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Original article

# Diagnostic value of progranulin in pediatric sepsis

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**Abstract:**

**Background**: Intensive care unit admissions are largely attributed to sepsis in pediatrics. It is essential to diagnose an infection correctly and monitor it closely to optimize treatment and outcomes. **Aim:** This research was conducted to estimate the diagnostic utility of serum progranulin in pediatric sepsis. **Patients and methods:** This case-control study included 50 pediatric sepsis patients and 40 healthy matched controls. A peripheral blood sample was taken from the patients and controls then progranulin levels were measured using ELISA. **Results:** Serum progranulin values were significantly greater in pediatric sepsis patients than in controls (median 180.15 vs. 96.0 ng/ml, respectively: Mann-Whitney $p < 0.001$). Serum progranulin had good diagnostic power and was the best of laboratory parameters in the diagnosis of pediatric sepsis after CRP with ROC area under the curve (AUC) = 0.998. Using a cutoff value of 116.3 ng/ml PGRN had a sensitivity of

86.0% and a specificity of 100% with a positive predictive value of 100% and a negative predictive value of 85.1%. Serum progranulin levels were positively correlated with body weight and CRP levels and negatively correlated with platelets and hemoglobin levels. Progranulin levels in survivors were not statistically different from those in non-survivors. **Conclusions and Recommendations:** Serum progranulin may be a good biomarker for sepsis diagnosis in pediatrics.

## 1. Introduction:

A dysregulated host's reaction to infection causes sepsis **(1)**. The term 'septic shock' refers to sepsis that is associated with profound alterations in circulation, cellular function, or metabolism, as well as a substantially increased mortality rate **(2)**. In the pediatric intensive care unit, the global burden of morbidity, mortality, and utilization of healthcare services continues to increase due to sepsis **(3)**. There is a wide range of mortality rates for children with sepsis, according to illness severity, risk factors, and the location where they live **(4)**.

The mortality and morbidity rates increase significantly when antibiotics are administered late **(5)**. It is therefore likely that biomarkers will be essential in identifying and treating sepsis as quickly as possible **(6)**.

Progranulin, a secretory protein rich in cysteine and composed of 593 amino acids, is considered to be a physiologically crucial growth factor **(7)**. Progranulin suppresses the degranulation of neutrophils and the transmission of tumor necrosis factor (TNF), contributing to its anti-inflammatory properties **(8)**. Compared to healthy controls, circulating progranulin was elevated in pediatric and adult patients with sepsis **(9)**.

## 2. Patients and Methods:

This case-control research executed in the Beni-Suef University Hospital Pediatric critical care unit from June 2022 to May 2023 included Group A with 50 pediatric sepsis cases and Group B with 40 healthy controls of the same age and gender as Group A. The study was approved by Ethical

Committee of Faculty of Medicine, Beni-Suef University. Approval No (FMBSUREC\09052021\Mesaaed).

Critically ill patients, (1 month-18 years), were included in this research if they fulfilled the pediatric sepsis diagnostic criteria in accordance with the 2005 International Pediatric Sepsis Consensus Conference which defined sepsis as a systemic inflammatory response syndrome (SIRS) with suspected or proven infection**.** Two of the following four criteria are required to diagnose SIRS, with total leucocytic count (TLC) or temperature being one of them **(10)**:

-Temperature >38.5◦C or <36◦C.

-Age-dependent increased or decreased heart rate.

-Increased respiratory rate or need for mechanical ventilation.

-Abnormal TLC or immature cells >10 percent.

Patients were excluded if aged less than 1 month or more than 18 years or lacked parental consent.

Serum electrolytes, kidney function tests, coagulation profile, blood gases, C-reactive protein, complete blood count, and blood culture were tested in all patients with suspected sepsis. A culture of other body fluids like cerebrospinal fluid or urine was requested if clinically indicated. Serum progranulin was measured in patients with proven sepsis and the clinical, and laboratory data were recorded.

**Progranulin measurement:**

Peripheral venous blood samples were collected, then samples were dispensed into plain tubes that were instantly centrifuged at approximately 1000×g for 15 minutes. Blood samples were processed within a few hours after collection for optimal results. After collection, samples were stored for up to 72 hours at 2-8 °C. Extracted serum was stored at -80 °C. Samples were not stored for long periods. Samples were sent on ice packs to the workplace. In accordance with the manufacturer's i nstructions (SinoGeneClon Biotech Co ., Ltd.), serum levels were measured by an enzyme-linked immunosorbent assay

(ELISA) kit using serum centrifuged at approximately 1000 x g.

**Statistical analysis:**

The qualitative data was provided as numbers and percentages to provide descriptive statistics (proportions). The mean and standard deviation were the two main statistical measures that were used to display the quantitative data. The necessary statistical tests were used to conduct an analysis of the relations between the variables, namely the Chi-square test for categorical data

comparison. A mean independent sample t-test was used to compare the two different groups. When the p-value was less than or equal to 0.05, the differences were determined as significant.

**Ethical considerations:**

The research ethics committee of Beni-Suef University's Faculty of Medicine approved the study protocol with No. FMBSUREC/09052021/Mesaaed. The study was conducted according to the Declaration of Helsinki.

## 3. Results:

The pediatric sepsis group included 26 males and 24 females while the controls group included 23 males and 17 females with no significant difference between the 2 groups. Table 1 summarizes the clinical and laboratory characteristics of both groups.

The median and interquartile range of the heart rate was 127 (110 – 144) beats per minute**,** respiratory rate was 48 (40.0 – 55.3) breaths per minute**,** systolic blood pressure was 80 (70 – 90) mmHg**,** diastolic blood pressure was 50 (48.8 – 60) mmHg while it was 39.0 (38.8-39) ◦C for temperature.

The most common cause of PICU admission was a respiratory compromise in 48% of patients followed by a neurologic compromise in 22% of patients. The most common primary site of infection was the respiratory system in 54% of patients followed by the bloodstream in 24% of patients. Around 26% of patients had a preexisting chronic disease. Around 48% of the patients were on an O2 mask, 38% were on mechanical ventilation, 10% were on nasal oxygen and 4% were off oxygen. 37% of patients were on inotropes. The length of PICU stay ranged from 2 – 54 days with a median (Interquartile range) of 11.5 (7.00- 21.25). Around 76% of patients recovered and 24% of patients died.

WBC, CRP, and absolute neutrophilic counts (ANC) were significantly higher in pediatric sepsis patients than in controls (P value < 0.001) while platelets and hemoglobin were significantly lower in pediatric sepsis patients than in controls (P value < 0.001) (Table 1).

Table 2 summarizes the bacteria isolated in blood cultures of pediatric sepsis patients. The most frequently isolated organism was Klebsiella pneumoniae (22 percent).

The sputum culture was done in 27 patients. Around 33% of them showed no growth, MRSA was detected in 7.4% of them, 18.5% were positive for Klebsiella, 11.1% were positive for E.

coli, 14.8% were positive for Acinetobacter while 18.5% were positive for Candida.

The CSF culture was done in 10 patients, 40% of them showed no growth, 50% were positive for CONS and 10% were positive for E. coli. The urine culture was done in 12 patients, 33.3% of them showed no growth, 41.7% were positive for Candida, 16.7% were positive for MRSA and 8.3% were positive for E. coli. The pleural culture was done in 4 patients, 1 of them showed no growth, 1 was positive for MRSA, and 2 were positive for Pseudomonas. 2 patients (4%) had positive PCR nasopharyngeal swabs for COVID-19.

Serum progranulin levels ranged from 101.2 – 286.3 ng/ml with a median and interquartile range of 180.15 (134.45 – 213.55) in pediatric sepsis patients while they ranged from 76.0 – 196.2 ng/ml with a median and interquartile range of 96.0 (85.5-145.0) in controls. They were significantly higher in pediatric sepsis patients than in controls (P value < 0.001) (Table 3), (Figure 1).

The median and interquartile range of progranulin levels in gram-negative and gram-positive sepsis were 181.5 (178.6 - 230.6) ng/ml, and 194.0 (139.2 - 238.0) ng/ml respectively with no significant differences between both.

The median and interquartile range of progranulin levels in survivors and non-survivors were 179.75 (129.73 - 201.68) ng/ml, and 180.15 (136.53-255.33) ng/ml respectively with no significant differences between both.

Serum progranulin was significantly and positively correlated with the weight of pediatric sepsis patients and CRP (r=0.386, 0.372, p value <0.001, 0.008 respectively), while they were significantly and negatively correlated with platelets, and hemoglobin levels (r=-0.46, -0.292, p value= 0.001 and 0.040 respectively) (Table 5).

**Table (1):** Clinical, and laboratory data among pediatric sepsis patients and controls

| **Variables** | **Group A (Pediatric sepsis patients)** | | **Group B (controls)** | | **U** | **P Value** |
|---|---|---|---|---|---|---|
| | Range | Median (Interquartile range) | Range | Median (Interquartile range) | | |
| **Age in years** | 0.16-13 | 1.1 (0.33 - 3.25) | 0.25 - 12 | 1.5 (1.13– 3) | 791.0 | 0.089 |
| **Weight in kg** | 4 – 24 | 9 (5.00 - 14.25) | 4 - 24 | 10 (7.0-12.0) | 951.0 | 0.690 |
| **TLC*$10^3$ (cell/$mm^3$)** | 3.4 - 39.1 | 13.4 (10.08 - 18.7) | 4.5 - 9.9 | 7 (5.4 – 7.8) | 217.5 | **<0.001*** |
| **CRP (mg/L)** | 12 - 362 | 71.0 (24.00 – 137.25) | 1 - 5 | 2.4 (1.6 – 3.0) | 0.000 | **<0.001*** |
| **Platelets*$10^9$/L** | 13 - 945 | 115.0 (77.8-190.0) | 200 - 450 | 277.00 (234.25-330.75) | 245.5 | **<0.001*** |
| **Hemoglobin (g/dl)** | 5.1 – 10 | 7.7 (6.7-8.4) | 11.8 - 15.6 | 13.2 (12.4 – 14.1) | 0.000 | **<0.001*** |
| **ANC*$10^3$ (cell/$mm^3$)** | 1.2-34 | 8.5 (4.3 – 13.2) | 2.1 – 5.8 | 3.5 (2.9-4.5) | 393.5 | **<0.001*** |
| **Progranulin (ng/ml)** | 101.2 - 286.3 | 180.15 (134.45 - 213.55) | 76.0 - 196.2 | 96.0 (85.5-145.0) | 4.00 | **<0.001*** |

*; significant, U; Mann Whitney U test

**Table (2):** Blood culture results of pediatric sepsis patients

| **Organism** | **N (%)**<br>**(n = 50)** |
|---|---|
| **Type of Organism in Blood culture * (Gram -ve/+ve):** | |
| No Growth | 21 (42%) |
| Gram -ve | 15 (30%) |
| Gram +ve | 16 (32%) |
| **Causative organism according to blood culture*** | |
| Klebsiella | 11 (22%) |
| MRSA | 10 (20%) |
| CONS | 6 (12%) |
| Pseudomonus | 2 (4%) |
| Acenitobacter | 2 (4%) |

*; More than 1 type can be present in the same patient

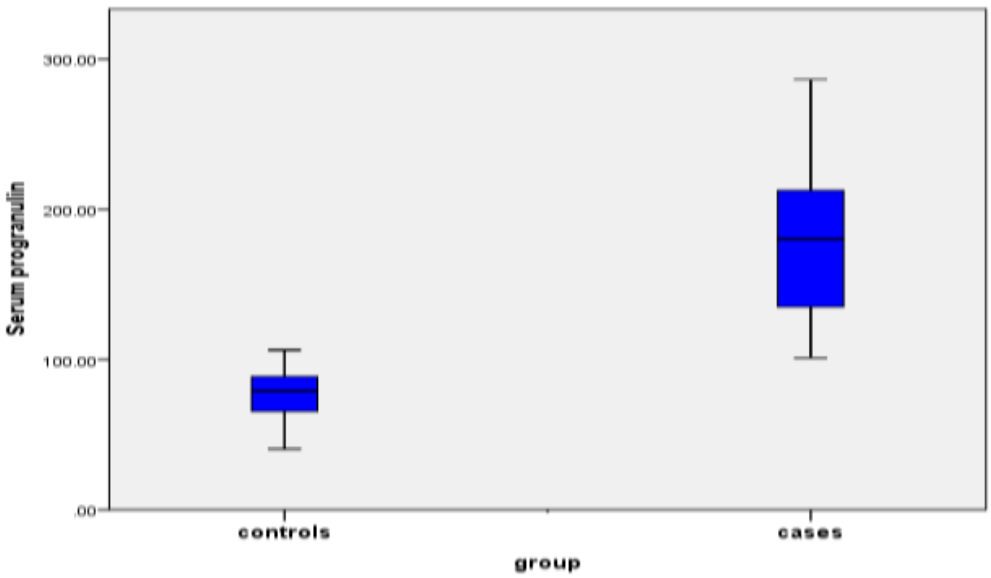


**Figure (1):** Serum progranulin among pediatric sepsis cases and controls

**Table (4):** Correlation of serum progranulin with clinical, and laboratory data among pediatric sepsis patients:

| **Variables** | **Serum progranulin** | |
|---|---|---|
| | **r** | **P value** |
| **Age** | 0.127 | 0.381 |
| **Weight** | 0.386 | **<0.001*** |
| **Length of PICU stay** | 0 235 | 0.101 |
| **Hemoglobin** | -0.292 | **0.040*** |
| **Platelets** | -0.460 | **0.001*** |
| **TLC** | 0.202 | 0.160 |
| **CRP** | 0.372 | **0.008*** |

*; significant, r; Pearson's correlation coefficient

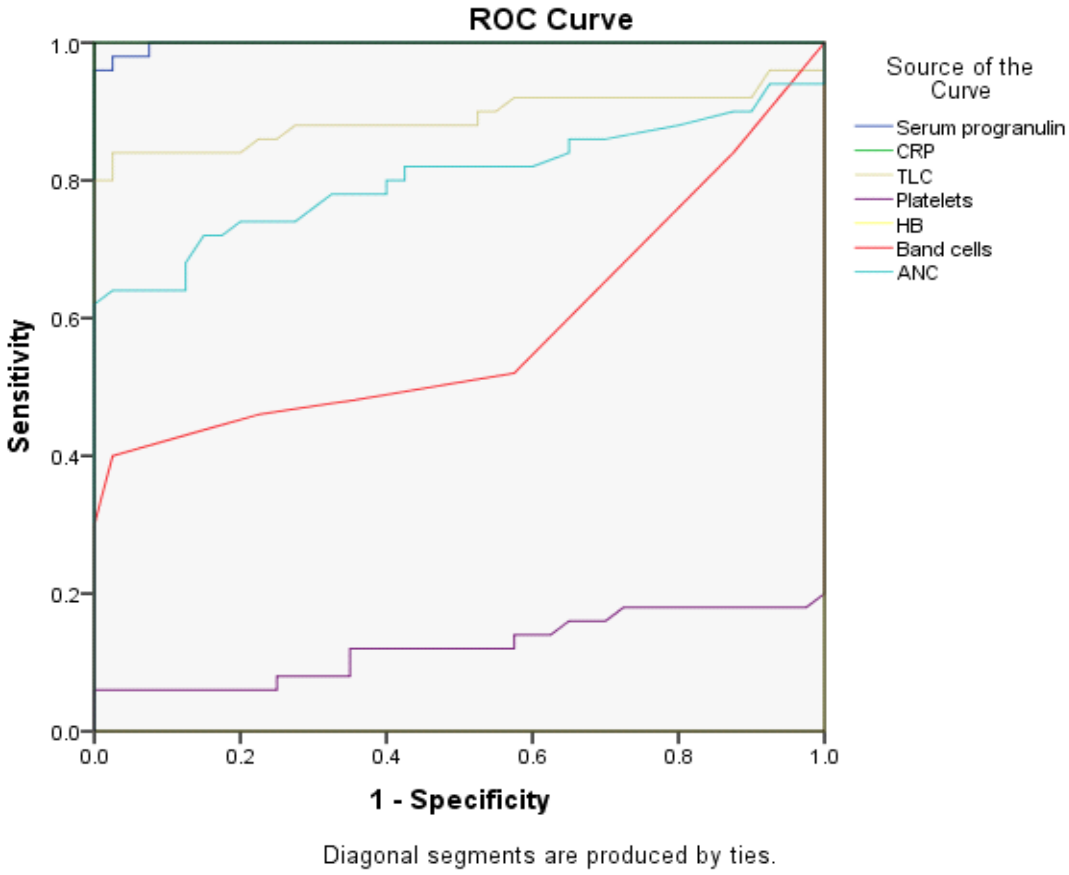


**Figure (2):** ROC curve for serum progranulin, and other laboratory investigations in diagnosing pediatric sepsis.

## 4. Discussion:

Globally, sepsis accounts for 19% of all deaths, with children younger than 5 years having the highest incidence (**11,12**). In the PICU, sepsis is a common cause of admission. In the United States, sepsis in children accounted for 0.7% of all hospitalizations **(13)**. The mortality in PICUs caused by pediatric sepsis has been found to be 1 in 4 based on epidemiological studies **(14)**.

Proper and early diagnosis are crucial for guiding treatment **(15)**. A biomarker detected during an infectious insult can be used in screening, diagnosis, prognosis, monitoring of treatment, and appropriate antibiotic use **((16)**.

Progranulin (PGRN), a precursor for granulin, is expressed in endothelial cells neurons, microglia, and astrocytes **(17)**. PGRN plays a major role in embryonic development, immunity, inflammation, tumorigenesis, and neurodegeneration **(18)**. During sepsis, hematopoietic cells produce

progranulin, which facilitates host protection against sepsis **(9)**.

This case-control study including 50 pediatric sepsis patients recruited from the PICU of Beni-Suef University Hospital and 40 healthy matched controls was conducted to assess the diagnostic value of progranulin in pediatric sepsis.

In the current study, most of the children were admitted for either respiratory or neurological causes. In a study by Gaafar et al., they reported that respiratory causes were the most common causes for admission after the exclusion of surgical causes **(19)**. In another study by Meligy and colleagues at Cairo University, the most common causes for PICU admission were neurological and respiratory causes **(20).**

In the current study, among primary infection sites, the respiratory system was the most frequent followed by bloodstream infection. In their review of pediatric sepsis, Cruz et al. also reported that the most frequent primary sites of infection are respiratory and bloodstream infections **(21)**. Another study of ICU pediatric patients in the Faculty of Medicine, Assiut University by NasrEldin and Ahmed revealed that the respiratory system was the most frequent primary site of infection **(22)**.

In the current study, blood culture results revealed that gram-positive bacteria were more frequent than gram-negative bacteria. Moreover, we found that MRSA was the most common gram-positive organism while Klebsiella pneumoniae was the most frequent gram-negative organism. Dierig and colleagues reported that 64% of isolated bacteria were gram-positive and 36% were gram-negative pathogens **(23)**. However, Ibrahiem et al. in their study in 2 PICUs at Cairo University Hospitals, reported that gram-negative bacteria were more common than gram-positive, and the most common gram-negative pathogen was Klebsiella followed by Pseudomonas aeruginosa while Staphylococcus aureus was the most common gram-positive one (**24**).

In our study, as regards the laboratory data of the patients, TLC, CRP, and absolute neutrophilic counts were significantly higher in children with sepsis than in controls while platelets and hemoglobin levels were significantly lower in children with sepsis than in controls. NasrEldin and Ahmed. also reported that TLC and CRP levels were higher in pediatric sepsis patients than in controls **(22)**. Patel et al. stated that the best-known biomarker for sepsis diagnosis is CRP **(25)**. However, Tamelytė et al. stated

that such markers as TLC, neutrophils, and CRP, especially when used alone, showed insufficient sensitivity to differentiate SIRS and sepsis, **(26)**.

In the current study, serum progranulin levels were significantly higher in pediatric sepsis patients than in controls. Many studies investigated the relationship between infection and progranulin with few studies in the pediatric age group. Song et al. found that progranulin was highly elevated in pediatric and adult patients with sepsis. Moreover, they reported that progranulin was lower in pediatric compared to adults **(9)**. Similarly, PGRN levels were found to be upregulated in adult patients with sepsis compared with those in healthy controls in another study **(27)**. In Luo and colleagues' study, serum PGRN was increased in adults with community-acquired pneumonia (CAP), independently of etiology **(18)**.

In neonates, the serum level of PGRN in suspected EOS has been found to be a strong indicator of bloodstream infection by Rao and colleagues. Their results indicated that in multivariate models, elevated serum PGRN levels showed the strongest risk prediction of EOS independent of PCT and CRP (**28)**. The receiver operating characteristic (ROC) curve of serum progranulin was used to assess the diagnostic accuracy in diagnosing pediatric sepsis. It showed that serum progranulin level has a good diagnostic power and it was the best of laboratory parameters in the diagnosis of pediatric sepsis after CRP with an Area under the ROC curve (AUC) =0.998. (Figure 2). Using a cutoff value of 116.3 ng/ml PGRN had a sensitivity of 86.0% and specificity of 100% with a positive predictive value of 100% and a negative predictive value of 85.1% (Table 6). In neonates, Rao et al. reported that a cutoff value for progranulin of > 37.89 ng/ml in neonates with EOS resulted in a sensitivity of 94.34% and an NPV of 91.7% with an AUC of 0.786 **(28)**.

There was no statistically significant difference in serum levels of progranulin between survivor and non-survivor children with sepsis. Song et al reported a similar result in their study of adult and pediatric patients with sepsis **(9)**. Contrary to this result, in the work of Shan and colleagues in adult patients with sepsis, PRGN was significantly higher in non□survivor patients compared with those in survivors. PGRN exhibited a higher predictive effect, especially the 28-day mortality when combined with acute physiology and chronic health evaluation II (APACHE II) or sepsis□related organ

failure assessment (SOFA) scores **(27)**. PGRN was also highly accurate in predicting 30-day mortality in the work of Luo et al in adult patients with CAP **(18)**.

There was no statistically significant difference in serum progranulin in both gram-negative and positive sepsis. This agrees with the results obtained by Song and colleagues **(9)**. Zou et al. also found increased PGRN production in the lungs and circulation of mice with gram-negative pneumonia and gram-positive pneumonia. In addition, PGRN-deficient mice had decreased bacterial clearance and higher mortality rates when infected with gram-positive or gram-negative pneumonia **(29)**.

Further, serum progranulin levels were significantly and positively correlated with body weight and CRP levels of pediatric sepsis patients (r = 0.386 and 0.372 respectively, p-value <0.001 and 0.008 respectively). In addition to that, serum progranulin was significantly and negatively correlated with platelets and hemoglobin levels of pediatric sepsis patients (r = -0.460 and -0.292 respectively, p-value =0.001 and 0.040 respectively). In the work of Shan et al, there was a positive correlation between PGRN and hypersensitive C-reactive protein, as well as procalcitonin levels **(27)**. In a study by Matsubara and colleagues, the body weight of granulin-deficient mice was lower than that of wild-type mice receiving a standard diet **(30)**. Another study reported that after a long-term diet intervention, progranulin levels decreased in overweight subjects **(31)**.

To our knowledge, no previous studies correlated serum progranulin with platelet levels in pediatric sepsis however ITP patients' plasma PGRN levels and platelet counts were negatively correlated, according to Yu et al. Moreover, they found that as a result of PGRN deficiency, a passive-transfer ITP murine model showed further decreases in platelet count. Recombinant PGRN, however, increased platelet counts in chronic ITP SCID mice **(32)**.

This study had some points of strength; It was a randomized case-control study. It was one of the few works that investigated serum progranulin in pediatric sepsis and correlated it with clinical and laboratory data. The relatively small sample size in this single-center study and just a single measurement of progranulin levels are the main study's limitations.

## 5. Conclusions:

This study concluded that pediatric patients with sepsis show high serum progranulin levels. Serum progranulin

levels are significantly positively correlated with CRP and body weight and significantly negatively correlated with platelets and hemoglobin levels in pediatric sepsis patients. No statistically significant difference in serum levels of progranulin in survived and non-survived children with sepsis. No statistically significant difference in serum levels of progranulin in both gram-negative and gram-positive sepsis. Serum progranulin could be a good biomarker for the diagnosis of sepsis in pediatrics.

## 6. Recommendations:

Further multicenter studies on a large number of populations with serial measurements of progranulin levels are recommended to further evaluate the role of progranulin in the diagnosis of pediatric sepsis and to detect the prognostic value of progranulin regarding mortality. Further studies are required to compare progranulin and other sepsis markers like procalcitonin. There is a need for further studies to determine whether progranulin combined with other inflammatory biomarkers can guide the decision of whether to start or discontinue empirical antibiotics. in pediatric patients with probable sepsis. Further studies are required to compare progranulin in SIRS, severe sepsis, and septic shock pediatric patients.

## 7. References:


1. Singer, M., Deutschman, C. S., Seymour, C. W., Shankar-Hari, M., Annane, D., Bauer, M., ... & Angus, D. C. (2016). The third international consensus definitions for sepsis and septic shock (Sepsis-3). Jama, 315(8), 801-810.
2. Shankar-Hari, M., Phillips, G. S., Levy, M. L., Seymour, C. W., Liu, V. X., Deutschman, C. S., ... & Singer, M. (2016). Developing a new definition and assessing new clinical criteria for septic shock: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Jama*, *315*(8), 775-787.
3. Weiss, S. L., Peters, M. J., Alhazzani, W., Agus, M. S., Flori, H. R., Inwald, D. P., ... & Tissieres, P. (2020). Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Intensive care medicine*, *46*(1), 10-67.
4. Ames, S. G., Davis, B. S., Angus, D. C., Carcillo, J. A., & Kahn, J. M. (2018). Hospital variation in risk-adjusted pediatric sepsis mortality. Pediatric critical care medicine: a

journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies, 19(5), 390.

5. Plunkett, A., & Tong, J. (2015). Sepsis in children. Bmj, 350.
6. Markanday, A. (2015, September). Acute phase reactants in infections: evidence-based review and a guide for clinicians. In Open forum infectious diseases (Vol. 2, No. 3, p. ofv098). Oxford University Press.
7. Tian, G., Jin, X., Wang, Q., Ye, T., Li, G., & Liu, J. (2020). Recent advances in the study of progranulin and its role in sepsis. International Immunopharmacology, 79, 106090.
8. Pogonowska, M., Poniatowski, Ł. A., Wawrzyniak, A., Królikowska, K., & Kalicki, B. (2019). The role of progranulin (PGRN) in modulating anti-inflammatory response in asthma. Central European Journal of Immunology, 44(1), 91-101.
9. Song, Z., Zhang, X., Zhang, L., Xu, F., Tao, X., Zhang, H., & Cao, J. (2016). Progranulin plays a central role in host defense during sepsis by promoting macrophage recruitment. American Journal of Respiratory and Critical Care Medicine, 194(10), 1219-1232.
10. Goldstein, B., Giroir, B., & Randolph, A. (2005). International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatric critical care medicine, 6(1), 2-8.
11. Fleischmann-Struzek, C., Goldfarb, D. M., Schlattmann, P., Schlapbach, L. J., Reinhart, K., & Kissoon, N. (2018). The global burden of paediatric and neonatal sepsis: a systematic review. *The Lancet Respiratory Medicine*, *6*(3), 223-230.
12. Rudd, K. E., Johnson, S. C., Agesa, K. M., Shackelford, K. A., Tsoi, D., Kievlan, D. R., ... & Naghavi, M. (2020). Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *The Lancet*, *395*(10219), 200-211.
13. Weiss, S. L., Fitzgerald, J. C., Maffei, F. A., Kane, J. M., Rodriguez-Nunez, A., Hsing, D. D., ... & Nadkarni, V. M. (2015). Discordant identification of pediatric severe sepsis by research and clinical definitions in the SPROUT international point prevalence study. *Critical care*, *19*(1), 1-10.
14. Schlapbach, L. J., Straney, L., Alexander, J., MacLaren, G., Festa, M., Schibler, A., ... & ANZICS Paediatric Study Group. (2015). Mortality related to invasive infections, sepsis, and septic shock in critically ill children in Australia and New Zealand, 2002–13: a multicentre

retrospective cohort study. *The Lancet Infectious Diseases*, *15*(1), 46-54.

15. Z Oikonomakou, M., Gkentzi, D., Gogos, C., & Akinosoglou, K. (2020). Biomarkers in pediatric sepsis: a review of recent literature. Biomarkers in Medicine, 14(10), 895-917.
16. Lanziotti, V. S., Póvoa, P., Soares, M., Barbosa, A. P., & Salluh, J. I. F. (2016). Use of biomarkers in pediatric sepsis: literature review. Revista Brasileira de terapia intensiva, 28, 472-482.
17. Jian, J., Konopka, J., & Liu, C. (2013). Insights into the role of progranulin in immunity, infection, and inflammation. Journal of leukocyte biology, 93(2), 199-208.
18. Luo, Q., He, X., Zheng, Y., Ning, P., Xu, Y., Yang, D., & Gao, Z. (2020). Elevated progranulin as a novel biomarker to predict poor prognosis in community-acquired pneumonia. Journal of Infection, 80(2), 167-173.
19. Gaafar, M. M., Mohammed, A. A., & Mokhtar, W. A. (2022). Incidence of Hyperammonemia among High-Risk Infants Admitted to Pediatric Intensive Care Unit. The Egyptian Journal of Hospital Medicine, 88(1), 2936-2941.
20. Meligy, B. S., Kamal, S., & El Sherbini, S. A. (2017). Mechanical ventilation practice in Egyptian pediatric intensive care units. Electronic physician, 9(5), 4370.
21. Cruz, A. T., Lane, R. D., Balamuth, F., Aronson, P. L., Ashby, D. W., Neuman, M. I., & Schlapbach, L. J. (2020). Updates on pediatric sepsis. Journal of the American College of Emergency Physicians Open, 1(5), 981-993.
22. NasrEldin, E., & Ahmed, K. (2019). The role of human monocyte-expressing markers (CD163 and MR/CD206) in pediatric sepsis. The Egyptian Journal of Haematology, 44(3), 163.
23. Dierig, A., Berger, C., Agyeman, P. K., Bernhard-Stirnemann, S., Giannoni, E., Stocker, M., & Swiss Pediatric Sepsis Study. (2018). Time-to-positivity of blood cultures in children with sepsis. Frontiers in pediatrics, 6, 222.
24. Ibrahiem, S. K., Galal, Y. S., Youssef, M. R. L., Sedrak, A. S., El Khateeb, E. M., & Abdel-Hameed, N. D. (2016). Prognostic markers among Egyptian children with sepsis in the intensive care units, Cairo University Hospitals. Allergologia et Immunopathologia, 44(1), 46-53.
25. Patel, K., & McElvania, E. (2019). Diagnostic challenges and laboratory

considerations for pediatric sepsis. The journal of applied laboratory medicine, 3(4), 587-600.

26. Tamelytė, E., Vaičekauskienė, G., Dagys, A., Lapinskas, T., & Jankauskaitė, L. (2019). Early blood biomarkers to improve sepsis/bacteremia diagnostics in pediatric emergency settings. Medicina, 55(4), 99.
27. Shan, Y., Zhang, X., Zhou, G., Ji, X., & Gu, Y. (2022). Increased progranulin as an independent predictive biomarker for poor prognosis in sepsis. Cytokine, 155, 155911.
28. Rao, L., Song, Z., Yu, X., Tu, Q., He, Y., Luo, Y., & Chen, D. (2020). Progranulin as a novel biomarker in diagnosis of early-onset neonatal sepsis. Cytokine, 128, 155000.
29. Zou, S., Luo, Q., Song, Z., Zhang, L., Xia, Y., Xu, H., & Cao, J. (2017). Contribution of progranulin to protective lung immunity during bacterial pneumonia. The Journal of infectious diseases, 215(11), 1764-1773.
30. Matsubara, T., Mita, A., Minami, K., Hosooka, T., Kitazawa, S., Takahashi, K., & Seino, S. (2012). PGRN is a key adipokine mediating high fat diet-induced insulin resistance and obesity through IL-6 in adipose tissue. Cell metabolism, 15(1), 38-50.
31. Blüher, M., Rudich, A., Klöting, N., Golan, R., Henkin, Y., Rubin, E., & Shai, I. (2012). Two patterns of adipokine and other biomarker dynamics in a long-term weight loss intervention. Diabetes care, 35(2), 342-349.
32. Yu, Y., Shi, Y., Zuo, X., Feng, Q., Hou, Y., Tang, W., & Peng, J. (2018). Progranulin facilitates the increase of platelet count in immune thrombocytopenia. Thrombosis research, 164, 24-31.