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Original Article

Predictive Factors for Failure of High-Flow Nasal Cannula Therapy in Pediatric Intensive Care Unit

Çocuk Yoğun Bakım Ünitesinde Yüksek Akışlı Nazal Kanül Tedavisinin Başarısızlığı için Öngörücü Faktörler

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ABSTRACT

Objective: High-flow nasal cannula (HFNC) therapy is widely used to manage respiratory distress in children. However, treatment failure requiring advanced respiratory support is associated with increased rates of morbidity and mortality. Identifying predictive factors for HFNC failure is crucial for optimizing patient outcomes. This study aimed to determine the predictive factors associated with HFNC therapy failure in pediatric patients with moderate to severe respiratory distress managed in the pediatric intensive care units (PICU).

Method: This cross-sectional study included patients aged one month to 18 years with moderate to severe respiratory distress treated with HFNC therapy in the PICU between October 2018 and January 2020. Patients with chronic lung disease or cyanotic congenital heart disease were excluded from the analysis. Clinical and laboratory data, including modified Respiratory Distress Assessment Instrument (mRDAI) scores and treatment outcomes, were analyzed. Statistical methods including Mann-Whitney U test, χ^2 test, receiver operating characteristic curve and multivariate logistic regression analyses were used.

Results: Analysis of 114 patients revealed an HFNC treatment failure rate of 31.6%. Multivariate logistic regression analysis revealed that the presence of medical comorbidities [odds ratio (OR): 25.8; 95% confidence interval (CI): 2.61-254.5; p=0.005], an increased mRDAI scores at the first hour of HFNC therapy (OR: 2.9, 95% CI: 1.32-6.48, p=0.008), and higher pediatric risk of mortality (PRISM) (OR: 2.1, 95% CI: 1.44-3.07, p<0.001) were significant predictors of HFNC failure.

Conclusion: Early identification of predictive factors such as medical comorbidities, mRDAI and PRISM scores can help improve management strategies and outcomes for pediatric patients with respiratory distress undergoing HFNC therapy.

Keywords: Risk factors, HFNC, non-invasive ventilation, treatment failure, pediatric intensive care unit, pediatrics

ÖZ

Amaç: Yüksek akışlı nazal kanül (HFNC) tedavisi çocuklarda solunum sıkıntısını yönetmek için sıklıkla kullanılmaktadır. Bununla birlikte, ileri hava yolu desteği gerektiren tedavi başarısızlığı, artmış morbidite ve mortalite ile ilişkilidir. HFNC başarısızlığı için öngörücü faktörlerin belirlenmesi, hasta sonuçlarının optimize edilmesi için hayati önem taşımaktadır. Bu çalışmanın amacı, çocuk yoğun bakım ünitesinde (ÇYBÜ) orta ila şiddetli solunum sıkıntısı olan çocuk hastalarda HFNC tedavi başarısızlığı ile ilişkili öngörücü faktörleri belirlemektir.

Yöntem: Bu kesitsel çalışmaya, Ekim 2018 ile Ocak 2020 tarihleri arasında ÇYBÜ'de HFNC tedavisi ile tedavi edilen orta ila şiddetli solunum sıkıntısı olan bir ay ila 18 yaş arasındaki hastalar dahil edildi. Kronik akciğer hastalığı veya siyanotik konjenital kalp hastalığı olan hastalar çalışma dışı bırakıldı. Solunum skorları modifiye solunum sıkıntısı değerlendirme aracı (mRDAI) ve tedavi sonuçları dahil olmak üzere klinik ve laboratuvar verileri analiz edildi. İstatistiksel yöntemler arasında Mann-Whitney U testi, χ^2 testi, alıcı işletim karakteristik analizi ve çok değişkenli lojistik regresyon yer aldı.

Bulgular: Yüz on dört hastanın analizi, HFNC tedavi başarısızlığı oranının %31,6 olduğunu ortaya koydu. Çok değişkenli lojistik regresyon, tıbbi komorbiditelerin varlığının [olasılık oranı (OR): 2,8, %95 güven aralığı (CI): 2,61-254,5, p=0,005], HFNC tedavisinin ilk saatinde artmış mRDAI skorunun (OR: 2,9, %95 CI: 1,32-6,48, p=0,008) ve daha yüksek pediatrik ölüm riski (PRIM) skorlarının (OR: 2,1, %95 CI: 1,44-3,07, p<0,001) HFNC başarısızlığının anlamlı öngörücüleri olduğunu göstermiştir.

Sonuç: Tıbbi komorbiditeler, mRDAI skorları ve PRISM skorları gibi öngörücü faktörlerin erken tanımlanması, solunum sıkıntısı nedeniyle HFNC tedavisi alan çocuk hastalar için yönetim stratejilerinin ve sonuçların iyileştirilmesine yardımcı olabilir.

Anahtar kelimeler: Risk faktörleri, HFNC, non-invaziv mekanik ventilasyon, tedavi başarısızlığı, çocuk yoğun bakım ünitesi, pediatri

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INTRODUCTION

High-flow nasal cannula (HFNC) therapy is a relatively safe and easily applicable management of respiratory distress in children[1-3]. It delivers heated and humidified oxygen at high flow rates through the nasal cannula, which creates positive airway pressure and improves gas exchange[1,3,4]. HFNC therapy is generally used safely in pediatric wards, pediatric emergency departments, and pediatric intensive care units (PICUs)[4-6]. Studies have shown that HFNC therapy reduces respiratory effort/scores, the need for advanced respiratory support, and the length of hospitalization by clearing the nasopharyngeal dead space, improving lung mucociliary clearance, and oxygen delivery[2,3,7-11].

However, despite its many advantages and widespread use, failure rates of HFNC therapy ranging between 12.7-31.9% have been reported[1,12-16]. HFNC therapy failure, defined as the transition to advanced airway support therapies in patients who do not respond to HFNC therapy, is associated with increased mortality and morbidity[13].

HFNC therapy may delay the inevitable need for advanced respiratory support therapy by masking signs of respiratory distress. Identifying the predictors of HFNC therapy failure, early diagnosis, and optimization of patient care are important factors for preventing adverse outcomes. This study aimed to determine the factors affecting HFNC therapy failure in patients with moderate to severe respiratory distress treated in the PICU.

MATERIALS and METHODS

Study Design and Setting

This is an observational, cross-sectional study conducted in a single center in Turkey. Behçet Uz Children's Hospital, which was included in the study as a single center, is a tertiary-level training and research hospital for pediatrics in İzmir. It has a 14-bed pediatric emergency department, a 24-bed third-level PICU, and three general pediatric wards with a total of 46 beds.

Sample Size

The sample size was calculated as 70 (at least 35 for each of the successful and failed HFNC therapy groups using G*Power[17] with 80% power and a 0.05 type 1 error rate, and using the data derived from the study of Er et al.[14]

Participants

Inclusion Criteria

All patients aged between 1 month and 18 years who were followed up in the PICU with the indication of moderate and severe respiratory distress and received HFNC respiratory support therapy between October 2018 and January 2020 were included in our study.

Exclusion Criteria

Patients aged over 18 years and younger than one month, those with chronic lung disease and cyanotic congenital heart disease (those with CO_2 retention or hypoxia in daily life, those receiving home oxygen therapy), patients with craniofacial malformations, trauma patients, hypotonic patients, patients with tracheostomy, patients using HFNC therapy for respiratory support after extubation, and those who did not agree to participate in the study were excluded.

HFNC Therapy Protocol

The HFNC device-flow driver and humidifier-(AIRVO 2® Nasal High Flow System, Fisher & Paykel Healthcare, Auckland, New Zealand) in our hospital consisted of an air-oxygen mixer and a heating and humidification system capable of providing fraction of inspired oxygen (FiO_2) from 21% to 100% and an airflow of 2-60L/min. The gas mixture was delivered to the patient via an age-appropriate nasal cannula (Optiflow™ interfaces, Fisher & Paykel Healthcare, Auckland, New Zealand) at 34 °C.

In patients receiving HFNC therapy, the nasal cannula was set to an initial flow rate of 2 L/kg/min. in infants and 1 L/kg/min. in children, and the flow rate was changed according to the discretion of the clinician who monitored the patient and symptomatic changes in the patient's respiratory distress (respiratory retraction, nasal flaring, and tachypnea)[8]. FiO_2 was initially adjusted appropriately according to the patient's requirements and then adjusted so that the patient's oxygen saturation (SpO_2) was maintained between 92-97%[1,3,10].

Data Collection and Measurements

Patient information, laboratory results, and nurse and physician records registered in electronic patient database of our hospital were investigated. Sex, age, diagnoses, pediatric risk of mortality (PRISM) III scores, cardiovascular system history, intubation history, indications, and duration of HFNC therapy, medical comorbidities, nasal respiratory polymerase chain

reaction results, hematocrit values, and incidence of mortality (if any) were recorded. Blood gas test results, respiratory rates (RRs), heart rates (HRs), SpO_2, FiO_2 values, SpO_2/FiO_2 (S/F) ratios, modified Respiratory Distress Assessment Instrument (mRDAI) and Pediatric Respiratory Severity Scores (PRESS), sedation, and side effects were recorded before, during the first hour, and in cases of failure of HFNC therapy.

Severity of respiratory distress was assessed using mRDAI and PRESS scores. Failure of HFNC therapy was defined as the need for advanced respiratory support treatment modalities [non-invasive mechanical ventilation (NIMV), continuous airway pressure and bilevel positive airway pressure or invasive mechanical ventilation (IMV)] within the first seven days after onset of respiratory distress. A 7-day failure period was chosen so as to evaluate both early and late HFNC therapy failures, providing a comprehensive assessment of its efficacy in our PICU population, where shorter periods may miss delayed deteriorations[16,18,19]. Intubation criteria were based on the discretion of the attending physician on the overall clinical situation, including breathing effort (chest retractions, and nasal flaring) and the ability to sustain this respiratory effort[20-22]. In addition, lethargy, cyanosis, poor perfusion, apnea, or inability to maintain adequate oxygen saturation were indications for intubation.

Study Registration and Guidelines

This study was registered at ClinicalTrials under the identifier NCT06146439. The design of our study adhered to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis + artificial intelligence (AI) statement (Appendix)[23].

Statistical Analysis

Distribution of data was checked using histograms, Q-Q plots, and the Kolmogorov-Smirnov test. Normally distributed quantitative data were expressed as mean (± Standard Deviation), whereas data that were not normally distributed were indicated as median and interquartile range (IQR=Q3-Q1). Categorical variables were expressed as numbers and percentages. Variables with more than 25% missing data were excluded from the analysis. Missing data were analyzed using Little's missing completely at random test. The missing data were determined to be missing completely at random mechanism, and the datasets were completed using the expectation-maximization algorithm. To eliminate the effect of extreme outliers in the data, we excluded these data using (25^{th} percentile - 3IQR) and (75^{th} percentile + 3IQR).

For comparisons of numerical data between paired groups, the Student's t-test was used for comparisons between normally distributed groups, and the Mann-Whitney U test for comparisons among non-normally distributed groups. Nominal and ordinal variables were compared by the χ^2 test. If a significant difference was found between the groups after application of the χ^2 test, the group or groups from which the difference originated from were evaluated by post hoc analysis using Tukey and Bonferroni tests.

Variables with a p-value less than 0.20 were included in univariate analyses to determine the factors affecting the risk of HFNC therapy failure. Nominal independent variables were designed as n-1 dummy variables. Multivariate logistic regression (LR) analysis was performed by including independent variables that were significant in the univariate analysis. The variance inflation factor (VIF) was used to detect multicollinearity among independent variables. Variables with a VIF of >3 were excluded from the analysis. Predictive factors were reported using multivariate odds ratios (ORs) and levels of significance (p) were adjusted for 95% confidence intervals (CIs). In the LR analysis, the fit of the predictions to the established model was tested using the Hosmer-Lemeshow test, and the ability of the independent variables to explain the dependent variables was tested using the Nagelkerke R^2 value. Receiver operating characteristic (ROC) analysis was used to evaluate the diagnostic decision-making properties of independent variables in predicting HFNC therapy failure. The area under curve (AUC) was used to determine the discrimination power of the variables and the Youden index (sensitivity+specificity-1) was used to determine the most appropriate threshold value and the best sensitivity and specificity values.

Statistical analyses and data visualization were performed using Jamovi (The Jamovi Project 2023, Sydney, Australia, version 2.3) and SPSS® (IBM® SPSS Statistics for Windows, version 26.0, Armonk, NY, USA). All analyses were conducted using two-tailed tests with a significance level of 0.05.

Ethical Considerations

Our study was conducted after receiving approval from Behçet Uz Children's Hospital Ethics Committee (approval number: 2018/239, dated: 10.08.2018). Informed consent was obtained from all participants or their parents.

RESULTS

A total of 187 patients applied to our Pediatric intensive care unit between October 2018 and January 2020 were included in our study (Figure 1). Sixty-three patients were excluded owing to missing data and reasons for exclusion. Of the 114 patients included in the analysis, 61.4% (n=70) were male, the median age was 6 (IQR:3-13) months, and the median weight was 7.0 (IQR:5.0-9.5) kilograms. The demographic and medical characteristics of the patients are shown in Table 1.

HFNC therapy was successful in 78 (68.4%) and failed in 36 (31.6%) patients. After the failure of HFNC therapy, 16.7% (n=6) of the patients received NIMV treatment, whereas 83.3% (n=30) of them received invasive ventilation after endotracheal intubation. The history of intubation, place of transfer to intensive care, diagnosis on hospitalization, indications, respiratory distress, medical comorbidity, PRISM scores, mortality rates, breastfeeding history, side effects, and duration of HFNC therapy were significantly different between the groups. History of intubation, transfer to the intensive care unit from another hospital, bronchopneumonia, type 1 respiratory failure, medical comorbidity (immunodeficiency), side effects (inability to tolerate HFNC therapy), and mortalities were significantly more frequent in the failure group (Table 1).

At the beginning of HFNC therapy, FiO_2 was higher, and the mRDAI score and S/F were lower in the failure group. In the first hour of HFNC therapy, pCO_2, lactate, HR, RR, FiO_2, mRDAI, and PRESS scores were higher, and the pH, SpO_2, and S/F ratio were lower in the failure group. A comparison of the clinical and laboratory data between the successful and failed groups at the beginning and first hour of HFNC therapy is presented in Table 2.

When the variables found to be significant in the univariate LR analysis were evaluated using multivariate LR analysis, the variables given in Table 3 formed the most appropriate model. The predictability and goodness-of- fit of the model were found to be high according to the Hosmer-Lemeshow test (χ^2: 3.5, degree of freedom 8, p=0.899), and its fit (Cox&Snell R^2=0.546 and Nagelkerke R^2=0.773) was similar to the real situation. According to the multiple LR model, the presence of medical comorbidities (OR:25.8, 95% CI:2.61-254.50, p=0.005), the mRDAI scores at the first hour of HFNC therapy (OR:2.9, 95% CI:1.32-6.48, p=0.008) and the PRISM scores (OR:2.1, 95% CI:1.44-3.07, p<0.001) were significantly associated with failure. The mRDAI scores at the beginning of HFNC therapy (OR:0.2, 95% CI:0.08-0.44, p<0.001) were significantly associated with success of the HFNC therapy. The results of the multiple LR model are presented in Table 3.

In the ROC analysis performed to determine the optimal cut-off values for quantitative variables for predicting HFNC failure, cut-off values of 17 for the PRISM score (AUC:0.736, p<0.001) and 4.5 for the mRDAI score in the first hour of HFNC therapy (AUC:0.779, p<0.001) were found (Table 4).

Table 1. Demographic and clinical data of the patients

Characteristics	Successful (n=78)	Failure (n=36)	Total (n=114)	p-value
Gender, % (n)				
Male	56.4 (44)	72.2 (26)	61.4 (70)	0.107
Female	43.6 (34)	27.8 (10)	38.6 (44)	
Age, median (IQR), months	5.75 (3-11)	9 (2.25-16.75)	12.1 (3-6)	0.326
Weight, median (IQR), kg	7 (5.5-9.57)	6.6 (4.5-9.75)	7.8 (5-7)	0.475
Congenital heart disease, % (n)	10.3 (8)	5.6 (2)	8.8 (10)	0.401
Intubation history, % (n)	15.4 (12)	33.3 (12)	21.1 (24)	**0.029**
Patients transferred to the PICU from, % (n)				
Another hospital	8.9 (7)	25 (9)*	14.03 (16)	**0.039**
Pediatric emergency room	79.4 (62)*	58.3 (21)	72.8 (83)	
Pediatric ward	11.5 (9)	16.7 (6)	13.1 (15)	

Table 1. Continued				
Characteristics	**Successful (n=78)**	**Failure (n=36)**	**Total (n=114)**	**p-value**
Indications for its use, % (n)				
Respiratory distress	94.9 (74)*	63.9 (23)	85.1 (97)	**<0.001**
Type 1 respiratory failure	5.1 (4)	25.0 (9)*	11.4 (13)	
Type 2 respiratory failure	0.0 (0)	11.1 (4)	3.5 (4)	
Respiratory distress according to mRDAI scores, % (n)				
Moderate	30.7 (24)	50 (18)	36.8 (42)	**0.048**
Severe	69.3 (54)	50 (18)	63.2 (72)	
Respiratory distress according to PRESS scores, % (n)				
Moderate	1.2 (1)	11.1 (4)	4.3 (5)	**0.034**
Severe	98.8 (77)	88.9 (32)	95.7 (109)	
PRISM scores, median (IQR)	14 (11-16)	18 (12-21)	14 (11-16)	**<0.001**
Baseline diagnoses, % (n)				
Bronchopneumonia	47.4 (37)	72.2 (26)*	55.2 (63)	**0.017**
Bronchiolitis	35.9 (28)*	11.1 (4)	28.1 (32)	
Reactive Airway Disease	14.4 (11)	0.0 (0)	9.6 (11)	
ARDS	0.0 (0)	11.1 (4)	3.5 (4)	
Chest X-ray findings, % (n)				
Normal	12.8 (10)	5.5 (2)	10.5 (12)	0.368
Consolidation	24.3 (19)	77.7 (28)	41.2 (47)	
PBM	53.8 (42)	75.0 (27)	60.5 (69)	
Air trapping	35.8 (28)	8.3 (3)	27.1 (31)	
Nasopharyngeal swap PCR, % (n)				
RSV	31.8 (14)	29.0 (9)	30.6 (23)	0.206
Rhinovirus	31.8 (14)	3.2 (1)	20.0 (15)	
Negative	4.5 (2)	12.9 (4)	8.0 (6)	
Medical comorbidities, % (n)				
None	71.6 (58)	41.6 (15)	64.0 (73)	**0.017**
Immunodeficiency	1.2 (1)	13.7 (5)*	5.2 (6)	
Prematurity	6.1 (5)	8.3 (3)	7.0 (8)	
Septic shock	6.1 (5)	0.0 (0)	4.3 (5)	
Epilepsy	3.7 (3)	11.0 (4)	6.1 (7)	
Inherited metabolic disorders	6.1 (5)	8.3 (3)	7.0 (8)	
Cerebral palsy	3.7 (3)	5.5 (2)	4.3 (5)	
Side effects, % (n)				
None	73.1 (57)	55.6 (20)	67.5 (77)	**<0.001**
Nasal trauma	24.4 (19)	16.7 (6)	21.9 (25)	
Intolerance	2.6 (2)	27.8 (10)*	10.5 (12)	
Sedation, % (n)				
No	80.8 (63)	77.8 (28)	79.8 (91)	0.711
Yes	19.2 (15)	22.2 (8)	20.2 (23)	

Table 1. Continued

Characteristics	Successful (n=78)	Failure (n=36)	Total (n=114)	p-value
Breastfeeding history, % (n)				
Never	6.4 (5)	27.8 (10)	13.2 (15)	**<0.001**
Still breastfeeding	78.2 (61)	36.1 (13)	64.9 (74)	
Weaned breastfeeding	15.4 (12)	36.1 (13)	21.9 (25)	
Hematocrit, mean (± SD), %	31.94 (3.94)	30.3 (4.99)	31.5 (4.31)	0.082
HFNC duration, median (IQR), hour	72 (60-96)	15 (4.5-35.5)	48 (16-84)	**<0.001**
Death, % (n)	0 (0)	25.2 (7)	6.14 (7)	**<0.001**

A p-value <0.05 marked in bold. *Indicates statistical significance in post-hoc analysis (p<0.05). ARDS: Acute respiratory distress syndrome, HFNC: High-flow nasal cannula, IQR: Interquartile range, mRDAI: Modified respiratory distress assessment instrument, PBM: Prominent broncho-vascular markings, PICU: Pediatric intensive care unit, PRESS: Pediatric Respiratory Severity score, RSV: Respiratory syncytial virus, SD: Standard deviations, PRISM: Pediatric risk of mortality score, PCR: Polymerase chain reaction

Table 2. Data at the beginning and first hour of HFNC treatment

	Successful (n=78)	Failure (n=36)	Total (n=114)	p-value
At the onset of HFNC therapy, median (IQR)				
pH	7.36 (7.3-7.4)	7.32(7.24-7.4)	7.35 (7.29-7.4)	0.08
pCO_2, mmHg	44.3 (37.9-48.5)	46 (41.5-55)	44.7 (39-50)	0.104
Lactate, mmol/L	2.1 (1.32-3)	2.1 (1.58-2.79)	2.1 (1.5-3)	0.91
HR, bpm	166 (155-180)	162 (146-175)	166 (150-180)	0.19
RR, bpm	60 (56-62)	60 (51-65)	60 (55-64)	0.85
SpO_2, %	90 (88-90)	88 (88-90)	90 (88-90)	0.19
FiO_2, %	21 (21-30)	30 (30-40)	30 (21-40)	**<0.001**
S/F ratio	419 (300-423)	293 (218-300)	313 (237-419)	**<0.001**
mRDAI scores	9 (8-10)	9 (7-9)	9 (8-10)	**0.04**
PRESS scores	4 (4-5)	4 (4-5)	4 (4-5)	0.499
First hour of HFNC therapy, median (IQR)				
pH	7.38 (7.35-7.4)	7.33 (7.28-7.38)	7.37 (7.33-7.4)	**<0.001**
pCO_2, mmHg	41 (38-44)	47 (40-53)	41.5 (38-46.6)	**0.001**
Lactate, mmol/L	1.45 (1.17-2.1)	2.16 (1.37-3.4)	1.6 (1.2-2.36)	**0.004**
HR, beats/min.	138 (125-148)	150 (141-167)	140 (130-154)	**<0.001**
RR, beats/min.	42 (40-50)	50 (44-55)	44 (40-50)	**<0.001**
SpO_2, %	98.5 (96-100)	94 (94-98)	98 (96-100)	**<0.001**
FiO_2, %	40 (30-40)	40 (40-50)	40 (30-40)	**<0.001**
S/F ratios	250 (245-320)	225 (188-246)	247 (235-320)	**<0.001**
mRDAI scores	3.5 (3-4)	5 (4-6)	4 (3-5)	**<0.001**
PRESS scores	2 (1-2)	3 (2-4)	2 (2-3)	**<0.001**

A p-value <0.05 marked in bold. FiO_2: Fraction of inspired oxygen, HFNC: High Flow Nasal Cannula, IQR: Interquartile range, pCO_2: Partial pressure of carbon dioxide, HR: Heart rate, mRDAI: modified respiratory distress assessment instrument, PRESS: Pediatric Respiratory Severity Score, RR: Respiratory rate, SpO_2: Oxygen saturation, S/F: Oxygen saturation/fraction of inspired oxygen ratio

Table 3. Results of multivariate logistic regression analysis

A. Model fit measures

Model summary			Hosmer and Lemeshow test			
-2 LogL	Cox & Snell R^2	Nagelkerke R^2	Step	χ^2	df	p-value
47.543	0.546	0.773	7	3.505	8	0.899

B. Model co-efficients

Predictors	B	SE	Wald	OR	95% CI		p-value
Medical comorbidities, Yes vs. No[a]	3.249	1.16	7.73	25.8	2.61	254.5	**0.005**
PRISM scores	0.741	0.19	14.64	2.1	1.44	3.07	**<0.001**
mRDAI scores, first hour of HFNC	1.074	0.40	7.01	2.9	1.32	6.48	**0.008**
mRDAI scores, beginning of HFNC	-1.664	0.43	14.74	0.2	0.08	0.44	**<0.001**
pCO_2, first hour of HFNC, mmHg	0.060	0.04	2.14	1.1	0.98	1.15	0.143

[a]Reference value. A p-value <0.05 is marked in bold. χ^2: Chi-square, CI: Confidence interval, df: Degree of freedom, HFNC: High-flow nasal cannula, LogL: Log-likelihood, mRDAI: Modified respiratory distress assessment instrument, pCO_2: Partial pressure of carbon dioxide, PRISM: Pediatric risk of mortality score, OR: Odds ratio, SE: Standard error

Table 4. ROC analysis results

Independent variables	AUC	SE	p-value	%95 CI			
mRDAI scores, first hour of HFNC	0.779	0.051	<0.001	0.678	0.879		
PRISM scores	0.736	0.060	<0.001	0.619	0.854		
Independent variables	**Cut-off value**	**Sensitivity (%)**	**Specificity (%)**	**Positive predictive value (%)**	**Negative predictive value (%)**	**LR test**	**Youden index**
mRDAI scores, first hour of HFNC	4.5	60	90	57.9	90.9	5	1.497
PRISM score	17	57.1	92.3	76.9	81.8	7	1.495

AUC: Area under the curve, CI: Confidence interval, HFNC: High-flow nasal cannula, LR: Likelihood ratio, mRDAI: Modified respiratory distress assessment instrument, PRISM: Pediatric risk of mortality score, SE: Standard error, ROC: Receiver operating characteristic

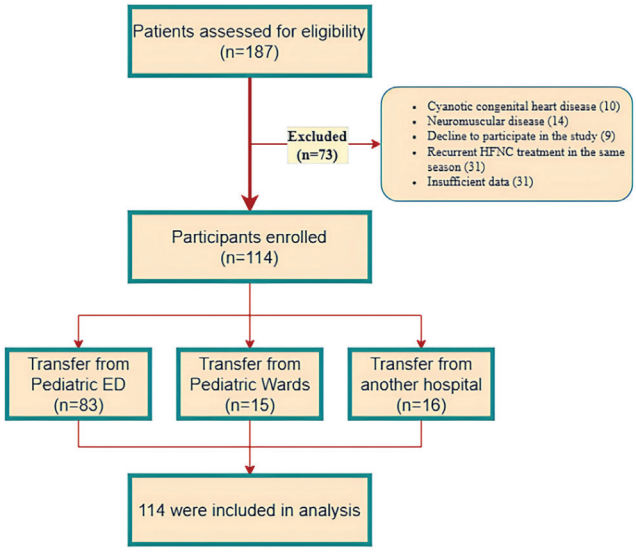

Figure 1. Flow diagram. Flowchart showing the stages of the study and the number of participants

DISCUSSION

Our study aimed to determine the factors affecting HFNC therapy failure in children with moderate to severe respiratory distress and revealed that HFNC therapy failure was 31.6%. The presence of medical comorbidities was associated with 25.8 times greater odds of HFNC therapy failure. The PRISM and mRDAI scores estimated at the first hour of treatment were associated with HFNC therapy failure, whereas interestingly, the mRDAI scores at the beginning of treatment were associated with successful HFNC therapy.

Studies to detect HFNC therapy failure in children have been conducted in pediatric emergency departments[14,15,24-26], pediatric wards[1,12,26-29], and PICUs[5,10,12,13,15,16,26,30-37] as in our study. To the best of our knowledge, we have reported one of the highest failure rates[1,12-16,32,36]. Pediatric HFNC failure has been evaluated at varying time intervals (30 minutes to 96 hours)[13,19,38].

Many studies[16,18,19] have evaluated HFNC failure within the first 24-hours after its application, whereas our study employed a 7-day assessment window. This extended duration of follow-up period likely allowed us to capture delayed failures that occur beyond the initial 24 hours, thereby contributing to a higher observed failure rate. In addition, this high failure rate we observed may be attributed to the exclusion of patients with mild respiratory distress and focusing on patients admitted to the PICU. The inclusion of patients with a higher prevalence of medical comorbidities, as confirmed by our LR analysis, further distinguishes our study from others that may have enrolled a broader, less critically ill pediatric population. Besides, higher proportion (83.3%) of the patients in our failure group required intubation and invasive respiratory support therapy when compared with HFNC therapy failure rates reported in other studies[5,14,36]. Only İleri et al.[15] reported the need for IMV similar to our study. This finding suggests that our cohort may represent a population in which HFNC is being used in patients near the threshold for invasive support, or that certain underlying pathologies common in our center are less responsive to HFNC alone. Additionally, variations in clinical management protocols, including different criteria for transition to invasive ventilation and local practices regarding monitoring respiratory parameters, may have contributed to the observed discrepancies.

The presence of medical comorbidities, which was the predictor factor with the highest odds ratio in our study, was reported to be significant in only one study[32]. Comorbidities of congenital heart disease were reported more frequently in patients who experienced HFNC failure in two studies[12,28]. Of these studies, only Sunkonkit et al.[12] applied LR analysis (RR: 6.36, 95% CI: 1.74–23.17; p = 0.005). In another study, the presence of hemato-oncologic disease was associated with treatment failure (OR: 3.79, 95% CI: 1.12–12.78, p=0.031)[39]. While other studies have identified comorbidities as risk factors, in our study a particularly striking link was detected between HFNC failure rates and these comorbidities. This finding may be indicative of the specific patient profile, severity, or multiplicity of comorbidities that are prevalent in the population that is served by our tertiary referral center. The broad CI (95% CI: 2.61-254.5) also suggests variability, emphasizing the need for future research to identify which specific comorbidities drive this profound risk.

To the best of our knowledge, the PRISM score, another important predictive factor in our study, was reported to be significant in three studies[13,16,34]. In their study evaluating both HFNC therapy and NIV, Ongun et al.[34], reported that the cut-off value for the PRISM score was lower than that in our study. The Pediatric Index of Mortality^2 Risk of Death score in one study and the Pediatric Early Warning System respiratory score in another study were reported to be associated with failure of HFNC therapy[10,36].

A study conducted in infants with bronchiolitis managed in the PICU reported that a modified Tal score greater than five at the fourth hour of HFNC therapy was a predictive factor (OR: 2.81, 95% CI: 1.04, 7.64; p=0.042) [33]. In our study, we found that the mRDAI score at the first hour of treatment was associated with treatment failure. This seemingly paradoxical result requires careful interpretation. One potential explanation for this phenomenon is that patients presenting with more pronounced, readily apparent respiratory distress (higher initial mRDAI scores), perhaps due to conditions highly responsive to the mechanisms of HFNC (e.g., work of breathing reduction), may exhibit a more dramatic and rapid positive response when therapy is initiated promptly. Conversely, patients with lower initial scores might harbor underlying pathologies less amenable to HFNC support, such as severe parenchymal disease or impending fatigue not yet fully reflected in the score. This phenomenon underscores the notion that a baseline score alone is insufficient to evaluate the efficacy of HFNC therapy; the trajectory of the score and the overall clinical picture, including factors like comorbidities and PRISM score have a paramount importance. The dynamic nature of respiratory distress in pediatric patients necessitates continuous reassessment, rather than reliance on initial presentations alone.

In addition to the predictive factors we found in our study; younger age[33], higher RR at triage[25,30,35], lower SpO_2 at admission[14], higher FiO_2 at admission[10], lower S/F ratio at admission[5,14,16,39], lower venous pH at admission[14,25], greater venous pCO_2 at admission[14,25,32,35,37], no improvement or decrease in RR[1,10,12,14,24,29,32], no improvement in the S/F ratio[14,39], low S/F ratio[5], no improvement in HR[10,12,24,32], decreased $PaCO_2/PaO_2$ ratio[13], decreased ROX index[13,40,41], lowest diastolic blood pressure[32], lobar infiltration on chest radiography[12], and maximum FiO_2[27,28] were also reported.

The diagnosis of bronchiolitis[25], duration of HFNC therapy[33], and a significant increase in the S/F ratio in the first hour of HFNC therapy[14] were reported as factors

affecting the success of HFNC therapy. In our study, the initial mRDAI score was associated with successful HFNC therapy.

HFNC is a relatively new treatment on which pediatricians have focused. HFNC therapy has several benefits. Clinical practice and the literature have reported these benefits many times. However, similar to any other therapy, HFNC therapy can fail. We must not forget its negative consequences.

Study Limitations

This study had several limitations. The study was conducted at a single center. We could not evaluate confounding factors such as clinicians' different approaches to HFNC therapy. This single-center design and the variabilities in the applications of HFNC therapy and disease management practices may limit the generalizability of our findings. Furthermore, the extended observation period used to define HFNC failure could have contributed to our higher reported failure rate compared to studies with shorter monitoring windows. In addition, we should have included patients on HFNC therapy whose transfer from the pediatric emergency department. to the PICU was delayed due to the heavy bed occupancy in the PICU in the comparative analyses which may have affected both the results and the validity of the predictive model. It is also important to note that variations in sample size, statistical methodologies, and the operational definition of HFNC failure across studies may have contributed to the observed discrepancies. Future multicenter studies with standardized protocols are needed to validate these results and further refine the predictive models.

CONCLUSION

Early identification of predictive factors -medical comorbidities, elevated mRDAI scores at the first hour, and higher PRISM scores- can guide clinicians in optimizing HFNC therapy and improving outcomes of pediatric respiratory distress managed in the PICUs.

Ethics

Ethics Committee Approval: Our study was conducted after receiving approval from Behçet Uz Children's Hospital Ethics Committee (approval number: 2018/239, dated: 10.08.2018).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

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Footnotes

Author Contributions

Surgical and Medical Practices: D.O., R.İ., Concept: D.O., R.İ., Design: D.O., R.İ., Data Collection or Processing: D.O., G.A., Analysis or Interpretation: D.O., G.A., R.İ., Literature Search: D.O., G.A., R.İ., Writing: D.O., G.A., R.İ.

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