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Research Article

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Pharmacogenomics in Critical Care: Advancing Precision Medicine for Optimized Drug Therapy and Improved Patient Outcomes

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Abstract

Background

Patients in the critical care unit often have complex, acute medical conditions requiring multiple drug regimens. Therapy relies on clinical guidelines and physician experience. This preliminary study evaluated functional polymorphisms in six genes affecting metabolism of drugs often used in ICU patients.

Methods

Blood samples from patients of Intensive Care Unit (ICU), Kamineni Hospitals, Hyderabad, India were collected over one month. Genomic DNA was extracted as done routinely for diagnostics. PCR was carried out for a functional variant in six pharmacologically relevant genes—ABCB1, CYP2B6, CYP2C9, CYP2C19, CYP3A4, and CYP3A5. The PCR products were analysed by Restriction Fragment Length Polymorphism (RFLP) or Sanger sequencing. The genotypes identified were categorized as normal, intermediate and poor metabolizers.

Results

The 41 patient samples showed significant genotypic variation with 29% who were poor transporters for ABCB1 (rs1045642), while 41% of them were poor metabolizers for CYP2B6 (rs3745274). Around 75% of samples had a genotype for CYP2C9 (rs1057910) which indicated normal metabolizers. 20% and 41% poor metabolizers were seen for CYP2C19 (rs4244285) and CYP3A5 (rs776746), respectively. Whereas CYP3A4 (rs2740574) had no poor metabolizers. These variations are responsible for the metabolism of commonly used ICU drugs like proton pump inhibitors, anticoagulants, antiepileptics, antibiotics, analgesics, etc.

Conclusion

This preliminary study indicates that a significant proportion of ICU patients would benefit from pharmacogenomic testing as 20-40% of the individuals exhibited genotypes associated with poor metabolism that may require dosage regulation. A larger study is warranted to develop appropriate panels for different types of patients admitted to ICU.

Keywords: Critical Care, Pharmacogenetics and Precision Medicine

Highlights

- In Critical care units polypharma is the norm. For the first time gene polymorphisms in 6 genes relevant for drug transport and metabolism were assessed in ICU patients from India.
- A significant proportion of patients exhibited genotypes associated with poor activity affecting drug metabolism and therapy.
- Pharmacogenomic testing can optimize drug selection and dosing, reducing adverse drug reactions and improving patient outcomes.

1. Introduction

Critical care medicine presents unique challenges where therapeutic efficacy and patient safety must be balanced amidst time-sensitive, high-stakes decision-making. Patients in the Critical Care Unit (ICU) often have complex, acute medical conditions requiring multiple drug regimens. Traditionally, drug therapies in this setting are selected and dosed empirically at the start, relying heavily on clinical guidelines and physician experience. However, the presence of inter-individual variability in drug response, driven by genetic differences, poses a significant challenge to this approach. These variations can lead to adverse drug reactions (ADRs), therapeutic failures, and complications that can prolong ICU stay and increase healthcare costs [1,2].

Pharmacogenomics, which examines the influence of genetic variations on drug metabolism, efficacy, and safety, provides an opportunity to personalize drug therapy, transforming critical care management. By identifying genetic polymorphisms that influence drug-metabolizing enzymes, drug transporters, and target receptors, pharmacogenomics can enable tailored therapeutic strategies in the ICU [3]. Pharmacogenomics has become a key force in advancing personalized medicine, with a growing number of individualized therapies now being integrated into clinical practice [4].

In the present study, six common gene polymorphisms that are responsible for metabolizing and transporting >60% of the drugs used in critical care settings were evaluated. These were assessed in ICU patients in a tertiary care hospital to evaluate in what percentage of our population the standard drugs/ dosages would be appropriate for management.

2. Methodology

Patients admitted in the Medical ICU of Kamineni Hospital, Hyderabad, India over a period of one month were included in the study. 2 ml EDTA blood sample was collected from them for molecular testing. Genomic DNA isolation and Polymerase Chain Reaction (PCR) were performed with specific primers encompassing functional variants of 6 genes which included ABCB1, CYP2B6, CYP2C9, CYP2C19, CYP3A4 and CYP3A5 genes followed by RFLP/ Sanger sequencing to identify the functional variants as done in our lab routinely [5].

3. Results

A total of 41 patients were included in the study. All the samples were processed for five common CYP variants and one drug transporter i.e., ABCB1. The results obtained are presented in (Table 1).

Gene	Genotype	Drugs	Metabolism	No. of patients (%)
ABCB1 rs 1045642 c.3435 T>C	TT/ *1*1	Proton pump inhibitors, anticoagulants, antibiotics, pain relief, antineoplastic and immunosuppressants.	Normal	06 (14.6%)
	TC/ *1*2		Intermediate	23 (56.09%)
	CC/ *2*2		Poor	12 (29.2%)
CYP2B6 rs3745274 c.516 G>T	GG/ *1*1	Antiemetics, antineoplastics, antiretrovirals, anaesthetics	Normal	07 (17.07%)
	GT/*1*6		Intermediate	17 (41.4%)
	TT/ *6*6		Poor	17 (41.4%)
CYP2C9 rs1057910 c.1075A>C	AA/*1*1	Antiepileptics, Nonsteroidal anti-inflammatory drugs, antifungals, anticoagulants.	Normal	31 (75.6%)
	AC/*1*3		Intermediate	08 (19.5%)
	CC/*3*3		Poor	02 (4.87%)
CYP2C19 rs4244285 c.681 G>A	GG/*17*17	Antiarrhythmic, antihypertensives, antiplatelets, proton-pump inhibitors, and antipsychotics.	Normal	16 (39.02%)
	GA/*1*3		Intermediate	17 (41.46%)
	AA/*3*3		Poor	08 (19.51%)
CYP3A4 rs2740574	AA/ *1*1	Antibiotics, antituberculosis, anti-epileptics and glucocorticoids.	Normal	32 (78.04%)
	AG/ *1*1B		Intermediate	09 (21.9%)
	GG/ *3*3		Poor	—
CYP3A5 rs776746 c.3435 T>C	AA/ *1*1	Antineoplastics, antipsychotics, and immunosuppressants.	Normal	04 (9.75%)
	AG/ *1*3		Intermediate	20 (48.7%)
	GG/ *3*3		Poor	17 (41.4%)

Table 1: Genes, Their Functional Polymorphisms, Drugs, and Percentages in The Samples Studied

The ABCB1 gene, or Multidrug Resistance Protein 1 (MDRP1), has a functional nucleotide variant, c.3435T>C, that affects its activity. Among the samples analysed, the CC genotype was seen in 29% of the samples, which was associated with poor activity, while the TC genotype was seen in 56%, indicating intermediate activity (table 1).

41% of the samples gave a GT genotype for CYP2B6indicative of intermediate metabolism, whereas another 41% were identified with TT genotype indicating poor metabolism. The latter may require either dose monitoring or alternatives, especially if receiving Antiemetics, antineoplastics, antiretrovirals, and anesthetics (table 1).

CYP2C9 only 5% had the CC genotype, indicating poor metabolism, while 19% presented with the AC genotype, indicative of intermediate metabolism, while the majority of patients (76%) had AA genotype and should benefit from the standard dose of drugs (table 1).

20% of samples had the AA genotype for CYP2C19, indicating poor metabolism, while 41% displayed the GA genotype, suggestive of intermediate metabolism. The remaining individuals showed GG genotype which is associated with normal metabolism (table 1).

CYP3A4 the *1B has higher promoter activity whereas *3 has decreased promoter activity, of the samples analysed, 22% showed the *1*3. While none of the samples showed *3*3 (table 1).

CYP3A5 49% showed the AG genotype, indicative of intermediate metabolism, and 41% had the GG genotype, which is associated with poor metabolism (table 1).

The total number of individuals who are poor metabolizers for ABCB1, CYP2B6, CYP2C9, CYP2C19 and CYP3A5 are 56. There are no individuals who showed poor metabolism for CYP3A4. Individuals who were found to be poor metabolizers for ABCB1 are 12 (21.42%), while 17 (30.35%) individuals were found to be poor metabolizers for CYP2B6 and CYP3A5, while 2 (3.57%) were poor metabolizers for CYP2C9, and 08 (14.20%) were poor metabolizers for CYP2C19 (Figure 1).

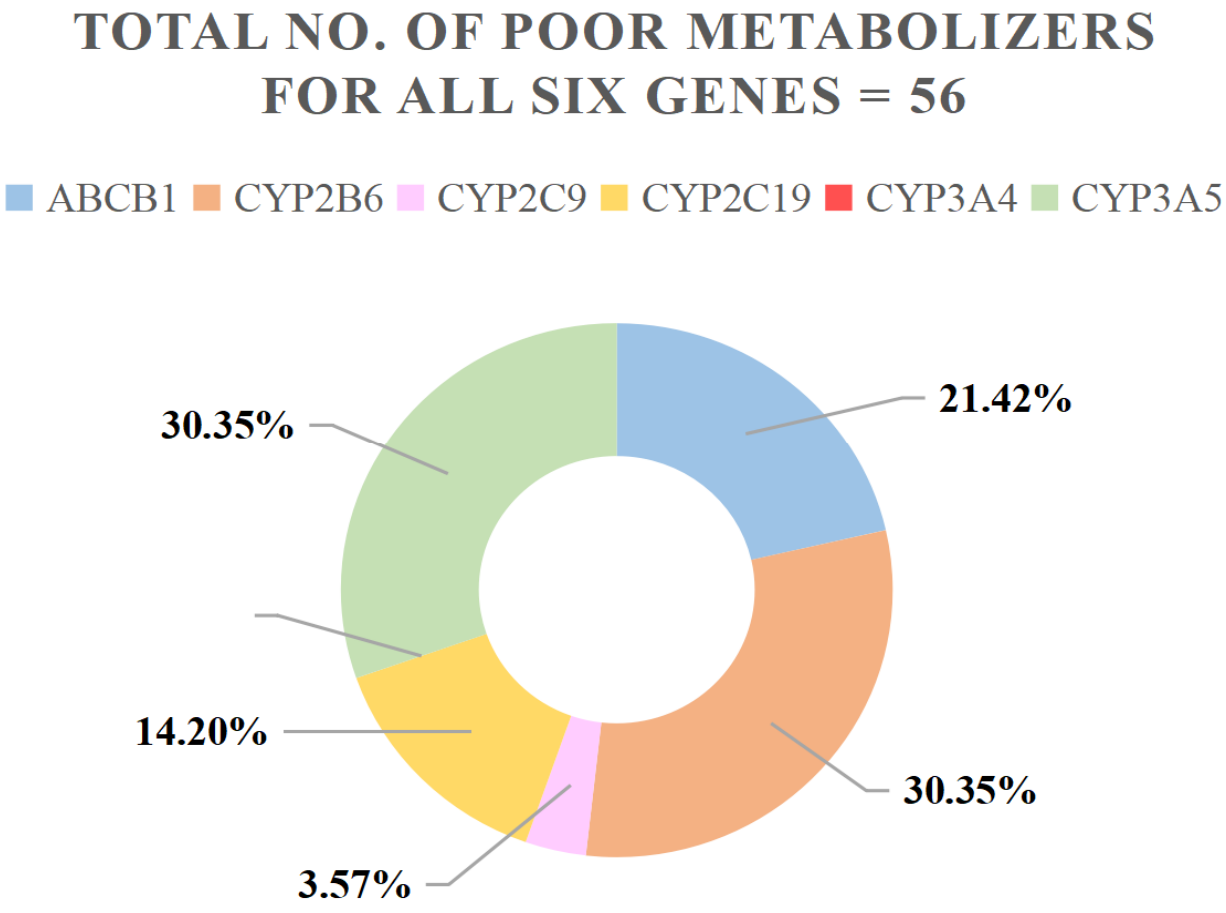

Figure 1: Number of Individuals Found to Be Poor Metabolizers For 6 Gene Polymorphisms.
*Note: CYP3A4 Had No Poor Metabolizers.

Poor metabolizers for any one gene were found in 15 (36.5%) individuals, 13 (31.7%) individuals were found to be poor metabolizers for two genes, while poor metabolizers for 3 genes were found in 05 (12.19%) patients and 08 (19.5%) individuals did not have any gene variant corresponding as poor metabolizers. (Figure 2).

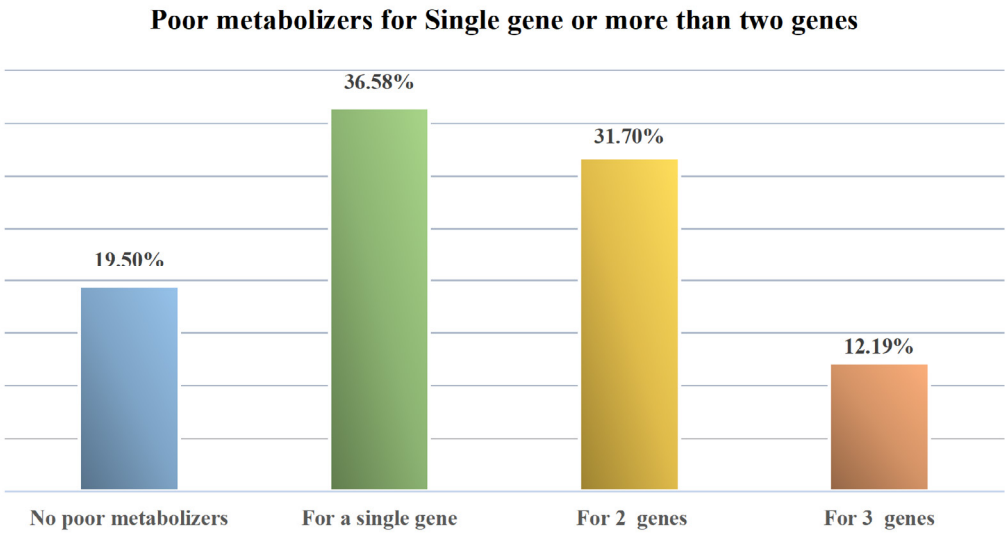

Figure 2: Graph Representing Individuals Who Are Poor Metabolizers for None To 3 Genes

4. Discussion

Pharmacogenomics (PGx) has emerged as a promising tool for optimizing drug therapy and personalized medicine. Very few studies have been carried out in the critical care setting, involving pharmacogenomics, and none of them are from India. Hence, this study, despite the small sample size, underscores the significant inter-individual differences in key pharmacogenomic genes involved in the metabolism of several drugs given in ICU and highlights the importance of genetic testing for patients in critical care setting.

Mackenzie and Hall (2016) and Dzierba et al. (2023) conducted narrative reviews analyzing genetic variations in cyps and drug transporters, which play a crucial role in the pharmacokinetics of commonly used ICU medications. Their findings highlight how genetic differences significantly impact drug metabolism, efficacy, and safety [6,7] Another comprehensive review by Zhou et al. (2018) indicated the importance of pharmacogenomics in critical care to improve patient outcomes using exome data from 60,706 individuals [8]. The key difference between these three papers and our present study is that, we have actually carried out genotyping in ICU patients to establish its importance in the clinical setting, while the others were reviews. A similar paper published in 2020 assessed pharmacogenomics in patients admitted to the ICU after cardiovascular surgery and found that 98% of patients had actionable or potentially actionable genotypic results [9]. However, this research was conducted on a Western population, which focussed primarily on patients in the U.S. and Europe.

Given the genetic diversity across populations, drug metabolism patterns observed in studies may not be fully transferable to Indian patients. To the best of our knowledge, ours is the first paper from India that has focussed on pharmacogenomics in an ICU setting. The results of our study indicate that poor transporters and metabolizers of ABCB1, CYP2B6, CYP2C9, CYP2C19, and CYP3A5 were several with 21.4% of individuals identified as poor transporters for ABCB1, 30.3% were poor metabolizers for CYP2B6 and CYP3A5, while CYP2C9 showed only 3.57% poor metabolizers, 14.2% were found to be poor metabolizers for CYP2C19, while there were no individuals identified as poor metabolizers for CYP3A4. This study also exhibited that 56.09% of individuals were poor metabolizers for a single gene, while 43.9% of individuals were poor metabolizers for two or more genes.

Gene	Drug class	Drugs	CPIC Level of evidence
ABCB1	Proton pump inhibitors, Anti-hypertensives, and Gastroprotective agents.	Pantoprazole, Omeprazole, Metoprolol	Class IA
CYP2B6	Antidepressants, antiretrovirals, first-line antitubercular agents.	Sertraline, efavirenz, rifampin, isoniazid.	Class IA

CYP2C9	NSAIDs, statins, antibiotics, anticoagulants, anticonvulsants, second-line antitubercular agents.	ibuprofen, tenoxicam, flurbiprofen, fluvastatin, streptomycin, warfarin, phenytoin, fosphenytoin, amikacin, kanamycin.	Class IA
CYP2C19	proton pump inhibitors, antifungals, antiplatelets, antidepressants.	pantoprazole, lansoprazole, omeprazole, voriconazole, clopidogrel, doxepin, trimipramine.	Class IA
CYP3A4	Antibiotics, Statins, pain management drugs.	Atorvastatin, paracetamol.	Class IA
CYP3A5	Immunosuppressants	Tacrolimus	Class IA

Table 2: Lists Out Commonly Used Drugs Metabolized by The Genes Tested with CPIC Level Class IA [10]

Critical care physicians should be aware of appropriate gene variant testing if they are prescribing any of the CPIC level class IA medication. If polypharma is required, then doing a panel of genes may be cost-effective.

Our results indicate that an overall number of individuals who can be treated with standard medication/dose based on genotyping are only 19.50% of individuals undergoing treatment in critical care can continue with the standard drug dosages, while the remaining 79.5%, based on their genotype, require dosage adjustments or drug replacement (Figure 2). This emphasizes that genotyping is a crucial step in optimizing drug therapy for critical care patients, who often require urgent, high-risk medications. The pharmacogenetic associations outlined in Table 1 highlight key genes (ABCB1, CYP2B6, CYP2C9, CYP2C19, CYP3A4, and CYP3A5). The influence they have on drug metabolism. Many of the listed drugs such as Warfarin, tacrolimus, pantoprazole, and clopidogrel are commonly used in cardiology, neurology, respiratory, transplant and in Intensive care unit, where precise dosing is critical (table 2).

By integrating pharmacogenetic testing into ICU protocols, healthcare providers can reduce hospital stay, minimize adverse drug reactions, and improve patient outcomes by tailoring drug therapy based on individual genetic profiles. In critical care, where therapeutic precision is often the difference between life and death, genotyping enables safer, more effective, and personalized treatment strategies.

Future directions should focus on large-scale clinical trials assessing the real-world impact of PGx-guided interventions, as well as advancements in rapid genetic testing and clinical decision support systems. By overcoming current barriers, pharmacogenomics could become an integral component of critical care pharmacotherapy, improving patient safety, and healthcare cost efficiency on a global scale.

The ABCB1 gene, which encodes the drug-efflux transporter P-glycoprotein, is known to influence drug absorption and resistance through common polymorphisms [11].

CYP2B6 is involved in the detoxification and bioactivation of approximately 8% of marketed drugs like antidepressants (sertraline), antiretrovirals (efavirenz), first-line antitubercular agents (rifampin, isoniazid). (Table 2). [12].

CYP2C9 accounts for approximately 18% of the cytochrome P450 enzymes in the liver and plays a crucial role in metabolizing over 100 therapeutic drugs. Common class IA drugs include anticoagulants like Warfarin, anti-epileptics such as Phenytoin, NSAIDs like Ibuprofen, and antibiotics like streptomycin. (Table 2) [13].

CYP2C19 is a key enzyme involved in metabolizing various class IA drugs, including antiplatelets (Clopidogrel), proton pump inhibitors (Omeprazole and Pantoprazole), and antifungal (voriconazole). (table 2). [14].

CYP3A5 and CYP3A4 function together and collectively metabolize approximately 30% of all drugs [15]. Some common class IA drugs are, Statins (Atorvastatin), pain management drugs (paracetamol), and Immunosuppressants (Tacrolimus) (Table 2).

Many of the listed drugs, such as warfarin, tacrolimus, pantoprazole, and clopidogrel, are commonly used in intensive care units (ICUs), where precise dosing is critical (Table 2). A large number of patients across various specialties, including cardiology, neurology, pulmonology, general medicine, transplant units, and oncology, rely on these drugs. Clinicians in critical care must be aware of CYP testing and genotyping to prescribe appropriate Class 1a drugs for admitted patients. Additionally, genotyping can prevent adverse drug reactions (ADRs), particularly in ICU patients who are vulnerable due to polypharmacy and organ dysfunction. By integrating pharmacogenetic testing into ICU protocols, healthcare providers can reduce hospital stays, minimize ADRs, and improve patient outcomes by tailoring drug therapy based on individual genetic profiles. In critical care, where therapeutic precision is often the difference between life and death, genotyping enables safer, more effective, and personalized treatment strategies.

Future directions should focus on large-scale clinical trials assessing the real-world impact of PGx-guided interventions, as well as advancements in rapid genetic testing and clinical decision support systems. By overcoming current barriers, pharmacogenomics could become an integral component of ICU pharmacotherapy, improving patient safety, treatment efficacy, and healthcare cost efficiency on a global scale.

5. Conclusion

Pharmacogenomics has the potential to transform critical care treatment by enabling clinicians to practice personalized drug therapy, reducing adverse drug reactions, and improving treatment outcomes. This is the first study to the best of our knowledge from India highlighting the significant inter-individual variability in key pharmacogenomic markers among ICU patients, emphasizing the importance of genetic testing in guiding drug selection and dosing. While international studies provide valuable insights about the importance of precision medicine, their applicability to Indian populations remains limited due to the ethnic genetic diversity. The findings reinforce the need for region-specific pharmacogenomic research and the development of tailored dosing guidelines to optimize therapy in critically ill patients. Integrating pharmacogenomics into ICU protocols, supported by rapid genetic testing and clinical decision support tools, can enhance precision medicine in critical care, ultimately improving patient safety and healthcare efficiency.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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None.

Author's Contributions

Conceptualization: QH, SK. Data curation: VRK, MSD, BKSN, SJ, GQ. Formal analysis: SJ, SKB. Writing- original draft: GQ. Writing- review & editing: QH, SK, GQ.

Ethical Clearance

The ethics committee of Kamineni Hospitals has exempted for full ethics approval of this manuscript, as the data utilized in this study was collected as routine diagnostics. Fully anonymized has been used in the manuscript. The analysis of de-identified, non-interventional data was collected retrospectively. Hence, the Ethical Board granted the approval as it qualifies for an exemption from full ethical review as per standard ethics guidelines.

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