To cite this article: Haznedar B, Kozan G, Ebik B. Effect of probiotic supplementation on hospital admission frequency and inflammatory markers in allergic rhinitis and irritable bowel syndrome patients. Turk J Clin Lab 2024; 3: 442-448

Research Article

Effect of probiotic supplementation on hospital admission frequency and inflammatory markers in allergic rhinitis and irritable bowel syndrome patients

Alerjik rinit ve irritabl bağırsak sendromu hastalarında probiyotik takviyesinin hastane yatış sıklığı ve inflamatuar belirteçler üzerine etkisi

Berzan Haznedar*[1], Günay Kozan[2], Berat Ebik[3]

[1]Department of Ear Nose Throat, University of Health Sciences, Gazi Yasargil Training and Research Hospital, Diyarbakır, Turkey,

[2]Department of Ear Nose Throat, Dicle University Faculty of Medicine, Diyarbakır, Turkey,

[3]Department of Gastroenterology, University of Health Sciences, Gazi Yasargil Training and Research Hospital, Diyarbakır, Turkey.

ABSTRACT

Aim: This study aimed to investigate the effect of short-term (3-6 months) probiotic use on patients with recurrent allergic rhinitis (AR) and irritable bowel syndrome (IBS), focusing on changes in inflammation indices and hospital admission frequency.

Material and Methods: This retrospective study included patients diagnosed with IBS and AR between 2020 and 2021, who used probiotic supplements for 3 to 6 months. Clinical data, including demographic characteristics, systemic inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), hemograms before and after probiotic use, and AR-related admission numbers, were collected. The probiotic intervention was compared to a control group receiving standard IBS treatment without probiotics.

Results: Of the 135 patients evaluated, a significant reduction in AR-related hospital admission frequency was observed in the probiotic-treated group compared to the control group ($p<0.001$). Both groups exhibited decreased IBS-related hospital admission frequency, with a higher effect size in the probiotic group (Cohen's d: 1.72 vs 0.55). Probiotic supplementation led to reductions in systemic inflammation indicators (SII, NLR, PLR, CRP) in the treatment group ($p<0.05$), whereas no significant changes were noted in the control group ($p>0.05$).

Conclusion: Probiotic use for at least 3 months in patients with IBS and AR demonstrated improvements in inflammation indices and a reduction in disease-related hospital admission frequency. This suggests a potential role for probiotics in modulating allergic responses and inflammation, providing a promising adjunctive therapy for managing AR, particularly in individuals with co-existing gastrointestinal conditions.

Keywords: probiotics, allergic rhinitis, irritabl bowel syndrome, inflammation indices, disease-releated hospital admission

Corresponding Author*: Berzan Haznedar, Department of Ear Nose Throat, University of Health Sciences, Gazi Yasargil Training and Research Hospital, Diyarbakır, Turkey.
E-mail: drberzanhaznedar@gmail.com
Orcid: 0000-0002-4990-5260
Doi: 10.18663/tjcl.1550711
Recevied: 15.09.2024 accepted: 24.09.2024

TJCL Volume 15 Number 3 p: 442-448

ÖZ

Amaç: Bu çalışma, tekrarlayan alerjik rinit (AR) ve irritabl bağırsak sendromu (IBS) olan hastalarda kısa süreli (3-6 ay) probiyotik kullanımının etkisini, özellikle inflamasyon indekslerindeki değişikliklere odaklanarak incelemeyi amaçlamıştır.

Gereç ve Yöntemler: Bu retrospektif çalışmaya 2020-2021 yılları arasında IBS ve AR tanısı almış ve 3-6 ay süreyle probiyotik takviyesi kullanan hastalar dahil edildi. Demografik özellikler, sistemik inflamasyon indeksi (SII), nötrofil-lenfosit oranı (NLR) ve trombosit-lenfosit oranı (PLR) gibi klinik veriler ile probiyotik kullanımı öncesi ve sonrası hemogram sonuçları ve AR ile ilişkili başvuru sayıları toplandı. Probiyotik müdahalesi, probiyotik içermeyen standart IBS tedavisi alan kontrol grubu ile karşılaştırıldı.

Bulgular: Değerlendirilen 135 hasta arasında, probiyotik tedavisi alan grupta kontrol grubuna kıyasla AR ile ilişkili hastane başvuru sıklığında anlamlı bir azalma gözlendi ($p<0.001$). Her iki grupta da IBS ile ilişkili hastane başvuru sıklığında azalma görülürken, probiyotik grubunda daha yüksek bir etki büyüklüğü tespit edildi (Cohen's d: 1.72 vs 0.55). Probiyotik takviyesi, tedavi grubunda sistemik inflamasyon indekslerinde (SII, NLR, PLR, CRP) azalmaya yol açtı ($p<0.05$), ancak kontrol grubunda anlamlı bir değişiklik gözlenmedi ($p>0.05$).

Sonuçlar: IBS ve AR hastalarında en az 3 ay boyunca probiyotik kullanımı, inflamasyon indekslerinde iyileşme ve hastalıkla ilişkili hastane başvuru sıklığında azalma sağladı. Bu, probiyotiklerin alerjik yanıtları ve inflamasyonu modüle etmede potansiyel bir rol oynayabileceğini ve özellikle gastrointestinal bozuklukları olan bireylerde AR yönetimi için umut verici bir yardımcı tedavi olabileceğini göstermektedir.

Anahtar Kelimeler: probiyotikler, alerjik rinit, İrritabl barsak sendromu, inflamasyon indeksleri, hastalığa bağlı hastaneye yatış

Introduction

Evidence indicates that imbalances in the composition of the intestinal microbiota and its interaction with the host may play a role in the development of allergic diseases [1, 2]. While certain bacterial species have been implicated in the onset of asthma and other allergic manifestations, the precise identification of the particular bacteria (or other microbes), their quantities, combinations, and the timing during the gut colonization process that could either prevent or contribute to allergic diseases and asthma remains uncertain [3, 4].

Bacterial colonization, a key determinant of future immunity, is influenced by various factors, notably the mode of childbirth—whether vaginal or cesarean—and the feeding method adopted during the initial months of a child's life [1]. In a comprehensive population-based cohort study, the intake of probiotics during pregnancy was linked to a diminished likelihood of eczema and rhinoconjunctivitis in the child [5]. Previous studies have suggested that a greater diversity in the intestinal microbiota during the initial week of life may correlate with a decreased likelihood of later eczema in infants at elevated risk of allergic disease. Thus, implementing interventions that boost microbial diversity early in life could offer an effective strategy for preventing eczema in high-risk infants [1, 6]. Probiotics may exhibit more promise, albeit with limitations, in preventing allergic diseases rather than treating already-established allergic diseases [7]. Given all of this, there is weak evidence to suggest probiotics in the treatment of allergic disease.

There is growing evidence suggesting potential links between the gastrointestinal and respiratory systems, often referred to as the "gut-lung axis" [8]. There is a higher prevalence of for irritable bowel syndrome (IBS) in individuals with allergic diseases, suggesting a potential link between the two conditions [9, 10]. On the other hand, it has been reported that the risk of developing allergic rhinitis (AR) is higher in patients with IBS compared to those without IBS [11, 12]. This findings suggests that disturbances in gut microbiota can influence systemic immune responses, potentially affecting distant organs such as the respiratory tract. The potential mechanism involves mast cells, which play a role in the pathogenesis of IBS, producing mediators that trigger allergic reactions, and IgE binding to receptors on these mast cells [13]. Atopic patients also exhibit increased intestinal permeability and a higher density of IgE-bearing mast cells compared to non-atopic patients [14]. There is limited evidence suggesting that the gut microbiome of adults with AR may have a reduced diversity and probiotics may have some benefits in the prevention of AR [15-17]. Since both IBS and AR are associated with immune dysregulation and altered microbiota, probiotic supplementation could offer valuable insights into the common mechanisms underlying inflammation and immune responses.

This study aimed to investigate the effect of short-term (3-6 months) probiotic use on patients with recurrent AR and IBS, focusing on changes in basic inflammation indices derived from hemograms during probiotic use and hospital admission frequency.

Material and Methods

This single-center retrospective study was conducted at Gazi Yaşargil Research and Training Hospital between 2020 and 2021. Patients were investigated with ICD code K58 for ISB and J30.9 for AR diagnoses, from the Hospital's software system. Participants who were admitted to the gastroenterology outpatient polyclinic and received a probiotic course as an adjuvant therapy for at least 3-6 months were included in the study and were followed for 2 years. The AR episodes and intensity of anti-allergic drug regimens pre- and post-treatment were compared using the national electronic health tracking system e-Nabiz and the local hospital admissions. A basic flow chart outlining the study design is provided (Figure 1).

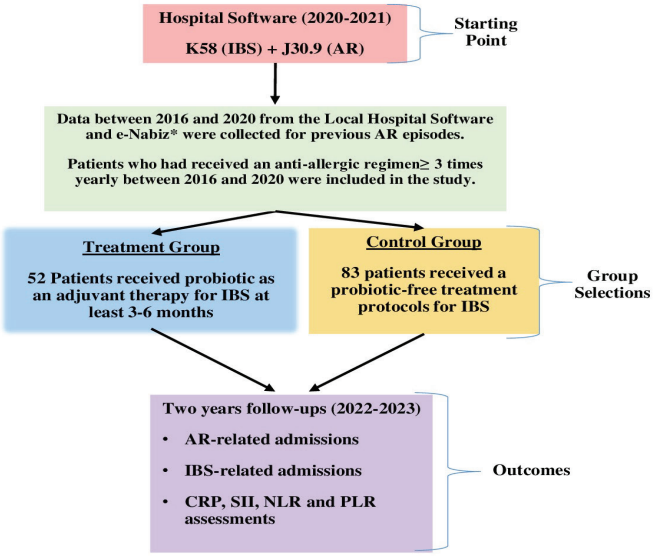

Figure 1. Study design and case selection. K58 and J30.9 (ICD codes for IBS; irritabl bowel syndrome and AR; allergic rhinitis). *e-Nabiz: Turkish Health Ministry National Patient Data Tracking System/registry.

Definitions

IBS: The diagnosis of IBS was based on the Rome IV criteria [18].

Allergic rhinitis: The diagnosis of AR was made based on a comprehensive history and physical examination, considering symptoms such as nasal discharge and congestion, swelling of the eyelids, sneezing, itching in the throat, mouth, and ears, sore throat, dry cough, headache, fatigue, watery and itchy eyes, and partial loss of the sense of smell.

Exclusion criteria

Participants who did not receive a probiotic regimen continuously and properly (cost-related issues, adverse effects, etc.), who received corticosteroids, who were actually under an anti-allergic regimen, or who experienced an acute illness (infectious or inflammatory) were excluded.

Establishing groups

Treatment Group: Patient who received a probiotic containing IBS treatment regimen.

Control Group: Patient who received a probiotic-free IBS treatment regimen.

Data collected

Data on age, gender, body mass index (BMI), C-reactive protein (CRP), complete blood count (CBC), and derived inflammation indices, including the systemic inflammation index (SII), the neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), were documented. Data collection occurred at two time points: initially at the study's commencement and subsequently after at least 24 months of probiotic supplementation in the treatment group. For the control group, data were collected at two points: two years before and two years after inclusion in the study. Probiotics were introduced as an adjunctive therapy for patients with persistent symptoms despite ongoing IBS management. The control group received supplementary pharmacotherapy excluding probiotics.

Calculations

The following formulas were used to calculate the SII, NLR, and PLR:

- SII = (Neutrophil count × Platelet count) / Lymphocyte count
- NLR = Neutrophil count / Lymphocyte count
- PLR = Platelet count / Lymphocyte count

Post-treatment SII, NLR, and PLR were obtained from participants' last hemogram results recorded in the hospital software.

Interventions with probiotics: A commercial product containing 10 billion probiotic organisms was administered daily in one capsule. According to the manufacturer's specifications, each capsule contained 1 billion organisms from the following species: Lactobacillus acidophilus, L. rhamnosus R0011, L. helveticus R0052, L. casei, L. paracasei 1, L. plantarum, L. salivarius, Bifidobacterium lactis, B. breve Br-03, and B. longum BB536. Participants were informed about potential adverse reactions, including abdominal pain, gas, bowel tenderness, diarrhea, and constipation.

IBS treatment: IBS patients received individualized treatment regimens tailored to their specific symptoms, including constipation and diarrhea. These regimens included antispasmodics, loperamide, laxatives, various tricyclic antidepressants, and personalized dietary advice.

Statistical Analysis

Statistical analyses were conducted using appropriate methods to compare demographic and clinical characteristics between the treatment and control groups. Continuous variables were expressed as means ± standard deviations (SD) and compared using independent t-tests or Mann-Whitney U tests, as appropriate. Categorical variables were presented as frequencies and percentages and compared using chi-square tests or Fisher's exact tests. Comparisons of inflammation indices (SII, NLR, PLR, CRP) between pre- and post-treatment periods within each group were conducted using paired t-tests or Wilcoxon signed-rank tests. Differences in AR-related and IBS-related hospital admission frequency between the treatment and control groups were assessed using independent t-tests or Mann-Whitney U tests. Effect sizes were calculated using Cohen's d to evaluate the magnitude of differences between groups. Correlations between inflammation indices and clinical parameters were examined using Pearson or Spearman correlation coefficients, depending on the normality of the data. All statistical tests were two-tailed, and p-values less than 0.05 were considered statistically significant. The analyses were performed using SPSS Version 15.0 for Windows.

Results

A total of 135 eligible patients were evaluated. Female predominance was observed among the participants (n = 91, 67.4%). The clinical and laboratory features of the participants are presented in Table 1. There were significant differences between the treatment and control groups in terms of female gender (98.1% vs. 48.2%, $p < 0.001$) and BMI (23.6 ± 4.3 vs. 25.6 ± 3.0, $p = 0.002$). Allergic rhinitis-related hospital admission frequency significantly decreased in the treatment group ($p < 0.001$), while no significant change was observed in the control group ($p = 0.367$). IBS-related hospital admission frequency decreased in both groups ($p = 0.001$ and $p = 0.021$, respectively) (Table 1). However, the Cohen's d effect size was higher in the treatment group (1.72 vs. 0.55).

Table 1. The clinical and laboratory characteristics of the two groups.

	Treatment Group n = 52	Control Group n = 83	P-value
Age, years	35.8 ± 10.6	38.3 ± 8.8	0.145
Gender, n (%) Male Female	 1 (1.9) 51 (98.1)	 43 (51.8) 40 (48.2)	 <0.001
BMI, kg/m2	23.6 ± 4.3	25.6 ± 3.0	0.002
Mean follow-up, months	17.1 ± 9.2	18.6 ± 7.3	0.133
AR-related hospital admissions frequency	5.1 ± 1.4[a] 2.2 ± 1.3[b]	5.3 ± 1.5[c] 5.2 ± 1.7[d]	a vs. c: 0.496 b vs. d: <0.001 a vs. b: <0.001 c vs. d: 0.367
IBS-related hospital admissions frequency	4.5 ± 1.5[a] 2.3 ± 1.0[b]	4.2 ± 1.5[c] 3.2 ± 1.6[d]	a vs. c: 0.496 b vs. d: <0.004 a vs. b: <0.001 c vs. d: 0.021

Numerical variables were presented as mean ± SD, and categorical variables as numbers (%). a: pre-treatment, b: post-treatment, c: pre-inclusion, and d: post-inclusion. Each superscript is assessed within its line. Abbreviations: BMI, body mass index; AR, allerghic rhinitis; IBS, irritable bowel syndrome.

In the treatment group, SII, NLR, PLR, and CRP levels were significantly reduced ($p < 0.05$), whereas no significant changes were observed in the control group ($p > 0.05$) (Table 2). Pre-treatment SII, NLR, and PLR were correlated with pre-treatment CRP levels in the treatment group ($r = 0.240$, $p = 0.035$; $r = 0.251$, $p = 0.041$; $r = 0.325$, $p = 0.002$, respectively). Age, sex, and BMI had no significant impact on SII, NLR, PLR, or CRP ($p > 0.05$) (Table 2).

According to the records, two patients experienced diarrhea and one patient had abdominal tenderness within the first week of probiotic use. However, the symptoms resolved quickly, and they continued the treatment.

Discussion

Probiotic use has shown benefits for patients with IBS in various clinical studies. However, their efficacy in the treatment of AR remains unclear. This study demonstrated that probiotic supplementation for more than 3 months in patients with both AR and IBS can lead to significant improvements in inflammation indices and reductions in disease-related hospital admission frequency. Our main findings were: (1) Probiotic use was associated with reductions in systemic inflammation markers, including CRP, SII, NLR, and PLR; (2) AR-related hospital admission frequency significantly decreased in the probiotic-treated group compared to the control group; (3) IBS-related hospital admission frequency also decreased in both groups, but the effect was more pronounced in the probiotic group.

Table 2. The comparison of the two groups for inflammation indices

	Treatment Group n = 52	Control Group n = 83	P-value
SII	1685.5 ± 607.9[a] 1452.6 ± 428.9[b]	1434.6 ± 533.9[c] 1458.8 ± 523.8[d]	a vs. c: 0.013 b vs. d: 0.356 a vs. b: 0.036 c vs. d: 0.825
NLR	8.2 ± 1.5[a] 7.2 ± 3.6[b]	7.70 ± 1.8[c] 7.92 ± 2.1[d]	a vs. c: 0.109 b vs. d: 0.035 a vs. b: 0.012 c vs. d: 0.152
PLR	316.5 ± 88.0[a] 279.2 ± 75.6[b]	304.8 ± 101.0[c] 302.9 ± 121.2[d]	a vs. c: 0.480 b vs. d: 0.066 a vs. b: 0.044 c vs. d: 0.911
CRP, mg/dl	1.6 ± 0.8[a] 1.2 ± 0.7[b]	1.35 ± 0.8[c] 1.32 ± 0.8[d]	a vs. c: 0.480 b vs. d: 0.688 a vs. b: 0.028 c vs. d: 0.268

Numerical variables were presented as mean ± SD. a: pre-treatment, b: post-treatment, c: pre-inclusion, and d: post-inclusion. Each superscript is assessed within its line. Abbreviations: SII, systemic inflammation index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelete-to-lymphocyte ratio.

Probiotics are live bacteria that colonize the gastrointestinal tract, exerting beneficial effects on the host's health when administered in adequate amounts [19]. Studies have shown that probiotics can enhance the production of systemic IFN, IL-10, and IL-12, thereby improving the pre-Th1 immune response while reducing Th2 cytokines [20]. Furthermore, Galdeano et al. suggest that the induction of cytokines from activated pro-T-helper type 1 cells, which promote the production of IgG over IgE, can improve the immune-allergic imbalance [19]. Consequently, probiotics have been proposed as modulators of the allergic response and are advocated as therapeutic and preventive interventions for allergic diseases [21, 22].

The rationale for the use of SII, NLR, and PLR in the assessment of various clinical entities is that they demonstrate the relationship between innate and adaptive immunity. AR is related to dysfunction of the acquired immune response, which manifests as oversensitization to allergens [23]. Therefore, changes in these indices can provide affordable, accessible, and objective data for evaluating AR. Several studies have reported that both NLR and PLR are useful markers for diagnosing AR and determining its severity [24, 25]. Our study revealed that SII, NLR, and PLR levels were elevated in individuals with AR and that probiotics could reduce these levels, likely by regulating signaling pathways between immune cells. The reduction in SII, NLR, and PLR is consistent with the observed reduction in CRP among probiotic users, emphasizing the alleviation of immune response. A comprehensive meta-analysis demonstrated significant improvements in most subjective outcomes, including quality of life, total nasal symptom score, total ocular symptom score, and daily total symptom score, following probiotic use in patients with AR [15]. Additionally, no serious adverse effects or cases requiring further intervention were reported after probiotic treatment [26].

Probiotics possess antibacterial, antiviral, and anti-inflammatory properties on mucous membranes, which may help reduce or halt the progression of post-infective IBS [27]. Yoon et al. carried out a randomized, double-blind, placebo-controlled trial to evaluate the effectiveness of multispecies probiotics in IBS patients, using the Rome III criteria. The study included 49 IBS patients, who were randomly assigned to receive either a placebo or multispecies probiotics twice daily for four weeks. By the end of the study, patients in the probiotics group experienced significant improvement in symptoms such as abdominal pain or discomfort, bloating, stool consistency, and frequency [28]. Similarly, previous studies have reported that probiotics reduce pain and symptom severity scores in IBS patients [29-31]. These results demonstrate the beneficial effects of probiotics compared to placebo in IBS management. In this study, both the treatment and control groups exhibited decreased IBS-related hospital admission frequency. However, the reduction was more pronounced in the treatment group, as evidenced by a higher effect size (Cohen's d: 1.72 vs. 0.55). This suggests that probiotic supplementation may lead to a more substantial reduction in the frequency and severity of IBS-related hospital admissions compared to standard IBS treatment without probiotics. Additionally, reductions in systemic inflammation indices (SII, NLR, PLR, and CRP) were observed in the treatment group following probiotic supplementation. This finding suggests that probiotics may exert anti-inflammatory effects, which could be beneficial in managing the inflammatory component of IBS.

This study has several limitations that should be considered. This study has several limitations. First, as a single-center study, the findings may not be generalizable to other populations or clinical settings, and multi-center studies with a more diverse population would improve the external validity. Second, the probiotic product contained multiple bacterial strains, making it difficult to determine the specific

contributions of each strain to the observed effects. Future research could investigate individual strains to clarify their distinct roles. Third, while the two-year follow-up period was adequate for assessing medium-term effects, longer follow-up is needed to evaluate the long-term efficacy and potential relapses. Finally, the study focused on a limited number of inflammatory markers (SII, NLR, PLR, and CRP), and the inclusion of additional immunological markers, such as cytokine levels or gut microbiota composition, could provide a more comprehensive understanding of the probiotic effects on immune modulation and inflammation.

Conclusion

This study highlights the potential benefits of probiotic supplementation in patients with allergic rhinitis and irritable bowel syndrome. The findings suggest that probiotics may contribute to a reduction in disease-related hospital admission frequency and improvements in inflammation indices, indicating a potential role in the management of both allergic and gastrointestinal conditions.

Funding

The authors declared that this study has received no financial support.

Conflicts of Interest

The authors declare they have no conflicts of interest.

Ethics Approval

The study was approved by the Gazi Yasargil Training and Research Hospital Clinical Research Ethics Committee (17.11.2023 - No: 567).

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Availability of Data and Material

The data that support the findings of this study are available on request from the corresponding author.

Authors' contribution

Concept – B.H., Design- B.H., Data collection and/or processing - B.H., G.K. and B.E., Analysis and/or interpretation - B.H., G.K. and B.E., Writing – B.H., Critical review- G.K. and B.E., All authors read and approved the final version of the manuscript.

References

1. Melli LC, do Carmo-Rodrigues MS, Araujo-Filho HB, Sole D, and de Morais MB. Intestinal microbiota and allergic diseases: A systematic review. Allergol Immunopathol (Madr). 2016;44(2):177-88. DOI: 10.1016/j.aller.2015.01.013.
2. Hevia A, Milani C, Lopez P, et al. Allergic Patients with Long-Term Asthma Display Low Levels of Bifidobacterium adolescentis. PLoS One. 2016;11(2):e0147809. DOI: 10.1371/journal.pone.0147809.
3. Simonyte Sjodin K, Vidman L, Ryden P, and West CE. Emerging evidence of the role of gut microbiota in the development of allergic diseases. Curr Opin Allergy Clin Immunol. 2016;16(4):390-5. DOI: 10.1097/ACI.0000000000000277.
4. Zimmermann P, Messina N, Mohn WW, Finlay BB, and Curtis N. Association between the intestinal microbiota and allergic sensitization, eczema, and asthma: A systematic review. J Allergy Clin Immunol. 2019;143(2):467-85. DOI: 10.1016/j.jaci.2018.09.025.
5. West CE. Gut microbiota and allergic disease: new findings. Curr Opin Clin Nutr Metab Care. 2014;17(3):261-6. DOI: 10.1097/MCO.0000000000000044.
6. Ismail IH, Oppedisano F, Joseph SJ, et al. Reduced gut microbial diversity in early life is associated with later development of eczema but not atopy in high-risk infants. Pediatr Allergy Immunol. 2012;23(7):674-81. DOI: 10.1111/j.1399-3038.2012.01328.x.
7. Tang RB, Chang JK, and Chen HL. Can probiotics be used to treat allergic diseases? J Chin Med Assoc. 2015;78(3):154-7. DOI: 10.1016/j.jcma.2014.08.015.
8. Enaud R, Prevel R, Ciarlo E, et al. The Gut-Lung Axis in Health and Respiratory Diseases: A Place for Inter-Organ and Inter-Kingdom Crosstalks. Front Cell Infect Microbiol. 2020;10:9. DOI: 10.3389/fcimb.2020.00009.
9. Powell N, Huntley B, Beech T, Knight W, Knight H, and Corrigan CJ. Increased prevalence of gastrointestinal symptoms in patients with allergic disease. Postgrad Med J. 2007;83(977):182-6. DOI: 10.1136/pgmj.2006.049585.
10. Shen TC, Lin CL, Wei CC, et al. Bidirectional Association between Asthma and Irritable Bowel Syndrome: Two Population-Based Retrospective Cohort Studies. PLoS One. 2016;11(4):e0153911. DOI: 10.1371/journal.pone.0153911.
11. Tobin MC, Moparty B, Farhadi A, DeMeo MT, Bansal PJ, and Keshavarzian A. Atopic irritable bowel syndrome: a novel subgroup of irritable bowel syndrome with allergic manifestations. Ann Allergy Asthma Immunol. 2008;100(1):49-53. DOI: 10.1016/S1081-1206(10)60404-8.
12. Mansueto P, D'Alcamo A, Seidita A, and Carroccio A. Food allergy in irritable bowel syndrome: The case of non-celiac wheat sensitivity. World J Gastroenterol. 2015;21(23):7089-109. DOI: 10.3748/wjg.v21.i23.7089.

13. Loo EXL, Wang Y, and Siah KTH. Association between Irritable Bowel Syndrome and Allergic Diseases: To Make a Case for Aeroallergen. Int Arch Allergy Immunol. 2020;181(1):31-42. DOI: 10.1159/000503629.
14. Lillestol K, Helgeland L, Arslan Lied G, et al. Indications of 'atopic bowel' in patients with self-reported food hypersensitivity. Aliment Pharmacol Ther. 2010;31(10):1112-22. DOI: 10.1111/j.1365-2036.2010.04261.x.
15. Iftikhar H, Awan MO, Awan MS, Mustafa K, Das JK, and Ahmed SK. Role of Probiotics in Patients with Allergic Rhinitis: A Systematic Review of Systematic Reviews. Int Arch Otorhinolaryngol. 2022;26(4):e744-e52. DOI: 10.1055/s-0042-1749370.
16. Watts AM, West NP, Zhang P, Smith PK, Cripps AW, and Cox AJ. The Gut Microbiome of Adults with Allergic Rhinitis Is Characterised by Reduced Diversity and an Altered Abundance of Key Microbial Taxa Compared to Controls. Int Arch Allergy Immunol. 2021;182(2):94-105. DOI: 10.1159/000510536.
17. Zhou MS, Zhang B, Gao ZL, et al. Altered diversity and composition of gut microbiota in patients with allergic rhinitis. Microb Pathog. 2021;161(Pt A):105272. DOI: 10.1016/j.micpath.2021.105272.
18. Schmulson MJ and Drossman DA. What Is New in Rome IV. J Neurogastroenterol Motil. 2017;23(2):151-63. DOI: 10.5056/jnm16214.
19. Maldonado Galdeano C, Cazorla SI, Lemme Dumit JM, Velez E, and Perdigon G. Beneficial Effects of Probiotic Consumption on the Immune System. Ann Nutr Metab. 2019;74(2):115-24. DOI: 10.1159/000496426.
20. Hajavi J, Esmaeili SA, Varasteh AR, et al. The immunomodulatory role of probiotics in allergy therapy. J Cell Physiol. 2019;234(3):2386-98. DOI: 10.1002/jcp.27263.
21. Isolauri E, Sutas Y, Kankaanpaa P, Arvilommi H, and Salminen S. Probiotics: effects on immunity. Am J Clin Nutr. 2001;73(2 Suppl):444S-50S. DOI: 10.1093/ajcn/73.2.444s.
22. Fiocchi A, Burks W, Bahna SL, et al. Clinical Use of Probiotics in Pediatric Allergy (CUPPA): A World Allergy Organization Position Paper. World Allergy Organ J. 2012;5(11):148-67. DOI: 10.1097/WOX.0b013e3182784ee0.
23. Pawankar R, Mori S, Ozu C, and Kimura S. Overview on the pathomechanisms of allergic rhinitis. Asia Pac Allergy. 2011;1(3):157-67. DOI: 10.5415/apallergy.2011.1.3.157.
24. Cansever M and Sari N. The association of allergic rhinitis severity with neutrophil-lymphocyte and platelet-lymphocyte ratio in children. North Clin Istanb. 2022;9(6):602-09. DOI: 10.14744/nci.2022.96236.
25. Goker AE, Ekincioglu E, Alagoz MH, et al. The association of allergic rhinitis severity with neutrophil-lymphocyte and platelet-lymphocyte ratio in adults. Eur Arch Otorhinolaryngol. 2019;276(12):3383-88. DOI: 10.1007/s00405-019-05640-0.
26. Zajac AE, Adams AS, and Turner JH. A systematic review and meta-analysis of probiotics for the treatment of allergic rhinitis. Int Forum Allergy Rhinol. 2015;5(6):524-32. DOI: 10.1002/alr.21492.
27. Ford AC and Talley NJ. Irritable bowel syndrome. BMJ. 2012;345:e5836. DOI: 10.1136/bmj.e5836.
28. Yoon JS, Sohn W, Lee OY, et al. Effect of multispecies probiotics on irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. J Gastroenterol Hepatol. 2014;29(1):52-9. DOI: 10.1111/jgh.12322.
29. Didari T, Mozaffari S, Nikfar S, and Abdollahi M. Effectiveness of probiotics in irritable bowel syndrome: Updated systematic review with meta-analysis. World J Gastroenterol. 2015;21(10):3072-84. DOI: 10.3748/wjg.v21.i10.3072.
30. Zhang Y, Li L, Guo C, et al. Effects of probiotic type, dose and treatment duration on irritable bowel syndrome diagnosed by Rome III criteria: a meta-analysis. BMC Gastroenterol. 2016;16(1):62. DOI: 10.1186/s12876-016-0470-z.
31. Konstantis G, Efstathiou S, Pourzitaki C, Kitsikidou E, Germanidis G, and Chourdakis M. Efficacy and safety of probiotics in the treatment of irritable bowel syndrome: A systematic review and meta-analysis of randomised clinical trials using ROME IV criteria. Clin Nutr. 2023;42(5):800-09. DOI: 10.1016/j.clnu.2023.03.019.