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Evaluation of off-label medication use and drug safety in a pediatric intensive care unit

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ABSTRACT

Safety and efficacy are essential in the process of disease treatment. However, off-label medication use is inevitable because various medications do not contain regulatory labels for pediatric use. We aimed to examine off-label medication use and analyze the risk factors correlated with adverse drug reactions (ADRs). This study was performed retrospectively using electronic medical data from a pediatric intensive care unit (PICU) of a tertiary hospital in Korea from July 2019 to June 2020. A total 6,183 prescribed medications from 502 PICU patients were examined in the present study. A total of 80% were infants or children, and 96.0% of them were treated with off-label medications. It was discovered that 4,778 off-label cases (77.2%) of the top 100 drugs had prescriptions with dosage (67.8%). Drugs prescribed to patients admitted to the cardiothoracic department (odds ratio [OR], 3.248; p = 0.019), total number of medications (OR, 1.116; p = 0.001), and length of PICU stay of $\geq$ 7 days (OR, 4.981; p = 0.008) were significantly associated with ADRs. ADRs were noted to be more severe in off-label use (p = 0.0426). For appropriate medication use, evidence regarding the safety of off-label medications is required and ultimately reflected in the official regulation.

1. Introduction

Both efficacy and safety should be considered when treating patients with medications. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) published strict guidelines for medicinal product examination in pediatric populations in section ICE11, including ethical conditions such as consideration of subject recruitment, consent from guardians, and minimization of risks and distress (European Medicines Agency, 2021); (Guidi et al., 2022). These limitations and inconsistencies are hurdles in the drug approval process of clinical trials relevant to the pediatric population (Caldwell et al., 2004). Therefore, several medications have been prescribed to children based on extrapolated data adapted from adult dosages (Tukayo et al., 2020).

Previous studies have shown that even with equally licensed drugs in children and adults, adverse drug reactions (ADRs) are more frequent in children than in adults (Liu et al., 2019); (Tukayo et al., 2020). In addition, several concerns persist regarding the safety and efficacy of off-label drug use. Because children are in the growth and development stages, they are estimated to have different pharmacokinetic (PK) properties than adults, such as drug metabolism or volume of distribution (Novak and Allen,

Abbreviations: ADRs, Adverse drug reactions; PICU, Pediatric intensive care units; EMRs, Electronic medical records; ATC, Anatomical Therapeutic Chemical Classification System; PK, Pharmacokinetic; PD, Pharmacodynamic; EMA, European Medicines Agency; MFDS, Ministry of Food and Drug Safety; RWD, Real World Data.

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2007); (O'Hara, 2016). In particular, critically ill children often present with impaired organ function due to disease conditions; their PKs and pharmacodynamic (PD) profiles may therefore vary from those of healthy children (Zuppa and Barrett, 2008). Importantly, critically ill patients in pediatric intensive care units (PICUs) are frequently exposed to drug-drug interactions due to the simultaneous prescriptions of a number of medications. Therefore, they are at high risk of ADRs related to drug-drug interactions. Nevertheless, off-label drug use in critically ill children has increased to 23.0–49.5% and 23.4–70.6% over two decades (1996–2006, 2007–2016, respectively) (Balan et al., 2018). Additionally, although critically ill children are more likely to be exposed to a risk of ADRs due to off-label drug use, data on this topic are limited.

In the present study, an effort to assess the status of frequently prescribed off-label drugs in the PICU and analyze the associated factors between reported ADRs and off-label agents using real-world data (RWD) is provided. In addition, this study attempted to collect evidence for safe drug use by identifying the frequency of the prescription of off-label drugs and their associated ADRs, including their type and severity.

2. Materials and methods

2.1. Study design and setting

This retrospective cohort study was performed in the PICU of a tertiary hospital in Korea between July 2019 and June 2020. The unit has 24 beds and is staffed 24 h a day, 7 days a week, by four pediatric intensivists. Clinical pharmacy services are provided 5 days a week by dedicated PICU clinical pharmacists who review the medication records of all PICU patients, including drug dosing, administration routes, drug concentrations, reported ADRs, and any drug-related queries (Choi et al., 2021).

2.2. Study population

The study population consisted of pediatric patients aged less than 19 years who were admitted to and discharged from the PICU during the study period (July 2019 to June 2020). Patients who stayed for less than 24 h or were re-admitted for the same indication within 72 h in the PICU were excluded from the study (Fig. 1). Patient ages were divided into the following four groups based on the European Medicines Agency (EMA) age classification: neonates (0–27 days), infants (28 days–23 months), children (2–11 years), and adolescents (12–18 years) (European Medicines Agency, 2000). Preterm neonates were excluded, and only those with a corrected age of 40 weeks or more were included in the study as full-term neonates.

2.3. Selection of study medications and data sources

After thoroughly reviewing all drugs prescribed to the eligible population during the study period, only prescriptions with signs of administration on the nursing record were collected and investigated. The prescribed medications were classified using the Anatomical Therapeutic Chemical Classification System (ATC) code, and the following ATC groups were then excluded: 1) B05 (blood substitutes and perfusate); 2) V06 (general nutrients); 3) A11 (vitamins); 4) A12 (inorganic supplements); and 5) J07 (vaccines). Antibiotics used for susceptibility skin tests and vitamin K formulas were also excluded. Finally, a list containing the top 100 drugs with high prescription frequencies was prepared for further evaluation in the present study (Supplementary Table 1).

Data were collected using electronic medical records (EMRs) to gather information on patients' basic characteristics, such as age, sex, medical department at admission, indications for PICU admission, and duration of stay in the PICU. Moreover, the information associated with medical history was investigated. The medical department was largely classified into three categories: cardiothoracic, pediatric surgical, and general pediatric. The cardiothoracic department includes the departments of pediatric cardiology and thoracic surgery. The pediatric surgical department includes surgical patients from the departments of pediatric otorhinolaryngology, pediatric orthopedic surgery, pediatric general surgery, and pediatric neurosurgery. General pediatrics includes medical patients only, not surgical patients.

2.4. Off-label prescription

An 'off-label prescription' was defined as a prescription that deviates from the approved drug label in terms of indication, age, route of administration, or dose sections, as specified in the Pharmaceutical Integrated Information System of the Ministry of Food and Drug Safety (MFDS) of Korea (Ministry of Food and Drug

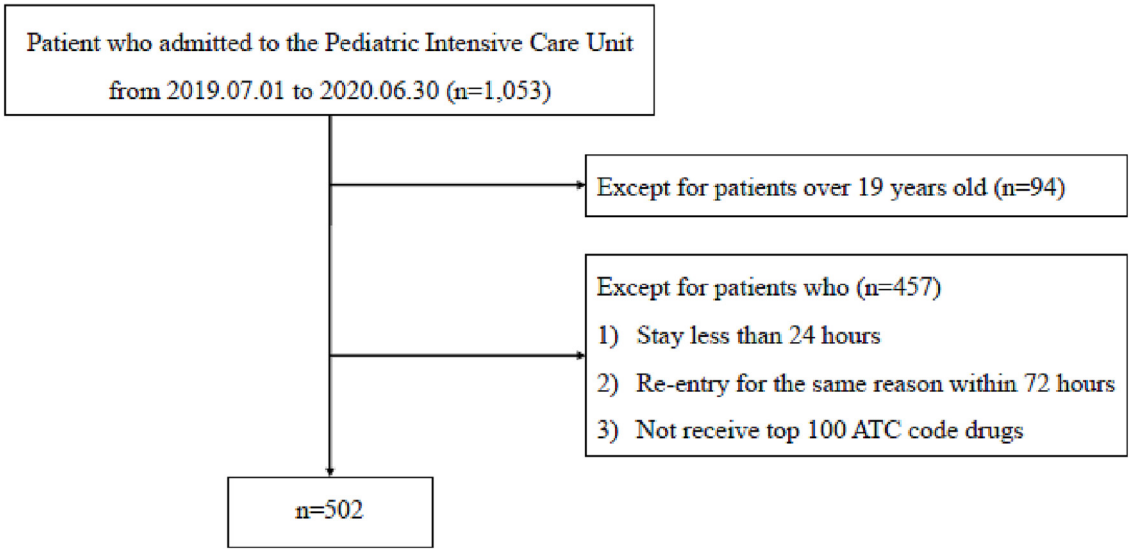

Fig. 1. Patient selection flowchart.

Safety (MFDS) of Korea., 2004, (Turner et al., 1998). The four categories are classified as follows:

1) Indications: When the use was not listed in the "efficacy and effects."
2) Age: When the use was not approved for age or weight. The use of all medications with ambiguous or limited permission for children such as "safety is not established," "administration is not recommended in children," and "do not administer in children."
3) Route of administration: When administered by a route other than the approved route of administration.
4) Dosage: When the total daily dose exceeded the permitted dose for continuous infusion drugs, when the administration rate was higher than the approved rate, or when pediatric dose information was not clearly described.

EMR data were retrospectively reviewed to verify whether the prescriptions of all selected medications were under the information on the labels or not, while the pediatric intensivist (author, YHC) confirmed the indication category evaluation if the clinical indication was unclear. In addition, a prescribed drug could occasionally be included in multiple off-label categories during the evaluation process. This study did not include an assessment of unlicensed drugs that did not provide information on the labels.

2.5. ADRs

ADRs are defined as responses to a medicinal product which is noxious and unintended (European Medicines Agency and Heads of Medicines Agencies. Guideline on good pharmacovigilance practices, 2017). In order to discover the correlation between off-label drug use and ADRs, data on ADR cases voluntarily reported to the ADR surveillance team of Seoul National University Children's Hospital, part of the regional pharmacovigilance center, were analyzed (Baek et al., 2016); (Kim et al., 2017). The reported events were classified into six categories based on the WHO-UMC causality assessment tool and were only selected in this study if they qualified for the following causality assessment categories: "certain," "probable/likely," or "possible" (Centre, 2018). ADRs, identified in our study, were categorized into three severity levels: mild, moderate, and severe. Mild ADRs refer to symptoms or signs that are perceptible to the patient but do not require treatment to alleviate them and have minimal impact on behavior or function. Moderate ADRs involve significant symptoms with mild effects on vital organs, while severe ADRs pose life-threatening risks and severely impacts vital organs. The grading system used in the hospital where the study was conducted is based on the criteria of the Korea Institute of Drug Safety & Risk Management (Korea Institute of Drug Safety & Risk Management, 2013). It follows the evaluation methodology consistent with the widely accepted international standards of the Common Terminology Criteria for adverse events (CTCAE) (U.S. Department of Health and Human Services, 2017). However, in accordance with the Korean context, ADRs classified higher according to CTCAE were defined as severe.

2.6. Statistical analysis

Continuous nonparametric and categorical variables were presented as medians with interquartile ranges and numbers with percentages, respectively. Descriptive statistics were used for demographics and to analyze the frequency of off-label prescriptions. A Pearson's chi-square test was conducted to assess the difference in off-label categories among the medical departments and the severity of ADRs between on-label and off-label use. Logistic regression was used to identify variables that were significantly associated with ADRs. Multivariate logistic regression analysis identified significant univariate variables and was performed using a backward elimination strategy. A p value of less than 0.05 was considered to have statistical significance, and statistical analyses were performed using the SPSS software version 25.0 (IBM, Armonk, NY, USA).

2.7. Ethics

This study was performed with the approval of the Institutional Review Board of Seoul National University Hospital, and consent from the study subjects was waived due to the retrospective nature of the study (IRB no. H-2007–093-1141).

3. Results

3.1. Patient characteristics

A total of 502 patients were included in this study (Table 1). The median age of the patients was 1.7 (0.4–6.5) years, and approximately 80% of patients were included in infant and children groups. The majority of patients (74.3%) were admitted to the PICU for postoperative or procedural care. In the PICU, patients received a median of 12 (IQR, 7–16) of the top 100 drugs. Among these drugs, the median number of off-label drugs was nine (IQR, 5–13). Almost all patients (500, 99.6%) were exposed to at least one off-label prescription. ADR was observed in 27 patients (5.4%). The patients stayed in the PICU for a median of 3.4 days (IQR

Table 1
General characteristics of the study population.

Characteristic	n (%) or median (IQR)
Patients exposed to at least one off-label prescription	500 (99.6)
Sex	
Male	285 (56.8)
Age (years)	1.7 (0.4–6.5)
0–27 days	31 (6.2)
28 days-23 months	231 (46.0)
2–11 years	176 (35.1)
12–19 years	64 (12.7)
Department	
Cardiothoracic department[a]	198 (39.4)
Pediatric surgical department[b]	194 (38.7)
General pediatrics	110 (21.9)
Indication for PICU admission	
Post-operative or procedural care	373 (74.3)
Acute respiratory failure	38 (7.6)
Shock	21 (4.2)
Neurological monitoring	20 (4.0)
Multiple organ failure	15 (3.0)
Other reasons[c]	35 (7.0)
Average number of prescribed medications per patient	
Total medications	12 (7–16)
off-label medications	9 (5–13)
Adverse drug reaction experience in PICU stay	27 (5.4)
Length of stay in PICU (days)	3.4 (1.9–6.9)
≤3	252 (50.2)
4–6	129 (25.7)
≥7	121 (24.1)
Survival to PICU discharge	484 (96.4)

PICU, pediatric intensive care unit.
[a] Included departments of pediatric cardiology and thoracic surgery.
[b] Included departments of pediatric otorhinolaryngology, pediatric orthopedic surgery, pediatric general surgery, and pediatric neurosurgery.
[c] Included chronic respiratory failure, continuous renal replacement therapy, post cardiac arrest care, and arrhythmia.

1.9–6.9) and half of them were discharged from the PICU within three days.

3.2. Classification of off-label drug prescriptions

A total of 6,183 prescriptions from the top 100 drugs were identified, and 77.2% of total prescriptions with off-label use were evaluated (Table 2, Supplementary Table 1). The "dose" was the major category of off-label drug prescription (67.8%), followed by "age" (50.1%) and "indication" (31.5%). The number of off-label prescriptions differed significantly by medical department (p less than 0.001). Additionally, the classification of off-label prescriptions, excluding "route of administration," showed statistically significant differences according to department (p less than 0.001).

Table 3 presents the top ten drugs with a high frequency of off-label prescriptions in each department. Remifentanil, midazolam, furosemide, and dopamine were predominantly used irrespective of the department, whereas others differed depending on the department.

3.3. Risk factors associated with ADR

The correlations between patient characteristics and risk of ADRs are summarized in Table 4. In the univariate logistic regression analysis, ADRs were significantly associated with the following factors: department, indication for PICU admission, number of prescribed medications per patient, and length of stay in the PICU. Based on multivariate logistic regression analysis, three variables, including department, number of prescribed medications per patient, and length of stay in the PICU, demonstrated statistically significant associations with ADRs. Patients in the general pediatric department had a three-fold higher likelihood of ADRs than patients in the cardiothoracic department (odds ratio [OR], 3. 248; p = 0.019), while no significant difference was observed between patients in the cardiothoracic and pediatric surgical department. Therefore, a statistically significant increase in the risk of ADRs was observed along with an increase in the total number of drugs, instead of the number of off-label drugs (OR, 1.116; p = 0.001) and length of stay of $\geq$ 7 days (OR, 4.98; p = 0.008).

3.4. Severity of ADRs in off-label drugs

Based on the subgroup analysis of 27 patients reporting ADRs, 61.7% of 67 ADRs (47 causative prescriptions) were statistically correlated with off-label use, and the type of moderate to severe adverse reactions were identified. The incidence of moderate or severe ADR events differed significantly between off-label and on-label drugs (69.0% vs. 38.9%, p = 0.0426) (Fig. 2). Moreover, Table 5 presents the ADRs and their associated drugs that the ADR surveillance team considered moderate or severe when using off-label medications.

Table 3
Top 10 off-label drugs in each department.

Cardiothoracic department[a]	Pediatric surgical department[b]	General pediatrics
Remifentanil	Esomeprazole	Midazolam
Famotidine	Acetylcysteine	Famotidine
Furosemide	Midazolam	Propacetamol
Nitroglycerin	Furosemide	Dexamethasone
Dopamine	Remifentanil	Cefazolin
Spironolactone	Piperacillin/Tazobactam	Remifentanil
Enalapril	Dexamethasone	Furosemide
Midazolam	Meropenem	Acetylcysteine, Pantoprazole
Epinephrine	Dopamine	Dopamine
Ambroxol	Salbutamol, UDCA	Levetiracetam

[a] Included departments of pediatric cardiology and thoracic surgery.
[b] Included departments of pediatric otorhinolaryngology, pediatric orthopedic surgery, pediatric general surgery, and pediatric neurosurgery.

4. Discussion

In this study, we characterized the current status of off-label drug use in critically ill children, with a focus on clinical characteristics. Furthermore, we identified the risk factors for ADRs and an association between off-label drug use and ADRs. To date, only a few studies exist on the prevalence, common drugs, and risk factors of off-label prescriptions in adults or children, with inconsistent results (Turner et al., 1999); (Choonara and Conroy, 2002); (Neubert et al., 2004); (Saiyed et al., 2015). In addition, research on the effects of exposure to off-label drugs in the PICU is limited. To our knowledge, this is the first study to assess the relationship between off-label drug use and ADR severity in critically ill children.

Although several steps should be carefully considered in the management of critically ill children, off-label prescriptions are frequently required. Our research revealed that most patients in the PICU were exposed to off-label drugs, and that approximately three-quarters of the administered drugs were related to off-label prescriptions. Similar to previous studies, this result supports the reality of the PICU faced by intensivists (Balan et al., 2018); (Nir-Neuman et al., 2018). However, contrary to a recent systematic review in which indication and age categories were the most frequent types of off-label drugs use, the dosage category appeared most frequently in this study (Magalhães et al., 2015). It could be assumed that indications for medication usage differed according to the references used; such as MFDS, FDA, or EMA regulations, and that some medications were not licensed in certain countries (Teigen et al., 2017); (Balan et al., 2018); (Costa et al., 2018); (Song et al., 2020). Additionally, since most of the patients in this study were aged under 12 years, most of the cases regarding dosage criteria were associated with insufficient information on pediatric doses, rather than overdoses. Thus, it is presumed that the cases in the dosage category of this study would be included in the age category of previous reports.

Table 2
Classification of off-label drug use according to department.

	Total	Cardiothoracic department	Pediatric surgical department	General pediatrics	p-value
Total prescription	6,183	3,116	1,559	1,508	
Off-label use	4,778 (77.3)	2,565 (82.3)	1,073 (68.8)	1,140 (75.6)	<0.001
Dose	4,192 (67.8)	2,215 (71.1)	920 (59.0)	1,057 (70.1)	<0.001
Age	3,098 (50.1)	1,787 (57.3)	716 (45.9)	595 (39.5)	<0.001
Indication	1,947 (31.5)	1,049 (33.7)	413 (26.5)	485 (32.2)	<0.001
Route of administration	38 (0.6)	21 (0.7)	6 (0.4)	11 (0.7)	0.396

Note: a drug may be off-label for more than one category.

Table 4
Risk factors associated with adverse drug reactions: Logistic regression analysis.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex				
Male	1		–	–
Female	1.983 (0.901–4.364)	0.089	–	–
Age				
0–27 days	1		–	–
28 days-23 months	0.865 (0.186–4.026)	0.853	–	–
2–11 years	0.424 (0.079–2.289)	0.319	–	–
12–19 years	1.781 (0.348–9.123)	0.489	–	–
Department				
Cardiothoracic department	1		1	
Pediatric surgical department	0.373 (0.097–1.428)	0.150	0.925 (0.217–3.948)	0.916
General pediatrics	4.043 (1.670–9.785)	0.002	3.248 (1.215–8.683)	0.019
Indication for PICU admission				
Post-operative or post-procedural	1		1	
Acute respiratory failure	4.735 (1.644–13.633)	0.004	1.156 (0.223–5.989)	0.862
Other reasons	6.500 (2.471–14.816)	<0.001	1.618(0.409–6.399)	0.493
Average number of prescribed medications per patient				
Total medications	1.199 (1.134–1.268)	<0.001	1.116 (1.045–1.193)	0.001
Off-label medications	1.215 (1.139–1.297)	<0.001	0.907 (0.693–1.187)	0.478
Length of stay in PICU (days)				
<7	1		1	
≥7	14.711 (6.173–45.242)	<0.001	4.981 (1.515–16.376)	0.008

PICU, pediatric intensive care unit.

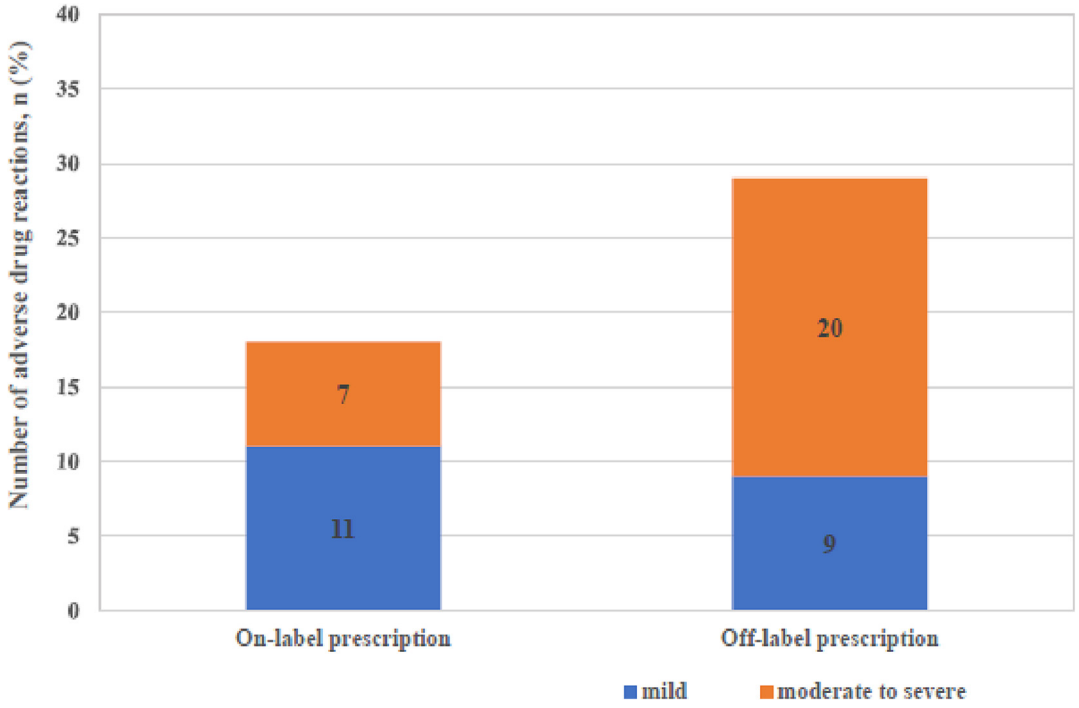

Fig. 2. Off-label drug use and severity of adverse drug reactions (n = 47).

In the present study, we discovered off-label prescription trends according to the department in which the patients were admitted. First, patients in the medical department were more likely to receive off-label drugs than those in the surgical department. Second, the distribution of off-label prescription categories differed by department. Third, drugs with high frequencies of off-label use also differed by department, except for the top four drugs. In general, prescribed medications may vary according to the general characteristics of inpatients (underlying diseases, severity of illness, reasons for hospitalization, etc.), clinician preference, and country-specific drug availability (Palmaro et al., 2015). Thus, it is estimated that the trend of off-label prescriptions can also be determined by department due to diverse patient characteristics between departments. Additionally, off-label drug use is expected to vary across PICUs owing to differences in patient composition. These findings suggest that the use of off-label drugs, according to the characteristics of the PICU, should be considered in further research.

Ultimately, the safety of off-label drug use for patients is a major concern in the clinical field. This study confirmed that the medical department, total number of medications, and length of stay in the PICU increased the risk of ADRs. The latter two results

Table 5
Cases of moderate to severe adverse drug reactions in off-label prescription drugs.

Severity	Drug	Adverse drug reaction
Moderate	Acyclovir	AST elevation
	Cefotaxime	Elevated liver enzymes
	Dopamine	Eosinophilia
	Esomeprazole	AST elevation
	Fosphenytoin	AST elevation
	Meropenem	Bilirubin elevation
	Milrinone	Thrombocytopenia
	Phenobarbital	Leucopenia, Thrombocytopenia
	Phenytoin	Pruritus, Rash
	Piperacillin/ Tazobactam	Bilirubin elevation, Eosinophilia, Elevated liver enzymes, Thrombocytopenia
	Remifentanil	Eosinophilia
	Tacrolimus	Convulsions
	Vancomycin	Diarrhea
Severe	Amphotericin-B	BUN and bilirubin elevation
	Chloral hydrate	Hypotension
	Colistin	BUN elevation
	Ertapenem	Bilirubin elevation
	Esomeprazole	Bilirubin elevation
	Ganciclovir	Leucopenia, Neutropenia, Thrombocytopenia
	Levofloxacin	Bilirubin elevation
	Meropenem	Bilirubin and BUN elevation
	Piperacillin/ Tazobactam	Bilirubin elevation, Elevated liver enzymes
	Tacrolimus	Bilirubin elevation

AST, aspartate transaminase; BUN, blood urea nitrogen.

are consistent with those in previous studies (Rashed et al., 2012); (Bellis et al., 2013). However, in the case of medical departments, the present results differed from those of previous studies. This might be due to the fact that medical patients tended to be exposed to a higher quantity drugs than surgical patients because of their multiple diagnoses and longer lengths of stay (Du et al., 2013). Interestingly, unlike previous studies that suggested that the use of off-label drugs was more likely to be associated with ADRs than with labeled drugs (Saiyed et al., 2015); the number of off-label drugs was not statistically associated with ADRs in this study. However, off-label drugs were found to increase the likelihood of moderate-to-severe ADR. To our knowledge, this is the first study to confirm the relationship between off-label drug use and ADR severity in critically ill children (Saiyed et al., 2015). Therefore, based on the results of the present study, it could be recommended that particular attention should be paid to safety when administering off-labels medications in the PICU.

Despite the uncertainty of off-label drug safety, it is not possible to monitor the effects of off-label drugs administered to patients due to the high proportion of off-label prescriptions in the PICU. The most frequently prescribed off-label drugs in this study were remifentanil, midazolam, furosemide, and dopamine, regardless of department. Three of these medications, excluding remifentanil, were also identified as frequently prescribed in other studies (Carvalho et al., 2003); (Bavdekar et al., 2009). Future research on widely used drugs should be conducted. Regulations for medication usage should be developed through research, so clinicians may focus on monitoring essential drugs. Therefore, the lack of sufficient data should be urgently assessed by producing reliable data. The development of a validated screening tool that can identify these data is also critical.

This study had some limitations. First, although the chosen research institute is one of the major tertiary hospitals in South Korea with a large-scale 24-bed PICU, the study was conducted at a single institution, limiting the representation and generalization of the findings. Therefore, a multicenter study with a longer study period is required to obtain more concrete information. Second, some ADRs might be underreported because we only evaluated the top 100 most frequently prescribed drugs and because ADRs were reported voluntarily in this institute. However, since the top 100 drugs accounted for 95.7% of all prescribed medications, the drugs selected in this study could be considered representative of those prescribed in the PICU. Moreover, mild ADRs might have been neglected, but moderate to severe ADRs, which were considered meaningful in this study, were closely monitored by a dedicated PICU pharmacist at the institute (Choi et al., 2021). Therefore, concerns about underreported ADRs were assumed to have a minimal impact on the results of this study.

5. Conclusions

In conclusion, a large proportion of patients in the PICU are exposed to off-label prescriptions due to insufficient information on pediatric indication. Moreover, off-label drug use is associated with moderate to severe ADRs. This highlights an urgent need to establish a feasible system that monitors the negative effects of off-label drug use in the PICU, especially based on the characteristics of critically ill children.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2023.101704.

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