use. Furthermore, procalcitonin (WBC), platelet count (PLT), white blood cell count, and C-reactive protein (CRP) are more sensitive indicators for diagnosing infectious illnesses in neonates [10].

In recent years, Numerous biomarkers, such as cell surface antigens, bacterial surface antigens, and genetic biomarkers, have been assessed. There is a lot of interest in using protein biomarkers, cytokines, and chemokines to detect neonatal sepsis [11, 12]. Currently, no single biomarker achieves optimal sensitivity and specificity, but combinations like RIP3 with hs-CRP and PLT show promise [1, 11].

The RIP kinase family includes receptor interacting protein (RIP) 3 [13]. According to recent data, RIP3-dependent necroptosis may be triggered in a number of illnesses [14–16]. Apoptosis is triggered when the tumor necrosis factor receptor attaches to a ligand due to biological or physicochemical events. It then uses RIP1, caspase-8, and Fas-associated protein with death domain (FADD) to

form complex I. [16]. By attaching to RIP3 and enlisting FADD and caspase-8 to form complex II, inhibiting caspase-8 activity prevents apoptosis and changes into a programmed necrosis pathway that promotes cell death and proliferation. Numerous damage-associated molecular patterns (DAMPs) emerge, which sets forth a strong inflammatory response. [17].

RIP3 might help with early sepsis diagnosis and treatment effect monitoring. Sepsis may be easier to detect when RIP3, hs-CRP, and PLT are detected together rather than separately [18]. Examining receptor interacting protein 3's possible diagnostic and prognostic use in neonatal sepsis is the goal of this investigation (RIP3).

METHODS

This study was carried out at Zagazig University's Pediatrics Department at the Faculty of Medicine on seventy people participated in this case-control study; thirty-five were sepsis cases and thirty-five were controls. The study was approved by ethical committee of Faculty of Medicine, Zagazig University (IRB number 10362-18-1-2023).

Before and after receiving antibiotic treatment, all patients underwent a complete history taking, a comprehensive clinical examination, comprehensive laboratory testing that measures the plasma levels of procalcitonin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and complete blood count (CBC). Plasma levels of RIP3 were measured using validated neonatal-specific ELISA kits

Statistical analysis:

SPSS 26.0 for Windows was used to gather, tabulate, and statistically analyze all of the data (SPSS Inc., Chicago, IL, USA). Numbers and percentages were used to describe the qualitative data. The mean, standard deviation, median, and range (minimum and maximum) were used to characterize quantitative data. Every statistical comparison was significant and two-tailed. The difference is considered significant if the P-value is less than 0.05, extremely significant if it is less than 0.001, and non-significant if it is greater than 0.05. The proportions of qualitative components were compared using the Chi-square (X2) test of significance. Two independent groups were compared using parametric quantitative data and the independent T-test. Through the use of receiver operating characteristic (ROC) curve analysis, the optimal cut-off value was determined, along with the detection of sensitivity and specificity at this cut-off value and the overall predictivity of the parameter.

RESULTS

There were 35 sepsis patients and 35 controls in this study. No statistically significant difference was found (p=0.149) between the two groups. The age (days) in the Sepsis group varied from 10 to 22 with mean ± SD = 15.74 ± 2.65, whereas the age (days) in the Control group ranged from 8 to 20 with mean ± SD = 14.83 ± 2.6. The two groups under study did not differ statistically significantly in terms of sex (p=0.806) (Table 1).

Outcomes of lab tests conducted on the study groups. In the Sepsis group, the WBC (× 109/L) ranged from 4.4 to 11.8 with mean ± SD = 7.47 ± 1.68, while in the Control group, it ranged from 7.6 to 10.8 with mean ± SD = 9.09 ± 0.94. The statistical significance of the difference between the two groups was very strong (p=<.001). The Sepsis group's PLT (×109/L) ranged from 128 to 249 with mean ± SD = 187 ± 30.88, whereas the Control group's PLT (×109/L) ranged from 167 to 250 with mean ± SD = 213.57 ± 25.19. The two groups' differences were highly statistically significant (p=<.001) (Table 2).

Procalcitonin (pg/dl) varied from 77 to 223 in the Sepsis group, with mean ± SD = 155.97 ± 35.52, and from 91 to 109 in the Control group, with mean ± SD = 99.43 ± 4. There was a highly statistically significant difference between the two groups (p=<.001). The hs-CRP (mg/l) varied between 1.2 and 11.8 in the Sepsis group, with mean ± SD = 6.32 ± 3.49, and between 1.2 and 3.3 in the Control group, with mean ± SD = 1.87 ± 0.6. The statistical significance of the difference between the two groups was very strong (p=<.001). In terms of blood culture, the two groups under study differed significantly (p=<.001).

Regarding comparing the outcomes of laboratory tests conducted on newborn sepsis patients before and after therapy. WBC (× 109/L) varied from 4.4 to 11.8 in the Sepsis group with mean ± SD = 7.47 ± 1.68, and from 3.7 to 10 in the Control group with mean ± SD = 6.35 ± 1.42. The difference between the two groups was statistically significant (p=0.004). PLT (×109/L) varied between 128 and 249 in the Sepsis group, with mean ± SD = 187 ± 30.88, and between 141 and 274 in the Control group, with mean ± SD = 205.74 ± 34.07; the two groups' differences were statistically significant (p=0.019).

The difference between the two groups was statistically significant (p=0.004). Procalcitonin

(pg/dl) ranged from 77 to 223 in the Sepsis group, with a mean ± SD of 155.97 ± 35.52. In contrast, the Control group it ranged from 65 to 190 with mean ± SD = 132.51 ± 30.21. Hs-CRP (mg/l) varied between 1.2 and 11.8 in the Sepsis group, with mean ± SD = 6.32 ± 3.49, and between 1.8 and 9.4 in the Control group, with mean ± SD = 5.95 ± 2.18. There was no statistically significant difference (p=0.598) between the two groups.

While the RIP3 (pg/mL) of the Control group ranged from 6148 to 19324 with mean ± SD = 11642.63 ± 3186.99, that of the Sepsis group ranged from 8968 to 28647 with mean ± SD = 19558.71 ± 6188. The differences between the two groups were statistically significant (p=<.001) (Figure 1).

RIP3 levels in sepsis neonates showed a significant increase (mean ± SD = 19,558.71 ± 6,188) compared to controls ($p < 0.001$), supporting its diagnostic utility (Figure 2).

The RIP3 plasma level's cut-off value, sensitivity, and specificity were used in a receiver operating characteristic (ROC) curve study to forecast neonatal sepsis. Regarding RIP3 (pg/mL), the AUC was 0.848, the cutoff value was 16375.5, the sensitivity was 74.3%, and the specificity was 97.1%. Regarding hs-CRP (mg/L), the AUC was 0.887, the cutoff value was 3.25, the sensitivity was 74.3%, and the specificity was 97.1%. Regarding PLT (×109/L), Figure 3 displays that the sensitivity was 80.0%, the specificity was 60.0%, the cutoff value was 189.5, and the AUC was 0.742.

Combining RIP3 and hs-CRP improves sensitivity (74.3%) and specificity (97.1%), suggesting a synergistic diagnostic role. For the RIP3 + PLT combination, the AUC was 0.851, the cutoff value was 16557.5, the sensitivity was 74.3%, and the specificity was 97.1%. For the hs-CRP + PLT combination, the AUC was 0.796, the cutoff value was 194.8, the sensitivity was 88.6%, and the specificity was 62.9%. For the RIP3 + hs-CRP + PLT combination, the AUC was 0.851, the cutoff value was 16560.75, the sensitivity was 74.3%, and the specificity was 97.1% (Figure 4).

Table 1: Baseline data among studied groups

	Sepsis group (n = 35)	**Control group (n = 35)**	**Test of Sig.**	**p**
Age (days)				
Mean ± SD.	15.74 ± 2.65	14.83 ± 2.6	**t = 1.458**	**0.149**
Median (IQR)	15 (14 - 17.5)	15 (14 - 16.5)		
Range (Min-Max)	12 (10 - 22)	12 (8 - 20)		
Sex				
Male	22 (62.86%)	21 (60%)	**X2 = 0.06**	**0.806**
Female	13 (37.14%)	14 (40%)		
Pregnancy data				
Multiple pregnancy	6 (17.14%)	7 (20%)	**X2 = 0.094**	**0.759**
Spontaneous pregnancy	32 (91.43%)	33 (94.29%)	**X2 = 0.215**	**0.643**
GDM	4 (11.43%)	4 (11.43%)	**X2 = 0**	**1**
PROM	5 (14.29%)	4 (11.43%)	**X2 = 0.128**	**0.721**
Delivery data				
Gestational age	33.03 ± 1.46	33.63 ± 1.42	**t = -1.742**	**0.086**
Birth weight	1539.8 ± 132.99	1584.29 ± 150.31	**t = -1.311**	**0.194**
Delivery mode -Vaginal delivery -CS	 19 (54.29%) 16 (45.71%)	 22 (62.86%) 13 (37.14%)	**X2 = 0.53**	**0.467**
APGAR 1m score (<7) APGAR 5m score (<7)	2 (5.71%) 0 (0%)	4 (11.43%) 0 (0%)	**X2 = 0.729** **$\chi 2 = 0$**	**0.393** **1**

Table 2: Lab investigations results among the study groups

	Sepsis group (n = 35)	Control group (n = 35)	Test of Sig.	p
WBC (× 109/L)			**t = -4.949**	**<0.001**
Mean ± SD.	7.47 ± 1.68	9.09 ± 0.94		
PLT (× 109/L)			**t = -3.945**	**<0.001**
Mean ± SD.	187 ± 30.88	213.57 ± 25.19		
Procalcitonin (pg/dl)			**t = 9.358**	**<0.001**
Mean ± SD.	155.97 ± 35.52	99.43 ± 4		
hs-CRP (mg/L)			**t = 7.436**	**<0.001**
Mean ± SD.	6.32 ± 3.49	1.87 ± 0.6		
Blood culture			**X2 = 70**	**<0.001**
Staphylococcus aureus	8 (22.86%)	0 (0%)		
Staphylococcus epidermidis	7 (20%)	0 (0%)		
E.coli	6 (17.14%)	0 (0%)		
Enterobacter	5 (14.29%)	0 (0%)		
E.coli+ Klebsiella	4 (11.43%)	0 (0%)		
Streptococcus pyogens	2 (5.71%)	0 (0%)		
Non-hemolytic streptococci	2 (5.71%)	0 (0%)		
Staphylococcus saprophyticus	1 (2.86%)	0 (0%)		
Negative (Sterile culture)	0 (0%)	35 (100%)		

Table 3: Comparison between Lab investigations results in children with neonatal sepsis before and after treatment

	Sepsis group before ttt (n = 35)	Sepsis group after ttt (n = 35)	Test of Sig.	p
WBC (× 109/L)			**t = 3.009**	**0.004**
Mean ± SD.	7.47 ± 1.68	6.35 ± 1.42		
PLT (× 109/L)			**t = -2.411**	**0.019**
Mean ± SD.	187 ± 30.88	205.74 ± 34.07		
Procalcitonin (pg/dl)			**t = 2.976**	**0.004**
Mean ± SD.	155.97 ± 35.52	132.51 ± 30.21		
hs-CRP (mg/L)			**t = 0.53**	**0.598**
Mean ± SD.	6.32 ± 3.49	5.95 ± 2.18		

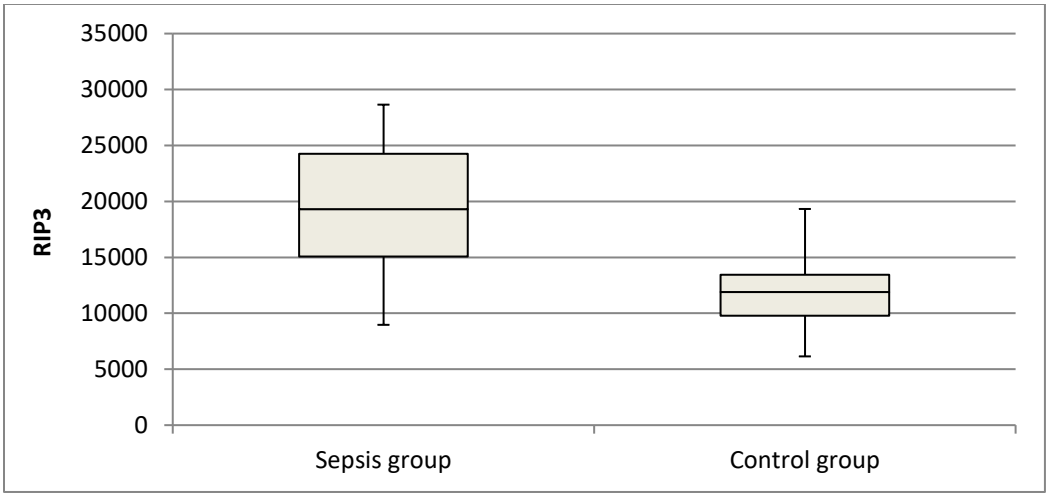

Figure 1: Box-plot showing difference between the study groups regarding RIP3 (pg/mL).

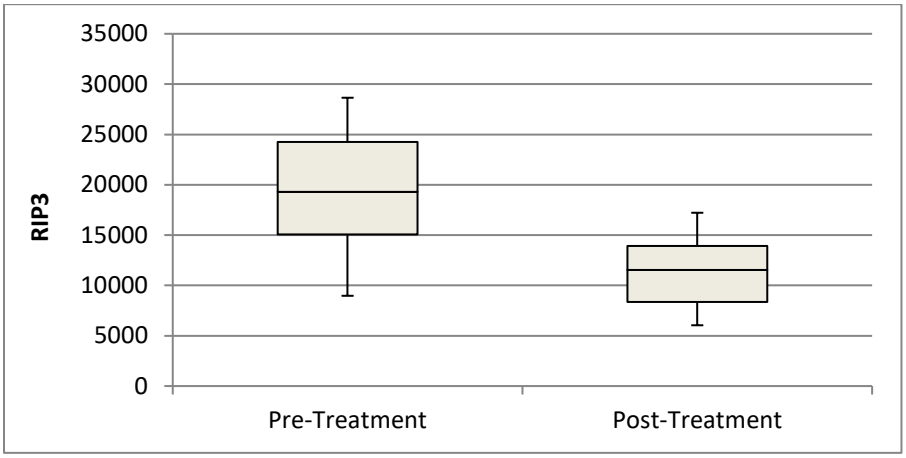

Figure 2: Box-plot showing difference between the study groups regarding RIP3 (pg/mL).

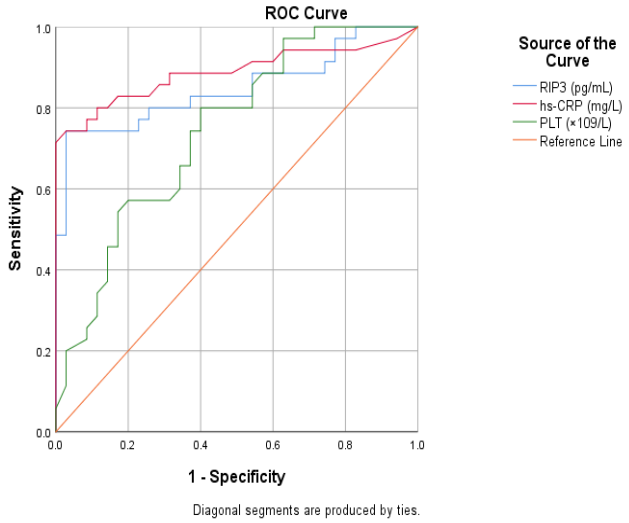

Figure 3: Receiver operating characteristic curve for RIP3, hs-CRP and PLT to predict neonatal sepsis**.**

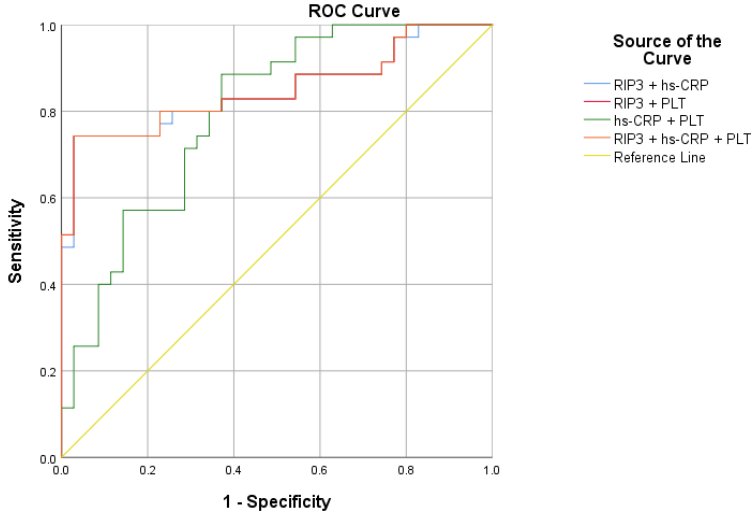

Figure 4: Receiver operating characteristic curve for biomarker combinations to predict neonatal sepsis.

DISCUSSION

Investigating the possible diagnostic and prognostic use of receptor interacting protein 3 (RIP3) in newborn sepsis was the goal of this investigation.

In the present investigation, we discovered that the two groups under investigation differed significantly in terms of WBCs, platelets, procalcitonin, hs-CRP, and blood culture.

These findings were in line with those of Gao et al. [20], who found that the sepsis group had pretreatment levels of hs-CRP and PLT of 7(1~25.4) mg/L and 191(111.5~267) ×109 /L, while the control group had levels of 1(1~3) mg/L and 278(215.5~353) ×109 /L. A follow-up comparison revealed that the sepsis group's hs-CRP levels were considerably greater than the control group's. The PLT levels of the infants in the control group were noticeably lower.

According to Iroh et al. [21], while WBC and PLT are commonly used in practice, they lack specificity, necessitating the use of more targeted biomarkers like RIP3.

Nakstad et al. [22] demonstrated that combining many biomarkers can increase the diagnostic value. Based on this, to examine the diagnostic usefulness of numerous signs together for newborn sepsis, another research was conducted. In the diagnosis of neonatal sepsis, the results showed that RIP3+hs-CRP+PLT performed better than RIP3+hs-CRP, RIP3+PLT, and hs-CRP+PLT in terms of sensitivity, specificity, positive predictive value, and negative predictive value. On the other hand, when utilized to diagnose neonatal sepsis, the combination of RIP3, hs-CRP, and PLT achieved the highest AUC (0.851), reflecting an improved diagnostic profile compared to individual markers.

Sharma et al. [23] demonstrated that > 6 mg/l is the typical, accepted cutoff for a substantial level of CRP. Compared to regular CRP, highly sensitive CRP (hsCRP) is more sensitive for diagnosing neonatal sepsis. Compared to traditional CRP assays, the hs-CRP assay has a lower cutoff value; a reading of less than 1 mg/l indicates a higher sensitivity for neonatal infection. When compared to noninfected neonates, Edgar et al. [24] found that both infected and culture-positive babies had significantly higher levels of hs-CRP. Abdollahi et al. [25] provided additional confirmation of these findings. In their comparison of IL-6, CRP, and hs-CRP as early indicators of newborn sepsis, Ganesan et al. [26] found that whereas IL-6 performed better in terms of sensitivity, hs-CRP performed better in terms of specificity and sensitivity than conventional CRP. A neonatal hs-CRP score of 3 mg/l in this study suggested a considerable risk of infection. Further research is required to assess the function of hs-CRP as a marker for neonatal sepsis.

The current study examined the plasma levels of RIP3 in children with neonatal sepsis before therapy versus healthy controls. RIP3 (pg/mL) varied between 8968 and 28647 in the sepsis group, with mean ± SD = 19558.71 ± 6188, while it varied between 6148 and 19324 in the control group, with mean ± SD = 11642.63 ± 3186.99. The statistical significance of the difference between the two groups was strong.

This was in line with the results of Gao et al. [18], who discovered that the control group had RIP3 levels of 11648 (9219~13530) pg/mL before therapy, but the sepsis group had 19202 (14646~24720) pg/mL. RIP3 levels were considerably greater in the sepsis group than in the control group, according to other comparison studies. The significantly increased levels of plasma RIP3 in the neonatal sepsis group before therapy compared to the control group suggest that plasma RIP3 may be a crucial biomarker of newborn sepsis.

Our results on the expression of plasma RIP3 in adult patients in ICUs are in line with those of Qing et al. [27]. The expression of RIP3 was significantly higher in the plasma of patients who died from sepsis than in the plasma of survivors, and it was demonstrated that RIP3 could be found in the plasma of adult patients with severe sepsis. This implies that a poor prognosis in sepsis may be predicted by aberrant RIP3 production or clearance.

Ma et al [28] patients in five intensive care units participated in a prospective study [28]. Indirect proof that elevated RIP3 expression could indicate the adverse effects of crucial illness was provided by the discovery that elevated plasma levels were linked to both in-hospital death and organ failure.

Our recent research unequivocally demonstrated that children with neonatal sepsis have different plasma levels of RIP3 before and after treatment. RIP3 (pg/mL) varied between 8968 and 28647 in pre-treatment studies, with mean ± SD = 19558.71 ± 6188, and between 6041 and 17219 in post-treatment studies, with mean ± SD = 11402.14 ± 3345.99. The statistical significance of the difference between the two groups was strong.

Our results are consistent with those of Gao et al. [18], who reported that RIP3, hs-CRP, and PLT levels in the sepsis group were

19202(14646~24720) pg/mL, 7(1~25.35) mg/L, and 191(111.5~267)×109 /L before to therapy, and 11411(7973~14158) pg/mL, 1(2~4) mg/L, and 240(170~332)×109 /L after treatment. Additionally, RIP3 and hs-CRP levels dramatically dropped following successful therapy compared to pretreatment levels, according to comparison study. However, PLT levels were noticeably higher than they were before to treatment. Following successful treatment, the plasma RIP3 level in the neonatal sepsis group dramatically dropped. RIP3 is thought to be useful in determining the prognosis and clinical effectiveness of newborn sepsis.

According to the results of the current study, the RIP3 (pg/mL) cutoff value was 16375.5, and the AUC was 0.848, the sensitivity was 74.3%, and the specificity was 97.1%.

Similar findings were made by Gao et al. [18], who discovered that 15464.72 pg/mL was the ideal cut-off value for plasma RIP3 level, with an area under the curve (AUC) of 0.872. RIP3 had a specificity of 91.4% and a sensitivity of 68.8%.

CONCLUSION:

RIP3 serves as a promising biomarker for early diagnosis and monitoring of therapeutic response in neonatal sepsis. The simultaneous measurement of RIP3, CRP, and PLT may be more helpful in the diagnosis of newborn sepsis than their individual detection.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interest.

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Citation

Gaafar, M., El-Sayed, A., Saad, A., Albanna, E. The Role of Plasma Receptor Interacting Protein3 in Early Detection of Neonatal Sepsis. ***Zagazig University Medical Journal*****, 2025; (1116-1123): -. doi: 10.21608/zumj.2024.339842.3706**