Open Access Research paper

ISSN: 2349-9818
March - April 2025, Vol. 12 (2), 22-33

Tropical Journal of Pharmaceutical and Life Sciences
(An International Peer Reviewed Journal)
Journal homepage: http://informativejournals.com/journal/index.php/tjpls

Potential and Clinically Significant CYP3A4 Mediated Drug Interactions in Hospitalized Patients: A Cross-Sectional Observational Study

Sai Keshava Reddy A[1], **Kiranmai Venkatagiri[2]***, Ambati Sandeep Reddy[2], Bhavya Sai Sakhamuri[2], Mitta Putta Pooja[2] and Ugandar RE[3]

[1]Associate Professor, Department of Pharmacy Practice, Santhiram College of Pharmacy, Nandyal, Andhra Pradesh, India
[2]Department of Pharmacy Practice, Santhiram College of Pharmacy, Nandyal, Andhra Pradesh, India
[3]Head Of Department of Pharmacy Practice, Santhiram College Of Pharmacy, Nandyal, Andhra Pradesh, India

ARTICLE INFO:
Received: 18th March 2025; **Received** in revised form: 29th March 2025; **Accepted:** 18th April 2025; **Available online:** 27th April 2025.

Abstract

Background:
Drug interactions occur due to the simultaneous administration of pharmacological agents that affect the efficacy of concomitant drugs.

Objective:
Estimate the prevalence of CYP3A4 enzyme-mediated drug interactions in a tertiary care hospital along with a focus on clinical significance.

Materials and Methods:
An observational cross-sectional study was conducted over three months. A total of 180 patients with polypharmacy and two or more CYP3A4-mediated drugs in the prescription were included. Data collected from patient case sheets and drug-drug interactions were analyzed using Micromedex, SuperCYP database, and literature along with consideration of personal habits (smoking and alcohol).

Results:
Among 180 patients, 132 CYP3A4-mediated drug interactions were noted. The prevalence of CYP3A4 interactions was 50.56%, with 40.56% being drug-drug interactions, 10.5% drug-alcohol interactions, and 1.66% food-drug interactions. The most common combination of interacting drugs and clinical factors associated with interacting drugs were reported. Clinically significant interactions were observed in 13 patients.

Conclusion:
We estimated the prevalence of CYP3A4 enzyme-mediated drug interactions both potential and clinically significant, and reported accordingly. The prescriber's understanding of CYP3A4-associated drug-drug

***Corresponding Author:**
Kiranmai Venkatagiri
DOI: https://doi.org/10.61280/tjpls.v12i2.172

interactions and the recognition of resultant consequences constitutes the primary approach for reducing patient distress, by timely interventions.

Keywords: Drug interactions, Cytochrome P450, CYP3A4, Drug metabolism, Potential interaction, Clinically significant interaction.

Introduction

Drug interactions occur due to simultaneous administration of pharmacological agents that will affect the efficacy of concomitant drugs. Outcomes of these interactions may vary clinically with some interactions causing serious adverse effects and some showing negligible clinical significance.[1] Actual estimation of prevalence of drug-drug interactions is difficult to establish and quantify because not all patient will experience the outcome of drug interaction even when taking a combination of drugs that are known to interact. Hence, we should distinguish between potential drug interactions and clinically relevant drug interactions. Recent systematic evaluations indicate a diverse range of prevalence rates, with clinically evident DDIs cited at 9.2%, and potential DDIs in non-ICU contexts at 33%, whereas ICU cohorts show a prevalence of 67%.[2] . One in ten individuals in the total Slovenian population is exposed to clinically relevant potential DDIs. Metabolic breakdown of drugs by specific enzymes is called as Biotransformation of a drug.

The most common drug metabolizing enzymes belongs to Cytochrome-P450 family. There are more than 50 CYP450 enzymes, but the CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 enzymes metabolize 90 percent of drugs. The primary site of expression of CYP-450 enzymes is liver followed by kidney, placenta, adrenal gland, gastrointestinal tract, and skin. CYP-mediated drug metabolism not only transforms lipophilic products into hydrophilic products that aid in elimination but also significantly influences treatment outcomes by altering drug action, safety, bioavailability, and drug resistance through metabolism. [3] Patients with chronic illness and comorbid conditions need multiple medications for better prognosis. In clinical practice it is common to provide many drugs concurrently to attain medication adherence although this may be a clinical strategy but it will increase the likelihood of causing drug-drug interactions.[4] CYP mediated metabolism is the primary route for drug elimination simultaneously more than one drug compete for same CYP enzyme resulting in CYP mediated drug-drug interactions.[5] The major mechanisms by which CYP enzymes mediated drug interactions are by Inhibition and induction that are further categorized to reversible (competitive or non-competitive) and irreversible mechanisms.

CYP mediated induction is one of the major concerns in clinical practice due to many reasons. The primary being reduction in therapeutic efficacy of co-administered drug by accelerating drug excretion and lowering its concentration. [6] As stated by Kazuhisa Kusuki etal Rifampicin induces CYP3A4 expression and accelerates metabolism of glucocorticoids. Thus, hydrocortisone dosage should be increased when a patient is treated with rifampicin. [7] Majority of DDIs were due to CYP mediated drug inhibition that usually results in increased drug concentration sometimes above the normal therapeutic window resulting in increased probability of occurrence of adverse events in the patient. [8] The pharmacist intervention made by Jayson P Jessop etal suggested changing atorvastatin to pravastatin in order to reduce the risk of statin-associated adverse drug events (ADEs) caused by CYP3A4 inhibition, and changing fluoxetine to citalopram in order to reduce the risk of uncontrolled anxiety and depression and to mitigate drug-drug interactions with carvedilol to reduce the risk of orthostatic hypotension in a 70year old woman. [9]

Among all the CYP enzymes CYP3A4 is the most common enzyme responsible for metabolism of about 50percent of total drugs available in the market. A review by Jacob George etal revealed a significant decrease in the activity of CYP3A4 due to aging and other chronic conditions including renal impairment in elderly patients leading to circulation of toxins in the body and it also emphasized on epigenetic transformations in elderly. [10] Around 80 percent and 40 percent of CYP3A4 is widely distributed along liver and small intestine and are simultaneously involved in first pass metabolism. [11] Studies have shown that several nuclear receptors

play an important role in the induction of CYP3A4, Pregnane X receptor (PXR), constitutively androstane receptor (CAR), HNF4, glucocorticoid receptor (GR), or vitamin D receptor are most common among them. PXR forms a complex with CYP3A4 and usually gets activated by steroids, antibiotics, antimycotics, bile acids, and hyperforin, a constituent of the herbal antidepressant St. John's Wort. [12] The impact of substance abuse, especially alcohol consumption, on various aspects of disease pathogenesis and treatment is well documented in the literature.

Chronic alcohol consumption leads to liver injury, brain damage, dyslipidemia and other cardio-vascular complications. Even low levels of alcohol consumption results in premature aging of brain. Research have shown that chronic alcohol exposure results in CYP3A4 activation through increased content of CYP2E1 which has high catalytic activity with ethanol, which indicated that CYP3A4 may play a role in ethanol metabolism. A retrospective study conducted by Xiaoqing Jia etal revealed that there is a strong relation between alcohol consumption and CYP3A4 polymorphism.

A significant proportion of individuals consume alcohol and at the same time take medications for any of the underlying medical conditions. The drugs may be prescription drugs or over the counter drugs but both have a potential to interact with alcohol affecting the dynamics or fate of drug action in the body. For example, Alcohol enhances the metabolism of acetaminophen into a toxic product potentially causing liver damage. [13,14] Regarding food-drug interactions pharmacist recognize that when some food and drugs are taken simultaneously can alter body's ability in utilization of drug resulting in adverse or sub therapeutic effects. According to a review by MT Holmberg etal therapeutic efficacy of clopidogrel involves metabolic activation by CYP2C19 and CYP3A4 and regular use of grapefruit juice results in impaired bioactivation of clopidogrel effecting the anti-platelet effect of drug. [15,16] The present study was carried out to estimate the prevalence of CYP3A4 enzyme mediated drug interactions in a tertiary care hospital along with focus on clinical significance and relevance of literature related documentation in a clinical setting.

Materials and Methods

Study design:

This Observational cross-sectional study was performed after the approval from Institutional Ethics Committee at Santhiram Medical College and General Hospital, Nandyal, Andhra Pradesh. The study was carried out for a period of three months in the inpatient department of Santhiram General Hospital. A total of 180 patients with polypharmacy (having five or more medications) and having two or more drugs related to CYP3A4 in their prescription were included in the study from medicine and allied departments. Necessary information such as age, sex, concomitantly existing diseases, prescribed drugs and information regarding past medication history along with personal history (smoking, alcohol, substance abuse) and information regarding food taken during hospitalization were obtained from patient case sheets and prescriptions. Data from all the prescriptions was entered in proforma by taking the consent of patients. Based on Micromedex and Literature search drug-drug interactions were analyzed in the prescriptions. We screened for interactions among drugs that were co-administered and omitted others that have no similar frequency and this data is obtained from nursing notes and case sheets followed up on a daily basis.

Subjects:

Inclusion Criteria:

The subjects 18–95 years of age, diagnosed with Cardiovascular, General medicine, Neurologic, Nephrological, pulmonary related diseases and Psychiatry disease along with medication regimen complexity and polypharmacy were included in the study. Patients with personal habits of Alcohol consumption and smoking that are exposed to two or more oral agents metabolized by CYP3A4 were also included in the study.

Exclusion criteria:

Patients were excluded if they had less than two oral medications. Special populations like Pregnant women, lactating mothers and pediatrics are excluded from the study. Out Patient Department prescriptions were also excluded from the study.

Data Collection:

Eligible cases were identified through case sheets of the patient. We reviewed each case file, and using a standard form purposely designed for the study – extracted data on sex, age, concomitantly existing disease, therapy regimen, personal habits and data related to clinical findings (laboratory investigations, imaging and sonological evidence). We tried to follow up the patient in his whole hospital stay and update the information regarding drug regimen, vitals and clinical examination on a daily basis for a complete picture of patient's prognosis.

Data Assessment:

We screened the prescriptions for drug-drug interactions and potential interactions were classified based on severity. DDI severity was classified as minor, moderate, major, contraindicated. They were analyzed for severity through Micromedex and Literature sources. Later we use a database called as SuperCYP . It is a comprehensive resource focused on CYP and drug metabolism. The SuperCYPsPred web server includes machine learning model based on Random Forest algorithm, and different types of data sampling method. The models present here discriminate the inhibitors and non-inhibitors for five major Cytochromes (CYPs) isoforms.[17] By using this database, we found the class of CYP enzyme responsible for drug interactions they're by interpreting mechanism, clinical consequences and risk associated with such potential interactions. We estimated the prevalence of CYP3A4 mediated drug interactions along with identification of substantial clinically significant interaction seen in patients based on monitoring parameters, clinical symptoms and patient interview.

Statistical Analysis:

General characteristics of study population were reported as means and standard deviation (SD) and percentage appropriately. Total number of patients exposed to CYP3A4 interactions were calculated on basis of absolute number. The most common combination of interacting drugs was represented in terms of frequency. A sub-analysis of interactions actually seen in patient is also conducted via Chi-square test. All analysis was performed using MS-Excel.

Results

General characteristics of study population:

The general characteristics are reported in Fig.1. Mean age was 53.72 among which men were 76.5% and women were 23.4% that were exposed to CYP mediated drug interactions. Out of 180 study population 64(35.5%) patients have comorbidities.

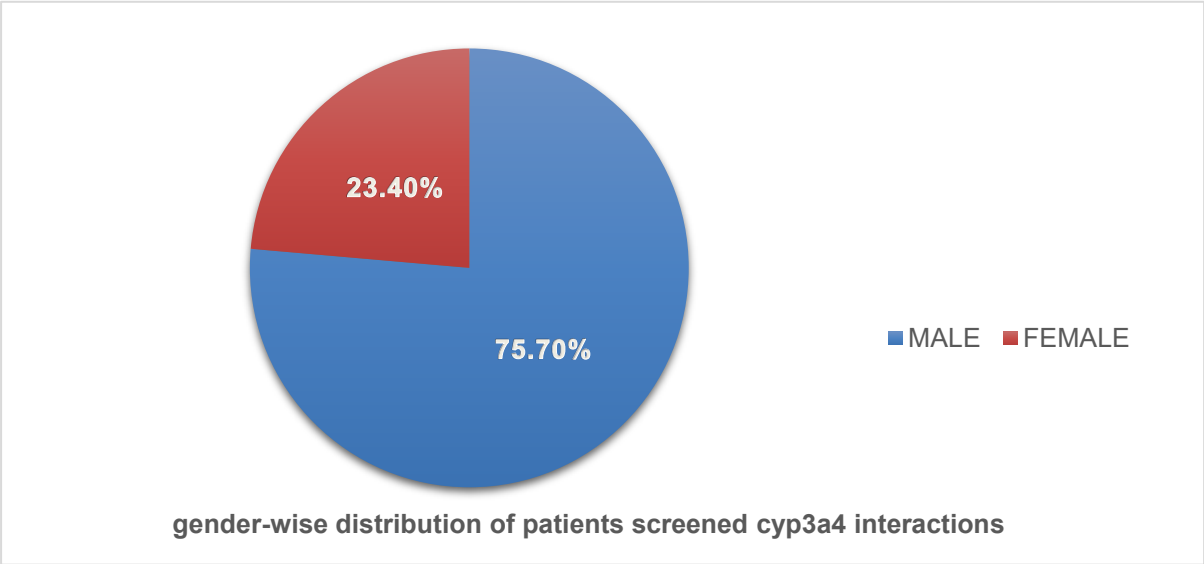

Figure1: gender-wise distribution of patients screened CYP3A4 interactions

Out of identified 132 CYP3A4 mediated drug interactions, 101 (75.70%) interactions are observed in male patients and 31 (23.40%) interactions in female patients.

CYP3A4 mediated drugs involved:

A total of 132 CYP3A4 mediated drug interactions were noted among 180 patients. The drug interactions were distributed across the medicine and allied departments as follows, emergency (14.39%), general medicine (13.63%), psychiatry (12.87%), neurology (18.93%), nephrology (15.15%), cardiology (15.15%), pulmonology (9.84%) (Fig.2). Out of 132 potential drug interactions 13 clinically significant interactions were observed in the patients. These interactions were identified based on available literature and through follow up of patient on a daily basis. The drugs most frequently involved in these interactions are cardiovascular drugs, anti-depressants, Anti-arrhythmic, anti-psychotics and certain antibiotics.

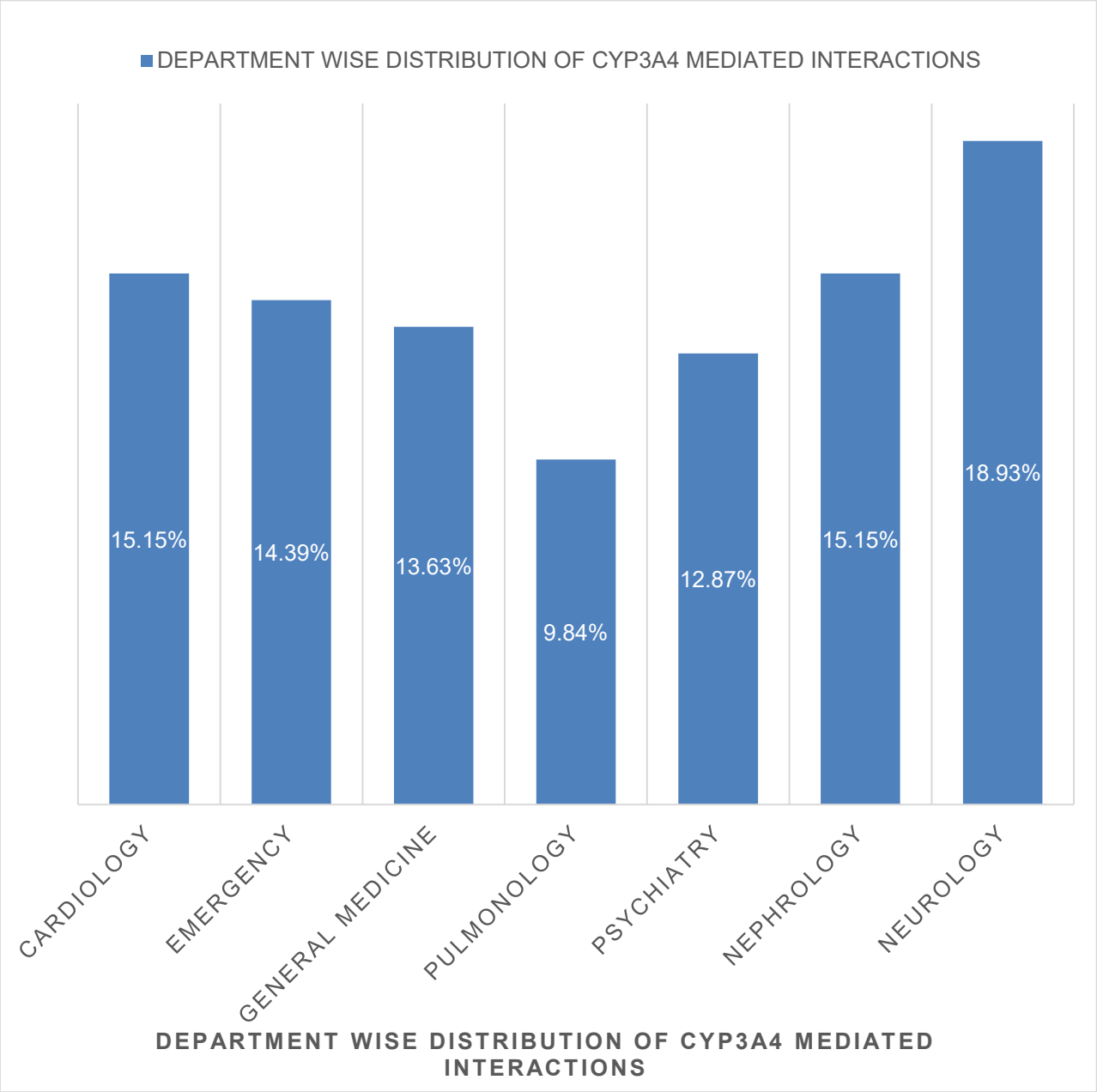

Figure 2: Department Wise Distribution of CYP3A4 mediated Drug Interactions

Out of 132 identified CYP3A4 mediated drug interactions, 25 (18.93%) interactions are observed in neurology, 20 (15.15%) interactions in cardiology, 20 (15.15%) interactions in nephrology, 19 (14.39%) interactions in emergency, 18 (13.63%) interactions in general medicine, 17 (12.87%) interactions in psychiatry and 13 (9.84%) interactions in pulmonology.

Prevalence of CYP3A4 interactions:

We reported a prevalence of 50.56% of CYP3A4 mediated drug interactions potentially seen in 91 patients. Prevalence of CYP3A4 drug-drug interactions was found to be 40.56% potentially seen in 73 patients followed by prevalence of CYP3A4 mediated drug alcohol interactions is 10.5% seen in 19 patients. CYP3A4 mediated food drug interactions were potentially seen in 3 patients with a prevalence rate of 1.66%. (Fig.3).

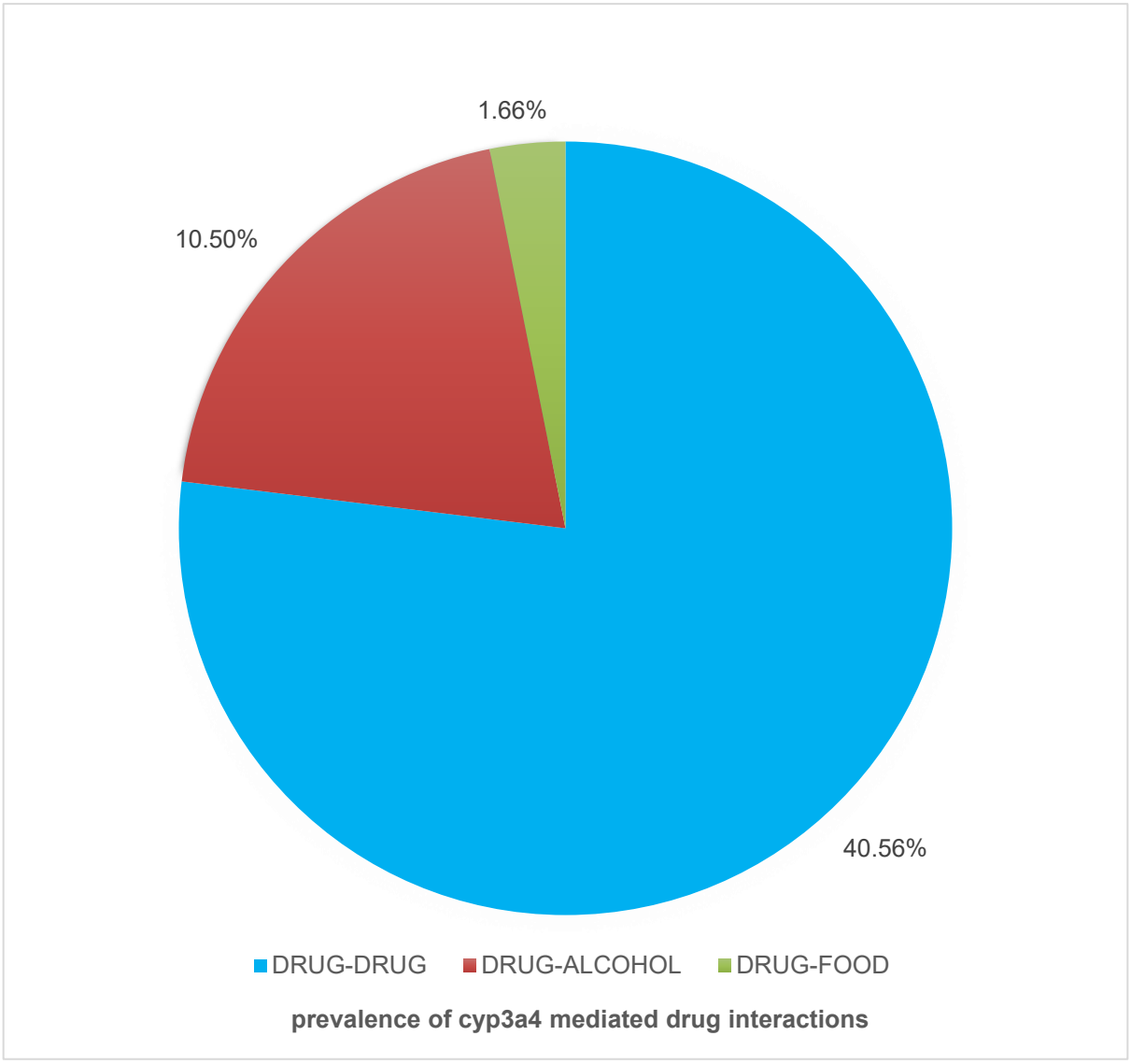

Figure 3: Prevalence of CYP3A4 Mediated Drug Interactions

The prevalence rate of CYP3A4 mediated drug-drug interactions is 40.56%, drug-alcohol interactions is 10.50% and drug-food interactions is 1.66%.

As a part of our study, we witnessed clinical effects due to CYP3A4 mediated drug interactions in 13 patients with a prevalence of 7.22%. the distribution of comorbidities among patients with CYP3A4 mediated potential interactions was represented in Fig.4. Chi square analysis was performed to know the association between comorbidities and clinically significant interactions seen in patient. We obtained p-value less than 0.05(0.304) indicating the above-mentioned association is not statistically significant.

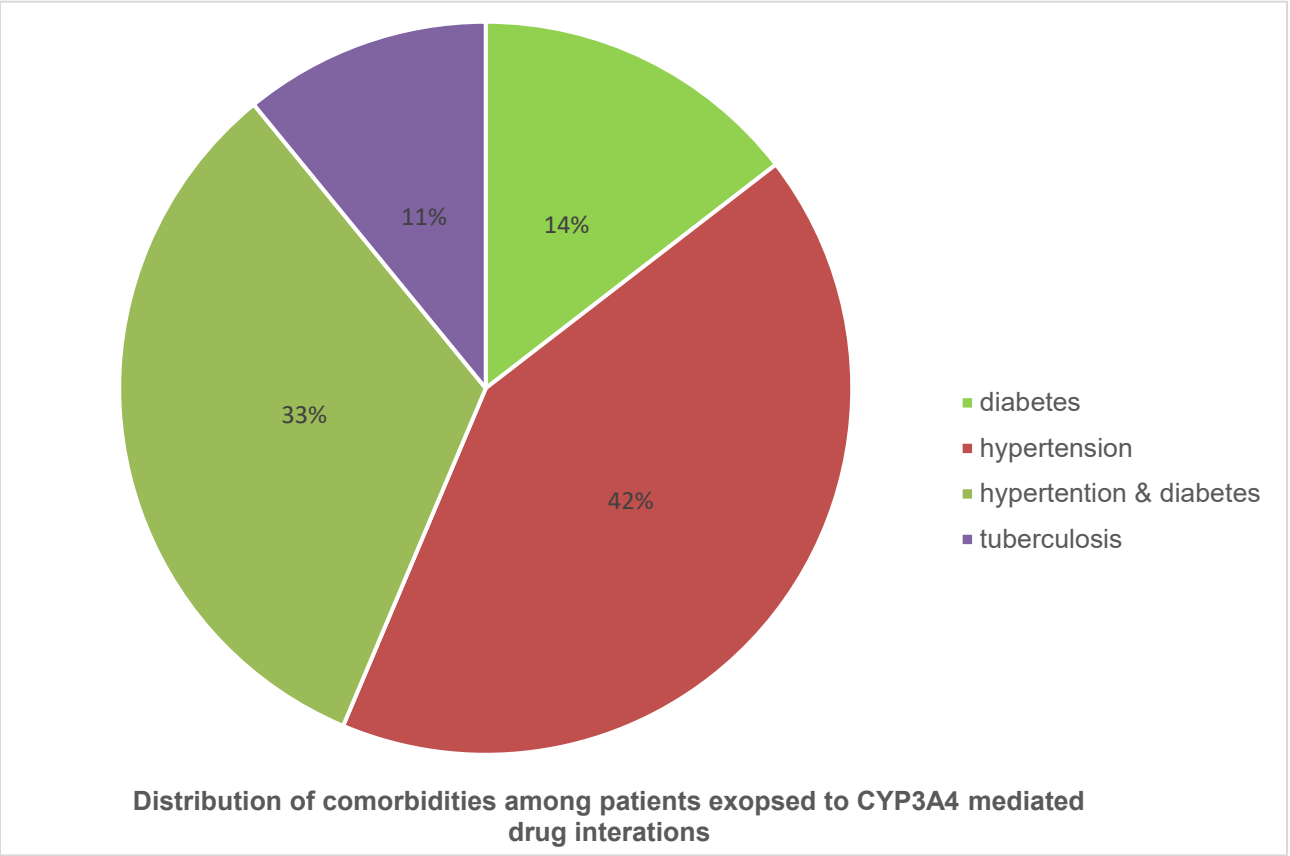

Figure 4: Distribution of Comorbidities Among Patients Exposed to CYP3A4 Mediated Drug Interactions

Out of selected 91 patients having CYPP3A4 mediated drug interactions, 64 patients have comorbidities among which 27 (42%) patients have Hypertension, 9 (14%) patients have Diabetes Mellitus, 21 (33%) patients have both Hypertension and Diabetes Mellitus and 7 (11%) patients have Tuberculosis.

The identified potential CYP3A4 mediated drug interactions were categorized into drug-drug, drug-alcohol, drug-food were represented in Table No.1, Table No.2, Table No.3 respectively.

Table No.1: Most frequent CYP3A4 mediated drug-drug interactions

S. No	Interacting Drugs	MOA	Severity	Frequenc
1	Atorvastatin & Clopidogrel	inhibition	moderate	26
2	Chlorpheniramine & Dextromethorphan	competitive inhibition	major	8
3	Atorvastatin & Azithromycin	inhibition	moderate	4
4	Acetaminophen & Isoniazid	inhibition	minor	3
5	Amiodarone & Levofloxacin	inhibition	major	2
6	Clonazepam & Valproic Acid	inhibition	moderate	2
7	Methylprednisolone & Tramadol	inhibition	major	2
8	Nortriptyline & Tramadol	inhibition	major	2
9	Amiodarone & Atorvastatin	inhibition	major	2
10	Pyrazinamide & Rifampicin	inhibition	major	2

Out of 105 identified CYP3A4 mediated drug-drug interactions, 53 (50.4%) interactions have a frequency greater than 1, of which 18 (33.9%) interactions are major, 32 (60.3%) interactions are moderate and 3 (5.6%) interactions are minor.

Table No.2: CYP3A4 mediated Drug-Alcohol Interactions

S.No	Interacting Drugs	MOA	Severity	Frequency
1	Alcohol & Chlordiazepoxide	Inhibition	Moderate	5
2	Alcohol & Propranolol	Inhibition	Minor	5
3	Acetaminophen & Alcohol	Inhibition	Major	3
4	Alcohol & Tramadol	Inhibition	Major	2
5	Alcohol & Clonazepam	Inhibition	Major	2
6	Alcohol & Alprazolam	Inhibition	Major	1
7	Alcohol & Amitriptyline	Inhibition	Moderate	1
10	Alcohol & Escitalopram	Inhibition	Moderate	1
11	Alcohol & Midazolam	Inhibition	Major	1
12	Alcohol & Nortriptyline	Inhibition	Moderate	1
13	Alcohol & Sertraline	Inhibition	Moderate	1
14	Alcohol & Cetirizine	Inhibition	Major	1

Out of 132 identified CYP3A4 mediated drug interactions, 24 are CYP3A4 mediated drug-alcohol interactions, of which 10 (41.6%) interactions are major, 9 (37.5%) interactions are moderate and 5 (20.8%) interactions are minor.

Table No.3: CYP3A4 mediated Drug-Food Interactions

S. No	Interacting Drugs	Mechanism	Severity	Frequency
1	Lorazepam & Orange Juice	Inhibition	Moderate	1
2	Alprazolam & Caffeine	Competitive Inhibition	Moderate	1
3	Caffeine & Chlordiazepoxide	Competitive Inhibition	Moderate	1

There are 3 identified potential drug food interactions, of which all the 3 (100%) are moderate in severity. Clinically significant CYP3A4 mediated drug interactions were identified in patients were represented in Table No.4 based on severity, parameters monitored and effect seen in patient.

Table No.4: Clinically significant CYP3A4 Drug Interactions

S. No	Interacting Drugs	Severity	Monitoring Parameter	Clinical Effect
1.	Acetaminophen & Alcohol[18]	Major	Liver Function Test	Increased Alkaline Phosphate
2.	Acetaminophen & Alcohol[18]	Major	Clinical Symptoms	Vomiting
3.	Acetaminophen & Alcohol[18]	Major	Liver Function Test	Increased Alkaline Phosphate
4.	Acetaminophen & Isoniazid[19]	Major	Clinical Symptoms	Tingling, Numbness and Weakness
5.	Alcohol & Propranolol[18]	Moderate	Vitals	Hypotension Was Observed
6.	Alcohol & Propranolol[18]	Moderate	Clinical Symptoms	Fainting Was Observed
7.	Alcohol & Zolpidem[18]	Major	Clinical Symptoms	Patient Was Sedative
8.	Amiodarone & Levofloxacin[20]	Major	Clinical Symptoms	Ataxia Noted
9.	Clopidogrel & Nicardipine[21]	Moderate	D-Dimer	Abnormal D-Dimer Levels
10.	Digoxin & Spironolactone[22]	Major	Electrocardiogram, Echo Cardiogram	Cardiac Arrythmia
11.	Hydrocortisone & Levofloxacin[23]	Major	Serum Electrolytes	Hypokalaemia Noted
12.	Mycophenolate Mofetil & Pantoprazole[24]	Moderate	Ultrasound-Sonography, Clinical Symptoms	Flareup Of Lupus, Nephritis Was Observed
13.	Phenytoin & Valproic Acid[25]	Major	Clinical Symptoms	Vertigo Noted

Out of 132 identified CYP3A4 mediated drug interactions, 13 (9.84%) interactions are clinically seen in patients, of which 9 (69.2%) interactions are major and 4 (30.8%) interactions are moderate.

Discussion

In this study we tried to document the prevalence of clinically important potential DDIs. We included patient characteristics along with drug related factors to obtain complete information of CYP3A4 mediated drug interactions. From this study we found that potential DDIs are occurring more frequently in a clinical setting particularly with cardiovascular drugs like Atorvastatin and Clopidogrel.[26] A significant number of interactions were CYP3A4 mediated drug-alcohol interactions and the most common being interaction between Alcohol and acetaminophen that involves both CYP3A4 and CYP2E1 enzymes. The above-mentioned interaction was seen in 3 patients where the laboratory investigations revealed increased Liver enzymes levels indicating hepatotoxicity without any hepatic comorbidities noted in patient giving us a inference that elevated liver enzymes might be due to significant chronic exposure of patient to alcohol and Acetaminophen from a long period of time[27].

A total of two patients has shown signs of drug intoxication due to CYP3A4 drug interactions. A patient of age 86 years admitted in the hospital for treatment of neurological and cardiological condition was prescribed with digoxin and spironolactone as oral agents over a period of 4 days, the 2D-Echo had shown EF as 38% hence was prescribed with Digoxin to treat CHF and Spironolactone was prescribed to treat oedemata condition. Patient had shown Cardiac arrythmias after a week of concurrent administration of both drugs. We ruled out other possible causes based on patient's conditions and hence concluded that it might be due to concomitant administration of these drugs. (same as table reference 3) Similarly a male patient of age 20 years was admitted in the hospital for treatment of CKD. The patient had an episode of cardiac arrest while he was hospitalized and had recurrent seizures during hospitalization. He was prescribed with Phenytoin and Valproic acid for

treatment of seizures. Both the drugs were administered there by resulting in development of mild nystagmus and vertigo by the patient. Upon relevant review of medications, we inferred that the fresh complaint experienced by patient might be clinical consequence of the interactions. Later the patient was put on anti-vertigo medications. The following are the common patterns seen in both the patients. Both patients were put on multiple medications(polypharmacy) and a long hospital stay (follow-up done for 1 month). The interactions in above scenarios belong to a special category of drugs called as Narrow therapeutic drugs. NTI drugs usually are those drugs where small differences in the plasma drug concentration leads to subtherapeutic failure or serious adverse effects.

Special attention must be given to patients receiving such NTI drugs as there is a risk of potential drug-drug interactions mostly due to drug pharmacokinetics hence periodic monitoring of prescriptions is necessary to promote safety, efficacy, cost effectiveness and rationale use of drug therapy and overall minimization of unintentional drug interactions. [28] The Chi-square test performed for comorbidities and drug interactions seen in patients had shown no statistical significance (p value <0.05) giving us an idea on inter individual variations among patients regarding outcome of drug interactions. These interactions can be wholly determined when we include biogenic factors, environmental factors, drug related factors along with genomic factors.[29]

Limitations

Errors or omissions in databases affect accuracy of drug interaction results for their reliability and comprehensiveness which could affect the results. This study is limited to specific regional health care setting which may not be generalized to larger populations. As it was not possible to integrate pharmacogenetic data (genetic polymorphism e.g., poor metabolizers vs ultra rapid metabolizers), the study misses the opportunity for advancement in personalized medicine approaches which aim to predict and prevent adverse drug interactions based on genetic profile.

Potential directions for future research

Characterization of polypharmacy risk in critical care settings helps in developing predictive models to assess interaction severity. Integrate pharmacogenetics into Electronic Health Records and develop guideline for dosing in CYP3A4 genotype for real time decision making. Develop in silico methods to predict impact of drugs on CYP3A4 by integrating tools like Clinical Decision Support Systems. Study the dynamics of CYP3A4 modulation in different patient populations by means of longitudinal studies.

Conclusion

We estimated the prevalence of CYP3A4 enzyme mediated drug interactions both potential and clinically significant ones, and reported accordingly. The prescriber's understanding on CYP3A4-associated drug-drug interactions, along with the recognition of resultant consequences, constitutes the primary approach for reducing patient distress, by timely interventions. Pharmacists can mitigate clinically relevant drug-drug interactions through enhanced medication management via continuous monitoring and patient education. Continuous review of prescriptions can help us identify clinically significant drug interactions in patients if not these adverse outcomes are masked due to patient related complexities hence pharmacist plays a huge role in clinical monitoring of drug regimen. From this study we inferred that patients with personal habits of smoking and alcohol have higher chance of being affected by clinically significant CYP3A4 mediated drug interactions. Hence early detection and reporting of such potential drug-drug interactions can improve the clinical outcomes of hospitalized patients along with promoting safe use of drugs in a clinical setting.

Acknowledgment: Nil.

Conflict of Interest: The authors declare no conflict of interest.

Abbreviations: CYP: Cytochrome-P, DDI: Drug-Drug Interactions, ICU: Intensive Care Unit, ADE: Adverse Drug Event, PXR: Pregane-X-Receptor, CAR: Constitutively Androstane Receptor, GR:

Glucocorticoid Receptor, SD: Standard Deviation, CHF: Congestive Heart Failure, EF: Ejection Fraction, CKD: Chronic Kidney disease, NTI: Narrow Therapeutic Index.

Funding Statement: This research received no specific grant from any funding agency in the public, commercial or non-profit sectors.

References:

1. Gabay M. Drug Interactions: Scientific and Clinical Principles.
2. Zheng WY, Richardson LC, Li L, Day RO, Westbrook JI, Baysari MT. Drug-drug interactions and their harmful effects in hospitalised patients: a systematic review and meta-analysis. Eur J Clin Pharmacol 2018;74(1):15–27.
3. Zhao M, Ma J, Li M, Zhang Y, Jiang B, Zhao X, et al. Cytochrome P450 Enzymes and Drug Metabolism in Humans. Int J Mol Sci 2021;22(23):12808.
4. Doan J, Zakrzewski-Jakubiak H, Roy J, Turgeon J, Tannenbaum C. Prevalence and Risk of Potential Cytochrome P450–Mediated Drug-Drug Interactions in Older Hospitalized Patients with Polypharmacy. Ann Pharmacother 2013;47(3):324–32.
5. Deodhar M, Al Rihani SB, Arwood MJ, Darakjian L, Dow P, Turgeon J, et al. Mechanisms of CYP450 Inhibition: Understanding Drug-Drug Interactions Due to Mechanism-Based Inhibition in Clinical Practice. Pharmaceutics 2020;12(9):846.
6. Lin JH. CYP Induction-Mediated Drug Interactions: in Vitro Assessment and Clinical Implications. Pharm Res 2006;23(6):1089–116.
7. Kusuki K, Watanabe S, Mizuno Y. Tuberculous Addison's disease with increased hydrocortisone requirements due to administration of rifampicin. BMJ Case Rep 2019;12(3):e228293.
8. Hakkola J, Hukkanen J, Turpeinen M, Pelkonen O. Inhibition and induction of CYP enzymes in humans: an update. Arch Toxicol 2020;94(11):3671–722.
9. Jessop JP, Russell J, DeJesus A, Bardolia C, Hanna A, Turgeon J, et al. Pharmacogenetic Testing in a 70-Year-Old Woman with Polypharmacy and Multiple Comorbidities: A Case Report. Am J Case Rep [Internet] 2023 [cited 2025 Jan 6];24. Available from: https://www.amjcaserep.com/abstract/index/idArt/938850
10. George J, Byth K, Farrell GC. Age but not gender selectively affects expression of individual cytochrome P450 proteins in human liver. Biochem Pharmacol 1995;50(5):727–30.
11. Patel KA, Bhatt MH, Hirani RV, Patel VA, Patel VN, Shah GB, et al. Assessment of potential drug–drug interactions among outpatients in a tertiary care hospital: focusing on the role of P-glycoprotein and CYP3A4 (retrospective observational study). Heliyon 2022;8(11):e11278.
12. Zhou SF. Drugs Behave as Substrates, Inhibitors and Inducers of Human Cytochrome P450 3A4. Curr Drug Metab 2008;9(4):310–22.
13. Jia X, Zhang X, Zhou T, Sun D, Li R, Yang N, et al. Cyp3A4 *1G polymorphism is associated with alcohol drinking: A 5-year retrospective single centered population-based study in China. PLOS ONE 2023;18(12):e0295184.
14. Weathermon R, Crabb DW. Alcohol and medication interactions. Alcohol Res Health J Natl Inst Alcohol Abuse Alcohol 1999;23(1):40–54.
15. Ased S, Wells J, Morrow LE, Malesker MA. Clinically Significant Food-Drug Interactions. Consult Pharm J Am Soc Consult Pharm 2018;33(11):649–57.
16. Holmberg MT, Tornio A, Neuvonen M, Neuvonen PJ, Backman JT, Niemi M. Grapefruit Juice Inhibits the Metabolic Activation of Clopidogrel. Clin Pharmacol Ther 2014;95(3):307–13.
17. Priyanka B. SuperCYPsPred [Internet]. Available from: https://insilico-cyp.charite.de/SuperCYPsPred/index.php?site=DrugDrugInteraction

18. Alcohol-Medication Interactions: Potentially Dangerous Mixes.
19. Zaoui A, Abdelghani A, Ben Salem H, Ouanes W, Hayouni A, Khachnaoui F, et al. Early-onset severe isoniazid-induced motordominant neuropathy: a case report. East Mediterr Health J 2012;18(3):298–9.
20. Kaur P, Kaur A, Sinha A, Khaliq W, Dumic I, Singh A. Amiodarone-Induced Nystagmus and Ataxia: Case Report and Systematic Review of Case Reports. J Clin Pharmacol 2023;63(12):1324–9.
21. Siller-Matula JM, Lang I, Christ G, Jilma B. Calcium-Channel Blockers Reduce the Antiplatelet Effect of Clopidogrel. J Am Coll Cardiol 2008;52(19):1557–63.
22. Wang M, Su C, Chan ALF, Lian P, Leu H, Hsu Y. Risk of digoxin intoxication in heart failure patients exposed to digoxin–diuretic interactions: a population-based study. Br J Clin Pharmacol 2010;70(2):258–67.
23. Veltri KT, Mason C. Medication-induced hypokalemia. P T Peer-Rev J Formul Manag 2015;40(3):185–90.
24. Xu L, Cai M, Shi BY, Li ZL, Li X, Jin HL. A Prospective Analysis of the Effects of Enteric-Coated Mycophenolate Sodium and Mycophenolate Mofetil Co-medicated With a Proton Pump Inhibitor in Kidney Transplant Recipients at a Single Institute in China. Transplant Proc 2014;46(5):1362–5.
25. Hwang WJ, Tsai JJ. Acute phenytoin intoxication: causes, symptoms, misdiagnoses, and outcomes. Kaohsiung J Med Sci 2004;20(12):580–5.
26. Lau WC, Waskell LA, Watkins PB, Neer CJ, Horowitz K, Hopp AS, et al. Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: a new drug-drug interaction. Circulation 2003;107(1):32–7.
27. Dangi B, Davydova NY, Maldonado MA, Abbasi A, Vavilov NE, Zgoda VG, et al. Effects of alcohol-induced increase in CYP2E1 content in human liver microsomes on the activity and cooperativity of CYP3A4. Arch Biochem Biophys 2021;698:108677.
28. Vivean SPR, Kumar MA, Shanmugasundaram P. Prospective Study On Drug-Drug Interactions Of Narrow Therapeutic Index Drugs. . E 8.
29. Turner RM, Park BK, Pirmohamed M. Parsing interindividual drug variability: an emerging role for systems pharmacology. Wiley Interdiscip Rev Syst Biol Med 2015;7(4):221–41.

How to cite this article: Sai Keshava Reddy A, Kiranmai Venkatagiri, Ambati Sandeep Reddy, Bhavya Sai Sakhamuri, Mitta Putta Pooja, and Ugandar R E. "POTENTIAL AND CLINICALLY SIGNIFICANT CYP3A4 MEDIATED DRUG INTERACTIONS IN HOSPITALIZED PATIENTS: A CROSS-SECTIONAL OBSERVATIONAL STUDY". *Tropical Journal of Pharmaceutical and Life Sciences*, vol. 12, no. 2, Apr. 2025, **DOI:** https://doi.org/10.61280/tjpls.v12i2.172

Published by:
Informative Journals
Jadoun Science Publishing Group India