IJPSR (2025), Volume 16, Issue 10 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 21 April 2025; received in revised form, 14 May 2025; accepted, 14 June 2025; published 01 October 2025

INFORMATIVENESS OF EPIGENETIC CHANGES IN THE SIGIRR GENE IN INFANTS WHO DIED FROM NECROTIZING ENTEROCOLITIS

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Keywords:

Necrotizing enterocolitis, Premature birth, SIGIRR gene, Epigenetic modification

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ABSTRACT: Necrotizing Enterocolitis (NEC) is a severe gastro-intestinal disease primarily affecting premature infants, especially those born at or before 32 weeks of gestation, and is associated with high morbidity and mortality rates, characterized by intestinal inflammation and necrosis. The purpose of this study was to investigate the role of genetic factors in the development of necrotizing enterocolitis, mortality cases, and potential links between these two conditions. A total of 44 infants were included in this study. Based on survival during the neonatal period, NEC were divided into two subgroups: those who survived (35 infants) and those who died 9 infants). SIGIRR gene methylations were identified through DNA isolation and standard PCR reactions. It was found that changes in the %C33, %C35, %C51 and %C102 gene loci are potential predictive markers for distinguishing infants who died from NEC from those without this pathology Genetic screening could help identify infants at a higher risk of developing NEC, allowing for timely, targeted intervention and personalized care measures.

INTRODUCTION: In modern healthcare, the delayed recognition and treatment challenges of certain neonatal conditions continue to cause stress for medical professionals. Necrotizing enterocolitis (NEC), a severe condition affecting premature infants, particularly those born before 32 weeks of gestation, has high mortality rates and impacts quality of life. It is characterized by intestinal inflammation and necrosis [1, 2]. As medical science advances, our understanding of this disease also deepens [3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.16(10).2776-82

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.16(10).2776-82

Necrotizing enterocolitis (NEC) is a serious gastrointestinal condition affecting premature infants, especially those born before 32 weeks, with high morbidity and mortality rates, marked by intestinal inflammation and necrosis. NEC, characterized by inflammation and tissue death in the intestines, represents a significant challenge in neonatal intensive care units worldwide.

Despite advancements in medical care, its etiopathogenesis remains complex, and neonatologists continuously strive to establish effective preventive and therapeutic strategies. Genetic, dietary, and environmental risk factors may increase susceptibility to NEC by impacting the intestinal mucosa and gut microbiome [4-6]. Studies on intestinal samples from preterm infants with NEC have shown an increase in the mediating genes and cytokines that positively regulate the

TLR signaling pathway, specifically TLR4 and MYD88, during NEC, while the negative regulators of the TLR pathway, single immunoglobulin interleukin-1-related receptor (SIGIRR) and A20, are observed to decrease [7]. High levels of TLR4 in the intestines of preterm infants and its activation in the postnatal gut can lead to ischemia, barrier disruption, and NEC [8].

These mechanisms explain the high susceptibility to NEC development in preterm infants, as this group consistently shows elevated TLR4 levels. Studies on human embryonic kidney and intestinal epithelial cells have shown that SIGIRR inhibits the inflammation induced by LPS from Gram-negative bacteria, which play a role in NEC development. The sequence of four nucleotides in DNA forms the genetic code, which is passed down to the next generation without changes at the cellular level. Alongside the genetic code, there is also an epigenetic code, methyl groups attached to the cytosine element of DNA [9].

According to Sampat *et al.* (2015), genetic variants of TLR in very low birth weight infants can alter NEC susceptibility, indicating that genetic diversity plays a significant role in NEC pathogenesis. Congenital defects in TLR regulation increase NEC susceptibility in preterm infants. It has been found that, in preterm infants with NEC, genetic variants of SIGIRR identified as losing their function result in an intensified inflammatory response to LPS [10]. Epigenetic changes or modifications involve functional and regulatory changes in genes without altering the DNA structure itself, and are often associated with the pathogenesis of relevant diseases. SIGIRR acts as a "brake" by preventing excessive TLR4 activation and inflammation in the intestines. SIGIRR regulates postnatal adaptation of the intestines. During NEC, mutations in SIGIRR have been observed. Mutation in the SIGIRR gene disrupts postnatal immune tolerance in the intestines [11]. The aim of the study was to investigate the role of genetic factors in the development of necrotizing enterocolitis, mortality cases, and the potential connections between these two conditions.

MATERIALS AND METHODS:

Patient Population: This study was approved by the Ethics Committee of Azerbaijan Medical University under Protocol No 22 issued in 04.02.2022. All methods were performed following the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants. A total of 44 infants were included in this study. Based on survival during the neonatal period, NEC were divided into two subgroups: those who survived (35 infants) and those who died 9 infants). The NEC group included newborns receiving treatment in the "Anesthesiology, Resuscitation, and Intensive Care" and "Pathology of Premature Infants" departments of the SRIP (Scientific Research Institute of Pediatrics). Conventionally healthy newborns were selected from Maternity Hospital No. 7. The study of the SIGIRR gene was conducted at the INTERGEN laboratory in Ankara. Considering the preterm status of the infants, the collected blood sample volume was limited to 0.5 ml. The changes in the SIGIRR gene profile in the children included in the study were investigated through DNA isolation and Sanger sequencing method.

DNA Isolation: DNA was isolated using the QIA amp DNA Blood Mini Kit (Qiagen Inc.), following the manufacturer's recommended protocol, with 200 µl of each whole blood sample used for the isolation process. The isolated DNA samples were stored at -20°C until the bisulfite conversion stage. Cleaned and standardized PCR reactions were prepared for the NGS phase using the Nextera XT Prep Kit (Illumina Inc.). Sequencing was performed on the MiSeq system (Illumina Inc.) using MiSeq Reagent Kit v2 2x150 cartridges (MS-102-2002, Illumina Inc.).

Statistical Analysis: All indicators in the study were analyzed using variation analysis (U-Mann-Whitney H-Kruskal Wallis test), discriminant analysis (Odds Ratio X2-Pearson), dispersion variance analysis (ANOVA-Fisher test, Fisher-Snedecor test), correlation (ρ(Rho) g-Spearman), and ROC analysis, and were verified using biostatistical methods in medicine [12]. For diagnostic purposes, a discriminant analysis algorithm was applied. At this stage, prognostic criteria were selected for further analysis. Proper application of probabilistic methods requires examining the correlation and interrelations among prognostic criteria.

To evaluate laboratory indicators (prognostic markers), ROC analysis was performed. Based on the coordinates of the ROC curve, cutoff points were identified, and sensitivity (Sn) and specificity (Sp) for the markers were calculated. The sensitive ROC test was based on laboratory indicators that showed statistically significant differences.

RESULTS: The gestational age of deceased group with NEC was 32.2 ± 0.4 (25-36) weeks. Birth weights were $1.596.3 \pm 79.8$ (500-2450) grams. The mean age of the mothers was 30.2±1.9 (18-51) years **Table 1.**

TABLE 1: THE GESTATIONAL AGE AND BIRTH WEIGHTS OF INFANTS WITH NEC ACCORDING TO STUDY GROUPS

	Study groups	Mean	Std. Error	Min	Max	P
Gestational age	Survived (N=35)	32.6	0.5	25	37	0.756
	Dead (N=9)	32.2	0.4	25	36	
Birth weights	Survived (N=35)	1625.8	86.5	450	2500	0.946
	Dead (N=9)	1596.3	79.8	500	2450	
Mothers' age	Survived (N=35)	28.4	1.1	18	37	0.562
	Dead (N=9)	30.2	1.9	18	51	

Among the infants, 16 (45.7%) in the survived group and 4 (44.4%) in the deceased group were from twin pregnancies. In the survived and deceased groups, 14 (40.0%) and 5 (55.6%) were from first-time pregnancies, while 21 (60.0%) and 4 (44.4%) were from subsequent pregnancies, respectively. A total of 7 pregnancies (15.9%) resulted from *in-vitro* fertilization following prolonged infertility. Regarding the mode of delivery, 10 infants (28.6%) in the survived group and 3 (33.3%) in the deceased group were born via natural birth, whereas 25 (71.4%) and 6 (66.7%) were delivered by cesarean section, respectively. Overall, 21 infants (47.7%) were male, and 23 infants (52.3%) were female (p=0.006) **Table 2.**

TABLE 2: ANAMNESTIC INDICATORS OF NEWBORNS ACCORDING TO STUDY GROUPS

		Survived		Dead		Total		
		Count	N %	Count	N %	Count	N %	Pχ^2
Gender	Male	13	37.1%	8	88.9%	21	47.7%	0.006
	Female	22	62.9%	1	11.1%	23	52.3%	
Numberof Infants	Single	19	54.3%	5	55.6%	24	54.5%	0.946
	Twin	16	45.7%	4	44.4%	20	45.5%	
İVF	No	30	85.7%	7	77.8%	37	84.1%	0.562
	Yes	5	14.3%	2	22.2%	7	15.9%	
Pregnancy	First-time	14	40.0%	5	55.6%	19	43.2%	0.401
	Subsequent	21	60.0%	4	44.4%	25	56.8%	
Mode of delivery	Natural	10	28.6%	3	33.3%	13	29.5%	0.780
	Cesarean	25	71.4%	6	66.7%	31	70.5%	

In the early neonatal period, 3 infants (8.6%) in survived group and 4 (44.4%) infants in deceased group required respiratory support (CPAP) (p=0.009). A total of 5 (11.4%) were born with asphyxia. Sepsis developed in 17 infants (38.6%): 10 infants (28.6%) in the survived group and 7 infants (77.8%) in the deceased group (p=0.007).

Respiratory distress syndrome (RDS) was identified in 4 infants (11.4%) in the survived group and in 8 infants (88.9%) in the deceased group ($p < 0.001$). In the survived group, Stage I necrotizing enterocolitis (NEC) was identified in 22 infants (62.9%), Stage II in 7 infants (20.0%), and Stage III in 6 infants (17.1%). In the deceased group, Stage I NEC was identified in 2 infants (22.2%), Stage II in 4 infants (44.4%), and Stage III in 3 infants (33.3%).

Of the infants with Stage I NEC, 13 (54.1%) began receiving breast milk by an average of the 5th day. For those with Stage II NEC, 3 infants (27.2%) began receiving breast milk by days 8–9, and for Stage III NEC, 5 infants (55.5%) began receiving it after day 9. It was found that 25 infants (56.8%) who developed NEC were fed with formula from the first days of life. Only 2 infants (4.5%) received exclusive breastfeeding from the first day of life.

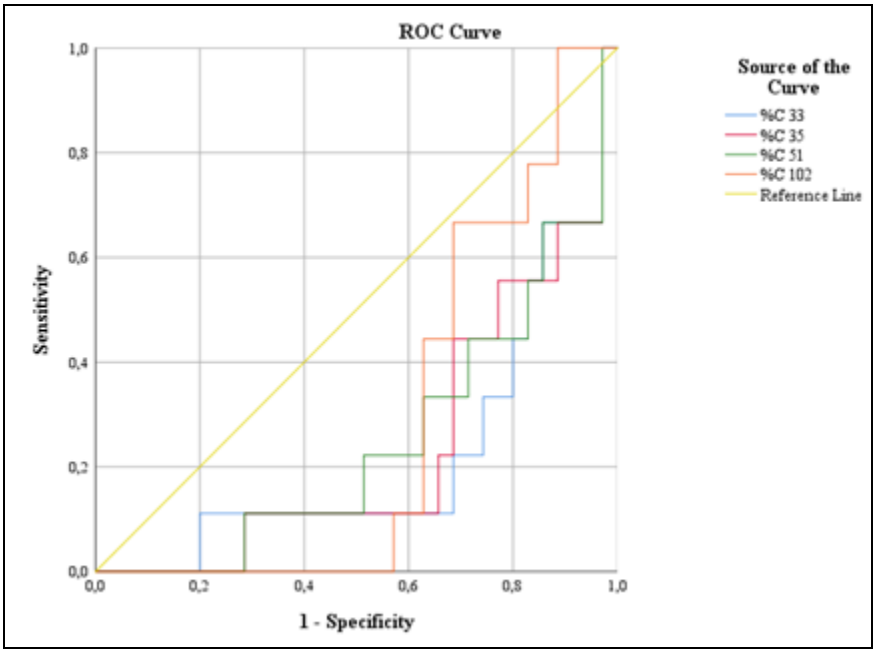
Among the NEC-affected infants, 11 (25.0%) underwent surgery: 6 infants (17.1%) in the survived group and 5 infants (55.6%) in the deceased group (p=0.018). **Table 3** presents a comparison of statistical differences in various parameters of SIGIRR gene locus indicators among NEC infants between two subgroups (D- survivors and D+ non-survivors). The table indicates a statistically significant difference of %C33, %C35, %C51 and %C102 between the groups of surviving and non-surviving infants.

TABLE 3: SIGIRR GENE LOCI IN NEC INFANTS

SİGİRR	Groups	n	M	Me	Q_1	Q_3	P_U
%C33	D-	35	30.69	2.01	25.33	35.4	0/010*
	D+	9	23.55	1.80	19.3	25.42	
%C35	D-	35	41.79	1.98	35.52	46.98	0.015*
	D+	9	32.39	2.99	27.17	38.63	
%C51	D-	35	44.08	1.79	38.07	48.61	0.022*
	D+	9	35.57	2.74	31.09	40.19	
%C102	D-	35	19.89	1.37	16.38	25.08	0.050*
	D+	9	16.15	1.00	14.47	18.3	

P_U - statistical significance of the difference according to the U-Mann-Whitney test

Fig. 1 presents the ROC curve of the SIGIRR gene profile in deceased NEC infants. As shown, the majority of the ROC curve for the %C33, %C35, %C51 AND %C102 loci lies below the central line. The AUC value for %C33 is 0.219 ± 0.088 within a 95% confidence interval (p=0.010), for %C35 it is 0.235 ± 0.084 (p=0.015), for %C51 it is 0.251 ± 0.088 (p=0.022) and for %C102 it is 0.286 ± 0.075 (p=0.050). Based on the ROC curves, the %C33, %C35, %C51 and %C102 loci of the SIGIRR gene hold high informational value for deceased NEC infants.



Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
%C 33	0,219	0,088	0,010	0,047	0,391
%C 35	0,235	0,084	0,015	0,070	0,400
%C 51	0,251	0,088	0,022	0,079	0,423
%C 102	0,286	0,075	0,050	0,138	0,433

FIG. 1: ROC CURVE OF THE SIGIRR GENE PROFILE IN DIED NEC INFANTS

Based on the analyzed data presented in **Table 4** the %C33, %C35, %C51 and %C102 loci of the SİGİRR gene have higher in formativeness, with the cut-off point for %C102 being lower than 19.

Its sensitivity (Sn), specificity (Sp), and overall diagnostic value (ODV) are 100.0%, 57.1±8.4%, and 65.9±7.1%, respectively. The evaluation of the positive and negative prognostic values demonstrated effectiveness rates of 37.5 ± 9.9 and 100.0, respectively. The perfect negative predictive value indicates that this marker is highly significant in predicting the prognosis of patients who died from NEC. According to the table, LR+ is 2.33 and LR- is 0.00, excellent, meaning a negative test completely rules out the disease.

TABLE 4: INFORMATIVE VALUE OF SIGIRR GENE LOCI IN NEC INFANTS

Statistical parameter	İndicators			
	%C 33	%C 35	%C 51	%C102
Cut off point	<9	<39.2	<40.7	<19
Sensitive (Sn)	0.0±0.0	88.9±10.5	77.8±13.9	100.0±0.0
Specificity (Sp)	97.1±2.8	65.7±8.0	62.9±8.2	57.1±8.4
Overall diagnostic value (ODV)	77.3±6.3	70.5±6.9	65.9±7.1	65.9±7.1
Effect of evaluation under positive predictive value (pPV)	0.0±0.0	40.0±11.0	35.0±10.7	37.5±9.9
Effect of evaluation under negative predictive value (nPV)	79.1±6.2	95.8±4.1	91.7±5.6	100.0±0.0
Likelihood ratio of positive result (LR+)	0.0 insufficient	2.59 moderate	2.09 moderate	2.33 moderate
Likelihood ratio of negative result (LR-)	1.03 insufficient	0.17 good	0.35 moderate	0.00 excellent

Cut-off point for %C35 and %C51 is lower than 39.2 and 40.7 respectively. Its sensitivity (Sn), specificity (Sp), and overall diagnostic value (ODV) are 88.9±10.5%, 65.7±8.0%, 70.5±6.9%, and 77.8±13.9%, 62.9±8.2%, 65.9±7.1 respectively. The evaluation of the positive and negative prognostic values demonstrated effectiveness rates of 40.0 ± 11.0, 95.8 ±4.1 and 35.0±10.7, 91.7±5.6 respectively. The very high nPV of 95.8 and 91.7, respectively, indicate that a negative result is highly reliable in predicting the prognosis of patients who died from NEC. According to the table, LR+ is 2.59, LR- is 0.17 for %C35, which is considered good, and suggests that a negative test result effectively rules out the disease. In contrast, the LR- for %C51 is 0.35, which is moderate, making it still useful but less conclusive.

Table 5 presents the analysis of the *SIGIRR* gene loci, revealing varying degrees of association with NEC prognosis based on odds ratios (OR), confidence intervals (CI), and statistical significance (p-values).

TABLE 5: ASSOCIATION OF SIGIRR GENE LOCI WITH NEC PROGNOSIS

SIGIRR	Odds ratio				Fischer-Snedecor test				
	OR	95%CI	95%CI	p	FS	EIF	LB_{95}	UB_{95}	p
%C 33	1.2	0.0	32.2	>0.05	0.0	0.0	0.0	9.3	0.911
%C 35	15.3	1.7	137.4	<0.05	13.5	24.3	17.0	31.7	0.001***
%C 51	5.9	1.1	32.9	<0.05	5.8	12.2	3.6	20.7	0.020*
%C102	25.1	1.4	465.6	<0.05	12.9	22.7	15.6	29.8	0.001***

For %C102 Locus, the OR is the highest at 25.1, with a 95% CI of 1.4–465.6, and a significant p-value (p <0.05). This suggests that the %C102 locus may be a particularly strong predictive marker for NEC prognosis, although the wide confidence interval indicates some variability in the estimate. FS=12.9, the effect estimate for Efficiency influence of factor (EIF) is 22.7, indicating a significant effect of the variable. LB95 (15.6), UB95 (29.8) further increase confidence in the strength of the OR, with the range between 15.6 and 29.8. There is a strong and highly significant association (p=0.001). The relatively narrow CI and high EIF reinforce this locus's value as a predictive marker.

For %C35, the OR is 15.3, with a 95% CI of 1.7–137.4, and a significant p-value (p <0.05). This suggests a strong association between the %C35 locus and NEC prognosis, indicating that newborns with this variant are more likely to exhibit related clinical outcomes. FS=13.5 | EIF: 24.3 | 95% CI: 17.0–31.7 | p = 0.001 There is a strong and highly significant association (p < 0.001).

The narrow CI and high EIF suggest this locus is strongly informative for predicting NEC prognosis. For %C51 locus, the OR is 5.9, with a 95% CI of 1.1–32.9, and a significant p-value ($p < 0.05$). FS=5.8, EIF: 12.2 | 95% CI: 3.6–20.7 ($p = 0.020$). Although the association is moderate compared to %C35, it still indicates a noteworthy relationship between this locus and NEC prognosis. For %C33 Locus, the OR is 1.2, with a wide 95% confidence interval (CI) ranging from 0.0 to 32.2. The p-value ($p = 0.911$) indicates no statistically significant association between this locus and NEC prognosis.

Table 6 presents the Spearman correlation (ρ - Rho) between Survival and different %C indicators. For %C 33 (ρ (Rho) = -0.393, p = 0.008), %C 35 (ρ (Rho) = -0.370, p = 0.013), %C 51 (ρ (Rho) = -0.348, p = 0.020), %C 102 (ρ (Rho) = -0.300, p = 0.048). Since all ρ (Rho) values are negative, there is an inverse relationship between %C indicators and Survival. This means that an increase in these indicators is associated with a decrease in survival probability, p-values ($p < 0.05$) indicate that these correlations are statistically significant.

TABLE 6: CORRELATION BETWEEN SURVIVAL AND DIFFERENT %C INDICATORS

		%C 33	%C 35	%C 51	%C 102
Survival	ρ (Rho)	-0.393**	-0.370*	-0.348*	-0.300*
	p	0.008	0.013	0.020	0.048
	N	44	44	44	44

All three gene loci %C102, %C35 and %C51 show a significant effect on the studied event: the %C35 and %C102 loci demonstrate the strongest and most statistically significant associations with NEC prognosis, the %C51 locus shows a moderate yet significant association. All results are statistically significant, suggesting that the observed effects are not due to chance. The %C33 locus does not exhibit a statistically significant relationship.

DISCUSSION: The SIGIRR gene encodes a protein that negatively regulates the toll-like receptor (TLR) signaling pathway. TLR4, a key component of this pathway, has been implicated in NEC development through its role in modulating inflammatory responses in the immature intestine. Studies have shown that excessive TLR4 activation leads to ischemia, disruption of the intestinal barrier, and inflammatory damage, all of which contribute to NEC onset and progression [13].

SIGIRR acts as an anti-inflammatory regulator, dampening TLR4-mediated responses and maintaining immune tolerance in the postnatal intestine [14]. Loss-of-function mutations in SIGIRR have been associated with heightened inflammatory responses, suggesting its critical role in protecting the intestinal epithelium [9]. The findings of this study highlight the significance of epigenetic changes in the SIGIRR gene as potential biomarkers for necrotizing enterocolitis (NEC) mortality. Specifically, alterations in the %C33, %C35, %C51 AND %C102 loci emerged as statistically significant indicators distinguishing deceased NEC infants from survivors. This suggests that genetic and epigenetic factors, particularly those affecting the regulation of intestinal immune responses, play a critical role in NEC progression and outcomes.

The identification of reliable biomarkers is critical for early diagnosis and risk stratification in NEC. Genetic studies have shown that polymorphisms and epigenetic modifications in TLR signaling-related genes, including SIGIRR, influence NEC susceptibility [10]. Methylation profiling offers a promising approach for identifying high-risk infants and tailoring interventions.

ROC curve analyses of methylation levels at the SIGIRR gene loci in deceased NEC infants revealed high discriminatory power, with significant differences in %C33, %C35, %C51 and %C102 methylation levels between survivors and non-survivors. These findings suggest that epigenetic modifications in SIGIRR could serve as predictive markers for NEC outcomes, enabling personalized neonatal care. Further research is needed to validate the clinical utility of SIGIRR methylation as a biomarker across diverse populations and to explore its interactions with environmental factors such as feeding practices and microbiome composition. Longitudinal studies could provide insights into the dynamic nature of epigenetic changes during NEC progression and recovery.

CONCLUSION: The AUC results for the %C33, %C35, %C51 and %C102 gene loci in deceased infants with necrotizing enterocolitis (NEC) indicate promising discriminative ability. The significant AUC values and low standard errors suggest that %C33, %C35, %C51 and %C102 may serve as valuable biomarkers for identifying infants at risk of mortality from NEC under these conditions.

However, further research and validation are warranted to confirm the clinical utility of %C33, %C35, %C51 and %C102 and to potentially enhance patient care. The wide confidence intervals, especially for %C102, suggest the need for further research with larger sample sizes to confirm these associations. Understanding the genetic basis of NEC offers significant potential for improving disease management and prevention strategies. Genetic screening may assist in identifying infants at high risk for NEC, enabling targeted interventions and personalized care. Additionally, insights into the genetic factors of NEC could lead to the development of new therapeutic approaches, including gene-based treatments and individualized therapies.

Authors' Contributions: AA conceived and designed the study, collected, analyzed and interpreted the data, wrote and edited the manuscript. IG conceived and designed the study, analyzed the data. AP, SN, and SM collected the data and revised the work critically.

CONFLICT OF INTEREST: The authors have no conflict of interest to declare.

ACKNOWLEDGEMENTS: Nil

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How to cite this article:
Aliyeva AM, Polukhova AA, Nasirova SR, Mekhdiyeva SA and Gafarov IA: Informativeness of epigenetic changes in the sigirr gene in infants who died from necrotizing enterocolitis. Int J Pharm Sci & Res 2025; 16(10): 2776-82. doi: 10.13040/IJPSR.0975-8232.16(10).2776-82.