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Image	200	No abstract	3	No table	3

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Conference proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561–5.

Scientific or technical report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

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ORIGINAL ARTICLE

Efficacy, tolerability, and safety of intravenous ferric carboxymaltose compared with oral ferrous sulfate for the treatment of iron deficiency anemia during the antepartum period

[1]Mustafa GÖKSU
[2]Ozan KARADENİZ

[1]Department of Obstetrics and Gynecology, Istanbul Health Sciences University, Kanuni Sultan Suleyman Training and Research Hospital, Istanbul, Turkey

[2]Department of Obstetrics and Gynecology, Basaksehir Cam ve Sakura City Hospital, Istanbul, Turkey

ORCID ID
MG : 0000-0002-6389-9178
OK : 0000-0002-2215-1198

ABSTRACT

Objective: This study aims to compare the efficacy, safety, and tolerability of intravenous ferric carboxymaltose to oral ferrous sulfate in pregnant women (gestation weeks 14–21) with antepartum anemia.

Material and Methods: A retrospective cohort study was conducted in a tertiary hospital comparing intravenous 1000 mg ferric carboxymaltose treatment during pregnancy (120 patients) to oral ferrous sulfate (100 mg) 2x1 treatment until delivery (120 patients) for the treatment of iron deficiency anemia in pregnancy. The patients' responses to treatment were assessed by measuring hemoglobin, hematocrit, and ferritin levels on the 60th day, 120th day, and postpartum 1st day following the initiation of the therapeutic intervention.

Results: There were no significant differences between the groups in terms of gestational age, parity, delivery patterns, or antepartum hemoglobin and hematocrit levels. On the 60th and postpartum first day of treatment, the IV ferric carboxymaltose group had significantly higher hemoglobin and hematocrit levels than the oral ferrous sulfate group ($p<0.05$). Ferritin levels improved rapidly on the 60th day of IV treatment. However, there was no significant difference in hemoglobin, hematocrit, or ferritin levels on the 120th day.

Conclusion: Intravenous ferric carboxymaltose proves to be safe and well-tolerated in the management of antepartum iron deficiency anemia. While short-term intravenous iron therapy leads to a quicker elevation of hemoglobin, hematocrit, and ferritin levels in women with antepartum anemia compared to oral ferrous sulfate therapy, over the long term, the levels tend to equalize.

Keywords: Antepartum iron deficiency anemia, ferric carboxymaltose, ferrous sulfate, intravenous treatment, oral treatment.

Cite this article as: Göksu M, Karadeniz O. Efficacy, tolerability, and safety of intravenous ferric carboxymaltose compared with oral ferrous sulfate for the treatment of iron deficiency anemia during the antepartum period. Zeynep Kamil Med J 2024;55(3):117–121.

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Correspondence: Mustafa GÖKSU, MD. Sağlık Bilimleri Üniversitesi, Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Kliniği, İstanbul, Türkiye.
Tel: +90 537 782 81 07 **e-mail:** mstfgks@gmail.com

INTRODUCTION

Anemia represents a significant global health concern, impacting newborns, pregnant and postpartum women, as well as adolescent girls. The burden of anemia is disproportionately borne by non-educated individuals and impoverished rural households residing in low- and middle-income countries. Globally, the prevalence of anemia among pregnant women aged 15–49 is reported at 36.5%.[1] The primary contributors to anemia encompass dietary iron deficiency, thalassemia, sickle cell trait, and malaria.[2] Iron deficiency anemia can manifest with symptoms such as fatigue, headache, dizziness, shortness of breath, palpitations, decreased cognitive function, and depression.

A singleton gestation imposes a need for roughly one gram of iron on expectant mothers. This augmented demand stems from heightened red cell mass, fetal-placental growth, and enlargement of maternal blood volume. Anemia poses a significant risk factor for both maternal and fetal morbidity. This will lead to adverse fetal, neonatal, and newborn outcomes such as preterm labor, fetal growth restriction (FGR), postpartum hemorrhage, cardiac hypertrophy, recurrent infections, and puerperal sepsis.[3,4]

The World Health Organization (WHO) suggests that all women receive daily oral iron supplements along with folic acid.[5] According to the Pregnancy Iron Support Program Guide issued by the Ministry of Health on January 31, 2007, in Türkiye, the use of appropriate daily iron supplements containing elemental iron (40–60 mg) is recommended from the beginning of the 4th month of pregnancy (second trimester) throughout the pregnancy, for a total duration of nine months, including six months postpartum.[6] Although numerous iron preparations are available for addressing iron deficiency anemia during pregnancy, oral forms are notable for their pronounced gastrointestinal side effects such as GI discomfort, vomiting, diarrhea, and a metallic taste in the mouth.[7] IV iron treatment shows better tolerability, fewer adverse effects, and rapid improvement in desired hemoglobin (Hb) levels compared to oral iron preparations.[8] Ferric carboxymaltose (FCM) is one of the modern intravenous iron formulations frequently employed in the management of iron deficiency during pregnancy. Hence, we conducted a retrospective cohort study at our tertiary research hospital to assess the tolerability, efficacy, and safety of a single dose of 1000 mg intravenous ferric carboxymaltose (FCM) in comparison to oral ferrous sulfate (FS).

MATERIAL AND METHODS

We conducted a retrospective cohort study at the Istanbul Health Sciences University Kanuni Sultan Suleyman Training and Research Hospital, a tertiary referral center, from November 2020 to November 2023. The study included patients referred to our outpatient clinics in the Department of Obstetrics and Gynecology and diagnosed with antepartum anemia based on their biochemical investigations. This investigation targeted women aged ≥18 years who encountered iron deficiency anemia (IDA) within the antepartum period, precisely in the second trimester (gestational weeks 14–21). Patients with serum ferritin levels ≤40 (μg/L) and IDA (Hb levels of 8.0–10.4 g/dL for gestation weeks 14–21) were included in the study. Pregnant women with severe postpartum vaginal bleeding, iron intolerance, a history of peripartum blood transfusions, myelosuppressive therapy, asthma, pulmonary thromboembolism, alcohol consumption, malabsorption syndrome, or renal-hepatic infections were excluded from the study. We followed the Helsinki Declaration guidelines and received clinical and ethical approval from the institutional review board (Approval number: KAEK/2023.11.171). Each participant provided written informed consent before enrollment.

An electronic medical database of the hospital was used to determine patients in the second trimester who had received either IV ferric carboxymaltose (total dosage 1000 mg) or oral ferrous sulfate (100 mg capsules taken twice daily; total dosage 200 mg) treatment until delivery during the antepartum period for the treatment of IDA. Demographic data, including age, BMI, gravida, parity, pre-treatment hemoglobin (Hb) levels, pre-treatment hematocrit (Hct) levels, and delivery type, were obtained from the patients' records. On the 60th day, 120th day, and postpartum 1st day of the treatment, the levels of hemoglobin (Hb), hematocrit (Hct), and ferritin were documented for both groups. Additionally, any treatment-emergent adverse events were recorded for efficacy, safety, and tolerability assessment.

The primary objective was to compare the effectiveness of the IV FCM and oral ferrous sulfate (FS) treatment for IDA during the antepartum period by measuring Hb and Hct levels from baseline. The secondary objective was to assess the tolerability of FCM and FS usage during pregnancy.

The data analysis was conducted using IBM Statistical Package for the Social Sciences version 20 (SPSS Inc., Chicago, IL, USA). Mean±standard deviations were provided for continuous variables, and percentages along with numerical values were presented for categorical variables. The normal distribution of groups was assessed using the Kolmogorov-Smirnov test, and based on the distribution results, comparisons of means were performed using either the Mann-Whitney U or Student's t-test. The Chi-square test and Fisher's exact test were employed to compare categorical variables. A p-value<0.05 was considered statistically significant in the results.

RESULTS

Routine assessment of hemoglobin levels during outpatient clinic admissions revealed values within the range of 8 to 11 g/dl for the enrolled patients. The oral iron supplementation (FS) group had an average age of 27.1±6.1 years, while the intravenous ferric carboxymaltose (IV FCM) group exhibited an average age of 27.7±7.0 years. There were no statistically significant differences observed between the groups regarding gravida, parity, or mode of delivery. The demographic and characteristic features of the patients are outlined in Table 1.

The mean pretreatment hemoglobin (Hb) levels for patients in the FS group were determined to be 10.1±1.2 g/L, with hematocrit (Htc) levels averaging 30.4±2.6 g/L. In contrast, the IV FCM group's mean pretreatment Hb levels were 10.3±1.2 g/L, and Htc levels averaged 30.6±2.7 g/L. The pretreatment Hb and Htc values among the groups showed no statistically significant differences.

Table 1: Characteristic and demographic features of the patients

	Group 1 Oral treatment (n=120)	Group 2 Intravenous treatment (n=120)	p
Age (year)	27.1±6.1	27.7±7.0	0.410
BMI (kg/m^2)	22.2±1.6	22.9±1.8	0.186
Gravida	2.2±1.1	2.3±1.2	0.110
Parity	2.0±1.1	2.1±1.1	0.097
Hb before treatment (g/dL)	10.1±1.2	10.3±1.2	0.060
Htc before treatment (%)	30.4±2.6	30.6±2.7	0.642
Mode of delivery, n (%)			0.786
Vaginal delivery	41 (34.1%)	43 (35.8%)	
Cesarean section	79 (65.9%)	77 (64.2%)	

BMI: Body mass index; Hb: Hemoglobin; Htc: Hematocrit.

Table 2: Hemoglobin, hematocrit, ferritin values on day 60, day 120 and postpartum day 1 of treatment

	Group 1 Oral treatment (n=120)	Group 2 Intravenous treatment (n=120)	p
Hb on day 60 of treatment (g/dL)	10.2±1.1	11.3±1.3	0.032
Htc on day 60 of treatment (%)	33.4±3.1	36.0±2.8	0.041
Ferritin on day 60 of treatment (μg/L)	91.7±80.8	398.1±186.8	0.012
Hb on day 120 of treatment (g/dL)	11.8±0.6	11.6±0.8	0.452
Htc on day 120 of treatment (%)	36.6±2.2	36.9±2.3	0.332
Ferritin on day 120 of treatment (μg/L)	198.4±76.5	236.7±89.9	0.090
Hb on postpartum day 1 of treatment (g/dL)	9.1±0.6	9.3±0.7	0.026
Htc on postpartum day 1 of treatment (%)	27.3±1.8	29.8±2.8	0.009
Ferritin on postpartum day 1 of treatment (μg/L)	28.5±20.6	33.8±29.7	0.156

Hb: Hemoglobin; Htc: Hematocrit

On the 60th day of treatment, the average Hb value in the FS group was determined to be 10.2±1.1 g/L, with a mean hematocrit value of 33.4±3.1 g/L. In the IV FCM group, the Hb average was 11.3±1.3 g/L, with a mean Htc value of 36.0±2.8 g/L. Upon comparing ferritin levels between the two groups on the 60th day of treatment, a statistically significant difference favoring the IV FCM group (398.1±186.8) was observed compared to the FS group (91.7±80.8) (p=0.012).

On the 120th day of treatment, there was no statistically significant difference between the groups in terms of hemoglobin (Hb), hematocrit (Htc), and ferritin levels (Table 2). However, on the postpartum 1st day, there was a significant difference in Hb and Htc levels among groups, favoring the IV FCM group. On the postpartum 1st day of treatment, the average Hb value in the FS group was determined to be 9.1±0.6 g/L, with a mean hematocrit value of 27.3±1.8 g/L. In the IV FCM group, the Hb average was 9.3±0.7 g/L, with a mean Htc value of 29.8±2.8 g/L.

No serious side effects were detected in either group. In the IV FCM group, 2 patients (1.6%) experienced headaches during the infusion of the drug, while flushing occurred in 9 women (7.5%). Four women (3.4%) reported a sensation of trembling, and 3 women (2.5%) mentioned feeling fatigued. However, none of these effects were persistent or progressive. No hemodynamic issues were observed during or after the infusion. Sixty-one patients (51%) in the FS group reported experiencing side effects. These side effects were generally related to the gastrointestinal system, such as dyspepsia and constipation. Thirty-two women (27%) reported a change in taste or a metallic taste sensation, while twenty-nine (24%) women reported constipation (Table 3). Despite these symptoms, patients adapted to the medication and completed the treatment. When comparing the groups regarding side effects, the rate of complaints related to side effects was significantly higher in the oral FS group (p<0.05).

Table 3: Treatment related side effects

	Group 1 Oral treatment (n=120)	Group 2 Intravenous treatment (n=120)	p
Fatigue	0	3 (2.5%)	
Constipation	29 (24%)	0	
Flushing	0	9 (7.5%)	
Trembling	0	4 (3.4%)	0.008
Change in taste	32 (27%)	0	
Headache	0	2 (1.6%)	
Total	61 (51%)	18 (15%)	

DISCUSSION

IDA is a major health problem affecting approximately 40% of women worldwide. Due to the elevated fetal iron requirements, ferritin levels decrease in approximately 30–50% of pregnant women throughout gestation.[9] IDA and acute bleeding are the main causes of anemia during the antepartum and postpartum periods.[10] IDA during pregnancy is associated with maternal and neonatal morbidity and mortality. To prevent complications and reduce the morbidity and mortality rates due to IDA, the National Institute for Health Care Excellence (NICE) recommends screening for hematological pathologies through a full blood count at 28 weeks of gestation, as well as at any point during pregnancy if anemia is suspected.[11] The Network for the Advancement of Patient Blood Management, Haemostasis, and Thrombosis (NATA) consensus statement advocates for the routine antenatal administration of oral iron (30–60 mg/day) and folic acid (400 μg/day) to mitigate the risk of low birth weight and IDA during pregnancy.[12] However, the gastrointestinal adverse effects of oral iron salts often impede the compliance of pregnant women with treatment. IV iron supplements are another route for treating IDA during pregnancy. It is usually administered in the second or third trimester, as there is no available data for first-trimester use. In this study, we aimed to compare the efficacy, tolerability, and safety of intravenous FCM over oral FS for treating IDA during pregnancy.

Many randomized controlled trials have compared the efficacy and safety of IV FCM with oral FS during pregnancy.[13–16] These studies consistently demonstrate that FCM is superior at rapidly increasing hemoglobin (Hb) levels without resulting in group 3 or 4 adverse outcomes. Additionally, this statement is supported by systematic reviews in the literature favoring IV iron preparations compared to oral forms in terms of efficacy, safety, and quality of life.[8,17] Both meta-analyses illuminate that intravenous iron formulations significantly enhance hemoglobin levels within 4 weeks following the initiation of treatment. Consistent with the literature, our results demonstrate that IV FCM is superior to oral FS in terms of rapidly improving hemoglobin levels and replenishing iron stores. Additionally, IV FCM exhibits fewer adverse effects compared to the oral FS group.

There is a significant reluctance to use intravenous iron preparations due to the high risk of anaphylactoid reactions. However, ferric carboxymaltose offers various advantages over other parenteral iron preparations. It does not contain dextran and does not react with dextran antibodies, hence eliminating the risk of anaphylactic reactions observed with iron dextran.[18] Additionally, ferric carboxymaltose possesses favorable characteristics compared to iron sucrose (VenoferTM, Vifor International, StGallen, Switzerland), including lower pH, lower osmolarity, and higher single-dose administration.[19] Its safety profile allows for short-term administration in outpatient facilities. Common adverse effects, such as metallic taste, flushing, and burning at the injection site, are observed at a rate of 0.5% for doses up to 200 mg.[20] It is well known that oral iron medications cause gastrointestinal side effects.[21] Gastrointestinal side effects are believed to be dose-dependent and occur more frequently at higher doses. Up to 30% of women treated with oral iron report gastrointestinal side effects.[22] Ferric carboxymaltose is well-tolerated by patients in single-dose administrations.[16] Consistent with findings from other studies, our study also supports a higher frequency of gastrointestinal disturbances in the iron sulfate group, while the incidence of side effects in the parenteral ferric carboxymaltose group was lower. Outside of a clinical trial setting, non-adherence to oral iron therapy is reported to be 10% after two weeks, 25% after one month, and 32% after two months.[23,24] Given these high rates of non-adherence, many patients are exposed to symptoms associated with anemia and increased interventions such as transfusions. In this study, ferric carboxymaltose provided clinical improvement in anemia without the need for prolonged adherence to oral iron therapy.

The interpretation of this study is subject to some limitations. One of the limitations was the retrospective nature of this study. Another limitation of this study is the lack of comprehensive records, the quality of the documents, and the inherent recollection bias associated with retrospective data collection. Additionally, we refrained from incorporating fetal outcomes in this study due to potential variations in the quality of available documents, which could introduce inconsistencies or errors in the data analysis.

CONCLUSION

In conclusion, our findings further support the evidence that IV FCM is both safe and efficacious for the treatment of IDA during pregnancy. In patients with intolerance to oral iron and a limited timeframe before delivery, IV FCM may be considered as an option. IV FCM could provide an alternative approach for managing IDA during the antepartum period, offering a safety profile comparable to oral formulations.

Statement

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Ethics Committee Approval: The Kanuni Sultan Suleyman Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 30.11.2023, number: KAEK/2023.11.171).

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REFERENCES

1. World Health Organization. The global health observatory data repository. Explore a world of health data. 2023. Available at: https://www.who.int/data/gho. Accessed Aug 6, 2024.
2. Global Health Metrics (2019) Anaemia—Level 1 Impairment. The Lancet, 393, R2.
3. Nair M, Churchill D, Robinson S, Nelson-Piercy C, Stanworth SJ, Knight M. Association between maternal haemoglobin and stillbirth: A cohort study among a multi-ethnic population in England. Br J Haematol 2017;179:829–37.
4. Tangeda PR, Patil S, Shastri N, Noorali SN. Maternal myocardial performance in second trimester of pregnancy with iron deficiency anaemia. J Clin Diagn Res 2016;10:CC16–8.
5. WHO. Guideline: Daily iron and folic acid supplementation in pregnant women. Geneva: World Health Organization, 2012. Available at: https://iris.who.int/bitstream/handle/10665/77770/9789241501996_eng.pdf. Accessed Aug 6, 2024.
6. Türkiye Cumhuriyeti Sağlık Bakanlığı. Gebelerde demir destek programı uygulaması genelgesi 2007/6. 2007. Available at: https://www.saglik.gov.tr/TR-11100/gebelerde-demir-destek-programi-uygulamasi-genelgesi-2007--6.html. Accessed Aug 6, 2024. [In Turkish]
7. Chawla S, Singh A, Jhamb D, Anupama CH. A randomised controlled trial to compare injection ferric carboxymaltose and oral iron in treating iron deficiency anemia during pregnancy. J Obstet Gynaecol India 2022;72:492–6.
8. Govindappagari S, Burwick RM. Treatment of iron deficiency anemia in pregnancy with intravenous versus oral iron: Systematic review and meta-analysis. Am J Perinatol 2019;36:366–76.
9. Benson AE, Shatzel JJ, Ryan KS, Hedges MA, Martens K, Aslan JE, et al. The incidence, complications, and treatment of iron deficiency in pregnancy. Eur J Haematol 2022;109:633–42.
10. Anemia in pregnancy: ACOG practice bulletin, number 233. Obstet Gynecol 2021;138:e55–e64.
11. National Institute for Health Care Excellence. Antenatal care 2021. Available at: https://www.nice.org.uk/guidance/ng201. Accessed Apr 27, 2023.
12. Muñoz M, Peña-Rosas JP, Robinson S, Milman N, Holzgreve W, Breymann C, et al. Patient blood management in obstetrics: Management of anaemia and haematinic deficiencies in pregnancy and in the post-partum period: NATA consensus statement. Transfus Med 2018;28:22–39.
13. Jose A, Mahey R, Sharma JB, Bhatla N, Saxena R, Kalaivani M, et al. Comparison of ferric Carboxymaltose and iron sucrose complex for treatment of iron deficiency anemia in pregnancy- randomised controlled trial. BMC Pregnancy Childbirth 2019;19:54.
14. Vanobberghen F, Lweno O, Kuemmerle A, Mwebi KD, Asilia P, Issa A, et al. Efficacy and safety of intravenous ferric carboxymaltose compared with oral iron for the treatment of iron deficiency anaemia in women after childbirth in Tanzania: A parallel-group, open-label, randomised controlled phase 3 trial. Lancet Glob Health 2021;9:e189–98.
15. Khalafallah AA, Hyppa A, Chuang A, Hanna F, Wilson E, Kwok C, et al. A prospective randomised controlled trial of a single intravenous infusion of ferric carboxymaltose vs single intravenous iron polymaltose or daily oral ferrous sulphate in the treatment of iron deficiency anaemia in pregnancy. Semin Hematol 2018;55:223–34.
16. Breymann C, Milman N, Mezzacasa A, Bernard R, Dudenhausen J; FER-ASAP investigators. Ferric carboxymaltose vs. oral iron in the treatment of pregnant women with iron deficiency anemia: An international, open-label, randomized controlled trial (FER-ASAP). J Perinat Med 2017;45:443–53.
17. Rogozińska E, Daru J, Nicolaides M, Amezcua-Prieto C, Robinson S, Wang R, et al. Iron preparations for women of reproductive age with iron deficiency anaemia in pregnancy (FRIDA): A systematic review and network meta-analysis. Lancet Haematol 2021;8:e503–12.
18. Burns DL, Mascioli EA, Bistrian BR. Parenteral iron dextran therapy: A review. Nutrition 1995;11:163–8.
19. Venofer: Iron sucrose injection USP. Full prescribing information. Available at: https://www.venofer.com/pdfs/venofer-prescribing-information.pdf. Accessed Aug 6, 2024.
20. Perewusnyk G, Huch R, Huch A, Breymann C. Parenteral iron therapy in obstetrics: 8 years experience with iron-sucrose complex. Br J Nutr 2002;88:3–10.
21. Crichton R, Danielson B, Geisser P. Iron therapy. Bremen, Germany: Uni-Med Verlag; 2005.
22. al-Momen AK, al-Meshari A, al-Nuaim L, Saddique A, Abotalib Z, Khashogji T, et al. Intravenous iron sucrose complex in the treatment of iron deficiency anemia during pregnancy. Eur J Obstet Gynecol Reprod Biol 1996;69:121–4.
23. Hallberg L, Ryttinger L, Sölvell L. Side-effects of oral iron therapy. A double-blind study of different iron compounds in tablet form. Acta Med Scand Suppl 1966;459:3–10.
24. Bonnar J, Goldberg A, Smith JA. Do pregnant women take their iron? Lancet 1969;1:457–8.

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ORIGINAL ARTICLE

Obstetric results of epileptic pregnant women: A retrospective analysis

[1]Meltem DURAKLI ULUKÖK
[2]Ufuk ATLIHAN
[3]Hüseyin Aytuğ AVŞAR
[3]Can ATA

[1]Department of Neurology, Çankaya Medical Center, Izmir, Turkey

[2]Department of Obstetrics and Gynecology, Private Karatas Hospital, Izmir, Turkey

[3]Department of Obstetrics and Gynecology, Buca Seyfi Demirsoy Training and Research Hospital, Izmir, Turkey

ORCID ID
MDU : 0000-0002-0985-0103
UA : 0000-0002-2109-1373
HAA : 0000-0003-0636-3104
CA : 0000-0002-0841-0480

ABSTRACT

Objective: Epilepsy is one of the most common neurological diseases on a global scale and the second most common neurological disease during pregnancy. The aim of our study is to evaluate the pregnancy outcomes and complications of pregnant women diagnosed with epilepsy followed in our clinic.

Material and Methods: Between March 2018–2022, 147 pregnant women who were followed up in our hospital and diagnosed with epilepsy were examined. Demographic and clinical findings of all patients were compared retrospectively according to drug use history and seizure frequency during pregnancy.

Results: There was no significant difference in mean birth weight and mean week of birth according to drug use groups (p=0.385, p=0.115, respectively). There was no significant difference between the drug use groups in terms of the presence of spontaneous abortion and history of preterm birth (p=0.360, p=0.210, respectively). No significant relationship was found between seizure frequency and seizure type (p=0.245). No significant relationship was found between seizure frequency and antiepileptic drug use (p=0.640). The average age of pregnant women with a history of polytherapy was 32.6±8.4 and was found to be significantly higher than the other groups (p=0.042). When the groups were evaluated according to drug use history, it was seen that the duration of epilepsy was significantly longer in the polytherapy group (p=0.044). When the groups were evaluated according to drug use history, it was seen that the cesarean section rate was significantly higher in the polytherapy group (p=0.038).

Conclusion: Today, we think that pregnant women diagnosed with epilepsy have a high probability of giving birth to a healthy baby, spontaneous miscarriages are not more common than expected, and there is no significant difference between birth weight or week of birth and the treatment applied during pregnancy. The study also shows that with an appropriate approach and follow-up, it is possible to achieve positive results similar to those in the general population.

Keywords: Antiepileptic drugs, epilepsy, pregnancy.

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Correspondence: Meltem DURAKLI ULUKÖK, MD. Çankaya Tıp Merkezi, Nöroloji Kliniği, İzmir, Türkiye.
Tel: +90 232 425 3131 / 0549 425 31 32 **e-mail:** sevimeltem@gmail.com
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INTRODUCTION

Epilepsy is one of the most common neurological diseases that affects 2% of the population on a global scale[1] as the second most common neurological disease in pregnancy after migraine, and a total of 18 million women have epilepsy in the World.[2] Pregnancy is an important decision process for women who have epilepsy. A balance must be established between the risks to the mother and fetus of uncontrolled seizures during pregnancy and the potential teratogenic effects of antiepileptic drugs (AEDs).[3] When an epileptic woman becomes pregnant, there are fetal or maternal risks of epilepsy during pregnancy, the medical treatment used, and the epileptic seizure.[4] Pregnancy also has effects on epilepsy and the AEDs used. There are studies in the literature reporting increased risks of miscarriage, premature birth, intrauterine infant death, intrauterine growth retardation, and long-term mental and psychomotor retardation in the newborn in cases of epilepsy and pregnancy.[5] Counseling before pregnancy, a correct and effective birth control method, and a planned pregnancy will allow the regulation of antiepileptic drugs, minimizing the related risks with folic acid prophylaxis in terms of fetal malformations and especially neural tube defects, and explaining the effects of epilepsy and epilepsy on pregnancy to the family.[6] It can be recommended for most women who have epilepsy to become pregnant because the malformation rates determined by recent studies are not significantly different from the general population.[7] In the treatment of epilepsy during pregnancy, the most critical point is to maintain the balance between control of maternal seizures and teratogenic risk.[8] Although AEDs increase the risk of major and minor congenital anomalies, the risk is lower than considered, and the majority of women who have epilepsy can give birth to healthy babies.[9] In the study conducted by Razaz et al.[10] in which 3586 epileptic pregnant women were examined, it was reported that AED use did not increase the risk of pregnancy and perinatal complications, except for a higher rate of labor induction. Although several studies report that seizures that develop in the first trimester increase the risk of malformations, there are also other studies reporting contrary outcomes.[11] Pregnancy complications such as hyperemesis gravidarum, vaginal bleeding, preeclampsia, eclampsia, vitamin D and K deficiencies, megaloblastic anemia because of decreased folate, premature birth, and postpartum bleeding are more common in epileptic women.[12] When the effects of pregnancy on epilepsy are evaluated, it is seen that seizures increase by approximately 25%.[13] The increase in seizure frequency occurs mostly at the end of the first trimester or the beginning of the second trimester[14] and the increase in seizure frequency during pregnancy is multifactorial. Drug incompatibility, decreased serum AED levels because of changes in the absorption and metabolism of the drug, sleep deprivation, and stress can be listed among the reasons for this.[9] The risk of hypertensive diseases and long-term hospitalization also increases in epileptic pregnant women. In the study conducted by Huang et al.[15] it was reported that abortion, bleeding during pregnancy, postpartum hemorrhage, hypertensive diseases, labor induction, cesarean section, preterm labor, and intrauterine growth retardation were seen at higher rates in epileptic pregnant women. In our study, the purpose was to present pregnancy outcomes and possible complications in pregnant epileptic patients followed in our pregnancy clinic.

MATERIAL AND METHODS

The study had a retrospective cross-sectional design and was conducted following the principles of the Declaration of Helsinki. Informed consent forms were obtained from the patients. The study was started after receiving ethics committee approval number 2023/209 from our hospital's ethics committee. The files of a total of 147 pregnant women who were diagnosed with epilepsy who applied to our hospital between March 2018 and March 2022 and whose pregnancy follow-ups were performed in our hospital were examined retrospectively. Demographic characteristics of all patients such as age, parity, week of birth, birth weight, 1st and 5th minute Apgar scores, types of epilepsy, and duration of epilepsy were evaluated retrospectively along with fetal malformations, abortion, premature birth, intrauterine growth retardation, antenatal and neonatal problems. Births after the 37th week were categorized as term birth, between 34 and 37 weeks as late preterm birth, and births under the 34th week were categorized as early preterm birth. The distinction of major anomalies from minor anomalies was made in line with the EUROCAT Guideline used in the evaluation of congenital anomalies. It was evaluated whether the patients had an attack during pregnancy. Quantitative data of the patients were reported as mean±standard deviation (SD) (minimum–maximum). Whether there was a relationship between the categorical variables was evaluated with the Chi-Square Test, and whether there was a difference between the independent groups was evaluated with the One-Way Analysis of Variance Test. The results were evaluated with a 95% Confidence Interval (CI). The p-value considered statistically significant was <0.05. The analyses were made with SPSS version 26.0 (IBM Inc., Chicago, IL, USA).

RESULTS

The mean age of the 147 patients who were evaluated in the study was 31.8±8.8 years. The mean parity of 130 patients with ongoing pregnancy was 1.6±0.5, birth week was 37±2.1, birth weight was 2960±752 g, 1st minute Apgar score was 8.1±0.8, and 5th minute Apgar score was 8.6±0.7. Among 147 pregnant women, 17 (11.5%) had a spontaneous abortion, 108 (73.4%) gave birth in the term period, 15 (10.2%) gave birth in the late preterm period, and 7 (4.7%) gave birth in the early preterm period. In addition, 80 (61.5%) pregnant women had a cesarean section and 50 (38.5%) had a normal spontaneous vaginal birth. The mean duration of epilepsy was 16.8±7.8 years. The average age of pregnant women with a history of polytherapy was found to be 32.6±8.4 years, which was significantly higher than the other groups (p=0.042). No significant difference was found between the groups in terms of parity number according to drug use history (p=0.850). Among the women included in the study group, the mean birth weight of those who did not receive any treatment during pregnancy was 3080±592 g, the mean birth weight of patients who had a history of monotherapy was 2960±505 g, and the mean birth weight of patients who had a history of polytherapy was 2820±610 g, and no significant differences were found between the groups (p=0.385). The mean birth week of women who did not receive any treatment during pregnancy was 38±1.9, the mean birth week of patients with a history of monotherapy was 37±1.9, and the mean week of birth of patients with a history of polytherapy was 36±2.4, and no significant differences were detected between the groups (p=0.115). No

Table 1: The relationship between treatment history and pregnancy outcomes

	Monotherapy	Polytherapy	Not receiving treatment	Total	p
Age, Mean±SD	30.5±7.9	32.6±8.4	30.2±8.1	31.8±8.8	0.042
Parity, Mean±SD	1.6±0.6	1.5±0.7	1.6±0.6	1.6±0.5	0.850
Birth weight (g), Mean±SD	2960±505	2820±610	3080±592	2960±752	0.385
Birth week, Mean±SD	37±1.9	36±2.4	38±1.9	37±2.1	0.115
1st minute Apgar score, Mean±SD	8.1±0.6	8.1±0.5	8.2±0.6	8.1±0.8	0.770
5th minute Apgar score, Mean±SD	8.7±0.6	8.6±0.5	8.6±0.5	8.6±0.7	0.640
Spontaneous abortion, n (%)	5 (29.4)	5 (29.4)	7 (41.1)	17 (11.5)	0.360
Duration of epilepsy (year), Mean±SD	15.5±7.5	18.1±6.1	15.5±7.7	16.8±7.8	0.044
Birth type, n (%)					0.038
C/S	44 (68.7)	18 (78.2)	18 (41.8)	80 (61.5)	
NSPD	20 (31.3)	5 (21.8)	25 (58.2)	50 (38.5)	
Birth period, n (%)					0.210
Term birth	59 (50)	18 (15.3)	41 (34.7)	108 (73.4)	
Late preterm birth	3 (50)	2 (33.3)	1 (16.7)	15 (10.2)	
Early preterm birth	2 (33.3)	3 (50)	1 (16.7)	7 (4.7)	

SD: Standard deviation; NSPD: Normal spontaneous perineal birth; C/S: Cesarean delivery.

significant difference was found between the groups in terms of 1st minute and 5th minute Apgar scores according to drug use history (p=0.770, p=0.640 respectively). Among the 17 patients who had a history of spontaneous abortion, 5 (29.4%) pregnant women had a history of monotherapy, 5 (29.4%) pregnant women had a history of polytherapy, and 7 (41.1%) pregnant women did not have any treatment history, and no significant differences were detected between the groups (p=0.360). When the groups were evaluated according to drug use history, the duration of epilepsy was found to be significantly higher in the polytherapy group (p=0.044). When the groups were evaluated according to drug use history, it was found that the cesarean section rate was significantly higher in the polytherapy group (p=0.038). Among the 130 pregnant women who gave birth live, 64 (49.2%) had a history of monotherapy, 23 (17.6%) had a history of polytherapy, and 43 (33%) patients did not receive any treatment. The number of pregnant women who gave birth at term was 118, 59 (50%) of the women in this group were in the monotherapy group, 18 (15.3%) were in the polytherapy group, and 41 (34.7%) pregnant women did not receive any treatment during pregnancy. The number of pregnant women who gave birth in the late preterm period was 6, 3 (50%) of them were in the monotherapy group, 2 (33.3%) were in the polytherapy group, and 1 (16.7%) pregnant woman did not receive any treatment during pregnancy. The number of pregnant women who gave birth in the early preterm period was 6, and 2 of the women (33.3%) in this group were in the monotherapy group, 3 (50%) were in the polytherapy group, and 1 (16.7%) pregnant woman did not receive any treatment during pregnancy, and no significant differences were detected between the groups (p=0.210) (Table 1).

Although 94 (63.9%) women included in the study group had at least one epileptic seizure during pregnancy, no seizures were detected in 53 (36.1%) women. Additionally, 50 (34%) patients in the study group did not use medication during pregnancy, 69 (46.9%) patients had a history of monotherapy, and 28 (19.1%) patients had a history of polytherapy. An increase in seizure frequency was de-

Table 2: The epilepsy prognosis of the patients

	n	%
Number of seizures		
≥1	94	63.9
0	53	36.1
Drug history		
Monotherapy	69	46.9
Polytherapy	28	19.1
No treatment	50	34
Seizure prognosis		
Increasing	40	27.2
Decreasing	50	34
No change	57	38.7
Seizure period		
1st trimester	15	10.2
2nd trimester	20	13.6
3rd trimester	12	8.1
2 separate trimesters	13	8.8
1-2-3rd trimesters	24	16.3

Table 3: The relationship between seizure prognosis and seizure type and history of epileptic drug use

	Increased seizures		Decreased seizures		No change		p
	n	%	n	%	n	%	
Seizure type							0.245
Partial	1	7.2	7	50	6	42.8	
Generalized	18	21.9	28	34.2	36	43.9	
Partial + generalized	16	47	9	26.5	9	26.5	
Antiepileptic drug use							0.640
Monotherapy	21	32.9	17	26.6	26	40.5	
Polytherapy	4	17.4	12	52.2	7	30.4	
Not receiving treatment	10	23.2	15	34.9	18	41.9	
Total	35	26.9	44	33.8	51	39.2	

tected in 40 (27.2%) women, a decrease in seizure frequency in 50 (34%) women, and no change in seizure frequency was detected in 57 (38.7%) women in the study group. Seizures were reported in 15 (10.2%) pregnant women in the 1st trimester, in 20 (13.6%) pregnant women in the 2nd trimester, in 12 (8.1%) pregnant women in the 3rd trimester, in 13 (8.8%) pregnant women in two separate trimesters, and in 24 (16.3%) pregnant women in all three trimesters (Table 2).

Among the 130 women who gave birth, an increase in seizure frequency was detected in 35 (26.9%) pregnant women during pregnancy, a decrease in seizure frequency in 44 (33.8%) pregnant women, and there were no changes in the seizure frequency in 51 (39.2%) pregnant women during pregnancy in the study group. When the relationship between seizure frequency, seizure type, and antiepileptic drug use was evaluated, no significant relationships were found between the groups (p=0.245, p=0.640, respectively) (Table 3).

DISCUSSION

The frequency of seizures decreased or remained unchanged during pregnancy in the majority of pregnant women in our study. The period with the lowest seizure frequency was the 2nd trimester. More than half of the patients had a history of seizures at least once during their pregnancy. In our study, the average age of pregnant women with a history of polytherapy was found to be significantly higher. The duration of epilepsy was found to be significantly longer in the polytherapy group, and the cesarean section rate was significantly higher in the polytherapy group. The average age of pregnant women with a history of polytherapy was significantly higher than in other groups. There are conflicting data in the literature in studies evaluating the relationship between age and epilepsy, both in pregnant women and outside the pregnancy period.[16,17] In our study, the high average age in the polytherapy group was associated with the long history of epilepsy in these patients. It has been shown in the literature that the duration of epilepsy is significantly higher in patients receiving multiple drug therapy.[18,19] In our study, it was observed that the duration of epilepsy was significantly longer in the polytherapy group, consistent with the literature. The reason for this relationship can be explained by the fact that patients diagnosed with severe epilepsy have a low remission rate over the years and are resistant to monotherapy.

The mean birth weight and birth week of the women who did not receive any treatment during pregnancy were higher than the mean birth weight and birth week of the infants with a history of monotherapy and polytherapy among the women in the study group, but this difference was not statistically significant. In the study conducted by Pennell et al.,[19] it was reported that the rate of low birth weight and prematurity increased in epileptic pregnant women. In the study conducted by Crawford et al.,[20] it was reported that the rate of premature birth increased in epileptic pregnant women. It is thought that the difference between the literature data and our study is the difference in the number of patients evaluated in the studies and the exclusion criteria. When patients who had a history of spontaneous abortion were evaluated according to their treatment history, no statistically significant differences were detected between those who did not receive medication and those who received polytherapy or monotherapy. In the study conducted by Adab et al.,[21] abortion rates were found to be significantly higher in the epilepsy group. It is thought that the difference between our study and literature data is since spontaneous abortion patients were not hospitalized in our study. Although studies report that complications during pregnancy are more common in pregnant women who have epilepsy, some studies do not support this result. In the study conducted by Annegers et al.,[22] no differences were detected in the rate of spontaneous miscarriage between pregnant women taking and not taking antiepileptic drugs. Although the rate of spontaneous abortion is not known exactly in normal pregnancies, it is reported to be between 10–40%.[23,24] In our study, spontaneous abortion was detected in 17 (11.5%) cases and no significant differences were detected when compared to normal pregnancies. The risk of congenital malformation increases in proportion to the increase in the number and dose of antiepileptic drugs used (i.e., polytherapy and monotherapy).[25] No major anomaly was found in the patients included in our study. A shift towards a higher rate of monotherapy and a change towards the choice of less teratogenic AEDs during the treatment of our patients may have contrib-

uted to the lower risk of malformations. A wide range of results were reported in the study of Mawer et al.,[25] indicating that the frequency of seizures during pregnancy might increase, decrease, or remain unchanged. Similarly, in our study, data regarding the frequency of seizures during pregnancy were found to be compatible with the literature. Although 94 (63.9%) women in the present study group experienced at least one epileptic seizure during pregnancy, no seizures were detected in 53 (36.1%). No increase was detected in seizure frequency in 40 (27.2%) women in the study group, no decrease in seizure frequency in 50 (34%) women, and no change in seizure frequency in 57 (38.7%) women. These findings were found to be compatible with other studies in the literature. No history of status epilepticus during pregnancy was detected in our study group.

The consensus is that there is no change in the frequency of epileptic seizures in most patients. The best indicator that can reflect the frequency of seizures during pregnancy is the frequency of seizures in the past year before the pregnancy.[23] Perhaps the most important factor that affects the increase in epileptic attacks is the discontinuation of drug use during pregnancy.[26] Expectant mothers stop using AEDs (especially in the first 3 months of pregnancy) to avoid the negative effects of the drugs on their children. It was found in the EURAP Study, in which 1736 pregnancies were evaluated, that 58.3% of the patients did not have seizures during pregnancy, 15.9% had a decrease in their seizures, 17.3% had convulsive seizures, and 1.8% had a history of status epilepticus.[27] In our study, the reason for the similar seizure frequency throughout the pregnancy period may be that the patients had regular neurology check-ups. In the study conducted by Schmidt et al.,[13] it was reported that the increase in seizure frequency was more evident in the 1st and 3rd trimesters, but it was reported in the study of Battino et al.[28] that there was a decrease in the frequency of seizures in the 1st trimester. Unlike the literature data, the fewest seizures were observed in our study in the second trimester. The findings of previous studies conducted on cesarean section rates in epileptic pregnant women are variable.[29] In our study, 38.5% of the pregnant women gave birth by normal vaginal birth and 61.5% by cesarean section, and the cesarean rate was observed to be quite high compared to studies in the literature. The high rate of cesarean sections due to patient request in Türkiye reveals the difference between the literature and our study. It was reported in another study that the mean birth weight of newborn infants of epileptic patients was lower than that of controls, but the difference was not at a statistically significant level.[30] AED polytherapy was suggested to be a risk factor for low birth weight compared to monotherapy.[31] In our study, no significant difference was observed in terms of pregnancy outcomes between patients with a history of polytherapy and patients with a history of monotherapy. However, it supports the view that polytherapy is a risk factor for low birth weight. Among the women included in the study group, the mean birth week of those who did not receive any treatment during pregnancy was higher than the mean birth week of those who received monotherapy and polytherapy, but this difference was not at a statistically significant level. The fact that all patients were followed up from a single center throughout their pregnancy is considered a strength of the study. However, the fact that the relationship between drug dose and drug group and perinatal period results in epileptic drug use was not examined can be considered a limitation of the present study.

CONCLUSION

We think that pregnant women diagnosed with epilepsy have a high probability of giving birth to healthy babies, spontaneous miscarriages are not more common than expected, and there are no significant differences between birth weight or week of birth and the treatment received during pregnancy in the present study. The study also shows that it is possible to obtain positive outcomes almost similar to the general population with an appropriate approach and follow-up.

Statement

Ethics Committee Approval: The Buca Seyfi Demirsoy Training and Research Hospital Non-Interventional Research Ethics Committee granted approval for this study (date: 27.12.2023, number: 2023/209).

Author Contributions: Concept – MDU; Design – UA; Supervision – CA; Resource – HAA; Materials – UA; Data Collection and/or Processing – HAA; Analysis and/or Interpretation – UA; Literature Search – MDU; Writing – MDU; Critical Reviews – UA.

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REFERENCES

1. Prevalence of self-reported epilepsy--United States, 1986-1990. JAMA 1994;272:1893.
2. Thomas SV, Sindhu K, Ajaykumar B, Sulekha Devi PB, Sujamol J. Maternal and obstetric outcome of women with epilepsy. Seizure 2009;18:163–6.
3. Battino D, Tomson T. Management of epilepsy during pregnancy. Drugs 2007;67:2727–46.
4. Tomson T, Battino D. Pregnancy and epilepsy: What should we tell our patients? J Neurol 2009;256:856–62.
5. Morrell MJ. Reproductive and metabolic disorders in women with epilepsy. Epilepsia 2003;44(Suppl 4):11–20.
6. Crawford P. Best practice guidelines for the management of women with epilepsy. Epilepsia 2005;46(Suppl 9):117–24.
7. Liporace J, D'Abreu A. Epilepsy and women's health: Family planning, bone health, menopause, and menstrual-related seizures. Mayo Clin Proc 2003;78:497–506.
8. Tomson T, Landmark CJ, Battino D. Antiepileptic drug treatment in pregnancy: Changes in drug disposition and their clinical implications. Epilepsia 2013;54:405–14.
9. Madazlı R, Öncül M, Albayrak M, Uludağ S, Eşkazan E, Ocak V. Gebelik ve epilepsi: 44 olgunun değerlendirilmesi. Cerrahpasa Tıp Derg [Article in Turkish] 2004;35:126–30.
10. Razaz N, Tomson T, Wikström AK, Cnattingius S. Association between pregnancy and perinatal outcomes among women with epilepsy. JAMA Neurol 2017;74:983–91.
11. Lindhout D, Meinardi H, Meijer JW, Nau H. Antiepileptic drugs and teratogenesis in two consecutive cohorts: Changes in prescription policy paralleled by changes in pattern of malformations. Neurology 1992;42(4 Suppl 5):94–110.

12. Yerby M, Koepsell T, Daling J. Pregnancy complications and outcomes in a cohort of women with epilepsy. Epilepsia 1985;26:631–5.
13. Schmidt D, Canger R, Avanzini G, Battino D, Cusi C, Beck-Mannagetta G, et al. Change of seizure frequency in pregnant epileptic women. J Neurol Neurosurg Psychiatry 1983;46:751–5.
14. Knight AH, Rhind EG. Epilepsy and pregnancy: A study of 153 pregnancies in 59 patients. Epilepsia 1975;16:99–110.
15. Huang CY, Dai YM, Feng LM, Gao WL. Clinical characteristics and outcomes in pregnant women with epilepsy. Epilepsy Behav 2020;112:107433.
16. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia 1993;34:453–68.
17. Morrell MJ. Epilepsy in women: The science of why it is special. Neurology 1999;53(4 Suppl 1):S42–8.
18. Battino D, Tomson T, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al. Seizure control and treatment changes in pregnancy: Observations from the EURAP epilepsy pregnancy registry. Epilepsia 2013;54:1621–7.
19. Pennell PB. 2005 AES annual course: Evidence used to treat women with epilepsy. Epilepsia 2006;47(Suppl 1):46–53.
20. Crawford P. CPD-Education and self-assessment: Epilepsy and pregnancy. Seizure 2001;10:212–9.
21. Adab N, Kini U, Vinten J, Ayres J, Baker G, Clayton-Smith J, et al. The longer term outcome of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2004;75:1575–83.
22. Annegers JF, Baumgartner KB, Hauser WA, Kurland LT. Epilepsy, antiepileptic drugs, and the risk of spontaneous abortion. Epilepsia 1988;29:451–8.
23. Patel SI, Pennell PB. Management of epilepsy during pregnancy: An update. Ther Adv Neurol Disord 2016;9:118–29.
24. Pernoll ML, DeCherney AH. Current obstetric & gynecologic diagnosis & treatment. 7th ed., USA: Appleton & Lange; 1991.
25. Mawer G, Clayton-Smith J, Coyle H, Kini U. Outcome of pregnancy in women attending an outpatient epilepsy clinic: Adverse features associated with higher doses of sodium valproate. Seizure 2002;11:512–8.
26. ACOG Committee on Practice Bulletins--Obstetrics. ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologists number 92, April 2008 (replaces practice bulletin number 87, November 2007). Use of psychiatric medications during pregnancy and lactation. Obstet Gynecol 2008;111:1001–20.
27. EURAP Study Group. Seizure control and treatment in pregnancy: Observations from the EURAP epilepsy pregnancy registry. Neurology 2006;66:354–60.
28. Battino D, Tomson T, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al. Seizure control and treatment changes in pregnancy: Observations from the EURAP epilepsy pregnancy registry. Epilepsia 2013;54:1621–7.
29. Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Pregnancy, delivery, and outcome for the child in maternal epilepsy. Epilepsia 2009;50:2130–9.
30. Soydinç HE, Turgut A, Sak ME, Özler A, Evsen MS, Başaranoğlu S, et al. Pregnancy and epilepsy: A retrospective analysis of 46 cases and comparison of perinatal outcomes with healthy pregnant women. Perinatal J 2013;21:12–6.
31. Rauchenzauner M, Ehrensberger M, Prieschl M, Kapelari K, Bergmann M, Walser G, et al. Generalized tonic-clonic seizures and antiepileptic drugs during pregnancy--a matter of importance for the baby? J Neurol 2013;260:484–8.

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ORIGINAL ARTICLE

Prediction of prognostic factors in endometrial cancer with PET-CT imaging

[1]Varol GÜLSEREN
[2]Mehmet DOLANBAY
[1]Mine DAĞGEZ
[3]Ümmühan ABDÜLREZZAK
[2]Fulya ÇAĞLI
[3]Ahmet TUTUŞ
[1]Bülent ÖZÇELİK
[1]Serdar SERİN
[4]Kemal GÜNGÖRDÜK

[1]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Erciyes University Faculty of Medicine, Kayseri, Turkey

[2]Department of Obstetrics and Gynecology, Erciyes University Faculty of Medicine, Kayseri, Turkey

[3]Department of Nuclear Medicine, Erciyes University Faculty of Medicine, Kayseri, Turkey

[4]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Mugla Sitki Kocman University Faculty of Medicine, Mugla, Turkey

ORCID ID
VG : 0000-0002-0779-8305
MD : 0000-0002-8332-1568
MDa : 0000-0001-5266-9652
ÜA : 0000-0002-7100-1866
FÇ : 0000-0002-6492-3379
AT : 0000-0002-6643-6363
BÖ : 0000-0003-3257-8088
SS : 0000-0002-7306-1184
KG : 0000-0002-2325-1756

ABSTRACT

Objective: The aim of our study is to evaluate the lymphovascular space involvement (LVSI) status using preoperative fluorine-18 (18F) fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET-CT) imaging.

Material and Methods: This retrospective study was based on a review of the records of patients who were diagnosed with endometrial cancer (EC) and underwent hysterectomy between January 2014 and 2021. The thickness, volume of the uterine lesion, and its standardized uptake value (SUV_{max}) as obtained using 18F-FDG PET-CT and pathology results of hysterectomy specimens were recorded.

Results: All 151 patients included in the study had endometrioid-type cancer. Recurrence was observed in 22 (14.6%) patients. To predict LVSI, deep myometrial invasion, cervical involvement, and lymph node (LN) metastasis preoperatively, ideal SUV_{max} values in PET-CT were analyzed according to receiver operating characteristic (ROC) analysis. Deep myometrial invasion, cervical involvement, LVSI, and LN metastasis, which are poor prognostic factors, were found to be significantly more common in high SUV_{max} values (≥14.65). The 5-year disease-free survival was 92.0% at low SUV_{max} and 71.1% in patients with high SUV_{max} values (p=0.004). Patients with low SUV_{max} had a higher mean 5-year overall survival than patients with high SUV_{max} (97.3% & 71.8%; p<0.001).

Conclusion: In order to predict the presence of LVSI in the preoperative period, the SUV_{max} value of the uterine lesion on PET-CT can be used. It may be helpful in planning the extent of the surgery and the level of LN dissection.

Keywords: Endometrial cancer, lymph node, lymphovascular space involvement, positron emission tomography.

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Correspondence: Varol GÜLSEREN, MD. Erciyes Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Jinekolojik Onkoloji Kliniği, Kayseri, Türkiye.
Tel: +90 352 207 66 66 **e-mail:** drvarolgulseren@gmail.com

INTRODUCTION

The most common gynecological cancer type in developed countries is endometrial cancer (EC).[1] Histological type, grade, depth of myometrial invasion, lymph node (LN) metastasis and lymphovascular space involvement (LVSI) are important prognostic factors for recurrence and survival.[2] EC is usually diagnosed at an early stage (75%) and has an excellent prognosis.[3]

LVSI is the first step in tumor metastasis and is defined as the invasion of tumor cells in lymphatic and/or blood vessels. The presence of LVSI is associated with metastatic spread to lymph nodes and distant sites.[4] LVSI status is assessed by examining the hysterectomy material.[5] On the other hand, LVSI can rarely be evaluated in biopsy specimens, with the hazard of a second surgery to confirm lymph node metastasis.[6,7] Recently, the European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) ESGO-ESTRO-ESP classification, based on final pathology taking into account both LVSI and lymph node status, identified four risk groups for recurrence and is used in adjuvant therapy.[7] Some authors have reported that pelvic and para-aortic lymphadenectomy in low-risk EC patients has no clinical benefit but causes an additional increase in the risk of complications and morbidities.[8] Although there were imaging studies evaluating LVSI preoperatively, no consensus was reached.[9] In addition, LVSI is now included in the 2023 EC staging system.[10]

The aim of our study is to evaluate the LVSI status using preoperative fluorine-18 (18F) fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET-CT) imaging.

MATERIAL AND METHODS

This retrospective study was based on a review of the records of patients who were diagnosed with EC and underwent hysterectomy at the Gynecologic Oncology Clinic of Erciyes University, Faculty of Medicine, Türkiye, between January 2014 and 2021. The patients' clinical files and pathological specimens were reviewed retrospectively. Study inclusion was limited to patients with EC who were operated on at our institution, for whom follow-up data were available, and who underwent PET-CT in the preoperative period. Collected data included patient age at diagnosis, tumor size, histological subtype, lymphovascular space invasion, The International Federation of Gynecology and Obstetrics (FIGO) stage, and comorbidities (hypertension, diabetes mellitus). The study was approved by the local Ethics Committee (Date=26.05.2021, Decision No=2021/365) and conducted in accordance with the principles of the Declaration of Helsinki.

All surgical operations were carried out by surgeons experienced in gynecological oncologic surgery. A vertical midline incision was preferred in all patients for ease of access during abdominal exploration and organ resection. After the peritoneal cavity had been entered, a peritoneal wash was obtained for cytology. Exploration of the abdominal cavity included systematic examination of the peritoneal surfaces, omentum, colon and small intestine, and para-colic, pelvic, mesenteric, and para-aortic sites, as well as palpation to locate suspicious lesions. The procedures included hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node sampling, resection of bulky lymph nodes, and omentectomy. Systematic retroperitoneal lymphadenectomy was performed at our oncology center in patients with (a) myometrial invasion ≥1/2, (b) positive pelvic LNs, (c) nonendometrioid tumors, and (d) grade 3 endometrioid cancer. The staging of all cases was re-evaluated according to the FIGO 2023 staging system by re-evaluating the pathological findings.[10] Pelvic lymphadenectomy consisted of removal of the lymphatic tissue over the external, internal, and common iliac vessels and in the obturator fossa. Para-aortic LN dissection was performed by removal of the lymphatic tissue over the inferior vena cava and aorta, beginning at the bifurcation and proceeding to the left renal vein if necessary.

Table 1: The demographic and clinical characteristics of the patient (n=151)

Characteristics	
Age, years, Mean±SD	59.7±10.8
CA125, Mean±SD	58.5±143.2
Hemoglobin, Mean±SD	12.1±2.0
Histological grade, n (%)	
1	81 (53.6)
2	45 (29.8)
3	25 (16.6)
Myometrial invasion, n (%)	
Limited in the cavity	10 (6.6)
<1/2	104 (68.9)
≥1/2	34 (22.5)
Serosal	3 (2.0)
Cervical invasion, n (%)	17 (11.3)
Adnexal involvement, n (%)	5 (3.3)
Lymphovascular space invasion, n (%)	35 (23.2)
Stage, n (%)	
IA1	10 (6.6)
IA2	79 (52.3)
IA3	1 (0.7)
IB	10 (6.6)
IIA	1 (0.7)
IIB	12 (7.9)
IIC	16 (10.6)
IIIC1	8 (5.3)
IIIC2	6 (4.0)
IVB	8 (5.3)
SUV_{max} (uterine lesion), Mean±SD	14.2±9.2
Vertical size of the tumor in PET, mm, Mean±SD	39.3±20.7
Horizontal size of the tumor in PET, mm, Mean±SD	29.2±16.9
The largest tumor size in pathology, cm, Mean±SD	3.6±2.0

SD: Standard deviation.

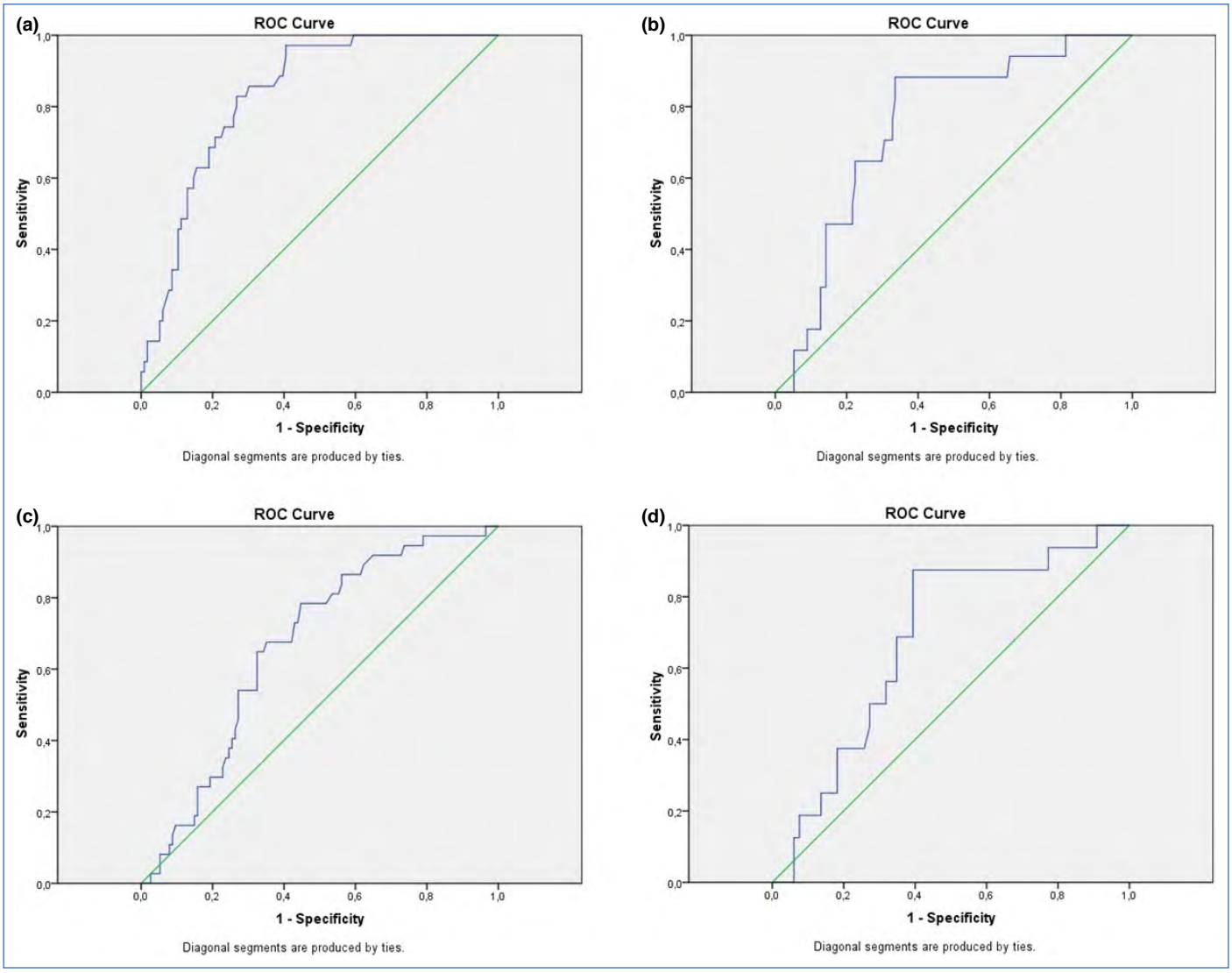

Figure 1: Determination of ideal cut-off values in PET-CT by ROC analysis to predict prognostic factors.

(a) LVSI & SUV_{max}, AUC: 0.834 (CI 95%: 0.769–0.899), p<0.001, cut-off: 14.6; sensitivity: 82.9% and 73.3% specificity. **(b)** Cervical involvement & SUV_{max}, AUC: 0.747 (CI 95%: 0.639–0.855), p=0.001, cut-off: 14.6; sensitivity: 88.2% and 66.4% specificity. **(c)** Deep myometrial invasion & SUV_{max}, AUC: 0.668 (CI 95%: 0.576–0.760), p=0.002, cut-off: 14.6; sensitivity: 64.9% and 67.5% specificity. **(d)** Lymph node metastasis & SUV_{max}, AUC: 0.680 (CI 95%: 0.544–0.817), p=0.026, cut-off: 14.6; sensitivity: 87.5% and 60.6% specificity.

All histological slides were reviewed by an expert gynecopathologist. Histological subtype, histological FIGO grade (according to the World Health Organization criteria), and mitotic index (number of mitoses per 10 high power fields) were evaluated both in the primary tumor and in curettage material. Uterine sections were selected from the anterior and posterior aspects of the cervix, the lower uterine segment, and the uterine corpus. A minimum of 6 sections, including the section showing the deepest tumoral invasion, was obtained for all specimens.

Diagnosis was confirmed histopathologically in all patients. The thickness and volume of the uterine lesion and its standardized uptake value (SUV_{max}) as obtained using 18F-FDG PET/CT and hysterectomy pathology results were recorded. Whole-body 18F-FDG PET/CT imaging was performed using a PET/CT scanner (Philips GeminiTF; Philips Healthcare, Andover, MA, USA), which consisted of a dedicated lutetium orthosilicate full-ring PET scanner and 16-slice CT. Both PET and low-dose CT scanning covered the skull to the proximal thigh. The protocol included 6 h of fasting before image acquisition, and all patients were asked to void before undergoing scanning. On the day of the examination, the serum glucose levels measured before 18F-FDG injections were found to be less than 140 mg/dL. Subsequently, 18F-FDG (6.5–13.4 µCi) was given intravenously 60 to 120 min before the CT scan, and the patients were instructed to rest in a semi-dark, temperate room between the injection and scanning. At 60 min after the administration of 18F-FDG, low-dose CT (50 mAs, 120 kV) covering the area from the skull to the proximal thighs was performed to attenuate the correction and precise anatomic localization. An emission scan was then conducted in the three-dimensional mode. All images were reconstructed and stored as axial, coronal, and sagittal slices. The total scanning time was about 20 min per patient. The SUV_{max} was estimated for each hypermetabolic lesion.

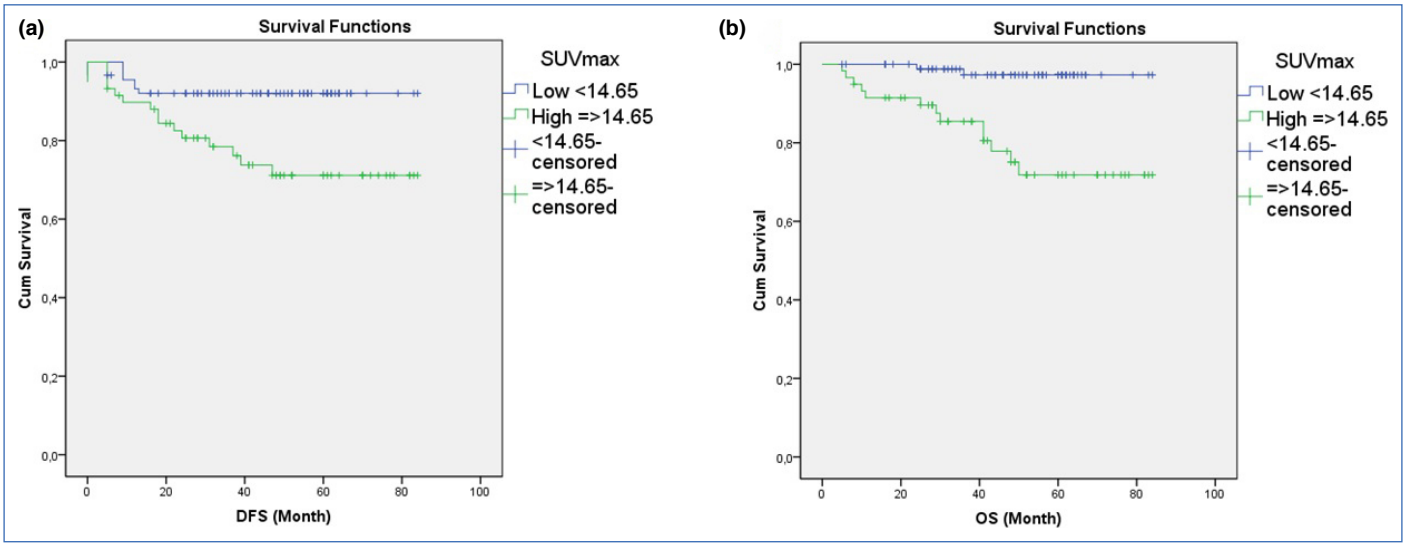

Figure 2: Disease-free **(a)** and overall **(b)** survival curves of low and high SUV_{max} values according to Kaplan-Meier.

The patients were followed up every 3–4 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Computed tomography or magnetic resonance imaging was performed annually. Disease-free survival was defined as the interval from the date of primary surgery to the detection of recurrence or the latest observation. Overall survival was defined as the interval from the date of primary surgery to death or the latest observation.

Statistical Analysis

Descriptive data are expressed as the mean±standard deviation or as a percentage. Chi-square was used to compare categorical data, and the Student t-test was used to compare nominal data. The optimal cut-off value of predictive prognostic factors in EC was identified using receiver operating characteristic (ROC) curve analysis. Logistic regression analysis was used to define the risk factors for lymph node involvement; the results were presented as the 95% confidence interval (CI) and odds ratio (OR). All statistical analyses were performed using SPSS software (ver. 20.0; IBM Corp., Armonk, NY, USA). A p value <0.05 was considered to indicate statistical significance.

RESULTS

All 151 patients included in the study were of the endometrioid adenocarcinoma histological type. One hundred forty-one (93.4%) patients were estrogen receptor positive and 134 (88.7%) patients were progesterone receptor positive. Type 1 hysterectomy was performed in 148 (98.0%) patients and type 3 hysterectomy in 3 (2.0%) patients. Pelvic LN dissection was performed in 110 (72.8%) patients and paraaortic LN dissection was performed in 83 (55.0%) patients. The mean number of pelvic LNs taken was 17.1±7.9 and the number of paraaortic LNs was 6.1±4.2. Pelvic LN metastasis was observed in 16 (10.6%) patients and paraaortic LN metastasis was observed in 9 (6.0%) patients. Seventy-four (49.0%) of the patients had hypertension and 49 (32.5%) had diabetes mellitus. The demographic and clinical characteristics of the patients are given in Table 1.

Sixty-eight (45.0%) patients received adjuvant radiotherapy; vaginal brachytherapy (VBT) was given to 57 (37.7%) patients and external beam radiotherapy (EBRT) to 31 (21.5%) patients. Adjuvant chemotherapy was given to 21 (13.9%) patients and all received carboplatin plus paclitaxel. Recurrence was observed in 22 (14.6%) patients. Recurrence locations were: vaginal cuff in 3 (2.0%) patients, pelvic in 4 (2.6%) patients, pulmonary in 3 (2.0%) patients, common in more than one area in 8 (5.3%) patients, and other regions in 4 (2.6%) patients.

In order to predict LVSI, deep myometrial invasion, cervical involvement, and LN metastasis, ideal SUV_{max} values in preoperative PET-CT were analyzed according to ROC analysis in Figure 1. The sensitivity, specificity, negative and positive predictive values of the cut-off values are given in Table 2. The average incidence of prognostic factors with respect to low and high SUV_{max} values are summarized in Table 3. The 5-year disease-free survival (148 patients) was 92.0% at low SUV_{max} (<14.65) and 71.1% in patients with high SUV_{max} (≥14.65) values (p=0.004) (Fig. 2a). Patients with low SUV_{max} (<14.65) had a higher mean 5-year overall survival (141 patients) than patients with high SUV_{max} (≥14.65) (97.3% & 71.8%; p<0.001) (Fig. 2b).

DISCUSSION

In EC, depending on the status of prognostic factors, the extent of surgery and adjuvant treatment is decided. However, it may not always be possible to identify prognostic factors preoperatively. LVSI is defined as the presence of adenocarcinoma, of any extent, in endothelial-lined channels of uterine specimens extracted at the time of surgery.[11] In particular, the status of LVSI is not considered reliable if it is negative in preoperative biopsies because the absence of LVSI in the biopsy area does not reflect the LVSI status in the rest of the specimen. In this regard, we conducted research to predict the LVSI status and other prognostic features of EC patients according to SUV_{max} values in PET-CT, with an aim to guide the surgery.

LVSI is an important prognostic factor for disease relapse and poor survival in EC, as is LN metastasis, in patients with EC.[12–14] LVSI is reported as positive in 13.2–51.8% of ECs.[4,12–15] There are

Table 2: The sensitivity, specificity, negative and positive predictive value of the cut-off values

	Sensitivite	Spesifisite	PPV	NPV
Deep myometrial invasion	64.9	67.5	38.3	84.6
Cervical invasion	88.2	66.4	25.0	97.8
Lymphovascular space invasion	82.9	73.3	48.3	93.4
Lymph node involvement	87.5	60.6	35.0	95.2

PPV: Positive predictive value; NPV: Negative predictive value.

Table 3: Incidence of prognostic factors according to low and high SUV_{max} values

	Low SUV_{max} (<14.65) (n=91)	High SUV_{max} (≥14.65) (n=60)	p
Deep myometrial invasion	14 (15.4%)	23 (38.3%)	0.002
Cervical invasion	2 (2.2%)	15 (25.0%)	<0.001
Lymphovascular space invasion	6 (6.6%)	29 (48.3%)	<0.001
Lymph node involvement	2 (4.8%)	14 (35.0)	0.001

SUV: Standardized uptake value.

studies in the literature evaluating the utilization of PET-CT in LVSI assessment. SUV_{max} value of the uterine lesion was found to be significantly higher in patients with positive LVSI.[13–18] However, studies investigating the ideal cut-off value to detect LVSI positivity have reported a wide range of SUV_{max} values changing between 6–16.[16,17] Sensitivity of SUV_{max} for determining LVSI was 71.4–88.2%.[16–18] In regression analysis, the SUV_{max} value was significantly correlated with LVSI.[19] Apart from that, the relationship between deep myometrial invasion, advanced stage, LN involvement, and SUV_{max} values was investigated and a significant result was found.[14,19] The rate of LVSI positivity in patients with EC was 23.2% in our study. In regard to determining the LVSI status, the cut-off value of SUV_{max} was 14.6 in the ROC analysis, and the area under the curve was 0.834. The sensitivity was 82.9%, the negative predictive value was 93.4%, and the positive predictive value was 48.3%. Additionally, for disease-free and overall survival outcomes, patients with higher SUV_{max} values were found to be statistically significantly worse.

The choice of optimal surgery for EC, particularly on the extension of lymphadenectomy, should be balanced in terms of surgical morbidity and oncological outcomes. Surgeons may stand in favor of more comprehensive surgery to overcome endometrial cancer with high-risk factors. On the other hand, it is known that more radical surgery is associated with increased morbidity. It is known that systematic total pelvic and paraaortic lymphadenectomy increases complication rates such as wound infection, lymphocyst, and lymphedema. Preoperative evaluation and imaging may help in planning the extent of surgery. In our cohort, 6.6% of patients with low SUV_{max} values had LVSI positivity, while approximately half of the patients with high values were LVSI positive. When performing LN dissection, a more systematic approach should be performed in cases where the SUV_{max} values are above the threshold. In the ESGO-ESTRO-ESP guidelines on EC, LVSI is accepted as an important risk factor for disease recurrence and having information on the status of LVSI preoperatively may provide clarity in management.[7,9,11] In addition, LVSI changes the stage in the 2023 FIGO staging system.[10]

This study has some limitations. First, it has a retrospective design, and secondly, the sample size was relatively small. Further studies with larger cohorts and prospective designs are recommended. Lastly, systematic LN dissection was not performed for all patients. Despite these limitations, the comparable demographic characteristics of the study population and the inclusion of expert pathologists increased the validity of our results and reduced these weaknesses.

CONCLUSION

In conclusion, in order to predict the presence of LVSI in the preoperative period, the SUV_{max} value of the uterine lesion on PET-CT can be used. It may be helpful preoperatively in determining prognosis.

Statement

Ethics Committee Approval: The Erciyes University Clinical Research Ethics Committee granted approval for this study (date: 26.05.2021, number: 2021/365).

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7–30.
2. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. Lancet 2016;387:1094–108.
3. Creasman WT, Odicino F, Maisonneuve P, Beller U, Benedet JL, Heintz AP, et al. Carcinoma of the corpus uteri. J Epidemiol Biostat 2001;6:47–86.
4. Boothe D, Wolfson A, Christensen M, Francis S, Werner TL, Gaffney DK. Lymphovascular invasion in endometrial cancer: Prognostic value and implications on adjuvant radiation therapy use. Am J Clin Oncol 2019;42:549–54.
5. Sadozye AH, Harrand RL, Reed NS. Lymphovascular space invasion as a risk factor in early endometrial cancer. Curr Oncol Rep 2016;18:24.
6. Ueno Y, Forghani B, Forghani R, Dohan A, Zeng XZ, Chamming's F, et al. Endometrial carcinoma: MR imaging-based texture model for preoperative risk stratification-a preliminary analysis. Radiology 2017;284:748–57.
7. Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer 2021;31:12–39.
8. Hidaka T, Kato K, Yonezawa R, Shima T, Nakashima A, Nagira K, et al. Omission of lymphadenectomy is possible for low-risk corpus cancer. Eur J Surg Oncol 2007;33:86–90.
9. Nougaret S, Reinhold C, Alsharif SS, Addley H, Arceneau J, Molinari N, et al. Endometrial cancer: Combined MR volumetry and diffusion-weighted imaging for assessment of myometrial and lymphovascular invasion and tumor grade. Radiology 2015;276:797–808.
10. Berek JS, Matias-Guiu X, Creutzberg C, Fotopoulou C, Gaffney D, Kehoe S, et al. FIGO staging of endometrial cancer: 2023. Int J Gynaecol Obstet 2023;162:383–94.
11. Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: A Gynecologic Oncology Group study. Gynecol Oncol 2004;92:744–51.
12. Mapelli P, Ironi G, Bergamini A, Mangili G, Rancoita PM, Taccagni GL, et al. Synergic role of preoperative 18F-fluorodeoxyglucose PET and MRI parameters in predicting histopathological features of endometrial cancer. Nucl Med Commun 2020;41:1073–80.
13. Kitajima K, Suenaga Y, Ueno Y, Maeda T, Ebina Y, Yamada H, et al. Preoperative risk stratification using metabolic parameters of (18)F-FDG PET/CT in patients with endometrial cancer. Eur J Nucl Med Mol Imaging 2015;42:1268–75.
14. Sürer Budak E, Toptaş T, Aydın F, Öner AO, Çevikol C, Şimşek T. Correlation of minimum apparent diffusion coefficient and maximum standardized uptake value of the primary tumor with clinicopathologic characteristics in endometrial cancer. Mol Imaging Radionucl Ther 2017;26:24–32.
15. Sahin H, Sarioglu FC, Bagci M, Karadeniz T, Uluer H, Sanci M. Preoperative magnetic resonance volumetry in predicting myometrial invasion, lymphovascular space invasion, and tumor grade: Is it valuable in international federation of gynecology and obstetrics stage I endometrial cancer? Int J Gynecol Cancer 2018;28:666–74.
16. Yahata T, Yagi S, Mabuchi Y, Tanizaki Y, Kobayashi A, Yamamoto M, et al. Prognostic impact of primary tumor SUVmax on preoperative 18F-fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography in endometrial cancer and uterine carcinosarcoma. Mol Clin Oncol 2016;5:467–74.
17. Sudo S, Hattori N, Manabe O, Kato F, Mimura R, Magota K, et al. FDG PET/CT diagnostic criteria may need adjustment based on MRI to estimate the presurgical risk of extrapelvic infiltration in patients with uterine endometrial cancer. Eur J Nucl Med Mol Imaging 2015;42:676–84.
18. Liu DD, Li J, Li X, Xie L, Qin L, Peng F, et al. Prognostic value of metabolic tumor volume and total lesion glycolysis from ^{18}F-FDG PET/CT in lymph node metastases and risk stratification of endometrial carcinoma. J Gynecol Oncol 2019;30:e89.
19. Lee HJ, Ahn BC, Hong CM, Song BI, Kim HW, Kang S, et al. Preoperative risk stratification using (18)F-FDG PET/CT in women with endometrial cancer. Nuklearmedizin 2011;50:204–13.

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ORIGINAL ARTICLE

Evaluation of first-trimester hematological indices in preeclampsia: A retrospective observational case-control study

[1]Esra KELEŞ
[2]Leyla KAYA
[3]Pınar KUMRU
[4]Zahide KAYA

[1]Department of Gynecologic Oncology, University of Health Sciences, Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Turkey

[2]Department of Midwifery, University of Health Sciences Faculty of Health Sciences, Istanbul, Turkey

[3]Department of Obstetrics and Gynecology, University of Health Sciences, Turkey. Istanbul Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center, Istanbul, Turkey

[4]Internal Medicine Clinic, Uskudar State Hospital, Istanbul, Turkey

ORCID ID
EK : 0000-0001-8099-8883
LK : 0000-0002-2199-0854
PK : 0000-0002-8905-1909
ZK : 0000-0002-7461-2013

ABSTRACT

Objective: Preeclampsia (PE) is one of the leading major causes of maternal and neonatal mortality and morbidity. Improving the outcome for preeclampsia necessitates early prediction of the disease to identify women at high risk. Evaluation of hematological parameters might provide prognostic and diagnostic clues to diseases. The purpose of this study is to investigate hematological changes in early pregnancy using complete blood counts in order to determine whether these measurements may provide useful information for the early diagnosis of preeclampsia.

Material and Methods: This retrospective observational case–control study was conducted at a tertiary referral center between August 2020 and February 2022. Medical records of women with preeclampsia and healthy controls were compared regarding clinical characteristics and first-trimester hematological parameters. Receiver operating characteristic curve analysis was performed to identify the optimal white blood cells level predicting preeclampsia.

Results: The white blood cells (WBC) values were significantly higher in the preeclampsia group compared with the control group ($p<0.049$). There were no significant differences in other hematological parameters between the groups. For WBC, the values of area under the curve were 0.605, and the p-value for this parameter statistically differed ($p=0.049$).

Conclusion: This study showed that WBC may be a useful marker in the prediction of preeclampsia in early pregnancy.

Keywords: Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, preeclampsia, white blood cells.

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Correspondence: Esra KELEŞ, MD. Sağlık Bilimleri Üniversitesi, İstanbul Kartal Dr. Lütfi Kırdar Şehir Hastanesi, Jinekolojik Onkoloji Kliniği, İstanbul, Türkiye.
Tel: +90 216 391 06 80 **e-mail:** dresrakeles@hotmail.com

INTRODUCTION

Preeclampsia (PE) is a significant complication that involves 2-8% of pregnant women and can lead to maternal and neonatal morbidity and mortality. It is a major cause of maternal death in developing countries, primarily due to eclampsia resulting from untreated preeclampsia.[1]

The cause of PE is placental dysfunction and hypoxia, which triggers immunological factors.[2–4] Despite extensive research, the root causes of the excessive systemic inflammation response in normal pregnancy and PE remain unclear.

The immune system can be assessed through a simple and cost-effective test named complete blood count (CBC). This test displays different cellular components of blood and their distribution, which is valuable in evaluating various obstetric complications such as PE.[5] Hematologic parameters derived from CBC can provide diagnostic and prognostic clues to diseases.[6–8]

While many studies have examined hematologic parameters in preeclampsia, uncertainty remains regarding their predictive value of first-trimester CBC parameters in PE. Early prediction of PE is crucial to improve outcomes and identify women at high risk. Therefore, this study was to compare CBC indices between preeclamptic and healthy pregnant women during the first trimester.

MATERIAL AND METHODS

This retrospective observational case-control study was carried out by primiparous singleton pregnant women aged 18-40 years and delivered at a tertiary hospital from August 2020 to February 2022. Our study was granted by the Ethics Committee (23.03.2022/39) and follows the tenets of the Declaration of Helsinki.

Women were stratified into two groups: a healthy control group and a group with PE, as determined by the American College of Obstetrics and Gynecology guidelines.[9] The healthy control group was randomly selected from patients with uncomplicated pregnancies hospitalized during the same period.

Patients with chronic systemic diseases, autoimmune disease, renal or hepatic diseases, cardiovascular disease, malignancies, thyroid disorders, any medication use, Body Mass Index ≥30 kg/m², a history of recurrent miscarriages or infertility, history of thrombophilia or any other medical condition requiring chronic drug treatment, the use of acetylsalicylic acid, complicated pregnancies, multiple gestations, inflammatory bowel diseases, smoking, anemia, hepatitis infections, ruptured membranes, or any active local or systemic infection which could affect maternal complete blood count results were excluded.

Sociodemographic information, obstetric, clinical characteristics, and laboratory results were extracted from electronic medical records. We collected the blood tests for all patients during the first trimester. When multiple CBC results were available, the result closest to 6 weeks of gestation was selected. The NLR and PLR were computed by dividing neutrophils and platelets by lymphocytes, respectively.

Statistical Analysis

Statistics were analyzed with SPSS v. 25.0. The variables were presented as mean±standard deviation. We utilized Chi-square test, Student's t-test, and the Mann-Whitney U test, when necessary.

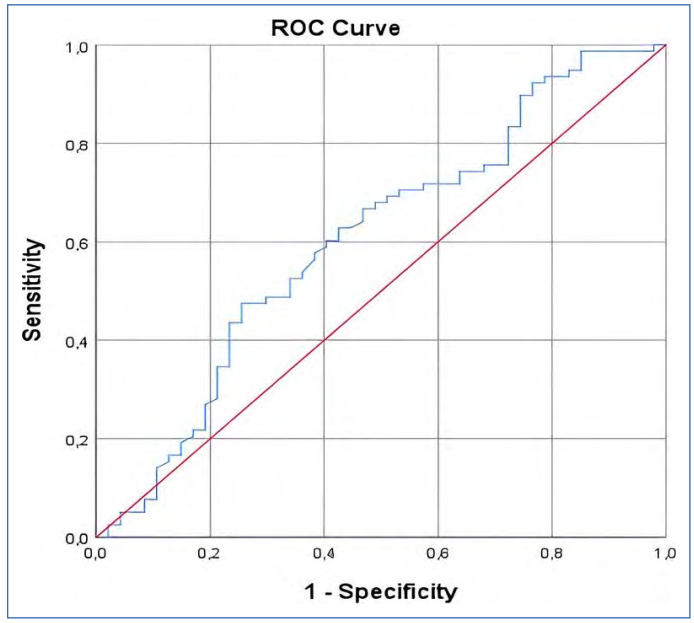

Figure 1: Area under the receiver operating characteristic curve for white blood cell measurement for predicting preeclampsia. The area under the curve was 0.605 (95% confidence interval 0.500–0.710).

Receiver operating characteristic (ROC) curves were constructed to determine the cut-off values, sensitivity, and specificity. Statistical significance was considered as $p<0.05$.

RESULTS

Seventy-eight pregnant women with PE and 47 healthy controls were enrolled in the study. The maternal age and gestational week at blood sampling did not differ between groups. The PE group had higher mean blood pressures and lower APGAR scores at 1- and 5-minute than the healthy control group (all p=0.001).

Hemoglobin, lymphocyte count, neutrophil count, platelet count, red blood cell distribution width (RDW), and MCV during the first trimester were comparable between the two groups. The first-trimester white blood cells (WBC) counts for the PE group were significantly higher in comparison to those of the healthy control group (p=0.049). NLR and PLR values were not significantly different between groups (Table 1).

ROC curves indicated that the cut-off point for WBC was 9.7×10^3/µL, exhibiting a sensitivity of 62.8% and a specificity of 57.4%. ROC curve analysis revealed an AUC of 0.605 (95% CI 0.500–0.710) (Fig. 1).

DISCUSSION

The study found that women with preeclampsia had higher levels of WBC in comparison to the healthy controls. Other hematologic parameters did not differ between groups. NLR and PLR are easily calculated, cost-effective inflammatory indexes. Evidence concerning the association between NLR and PLR values and preeclampsia is contradictory.[1,10–12] While Gogoi et al.[13] observed significantly higher values of NLR and PLR in women with PE, the present study found no differences in these indices between groups. These results were in agreement with those of Örgül et al.,[14] who also concluded that

Table 1: Comparison of demographic, clinical characteristics and hematological results of preeclampsia group and the control group

	Preeclampsia group (n=78) Mean±SD	Control group (n=47) Mean±SD	p*
Maternal age (years)	29.9±5.8	28.8±5.1	0.326
Gestational age at delivery (weeks)	36.2±4.0	38.5±2.5	0.001
Neonatal birth weight (g)	2576.0±857.6	3131.7±686.4	0.001
APGAR Score 1-minute	6.9±1.3	7.7±0.7	0.001
APGAR Score 5-minute	8.5±0.8	8.9 ±0.5	0.001
Systolic blood pressure (mmHg)	140.8 ±19.8	116.6 ±15.5	0.001
Diastolic blood pressure (mmHg)	90.4 ±14.0	76.8 ±21.6	0.001
Gestational age at blood sampling (weeks)	14.2±4.3	14.4 ±4.1	0.810
Hemoglobin	12.1±1.2	14.0 ±3.9	0.275
White blood cells	10.6±3.0	9.8 ±3.7	**0.049**
Neutrophils (10^3/mm–3)	7.8±2.9	15.2±10.7	0.208
Lymphocytes (10^3/mm–3)	3.1±0.5	2.0±0.6	0.532
Platelets (10^3/mm–3)	259.9±66.5	254.1±67.4	0.638
Mean corpuscular volume (MCV) (fL)	9.5±1.2	9.3±0.9	0.623
Red cell distribution width (RDW)	13.9±1.6	14.3±2.3	0.994
Neutrophil to lymphocyte ratio	4.1±2.5	5.0±5.4	0.723
Platelet to lymphocyte ratio	138.6±76.4	137.2±49.7	0.889

*: P-value≤0.05 statistically significant difference between pre-eclampsia group and control group.

NLR and PLR are not significant predictors in preeclampsia. Similarly, Yavuzcan et al.[15] did not observe a significant increase in NLR in women with PE compared to healthy pregnant women. It should be noted, however, that the insignificant results in this research may be attributed to the small sample size.

Anemia has been shown to have no association with PE, according to a recent systematic meta-analysis,[16] and our study also found no differences in anemia parameters between the preeclamptic and healthy controls. Red blood cell distribution width (RDW), another parameter that is measured during CBC tests, has been associated with inflammation. It has been established that increased RDW levels during pregnancy were related to the occurrence and severity of PE.[1,17] However, in contrast to previous studies, our findings did not show significant differences in RDW values between groups.

This study indicated that women with PE had higher WBC counts in comparison to the controls. In addition, a WBC count >9.7×10³/μL was associated with PE. These findings were comparable to those of Örgül et al.,[14] who also concluded that an increased first-trimester WBC count is linked to early-onset PE. However, no difference was observed with regard to eosinophils, basophils, monocytes, and lymphocytes. It has been suggested that the increased WBC levels in the first trimester are caused by endothelial dysfunction in PE.

Our study has some limitations due to its single-center design and small sample size. However, it is worth noting that the dataset collected during the study is one of the few rigorously collected datasets regarding PE. Further multicenter research is necessary to confirm the changes in hematological values that occur during the first trimester of pregnancy that is complicated by PE. These findings may contribute to the development of effective diagnostic tools and therapeutic interventions for PE.

CONCLUSION

The present study found that first-trimester increased WBC levels were associated with PE, while other inflammation markers did not exhibit any significant differences between groups.

Statement

Ethics Committee Approval: The Istanbul Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center Clinical Research Ethics Committee granted approval for this study (date: 23.03.2022, number: 39).

Author Contributions: Concept – EK, LK, PK, ZK; Design – EK, LK, PK, ZK; Supervision – EK, LK, PK, ZK; Resource – LK, ZK; Materials – LK, ZK; Data Collection and/or Processing – LK, ZK; Analysis and/or Interpretation – PK; Literature Search – EK, LK, PK, ZK; Writing – EK, LK, PK, ZK; Critical Reviews – EK, LK, PK, ZK.

Conflict of Interest: The authors have no conflict of interest to declare.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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REFERENCES

1. Yücel B, Ustun B. Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, mean platelet volume, red cell distribution width and plateletcrit in preeclampsia. Pregnancy Hypertens 2017;7:29–32.
2. Phipps EA, Thadhani R, Benzing T, Karumanchi SA. Pre-eclampsia: Pathogenesis, novel diagnostics and therapies. Nat Rev Nephrol 2019;15:275–89.
3. Guerby P, Tasta O, Swiader A, Pont F, Bujold E, Parant O, et al. Role of oxidative stress in the dysfunction of the placental endothelial nitric oxide synthase in preeclampsia. Redox Biol 2021;40:101861.
4. Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia: Pathophysiology, challenges, and perspectives. Circ Res 2019;124:1094–112. Erratum in: Circ Res 2020;126:e8.
5. Kirbas A, Ersoy AO, Daglar K, Dikici T, Biberoglu EH, Kirbas O, et al. Prediction of preeclampsia by first trimester combined test and simple complete blood count parameters. J Clin Diagn Res 2015;9:QC20–3.
6. Seo IH, Lee YJ. Usefulness of Complete Blood Count (CBC) to assess cardiovascular and metabolic diseases in clinical settings: A comprehensive literature review. Biomedicines 2022;10:2697.
7. Kara SS, Keles E, Sivri Aydın D, Mat E, Yıldız G, Temoçin RB, et al. Utility of preoperative neutrophil–lymphocyte and platelet–lymphocyte ratios in differential diagnosis of benign, borderline, and malignant ovarian tumors. J Exp Clin Med 2023;40:333–6.
8. Pinna A, Carlino P, Serra R, Boscia F, Dore S, Carru C, et al. Red Cell Distribution Width (RDW) and complete blood cell count-derived measures in non-arteritic anterior ıschemic optic neuropathy. Int J Med Sci 2021;18:2239–44.
9. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol 2020;135:e237–60.
10. Mannaerts D, Heyvaert S, De Cordt C, Macken C, Loos C, Jacquemyn Y. Are neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and/or mean platelet volume (MPV) clinically useful as predictive parameters for preeclampsia? J Matern Fetal Neonatal Med 2019;32:1412–9.
11. Wang J, Zhu QW, Cheng XY, Liu JY, Zhang LL, Tao YM, et al. Assessment efficacy of neutrophil-lymphocyte ratio and monocyte-lymphocyte ratio in preeclampsia. J Reprod Immunol 2019;132:29–34.
12. Kang Q, Li W, Yu N, Fan L, Zhang Y, Sha M, et al. Predictive role of neutrophil-to-lymphocyte ratio in preeclampsia: A meta-analysis including 3982 patients. Pregnancy Hypertens 2020;20:111–8.
13. Gogoi P, Sinha P, Gupta B, Firmal P, Rajaram S. Neutrophil-to-lymphocyte ratio and platelet indices in pre-eclampsia. Int J Gynaecol Obstet 2019;144:16–20.
14. Örgül G, Aydın Haklı D, Özten G, Fadiloğlu E, Tanacan A, Beksaç MS. First trimester complete blood cell indices in early and late onset preeclampsia. Turk J Obstet Gynecol 2019;16:112–7.
15. Yavuzcan A, Cağlar M, Ustün Y, Dilbaz S, Ozdemir I, Yildiz E, et al. Mean platelet volume, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in severe preeclampsia. Ginekol Pol 2014;85:197–203.
16. Rahman MM, Abe SK, Rahman MS, Kanda M, Narita S, Bilano V, et al. Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: Systematic review and meta-analysis. Am J Clin Nutr 2016;103:495–504.
17. Adam I, Mutabingwa TK, Malik EM. Red cell distribution width and preeclampsia: A systematic review and meta-analysis. Clin Hypertens 2019;25:15.

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ORIGINAL ARTICLE

Retrospective evaluation of amniocentesis results: A tertiary center data

[1]Mustafa BAĞCI
[1]Kazım UÇKAN
[1]Hanım GÜLER ŞAHİN
[2]Onur KARAASLAN
[2]Yusuf BAŞKIRAN
[3]Erbil KARAMAN

[1]Division of Perinatology, Department of Obstetrics and Gynecology, Van Yuzuncu Yil University Faculty of Medicine, Van, Turkey

[2]Department of Gynecology and Obstetrics, Van Yuzuncu Yil University Faculty of Medicine,Van, Turkey

[3]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Van Yuzuncu Yil University Faculty of Medicine, Van, Turkey

ORCID ID
MB : 0000-0003-1042-2920
KU : 0000-0002-5576-6789
HGŞ : 0000-0002-8596-0734
OK : 0000-0002-4599-1173
YB : 0000-0003-1123-6062
EK : 0000-0003-1058-2748

ABSTRACT

Objective: The aim of this study is to contribute to the literature by retrospectively analyzing the indications, results, culture successes, and pregnancy results of patients who underwent amniocentesis in our clinic between 2021–2022.

Material and Methods: Our study includes the results of 132 patients who underwent amniocentesis. Demographic characteristics, weeks of gestation, amniocentesis indications, results, complications, and pregnancy outcomes of the patients were evaluated.

Results: In our study, the most common indication for amniocentesis was patients with fetal anomaly detected in ultrasonography (US) with a rate of 38.6% (51/132). The culture success rate was 98.5%. Chromosome anomaly was detected as 18.2% (24/132) in the culture results. Chromosome anomaly was found in 15.7% (8/51) of patients with a fetal anomaly in US. The most common numerical anomalies in culture were Trisomy 21 and Trisomy 18. Among the chromosomal microarray analysis (CMA) results, 4.9% (2/41) were found to be pathogenic and 4.9% (2/41) were classified as variants of uncertain significance (VUS). The pregnancy of 13 patients with chromosomal anomalies was terminated, and three had stillbirths. No maternal or fetal complications related to amniocentesis were observed.

Conclusion: Amniocentesis is a reliable and successful prenatal diagnosis test. The results of our study can provide a database for the literature to provide appropriate genetic counseling.

Keywords: Amniocentesis, chromosomal abnormality, prenatal diagnosis, ultrasonography.

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Correspondence: Mustafa BAĞCI, MD. Van Yüzüncü Yıl Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Perinatoloji Kliniği, Van, Türkiye.
Tel: +90 432 215 04 70 **e-mail:** mustafabagci@outlook.com.tr

INTRODUCTION

Structural anomalies in the fetus are seen in approximately 3% of live births.[1] Its etiology is based on environmental factors together with genetic factors or the combination of both factors. The risk of chromosomal anomaly and genetic molecular defect increases in fetuses with structural anomalies.[2] It has been determined that fetal chromosomal anomaly is seen at a rate of 2–18% in structurally isolated fetal anomalies and 13–35% in multiple anomalies.[2,3]

Amniocentesis, which is based on the aspiration of amniotic fluid by the transabdominal route, was first performed for the determination of sex cells in the 1950s.[4] Karyotype analysis was started in 1966 by obtaining and culturing the skin and gastrointestinal system cells of the fetus from amniotic fluid.[5]

According to ACOG (American College of Obstetricians and Gynecologists), high risk in first or second-trimester screening tests, abnormality in fetal ultrasonography (US), fetal infections, advanced maternal age, history of habitual abortion, history of a child with a chromosomal abnormality, maternal anxiety, detection of mosaicism in chorionic villus sampling, constitutes some of the indications for amniocentesis.[6]

When amniocentesis is applied in early gestational weeks, the probability of fetal loss is high, and when it is applied after the 20th gestational week, it is usually difficult to reproduce in the amniocyte culture and the result can be obtained in the advancing gestational weeks. It is done between 16-20 weeks of pregnancy.[7]

In this study, our aim is to evaluate the amniocentesis procedures performed between 2021-2022, in our clinic, with indications, desired genetic tests and their results, pregnancy results of patients with chromosomal anomalies and contribute to the literature.

MATERIAL AND METHODS

In this study, 132 patients who underwent amniocentesis between January 1, 2021, and December 31, 2022, in Van Yüzüncü Yıl University, Department of Perinatology were evaluated. Approval for the study was obtained from the local ethics committee of the Van Yüzüncü Yıl University (Date/number of ethics committee: 14.04.2023/number:2023/04-05). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Demographic characteristics of the patients, indications of amniocentesis, fetal US findings, cytogenetic culture successes, all desired genetic results, and pregnancy outcomes were evaluated retrospectively.

Patients were consulted with the genetics department before the procedure. All patients and their spouses were informed verbally about how amniocentesis was performed before the procedure, its possible complications, and the benefits of the genetic result to be obtained after the procedure. Written informed consent was obtained from the couples who agreed to undergo amniocentesis before starting the procedure. Before the procedure, blood samples were taken from all patients and screened for Hepatitis B, Hepatitis C, and HIV infections. Blood groups were studied from all patients, and 300 mcg Rh IgG was administered intramuscularly to those with Rh incompatibility after the procedure. Prophylactic cefazolin (1 gr) was administered prior to the procedure. Amniocentesis procedures were performed in accordance with the interventional procedures practice guide for prenatal diagnosis published by ISUOG (The International Society of Ultrasound in Obstetrics and Gynecology) in 2016.[8] During the procedure, a convex ultrasound transducer of 2–5 MHz of GE Voluson E6 (General Electric Healthcare, ABD) was used. Ultrasonographic evaluation including placental localization, amniotic fluid amount, and systematic fetal anatomical examination was performed before the procedure. Using a spinal 20 G (BD) needle, the first 2 ml of amniotic fluid was discarded to prevent maternal contamination. Then, a 20 ml amniotic fluid sample was taken with 2 different pistonless injectors and sent to the genetics laboratory. Quantitative fluorescent polymerase chain reaction (QF-PCR) and cytogenetic culture were requested from all patients. Maternal contamination was excluded in all patients by the short tandem repeat sequences (STR) analysis method. During the period when the genetics laboratory was able to work, chromosomal microarray analysis (CMA) and other genetic examinations were performed according to the recommendations of the genetics department. After the procedure, ultrasonographic evaluation was performed for amniotic fluid index, fetal heart rate, and other possible complications.

In the study, for increased nuchal translucency (NT), which is one of our amniocentesis indications, NT measurement according to crown-rump length (CRL) was accepted to be ≥95th percentile.[9]

Statistical Analysis

While evaluating the findings obtained in the study, SPSS 22 for Windows (Statistical Package for Social Sciences, IBM SPSS Inc.) program was used for statistical analysis. Total count, median, and percentage values are given as descriptive statistics.

RESULTS

In our study, 132 patients who underwent amniocentesis were found to be a median of 30 years old (range 18–46). The median gestational week at which the procedure was performed was 19+0 (range 15+0-20+6).

The amniotic fluid index was sufficient in 96.2% of the patients on the day of amniocentesis. The placenta was posterior in 51.5% of patients and anterior in 40.9% of patients. An adequate amount of fluid was obtained in 123 (93.2%) patients with a single needle entry and in nine (6.8%) with two needle insertions. Two needle insertions were performed in six patients because they moved during the procedure, causing the angle of the needle to change, and in three patients, the fetal position changed. Ultrasonographic features of the patients and the number of interventions performed on the patients are shown in Table 1.

QF-PCR and chromosome analysis were performed on the samples taken from all patients. During the period when the genetics laboratory was able to work, CMA in 41 patients, molecular deletion duplication analysis for Duchenne Muscular Dystrophy (DMD) in two patients, molecular deletion duplication analysis for Spinal Muscular Atrophy (SMA) in one patient, 22q11.2 deletion analysis by Fluorescent in situ hybridization (FISH) method in four patients, and PTPN11 whole

Table 1: Ultrasonographic features of the patients and the number of interventions performed on the patients

Classification	Number of patient (n)	%
Pregnancy		
Single	129	97.7
Twin	3	2.3
Amniotic Fluid Index		
Adequate	127	96.2
Polyhydramniosis	4	3.0
Oligohydramnios	1	0.8
Placenta		
Posterior	68	51.5
Anterior	54	40.9
Lateral	10	7.6
Number of puncture		
1	123	93.2
2	9	6.8

Table 2: Examinations requested from the patients

	Number of patient (n)
Chromosome analysis	132
QF-PCR	132
CMA	41
22q11.2 deletion analysis	4
PTPN11 whole gene analysis	3
Molecular deletion duplication analysis for DMD	2
Molecular deletion duplication analysis for SMA	1

CMA: Chromosomal microarray analysis; DMD: Duchenne muscular dystrophy; QF-PCR: Quantitative fluorescent polymerase chain reaction; SMA: Spinal muscular atrophy.

gene analysis for Noonan Syndrome in three patients were studied. The examinations requested from the patients are shown in Table 2.

Fetal structural anomalies were the most common indication for amniocentesis in 51 (38.6%) patients. Eight of them (15.7%) were found to have a chromosomal anomaly. Among the fetal anomalies, 39.2% were central nervous system anomalies, 19.6% were cardiac anomalies, 19.6% were multiple system anomalies, and 11.8% were diaphragmatic hernia anomalies. The second most common indication for amniocentesis was 47 (35.6%) patients with high risk in the combined test, triple screening test, and non-invasive prenatal test (NIPT). A chromosomal anomaly was detected in five (10.6%) of these cases. Increased NT 7.6%, cystic hygroma 5.3%, hydrops fetalis 3.8%, genetic disease in the previous child 3.8%, carrier of genetic disease in the mother 2.3%, multiple soft markers 1.5%, advanced maternal age other amniocentesis indications were 1.5%. The distribution of amniocentesis indications in the patients is shown in Table 3.

Table 3: Indications of amniocentesis

Indication	Number of patient (n)	%
Fetal structural anomaly	51	38.6
High risk in prenatal triple screening test	25	18.9
High risk in prenatal combined screening test	20	15.2
Increased NT	10	7.6
Cystic hygroma	7	5.3
Hydrops fetalis	5	3.8
Genetic disease in the previous child	5	3.8
Carrier of genetic disease in the mother	3	2.3
Multiple soft markers	2	1.5
Advanced maternal age	2	1.5
High risk in NIPT	2	1.5

NIPT: Non-invasive prenatal test; NT: Nuchal translucency.

In QF-PCR, no result could be obtained in one (0.8%) of the patients. Maternal contamination was detected in one (0.8%) patient. Trisomy 21 and 18 were detected most frequently in QF-PCR. The QF-PCR and amniocyte culture results of the patients are shown in Table 4.

Culture results could not be obtained in two (1.5%) patients. The amniocentesis karyotype culture success rate was 98.5%. The rate of chromosomal anomaly in culture results was found to be 18.2% (24/132). Numerical anomalies were detected most frequently with 18 (74.8%) cases among chromosomal anomalies in culture. Trisomy 21 (33.2%) and Trisomy 18 (29.0%) were the most common numerical anomalies. QF-PCR and amniocyte culture results are shown in Table 4, and the distribution of chromosomal abnormalities in culture is shown in Table 5.

Abnormal results were obtained in four (9.8%) of 41 patients for whom CMA was requested. Two (4.9%) of the CMA results were found to be pathogenic and two (4.9%) were in the variant of uncertain significance (VUS) classification.

Hemizygous duplication, which would be compatible with DMD clinic, was found in one of the 10 pregnant women who requested 22q11.2 deletion analysis, PTPN11 whole gene analysis, DMD molecular deletion duplication analysis, and molecular deletion duplication analysis for SMA.

All patients who were found to have chromosomal anomalies as a result of amniocentesis were informed about the prognosis, pregnancy outcomes, and pregnancy termination options. Genetic consultation was requested for all patients. The most common indication for amniocentesis in pregnant women with chromosomal anomalies was anomalies found in the fetus. A total of 13 patients terminated their pregnancies upon their and their husband's request. The pregnancies of three patients with trisomy 21 were terminated

Table 4: QF-PCR and amniocyte culture results of patients

QF-PCR results	n	%	Culture results	n	%
No aneuploidy	115	87.1	Normal karyotype	106	80.3
Trisomy 21	8	6.0	Numerical anomalies	18	13.7
Trisomy 18	7	5.3	Structural anomalies	4	3.0
Maternal contamination	1	0.8	Structural ve numerical anomalies	2	1.5
No result	1	0.8	No result	2	1.5

QF-PCR: Quantitative fluorescent polymerase chain reaction.

Table 5: Distribution of chromosomal abnormalities in culture (n=24)

Numerical anomalies (74.8%)			Structural anomalies (16.8%)			Structural ve numerical anomalies (8.4%)		
Results	**n**	**%**	**Results**	**n**	**%**	**Results**	**n**	**%**
Trisomy 21	8	33.2	46....ins(4;2)(q25;p12p2?)	1	4.2	47.X*.+mar[2]/46.X*[83]	1	4.2
Trisomy 18	7	29.0	46.X*.der(7)add(7)(q22)	1	4.2	47.X*.der(12)i(12)(p10)[79]/46.X*[6]	1	4.2
45.X[2]/46.X*[77]	1	4.2	46.X*.inv(9)(p11q13)	1	4.2			
47.X*.+13[1]/46.X*[134]	1	4.2	46.X*.15ps+	1	4.2			
45.X[1]47.X*.+21[1]/47.X*.+13[1]/46.X*[119]	1	4.2						

add: Addition; der: Derivative; ins: Insertion; inv: Inversion; mar: Marker chromosome; ps+: Satellite increase in the p arm of the chromosome.

upon their request. Four patients with trisomy 21 gave live birth. A patient who wanted to continue her pregnancy had a stillbirth due to the intrauterine death of the fetus in the third trimester. Pregnancies of five patients with trisomy 18 were terminated upon their request. Two patients with trisomy 18 wanted to continue their pregnancies and had stillbirths due to intrauterine death of the fetuses in the third trimester. Amniocentesis indications and pregnancy results of patients with chromosomal abnormalities as a result of amniocentesis are shown in Table 6.

No maternal and fetal complications related to the amniocentesis procedure were detected.

Of the patients included in our study, 129 (97.7%) were singleton pregnancies and three (2.3%) were dichorionic diamniotic twin pregnancies. Amniocentesis was performed after polyhydramnios, inlet type ventricular septal defect (VSD), and choroid plexus cyst were detected in one baby of one of the twins. Trisomy 18 was detected in the baby with the anomaly. The patient did not accept the selective fetocide procedure. In the follow-up of the patient, the fetus with trisomy 18 was found to be intrauterine exitus at the 28th gestational week. The patient gave birth at term. Amniocentesis was performed because NT increase was detected in one of the fetuses in the other twin pregnancy. Trisomy 21 was detected in the fetus with increased NT. The patient did not accept the selective fetocide procedure. In the follow-up, the patient gave birth at 32 weeks of gestation.

DISCUSSION

Amniocentesis is usually done for prenatal diagnosis between the 15th-20th weeks of pregnancy. It is a more reliable procedure than other diagnostic methods with a 0.1% risk of failed culture and a risk of fetal loss of 0.1%.[8] No fetal or maternal complications were found in our study. Since the complication rate due to amniocentesis is generally low, the evaluation of complications related to amniocentesis in multicenter studies or studies with more participants will enable us to obtain more accurate results.

In our study, the most common indications for amniocentesis were fetal anomalies (38.6%) and high risk in screening tests (35.6%). In a study that included 12,365 patients who underwent amniocentesis, the most common indications for amniocentesis were found to be abnormal screening tests (40.1%), advanced maternal age (34.5%), and anomaly on US (8.1%).[10] In another study evaluating 632 patients who underwent amniocentesis, it was found that abnormal screening tests (72.6%)

Table 6: Amniocentesis indications and pregnancy outcomes of patients with chromosomal anomaly as a result of amniocentesis

Maternal age (year)	Gestational age (week+day)	Indication	Karyotypes	Pregnancy outcome
46	15+0	High risk in NIPT	Trisomy 21	Termination
43	20+0	High risk in NIPT	Trisomy 21	Termination
34	16+5 (twin pregnancy)	Increased NT in one of the fetuses	One fetus Trisomy 21 + other fetus normal karyotype	Delivery
36	16+0	High risk in prenatal combined screening test	Trisomy 21	Delivery
34	17+0	High risk in prenatal combined screening test	Trisomy 21	Delivery
31	19+0	Hypoplastic nasal bone	Trisomy 21	Termination
22	17+1	Cystic hygroma	Trisomy 21	Delivery
36	17+3	High risk in prenatal triple screening test	Trisomy 21	Stillbirth at 36th gestational week
40	16+0	Cystic hygroma	Trisomy 18	Stillbirth at 34th gestational week
26	20+5	Clubfoot + choroid plexus cyst + polyhydramniosis	Trisomy 18	Termination
38	20+5 (twin pregnancy)	Ventricular septal defect + choroid plexus cyst + polyhydramniosis in one of the fetuses	One fetus Trisomy 18 + other fetus normal karyotype	Anomaly fetus intrauterine ex at 28th gestational week + Other fetus live birth
38	20+3	Hypoplastic nasal bone + clenched hands + polyhydramniosis	Trisomy 18	Termination
22	16+3	Cystic hygroma	Trisomy 18	Termination
28	20+2	Ventricular septal defect + choroid plexus cyst + polyhydramniosis + clenched hand + single umbilical artery	Trisomy 18	Termination
36	19+2	Ventricular septal defect + choroid plexus cyst + polyhydramniosis + clenched hand	Trisomy 18	Termination
25	15+1	Cystic hygroma + omphalocele	46....ins(4;2)(q25;p12p2?) + arr[GRCh38] 2p24.2p24.1(18761580-20227386)x1	Termination
28	17+1	Cystic hygroma + diaphragmatic hernia	47.X*.der(12)i(12)(p10)[79]/46.X*[6] +arr [GRCh38] 12p13.33p11.1(64.62134.629.700)x4mos	Termination
35	17+6	Paternal DiGeorge Syndrome	arr[GRCh37]22q11.21(18844632_21462353)x1	Delivery
35	18+1	Dandy-Walker Syndrome	46.X*.der(7)add(7)(q22)	Termination
24	20+5	High risk in prenatal combined screening test	45.X[2]/46.X*[77]	Delivery
21	20+4	Open spina bifida	46.X*.inv(9)(p11q13)	Termination
20	16+0	Maternal DMD carrier	Hemizygous duplication in the DMD gene	Termination

NIPT: Non-invasive prenatal test; NT: Nuchal translucency; add: Addition; der: Derivative; ins: Insertion; inv: Inversion; DMD: Duchenne muscular dystrophy.

and anomaly detection on US (12.8%) were the most common indications for amniocentesis.[11] In their study, Güven et al.[12] found that the most common indication for amniocentesis was abnormal screening tests, with a rate of 43%. In another study, the most common indication for amniocentesis was found to be abnormal screening tests, with a rate of 29.9%.[13] Fetal structural anomalies were the most common cause of amniocentesis in our study. This may be due to the fact that our center serves as a tertiary center for neighboring provinces and that all anomalies detected in fetuses in these regions were referred to our center.

In our study, the number of pregnant women who underwent NIPT, which has had the highest success among screening tests in recent years, was found to be only two. It was thought that the fact that it was an expensive test in our country and that it was not covered by the social security institution caused it to not be used widely.

In our study, the amniocentesis culture success rate was found to be 98.5%. In their study, Acar et al.,[14] which analyzed 3721 patients, found the culture success rate to be 99.3%, similar to our study. In another study performed by Tao et al.,[15] evaluating 4761 patients, the success rate of culture was found to be 98.3%. Balcı et al.[16] and Gündüz et al.[11] found a culture success rate of 97.9%. The culture success rate in our study is consistent with the literature.

In our study, the rate of chromosomal anomalies was found to be 18.2%, and numerical anomalies were the most common. Acar et al.[14] found the chromosomal anomaly rate to be 3.6%, which is lower than our study. In the same study, similar to our study, it was found that 80.9% of chromosomal anomalies were numerical anomalies and Trisomy 21 was the most common of these. Tao et al.[15] determined the rate of chromosomal anomaly as 2.8% and stated that 89.1% of them were numerical and 10.9% were structural anomalies. Gündüz et al.[11] reported the rate of chromosomal anomaly in their study as 22.4%, similar to our study. In the same study, unlike our study, numerical anomalies were found in 30.2% and structural anomalies in 69%. There are different rates in the studies conducted in the literature. We thought that the indications for performing amniocentesis, the technique of performing amniocentesis, and the rates depending on the laboratory where the material was studied may vary. We thought that the high rate of chromosomal anomaly detected in our study was due to the fact that we are a tertiary center serving a large population and that our most common indication for amniocentesis is fetal anomalies.

There are studies in the literature that found the rate of chromosomal anomaly to be seen in fetuses found to have an anomaly on US between 6.8% and 27.1%.[17,18] The inclusion of soft markers in abnormal US findings in some studies may decrease the rate of detected chromosomal abnormalities. Soft markers were not evaluated as fetal anomalies in our study. We thought that this caused a high rate of chromosomal anomaly in patients who underwent amniocentesis due to fetal anomaly.

Hsiao et al.[19] found chromosomal anomalies in 10.6% of pregnant women and pathological chromosomal anomalies in 2.9% of pregnant women. CMA is especially requested in cases where the fetal anomaly is detected in US. It was thought that the fact that it is an expensive test in our country and that it is not studied in some genetic laboratories caused the test not to be widely used. More studies on CMA will be done as its use becomes more widespread.

The limitation of our study is the lower number of patients compared to some other studies conducted in our country. It was thought that the low number of amniocentesis performed may be due to the region not wanting to have an amniocentesis done due to socio-economic and socio-cultural factors. Obtaining the data from a single center increases confidence in the results and creates the superiority of the study.

CONCLUSION

In our study, the rate of chromosomal anomaly was found to be 18.2%. Our most common indication for amniocentesis was fetal anomalies detected on US. There were no maternal or fetal complications related to amniocentesis. Amniocentesis is a very reliable and successful prenatal diagnostic test.

Statement

Ethics Committee Approval: The Van Yüzüncü Yıl Clinical Research Ethics Committee granted approval for this study (date: 14.04.2023, number: 2023/04-05).

Author Contributions: Concept – HGŞ, MB, KU; Design – HGŞ, EK; Supervision – HGŞ, MB, EK; Resource – MB; Materials – KU; Data Collection and/or Processing – OK, YB; Analysis and/or Interpretation – OK; Literature Search – YB, MB; Writing – MB, KU, YB; Critical Reviews – EK, OK.

Conflict of Interest: The authors have no conflict of interest to declare.

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REFERENCES

1. McCormick AC, McIntosh JJ, Gao W, Hibbard JU, Cruz MO. The impact of fetal anomalies on contemporary labor patterns. Am J Perinatol 2019;36:1423–30.
2. Staebler M, Donner C, Van Regemorter N, Duprez L, De Maertelaer V, Devreker F, et al. Should determination of the karyotype be systematic for all malformations detected by obstetrical ultrasound? Prenat Diagn 2005;25:567–73.
3. Bijok J, Massalska D, Kucińska-Chahwan A, Posiewka A, Ilnicka A, Jakiel G, et al. Complex malformations involving the fetal body wall - definition and classification issues. Prenat Diagn 2017;37:1033–9.
4. Drugan A, Johnson MP, Evans MI. Amniocentesis. In: Evans MI, editor. Reproductive risks and prenatal diagnosis. Norwalk, CT: Appleton & Lange; 1992. p.191–200.
5. Steele MW, Breg WR Jr. Chromosome analysis of human amniotic-fluid cells. Lancet 1966;1:383–5.
6. Practice Bulletin No. 162: Prenatal diagnostic testing for genetic disorders. Obstet Gynecol 2016;127:e108–22.
7. Hoehn H, Bryant EM, Karp LE, Martin GM. Cultivated cells from diagnostic amniocentesis in second trimester pregnancies. I. Clonal morphology and growth potential. Pediatr Res 1974;8:746–54.
8. Ghi T, Sotiriadis A, Calda P, Da Silva Costa F, Raine-Fenning N, Alfirevic Z, et al. ISUOG Practice Guidelines: Invasive procedures for prenatal diagnosis. Ultrasound Obstet Gynecol 2016;48:256–68.

9. Nicolaides KH. 11-13+6 weeks scan. London: Fetal Medicine Foundation: 2004. p.7-110.
10. Xiao H, Yang YL, Zhang CY, Liao EJ, Zhao HR, Liao SX. Karyotype analysis with amniotic fluid in 12365 pregnant women with indications for genetic amniocentesis and strategies of prenatal diagnosis. J Obstet Gynaecol 2016;36:293–6.
11. Gündüz R, Yaman Tunç S, Buğday R, Oral D, Tekeş S, Yalınkaya A. İkinci trimester amniyosentez olgularının değerlendirilmesi: Tersiyer bir merkezin 10 yıllık deneyimi. Perinatol Derg [Article in Turkish] 2021;29:63–70.
12. Güven MA, Ceylaner S. Amniyosentez ve kordosentez ile prenatal tanı: 181 olgunun değerlendirilmesi. Perinatol Derg [Article in Turkish] 2005;13:25–30.
13. Timur A, Uyar İ, Gülhan İ, Saz NT, İleri A, Özeren M. Genetik amniyosentez yapılan 16-22 haftalık gebelerin amniyosentez sonuçlarının değerlendirilmesi. Perinatol Derg [Article in Turkish] 2013;21:101–6.
14. Acar A, Ercan F, Yıldırım S, Görkemli H, Gezginç K, Balcı O, et al. Genetic amniocentesis results: Analysis of the 3721 cases. Med Bull Sisli Etfal Hosp [Article in Turkish] 2016;50:33–8.
15. Tao H, Xiao J, Yang C, Wang J, Tang Y, Guo C, et al. Retrospective analysis of 4761 cases who underwent amniocentesis in southeast China. J Obstet Gynaecol 2018;38:38–41.
16. Balcı O, Büyükdoğan M, Özdemir S, Mahmoud AS, Acar A, Zamani A. The evaluation of amniocentesis cases made for genetic examination in one-year period. Selçuk Üniv Tıp Derg [Article in Turkish] 2011;27:6–10.
17. Rizzo N, Pittalis MC, Pilu G, Orsini LF, Perolo A, Bovicelli L. Prenatal karyotyping in malformed fetuses. Prenat Diagn 1990;10:17–23.
18. Dallaire L, Michaud J, Melancon SB, Potier M, Lambert M, Mitchell G, et al. Prenatal diagnosis of fetal anomalies during the second trimester of pregnancy: Their characterization and delineation of defects in pregnancies at risk. Prenat Diagn 1991;11:629–35.
19. Hsiao CH, Chen JS, Shiao YM, Chen YJ, Chen CH, Chu WC, et al. Prenatal diagnosis using chromosomal microarray analysis in high-risk pregnancies. J Clin Med 2022;11:3624.

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ORIGINAL ARTICLE

Predictive value of first-trimester screening tests (PAPP-A and free βhCG) for placenta previa and placenta accreta spectrum disorders

[1]Çiğdem YAYLA ABİDE
[2]Çetin KILIÇÇI
[3]Önder SAKİN
[2]Resul KARAKUŞ
[2]Belgin DEVRANOĞLU
[2]Aysel ÖCAL
[2]İrem ÇOKELİER

[1]Department of Obstetrics and Gynecology, Uskudar University Faculty of Medicine, Istanbul, Turkey

[2]Department of Obstetrics and Gynecology, University of Health Sciences, Turkey. Istanbul Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center, Istanbul, Turkey

[3]Department of Obstetrics and Gynecology, Bahceci Umut IVF Center, Istanbul, Turkey

ORCID ID
ÇYA : 0000-0001-5437-7987
ÇK : 0000-0002-9674-2505
ÖS : 0000-0001-6036-9975
RK : 0000-0001-7386-3833
BD : 0009-0007-0711-9679
AÖ : 0000-0002-1491-4079
İÇ : 0000-0002-6195-8090

ABSTRACT

Objective: Placenta previa and the placenta accreta spectrum (PAS) represent critical conditions in pregnant women, carrying a life-threatening risk of bleeding and adverse obstetric outcomes. Timely diagnosis and intervention play a pivotal role in mitigating the potential risks associated with these conditions. Our study seeks to evaluate the significance of serum pregnancy-associated plasma protein-A (PAPP-A) and beta-human chorionic gonadotropin (βhCG) as early biomarkers for predicting placenta accreta spectrum disorders and placenta previa. This research is essential as further investigations are warranted to enhance our understanding of this significant medical condition.

Material and Methods: A retrospective study was carried out on 254 pregnant individuals with placenta previa who underwent cesarean section delivery at our hospital. Excluding 187 pregnant women who had placenta previa with or without placenta accreta spectrum but lacked PAPP-A and βhCG test results in the second trimester, the study focused on 30 cases of placenta previa with PAS, 37 cases of placenta previa without PAS, and 30 cases of body mass index (BMI)-matched healthy pregnant controls with available second-trimester test results. The comparison of PAPP-A and βhCG MoMs (Multiples of the Median) between these groups was conducted to assess significant differences.

Results: The ages of the individuals ranged from 22 to 41 years, with a mean of 32.29±4.14 years. BMI measurements ranged from 18 to 40 kg/m^2, with a mean of 26.22±4.48 kg/m^2. BMI, PAPP-A, and βhCG measurements did not show statistically significant differences between the groups ($p>0.05$). The mean age of the PAS group was significantly higher than that of the control group ($p<0.05$).

Conclusion: Our study did not find significant predictive value for PAPP-A and βhCG in placenta accreta spectrum. However, conflicting results from previous studies suggest the need for further research. Larger prospective studies are necessary to clarify the role of these biomarkers.

Keywords: Abnormally invasive placentation, free βhCG, placenta accreta spectrum, placenta previa, pregnancy-associated plasma protein-A.

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Correspondence: Çiğdem YAYLA ABİDE, MD. Üsküdar Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, İstanbul, Türkiye.
Tel: +90 506 601 56 00 **e-mail:** cigdemabide@gmail.com

INTRODUCTION

The placenta accreta spectrum (PAS) represents a serious pregnancy disorder characterized by an abnormally firm attachment and deep infiltration of the placenta into the uterine layers.[1] Due to the increasing rates of cesarean sections (C/S) over the past two decades, the incidence of placenta accreta has increased approximately 13-fold.[2]

Clinically, PAS is associated with an increased risk of life-threatening maternal mortality, high rates of intrapartum hemorrhage, hysterectomy, blood transfusions, widespread coagulopathy, acute respiratory failure, renal failure, and postpartum hemorrhage.[3–5] While various surgical strategies can effectively minimize blood loss in the treatment of women diagnosed with PAS,[6] the key to successful management lies in the early identification of high-risk individuals.[7] Referral to a high-volume surgical center for women undergoing peripartum hysterectomy can also reduce maternal mortality rates by up to 70%.[8]

Preoperative management of PAS relies heavily on effective antenatal diagnosis, which typically involves the utilization of various imaging modalities. However, relying solely on radiological strategies, such as ultrasound technology and magnetic resonance imaging (MRI), may not be sufficient for accurate PAS diagnosis.[9] Also noteworthy is the observation that the sensitivity and specificity of these imaging techniques in detecting placenta accreta decrease significantly between the 15th and 20th weeks of gestation.[10] Therefore, the diagnosis of accreta necessitates a high-resolution setting and well-trained clinicians.[11]

Due to the ongoing debates regarding the reliability of currently available imaging modalities, the utilization of biomarkers has been proposed as an adjunct for the prediction of PAS risk. This approach is recommended because it offers several advantages, including convenience, repeatability, and ease of comparison.[12] For the purpose of validating a PAS diagnosis, several biomarkers, such as PAPP-A and βhCG, have been investigated for their usefulness in predicting PAS risk.[12–14]

The aim of our study was to evaluate the diagnostic value of serum PAPP-A and βhCG levels for the prediction of placenta accreta spectrum.

MATERIAL AND METHODS

The study cohort consisted of 254 pregnant women admitted to the Zeynep Kamil Maternity and Children Training and Research Hospital with a diagnosis of either placenta previa alone or placenta accreta concurrent with placenta previa and who had delivered between December 2015 and September 2021. Of these patients, only those with available first-trimester screening test results were included in the study. The patients were categorized into four groups: 1) placenta previa with PAS (PAS group), 2) placenta previa without PAS, 3) a control group consisting of healthy pregnant women with a history of previous cesarean section and normal placental location, and 4) a previa group that included all pregnant patients with placenta previa with and without PAS.

The first-trimester PAPP-A and BhCG MoM values were compared between these groups, particularly with the control group. The control group comprised patients who had undergone cesarean section after completing a 37-week pregnancy, were free of any diseases, and did not exhibit either previa or accreta.

Patients with placenta previa and coexisting accreta (PAS Group) were categorized based on histopathological examination results for those who had undergone hysterectomy or segmental resection and based on surgical records for those who were managed conservatively.

The Institutional Review Board of the Zeynep Kamil Maternity and Children Training and Research Hospital approved the study protocol. The study was conducted in accordance with the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000.

Demographic and obstetric data were gathered from the surgical and prenatal follow-up records within the patient database of Zeynep Kamil Maternity and Children Training and Research Hospital. These parameters included the gestational age at delivery, previous delivery mode, requirement for blood transfusion during cesarean section, and newborn birth weight.

The exclusion criteria included pregnant women without clinical and first-trimester screening test records and those with multiple pregnancies, fetal chromosomal abnormalities, miscarriages or stillbirths, and diagnoses of diabetes, hypertension, or preeclampsia.

Multiples of the median (MoM) values for βhCG and PAPP-A were extracted from first-trimester screening test reports. The maternal serum markers were measured using automated equipment (Clinical Laboratory Improvement Amendments CLIA kit). The MoM values of the markers were adjusted for gestational age, maternal weight, diabetes, and smoking status using logistic regression analysis.

Statistical Analysis

In the evaluation of the findings obtained in the study, IBM SPSS Statistics 22.0 software was utilized for statistical analysis. The normal distribution of parameters was assessed using the Kolmogorov-Smirnov test. For parameters demonstrating normal distribution, group comparisons were conducted using the One-Way ANOVA test, and the Post-Hoc Tukey HSD test was employed to identify the source of differences. Group comparisons of parameters not showing normal distribution were performed using the Kruskal-Wallis test. For comparisons between two groups of parameters demonstrating normal distribution, the Student's t-test was used, while the Mann-Whitney U test was employed for parameters not exhibiting normal distribution. The Chi-square test was used for the evaluation of qualitative data. Significance was evaluated at the $p<0.05$ level.

RESULTS

The study was conducted with a total of 97 cases: 30 were in the control group and 67 were in the previa group. All included patients were treated at our hospital between the years 2015 and 2021. The ages of the cases ranged from 22 to 41 years, with a mean age of 32.29±4.14 years. BMI measurements ranged from 18 to 40 kg/m², with a mean of 26.22±4.48 kg/m². No statistically significant differences were detected in BMI, PAPP-A, and fβhCG measurements between the groups ($p>0.05$) (Table 1).

The mean age was statistically significantly higher in the previa group than in the control group ($p<0.01$) (Table 1). The mean birth weight was statistically significantly higher in the control group than

Table 1: Evaluations according to groups

	Control (n=30)	Previa (n=67)	p
Age (years), Mean±SD	30.57±2.57	33.06±4.47	[1]0.001**
Body mass index (k/m^2), Mean±SD	25.34±3.95	26.64±0.69	[1]0.208
PAPP-A (MoM), Mean±SD (Median)	1.04±0.46 (1.01)	1.23±0.96 (0.99)	[2]0.785
βhCG (MoM), Mean±SD (Median)	0.96±0.43 (0.86)	1.17±0.75 (0.85)	[2]0.437
Birth weight (gram), Mean±SD	3173.33±420.63	2572.38±712.04	[1]0.001**
Gestational week at delivery, Mean±SD	38.20±1.27	34.62±3.44	[1]0.001**
Ceserean history, n (%)			[5]0.019*
0	8 (26.7)	31 (46.3)	
1	18 (60)	20 (29.9)	
≥2	4 (13.3)	16 (23.9)	
Blood transfusion, n (%)			[5]0.001**
–	30 (100)	35 (53)	
+	0 (0)	31 (47)	

1: Student t Test; 2: Mann-Whitney U test; 5Ki-Kare test; *: P<0.05; **: P<0.01; n: Number; PAPP-A: Pregnancy-associated plasma protein-A; MoM: Multiples of the median; βhCG: Beta-human chorionic gonadotropin.

Table 2: Evaluations according to groups

	Control (n=30)	Plasenta previa without PAS (n=37)	Placenta previa with PAS (n=30)	p
Age (years), Mean±SD	30.57±2.57	32.86±4.29	33.30±4.76	[3]0.020*
Body mass index (k/m^2), Mean±SD	25.34±3.95	25.76±4.21	27.75±5.08	[3]0.106
PAPP-A (MoM), Mean±SD (Median)	1.04±0.46 (1.01)	1.29±1.13 (0.99)	1.16±0.70 (0.99)	[4]0.963
βhCG (MoM), Mean±SD (Median)	0.96±0.43 (0.86)	1.08±0.72 (0.84)	1.27±0.79 (1.06)	[4]0.379
Birth weight (gram), Mean±SD	3174.3±420.6	2680.2±709.6	2434.8±703.3	[3]0.001**
Gestational week at delivery Mean±SD	38.20±1.27	35.41±3.42	33.62±3.26	[3]0.001**
Ceserean history, n (%)				[5]0.001**
0	8 (26.7)	25 (67.6)	6 (20)	
1	18 (60)	12 (32.4)	8 (26.7)	
≥2	4 (13.3)	0 (0)	16 (53.3)	
Blood transfusion, n (%)				[5]0.001**
–	30 (100)	31 (83.8)	4 (13.8)	
+	0 (0)	6 (16.2)	25 (86.2)	

3: Oneway ANOVA Test; 4: Kruskall Wallis H Test; 5: Ki-Kare Test; *: P<0.05; **: P<0.01; n: Number; PAPP-A: Pregnancy-associated plasma protein-A; MoM: Multiples of the median; βhCG: Beta-human chorionic gonadotropin.

in the previa group (p<0.01) (Table 1). The gestational age at birth was statistically significantly higher in the control group than in the previa group (p<0.01) (Table 1). A statistically significant difference in the rates of blood transfusion was determined between the groups (p<0.01), with the rate of blood transfusion significantly higher in the previa group than in the control group (Table 1).

A statistically significant difference was also detected in the mean ages between the groups (p<0.05). Pairwise comparisons to determine the source of this difference revealed that the mean age was significantly higher in the PAS group than in the control group (p<0.05). No significant difference was noted in the mean ages between the placenta previa without PAS group and control group (p>0.05) (Table 2).

Table 3: Evaluations according to groups

	Control (n=30)	With hysterectomy (n=53)	Without hysterectomy (n=14)	p
Age (years), Mean±SD	30.57±2.57	33.11±4.12	32.86±5.81	[3]0.021*
Body mass index (k/m^2), Mean±SD	25.34±3.95	26.37±4.58	27.69±5.16	[3]0.300
PAPP-A (MoM), Mean±SD (Median)	1.04±0.46 (1.01)	1.24±1.01 (0.99)	1.21±0.78 (1.04)	[4]0.951
βhCG (MoM), Mean±SD (Median)	0.96±0.43 (0.86)	1.07±0.66 (0.84)	1.52±0.99 (1.45)	[4]0.249
Birth weight (gram), Mean±SD	3174.33±420.63	2603.98±769.92	2455.0±436.63	[3]0.001**
Gestational week at delivery, Mean±SD	38.20±1.27	34.92±3.73	33.50±1.65	[3]0.001**
Ceserean history, n (%)				[5]0.001**
0	8 (26.7)	30 (56.6)	1 (7.1)	
1	18 (60)	17 (32.1)	3 (21.4)	
≥2	4 (13.3)	6 (11.3)	10 (71.4)	
Blood transfusion, n (%)				[5]0.001**
–	30 (100)	34 (65.4)	1 (7.1)	
+	0 (0)	18 (52)	13 (92.9)	

3: Oneway ANOVA Test; 4: Kruskall Wallis H Test; 5: Ki-Kare Test; *: P<0.05; **: P<0.01; n: Number; With Hysterectomy:Hysterectomy (+); With Hysterectomy:Hysterectomy (-); PAPP-A: Pregnancy-associated plasma protein-A; MoM: Multiples of the median; βhCG: Beta-human chorionic gonadotropin.

A statistically significant difference was found in birth weights between the groups (p<0.01). Pairwise comparisons to determine the source of the difference revealed that the mean birth weight was significantly higher in the control group than in either the placenta previa without PAS group or the PAS group (Table 2).

A statistically significant difference was determined in the gestational ages at birth between the groups (p<0.01). Pairwise comparisons to determine the source of the difference showed that the mean gestational age at birth was significantly higher in the control group than in either the placenta previa without PAS group or the PAS group. The gestational age at birth was also significantly higher in the placenta previa without PAS group than in the PAS group (Table 2).

A statistically significant difference was observed in the history of C/S between the groups (p<0.01). The number of C/S cases was significantly higher in the PAS group than in either the control group or the placenta previa without PAS group (Table 2).

A statistically significant difference was detected in the rates of blood transfusion between the groups (p<0.01). The rate of blood transfusion was significantly higher in the PAS group than in either the control or the placenta previa without PAS group (Table 2).

The mean birth weight of the control group was significantly higher than both the Hysterectomy (-) and Hysterectomy (+) groups. Additionally, the mean gestational age of the control group was significantly higher than both the Hysterectomy (-) and Hysterectomy (+) groups. The C-section rate in the Hysterectomy (+) group was significantly higher than both the control group and the Hysterectomy (-) group (Table 3).

DISCUSSION

Disorders within the placenta accreta spectrum represent a range of abnormalities in placental attachment. Subtypes of PAS include placenta accreta (creta or adherenta, PA), placenta increta (PI), and placenta percreta (PP). The incidence of PAS has undergone a dramatic increase in recent years. A study by Matsuzaki et al.[15] reported a prevalence of PAS of 0.29% among women undergoing cesarean delivery with live births in the United States. Women diagnosed with PAS face elevated risks of hemorrhage, bladder and urinary tract injuries, and the need for hysterectomy during childbirth. Early and accurate diagnosis, along with appropriate treatment planning for PAS pregnancies, is of paramount importance for preoperative multidisciplinary management and planning of PAS deliveries.

A diagnosis of PAS is preferably made through ultrasonographic evaluation, although this is operator-dependent and limited in terms of accuracy in determining the degree of posterior placental invasion and parametrial extension. In these situations, magnetic resonance imaging (MRI) is helpful, but MRI is not recommended as a routine diagnostic approach due to its high cost and limited clinical value.[16] Thus, the true performance of MRI remains to be confirmed by independent studies.[17]

At present, radiological strategies, such as ultrasound technology, remain the primary approach for diagnosing PAS. Early prediction of PAS in pregnancy therefore relies primarily on the position of the gestational sac, but this may not provide sufficient information for a diagnosis of PAS.[18] Improving the diagnosis, assessing the severity of PAS, and predicting perioperative outcomes still require further exploration of additional diagnostic methods. In this respect, the process of detecting maternal circulation biomarkers offers an objective, non-invasive, and cost-effective method for PAS diagnosis.

Some studies have shown that biomarkers may have potential significance in the diagnosis of PAS. However, no biomarker has yet been definitively proven useful in PAS diagnosis; therefore, these biomarkers are not yet utilized in clinical practice. Nevertheless, due to the importance of early diagnosis, research on biomarkers for the early detection of PAS is continuing to increase.[16] Unlike imaging methods, which can only establish a diagnosis in advanced gestational weeks, numerous serum markers have been investigated to make earlier diagnoses.[2–4,13–18] Of these markers, PAPP-A and fβhCG are considered placental markers and have been utilized in multifactorial tests aimed at predicting placental function.[19]

Although the exact function of PAPP-A remains incompletely understood, it is known to participate in the proteolysis of insulin-like growth factor-binding protein 4 (IGFBP-4), suggesting a role for PAPP-A in placental growth. Physiologically, placental syncytiotrophoblasts secrete PAPP-A in increasing concentrations into the maternal circulation,[20] where it acts as a zinc metalloproteinase. Additionally, PAPP-A may serve as a potential marker for healthy placental trophoblasts,[21] as it is overexpressed in the first trimester and may be involved in trophoblast invasion that could lead to the pathogenesis of PAS.[22]

A recent meta-analysis assessed eight research studies (seven retrospective and one prospective) involving 243 PAS patients and 1599 non-PAS pregnant women. The age range was between 32 and 35 years, and the MoM values were compared. Five studies reported an association between PAPP-A and PAS, while three studies found no clear association. The limitations of the meta-analysis included the small number of patients, the reliance on mostly retrospective studies and, most importantly, the inability to confirm a causal relationship between high PAPP-A levels and the development of PAS during pregnancy. Based on the meta-analysis results, the authors concluded that further studies are needed to investigate the optimal cut-off points for serum PAPP-A levels in the first trimester when attempting to use PAPP-A as a predictor of PAS.[7] In our study, neither the BMI nor the PAPP-A or free βhCG measurements showed statistically significant differences between any of the groups ($p>0.05$).

Serum levels of free beta hCG (fβhCG) have also been proposed as another PAS indicator in the first trimester. The screening test probes for the beta subunit of the glycoprotein hormone hCG. While predominantly produced by syncytiotrophoblasts, this hormone is also synthesized by fetal kidney and liver tissues. Thus, the concentrations of fβhCG gradually increase during early pregnancy, peaking between the 8th and 10th weeks of gestation. Besides sustaining the function of the corpus luteum, fβhCG also plays a role in promoting angiogenesis, cytotrophoblast differentiation, immunosuppression, and inhibiting the phagocytosis of invading trophoblast cells.[23,24]

Several studies in the literature have assessed βhCG levels. For example, Desai et al.[13] did not observe a significant difference in first-trimester βhCG levels in their PAS group. By contrast, two other studies indicated increases in βhCG MoM values of up to 1.5 times in cases of accreta.[14,25] The latter authors concluded that βhCG MoM values still exhibit differences and require further evaluation through advanced research.[13] In the present study, our results indicated no significant differences in the βhCG MoM values in our groups.

The disadvantage of using biomarkers, such as PAPP-A and βhCG, for the diagnosis of PAS is that these biomarkers are often not specific to PAS and are also associated with other comorbidities and adverse complications that can arise during pregnancy.[26,27] In addition, PAPP-A levels are influenced by ethnic origin and BMI.[7,13,14,28,29] In our study, the pregnant women selected for the control group had similar ethnic backgrounds and their BMI averages were also within similar ranges, but we assumed that our study results were not influenced by these variables. Another finding in the literature is that PAS patients tend to be older. In our study, the average age of our patients was significantly higher in the PAS group than in the control group.

CONCLUSION

Whether PAPP-A and βhCG are involved in the pathogenesis of PAS remains unclear. Investigating these markers in combination with ultrasound and MRI may provide more useful information. Further prospective research is needed to evaluate these aspects of PAS.

Statement

Ethics Committee Approval: The Istanbul Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center Clinical Research Ethics Committee granted approval for this study (date: 23.06.2021, number: 134).

Author Contributions: Concept – ÇYA; Design – ÇYA; Supervision – ÇK, ÇYA; Resource – BD; Materials – RK; Data Collection and/or Processing – AÖ, ÇK, RK, İÇ; Analysis and/or Interpretation – BD, ÇK; Literature Search – ÖS, RK; Writing – ÇYA, ÖS; Critical Reviews – ÇYA, RK, ÖS.

Conflict of Interest: The authors have no conflict of interest to declare.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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REFERENCES

1. Silver RM, Branch DW. Placenta Accreta Spectrum. N Engl J Med 2018;378:1529–36.
2. Wu S, Kocherginsky M, Hibbard JU. Abnormal placentation: twenty-year analysis. Am J Obstet Gynecol 2005;192:1458–61.
3. Capannolo G, D'Amico A, Alameddine S, Di Girolamo R, Khalil A, Calì G, et al. Placenta accreta spectrum disorders clinical practice guidelines: A systematic review. J Obstet Gynaecol Res 2023;49:1313–21.
4. Einerson BD, Gilner JB, Zuckerwise LC. Placenta accreta spectrum. Obstet Gynecol 2023;142:31–50.
5. Publications Committee, Society for Maternal-Fetal Medicine; Belfort MA. Placenta accreta. Am J Obstet Gynecol 2010;203:430–9.
6. Dai M, Zhang F, Li K, Jin G, Chen Y, Zhang X. The effect of prophylactic balloon occlusion in patients with placenta accreta spectrum: A Bayesian network meta-analysis. Eur Radiol 2022;32:3297–308.
7. Li Y, Meng Y, Chi Y, Li P, He J. Meta-analysis for the relationship between circulating pregnancy-associated plasma protein A and placenta accreta spectrum. Medicine (Baltimore) 2023;102:e34473.
8. Wright JD, Herzog TJ, Shah M, Bonanno C, Lewin SN, Cleary K, et al. Regionalization of care for obstetric hemorrhage and its effect on maternal mortality. Obstet Gynecol 2010;115:1194–200.

9. Berkley EM, Abuhamad A. Imaging of placenta accreta spectrum. Clin Obstet Gynecol 2018;61:755–65.
10. Comstock CH, Love JJ Jr, Bronsteen RA, Lee W, Vettraino IM, Huang RR, et al Sonographic detection of placenta accreta in the second and third trimesters of pregnancy. Am J Obstet Gynecol 2004;190:1135–40.
11. Warshak CR, Eskander R, Hull AD, Scioscia AL, Mattrey RF, Benirschke K, et al. Accuracy of ultrasonography and magnetic resonance imaging in the diagnosis of placenta accreta. Obstet Gynecol 2006;108:573–81.
12. Bartels HC, Postle JD, Downey P, Brennan DJ. Placenta accreta spectrum: A review of pathology, molecular biology, and biomarkers. Dis Markers 2018;2018:1507674.
13. Desai N, Krantz D, Roman A, Fleischer A, Boulis S, Rochelson B. Elevated first trimester PAPP--a is associated with increased risk of placenta accreta. Prenat Diagn 2014;34:159–62.
14. Büke B, Akkaya H, Demir S, Sağol S, Şimşek D, Başol G, et al. Relationship between first trimester aneuploidy screening test serum analytes and placenta accreta. J Matern Fetal Neonatal Med 2018;31:59–62.
15. Matsuzaki S, Mandelbaum RS, Sangara RN, McCarthy LE, Vestal NL, Klar M, et al. Trends, characteristics, and outcomes of placenta accreta spectrum: A national study in the United States. Am J Obstet Gynecol 2021;225:534.e1–e38.
16. Guo Z, Yang H, Ma J. Maternal circulating biomarkers associated with placenta accreta spectrum disorders. Chin Med J (Engl) 2023;136:995–7.
17. Kapoor H, Hanaoka M, Dawkins A, Khurana A. Review of MRI imaging for placenta accreta spectrum: Pathophysiologic insights, imaging signs, and recent developments. Placenta 2021;104:31–9.
18. Shainker SA, Coleman B, Timor-Tritsch IE, Bhide A, Bromley B, Cahill AG, et al. Special report of the society for maternal-fetal medicine placenta accreta spectrum ultrasound marker task force: Consensus on definition of markers and approach to the ultrasound examination in pregnancies at risk for placenta accreta spectrum. Am J Obstet Gynecol 2021;224:B2–14.
19. Costa SL, Proctor L, Dodd JM, Toal M, Okun N, Johnson JA, et al. Screening for placental insufficiency in high-risk pregnancies: Is earlier better? Placenta 2008;29:1034–40.
20. Boldt HB, Conover CA. Pregnancy-associated plasma protein-A (PAPP-A): A local regulator of IGF bioavailability through cleavage of IGFBPs. Growth Horm IGF Res 2007;17:10–8.
21. Christians JK, Beristain AG. ADAM12 and PAPP-A: Candidate regulators of trophoblast invasion and first trimester markers of healthy trophoblasts. Cell Adh Migr 2016;10:147–53.
22. Illsley NP, DaSilva-Arnold SC, Zamudio S, Alvarez M, Al-Khan A. Trophoblast invasion: Lessons from abnormally invasive placenta (placenta accreta). Placenta 2020;102:61–6.
23. Cole LA. Biological functions of hCG and hCG-related molecules. Reprod Biol Endocrinol 2010;8:102.
24. Shi QJ, Lei ZM, Rao CV, Lin J. Novel role of human chorionic gonadotropin in differentiation of human cytotrophoblasts. Endocrinology 1993;132:1387–95.
25. Dreux S, Salomon LJ, Muller F, Goffinet F, Oury JF; ABA Study Group, et al. Second-trimester maternal serum markers and placenta accreta. Prenat Diagn 2012;32:1010–2.
26. Zhang T, Wang S. Potential serum biomarkers in prenatal diagnosis of placenta accreta spectrum. Front Med (Lausanne) 2022;9:860186.
27. Buhimschi IA, Zhao G, El Helou Y, Frye LJ, Winikoff B, Raymond EG. Analytical comparison of Pregnancy-Associated Plasma Protein-A (PAPP-A) immunoassays for biochemical determination of gestational age. J Appl Lab Med 2021;6:1517–32.
28. Jauniaux E, Grønbeck L, Bunce C, Langhoff-Roos J, Collins SL. Epidemiology of placenta previa accreta: A systematic review and meta-analysis. BMJ Open 2019;9:e031193.
29. Gagnon A, Wilson RD; Society of Obstetricians and Gynaecologists of Canada Genetics Committee. Obstetrical complications associated with abnormal maternal serum markers analytes. J Obstet Gynaecol Can [Article in English, French] 2008;30:918–32.

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ORIGINAL ARTICLE

Evaluation of inhalant allergen sensitivity in children diagnosed with atopic dermatitis

[1]Seda ÇEVİK
[1]Uğur ALTAŞ
[2]Zeynep Meva ALTAŞ
[1]Mehmet Yaşar ÖZKARS

[1]Department of Pediatric Allergy and Immunology, University of Health Sciences, Umraniye Training and Research Hospital, Istanbul, Turkey

[2]Department of Public Health, Umraniye District Health Directorate, Istanbul, Turkey

ORCID ID
SÇ : 0000-0002-1124-4137
UA : 0000-0001-5871-2033
ZMA : 0000-0003-0475-8946
MYÖ : 0000-0003-1290-8318

ABSTRACT

Objective: Atopic dermatitis (AD) is a recurrent and inflammatory chronic skin disease, particularly common in children. In the context of our study, the aim is to determine the frequency of respiratory allergen sensitivity in children diagnosed with atopic dermatitis.

Material and Methods: In this descriptive study, conducted between October 2022 and October 2023, the medical records of patients aged 0-18 with atopic dermatitis who presented to the Pediatric Allergy and Immunology Clinic were retrospectively reviewed. The analysis included age, gender, eosinophil counts, and total IgE levels. The patients' IgE and eosinophil values were measured during their initial visit when they had complaints.

Results: When examining the food and inhalant allergen sensitivity of patients, the most common sensitivity was to house dust mites (30.6%), followed by egg allergen sensitivity (28.6%). Eosinophil percentage and total IgE levels were also statistically significantly higher in those with inhalant allergen sensitivity compared to those without ($p=0.003$ and $p<0.001$, respectively). The cut-off point for total IgE in predicting inhalant allergen sensitivity was determined to be 99.5. Sensitivity and specificity values for the cut-off point of total IgE were 71.6% and 70.9%, respectively.

Conclusion: In conclusion, this article assessed the frequency of inhalation allergen sensitivity in atopic dermatitis. Sensitivity to allergens such as house dust mites, eggs, and milk was determined to be increased, emphasizing the potential critical role of indoor environments in the pathogenesis of AD. Additionally, it was found that eosinophil percentage and total IgE values were significantly higher in those with inhalation allergen sensitivity. These findings are important for understanding the clinical characteristics of patients and developing effective treatment strategies.

Keywords: Atopic dermatitis, house dust mites, inhalant allergen.

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Correspondence: Seda ÇEVİK, MD. Sağlık Bilimleri Üniversitesi, Ümraniye Eğitim ve Araştırma Hastanesi, Çocuk Alerji ve İmmünoloji Kliniği, İstanbul, Türkiye.
Tel: +90 216 632 18 18 **e-mail:** drsedacevik@hotmail.com
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INTRODUCTION

Atopic dermatitis (AD) is a recurrent and inflammatory chronic skin disease, particularly common in children.[1] AD is a dermatosis observed in individuals with an atopic tendency, affecting approximately 20–25% of children and 2–3% of adults.[2] Genetic factors, immune dysregulation, impaired skin barrier function, environmental factors, and nutrition play significant roles in the pathogenesis of atopic dermatitis.[3]

According to the atopic march theory, the presence of atopy implies that children with eczema may develop airway allergies such as asthma or allergic rhinitis (AR) in later years.[4] Understanding the allergens that trigger the atopic process is crucial.[5] The identification of IgE-mediated allergies suspected based on the history and examination in childhood should rely on validated tests such as skin prick tests and serum-specific IgE tests. Allergy tests are essential for allergen avoidance, disease monitoring, treatment planning, and specific immunotherapy.[6] Allergens typically manifest as food allergies in early childhood but become more relevant as inhalant allergen sensitivity in older children and adolescents.[5] Well-known inhalant allergens include house dust mites, animal epithelia, pollens, and molds.[7,8]

As inhalant allergen sensitivity is frequently observed in patients with AD, where skin involvement is prominent, determining the frequency of sensitivity to these allergens is crucial for preventing exposure in the clinical control of the disease. In the context of our study, the aim is to determine the frequency of respiratory allergen sensitivity in children diagnosed with atopic dermatitis.

MATERIAL AND METHODS

Study Type and Design

In this descriptive study, conducted between October 2022 and October 2023, the medical records of patients aged 0–18 with atopic dermatitis who presented to the Pediatric Allergy and Immunology Clinic were retrospectively reviewed. During this period, patients with available records and diagnosed with atopic dermatitis were included in the study. The diagnosis of atopic dermatitis was made according to the Hanifin-Rajka diagnostic criteria. This study was conducted in accordance with the Declaration of Helsinki.

Measurements

The analysis included age, gender, presence of additional allergic diseases, eosinophil counts, and total IgE levels. The patients' IgE and eosinophil values were measured during their initial visit when they had complaints. The eosinophil count was determined from the peripheral blood smear or counter and values higher than 4% were considered eosinophilia. Specific IgE testing was performed to identify food and inhalant allergens in patients. Allergen-specific IgE measurements were conducted using ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden). Specific IgE values equal to or greater than 0.35 kU/L were considered positive. For those with negative results in the specific IgE test, a skin prick test was also conducted. Epidermal skin prick tests were performed using allergen extracts (ALK-Abello, Madrid, Spain) along with a positive control (10 mg/dL of histamine phosphate) and a negative control (0.9% sterile saline). Horizontal and vertical measurements were performed for the indurations. Indurations were considered positive if the average diameter was at least 3 mm greater than the negative control. Allergen sensitivity was defined as a positive result either in the specific IgE test or the skin prick test.

Table 1: Patients' laboratory values

	n (%)
Gender (female/male)	127 (51.2)/ 121 (48.8)
	Median (min–max)
Age	3 years (1 month–18 years)
Absolute eosinophil count 10^3/uL	290.0 (10–1840)
Eosinophil (%)	3.3 (0.1–51.0)
IgE IU/ml	72.5 (1.0–8910.0)

IgE: Immunoglobulin E.

Statistical Analysis

For statistical analysis and recording of the data, SPSS for Windows 25.0 program was used. Descriptive results were presented with median, minimum and maximum values, numbers (n), and percentages (%). The normal distribution was evaluated with visual (graphics) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests). For non-normally distributed data, the Mann–Whitney U test was used to compare two independent variables. Chi-square test was used for the comparison of categorical data. $P<0.05$ was accepted as the statistical significance level. Receiver Operating Characteristics (ROC) curve analysis was used for the predictive capacity of eosinophils (absolute) and eosinophils (%) values and serum total IgE for inhalant allergen sensitivity. Sensitivity and specificity values were calculated for cut-off points.

Ethics

The study was conducted with ethical approval obtained from the Ethics Committee of the Umraniye Training and Research Hospital, as per the decision numbered 449 dated 23/11/2023.

RESULTS

Fifty-one point two percent (n=127) of the patients were female and 48.8% (n=121) were male. The median age was 3.0 years, with a minimum age of one month and a maximum age of 18 years.

The median values for absolute eosinophil count, eosinophil percentage, and total IgE were 290.0 10^3/uL (10–1840), 3.3% (0.1–51.0), and 72.5 IU/mL (1.0–8910.0), respectively (Table 1).

When examining the food and inhalant allergen sensitivity of patients, the most common sensitivity was to house dust mites (30.6%), followed by egg allergen sensitivity (28.6%). After egg, milk sensitiv-

Table 2: Patients' food and inhalant allergen sensitivity

Food and inhalant allergen sensitivity	n	%
Inhalant allergen sensitivity		
House dust mites	76	30.6
Cat	31	12.5
Pollen	25	10.1
Food allergen sensitivity		
Egg	71	28.6
Cow milk	36	14.5
Peanut	19	7.7
Hazelnut	17	6.9
Walnut	5	2.0
Pistachios	1	0.4

ity was observed in 14.5% (n=36) of cases in terms of food allergen sensitivity. Among inhalant allergens, sensitivities to cat and pollen were 12.5% (n=31) and 10.1% (n=25), respectively (Table 2).

In patients, inhalant allergen sensitivity was detected in 35.5% (n=88), while food allergen sensitivity was identified in 34.3% (n=85). When evaluating factors associated with allergen sensitivity, it was observed that children with food allergen sensitivity were statistically significantly younger compared to those without food allergen sensitivity (p<0.001). Absolute eosinophil count, eosinophil percentage, and total IgE levels were considerably higher in children with food allergen sensitivity compared to those without (p<0.001, p=0.001, and p=0.006, respectively). There was no relationship detected between the presence of food and inhalant allergen sensitivity and gender (p>0.05). The age of children with inhalant or food allergen sensitivity was significantly higher than those without sensitivity (p<0.001). Total IgE levels and eosinophil percentage were also statistically significantly higher in those with inhalant allergen sensitivity compared to those without (p<0.001 and p=0.019, respectively). Absolute eosinophil count, eosinophil percentage, and total IgE levels were also statistically significantly higher in those with food allergen sensitivity compared to those without (p<0.001, p=0.001, p=0.006, respectively) (Table 3).

ROC analysis was performed to assess the predictive capacity of eosinophil and total IgE values for aeroallergen sensitivity in patients. The ROC analysis indicated low Area Under the Curve (AUC) values for absolute eosinophil and eosinophil percentage (0.549 and 0.590, respectively). Therefore, cut-off points, sensitivity, and specificity were not calculated for absolute eosinophil and eosinophil percentage. The cut-off point for total IgE in predicting inhalant allergen sensitivity was determined to be 99.5. The Area Under the Curve (95% CI) was found to be 0.797 (0.739–0.856) (p<0.001). Sensitivity and specificity values for the cut-off point of total IgE were 71.6% and 70.9%, respectively (Table 4).

Table 3: Factors associated with patients' allergen sensitivity

	Food allergen sensitivity		p	Inhalant allergen sensitivity		p
	No (n=163) Median (min–max)	Yes (n=85) Median (min–max)		No (n=160) Median (min–max)	Yes (n=88) Median (min–max)	
Age (years)	4.0 (0–18.0)	1.0 (0–16.0)	**<0.001**	1.5 (0–18.0)	5.5 (0–17.0)	**<0.001**
Absolute eosinopil count 10^3/uL	240.0 (20.0–1420.0)	390.0 (10.0–1840.0)	**<0.001**	280.0 (10.0–1700.0)	330.0 (0–1840.0)	0.204
Eosinopil (%)	2.9 (0.1–51.0)	4.3 (0.1–16.5)	**0.001**	3.1(0.1–12.7)	3.95 (0.1–51.0)	**0.019**
Total IgE (IU/ml)	59.0 (1.0–5627)	115.0 (2.0–8910.0)	**0.006**	37.0 (1.0–3942)	388.5 (6.0–8910.0)	**<0.001**
	n (%)	**n (%)**	**p**	**n (%)**	**n (%)**	**p**
Gender			0.081			0.777
Female	90 (55.2)	37 (43.5)		83 (51.9)	44 (50.0)	
Male	73 (44.8)	48 (56.5)		77 (48.1)	44 (50.0)	

IgE: Immunoglobulin E.

Table 4: Cut-off value, sensitivity, and specificity of total IgE in predicting inhalant allergen sensitivity

Total IgE	Sensitivity	Specificity	AUC	95% CI	p
Cut off value: 99.5	71.6%	70.9%	0.797	0.739–0.856	<0.001

AUC: Area under the curve; CI: Confidence interval; IgE: Immunoglobulin E.

DISCUSSION

In our study, the total IgE and eosinophil percentage of patients with detected inhalant allergen sensitivity were found to be significantly higher compared to those without detected sensitivity. Atopic dermatitis (AD) is a skin disease that typically arises from complex interactions between environmental factors, genetic predisposition, and allergic reactions. In this context, the role of inhalant allergen sensitivity in the development of AD is increasingly gaining importance. This article aims to assess the frequency of inhalant allergen sensitivity in atopic dermatitis and understand its impact on the course of the disease.

In patients, inhalant allergen sensitivity was detected in 35.5%, and food allergen sensitivity was identified in 34.3%. When examining patients' food and inhalant allergen sensitivity, the most common sensitivity was to house dust mites (30.6%), followed by egg allergen sensitivity (28.6%). Milk sensitivity was the second most common food allergen sensitivity after eggs, observed in 14.5% of cases. In another study conducted in our clinic, food allergen sensitivity was identified in 34.2% of AD patients, with 26.4% showing sensitivity to eggs and 12.2% to cow's milk.[9] In our study, sensitivities to inhalant allergens, specifically cat and pollen, were detected at rates of 12.5% and 10.1%, respectively. One of the key findings of our study is the notably high sensitivity to house dust mites. This suggests a critical role, particularly of indoor environments, in the pathogenesis of AD and the potential triggering of patients' symptoms. A study on inhalant allergen sensitivity in children with atopic dermatitis revealed significant variation in sensitivity rates among countries. Sensitivity to house dust mites was found to be 40% in South Africa and 33% in Australia, while sensitivity to cat epithelium was 21% in the United Kingdom, 21% in France, 20% in the Netherlands, and 19% in Australia. Sensitivity to pollen was reported as 16% in the United Kingdom and 14% in France.[10] Sensitivity to house dust mites and pollen in our study is comparable, while sensitivity to cat epithelium is found to be lower compared to the literature. In a study conducted in Kahramanmaraş, Türkiye, the most common inhalant allergen for preschool and school-age children was identified as grass pollen.[11] Compared to this study conducted in a different region, it can be said that in the Marmara region, the primary factor causing inhalation allergen sensitivity is house dust mites. The lower number of house dust mites in regions with a continental climate and at high altitudes, coupled with the increase in house dust mite numbers in coastal areas with a humid climate, may contribute to this difference.[12]

In our study, eosinophil percentage and total IgE values were statistically considerably higher in those with inhalant allergen sensitivity compared to those without sensitivity. In 80–85% of patients with atopic dermatitis, serum IgE antibody levels are elevated.[13] Eosinophils are a cell type that commonly increases in allergic reactions. In a study by Özçeker et al.,[14] it was found that in patients with atopic dermatitis and IgE levels >100 kU/L, there was a higher prevalence of allergen sensitivity. In patients with AD, there is a decrease in the number of T suppressor cells and circulating T lymphocytes.[15] As a result of T lymphocyte suppression, B lymphocytes increase IgE production. IL-4 acts by increasing IgE production from B lymphocytes, while IL-5 influences by activating eosinophils.[16–19]

In our study, the Area Under the Curve (AUC) values for absolute eosinophil and eosinophil percentage in ROC analysis, assessing the predictive capacity of eosinophil and total IgE values for aeroallergen sensitivity, were found to be low. The cut-off point for total IgE in predicting inhalant allergen sensitivity was determined to be 99.5. Sensitivity and specificity values for the cut-off point of total IgE were found to be 71.6% and 70.9%, respectively. In a study conducted by Saglam et al.,[20] the predictive capacity of absolute eosinophil, eosinophil percentage, and total IgE values for test positivity (skin prick test and/or specific IgE positivity) was evaluated using ROC curve analysis. The cut-off point for total IgE was 104.5 in all patients (AUC: 0.789). Sensitivity and specificity were 72.0% and 71.9%, respectively. In our study, the cut-off point for predicting inhalant allergen sensitivity with total IgE was found to be lower compared to this study, with similar sensitivity and specificity ratios determined.

Limitations and Strengths

The retrospective nature of our study, the small number of patients, and its conduct at a single center constitute limitations in terms of the generalizability of the results. Additionally, evaluating laboratory findings such as IgE and eosinophils in patients with allergen sensitivity provides a broad perspective and constitutes strengths of the study.

CONCLUSION

In conclusion, this article assessed the frequency of inhalation allergen sensitivity in atopic dermatitis. Sensitivity to allergens such as house dust mites, eggs, and milk was determined to be increased, emphasizing the potential critical role of indoor environments in the pathogenesis of AD. Additionally, it was found that eosinophil percentage and total IgE values were considerably higher in those with inhalation allergen sensitivity. These findings are important for understanding the clinical characteristics of patients and developing effective treatment strategies. Evaluating inhalation allergen sensitivity in the treatment of atopic dermatitis can be a crucial step in managing patients.

Statement

Ethics Committee Approval: The Ümraniye Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 23.11.2023, number: 449).

Author Contributions: Concept – UA, SÇ; Design – ZMA; Supervision – SÇ; Resource – MYÖ; Materials – UA; Data Collection and/or Processing – MYÖ; Analysis and/or Interpretation – ZMA; Literature Search – SÇ; Writing – UA; Critical Reviews – ZMA, SÇ.

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REFERENCES

1. Weidinger S, Novak N. Atopic dermatitis. Lancet 2016;387:1109–22.
2. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, et al. Guidelines of care for the management of atopic dermatitis: Section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol 2014;70:338–51.
3. Trikamjee T, Comberiati P, D'Auria E, Peroni D, Zuccotti GV. Nutritional factors in the prevention of atopic dermatitis in children. Front Pediatr 2021;8:577413.
4. Spergel JM. From atopic dermatitis to asthma: The atopic march. Ann Allergy Asthma Immunol 2010;105:99–117.
5. Hon KL, Tsang S, Wong CY, Tse PM, Wong C, To WH, et al. Atopy in children with eczema. Indian J Pediatr 2010;77:519–22.
6. Eigenmann PA, Atanaskovic-Markovic M, O'B Hourihane J, Lack G, Lau S, Matricardi PM, et al. Testing children for allergies: Why, how, who and when: An updated statement of the European Academy of Allergy and Clinical Immunology (EAACI) Section on pediatrics and the eaacı-clemens von pirquet foundation. Pediatr Allergy Immunol 2013;24:195–209.
7. Akdis CA, Akdis M, Bieber T, Bindslev-Jensen C, Boguniewicz M, Eigenmann P, et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL consensus report. J Allergy Clin Immunol 2006;118:152–69.
8. Sidbury R, Tom WL, Bergman JN, Cooper KD, Silverman RA, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: Section 4. Prevention of disease flares and use of adjunctive therapies and approaches. J Am Acad Dermatol 2014;71:1218–33.
9. Altaş U, Akman E, Altaş ZM, Çiçek F, Özkars MY. Determination of the frequency of food allergen sensitivity in children with atopic dermatitis. J Health Sci Med 2023;6:1322–6.
10. de Benedictis FM, Franceschini F, Hill D, Naspitz C, Simons FE, Wahn U, et al. The allergic sensitization in infants with atopic eczema from different countries. Allergy 2009;64:295–303.
11. Özkars MY, Kirik S. Determination of aeroallergen prevalence in children aged 1-16 years in the provincial center of Kahramanmaras. Ann Med Res 2021:27;903–6.
12. Demirtaş N. Astımlı hastalarda ev içi ortam değerlendirmesi ve atopi özellikleri. Uzmanlık Tezi. Aydın: Aydın Adnan Menderes Üniversitesi; 2008.
13. Leung DYM, Soter NA. Cellular and immunologic mechanisms in atopic dermatitis. J Am Acad Dermatol 2001;44:S1–S12.
14. Özçeker D, Durak C, Kardelen AD, Güler N, Tamay Z. Atopic dermatitis in children: How much atopic? Asthma Allergy Immunol [Article in Turkish] 2017:15;135–9.
15. Dahl MV, Lobitz WC, Dobson RL. Atopic dermatitis. In: Demis DJ, Dahl MV, Smith EB, Thiers BH, Crouse RG, Dobson RL, Mcguine JS, editors. Clinical dermatology. 14th ed. Philadelphia: HarperRow; 1987. p.1–35.
16. Degreef H, Cerio R. Mechanisms in allergic skin disorders, therapy of atopic dermatitis. J Acad Dermatol Venereol 1997;8(Suppl 1):2–10.
17. Leung DYM, Rhodes AR, Geha RS, Schreider L, Ring J. Atopic dermatitis. In: Fitzpatrick TB, Freedberg MI, Austen FK, Wolff K, editors. Dermatology in general medicine. 5th ed. New York: Mc Graw-Hill; 1999. p.1464–79.
18. Solomon LM. Atopic dermatitis. In: Moshella SL, Hurley HJ, editors. Dermatology. Philadelphia: WB Saunders Co; 1985. p.334–53.
19. Bos JD, Wierenga EA, Sillevis Smitt JH, van der Heijden FL, Kapsenberg ML. Immune dysregulation in atopic eczema. Arch Dermatol 1992;128:1509–12.
20. Saglam NO, Ozkars MY, Altas U, Altas ZM. Evaluation of the predictive value of total IgE and absolute eosinophil levels on allergy test positivity. North Clin Istanb 2023;10:602–8.

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ORIGINAL ARTICLE

Assessment of vitamin D levels in pediatric patients: A retrospective analysis from a tertiary hospital

[1]Fedli Emre KILIÇ
[2]Osman KÜÇÜKKELEPÇE

[1]Department of Pediatrics, Kahta State Hospital, Adiyaman, Turkey

[2]Department of Public Health, Adiyaman Provincial Health Directorate, Adiyaman, Turkey

ORCID ID
FEK : 0000-0002-0964-5572
OK : 0000-0002-7138-692X

ABSTRACT

Objective: We aimed to assess the vitamin D levels in patients who visited the pediatric outpatient clinic for various reasons.

Material and Methods: The study was conducted retrospectively. Demographic information, vitamin D levels, place of residence (rural or urban), and vitamin D levels of 6939 patients, all obtained from the medical records of children aged 0–18 years who visited the outpatient pediatric clinic at Adıyaman Training and Research Hospital for any reason between January 1, 2022, and December 31, 2022, were meticulously recorded in an Excel file.

Results: Of the patients, 44.2% had adequate vitamin D levels. When examining these levels, it was observed that boys had a significantly higher proportion of sufficient vitamin D levels than girls ($p<0.001$). A significant difference in vitamin D levels was also observed among the 0–5 years, 6–11 years, and 12–18 years ($p<0.001$). Furthermore, vitamin D deficiency was notably more prevalent in children residing in urban areas than in rural areas.

Conclusion: It has been observed that vitamin D insufficiency/deficiency has a significant rate in childhood. To protect children against vitamin D insufficiency/deficiency, adopting a protective lifestyle that includes increasing sun exposure, gradually increasing vitamin D supplementation as they age, and periodically checking their vitamin D levels can be beneficial in preventing complications.

Keywords: Child nutrition, vitamin D, vitamin D deficiency, vitamin D insufficiency.

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Correspondence: Osman KÜÇÜKKELEPÇE, MD. Adıyaman İl Sağlık Müdürlüğü, Halk Sağlığı Daire Başkanlığı, Adıyaman, Türkiye.
Tel: +90 416 225 10 21 **e-mail:** osmankkelepce@hotmail.com

INTRODUCTION

Vitamin D is a vitamin synthesized from our skin with the effect of ultraviolet B in sunlight and has biologically significant effects.[1] A vital component of bone-mineral metabolism, this vitamin is fat soluble. In studies conducted in the last two decades, the vitamin D receptor has been shown on many tissues, and it has been reported to be effective in general health and the protection of bone health.[2] The primary source of vitamin D is the synthesis that occurs in the skin when exposed to sunlight, although it can also be obtained through dietary intake. From a physiological perspective, approximately 90–95% of the vitamin D in the human body is produced through exposure to sunlight, whereas the remaining 5–10% is acquired through dietary means (milk, eggs, fish, animal fats, offal, etc.). Vitamin D, synthesized in our skin by diet and sunlight, is biologically inactive and must pass through several enzymatic pathways to be converted into active metabolites. The main factors affecting vitamin D levels are inadequate synthesis, intake, or absorption of vitamin D.[3,4] Vitamin D deficiency has been associated with various other diseases (autoimmune diseases, rheumatoid arthritis, cardiovascular diseases, etc.) as well as rickettsia, characterized by a deformity of bones and inadequate growth in children. Vitamin D deficiency and rickets continue to be insufficiently acknowledged clinical issues in numerous populations. Their significance goes beyond bone health, encompassing the non-classical functions of vitamin D, which include influencing various immune-related diseases. Compelling evidence supports the effectiveness of vitamin D supplementation in lowering infection rates among pediatric populations.[5] Reports indicate that vitamin D inadequacy or deficiency constitutes a significant global public health issue, affecting as many as 30% of children and 60% of adults.[4,6]

Epidemiological investigations have established that living in regions with higher latitudes and reduced sun exposure serve as indicators for the risk of having insufficient vitamin D levels. Furthermore, in various populations across the world, sun avoidance practices and conservative clothing in more southern areas contribute to vitamin D deficiency. The risk of vitamin D deficiency is prevalent at all life stages, including during pregnancy, infancy, childhood, and adulthood. In infants, this risk can be compounded by recommended sun avoidance practices, limited vitamin D stores, potential inadequacy of vitamin D in exclusively breastfed infants, and a lack of awareness regarding systematic vitamin D supplementation in certain cultural contexts. Epidemiological studies have shown that vitamin D levels are lower in children residing at higher latitudes because they are less exposed to the sun.[5] Türkiye is located between the 36th and 42nd latitudes in the northern hemisphere and is in a region where sun rays can be utilized at an optimum level. While vitamin D deficiency is expected to be less common in our country, studies have found that vitamin D insufficiency/deficiency is a severe public health problem.[1,7]

Since 2008, support programs covering all age groups have been carried out worldwide to prevent vitamin D deficiency/insufficiency. In their 2011 guideline publication, the Endocrine Society advised a vitamin D supplementation regimen of 400 IU per day for infants from the day of birth until their first year and 600 IU per day for children between the ages of 1 and 18, specifically for those without risk factors for vitamin D deficiency. For infants with risk factors for vitamin D deficiency, the recommended supplementation ranged from 400 to 1000 IU per day from birth to one year and 600 to 1000 IU per day for children aged 1 to 18.[8] Since 2005, in Türkiye, the "Prevention of Vitamin D Deficiency and Promotion of Bone Health" initiative has been carried out for all newborns to combat vitamin D insufficiency and deficiency. As part of this program, a daily oral vitamin D supplement of 400 IU (equivalent to 3 drops) is provided to all infants.[1] In this research, we aimed to assess the vitamin D levels of patients who presented to the pediatrics outpatient clinic for any reason and were examined for vitamin D.

Table 1: Descriptive characteristics and vitamin D status of the patients

	Number	Percent
Age		
0–5 years	2983	43.0
6–11 years	2180	31.4
12–18 years	1776	25.6
Gender		
Male	3273	47.2
Female	3666	52.8
Place of residence		
Urban	6153	88.7
Rural	786	11.3
Vitamin D status		
Severe deficiency	124	1.8
Deficiency	2306	33.2
Inadequate	1439	20.7
Normal	3070	44.2

MATERIAL AND METHODS

This retrospectively descriptive research was carried out in Adıyaman province, situated in the Southeastern Anatolia region of Türkiye. The demographic data, vitamin D levels, place of residence (rural, urban), and vitamin D levels of 6939 children aged 0–18 years who applied to the outpatient pediatrics clinic of Adıyaman Training and Research Hospital for any reason between 01.01.2022 and 31.12.2022 were investigated and recorded in an Excel file. It was planned to reach the entire universe without conducting a sample calculation that collects Hospital Information Management System (HIMS) data from the hospital. Patients with chronic diseases (epilepsy, congenital heart disease, chronic renal failure, etc.) and foreign patients were excluded from the study. The assessment of vitamin D levels in children, following the guidelines of the American Pediatric Endocrine Society, resulted in the following categories:

- Less than 5 ng/ml: Severe deficiency
- 5–15 ng/ml: Deficiency
- 15–20 ng/ml: Insufficiency
- Greater than 20 ng/ml: Normal.[9]

Table 2: Comparison of vitamin D status according to descriptive characteristics

	Vitamin D status								p
	Severe deficiency		Deficiency		Inadequate		Normal		
	Number	%	Number	%	Number	%	Number	%	
Gender									<0.001
Male	24	0.7	807	24.7	712	21.8	1730	52.9	
Female	100	2.7	1499	40.9	727	19.8	1340	36.6	
Age (years)									<0.001
0–5 years	24	0.8	659	22.1	536	18.0	1764	59.1	
6–11	18	0.8	703	32.2	547	25.1	912	41.8	
12–18	82	4.6	944	53.2	356	20.0	394	22.2	
Place of residence									0.011
Urban	117	1.9	2074	33.7	1257	20.4	2705	44.0	
Rural	7	0.9	232	29.5	182	23.2	365	46.4	

Statistical Analysis

The findings obtained from the files were evaluated with SPSS 26 package program. Descriptive statistics were expressed as numbers and percentages. The chi-square test was utilized to examine categorical variables among unrelated groups, with a significance level set at $p<0.05$.

Ethics Statement

Approval was obtained from the Ethics Committee for Non-Interventional Studies at Fırat University Faculty of Medicine (date: 08.06.2023, number: 2023/08-20). Institutional approval was obtained from Adıyaman University, Adıyaman Training and Research Hospital (date: 29.09.2023, number: 225654554). Since this is a retrospective study, obtaining any verbal or written consent from the participants was impossible. Helsinki Declaration rules were followed throughout the study.

RESULTS

The study included a total of 6939 participants. Among these individuals, 3666 (52.8%) were female, and 6153 (88.7%) resided in the city center. According to age groups, there were 2983 patients (43.0%) in the 0–5 age group, 2180 patients (31.4%) in the 6–11 age group, and 1776 patients (25.6%) in the 12–18 age group. According to vitamin D status, 124 (1.8%) were severely deficient, 2306 (33.2%) were deficient, 1439 (20.7%) were insufficient, and 3070 (44.2%) were at normal levels (Table 1).

In the analysis of vitamin D levels, it was observed that 1730 (52.9%) males and 1340 (36.6%) females had normal levels, and a significant difference was noted between the two groups ($p<0.001$). In the age analysis, it was determined that 1764 (59.1%) individuals were in the 0–5 years age group, 912 (41.8%) in the 6–11 years age group, and 944 (53.2%) in the 12–18 years age group, all of whom exhibited deficient levels of vitamin D. There was a significant difference observed among the age groups ($p<0.001$). Among urban residents, 2705 (44.0%) had normal vitamin D levels, whereas 365 (46.4%) of rural residents had normal vitamin D levels. A significant difference was observed between these two groups ($p=0.011$) (Table 2).

In subgroup analyses based on gender, a significant difference was identified in the vitamin D status of males concerning both age groups and place of residence ($p<0.001$ and $p=0.004$, respectively). Conversely, among females, a significant difference was observed among age groups in terms of vitamin D status ($p<0.001$), while no significant difference was noted based on place of residence ($p=0.148$) (Table 3).

DISCUSSION

Vitamin D deficiency/insufficiency is a prevalent health issue, especially in developing countries like Türkiye. Although it is located in the northern hemisphere and receives enough sunlight, vitamin D levels still need to be increased.[7] In this case, the importance of vitamin D-enriched foods or vitamin D supplementation therapy increases. No threshold 25-hydroxy D vitamin level is determined for vitamin D deficiency in children. Different threshold values have been taken as criteria in studies investigating vitamin D deficiency and insufficiency. The Endocrine Society published a report on this subject in 2016. In this report, a 25-OH D level was defined as vitamin D deficiency if <12 ng/ml, vitamin D insufficiency if 12–20 ng/ml, and normal vitamin D level if >20 ng/ml.[10] The American Pediatric Endocrinology Association defines a 25-OH D level as normal if it is >20 ng/ml, insufficiency if it is between 15–20 ng/ml, deficiency if it is between <5–15 ng/ml, and severe deficiency if it is <5 ng/ml.[11] In this study, the American Association of Pediatric Endocrinology's vitamin D ranges were considered.

In various epidemiological studies conducted across the globe, vitamin D deficiency has been documented with frequencies ranging from 7% to 68%, while vitamin D insufficiency has been observed with frequencies ranging from 19% to 61% among healthy children and

Table 3: Comparison of vitamin D status according to gender and descriptive characteristics

	Vitamin D status								p
	Severe deficiency		Deficiency		Inadequate		Normal		
	Number	%	Number	%	Number	%	Number	%	
Male									
Age (years)									<0.001
0–5	9	0.6	317	20.6	264	17.1	950	61.7	
6–11	7	0.7	265	25.0	273	25.7	517	48.7	
12–18	8	1.2	225	33.5	175	26.1	263	39.2	
Place of residence									0.004
Urban	23	0.8	732	25.6	615	21.5	1488	52.1	
Rural	1	0.2	75	18.1	97	23.4	242	58.3	
Female									
Age (years)									<0.001
0–5	15	1.0	342	23.7	272	18.8	814	56.4	
6–11	11	1.0	438	39.2	274	24.5	395	35.3	
12–18	74	6.7	719	65.1	181	16.4	131	11.9	
Place of residence									0.148
Urban	94	2.9	1342	40.7	642	19.5	1217	36.9	
Rural	6	1.6	157	42.3	85	22.9	123	33.2	

adolescents.[10] Many studies conducted and published in Türkiye reveal significant levels of vitamin D deficiency/insufficiency in children and adults. In Türkiye, the prevalence of vitamin D deficiency among children and adolescents ranges from 8% to 61%, and this prevalence varies depending on factors such as age, gender, and season.[11] In a study conducted by the Ministry of Health in 2011, involving 2504 children aged 6–17 months and their mothers in Türkiye, it was reported that vitamin D deficiency was present in 26.8% of the participants. Additionally, vitamin D insufficiency was found to affect 66.7% of the individuals. The study aimed to assess vitamin D levels and the status of iron deficiency anemia in this population and evaluate the programs conducted in 2011.[8] In a study conducted by Akman et al.[12] during the spring season in Ankara, vitamin D deficiency was observed in 8% of the 420 children aged 1–16 years, while vitamin D insufficiency was present in 25.5% of the participants. In a study conducted on children applied to the pediatric endocrine outpatient clinic, vitamin D deficiency was found to be 51.5%, and vitamin D insufficiency was found to be 35.1%.[13] A 2018 study conducted in the Erzincan province, involving 2346 children, revealed that severe vitamin D deficiency was detected in 8.36% of the participants.[14] Türe et al.,[15] in a study with 4153 children and adolescents, found vitamin D deficiency in 65.0% (n=2700) and vitamin D insufficiency in 23.1% (n=959) of the patients. In a study carried out in Ankara province, a significant prevalence of vitamin D deficiency (51.8%) and vitamin D insufficiency (20.7%) was observed.[16] Okan et al.[17] reported that 58.4% of children and adolescents had vitamin D deficiency. A study by Pearse et al.[18] in the UK revealed that vitamin D deficiency was prevalent in over 50% of the adult population during the winter and spring seasons, with severe vitamin D deficiency affecting 16%. A study conducted in Greece reported that 52.5% of 2386 school children aged 9–13 years had vitamin D deficiency.[19] Additionally, in an observational study conducted in Spain, 66% of children and adolescents aged 5–15 years were found to have vitamin D deficiency.[20] In the current study, among 6939 children, the prevalence of severe vitamin D deficiency was 1.8%, deficiency was observed in 33.2%, insufficiency in 20.7%, and normal levels in 44.2%. More than half (55.8%) had low vitamin D levels. This was considered to be compatible with the literature.

In a 2014 study conducted by Karagüzel et al.[21] in Trabzon, involving 746 healthy school-age children, it was observed that girls exhibited a higher prevalence of vitamin D deficiency compared to boys. Topal et al.'s[14] study revealed a significant difference (p<0.001) in vitamin D levels between boys and girls, with boys exhibiting higher levels. In Demiral et al.'s[13] study, it was observed that 25-OH D levels were significantly lower in girls compared to boys (p<0.001). In a study conducted by Badem et al.[22] involving 2672 adolescents, it was found that 84.9% of girls had vitamin D deficiency, while 12.1% had vitamin D insufficiency. In contrast, this rate was 59.5% and 31.4% in boys. In a study conducted on school children in Kuwait, it was observed that male students had significantly higher 25(OH) vitamin D levels compared to their female counterparts.[23] In a study conducted in Colombia, 25 hydroxy D vitamin levels were lower in female students than male students.[24] It is evident that research conducted both within Türkiye and internationally consistently indicates that girls tend to have lower levels of vitamin D. In our study, boys' low

vitamin D levels were 47.1%, whereas this rate was 63.4% in girls. It is evident that vitamin D deficiency was notably more prevalent in girls compared to boys (p<0.001). It was thought that this might be because girls dress more closed due to sociocultural or religious obligations and that girls spend less time in open areas, so their bodies are not sufficiently exposed to the sun and cannot synthesize vitamin D. Further studies are needed to make more precise interpretations about the cause. The current research aligns with existing literature, demonstrating a higher prevalence of vitamin D deficiency in girls.

The period of adolescence is a crucial phase for skeletal growth and development. The rapid increase in height during puberty necessitates a greater intake of calcium and vitamin D, both of which are often deficient during this time. As a result, it is standard practice to recommend calcium and vitamin D supplementation for adolescents during their pubertal years.[11] A research carried out in the Erzincan region of Türkiye revealed that vitamin D levels declined as individuals grew older.[14] In a study involving adolescent girls in Kocaeli, a vitamin D deficiency or insufficiency rate of 64.8% was documented.[25] In a study conducted by Okan et al.,[17] it was noted that 25(OH)-D vitamin D levels exhibited variations among different age groups, with the highest levels observed in the 1–6 age group and the lowest levels in the 7–17 age group (p<0.001). There exists an inverse correlation between age and vitamin D levels. The current study noted a significant decline in vitamin D levels among the older age groups. While the rate of children aged 0–5 years with low vitamin D levels was 40.9%, this rate was 77.8% in the 12–18 age group. This was consistent with the literature. It is considered that the free vitamin D support given to all babies from birth up to a certain age in Türkiye may also have an effect.

In some studies, spending more time at home, not taking children out of the house due to cultural reasons or screen addiction, having houses without balconies, or living in neighborhoods with dense apartment buildings that block sunlight cause people not to benefit from the sun sufficiently.[3] There is a scarcity of studies that assess vitamin D levels in children residing in both urban and rural areas. In a retrospective study conducted in the Tokat region of Türkiye, involving 5356 pediatric patients, it was observed that there was no significant difference in vitamin D levels between children residing in the city center and those living in rural areas (p=0.673).[17] In the current study, variations in vitamin D levels were noted based on the participants' places of residence. The vitamin D levels of children residing in the city center were markedly lower when compared to those living in rural areas (p=0.011). The reason for this was thought to be that children living in the city did not go out in the sun much and stayed in the buildings, whereas those living in the countryside benefited more from sunlight and thus had higher vitamin D levels.

The most important limitation of this study is that since it was a retrospective study, information such as living conditions, complaints, duration of contact with the sun, whether the skin color was dark or not, dietary characteristics, whether they used vitamin D supplements or not and sunscreen use could not be obtained. At the same time, the fact that the study was single-centered prevents the generalisability of the results. Most of the demographic characteristics of the study group could not be reached because the data were collected through hospital information systems, and the patients could not be interviewed one-on-one.

CONCLUSION

The study findings indicate a notable prevalence of vitamin D deficiency/insufficiency during childhood, with an increase in prevalence as age advances and a higher incidence among girls. Vitamin D deficiency was more prevalent among children residing in urban areas compared to those living in rural areas. Adopting a protective lifestyle against vitamin D deficiency/insufficiency in children, increasing exposure to the sun, increasing vitamin D supplementation with increasing age, and checking vitamin D levels from time to time may be helpful in terms of preventing complications.

Statement

Ethics Committee Approval: The Fırat University Non-Interventional Clinical Research Ethics Committee granted approval for this study (date: 08.06.2023, number: 2023/08-20).

Author Contributions: Concept – FEK, OK; Design – FEK, OK; Supervision – FEK, OK; Resource – FEK, OK; Materials – FEK, OK; Data Collection and/or Processing – FEK, OK; Analysis and/or Interpretation – FEK, OK; Literature Search – FEK, OK; Writing – FEK, OK; Critical Reviews – FEK, OK.

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REFERENCES

1. Şenkal E, Ünüvar E, Seren L, Göl C, Durankuş F. Necessity of determination and interpretation of the serum vitamin D levels. J Child 2018;18:97–102.
2. Elitok GK, Bülbül L, Turan B, Akın TY, Uslu S, Bülbül A. Knowledge, attitudes and practices the mothers regarding recommendation of Vitamin D supplementation to children. Sakarya Med J 2020;10:231–9.
3. Makhsudov J, Yılmaz R. Vitamin D deficiency in children. Chron Precis Med Res 2020;1:8–19.
4. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 2004;80(6 Suppl):1678S–88S.
5. Mailhot G, White JH. Vitamin D and immunity in infants and children. Nutrients 2020;12:1233.
6. Peroni DG, Trambusti I, Di Cicco ME, Nuzzi G. Vitamin D in pediatric health and disease. Pediatr Allergy Immunol 2020;31(Suppl 24):54–7.
7. Seremet Kürklü N, Suna G, Kamarlı Altun H, Karaçil Ermumcu MŞ. The state of vitamin D supplement use and knowledge levels of mothers with 0-12 month-old infants. BANU J Health Sci Res 2022;4:94–102.
8. Saggese G, Vierucci F, Boot AM, Czech-Kowalska J, Weber G, Camargo CA Jr, et al. Vitamin D in childhood and adolescence: An expert position statement. Eur J Pediatr 2015;174:565–76.
9. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M; Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. Vitamin D deficiency in children and its management: Review of current knowledge and recommendations. Pediatrics 2008;122:398–417.

10. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, et al. Global consensus recommendations on prevention and management of nutritional rickets. J Clin Endocrinol Metab 2016;101:394–415.
11. Özkan B, Karagüzel G. Çocuklarda D vitamini eksikliği, tanı, tedavi ve korunma. In: Saka N, Akçay T, editörler. Çocuk endokrinolojisinde uzlaşı. 2. baskı. İstanbul: Çocuk Endokrinolojisi ve Diyabet Derneği Yayınları; 2014. p.183–9. [In Turkish]
12. Akman AO, Tumer L, Hasanoglu A, Ilhan M, Caycı B. Frequency of vitamin D insufficiency in healthy children between 1 and 16 years of age in Turkey. Pediatr Int 2011;53:968–73.
13. Demiral M, Sırmagül B, Kirel B. Vitamin D levels in children admitted to the endocrine outpatient clinic. J Curr Pediatr 2016;14:60–6.
14. Topal İ, Mertoğlu C, Arslan YK, Gümüş A, Sürücü Kara İ, Peker N. Erzincan bölgesindeki çocukların D vitamini seviyelerinin yaş, cinsiyet ve mevsimlere göre değerlendirilmesi. Fırat Med J [Article in Turkish] 2018;23:168–72.
15. Türe E, Müderrisoğlu S, Acı R, Çubukçu M, Erdem MA. Adölesan ve çocuklarda D vitamini düzeylerinin yaş, cinsiyet ve mevsimsel özelliklere göre değerlendirilmesi. Ankara Med J [Article in Turkish] 2020;20:380–6.
16. Uçar F, Taşlıpınar MY, Soydaş AÖ, Özcan N. 25-OH Vitamin D levels in patients admitted to Ankara Etlik İhtisas training and research hospital. Eur J Basic Med Sci 2012;2:12–5.
17. Okan S, Okan F, Demir O. Association of vitamin D level with age, gender, living place and season of the year in children and adolescents. J Health Sci 2020;29:114–8.
18. Pearce SH, Cheetham TD. Diagnosis and management of vitamin D deficiency. BMJ 2010;340:b5664.
19. Manios Y, Moschonis G, Hulshof T, Bourhis AS, Hull GLJ, Dowling KG, et al. Prevalence of vitamin D deficiency and insufficiency among schoolchildren in Greece: The role of sex, degree of urbanisation and seasonality. Br J Nutr 2017;118:550–8.
20. Fernández Bustillo JM, Fernández Pombo A, Gómez Bahamonde R, Sanmartín López E, Gualillo O. Vitamin D levels in a pediatric population of a primary care centre: A public health problem? BMC Res Notes 2018;11:801.
21. Karagüzel G, Dilber B, Çan G, Ökten A, Değer O, Holick MF. Seasonal vitamin D status of healthy schoolchildren and predictors of low vitamin D status. J Pediatr Gastroenterol Nutr 2014;58:654–60.
22. Badem ND. Kırıkkale ve çevresinde ergen bireylerde D vitamini düzeyi değerlendirmesi. Ankara Eğit Arş Hast Tıp Derg [Article in Turkish] 2019;52:223–38.
23. Alyahya KO. Vitamin D levels in schoolchildren: A cross-sectional study in Kuwait. BMC Pediatr 2017;17:213.
24. Gilbert-Diamond D, Baylin A, Mora-Plazas M, Marin C, Arsenault JE, Hughes MD, et al. Vitamin D deficiency and anthropometric indicators of adiposity in school-age children: A prospective study. Am J Clin Nutr 2010;92:1446–51.
25. Hatun S, Islam O, Cizmecioglu F, Kara B, Babaoglu K, Berk F, et al. Subclinical vitamin D deficiency is increased in adolescent girls who wear concealing clothing. J Nutr 2005;135:218–22.

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ORIGINAL ARTICLE

The association of phototherapy for neonatal hyperbilirubinemia and childhood allergic disease

[1,2]Mehtap KAYA
[2,3]Fatih ÇİÇEK
[2]Feyza Mediha YILDIZ
[4,5]Mahmut DOĞRU

[1]Division of Pediatric Nephrology, Department of Pediatrics, Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Turkey

[2]Department of Pediatrics, University of Health Sciences, Turkey. Istanbul Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center, Istanbul, Turkey

[3]Department of Pediatric Allery and Immunology, Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Turkey

[4]Department of Pediatric Allergy and Immunology, Memorial Sisli Hospital, Istanbul, Turkey

[5]Division of Pediatric Allergy and Immunology, University of Health Sciences, Turkey. Istanbul Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center, Istanbul, Turkey

ORCID ID
MK : 0000-0002-6750-5172
FÇ : 0000-0001-7348-7081
FMY : 0000-0002-8684-0101
MD : 0000-0001-9728-8028

ABSTRACT

Objective: The prevalence of allergic diseases is increasing worldwide. Phototherapy has been identified as a potential risk factor associated with childhood allergic diseases, including allergic asthma, allergic rhinitis (AR), and atopic dermatitis (AD). In this study, our aim is to assess the relationship between phototherapy and these common childhood allergic diseases.

Material and Methods: We analyzed 621 children between the ages of 3-17, including a patient group of 371 who received phototherapy during the neonatal period and a control group of 250 who did not receive phototherapy. The International Study of Asthma and Allergy in Childhood (ISAAC) survey was administered to all cases. For participants with allergic diseases, plasma eosinophil and total immunoglobulin (Ig) E levels were analyzed, and a skin prick test was conducted.

Results: There was no statistically significant association between the patient and control groups in terms of the diagnosis of wheeze/asthma, AR, AD, and phototherapy treatment. The percentage of eosinophilia was significantly higher in the patient group ($p=0.01$). Cesarean section was more frequent in the control group ($p<0.05$).

Conclusion: According to our study, there was no significant relationship between phototherapy treatment and the incidence of childhood asthma, AR, and AD.

Keywords: Allergic asthma, allergic rhinitis, atopic dermatitis, children, phototherapy.

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Correspondence: Mehtap KAYA, MD. Kartal Dr. Lutfi Kırdar Şehir Hastanesi, Çocuk Sağlığı ve Hastalıkları Kliniği, Çocuk Nefrolojisi Bölümü, İstanbul, Türkiye.
Tel: +90 505 949 21 09 **e-mail:** mehtap_ky@hotmail.com

INTRODUCTION

Allergy can be defined as an exaggerated immune response of the body against allergens and antigens. Allergic diseases, including asthma, allergic rhinitis (AR), and atopic dermatitis (AD), are frequently observed in childhood, and their frequency has been increasing over the last 30 years, especially in developing countries.[1] They represent a significant cause of morbidity in children. Therefore, it is essential to identify and prevent risk factors associated with allergic diseases. These risk factors include genetic predisposition, obesity, gender, and emotional and environmental factors.[2] Additionally, several perinatal and neonatal factors have been linked to childhood allergic diseases, such as low gestational age, preterm birth, low birth weight, breastfeeding, hyperbilirubinemia, and phototherapy.[3]

Neonatal hyperbilirubinemia/jaundice results from the production of unconjugated bilirubin in newborns. This condition results from a metabolic dysregulation that leads to increased bilirubin production surpassing the capacity of bilirubin elimination via the liver and intestines, posing a risk of neurological impairment if not adequately managed.[4] Every year 60% of term and 80% of preterm babies develop neonatal hyperbilirubinemia within the first two weeks of life.[5] Therefore, it is crucial for clinicians to evaluate the short-term and lasting impacts of elevated bilirubin levels and phototherapy.

Bilirubin is produced as the final result of breaking down heme, a process initiated by the enzyme heme oxygenase, which catalyzes the decomposition of heme. This is followed by the conversion of biliverdin into bilirubin through reduction.[6] At a physiological level, bilirubin has been shown to be a naturally occurring antioxidant.[6] The mainstay of hyperbilirubinemia treatment is phototherapy. It converts unconjugated bilirubin into water-soluble forms.[7] Phototherapy has both acute and late side effects. Acute side effects involve disruption of the relationship between child and mother, imbalances in body temperature and fluid-electrolyte levels, bronze baby syndrome, skin damage, changes in blood composition, intestinal paralysis, an open ductus arteriosus, and eye problems. Late side effects involve tumors, skin damage, and allergic conditions.[8]

The pathophysiology of allergic diseases is based on the balance between oxidants and antioxidants. Phototherapy leads to an increase in pro-inflammatory cytokines and a decrease in the T helper 2 (Th2) to T helper 1 (Th1) switching, as well as a decrease in interleukin 6 (IL-6), which is an anti-inflammatory cytokine.[9] These changes all contribute to an increased risk of allergic diseases and inflammatory conditions. Many studies have demonstrated that phototherapy can cause damage to DNA and induce lymphocyte apoptosis.[10] Additionally, phototherapy suppresses T lymphocyte activity, resulting in DNA chain breaks and mutations.[11] It is also reported that bilirubin suppresses T-cell proliferation, activation, and IL-2 production. The inhibition of T-cell function leads to an increased risk of developing allergic diseases by reducing regulatory T cells (Treg).[12] Despite the effects of hyperbilirubinemia and phototherapy on the development of allergic diseases, the results of the studies are challenging.

In our study, we aimed to assess the relationship between phototherapy and common childhood allergic diseases: allergic asthma, AR, and AD.

MATERIAL AND METHODS

This is a prospective study conducted at Zeynep Kamil Maternity and Children Training and Research Hospital. We analyzed a total of 621 children between the ages of three and 17, comprising 366 males and 255 females. This cohort included a patient group of 371 who received phototherapy during the neonatal period and a control group of 250 patients who did not receive phototherapy. The International Study of Asthma and Allergies in Childhood (ISAAC) survey was administered to all 621 cases to assess allergic diseases.

We planned to analyze eosinophil and total IgE levels and conduct a skin prick test in cases with allergic diseases. The questionnaire included the ISAAC survey and information on demographics, birth data, maternal pregnancy history, and family history of allergies.

The study received approval from the Zeynep Kamil Maternity and Children Training and Research Hospital Ethical Committee (date, 25.04.2014; decision number: 54). All procedures adhered to the ethical principles outlined in the Declaration of Helsinki. Written consent forms were obtained from the parents.

Skin Prick Test

Skin prick tests with common aeroallergens, including Dermatophagoides pteronyssinus, Dermatophagoides farinae, Alternaria alternata, cockroaches (Blattella germanica), cat dander, dog dander, a mixture of grass pollens (Lolium perenne, Dactylis glomerata, Phleum pratense, Anthoxanthum odoratum, Poa pratensis, Festuca elatior, Agrostis vulgaris, Holcus lanatus, Cynodon dactylon, Avena sativa, Avena fatua, Lotus corniculatus), a mixture of grain pollens (oats, wheat, barley, corn), a mixture of tree pollens (Acer pseudoplanatus, Aesculus hippocastanum, Robinia pseudoacacia, Tilia platyphyllos, Platanus vulgaris), and weed mix pollens (Medicago sativa, Trifolium pratense, Brassica nigra, Urtica dioica, Rumex acetosa; Stallergenes SA, Antony, France), were conducted with a lancet. The anterior surface of the forearm was used for administration. Histamine (10 mg/ml) and physiological saline were used as positive and negative references, respectively. Skin reactions were assessed 20 minutes after the skin test application, with indurations of ≥3mm deemed to signify a positive response.

Serum Total Immunoglobulin E and Eosinophil Counts

Serum total IgE levels were analyzed using the nephelometry system (Siemens Healthcare Diagnostics Inc., Deerfield, Germany), and values over 100 IU/ml were considered high. The total number of eosinophils and blood eosinophils percentage were determined through an automated blood analyzer, the ABX Pentra 80 (HORIBA Medical, Montpellier, France), with percentages above 4% regarded as elevated.

Statistical Analysis

All analyses were conducted using Statistical Package for the Social Sciences (SPSS) Version 15. For statistical analyses of qualitative data and comparisons between two groups, the Pearson chi-squared test and the independent Mann-Whitney U test were employed, respectively. Findings were estimated with a 95% confidence interval, and statistical significance was determined with a two-tailed corrected p-value of <0.05.

Table 1: Age and gender distribution of patient and control groups

	Patient group (n=371)	Control group (n=250)	p
Gender			0.578*
Boys, n (%)	222 (%59.8)	144 (%57.6)	
Girls, n (%)	149 (%40.2)	106 (%42.4)	
Age (years)	7.65±3.75	7.19±1.79	0.563**

*: Chi-Square Test; **: Mann-Whitney U test.

Table 2: Demographics, birth data, background of mother's pregnancy and family history of allergy of patient and control groups

	Patient group (n=371)		Control group (n=250)		p
	n	%	n	%	
Consanguinity	61	16.4	51	20.4	>0.05
Family history of allergic disease	117	31.5	75	30	>0.05
Gestational diabetes	18	4.8	20	8	>0.05
Pre-eclampsia	14	3.7	7	2.8	>0.05
Maternal smoking during pregnancy	34	9.1	31	12.4	>0.05
Delivery method					
Vaginal delivery	216	58.2	102	40.8	>0.05
Caesarean section	149	40.1	143	57.2	*0.01

*: Significant difference between the patient and control groups, p<0.05.

RESULTS

In total, 621 children were evaluated: 366 boys (58.9%) and 255 girls (41.1%). Among them, 371 children received phototherapy for neonatal jaundice, with 222 boys (59.8%) and 149 girls (40.2%). The control group consisted of 250 children, including 144 boys (57.6%) and 106 girls (42.4%). There was no significant difference in gender distribution (p=0.578). The mean age of the patient group was 7.19±1.79 years, and for the control group, it was 7.65±3.75 years. There was no significant difference in age distribution (Table 1).

There were no statistically significant differences in consanguinity, a family history of allergic disease, gestational diabetes, a history of preeclampsia, tobacco smoke exposure, or tobacco smoking during pregnancy between the patient and control groups (p>0.05). Cesarean section was more frequent in the control group (p<0.05) (Table 2).

The mean total serum bilirubin (TSB) level of the patient group was 19.6±3.7 mg/dL. Children received phototherapy for an average of 58.7±28.6 hours (ranging from 24 to 240 hours). We analyzed the etiology of hyperbilirubinemia in the patient group; the reason was unknown in 227 patients (61.2%), ABO incompatibility was detected in 62 patients (16.7%), Rh incompatibility in 28 patients (7.5%), dehydration in 22 patients (5.9%), subgroup incompatibility in 16 patients (4.3%), sepsis in 13 patients (3.5%), glucose-6-phosphate dehydrogenase deficiency (G6PD) in two patients (0.5%), and hereditary spherocytosis in one patient (0.3%). There was no statistically significant association between the patient and control groups in terms of the diagnosis of wheeze/asthma, nighttime coughing, exercise-induced wheeze, AR, and AD, with a p-value >0.05 (Table 3).

Doctor-diagnosed allergic asthma and/or allergic rhinitis and/or atopic dermatitis were detected in 87 (23.5%) children in the patient group and 68 (27.2%) children in the control group; however, there was no statistical significance with a p-value of 0.29 (Table 3).

The prick test could be applied to 32 of the 82 cases in the patient group and 38 of the 68 cases in the control group with doctor-diagnosed allergic disease. Additionally, total IgE levels and the percentage of eosinophilia were analyzed. The percentage of eosinophilia was higher in the patient group (p=0.012). On the other hand, the presence of atopy detected in the prick test and total IgE levels showed no difference between the patient and control group (p=0.509 and p=0.327, respectively) (Table 4).

DISCUSSION

Phototherapy/hyperbilirubinemia has been mentioned as a potential risk factor for the development of allergy.[13] However, we did not find a significant association between phototherapy and the risk of developing childhood asthma, AR, and AD in our study. Despite the

Table 3: Comparison of diagnosis of allergic disease according to ISAAC questionnaire between patient and control groups

	Patient group		Control group		p
	n	%	n	%	
Diagnosis of wheeze/asthma	137	36.9	96	38.4	0.710*
Nighttime coughing	21	5.7	17	68	0.568*
Exercise induced wheeze	23	6.2	15	6	0.907*
Allergic rhinitis	58	15.6	52	20.8	0.098*
Atopic dermatitis	25	6.7	13	5.2	0.433*
Doctor diagnosed allergic asthma	57	15.4	38	15.3	0.972*
Doctor diagnosed allergic rhinitis	45	12.1	36	14.4	0.399*
Doctor diagnosed atopic dermatitis	15	4	11	4.4	0.820*

*: Chi-Square Test.

Table 4: Values of eosinophilia and immunoglobulin E levels

	Patient group (n=22)	Control group (n=32)	p
Percentage of eosinophilia (%)	4.1+2.8	3.2+2.9	0.012*
Immunoglobulin E levels (IU/mL)	232+404	222+397	0.327

*: Significant difference between patient and control group, p<0.05.

potential enhancing effects of phototherapy/hyperbilirubinemia on allergic inflammation, different results have been obtained on this issue. These discrepancies may be attributed to variations in factors such as study design, patient population, and diagnostic criteria for allergic diseases.

The first study about the relationship between asthma and neonatal phototherapy/hyperbilirubinemia was conducted in 2007 by Aspberg et al.[9] They assessed children admitted to the hospital diagnosed with asthma and showed that neonatal phototherapy or neonatal hyperbilirubinemia was independently associated with an increased risk for developing childhood asthma. In another study conducted by Aspberg et al.,[13] any prescribed asthma medication was accepted as a diagnosis of asthma, and they obtained results similar to their previous study. Kuzniewicz et al.[14] conducted a study involving 109,212 infants. For the diagnosis of asthma, they used the criteria of at least two physician-diagnosed asthma attacks and/or at least two prescriptions for asthma medication after the age of two years. According to their study, even though modest levels of hyperbilirubinemia were associated with asthma, higher bilirubin levels were not associated with it. In 2018, Tham et al.[15] did not observe any association between phototherapy and the frequency of allergic diseases in the first five years of life in a prospective study involving 135 children. Similarly, we did not find a relationship between asthma and phototherapy treatment, which is consistent with this study. These differences among studies in this area may be attributed to the parabolic relationship between hyperbilirubinemia and asthma, in addition to factors such as study design, diagnostic criteria, and sample selection. It is exceedingly challenging to separate the impacts of high bilirubin levels and phototherapy treatment on allergic diseases due to their strong association. There is a need for more comprehensive studies.

Allergic rhinitis was another allergic condition we evaluated in our study. The first study investigating the relationship between neonatal hyperbilirubinemia and allergic rhinitis was conducted by Sun et al.[16] In this study, 11,328 children born between 1997 and 2000 were followed up until the age of ten. They discovered a significant association between neonatal hyperbilirubinemia and AR.[16] In another study, babies born between 2000 and 2007 were monitored until 2008. Across all age groups, the incidence of all allergic diseases was higher in the neonatal jaundice cohort than in the non-neonatal jaundice cohort.[17] Safar et al.[18] compared 300 allergic children with a mean age of 3.4–3.7 years to 300 controls. They concluded that hyperbilirubinemia and phototherapy have a statistically significant association with the development of allergic diseases. In contrast to these studies, Tham et al.[15] followed 1058 infants up to the age of five years and found no difference in AR between those who received phototherapy and those who did not. Our results were consistent with this study.

The last allergic disease we investigated in our study was AD. The most comprehensive study on this subject is the study by Egeberg et al.[19] They encompassed 85,743 children who developed AD within the first five years of their life and concluded that neonatal hyperbilirubinemia was associated with an increased risk of AD. A population-based study conducted in Taiwan revealed similar results to Egeberg et al.[19,20] In contrast to these studies, Tham et al.[15] found no relationship between receiving phototherapy and the development of AD. Likewise, we did not find a significant association between AD and phototherapy treatment.

Additionally, there are two systematic reviews that have evaluated the association between allergic diseases and hyperbilirubin-

emia/receiving phototherapy. One of these systematic reviews was conducted by Das et al.[21] They published a systematic review that included seven high-quality studies on childhood allergic diseases and neonatal hyperbilirubinemia. They concluded that there was a significant association between childhood allergic diseases and neonatal hyperbilirubinemia and/or neonatal phototherapy. However, the evidence obtained was deemed to be 'low-quality'.[21]

The review conducted by Kuniyoshi et al.[22] included fourteen studies. This review revealed that neonatal hyperbilirubinemia was associated with a higher risk of childhood asthma. Neonatal phototherapy was also linked to an increased likelihood of developing asthma and AR in childhood. In conclusion, this review suggests that neonatal hyperbilirubinemia and phototherapy may be considered as potential etiological factors for allergic diseases developing in childhood; however, the associations appear to be weaker than previously estimated.[22]

In 2010, Gloria-Bottini et al.[23] conducted a study on Adenosine Deaminase locus 1 (ADA1) polymorphisms. The study has shown that the ADA12 allele was linked to elevated bilirubin levels in newborn infants and it was a defense mechanism against asthma. Individuals carrying the ADA12 allele are found to be less common in people with asthma compared to those in the control group ($p<0.05$). In the group analyzed from birth, allergic rhinitis and/or conjunctivitis occurred more often in newborns who underwent phototherapy than among those who did not receive it ($p=0.046$). In conclusion, these findings back the theory that the ADA12 allele, by raising bilirubin levels in newborns, could shield infants from oxidative stress. This genetic trait may lead to a shift towards a Th1 immune response, hence reducing the likelihood of allergic symptoms in later life. The ADA12 allele may play an effective role in the parabolic relationship between allergic diseases and jaundice/phototherapy.[23] There is a need for further research to obtain more precise information.

One of the limitations of our study is the small number of patients. Additionally, there was a high frequency of caesarean section deliveries in our control group, which is known to be a risk factor for allergic diseases.[24] While there were no differences in other factors that may influence the development of allergic diseases between our control and patient groups, the disparity in caesarean section deliveries may have an impact on the prevalence of allergic diseases in our control group.

The strength of our study lies in the inclusion of patients across a wide age range, from three to 18 years old. In other studies examining the relationship between the development of allergic diseases and neonatal hyperbilirubinemia, cases within a limited age range were assessed. Due to the broad age range in our study, we believe it is important in providing a more accurate reflection of real-life data.

CONCLUSION

In conclusion, our study did not find a significant relationship between phototherapy treatment and the incidence of childhood asthma, AR, and AD. This result, which contradicts the findings of most previous studies, may be attributed to the inclusion of only patients who received phototherapy in our study. More extensive research is required in this area.

Statement

Ethics Committee Approval: The University of Health Sciences, Turkey. Istanbul Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center Clinical Research Ethics Committee granted approval for this study (date: 25.04.2014, number: 54).

Author Contributions: Concept – MK, FÇ, MD, FMY; Design – MK, FÇ, MD, FMY; Supervision – MK, FÇ, MD, FMY; Resource – MK, FÇ; Materials – MK, FÇ; Data Collection and/or Processing – MK, FÇ; Analysis and/or Interpretation – MK, FÇ, MD, FMY; Literature Search – MK, FÇ; Writing – MK; Critical Reviews – MD, FMY.

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REFERENCES

1. Kansen HM, Lebbink MA, Mul J, van Erp FC, van Engelen M, de Vries E, et al. Risk factors for atopic diseases and recurrent respiratory tract infections in children. Pediatr Pulmonol 2020;55:3168–79.
2. Hallit S, Raherison C, Malaeb D, Hallit R, Kheir N, Salameh P. The AAA risk factors scale: A new model to screen for the risk of asthma, allergic rhinitis and atopic dermatitis in children. Med Princ Pract 2018;27:472–80.
3. Yu B, Dai L, Chen J, Sun W, Chen J, Du L, et al. Prenatal and neonatal factors involved in the development of childhood allergic diseases in Guangzhou primary and middle school students. BMC Pediatr 2019;19:479.
4. Olusanya BO, Kaplan M, Hansen TWR. Neonatal hyperbilirubinaemia: A global perspective. Lancet Child Adolesc Health 2018;2:610–20.
5. UNICEF. The state of the world's children 2017. Children in a digital world. December, 2017. Available at: https://www.unicef.org/reports/state-worlds-children-2017. Accessed Mar 25, 2018.
6. Maruhashi T, Kihara Y, Higashi Y. Bilirubin and endothelial function. J Atheroscler Thromb 2019;26:688–96.
7. Bhutani VK; Committee on Fetus and Newborn; American Academy of Pediatrics. Phototherapy to prevent severe neonatal hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2011;128:e1046–52.
8. Faulhaber FRS, Procianoy RS, Silveira RC. Side effects of phototherapy on neonates. Am J Perinatol 2019;36:252–7.
9. Aspberg S, Dahlquist G, Kahan T, Källén B. Is neonatal phototherapy associated with an increased risk for hospitalized childhood bronchial asthma? Pediatr Allergy Immunol 2007;18:313–9.
10. Yahia S, Shabaan AE, Gouida M, El-Ghanam D, Eldegla H, El-Bakary A, et al. Influence of hyperbilirubinemia and phototherapy on markers of genotoxicity and apoptosis in full-term infants. Eur J Pediatr 2015;174:459–64.
11. Rosenstein BS, Ducore JM. Enhancement by bilirubin of DNA damage induced in human cells exposed to phototherapy light. Pediatr Res 1984;18:3–6.
12. Liu Y, Li P, Lu J, Xiong W, Oger J, Tetzlaff W, et al. Bilirubin possesses powerful immunomodulatory activity and suppresses experimental autoimmune encephalomyelitis. J Immunol 2008;181:1887–97.

13. Aspberg S, Dahlquist G, Kahan T, Källén B. Confirmed association between neonatal phototherapy or neonatal icterus and risk of childhood asthma. Pediatr Allergy Immunol 2010;21:e733–9.
14. Kuzniewicz MW, Niki H, Walsh EM, McCulloch CE, Newman TB. Hyperbilirubinemia, phototherapy, and childhood asthma. Pediatrics 2018;142:e20180662.
15. Tham EH, Loo EXL, Goh A, Teoh OH, Yap F, Tan KH, et al. Phototherapy for neonatal hyperbilirubinemia and childhood eczema, rhinitis and wheeze. Pediatr Neonatol 2019;60:28–34.
16. Sun HL, Lue KH, Ku MS. Neonatal jaundice is a risk factor for childhood allergic rhinitis: A retrospective cohort study. Am J Rhinol Allergy 2013;27:192–6.
17. Wei CC, Lin CL, Shen TC, Kao CH. Neonatal jaundice and risks of childhood allergic diseases: A population-based cohort study. Pediatr Res 2015;78:223–30.
18. Safar H, Elsary AY. Neonatal jaundice: The other side of the coin in the development of allergy. Am J Perinatol 2020;37:1357–63.
19. Egeberg A, Andersen YM, Gislason G, Skov L, Thyssen JP. Neonatal risk factors of atopic dermatitis in Denmark - Results from a nationwide register-based study. Pediatr Allergy Immunol 2016;27:368–74.
20. Gau C-C, Lee WF, Lu I-C, Lin LL, Wu CY, Tsai HJ, et al. Neonatal jaundince and risk of allergic diseases by 6 years of age: A cohort study. J Allergy Clin Immunol 2018;141:AB5.
21. Das RR, Naik SS. Neonatal hyperbilirubinemia and childhood allergic diseases: A systematic review. Pediatr Allergy Immunol 2015;26:2–11.
22. Kuniyoshi Y, Tsujimoto Y, Banno M, Taito S, Ariie T. Neonatal jaundice, phototherapy and childhood allergic diseases: An updated systematic review and meta-analysis. Pediatr Allergy Immunol 2021;32:690–701.
23. Gloria-Bottini F, Bottini E. Is there a role of early neonatal events in susceptibility to allergy? Int J Biomed Sci 2010;6:8–12.
24. Gerlich J, Benecke N, Peters-Weist AS, Heinrich S, Roller D, Genuneit J, et al. Pregnancy and perinatal conditions and atopic disease prevalence in childhood and adulthood. Allergy 2018;73:1064–74.

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ORIGINAL ARTICLE

Investigation of factors by real-time polymerase chain reaction analysis in hospitalized patients with acute lower respiratory tract infections

[1]Ceren YAPAR GÜMÜŞ
[2]Feyza Mediha YILDIZ

[1]Department of Pediatrics, Ordu University Faculty of Medicine, Ordu, Turkey

[2]Department of Pediatrics, University of Health Sciences, Turkey. Istanbul Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center, Istanbul, Turkey

ORCID ID
CYG : 0000-0001-6349-2514
FMY : 0000-0002-8684-0101

ABSTRACT

Objective: Acute bronchiolitis and/or pneumonia are generally referred to as lower respiratory tract infections (LRTI). It was aimed to investigate the agents in LRTI, which is one of the most important causes of childhood deaths, by real-time polymerase chain reaction (PCR) method from the nasopharyngeal aspirate.

Material and Methods: In our study, chest radiographs, clinical, demographic, laboratory characteristics, and disease agents obtained by real-time PCR were examined in patients aged 1 month to 18 years who were hospitalized with a prediagnosis of LRTI in the pediatric service during the year 2019.

Results: The patients' mean age was 25.89±36.72 months, and 57.05% (n=279) of the study group were male. Patients are grouped monthly; of the study group, 69.3% were between the ages of one and 24 months, and 16.0% were between the ages of 24 and 60 months. In the study group, 38% (n=186) of 489 patients had a fever. In 93.9% of cases, a cough was present. Of the 489 patients in the study group, 175 (35.7%) had no detectable causative agent, while 314 (64.3%) had one or more. After analyzing individual factors, 28.34% of the study group had Rhinovirus as the causative agent.

Conclusion: The most frequent cause of LRTI was determined to be Rhinovirus in our investigation, in contrast to the general literature in our nation. Other data appear to be generally compatible with national and international literature.

Keywords: Lower respiratory tract infections, pediatric, RT-PCR.

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Correspondence: Ceren YAPAR GÜMÜŞ, MD. Ordu Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Ordu, Türkiye.
Tel: +90 452 226 52 14 **e-mail:** cerenyapar91@gmail.com

INTRODUCTION

Pneumonia, bronchopneumonia, and acute bronchiolitis are commonly referred to as lower respiratory tract infections (LRTIs). Acute bronchiolitis is the most common presentation of LRTI in the first years of life. In this age period, almost one out of every three children is diagnosed with acute bronchiolitis based on clinical findings, and hospitalization is considered appropriate in approximately 2–3% of children.[1] In a clinical study conducted in Türkiye, it was reported that the rate of hospitalization due to acute LRTI in children under two years of age was 20.5 per 1000 children and that half of these hospitalizations were acute bronchiolitis cases and the causative agent detected in 41% of these cases was Respiratory syncytial virus (RSV).[2] LRTI was responsible for 13.9% of the 5.30 million deaths in children under five in 2019, making it the most common cause of death for children aged one to fifty-nine months.[3] In children under two years of age, viral agents are responsible for 80% of the disease.[4] Among viral pathogens, RSV ranked first with 40%, followed by Adenovirus, Bocavirus, Parainfluenza, Rhinovirus, Human metapneumovirus (HMPV), Coronavirus, Parainfluenza, Influenza A and B.[5] Studies on the etiology and clinical outcomes of LRTI, which have significant morbidity and mortality rates, are of utmost importance. For this reason, in our study, we aimed to define the demographic and clinical characteristics of pediatric patients aged between 1 month and 18 years who were hospitalized with a prediagnosis of LRTI in the pediatric service of our hospital and to investigate the causative agents of the disease.

MATERIAL AND METHODS

Study Design: The study population consisted of patients between the ages of one month to 18 years who applied to a tertiary care training and research hospital in Istanbul in 2019 and were hospitalized in the pediatric service with a prediagnosis of LRTI and met the inclusion criteria. The medical records of the patients were retrospectively reviewed and chest radiographs taken during hospitalization were evaluated by an experienced pediatric radiologist. The number of study participants when the inclusion/exclusion criteria were applied was 489.

The inclusion criteria were as follows: The patient was between the ages of 1 month and 18 years, did not have any additional cardiac disease, and was hospitalized and treated with a prediagnosis of LRTI in the pediatric service of our hospital.

Exclusion criteria: Age <1 month, presence of additional cardiac disease, voluntary refusal of hospitalization by the patient's family/legal guardian.

The agents detected by real-time PCR in our hospital are Klebsiella pneumoniae, Influenza A, Influenza B, Parainfluenza Type 1, Parainfluenza Type 2, Parainfluenza Type 3, Parainfluenza Type 4, Mycoplasma pneumoniae, Enterovirus, HPMV, RSV A/B, Bocavirus, Rhinovirus, Coronavirus, Pandemic H1N1, Seasonal H1N1. The results of real-time PCR tests taken at the time of hospitalization of patients hospitalized with a prediagnosis of LRTI were reported as positive and negative.

Age groups were categorized as >60 months, 24–60 months, and 1–24 months. Initially, patients were classified as either causative or non-causative based on real-time PCR detection of the causative agent. The group in which the causative agent was detected was divided into subgroups as two and three causative agents detected/single causative agent detected.

Chest X-ray findings of the study population were evaluated by a pediatric radiologist. Findings were recorded as normal, atelectasis, peribronchial infiltration, increased aeration, reticulonodular infiltration, consolidation, increased vascular central markings, and blunting of the sinus. The study group was further subdivided into two subgroups: those with both of these findings and those with more than two radiologic findings.

According to medical history, clinical course, physical examination, and imaging findings, the study group was divided into four diagnostic groups: pneumonia, lobar pneumonia, bronchopneumonia, and bronchiolitis.

Statistical Analysis

The Statistical Package for the Social Sciences, version 22.0 software (SPSS Inc., Chicago, IL, USA) was used to analyze the study data. Descriptive data were presented as frequency and numerical data were presented as median (min–max) or mean±SD. The Kolmogrov-Smirnov test was used to evaluate the conformity of the data to normal distribution.

The chi-square test was used for the comparison of categorical data between groups. Pearson test or Fisher exact test was preferred according to the number of groups. The Mann-Whitney U test was used for intergroup comparison of numerical data not conforming to a normal distribution, and the independent sample t-test was used for intergroup comparison of numerical data conforming to a normal distribution. A logistic regression test was used to determine the predictive function and cause-effect relationship of the presence of a viral agent using binary or multiple variables.

Data are presented at a 95% confidence interval, $p<0.05$ was considered statistically significant, and $p=0.000$ values were presented as $p<0.001$.

Ethics Statement

The study was approved by the Zeynep Kamil Women and Children's Diseases Training and Research Hospital Clinical Research Ethics Committee on 21.08.2019 with decision number 82. This study was conducted by adhering to the Declaration of Helsinki.

RESULTS

Main Characteristics of the Study Group: The median age of the patients was 8.00 (1–196) months and the mean age was 25.89±36.72 months. There were 42.95% (n=210) females and 57.05% (n=279) males in the study group. When the patients were grouped based on months, 16.0% of the study group was between 24–60 months and 69.3% was between 1–24 months. When the patients were evaluated according to the months of admission to the hospital, it was found that admissions in January and December were more frequent than the other months. While 12.7% (n=62) of the patients were admitted in January, 19% (n=93) were admitted in December. Table 1 shows the study group's laboratory parameters.

Table 1: Laboratory parameters of the study group

Parameters	Mean	Standard deviation	Median	Minimum	Maximum
Hb (g/dL)	11.20	1.46	11.1	6.90	17.7
WBC (10^3/µL)	12.44	5.68	11.24	1.06	36.28
PLT (10^3/µL)	366.34	140.62	346.00	21.00	1011.00
CRP (mg/dL)	2.35	4.15	0.69	0.2	34.00

Hb: Hemoglobin; WBC: White blood cell count; PLT: Platelet count; CRP: C-reactive protein.

Fever, cough, sibilant rhonchi, prolonged expiratory phase of respiration, tachypnea, and crepitant rales were all noted as the patient's clinical findings upon admission. Cough was present in 93.9% of the 489 patients and constituted the most common finding.

The median duration of hospitalization in the study group was 5.00 (1–82) days and the mean was 7.89±5.48 days.

In the study group, one or more agents were detected in 314 (64.3%) of 489 patients, while no agent was detected in 175 (35.7%). When single agents were analyzed, seasonal H1N1 Influenza A was detected in 1 of 314 patients, Parainfluenza 2 in 1, Parainfluenza 4 in 2, Pandemic H1N1 Influenza A in 3, Enterovirus in 3, Influenza A in 3 patients, Coronavirus in 4 patients, Klebsiella pneumoniae in 5 patients, Mycoplasma pneumoniae in 7 patients, Parainfluenza 1 in 7 patients, Influenza B in 7 patients, Parainfluenza 3 in 9 patients, Bocavirus in 16 patients (5.09%), HMPV in 17 patients (5.41%), RSV in 69 patients (21.97%), and Rhinovirus in 89 patients (28.34%). While there were 16 patients with 3 or more agents, there were 55 patients (17.5%) with two viral agents. When the radiologic findings during hospitalization were analyzed, no pathologic radiologic findings were found in 36.2% of the cases (n=177). The most common single pathologic radiologic finding was consolidation with 20.2% (n=99), followed by peribronchial infiltration (n=68). The frequencies of radiologic findings are given in detail in Table 2.

Regarding the diagnosis, it was determined that 38.2% (n=187) of the patients had bronchiolitis and 41.7% (n=204) had bronchopneumonia. 67 patients were diagnosed with pneumonia and 31 with lobar pneumonia.

Table 2: Imaging findings of the study group

Imaging findings	Study group (n=489)	
	n	%
Normal	177	36.2
Single radiologic finding		
Atelectasis	14	2.9
Peribronchial infiltration	68	13.9
Increased aeration	8	1.6
Reticulonodular infiltration	12	2.5
Consolidation	99	20.2
Total	201	41.10
Dual Radiologic Findings		
Peribronchial + reticulonodular infiltration	5	1.0
Atelectasis + peribronchial infiltration	13	2.7
Consolidation + peribronchial İnfiltrasyon	29	5.9
Atelektasis + Retikülonodüler infiltration	5	1.0
Peribronchial infiltration + increased aeration	1	0.2
Atelectasis + consolidation	15	3.1
Consolidation + reticulonodular infiltration	6	1.2
Sinus Blunting + consolidation	5	1.0
Sinus Blunting + atelectasis	4	0.8
Sinus Blunting + peribronchial infiltration	2	0.4
Total	86	17.6
>2 radiologic findings	25	5.1

Statistical Analysis of Agents Detected by Real-time PCR

Eighteen (10.28%) of 175 patients, whose pathogen was not detected as a result of PCR, were admitted in summer, 30 (17.14%) in autumn, 37 (21.14%) in spring, and 90 (51.42%) in winter. Of the 243 patients who were found to have a single respiratory tract infection agent as a result of PCR, 22 (9.05%) were admitted to the hospital in summer, 54 (22.22%) in autumn, 77 (31.68%) in spring, and 90 (37.03%) in winter. Of 71 patients with more than one respiratory tract infection factor detected by PCR, 9 (12.67%) were admitted to the hospital in summer, 18 (25.35%) in spring, 20 (28.16%) in autumn, and 24 (33.8%) in winter. The frequency of admission to the hospital in the winter season in cases with no causative agents in PCR results is significantly higher than in patients with single or more than one respiratory tract agent (p=0.025).

Rhinovirus (68.51%) was detected in 37 of 54 patients admitted to hospital in the autumn season. No patient had RSV as the single respiratory tract infection agent this season.

Of the 90 patients admitted to the hospital in the winter season, RSV was detected in 53 (58.88%), Rhinovirus in 10 (11.11%), Bocavirus in 9 (10%), Pandemic H1N1-A, Influenza A, Mycoplasma pneumoniae, and HMPV in 3 cases each (3.33%). Parainfluenza 1 and Coronavirus were detected in 2 patients each.

Table 3: The relationship between laboratory parameters of cases with and without causative agents

Laboratory parameters	Causative agent	No causative agent	p
Hb (g/dL), Mean±SD	11.11±1.41	11.37±1.53	0.059
WBC (10^3/µL), Mean±SD	12.42±5.93	12.48±5.23	0.911
PLT (10^3/µL), Mean±SD	365.74±13.73	367.43±14.67	0.899
CRP (mg/dL), Median (Min–Max)	0.51 (0.2–25.76)	1.16 (0.20–34.00)	**0.003**

Hb: Hemoglobin; WBC: White blood cell count; PLT: Platelet count; CRP: C-reactive protein; Min: Minimum; Max: Maximum; SD: Standard deviation.

Of the 77 patients admitted in the spring season and the only respiratory tract infection agent detected by PCR, Rhinovirus was detected in 32 (41.55%), RSV in 16 (20.77%), HMPV in 8 (10.39%), and Influenza B in 7 (9.09%).

Rhinovirus was detected in 10 (45.5%), Bocavirus in 2 (9.09%), Parainfluenza Type 3, Mycoplasma pneumoniae, and Klebsiella pneumoniae in 3 (13.63%) of 22 patients admitted in the summer season. In this season, no patient had RSV as the single respiratory tract infection agent.

The age of 74.9% (n=182) of the 243 cases in which a single respiratory tract infection agent was detected by PCR was between 1 and 24 months. The age of 80% (n=4) of the patients with Klebsiella pneumoniae was between 1–24 months. 94.7% (n=18) of all Parainfluenza cases, 100% (n=4) of Coronavirus cases, 92.8% (n=64) of RSV cases, and 82.4% of HMPV cases were between 1–24 months of age.

Between the age groups of patients with one respiratory tract infection agent and patients with multiple respiratory tract infection agents, there was no statistically significant difference (p=0.701).

The frequency of negative PCRs obtained during hospitalization in patients with a diagnosis of lobar pneumonia was statistically significantly higher than in other patient groups (p<0.001).

Compared to other months, there was a significant increase in the probability of detecting a viral agent in September and January (p<0.001).

The CRP median of the group with no causative agent was statistically significantly higher than the CRP median of the group with a causative agent (p=0.003). The relationship between laboratory parameters of cases with and without causative agents is shown in Table 3.

The mean age (months) of the cases in which the agent was detected was significantly lower than the mean age of the cases in which the agent was not detected (20.54 vs. 35.51 months) (p<0.001).

The median duration of hospitalization in the study group was 5.00 (1–82) days, while the mean was 7.89±5.48 days. The mean duration of hospitalization in cases without causative agents was statistically significantly higher than in cases with causative agents (9.01 vs. 7.26; p<0.001).

Statistical Analysis of Data by Age Groups

The study group was categorized as >60 months (n=72), 24–60 months (n=78), and 1–24 months (n=339). The frequency of physical examination findings and the relationship between clinical findings and age groups are shown in Table 4.

The frequency of crepitant rales and fever was significantly lower in patients aged 1–24 months in the study group compared to other age groups (p<0.001), whereas the frequency of tachypnea, prolonged expiration, and rhonchi was significantly higher (p<0.001).

The frequency of radiologic findings according to age groups is presented in Table 5.

When the presence of pathologic imaging findings was analyzed according to age groups, it was observed that the frequency of pathologic imaging findings in children increased significantly with increasing age. While 93.1% of children older than 60 months had pathologic findings, 53.7% of children aged 1–24 months had at least one pathologic finding (p<0.001).

When the median length of hospitalization was analyzed according to age groups, the median length of hospitalization for children between 24–60 months and 1–24 months was 7 days (7 (4–24) days for 24–60 months; 7 (1–82) days for 1–24 months), while the median length of hospitalization for children over 60 months was 8 (3–53) days. Compared to other age groups, the median length of hospitalization for children over 60 months was found to be statistically significantly higher (p=0.009).

When the relationship between diagnoses and age groups was evaluated, pneumonia constituted 36.1% of the diagnoses in children older than 60 months, 15.4% in children aged 24–60 months, and 8.6% in children aged 1–24 months. There was a statistically significant correlation between the increase in the frequency of pneumonia and increasing age (p<0.001).

DISCUSSION

In the pediatric population, viral respiratory infections are a serious public health problem and an important cause of morbidity and mortality.[6,7] It has been emphasized that the prevalence of viral respiratory infections, which are responsible for 5 million child deaths annually in children under five years of age, is 2–3 times higher in children than in adults in developing countries.[8,9]

Viruses are the main pathogens in LRTI.[10] Real-time PCR analysis is a sensitive, rapid, and specific test for the detection of respiratory viruses, unlike conventional diagnostic methods to date. Literature studies show that the sensitivity of real-time PCR in detecting respiratory tract pathogens ranges between 95% and 100%, and the specificity between 91.3% and 100%.[11]

Table 4: The frequency of physical examination findings and the relationship between clinical findings and age groups

Description	1–24 months (n)	24–60 months (n)	>60 months (n)	p
Fever				**<0.001**
Yes	100	38	48	
No	239	40	24	
Cough				0.67
Yes	319	74	66	
No	20	4	6	
Sibilant rhonchi				**<0.001**
Yes	141	27	13	
No	198	51	59	
Prolonged expiratory phase of respiration				**<0.001**
Yes	288	57	33	
No	51	21	39	
Tachypnea				**<0.001**
Yes	215	29	20	
No	124	49	52	
Crepitant rales				**<0.001**
Yes	156	49	49	
No	189	29	23	

Table 5: Frequency of imaging findings by age groups

Radiological findings	1–24 months	24–60 months	>60 months	Total
Normal	157	15	5	177
Atelectasis	9	5	0	14
Peribronchial infiltration	56	9	3	68
Increased aeration	7	1	0	8
Reticulonodular infiltration	8	0	4	12
Consolidation	37	26	36	99
Dual findings	51	15	20	86
>2 findings	14	7	4	25
Total	339	78	72	**489**

In our study, we investigated the disease agents by real-time PCR, and the demographic, clinical, laboratory, and radiological imaging characteristics of patients aged between 1 month and 18 years admitted to a tertiary care training and research hospital in Istanbul in 2019 and hospitalized in the pediatric service with a prediagnosis of LRTI.

Although the pathogens of viral LRTI vary according to years and seasons, RSV is the most common agent in the literature. In a 2008 research performed by Mansbach et al.,[12] RSV was detected in 72% of the study group. In a study by Sarkar et al.,[13] in children with LRTI, RSV was found to be the causative agent in 40.68% of children. If we look at the studies in Türkiye, the prevalence of RSV ranges between 20% and 50%.[14–16] In our study, RSV was found to be a pathogen in 21.97% of 314 cases with causative agents. However, contrary to the literature, the major causative agent in our study was Rhinovirus (28.34%). According to the literature, these differences in rates may be attributed to the frequency of hospitalization, season of hospitalization, and age group.

In this study, RSV was detected as the predominant causative agent in the winter season, and Rhinovirus was found to be the predominant causative agent except in the winter season. Rhinovirus

dominance was also observed in the autumn season in the study performed by Jiang et al.[17] Although the causes of respiratory tract infections have their specific seasons, subgroup analysis did not provide a statistically significant result because there were not enough numbers for other subgroups in our study.

Analysis of the correlation between agent positivity and symptoms revealed that, aside from tachypnea frequency, there was no statistically significant difference between the agent's presence and other symptoms. Kamata et al.[18] found that patients infected with RSV were more likely to have rhonchi. In the study by Bharaj et al.,[19] no significant difference was found in the frequency of symptoms between cases with and without the causative agent. Similar results were obtained in the study by Papadopoulos et al.[20] Our study was found to be consistent with the literature in this regard.

In our study, it was shown that the median CRP of the group with no causative agents was statistically significantly higher than the group with the causative agent. This situation has revealed the prediction that some bacterial pathogens that cannot be demonstrated by PCR may also accompany the clinical picture.

The mean length of hospitalization of patients in whom the causative agent was not detected was statistically significantly higher than that of patients in whom the causative agent was detected (9.01 vs. 7.26; $p<0.001$). This was attributed to the advanced investigations performed in patients in whom the causative agent was not detected and the longer duration of treatment in LRTI cases caused by bacterial infections that could not be detected by the PCR method.

When the study population is analyzed according to age groups, it provides valuable information to make new contributions to the literature. In patients aged 1–24 months, the frequency of crepitant rales and fever was statistically significantly lower, and the frequency of prolonged expiration, rhonchi, and tachypnea was noticeably higher in the study group when compared to other age groups. In previous studies, it was observed that agent frequency analyses were performed according to age groups, and the frequency of findings was evaluated according to the agents. Therefore, this result is important in terms of its contribution to the literature.

When the presence of pathologic chest radiograph findings was analyzed according to age groups, it was observed that the frequency of pathologic findings increased significantly with increasing age in the study population. This can be evaluated together with the relationship between age and the causative agent detected. Further studies on this subject are needed.

It was found that the median duration of hospitalization was statistically significantly higher in patients aged over 60 months compared to other age groups. This result is important for pediatricians in the management of lower respiratory tract infections that require a multidisciplinary approach.

The first limitation of our study is its retrospective design. In this study, in which hospitalizations in the period before the COVID-19 pandemic period were evaluated, Coronavirus cases were few. Due to the statistically insufficient number of all agents found in the respiratory viral panel, we could not effectively compare our study with literature studies examining clinical features associated with specific viral respiratory tract pathogens, which constitutes a shortcoming of this study.

CONCLUSION

Contrary to the general literature in our country, Rhinovirus was found to be the most common cause of LRTI in our study. Other data are largely consistent with the national and international literature. Our study may guide planning general patient management according to age groups. The findings of this investigation will offer more information about the epidemiology and appropriate management of LRTIs in our country and help to reduce morbidity and mortality rates related to LRTIs.

Statement

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REFERENCES

1. National Institute for Health and Care Excellence. Bronchiolitis in children: Diagnosis and management guidance. 2021. Available at: https://www.nice.org.uk/guidance/ng9/evidence. Accessed Sep 30, 2022.
2. Hacımustafaoğlu M, Celebi S, Bozdemir SE, Ozgür T, Ozcan I, Güray A, et al. RSV frequency in children below 2 years hospitalized for lower respiratory tract infections. Turk J Pediatr 2013;55:130–9.
3. Perin J, Mulick A, Yeung D, Villavicencio F, Lopez G, Strong KL, et al. Global, regional, and national causes of under-5 mortality in 2000-19: An updated systematic analysis with implications for the Sustainable Development Goals. Lancet Child Adolesc Health 2022;6:106–15.
4. Hamano-Hasegawa K, Morozumi M, Nakayama E, Chiba N, Murayama SY, Takayanagi R, et al. Comprehensive detection of causative pathogens using real-time PCR to diagnose pediatric community-acquired pneumonia. J Infect Chemother 2008;14:424–32.
5. Drummond P, Clark J, Wheeler J, Galloway A, Freeman R, Cant A. Community acquired pneumonia--a prospective UK study. Arch Dis Child 2000;83:408–12.
6. Heikkinen T. Respiratory viruses and children. J Infect 2016;72(Suppl):S29–33.
7. Liolios L, Jenney A, Spelman D, Kotsimbos T, Catton M, Wesselingh S. Comparison of a multiplex reverse transcription-PCR-enzyme hybridization assay with conventional viral culture and immunofluorescence techniques for the detection of seven viral respiratory pathogens. J Clin Microbiol 2001;39:2779–83.
8. Ozdemir S, Ozturk TC, Metiner Y, Ak R, Ocal O. Evaluation of the prescriptions written for upper respiratory tract infections. North Clin Istanb 2015;2:107–14.

9. Templeton KE. Why diagnose respiratory viral infection? J Clin Virol 2007;40(Suppl 1):S2–4.
10. Tregoning JS, Schwarze J. Respiratory viral infections in infants: Causes, clinical symptoms, virology, and immunology. Clin Microbiol Rev 2010;23:74–98.
11. Mahony JB. Detection of respiratory viruses by molecular methods. Clin Microbiol Rev 2008;21:716–47.
12. Mansbach JM, Piedra PA, Teach SJ, Sullivan AF, Forgey T, Clark S, et al. Prospective multicenter study of viral etiology and hospital length of stay in children with severe bronchiolitis. Arch Pediatr Adolesc Med 2012;166:700–6.
13. Sarkar S, Ratho RK, Singh M, Singh MP, Singh A, Sharma M. Comparative analysis of epidemiology, clinical features, and cytokine response of respiratory syncytial and human metapneumovirus ınfected children with acute lower respiratory ınfections. Jpn J Infect Dis 2022;75:56–62.
14. Sancakli O, Yenïgün A, Kırdar S. Results of polymerase chain reaction in nasopharyngeal swab specimens of patients with lower respiratory tract infection. J Pediatr Inf 2012;6:84–9.
15. Bicer S, Giray T, Çöl D, Erdağ GÇ, Vitrinel A, Gürol Y, et al. Virological and clinical characterizations of respiratory infections in hospitalized children. Ital J Pediatr 20137;39:22.
16. Akçalı S, Yılmaz N, Güler Ö, Şanlidağ T, Anıl M. The frequency of respiratory tract viral agents in children with lower respiratory tract infections. Turk Arch Pediatr 2013;48:215–20.
17. Jiang H, Yang T, Yang C, Lu Y, Yi Z, Zhang Q, et al. Molecular epidemiology and clinical characterization of human rhinoviruses circulating in Shanghai, 2012-2020. Arch Virol 2022;167:1111–23.
18. Kamata K, Thein KN, Di Ja L, Win NC, Win SMK, Suzuki Y, et al. Clinical manifestations and outcome of viral acute lower respiratory infection in hospitalised children in Myanmar. BMC Infect Dis 2022;22:350.
19. Bharaj P, Sullender WM, Kabra SK, Mani K, Cherian J, Tyagi V, et al. Respiratory viral infections detected by multiplex PCR among pediatric patients with lower respiratory tract infections seen at an urban hospital in Delhi from 2005 to 2007. Virol J 2009;6:89.
20. Papadopoulos NG, Moustaki M, Tsolia M, Bossios A, Astra E, Prezerakou A, et al. Association of rhinovirus infection with increased disease severity in acute bronchiolitis. Am J Respir Crit Care Med 2002;165:1285–9.