MARMARA
MEDICAL JOURNAL

Original Article

https://dergipark.org.tr/tr/pub/marumj

Comparison of respiratory morbidity in late preterm infants and intrauterine growth retarded infants at school-age

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Submitted: 31.03.2022 **Accepted:** 17.06.2022

ABSTRACT

Objective: We aimed to determine respiratory morbidity of late preterm infants versus infants with intrauterine growth retardation (IUGR) at school-age.

Patients and Methods: Late preterm appropriate for gestational age (AGA) infants (34-36, 6/7 weeks) (Group 1), IUGR infants (Group 2), extremely preterm AGA (Group 3) and term AGA infants (Group 4) born between 2004 and 2008 were included in this case-control study and assessed for respiratory morbidity at school-age. We evaluated the impact of late preterm compared with IUGR and term gestation on respiratory morbidity by using validated American Thoracic Society – Division of Lung Diseases (ATS-DLD-78-C) and the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires. Questionnaires on wheezing, infectious respiratory morbidity, and physician-diagnosed asthma panels were constituted and groups were compared.

Results: A total of 160 patients were enrolled in the study and 97 (60.6%) of them were boys. Respiratory morbidities at school-age were found to be significantly higher in both late preterm and IUGR groups when compared to term controls. Each weekly increase in gestational age reduced the risk for wheezing episodes (OR perGW:0.82,95%CI:0.71-0.97, p:0.02). Regarding infectious respiratory morbidities, there was a significant increase when the number of people living at home increased (OR perperson:1.79,95%CI:1.12-2.87, p:0.01), and a decrease in female gender (OR:0.41,95%CI:0.17-0.99, p:0.04) and in the week of gestation (OR perGW:0.84,95%CI:0.71-1.00, p:0.04). Atopic dermatitis (OR:5.26,95%CI:1.57-17.69, p<0.01) and maternal asthma (OR:5.38,95%CI:1.17-24.60, p:0.03) history were found to be risk factors for asthma.

Conclusion: Being IUGR may be an important risk factor for respiratory morbidity at school-age. Further studies are needed on this subject.

Keywords: Premature Birth, Late preterm, Fetal Growth Retardation, Asthma, School-age

1. INTRODUCTION

Preterm births have increased from 9.5% to 12.7% in the last 3 decades and 60-70% of this change is due to the increased prevalence of late preterm births [1]. Until recently, protocols prepared for term babies were used for late preterm infants, which include the most important part of this increase observed in preterm births. However, it was shown that these babies face increased morbidity and mortality, especially in respiratory and neurodevelopmental aspects both in the neonatal period and in school-age period when compared to term infants [2]. Neonatal morbidities such as respiratory distress syndrome (RDS), transient tachypnea of the newborn and neonatal pneumonia were more common in preterm infants than terms; and at school-age decreased lung capacity, increased bronchial asthma episodes and respiratory tract infections were more frequently found. In a study by Kotecha et al., respiratory morbidity was found to be 10 times higher in this group compared to term infants [1].

On the other hand, IUGR causes respiratory problems in later life by giving rise to decreased lung function and early respiratory morbidity, as well as impaired lung function in infancy [3]. However, few studies have been conducted on the comparative evaluation of school-age respiratory morbidity of late preterm infants and newborns with IUGR [4]. The presence of prematurity in IUGR infants causing respiratory morbidity is important to determine the risk group for long-term follow-up.

Our hypothesis was that those children with late preterm and IUGR birth history have increased respiratory morbidity at school age compared to their healthy term birth history peers. We

How to cite this article: Us MC, Vatansever U, Duran R, Acunas B. Respiratory morbidity of late preterm vs intrauterine growth retarded infants at school-age. Marmara Med J 2022; 3; 35(3):335-342. doi: 10.5472/marumj.1195309

ISSN: 1309-9469

http://doi.org/10.5472/marumj. 1195309
Marmara Med J 2022;35(3): 335-342

aimed to evaluate respiratory morbidity of children who have late preterm and IUGR history and compare them with healthy peers at school age and point out the effects of risk factors encountered in the neonatal period for respiratory morbidity at school age.

2. PATIENTS and METHODS

Our study is a case-control study in which the school-age respiratory morbidity of newborns with late preterm and IUGR birth history who were followed and treated in the neonatology department between January 2006 and December 2008 were evaluated.

A total number of 160 children were included in the study. Children who were admitted to the neonatal intensive care unit and/or those who were born in our hospital and followed up with their mothers between January 2006 – December 2008 and reevaluated at school age (5-7 years old) during the study, were divided into three main groups: a) Late preterm appropriate for gestational age (AGA) infants (n:50): according to the new BALLARD scoring system [5] with gestational age 34-36 6/7 and were at the 10-90th percentile according to the Fenton growth curves [6] (Group 1) b) Newborns with IUGR (n:50): term or preterm infants below 10th percentile according to the values calculated according to Fenton growth curves [6] (Group 2) and, c) the healthy term (gestation week 38-42 weeks), AGA newborns (n:50) born between January 2006 and December 2008, were included in the study as the control group (Group 4). In addition to these main groups, group 2 was divided into two subgroups to compare the effect of IUGR in different gestational ages: preterm IUGR infants (<34 weeks of gestation) (n:10) (Group 2a), late preterm (between 34-36 6/7 gestational age) IUGR infants (n:19) (Group 2b) were divided into subgroups. An equal number of preterm AGA infants (<34 weeks of gestation) was added as the last group to compare the effect of being IUGR in preterms' (Group 3) (n:10) (Figure 1 Flow Chart of the study). Patients with major anomalies, patients who did not come to the school-age assessment or /and rejected to sign the informed consent form were excluded from the study.

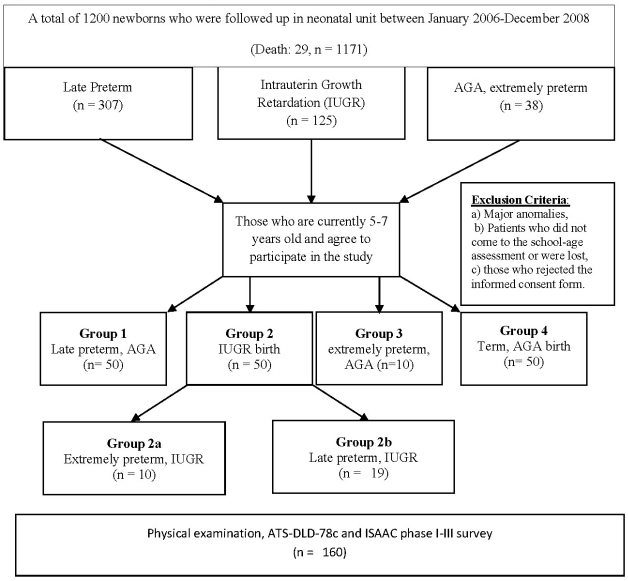

Figure 1. Flow chart of the study

Early (perinatal-neonatal), natal and postnatal period data were recorded from the hospital database system and patient files. The morbidities observed during the follow-up of the newborns, the duration of hospitalization, need for oxygen, surfactant administration, positive pressure ventilation requirement, and need for mechanical ventilation support and duration were documented from patient file records. During the study, the study and control group cases that were of school age and had perinatal parameters as defined above were contacted by telephone and invited to the outpatient clinic. Anthropometric measurements of all patients were taken (TBS model, scale with serial number 1212430 and height meter, Tartımsan, Istanbul, Turkiye). Demographic information, socioeconomic level, mother/father education level, mother's smoking status and medical history were questioned, and physical examinations of the patients were performed. The validated Turkish forms of American Thoracic Society – Division of Lung Diseases (ATS-DLD-78-C) [7] and International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires [8] were tested on 10 randomly selected patients by 2 different investigators to evaluate their intelligibility for screening respiratory diseases. The ATS-DLD-78-C questionnaire consisted of 46 questions with 3 options (yes, no, unknown) in 7 sections (socio-demographic characteristics, cough, sputum, wheezing, chest diseases, other diseases, and family history). The ISAAC questionnaire consisted of 31 questions in 2 parts (environmental factors, wheezing) most of which had 2 answer options (yes, no). In the wheezing section of the questionnaire the presence of wheezing was questioned in the first 2 questions, the number of symptom days in the following 3 multiple-choice questions, and the exercise and symptoms, nighttime symptoms, and asthma in the last 3 questions. The questionnaires were applied separately to both mother and father. After comparing the answers, it was decided that the questions were understandable. After the physical examination, the questionnaire forms were filled in face-to-face by the research doctor who did not know the patient's medical history (M.C.U).

Responses with "yes" to the survey questions include; the presence of wheezing/wheezing in the chest independent of having a cold, presence of wheezing in the chest day/night, presence of two or more wheezing episodes causing shortness of breath, the need of using medication during wheezing attacks causing shortness of breath, one or more of the presence of wheezing episodes after exercise or playing games "Respiratory morbidity 1 – wheezing panel", presence of hospitalization due to severe respiratory infection under 2 years of age, having had more than 1 previous bronchiolitis/bronchitis/pneumonia or two or three of them, more than 3 days in the last 3 years of chest disease, cough/sputum attacks lasting at least for a week or longer, sputum, breast fullness, cough present for more than 3 months of the year "Respiratory morbidity 2 – infectious respiratory morbidity panel", presence of physician-diagnosed asthma history, current asthma, and the presence of a history of being followed up with a diagnosis of asthma "Respiratory morbidity 3 – physician-diagnosed asthma panel" [9-13].

Ethics committee approval was obtained for the study from the Trakya University Faculty of Medicine Local Ethics Committee numbered 18/5 and protocol number TÜTF-GOKAEK 2013/150, and registered with Clinical Trials (NCT04849494).

http://doi.org/10.5472/marumj.1195309
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Statistical Analysis

SPSS version 19 license number: 10240642 was used as a statistics program in the study. The minimum sample size required to obtain statistically significant results using the random sampling method was 160 in total, and it was determined a minimum of 50 for each group in late preterm, IUGR and the control groups (Pi1: 0.198, Pi2: 0.028, Alpha: 0.05, n: 50. power 80%). There was no missing data. While evaluating the study data, T-test or Mann-Whitney U test were used in samples independent of one-way analysis by evaluating the normal distribution of the data in comparing the quantitative data. A Chi-square test was used for comparing qualitative data between the two groups. Logistic regression analysis (Likelihood Ratio) method was used, taking respiratory morbidity as the dependent variable and risk factors as the independent variables. A value of p <0.05 was accepted as the limit for a significant difference.

3. RESULTS

When the early demographic data of the study and control groups were compared, no statistically significant difference was found between groups in terms of gender. Cesarean birth and multiple pregnancy rates in the study groups (Group 1, Group 2 and Group 3) were found to be statistically significantly higher when compared to Group 4 (respectively p <0.01, p <0.01). In terms of the week of gestation there was a statistically significant difference between the study Groups and Group 3 was significantly lower (p<0.001). As expected, it was found that the mean birth weight, birth length and birth head circumference of Group 1 cases were statistically significantly higher than Group 2 and Group 3 (p <0.01 for all). The 1st minute Apgar score was found significantly higher in Group 1 cases (p: 0.04). No statistically significant difference was found between the groups in the 5-minute Apgar median (Table I). There was no statistically significant difference between the groups in terms of anthropometric measurements at school-age. The socioeconomic levels of the groups were found to be similar (Table I).

Table I. *Comparison of demographic, socioeconomic and perinatal data of groups*

		Group 1 (n: 50)		Group 2 (n: 50)		Group 3 (n: 10)		Group 4 (n: 50)	p*
		n (%)		**n (%)**		**n (%)**		**n (%)**	
Gender	**Male**	29 (58)		32 (64)		7 (70)		30 (60)	0.82
	Female	21 (42)		18 (36)		3 (30)		20 (40)	
Type of Delivery	**Normal Birth**	9 (18) [a]		8 (16) [a]		2 (20) [a]		38 (76) [b]	**<0.01**
	Caesarean section	41 (82)		42 (84)		8 (80)		12 (24)	
Multiple pregnancy		24 (48) [a]		25 (50) [a]		6 (60) [a]		0 (0) [b]	**<0.01**
Mechanical ventilator requirement		3 (6) [a]		11 (22) [b]		4 (40) [c]			**0.02**
		Mean, SD	**Median**	**Mean, SD**	**Median**	**Mean, SD**	**Median**		p**
Gestational age (week±SD)		35.2± 0.9	35	34.8± 2.1	35	30.3±1.9	30		**<0.01**
Birth weight (gram±SD)		2210.4±533.7	2105	1662.2±341.1	1620	1353.3±245.5	1347		**<0.01**
Birth height (cm±SD)		44.9±2.8	44	42.6±3.3	43.5	39.6±2.2	38.5		**<0.01**
Birth head circumference (cm±SD)		31.5±1.8	31.25	29.9±2.3	30.1	27.9±2.2	27.5		**<0.01**
Apgar score	**Minute 1**	8.3±1.1	9	7.6±1.7	8	6.8±1.8	6.5		**0.04**
	Minute 5	9.5±0.8	10	9.2±1.2	9	8.6±1.1	8.5		0.10
Number of days of mechanical ventilation		2.0±1.4	1	3.6±2.3	5	4.1±3.3	4		0.44
Total number of days with oxygen		2.3±5.8	0	2.8±8.3	1	8.6±17.6	4.5		0.33
Length of hospital stay (day)		10.1±8.9	9	14.9±16.2	9	27.8±23.2	24		0.16
		Mean,SD		**Mean,SD**		**Mean,SD**		**Mean,SD**	p**
Age (month)[a]		75.3±8.4		79.6±7.7		74.9±6.3		76.4±8.3	0.20
Weight (kg)[a]		22.5±5.1		23.0±4.8		22.4±4.2		21.6±3.5	0.29
Height (cm)[a]		119±7		122±6		120±6.2		116±7	0.10
BMI (kg/m^2)[a]		15.5±2.5		15.1±1.8		15.3±1.0		15.7±1.7	0.33
Number of people living in the house		4.3±0.6		4.3±0.7				4.36±0,7	0.93
		n (%)		**n (%)**		**n (%)**		**n (%)**	p*
Socioeconomic Level	**Good**	3 (6)		2 (4)		1 (10)		3 (6)	0.95
	Avarage	45 (90)		47 (94)		8 (80)		46 (92)	
	Low	2 (4)		1 (2)		1 (10)		1 (2)	
Physician diagnosed GOR		14 (28) [a]		13 (26) [a]		2 (20) [a]		5 (10) [b]	**0.04**
History of atopic dermatitis		10 (20) [a]		11 (22) [a]		3 (40) [a]		1 (2) [b]	**0.02**
Having a pet in the house		11 (22)		8 (16)		0 (0)		15 (30)	0.24
Maternal smoking		14 (28)		19 (38)		3 (30)		20 (40)	0.40
Maternal asthma history		9 (18) [a]		15 (30) [a]		1 (10) [b]		5 (10) [b]	**0.03**

*Chi-square; ** Kruskal-Wallis test; PPV: Positive pressure ventilation, same letters indicates no significant relationship between groups and each different letter indicates a statistically significant difference at the p<0.05 level; MAS: Meconium aspiration syndrome, BMI: Body mass index, GOR: gastroesophageal reflux.[a] measurements and sociodemographic data has assessed at school-age

http://doi.org/10.5472/marumj.1195309
Marmara Med J 2022;35(3): 335-342

Table II. *Respiratory morbidity questionnaires of study and control groups*

	Group 1 (n: 50)	Group 2 (n: 50)	Group 4 (n: 50)	p*
	n (%)	n (%)	n (%)	
Congested in chest or bring up phlegm apart from colds	9 (18)	4 (8)	1 (2)	**0.01**[a,b]
Congested or bring up phlegm, sputum or mucus from his/her chest 3 months a year	6 (12)	4 (8)	0 (0)	**0.04** [a,b]
Attacks of cough, chest congestion or phlegm lasting for ≥1 week /year	22 (44)	23 (46)	9 (18)	**<0.01** [a,b]
Wheezy or whistling occasionally apart from cold	6 (12)	11 (22)	0 (0)	**<0.01** [a,b]
Attack of wheezing causing short of breath	13 (26)	16 (32)	3 (6)	**<0.01** [a,b]
Attacks of wheezing after exercising	9 (18)	8 (16)	2 (4)	**0.04** [a,b]
During past 3 years any chest illness keeping him/her from usual activities for as much as 3 days	15 (30)	23 (46)	1 (2)	**<0.01** [a,b]
More congested than usual with any of these illness	15 (30)	20 (40)	0 (0)	**0.02** [a,b]
Doctor diagnosed asthma	9 (18)	15 (30)	5 (10)	**0.03** [a,b]
Hospitalization for severe chest illness/cold <age 2	10 (20)	16 (32)	4 (8)	**<0.01** [a,b]
Severe chest illness/cold <age 2	14 (28)	25 (50)	8 (16)	**<0.01** [a,b]
Doctor diagnosed allergic reaction to pollen or dust	8 (16)	8 (16)	1 (2)	**0.01** [a,b]
Hospitalization for severe chest illness /cold <age 2	10 (20)	16 (32)	-	**0.01**
Any other severe chest illness or chest cold < age 2	14 (28)	25 (50)	-	**0.02**
≥2 attack of wheezing causing shortness of breath	13 (26)	16 (32)	-	**0.02**

*Chi-square, a: Significant relationship between Group1 and Group 4, b: Significant relationship between Group 2 and Group 4, a,b: Significant relationship between both Group 1 and 4 and Group 2 and 4

Table III. *Comparison of the groups in terms of Respiratory morbidity panels*

	Group 1 (n: 50)	Group 2 (n: 50)	Group 4 (n: 50)	p*	Group 1 (n: 50)	Group 2b (n: 19)	p*	Group 2a (n: 10)	Group 3 (n: 10)	p*
	n (%)	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Respiratory morbidity 1	27 (54)[a]	24 (48)[b]	13 (26)[a,b]	**0.01**	27 (54)	7 (36.8)	0.20	9 (90)	1 (10)	**0.002**
Respiratory morbidity 2	16 (32)	13 (26)	9 (18)	0.27	16 (32)	2 (10.5)	0.07	6 (60)	5 (50)	0.46
Respiratory morbidity 3	9 (18)[a]	15 (30)[b]	4 (8)[a,b]	**0.01**	9 (18)	3 (15.8)	0.82	5 (50)	1 (10)	**0.05**
Total respiratory morbidity	28 (56)[a]	24 (48)[b]	18 (36)[a,b]	**0.05**	28 (56)	7 (36.8)	0.15	9 (90)	5 (50)	0.18

*Chi-square, a: Significant relationship between Group1 and Group 4, b: Significant relationship between Group 2 and Group 4, a,b: Significant relationship between both Group 1 and 4 and Group 2 and 4; Respiratory morbidity 1 wheezing panel, Respiratory morbidity 2 infectious respiratory morbidity panel, Respiratory morbidity 3 physician-diagnosed asthma panel.

Compared with term gestation, both late preterm gestation and being IUGR were associated with a significant increase in most of the respiratory morbidities at school-age such as physician-diagnosed asthma, allergic rhinitis, wheezing and whistling episodes, exercise-induced wheezing, and episodes of shortness of breath, etc. Furthermore, the presence of IUGR was significantly associated with an increase in >2 episodes of shortness of breath (p=0.02), hospital admission for severe respiratory infection before age 2 (p=0.01), and severe chest disease before the age of 2 (p=0.02) (Table II).

Respiratory morbidity 1-3 and total respiratory morbidity were significantly higher in infants with both late preterm and IUGR history compared to the control group. When late preterm AGA and IUGRs were compared, no statistically significant difference was found between the groups. Respiratory morbidity 1 and 3 were found to be statistically significantly higher in extremely preterm patients with IUGR compared to AGA controls (Table III).

Logistic regression analysis was performed to show the effects of factors on wheezing phenotype, infectious respiratory morbidity, and physician-diagnosed asthma. When the effect of variables on wheezing (respiratory morbidity 1) was examined, gestational age (p: 0.02, OR: 0.83, 95% confidence interval: 0.71-0.97) was found to be significant. When the effect of variables on infectious respiratory morbidity (respiratory morbidity 2) was examined, gestational age (p: 0.04, OR: 0.84, 95% confidence interval: 0.71-1.00) and the number of people living in the house (p: 0.01, OR: 1.79, 95% confidence interval: 1.12-2.87) were found to be significant. Accordingly, infectious respiratory morbidity decreased 0.84 times with each weekly increase in the week of gestation, while the number of people living at home increased 1.79 times. Examining the effect of variables on the physician-diagnosed asthma panel (respiratory morbidity 3), maternal asthma diagnosis (p: 0.03, OR: 5.38, 95% confidence interval: 1.17-24.60) and the presence of atopic dermatitis in the patient (p: <0.01, OR: 5.26, 95% confidence interval: 1.57-17.69) were found to be significant. The probability of physician-diagnosed asthma increased by 5.38 times in the mother, while the history of atopic dermatitis increased by 5.26 times (Table IV).

http://doi.org/10.5472/marumj.1195309
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Table IV. *Logistic regression analysis of respiratory morbidity panels*

	Respiratory morbidity 1			Respiratory morbidity 2				Respiratory morbidity 3			
Variables	Odds ratio	95% CI	p*	Variables	Odds ratio	95% CI	p*	Variables	Odds ratio	95% CI	p*
Gender Female	0.69	0.34-1.42	0.32	Gender Female	**0.41**	**0.17-0.99**	**0.04**	Gender Female	0.53	0.19-1.49	0.23
Having a pet in the house	1.47	0.63-3.40	0.36	Having a pet in the house	0.60	0.21-1.73	0.35	Having a pet in the house	0.47	0.12-1.87	0.28
Maternal smoking	1.34	0.65-2.79	0.42	Maternal smoking	0.84	0.34-2.03	0.70	Maternal smoking	1.18	0.42-3.27	0.74
Maternal asthma history	0.98	0.23-4.19	0.98	Maternal asthma history	2.17	0.45-10.33	0.32	Maternal asthma history	**5.38**	**1.17-24.60**	**0.03**
IUGR	1.20	0.53-2.69	0.65	IUGR	1.60	0.62-4.11	0.32	IUGR	0.46	0.16-1.33	0.15
Gestation week	**0.83**	**0.71-0.97**	**0.02**	Gestation week	**0.84**	**0.71-1.00**	**0.04**	Gestation week	0.89	0.73-1.10	0.30
Number of people living in the house	0.81	0.53-1.22	0.31	Number of people living in the house	**1.79**	**1.12-2.87**	**0.01**	Number of people living in the house	1.09	0.63-1.91	0.73
History of atopic dermatitis	1.81	0.61-5.37	0.28	History of atopic dermatitis	1.70	0.52-5.56	0.37	History of atopic dermatitis	**5.26**	**1.57-17.69**	**<0.01**
Physician diagnosed GOR	1.62	0.12-20.89	0.71	Physician diagnosed GOR	0.80	0.05-12.1	0.87	Physician diagnosed GOR	2.40	0.17-33.56	0.51
Constant	**7.30**		**0.01**	Constant	3.95		0.23	Constant	3.57		0.36

*Stepwise lojistic regression model (enter), GOR: gastroesophageal reflux, CI: confidence interval; Respiratory morbidity 1 wheezing panel, Respiratory morbidity 2 infectious respiratory morbidity panel, Respiratory morbidity 3 physician-diagnosed asthma panel.

Respiratory morbidity increased 1.8 times with an increase on the day of hospitalization (p: 0.003, OR 1.80, 95% confidence interval: 1.02-1.14), it was seen 0.02 times less in infants requiring mechanical ventilation (p: 0.04, OR: 0.01-0.75, 95% confidence interval: 0.01-0,75). Accordingly, each daily increase on the day of hospitalization caused a 1.8 times increase in respiratory morbidity, while it was 0.002 times less in those who did not require a mechanical ventilator other factor, especially IUGR, did not have statistically significant effects on respiratory morbidity (Table V).

Table V. *Logistic regression analysis of total respiratory morbidity panel*

Variables	Odds ratio	%95 %CI	p*
Gender Male	1.42	0.69-2.94	0.33
Total number of days with oxygen	1.05	0.91-1.21	0.44
Length of hospital stay (day)	**1.80**	**1.02-1.14**	**0.003***
Presence of physician diagnosed GOR	2.32	0.10-51.44	0.59
Presence of history of atopic dermatitis	1.67	0.54-5.14	0.37
Presence of mechanical ventilator requirement	**0.002**	**0.01-0.75**	**0.04***
Constant	0.95		0.004

*Stepwise lojistic regression model (enter), GOR: gastroesophageal reflux, CI: confidence interval

4. DISCUSSION

Late preterm birth and IUGR birth, have increased due to many etiological factors, like assisted reproductive techniques and the increase in risky pregnancies, bring many problems. Few studies have been conducted on the comparative evaluation of school-age respiratory morbidities of late preterm infants and newborns with IUGR, as well there is no study comparing the effects of late preterm birth and IUGR [4]. The frequency of wheezing due to airway obstruction during follow-up was observed in the first two years of life in prematurely born infants [14].

Studies have reported that there is a significant increase in admissions because of lower respiratory tract infections (LRTI) or bronchiolitis during infancy and early childhood in late preterms compared with term infants [15-19]. Similarly, studies including early and late preterm born adolescents have shown that admissions due to both infectious and non-infectious respiratory tract diseases are significantly increased compared to those who were term infants [20, 21]. Hoo et al., found that the frequency of wheezing and/or LRTI in the first year of life in late preterm infants was significantly higher than in term babies in which male gender and low gestational age were independent risk factors [22]. In the study of Coathup et al., it was stated that the rates of infection-related (acute bronchitis/bronchiolitis, pneumonia, upper and LRTI) hospital admissions from birth to 10 years of age were significantly higher in late preterm infants compared to term peers [23]. Similar to the literature, in our study, the frequency of upper respiratory tract infections in late preterm infants was found to be significantly higher than in term infants. Late preterm infants got sick more frequently and had more LRTIs' in the first 2 years of life, therefore hospitalization rates were found to be significantly higher. Also, respiratory morbidity due to infection, significantly increased in parallel with a decrease in the week of gestation, male gender and with an increase in number of people living at home.

The relationship between late preterm birth and asthma has not been clarified yet. It has been shown that the frequency of admission to the hospital in the first 6 years of life due to asthma is significantly higher in late preterms compared to term infants [18, 24]. The risk of asthma increased 2 times in late preterm infants compared to terms and male gender, low gestational age, maternal smoking during pregnancy and maternal asthma history were risk factors for asthma [25, 26]. In a recent study, it was shown that children with a history of late preterm labour had more frequent medication use and a need for hospitalization for asthma compared to their term-born controls when followed

http://doi.org/10.5472/marumj.1195309
Marmara Med J 2022;35(3): 335-342

up until the age of 7 [27]. However, it has been shown that there is no significant relationship between the use of treatment for asthma in young adults and the presence of a history of late preterm labour [28]. In the meta-analysis of Jaakkola et al., it was found that the asthma risk in individuals with a birth history below the 37th week of gestation was 1.07 times higher [29]. Contrastly, Voge et al., also found no relationship between late preterm birth and the risk of asthma [30]. In our study, similar to the literature, infectious wheezing at school-age was found to be significantly higher in late preterm infants. Also, the presence of wheezing attacks causing shortness of breath, wheezing attacks triggered by exercise and the presence of physician-diagnosed asthma were found to be statistically significantly higher in the late preterm group. Furthermore, the frequency of physician-diagnosed dust and pollen allergy, allergic rhinitis, allergic conjunctivitis, and atopic dermatitis in late preterm infants was significantly higher than in term controls.

IUGR has long-term consequences such as asthma and bronchiolitis [31]. Recent studies have shown that there is a relationship between IUGR and the development of wheezing, bronchial reactivity, asthma, LRTI and develop lower lung function at school-age [32], regardless of the gestational age [33-36]. In the study by Barker et al., it was shown that each unit's decrease in birth weight and birth height was associated with bronchitis, pneumonia, or cough in the first 5 years [37]. Contrastly, Sonnenschein-van der Voort et al., stated that the main reason for an increased risk factor for asthma and its symptoms was preterm delivery, not low birth weight [38]. In the study conducted by Lopuhaa et al., on adults, the frequency of obstructive airway disease and respiratory symptoms increased 1.7 times in those who were exposed to famine during the midgestation period [39]. In another study by Kotecha et al., the frequency of previous or ongoing asthma and wheezing was found to be similar between those who had an age-appropriate growth catch-up and those who did not and control groups [10]. In the study of Rona et al., it has been shown that the risk of wheezing decreases by 10% with each increased week of gestation [11]. In our study, the frequency of wheezing, physician-diagnosed asthma and other allergic conditions increased in IUGRs. Although, we found that wheezing, asthma and respiratory morbidity were significantly higher in both the late preterm group and the IUGR group compared to term controls; there was no significant difference between the late preterm AGA and IUGR groups. We concluded that IUGR may negatively affect allergic respiratory morbidity for advanced preterms, but not for late preterm infants and that the main determinant factor for respiratory morbidity for later periods of pregnancy is the gestational age. We found that the presence of maternal asthma and atopic dermatitis history in children increases the frequency of asthma at school age, and also each weekly increase in the gestational age reduces the risk for wheezing attacks.

In the study, which is based on parental reports, IUGRs were more likely to have upper respiratory tract infections [40]. With a 2-year follow-up of IUGRs, 50% of children coughed and approximately 58% of the children used treatments such as a bronchodilator, inhaled corticosteroid, and antibiotics due to chest diseases. It has been shown that there is a negative correlation between the birth weight Z score and hospital admission because of respiratory illness [13]. It was shown that being IUGR was significantly related to the increased infection-related hospital admissions during the first 10 years of age and modified the effect of gestational age; specifically, among the history of being both preterm and IUGRs [23]. In our study, although the respiratory infections and therefore hospitalization requirements in patients with a history of IUGR were found significantly increased compared to term controls, there was no significant difference between both late preterm AGA and late preterm IUGR groups, extremely preterm AGA and IUGR groups.

Since, spirometric measurements were not performed in our study, the negative effect of IUGR shown in the literature on lung volume and flows could not be shown. And low patient follow-up rates were also limitations of our study. As a result, it was thought that the decrease in gestational age was effective in respiratory diseases and symptoms. We concluded that IUGR negatively affects respiratory morbidity for extreme preterms, although, not for late preterm infants, this relationship cannot be demonstrated for later periods of pregnancy.

Late preterm births and IUGR, which are on the rise today, can bring many problems both in perinatal, neonatal, infancy and later life. We think that the follow-up during pregnancy, perinatal period, delivery room, and neonatal period should be reviewed, and detailed guidelines should be prepared to start with birth planning. For these children, long-term follow-up protocols should be determined, and follow-up timelines should be established instead of risk-free routine healthy term child follow-up. The effect of late preterm birth and IUGR history on negative respiratory outcomes in school-age and later should be investigated with further studies.

Acknowledgements: The authors acknowledge Prof. Necdet Sütcü for statical analyses.

Compliance with Ethical Standards

Ethical Approval: Ethics committee approval was obtained for the study from the Trakya University Faculty of Medicine Local Ethics Committee numbered 18/5 and protocol number TÜTF-GOKAEK 2013/150, and registered with Clinical Trials (NCT04849494).

Financial Support: The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work.

Conflict of Interest Statement: The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the article.

Authors' contributions: MCU and BA: Concept and design of the study, MCU and UV: Acquisition and analysis of data, MCU, UV, RD and BA: Drafting the manuscript, tables and figures. All authors read and approved the final version of the article.

REFERENCES

[1] Kotecha SJ, Watkins WJ, Paranjothy S, Dunstan FD, Henderson AJ, Kotecha S. Effect of late preterm birth on longitudinal lung spirometry in school age children and adolescents. Thorax 2012;67:54-61. doi: 10.1136/thoraxjnl-2011-200329.

[2] Melamed N, Klinger G, Tenenbaum-Gavish K et al. Short-term neonatal outcome in low-risk, spontaneous, singleton, late preterm deliveries. Obstet Gynecol 2009;114(2 Pt 1):253-60. doi: 10.1097/AOG.0b013e3181af6931.

[3] Pike K, Jane Pillow J, Lucas JS. Long term respiratory consequences of intrauterine growth restriction. Semin Fetal Neonatal Med 2012;17:92-8. doi: 10.1016/j.siny.2012.01.003.

[4] Lima RdC, Victora CG, Menezes AMB, Barros FC. Respiratory function in adolescence in relation to low birth weight, preterm delivery, and intrauterine growth restriction. Chest 2005;128:2400-7. doi: 10.1378/chest.128.4.2400.

[5] Marin Gabriel MA, Martin Moreiras J, Lliteras Fleixas G et al. [Assessment of the new Ballard score to estimate gestational age]. An Pediatr (Barc) 2006;64:140-5. doi: 10.1157/13084173.

[6] Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatrm2013;13:59. doi: 10.1186/1471-2431-13-59.

[7] Esteves A, Solé D, Ferraz M. Adaptation and validity of the ATS-DLD-78-C questionnaire for asthma diagnosis in children under 13 years of age. Braz Ped News 1999;1:5.

[8] Mallol J, Crane J, von Mutius E et al. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three: a global synthesis. Allergol Immunopathol (Madr) 2013;41:73-85. doi: 10.1016/j.aller.2012.03.001.

[9] Bayram I, Guneser-Kendirli S, Yilmaz M, Altintas DU, Alparslan N, Bingol-Karakoc G. The prevalence of asthma and allergic diseases in children of school age in Adana in southern Turkey. Turk J Pediatr 2004;46:221-5. PMID: 15503474.

[10] Kotecha SJ, Watkins WJ, Heron J, Henderson J, Dunstan FD, Kotecha S. Spirometric lung function in school-age children: effect of intrauterine growth retardation and catch-up growth. Am J Respir Crit Care Med 2010;181:969-74. doi: 10.1164/rccm.200.906.0897OC.

[11] Rona R, Gulliford M, Chinn S. Effects of prematurity and intrauterine growth on respiratory health and lung function in childhood. BMJ 1993;306(6881):817. doi: 10.1136/bmj.306.6881.817.

[12] Wjst M, Popescu M, Trepka MJ, Heinrich J, Wichmann H. Pulmonary function in children with initial low birth weight. Pediatr Allergy Immunol 1998;9:80-90. doi: 10.1111/j.1399-3038.1998.tb00308.x

[13] Peacock JL, Lo JW, D'Costa W, Calvert S, Marlow N, Greenough A. Respiratory morbidity at follow-up of small-for-gestational-age infants born very prematurely. Pediatr Res 2013;73(4 Pt 1):457-63. doi: 10.1038/pr.2012.201.

[14] Greenough A. Late respiratory outcomes after preterm birth. Early Hum Dev 2007;83:785-8. doi: 10.1016/j.earlhumdev.2007.09.006.

[15] Helfrich AM, Nylund CM, Eberly MD, Eide MB, Stagliano DR. Healthy Late-preterm infants born 33–36+ 6 weeks gestational age have higher risk for respiratory syncytial virus hospitalization. Early Hum Dev 2015;91:541-6. doi: 10.1016/j.earlhumdev.2015.06.009.

[16] Lanari M, Prinelli F, Adorni F et al. Risk factors for bronchiolitis hospitalization during the first year of life in a multicenter Italian birth cohort. Ital J Pediatr 2015;41:40. doi: 10.1186/s13052.015.0149-z.

[17] Odibo IN, Bird TM, McKelvey SS, Sandlin A, Lowery C, Magann E. Childhood Respiratory Morbidity after Late Preterm and Early Term Delivery: a Study of Medicaid Patients in South Carolina. Paediatr Perinat Epidemiol 2016;30:67-75. doi: 10.1111/ppe.12250.

[18] Haataja P, Korhonen P, Ojala R et al. Hospital admissions for lower respiratory tract infections in children born moderately/late preterm. Pediatr Pulmonol 2018;53:209-17. doi: 10.1002/ppul.23908.

[19] Kotecha SJ, Lowe J, Kotecha S. Does the sex of the preterm baby affect respiratory outcomes? Breathe (Sheff) 2018;14:100-7. doi: 10.1183/20734.735.017218.

[20] Srinivasjois R, Slimings C, Einarsdóttir K, Burgner D, Leonard H. Association of gestational age at birth with reasons for subsequent hospitalisation: 18 years of follow-up in a Western Australian population study. PloS One 2015;10:e0130535. doi: 10.1371/journal.pone.0130535.

[21] Hoo AF, Dezateux C, Henschen M, Costeloe K, Stocks J. Development of airway function in infancy after preterm delivery. J Pediatr 2002;141:652-8. doi: 10.1067/mpd.2002.128114.

[22] Coathup V, Carson C, Kurinczuk JJ, et al. Associations between gestational age at birth and infection-related hospital admission rates during childhood in England: Population-based record linkage study. PLoS One 2021;16:e0257341. doi:10.1371/journal.pone.0257341

[23] Leung JY, Lam HS, Leung GM, Schooling CM. Gestational Age, Birthweight for Gestational Age, and Childhood Hospitalizations for Asthma and Other Wheezing Disorders. Paediatr Perinat Epidemiol 2016;30:149-59. doi: 10.1111/ppe.12273.

[24] Abe K, Shapiro-Mendoza CK, Hall LR, Satten GA. Late preterm birth and risk of developing asthma. J Pediatr 2010;157:74-8. doi: 10.1016/j.jpeds.2010.01.008.

[25] Harju M, Keski-Nisula L, Georgiadis L, Raisanen S, Gissler M, Heinonen S. The burden of childhood asthma and late preterm and early term births. J Pediatr 2014;164:295-9 e1. doi: 10.1016/j.jpeds.2013.09.057.

[26] Haataja P, Korhonen P, Ojala R et al. Asthma and atopic dermatitis in children born moderately and late preterm. Eur J Pediatr 2016;175799-808. doi: 10.1007/s00431.016.2708-8.

[27] Crump C, Winkleby MA, Sundquist J, Sundquist K. Risk of asthma in young adults who were born preterm: a Swedish national cohort study. Pediatrics. 2011;127:e913-20. doi: 10.1542/peds.2010-2603.

[28] Jaakkola JJ, Ahmed P, Ieromnimon A, et al. Preterm delivery and asthma: a systematic review and meta-analysis. J Allergy Clin Immunol 2006;118:823-30. doi: 10.1016/j.jaci.2006.06.043.

[29] Voge GA, Carey WA, Ryu E, King KS, Wi CI, Juhn YJ. What accounts for the association between late preterm births and risk of asthma? Allergy Asthma Proc 2017;38:152-6. doi: 10.2500/aap.2017.38.4021.

[30] Eriksson L, Haglund B, Odlind V, Altman M, Ewald U, Kieler H. Perinatal conditions related to growth restriction and inflammation are associated with an increased risk of bronchopulmonary dysplasia. Acta Paediatrica 2015;104:259-63. doi: 10.1111/apa.12888.

[31] Arigliani M, Stocco C, Valentini E et al. Lung function between 8 and 15 years of age in very preterm infants with fetal growth restriction. Pediatr Res 2021;90:657-63. doi: 10.1038/s41390.020.01299-0.

[32] Pike KC, Crozier SR, Lucas JS et al. Patterns of fetal and infant growth are related to atopy and wheezing disorders at age 3 years. Thorax 2010;65:1099-106. doi: 10.1136/thx.2010.134742.

[33] Ronkainen E, Dunder T, Kaukola T, Marttila R, Hallman M. Intrauterine growth restriction predicts lower lung function at school age in children born very preterm. Arch Dis Child Fetal Neonatal Ed 2016;101:F412-F7. doi: 10.1136/archdischild-2015-308922.

[34] Kotecha SJ, Watkins WJ, Henderson AJ, Kotecha S. The effect of birth weight on lung spirometry in white, school-aged children and adolescents born at term: a longitudinal population based observational cohort study. J Pediatr 2015;166:1163-7. doi: 10.1016/j.jpeds.2015.01.002.

[35] Chan KN, Noble-Jamieson CM, Elliman A, Bryan EM, Silverman M. Lung function in children of low birth weight. Arch Dis Child 1989;64:1284-93. doi: 10.1136/adc.64.9.1284.

[36] Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. BMJ 1991;303(6804):671-5. doi: 10.1136/bmj.303.6804.671.

[37] Sonnenschein-van der Voort AM, Jaddoe VW, Raat H, et al. Fetal and infant growth and asthma symptoms in preschool children: the Generation R Study. Am J Respir Crit Care Med 2012;185:731-7. doi: 10.1164/rccm.201.107.1266OC.

[38] Lopuhaa CE, Roseboom TJ, Osmond C, et al. Atopy, lung function, and obstructive airways disease after prenatal exposure to famine. Thorax 2000;55:555-61. doi: 10.1136/thorax.55.7.555.

[39] Hoo AF, Stocks J, Lum S, et al. Development of lung function in early life: influence of birth weight in infants of nonsmokers. Am J Respir Crit Care Med 2004;170:527-33. doi: 10.1164/rccm.200.311.1552OC.