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Research Article

The Frequency and Severity of Nasal Trauma Secondary to Nasal Continuous Positive Airway Pressure in Neonates

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Abstract

Background: Nasal trauma is a well-recognized iatrogenic complication in neonates with respiratory distress using nasal continuous positive airway pressure (NCPAP). The severity of nasal injury ranges from mild erythema to necrosis. ***Objective***: to determine the frequency of nasal trauma and risk factors associated with the severity progression secondary to NCPAP. ***Methods***: A prospective observational study was conducted in Mosul City. Newborns who received NCPAP were included to assess nasal trauma and its severity. Univariate and multivariate logistic regression were used to identify factors associated with the nasal trauma. The Mann-Whitney U test was used to compare continuous variables and nasal trauma stages, and the effect sizes were reported. ***Results***: The incidence of nasal trauma was 46.2%. In univariate analysis, factors associated with increased odds of trauma were lower gestational age (OR=3.367; p<0.001), lower birth weight (OR=2.923; *p*<0.001), and NICU stay ≥7 days (OR=2.507; *p*=0.049), while the duration of NCPAP was not statistically significant (OR=1.341; *p*=0.515). However, in the multivariate analysis, none of the factors emerged as an independent predictor. NICU stay ≥7 days in the Mann-Whitney U test was the only significant predictor of severity progression (*p*=0.034), with a medium to large effect size. ***Conclusions***: Nasal trauma is a common and significant complication of NCPAP in neonates. Severity is usually mild, but moderate and severe cases do occur. Lower gestational age, lower birth weight, and longer NCPAP duration are risk factors for nasal injury, but prolonged NICU stay appeared to be a strong predictor for nasal trauma progression.

Keywords: NCPAP; Nasal trauma; Neonates; Pressure injury; Risk Factors; Severity progression.

تكرار وشدة إصابة الأنف الثانوية لضغط مجرى الهواء الإيجابي المستمر في الأنف عند المواليد الجدد

الخلاصة

الخلفية: إصابة الأنف هي مضاعفات علاجية معروفة لدى الأطفال الذين يعانون من ضيق تنفسي باستخدام ضغط الهواء الإيجابي المستمر في الأنف (NCPAP). تتراوح شدة إصابة الأنف من احمرار خفيف إلى نخر. **الهدف**: تحديد تكرار إصابات الأنف وعوامل الخطر المرتبطة بتقدم شدة المرض الناتج عن NCPAP. **الطرائق**: أجريت دراسة رصدية مستقبلية في مدينة الموصل. تم تضمين المواليد الجدد الذين تلقوا NCPAP لتقييم إصابات الأنف وشدتها. تم استخدام الانحدار اللوجستي أحادي المتغير ومتعدد المتغيرات لتحديد العوامل المرتبطة بإصابة الأنف. تم استخدام اختبار مان-ويتني U لمقارنة المتغيرات المستمرة ومراحل إصابة الأنف، وتم الإبلاغ عن أحجام التأثير. **النتائج**: كانت نسبة إصابة الأنف 46.2٪. في التحليل الأحادي المتغير، كانت العوامل المرتبطة بزيادة احتمالية الإصابة هي انخفاض عمر الحمل (OR=3.367 ؛p<0.001)، ووزن الولادة الأقل (OR=2.923 ؛p<0.001)، والبقاء في وحدة العناية المركزة لحديثي الولادة ≤7 أيام (OR=2.507 ؛p=0.049)، بينما لم تكن مدة NCPAP ذات دلالة إحصائية (OR=1.341 ؛p=0.515). ومع ذلك، في التحليل متعدد المتغيرات، لم يظهر أي من العوامل كمتنبئ مستقل. كان البقاء في وحدة العناية المركزة لحديثي الولادة ≤7 أيام في اختبار مان-ويتني U هو المؤشر الوحيد الكبير على تقدم الشدة (*p=0.034*)، مع حجم *تأثير متوسط إلى كبير*. **الاستنتاجات**: إصابة الأنف هي مضاعفات شائعة ومهمة لعلاج NCPAP لدى حديثي الولادة. عادة ما تكون شدتها خفيفة، لكن الحالات المتوسطة والشديدة تحدث. انخفاض عمر الحمل، وانخفاض وزن الولادة، ومدة NCPAP الأطول هي عوامل خطر لإصابة الأنف، لكن البقاء المطول في وحدة العناية المركزة لحديثي الولادة كان مؤشرا قويا على تقدم إصابة الأنف.

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INTRODUCTION

Nasal continuous positive airway pressure (NCPAP) has become a cornerstone of respiratory support in neonatal intensive care units (NICUs). It is useful in managing preterm infants with respiratory distress syndrome, as it provides effective stabilization without the need for invasive ventilation [1]. However, the extended NCPAP application can lead to nasal trauma in neonates [2]. Nasal trauma damages the nasal skin, mucosa, or overall structure that develops due to sustained compression from noninvasive respiratory interfaces [3,3], including prongs and masks. It is considered a specific form of device-associated pressure injury [5]. Clinically, nasal complications may manifest as bleeding, mucosal ulceration, septal injury, vestibular narrowing,

deformation of the nasal ala, or breakdown of the overlying skin [6]. Nasal trauma incidence has been reported to range between 20% and 60% [6,7]. The wide variation in reported incidence is mainly due to differences in gestational age of study populations, absence of a standardized nasal injury classification system, variations in the type of nasal interface used, nursing care quality, and duration of noninvasive ventilation [8]. Major risk factors include prematurity, low birth weight, and prolonged exposure to NCPAP [9]. Nasal trauma can lead to structural deformity and residual scarring [10]. In severe cases, corrective plastic surgery may be required for reconstruction. Such complications not only increase healthcare costs but also cause significant emotional strain in the affected neonates' families [11]. Strategies used to prevent nasal trauma include careful NCPAP interface selection, alternating between nasal prongs and masks, and use of prophylactic dressings to minimize pressure-related injury [12]. However, despite these measures, nasal injury continues to occur frequently. In settings with restricted resources, this challenge is even more evident, where variations in equipment quality, interface design, and staff expertise may increase the risk of nasal trauma. Therefore, this study aimed to determine nasal injury frequency and to identify factors contributing to nasal trauma severity secondary to NCPAP.

METHODS

Study design and setting

A prospective observational study was executed in the neonatal intensive care unit (NICU) at Al-Batool Teaching Hospital in Mosul City, Iraq, over six months from May to October 2025. During the study period, about 750 neonates were admitted to our unit. The NICU has 40 incubators and can provide non-invasive ventilation by CPAP to up to 14 patients.

Inclusion criteria

Newborns who underwent NCPAP use on admission and those receiving NCPAP after weaning from ventilation were regarded as eligible. The enrolled neonates were observed by a pediatric resident or by a nurse to detect nasal trauma from the first day until they were weaned.

Exclusion criteria

NCPAP treatment duration less than 24 hours, pre-existing nasal deformities, lesions due to nasotracheal intubation, upper airway malformations, or neonatal sepsis.

Intervention and outcomes measurement

Standard policy in our NICU is to use NCPAP within minutes after birth for all newborns with respiratory distress, regardless of etiology. Neonates were commenced on NCPAP at a positive end expiratory pressure of 5 cmH_2O or up to 8 cmH_2O and a fraction of inspired oxygen of 30% or up to 60% to maintain an oxygen saturation above 90%. A CPAP system SLE1000 (SLE Ltd., London, United Kingdom) was used. The nasal prongs' size was adapted to the nose and nostrils. Typically, they used a prong size of 80-85% of the nostril opening size, and the cap size depends on the occipital-frontal circumference of a neonate. Before connecting the NCPAP, infants were positioned supine, the external nares were cleaned with water, and suction was gently applied if needed. They placed prongs at least 2 mm from the septum to avoid pressure necrosis and secured them using a head cap and Velcro felt. Nursing care included good alignment and preventing excessive movement of the nasal prong. Every 4 hours, the nurse lifts the prong for 10 minutes, gently massages pressure points, and washes the nose with normal saline. When they noted a nasal trauma, an ointment (sodium fusidate 20 mg) was applied. In a case of persistent trauma, they placed cotton soaked with normal saline between the pressure points and the nasal prong. After 5 days, the nurse washes the prong and reuses it. The assessment of Nasal trauma severity was based on Fischer et al.'s nasal injury grading system. Stage I: non-blanching erythema; stage II: partial-thickness skin loss (superficial ulcer); stage III: full-thickness skin loss (necrosis) [6]. When a neonate presented with a nasal trauma of different stages, only the most severe stage was used, and each neonate was included only once in the analysis. To collect and establish lesions caused by the NCPAP, the prongs were briefly removed from newborns' noses, their skin and nostrils were checked, and the prongs were immediately replaced. Because inspection was external and not instrumented, isolated internal trauma of the nostrils could be missed. The stage of nasal trauma, use of protection, size of prongs used, and other complementary data were extracted from the neonatology charts, medical evaluation records, and nursing files.

Ethical considerations

The Ethical Committee of the College of Medicine, University of Mosul, approved this study (UOM/COM/MREC/24-25/FEB11). Written consent was obtained from the parents.

Statistical analysis

Data were analyzed using SPSS version 23.0. The Shapiro-Wilk normality test was used to assess normality. Descriptive statistics were used to summarize the characteristics of the study population, including the median and interquartile range (IQR) for continuous variables and frequencies and percentages for categorical variables. Chi-square testing assessed the significance of the association between categorical

variables (frequencies), and the Mann-Whitney U test was used to find the importance of the association between continuous variables. The effect sizes for the Mann-Whitney U test were reported using common language effect size (CLES) and rank-biserial correlation (rrb). For the chi-square test, we considered Cramer's V. Univariate logistic regression was used to assess the association between each independent variable and nasal trauma (dependent variable). The Chi-Square or Fisher's Exact Test was used to calculate Odds Ratios (OR) with 95% Confidence Intervals (CI), and to identify factors independently associated with nasal trauma, we used multivariable logistic regression analysis. Adjusted Odds Ratios (AOR) with 95% CI and p-values were calculated for each predictor. Variables with a *p*-value < 0.05 in the univariate analysis or clinically relevant factors were included in the multivariate models to minimize the risk of excluding potentially clinically relevant factors and to account for the sample size. *A p-value* < 0.05 was statistically significant. Finally, results and findings were presented in tables and figures.

RESULTS

As shown in Table 1, a total of 135 newborns were enrolled in this study; 16 patients were excluded (five diagnosed with sepsis, seven treated with NCPAP for less than 24 hours, and four who died). The final sample that met the inclusion criteria was 119 neonates. We observed nasal trauma in 55 cases (46.2%), which was slightly higher in males (60%) than in females (40%), but this was not statistically significant (p= 0.342) and had a negligible effect size (Cramer's V= 0.091).

Table 1: Frequency of nasal trauma and baseline characteristics of the study population

Characteristic	Total (n=119)	Nasal trauma (n=55)	No nasal trauma (n=64)	*p*-value	Effect size
Sex n(%)					
Male	77(64.7)	33(60)	44(68.8)	0.342[f]	0.091[v]
Female	42(35.3)	22(40)	20(31.3)		
Gestational age (week); median (IQR)	33(30-36)	31(28-33)	35(32-37)	<0.001[m]	-0.527[a] 0.236[b]
Gestational age (week) n(%)					
<28	13(10.9)	10(18.2)	3(4.7)	<0.001[c]	0.466[v]
28-32	29(24.4)	22(40)	7(10.9)		
32-36/6	57(47.9)	20(36)	37(57.8)		
≥ 37	20(16.8)	3(5.5)	17(26.6)		
Birth weight (gm); median (IQR)	1800 (1250-2500)	1500 (1000-1900)	2350 (1700-2800)	<0.001[m]	-0.540[a] 0.229[b]
Birth weight (gm) n(%)					
<1000	14(11.8)	11(20)	3(4.7)	<0.001[c]	
1000-1499	22(18.5)	15(27.3)	7(10.9)		0.465[v]
1500-2499	47(39.5)	24(43.6)	23(35.9)		
≥ 2500	36(30.3)	5(9.1)	31(48.4)		
Duration of NCPAP use (day); median (IQR)	3(2-4)	3(3-5)	2(2-4)	0.004[m]	-0.301[a] 0.036[b]
Duration of NCPAP use (day) n(%)					
<5	94(79)	42(76.4)	52(81.3)	0.652[f]	0.062[v]
>5	25(21)	13(23.6)	12(18.8)		
Time in NICU (day); median (IQR)	4(3-6)	4(3-7)	3(2-6)	0.006[m]	-0.288[a] 0.355[b]
Time in NICU (day) n(%)					
<7	94(79)	39(70.9)	55(85.9)	0.070[f]	0.184[v]
>7	25(21)	16(29.1)	9(14.1)		

IQR, interquartile range; n, number; NCPAP, nasal continuous positive airway pressure; NICU, neonatal intensive care unit; [a] rank-biserial correlation; [b] common language effect size; [c] Chi-square test; [f] Fisher's exact test; [m] Mann-Whitney U test; [v] Cramer's V.

The median gestational age was significantly lower in the trauma group (31 weeks versus 35 weeks; p< 0.001; CLES = 0.236). Also, the distribution across gestational age groups was significantly different (p< 0.001), with infants aged < 28 weeks and 28-32 weeks constituting a larger proportion of the nasal trauma groups, with a large effect size (Cramer's V = 0.466). Similarly, the median birth weight was significantly lower in neonates with nasal trauma (1500 g versus 2350 g; p< 0.001). A large negative rank-biserial effect (rrb = −0.540; CLES = 0.229) confirmed this association, with a greater percentage of extremely low birth weight (< 1000 g) and very low birth weight (1000-1499 g) infants having trauma (p< 0.001; Cramer's V = 0.465). Regarding the duration of NCPAP use, neonates in the trauma group had a significantly longer median duration (3 days versus 2 days; p= 0.004). The effect size (rrb = −0.301) indicated a small to medium negative association. However, when categorized into groups (<5 days and ≥5 days), no statistically significant difference was observed (p= 0.652), and the effect size was negligible (Cramer's V= 0.06). Finally, time in the NICU also showed a statistically significant difference. Neonates with nasal trauma had a longer median NICU stay (4 days versus 3 days; p= 0.006). This constituted a small to medium negative association (rrb = −0.288; CLES = 0.355). In contrast, the categorical analysis of NICU stays (<7 days and ≥7 days) did not yield a statistically

significant difference (p= 0.07), with a small effect size (Cramer's V= 0.184). Table 1 details the baseline demographic and clinical characteristics, disaggregated by the presence or absence of nasal trauma. In univariate analysis, the factors significantly associated with increased odds of nasal trauma were lower gestational age category (OR= 3.367; p< 0.001), lower birth weight category (OR= 2.923; p< 0.001), and NICU stay ≥7 days (OR= 2.507; p= 0.049). The duration of NCPAP use was not statistically significant in the univariate model (OR = 1.341; p= 0.515). However, in the multivariate analysis, none of the factors emerged as an independent predictor of nasal trauma. Table 2 presents the results of univariate and multivariate logistic regression analysis examining factors associated with nasal trauma.

Table 2: Factors associated with nasal trauma

Variables	Nasal trauma (n=55)	No nasal trauma (n=64)	Univariate logistic regression		Multivariate logistic regression	
			OR (95%CI)	*p*-value	AOR (95%CI)	*p*-value
Gestational age (week) n(%)						
<28	10(76.9)	3(23.1)				
28-32	22(75.9)	7(24.1)	3.367	<0.001	1.926	0.160
32-36/6	20(35.1)	37(64.9)	(1.949-5.813)		(0.771-4.830)	
≥ 37	3(15)	17(85)				
Birth weight (gm) groups; n (%)						
<1000	11(78.6)	3(21.4)				
1000-1499	15(68.2)	7(31.8)	2.923	<0.001	1.785	0.158
1500-2499	24(51.1)	23(48.9)	(1.814-4.716)		(0.798-4)	
≥ 2500	5(13.9)	31(86.1)				
Duration of NCPAP use (day) n(%)						
<5	52(55.3)	42(44.7)	1.341	0.515	1.786	0.270
>5	12(48)	13(52)	(0.554-3.246)		(0.637-5.011)	
Time in NICU (day) n(%)						
<7	39(41.5)	55(58.5)	2.507	0.049	1.720	0.291
>7	16(64)	9(36)	(1.005-6.253)		(0.629-4.705)	

AOR: adjusted odds ratio; CI: confidence interval; n: number; NCPAP: nasal continuous positive airway pressure; NICU: neonatal intensive care unit; OR: odds ratio.

Among neonates who developed nasal trauma (n = 55), a comparison was made between those with Stage I (mild) injury (n = 44) and Stage II (moderate) injury (n = 10), based on continuous clinical variables (Table 3). The median gestational age was 31.5 weeks for Stage I trauma and 30 weeks for Stage II trauma. This difference was not statistically significant (p= 0.248), and the effect size was small (rrb= −0.23; CLES= 0.38). Similarly, the median birth weight for Stage I was 1500 g compared to 1250 g for Stage II, with no significant difference (p= 0.326). The effect size was also small (rrb = −0.20; CLES = 0.40). Finally, the median duration of NCPAP use did not show a statistically significant difference, with a median of three days for Stage I and Stage II and a small effect size (rrb = −0.24; CLES = 0.38).

Table 3: Mann-Whitney U test results comparing continuous variables between nasal trauma stages I and II

Variable	Stage I (mild) (n=44)	Stage II (moderate) (n=10)	Mann-Whitney (U)	*p*-value	Effect size
Gestational age (week), median (IQR)	31.5 (31.5-33)	30 (27.75-32)	168.5	0.248	-0.23[a] 0.38[b]
Birth weight (gm), median (IQR)	1500 (1000-2000)	1250 (962.5-1650)	176	0.326	-0.20[a] 0.40[b]
Time in NICU (day), median (IQR)	4 (3-6)	7 (4-7.50)	126.5	0.034	-0.43[a] 0.29[b]
Duration of NCPAP use (day), median (IQR)	3 (2-4)	3 (3-6.25)	168	0.232	-0.24[a] 0.38[b]

IQR: interquartile range; NCPAP: nasal continuous positive airway pressure; n: number; [a] rank-biserial correlation; [b] common language effect size.

On the other hand, neonates with Stage II trauma had a statistically significantly longer median NICU stay of 7 days compared to 4 days for Stage I trauma (p= 0.034). This association had a medium to large effect size (rrb = −0.43; CLES = 0.29). Figure 1 illustrates the distribution of time in the NICU across the observed stages of nasal trauma. We exclude Stage III trauma due to a significant limitation of a very small number (n=1), which made it difficult to draw meaningful statistical conclusions involving this group. Regarding the association between categorical variables and nasal trauma severity (Table 4), the analysis revealed male neonates were 56.8% of Stage I, 70% of Stage II, and the sole case of Stage III, and females comprised 43.2% of Stage I and 30% of Stage II. However, no statistically significant association was found between sex and nasal trauma severity (p= 0.530), with a small effect size (Cramer's V= 0.152). For gestational age groups, Stage I trauma was most frequently observed in the 32-36/6 weeks category, with 43.2%, while 60% of Stage II and

100% of Stage III occurred in the 28-32 weeks category, which was not significant (p= 0.326), with a small to medium effect size (Cramer's V= 0.251). Similarly, birth weight groups did not show a significant association with nasal trauma severity (p= 0.600). The highest percentage for Stage I (45.5%) and for Stage II (40%) occurred in the 1500-2499 g category. The single Stage III case was observed in the 1000-1499 g category. The effect size was small to medium (Cramer's V = 0.204).

DISCUSSION

Our study revealed that the incidence of nasal trauma in neonates using NCPAP was 46.2%, which aligns with findings reported by other studies [6,13,14]. This highlights that nasal trauma remains an important complication even in a mixed neonatal population, underscoring the ongoing need for more effective monitoring and prevention strategies. A key result of this study was the significant association between nasal trauma and both lower gestational age and lower birth weight, which was consistent with studies emphasizing extreme prematurity and low birth weight as independent risk factors [9,10,15], this due to underdeveloped skin integrity, reduced subcutaneous tissue, and prolonged dependency on CPAP.

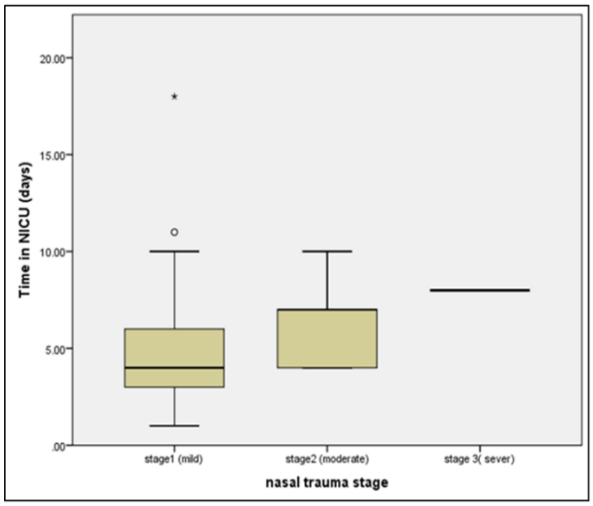

Figure 1: Comparison of median time in NICU (days) with nasal trauma stages. The neonates with Stage II have a higher median and wider variability in NICU days in the boxplot compared with Stage I, while the single Stage III case appears as a fixed value. The distribution also showed mild (○) and extreme (*) outliers within the Stage I group, reflecting a small number of infants requiring unusually prolonged hospitalization for reasons unrelated to trauma severity.

Table 4: Association between categorical variables and nasal trauma severity

Variable	Stage I (mild) n(%)	Stage II (moderate) n(%)	Stage III (severe) n(%)	chi^2	p-value	Effect size Cramer's V
Sex n(%)						
Male	25(56.8)	7(70)	1(100)	1.269	0.530	0.152
Female	19(43.2)	3(30)				
Gestational age (week) n(%)						
<28	7(15.9)	3(30)	1(100)	6.947	0.326	0.251
28-32	15(34.1)	6(60)				
32-36/6	19(43.2)	1(10)				
>37	3(6.8)	0				
Birth weight (gm) n(%)						
<1000	8(18.2)	3(30)	1(100)	4.573	0.600	0.204
1000-1499	11(25)	3(30)				
1500-2499	20(45.5)	4(40)				
>2500	5(11.4)	0				

n: number.

Additionally, prolonged NCPAP use and longer NICU stays were significantly associated with nasal trauma. This aligns with studies that identified extended NCPAP duration and NICU stay as critical risk factors that compromise skin integrity by prolonged pressure effect and reduce blood flow [4,16,17]. While our finding of the non-significance of the categorical variable suggests a continuous dose-response rather than fixed thresholds, this is possibly due to power loss or suboptimal categorization of NCPAP duration and NICU stay. Notably, no significant association was found between sex and nasal trauma. This finding is consistent with other research, which reported no gender predisposition to NCPAP-related nasal trauma [18]. This might indicate that skin and mucosal vulnerability are more biologically affected by gestational age and weight rather than by sex. Contrary to our study, Pascual and Wielenga [19] found that male infants had an increased risk of nasal injury. Our univariate and multivariate models for NCPAP duration revealed no significant effect of categorized duration, aligning with other research [20]. On the other hand, Wu et al. and Ribeiro et al [3,16]. identified prolonged NCPAP use as a significant risk factor. The univariate analysis showed significant associations between lower gestational age, lower birth weight, and NICU stay ≥7 days with increased odds of nasal trauma, echoed by other studies [4,19,21] While reinforcing baseline observations and literature, these lost significance in multivariate models, consistent with Naha et al. [20]. This suggests limited predictive power for broad categories, likely due to high intercorrelation among factors like prematurity, low birth weight, and hospital stay. Our analysis of the continuous clinical and categorical variables associated

with nasal trauma severity found that while prematurity, low birth weight, and duration of NCPAP use predispose infants to develop an injury, they may not be the primary predictors of its severity. In fact, the single case of stage III trauma in our study occurred in a neonate in the 28-32-week, 1000-1499 g group, underscoring that a severe outcome is not limited to the most extreme preterm neonates, which contrasts with other studies [3,9,19]. This suggests that when an initial injury has occurred, other factors play a more critical role in its progression. This interpretation is consistent with research [8,10,12], highlighting that nasal trauma severity was affected by other factors such as interface type, hydrocolloid dressings used, and interface rotation strategies, rather than neonatal characteristics. The most important finding in our analysis was the significant association between a longer NICU stay and the progression to more severe (Stage II) trauma. This aligns with previous studies that have found prolonged hospitalization was a risk factor for nasal trauma [4,6,21]. This supports a cumulative, dose-response model in which risk accumulates over a prolonged, complex clinical course, and other unmeasured confounders, such as nursing care practices and skin integrity protocols, contribute to a worse outcome.

Study limitations

Several limitations should be taken into account in this study: a relatively small sample size and a single-center study, which limits its generalizability. Furthermore, our NICU experiences an unusually heavy service burden, with about 125 admissions per month, and a nurse-to-neonate ratio of 1:5 may have contributed to resource strain and variability in nursing care delivery, particularly in low- and middle-income countries. In addition, differences in severity assessment classification, nasal interface types, and a lack of standardized NCPAP care protocols limit the comparability across studies. Finally, isolated internal nasal trauma could be missed because inspection was external and not instrumented.

Conclusion

Nasal trauma is a frequent complication of NCPAP across a mixed neonatal population. While lower gestational age, lower birth weight, and duration of NCPAP use are strong predictors of nasal injury, they may not predict its progression to more severe stages. However, prolonged NICU stay appeared to be the major risk factor responsible for nasal trauma progression, suggesting a continuous dose-response relationship between patient vulnerability and unmeasured confounding variables. So, we recommend regular interface inspection and rotation protocols and use of prophylactic dressings as a skin prevention strategy in neonates requiring prolonged NICU stays. Future multicenter research should consider a more detailed analysis of care practices alongside demographic and clinical factors.

Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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