Research Article

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Potential Drug-Drug Interactions in Pediatric Patients of a Teaching Hospital In Northern Cyprus: A Retrospective Study

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ABSTRACT

Hospitalized infants and children are exposed to various medications, leading to potential drug-drug interactions (pDDIs). A retrospective observational study was conducted in a Northern Cyprus tertiary hospital to determine the frequency, types, and associated factors of pDDIs in hospitalized pediatric patients. All charts of pediatric patients hospitalized between September 1st, 2017, and August 30, 2018, were reviewed. Medications used concomitantly during hospitalization were screened for pDDIs using three DDI databases; Lexicomp TM 3.0.2, drugs.com, and Medscape. Of the 332 patients examined, 230 (69.2%) patient files met the inclusion criteria. The prevalence rates of pDDIs were 27.8%, 24.8%, and 23%, according to Lexicomp, Drugs.com, and Medscape databases, respectively. Young children (aged 2-6) had the highest percentage of pDDIs with a significant difference between databases ($P < 0.05$).Patients with pDDIs had longer hospital stays and were on more medications than those without ($P < 0.05$). Our study revealed that moderate severity pDDIs were common, and there were significant variations between databases. While severe pDDIs are rare, they may be life threatening. Collaborative efforts involving pediatricians and clinical pharmacists are necessary to address pDDIs in pediatric medication management. Utilizing multiple databases to enhance pDDI identification and prevention is also crucial.

Keywords: Drug interactions, Pediatrics, Drug safety, Clinical pharmacist, Hospital stay

1. Introduction

Drug interactions (DIs) are becoming more common in daily practice because of the increasing number of drugs available and the rising incidence of diseases across all age groups, including pediatrics, adults, and the elderly [1]. Many drugs are introduced annually, and new drug interactions are increasingly reported [1]. Although the number of pediatric drug-drug interaction studies is limited, data collected from clinical trials before drug approval and post-marketing studies are usually extrapolated for use in pediatric patients with different physical profiles and pharmacokinetic processes [2]. Fatal adverse drug effects rank the fourth and sixth major cause of death in the US, and it is reported that 20%–30% of all adverse reactions to drugs are caused by interactions between drugs [3]. Children can be more susceptible to potential drug-drug interaction (pDDIs) than adults, as some hospitalized children may receive more than 25 drugs during their stay [4]. In addition, they can react differently to drug administration than adults, which is explained by changes in absorption, distribution, metabolism, excretion, and the administration of unlicensed and off-label prescription drugs [5]. In the pediatric population, the prevalence of pDDIs ranges from 3.8% to 75% [6]. Recent research shows several risk factors are associated with pDDIs in hospitalized children. These risk factors include patient age, the average number of prescriptions per visit, the number of visits per year, specific diagnoses such as epilepsy, leukemia, and rheumatoid arthritis, as well as specific groups of drugs such as antiepileptic, anti-neoplastic, systemic antifungal and immunosuppressant drugs, as well as those used for respiratory tract obstructive conditions [7].

Evaluating the potential for drug-drug interactions (DDIs) in pediatric patients poses ethical, logistical, and methodological challenges [8]. According to regulatory guidelines, DDI studies in pediatric patients must be performed on those receiving the drug as part of their care [9]. However, analyzing DDI data in this context can be complex, as it requires separating the effect of the DDI of interest from other medications and disease states. Limited DDI data exists for neonates and infants, despite their expected considerable differences in pDDI [8].

Due to the lack of clinical trials focusing on pediatric patients' safety, efficacy, and dosing parameters, physicians may need to resort to "off-label" prescribing. With the limited availability of evidence-based protocols and practice guidelines, clinicians often rely on their best clinical judgment when managing pharmacotherapy for pediatric patients with multiple or complex disease states [10]. While it may be challenging for clinical practitioners to recall all possible drug-drug interactions, improving their awareness of clinically significant DDIs can substantially lower the likelihood of adverse events [11].

Despite the available information, our knowledge of drug-drug interactions in the pediatric population in North Cyprus is limited. Consequently, it is crucial to conduct further research to identify potential risk factors and evaluate the prevalence and severity of these interactions. With this in mind, our study aims to determine the most common pDDIs found in hospitalized pediatric patients, as well as to classify their severity and identify any associated risk factors. Through this study, we aim to raise awareness of this important issue and improve patient safety.

2. Materials and Methods

2.1. Study Design and Data Collection

A retrospective analysis was conducted on the clinical records of pediatric patients aged< 12 years old who used more than one drug and presented in the pediatric clinics of Near East University Hospital in North Cyprus from September 1st, 2017, till August 30, 2018. Patients with uncompleted files were excluded**.** Data were collected using particular forms, which involve demographic data of the patients, age, gender, and the number of medications used during the hospitalization and stay periods. Drugs information record includes the name of the drugs, DDI severity, mechanism of drug interaction, risk rating, and the recommendation for the DDI. Generic names were used in all study procedures. Ethics approval for this study was obtained from the Institutional Review Board (IRB) of Near East University Hospital (YDU/2018/62-656). The research was conducted in accordance with the Declaration of Helsinki. Patients' privacy was taken into consideration by the researchers.

2.2. Study Procedure

All drugs the patients used during their hospitalization were screened using three different DDIs checkers; Lexicomp Online™3.0.2, drugs.com, and the

online Medscape drug interaction checker. Mechanisms of DDIs in all databases used were categorized as pharmacodynamic, pharmacokinetic, and unknown. Based on Lexicomp, levels of interaction are classified into five categories (A, B, C, D, and X).Interaction levels of X, D, and C were regarded as clinically important, and the need to modify the medications and dosages or avoid combinations based on assessment. In the Drugs.com database, DDIs are classified according to the severity of interaction into major, moderate, and minor, while in Medscape, they are classified as minor, monitored closely, and serious.

2.3. Statistical Analysis

The collected data were organized and analyzed using Microsoft Excel 2016 and Statistical Package for the Social Sciences (SPSS) statistical software (version 20, IBM, SPSS). Descriptive statistics were used to present categorical variables as frequency and percentages, whereas arithmetic means, standard deviation, median, minimum, and maximum values were calculated for continuous data. Independent samples Mann Whitney U test was applied to compare two categorical variables. Pearson Chi-square and Fisher's exact tests were performed to test the association between different categorical variables. Values<0.05 were considered statistically significant.

3. Results and Discussion

3.1. Demographics of the Patients

Totally 332 patients file were screened during the study period, and only 230 files fit the inclusion criteria and screening for pDDI. One hundred eighteen (51.3%) were female patient files (**Table 1**). Referring to the Food and Drug Administration (FDA) age categories of the patients, more than half of the patients (n=127; 55.2%) were neonates (0-1 month) (**Table 1**). The mean days of hospitalization were 2.8 ± 4.5, with the mean number of medications used during hospitalization 3.6 ± 2.0 (ranging from 2 to 15 medications). Fever was the most common cause of hospitalization (23%), while 20% documented as pneumonia patients.

3.2. Drug Interactions

The total number of the DDIs identified using the tools differed according to their classifications. Lexicomp identified 64 (27.8%) patients to have at least a DDI, while Drugs.com and Medscape identified 57 (24.8%) and 53 (23%) patients with a DDI, respectively. In the three databases, a longer duration of stay (5.17 ± 6.88 versus 2.01± 2.89 P <0.05) and a more significant number of medications (6.01 ± 2.68 versus 2.88 ± 0.88, P <0.05) were seen respectively for those who had an interaction compared to those who did not record any interaction.

Regarding the mechanism of interaction, the most frequent mechanism recorded using Lexicomp was PD (45.3%) as well in drugs.com (55.3%) and less in Medscape (38.5%).Referring to the severity of the DDI identified, most DDIs were moderate (85.1%), while major represented only 2.2% of the total interactions reported using Lexicomp. In Drugs.com, the major severity of interaction was 3.9%, and there was 20.2% major interaction from the total interactions reported using Medscape (**Table 2**).

According to Lexicomp, the total number of DDIs recorded was 181. The highest percentage of interactions was noticed in young children (70%) and neonates (7.87%) (**Figure 1**). These findings can conclude that there is an association between age and the DDIs in the Lexicomp tool (X2=66.28, P <0.05). Based on the gender of the patients, 71.4% of the males had no interaction, and 72.9% of the females recorded no interaction. According to drugs.com, the total number of DDI recorded was 179. Fifty percent of hospitalized young children and 13.4% of neonates had interactions (**Figure 1**). These findings indicated an association between age groups and the presence of DDIs (X^2 = 24.37, P <0.05). According to Medscape, only 23% of the drugs used during hospitalization recorded interaction. The number of interactions ranged from one to seven per patient. Thus prevalence of pDDI within different age groups is not equal to 100 in same database (**Figure 1**). Regarding the patients' age, 92.10% of the neonates recorded no interaction, while only 7.87% recorded interactions. Out of young children, 57% had an interaction (**Figure 1**). From these findings; we can conclude that there is an association between age groups and the presence of interactions (X^2 = 46.20, P < 0.05).

Lexicomp reported the most frequent interaction between budesonide and salbutamol, occurring 29 times, whereas drug.com identified the most frequent interaction between salbutamol and clarithromycin, appearing 26 times. For Medscape, the most frequent

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Table 1. Age categories prevalence and their medications mean

Age categories	Prevalence of patients according to the age category	The mean ± SD of medication used regarding the age category
Neonate (0-1 month)	127 (55.2%)	(3.02 ± 1.43)
Infant (2 months-2 years)	32 (13.9%)	(4.09 ± 2.21)
Young child (3-6 years)	40 (17.4%)	(5.07 ± 2.37)
Child (7-12 years)	31 (13.5%)	(4.00 ± 2.50)

SD = standard deviation.

Table 2. The total number of the DDIs and DDIs mechanism of interactions and severity

DDI Checker tool		Lexicomp	Drugs.com	Medscape
Number of DDIs		n=181	n= 179	n=109
Mechanism of interactions	Pharmacokinetics	74 (40.9%)	28 (15.6%)	32 (29.4%)
	Pharmacodynamics	82 (45.3%)	99 (55.3%)	42 (38.5%)
	Unknown	25 (13.8%)	52 (29.1%)	35 (32.2%)
Severity	N/A	2 (1.1%)	--	--
	Minor	21 (11.6%)	46 (25.7%)	11 (10.1%)
	Moderate	154 (85.1%)	126 (70.4%)	76 (69.7%)
	Major	4 (2.2%)	7 (3.9%)	22 (20.2%*)

DDI = drug-drug interaction; N/A = xxxxx.
*The data showed that there is a significant association between the programs and interaction (X^2 =35.53, P < 0.05)

interaction was between (salbutamol × ibuprofen) 20 times (**Tables 3-5**).

Regarding the severity of DDI, most DDIs were moderate (85.1%), while major interactions were only 2.2% of the total interactions reported using Lexicomp. The severity of DDI screened via drugs.com was mostly moderate (70.4%), and only 3.9% were major interactions. Medscape reported more major DDIs (22%) (Tables 2-6).

The mean ± standard deviation number of medications used in males was significantly higher than in females (3.45 ±1.96) (3.85± 2.11) (P < 0.05).No significant difference was seen in the mean staying period of different genders (P >0.05).

The data on the presence of interaction regarding Lexicomp, drugs.com, and Medscape showed that the mean ± standard deviation of the number of medications used was significantly higher in patients with interactions than those with no interaction (5.85 ± 2.56 versus 2.81 ± 0.84 in Lexicomp;6.01 ± 2.68 versus 2.88 ± 0.88 in drugs.com and 6.26 ± 2.60 versus 2.88 ± 0.89 in Medscape; P-values< 0.05). Similar to the number of drugs, the staying period in the three databases showed that there is a significant difference between the mean ± standard deviation of the staying period for those who have interaction compared to those who did not record any interaction (5.17 ± 6.88 versus 2.01± 2.89 in Lexicomp; 6.63 ± 7.90 versus 1.66± 1.25 in drugs.com; 5.43 ± 6.64 versus 2.13± 3.44 in Medscape; P-values <0.05).

DDIs have received a great deal of recent attention from the regulatory, scientific, and healthcare communities worldwide. In medical practice, it is common to use drug combinations with the capability to interact. Although not all pDDIs detected in a patient may occur as DDI, their identification is relevant since they can increase the risk for adverse drug reactions (ADRs), toxicity, or loss of treatment efficacy, which in addition to negative consequences for patients, can increase days of hospital stay and costs [1].

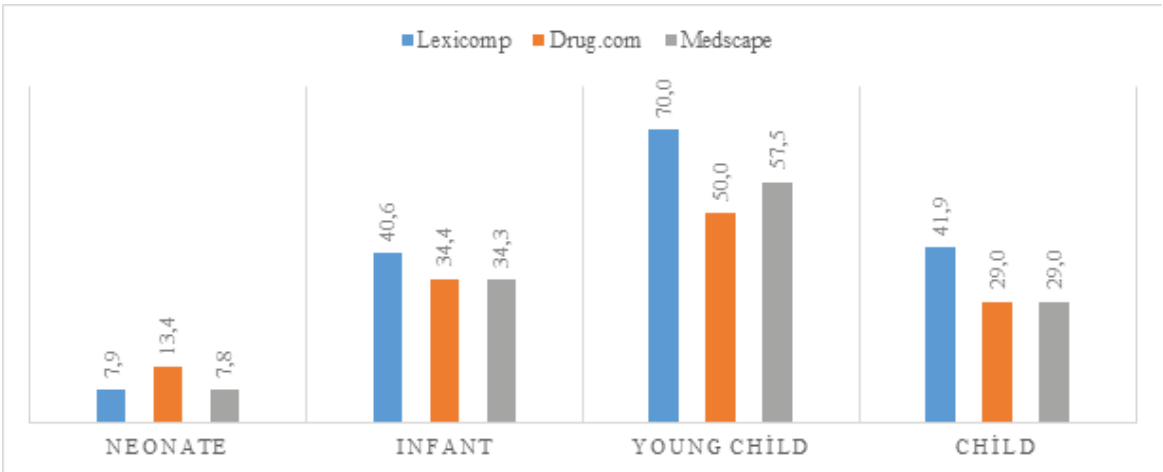

Figure 1. The prevalence of drug-drug interactions (DDIs) within the age groups

Table 3. Most frequent five DDIs in Lexicomp

Drug A	Drug B	M. Of Interaction	Severity	Clinical Significance	Recommendation	Frequency
Budesonide	Salbutamol	PD	Moderate (B)	Cs enhance the hypokalemia effect of B2 agonist	No action required	29
Clarithromycin	Budesonide	PK	Moderate(C)	CYP3A4 inhibitors increase the serum concertation of budesonide	Monitor for signs and symptoms of Cs toxicity	23
Prednisolone	Salbutamol	PD	Moderate(B)	Cs enhance the hypokalemia effect of b2 agonist	No action required	18
Clarithromycin	Ranitidine	PK	Moderate(C)	P-glycoprotein inhibitor may increase the serum concentration of ranitidine	Monitor therapy	10
Clarithromycin	Prednisolone	PK	Moderate(C)	CYP3A4 inhibitors increase the serum concertation of prednisolone	Monitor for increased steroid–related adverse effect	16

PD = pharmacodynamics; PK = pharmacokinetic.

Table 4. Most frequent five DDIs in Drugs.com

Drug A	Drug B	M. of interaction	Severity	Clinical significance	Recommendation	Frequency
Salbutamol	Clarithromycin	PD	Moderate	Increased risk of irregular heart rhythm	Monitor therapy	26
Budesonide	Clarithromycin	PK	Moderate	Clarithromycin increases the absorption of budesonide	Monitor side effects:depression,high BP. and blood glucose	25
Prednisolone	Salbutamol	unknown	Minor	____	No action required	19
Clarithromycin	Prednisolone	PD	Moderate	Clarithromycin increases the blood level of prednisolone	Monitor side effects:depression,high BP. and blood glucose	14
Gentamycin	Ampicillin +Sulbactam	PD	Moderate	Ampicillin reduces the effect of gentamycin	Monitor therapy	12

DDIs = drug-drug interactions; PD = pharmacodynamics; PK = pharmacokinetic; BP = xxxxxxxx.

In the literature, the studies that evaluated more than one DDI software program usually emphasized the difference between each software program that was compared, especially on their severity classifications. However, the three DDI software programs evaluated in the present study had similar classification

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Table 5. Most frequent five DDIs in Medscape

Drug A	Drug B	M. Of Interaction	Severity	Clinical Significance	Recommendation	Frequency
Salbutamol	Ibuprofen	unknown	Monitor closely	Ibuprofen increase and salbutamol decrease serum K	Use caution	20
Prednisolone	Ibuprofen	PD (synergism)	Monitor closely	Both drugs increase the risk of GI ulceration	Use caution	14
Gentamycin	Ibuprofen	unknown	Monitor closely	Ibuprofen increase and gentamycin decrease serum K	Use caution	4
Gentamycin	Midazolam	PK	Monitor closely	Midazolam reducesthe effect of gentamycin	Use caution	3
Levothyroxine	Furosemide	PK	Minor	Increased toxicity of levothyroxine	no action need	1

PD = pharmacodynamics; PK = pharmacokinetic.

Table 6. Most frequent major DDI in all tools

Drug A	Drug B	M. Of Interaction	Severity	Clinical Significance	Recommendation	Frequency	DDI Checker
Ipratropium	Cetrizine	PD	Major-X	Enhance the anticholinergic effect	Monitor for anticholinergic related toxicity (urinary retention, constipation, tachycardia)	1	Lexicomp
Pethidine	Tramadol	PD	Major-D	Enhance the CNS depressant effect of opioid analgesics	Monitor CNS depressant	1	Lexicomp
Ondansetron	Phenytoin	PK	Major-D	Increase the metabolism of ondansetron	Consider therapy modification	1	Lexicomp
Captopril	Spironolactone	PD	Major –C	Enhance the hyperkalemia effect of ACEI	Monitor therapy	1	Lexicomp
Fluticasone	clarithromycin	PK	Major	Increase side effects (high blood pressure,weight gain)	Avoid combination	1	Drugs.com
Furosemide	Gentamycin	PD	Major	Increase side effects of gentamycin (hearing loss, kidney problems)	Avoid combination	5	Drugs.com
Pethidine	Tramadol	PD	Major	Increase side effects (respiratory distress,coma)	Avoid combination	2	Drugs.com
Spironolactone	Captopril	PD	Major	Increase the level of blood potassium	Avoid combination	1	Drugs.com
Prednisolone	Clarithromycin	PK	Serious	Increase prednisolone effects	Use alternative	18	Medscape
Gentamicin	Furosemide	PD	Serious	Increase ototoxicity ad nephrotoxicity	Use alternative	2	Medscape
Pethidine	Tramadol	PD	Serious	Increase sedation	Use alternative	1	Medscape

systems when assessing the clinical consequences of each possible DDI [1].

A retrospective cross-sectional study assessed the occurrence of pDDIs in the pediatric population. The prevalence and nature of pDDIs have been reported in 384 pediatric patients. The study revealed that the overall prevalence of at least one pDDI per patient was 45.8% [12].This is comparable to the Feinstein et al. study, in which 49% of pDDIs in hospitalized pediatric patients were also reported [7]. In our study, the number of interactions that occurred according to Lexicomp, Drugs.com, and Medscape was (27.8%), (24.5%) and (23%), respectively, which is in contrast to the two studies mentioned above low. This difference in prevalence may be attributed to the difference in disease type and the number of medications used during hospitalization, where most of our patients were neonates and infants. In our study, the most common diagnosis was fever, followed by pneumonia. In contrast, in Feinstein et al. study, respiratory system diseases and congenital anomalies were among the most common diagnoses [7]. Additionally, nearly 70% of patients in Feinstein et al. had at least one category of complex chronic conditions, which could have contributed to the higher incidence of pDDIs.

In 2020, two studies independently found that the prevalence of pDDIs was 42%. The first study examined 510 pediatric inpatients using Lexi-interact to check for pDDIs and reported this finding [13]. The second study examined 88 pediatric inpatients in a Mexican hospital and found that 42% had some form of pDDI using Micromedex [14]. Our study found a lower prevalence of pDDIs than both studies, with only 27.8% of pediatric patients showing pDDIs based on Lexicomp. However, it is worth noting that our study included pediatric patients under 12 years old and most young children (57 %) recorded pDDIs in our study. The difference in prevalence between our study and the others may be attributed to the fact that most of our study population consisted of neonates, while mentioned studies included pediatric patients up to 18 years old [13-14].

The other result of this study showed that the age group has a statistically significant association with pDDIs which occurred more frequently in the 2–6 years age group than any other age group of pediatrics ($P < 0.029$) [12]. These findings were similar to our results in that there is an association between the presence of interactions and the age groups in three different tools, similar to ours; most of the interactions occurred in young children ($P < 0.05$).

Our findings regarding the mechanism of interactions showed that there is no significant association between the presence of interactions and the mechanism in all interaction checker tools ($P > 0.05$), with the most frequent mechanism being pharmacodynamics in Lexicomp, Drugs.com, and Medscape (45.3%), (55.3%) and (38.5%), respectively. In contrast to these findings, a study performed in 2016 concluded that pharmacokinetics interactions were the most frequent interactions among their patients [12].

Of 176 patients with at least one pDDI, major interactions were found in 19.9% (n = 35) of pediatric patients [12]. These findings were higher than Ismail et al., in which overall interaction was 25%, and major interaction was 10.7% (n = 43) [15]. However, they were less than the results of Feinstein et al., which found exposure to the major interaction of pDDIs in 41% of pediatric patients [7]. These studies contrasted our study, in which only 2.2% of interactions were major regarding Lexicomp, and 3.9% and 20.1% were major interactions in Drugs.com and Medscape, respectively.

A study conducted on pediatric inpatients across pediatric wards and intensive care units found that the average number of medications per prescription/patient was 9.0±4.8 and 8.7±5.2, respectively. This study reported that the prevalence of D and X interactions was 10.2% and 14.6% for pediatric wards and pediatric intensive care units, respectively, according to Lexicomp [16].

In contrast, our study found a lower mean number of medications used per prescription (3.6 ± 2.0), and a lower incidence of major interactions (D and X), recorded at 2.2%, according to Lexicomp. However, Medscape reported a higher rate of major interactions, with 20.2% classified as major. These differences in the drug-drug interactions may be due to different software used to detect pDDIs, the age of the patients, and the number of medications used per prescription.

According to the Bebitoglu et al. study in 2020, the most common pDDIs involved clarithromycin 37 times, mainly with budesonide and methylprednisolone [13]. Similarly, our study found that clarithromycin interacted 49 times, mainly with budesonide

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(n=23) and prednisolone (n=16), and was responsible for 27% of all the pDDIs analyzed using Lexicomp.

In addition to our study, in previous studies, clarithromycin and corticosteroids have been reported as drugs that often interact with other medications. A study on pediatric inpatients noted that these two drugs were involved in the most prevalent moderate drug interactions [17]. Similarly, another study conducted in an intensive care unit in India found that clarithromycin and hydrocortisone were among the drugs that frequently interacted with other medications [18]. As shown in our study and previous research, clarithromycin and corticosteroids may pose a risk for pDDIs.

Pharmacists are essential in identifying and preventing drug interactions in developed healthcare systems. They help ensure patients are informed about drug interactions and their possible side effects and can manage any harmful effects through interventions on either patient or prescriber level [19].

The American Academy of Pediatrics in 2003 proposed that including a pharmacist in the critical care team could help decrease medication errors. There is strong evidence to support the involvement of pharmacists as members of the health care team for pediatric patients. Yet this practice remains uncommon in many developing countries [20].

Despite the availability of electronic drug interaction screening systems, health professionals may still fail to detect potentially harmful combinations. Prescribers and pharmacists must possess the necessary drug interaction knowledge to identify potentially harmful combinations correctly, evaluate the risks for specific patients, and take action to minimize the risk of harm if appropriate [21]. Computerized provider order entry in electronic health record (EHR) systems has been identified as one of the interventions with the most significant potential to reduce medication errors and associated harm in the pediatric inpatient setting [22].

This is the first study that evaluates three different tools for detecting DDI in pediatric patients in North Cyprus. Relatively a representative large sample of patients was involved in the study. Despite this, the study has some limitations. One of the major limitations of this study is that some factors that may affect the prevalence of interaction were not considered, such as patient weight, genetic factors, major organ function status, and drug compliance.

Another area for improvement is that this study took place in a single hospital, so the findings may not be generalized, and it covered only drug-drug interactions. Drug-food and drug-herbal interactions also were not assessed in this study.

4. Conclusion

Hospitalized pediatric patients are commonly exposed to pDDIs, but the subsequent probability of occurrence and magnitude of patient harm requires further empirical substantiation. Although our data showed low prevalence rates of severe DDIs, life-threatening interactions may develop. Though Medscape detects more major interactions than the other two databases, Lexicomp was the most inclusive of all three databases and was more user-friendly and better guided to clinical recommendations than the others. Collaborative approaches involving pediatricians and clinical pharmacists and sharing the data of prevalence studies are needed to address pDDIs when prescribing medications to pediatrics and consider multiple databases.

Conflict of Interest

The authors declare no conflict of interest.

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Statement of Contribution of Researchers

AA: supervised the study and coordinated the participation of other contributors.

RD: directed the study, participated in the study design and data collection, performed the statistical analysis and writing the manuscript.

DA: participated in writing the manuscript, reviewing and improving the manuscript.

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