European Journal of Clinical Pharmacy

Print ISSN: 2385-409X **Online ISSN**: Applied
Website: https://farmclin.com/

Original Research Article

To Measure the Incidence and Risk Factors of Iatrogenic Withdrawal Syndrome in Mechanically Ventilated Children Admitted in Paediatric Intensive Care Unit

Article History:

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Received: 16-10-2025
Revised: 09-12-2025
Accepted: 21-12-2025
Published: 30-12-2025

Abstract:

Introduction: Iatrogenic withdrawal syndrome (IWS) is a clinically important complication of prolonged opioid and sedative exposure in the pediatric intensive care unit (PICU). Recent guidelines emphasize routine monitoring with validated tools and structured prevention strategies, yet implementation remains inconsistent across the units.

Objective: We evaluated the incidence of WAT-1–defined withdrawal and examined the factors associated with withdrawal in ventilated children.

Study Design: prospective observational study.

Place and Duration of Study: PICU of The Indus Hospital from 12 June 2025 to 12 October 2025.

Methodology: We conducted this study in mechanically ventilated children admitted to the PICU. WAT-1 assessment was conducted every 12 hours during weaning and for at least 48 hours after discontinuation, and SBS was used for sedation assessment. Withdrawal was defined as a WAT-1 score ≥3, consistent with the protocol materials based on pediatric literature. Continuous data were summarized with medians and interquartile ranges (IQR); group comparisons was done by Mann-Whitney U, chi-square, or Fisher exact tests. Multivariable logistic regression was limited to adequate variables.

Results: Thirty-five of one hundred children met criteria for withdrawal (35.0%). WAT-1 severity was mild in sixteen, moderate in fourteen, and severe in five patients. Median time to onset was 0.6 days (IQR 0.4–0.9), and median symptom duration was 3.0 days (IQR 2.0–4.0). Withdrawal was associated with longer ventilation duration, longer analgesic exposure, longer PICU stay, malnutrition/wasting, metabolic comorbidity, prior withdrawal history, additional interventions, and non-nalbuphine exposure. In the multivariable model, longer ventilation duration (adjusted odds ratio [aOR] 1.85 per day, 95% CI 1.38–2.47), younger age (aOR 0.99 per month, 95% CI 0.97–1.00), and malnutrition/wasting (aOR 6.15, 95% CI 1.85–20.44) remained associated with withdrawal.

Conclusion: IWS affected more than one-third of ventilated children and occurred more in younger, nutritionally vulnerable patients with longer ventilation. Routine WAT-1 surveillance and a standard sedation-weaning protocol are justified for caring for these children.

Keywords: Pediatric intensive care; iatrogenic withdrawal syndrome; mechanical ventilation; WAT-1; sedation weaning; analgesia; risk factors; critical care.

INTRODUCTION

Prolonged sedation and analgesia are commonly required for pediatric patients undergoing mechanical ventilation to ensure comfort, reduce stress, and improve synchronization with the ventilator. [1] However, extended use of sedatives and opioids can lead to physical dependence, making these patients susceptible to withdrawal syndrome upon cessation or tapering of medications. [2] Withdrawal syndrome is characterized by a constellation of symptoms, including sweating, agitation, tachycardia, hypertension, vomiting, and diarrhea, which can complicate recovery and

prolong hospital stay. [3,4] The prevalence of withdrawal syndrome in pediatric intensive care units (PICUs) varies widely, depending on the population studied, the duration and type of sedation used, and the tapering of sedation protocols. [5] There is variability in the duration of sedation in adults and children that may lead to withdrawal symptoms. Zerrouki et al. prospectively studied twenty-nine patients who required mechanical ventilation and opioid administration for at least 72 h. Six patients (20.7%) developed withdrawal syndrome within a median of 3 days from opioid weaning. [6] Withdrawal not only impacts the patient's physiological and psychological well-being but also increases the burden on healthcare systems by extending PICU stays and requiring additional interventions. [7] Despite its clinical and economic implications, research on withdrawal syndrome in children remains limited compared to adult populations.

Many studies have highlighted the need for early identification and management of withdrawal syndrome in pediatric patients. Validated tools such as the Withdrawal Assessment Tool-1 (WAT-1) and the Sophia Observation Withdrawal Symptoms scale (SOS) have been developed to facilitate standardized assessment. [8] However, the applicability of these tools in various clinical settings and patient populations requires further investigation. [9] Moreover, the risk factors contributing to withdrawal syndrome, including cumulative medication doses, duration of sedation, and individual patient features, remain poorly understood. [9,10] Addressing these gaps may be challenging and helpful for developing evidence-based guidelines to prevent and manage withdrawal syndrome effectively.

Objective

This study was designed to measure the incidence of withdrawal syndrome in ventilated children and to identify associated factors in a PICU population. By identifying modifiable risk factors and characterizing the clinical course of withdrawal syndrome, this research aims to inform the development of targeted interventions for improving and optimizing patient outcomes and resource utilization in PICUs.

METHODOLOGY

We conducted a prospective observational study in the PICU of The Indus Hospital from 12 June 2025 to 12 October 2025 with the inclusion of children aged 1 month to 14 years who were mechanically ventilated for more than 72 hours, with WAT-1 used during weaning. The SBS served as a tool to evaluate comfort throughout the ventilation process. The primary outcome was iatrogenic withdrawal syndrome, defined as WAT-1 score ≥3. According to the withdrawal assessment, symptoms were measured using standardized instruments like the Withdrawal Assessment Tool-1 (WAT1). Assessment frequency was done every 12 hours during active weaning and for 48 hours post-weaning. [1,11] This threshold was clinically consistent with prior WAT-1 literature and commonly used to indicate clinically relevant withdrawal symptoms in pediatric critical care. We also differentiated the Tolerance and dependence. Tolerance refers to a physiological phenomenon where, over time, a child requires increasing amounts of a substance (such as a medication) to achieve the same therapeutic or desired effect due to neuroadaptive changes in the brain. While dependence describes a state where a child develops physiological adaptation to a substance, leading to withdrawal symptoms if the substance is reduced or discontinued abruptly. [12,13]

WAT-1 severity was classified as follows: 0–2: no or minimal withdrawal, 3–5: mild withdrawal, 6–8: moderate withdrawal, 9–12: severe withdrawal. [14] We included the age, sex, weight, mechanical ventilation duration, duration of analgesic exposure, PICU length of stay, nutritional status, metabolic conditions, prior withdrawal history, need for additional interventions, primary sedative/analgesic agent, WAT-1 score, time to onset of withdrawal, and duration of withdrawal symptoms. Our data also contained medication doses, but these were entered in heterogeneous formats that did not allow reliable normalization into standardized opioid- or sedative-measures. Therefore, cumulative dose-response analyses were not performed.

Median and interquartile range (IQR) were used to present continuous variables, while categorical variables were shown as counts and percentages. Comparisons between children with and without withdrawal were made using Mann-Whitney U tests for continuous variables and chi-square or Fisher exact tests for categorical variables. Logistic regression was used to explore independent associations with withdrawal. As several variables displayed complete or quasi-complete separation, the main multivariable model was intentionally parsimonious and included age, mechanical ventilation duration, and malnutrition/wasting. A secondary exploratory model examined the primary recorded drug group in simplified form. The research was approved by the IRB of the institution (IRB No: IHHN_IRB_2025_03_005).

RESULTS

We studied one hundred children in our research. Median age was 36.0 months (IQR 9.0– 96.0), median weight was 12.0 kg (IQR 6.0–20.5), and 60% were male. Median mechanical ventilation duration was 5.0 days (IQR 3.0–6.0), median analgesic exposure duration was 4.0 days (IQR 3.0–5.0), and median PICU length of stay was 7.0 days (IQR 6.0–10.0) (Table 1).

Values are median (IQR) or n (%).

Table 1. Baseline demographic and clinical characteristics of the study population (N=100)

Variable	Value
Age, months	36.0 (9.0–96.0)
Weight, kg	12.0 (6.0–20.5)
Male sex	60 (60.0%)

Mechanical ventilation duration, days	5.0 (3.0–6.0)
Analgesic exposure duration, days	4.0 (3.0–5.0)
PICU length of stay, days	7.0 (6.0–10.0)
Malnutrition/wasting	27 (27.0%)
Metabolic condition recorded	6 (6.0%)
Previous withdrawal history	8 (8.0%)
Additional intervention required	26 (26.0%)
Primary recorded sedative/analgesic agent	
Agent	n (%)
Nalbuphine	49 (49.0%)
Midazolam	23 (23.0%)
Dexmedetomidine	14 (14.0%)
Morphine	13 (13.0%)
Fentanyl	1 (1.0%)
WAT-1 severity distribution	
Category	n (%)
No/minimal (0–2)	65 (65.0%)
Mild (3–5)	16 (16.0%)
Moderate (6–8)	14 (14.0%)
Severe (9–12)	5 (5.0%)

Among affected patients, the median time to symptom onset after tapering was 0.6 days (IQR 0.4–0.9), equivalent to about 14 hours, and the median withdrawal duration was 3.0 days (IQR 2.0–4.0). Notably, all withdrawal cases occurred in children ventilated for at least 3 days; none of the fourteen children ventilated for less than 3 days developed WAT-1–defined withdrawal (Table 2).
Values are median (IQR) or n (%).

Table 2. Comparison of children with and without withdrawal syndrome

Variable	No withdrawal (n=65)	Withdrawal (n=35)	p value
Age, months	36.0 (11.0–96.0)	30.0 (7.5–72.0)	0.615
Weight, kg	12.0 (7.0–22.0)	9.0 (5.2–14.0)	0.173
Mechanical ventilation duration, days	4.0 (3.0–5.0)	6.0 (4.0–7.0)	<0.001
Analgesic exposure duration, days	4.0 (3.0–5.0)	5.0 (4.0–6.0)	<0.001
PICU length of stay, days	6.0 (6.0–8.0)	10.0 (8.0–15.0)	<0.001
Male sex	39 (60.0%)	21 (60.0%)	1.000
Malnutrition/wasting	12 (18.5%)	15 (42.9%)	0.017
Metabolic condition	0 (0.0%)	6 (17.1%)	0.001
Previous withdrawal history	0 (0.0%)	8 (22.9%)	<0.001
Additional intervention	0 (0.0%)	26 (74.3%)	<0.001

Children with withdrawal had longer ventilation durations than those without withdrawal: median 6.0 days (IQR 4.0–7.0) versus 4.0 days (IQR 3.0–5.0), p<0.001. (Figure 2) Analgesic exposure duration was also longer in the withdrawal group: 5.0 days (IQR 4.0–6.0) versus 4.0 days (IQR 3.0–5.0), p<0.001. PICU stay was substantially longer among children with withdrawal: 10.0 days (IQR 8.0–15.0) versus 6.0 days (IQR 6.0–8.0), p<0.001. Age and weight trended lower in the withdrawal group, but only age retained a signal in adjusted modelling. Sex was not associated with withdrawal. Several categorical factors were strongly associated with withdrawal on univariate analysis. Malnutrition/wasting was more common in affected patients (42.9% vs 18.5%, Fisher p=0.017) (Table 3).

Table 3. Medication pattern and concurrent therapy by withdrawal status

Variable	No withdrawal (n=65)	Withdrawal (n=35)	p value
Primary recorded agent			0.001
Nalbuphine	42 (64.6%)	7 (20.0%)	
Midazolam	9 (13.8%)	14 (40.0%)	
Morphine	6 (9.2%)	7 (20.0%)	
Dexmedetomidine	7 (10.8%)	7 (20.0%)	
Fentanyl	1 (1.5%)	0 (0.0%)	
Concurrent medication group			0.348
Antimicrobials only	9 (13.8%)	2 (5.7%)	
Antimicrobials + steroids	35 (53.8%)	16 (45.7%)	

Antimicrobials + steroids oncology therapy	19 (29.2%)	15 (42.9%)	
Antimicrobials + steroids catecholamines	2 (3.1%)	2 (5.7%)	

In the Multivariable analysis, Ventilation duration (95% CI 1.38–2.47; p<0.001), age (95% CI 0.97–1.00; p=0.015), and Malnutrition/wasting (95% CI 1.85–20.44; p=0.003) were associated with withdrawal (Table 4).

P value significance: < 0.05

Table 4. Univariate and multivariable analysis of factors associated with withdrawal syndrome

Variable	Univariate estimate	p value	Adjusted OR (95% CI)	p value
Mechanical ventilation duration	—	<0.001	1.85 2.47)	<0.001
Age (months)	—	0.615 in unadjusted group comparison	0.99 1.00)	0.015
Malnutrition/wasting	OR 3.31	0.017	6.15 20.44)	0.003
Male sex	OR 1.00	1.000	Not retained	—

Thirty-five children met the primary definition of withdrawal, giving an incidence of 35 %. WAT1 severity was: no/minimal withdrawal in sixty-five, mild withdrawal in sixteen, moderate withdrawal in fourteen, and severe withdrawal in five. (Figure 1)

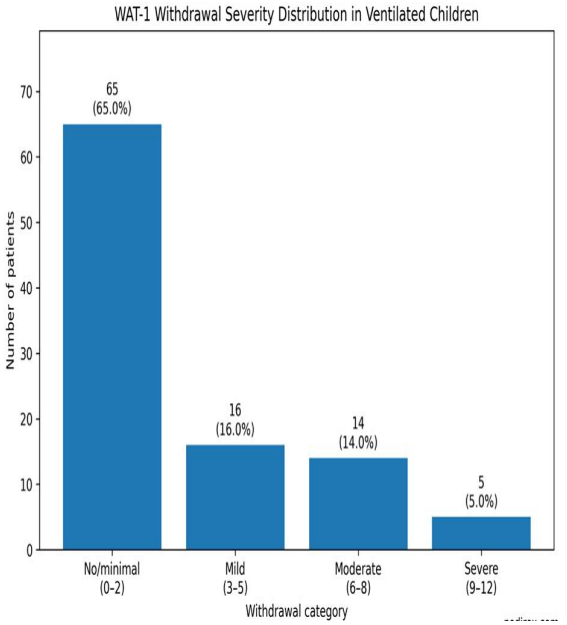

Figure 1. WAT-1 withdrawal severity distribution in mechanically ventilated children

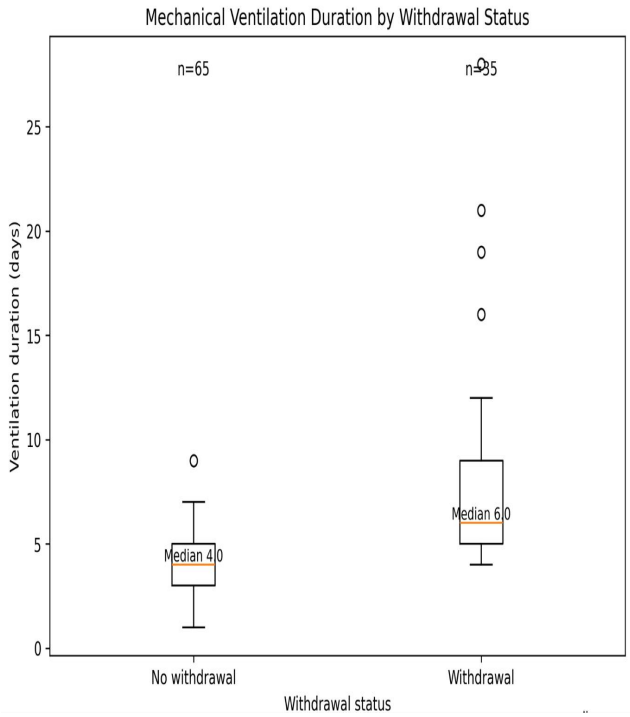

Figure 2. Mechanical ventilation duration by withdrawal status

Among the thirty-five withdrawal cases, the most frequently recorded components were fever >37.8°C (80.0%), loose/watery stools (74.3%), distressed state behaviour (71.4%), moderate/severe startle to touch (71.4%), vomiting/retching/gagging (42.9%), and increased muscle tone (37.1%). Recovery time greater than 2 minutes after stimulation was recorded in 91.4% of withdrawal cases. This pattern is clinically coherent with autonomic, gastrointestinal, and behavioural manifestations expected in pediatric withdrawal (Table

5).
Values are median (IQR) or n (%).

Table 5. Clinical profile of withdrawal episodes (n=35)

Variable	Value
WAT-1 score	6.0 (4.0–7.0)
Mild withdrawal (WAT-1 3–5)	16 (45.7%)
Moderate withdrawal (WAT-1 6–8)	14 (40.0%)
Severe withdrawal (WAT-1 9–12)	5 (14.3%)
Time to onset after tapering, days	0.6 (0.4–0.9)
Withdrawal duration, days	3.0 (2.0–4.0)
Loose/watery stools	26 (74.3%)
Vomiting/retching/gagging	15 (42.9%)
Temperature >37.8°C	28 (80.0%)
Distressed state behavior	25 (71.4%)
Moderate/severe tremor	9 (25.7%)
Sweating	11 (31.4%)
Uncoordinated/repetitive movements	10 (28.6%)
Yawning/sneezing ≥2	2 (5.7%)
Moderate/severe startle to touch	25 (71.4%)
Increased muscle tone	13 (37.1%)
Recovery time >2 min	32 (91.4%)

DISCUSSION

In this cohort, more than one-third of mechanically ventilated children developed WAT-1– defined withdrawal. That incidence is clinically important and aligns with the broader literature showing that IWS is a common complication of prolonged analgesia and sedation. [15] The observed burden in our study is lower than the 52% reported by Geslain et al in a surgical PICU cohort, yet the overall signal is directionally similar: withdrawal remains frequent even in contemporary practice and continues to track with treatment intensity and complexity. [16] The strongest association in our dataset was the duration of mechanical ventilation. This is biologically and clinically reasonable. Longer ventilation usually reflects longer exposure to opioids and sedatives, repeated titration, greater cumulative dependence, and a weaning challenge. That pattern is highly consistent with the systematic review by Best et al, which identified exposure duration and cumulative burden as dominant recurrent risk domains, and with later observational work from Best et al showing that younger age and greater preweaning exposure intensify withdrawal risk. [9,10] Our study could not reliably quantify standardized cumulative doses, but the duration signal was sufficiently strong to persist after adjustment. Younger age also emerged as an independent correlate. Younger children showed the altered pharmacokinetics, less physiologic reserve, and more limited behavioral communication, making both dependence and detection more challenging. [17,18] The persistence of age as a significant indicator in a limited single-center study implies that developmental vulnerability continues to be an important factor contributing to withdrawal risk.

An additional finding was the association between malnutrition and withdrawal. Because previous research has placed less emphasis on this variable, it is important to interpret it with caution. Malnutrition may reflect chronic illness, altered body composition, modified drug distribution, reduced protein binding, or greater overall physiologic fragility. [19,20] It may also function as a surrogate for case complexity rather than a causal risk factor. However, from a pediatric intensivist's perspective, this is a clinical possibility and important signal: nutritionally vulnerable children may be the group in whom exposure accumulates quietly while recovery remains slow. The medication-pattern analysis suggested lower withdrawal frequency in children whose primary recorded agent was nalbuphine, with greater withdrawal among those exposed to midazolam, morphine, or dexmedetomidine. As an exploratory binary contrast, nonnalbuphine exposure was associated with withdrawal. This observation should not be overread. Our data lacked complete multimodal exposure histories, cumulative dose standardization, and formal time-linked weaning data. So, drug-group comparisons remain vulnerable to confounding by indication. That is why we suggest interpreting this as a treatment-pattern hint rather than evidence of drug-specific protection.

Our findings also reinforce the clinical value of structured surveillance. The WAT-1 was designed by Franck et al as a practical bedside tool to detect the withdrawal symptom clusters in pediatric patients receiving opioids and benzodiazepines, and its later validation work supported broader generalizability. [1,11] Current guidelines from Smith et al recommend routine monitoring of withdrawal with validated tools, and more recent reviews by Amigoni et al, Mondardini et al, and MacDonald et al also support the algorithm-based approaches to pain, sedation, and withdrawal management in pediatric intensive care. [14,21–24] Though our data did not evaluate a protocol, it has provided a strong local rationale for implementing one.

Limitations

A few limitations of our study deserve emphasis. First,

this was a single-centre cohort with a modest sample size and heterogeneous diagnoses. Second, although the conceptual study framework targeted prolonged ventilation, some children were ventilated for less than 72 hours, but they were receiving opioids as oncological pain therapy. Third, illness-severity scores such as PRISM III or PELOD-2 were not applied, so residual confounding is unavoidable.

Even with these limitations, the clinical implications are straightforward. Withdrawal affected a substantial fraction of ventilated children, usually appeared early after tapering, and was associated with longer intensive care exposure. A pragmatic PICU response would include routine WAT-1 monitoring during weaning, earlier identification of high-risk patients, and development of a structured sedation-reduction pathway.

CONCLUSION

It is concluded that in patients undergoing PCI with Iatrogenic withdrawal syndrome affected more than one-third of mechanically ventilated children and was associated with longer ventilation, younger age, malnutrition/wasting, and prolonged PICU stay. The findings are directionally consistent with pediatric critical care literature and strengthen the case for routine WAT-1 monitoring and standardized weaning practice.

Funding: None

Conflict of interest: None

Acknowledgment: We are thankful for the IRB team and PICU staff of The Indus Hospital for helping us in form collection and data management of this research.

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