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Factors affecting mortality in neonatal pneumothorax

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Abstract
Aim: We aimed to determine the prevalence, demographic and clinical features of neonatal pneumothorax (NP) and to investigate the effects of these variables on mortality.
Material and Methods: The medical records of patients with NP who were treated with tube thoracostomy method between 2004 and 2018 were examined. The causes, clinical features, additional anomalies, demographic data and mortality rate of NP patients were investigated. The results were compared with chi-square, Mann-Whitney U, ROC (receiver operating characteristic) analysis and Binary Logistic Regression test.
Results: NP prevalence in our setting was 1.56%. Sixty-six of the patients were girls and 54 were boys. Mortality was significantly higher in female newborns ($p = 0.005$), mechanical ventilator support ($p = 0.005$), cardiopulmonary resuscitation history ($p = 0.001$), birth-weight of < 1380 g ($p = 0.001$) and gestational age of < 30 weeks ($p = 0.001$) and diagnosis time of > 5 days ($p = 0.001$). Among congenital heart diseases, mortality was also significantly higher in patients with patent foramen ovale + patent ductus arteriosus and atrial septal defect + patent ductus arteriosus ($p = 0.032$). In addition, mortality was significantly higher in the patients with respiratory distress syndrome ($p = 0.01$). However, mode of delivery, pneumothorax side, presence of additional anomalies, Apgar score, age of diagnosis did not have significant effect on mortality ($p > 0.005$).
Discussion: The neonates with ≤ 1400 g birth-weight, 33 weeks gestational age, > 5 postnatal days, history of CPR and mechanical ventilator support, and female gender constitute a sensitive population for development of pneumothorax and therefore should be closely monitored.

Keywords
Respiratory Distress Syndrome, Neonate, Pneumothorax, Risk Factor, Mortality

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Introduction

Pneumothorax is the presence of air in the space between the parietal and visceral pleura [1]. Symptomatic pneumothorax occurs in 0.05% of newborns [2]. Although there are many factors in the etiology of neonatal pneumothorax (NP), prematurity and mechanical ventilator therapies are among the most important factors. The prevalence of pneumothorax was reported to be higher in newborns treated by the mechanical ventilator (6-33%) [3]. NP is also increasing in the presence of some pulmonary diseases such as meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), pneumonia and pulmonary hypoplasia [1-3]. Although NP is one of the treatable respiratory problems, which usually occurs in the first days of life, its mortality rate is still high (30-36%) [4,5]. Though there are many studies in the literature on the etiology and frequency of NP, there are not enough studies on the prediction of mortality by affecting factors in these cases.

In this study, it was aimed to determine the prevalence, demographic and clinical features of NP cases and to define the effect of these variables on mortality.

Material and Methods

Study Design

The medical records of 128 patients with pneumothorax who were treated with tube thoracostomy between January 1, 2004 and January 30, 2018 were analyzed retrospectively. Eight out of 128 patients were excluded from the study because of incomplete records. Patients' gestational age, gender, mode of delivery, birth-weight, Apgar score at 5 minutes, diagnosis time, duration of tube thoracostomy drainage, history of mechanical ventilator treatment, accompanying diseases or anomalies, cardiopulmonary resuscitation history, pneumothorax side (right, left, or bilateral) and outcome were investigated. It is defined that preterm delivery < 37 completed weeks and full-term delivery ≥ completed 37 weeks.

The diagnosis was made clinically and radiologically on the basis of chest X-ray, and for selected cases, using computed tomography (CT). An 8-12 Fr thorax tube was used for the treatment of pneumothorax. All interventions were performed by a pediatric surgeon. Thoracal tubes were placed in the area where the pre-axillary line was connected with the 4th intercostal line. The control chest X-ray was checked for localization of the tube, and then, in the absence of accumulation of air on the radiograph taken, the tube was removed and the incision was closed for 3 days.

This study was conducted with the approval of the Non-Interventional Research Ethical Committee of Fırat University (approval date/no: 22.11.2018 / 19-7). This study was not supported by any foundation.

Statistical Analysis

Data were analyzed using SPSS statistics (SPSS statistics Inc., Chicago, USA) version 22, Java state and MS Excel Software. The Shapiro-Wilk test was used to determine the normal distribution of the data. Descriptive statistics are expressed as the median (minimum, maximum) for variables that do not show a normal distribution in continuous data, and as a percentage [% (n)] for categorical variables. The Mann-Whitney U test was used to compare two groups that were not normally distributed. The Chi-square test was used to analyze categorical data. The ROC (receiver operating characteristic) analysis was performed to determine the cut-off value of the variables to evaluate the mortality. The relevant values are given with area under the curve (AUC) and standard deviation, 95% confidence interval, sensitivity and specificity. The relevant cut-off values are calculated according to the Youden index. Binary logistic regression analysis was used to analyze the effect of independent variables on two outcome- dependent variables. The significance level was determined as $p < 0.05$.

Results

A total of 8161 newborn infants were admitted to the neonatal intensive care unit (NICU) during the study period. One hundred twenty-eight of them were diagnosed with NP. Eight patients were excluded from the study due to incomplete records. According to this, the NP prevalence was 1.56%. Fifty-four of patients were male (45%) and 66 were female (55%). The mortality rate for all patients was 56.7% (n: 68). The mortality rate was significantly higher in females (n: 45, 68.2%) than in males (n: 23, 42.6%) ($p = 0.005$).

The characteristics of the patients like birth-weight, gestational age, admission time, age of diagnosis, duration of tube thoracostomy drainage, Apgar score at 5 minutes, and mortality rates in relation to these variables are given in Table 1. In terms of accompanying diseases, the mortality rate was significantly higher in patients with RDS. This disease was followed by MAS, and hypoxic-ischemic encephalopathy (HIE) ($p = 0.001$). The mortality rates of the patients according to the accompanying diseases are given in Table 2. Mortality was significantly higher in patients required mechanical ventilation ($p = 0.001$) and in patients underwent cardio-pulmonary resuscitation (CPR) ($p = 0.001$). The mortality rates of the patients according to mechanical ventilator support, type of delivery, CPR history, side of pneumothorax, and presence of congenital heart disease (CHD) are given in Table 3. Sixty patients (50%) had congenital heart disease. Mortality occurred in 30 (50%) of these patients. Although the mortality rate was not significantly high in patients with CHD ($p = 0.197$). In 8 (30.8%) of 26 (43.3%) patients with patent foramen ovale (PFO) + patent ductus arteriosus (PDA) and in 7 (58.3%) of 12 (20%) patients with atrial septal defect (ASD) + PDA had developed mortality. Mortality was significantly higher in these patients ($p = 0.032$).

Table 1. The mortality rates in relation to patients' characteristics

Mortality		Birth-weight (g)	Gestational age (weeks)	Admission time (days)	Diagnosis time (days)	Duration of tube drainage (days)	Apgar score at 5 minute
NO (n=52)	Median	2650	37	1	3	9	8
	Minimum	980	24	1	1	1	5
	Maximum	4000	38	10	19	22	10
YES (n=68)	Median	1380	30	1	5	5	8
	Minimum	580	23	1	1	0	3
	Maximum	3410	40	12	37	19	10
TOTAL (n=120)	Median	2130	35	1	4	7	8
	Minimum	580	23	1	1	0	3
	Maximum	4000	40	12	37	22	10
p		0.0001	0.0001	0.906	0.001	0.0001	0.189

Five of 10 (16.7%) patients with atrial septal aneurysm (ASA) + PFO + PDA, 2 of 4 patients with ASD, 6 of 6 patients with ventricular septal defect (VSD) + PFO + PDA and 2 of 2 patients with Tetralogy of Fallot developed mortality.

ROC analysis of the patients' birth weight, gestational age, age of diagnosis and duration of tube thoracostomy drainage was performed to determine the critical threshold for mortality. Binary logistic regression analysis demonstrated that gestational age, duration of tube thoracostomy drainage, and accompanying additional anomalies significantly increased mortality compared to other variables.

Table 2. Mortality rates according to accompanying diseases

	Mortality n (%)		Total n (%)
	NO	YES	
Respiratory distress syndrome	9 (17.4)	34 (50.1)	43 (35.7)*
Meconium aspiration syndrome	7 (13.6)	8 (11.8)	15 (12.5)*
Hypoxic-ischemic encephalopathy	2 (3.8)	8 (11.8)	10 (8.3)*
Esophageal atresia	8 (15.5)	0 (0)	8 (6.7)
Intrauterine growth retardation	4 (7.7)	4 (5.9)	8 (6.7)
Intestinal atresia	4 (7.7)	2 (2.9)	6 (5)
Transient tachypnea of the newborn	6 (11.5)	0 (0)	6 (5)
Bronchopulmonary dysplasia	0 (0.0)	4 (5.9)	4 (3.3)
Congenital heart disease	2 (3.8)	2 (2.9)	4 (3.3)
Pneumomediastinum	2 (3.8)	2 (2.9)	4 (3.3)
Diaphragmatic hernia	2 (3.8)	0 (0)	2 (1.7)
Inborn error of metabolism	0 (0)	2 (2.9)	2 (1.7)
Congenital pulmonary malformation	2 (3.8)	0 (0)	2 (1.7)
Omphalocele	2 (3.8)	0 (0)	2 (1.7)
Congenital pneumonia	0 (0)	2 (2.9)	2 (1.7)
No	2 (3.8)	0 (0.0)	2 (1.7)
Total	52 (100)	68 (100)	120 (100)

*: p = 0.001

Table 3. The mortality rates of the patients according to their clinical characteristics

		Mortality n (%)		Total n %	p
		NO	YES		
Gender	Female	21 (31.8)	45 (68.2)	66 (55)	0.005*
	Male	31 (57.4)	23 (42.6)	54 (45)	
Mechanical ventilator requirement	No	8 (15.5)	0 (0)	8 (6.7)	0.001*
	Yes	44 (84.6)	68 (100)	112 (93.3)	
Type of delivery	Vaginal birth	40 (76.9)	50 (73.5)	90 (75)	0.671
	C-section	12 (23.1)	18 (26.5)	30 (25)	
Cardio-pulmonary resuscitation	No	48 (92.3)	0 (0)	48 (40)	0.001*
	Yes	4 (7.7)	68 (100)	72 (60)	
Side of pneumothorax	Right	37 (71.2)	51 (75)	88 (73.3)	0.524
	Left	7 (13.5)	11 (16.2)	18 (15)	
	Bilateral	8 (15.4)	6 (8.8)	14 (11.7)	
Congenital heart disease	No	22 (42.3)	38 (55.9)	60 (50)	0.197
	Yes	30 (57.7)	30 (44.1)	60 (50)	

*: Statistically significant

Discussion

In this study, the clinical and demographic characteristics of a sensitive population who developed pneumothorax, as well as risk factors that were affecting the mortality were demonstrated. NP is a common and life-threatening condition for NICU patients. NP prevalence is between 0.5-1% in term infants in NICU. In this study, the NP prevalence in NICU was found to be 1.56%. When the demographic data were analyzed, NP was reported to be more common in low birthweight infants [6,7]. It was reported as 13% in infants with a birth weight of 500-750 g and 2% in infants with a birth weight of 1251-1500 g [7].

It has been reported that mortality significantly increases, especially in < 2500 g infants [5-7]. In addition, Verma et al. [8] reported that the risk of bronchopulmonary dysplasia was 13-fold higher in the < 1500 g infants who developed pneumothorax. In our study, the median birthweight of the surviving patients was 2650 g, and the median birth-weight of deceased patients was 1380 g. A birth-weight of 1400 g was found as a critical limit for mortality. According to this, patients with low birthweight should be followed up closely for the development of pneumothorax and mortality in the event of a sudden deterioration.

Studies have shown that mortality is more common in preterm cases with NP [9,10]. On the contrary, another study reported that there was no difference in mortality between preterm and term babies with NP. In our study, the median gestational age was 30 weeks in the dead patients, and a < 33 gestational week was found to be a critical limit for mortality.

It was found that one of the effective parameters of mortality was female sex. However, although NP prevalence was found to be higher in boys, the effect of gender on mortality was not reported some studies [5,7,9,11,12]. In contrast to the previous studies, the present study found that the female gender significantly increased both the prevalence and mortality rate of NP.

Studies have reported that NP occurs more frequently in the first three days of life [9,13]. In our study, the median age of NP development was 4 days. However, it was found to be 5 days in dead patients. The mortality rate was significantly high in patients who developed NP after the postnatal fifth day.

In patients with NP, comorbidities of RDS, MAS, pneumonia, premature rupture of membranes (PROM), oligohydramnios, and perinatal asphyxia are frequently reported. Madansky et al. [14] reported that 41% of newborns diagnosed with MAS developed NP; likewise, Santos Silva et al. [15] reported that 3.8 % of patients with NP had MAS, 30 % had RDS. Apiliogullari et al [9] also reported that 43% of cases with NP had RDS and 17% had RDS and MAS. In studies, it was found that 89% of patients with NP had PROM with a 26% mortality rate, 38% had RDS, 22% had MAS, 14% had transient tachypnea of the newborn, and 12% had pneumonia [5,13]. Likewise, 35.7% of our patients had RDS, 12.5% had MAS, and 8.3% had HIE. Mortality was significantly higher in patients with comorbidities of RDS, MAS, HIE and mortality of these three diseases constituted 73.7% of the overall mortality. In the studies, it was reported that the pneumothorax developed more on the right side (73%), but it

did not have any effect on mortality if it developed on the right, left or bilaterally [9,13]. In addition, the type of delivery (vaginal or C/S) and the Apgar score at 5 minutes have been reported to have no effect on the development of NP [5,13,16]. In our study, in accordance with the literature, pneumothorax was seen more on the right side; however, it was determined that the side of pneumothorax, the type of delivery and the Apgar score at 5 minutes did not differ in terms of mortality.

It has been described in the studies that mechanical ventilator treatment is a predisposing factor for NP development [10,17]. Zenciroğlu et al. [10] reported that 90.6% of deceased patients had received mechanical ventilation therapy. In our study, mechanical ventilation therapy was required in 93% of the cases. While there was no mortality in patients without mechanical ventilation requirement, the mortality rate was 60% of those who needed mechanical ventilation. Because this significantly increases mortality in patients with NP, NICU practitioners should develop their mechanical ventilation strategies to reduce pulmonary complications and improve long-term outcomes.

In the study of Apiliogullari et al. [9], 10 out of 30 patients with NP died, while 9 of them had CPR history. In addition, Zenciroğlu et al. [10] reported that CPR had increased mortality in NP cases. In our study, all patients who died had a CPR history, while no mortality was noticed in patients without CPR history. The increased mortality in patients undergoing CPR may be due to respiratory and circulatory collapse.

In a study, the number of CHD was significantly higher (55%) in patients with symptomatic NP compared to the control group [7]. In the present study, 50% of the cases had CHD. The most common CHDs were the associations of PFO + PDA and ASD + PDA. Mortality was significantly higher in these two associations. The addition of circulatory collapse to respiratory collapse in NP patients with CHD might have been effective in increasing the mortality in these patients.

Conclusion

Neonatal pneumothorax is a fatal respiratory disease which is more common in the first days of life with increased prevalence due to accompanying additional diseases and anomalies, and can be treated with early diagnosis. The cases with birth weight ≤ 1400 g, 33 weeks gestational age, > 5 postnatal days, history of CPR and mechanical ventilator support, and female gender constitute a sensitive population for development of pneumothorax and therefore should be closely monitored.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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