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Original Article

Predictors and outcomes of extubation failures in a pediatric intensive care unit: A retrospective study

Khouloud A. Al-Sofyani, PhD

Department of Pediatric, Pediatric Critical Care Unit, Faculty of Medicine, King Abdulaziz University, Jeddah, KSA

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المركزة، ومتطلبات طويلة الأمد للتهوية الميكانيكية قبل نزع الأنبوب، وحالة التشخيص الأولية. وقد لوحظ أن الديكساميثازون فعال في التخفيف من حدوث فشل نزع الأنبوب. هناك حاجة إلى مزيد من البحث الذي يتضمن تصميم دراسة أكثر جوهرية قائمة على الأدلة لإثبات العوامل المذكورة كمنبئات لفشل نزع الأنبوب ووضع استراتيجيات للحد منه.

الكلمات المفتاحية: ديكساميثازون؛ فشل نزع الأنبوب؛ التهوية الميكانيكية؛ وحدة العناية المركزة للأطفال؛ البقاء

Abstract

Objectives: This study was aimed at determining the extubation failure (EF) rate in a pediatric intensive care unit (PICU), and assessing the etiology, associated risk factors, and outcomes.

Methods: We conducted a retrospective study on 335 pediatric patients admitted to King Abdulaziz University Hospital between 2018 and 2020, ranging in age from 1 month to 14 years, who required invasive mechanical ventilation (MV) for >24 h. Extubation readiness was determined by the attending pediatric intensive care physician, according to the patients' clinical status and extubation readiness criteria.

Results: In the cohort of 335 patients, 42 experienced issues during extubation (failure rate, 12.5%). Cardio-vascular disease (42.9%) was the main primary admission condition in patients with EF. Younger age (median, interquartile range [IQR]: 4, 1.38–36 months) was strongly associated with EF compared with successful extubation (median, IQR: 12, 2–48; p = 0.036), and with a high predicted mortality rate (10.9%; p < 0.001) and Pediatric Risk of Mortality III (PRISM) score (13; p < 0.001). Furthermore, prolonged ICU stay (25.5 days; p < 0.001) and longer MV requirements (4 days; p < 0.001) before extubation in patients with EF were

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الملخص

أهداف البحث: تهدف هذه الدراسة إلى تحديد معدل فشل نزع الأنبوب في وحدة العناية المركزة للأطفال والتأكيد على المسببات وعوامل الخطر المرتبطة بها والنتيجة.

طريقة البحث: أجرينا دراسة بأثر رجعي على 335 مريضا من الأطفال الذين تم إدخالهم إلى مستشفى جامعة الملك عبد العزيز في الفترة من 2018 إلى 2020، وتتراوح أعمار هم بين شهر واحد و14 عاما، ويحتاجون إلى تهوية ميكانيكية غزوية لمدة تزيد عن 24 ساعة. تم تحديد جاهزية نزع الأنبوب للمرضى من قبل طبيب العناية المركزة للأطفال المعالج بناء على الحالة السريرية ومعايير الاستعداد لنزع الأنبوب.

النتائج: ومن بين مجموعة مكونة من 335 مريضا، واجه 42 فردا مشكلات أثناء عملية نزع الأنبوب، وبلغت ذروتها بمعدل فشل قدره 2.5%. كانت أمراض القلب والأوعية الدموية (42.9%) هي حالة القبول الأولية الملحوظة إلى حد كبير لدى مرضى فشل نزع الأنبوب. كان المرضى الأصغر سنا مرتبطين بشكل كبير بحدوث فشل نزع الأنبوب مقارنة بالمرضى الذين تم نزع أنبوبهم بنجاح مع ارتفاع معدل الوفيات المتوقع ودرجة معيار خطر وفيات الأطفال 3. علاوة على ذلك، لوحظت فترات الإقامة الطويلة في وحدة العناية المركزة ومتطلبات أطول للتهوية الميكانيكية قبل نزع الأنبوب لدى مرضى فشل نزع الأنبوب المرتبطين بمعدل وفيات مرتفع. ومن المثير للاهتمام أن إعطاء الأنبوب لدى المرضى. الأنبوب لدى المرضى.

الاستنتاجات: توضح دراستنا ارتفاع معدل فشل نزع الأنبوب لدى المرضى الأصغر سنا الذين يحتمل أن يكونوا مرتبطين بإقامات أطول في وحدة العناية

Corresponding address: Pediatrics Intensive Care Consultant, Department of Pediatric, Pediatric Critical Care Unit, Faculty of Medicine, King Abdulaziz University, PO Box: 80215, Jeddah, 215 85, KSA.

E-mail: kalsofyani@kau.edu.sa

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associated with a high mortality rate (~12%; p < 0.001). Interestingly, dexamethasone administration before extubation significantly alleviated EF risk (28.3%; p < 0.001).

Conclusion: A higher EF rate in younger patients may potentially be associated with longer ICU stays, prolonged MV requirements before extubation, and the primary diagnostic condition. Dexamethasone effectively alleviated EF incidence. Further research with a rigorous evidence-based study design is necessary to substantiate the factors identified as predictors of EF and to develop strategies to avoid EF.

Keywords: Dexamethasone; Extubation failure; Mechanical ventilation; Pediatric intensive care unit; Survival

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Introduction

Invasive mechanical ventilation (IMV) is crucial life support measure used extensively in $\sim 30-60\%$ of severely ill patients hospitalized in pediatric intensive care units (PICUs).¹⁻³ However, the clinical necessity and prolonged use of mechanical ventilation (MV) in the PICU setting have been associated with potential adverse effects and risks of progression to clinical respiratory conditions including cardiovascular dysfunction, ventilator-associated pneumonia, glottic edema, airway-passage injury, diaphragmatic dysfunction, airway stenosis, and vocal cord paralysis. These adverse outcomes further contribute to prolonged use of MV and increased lengths of PICU stay, thereby substantially increasing the risks of morbidity and mortality.⁴⁻⁶ Attending physicians must perform timely monitoring of vital clinical parameters and associated factors to accurately determine patients' extubation readiness, thereby avoiding medical complications and making efficient use of these modalities.

Extubation failure (EF) is defined as the requirement for reintubation (placement of a breathing tube) within 48 h after prior tube removal.⁷ Premature extubation, primary illness severity, etiological condition, prolonged PICU stay, prolonged use of analgesics and sedatives, and population demographics may result in 2-20% of EFs with associated unfavorable clinical outcomes and increased mortality, as reported in several studies.^{8–11} Upper airway obstruction (UAO) is a major contributor to reported cases of EF caused by tracheal inflammation, glottis, and laryngeal edema, leading to distress and stridor. Other clinical factors include respiratory muscle weakness, diaphragm dysfunction, neurological impairment, and cardiac dysfunction.^{12–14}

The potent anti-inflammatory properties of dexamethasone have been explored to treat UAO by decreasing glottis, laryngeal edema, and EF with various dosage combinations. However, the effectiveness and efficacy of dexamethasone administration are unclear, given the contradictory observations in prior studies.^{15–17} Several studies have reported operational protocols for ventilator weaning and extubation readiness to alleviate complications with EF and post-extubation stridor.^{7,18} The complications associated with EF and the high hospitalization and treatment costs necessitate the evaluation of various associated risk factors and prophylactic benefits of dexamethasone administration to determine the probability of occurrence, increase extubation success, and avoid reintubation. In this retrospective cohort study, we aimed to evaluate potential etiological and demographic EF risk factors—such as age, primary condition, prolonged MV support, and length of stay in a PICU—leading to high morbidity and mortality. Furthermore, we evaluated the effect of dexamethasone on alleviating EF incidence in severely ill patients.

Materials and Methods

Study design, demography, and PICU setting

This retrospective cohort study was conducted on pediatric patients admitted between 2018 and 2020 to the PICU of King Abdulaziz University Hospital (Figure 1). The study enrolled 335 pediatric patients (both boys and girls) 1 month to 14 years of age, who received mechanical ventilator support for >24 h. Our PICU comprises a 12-bed setup equipped with advanced medical infrastructure and timely monitoring of the medical status by an experienced multidisciplinary team of pediatric intensive care physicians, nurses, respiratory therapists, nutritionists, clinical pharmacists, social workers, and physical therapists.

Extubation characteristics and data collection

On the basis of the patients' clinical condition, the attending pediatric intensive care physician made the decision to initiate the weaning and extubation protocol^{7,18} after determining the following parameters: (i) fulfillment of the MV criterion: fraction of inspired oxygen $(F_{iO2}) \leq 0.5$ (50%), PaO₂ > 60 mmHg, peak inspiratory pressure <25 cm H₂O, and positive end-expiratory pressure ≤ 8 cm H₂O; (ii) patients with moderate MV moving toward successful completion of a spontaneous breathing test for 20–30 min with pressure support mode of ≤ 10 cm H₂O and positive end-expiratory pressure of 5 cm H₂O; (iii) decreased or no requirement for inotrope administration; (iv) balanced acid-base levels (pH \sim 7.25–7.45); (v) hemodynamic stability with normal electrolytes and no fluid overload; (vi) recovery from medical status indicating the need for intubation; (vii) awake status and adequate muscle tone; and (viii) ameliorated signs and symptoms of pneumonia. Patients with laryngomalacia or tracheomalacia, gastroesophageal reflux disease with airway edema, difficult airway intubation, and an absence of leak round-tracheal intubation were administered six doses (0.5 mg/kg/dose) of dexamethasone 12 h before extubation. EF was characterized by the need for reintubation within 48 h after extubation.

Electronic clinical data for the enrolled patients were collected in a 4-month period and compiled categorically into spreadsheets by (a) age, (b) sex, (c) medical diagnosis at the time of admission, (d) dexamethasone administration, (e) use of non-invasive ventilation, (f) MV duration before the first extubation, and (g) duration of hospital and ICU stay. Data regarding the extubation readiness method and reasons for the delay in extubation were also collected.

Exclusion criteria

Patients who received MV for <24 h, were accidentally extubated, underwent tracheostomy, showed airway anomalies, had an order not to resuscitate, or had chronic ventilator dependency were excluded from the study. In addition, patients with incomplete clinical medical records and those who died in the PICU without receiving extubation support were excluded.

Statistical analysis

The annotated medical records of the patients were categorized and coded for analysis in SPSS software version 20.0 for Windows, developed by IBM (Armonk, NY, USA). Categorical variables are reported as absolute frequencies and corresponding percentages. Continuous variables with non-uniform distribution are presented as medians and interquartile ranges (IQRs, spanning quartile 1 to quartile 3). We used the chi-square test to analyze qualitative variables, and we evaluated quantitative data with the Mann–Whitney U test. The demographic characteristics and various risk factors associated with EF compared with extubation success were assessed with the Mann–Whitney U test and chi-square test. A *p*-value <0.05 was considered to indicate statistical significance.

Results

Weaning from IMV and the extubation readiness of the patients were determined by the attending pediatric intensive care physician according to the patients' clinical status and fulfillment of the extubation readiness test criteria.^{7,18} Of 335 patients, 42 underwent reintubation; an EF risk of 12.5% was observed, and was comparable between boys (n = 20)



Figure 1: Schematic of patients enrolled in the study.

Table 1: Univariate analysis of the epidemiological characteristics of patients in the pediatric ICU with their extubation failure and success rates (N = 335).

Parameters	Variables	Extubation failure (N = 42) Frequency (Percent) n (%)	Extubation success (N = 293) Frequency (Percent) n (%)	<i>p</i> -value
Qualitative variables ^a				
Gender	Female	22 (15.7)	118 (84.3)	0.137
	Male	20 (10.3)	175 (89.7)	
Primary Diagnosis	ENT	4 (13.3)	26 (86.7)	< 0.001*
	Neurological	5 (13.5)	32 (86.5)	
	Neurosurgery	0 (0)	34 (100)	
	Oncology	0 (0)	10 (100)	
	Pediatric Surgery	0 (0)	59 (100)	
	Cardiovascular	9 (42.9)	12 (57.1)	
	Renal	0 (0)	1 (100)	
	Respiratory	4 (7.7)	48 (92.3)	
	Sepsis	8 (15.1)	45 (84.9)	
	Trauma	0 (0)	7 (100)	
	Others	12 (38.7)	19 (61.3)	
Use of Dexamethasone prior to extubation	No	12 (5.2)	217 (94.8)	< 0.001*
	Yes	30 (28.3)	76 (71.7)	
Use of NIV post extubation	No	19 (7)	251 (93)	< 0.001*
	Yes	23 (35.4)	42 (64.6)	
Mortality	Survived	37 (11.2)	293 (88.8)	< 0.001*
	Died	5 (100)	0 (0)	
Quantitative variables ^b				
Parameters		Median (Q1–Q3)	Median (Q1–Q3)	p-value
Age (months)		4 (1.38–36)	12 (2-48)	0.036*

Parameters	Variables	Extubation failure ($N = 42$)	Extubation success ($N = 293$)	<i>p</i> -value
		Frequency (Percent) n (%)	Frequency (Percent) n (%)	
Weight (kg)		4.15 (2.8–14.2)	8.2 (3.6–14)	0.039*
PRISM		13 (8–16)	7 (0-13)	< 0.001*
Predicted mortality %		10.9 (3.1–18.7)	3.1 (0.8-9.1)	< 0.001*
MV duration prior to extubation (days)		4 (2-10)	2 (1-5)	< 0.001*
Reintubation time (hours)		24(12-24)	0(0-0)	< 0.001*
ICU stay duration (days)		25.50(13-49)	6.00(3-10)	< 0.001*

NIV: Non-invasive ventilation; ENT: Ear, nose, and throat; ICU: Intensive care unit; MV: Mechanical ventilation; PRISM: Pediatric Risk of Mortality III. * A p-value of < 0.05 was used to evaluate the statistical significance.

Variables are presented as absolute frequency and percent or median (interquartile range).

^a Chi-square test was employed for qualitative variables.

^b Mann-Whitney U test was employed for quantitative variables.

and girls (n = 22) (Table 1). To evaluate the potential risk factors associated with the probability of EF, we compared the epidemiological characteristics of patients with EF versus successful extubation (Table 1). On the basis of the median distribution of patient age, EF risk was found to be significantly higher in younger patients (median, IQR: 4, 1.38–36 months) than in patients who were successfully extubated (median, IQR: 12, 2–48; p = 0.036). A similar trend was observed in weights: patients with EFs (4.15 kg;

IQR: 2.8–14.2 kg) had a lower median weight than patients with extubation success (8.2 kg; IQR: 3.6–14 kg). Cardiovascular disease was the primary clinical condition associated with EF (42.9%; p < 0.001). In many studies, the use of corticosteroids such as dexamethasone for treating UAO has been observed to significantly decrease EFs. In our retrospective study in 335 patients, dexamethasone was administered to 106 patients (31.6%) before extubation, after evaluation of clinical status. The

Parameters	Variables	$\frac{\text{Survived}}{(N = 330)}$ Frequency (Percent) n (%)	Died (N = 5) Frequency (Percent) n (%)	<i>p</i> -value
Gender	Female	138 (98.6)	2 (1.4)	0.935
	Male	192 (98.5)	3 (1.5)	
Primary Diagnosis	ENT	30 (100)	0 (0)	0.213
	Neurological	36 (97.3)	1 (2.7)	
	Neurosurgery	34 (100)	0 (0)	
	Oncology	10 (100)	0 (0)	
	Pediatric Surgery	59 (100)	0 (0)	
	Cardiovascular	19 (90.5)	2 (9.5)	
	Renal	1 (100)	0 (0)	
	Respiratory	52 (100)	0 (0)	
	Sepsis	52 (98.1)	1 (1.9)	
	Trauma	7 (100)	0 (0)	
	Others	30 (96.8)	1 (3.2)	
Use of Dexamethasone prior to extubation	No	226 (98.7)	3 (1.3)	0.686
-	Yes	104 (98.1)	2 (1.9)	
Use of NIV post extubation	No	269 (99.6)	1 (0.4)	0.001*
	Yes	61 (93.8)	4 (6.2)	
Extubation status	Failure	37 (88.1)	5 (11.9)	0.001*
	Success	293 (100)	0 (0)	
Quantitative variables ^b				
Parameters		Median (Q1-Q3)	Median (Q1-Q3)	
Age (months)		12(2-48)	0.56(0.33-3)	0.008^{*}
Weight (kg)		8(3.5-14)	4(2.8-4.5)	0.051
PRISM		8(0-13)	15(12-16)	0.024*
Predicted mortality (%)		3.48(0.8-10.8)	15.7(9.2-18.7)	0.018*
MV duration prior to extubation (days)		3(1-5)	8(3-10)	0.172
Reintubation time (hours)		0(0-0)	24(12-24)	$< 0.001^{*}$
ICU stay duration (days)		7(3-12)	39(28-56)	0.001*

NIV: Non-invasive ventilation; ENT: Ear, nose, and throat; ICU: Intensive care unit; MV: Mechanical ventilation; PRISM: Pediatric Risk of Mortality III. * A p-value of < 0.05 was used to evaluate the statistical significance.

Variables are presented as absolute frequency and percent or median (interquartile range).

^a Chi-square test was employed for qualitative variables.

^b Mann-Whitney U test was employed for quantitative variables.

EF rates were significantly lower in patients with than without dexamethasone administration (28.3%; p < 0.001). However, no pronounced effect was observed on survival (p = 0.686) (Table 2).

A death rate of ~12% was observed in patients with EF, who had significantly higher Pediatric Risk of Mortality III (PRISM) scores (median, IQR: 13, 8–16; p < 0.001) and predicted mortality rates (median, IQR: 10.9, 3.1–18.7; p < 0.001) than successfully extubated patients. EFs were also significantly associated with the duration of ICU stay (median, IQR: 25.50, 13–49 days; p < 0.001) and prolonged MV requirement (median, IQR: 4, 2–10 days; p < 0.001) before the weaning process could be initiated (Table 1). The elevated risk of EF was significantly associated with the requirement for non-invasive ventilation support post-extubation (54.8%; p < 0.001).

Death among patients with unsuccessful extubation attempts, compared with the surviving patients, correlated with diagnostic and clinical characteristics (Table 2). Notably, the significant correlation between the potential risk factors and EF incidence (Table 1) was also reflected in the prognosis regarding death, because of the severity of clinical status. Death was observed significantly more frequently in infants than older children (median, IQR: 0.56, 0.33–3 months; p = 0.008). Longer ICU stays and the requirement for prolonged MV support before extubation in patients with high predicted mortality rates and PRISM scores were significantly associated with death risk in patients with EF (Table 2).

Discussion

Extubation is the removal of invasive MV, thereby allowing patients to spontaneously breathe or to require less invasive respiratory support (nasal or nasopharyngeal CPAP, HHFNC, or an oxygen mask). Failure of the transition to extubation is characterized by a need to re-intubate with MV support within 48 h. We observed an EF rate of 12.5% among the 335 enrolled pediatric patients, in excellent agreement with earlier reports of 2-20% in various similar studies.⁸⁻¹¹ Extubation readiness protocols are less well established for pediatric than adult patients, and definitive and reliable markers to extubate pediatric patients are lacking.¹⁹ Therefore, the decision to extubate depends solely on the adequacy of the clinical assessment of patient medical status by the attending expert intensive care physician, and the conservative strategies used contribute to the variations observed in the EF rate in various hospital settings.^{3,9,20,21} Clinical and observational studies have made extensive efforts to identify predictors and definitive markers, and develop integrated and indexed standard practices and protocols for effective extubation. In a meta-analysis by Ng et al. evaluating the pre-extubation assessment and its diagnostic accuracy in predicting EF, 55 unique pre-extubation assessments were found to be poor predictors of EF.²²

Extubation failures result in longer MV durations and ICU stays—these major risk factors that may lead to severe clinical conditions and consequently increase mortality rates.⁶ Therefore, in this study, we evaluated various etiological risk factors and demographic characteristics associated with the incidence of EFs and prognosis regarding death. EF is a major risk factor in neonates and

infants, as observed in earlier studies,^{3,7,18,23} potentially because of the high airway resistance, immature respiratory system, neurological factors, and smaller airway with low elastance of the ribcage in these children.²⁴ Our study identified younger age as a high-risk factor associated with death in patients with EF, thus corroborating earlier reports.

Several other risk factors, such as admission etiology, mechanical ventilation time, length of PICU stay, and prolonged use of sedative drugs, are associated with EF risk. These risk factors are generally associated with greater severity of the prognosis to post-extubation clinical complications and worsening of health status, thus ultimately increasing morbidity and mortality rates.^{4,7,25,26} The clinical data in our study from 42 of 335 patients who underwent EF demonstrated a requirement for prolonged MV support and PICU lengths of stay. Furthermore, these factors were significantly elevated in patients who died after unsuccessful extubation. Our findings were similar to those of Al Ghafri et al., who have also observed that EF is positively associated with preoperative mechanical ventilation duration and escalation of the inotropic score.² Length of PICU stay may be affected by various factors, including the clinical admission etiology, severity of medical status, age, sex, individual immune response, use of prophylactic drugs, and treatment strategies. However, EF is also a highly influential factor directly associated with the need for additional rounds of ventilator weaning, additional use of sedative and prophylactic drugs, prolonged recovery times, and respiratory muscle weakness.

The increased lengths of hospital stay with prolonged ventilator support may be linked to atelectasis, ventilatorassociated pneumonia, and other several induced clinical complications, thus further increasing treatment times and hospitalization costs.^{4,7,28,29} Therefore, healthcare specialists should carefully consider these potential risk factors requiring close speculation and constant monitoring for timely initiation of the weaning process, thereby alleviating ventilator-induced clinical complications. Interestingly, we observed a significant contribution of cardiovascular disease (42.9%) as a primary diagnostic condition in the incidence of EF, in excellent agreement with findings from Baisch et al. and Heubel et al.^{8,30}

Laryngeal edema may arise from the mechanical irritation and pressure induced by IMV, and may result in the development of UAO and post-extubation stridor, thereby increasing the risk of development of ventilator-associated pneumonia. Laryngeal edema post-extubation is more common in pediatric than adult patients, primarily because of differences in respiratory tract anatomy; an occurrence rate of 4-37% has been reported in earlier studies with varying population demographics.^{6,23,31,32} Several studies have explored the effectiveness and efficacy of corticosteroids such as dexamethasone in treating UAO, larvngeal edema, and post-extubation stridor, through anti-inflammatory effects. However, the results of the prophylactic use of dexamethasone have not been standardized, because of contradictory reports among clinical studies. However, this treatment has been demonstrated to be beneficial in risk-prone patients, including both children and adults. A randomized controlled trial by Ritu et al., in 42 children receiving dexamethasone and 38 children receiving placebo, has reported that a 0.15 mg/kg/dose of dexamethasone is not beneficial in decreasing post extubation stridor.³³ Similarly, Saleem et al. have reported that prophylactic use of dexamethasone (0.5 mg/kg/dose), compared with a control of no medication, is ineffective in decreasing reintubation rates in children (n = 30).³⁴ Several other studies have also reported the ineffectiveness of dexamethasone in decreasing EF and post extubation stridor in children.^{15,16}

Meta-analyses by Kuriyama et al., Khemani et al., McCaffrey et al., and Kimura et al. have evaluated the effectiveness of dexamethasone and reported beneficial effects in preventing laryngeal edema, EFs, and post-extubation stridor.^{17,35–37} A network meta-analysis by Iyer et al. has shown that administration of a 0.5 mg/kg/dose of dexamethasone in patients >12 h before extubation is effective strategy for decreasing reintubation rates in children.³⁸ Interestingly, dexamethasone administration (0.5 mg/kg/dose) 12 h before extubation in patients with laryngomalacia, tracheomalacia, or gastroesophageal reflux disease has been shown to significantly alleviate EF incidence (31.6%). Our results corroborate the findings of Iyer et al. and Khemani et al.^{17,38} Thus, the administration of dexamethasone can be considered clinically relevant in increasing the chance of survival and decreasing the death rate in critically ill pediatric patients admitted to the PICU, as well as avoiding post-extubation stridor, laryngeal edema, and respiratory distress.

We also observed that higher PRISM scores and predicted mortality rates were potentially associated with EF and death risks, thereby corroborating findings from earlier studies.^{39,40} However, Wratney et al. have not observed a significant association between higher PRISM scores and EFs.⁴¹

Limitations

One limitation of this study is its retrospective nature. However, to minimize any potential bias, the data were reviewed by two senior nurses, and patients were excluded from the study if any significant data were missing. Another limitation is that the data were obtained from a single center serving a niche population; thus, the findings cannot be directly correlated to a broader population. A multi-center data analysis would aid in better assessment of the risk factors.

Conclusions

This study delineated potential risk factors that significantly contribute to elevated incidence of EFs. Younger age, cardiovascular disease, longer length of ICU stay, and prolonged requirement for MV before extubation were identified to severely influence EF rates. These factors were found to be associated with elevated death risk in patients with higher PRISM scores and to predict mortality rates. Dexamethasone administration before extubation in severe cases markedly alleviated the chance of EFs in pediatric patients. Variations in extubation assessment practices at the institutional level eventually lead to delays in weaning from IMV. Further prospective studies should be conducted to assess the improvements in extubation time while maintaining a very low EF incidence.

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Conflict of interest

We have no conflicts of interest to declare.

Ethical approval

The research design and protocol were reviewed and approved by the Institute Research Ethics Committee, Unit of Biomedical Ethics, Faculty of Medicine, King Abdulaziz University (registration number HA-02-J-008; January 1, 2022).

Authors contributions

KAA conceived, designed, and conducted the research; collected and analyzed the data; and drafted, critically reviewed, and approved the final draft of the manuscript. She is responsible for all aspects of the work. All authors have critically reviewed and approved the final draft, and are responsible for the content and similarity index of the manuscript.

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