

An Evaluation of the Levels of IL-1 β and IL-7 in Children With Viral Gastroenteritis

Saja Mohammed Mohsen¹, Asmaa Haseeb Hwaid^{2*}, Maha Falih Nazzal²

¹ Department of Medical Laboratories Techniques, Baqubah-Technical College, Diyala, Iraq

² Department of Biology, College of Education for Pure Sciences, University of Diyala, Diyala, Iraq

Received: Jun. 2024; Accepted: Dec. 2024

Abstract- Gastroenteritis is associated with high rates of morbidity and mortality in the general population, especially in children. To investigate the predictive role of interleukins (IL-1 β and IL-7) in children with viral gastroenteritis as potential diagnostic biomarkers. This cross-sectional study included children who were diagnosed with gastroenteritis at private clinics and Al-Batoul Teaching Hospital for Maternity and Childhood, Diyala, Iraq. The present study was conducted from May 2023 to May 2024. Ninety blood samples were collected from children with gastroenteritis, and 50 blood samples were taken from healthy children and those in the control group. Additionally, 90 samples of the stool were collected. The ELIZA technique was used for exploring IL-1 β and IL-7 in blood samples and for detecting viral antigens (Norovirus, Adenovirus and Astrovirus) in stool samples. The data were analyzed statistically via SPSS v. 24 and Prism v. 10. There was a statistically significant increase in the incidence of infectious gastroenteritis in thin children aged 1-3 years who were living in rural areas. As indicated in this study, the most common symptoms were diarrhoea, vomiting and fever, and the differences were significant. Compared with those in the control group, there were significant differences in the levels of IL-1 β and IL-7 among the children infected with gastroenteritis. ROC analysis of IL-1 β and IL-7 interleukins revealed moderate sensitivity (79% and 88%, respectively) and low specificity (64% and 69%, respectively) at cut-off values of 8.52 and 7.01. The occurrence of norovirus occurred in 30% of the total samples, followed by Adenovirus in 20% and Astrovirus in 11%. The serum levels of IL-1 β and IL-7 were high among children infected with gastroenteritis. Nevertheless, these parameters cannot be considered reliable vital indicators that are sufficient for diagnosing infections caused by gastroenteritis.

© 2025 Tehran University of Medical Sciences. All rights reserved.

Acta Med Iran 2025;63(January-February):19-24.

<https://doi.org/10.18502/acta.v63i1.18590>

Keywords: Gastroenteritis; Viral infections; Interleukins; Interleukin-1 beta (IL-1 β); Interleukin-7 (IL-7)

Introduction

Paediatric gastroenteritis is a common disease caused by viruses, bacteria, and some intestinal parasites. Gastroenteritis is responsible for 20% of paediatric morbidity and mortality (1,2). Children under the age of 3, regardless of sex, demonstrate a greater susceptibility to contracting acute viral gastroenteritis, as evidenced by various studies (3). Within developed countries experiencing economic growth, the annual incidence of diarrhoea in children younger than 3 years of age averages 1.2 episodes, whereas this frequency

significantly increases in developing countries (4-6). The duration of incubation typically ranges from 12 to 72 hours, depending on the specific causative viral agent. The primary clinical manifestations of acute viral gastroenteritis include vomiting and diarrhoea, frequently accompanied by malaise, nausea, abdominal cramping, and fever (7). Often, these conditions tend to be self-limiting and require primarily supportive care. However, antimicrobial agents play a pivotal role in the management of sudden severe diarrhoea. Prompt identification of the underlying aetiology may avoid the necessity of antimicrobial therapy, thus reducing

Corresponding Author: A. Haseeb Hwaid

Department of Biology, College of Education for Pure Sciences, University of Diyala, Diyala, Iraq
Tel: +964 07732438740, E-mail address: asmaa.haseeb@ymail.com

Copyright © 2025 Tehran University of Medical Sciences. Published by Tehran University of Medical Sciences

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International license (<https://creativecommons.org/licenses/by-nc/4.0/>). Non-commercial uses of the work are permitted, provided the original work is properly cited

morbidity and mortality rates (8).

Previous studies have shown a significant increase in the levels of proinflammatory cytokines, including interleukin-1 β (IL-1 β) and tumour necrosis factor- α (TNF- α), in most cases of gastrointestinal inflammation (9). IL-1 β is engaged in the initiation and enhancement of the inflammatory reaction that results in intestinal damage. It has been demonstrated that IL-1 β is crucial for the development of intestinal inflammation in IBD and in animal models. Elevated levels of IL-1 β are observed in the intestinal tissue of individuals with IBD (10). In individuals with gastroenteritis, researchers have found that higher levels of IL-1 β are associated with more severe disease (11). According to recent studies, interleukin 1 β (IL-1 β) promotes intestinal inflammation by disrupting the barriers of intestinal tight junctions (TJs) and promoting the intestinal penetration of luminal antigens (12). On the other hand, it has been documented (13), an increase in IL-1 β levels in patients with stomach cancer. Also, in another research, it has been reported (14) elevated IL-1 β levels in patients with gastritis caused by *H. pylori*.

IL-7 is a cytokine that originates from the stroma and is produced by cells in the fetal liver, stromal cells within the bone marrow and thymus, and intestinal epithelial cells (IECs). The IL-7 receptor is expressed on the surfaces of T and B lymphocyte precursors, innate lymphocytes, antigen-presenting cells (APCs), and mature T cells (15,16). High IL-7 gene expression in CD8⁺ T cells is significantly associated with a more aggressive course of IBD. However, the involvement of IL-7 activity in the pathogenesis of inflammatory bowel disease in humans is uncertain (17,18). Previous studies did not examine the relationship between IL-1 β and IL-7 with gastroenteritis, so the aim of the present study was to evaluate the predictive role of interleukins (IL-1 β and IL-7) and their relationship with gastroenteritis as a diagnostic biomarker and to detect the most important viral causes related to gastroenteritis in children.

Objectives

The objective of this work was to investigate the predictive role of interleukins (IL-1 β and IL-7) in children with viral gastroenteritis as potential diagnostic biomarkers.

Materials and Methods

Study design

This cross-sectional study included children who suffered from gastroenteritis and were selected from

among those who attended private clinics and the Al-Batoul Teaching Hospital for Maternity and Childhood, Diyala, Iraq, from May 2023 to May 2024. Ninety blood samples were collected from children with gastroenteritis after being clinically diagnosed by paediatricians, and 50 blood samples from healthy children were included in the study as a control group. IL-1 β and IL-7 interleukins were investigated via the ELISA technique (CUSABIO, China). In addition, 90 stool samples were collected for the exploration of viral antigens via ELISA (Diagnostic Automation, Inc., USA). The researcher previously prepared a questionnaire for gathering demographic information about age, sex, BMI, residence, and symptoms. Only 5 ml blood samples were taken from patients and healthy children and centrifuged to obtain the serum. The serum samples were kept at -20° C and then used for IL-1 Beta and IL-7 detection according to the manufacturer's instructions. The stool samples were collected and placed in sterile containers. Then, they were diluted in a buffer solution with neutral pH=7. A 10% suspension of each sample was prepared in sterile test tubes. The samples were mixed by vortex and centrifuged via a centrifuge. According to the manufacturer's instructions, ELISA was used to detect the viral antigens.

Statistical analysis

The researchers calculated the mean $\pm$ standard deviation (SD) for the quantitative data of the levels of IL-1 β and IL-7. The demographic and clinical data are expressed as numbers and percentages. Pearson's chi-square test was used to compare the variables. To be statistically significant, a *P* must be less than 0.05. Receiver operating characteristic (ROC) curves were drawn to estimate the accuracy of the diagnostic tests of the IL-1 β and IL-7 interleukins indicators by counting the areas under the area under the curve (AUC) curves for comparison (sensitivity, specificity, and cut-off value). The data were analysed statistically via SPSS v. 24 and Prism v. 10.

Results

Table 1 shows that (69%) of the children with gastroenteritis were thin in comparison with the healthy children. This difference was statistically significant (*P*<0.05). Most of those infected children lived in rural areas (64%). On the other hand, the statistical analysis indicated a significant difference in the age of the children who suffered from gastrointestinal infections who were included in the current study. There were more acute gastrointestinal viral infections in children 1-2 years old

and 3-5 years old than in children younger than one year old. This difference was statistically significant ($P<0.05$). Regarding the clinical manifestations, all diarrhoea, vomiting, and fever plus mild and moderate dehydration were correlated with most cases of gastroenteritis. This difference was statistically significant ($P<0.05$).

The most common viral pathogens detected in stool samples using ELISA were norovirus (30%), followed by adenovirus (20%) and astrovirus (11%), as shown in Table 2. The differences were statistically significant ($P<0.05$).

Regarding the levels of interleukin under study, laboratory results revealed significantly greater levels of interleukin IL-1 β and IL-7 in the sera of children

suffering from gastroenteritis was (13.45 ± 5.84 and 11.74 ± 4.48 , respectively) than in those of healthy children (7.88 ± 3.20 and 5.52 ± 2.03 , respectively) ($P<0.05$; Table 3 and Figure 1).

The values of IL-1 β and IL-7 were estimated by receiver operating characteristic (ROC) curve analysis. There was moderate sensitivity and low specificity determined by the area under the curve for IL- IL-1 β and IL-7 (AUC 0.807 and 0.861, respectively) (Table 4). The optimal cut-off value for IL-1 β was 8.52 pg/mL, with a sensitivity and specificity of 79% and 69%, respectively, while the optimal cut-off value for IL-7 was 7.01 pg/ml, with a sensitivity and specificity of 88% and 64%, respectively (Figure 2).

Table 1. Distribution of patients according to demographic and clinical features.

Demographic and clinical features	No.	%	P
Age groups (years)	<1	21	23%
	1-2	28	31%
	2-3	41	46%
Gender	Males	48	53%
	Females	42	47%
BMI	Lean	62	69%
	Obese	28	31%
Living	Rural	58	64%
	Urban	32	36%
Symptoms	Diarrhoea	84	93%
	Vomiting	77	86%
	Fever	61	68%
Dehydration	All above	82	91%
	Mild	32	36%
	Moderate	39	43%
	Sever	19	21%

Table 2. Positivity rate of viral infection in children with acute gastroenteritis

Viruses	No.	%	P
Norovirus	27	30%	$P<0.01^{**}$
Adenovirus	18	20%	
Astrovirus	10	11%	
Total	55	61%	

Table 3. The levels of interleukin IL-1 β and IL-7 in patients and control groups

		No.	Mean	SD	P
IL-1Beta (Pg/ml)	Patients	90	13.45	5.84	$P<0.001^{***}$
	Healthy	50	7.88	3.20	
IL-7 (Pg/ml)	Patients	90	11.74	4.48	$P<0.001^{***}$
	Healthy	50	5.52	2.03	

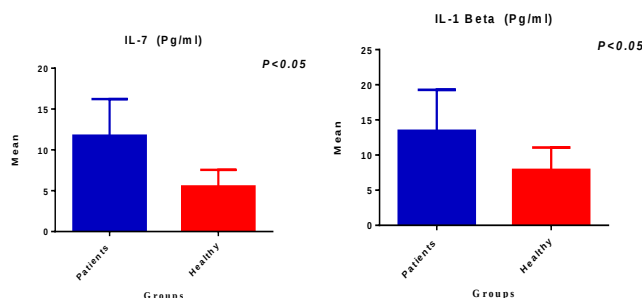


Figure 1. The mean levels of IL-1 β and IL-7 in the study groups

Table 4. AUC, cut-off, sensitivity, and specificity of interleukins

Variables	AUC*	Std. Error ^a	P	cut-off	Sensitivity %	Specificity %
IL-1 β (Pg/ml)	0.807	0.049	$P<0.001^{***}$	8.52	79%	69%
IL-7 (Pg/ml)	0.861	0.041	$P<0.001^{***}$	7.01	88%	64%

*AUC= Area under the curve

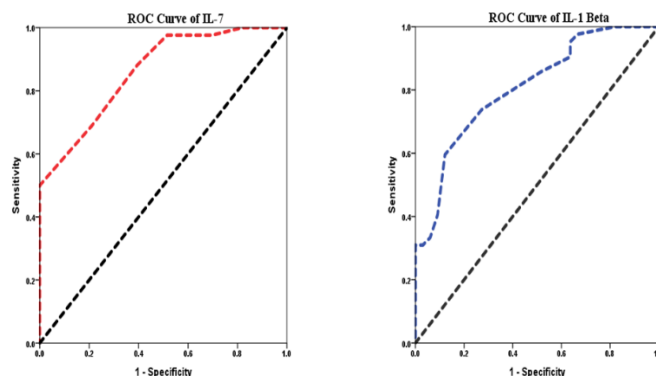


Figure 2. ROC curve of interleukins

Discussion

Gastroenteritis is a disease caused by many viral and bacterial pathogens. The infection is usually transmitted through the feces and mouth. Children are more susceptible to gastroenteritis. It has been reported (19) that most gastroenteritis patients were children aged 1-3 years, and these results were consistent with the results of the present study. On the other hand, in a recent study, it has been reported (20) a higher incidence of gastroenteritis in infants less than one year old than in older children. Several reasons can explain these differences, such as weak immunity in children, the adoption of artificial feeding and decreased breastfeeding, and a lack of interest in prevention and sterilization procedures. It is possible that the prevalence of infections among the population of the studied sample can be attributed to these reasons.

Most cases of gastroenteritis in the current study involved thin children, and these findings are consistent with previous research (21), who reported that most cases of gastrointestinal infections occurred in underweight and normal weight children. On the other hand, overweight and obesity are risk factors that play a role in increasing gastrointestinal inflammation (22). In this work, most cases of gastrointestinal infections were observed among residents of rural areas, and the findings of previous research (23) were consistent with our findings. The lack of health awareness and poverty indices in these areas may play a major role in this aspect. Previous studies have indicated that most patients with gastrointestinal

infections admitted to emergency departments have diarrhoea, fever, vomiting, and mild dehydration (24), which was also observed among the participants in the present study.

Acute viral gastroenteritis contributes to notable morbidity rates in developed countries and significant mortality rates in developing countries. It is a serious problem, especially for children and adolescents of all ages (25). Multiple studies from around the world have documented findings similar to ours, demonstrating that norovirus, adenovirus, and astrovirus are significantly involved in the occurrence of these gastrointestinal infections in children (26). Noroviruses have become increasingly prominent as the primary etiological agent of acute gastroenteritis, particularly in nations where universal rotavirus immunization has been implemented (27).

Proinflammatory cytokines induce the activation of macrophages and neutrophils, promoting the generation of reactive oxygen species as a defence mechanism against infection. Serological tests revealed a significant increase in the level of IL-1 β in children with gastroenteritis compared to the control group. The scientific literature has not studied the relationship between this interleukin and gastrointestinal infections. However, it has been reported (28) an increase in the level of IL-1 β in children with acute diarrhoea because of rotavirus infection. IL-1 β is a proinflammatory cytokine that plays an important role in inflammation of the stomach and intestine (29). Multiple studies have reported elevated serum concentrations of IL-1 β in

patients with ulcerative colitis and Crohn's disease (30). Other studies have shown similar observations of elevated IL-1 β concentrations in the mucosa and stool of children and adults with inflammatory bowel diseases (31,32). Due to its proinflammatory effect, a recent study has shown that anti-IL-1 β plays a key role in the treatment of many diseases, such as infectious diseases, systemic diseases, autoimmune diseases, and malignancies (33).

Children with gastroenteritis had significantly greater IL-7 levels than healthy children. This study is the first to document a relationship between gastroenteritis and IL-7 levels. In contrast to our results, it has been reported (34) that it did not observe an increase in the level of IL-7 in patients with gastric cancer. High levels of IL-7 in patients are related to proinflammatory effects (35). It has been reported (36) that IL-7 acts as a regulator of intestinal epithelial cell homeostasis, colonic function, and the composition of commensal bacteria. Therefore, elevated serum levels of IL-7 because of gastrointestinal infections may cause an imbalance in intestinal epithelial cells and affect commensal bacteria and colon function.

The present work evaluated the value of serum IL-1 β and IL-7 as biomarkers that can be used to predict the prognosis of patients with viral gastroenteritis in infected and healthy groups. Although the serum levels of these interleukins were significantly greater in the group of children with gastroenteritis, the sensitivity and specificity of IL-1 β and IL-7 were moderate and low, respectively, as shown by ROC curve analysis. This study is the first to determine the value of IL-1 β and IL-7 levels as predictors of viral gastroenteritis in children. There have been no previous studies using these interleukins as predictive biomarkers for the diagnosis of gastroenteritis, so researchers recommend additional future studies to confirm the results of this study.

The serum levels of IL-1 β and IL-7 were high among the children with gastroenteritis. Nevertheless, these parameters cannot be considered reliable vital indicators that are sufficient for diagnosing infections caused by gastroenteritis. There is a need for additional future studies to enhance these results and examine other interleukins that are strongly related to gastroenteritis among children.

Limitations

Limitations of the study included the small sample size, the short period of time for the study, and the limited clinical information. Future studies should include as many children as possible in different seasons and use

genetic diagnostic methods to diagnose enteroviruses.

Acknowledgements

The researchers would like to thank the people who helped complete this project.

References

1. Soltan Dallal MM, Rajabi Z, Papizadeh M, Amiri S, Foroushani AR, Naser A, et al. Prevalence of extended-spectrum β -lactamase (ESBL)-producing *Escherichia coli* associated with outbreaks of food-borne gastroenteritis in Tehran. *Cell Mol Biomed Rep* 2024;4:199-207.
2. Horne RG, Freedman SB, Johnson-Henry KC, Pang XL, Lee BE, Farion KJ, et al. Intestinal microbial composition of children in a randomized controlled trial of probiotics to treat acute gastroenteritis. *Front Cell Infect Microbiol* 2022;12:883163.
3. Monroe SS. Control and prevention of viral gastroenteritis. *Emerg Infect Dis* 2011;17:1347-8.
4. Leung A, Prince T, Society CP, Nutrition, Committee G. Oral rehydration therapy and early refeeding in the management of childhood gastroenteritis. *Paediatr Child Health* 2006;11:527-31.
5. Koteswari P, Lakshmi PA, Yaseen M, Sultana S, Tabassum A, Soumya P, et al. Preterm birth: causes and complications observed in tertiary care hospitals. *Cell Mol Biomed Rep* 2022;2:202-12.
6. Amjadi N, Talayeh M, Momeni M, Mansouri N. The comparison of umbilical cord artery pH in newborns with and without thick meconium stained amniotic fluid. *Cell Mol Biomed Rep* 2023;3:222-6.
7. Bánai K, Estes MK, Martella V, Parashar UD. Viral gastroenteritis. *Lancet* 2018;392:175-86.
8. Huang Y, Zhou N, Zhang S, Yi Y, Han Y, Liu M, et al. Norovirus detection in wastewater and its correlation with human gastroenteritis: a systematic review and meta-analysis. *Environmental Science and Pollution Research*. 2022;29:22829-42.
9. Kaminsky LW, Al-Sadi R, Ma TY. IL-1 β and the intestinal epithelial tight junction barrier. *Front Immunol* 2021;12:767456.
10. Isaacs KL, Sartor RB, Haskill S. Cytokine messenger RNA profiles in inflammatory bowel disease mucosa detected by polymerase chain reaction amplification. *Gastroenterology* 1992;103:1587-95.
11. Mao L, Kitani A, Strober W, Fuss IJ. The role of NLRP3 and IL-1 β in the pathogenesis of inflammatory bowel disease. *Front Immunol* 2018;9:2566.
12. Rawat M, Nighot M, Al-Sadi R, Gupta Y, Viszwapriya D,

- Yochum G, et al. IL1B increases intestinal tight junction permeability by up-regulation of MIR200C-3p, which degrades occludin mRNA. *Gastroenterology* 2020;159:1375-89.
13. Man SM. Inflammasomes in the gastrointestinal tract: infection, cancer and gut microbiota homeostasis. *Nat Rev Gastroenterol Hepatol* 2018;15:721-37.
14. Outlioua A, Badre W, Desterke C, Echarki Z, El Hammani N, Rabhi M, et al. Gastric IL-1 β , IL-8, and IL-17A expression in Moroccan patients infected with *Helicobacter pylori* may be a predictive signature of severe pathological stages. *Cytokine* 2020;126:154893.
15. Zhang W, Du JY, Yu Q, Jin JO. Interleukin-7 produced by intestinal epithelial cells in response to *Citrobacter rodentium* infection plays a major role in innate immunity against this pathogen. *Infect Immun* 2015;83:3213-23.
16. Fry TJ, Mackall CL. The many faces of IL-7: from lymphopoiesis to peripheral T cell maintenance. *The J Immunol* 2005;174:6571-6.
17. Lee JC, Lyons PA, McKinney EF, Sowerby JM, Carr EJ, Bredin F, et al. Gene expression profiling of CD8+ T cells predicts prognosis in patients with Crohn disease and ulcerative colitis. *J Clin Invest* 2011;121:4170-9.
18. Belarif L, Danger R, Kermarrec L, Nerrière-Daguin V, Pengam S, Durand T, et al. IL-7 receptor influences anti-TNF responsiveness and T cell gut homing in inflammatory bowel disease. *J Clin Invest* 2019;129:1910-25.
19. Lin FJ, Huang YC, Huang YC, Huang LM, Liu CC, Chi H, et al. Clinical and epidemiological features in hospitalized young children with acute gastroenteritis in Taiwan: a multicentered surveillance through 2014–2017. *J Formos Med Assoc* 2022;121:519-28.
20. Khan MA. Epidemiological studies on gastroenteritis in children in the Bannu district, Khyber Pakhtunkhwa, Pakistan. *Z Gesundh Wiss* 2023;31:739-46.
21. Cai H, Shao Y, Yu W. Prevalence and associated factors of acute gastroenteritis in children and adolescents aged from 6 to 17 years old: a cross-sectional study based on the National Health and Nutrition Examination Survey database 1999–2018. *BMJ Open* 2023;13:e068319.
22. Chaucheyras-Durand F, Sacy A, Karges K, Apper E. Gastro-intestinal microbiota in equines and its role in health and disease: The black box opens. *Microorganisms* 2022;10:2517.
23. Moon RC, Bleak TC, Rosenthal NA, Couturier B, Hemmert R, Timbrook TT, et al. Relationship between diagnostic method and pathogen detection, healthcare resource use, and cost in US adult outpatients treated for acute infectious gastroenteritis. *J Clin Microbiol* 2023;61:e01628-22.
24. Robson K, Bouchoucha S, Considine J. Emergency department assessment and management of children with gastroenteritis. *Australas Emerg Care* 2024;27:81-7.
25. Leung AK, Hon KL. Paediatrics: how to manage viral gastroenteritis. *Drugs Context* 2021;10:2020-11-7.
26. Kılıçaslan O, Sav N, Karaca S, Şahin I, Öksüz S, Kocabay K. Role of routine laboratory markers in the diagnosis of rotavirus and adenovirus gastroenteritis. *J Med Sci Res* 2022;10:76-81.
27. Koo HL, Neill FH, Estes MK, Munoz FM, Cameron A, DuPont HL, et al. Noroviruses: the most common pediatric viral enteric pathogen at a large university hospital after introduction of rotavirus vaccination. *J Pediatric Infect Dis Soc* 2013;2:57-60.
28. Al-Saffar VH. Rotavirus Stimulates Secretion of Interleukin-1beta (IL-1 β) in Children with Gastroenteritis. *Int J Psychosoc Rehabil* 2020;24.
29. Lu Z, Zou J, Hu Y, Li S, Zhou T, Gong J, et al. Serological markers associated with response to immune checkpoint blockade in metastatic gastrointestinal tract cancer. *JAMA Netw Open* 2019;2:e197621.
30. Hyams JS, Fitzgerald JE, Wyzga N, Treem WR, Justinich CJ, Kreutzer DL. Characterization of circulating interleukin-1 receptor antagonist expression in children with inflammatory bowel disease. *Dig Dis Sci* 1994;39:1893-9.
31. Raab Y, Hällgren R, Gerdin B. Enhanced Intestinal Synthesis of Interleukin-6 Is Related to the Disease Severity and Activity in Ulcerative Colitis. *Digestion* 1994;55:44-9.
32. Wedrychowicz A, Stopyrowa J, Fyderek K, Miezyński W. Stool interleukin 1 β and interleukin 1 receptor antagonist concentrations in children with active ulcerative colitis and during recovery. *Eur J Pediatr* 2003;162:541-2.
33. Villatoro A, Cuminetti V, Bernal A, Torroja C, Cossío I, Benguría A, et al. Endogenous IL-1 receptor antagonist restricts healthy and malignant myeloproliferation. *Nat Commun* 2023;14:12.
34. Bednarz-Misa I, Diakowska D, Krzystek-Korpacka M. Local and systemic IL-7 concentration in gastrointestinal-tract cancers. *Medicina (Kaunas)* 2019;55:262.
35. Winer H, Rodrigues GO, Hixon JA, Aiello FB, Hsu TC, Wachter BT, et al. IL-7: comprehensive review. *Cytokine* 2022;160:156049.
36. Shalapour S, Deiser K, Kühl AA, Glauben R, Krug SM, Fischer A, et al. Interleukin-7 links T lymphocyte and intestinal epithelial cell homeostasis. *PloS One* 2012;7:e31939.