Evaluating Drug-Drug Interactions in Intensive Care Unit Patients of a Private Tertiary Hospital

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ABSTRACT

Objectives: In the Intensive Care Unit (ICU), numerous drug administrations were often overlooked in patients, which could result in drug-drug interactions (DDIs) with reduced therapeutic efficacy or severe adverse reactions. The study aimed to evaluate the DDIs that occurred with the recorded administered medications in medical charts of ICU patients.

Methods: This research was a quantitative, descriptive, cross-sectional study among 97 existing medical charts with at least two drug prescriptions dated from March 2023 to December 2023. It utilized a total enumeration sampling technique, eligible medical record had a designated number which was subjected to a random number generator. The Lexicomp® Database from UpToDate was used to review the DDIs. Determination of the prevalence of DDI, type of DDIs, severity, and intervention made were analyzed using frequency and percentage. The 95% confidence interval was also calculated.

Results: Among the analyzed records, the majority of the results revealed that the DDIs had a frequency of more than four per record, and only a few with 1-2 DDIs. The predominant type of DDI was synergistic. Majority were classified as moderate severity with recommended interventions of monitoring therapy.

Conclusion: This study revealed that the physician's capacity to recognize and manage DDIs should be emphasized wherein the majority of the detected DDIs were classified as moderate in severity that could potentially aggravate the health condition of ICU patients with their pharmacotherapeutic regimen. The detection of DDIs showed importance in maximizing the therapeutic strategy and safety of the patients.

Key words: Drug-drug interaction, intensive care unit (ICU), medications, interventions

The consecutive administration of various drugs raises concerns regarding the potential impacts on the result of the treatment. A complex web of interactions can occur when different medications are combined, resulting in unforeseen consequences that may range from reduced treatment efficacy to severe adverse reactions. Although there are several therapeutically beneficial drug interactions, there are also risks that should be observed. In cases of intensive care, where patients are subjected to different combinations of medications to address their conditions, the assessment of drug interactions takes on paramount importance. However, these can be overlooked due to insufficient knowledge of possible interactions of drugs commonly administered to intensive care unit (ICU) patients. Little to no involvement of clinical pharmacists in monitoring and managing patient medication may also pose an additional drug-drug interaction (DDI) risk. DDIs occur when various drugs affect one another. Based on its type, these

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interactions can result in either the ineffectiveness of the intended treatment or the emergence of severe, potentially life-threatening adverse drug reactions (ADRs), thereby posing substantial threats to patient safety, especially for those admitted to the ICU. Considering the various factors present in the ICU that influence the pharmacokinetics, such as issues with absorbing medications, slower metabolism, renal problems, and taking multiple drugs at once, the incidence of potential DDIs (pDDIs) is expected to be high. The lack of knowledge of the common drugs used in the ICU and their corresponding interactions as well as the inadequate training and interventions on DDIs may also contribute to its pervasiveness. Furthermore, when these interactions cause ADRs, it is associated with high morbidity and mortality rates, longer time spent in the ICU, and higher costs for these patients.

DDIs are considered to be one of the most highly reported prescribing errors worldwide.[1] A study in 2022 among 101 patients admitted to the ICU of a tertiary care hospital in Nepal, 490 different medication interactions were also noted, of which 311 (63.46%) were rated as moderately severe on the severity scale, while 303 (61.83%) were rated as category C in terms of risk (Ghimire et al., 2022). Wang et al. (2022)[2] found that anticoagulants and antiplatelet drugs were involved in a third of drug-drug interactions in the cardiovascular intensive care unit (CCU), with aspirin/clopidogrel being the most common and causing major severity. Other drug combinations like aspirin/nitroglycerin, aspirin/insulin, and methylprednisolone/insulin produced moderate severity. The interaction between moxifloxacin/amiodarone was one of the top 10 frequently occurring DDIs. Taking anticoagulant and antiplatelet drugs with nonsteroidal anti-inflammatory drugs can result in increased risks of bleeding. Similarly, analgesics, antifungals, antidiabetics, antithrombotics, beta-blockers, and ECA inhibitors were the 10 most involved drugs in potential drug-drug interactions in the ICU. The study suggests the need for careful monitoring of drug combinations and possible interactions in the CCU and ICU. In addition, the prevalence of DDIs among hospitalized patients is 9.2% (de Andrade Santos et al., 2020), with critically ill patients being particularly vulnerable to adverse events from drug interactions because they take multiple medications and are more likely to have multiple comorbid conditions, which can complicate the management of their medications.[3] A similar study was done in the Philippines, with pDDIs observed in 8% of drugs prescribed to adult Filipinos at the Family Medicine Clinic in a government hospital; 15% had pharmacokinetic interactions; and 74% of the drug pairs with pDDIs were pharmacodynamic.[4] As of now, the previously mentioned data is the only published local data. Thus, published local studies regarding DDIs and clinical pharmacists' interventions for ICU patients with DDIs are limited. In fact, the majority of the provided data is derived from case reports and articles about DDI incidents in non-invasive care settings. DDIs were also managed and involved a range of interventions tailored to patient factors and the nature of the interactions, with a focus on enhancing medication safety and minimizing potential risks. Monitoring strategies like adding gastric protection, conducting ECGs, and clinical monitoring to mitigate risks, as well as, increasing healthcare providers' knowledge of pharmacotherapy can reduce the occurrence of potential DDIs.[5] In addition, Siddiqui (2023) has noted that interventions for DDIs may also include prescribing alternative medications, adjusting doses, conducting lab tests to monitor drug effects, counseling patients and caretakers, and ensuring vigilant medication administration. Clinical pharmacists play a crucial role in the management of medications, and providing interventions to DDIs. They are also given opportunities to contribute, identify, and prevent ADRs. 26% of all ADR-related hospital admissions are caused by DDIs and interventions of clinical pharmacists in various treatments showed a positive impact on hospitalized patients.[6] In fact, with clinical pharmacists' interventions, preventable adverse drug events (ADE) decreased by 66% from 10.4 per 1000 patient-days to 3.5/1000 patient-days. Furthermore, ADEs in ICUs also decreased from 33 to 11.6 per 1000 patient days.[7]

This study aimed to evaluate DDIs in ICU patients within a tertiary private hospital. The research focuses on determining the frequency, type, and severity of DDIs that can occur in the combinations of drugs given to ICU patients, and identifying the interventions done by the clinical pharmacists to address the DDIs that can occur in the ICU. The medical documents were created by the Antimicrobial Stewardship (AMS) and Unit Dose Drug Distribution (UDDS) teams of the Pharmacy department of the said hospital. The UDDS is involved with the profiling of the patients. Included in this profile are the drugs that the ICU patients take for 24 hours. The AMS, on

the other hand, is involved with checking the DDIs in which, upon the completion of the patient profile, the drugs are inputted in the UpToDate - Lexicomp® to check the DDIs of the patient. The significance of this study lies in its ability to enhance patient safety and improve medical care in the ICU by providing an analysis of DDIs. Understanding the incidence and severity of these interactions is vital for healthcare professionals. This knowledge enables clinicians to make better decisions to reduce risks linked to drug interactions and improve the quality of care in ICU patients leading to improved patient outcomes and safety.

MATERIALS AND METHODS

Study Design

This research used a quantitative, descriptive, cross-sectional design that utilized a retrospective review of patient medical records to assess drug-drug interactions (DDIs) among patients who were admitted in the Intensive Care Unit (ICU) of Far Eastern University- Nicanor Reyes Medical Foundation (FEU-NRMF).

Setting

This study was conducted using the medical charts of patients who were admitted to the ICU of FEU-NRMF Hospital from March 2023-March 2024. However, the obtained medical records were only from March 2023-December 2023 brought by limited manpower resources available for data collection during the later months of the study period. Inclusion criteria included medical charts of patients admitted to the ICU from March 2023 to December 2023 containing at least two documented drug prescriptions per day. Medical chart records with nonreadable and illegible handwriting were excluded from the study after extensive efforts to counter-check the information using the database of Lexicomp.

Variables

Data collected included the patient's age, sex, condition/s or illness, duration of ICU stay, medications or drugs administered per day, drug-drug interactions (DDIs), and interventions on the detected DDIs. DDIs were defined as pairs of drugs exhibiting interactions identified by the Lexicomp® database from UpToDate, which is also being used by the pharmacists in the FEU-NRMF Hospital. Multiple DDIs may be identified in the patient's medical chart, and these DDIs were categorized by the database according to type (additive, synergistic, antagonistic), and severity (minor, moderate, major). While interventions are the recommendations based on the Lexicomp® database with the DDIs detected including no action needed, monitor therapy, therapy modification, and avoid combination.

Data Sources/Measurement

For this study, the data were collected from the patient's medical records. The identified interacting drug pairs per medical chart were categorized as a frequency of 1-2, 3-4, and 5 & above. The patient's demographics (age, sex), severities of the detected DDIs, and interventions were analyzed using frequency and percentage. The 95% confidence interval was also calculated.

A multidisciplinary team, including the principal investigator and designated student researchers, accessed medical records to extract relevant data. A letter requesting access to medical records was submitted to the medical director, chief pharmacist, head of medical records, and head nurse of the ICU which was coursed through the Data Protection Officer. The letters contained the objectives of the study, the duration of the study, and the information to be gathered from these charts. Data collection involved recording patient demographics, medications, DDIs, severity of interactions, and clinical pharmacist interventions.

The Lexicomp® Database from UpToDate served as the primary tool for reviewing drug interactions. This database provided comprehensive information on drug dosing, interactions, and adverse effects, aligning with standard practice in pharmacotherapy.

Bias

Total enumeration sampling was employed to capture all eligible medical records of ICU patients from March 2023 to December 2023. This approach minimizes selection bias by ensuring all patients within the defined time frame were included in the study.

Study Size

Sample size was calculated based on the estimation of population of DDIs assumed to be 90.02%, (Abideen et al, 2014) with a maximum allowable error of 5% and a reliability of 90%. The minimum sample size required was 97 medical charts. This sample size ensured that adequate medical charts were collected and could represent the population even if total enumeration was employed.

Statistical Methods

Each medical record included in the study was assigned a unique alphanumeric code. This code was randomly generated and ensured that the data could not be traced back to individual patients, thereby maintaining confidentiality. All collected data were processed and encoded using Microsoft Excel 2019. To further protect the confidentiality and integrity of the data, the Excel file was encrypted and could only be accessed by the investigators involved in the study. The encrypted file was securely stored and is expected to be retained until the completion of the study course in May 2024.

In terms of data analysis, the prevalence of Drug-Drug Interactions (DDIs), types of DDIs, severity levels, and interventions made were examined using frequency and percentage calculations. Additionally, a 95% confidence interval was computed to provide a measure of the precision of the prevalence estimate.

Ethical Considerations

The study adhered to ethical guidelines and obtained approval from the Institutional Review Board of FEU-NRMF Hospital. Measures were implemented to safeguard patient confidentiality, including the use of anonymized data and encryption of files. Researchers disclosed any potential conflicts of interest to ensure transparency and research integrity.

RESULTS

Participants

The calculated minimum sample size for the present study comprises 97 medical records from patients in the ICU.

Descriptive Data

Among these 97 records, 41.23% were male patients while 58.76% were female patients. The patients' ages ranged from 27 to 99 years, with the majority falling in the 60 and above age group (Table 1).

Table 1. Patient's age

Age (in years)	n (%)
20 - 39	15 (15.46%)
40 - 59	30 (30.93%)
60 and above	52 (53.61%)
Total	97

Number of DDIs detected in the ICU in relation to the medical charts were tallied. Among the 97 medical records analyzed, the majority of the records had 5 and above DDIs detected followed by 3-4 DDIs then 1-2. There were 4 medical records that had no DDIs or were given the rating of "no interactions of risk level A or greater identified" (Table 2).

Table 2. DDIs in the ICU

	Frequency		
DDI	1-2 n (%)	3-4 n (%)	5 & Above n (%)
	23 (24.7%)	18 (19.3%)	52 (55.9%)
Total	93		

Main Results

Various types of DDIs are identified in the ICU. Based on the literature, DDIs are usually classified as additive, synergistic, and antagonistic. A total of 1,480 DDIs were classified wherein majority of them were classified as synergistic followed by antagonistic, then additive (Table 3).

Table 3. Types of DDIs in the ICU

DDIs	n (%)	95% CI
Additive	326 (22.03%)	(19.92) to (24.14)
Synergistic	777 (52.5%)	(49.96) to (55.04)
Antagonistic	377 (25.47%)	(23.25) to (27.69)
Total	1,480	

The severity of DDIs is discussed, with a total of 1,461 recorded from the medical charts. The majority of these DDIs exhibit a moderate severity, followed by minor, then major (Table 4). Additionally, a 95% confidence interval was employed to ascertain the upper and lower limits.

Table 4. Severity of DDIs

Severity of DDI	n (%)	95% CI
Minor	275 (18.8%)	(16.82) to (20.83)
Moderate	1062 (72.7%)	(70.41) to (74.97)
Major	124 (8.49%)	(7.06) to (9.92)
Total	1,461	

Out of the 1,461 detected DDIs, the majority of the DDIs received a risk category of C which refers to monitor therapy. It was followed by risk category B or no action needed while only a small percentage of the detected DDIs received a risk category of X which refers to avoid therapy combination (Table 5). These interventions were based on the database's recommendations and act as a guide to the personalized therapeutic recommendations of the pharmacist.

Table 5. Interventions for DDIs detected in the ICU

Interventions	n (%)	95% CI
No action needed	319 (21.8%)	(19.72) to (23.95)
Monitor therapy	916 (62.7%)	(60.22) to (65.18)
Consider therapy modification	183 (12.5%)	(10.83) to (14.22)
Avoid combination	43 (2.9%)	(2.08) to (3.81)
Total	1,461	

In the ICU, several types of DDIs were detected. The Top 5 DDIs are shown in Table 6. Drug pairs, Atorvastatin-Azithromycin and Clopidogrel-Atorvastatin, exhibited a moderate severity with a risk category of B which refers to no action needed, the Atorvastatin-Amlodipine exhibited a minor severity with a risk category of B which refers to no action needed, the Atorvastatin-Telmisartan-Amlodipine exhibited a minor severity with a risk category of B which refers to no action needed, and the Enoxaparin-Aspirin exhibited a moderate severity with a risk category of D which refers to consider therapy modification.

Table 6. Specific drug interactions

Interactions	n (%)	95% CI
Atorvastatin-Azithromycin	20 (1.4%)	(0.77) to (1.97)
Clopidogrel-Atorvastatin	20 (1.4%)	(0.77) to (1.97)
Atorvastatin-Amlodipine	18 (1.2%)	(0.66) to (1.80)
Atorvastatin-Telmisartan-Amlodipine	18 (1.2%)	(0.66) to (1.80)
Enoxaparin-Aspirin	17 (1.6%)	(0.61) to (1.71)
Total DDI	1,461	

DISCUSSION

Most of the medical charts had more than 4 detected DDIs (Table 2). In modern medicine, drug combinations have become increasingly significant, offering new opportunities for more effective and tailored patient care. In the study of Jonker et al. (2005)[8], drug combinations during intravenous administration of drugs are common. Additionally, patients in the ICU experience pain due to underlying illness or injury, recent surgical procedures, or other noxious stimuli caused by the different interventions, and for this reason, they are given pain medications on top of other medications. This practice introduces the possibility of interactions between these drugs, which can either enhance or counteract their intended effects. However, Tekin et al. (2016)[9] also elaborated that the efficacy and efficiency of these combination drugs are significantly influenced by how the specific medications interact. Consequently, a comprehensive analysis and quantification of potential drug interactions is of paramount importance. Additionally, research has shown that DDIs are more frequent in elderly patients who are hospitalized for a longer period, are prescribed a higher number of medications daily, and suffer from severe comorbidities (Murtaza et al., 2016). In this study, the age group most represented, making up 53.61% of the total sample, consisted of old adults, defined as those 60 years of age and older. This coincides with the study of Murtaza et al. (2016) wherein majority of the DDIs occurred in elderly patients. Young adults, those aged 20 to 30 years old, make up 15.46% of the overall sample, and comprise the age group with the lowest representation. The intricate interplay of DDIs manifests as a substantial contributor to an estimated 5% of hospital admissions, specifically in the geriatric cohort. This phenomenon arises from a confluence of factors, such as age-related alterations in pharmacokinetics and pharmacodynamics, that escalate the intricacy of therapeutic management.[10]

Most of the DDIs were classified to have the synergistic type of interaction, followed by antagonistic interaction, and then additive interaction (Table 3). In the study by Lee (2010)[11], drug interactions were categorized as synergistic, wherein the response is stronger than expected or may be more effective in achieving a desired outcome. Antagonistic interactions signify diminished combined effects wherein one drug counteracts or weakens the effect of the other drug. Additive interactions indicate a combined effect equal to the sum of the individual effects. These drug interactions are important since the efficacy of these drug combinations is significantly influenced by how specific medications interact.[9]

Majority of the DDIs were classified as moderate in severity, which meant considerable potential to deteriorate the patient's condition and may require medical treatment (Table 4). The results of the current study are similar to various research studies conducted among ICU patients.[12,13] A retrospective study by Ali et al. (2020)[14] identified 422 pDDIs, 66.6% of which were moderate interactions, followed by minor and major with 23.7% and 9.7%, respectively. However, the severity of DDIs, specifically among pediatric patients, was mostly of major severity.[15,16] According to González & Sinha (2021)[17], the extent of DDIs in pediatric patients may diverge from that in adults due to age-related physiological alterations affecting drug disposition or response, along with additional variables associated with the drug (e.g., dosage, formulation). Moreover, there have been reports of discrepancies between different drug interaction database programs.[18,19]

Risk ratings can also be seen in the Lexicomp ® database which serves as a guide for the interventions on the interactions of the drug pairs. It uses the letters A, B, C, D, and X. Drug pairs under the risk rating "A" are said to have no known interaction, and thus no interventions were recommended. However, other interactions may require monitoring the therapy, changing the therapy, avoiding the combination of drugs, or may not need any intervention. The majority of the DDIs detected were categorized as "C" (Monitor therapy), followed by "B" (No action needed), "D" (Consider therapy modification), and then "X" (Avoid combination) (Table 5). From the study of Aghili & Kasturirangan (2021)[20], drugs classified under the category of "C" require therapy monitoring. This may include monitoring of the patient's clinical outcomes, such as blood pressure, heart rate, blood glucose, serum electrolytes, and serum creatinine more frequently or more closely. In contrast, for DDIs categorized as "D" and "X" risk categories, the software recommends considering treatment modifiers and avoiding the combination, respectively. In a study by Siddiqui (2023)[21], modifications done after accepting the interventions included prescribing alternative medications, and adjusting to the lowest possible dose as per the needs of the patient. Clinical pharmacists may provide more tailored interventions for drug pairs with unique interactions, according to their expertise and their assessment of the patient's needs.

Interventions on DDIs come in different ways and may differ depending on patient factors. Different cases may require specific management to achieve optimum patient health care. Thus, these common interventions of DDIs might not be a management plan that fits all kinds of patients. The implementation of these interventions underscores the importance of close and comprehensive teamwork between healthcare professionals in assessing, overseeing, and controlling medication plans for severely ill patients.[20] Alternative regimens must be created depending on patient factors and disease patterns presented. In the study presented by Siddiqui (2023)[21], conducting periodic lab tests to monitor the drug effects can be done, as well as counseling caretakers and patients to be watchful and immediate reporting of any anticipated effects from DDIs were suggested. Additionally, vigilant monitoring of the administration of medications prone to interactions was done by the nurses to prevent errors. However, developing these new regimens can be resource-costly and time-consuming.[22]

The most common DDIs in the ICU were Atorvastatin-Azithromycin and Clopidogrel-Atorvastatin (Table 6). Both of these drug pairs had a moderate severity but no action was needed. The result of the study is aligned to a research conducted on DDIs by Sharma et al. (2014)[23], which identified atorvastatin-azithromycin as one of the most common interacting pairs. They related it to the fact that atorvastatin is one of the most commonly prescribed medicines in their study. Clopidogrel and enoxaparin, which are antithrombotics, also showed multiple interactions. A study by Rodrigues et al. (2017)[24] found that analgesics, antifungal, antidiabetics, antithrombotics, beta-blockers, and ECA inhibitors drugs were the 10 most involved in pDDIs in ICU of a Brazilian teaching hospital. Additionally, patients on antithrombotic or anticoagulant therapy are at higher

risk for DDIs (Guidoni et al., 2014). The specific drug interactions were of different severity and will require different interventions depending on its category.[20]

Limitations

As a retrospective study, the results may be altered by the inability to control confounding variables such as patients' age, sex, and comorbidities, which all can influence DDIs. The study also relies on pre-existing data where the focus is only on a single hospital where patient demographics, hospital protocol, and practices vary from one another and could potentially influence the DDIs observed. Furthermore, limitations from human typographical errors may give rise to inconsistency in data collection. The data gathered were from handwritten charts that were scanned to be accessed digitally; hence, the transfer of data can also lead to inaccuracy and change in interpretations. While efforts were made to minimize errors, human typographical errors cannot be ruled out.

Interpretation

The study shows a significant prevalence of drug-drug interactions (DDIs) in the ICU setting, with the majority of the medical charts showing multiple detected DDIs with moderate severity of these interactions, with majority categorized as synergistic interactions. The predominance of these interactions suggests a potential to aggravate patient health, requiring close monitoring and dose adjustments in their pharmacotherapeutic regimen. Notably, the study also aligns with previous literature emphasizing the complications of managing DDIs in ICU patients receiving multiple medications for pain management and treatment of underlying conditions. However, it was also observed that not all DDIs led to adverse events, as certain DDIs enhance the desired effects of some of the drugs administered, still requiring close monitoring. This was also described in the study of Niu et al (2019)[25], wherein DDIs can be beneficial and be used to optimize therapeutic outcomes.

Implications

Enhancing the capacity of clinicians to discern potentially detrimental DDIs assumes paramount importance in optimizing patient care, especially in geriatric populations where the chances are high. Given the multifaceted nature of DDIs, it is imperative to equip healthcare professionals with robust tools and resources to properly manage prescribed medications while minimizing adverse effects. To optimize patient therapy, healthcare professionals must utilize a comprehensive approach that encompasses several key strategies, such as carefully selecting medications based on factors like efficacy, potential side effects, cost, alternative medication, or tailoring the dosage treatment to the individual patient. Regular assessment and monitoring of the patient's response to the therapy allows for adjustments as needed. Furthermore, patient lifestyle modification and collaborative care to further complement the pharmacological therapy can enhance the overall treatment outcome and improve the quality of life of the patient while minimizing the risk of adverse effects.

CONCLUSION

This study highlights the prevalence and clinical significance of the nature of drug-drug interactions (DDIs) in the ICU setting, particularly among patients who are receiving multiple medications. Majority of the interactions found were classified as moderate in severity, meaning that they needed to be monitored and provided with intervention because they could potentiate negative health outcomes. Regarding the high proportion of DDIs within the institution, the establishment of a thorough DDI screening protocol in the ICU with the increased involvement of hospital pharmacists along with regular training can be done to identify potential interactions before administering medications. This study aligns with existing literature emphasizing the challenge in managing DDIs, especially in vulnerable groups such as the elderly, where age-related changes in medication response and physiological variations might make treatment even more difficult. Moreover, the results of the study underscore the significance of thorough collaboration among healthcare practitioners in evaluating, supervising, and managing pharmaceutical regimens, with customized treatments based on patient demographics and illness. Specifically, clinical pharmacists should assess DDIs, and recommend appropriate adjustments to therapeutic regimens. Their specialized training enables them to collaborate closely with physicians in order to mitigate risks associated with DDIs, thereby optimizing treatment outcomes and patient safety. However, it should be highlighted that putting these treatments into practice can be time-consuming and

resource intensive, requiring strategic planning for the allocation of resources and support to optimize patient-care outcomes. The retrospective design and dependence on previously collected data, highlight the necessity of interpreting the findings cautiously. However, the consequences are evident that there is a need to enhance physician's capacity to recognize and handle DDIs as crucial to maximizing patient care, especially in groups at risk for polypharmacy and related complications. In order to help healthcare practitioners navigate the complexities of drug interactions and minimize negative effects, it is necessary to develop robust tools and resources.

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