T.C.

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DEPARTMENT OF CLINICAL PHARMACY

EVALUATION OF DRUG-DRUG INTERACTION CHECKERS ALONG CLINICALLY RELEVANT ADVERSE DRUG EVENTS IN ONCOLOGY AND HEMATOLOGY PEDIATRIC PATIENTS

MASTER THESIS

Adnan Aleklah, M. Pharm

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APPROVAL

This thesis has been deemed by the jury in accordance with the relevant articles of Yeditepe University Graduate Education and Examinations Regulation and has been approved by Administrative Board of Institute with decision dated ..... and numbered .....

Prof. Dr. Bayram YILMAZ

Director of Institute of Health Sciences

DECLARATION

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which has been accepted for the award of any other degree except where due acknowledgment has been made in the text.

Date

Signature

Name Surname

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DRPs	Drug-Related Problems
DDIs	Drug-Drug Interactions
FDA	Food and Drug Administration
EMA	European Medicines Agency
PD	Pharmacodynamic
PK	Pharmacokinetic
MAO	Monoamine Oxidase
ADRs	Adverse Drug Reactions
GFR	Glomerular Filtration Rate
ICU	Intensive Care Unit
MTX	Methotrexate
CNS	Central Nervous System
BMT	Bone Marrow Transplantation
CINV	Chemotherapy-Induced Nausea and Vomiting
CDSS	Computerized Decision Support Systems
BNF	British National Formulary
AI	Artificial Intelligence
LLM	Large Language Model
SPSS	Statistical Package for the Social Sciences

ABSTRACT

Evaluation of Drug-Drug Interaction Checkers Along Clinically Relevant Adverse Drug Events in Oncology and Hematology Pediatric Patients

Background and Objective: Pediatric patients are vulnerable to drug-drug interactions (DDIs), studies on Pediatric patient are generally limited particularly in Hemato-Oncology patients, the aim of this study is to evaluate the performance of DDIs checkers, along with most frequent DDIs and its prevalence.

Materials and Methods: A retrospective observational study was conducted at the Yeditepe Hospital's Oncology Center from 2019 to 2023. Two different tools, Drugs.com and Lexicomp were utilized, and the agreement between these tools was assessed using the Kappa value. Tools' sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) was determined to evaluate the accuracy of these tools compared to Stockley's interaction book. The Spearman correlation test to compare the length of hospitalization with exposure to DDIs. Statistical significance was defined as a p-value of < 0.05. Logistic regression was performed to identify variables associated with the patients' final status and length of hospitalization (LOS). The consistency of ChatGPT was assessed using the Intraclass Correlation Coefficient (ICC). the study design was approved by an ethics committee. Statistical analysis was carried out using SPSS 25.

Results: A total of 155 patients were initially screened, with 80 met the inclusion criteria. Drugs.com and Lexicomp identified 752 and 473 unique drug-drug interactions (DDIs), respectively, resulting in an average DDI prevalence of 78%. Spearman was 0.79 and 0.85 for Lexicomp and Drugs.com, respectively. The Mann-Whitney showed a significant difference in DDI exposure between surviving and deceased patients. The performance of Lexicomp and Drugs.com revealed sensitivity values 0.5 - 0.77, specificity values 0.5 - 0.36, PPV values 0.31 - 0.36, and NPV values 0.31 - 0.77. The accuracy for both tools was 0.5, and Kappa value was 0.575. ICC for ChatGPT's consistency, showed a poor result with a Cronbach's Alpha of 0.630.

Conclusion: The study revealed that pediatric patients with hematologic oncology diseases are at a high risk of drug-drug interactions (DDIs). The accuracy of the tools used in this study was found to be moderate, and there was poor agreement between these tools.

Keywords: Drug interaction checker, Adverse effect, DDIs, Online software, Oncology

ABSTRACT (Turkish)

İlaç-İlaç Etkileşimi Kontrol Cihazlarının Onkoloji ve Hematoloji Pediatrik Hastalarda Klinik Olarak İlgili İlaç Yan Etkileri Üzerindeki Değerlendirmesi

Arka Plan ve Amaç: Pediatrik hastalar ilaç-ilac etkileşimlerine (İİE) karşı hassastır, pediatrik hastalarla ilgili çalışmalar genellikle sınırlıdır, özellikle Hemato-Onkoloji hastaları için. Bu çalışmanın amacı, İİE kontrol araçlarının performansını, en sık karşılaşılan İİE'leri ve yaygınlığını değerlendirmektir.

Materyal ve Yöntemler: Retrospektif bir gözlemsel çalışma 2019-2023 yılları arasında Yeditepe Hastanesi Onkoloji Merkezi'nde gerçekleştirildi. İki farklı araç olan Drugs.com ve Lexicomp kullanıldı ve bu araçlar arasındaki uyum, Kappa değeri kullanılarak değerlendirildi. Bu araçların doğruluğunu değerlendirmek için programların hassasiyetini, özgüllüğünü, Pozitif Tahmin Değeri'ni (PTD) ve Negatif Tahmin Değeri'ni (NTD) belirledik. İstatistiksel anlamlılık, $p < 0.05$ olarak tanımlandı. Yazılı onam alındı ve çalışma tasarımı bir etik kurul tarafından onaylandı. Hastaların son durumu ve hastanede kalma süresi (HKS) ile ilişkilendirilen değişkenleri belirlemek için lojistik regresyon yapıldı. ChatGPT'nin tutarlılığı, Intraclass Correlation Coefficient kullanılarak değerlendirildi. İstatistiksel analiz SPSS sürüm 25 kullanılarak gerçekleştirildi.

Sonuçlar: Toplamda 155 hasta başlangıçta tarandı, bunlardan 80'i dahil edilme kriterlerini karşıladı. Drugs.com ve Lexicomp sırasıyla 752 ve 473 benzersiz ilaç-ilac etkileşimi (İİE) tespit etti, bu da ortalama İİE yaygınlığını %78 olarak sonuçlandırdı. Spearman, Lexicomp için 0.79 ve Drugs.com için 0.85 idi. Mann-Whitney, hayatta kalan ve vefat eden hastalar arasındaki İİE maruziyetinde anlamlı bir fark gösterdi. Lexicomp ve Drugs.com'un performansı, hassasiyet değerlerini 0.5 - 0.77, özgüllük değerlerini 0.5 - 0.36, Pozitif Tahmin Değeri (PPV) değerlerini 0.31 - 0.36 ve Negatif Tahmin Değeri (NPV) değerlerini 0.31 - 0.77 olarak gösterdi. Her iki araç için doğruluk değeri 0.5, Kappa değeri ise 0.575 idi. ChatGPT'nin tutarlılığı için ICC, Cronbach Alfa'sı 0.630 olan zayıf bir sonuç gösterdi.

Çözüm: Çalışma, hematolojik onkoloji hastalıkları olan pediatrik hastaların ilaç-ilac etkileşimlerine (İİE) yüksek risk altında olduğunu gösterdi. Bu çalışmada kullanılan araçların doğruluğu orta seviyede bulundu ve bu araçlar arasında zayıf bir uyumsuzluk bulunmaktadır.

Anahtar Kelimeler: İlaç etkileşimi kontrol aracı, İstenmeyen etki, İİE, Çevrimiçi yazılım, Onkoloji.

1. INTRODUCTION

Over the past few decades, there has been an incredible surge in the number of medications approved, with over 20 thousand medications being reviewed and approved (1). Although, this represents a significant breakthrough in the healthcare industry, it is important to recognize that these discoveries can have dualistic nature, one side of the findings pertains to the potential benefits of therapeutic interventions, while the other side encompasses drug-related problems (DRPs) that may arise in the context of therapy. DRPs is defined as an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes (2). DRPs can involve various issues related to medication use, such as medication errors, drug-drug interactions (DDIs), adverse drug events, non-adherence, and inappropriate drug use (3).

DRPs such as drug-drug interactions (DDIs) have become a growing concern in clinical practice, DDIs are responsible for approximately 30% of adverse drug events and it has been reported to contribute to a mean incidence of 5.6% of inpatient deaths, making it the fourth leading cause of mortality. Moreover, the financial burden associated with ADRs is staggering, exceeding $136 billion in total costs. Urgent action is needed to address this critical issue and ensure patient safety (4),(5).

Although, The Food and Drug Administration (FDA), European Medicines Agency (EMA) and other authoritative bodies periodically release updated guidelines for pharmaceutical industries regarding DDIs studies, which essentially are conducted on healthy adult volunteers (6). However, limited studies have evaluated the drug interactions in oncology pediatrics patients due to the fact of ethical, methodological and logistical challenges. Therefore, Adult DDIs data's is extrapolated to pediatric patients without accounting age-dependent physiological changes that can alter Pharmacodynamic (PD) and Pharmacokinetic (PK) properties (7).

The risk of drug-drug interactions (DDIs) is prevalent in pediatrics Hematology and Oncology settings, primarily due to the high incidence of polypharmacy among patients. Furthermore, cancer patients commonly experience multiple comorbidities and a decline in hepatic and renal functions, rendering them more vulnerable to DDIs (8). In addition, the toxic nature of anticancer drugs, coupled with their narrow therapeutic index, and the frequent updates of guidelines and new anticancer agents that displace old regimens, considerably complicate the management of drug interactions. For instance, between 2016 and 2021, 207 novel chemotherapeutic agents were approved with 42% were introduced as first line therapy (9). Thus, healthcare providers face significant challenges in comprehending all possible drug interactions that their patients may experience. Therefore, effective strategies for managing DDIs, such as computerized drug interactions software are crucial to minimize serious ADEs resulted by DDIs (10).

The emergence of a computerized drug interaction software represents a significant breakthrough in the management of DDIs, providing healthcare providers with a powerful tool for optimizing medication regimens and reducing the risk of adverse drug events (11). However, huge discrepancies and alert fatigue have been observed between different software in term of their sensitivity, specificity, severity classifications and comprehensiveness. Even though, some studies used a standard to evaluate the sensitivity of different databases, the result were varied due to patients' status, populations, drug pairs, and the area these databases were used in (12)(13)(14).

1.1 Aim

In this study, the focus is on exploring clinically relevant drug-drug interactions (DDIs) in pediatric Oncology and hematology patients of Yeditepe hospital in Turkey and evaluating the performance of commonly used software using different gold standards and parameters. The investigation also includes the ability of the new artificial intelligence tool "ChatGPT" to detect DDIs in these patients. The research aims to assist healthcare professionals in making informed decisions when prescribing medication to pediatric oncology patients, helping to avoid potential drug interactions.

2. LITERATURE REVIEW

2.1 Drug-Drug interactions background

In the 1960s, it was believed that one of the first drug interactions with food was observed in patients taking monoamine oxidase (MAO) inhibitors as an antidepressant medication, they experienced acute attacks of hypertension, particularly after consuming cheese (15). Later, this phenomenon was attributed to the high levels of tyramine present in certain types of cheese and aged fermented products. Normally, our bodies eliminate tyramine by metabolizing it through the effect of intestinal and liver MAO enzymes. However, when MAO inhibitor drugs are present, the breakdown of tyramine is inhibited, leading to a build-up of this compound in the bloodstream. which can cause the release of norepinephrine, a neurotransmitter that is responsible for regulating blood pressure. The resulting increase in blood pressure can trigger a hypertensive crisis, this phenomenon was later coined the 'cheese effect' (16).

The term "drug interactions" is not limited to DDIs only, but extends to a wider range of interactions that can arise between drugs and concomitant agents, potentially altering the intended therapeutic outcome, unexpected adverse effects, therapeutic failure, or mortality. These interactions can be categorized into various types based on the causative agent, including: drug-drug interactions (DDIs), drug-food interactions, and drug-condition interactions (17).

DDIs can be further scientifically classified into two distinct categories Figure (1), pharmacokinetic (PK) interactions and pharmacodynamic (PD) interactions. PK interactions occur when the kinetic properties (absorption, distribution, metabolism, and excretion "ADME") of a particular drug are altered by the presence of another drug. On the other hand, PD interactions occur when the pharmacological properties of particular drug (Drug's Action) altered by the presence of another drug, leading to additive, synergistic, or antagonistic effects. Both PK and PD interactions are

resulting in changes in the intended therapeutic effect or in the manifestation of adverse drug reactions (18).

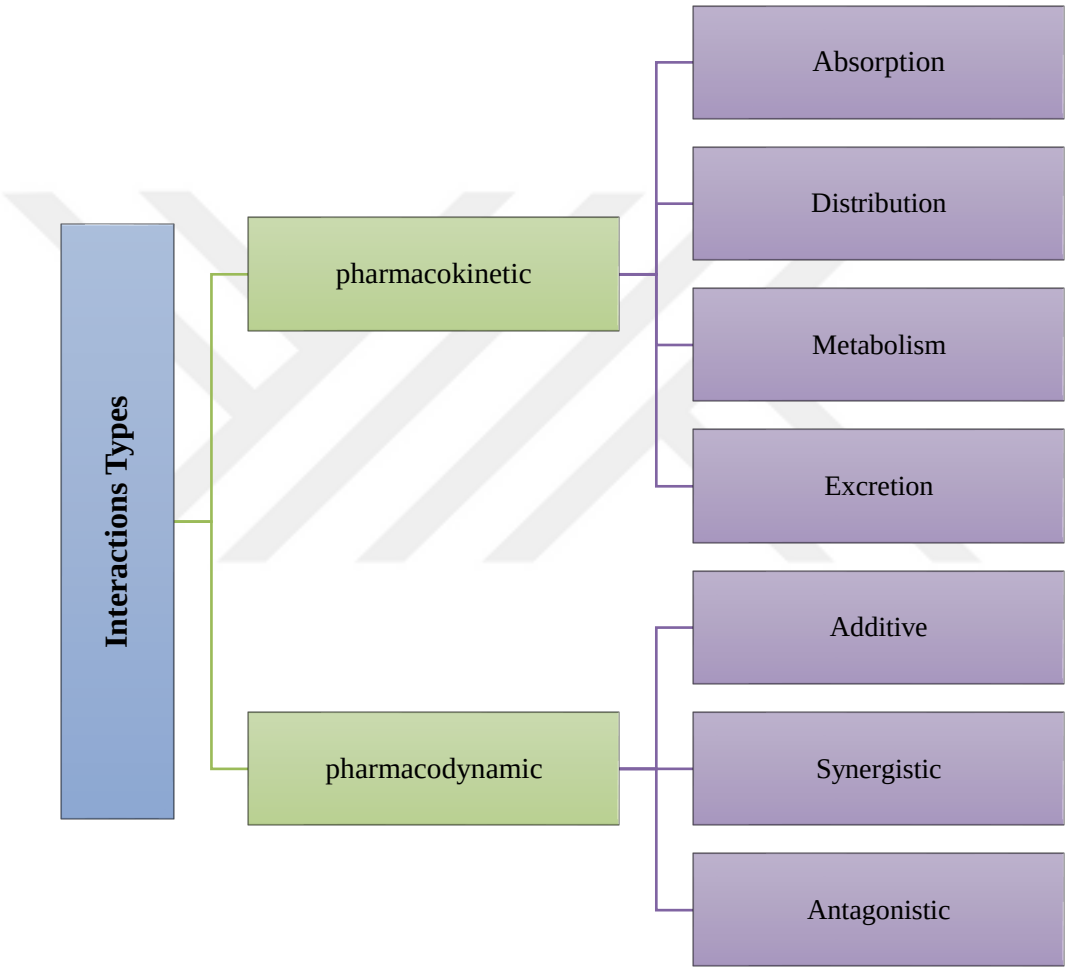

Figure 1 Drug-Drug Interactions Classifications

2.1.1 The Epidemiology of DDIs in Clinical Practice

It is imperative to note that not all drug interactions are clinically relevant, as some of the data regarding them is not supported by clinical or laboratory evidence. In fact, some of the reported drug interactions have been found to be theoretical in nature, and not actually observed in clinical practice. Clinical relevance interactions are those required medical interventions (19). Thus, it is important for healthcare professionals to be aware of the potential drug interactions and each case should be analyzed separately, as they can encompass a spectrum of outcomes, ranging from beneficial to even life-threatening interactions. Organic acid such as ascorbic acid with non-heme iron represents a well-known beneficial drug interaction, which is known to significantly enhance the absorption of iron. The mechanism behind this interaction involves the reduction of ferric to ferrous by ascorbic acid, resulting in the conversion of iron into its absorbable state (20).

Although 46% of drug-drug interactions (DDIs) appear to be preventable by proper patient centered practice and early detection. However, they still remain one of the main causes of increased hospitalization rates, cost and readmission (21). According to literature, DDIs are responsible for a significant proportion of adverse drug reactions (ADRs), accounting for 30% of total cases of ADRs (5). Notably, ADRs contribute to a considerable proportion of hospital-related mortality and morbidity, with one out of five deaths or injuries among hospitalized patients alone. This alarming statistic positions ADRs as the fourth leading cause of death, outranking several chronic diseases and accidents (4).

In community pharmacy, the prevalence of potential DDIs varies across different studies due to multiple factors such as differences in DDIs definitions, documentation, studied population, and settings. In a cross-sectional study conducted in Iran, the study aimed to examine the occurrence of drug interactions in medication prescriptions collected from various types of pharmacies, including community and hospital pharmacies. 34.5% of 765 medication prescriptions collected from community pharmacies showed at least one occurrence of drug interaction when analyzed using Lexi Comp on Desktop drug interaction software (22). In recent study conducted in Turkey aimed to investigate the

prevalence of potential drug-drug interactions (DDIs) in medication prescriptions collected from 50 community pharmacies. The study utilized a multiple drug interaction checking software to analyze 1000 prescriptions and found that 39% of the total prescriptions had at least one potential DDI (23). Within the Dutch community pharmacy setting, analysis of the pharmacy information system Pharmacom® revealed that 43% of prescription generated at least one drug safety alert (24) However, more recent studies have reported higher rates of potential DDIs. For instance, a study conducted in Nineveh Governorate-Iraq found that 57.6% of 1000 prescriptions gathered from community pharmacies had potential DDIs, which is much higher than the rates reported in the previous studies (25). In contrast, a study from Thailand reported a lower percentage of potential DDIs in gathered prescriptions at 27.9% (26). And 18.5% in Greece (27).

The prevalence of drug-drug interactions (DDIs) in the context of prescription dispensing at community pharmacies has been documented to range widely, from as low as 18% to exceeding 50% of the analyzed prescriptions. These variations in potential DDIs prevalence have been attributed to many factors; in a study aimed to measure the ability of pharmacists to detect potential DDIs in community pharmacy using simulated drug profiles has shown, a pharmacist with higher years of experience and education was able to detect more potential DDIs (28). Similarly, a study of simulated patient visits in Sudan found that community pharmacists demonstrated inadequate knowledge of drug-drug interactions (DDIs) in the presented scenarios (29). Another contributing factor of DDIs is ‘Prescribing cascade’ which is a frequent but often unrecognized issue in healthcare. This term describes a series of events that occur when a medication error including DDIs is misinterpreted as a new medical problem, resulting in addition of another medication to treat the problem (30).

2.1.2 Drug-Drug Interaction in Hospital Settings

Hospitalized and critically ill patients are at a greater risk of experiencing adverse drug events (ADE) resulted from DDIs than those in community pharmacies, primarily due to multiple factors as an increased in vulnerability, higher likelihood of multimorbidity and polypharmacy, and, unsurprisingly, advanced age (31),(32),(33). Polypharmacy is typically defined as the concurrent use of five or more medications by a patient, the prevalence of polypharmacy in literature is varied. In a large published study including 1,742,336 older adults, has shown a 44% prevalence of Polypharmacy in the studied participants and 80% in patients with more than 5 medications (34),(35). Although, Polypharmacy might be detected in safe regimen, it is still associated with higher risk of potential DDIs. As potential DDIs substantially increase as the number of prescribed medications rises (36) . Upon reviewing the literature, it is evident that the factors contributing to DDIs are often interconnected, which can influence one another, Ultimately leading to higher DDIs prevalence. for instance, multiple -morbidities as predictor of potential DDIs has been associated with higher Polypharmacy rate (37)(38).

The majority of drugs undergo hepatic metabolism and renal clearance as part of their normal excretion process. During these processes, drugs undergo chemical changes that may affect their action in the body (39). However, aging can significantly impact the pharmacokinetics and pharmacodynamics of drugs. In older individuals, there are alterations in the glomerular filtration rate (GFR) and hepatic metabolizing activity. These changes are attributed to factors such as decreased blood flow, organ size, and cytochrome P450 activity. Furthermore, aging can lead to changes in the activity and expression of receptors and channels, which can further impact the pharmacodynamic activity of drugs(40). These age-related changes can result in alterations in serum drug concentrations, an increased incidence of drug-drug interactions, and a higher risk of adverse drug effects in the elderly population.(41)

The prevalence and impact of drug-drug interactions (DDIs) in hospital settings have been found to vary significantly in the literature, an examination of data from the 1990s onwards clearly indicates a growing focus on drug interactions. By comparing the

findings of two reviews, one spanning the years 1990-2007 and the other 2000-2016, it becomes apparent that there has been a significant 13% rise in the prevalence of drug-drug interactions (DDIs) (42),(43). Although, a large study from Denmark, which included 12 public hospitals and recorded 945,475 general patients' admissions during the study period 2008-2016, it was found that 70% of patients experienced at least one DDI during their hospital admissions, The result of this study was not concomitant or even close to the previous review result, which covered the same period and reported a rate of 33%, indicating a substantial difference between the two studies (44). A consensus agreement on the administration of cardiovascular agents, antithrombotic medications, and antibiotics has been consistently associated with a higher incidence of adverse events, notably resulting in prolonged hospitalization, increased healthcare expenditures, and elevated mortality rates (45),(46). However non-standardized definitions of drug interactions, different methods, settings and clinical relevancy concept could be attributed to discrepancies between studies (47).

Intensive care unit (ICU) patients, being the most vulnerable among all inpatients, require meticulous medication management due to their high risk of drug-drug interactions (DDIs). In fact, ICU patients account for more than 64% of all DDIs occurrences across various inpatients settings (48). In this particular population, the risks associated with their critical conditions often outweigh the potential risks of drug interactions from physicians' perspectives. Therefore, healthcare providers often prioritize the management of their underlying conditions, recognizing that the benefits of administering necessary medications outweigh the potential risks of interactions(49), moreover, the list of medications and their dosages differ significantly from those used for other inpatient types due to the unique and critical nature of their conditions. Notably, there are 20 pairs of medications identified as responsible for more than 90% of DDIs that occur within the ICU setting(50).

2.1.3 Drug-Drug Interactions in Oncology-Hematology Pediatric Patients

Children encompass a diverse group, ranging from preterm neonates to post-pubertal adolescents, and should not be viewed as miniature adults. Their clinical presentation of disease often follows a distinct pattern compared to adults (51). Furthermore, they possess

physiological, pharmacological, and developmental features have not been completely unraveled yet (52). Their pharmacokinetic effects in this context may lead to the production of different metabolites, unexpected side effects, therapeutic failure, or drug interactions if all aspects are not taken into consideration (53). For example, in young children, the primary metabolic pathway for acetaminophen is sulfation, whereas in adults, the predominant mechanism for metabolic elimination is glucuronidation (54). Similarly, the phenomenon of paradoxical hyperactivity induced by phenobarbital is observed exclusively in children, attributed to variances in pharmacodynamics between pediatrics and adult populations (55).

Unlike adults, conducting clinical trials in this population is limited, clinical trials for pediatric patients often face various barriers, including ethical considerations such as the principles stated in the declaration of Helsinki for protection the rights of research participants, methodological concerns, and limited funding (56). Most pharmaceutical companies tend to prioritize funding adult trials, leaving only 12% of drug trials focused on pediatric patients. Consequently, data from adults are frequently extrapolated to children (57) (58).

In pediatric settings, it has been demonstrated that the potential rate of adverse drug events (ADEs) is three times higher compared to adults, irrespective of the cause (59). Similar to adults, the presence of poly-pharmacy among hospitalized pediatric patients is not unusual. Furthermore, multiple co-morbidities and chronic diseases are considered additional contributing factors to drug interactions, and both poly-pharmacy and co-morbidities have been associated with a higher prevalence rate in this population (60) (61).

In a retrospective study aimed at assessing the prevalence of drug interactions and the types of these interactions in 498,956 pediatric hospitalizations in the US, it was found that 49% of all hospitalized pediatric patients were exposed to a potential drug-drug interaction (PDDI). Among all hospitalizations, 5% involved exposure to a contraindicated PDDI, while 41% involved exposure to a major PDDI and 28% involved exposure to a moderate PDDI. The most common potential adverse drug events included additive respiratory depression, bleeding risk, QT interval prolongation, reduced iron

absorption/availability, central nervous system depression, hyperkaliemia, and altered diuretic effectiveness (60). Drug interactions occurrence in pediatric intensive care unit (ICU) is not better and often coincide with abnormal organ function, which is already prevalent in these patients due to their critical status and factors such as an organ dysfunction, chronic diseases, co-morbidities, and the necessity for a complex pharmacotherapeutic approach. These combined factors contribute to the complexity of managing medication regimens in ICU patients (62) (63).

In the realm of Oncology practice, the profound impact of drug interactions becomes evident, particularly when considering patients who are already experiencing serious side effects due to the toxic nature of chemotherapeutic agents, narrow therapeutic window, inter/intra-patient variability, organ dysfunction, and immunocompromised (64). When these factors are combined with drug interactions, it is clear that the resultant interactions cannot be underestimated. More importantly, over-the-counter medications, herbal remedies, and nutritional supplements can interact with anticancer and give rise to dire consequences, Considering the severe repercussions linked to both overdosing and undertreatment in this specific population, the potential outcomes can be fatal (65). Supplements such as St. John's wort, commonly used as an herbal antidepressant, and grapefruit juice, both pose significant risks when combined with chemotherapy. The fact that being derived from natural sources, patients may mistakenly perceive them as safe due to general public beliefs and often are overlooked by healthcare providers (66) (67).

When considering Vitamin C as a supplement widely consumed, known for enhancing the immune system and providing antioxidant benefits, it is generally assumed to be safe, Nevertheless, it is crucial to recognize that its interaction with Methotrexate (MTX). MTX is an antimetabolite chemotherapy agent used in oncology and autoimmune disorders. It exerts its action by inhibiting enzymes responsible for nucleotide synthesis, including dihydrofolate reductase, thymidylate synthase, and other enzymes. This inhibition of nucleotide synthesis prevents cell division(68). However, MTX is a weak

acid that is primarily excreted unchanged through urine and is soluble at higher pH values (alkaline) (69). Due to this reason, the administration of vitamin C will acidify the urine, leading to the precipitation of MTX crystals and consequently resulting in MTX-induced nephrotoxicity(70).

The types and distribution of pediatric malignancies differ significantly from those observed in adults and also vary among different age groups of children. Leukemias, myeloproliferative and myelodysplastic diseases constitute the most prevalent cancers in childhood, accounting for 34% of cases. Subsequently, central nervous system (CNS) tumors and miscellaneous intracranial and intraspinal neoplasms contribute to 23% of pediatric cancer cases. Following these, lymphomas and reticuloendothelial neoplasms represent approximately 12% of pediatric malignancies (71). figure (2)

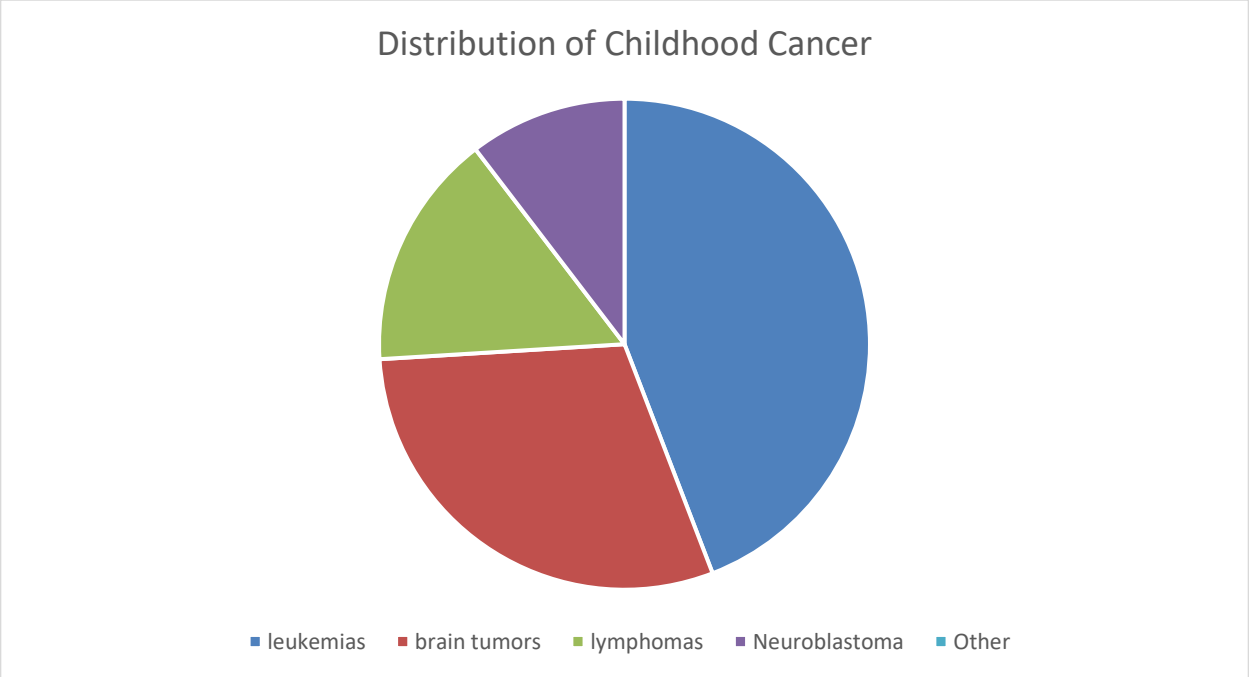

Figure 2 Childhood Cancer Distribution (71).

Seizures commonly occur during cancer therapy, particularly in children, either as a result of chemotherapy agents or due to the nature of cancer itself. Children diagnosed with cancer tend to experience seizures at a higher rate compared to adults (72). The majority of seizures are observed in children with acute leukemia, where they are often triggered by medications administered during bone marrow transplantation (BMT). Additionally, other oncological conditions such as lymphomas, neuroblastomas, and sarcomas are also associated with seizures (73). The majority of conventional anticonvulsant medications (such as phenytoin, carbamazepine, phenobarbital, and valproic acid) have the potential to either induce or inhibit CYP450 enzymes (74). When anticonvulsants are administered alongside chemotherapy drugs that are metabolized through the CYP450 system, it can lead to therapeutic failure or increased toxicity of these medications. A clinical trial revealed that, the use of phenytoin or phenobarbital caused a 1·5-fold increase the clearance of etoposide, this finding clearly implicates the involvement of hepatic cytochrome P450 enzyme systems in the metabolism of etoposide. (75).

Whenever feasible, alternative antiepileptic drugs that are less likely to interfere with drug-metabolizing enzymes (such as levetiracetam, gabapentin, and topiramate) should be taken into consideration.

Chemotherapy-induced nausea and vomiting (CINV) is a serious side effect of chemotherapy treatment that significantly impacts patients' quality of life. The use of antiemetic drugs can greatly alleviate patients' struggle (76); however, it also imposes the risk of drug interactions. Among these medications, Aprepitant and Dexamethasone are used in combination as valuable antiemetics. However, a clinical trial has observed a significant increase in dexamethasone plasma concentration when administered concomitantly with Aprepitant (77), Hence, it is recommended to reduce the dosage of dexamethasone when administered concurrently with Aprepitant, as Aprepitant has been observed to exhibit moderate inhibition of CYP3A4 during coadministration (78).

Table (1) presents a list of commonly used drugs in cancer patients, specifically focusing on their interactions with other medications. The table provides information regarding the type of interactions that can occur when these drugs are combined with other substances, such as concurrent chemotherapy agents, supportive care medications, or drugs used to manage comorbid conditions (79).

Table 1 list of commonly used drugs in cancer patients (79).

First Medication	Second Medication	Mechanism of Interaction	Increase / decreased activity of Chemotherapeutic agent
Allopurinol	Mercaptopurine Azathioprine	Inhibit clearance by blocking Xanthine oxidase activity	Increased Mercaptopurine/ Azathioprine Plasma Concentration
Omeprazole	Methotrexate MTX	Delay Methotrexate elimination	Increased MTX Plasma Concentration
Proton pump inhibitors PPIs and Antacid	Tyrosine kinase inhibitor (TKIs)	Interfere with absorption of TKIs	Decreased TKIs Plasma Concentration
Azole Antifungal	Vinca Alkaloid	Liver enzyme inhibitions	Increased Vinca Alkaloid Plasma Concentration
Azole Antifungal	Cyclosporin/Tacrolimus	Liver enzyme inhibitions	Increased Cyclosporin/Tacrolimus plasma concentration
Penicillin	Methotrexate	Interferes with MTX renal excretion	Increased MTX plasma Concentration

2.2 Managing Drug-Drug Interactions: Key Interventions

Pharmacists play a vital role in minimizing drug interactions by assessing patient profiles and suggesting appropriate medication adjustments. Online software enhances detection with real-time alerts and comprehensive drug databases. Artificial Intelligence analyses patient data to identify subtle interactions, aiding in personalized treatment plans. Together, these interventions optimize patient safety and treatment outcomes for those taking multiple medications.

2.2.1 Clinical Decision Support System and Digitalization of healthcare Service

It is undeniable that the emergence of computerized systems in healthcare facilities has been a groundbreaking transition, aiding stakeholders in making informed decisions and potentially reducing drug-related errors (80). Numerous computerized decision support systems (CDSS) have been designed to flag the potential drug-drug interactions (DDIs) among thousands of drug pairs, which surpasses the capacity of human memory. However, the utilization of Clinical Decision Support Systems (CDSS) has resulted in a phenomenon known as 'alert fatigue,' which arises from repetitive exposure to irrelevant alerts. Consequently, healthcare practitioners tend to be less receptive to these alerts as their frequency increases, especially when they are repeated (81).

Not all CDSS works similarly, as they showed differences in their performance. Upon reviewing the literature, the term performance or the best CDSS tool has many meanings based on the author, there is no crystal-clear definition of the best. Thus, evaluating drug interaction checkers is a challenging task, necessitating consideration of multiple factors. Numerous studies have been conducted to explore this subject.

In a comparative study that focused on three specific tools - the British National Formulary (BNF), Thesaurus, and Micromedex - the investigation assessed interacting drug pairs, severity rating, evidence rating, and clinical management recommendations. The study outcomes revealed inconsistencies and a lack of harmonization among the examined tools (82).

Not all CDSS works similarly, as they exhibit disparities in their performance and presentation of result. Moreover, an examination of the literature reveals that the term "performance" or the identification of the optimal CDSS tool carries diverse interpretations based on the author standpoints, as authors employ different methodologies and parameters to assess their effectiveness. Also, the difference in severity ranking has not been evaluated in many studies (14).

Four studies were conducted with the aim of identifying drug interactions software, specifically focusing on the most widely utilized tools, namely Lexicomp and Micromedex. It is noteworthy that a gold standard was employed to standardize the output of the tested tools, and variations were observed in the studied populations across these studies. The outcomes of these studies indicated discrepancies among the tested tools. Upon separate evaluation, the sensitivity and specificity values for Micromedex and Lexicomp were determined as follows: (0.36-0.43), (0.88-0.87), (0.83-1.0), and (0.53-0.72). (83), (84), (85), (86).

2.2.2 The Role of Clinical Pharmacists in Minimizing Drug Interaction Occurrence

The pharmacist, together with the prescriber, must guarantee that patients are informed about the potential side effects and the appropriate steps to take if they occur. Drawing upon their extensive understanding of medications, pharmacists can connect unforeseen symptoms reported by patients to potential adverse effects of their drug treatment. Clinical pharmacy practices additionally help reduce adverse drug reactions (ADRs) by avoiding medications with known side effects in vulnerable patients. Consequently, the pharmacist plays a significant part in preventing, detecting, and reporting ADRs including DDIs (87).

The significance of clinical pharmacists within the healthcare system is widely acknowledged. Regrettably, the role of clinical pharmacists remains inadequately established in numerous low- and middle-income countries (88). Notably, in Germany, the introduction of pharmaceutical care services in cardiology departments has yielded notable outcomes, including a reduction in drug-related events, decreased readmissions, and improved overall management (89).

The available evidence in literature indicates that integrating clinical pharmacists into the healthcare system leads to a decrease in the occurrence of potential drug-drug interactions DDI, improved adherence to therapy, and enhanced support for physicians in managing adverse drug events associated with DDI by identifying interactions that had gone undetected during routine clinical practice (90) (91). Likewise, in a study aimed to compare the clinical importance of DDI between CDSS and clinical pharmacist, a disparity has been identified between the existing local clinical decision support system (CDSS) and the current clinical practices (92).

Clinical pharmacist intervention in oncology practice has been shown to have a significant impact on various outcomes. This includes a reduction in unscheduled and emergency hospital admissions, as well as the early detection of side effects and drug-drug interactions (DDIs). Moreover, the involvement of clinical pharmacists has been associated with improvements in patients' quality of life and positive economic outcomes. These findings highlight the valuable role of clinical pharmacists in oncology care, emphasizing the importance of their intervention in optimizing patient outcomes (93) (94).

2.2.3 Artificial Intelligence (AI) In Healthcare

Artificial Intelligence (AI) is a broad concept encompassing the utilization of computers to emulate intelligent behavior, typically requiring minimal human intervention. The inception of AI is commonly attributed to the development of robots (95). AI is undergoing advancements in the realm of healthcare and biomedical literature.

Its emergence in healthcare is varied by enhancing the precision, problem-solving, and efficacy of decision-making processes. AI algorithms possess the capability to analyze extensive datasets, detect intricate patterns, and generate prognostications that surpass the capabilities of human (96).

The domain of artificial intelligence AI has witnessed a significant surge in growth and advancement in recent years, finding applications across various fields, including healthcare. Many initiatives have already started in molecular medicine, biochemistry, and cell biology. The pressing need for automation in these areas has led to the development of numerous machine learning models capable of identifying and classifying cellular and tissue damage, as well as predicting various biochemical processes and physiological mechanisms (97). While the integration of these models into current research and therapeutic protocols may require some time, a considerable number of scientists believe that artificial intelligence holds great promise in advancing toxicology-based methodological approaches(98).

Likewise, Pharmacovigilance is primarily focused on ensuring the safe and efficient utilization of medications while prioritizing public health and safeguarding patient safety by avoiding adverse effect of treatment including DDIs. A fundamental aspect of pharmacovigilance involves the systematic collection and comprehensive analysis of safety information associated with pharmaceutical substances (99). The employment of AI in pharmacovigilance in order to address drug interactions may enable healthcare providers to make quicker and well-informed decisions regarding patient safety and could predict potential interactions between new drug candidates and existing drugs by analyzing extensive data (100).

Dealing with a large language model (LLM) which is a type of artificial intelligence (AI) algorithm, it requires finely tuned queries "prompt" to obtain clear and scientifically accurate outputs. Prompts in AI are instructions or guidelines provided to an AI system, enabling users from various fields to customize its behavior (101). By crafting prompts effectively, users can enforce rules, automate processes, and ensure specific qualities and quantities of the generated output. Prompts can take the form of text-based instructions, queries, or descriptions, depending on the task at hand (102). They serve as a means of

communication between the expert and the AI system, guiding its behavior and enabling it to meet specific needs. Through the strategic use of prompts, users can leverage AI systems to streamline tasks and achieve tailored outcomes in their respective domains. This process is known as prompt engineering (103) (104) .

Among these LLMs is ChatGPT, it is a cutting-edge LLM and the fastest growing app in the internet history developed by OpenAI. It's a powerful learning model that has been trained extensively on a vast amount of text data from the internet. This extensive training enables ChatGPT to generate highly realistic and contextually appropriate responses in conversations. It has found applications in chatbots, virtual assistants, and other text-based interfaces, where it can provide human-like interactions and assistance (105).

The Department of Computer Science at Vanderbilt University in Tennessee recently published a paper describes a catalogue of prompt engineering techniques presented in pattern form that have been applied to solve common problems when conversing with learning models such as ChatGPT (102), to apply the prompt engineering concept, while utilizing ChatGPT for detecting drug interactions, based on the catalogue, it is crucial to formulate an appropriate inquiry that suits this task. This can be achieved by writing 'Act as (X),' where X represents the desired profession or persona for the model to assume. By providing a clear and specific input, we can minimize artificial hallucination and ensure the generation of excellent output (102).

Aysha et al. tested ChatGPT ability to detect drug interactions in 40 drug interactions pairs retrieved from literature, then each pair of the drugs were searched with two questions - “can I take X and Y together?” and “why should I not take X and Y together?’’ (106). And concluded that ChatGPT is a partially effective tool for predicting and explaining DDIs.

Consequently, it appears that Aysha et al. did not adequately consider the importance of crafting professional queries in their study. The structure of their questions was found to be vague and targeted towards customers rather than healthcare professionals. As a result, the lack of attention to crafting professional queries may have led to suboptimal responses or limited the model's ability to provide relevant and reliable information (102) (107).

3. MATERIALS AND METHODS

3.1 Study Design and Setting:

A retrospective observational study was conducted in Pediatric oncology hematology setting. for a period between 2019-2023.The data were gathered from patient files at the archive and electronic system records in Yeditepe hospital, for pediatric male and female who admitted and hospitalized.

Yeditepe University Koşuyolu Hospital, with approximately 35,000 m2 of closed area, has a capacity of 180 beds, including 6 intensive care units. It also comprises nine operating rooms and a medical staff of around 100 specialists and academic physicians

3.2 Study subjects

All the oncology hematology pediatric patient files of patients who have been hospitalized within the stipulated study period between Jan/2019 to Jan/2023 were considered.

3.3 Sample size and Sampling of the Study:

The total population of patients who have been hospitalized were 156 patients from 2019 till 2023. The estimated sample size (n=385) was calculated using the following:

SS=Z2 × p× (1 − p)/c2, where Z represents the confidence level (for example, 1.96 confidence level for 95%), p is the choice of estimated percentage (assigned 50%) and c is the desired level of precision, i.e., 0.05.[12]. For this, the minimum sample size is considered 385 and a random sampling approach will be used by which all patients' files are organized in order then the odd numbers are selected to review.

❖ **Inclusion**

The study comprised the following patient files:

- Patients hospitalized at oncology hematology center during the period from January 2019 to January, 2023.
- Prescriptions with 2 or more drugs.
- Patients aged less than 18 years.

❖ **Exclusion**

- Patients who their files were uncompleted or missing.
- Patient hospitalized less than 2 days

3.4 Data Collection Tools/Materials:

Data were obtained using Word Microsoft Office, which included demographic information on the patients, such as Age, Gender, length of stay, drug list including time and date of administration, number of drugs receiving during hospitalization and generic names of drugs.

3.5 Study procedure

All the medications administered to the patients which documented by nurses in ‘*’Medical treatment tracking form’’* during their hospitalization were assessed for potential drug-drug interactions using two different drug interaction tools: Lexicomp and Drugs.com. However, Onco-hematology patients often have extended hospital stays, making it impractical to check for drug-drug interactions (DDIs) on a daily basis. Instead, in this research, DDIs are assessed only on days when new medications are introduced. DDIs are considered significant with (C/D/X) Moderate/Major risk ranking in Lexicomp and Moderate/Major severity ranking in Drugs.com.

Additionally, ChatGPT was tested as tool for checking drug interactions.
The researcher was responsible for all screening and documentation processes.

3.6 Drug-drug interaction identification and categorization

3.6.1 Lexi-Interact:

Lexicomp drug interaction checker was used to check the interaction pairs. Lexicomp is produced by Wolters Kluwer Health. Lexi-comp is the most comprehensive medication resource, Lexicomp classified interaction levels into five categories (A, B, C, D, and X), with interaction levels X, D, and C being very important therapeutically and clinically significant, necessitating the modification of drugs and dosages or the avoidance of combinations Table 2

Table 2 Interaction levels categories by Lexicomp(108)

Risk rating	Action	Description
A	No interaction	No evidence of pharmacodynamic or pharmacokinetic interactions between the agents has been found.
B	No action needed	Data show that the listed drugs can interact with one another, however there is little to no evidence of clinical risk as a result of their concurrent usage.
C	Monitor therapy	Data show that the listed drugs can interact with one another in a clinically significant way. The benefits of taking these two drugs together generally exceed the hazards. To identify potential detrimental impacts, a suitable monitoring plan should be created. In a small number of patients, one or both drugs, dosages may need to be adjusted.
D	Modify regimen	Data show that the two drugs may have clinically significant interactions with one another. To establish if the advantages of concomitant therapy outweigh the dangers, a patient-specific assessment must be performed. Specific activities must be made in order to reap the benefits and/or reduce the toxicity caused by the agents; concurrent use. These efforts may include intensive monitoring, empiric dosage adjustments, and the Selection of alternate medications.
X	Avoid combination	Data show that the listed drugs can interact with one another in a clinically significant way. The dangers of using these medicines concurrently usually outweigh the benefits. These medications are typically regarded as contraindicated.

3.6.2 Drugs.Com:

Drugs.com is an independent online pharmaceutical encyclopedia, offering drug information for consumers and healthcare professionals in the United States. The website, owned by the Drugsite Trust, provides details on around 24,000 drugs and receives approximately 50 million monthly visitors. It operates on the IBM Cloud and ensures fast access to its content. The site's library includes data from reputable sources like Cerner Multum, FDA, Mayo Clinic, and others. Drugs.com is certified by TRUSTe and the HONcode for user privacy and credibility. It offers free subscription services, encompassing drug information, consumer resources, health professional database, natural products info, and poison control center. Table 3.

Table 3 Drugs.com Severity ranking(109)

Severity	Action	Description
Major	Avoid combination	The interaction is highly clinically significant, and the risk outweighs the benefit.
Moderate	Usually avoid combinations	It is moderately clinically significant; usage only in exceptional conditions.
Minor	No action need	Minimally clinically significant, assess risk and consider an alternative drug, take steps to circumvent the interaction risk and/or institute a monitoring plan.

3.7 Tools Concordance:

The degree of agreement between Lexicomp and Drugs.com tools is measured by Cohen's kappa coefficient where, the Kappa result be interpreted as follows: values ≤ 0 as indicating no agreement and 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41– 0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement (110).

3.8 Evaluating the Performance Tools Against the Gold Standard

To evaluate the performance of tools, we measure their specificity, sensitivity ositive predictive value (PPV), and negative predictive value (NPV). We then cross-check the major DDIs from Drugs.Com and (C/D/X) Major+ X Moderate DDIs from Lexicomp against Stockley's Drug Interaction book. Definitions of sensitivity and specificity, are given in table 4:

Table 4 Definitions of sensitivity, specificity

sensitivity	True Positive (TP) / True Positive (TP) + False Negative (FN)
specificity	True Negatives (TN) / True Negatives (TN) + False Positive (FP)

3.9 ChatGPT Consistency

The consistency of ChatGPT was measured by intra-rater reliability, and it was calculated by asking ChatGPT to answer the questions with the same format twice. This assessment aimed to evaluate how consistent ChatGPT's responses when presented with the same set of questions on two separate occasions. Both responses were analyzed to obtain

Cronbach's alpha that quantifies the level of agreement on a standardized 0 to 1 scale. Higher values indicate higher agreement between items.

procedure

20 prescriptions have been selected randomly from patients collected forms. The selected 20 prescriptions entered into ChatGPT twice to check the potential DDIs, the format of the question is established in accordance with prompt engineering principles. it was calculated by asking ChatGPT.

Question format:

''Act as a clinical pharmacist and check these medications out if there are any moderate or severe drug-drug interactions only, present answer in table. avoid explanations, unnecessary details, and non-interacted pairs: (prescriptions)''

3.10 Ethical Considerations:

3.10.1 Permission:

Ethical approval for this study was obtained from Non-Interventional Clinical Research Ethics Committee of Yeditepe University.

Approval number: E.83321821-805.02.03-131

3.10.2 Informed consent:

Because the files were reviewed retrospectively, informed consent was not

required for this research.

3.11 Statistical analysis:

The collected data was entered in Microsoft Office Excel 2016 and Statistical Package for the Social Sciences (SPSS) statistical software version 23. Descriptive statistics were employed to evaluate categorical data, which was presented in frequency and percentage. In addition, certain categorical data is shown in graphs using Microsoft Office Excel 2016. the Spearman correlation coefficient was used to assess the association between Length of Hospitalization (LOS) and the number of unique DDIs experienced by patients. Regarding the comparisons between variables Mann-Whitney U test, Logistic Regression. A p-value of < 0.05 was considered as statistically significant.

4.RESULTS

4.1 Patients Demographics:

During the selected period, there were a total of 155 pediatric patients hospitalized at the Oncology Hematology Center. According to the inclusion/exclusion criteria, only 80 patients were eligible.

46 (57.5 %) of the 80 patients were male, while only 34 (42.5%) were female. The mean age of patients is 6.48 years. The patients' ages were between 3 months - 16 years old with median 6 years, age divided into four groups, 0 - 23 months old ,2-5 years old, 6-11 years old and 12-18 years old respectively. 45% of patients were between 6-11 years.

The hospitalization period was divided into four groups: less than 10 days, 10-30 days, 30-90 days, and more than 90 days. In each respective group, 17 patients were hospitalized for less than 10 days, 12 patients for 10-30 days, 24 patients for 30-90 days, and 27 patients for more than 90 days.

Out of 80 patients enrolled in the study, 21.25% (n=17) cured, while 15% (n=12) dead, 61.25% (n=49) stable discharged and 2.5% (n=2) transferred. 8 deceased individuals had lymphocytic leukemia and Myeloid Leukemia. the cause of death was attributed to cardiac arrest, multiple organ failure, and neutropenic sepsis.

Detailed information about patients' demographics is in table 5

Table 5 Patients Demographics

Characteristics	Frequency	Percent %
Gender		
Female	34	42.50 %
Male	46	57.50 %
Age (years)		
0 - 23 months	7	8.75 %
2 - 5 years	25	31.25 %
6 - 11 years	36	45 %
12 - 18 years	12	15 %
Hospital stay LOS (days)		
< 10 days	17	21.25 %
10-30 days	12	15 %
30-90 days	24	30 %
> 90 days	27	33.75 %
Final status of patient		
Cured	17	21.25 %
Stable	49	61.25 %
Dead	12	15 %
Transferred	2	2.50 %

4.2 Diseases Distribution and Relation with Hospitalization Length:

Patient's diagnosis was classified based on International Classification of Diseases (ICD-10)- version: 2019.

Lymphoid leukemia and Thrombocytopenia were the most prevalent conditions, each accounting for 46.25 % of the cases, followed by Myeloid Leukemia and Aplastic Anemia, 10 % and 8.75 % respectively. Table 6

Table 6 frequency of oncology hematology diseases

Disease types	Frequency	%
Lymphoid leukemia	24	30 %
Thrombocytopenia	13	16.25 %
Myeloid leukemia	8	10 %
Aplastic Anemia	7	8.75 %
Malignant neoplasm of brain	6	7.5 %
Beta thalassemia	5	6.25 %
Non-Hodgkin lymphoma	4	5 %
Hodgkin lymphoma	3	3.75 %
Other types	10	12.5 %
Total	**80**	**100 %**

After conducting a normality test, it was established that the data exhibited a non-normal distribution. Consequently, the median was employed as the measure to assess the length of hospital stay. Patients with Aplastic Anemia and Lymphoid leukemia experienced the longest hospitalization durations, with median lengths of 103 and 100 days, respectively. Lowest hospitalization was seen in Thrombocytopenic patients with median 4 days. Table 7

Table 7 The Median Length of Hospitalization for most frequent diseases by Days

Disease types	**The Median Hospitalization Stay Duration (**Days**)**
Lymphoid leukemia	103
Thrombocytopenia	4
Myeloid leukemia	58
Aplastic Anemia	100
Malignant neoplasm of brain	21
Beta thalassemia	78
Non-Hodgkin lymphoma	79
Hodgkin lymphoma	15

4.3 Prevalence of Drug-Drug Interactions:

Assessing the prevalence of drug interactions using two different drug interaction databases, Lexicomp and drug.com. The results showed that, 81.25 % (65 patients) have experienced at least one drug-drug interaction during their treatment course based on Drugs.com evaluations and 75% (60 patients) by Lexicomp Evaluations figure 3.

Figure 3 Frequency of patients with DDIs detected each tool

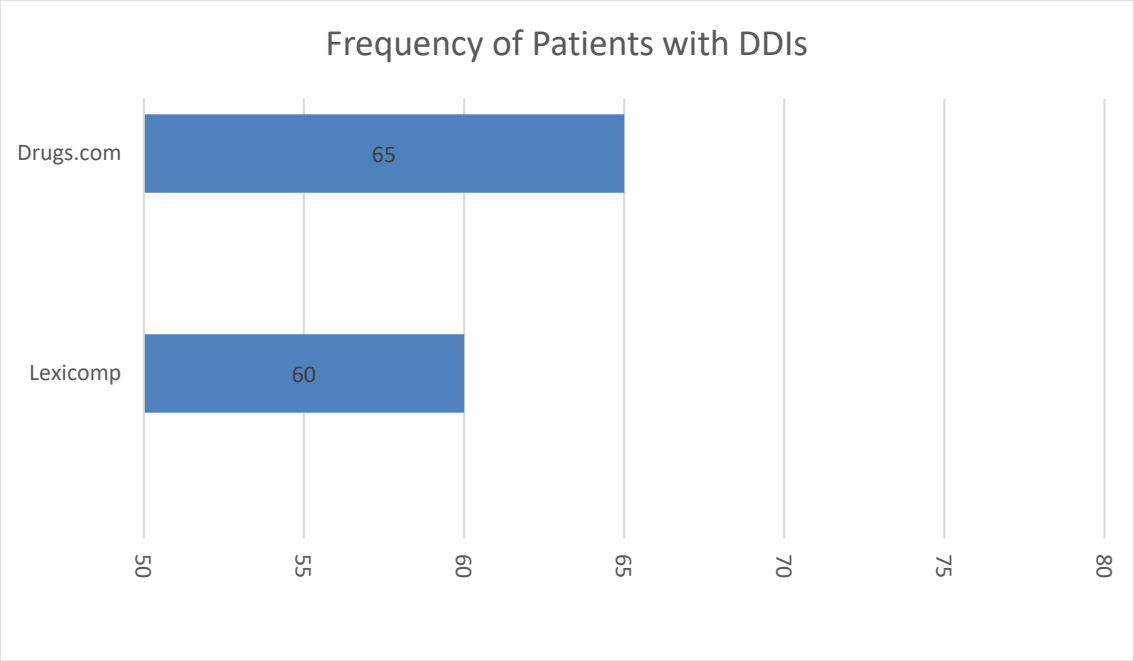

Figure 4, presents the number of unique drug-drug interactions (DDIs) detected by the tools. These unique DDIs were obtained after removing duplicated pairs. Drugs.com detected more unique DDIs than Lexicomp, with 752 and 473 pairs, respectively Table 8.

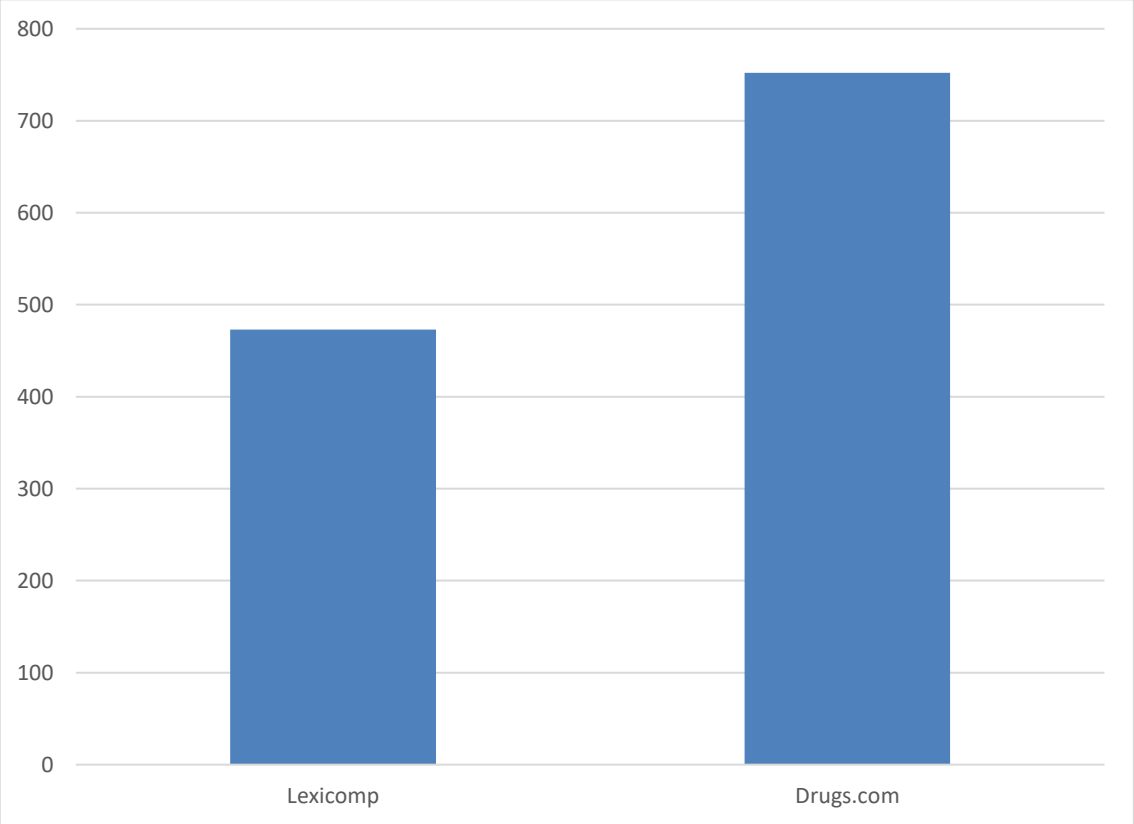

Figure 4 Number of unique DDIs Detected by each tool

Table 8 Drug interaction type and frequency by level of severity

Tools	Level	Frequency % (n)	Total
Lexicomp	Major (C/D/X)	16.84% (79)	473
	Moderate (C/D/X)	83.16% (394)	
Drugs.Com	Major	16.49% (124)	752
	Moderate	83.51% (628)	

4.4 Drug-Drug Interactions Relation to Hospitalization length

As the data were not normally distributed, the Spearman correlation coefficient was used to assess the association between Length of Hospitalization (LOS) and the number of unique DDIs experienced by patients.

There is a significant correlation between the LOS and the number of unique DDIs, regardless of whether Lexicomp or Drugs.com is used as the detection tool. (p-value < 0.001, Spearman correlation coefficient = 0.79) for Lexicomp and (p-value < 0.001, Spearman correlation coefficient = 0.853) for Drugs.com. Table (9), (10)

Table 9 Spearman Correlation between LOS and DDIs number by Lexicomp

			DDIs by Lexicomp
Spearman	**LOS**	**Correlation Coefficient**	0.79
		p-value	0.000

Table 10 Spearman Correlation between LOS and DDIs number by Drugs.com

			DDIs by Drugs.com
Spearman	**LOS**	**Correlation Coefficient**	0.853
		p-value	0.000

4.5 Patients Outcomes in relation to DDIs

A Mann-Whitney U test was conducted to examine whether there were significant differences in drug-drug interactions exposure by both tools with patients' outcome, specifically categorized as 'alive' or 'deceased'.

The results of Mann-Whitney U test indicated that, exposure to DDIs by Lexicomp and Drugs.Com was significantly higher in deceased patients (n=12) compared to alive patients (n=68), U = [94.5], z = [4.258], p = [<0.05] and U = [128], z = [3.786], p = [< 0.05] respectively.

4.6 Factors Associated with Patient Final Status and Length of Hospitalization

Binary and Multinomial logistic regression model were performed to see whether age and gender variables predict the odds of patient's final status and length of hospitalization with > 90 days hospitalization used as a reference, Table 11 and Table 12.

İt found that, there is a significant association between age and hospitalization period particularly 30-90 days period of stays.

Table 11 Binary Logistic Regression for patient's final status

					95% C.I.for EXP(B)	
Variables	**B**	**Wald**	***p*-value**	**OR**	**Lower**	**Upper**
Age	-0.008	0.009	0.924	0.992	0.848	1.161
Gender	0.04	0.004	0.948	1.042	0.300	3.617
Constant	1.76	7.069	0.008	5.856		

Table 12 Multinomial Logistic Regression for Length of Hospital Stay

Variables	**Reference > 90**	**< 10 Days**		**10-30 Days**		**30-90 Days**	
		OR (95% C. I)	***P*-Value**	**OR (95% C. I)**	***P*-Value**	**OR (95% C. I)**	***P*-Value**
Gender		0.77 (0.22-2.68)	0.691	0.7 (0.16-2.96)	0.637	0.64 (0.21-1.9)	0.445
Age		0.66 (0.31-1.41)	0.287	3.0 (1.1-8.1)	0.03	1 (0.505-1.99)	0.992

4.7 Most Frequent drug Interactions Among Patients:

İn this research, DDIs are considered significant with Moderate/Major (C/D/X) risk ranking in Lexicomp and Moderate/Major severity ranking in Drugs.com. Only the 25 most frequent DDIs among patients with both Lexicomp and Drugs.com are mentioned.

From the Lexicomp database, several significant interaction pairs were identified. Among them, (Allopurinol - furosemide), (furosemide - Dexamethasone) and (Voriconazole - Pantoprazole) were the most frequently encountered interactions occurred in 30 Patients with C-Moderate severity ranking. (Methotrexate - Pantoprazole) with D-Moderate severity ranking interaction has been noticed in 22 (27.5%) patients. (Cotrimoxazole - Metronidazole) and (Midazolam - Voriconazole) interaction is the most severe ranked DDI detected by Lexicomp and was seen in 19 (23.75%) and 17(21.25%) respectively of patients. The other frequent DDIs by Lexicomp are in table (11) and appendix.

On the other hand, from the Drugs.com database, (Furosemide - pantoprazole), (Amikacin - pantoprazole), (Voriconazole - pantoprazole) and (Dexamethasone - furosemide) were the most frequently detected interactions, occurring in 37(46.25%), 30(37.5%), 30 (37.5%) and 30 (37.5%) patients respectively. (ketamine - Midazolam), (furosemide - Amikacin), (Cyclosporine - Cotrimoxazole), (methotrexate - Pantoprazole) and (Amikacin - Privigen) are ranked as a major DDIs and were seen in more than 20% of the patients. The other frequent DDIs by drugs.com are in table (12) and appendix

Table 13 The most frequent DDIs detected by Lexicomp

First Drug	Second Drug	Severity Ranking	Frequency of DDIs among patients
Allopurinol	Furosemide	C Moderate	37.5% (30)
Furosemide	Dexamethasone	C Moderate	37.5% (30)
Voriconazole	Pantoprazole	C Moderate	37.5% (30)
Furosemide	Prednisolone	C Moderate	35% (28)
Furosemide	Methotrexate	C Moderate	32.5% (26)
ketamine	Midazolam	C Moderate	31.25% (25)
Amikacin	Furosemide	C Moderate	28.75% (23)
Methotrexate	Pantoprazole	D Moderate	27.5% (22)
Cyclosporine	Cotrimoxazole	C Moderate	27.5% (22)
Furosemide	Cyclosporine	C Moderate	26.25% (21)
Ondansetron	Voriconazole	C Moderate	26.25% (21)
ketamine	Voriconazole	C Moderate	25% (20)
Amikacin	Metamizole	C Moderate	25% (20)
Amphotericin	Furosemide	C Moderate	25% (20)
Cotrimoxazole	Metronidazole	X Major	23.75% (19)

Table 14 The most frequent DDIs detected by Drugs.com

First Drug	Second Drug	Severity Ranking	Frequency of DDIs among patients
furosemide	pantoprazole	Moderate	46.25% (37)
Amikacin	pantoprazole	Moderate	37.5% (30)
pantoprazole	Voriconazole	Moderate	37.5% (30)
furosemide	Dexamethasone	Moderate	37.5% (30)
furosemide	Prednisolone	Moderate	35% (28)
ketamine	midazolam	Major	31.25% (25)
Acyclovir	Cyclosporine	Moderate	28.75% (23)
furosemide	Amikacin	Major	28.75% (23)
Cyclosporine	Cotrimoxazole	Major	27.5% (22)
methotrexate	pantoprazole	Major	27.5% (22)
Cyclosporine	pantoprazole	Moderate	27.5% (22)
Amphotericin	pantoprazole	Moderate	27.5% (22)
ondansetron	Voriconazole	Moderate	26.25% (21)
furosemide	Cyclosporine	Moderate	26.25% (21)
Dexamethasone	Vincristine	Moderate	26.25% (21)

4.8 Measurement of Agreement Between the Tools:

To evaluate the concordance between Lexicomp and Drugs.com, we selected clinically relevant pairs that were identified as "X Major," "C Major," "D Major," and "X Moderate" on Lexicomp, and then matched them against pairs that were classified as "Major" on Drugs.COM.

Lexicomp identified 91 unique pairs, whereas, Drugs.Com detected 124 unique pairs. Only 33 pairs were identified by both tools. Table (13)

Table 15 Common Major DDIs between Lexicomp and Drugs.com

Tools	Lexicomp	Drugs.com	Total Pairs
Identified Exclusively pairs	91	124	182
Commonly identified pairs By both tools	33		

The kappa (κ) coefficient value of 0.171 showed that there is no agreement between the two tools (Lexicomp and Drugs.com). Table (14).

Table 16 Agreement between tools

	Value	Asymptotic Standard Error[a]	Approximate T[b]	P Value
Measure of Agreement Kappa	0.100	0.15	6.349	0.000

4.9 Evaluating the Performance and Agreement of Tools Against the Gold Standard

To evaluate the performance of tools, we measure their specificity, sensitivity, Positive predictive value (PPV), and negative predictive value (NPV) by cross-checking the Major DDIs from Drugs.Com and (C/D/X) Major+ X Moderate DDIs from Lexicomp against Stockley's Drug Interaction book.

The total number of selected DDIs is 182 pairs, the true and false DDIs by Lexicomp and Drugs.Com are presented in Table (15) and Table (16):

Table 17 Positive and negative DDIs by Lexicomp against Stockley's Book

	True	False
Positive	29	62
Negative	62	29

Table 18 Positive and negative DDIs by Drugs.com against Stockley's Book

	True	False
Positive	46	79
Negative	46	13

The sensitivity of Lexicomp and Drugs.Com against Stockley's interaction book were (0.5 - 0.77), the specificity are (0.5 - 0.36), PPV are (0.31 - 0.36) and NPV are (0.31 - 0.77) respectively. The accuracy was 0.5 for both tools.

4.10 ChatGPT Consistency:

Intraclass correlation coefficient (ICC) test for the intra-rater reliability analysis was calculated by asking ChatGPT to answer the questions with the same format twice.
Both responses from ChatGPT were analyzed to obtain Cronbach's alpha that quantifies the level of Consistency on a standardized 0 to 1 scale. Higher values indicate higher agreement between items. Table (17)

Table 19 Cronbach' Alpha Value

Cronbach's Alpha	Cronbach's Alpha Based on Standardized Items
0.608	0.630

6. DISCUSSION AND CONCLUSION

The present study aimed to investigate the characteristics of pediatric patients hospitalized in Hemato-Oncology department, as well as the prevalence of drug interactions identified using two different drug interaction databases, namely Lexicomp and Drugs.com. The study analyzed 156 patient files, out of which 80 met the inclusion criteria after excluding patients hospitalized for less than 2 days and those with incomplete files.

The demographic analysis of the 80 patients included in the study unveiled significant sex disparities in cancer incidence. A higher proportion of males (57.5%) were affected compared to females (42.5%); This finding aligns with previous research findings (111). The mean age of the patients was 6.48 years, with 45% falling into the age group of 6-12 years. The age range varied from 3 months to 16 years, with a median age of 6 years.

Regarding the hospitalization period, it was categorized into four groups: less than 10 days, 10-30 days, 30-90 days, and more than 90 days. Over 60% of patient has been hospitalized for more month.

In terms of patient outcomes, 21.25% of the enrolled patients were reported cured, 15% deceased, and 61.25% stable upon discharge. The causes of death in the deceased patients were attributed to cardiac arrest, multiple organ failure, and neutropenic sepsis.

Acute Lymphocytic Leukemia (ALL), Thrombocytopenia and Myeloid leukaemia were the most prevalent medical conditions, accounting for over 50% of the cases. Interestingly, patients with Aplastic Anemia and ALL experienced the longest hospitalization durations, with over 90 days Hospitalization, while patients with Thrombocytopenia had the shortest median hospital stay of 4 days.

The primary objective of the study was to investigate drug interactions by utilizing both the Lexicomp and Drugs.com databases. The prevalence of drug-drug interactions (DDIs) among patients was determined to be 76.25% according to Lexicomp and 81.25% according to Drugs.com. This finding demonstrates a higher prevalence when compared to the study conducted by Chelsea et al.(112), which included both adult and pediatric populations and assessed the prevalence of DDIs upon admission to Texas Children's Hospital for chemotherapy, revealing that 49% of admissions experienced at least one DDI.

Among the analyzed interactions, (Allopurinol - furosemide), (furosemide - Dexamethasone) and (Voriconazole - Pantoprazole) were the most frequently encountered interactions occurred in more than 30% of patients by Lexicomp. According to the Drugs.com database, interactions involving (Furosemide - Pantoprazole), (Amikacin - Pantoprazole), (Voriconazole - Pantoprazole), and (Dexamethasone - Furosemide) were the most commonly observed interactions, occurring in more than 30% of patients.

The calculated Cohen's κ coefficient of 0.171 indicates poor agreement between the two databases in terms of identifying major drug interactions. This suggests that the databases may yield different results when it comes to identifying significant interactions, which highlights the importance of using multiple drug interaction databases for comprehensive drug safety assessments. Furthermore, the sensitivity of the tools was assessed, and it was found that Drugs.com exhibited higher sensitivity than Lexicomp but had relatively lower specificity. These findings align with those in the literature, which have also reported significant variations among different drug-drug interaction (DDI) checkers (12) (13) (14).

In this study, the reliability of ChatGPT was evaluated, and it was concluded that the inconsistency in ChatGPT's responses undermines its reliability as a tool for detecting drug-drug interactions.

Overall, this study provides valuable insights into the characteristics of Hemato-Oncology pediatric patients and the prevalence of drug interactions in this population with evaluation of DDIs chekcers.

Limitation

It is important to acknowledge the limitations of this study. Firstly, we only included two freely available software tools commonly used in oncology departments, while other tools were not considered. Another limitation is that our study was retrospective in design, which means we had no opportunity to monitor vital signs, liver and kidney function that could potentially result from the effects of drug-drug interactions (DDIs).

Recommendation

In clinical practice, the issue of drug interactions is evolving with the introduction of new drugs and guidelines. To address this issue effectively, we recommend breaking it down into smaller tasks across various hospital settings. It is advisable to adopt a multidisciplinary team approach involving physicians, nurses, and clinical pharmacists, combined with the use of different online software. This approach aims to create a comprehensive and clinically evident reference list for significant drug-drug interactions (DDIs) in a specific setting. Subsequently, this approach can be extended to different hospital departments. For future work

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8.Appendices

Frequent DDIs deteceted by Lexicomp

prednisolone - Voriconazole	Mercaptopurine - Cotrimoxazole	Linezolid - Ondansetron
Cotrimoxazole - Ciprofaloxacin	Amphotericin - Prednisolone	Atgam - Fludarabine
Methotrexate - Cyclosporine	Enoxaparin - Metamizole	Defibrotide - Metamizole
Voriconazole - Dexamethasone	propranolol - Ciprofaloxacin	Amphotericin - Spironolactone
Amikacin - Vancomycin	Digoxin - Furosemide	Midazolam - Hydroxyzine
Cyclosporine - Amikacin	Dexamethasone - Metamizole	Amphotericin - dexamethasone
Midazolam - Voriconazole	Ciprofloxacin - Metamizole	Mercaptopurine - Methotrexate
Furosemide - Metamizole	Mycophenolate - Cyclosporine	Midazolam - Fluconazole
Ciprofloxacin - Prednisolone	Levetiracetam - Hydroxyzine	Cyclosporine - Spironolactone
Voriconazole - Metamizole	Cyclosporine - Cyclophosphamide	Dexamethasone - Fluconazole
Cyclosporine - Amphotericin	Amikacin - Ceftazidime	Ciprofloxacin - Spironolactone
Ceftazidime - Furosemide	Atgam - Cyclosporine	Amlodipine - Furosemide
Cyclosporine - Voriconazole	Fosaprepitant - Fluconazole	Captopril - Cotrimoxazole
Cyclosporine - Allopurinol	Ciprofloxacin - Dexamethasone	Captopril - Enoxaparin
Mycophenolate - Pantoprazole	Voriconazole - Methotrexate	Linezolid - Pheniramine
Atgam - Prednisolone	Captopril - Furosemide	Amikacin - cefepime
Amphotericin - Voriconazole	Clindamycin - Voriconazole	Voriconazole - Clarithromycin
Fluconazole - Ondansetron	Cyclophosphamide - Allopurinol	Amphotericin - Captopril
Mycophenolate - Ciprofaloxacin	Midazolam - Cyclosporine	Gantamicin - Furosemide
Acyclovir - Mycophenolate	propranolol - Metamizole	Doxorubicin - Cyclophosphamide
Enoxaparin - Defibrotide	Voriconazole - Fluconazole	Atgam - Cyclophosphamide
Levetiracetam - Midazolam	Cyclosporine - Metamizole	Digoxin - propranolol
prednisolone - Metamizole	Cyclosporine - Fluconazole	Atgam - Dexamethasone
Mycophenolate - Metronidazole	Methotrexate - Ciprofaloxacin	Cetirizine - Levetiracetam
Spironolactone - Furosemide	Amphotericin - propranolol	pheniramine - Hydroxyzine
Cetirizine - Pheniramine	Methotrexate - Levetiracetam	Digoxin - Amphotericin
Amphotericin - Ganciclovir	Cefepime - Furosemide	Cetirizine - Midazolam
cefixime - Furosemide	Midazolam - Metamizole	Captopril - Spironolactone
Furosemide - Hydrocortisone	Hydrocortisone - Voriconazole	Midazolam - Pheniramine
ketamine - Hydroxyzine	DiPhenhydramine - Levetiracetam	Spironolactone - Cotrimoxazole
Vancomycin - Metamizole	Linezolid - Metamizole	Cyclosporine - Fosaprepitant
Levetiracetam - Pheniramine	Cyclophosphamide - Fluconazole	Amlodipine - Voriconazole
Cyclosporine - Ganciclovir	Midazolam - Ciprofaloxacin	Colistimethate - Vancomycin
Digoxin - Cotrimoxazole	ketamine - Levetiracetam	tacrolimus - Prednisolone
Cetirizine - ketamine	Cyclosporine - Famotidine	Cytarabine - Metamizole
Cetirizine - Hydroxyzine	Amphotericin - Methotrexate	
Eltrombopag - Cyclosporine	Cotrimoxazole - Linezolid	

Frequent DDIs deteceted by Drugs.Com

Furosemide - Amphotericin	Cytarabine - Mercaptopurine	Allopurinol - Cyclophosphamide
Metronidazole - Voriconazole	fluconazole - Prednisolone	Fluconazole - Cyclosporine
Metronidazole - Ondansetron	fluconazole - Ondansetron	Vincristine - Asparaginase
Amikacin - Privigen	mycophenolate - pantoprazole	methotrexate - Voriconazole
methotrexate - Cyclosporine	Allopurinol - Cyclosporine	Ciprofloxacin - Methotrexate
Ciprofloxacin - Voriconazole	Cyclosporine - Metronidazole	Amphotericin - Prednisolone
Ciprofloxacin - Ondansetron	Ciprofloxacin - Vancomycin	Ciprofloxacin - fosaprepitant
furosemide - midazolam	Daunorubicin - Ondansetron	Clindamycin - Voriconazole
prednisolone - Voriconazole	hydrOXYzine - Voriconazole	Ciprofloxacin - Fluconazole
Amphotericin - Amikacin	Doxorubicin - Ondansetron	Amphotericin - Vancomycin
Acyclovir - Vancomycin	midazolam - Levetiracetam	Dexamethasone - Doxorubicin
Cotrimoxazole - Vancomycin	Cyclosporine - mycophenolate	methotrexate - Vincristine
propranolol - Furosemide	Vancomycin - Privigen	cyclophosphamide - Cyclosporine
Cyclosporine - Prednisolone	Ceftazidime - Cyclosporine	prednisolone - Asparaginase
propranolol - Voriconazole	Metronidazole - Hydroxyzine	Cyclosporine - Vancomycin
Amikacin - Vancomycin	furosemide - linezolid	Cytarabine - etoposide
furosemide - Vancomycin	fluconazole - Metronidazole	Ceftazidime - Amikacin
Cyclosporine - Amikacin	enoxaparin - defibrotide	Furosemide - Cefixime
Cyclosporine - Privigen	Amikacin - mycophenolate	propranolol - Dexamethasone
ondansetron - Hydroxyzine	cyclophosphamide - Metronidazole	cyclophosphamide - Mercaptopurine
Ciprofloxacin - Prednisolone	Paracetamol - Methotrexate	Cytarabine - Thioguanine
fluconazole - pantoprazole	Cotrimoxazole - Mercaptopurine	Metronidazole - fludarabine
Amphotericin - Cyclosporine	Cotrimoxazole - Asparaginase	Cytarabine - IDArubicin
Dexamethasone - Voriconazole	Ceftazidime - Cotrimoxazole	Ganciclovir - Amphotericin
furosemide - Hydroxyzine	captopril - Prednisolone	Ceftazidime - Amphotericin
Ciprofloxacin - mycophenolate	captopril - Cyclosporine	fluconazole - Voriconazole
Cyclosporine - Voriconazole	Furosemide - Digoxin	Amphotericin - Privigen
Acyclovir - Ceftazidime	Ciprofloxacin - Dexamethasone	Ciprofloxacin - Cyclosporine
propranolol - Prednisolone	furosemide - hydrocortisone	Metronidazole - mycophenolate
Ceftazidime - Furosemide	Vancomycin - mycophenolate	captopril - Furosemide
mycophenolate - meropenem	methotrexate - Dexamethasone	hydrOXYzine - Levetiracetam
midazolam - Voriconazole	Ciprofloxacin - Hydroxyzine	fluconazole - fosaprepitant

Curriculum Vitae

Personal Informations

Name	Adnan	**Surname**	Aleklah

Education

Degree	Department	The name of the Institution Graduated From	Graduation year
Doctorate			
Master	Clinical Pharmacy	Yeditepe Univeristy	2023
University	Pharmacy	Alexandria University	2018
High school	-		

[#] All the grades must be listed if there is more than one (KPDS, ÜDS, TOEFL; EELTS vs),

Languages	**Grades ([#]))**
Arabic	Native
English	TOEFL IBT 83
Turkish	Intermediate

Work Experience (Sort from present to past)

Position	**Institute**	**Duration (Year - Year)**
Pharmacist	Community pharmacy	2018-2019
		-

Computer Skills

Program	**Level**
Microsoft Office	Good

***Excellent, good, average or basic**