

ISSN Print: 1813-176x
ISSN Online: 1994-4624

International Journal of Molecular Medicine and Advance Sciences
https://ijmmas.com/

Research Article

Association of Pharmacogenomic Variants with Adverse Drug Reactions in Patients Receiving Multiple Medications: A Prospective Observational Study.

Sagarika Mahapatra.
Molecular Pathology and Cytogenomics Fellowship Student D Y Patil University,

Correspondence:
Sagarika Mahapatra.

Received: 06-10-2026
Revised: 17-10-2026
Accepted: 29-10-2026
Published: 02-11-2026

DOI: 10.61336/ijmmas.22-04-23

Abstract: ***Background:*** Pharmacogenomic variation may contribute to adverse drug reactions (ADRs), particularly in patients exposed to polypharmacy. This study evaluated the association between clinically relevant drug–gene interactions and ADR occurrence. ***Methods:*** In this prospective observational study, 200 adults receiving ≥5 medications were followed for 90 days. Clinically actionable pharmacogenomic variants were assessed, and drug–gene interactions were defined by the presence of an actionable variant together with exposure to the corresponding medication. ADRs were evaluated for causality and severity. ***Results:*** ADRs occurred in 55 patients (27.5%). Actionable pharmacogenomic variants were identified in 45.0%, while 22.5% had a relevant exposure-matched drug–gene interaction. ADRs occurred in 44.4% of patients with relevant interactions compared with 22.6% without such interactions. Relevant drug–gene interactions independently predicted ADRs (adjusted OR 2.93, 95% CI 1.35–6.36). Greater medication burden was also independently associated with ADR risk. Most ADRs were mild or moderate. ***Conclusion:*** Exposure-matched pharmacogenomic interactions were associated with increased ADR risk during polypharmacy and may improve identification of patients requiring closer medication monitoring.

Keywords: Pharmacogenomics; Adverse drug reactions; Polypharmacy; Drug–gene interaction; Precision medicine; Pharmacovigilance.

Copyright @ 2026: This is an open-access article distributed under the terms of the Creative Commons Attribution license which permits unrestricted use, distribution and reproduction in any medium for non-commercial use (NonCommercial, or CC-BY-NC) provided the original author and source are credited.

INTRODUCTION

Adverse drug reactions (ADRs) are a significant contributor to preventable morbidity, hospitalization, extended treatment duration and health care costs. They are affected by patient characteristics, comorbidity, organ function, medication burden and drug-drug interactions. A large prospective study by Pirmohamed et al. showed that the proportion of hospital admissions due to ADRs was clinically significant and therefore medication-related harm is an important patient safety issue [1]. The issue becomes more relevant in patients who are taking more than one drug, as the more drugs prescribed, the greater the likelihood of pharmacokinetic and pharmacodynamic interactions. At the population level, there have also been significant increases in the prevalence of polypharmacy and potentially serious drug–drug interactions over time [2].

However, clinical factors and drug burden do not account for all interindividual differences in drug response. Variability in genes related to drug metabolism, drug transport, drug receptors, and immune-mediated drug responses could significantly affect drug exposure, drug efficacy, and drug toxicity [3,4]. Pharmacogenomics offers a tool to identify such genetically based variations and to use them to inform personalized prescribing. Examples of established polymorphisms are the CYP2C9 gene and warfarin response, the VKORC1 gene and warfarin response, the CYP2D6 gene and disposition of various opioids and cardiovascular drugs, the CYP2C19 gene and response to clopidogrel and selected proton-pump inhibitors, and the SLCO1B1 gene and susceptibility to statin-associated muscle toxicity [3,4].

Structured prescribing guidelines and curated knowledge resources have been vital to the movement of pharmacogenomics from discovery to implementation in the clinic. The Clinical Pharmacogenetics Implementation Consortium (CPIC) was created to offer evidence-based recommendations for the use of available genetic information in the context of specific drugs [5]. PharmGKB complements this approach by systematically curating gene–drug associations, genotype–phenotype relationships, drug labels, and prescribing recommendations [6]. The CPIC and Dutch Pharmacogenetics Working Group guidance have been compared, revealing significant agreement for a number of established drug–gene pairs and variations in interpretation and implementation methodology [7].

In addition, pre-emptive panel-based testing has increased the scope of the clinical use of pharmacogenomics by identifying multiple actionable variants prior to a patient taking the medications associated with those variants. The creation of the PGx-Passport illustrated the potential to create a clinically relevant panel of germline variants associated with clinically accepted prescribing recommendations [8]. However, the clinical impact of a pharmacogenomic variant can vary greatly depending on exposure to the drug affected by that variant. In patients with polypharmacy, genetic susceptibility may be combined with

advanced age, multiple comorbidities, organ dysfunction and drug–drug interactions, which is why this consideration is especially relevant.

Although the implementation of pharmacogenomics has grown, there is still limited prospective evidence that investigates the association of pharmacogenomic variants with exposures matched to the specific variant and with ADRs in patients taking multiple medications, especially in the context of routine tertiary-care practice. The aim of the present study was therefore to identify the distribution of clinically relevant pharmacogenomic variants, describe the occurrence of ADRs and assess whether clinically relevant drug–gene interactions are independently associated with ADRs, after adjusting for conventional clinical and medication-related risk factors.

MATERIALS AND METHODS

Study design and participants

It was a prospective observational cohort study that was carried out in a tertiary care hospital during 2026. Adult patients (age ≥18 years) taking 5 or more regularly prescribed systemic medications were screened for inclusion. The planned number of patients for recruitment was 220 to yield about 200 evaluable patients in the event of incomplete genotyping or follow-up.

Patients were eligible if they were to continue with their prescribed medication for at least 30 days, had a complete medication history, had been tested for pharmacogenomics, and were available for prospective follow-up. Patients who had end-of-life conditions, drug poisoning or intentional overdose, lacked a reliable history of medication use, lacked a complete pharmacogenomic evaluation, or lacked adequate follow-up were excluded.

Evaluation of clinical and medication status

Baseline data consisted of age, gender, body mass index, smoking and alcohol habits, comorbidities, renal and hepatic function, and laboratory parameters. All medications prescribed regularly were recorded, including the type of medication, the dose, how often the medication was given and for how long. Polypharmacy was categorized as 5–7, 8–10, or >10 medications. Potential drug–drug interactions, high-risk drugs and the number of comorbidities were also documented.

Pharmacogenomic assessment

Pharmacogenomic genotyping and interpretation

Peripheral venous blood was collected in EDTA tubes, and genomic DNA was extracted using a standard silica-column-based DNA extraction method. Targeted pharmacogenomic genotyping was performed for clinically relevant variants in CYP2C19, CYP2C9, VKORC1, CYP2D6, SLCO1B1, NUDT15, TPMT, and HLA-B*15:02; DPYD variants were assessed when fluoropyrimidine exposure was clinically relevant.

Single-nucleotide variants were genotyped using allele-specific real-time PCR assays. CYP2D6 copy-number variation was assessed separately using a quantitative TaqMan copy-number assay to identify whole-gene deletion or duplication where applicable. HLA-B*15:02 carrier status was determined using allele-specific/sequence-specific PCR. Genotype calls that were ambiguous or failed prespecified quality-control criteria were repeated, with confirmatory sequencing used when required.

Alleles and diplotypes were assigned using established pharmacogene nomenclature, and genotype-to-phenotype translation was based on gene-specific Clinical Pharmacogenetics Implementation Consortium (CPIC) recommendations and PharmGKB/ClinPGx guideline annotations available at the time of analysis [5–7]. CYP phenotypes were classified as poor, intermediate, normal, rapid, or ultrarapid metabolizer, as applicable. SLCO1B1 was classified according to transporter function, while HLA-B*15:02 was treated as carrier/non-carrier status. VKORC1 interpretation was considered drug specific rather than assigned as a generalized metabolizer phenotype.

Classification of actionable pharmacogenomic findings

A pharmacogenomic finding was classified as actionable when the identified genotype or predicted phenotype corresponded to a gene–drug pair for which an established pharmacogenomic guideline recommended a change in prescribing, drug selection, or dosage. CPIC level A or B gene–drug pairs were considered actionable because these levels support a prescribing action. PharmGKB/ClinPGx clinical annotations and guideline annotations were used to cross-check the clinical significance of individual variants; evidence levels 1A, 1B, 2A, and 2B were considered supportive evidence but were not, by themselves, sufficient to define clinical actionability in the absence of a prescribing recommendation.

A relevant drug–gene interaction was considered present only when a patient carrying an actionable genotype or phenotype was concurrently exposed to a medication whose prescribing, dosage, efficacy, or toxicity was affected by that

pharmacogenomic finding. Actionable findings without exposure to the corresponding drug were therefore retained as genetic findings but were not classified as active drug–gene interactions.

Classification of high-risk drug–gene interactions

Exposure-matched drug–gene interactions were further classified according to the intensity of the pharmacogenomic prescribing recommendation. A high-risk drug–gene interaction was defined as an actionable exposure in which the applicable guideline recommended avoidance or substitution of the implicated drug, a major genotype-guided dose reduction, or identified a substantially increased risk of serious toxicity. Examples included high-risk HLA-associated hypersensitivity, markedly reduced thiopurine metabolism related to NUDT15 or TPMT, reduced DPYD activity during fluoropyrimidine treatment, or other gene–drug combinations for which guideline-directed substantial modification of therapy was indicated.

All remaining exposure-matched actionable combinations for which genotype-informed monitoring, moderate dose adjustment, or treatment modification was recommended were classified as relevant drug–gene interactions without meeting the prespecified high-risk definition. Classification was performed before analysis using the same decision rules for all participants.

Adverse drug reaction assessment

Participants were followed prospectively for 90 days for the occurrence of adverse drug reactions (ADRs). Suspected ADRs were detected by clinical review, patient reporting, medical records, laboratory abnormalities, and treatment modifications.

The suspected medication, time to onset, organ system involved, clinical manifestations, management and outcome were recorded for each ADR. Causality was determined by the WHO–UMC causality system and divided into certain, probable/likely, possible, and unlikely. The severity of the adverse drug reaction (ADR) was defined as mild, moderate, or severe, with additional documentation of serious reactions requiring hospitalization, prolonged hospitalization, drug withdrawal, dose modification, or specific treatment.

Study outcomes

The main outcome was the development of at least one ADR within 90 days of the follow-up period.Secondary outcomes were the number and distribution of pharmacogenomic variants, the severity and causality of the ADRs, the incidence of serious ADRs, and the association between specific drug–gene interactions and clinically compatible adverse reactions.

Statistical analysis

Continuous variables were presented as mean ± SD or median (IQR) depending on the distribution of data and categorical variables were presented as frequencies and percentages. The baseline characteristics were compared between the two groups (with and without ADRs) by Welch's independent-samples t test for continuous variables and by chi-square or Fisher exact test for categorical variables. Univariable logistic regression was used to first assess the association between clinically relevant drug–gene interactions and the occurrence of ADRs. A parsimonious multivariable logistic regression model was then used to assess whether pharmacogenomic risk was an independent predictor of ADRs, after clinically relevant covariates such as age, medication burden, renal impairment, comorbidity burden and potential drug–drug interactions were adjusted for. Time to first ADR was compared according to relevant drug–gene interaction status using Kaplan–Meier analysis and the log-rank test. Discrimination of the clinical model with and without pharmacogenomic interaction status was evaluated using receiver-operating-characteristic analysis and area under the curve with bootstrap 95% confidence intervals Results were expressed as crude and adjusted odds ratios with 95% confidence intervals. Gene-specific drug–ADR associations were explored when sufficient exposure and event numbers were available. All tests were two-sided, and $p<0.05$ was considered statistically significant.

Ethical considerations

The study protocol was approved by the Institutional Ethics Committee of the participating tertiary-care hospital. Written informed consent was obtained from all participants before enrolment. Genetic and clinical information was handled confidentially and used only for the purposes approved in the study protocol.

RESULTS

Participant characteristics

The final analysis included 200 patients receiving at least five regularly prescribed medications. Mean age was 61.1 ± 11.6 years, 89 (44.5%) were female, and the median medication burden was 8 [6–9] medications. Patients who developed an adverse drug reaction (ADR) had a greater comorbidity burden, higher medication burden, more potential drug–drug interactions, and were more likely to have a relevant drug–gene interaction (Table 1).

Table 1. Baseline demographic, clinical, and medication characteristics according to ADR status

Characteristic	Overall (N=200)	ADR (n=55)	No ADR (n=145)	Test statistic	p-value
Age, years	61.1 ± 11.6	63.4 ± 13.0	60.3 ± 10.9	t=1.56	0.122
Female sex	89 (44.5%)	25 (45.5%)	64 (44.1%)	χ^2=0.03	0.867
BMI, kg/m²	25.1 ± 3.9	25.8 ± 4.4	24.8 ± 3.7	t=1.55	0.125
Number of comorbidities	3 [2–5]	4 [3–5]	3 [2–4]	U=4946.5	0.008
Chronic kidney disease	49 (24.5%)	18 (32.7%)	31 (21.4%)	χ^2=2.78	0.096
Chronic liver disease	15 (7.5%)	3 (5.5%)	12 (8.3%)	Fisher exact	0.764
eGFR, mL/min/1.73 m²	77.2 [61.7–95.8]	72.9 [58.1–95.8]	78.7 [64.1–95.3]	U=3600.0	0.290
AST, U/L	28 [23–33]	27 [23–32]	28 [23–33]	U=3717.0	0.460
ALT, U/L	30 [25–40]	30 [24–36]	31 [25–40]	U=3603.0	0.293
Number of medications	8 [6–9]	9 [8–10]	7 [6–9]	U=5544.5	<0.001
≥10 medications	47 (23.5%)	23 (41.8%)	24 (16.6%)	χ^2=14.16	<0.001
High-risk medication use	142 (71.0%)	45 (81.8%)	97 (66.9%)	χ^2=4.31	0.038
Potential drug–drug interactions, n	1 [0–3]	2 [1–4]	1 [0–2]	U=5441.5	<0.001
Relevant drug–gene interaction	45 (22.5%)	20 (36.4%)	25 (17.2%)	χ^2=8.36	0.004

Values are mean ± SD, median [IQR], or n (%), as appropriate. Continuous variables were compared using Welch's t test or Mann–Whitney U test; categorical variables used Pearson χ^2 or Fisher exact test as appropriate. ADR, adverse drug reaction; BMI, body mass index; eGFR, estimated glomerular filtration rate.

Pharmacogenomic variant distribution

At least one prespecified actionable pharmacogenomic variant was identified in 90 (45.0%) patients. The most frequent non-reference/actionable genotypes involved CYP2C19, SLCO1B1, CYP2D6, and CYP2C9. Genotype and predicted phenotype distributions for the full panel are summarized in Table 2.

Table 2. Distribution of pharmacogenomic genotypes and predicted phenotypes

Gene	Genotype/variant, n (%)	Predicted phenotype/function, n (%)
CYP2C19	*1/*1: 153 (76.5%) *1/*17: 14 (7.0%) *1/*2: 26 (13.0%) *17/*17: 2 (1.0%) *2/*17: 1 (0.5%) *2/*2: 4 (2.0%)	Intermediate metabolizer: 27 (13.5%) Normal metabolizer: 153 (76.5%) Poor metabolizer: 4 (2.0%) Rapid metabolizer: 14 (7.0%) Ultrarapid metabolizer: 2 (1.0%)
CYP2C9	*1/*1: 171 (85.5%) *1/*2: 12 (6.0%) *1/*3: 12 (6.0%) *2/*3: 2 (1.0%) *3/*3: 3 (1.5%)	Intermediate metabolizer: 24 (12.0%) Normal metabolizer: 171 (85.5%) Poor metabolizer: 5 (2.5%)
VKORC1	-1639 A/A: 28 (14.0%) -1639 G/A: 81 (40.5%) -1639 G/G: 91 (45.5%)	Exposure-specific warfarin sensitivity was assigned only among warfarin users
CYP2D6	*1/*1: 167 (83.5%) *1/*4: 14 (7.0%) *1/*5: 4 (2.0%) *1xN/*1: 2 (1.0%) *4/*4: 13 (6.5%)	Intermediate metabolizer: 18 (9.0%) Normal metabolizer: 167 (83.5%) Poor metabolizer: 13 (6.5%) Ultrarapid metabolizer: 2 (1.0%)
SLCO1B1	c.521CC: 8 (4.0%) c.521TC: 27 (13.5%) c.521TT: 165 (82.5%)	Decreased function: 27 (13.5%) Normal function: 165 (82.5%) Poor function: 8 (4.0%)
NUDT15	*1/*1: 192 (96.0%) *1/*3: 7 (3.5%) *3/*3: 1 (0.5%)	Intermediate metabolizer: 7 (3.5%) Normal metabolizer: 192 (96.0%) Poor metabolizer: 1 (0.5%)
TPMT	*1/*1: 190 (95.0%) *1/*3A: 10 (5.0%)	Intermediate metabolizer: 10 (5.0%) Normal metabolizer: 190 (95.0%)
HLA-B*15:02	No: 190 (95.0%) Yes: 10 (5.0%)	Not applicable

DPYD	No decreased-function variant: 197 (98.5%) c.1905+1G>A heterozygous: 2 (1.0%) c.2846A>T heterozygous: 1 (0.5%)	Intermediate activity: 3 (1.5%) Normal activity: 197 (98.5%)

Percentages use the full cohort denominator (N=200). VKORC1 warfarin sensitivity was assigned only among patients receiving warfarin; HLA-B*15:02 is reported as carrier status.

Adverse drug reactions

During follow-up, 55 (27.5%) patients experienced at least one ADR. Most affected patients had a single event, and most ADRs were mild or moderate. Bleeding and gastrointestinal reactions were the most frequent organ-system categories, while severe and serious events were uncommon. Metoprolol, simvastatin, and clopidogrel were the most frequently implicated individual drugs (Table 3)

Table 3. Characteristics of observed adverse drug reactions

Characteristic	Category	n (%)
Overall ADR incidence	Any ADR	55 (27.5)
Number of ADRs among affected patients	1	42 (76.4)
	2	12 (21.8)
	3	1 (1.8)
Suspected drug	Metoprolol	8 (14.5)
	Simvastatin	5 (9.1)
	Clopidogrel	5 (9.1)
	Aspirin	3 (5.5)
	Pantoprazole	3 (5.5)
	Apixaban	3 (5.5)
	Gabapentin	3 (5.5)
	Paracetamol	3 (5.5)
	Other suspected drugs	22 (40.0)
ADR system organ class	Bleeding	10 (18.2)
	Gastrointestinal	10 (18.2)
	CNS/sedation	7 (12.7)
	Myopathy/muscle symptoms	7 (12.7)
	Bradycardia	6 (10.9)
	Hypotension	4 (7.3)
	Rash	3 (5.5)
	Electrolyte disturbance	2 (3.6)
	Hepatotoxicity	1 (1.8)
	Hypoglycemia	1 (1.8)
	Other	4 (7.3)
WHO–UMC causality	Certain	3 (5.5)
	Probable/Likely	21 (38.2)
	Possible	30 (54.5)
	Unlikely	1 (1.8)
ADR severity	Mild	32 (58.2)
	Moderate	19 (34.5)
	Severe	4 (7.3)
Serious ADR	Yes	5 (9.1)
Required hospitalization	Yes	4 (7.3)
Prolonged hospitalization	Yes	1 (1.8)
Required drug discontinuation	Yes	17 (30.9)
Required dose reduction	Yes	13 (23.6)
Required specific treatment	Yes	18 (32.7)
PGx-attributed ADR	Yes	18 (32.7)

Percentages for ADR characteristics use patients with ≥1 ADR (n=55) as the denominator unless otherwise stated. The overall incidence uses the full cohort denominator (N=200). Less frequent suspected drugs are grouped as 'Other suspected drugs'.

Pharmacogenomic interaction and ADR occurrence

A relevant exposure-matched drug–gene interaction was present in 45 (22.5%) patients, including 19 (9.5%) with a high-risk interaction. ADRs occurred in 20 (44.4%) patients with a relevant interaction compared with 35 (22.6%) without one. The high-risk interaction subgroup had the highest ADR frequency (Table 4; Figure 1).

Table 4. ADR occurrence according to pharmacogenomic risk status

PGx status	N	ADR n	ADR rate	Odds ratio	95% CI	Test statistic	p-value
Actionable variant absent	110	27	24.5%	Reference	—	—	—
Actionable variant present without relevant interaction	45	8	17.8%	0.66	0.28–1.60	χ^2=0.84	0.360
Relevant drug–gene interaction present	26	8	30.8%	1.37	0.53–3.49	χ^2=0.43	0.514
High-risk drug–gene interaction present	19	12	63.2%	5.27	1.88–14.74	χ^2=11.45	<0.001
Any relevant DGI present vs absent	45	20	44.4%	2.74	1.36–5.51	χ^2=8.36	0.004

Odds ratios are unadjusted. The first four rows use actionable-variant-absent patients as the reference group. The final row compares any relevant drug–gene interaction with no relevant interaction.

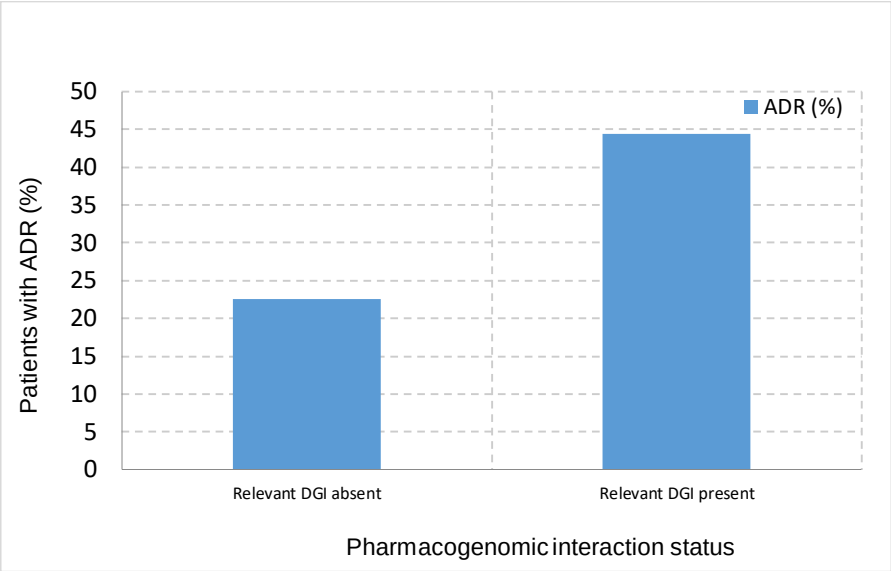


Figure 1. Frequency of adverse drug reactions according to relevant drug–gene interaction status.

Univariable and multivariable predictors of ADR

Relevant drug–gene interaction status, medication burden, comorbidity burden, potential drug–drug interactions, and high-risk medication use were associated with ADR occurrence in univariable analyses (Table 5). In the parsimonious multivariable model, a relevant drug–gene interaction remained independently associated with ADR occurrence (adjusted OR 2.93, 95% CI 1.35–6.36; z=2.72, p=0.007), as did medication count (adjusted OR 1.34 per additional medication, 95% CI 1.09–1.66; z=2.76, p=0.006). Other model covariates were not independently associated with ADRs (Table 6; Figure 2).

Table 5. Univariable predictors of adverse drug reactions

Predictor	Crude OR	95% CI	Test statistic	p-value
Relevant drug–gene interaction	2.74	1.36–5.51	z=2.83	0.005
Age, per 10 years	1.26	0.96–1.66	z=1.68	0.093
Female sex	1.05	0.57–1.97	z=0.17	0.867
Number of medications	1.41	1.20–1.66	z=4.15	<0.001
Chronic kidney disease	1.79	0.90–3.56	z=1.65	0.098
Liver dysfunction	0.73	0.23–2.33	z=-0.52	0.600
Number of comorbidities	1.28	1.06–1.54	z=2.56	0.010
Potential drug–drug interactions	1.40	1.17–1.67	z=3.67	<0.001
High-risk medication use	2.23	1.03–4.80	z=2.04	0.041

Crude odds ratios are from separate univariable logistic regression models. Age is scaled per 10-year increase.

Table 6. Multivariable predictors of adverse drug reactions

Predictor	Adjusted OR	95% CI	Test statistic	p-value	VIF
Relevant drug–gene interaction	2.93	1.35–6.36	z=2.72	0.007	1.01
Age, per 10 years	1.22	0.90–1.65	z=1.28	0.200	1.08
Number of medications	1.34	1.09–1.66	z=2.76	0.006	1.68
Chronic kidney disease	1.48	0.67–3.26	z=0.98	0.328	1.06
Potential drug–drug interactions	1.14	0.91–1.44	z=1.14	0.255	1.70

Parsimonious logistic regression model. Maximum variance inflation factor=1.70. Age is scaled per 10-year increase; medication count and potential drug–drug interaction count are modeled per unit increase.

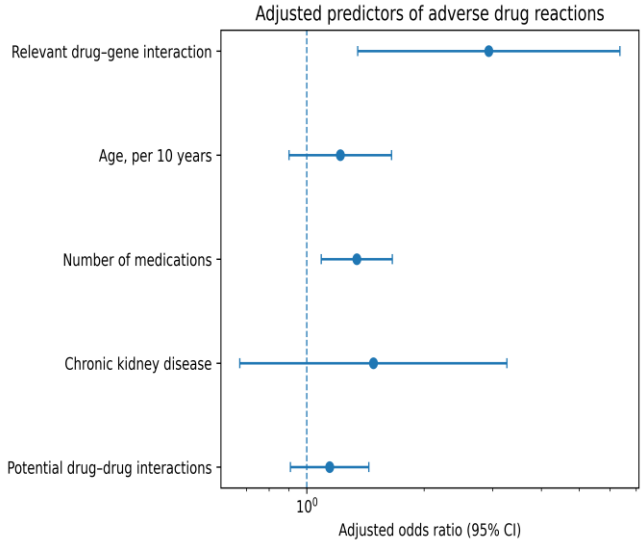


Figure 2. Adjusted predictors of adverse drug reactions in the multivariable logistic regression model.

Time-to-event and predictive performance

Time to first ADR differed according to relevant drug–gene interaction status (log-rank χ^2=11.36, p<0.001). The clinical model had an AUC of 0.718 (bootstrap 95% CI 0.633–0.799), which increased to 0.757 (0.685–0.826) after addition of relevant pharmacogenomic interaction status. The magnitude of this difference was modest.

Gene-specific exploratory findings

Gene-specific analyses were limited by the number of exposed patients for several drug–gene pairs. CYP2D6-related beta-blocker/opioid exposure was the most informative exploratory subgroup, whereas CYP2C9/warfarin, NUDT15/TPMT/azathioprine, and other low-frequency pairs were interpreted descriptively because of small exposure counts.

DISCUSSION

The present study revealed that adverse drug reactions (ADRs) occurred more often when an actionable pharmacogenomic variant was present along with the respective drug. In total, 27.5% (55/200) of the patients had at least one ADR. Forty-five percent had an actionable pharmacogenomic variant, though only 22.5% had a clinically-relevant exposure-matched drug–gene interaction. The incidence of ADRs was higher in patients who had a relevant interaction (44.4%) than in those who did not (22.6%) and the association was still present after adjustment for clinical covariates (adjusted OR 2.93, 95% CI 1.35–6.36). The increased ADR frequency in patients with high-risk interactions also highlights the need to take genotype into account in addition to actual drug exposure.

These results are similar to those of the PREPARE implementation study by Swen et al. [9] that assessed 6,944 patients in seven European countries. For patients with an actionable genotype, genotype-guided prescribing decreased the number of clinically relevant ADRs from 27.7% to 21.0% (OR 0.70). A similar decrease was seen in the entire evaluable population. The present findings complement this evidence by demonstrating that unmodified exposure to a pharmacogenomically relevant drug may be linked to an increased risk of ADRs.

Medication burden was also an independent predictor of the occurrence of ADRs, with an increase in medication burden being linked to an increase in the adjusted odds of an event. Davies et al. [10] conducted a prospective study of 3,695 hospital patient-episodes, with ADRs occurring in 14.7%. Patients with ADRs were prescribed a median of nine medications, while those without ADRs were prescribed six medications, with each additional medication being associated with a 14% increase in the hazard of an ADR. The increased ADR frequency in the current cohort is consistent with the fact that the cohort was restricted to patients taking at least five medicines and reflects the combined effects of polypharmacy and genetic susceptibility.

The reactions observed with metoprolol are biologically consistent with CYP2D6-mediated variability. Fux et al. [11] showed that there was a significant gene-dose effect for CYP2D6 on metoprolol exposure, with significantly higher dose-normalized concentrations observed in poor metabolizers compared with extensive or ultrarapid metabolizers. The overall rates of adverse events were comparable between the phenotypes, but cold extremities were more common in poor/intermediate metabolizers. These results show that the pharmacokinetic differences could lead to increased susceptibility without necessarily causing clinical toxicity.

Similar exposure dependent relationships have been shown for SLCO1B1 and statin-associated myopathy. In the SEARCH study [12] the risk of myopathy was found to be approximately 4.5 fold higher per allele of SLCO1B1 rs4149056 C allele and approximately 17 fold higher in CC homozygotes compared to TT homozygotes during high dose simvastatin therapy. In this cohort, simvastatin was among the more frequently implicated drugs and muscle-related symptoms were responsible for 12.7% of ADRs, highlighting the importance of transporter-mediated susceptibility in statin-treated patients.

The distinction between variant carriage and clinically relevant drug exposure is further supported by evidence from thiopurine pharmacogenetics. Similar overall hematological ADR rates were observed by Coenen et al. [13] with both genotype-guided and conventional thiopurine treatment, but among TPMT variant carriers, toxicity decreased from 22.9% to 2.6% with genotype-adjusted dosing. This observation is similar to the current finding that the most informative pharmacogenomic variants were those that were paired with an interacting medication.

Further evidence for the potential of pharmacogenomic information to minimise drug-related toxicity is provided by randomized trials of warfarin, where it is used appropriately. Gage et al. [14] reported in the GIFT trial that genotype-guided dosing lowered the composite of major bleeding, INR ≥4, thromboembolism or death from 14.7% to 10.8% and slightly increased time in therapeutic range (TTR). Likewise, Pirmohamed et al. [15] reported that genotype-directed dosing resulted in improved time in therapeutic range (60.3% to 67.4%), reduced excessive anticoagulation and decreased time to therapeutic INR. The COAG trial by Kimmel et al. [16] demonstrated no improvement in the time spent in the therapeutic range with genotype guidance, and identified important variation in performance across racial groups. Together, these studies highlight the importance of the gene panel, ancestry, drug exposure, and implementation strategy on pharmacogenomic utility.

The ADR profile of this cohort also highlights that genetic predisposition is just one aspect of medication safety. Bleeding and gastrointestinal reactions were the most common categories, followed by CNS/sedative effects and muscle reactions. The majority of reactions were mild or moderate, while a small number were serious or required hospitalization, treatment modification, or drug discontinuation. These results are consistent with the idea of incorporating the pharmacogenomic data with the traditional risk factors (medication burden, renal and hepatic function, comorbidities, and drug–drug interactions) rather than relying on pharmacogenomic data alone.

The major strengths of this study are the prospective assessment, risk classification based on exposure-matched drug–gene interactions, and the evaluation of multiple clinically relevant pharmacogenomic variants. There are some limitations, such as the single-centre design, the modest sample size, and the small number of cases for each gene–drug combination, especially for the less common variants. In patients on multiple medications, causality assessment of the ADR may also be difficult and residual confounding due to dose, compliance, severity of the disease and unmeasured interactions cannot be ruled out.

CONCLUSION

Clinically relevant, exposure-matched pharmacogenomic interactions were associated with a higher risk of adverse drug reactions in patients receiving polypharmacy. Integrating pharmacogenomic information with medication burden and conventional clinical risk factors may improve individualized medication safety.

REFERENCES

1. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ. 2004;329(7456):15–19. doi: 10.1136/bmj.329.7456.15.
2. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995–2010. BMC Med. 2015;13:74. doi: 10.1186/s12916-015-0322-7.
3. Relling MV, Evans WE. Pharmacogenomics in the clinic. Nature. 2015;526(7573):343–350. doi: 10.1038/nature15817.
4. Weinshilboum RM, Wang L. Pharmacogenomics: precision medicine and drug response. Mayo Clin Proc. 2017;92(11):1711–1722. doi: 10.1016/j.mayocp.2017.09.001.
5. Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. Clin Pharmacol Ther. 2011;89(3):464–467. doi: 10.1038/clpt.2010.279.
6. Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, Sangkuhl K, Thorn CF, et al. Pharmacogenomics knowledge for personalized medicine. Clin Pharmacol Ther. 2012;92(4):414–417. doi: 10.1038/clpt.2012.96.
7. Bank PCD, Caudle KE, Swen JJ, Gammal RS, Whirl-Carrillo M, Klein TE, et al. Comparison of the guidelines of the Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group. Clin Pharmacol Ther. 2018;103(4):599–618. doi: 10.1002/cpt.762.
8. van der Wouden CH, van Rhenen MH, Jama WOM, Ingelman-Sundberg M, Lauschke VM, Konta L, et al. Development of the PGx-Passport: a panel of actionable germline genetic variants for pre-emptive pharmacogenetic testing. Clin Pharmacol Ther. 2019;106(4):866–873. doi: 10.1002/cpt.1489.
9. Swen JJ, van der Wouden CH, Manson LE, Abdullah-Koolmees H, Blagec K, Blagus T, et al. A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. Lancet. 2023;401(10374):347–356. doi: 10.1016/S0140-6736(22)01841-4.
10. Davies EC, Green CF, Taylor S, Williamson PR, Mottram DR, Pirmohamed M. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. PLoS One. 2009;4(2):e4439. doi: 10.1371/journal.pone.0004439.
11. Fux R, Mörike K, Pröhmer AMT, Delabar U, Schwab M, Schaeffeler E, et al. Impact of CYP2D6 genotype on adverse effects during treatment with metoprolol: a prospective clinical study. Clin Pharmacol Ther. 2005;78(4):378–387. doi: 10.1016/j.clpt.2005.07.004.
12. SEARCH Collaborative Group. SLCO1B1 variants and statin-induced myopathy—a genomewide study. N Engl J Med. 2008;359(8):789–799. doi: 10.1056/NEJMoa0801936.
13. Coenen MJH, de Jong DJ, van Marrewijk CJ, Derijks LJJ, Vermeulen SH, Wong DR, et al. Identification of patients with variants in TPMT and dose reduction reduces hematologic events during thiopurine treatment of inflammatory bowel disease. Gastroenterology. 2015;149(4):907–917.e7. doi: 10.1053/j.gastro.2015.06.002.
14. Gage BF, Bass AR, Lin H, Woller SC, Stevens SM, Al-Hammadi N, et al. Effect of genotype-guided warfarin dosing on clinical events and anticoagulation control among patients undergoing hip or knee arthroplasty: the GIFT randomized clinical trial. JAMA. 2017;318(12):1115–1124. doi: 10.1001/jama.2017.11469.
15. Pirmohamed M, Burnside G, Eriksson N, Jorgensen AL, Toh CH, Nicholson T, et al. A randomized trial of genotype-guided dosing of warfarin. N Engl J Med. 2013;369(24):2294–2303. doi: 10.1056/NEJMoa1311386.
16. Kimmel SE, French B, Kasner SE, Johnson JA, Anderson JL, Gage BF, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. N Engl J Med. 2013;369(24):2283–2293. doi: 10.1056/NEJMoa1310669.