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Microbial metabolites and biomarkers in differential diagnosis of infection in children with cancer

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INTRODUCTION & AIM

In the treatment of pediatric cancer, finding ways to early detect complications to improve treatment outcomes is of great importance. Changes in the concentrations of aromatic microbial metabolites and inflammatory biomarkers are considered one way to identify sepsis as a manifestation of the most severe metabolic dysfunction. It has been shown that the proportion of sepsis-associated metabolites in the intestinal contents of healthy donors did not exceed 5%. However, in patients with sepsis, the proportion of sepsis-associated acids was significantly higher than FMA, 4-HFAA, and 4-HFMA (40% of the total metabolites) [1].

The three most significant aromatic metabolites are called sepsis-associated, these are phenyllactic acid, 4-hydroxyphenyllactic acid, and 4-hydroxyphenylacetic acid. In 2018, an article was published on the involvement of aromatic microbial metabolites in the development of septic shock, which presented a hypothesis about the mechanism and clinical evidence [2].

AIM To evaluate the diagnostic value of inflammation biomarkers and aromatic microbial metabolites in children during the treatment of malignant oncological diseases.

MATERIALS AND METHODS

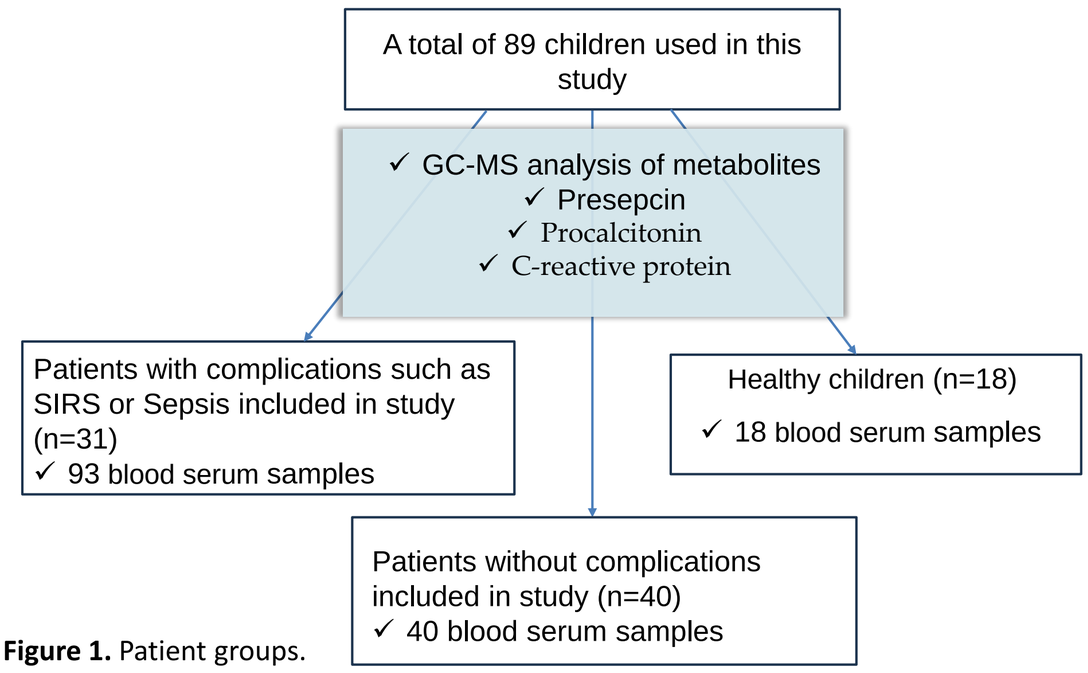
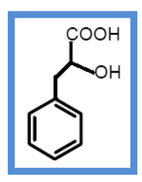
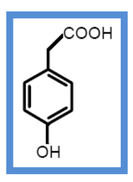


Figure 1. Patient groups.

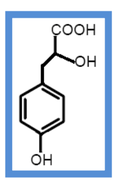
Sepsis-associated microbial metabolites that result from the metabolism of amino acids such as phenylalanine and tyrosine



Phenyllactic acid



p-Hydroxyphenylacetic acid



p-Hydroxyphenyllactic acid

- **The concentration of metabolites** in blood serum was determined by gas chromatography-mass spectrometry using equipment from Shimadzu, Tokyo, Japan.

Blood serum samples → **Sample preparation**

- ✓ Adding internal standard;
- ✓ Liquid-liquid extraction;
- ✓ Evaporation to dryness;
- ✓ Silylation;
- ✓ Dilute with hexane.

→ **GC-MS analysis**

- **Presepsin** was determined using a Pathfast chemiluminescence immunoassay analyzer (Mitsubishi Chemical Medience Corporation, Tokyo, Japan).
- **Procalcitonin and C-reactive protein** were determined using an electrochemiluminescence analyzer (Cobas e411, Roche Diagnostics, Switzerland).

RESULTS & DISCUSSION

Metabolites, µmol/L /Biomarkers	Healthy Children (n = 18)	Patients without Complications (n = 40)	Patients with Complications (n = 31)	p-Value
Phenyllactic acid	<0.5 (<0.5; <0.5)	<0.5 (<0.5; <0.5)	<0.5 (<0.5; 0.9)	-
p-hydroxyphenylacetic acid	<0.5 (<0.5; <0.5)	<0.5 (<0.5; 0.6)	<0.5 (<0.5; 1.0)	-
p-hydroxyphenyllactic acid	1.4 (1.1; 1.8)	0.9 (0.7; 1.1)	1.1 (0.8; 1.7)	**<0.001**
Σ3AMM*	2.2 (1.5; 2.6)	1.5 (1.1; 1.8)	2.0 (1.6; 3.3)	**0.001**
C-reactive protein (mg/L)	0.3 (0.2; 3.8)	1.35 (0.9; 2.4)	128 (66; 201)	**<0.001**
Procalcitonin (ng/mL)	0.06 (0.03; 0.07)	0.07 (0.05; 0.12)	4.2 (0.6; 11.8)	**<0.001**
Presepsin (pg/mL)	93 (72; 111)	108 (91; 122)	526 (331; 917)	**<0.001**

Table 1. Metabolites and biomarkers in healthy children (n = 18), patients with oncology without complications (n = 40), and patients with complications (SIRS, sepsis, and septic shock) (n = 31), and the results of the Kruskal-Wallis U test.

- Σ 3 AMM the sum of three sepsis-associated aromatic microbial metabolites, which consists of phenyllactic, *p*-hydroxyphenylacetic, and *p*-hydroxyphenyllactic acids.

A comparison of biomarkers in the three groups showed statistically significant differences between the groups of patients with complications and the group of healthy children and the group of patients with a diagnosis but without complications (Table 1). At the same time, a pairwise comparison of each group revealed that statistically significant differences were present between the groups of healthy donors and patients with complications, as well as between the groups with oncology without complications and with complications. When comparing the group of healthy children and group of patients without complications, no significant differences in biomarker values were observed. Patients who developed complications during treatment had statistically significant differences in the values of biomarkers such as PSP, PCT, and CRP in comparison with both healthy children and patients without complications.

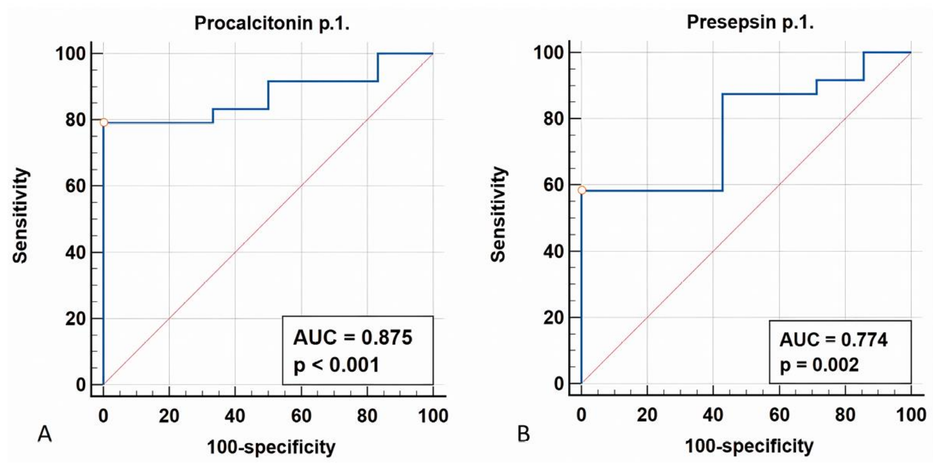


Figure 1. AUROC curve for procalcitonin (A) and presepsin (B) levels at time point 1

High diagnostic ability of procalcitonin and presepsin for detecting sepsis was observed: AUROC=0.875, with a cutoff value (Youden index) of 0.913 ng/ml, and AUROC=0.774, with a cutoff value (Youden index) of 526 pg/ml, respectively (Figure 1).

CONCLUSION

- Decreased concentrations of sepsis-associated aromatic microbial metabolites in cancer patients indicate microbiota dysfunction, which may indicate the need for its timely targeted correction. This study also revealed the high diagnostic ability of procalcitonin and presepsin for detecting sepsis.
- A significant increase in aromatic microbial metabolites and biomarkers in non-survivor patients that is registered already in the first days of the development of complications indicates the appropriateness of assessing metabolic dysfunction for its timely targeted correction.

FUTURE WORK / REFERENCES

1. Chernevskaya E.A., Getsina M.L., Cherpakov R.A., Sorokina E.A., Shabanov A.K., Moroz V.V., Beloborodova N.V. Sepsis-Associated Metabolites and Their Biotransformation by Intestinal Microbiota. *General Reanimatology*. 2023;19(6):4-12. https://doi.org/10.15360/1813-9779-2023-6-4-12
2. Beloborodova N.V., Sarshor Yu.N., Bedova A.Yu., Chernevskaya E.A., Pautova A.K. Involvement of Aromatic Metabolites in the Pathogenesis of Septic Shock. // SHOCK 50(3):273-279, 2018, DOI : 10.1097/SHK.0000000000001064