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Original Article

Is Transient Tachypnea of the Newborn a Risk Factor for Bronchiolitis in the First Two Years of Life? A Population-Based Birth Cohort Study

Yenidoğanın Geçici Takipnesi Yaşamın İlk İki Yılında Bronşiyolit için Bir Risk Faktörü mü? Nüfus Temelli Doğum Kohort Çalışması

Sinem CAN OKSAY[1], Mustafa Kursat SAHIN[2], Gulay BILGIN[3], Deniz MAVI TORTOP[4], Zeynep Reyhan ONAY[1], Yetkin AYHAN[1], Askın KESKIN KAPLAN[5], Saniye GIRIT[1]

[1]Istanbul Medeniyet University Goztepe Prof. Dr. Suleyman Yalcın City Hospital, Department of Pediatrics, Division of Pediatric Pulmonology, Istanbul, Türkiye
[2]On Dokuz Mayıs University, Faculty of Medicine, Department of Family Medicine, Samsun, Türkiye
[3]University of Health Sciences Türkiye, Eskisehir City Hospital, Department of Pediatrics, Division of Pediatric Pulmonology, Eskisehir, Türkiye
[4]Sanlıurfa Education and Training Hospital, Department of Pediatrics, Division of Pediatric Pulmonology, Sanlıurfa, Türkiye
[5]Maltepe University, Faculty of Medicine, Department of Family Medicine, Istanbul, Türkiye

ABSTRACT

Objective: Transient Tachypnea of the Newborn (TTN) is a common cause of respiratory distress in term infants, associated with delayed pulmonary fluid clearance resulting from dysfunction of the epithelial sodium channel. Although generally self-limiting, TTN may increase early childhood wheezing and asthma risk. This study aimed to assess the incidence and characteristics of acute bronchiolitis in TTN infants compared to those in healthy controls within a large birth cohort.

Methods: We conducted a population-based cohort study that included all live births in Istanbul from January 2016 to December 2018, utilizing the Turkish Ministry of Health's e-Nabız database. Infants diagnosed with isolated TTN (International Classification of Diseases [ICD]-10 P22.1) formed the study group. A randomly selected control group of healthy infants without respiratory diagnoses was included in the study. Both groups were followed for two years to identify episodes of acute bronchiolitis (ICD-10 J21*), excluding cases within the first month of life. The data collected included bronchiolitis incidence, recurrence, age at the time of the episode, and hospitalizations.

Results: Among 1,002,261 live births, 14,389 TTN infants and 14,500 controls were analyzed. Acute bronchiolitis occurred in 42.4% of TTN infants and 35.8% of controls (p<0.001). TTN infants had higher rates of single episodes, while controls experienced more recurrent episodes (p<0.001). Hospitalization was more frequent in the control group (p<0.001), with single hospitalizations predominating in the TTN group and multiple hospitalizations in the control group. The first episodes in TTN infants mainly occurred between 1-6 months, with controls showing more episodes early but fewer later (p<0.001). Recurrence was correlated with an earlier age of the first episode in both groups (p<0.001).

Conclusions: TTN infants experience more bronchiolitis episodes early in life, though recurrent episodes are more common among healthy controls.

ÖZ

Amaç: Yenidoğanın Geçici Takipnesi (YGT) zamanında doğan bebeklerde solunum sıkıntısının yaygın bir nedenidir ve epitelyal sodyum kanal disfonksiyonundan kaynaklanan gecikmiş pulmoner sıvı klirensi ile ilişkilidir. Genellikle kendi kendini sınırlasa da TTN erken çocukluk döneminde hışıltılı solunum ve astım riskini artırabilir. Bu çalışmada, geniş bir doğum kohortunda YGT öyküsü olan bebeklerde akut bronşiolit insidansı ve özellikleri, sağlıklı kontrollerle karşılaştırmalı olarak değerlendirildi.

Yöntemler: TC. Sağlık Bakanlığı e-Nabız veri tabanı kullanılarak, Ocak 2016-Aralık 2018 arasında Istanbul'da gerçekleşen tüm canlı doğumlar üzerinden toplum temelli bir kohort çalışması yürütüldü. İzole YGT (ICD-10: P22.1) tanısı konan bebekler çalışma grubunu oluşturdu. Solunum tanısı olmayan sağlıklı bebeklerden oluşan bir kontrol grubu ile eşleştirildi. Her iki grup, yaşamın ilk ayında görülen vakalar hariç tutularak, iki yıl boyunca akut bronşiolit (ICD-10: J21*) atakları açısından izlendi. Veriler arasında atak insidansı, nüks, atak sırasındaki yaş ve hastane yatışları yer almıştır.

Bulgular: 1.002.261 canlı doğumdan 14.389 YGT bebeği ve 14.500 kontrol grubu analiz edilmiştir. Bronşiolit, YGT grubunda %42,4; kontrol grubunda %35,8 oranında görülmüştür (p<0,001). YGT tanısı olan bebeklerde tek atak daha yüksek oranda görülürken, kontrol grubunda daha fazla tekrarlayan atak görülmüştür (p<0,001). Hastaneye yatış ise kontrol grubunda daha sıktır (p<0,001). İlk ataklar YGT grubunda 1-6 ayda yoğunlaşmıştı. Nüks, her iki grupta da erken ilk atak yaşı ile ilişkiliydi (p<0,001).

Sonuçlar: YGT'li bebeklerde yaşamın ilk iki yılında bronşiolit atağı geçirme sıklığı daha yüksek ancak tekrarlayan atak oranı sağlıklı bebeklerden daha düşüktür. Bu bulgular, YGT'nin ileride gelişebilecek astım ve hışıltılı solunumla ilişkisini araştıracak ileri çalışmalara temel oluşturabilir.

Address for Correspondence: S. Can Oksay, Medeniyet University Goztepe Prof. Dr. Suleyman Yalcın City Hospital, Clinic of Pediatrics, Division of Pediatric Pulmonology, Istanbul, Türkiye
E-mail: drsinemcan@gmail.com **ORCID ID:** orcid.org/0000-0001-9801-3181

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Further studies are warranted to investigate the relationship between TTN and the development of wheezing and asthma.

Keywords: Transient tachypnea of the newborn, acute bronchiolitis, population-based cohort study

Anahtar kelimeler: Yenidoğanın geçici takipnesi, akut bronşiolit, toplum temelli kohort çalışması

INTRODUCTION

The presence of tachypnea defines the diagnosis of Transient Tachypnea of the Newborn (TTN) within the first 6 hours after birth. This includes the persistence of tachypnea for at least 12 hours and characteristic findings on at least one chest radiograph, such as prominent central vascular markings, thickened interlobar fissures, symmetric perihilar congestion, flattened diaphragmatic domes, or an increased anteroposterior diameter indicating hyperaeration, in the absence of other known causes of respiratory distress[1]. It is a common cause of respiratory distress in term newborns[2]. Respiratory distress occurs in approximately 1% of newborns, with TTN accounting for about 4.0% to 5.7% of these cases. The remaining cases are attributed to other causes such as meconium aspiration syndrome, pneumonia, sepsis, and pneumothorax[3]. Known risk factors for TTN include prematurity, cesarean delivery, multiple gestation, infants of diabetic mothers, macrosomia, maternal asthma, male sex, rapid or prolonged labor, delayed cord clamping, and low appearance, pulse, grimace response, activity, respiration scores[4].

The incidence of TTN ranges from 0.6% to 1.57%, depending on the presence of risk factors. Its frequency has been increasing mainly due to rising rates of elective cesarean deliveries[4,5,6]. However, the exact pathophysiology of TTN remains unclear. One of the leading hypotheses implicates impaired function of the epithelial sodium channels (ENaC) in the alveolar epithelium. Typically, ENaC expression increases near term to promote alveolar fluid clearance; however, in TTN, despite adequate surfactant levels, reduced ENaC activity leads to delayed fluid resorption and consequent respiratory distress after birth. Although TTN is considered a self-limiting condition, it may increase the incidence of wheezing respiratory episodes and asthma during early life[7,8]. Over the past three decades, randomized controlled trials and studies have investigated the pathogenesis and clinical manifestations of asthma related to ENaC and chloride ion channels[9]. Moreover, similarities in pathophysiology between TTN and viral bronchiolitis, particularly bronchiolitis caused by respiratory syncytial virus (RSV), have been proposed, with ENaC dysfunction playing a central role[10,11]. The relationship between TTN and RSV bronchiolitis has been extensively investigated. Among the most significant risk factors identified for hospitalizations due to viral bronchiolitis, particularly RSV, are prematurity, chronic pulmonary disease, and congenital heart disease[12]. However, most children hospitalized for RSV are previously healthy, leaving the reasons for increased disease severity in these patients unclear[10,11].

Wheezing is a symptom observed in both children with asthma and those with bronchiolitis. However, it can also indicate other conditions with different pathophysiology, clinical courses, and outcomes. When the characteristics, onset, progression, and associated illnesses of wheezing are considered together, it becomes evident that multiple pathologies can cause this symptom. Especially during the first two years of life, wheezing episodes may be due to viral bronchiolitis or early manifestations of childhood asthma. Given the challenges in accurately diagnosing asthma in preschool children, we investigated the relationship between TTN and recurrent bronchiolitis.

Our aim was to investigate the incidence and characteristics of bronchiolitis during the first two years of life in infants diagnosed with TTN, compared to a healthy control group, using a population-based birth cohort study conducted in the most populous and cosmopolitan province, which represents all regions of our country.

MATERIALS and METHODS

This study is a population-based cohort including all live births in Istanbul between January 1, 2016, and December 31, 2018. Data from the Ministry's National Health Information System (e-Nabız) were utilized in collaboration with the Ministry of Health of the Republic of Türkiye. In the initial phase, individuals to be included in the study, those to be excluded, or those assigned to the control group were identified based on the International Statistical Classification of Diseases and Related Health Problems (ICD) diagnostic codes within the online national database.

All live-born infants with the TTN ICD-10 diagnosis code (P22.1) and no additional diagnoses composed the main study group. Exclusion criteria for the study group included infants with specific ICD-10 diagnosis codes that

could cause diagnostic confusion or negatively affect the identification of risk factors. These comprised stillbirths, premature infants, and/or those weighing less than 500 grams at birth; infants with congenital malformations, including cardiac anomalies starting with the ICD-10 code Q; and infants diagnosed with congenital malformations, deformations, or chromosomal abnormalities coded as Z13.7 in the ICD-10 classification.

Selection of the Control Group and the Randomization Process

To enable comparative analysis, a control group was required, consisting of infants without a TTN diagnosis but with similar sociodemographic characteristics. For this purpose, infants born within the same timeframe and geographical region Istanbul as the TTN cases were identified using the Ministry of Health's National Health Information System (e-Nabız) database. These infants had no respiratory disease diagnoses during the first month of life and had only visited healthcare facilities for routine check-ups (ICD-10 codes: Z00.0, Z00.1, Z00.8). Following this initial selection, infants meeting the exclusion criteria-such as prematurity, congenital malformations, stillbirth, or any respiratory diagnosis-were excluded. From the remaining eligible control candidates, a total of 14,500 infants were randomly selected to match as closely as possible the number of TTN cases (n=14,234), approximating an approximate 1:1 sampling ratio. The randomization process was conducted as follows:

Creation of the Data Pool

A pool of infants was formed who met the exclusion criteria and had received healthcare services only with the diagnoses of Z00.0 (General medical examination), Z00.1 (Routine child health examination), or Z00.8 (Other general examinations), without any TTN or other respiratory diagnoses.

Random Number Assignment

Each individual in the pool was assigned a random number linked to their unique identification number. These random numbers were generated using the Excel RAND function, and the overall distribution of the generated numbers was examined.

Ranking and selection based on random numbers: All individuals were ranked according to their assigned random numbers, and the first 14,500 were automatically selected without any manual intervention to form the control group.

Bronchiolitis Diagnosis Status

Among the individuals initially included in the control group, those who had received a diagnosis of acute bronchiolitis or any respiratory condition other than TTN within the first 30 days of life were subsequently excluded. Therefore, the final sample was standardized as a control group with a "clean respiratory history" at baseline concerning bronchiolitis.

Using this method, an objective and representative control group was obtained, consisting of individuals born during the same period as those diagnosed with TTN and without a history of exclusionary conditions, thereby avoiding systematic error or selection bias during selection.

The randomization process was designed and implemented in accordance with classical epidemiological principles, aiming to create a comparison group with similar characteristics to the study group but without a TTN diagnosis. The selected method was based on the principle of simple random sampling and was carefully structured to minimize the potential impact of confounding factors.

In the second phase, follow-up records from January 1, 2018, to December 31, 2020, were reviewed for all infants in both the study and control groups who were born between January 1, 2016, and December 31, 2018. This allowed for the collection of complete data on each case up to two years of age. These records were linked using a unique personal identification number assigned to every individual in the country.

After the first postnatal month, infants with ICD-10 diagnosis codes J21 (Acute bronchiolitis), J21.0 (Acute bronchiolitis due to RSV), J21.8 (Acute bronchiolitis due to other specified organisms), or J21.9 (Acute bronchiolitis, unspecified) were identified as having experienced a bronchiolitis episode. Those diagnosed with bronchiolitis during the first month of life were excluded due to the potential difficulty in differential diagnosis. The age at the time of each bronchiolitis episode, the number of recurrent episodes, and any hospital admissions were recorded. The age at the time of bronchiolitis episodes was also categorized into groups for analysis (1-6 months, 7-12 months, 13-18 months, 19-24 months).

Maternal diabetes (P70.0, P70.1) and maternal asthma (J45) were identified through the database as potential risk factors for TTN in infants. However, due to the insufficient maternal diagnostic data available in the records, these variables could not be included in the final analysis. Similarly, an attempt was made to assess

the association between maternal asthma diagnosis and the number of acute bronchiolitis episodes in infants within the control group. Still, maternal asthma records were not available for evaluation.

The primary outcome was to compare the incidence of acute bronchiolitis episodes during the first two years of life between infants with TTN and healthy controls. Secondary outcomes were to compare the characteristics of bronchiolitis episodes (recurrence, age at first episode, and hospitalization rates) between the two groups, and to examine associations between age at first episode and recurrence.

Since this study was based on data from the national health records system and no direct contact was made with any individuals, obtaining ethical approval from participants was not required. However, ethical approval for conducting the study was obtained from the Ethics Committee of Istanbul Medeniyet University (approval number: 2020/0633, date: 05.03.2025).

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA) and Microsoft Excel 2016 software. Descriptive statistics were presented as frequencies and percentages for categorical variables, and as mean ± standard deviation or median (with minimum and maximum values) for continuous variables. The normality of the variables was assessed using the Kolmogorov-Smirnov test.

Pearson's chi-square test was used to compare categorical variables between groups. For multilevel categorical variables such as episode count, frequency of hospitalizations, and age distribution of episodes, statistical significance was assessed using Pearson's chi-square test in conjunction with cross-tabulation. Significant differences in pairwise comparisons were identified using post-hoc analysis methods with Bonferroni correction.

Column proportion comparison analyses were also performed to test the significance of differences in proportions between groups, with cells showing significant differences marked using the Bonferroni correction. Additionally, the distribution of acute bronchiolitis episodes was evaluated separately across subgroups defined by time intervals to assess the effect of age ranges on the frequency of bronchiolitis attacks.

A two-sided p-value of less than 0.05 was considered statistically significant in all analyses.

RESULTS

During the specified two-year period, the number of births in Istanbul was 1,008,655. Of these, 6,394 were stillbirths (0.63%). Among the 1,002,261 live-born infants, 14,389 (1.43%) had an isolated diagnosis of TTN and constituted the study group. The control group included 14,500 infants (Figure 1).

During the first two years of life, 42.4% of the TTN group experienced an acute bronchiolitis episode, compared to 35.8% in the control group ($p<0.001$).

Regarding the number of acute bronchiolitis episodes, 46.5% of patients in the TTN group experienced one episode, 22.7% had two episodes, and 30.9% had three or more episodes. In the control group, 23.6% of patients had one episode, 22.3% (n=1,160) had two episodes, and 54.1% experienced three or more episodes (Table 1).

The rate of experiencing a single episode was significantly higher in the TTN group. In contrast, the rate of having three or more episodes was considerably higher in the healthy control group ($p<0.001$).

Due to episodes of acute bronchiolitis, 13.4% of the TTN group and 15.6% of the control group were hospitalized for treatment ($p<0.001$). Among the TTN group, 71% were hospitalized once, 18.7% were hospitalized twice, and 10.2% were hospitalized three or more times between birth and two years of age.In the control group, among those who experienced acute bronchiolitis episodes, 61.1% were hospitalized once, 22.2% were hospitalized twice, and 16.7% were hospitalized three or more times for treatment (Table 1). When comparing the hospitalization frequency between the two groups, the rate of single hospitalizations was significantly higher in the TTN group. In contrast, multiple hospitalizations were more frequent in the control group ($p<0.001$).

In the TTN group, 44.0% experienced their first bronchiolitis episode between 1-6 months, 33.4% between 7-12 months, 14.4% between 13-18 months, and 8.1% between 19-24 months. In the control group, these rates were 47.8%, 33.1%, 12.5%, and 6.6% for the respective age intervals. Comparison of the groups revealed that the control group experienced a significantly higher rate of acute bronchiolitis episodes between 1 and 6 months, whereas the TTN group showed a significantly higher number of episodes during the 12-24 month period ($p<0.001$) (Table 1).

The age distribution of the first bronchiolitis episode was compared, based on the number of bronchiolitis attacks, between children with and without a history of

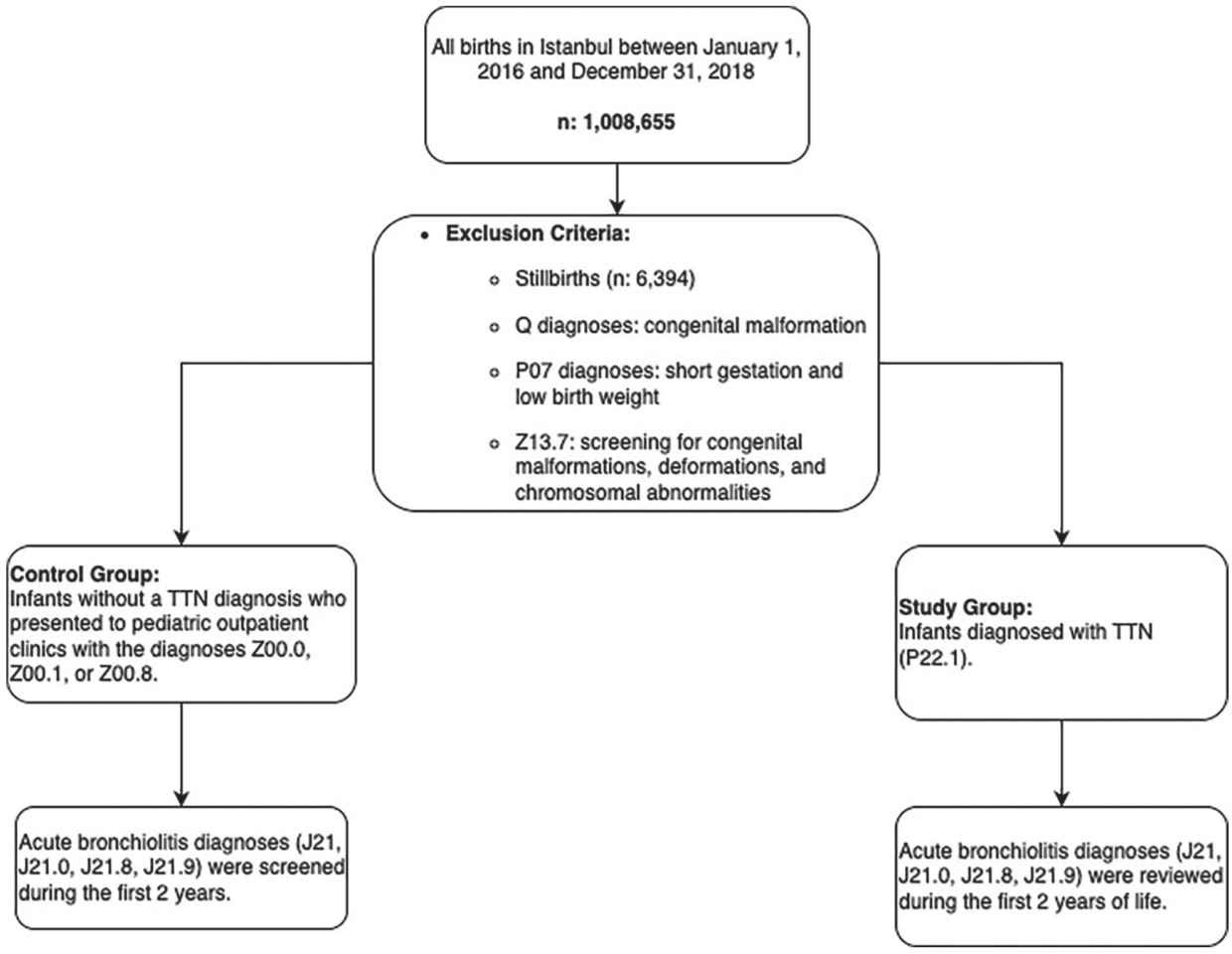

Figure 1. Flow diagram

TTN: Transient tachypnea of the newborn

TTN (Table 2). In the control group, 26.8% of those with a single bronchiolitis episode experienced their first attack between 1-6 months, increasing to 41.1% among those with two episodes and 59.7% among those with three or more episodes. Similarly, the proportions of first attacks occurring between 7 and 12 months were 32.2%, 37.9%, and 31.5%, respectively. A marked decrease in the incidence of first attacks was observed with increasing age: in the 13-18 month group, these rates were 22.9% (one episode), 14.4% (two episodes), and 7.3% (three or more episodes), while in the 19-24 month group, they declined to 18.2%, 6.6%, and 1.5%, respectively.

A similar pattern was observed in the TTN group, although the rates of bronchiolitis episodes between 1- to 6-months were higher across all groups. In this group, 32.7% of those with one episode, 44.7% of those with two episodes, and 60.6% of those with three or more episodes experienced their first attack within the first six months of life. The proportions of first attacks occurring between 7 and 12 months were 33.6%, 36.4%, and 31.1%, respectively. These rates declined markedly in older age groups: 20.0% (one episode), 13.0% (two episodes), and 7.1% (three or more episodes) in the 13- to 18- month group; and 13.7%, 5.9%, and 1.3% in the 19- to 24- month group.

Statistical analyses performed with Bonferroni correction for multiple comparisons revealed that, in both the TTN and control groups, an increasing number of bronchiolitis episodes was significantly associated with the first episode occurring earlier in life ($p<0.001$). Specifically, the proportion of children experiencing their first bronchiolitis episode within the first six months was 26.8% in the control group and 32.7% in the TTN group among those with a single episode. This rate increased to 59.7% in the control group and 60.6% in the TTN group among children with three or more episodes. Conversely,

Table 1. Frequency and clinical characteristics of acute bronchiolitis in children with a history of TTN compared to controls.

Variables	Category	Control group n (%)	TTN group n (%)	p-value
Acute bronchiolitis	No	9303 (64.20)	8293 (57.60)	**<0.001**
	Yes	5197 (35.80)	6096 (42.40)	
Hospitalization	No	12235 (84.40)	12462 (86.60)	**<0.001**
	Yes	2265 (15.60)	1927 (13.40)	
Number of hospitalization	1	1384 (61.10)	1369 (71.00)	**<0.001**
	2	502 (22.20)	361 (18.70)	
	≥3	379 (16.70)	197 (10.20)	
Number of bronchiolitis attack	1	1228 (23.60)	2834 (46.50)	**<0.001**
	2	1160 (22.30)	1381 (22.70)	
	≥3	2809 (54.10)	1881 (30.90)	
Age at bronchiolitis (months)	1-6	2481 (47.80)	2682 (44.00)	**<0.001**
	7-12	1720 (33.10)	2037 (33.40)	
	13-18	651 (12.50)	880 (14.40)	
	19-24	342 (6.60)	494 (8.10)	

TTN: Transient tachypnea of the newborn

Table 2. Comparison of the age and number of attacks in the TTN group and the control group.

	Number of bronchiolitis attacks) / Age at bronchiolitis (months)	1 n(%)	2 n(%)	≥3 n(%)	p-values
Control group	**0-6**	328 (26.8) A	477 (41.1) A B	1676 (59.7) B	**<0.001**
	7-12	394 (32.2) A C	440 (37.9) C	886 (31.5) A	
	13-18	280 (22.9) B C	167 (14.4) C	204 (7.3)	
	19-24	223 (18.2) B C	76 (6.6) C	43 (1.5)	
TTN group	**0-6**	926 (32.7) A	617 (44.7) A B	1139 (60.6) B	**<0.001**
	7-12	950 (33.6) A C	502 (36.4) C	585 (31.1) A	
	13-18	567 (20.0) B C	180 (13.0) C	133 (7.1)	
	19-24	388 (13.7) B C	82 (5.9) C	24 (1.3)	

*Based on column proportion comparisons with Bonferroni correction, comparison letters (A, B, C) were assigned to each cell. Cells bearing different letters within the same age row indicate statistically significant differences ($p<0.05$, Bonferroni correction applied).

TTN: Transient tachypnea of the newborn

the occurrence of first episodes between 13 and 24 months significantly decreased with increasing episode count in both groups.

DISCUSSION

We observed that children with a history of TTN experienced bronchiolitis episodes more frequently than healthy controls. In the TTN group, bronchiolitis episodes were predominantly observed within the first six months of life, whereas in the control group, they tended to occur between 12 and 24 months of age. Interestingly, hospitalisation rates and the occurrence of multiple admissions due to bronchiolitis were found to be higher among the healthy controls.

TTN, though generally benign and self-limiting, has been associated with increased long-term pulmonary morbidity. Several studies have suggested that infants diagnosed with TTN are at a higher risk of developing asthma and wheezing episodes during the preschool years[13]. RSV is a major contributor to viral bronchiolitis in infancy, with about two-thirds of affected infants developing wheezing within the first five months of

life[11,14]. Most infants hospitalized due to RSV bronchiolitis are previously healthy[6]. Therefore, the underlying reasons for increased disease severity in these cases remain unclear[10]. Studies in animal models and cell cultures have demonstrated that RSV increases alveolar fluid accumulation by inhibiting sodium-dependent pulmonary fluid clearance[9]. A similar pathophysiological mechanism has also been implicated in TTN.

Heinonen et al.[6] reported a novel association between TTN diagnosed at birth and the subsequent development of RSV bronchiolitis during the first year of life, proposing a potential mechanism involving ENaC within the alveolar epithelium. A birth cohort study in the literature reported higher rates of RSV-related hospitalizations among children with a history of TTN, while another study identified younger chronological age as an independent risk factor[6,14]. In contrast, our findings differed markedly; we observed a higher number of hospital admissions in the control group. However, it is essential to note that our study did not exclusively evaluate RSV bronchiolitis. Instead, it included all bronchiolitis episodes, which may account for this discrepancy. The studies mentioned above included only RSV- confirmed cases of bronchiolitis. In our study, however, we performed an analysis based on ICD-10 diagnoses from a birth cohort using a national health database, which included data from all levels of healthcare institutions-primary, secondary, and tertiary. As such, we recognize that in many of these settings, microbiological identification of the causative pathogen was not routinely performed. Therefore, the bronchiolitis cases without confirmed pathogen testing may also include a significant number of RSV-related episodes. We found that children with a history of TTN experienced more bronchiolitis episodes than their healthy counterparts. Among TTN infants, single bronchiolitis episodes were more common, whereas multiple episodes were more frequently observed in the control group and were also associated with a higher rate of hospitalization. Moreover, in TTN infants who had recurrent bronchiolitis, these episodes were predominantly concentrated within the first six months of life. From this perspective, it may be inferred that bronchiolitis was more severe in the TTN group. Given that RSV bronchiolitis typically peaks during the first six months of life, we speculate that the majority of early-life bronchiolitis episodes in TTN cases were likely attributable to RSV. Prospective studies involving larger patient populations with confirmed RSV diagnoses may clarify this relationship and potentially support including TTN in risk profiling for RSV- related hospitalizations.

In another retrospective study, 103 children with TTN and healthy controls were evaluated at two years of age through direct physical examination, review of medical history, and investigations. The study assessed factors such as the timing and frequency of wheezing episodes, as well as hospitalizations due to wheezing. The authors concluded that TTN is an independent risk factor for wheezing[5]. In this study, although the diagnosis of asthma in cases was considered more reliable than in questionnaire-based studies, the small sample size may limit the generalizability of the findings.

The relationship between TTN and wheezing or bronchiolitis episodes, as well as childhood asthma, has been extensively explored. We consider this inquiry natural, as diagnosing childhood asthma is challenging and requires careful differentiation of the causes of wheezing. Furthermore, severe bronchiolitis in early childhood-particularly following rhinovirus or RSV bronchiolitis-is known to be associated with an increased risk of developing asthma[15,16]. Additionally, recurrent wheezing episodes resembling bronchiolitis may represent early signs of asthma that develop later in life. The literature supports that having three or more wheezing attacks is associated with a higher likelihood of progression toward asthma[17]. A study aiming to identify potential risk factors for TTN and early childhood asthma selected infants with TTN and healthy births from a hospital database. Subsequently, families were contacted by phone and administered the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire to assess the presence of asthma. The association between TTN and asthma was found to be stronger than that of other factors, such as elective cesarean delivery and maternal asthma[18]. The ISAAC questionnaire used in this study assesses wheezing episodes, their characteristics, and other differential diagnostic factors. However, since the ISAAC questionnaire serves only as a screening tool for asthma, the results may differ from physician-confirmed diagnoses, which could potentially affect the reliability of the data. In another birth cohort study, based on hospital electronic medical records, infants with TTN and healthy controls were initially selected. Asthma diagnoses were then investigated using ICD codes recorded during the 2 to 5 years following birth at the same hospital[13]. TTN was found to be independently and significantly associated with a diagnosis of childhood asthma. The authors highlighted that TTN may serve as a marker of pulmonary dysfunction, reflecting a genetic predisposition to asthma[13]. Since we utilized the entire national database in our study, we were able to access all records, regardless of which hospital or district the cases were seen in. However, the referenced study relied solely on records from the hospital where the birth occurred. When interpreting their results, it is crucial to consider

that this approach may not fully capture the complete medical history of the cases.

In a study by Shohat et al.[19], 58 children aged 4 to 5 years with a history of TTN at birth were compared to age-matched controls without a TTN history. The TTN group showed significantly higher rates of atopic manifestations, a family history of atopy in first-degree relatives, more than two wheezing episodes, and a clinical diagnosis of childhood asthma compared to the control group[19].

In contrast to previous studies, our findings showed that the TTN group experienced more single episodes of bronchiolitis, while the frequency of three or more episodes was higher in the control group. Although recurrent bronchiolitis attacks can have multiple causes, they are often considered an early sign of asthma. Based on this information, our study suggests that progression to asthma was not more common in the TTN group compared to the control group.

The consistency of similar findings across various studies using different methods-such as surveys, clinical examinations, and ICD diagnosis codes-strengthens the association between wheezing/bronchiolitis episodes and TTN.

Strengths of the Study

This study has several important strengths that enhance its scientific validity and potential clinical contributions. Foremost, it is a population-based, large-scale birth cohort study conducted in Istanbul, the largest metropolitan area in Türkiye. The dataset, which covers over one million live births between 2016 and 2018, was obtained through the standardized electronic health record system (e-Nabız) of the Turkish Ministry of Health. This approach minimizes selection bias and ensures that the sample highly represents the general population.

Another significant strength of the study is its large sample size. Both the TTN and control groups included over 14,000 infants, which increased the statistical power and allowed the detection of small but clinically meaningful differences. Additionally, the carefully defined exclusion criteria eliminated the effects of congenital anomalies, severe prematurity, and other respiratory diseases, resulting in a homogeneous cohort with high internal validity.

A simple random sampling method was used to select the control group, which included only infants who had undergone healthy check-ups during the neonatal period. This approach ensured that the comparison group and the TTN group were similar in baseline characteristics, thereby minimizing the influence of confounding variables. Furthermore, the continuous follow-up of infants for 24 months from birth allowed detailed analysis of both the timing and frequency of acute bronchiolitis episodes.

The use of real-world data represents another key strength of this study, enhancing its applicability to health policy. By using nationally standardized health data, researchers ensured that the findings are not limited to Istanbul alone but can be generalized to broader populations with similar healthcare infrastructures. Moreover, these results may provide valuable insights for identifying target groups for preventive strategies against viral infections such as RSV.

Study Limitations

Limitations of the study include the fact that participants' health records encompassed all healthcare facilities, ranging from small health clinics to tertiary hospitals. In smaller centers, such as health clinics, specific ICD codes for bronchiolitis subtypes, like RSV bronchiolitis, may have been underreported, as confirmation of these specific diagnoses was not consistently possible at every facility.

CONCLUSION

Infants with TTN experience more bronchiolitis episodes during the first two years of life compared to healthy term infants. However, recurrent bronchiolitis attacks are less frequent in the TTN group than in healthy controls. Future studies employing new methodologies that retrospectively investigate the history of TTN in children with asthma and wheezing may provide further insights into this relationship.

Ethics

Ethics Committee Approval: Ethical approval for conducting the study was obtained from the Ethics Committee of Istanbul Medeniyet University (approval number: 2020/0633, date: 05.03.2025).

Informed Consent: Since this study was based on data from the national health records system and no direct contact was made with any individuals, obtaining ethical approval from participants was not required.

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We acknowledge that we employed ChatGPT 3.5 and 4 to assist us in refining the clarity of our writing while developing the draft of this case report. We always maintained continuous human oversight (editing-revising) and verified the artificial intelligence-generated output. We never used AI to find, locate, or review the literature or resources, summarize the articles, analyze the selected articles, or synthesize the findings. The authors completed all analyses with higher-level efforts.

Footnotes

Author Contributions

Surgical and Medical Practices: S.C.O., S.G., Concept: S.C.O., M.K.S., G.B., A.K.K., S.G., Design: S.C.O., M.K.S., D.M.T., Z.R.O., A.K.K., S.G., Data Collection and/or Processing: S.C.O., M.K.S., D.M.T., Y.A., S.G., Analysis and/or Interpretation: S.C.O., M.K.S., D.M.T., S.G., Literature Search: S.C.O., G.B., D.M.T., Z.R.O., Y.A., A.K.K., S.G., Writing: S.C.O., M.K.S., G.B., S.G.

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

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