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Original article

Diagnostic Value of Progranulin in Neonatal Sepsis

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Abstract

Background: The symptoms of neonatal sepsis are often hard to identify, which can lead to misdiagnosis. Because of the shortcomings of relying solely on blood cultures for diagnosis, surrogate biomarkers of sepsis are frequently employed. Progranulin is a secreted protein that acts as an anti-inflammatory agent and has a protective effect in sepsis and endotoxic shock. **Objectives:** Evaluating the diagnostic value of serum progranulin in neonatal sepsis could potentially lead to earlier detection and improved prognosis for affected neonates. **Patients and methods:** The study included 45 neonatal sepsis patients and 45 healthy controls of the same age and gender. Participants in the study underwent comprehensive history taking, thorough clinical examination, and tests involving CBC, blood culture, C-reactive protein, and serum progranulin measurement using an ELISA kit. **Results:** Serum progranulin levels were significantly greater in cases with neonatal sepsis contrasted with the control group. There was a significant +ve correlation among serum progranulin & CRP

levels. Furthermore, serum progranulin was the most effective laboratory parameter in diagnosing neonatal sepsis, with the highest area under the ROC curve following CRP. No link was found between progranulin levels and the outcome of Sepsis in neonates. The most prevalent risk factors for sepsis were premature rupture of membranes and prematurity. In terms of prevalence among gram-negative organisms, Klebsiella pneumoniae was found to be the most common., MRSA and CoNS were identified as the most frequently isolated gram-positive organisms. **Conclusions:** Progranulin levels in the serum could serve as a promising diagnostic biomarker for neonatal sepsis.

1. Introduction:

Neonatal sepsis is a medical illness defined as changes in blood flow and other general symptoms, caused by the existence of hazardous microorganisms like viruses, bacteria, or fungus in usually sterile fluids such as blood or cerebrospinal fluid within the 1st 28 days of life [1]. Neonatal sepsis is a prominent factor contributing to morbidity and illness in newborn infants [2]. It's estimated that out of every 100,000 live births, 2,202 newborns develop neonatal sepsis, with a mortality rate of 11-19 percent. This translates to approximately 3 million individuals of neonatal sepsis each year [3]. The identification of new biomarkers for diagnosing neonatal sepsis is crucial, as early diagnosis improves the prognosis [4]. Progranulin, a secretory protein consisting of 593 amino acids and rich in cysteine, is expressed in macrophages, neurons, adipose tissues, epithelial cells, fibroblasts, and chondrocytes. It acts as an anti-inflammatory agent and plays a protective role in sepsis and endotoxic shock [5]. Studies have found that progranulin levels in the bloodstream are significantly higher in adult and pediatric cases with sepsis than in healthy individuals [6], also in newborns with early-onset sepsis compared to uninfected newborns [4].

2. Aim of the Work:

Evaluating the diagnostic value of serum progranulin in neonatal sepsis could potentially lead to earlier detection and improved prognosis for affected neonates.

3. Patients & Methods:

This prospective case-control study took place in the Neonatal Intensive Care Unit at

Beni-Suef University Hospital.The study commenced in January 2021 and continued until the desired number of cases was reached.

Newborns were eligible for the study if they met the diagnostic criteria for neonatal sepsis, which was defined as a positive blood culture along with clinical & laboratory signs of infection [1]. Symptoms of sepsis included [7]: Respiratory distress or apnea, tachycardia or bradycardia, Seizure, irritability, floppy infant, or lethargy , hypothermia or hyperthermia, arterial hypotension and/or poor perfusion and vomiting or feeding intolerance or ileus.

The research excluded newborns with: major congenital malformations, chromosomal abnormalities, perinatal asphyxia. And inborn errors of metabolism.

The study involved 45 neonatal sepsis patients and 45 healthy controls matched by age and sex.

The determination of the sample size was performed by a two-tailed t-test to evaluate the difference between two independent means (two groups). The parameters for this calculation were as follows:

- The effect size (d) was set at 0.82.
- The probability of a Type I error (α err prob) was set at 0.05.
- The power of the test (1-β err prob) was set at 0.97.
- The allocation ratio (N2/N1) was set at 1.

As a result of these parameters, the calculated sample sizes were 45 for both group 1 and group 2, leading to a total sample size of 90.

Procedures All cases underwent the following:

1. Comprehensive history taking, including: Maternal infection during pregnancy or childbirth, gestational age, multiple births, duration of rupture of membranes, complicated delivery, and medical interventions such as endotracheal intubation, parenteral nutrition, or surgery.
2. Detailed clinical examination, including: birth weight, vital signs (heart rate, blood pressure, temperature & respiratory rate), neonatal reflexes e.g. Moro and suckling and full examination of all systems (cardiac, respiratory, neurological, and abdominal).
3. Laboratory tests, including: CBC, CRP and blood culture.

   The measurement of serum progranulin was conducted using an ELISA kit at the Clinical Pathology Laboratory, Clinical & Chemical Pathology Department, Beni-Suef University Hospital. The process was as follows:

A. Sample Collection: Blood samples were drawn from the peripheral veins of both patients and controls. These samples were then placed into a plain tube and immediately centrifuged at approximately 1000×g for 15 minutes to

extract the serum. For optimal results, blood samples were processed within a few hours of collection.

B. Storage and Transport:

- Storage: Post-collection, samples were stored at temperatures between 2-8 °C for a maximum of 72 hours. The extracted serum was stored at -80 °C. Long-term storage of samples was avoided.
- Transport: For transport, samples were maintained at 2-8 °C and dispatched to the workplace using ice packs.

C. Serum Progranulin Testing: The serum levels were evaluated utilizing a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kit, as per the manufacturer's instructions (SinoGeneClon Biotech Co., Ltd). The serum had been centrifuged at approximately 1000 x g prior to testing.

Statistical Methods:

The data was analyzed by the Statistical Package for the Social Sciences (SPSS). Quantitative variables have been assessed by descriptive statistics such as standard deviation, mean, median, or range. Qualitative variables were described by frequency & percentages, as appropriate. The Pearson correlation was employed to correlate qualitative variables that adhered to a normal distribution. The specificity and sensitivity of progranulin in identifying neonatal sepsis were identified by a Receiver Operating Characteristic (ROC) curve. A p-value was computed and deemed non-significant if it was greater than 0.05, significant if below 0.05, and highly significant if below 0.01.

Regarding ethical considerations, parents were thoroughly briefed about the research. Following approval from the Local Ethical Committee (FMBSUREC/07022021/Ahmed), the parents of those participating in the research provided written informed consent.

4. Results:

This research involved 90 participants from the NICU of Beni-Suef University Hospital, separated into two groups: Group A (45 individuals diagnosed with neonatal sepsis) and Group B (45 healthy controls). The delivery method for 84.4% of neonatal sepsis individuals and 93.3% of controls was cesarean section, with no significant variation among the two groups (Table 1).

Table 1: Personal data among neonatal sepsis patients and controls.

Variables	Group A (Cases) (Neonatal sepsis patients)		Group B (controls)		Test of significant*	P Value
	Range	Median (Interquartile range)	Range	Median (Interquartile range)		
Gastational-age in weeks	29 – 40	37 (33 – 38)	29 – 40	37 (35 – 38)	U= 947.5	0.589
Post-natal age in days	2-30	6 (3.5 – 17)	2 – 30	7 (5 – 7)	U= 989.0	0.849
Weight in Kg	1.7 – 4	2.5 (1.9 – 3.2)	1.8- 4.5	2.9 (2.5 – 3)	U = 806.5	0.095
Sex: • **Male** • **Female**	N= 26 (57.8%) N= 19 (42.2%)		N= 21 (46.7%) N= 24 (53.3%)		X^2 = 1.113	0.291
Mode of delivery • **Vaginal** • **Cesarean section**	N= 7 (15.6%) N= 38 (84.4%)		N= 3 (6.7%) N= 42 (93.3%)		X^2 = 1.80	0.180

**; significant, U; Mann-Whitney U test, X^2; Chi-square test*

CRP levels were notably higher in neonatal sepsis cases than in controls, with a median and interquartile range of 48 (24 – 96) in neonatal sepsis patients and 3 (2 – 4) in controls (Table 2).

Table 2: Laboratory data among neonatal sepsis patients and controls.

Variables	Group A (neonatal sepsis patients)		Group B (controls)		Test of significant	P Value
	Range	Median (Interquartile range)	Range	Median (Interquartile range)		
Hemoglobin (gm/dl)	8.2– 18	12.996 ±2.489 **	9.3-19.3	14.85±2.48	t = 3.538	0.001*
Platelets*10^3 (cell/mm^3)	17-834	155 (84 – 273)	158 – 658	280 (236 – 351)	U = 447.5	<0.001*
WBCs*10^3 (cell/mm^3)	2.3 – 33.3	11.80 (7.65 – 17.00)	3.8 – 20	10 (8 – 12.9)	U = 824	0.128
CRP	1.5 - 192	48 (24 – 96)	1 – 5.5	3 (2 – 4)	U = 92.0	<0.001*

**; significant, **; Mean ± SD, U; Mann-Whitney U test, t; Independent samples t-test*

Serum progranulin was significantly elevated in neonatal sepsis individuals in contrast to controls (Table 3).

Table 2: Serum progranulin among neonatal sepsis patients and controls.

Variables	**Group A (Neonatal sepsis patients)**		**Group B (Controls)**	
	Range	**Median (Interquartile range)**	**Range**	**Median (Interquartile range)**
Serum progranulin (ng/ml)	83.6 – 318.9	158.5 (129.1-190.2)	53.9-162.9	105.60 (80.2 - 128.35)
Test of significant	U = 237			
P Value	<0.001*			

**; significant, U; Mann-Whitney U test*

The causative organisms were Klebsiella Spps. in 33.3% of cases, Staphylococcus aureus (MRSA) in 26.7% of cases, coagulase negative staphylococci in 22.2% of cases, E-coli in 15.5% of cases, and Acinetobacter Spps. in only 2.3% of the cases (Table 4).

Table 3: Descriptive data of neonatal sepsis patients:

Variables	**N (%) (n = 45)**
Type of sepsis • LOS • EOS	 34 (75.6%) 11 (24.4%)
Risk factors of neonatal sepsis* • Premature rupture of membranes • Prematurity • Intubation • Multiple pregnancy	 26 (57.8%) 21 (46.7%) 9 (20%) 6 (13.3%)
Outcome • Improved • Died	 27 (60%) 18 (40%)
Causitive organism • Klebsiella • Staph (MRSA) • Staph cons (coagulase -ve staph) • Ecoli • Acinetobacter	 15 (33.3%) 12 (26.7%) 10 (22.2%) 7 (15.6%) 1 (2.3%)

O2 delivery mechanism • Mechanical ventilation • CPAP • Nasal • Off oxygen	 6 (13.3%) 21 (46.7%) 17 (37.8%) 1 (2.2%)
Use of +ve Inotropes	12 (26.7%)
Laboratory data in cases • I/T ratio • ANC	 0.160 ± 0.1248** 7176 (4070 – 10710) #

There was no significant association among serum progranulin levels and any of the personal data of neonatal sepsis patients (Table 5).

Table 4: Correlation of serum progranulin and personal data among neonatal sepsis patients:

Variables	**Serum progranulin**	
	R	**P value**
Gastational-age in weeks	0.108	0. 482
Post- natal age in days	- 0.172	0.259
Weight	-.119	0.437

Serum progranulin levels showed a significant and positive correlation with CRP levels of neonatal sepsis patients (Table 6).

Table 5: Correlation of serum progranulin and laboratory data among neonatal sepsis patients:

Variables	**Serum progranulin**	
	R	**P value**
Platelets	0.099	0.516
WBCs	0.008	0.956
Hemoglobin	0.162	0.286
CRP	0.507	<0.001*
I/T ratio	0.161	0.290
ANC	0.029	0.852

**; significant, r; Pearson's correlation coefficient*

Serum progranulin levels were significantly and positively associated with CRP levels of early-onset neonatal sepsis patients (Table 7).

Table 6: Correlation of serum progranulin and CRP among early-onset neonatal sepsis patients:

Variables	**Serum progranulin**	
	R	**P value**
CRP	0.868	0.001*

**; significant, r; Pearson's correlation coefficient*

There was no significant distinction in serum progranulin levels among different types of sepsis, between preterm and full-term, or between improved and deceased patients (Table 8).

Table 7: Serum progranulin levels in early and late-onset sepsis, preterm and full-term, improved and dead neonates.

Variables	**Range**	**Median (Interquartile range)**	**U**	**P Value**
Type of sepsis • LOS • EOS	 83.6 - 282.7 109.7 - 318.9	 159.70 (128.58 - 189.43) 129.3 (158.5 - 192.5)	175.5	0.761
Prematurity • Full term • Preterm	 83.6 - 318.9 115.2 - 264.1	 162.45 (128.93 - 96.15) 153.5 (131.95 - 190.2)	244.5	0.864
Outcome • Improved • Died	 83.6 - 318.9 109.7 - 264.1	 166.4 (130.3 - 201.4) 153.00 (122.03 - 178.60)	187	0.194

Serum progranulin level was the most effective laboratory parameter after CRP in diagnosing neonatal sepsis, with an Area under the ROC curve (AUC) of 0.883 (Table 9).

Table 8: Cutoff value of serum progranulin that can discriminate between patients with neonatal sepsis and sepsis-free neonates.

Area under the ROC curve (AUC)	0.883
95% CI*	0.817 - 0.949
Value	132.56
Sensitivity	68.9%
Specificity	80.00%
PPV*	77.5%
NPV*	72%

** PPV; Positive predictive value, NPV; Negative predictive value, CI; Confidence interval*

4. Discussion

Sepsis is a critical condition that poses a threat to life. It's defined by the sudden failure of organs [8]. Globally, it's estimated that over 31.5 million people are affected by sepsis, leading to almost 5.3 million deaths due to ongoing or repeated organ failure [9]. Survivors of sepsis often face long-term negative impacts, including severe & lasting functional disabilities, and a diminished quality of life related to health [10]. Sepsis frequently results in hospital admissions and high rates of readmission [11].

Diagnosing sepsis is a challenge due to the absence of a definitive standard. Additionally, the lack of standardized definitions hinders the comparison of findings from clinical and epidemiological investigations [5]. The existing sepsis criteria are being revised because they fail to distinguish between infection and sepsis [12]. Therefore, there's a critical need for new diagnostic tools for sepsis.

Progranulin is a multifunctional factor that is broadly exhibited. and involved in numerous physiological and pathological processes [5]. Anti-inflammatory effects are attributed to its ability to increase interleukin-10 production and decrease TNF1 signaling [13,14]. Previous research has linked elevated progranulin levels to a number of inflammatory disorders, involving systemic

lupus erythematosus [15], rheumatoid arthritis or osteoarthritis [16], as well as diabetes type 2 [17].

The pivotal regulatory role of progranulin in the immune response, together with the observation of elevated plasma progranulin levels in cases with sepsis [6] & bacterial pneumonia [18] from small-scale observational studies, implies that this compound could potentially serve as a biomarker for these conditions [19].

The purpose of this research was to evaluate the diagnostic value of progranulin in the serum of neonates with sepsis. Late-onset neonatal sepsis (LOS) was more prevalent than early-onset neonatal sepsis (EOS) (75.6% & 24.4% respectively). Shehab El-Din et al. also found that LOS was more common than EOS (55.8% and 44.2% respectively) in their study in Mansoura, Egypt [20]. In another study conducted in the NICUs of Ain Shams University's Children's Hospital and Al-Azhar University's El-Hussein Hospital, Egypt, the occurrence of early-onset sepsis was 35.4%, while late-onset sepsis accounted for 64.6% [21].

In this research, it was observed that the levels of CRP were significantly elevated in the case group compared to the control group. Conversely, both Hb and platelet levels were significantly reduced in the case group in comparison to the controls.

Numerous studies align with these findings. For instance, a study by Tam & Bendel found that CRP was an independent predictor of a positive blood culture upon adjusted analysis [22]. In another study by Benitz et al., which involved serial CRP measurements in neonates, both sensitivity and specificity were initially poor but showed significant improvement with multiple measurements. This study also reported a nonspecific physiological increase over a 3-day period, influenced by non-infectious perinatal and maternal factors [22]. According to Hornik et al., low platelet counts were also linked to late-onset sepsis [23]. Contrary to our results, Shoukry et al. stated that anemia is not a consistent characteristic in neonates with a positive blood culture [24].

In their systematic review of fifteen studies involving 11,009 records, Murthy et al. also found that a gestational age below 37 weeks and a premature rupture of membranes were the most commonly documented risk factors for sepsis [25].

In this research, Klebsiella pneumoniae was the predominant gram-negative bacterium, whilst MRSA and coagulase-negative staph (CoNS) were the most frequent gram-positive bacteria. This is consistent with research conducted at Al Demerdash and Ain Shams University Specialized Hospital, where Klebsiella was shown to be the most commonly seen gram-negative bacteria, whereas CoNS was most often encountered gram-positive organism [26]. Nevertheless, in separate research carried out at the Neonatal

Intensive Care Units (NICUs) of the Children's Hospital of Ain Shams University as well as El-Hussein Hospital, Al-Azhar University, Egypt, Escherichia coli was shown to be the most common pathogen that was isolated [21].

According to the findings of this research, the levels of serum progranulin among newborn people with sepsis were found to be significantly higher than those found in the control group. Infection and progranulin have been the subject of a great number of investigations that have been conducted. Take, for example, a study that was conducted on 121 newborns who were hospitalized with suspected EOS and had a gestational age of over 34 weeks. The researchers discovered that septic neonates had significantly higher levels of progranulin in comparison to healthy controls [4]. Similar results were obtained by Yang et al., who revealed that There was a time-dependent rise in the predictive efficacy of progranulin, as serum progranulin levels rose in the EOS newborns but did not in the non-EOS neonates [27]. Song et al. observed that the levels of progranulin were significantly higher in both adult and pediatric cases suffering from sepsis, compared to their respective healthy adult and pediatric control subjects [6]. Brandes et al. observed that plasma progranulin concentrations were significantly greater in adult cases with sepsis and community-acquired pneumonia (CAP) than in healthy control subjects, in cases with sepsis than those with SIRS, in individuals with COVID-19 pneumonia than those with non-COVID-19 CAP, and in cases with CAP than those with an abdominal or other septic focus [19].

According to the findings of our investigation, progranulin had a sensitivity of 68.9 percent & a specificity of 80 %, with a positive predictive value of 77.5 % & a negative predictive value of 72 %. The cutoff value for progranulin was 132.56 ng/ml. To differentiate among septic & non-septic newborns, the area under the curve (AUC) for progranulin was found to be 0.883. The optimal cut-off values of progranulin for the prediction of neonatal sepsis varied between different studies with variable sensitivities and specificities reported. Progranulin had a sensitivity of 67.1 percent, a specificity of 80.3 percent, and AUC of 0.760 when it was utilized to predict EOS within 72 hours of delivery, according to the research conducted by Yang et al. [27]. In the work of Rao et al. in neonates with suspected EOS, a cut-off value for progranulin of more than 37.89 ng/ml resulted in a sensitivity of 94.34% & an NPV of 91.7% with an AUC of 0.786 [4]. Additionally, progranulin levels were lower in pediatric cohorts in comparison with adult cohorts, which raises the possibility that progranulin production throughout sepsis is, at least in part, age-dependent [6].

In our trail, there was no significant variation in serum levels of progranulin among non-

survivor neonates with sepsis compared to the survivor group. Similar results were obtained by Song et al. and Brandes et al. [19,6]. In contrast to this result, Luo et al assessed progranulin as a potential new biomarker for forecasting adverse outcomes in cases of community-acquired pneumonia. according to the results, progranulin was the most accurate predictor of 30-day death in CAP participants. [18].

Moreover, we found in the recent trail that the levels of serum progranulin were shown to have a strong positive correlation with the levels of C-reactive protein (r=0.507). Similarly, Rao et al. found that there was significant positive association among progranulin & CRP in their research. [4].

The relatively small sample size in this single-center study and just a single measurement of progranulin levels are the main study's limitations, but its key strength is that we only included neonates with sepsis that were confirmed by blood culture.

5. Conclusions:

The levels of progranulin in the serum could potentially act as a promising diagnostic indicator for neonatal sepsis. There is a significant positive association among serum progranulin & CRP levels. No link was observed between progranulin levels and the prognosis of neonatal sepsis.

6. Recommendations:

We recommend conducting additional multicenter studies involving large populations, with repeated measurements of progranulin levels. This would allow for a more comprehensive evaluation of progranulin's role in diagnosing neonatal sepsis, determining its prognostic value concerning mortality, and assessing whether the combination of progranulin with other inflammatory biomarkers can provide a safe basis for decisions to start or discontinue empirical antibiotic treatment in neonates suspected of having sepsis.

7. References:

1. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. The lancet. 2017 Oct 14;390(10104):1770-80.
2. Mersha A, Worku T, Shibiru S, Bante A, Molla A, Seifu G, et al. Neonatal sepsis and associated factors among newborns in hospitals of Wolaita Sodo Town, Southern Ethiopia. Research and Reports in Neonatology. 2019;9:1.
3. Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, Schlapbach LJ, Reinhart K, Kissoon N. The global burden of pediatric and neonatal sepsis: a systematic review. The Lancet Respiratory Medicine. 2018 Mar 1;6(3):223- 30.
4. Rao L, Song Z, Yu X, Tu Q, He Y, Luo Y et al. Progranulin as a novel biomarker in diagnosis of early-onset neonatal sepsis. Cytokine. 2020 Apr 1;128:155000.
5. Tian G, Jin X, Wang Q, Ye T, Li G, Liu J. Recent advances in the study of progranulin and its role in sepsis.

International Immunopharmacology. 2020 Feb 1;79:106090.

6. Song Z, Zhang X, Zhang L, Xu F, Tao X, Zhang H et al. Progranulin plays a central role in host defense during sepsis by promoting macrophage recruitment. American journal of respiratory and critical care medicine. 2016 Nov 15;194(10):1219-32.
7. Stocker M, Van Herk W, El Helou S, Dutta S, Fontana MS, Schuerman FA et al. Procalcitonin-guided decision making for duration of antibiotic therapy in neonates with suspected early-onset sepsis: a multicentre, randomised controlled trial (NeoPIns). The Lancet. 2017 Aug 26;390(10097):871-81.
8. Napolitano, L. M.Definitions and guideline changes. Surgical infections, 2018;19(2), 117-125.
9. Fleischmann, C., Scherag, A., Adhikari, N. K., Hartog, C. S., Tsaganos, T., Schlattmann, P., et al. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. American journal of respiratory and critical care medicine, 2016;193(3), 259-272.
10. Scherag, A., Hartog, C. S., Fleischmann, C., Ouart, D., Hoffmann, F., König, C., et al. A patient cohort on long-term sequelae of sepsis survivors: study protocol of the Mid-German Sepsis Cohort. BMJ open, 2017;7(8), e016827.
11. Guirgis, F. W., Brakenridge, S., Sutchu, S., Khadpe, J. D., Robinson, T., Westenbarger, R et al. The long-term burden of severe sepsis and septic shock: sepsis recidivism and organ dysfunction. Journal of Trauma and Acute Care Surgery,2016; 81(3), 525-532.
12. Cohen, J., Vincent, J. L., Adhikari, N. K., Machado, F. R., Angus, D. C., Calandra, T, et al. Sepsis: a roadmap for future research. The Lancet infectious diseases, 2015;15(5), 581-614.
13. Abella, V., Pino, J., Scotece, M., Conde, J., Lago, F., Gonzalez-Gay, M. A et al. Progranulin as a biomarker and potential therapeutic agent. Drug discovery today, 2017;22(10), 1557-1564.
14. Tang, W., Lu, Y., Tian, Q. Y., Zhang, Y., Guo, F. J., Liu, G. Y. et al. The growth factor progranulin binds to TNF receptors and is therapeutic against inflammatory arthritis in mice. Science, 2011;332(6028), 478-484.
15. Tanaka Y. Systemic lupus erythematosus. Best Practice & Research Clinical Rheumatology. 2022: 36;4.
16. Cerezo LA, Kuklová M, Hulejová H, Vernerová Z, Kaspříková N, Veigl D et al. Progranulin Is Associated with Disease Activity in Patients with Rheumatoid Arthritis. Mediators Inflamm.2015:740357.
17. Youn BS, Bang SI, Klöting N, Park JW, Lee N, Oh JE et al. Serum progranulin

concentrations may be associated with macrophage infiltration into omental adipose tissue. Diabetes. 2009 Mar;58(3):627-36.

18. Luo, Q., He, X., Zheng, Y., Ning, P., Xu, Y., Yang, D et al. Elevated progranulin as a novel biomarker to predict poor prognosis in community-acquired pneumonia. Journal of Infection, 2020;80(2), 167-173.
19. Brandes, F., Borrmann, M., Buschmann, D., Meidert, A. S., Reithmair, M., Langkamp, M. et al. Progranulin signaling in sepsis, community-acquired bacterial pneumonia and COVID-19: a comparative, observational study. Intensive Care Medicine Experimental, 2021;9(1), 1-22.
20. Shehab El-Din, E. M. R., El-Sokkary, M. M. A., Bassiouny, M. R., & Hassan, R. Epidemiology of neonatal sepsis and implicated pathogens: a study from Egypt. BioMed research international, 2015.
21. Awad, H. A., Mohamed, M. H., Badran, N. F., Mohsen, M., & Abd-Elrhman, A. S. A. Multidrug-resistant organisms in neonatal sepsis in two tertiary neonatal ICUs, Egypt. Journal of the Egyptian Public Health Association, 2016;91(1), 31-38
22. Tam, P. Y. I., & Bendel, C. M. Diagnostics for neonatal sepsis: current approaches and future directions. Pediatric research, 2017; 82(4), 574-583.
23. Hornik, C. P., Benjamin, D. K., Becker, K. C., Benjamin Jr, D. K., Li, J., Clark, R. H. et al. Use of the complete blood cell count in early-onset neonatal sepsis. The Pediatric infectious disease journal,2012; 31(8), 799-802
24. Shoukry, L. R., Mohamed, A. N., Sharaf, A. E., & Osman, O. B. Diagnostic markers for early detection of neonatal sepsis. Journal of Scientific Research in Medical and Biological Sciences,2021; 2(3), 13-26.
25. Murthy, S., Godinho, M. A., Guddattu, V., Lewis, L. E. S., & Nair, N. S. Risk factors of neonatal sepsis in India: A systematic review and meta-analysis. PloS one, 2019;14(4), e0215683.
26. Abdelkader, H., Fahim, N. A. E., Hagras, A. M., Ahmed, A. A. A., Shawky, A & ،. Hassan, F. (2022). Molecular Identification of Multi Drug-resistant Klebsiella pneumoniae Isolated from Neonates with Sepsis in Egypt. Journal of Pharmaceutical Research International, 2022;77-89.
27. Yang, K. D., He, Y., Xiao, S., Ai, Q., & Yu, J. L. Identification of progranulin as a novel diagnostic biomarker for early-onset sepsis in neonates. European Journal of Clinical Microbiology & Infectious Diseases, 2020;39(12), 2405-2414.