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Review

Pharmacogenomic Determinants of Adverse Drug Effects: A Systematic Review and Meta-analysis

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Abstract. *Background/Aim: Genomic variants can predispose individuals to adverse drug effects (ADEs), implying the potential for personalised therapy based on genetic data to prevent them. However, existing pharmacogenomic databases lack a comprehensive list of such variants due to irregular updates and incomplete literature coverage. To facilitate the assessment of the feasibility of using pharmacogenetic testing on a larger scale and identify existing gaps in the literature, this study sought to compile a comprehensive list of genomic variants associated with ADEs, with a focus on serious ADEs. Patients and Methods: To identify relevant pharmacogenetic studies within randomised controlled trials (RCTs), post-hoc studies of RCTs and meta-analyses, two literature searches were performed across multiple databases. The compiled list of variants associated with ADEs was refined to create a set of variant–drug pairs significantly associated with serious ADEs. Results: We identified 254 RCTs/post-hoc studies and 207 meta-analyses investigating variants associated with ADEs. Among the 254 RCTs/post-hoc studies identified, 24 meta-analyses were conducted. Among these, only G6PD A− showed a significant association with severe anaemia in patients receiving artemisinin-based treatment for malaria. Conclusion: This systematic review provides a comprehensive list of variants associated with ADEs and a set of variant–drug pairs significantly associated with serious ADEs. These resources serve as valuable references for regulatory agencies, researchers, and healthcare professionals. This study, however, underscores the need for improved indexing and standardised definitions of ADE seriousness in the literature.*

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Clinical and experimental studies demonstrated that specific genomic variants may predispose individuals to particular adverse drug effects (ADEs) (1). However, an up-to-date, comprehensive list of pharmacogenomic variants associated with ADEs is lacking. While PharmGKB serves as a global resource for pharmacogenomic biomarker information, it may not always provide up-to-date coverage of the literature in its totality (2). Concerns regarding false positives and methodological quality in pharmacogenomic research have also been raised (3). Thus, there is a need for a systematic and reproducible synthesis of the available literature to provide robust evidence for the pharmacogenomics of ADEs.

By dominating the top of the pyramid of evidence (4), well-conducted systematic reviews of randomised controlled trials (RCTs) in the context of clinical decision-making have progressively become the gold standard for evidence-based medicine (5-7). RCTs offer higher quality evidence compared to non-randomised studies (8-10), in which pharmacogenomic effects tend to be overestimated. Nearly all well-conducted RCTs collect, grade, and provide a detailed summary of their intervention's safety data, allowing for accurate attribution of observed effects to the therapy used (11).

Efforts are made in RCTs to reduce the risk of confounding variables and selective reporting (12, 13). However, ethical concerns may preclude the implementation of RCTs in certain situations (14, 15). Furthermore, some

Table I. *The PICO's four key components in this study.*

Population	Patients or participants of any age, sex, ethnicity, stage of disease, comorbidity
Intervention	Pharmacological interventions at any dose, frequency, timing, route of delivery or in any treatment settings
Comparison	Comparison to the intervention can be either placebo or active comparator
Outcome	Incidence of at least one toxicity outcome of any grade or type whether acute, chronic or late-onset, as either a primary or secondary outcome

Table II. *Eligibility criteria for inclusion in the systematic review.*

Inclusion criteria	Exclusion criteria
English-language publications	Non-human studies
Articles in journals, theses, dissertations	Editorial articles, case reports, study protocols, ongoing studies
Single or multi-centre RCTs of any design, length, follow-up period, setting	No access to full text, meeting abstracts, conference proceedings
Post-hoc analyses of RCTs	Non-randomised trials, single-arm trials, case-control, cohort studies (unless nested in RCTs)
Meta-analyses	RCTs with concerns over the integrity of trial design or the randomisation process
Any germline genomic variants	Systematic or narrative reviews without meta-analysis
Studies in which carriers of specific genotype(s) were only eligible or ineligible for enrolment	GWAS/Meta-analyses of GWAS
Metaboliser status, phenotypes or activity scores defined based on genotypes	Gene expression, pathogenic variant, somatic variants, bacterial or viral genome variants
Any length of intervention or follow-up	Metaboliser status or phenotypes determined by biochemical assays
Comparison to the intervention can be either placebo or active comparator	Treatment algorithms (studies examined the combined genetic with clinical moderator)
Toxicity outcome of any grade	Genotype-guided treatment or pretreatment PG screening studies
Toxicity-related death or discontinuation of therapy	Irrelevant investigations (*e.g.*, recreational drugs)
Composite outcomes provided included at least one ADEs as clinical endpoints	Studies of radiation-induced toxicities or toxicity to organophosphate insecticides
	Radio-chemotherapy or chemo-radiation with radiotherapy not applied on both treatment arms analysed
	Drug–drug interactions
	Surrogate measurements or biomarker levels for toxicities as an endpoint using *in vitro* assays
	Pharmacokinetics/pharmacodynamics studies
	Adverse events or mortality due to reduced response to treatment
	Studies of response, disease progression, prognosis, recurrence, survival, treatment resistance, treatment failure, disease-related death, all-cause mortality
	Adverse outcomes, such as addiction or physical/psychological dependence
	Acute/chronic transplant rejection due to reduced efficacy
	Economic evaluation studies

RCTs: Randomised controlled trials; ADEs: adverse drug effects.

ADEs might not have been identified or anticipated when the RCTs were originally designed. The scarcity of well-designed RCTs in the context of the pharmacogenomics of ADEs is particularly evident (16). Therefore, both RCTs and *post-hoc* analyses of RCTs may need to be considered in the context of the pharmacogenomics of ADEs. Other study designs, including meta-analyses, further enhance precision and minimise false findings (17).

This study aimed to assess the current state of the art in pharmacogenomics of ADEs, compile a list of genomic variants associated with ADEs and subsequently identify variant–drug pairs significantly linked to serious ADEs, given their notable association with morbidity and mortality. This was achieved through systematic literature reviews targeting RCTs/*post-hoc* analyses and meta-analyses.

Patients and Methods

Data sources and search strategy. To identify genomic variants associated with toxicities or ADEs from RCTs and meta-analyses, we conducted two separate systematic reviews using databases including MEDLINE, Embase and Cochrane CENTRAL/Cochrane Register of Controlled Trials. Additionally, to retrieve reports from journals not

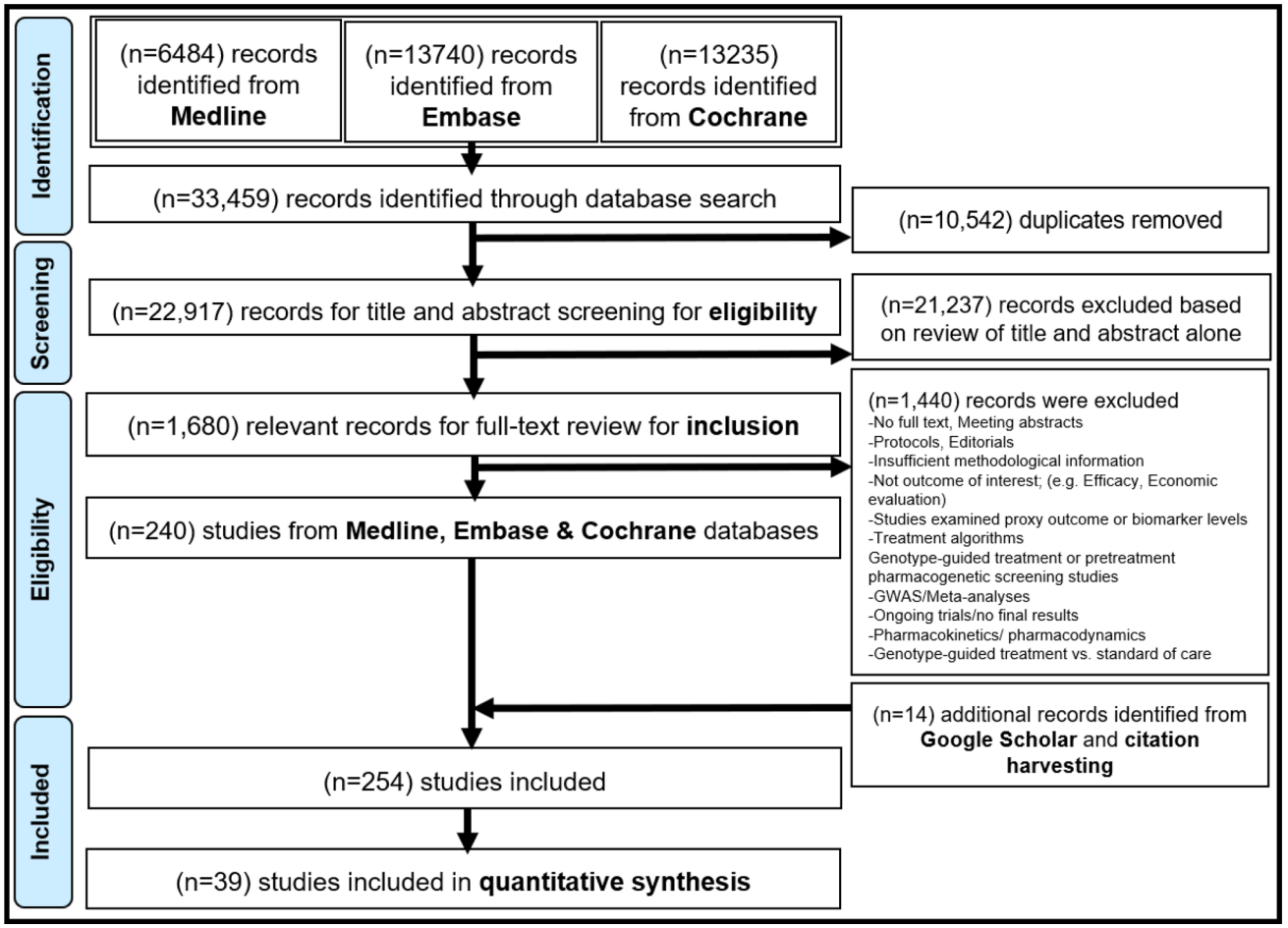

Figure 1. *PRISMA flow chart of systematic literature search and selection process of randomised controlled trials (RCTs) and posthoc studies of RCTs.*

indexed in these databases, we performed supplementary searches on Google Scholar's Advanced Search Portal. Database-specific search strategies are provided in Supplementary Tables S1-S7.

In addition to peer-reviewed articles, we endeavoured to include unpublished studies to mitigate publication bias (18, 19). This involved searching for subsequent or follow-up reports from dissertations, theses, conference abstracts, and independently-conducted investigations. To ensure thoroughness, we conducted retrospective reference harvesting of landmark and highly salient studies. We also reviewed the study methodology in articles that merited further scrutiny and cross-referenced them with trial registers to examine whether the initials, acronyms, or unique identification codes used in the titles or abstracts were RCTs. For clarification or missing data, as well as to identify any later unpublished articles, the original investigators were contacted.

Eligibility criteria. To compile a list of variants associated with ADEs, we established eligibility criteria using the PICO framework (Population, Intervention, Comparison, Outcome) (Table I). Articles meeting the inclusion criteria and none of the exclusion criteria were considered. We excluded prospective genotype-guided treatment trials and pre-treatment pharmacogenomic screening studies due to significant differences in randomisation design (Table II).

The list of variants associated with ADEs was further refined to create a set of variant–drug pairs significantly associated with serious ADEs. We introduced the term medically important adverse drug effects (MIADEs) to address the heterogeneity in the terminology used in the literature to describe the seriousness of ADEs. MIADEs are adverse drug effects that investigators have classified as serious or severe, meet WHO criteria for seriousness (20, 21), are classified as severe (22), or are recognised as designated or important medical events (23, 24). Composite toxicity outcomes were included if at least one incorporated endpoint satisfied MIADE criteria, but underspecified toxicity outcomes and unspecified treatment discontinuation were excluded. Haplotypes and star alleles were interpreted using relevant allele nomenclature to create more precise and interrogable genotypes. We excluded genomic variants related to cancer chemotherapy unless their indications overlapped with indications for other therapeutic classes (*e.g.,* Methotrexate).

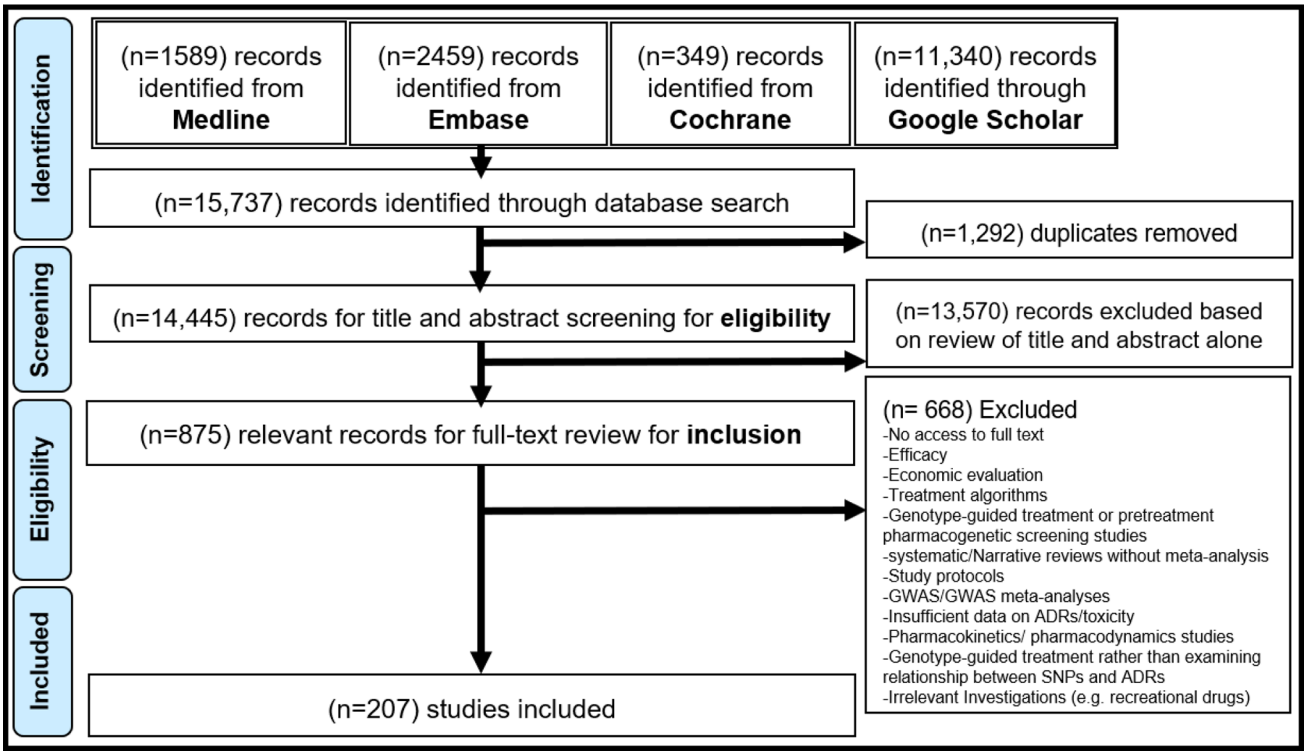

Figure 2. *PRISMA flow chart of systematic literature search and selection process of meta-analyses studies.*

Study selection. Search results from various databases were extracted and merged using Mendeley. Manual removal of duplicated citations was performed. Two independent reviewers (KM, LJ) conducted abstract and title screening, and irrelevant items were removed after screening. Relevant records underwent a full-text assessment based on pre-specified criteria for inclusion. Decisions as to which studies to include were made through consensus and tangentially relevant records were excluded.

Data extraction. The key characteristics of the studies were documented including treatment modality, toxicity outcomes, interventions(s) or culprit drug(s), genomic variant(s) and reference (containing study's authors and year of publication). For the meta-analysis, quantitative data were extracted from eligible studies.

Quantitative data synthesis and statistical analysis. Quantitative data from eligible studies were combined *via* meta-analysis. Consideration was given to both clinical and statistical aspects to determine appropriateness. A meta-analysis was conducted by combining studies that examined the same treatments and variants with similar measures of related toxicity outcomes and excluding those with different or tangentially-related outcomes. In cases where multiple studies used data from the same cohort, only the study with the largest analysis and/or longest follow-up period was included to prevent overrepresenting patient data in the meta-analysis. When necessary, effect sizes were transformed into a uniform metric for meta-analysis after being calculated using standard procedures. Forest plots were generated to visualise overall patterns and funnel plots were used to evaluate publication bias when applicable. We employed random-effects models to address the anticipated heterogeneity resulting from the broad range of study characteristics that satisfied our eligibility criteria. The Bonferroni correction was applied to the *p*-values to account for multiple hypothesis testing. R version v4.1 (Foundation for Statistical Computing, Vienna, Austria) and Stata/SE version 16.0 (StataCorp, College Station, TX, USA) were used for the statistical analyses. Both I^2 and *p*-values for *Q*-statistic were displayed in forest plots.

Results

This study identified 254 RCTs/post-hoc analyses and 207 meta-analyses. The initial search identified 33,459 potential RCTs and 15,737 potential meta-analyses. In the final synthesis, 254 RCTs/*post-hoc* analyses and 207 meta-analyses were included (Figure 1 and Figure 2). Of these, 93 (37%) and 52 (25%) studies did not report any significant associations, respectively. The full lists of variants associated with ADEs are shown in Supplementary Tables S8 and S9. Variants associated with ADEs were annotated with font colours: black for increased risk, green for decreased risk, and red for no significant association.

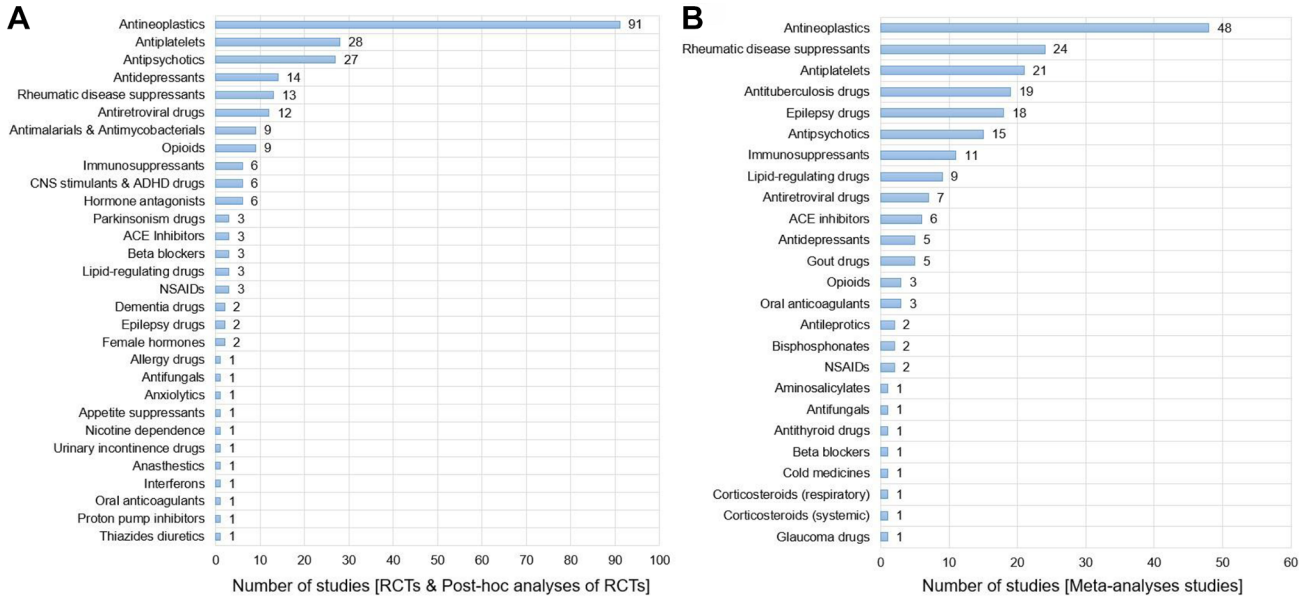

Figure 3. *The therapeutic classes investigated in studies included in this systematic review. (A) Randomised controlled trials (RCTs) & post-hoc analyses of RCTs studies. (B) Meta-analyses studies. This bar chart shows that chemotherapy-based cytotoxic regimens are the most commonly examined therapeutic modalities in PGx reports included in this systematic review. Antiplatelet drugs were the second, antipsychotic drugs were the third most frequently therapeutic classes investigated in RCTs & post-hoc analyses of RCTs studies, whilst in meta-analyses rheumatic disease suppressant drugs were the second with antiplatelets ranking third.*

Antineoplastics were the most commonly investigated therapeutic modality. Chemotherapy-based cytotoxic regimens were the most studied therapeutic modality, followed by antiplatelet drugs like Clopidogrel, antipsychotic drugs, and rheumatic disease suppressant drugs (mainly Methotrexate) (Figure 3).

Only one of the meta-analyses of RCTs performed in the current study was statistically significant. We conducted 24 meta-analyses involving 39 studies from identified RCTs/*post-hoc* analyses. After correcting for multiple testing (corrected *p*-value=0.05/24=0.002), the only statistically significant meta-analysis was the association between *G6PD A−* and severe anaemia in patients taking artemisinin-based combination therapy or Chlorproguanil-Dapsone-Artesunate (CDA) for malaria in seven studies (25-31) with pooled OR [95%CIs]=15 [10.27, 21.9], $p<0.0001$ (Figure 4). No other pooled effect sizes were significant. Detailed results are shown in Supplementary Table S10. Examples of the forest and funnel plots are shown in Supplementary Figure S1 and Figure S2.

This study generated a set of variant-drug pairs significantly associated with MIADEs. Having excluded variants associated with ADEs related to chemotherapy for cancer, we generated a set of variant-drug pairs significantly associated with MIADEs from 34 RCTs/*post-hoc* analyses and 86 meta-analyses (Figure 5). These pairs are listed in Table III.

Discussion

Owing to insufficient up-to-date coverage of the literature in its entirety, the available pharmacogenomic databases do not provide a complete list of genomic variants. Hence, this study systematically reviewed the literature to compile a comprehensive list of genomic variants associated with ADEs. Our list can serve as a reliable resource for regulators, researchers, and healthcare professionals. Due to their significant clinical implications for morbidity and mortality, this study synthesised a set of variant-drug pairs associated with MIADEs. The seriousness and clinical importance of ADEs are the most influential factors to weigh in the implementation of these tests on a broader scale (32). The paucity of RCTs in pharmacogenomic studies of ADEs was notable, with the majority being *post-hoc* analyses rather than RCTs, with randomisation status often unclear.

Findings from most individual studies were not statistically significant with mixed results and a noticeable lack of replication in other populations. The body of evidence supporting the clinical validity and utility of pharmacogenetic testing for ADEs requires replication in

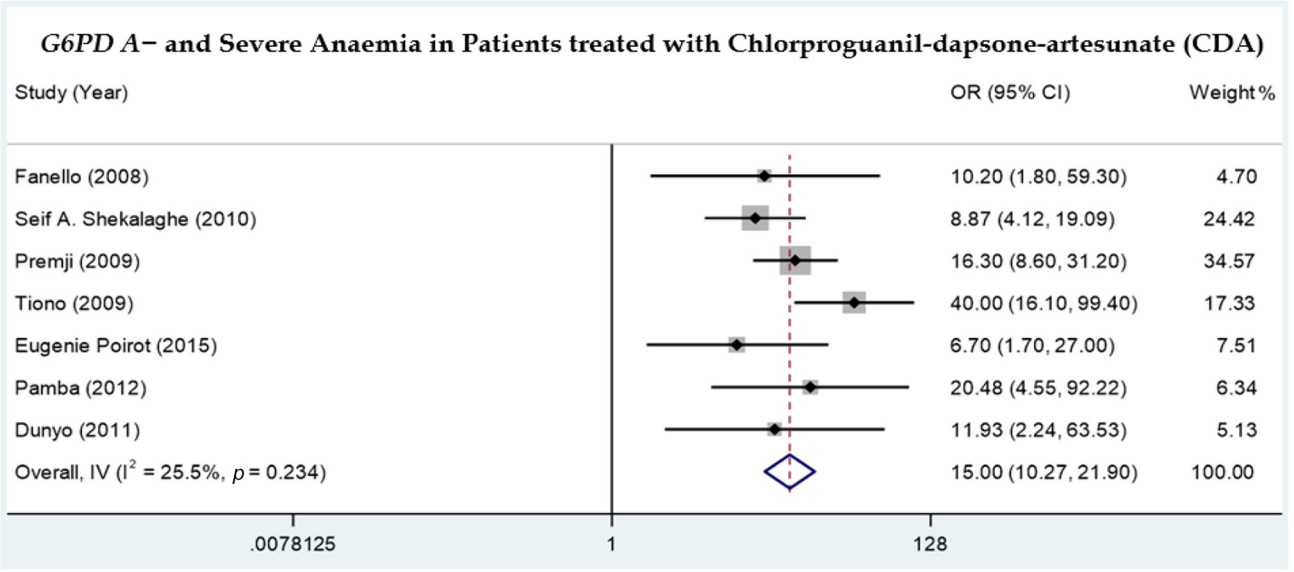

Figure 4. *Meta-analysis of G6PD A− and severe anaemia in patients taking CDA or artemisinin-based combination therapy for malaria. Meta-analysis of seven studies examined G6PD A− and severe anaemia in patients taking CDA or artemisinin-based combination therapy for malaria. Individual and pooled odds ratios from studies were reported in the forest-plot. Squares represent study-specific effect estimates and the size of the square reflects the study-specific weight (i.e., the inverse of the variance). The diamond represents the summary effect estimate with 95% confidence interval, and the horizontal lines indicate 95% confidence intervals. OR: Odds ratios; 95%CI: 95% confidence interval.*

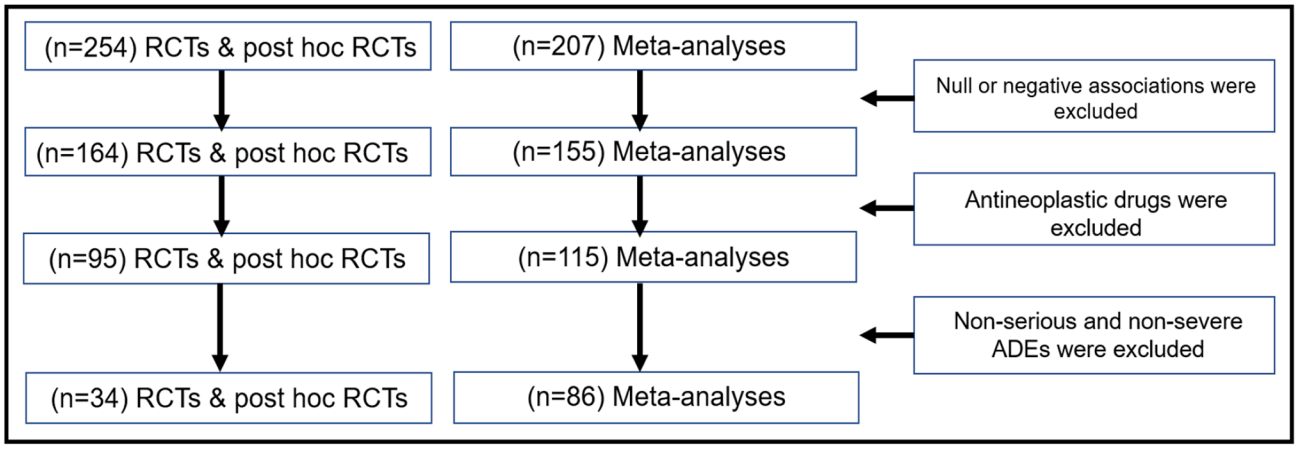

Figure 5. *The process of synthesising the set of variant-drug pairs significantly associated with MIADEs. Variants associated with adverse drug effects (ADEs) related to cancer chemotherapy were excluded, and only variant-drug pairs significantly associated with MIADEs were included. The set of variant-drug pairs was identified from 34 randomised controlled trials (RCTs)/post-hoc analyses of RCTs and 86 meta-analyses.*

larger cohorts with longer follow-ups. Except for the association between severe anaemia and *G6PD A−* in malaria patients on artemisinin-based therapy or CDA, none of the meta-analyses of RCTs/*post-hoc* analyses performed in the current study showed significance. However, concerns about severe haemolytic anaemia led to the premature termination of CDA therapy (33).

Substantial heterogeneity in study designs, interventions, outcomes, follow-up periods, participant characteristics and statistical methods was observed. Inconsistencies were noted in toxicity outcome reporting and definitions of seriousness, emphasising the need for standardised terminology to reduce the risk of erroneously designating seriousness (34). ADEs were inconsistently indexed or reported in the literature. Most

Table III. *The set of variant-drug pairs significantly associated with MIADEs*.

Treatment or Drug(s)	Variant(s)
Abacavir	HLA-B*57:01
Antiretroviral therapy (Nevirapine, Abacavir)	HLA-A*24, HLA-B*18, HLA-*35, HLA-B *39, HLA-B*51, HLA-B*81, HLA-C*04
Nevirapine	HLA-B*58:01, HLA-DRB1*01
Atazanavir	UGT1A1*1/*28, UGT1A1*28/*28
Efavirenz	ABCB1 3435C>T
Ribavirin	ITPA rs1127354 CC, ITPA rs7270101 AA, ITPA rs6051702 AA, Absent ITPase deficiency haplotype
Ritonavir-boosted Atazanavir	UGT1A1 rs887829 T/T, UGT1A1*28/*28
Antituberculous agents[1]	CYP2E1 RsaI/PstI polymorphism [RsaI is –1053C>T (rs2031920), PstI is –1293G>C (rs3813867)], CYP2E1 96-bp homozygous insertion allele (*1D/*1D), CYP2E1 homozygous (*1A/*1A), NAT2 481C>T (rs1799929), NAT2 590G>A (rs1799930), NAT2 857G>A (rs1799931), NAT2 282C-T (rs1041983), NAT2 slow acetylators or NAT2 ultra-slow acetylator [*5B/*6A, *5B/*7A, *6A/*6A, *6A/*7B, *7B/*7B], GSTT1 (null/null), GSTM1 null
CDA or Chlorproguanil-dapsone	G6PD A–
Dapsone	G6PD A–, HLA-B*1301
Antipsychotics	DRD3 Ser9Gly, Taq1A in DRD2 the A2 variant, CYP2D6*3, *4, *5, *6, *7, *12, *14, homozygotes for the *2 or *10 alleles
Aripiprazole	VNTR polymorphism in DAT1/SLC6A3 (rs28363170)
Trazodone	ABCB1 C3435T T/T
Atomoxetine	CYP2D6 PM [2 non-functioning alleles CYP2D6*3, *4, *5, *6, *7, *8]
Citalopram	GRIA3 rs4825476, GRIK2 rs2518224
Paroxetine	HTR2A -1438G/G
Aromatic antiepileptic drugs	HLA-A*24:02, HLA-B*15:02
Carbamazepine	HLA-B*15:02, HLA-B*1511, HLA-A*31:01, HLA-B*57:01
Lamotrigine	HLA-A*2402
Oxcarbazepine	HLA-A*3101, HLAB*1502
Phenytoin	HLA-B*13:01, HLA-B*15:02, HLA-B*51:01, CYP2C9*3
NSAIDs[2]	HLA-DRB1*11
NSAIDs[3]	CYP2C8*3 (rs11572080; rs10509681), CYP2C9*2 (rs1799853), CYP2C9*3 (rs1057910)
Celecoxib	ALOX15 (rs2255888), EP4 (rs4133101, rs13186505), GPX3 (rs8177406), PGES (rs2241271, rs2302821), CRP (rs1800947), SRC (rs6017996, rs6018256, rs6018257), CYP2C9*2 (R144C), CYP2C9*3 (I359L)
Oxycodone	ABCB1 G2677T/A
ACE inhibitors	MME rs989692, CRB1 rs2786098 T allele, ETV6 rs2724635 G allele
ACE inhibitors or ARBs	KCNMA1 rs2253202
Metoprolol	CYP2D6 PM
Statins[4]	LILRB5 (rs12975366: T>C: Asp247Gly), SLCO1B1 (rs4149056: c.521T>C: Val174Ala)
Clopidogrel	ABCB1 rs1045642 (c.3435C>T), CYP2C19*17 rs12248560 (4195C→T/A)
Warfarin	CYP2C9*2 (rs1799853), *3 (rs1057910)
Methotrexate	MTHFR C677T (rs1801133), MTHFR A1298C (rs1801131), ATIC 347C/G (rs2372536), ALDH2 rs671, SLC19A1 80G>A
Thiopurine-based drugs (Azathioprine or 6-mercaptopurine)	NUDT 15 c.415C>T, NUDT 15 c.52G>A, TPMT variants (*2,*3A,*3B,*3C,*3D,*4,*5,*6,*7,*8,*10,*12,*21,*37,*40), ITPA 94C>A (rs1127354), ITPA IVS2 + 21A>C (rs7270101), NUDT15 R139C, NUDT15 c.36_37ins/delGGAGTC, NUDT15 rs116855232
Tacrolimus plus everolimus or mycophenolate	FKBP2 c.-2110GG
Sulfasalazine	NAT2 slow acetylators
Glucocorticoid[5]	PAI-1 –675 4G/5G (rs1799889), ABCB1 C3435T C allele
Glucocorticoids[6]	GSTM1 (null/null) (homozygous deletion)
Inhaled corticosteroids±Additional corticosteroids[7]	PDGFD rs591118
Hormone therapy[8]	GP6 13254 TC+CC genotypes, GP1BA –5TT genotype
Letrozole or Tamoxifen	CYP19A1 rs700518, ESR2 rs4986938
Tamoxifen	CYP19A1 rs10046
Exemestane	ESR1 rs9322336
Antithyroid drugs (Carbimazole/Methimazole)	HLA-B*27:05, HLA- B*38:02, HLA-DRB1*08:03
Bisphosphonates	CYP2C8 rs1934951, VEGF rs3025039
Allopurinol	HLA-B*58:01, HLA-A*33:03, HLA-C*03:02
Lansoprazole	CYP2C19 PMs [CYP2C19*2, *3, *8, or *9]

ACEIs: Angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; CDA: Chlorproguanil-dapsone-artesunate; NSAIDs: Non-steroidal anti-inflammatory drugs. [1]Isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin; [2]Dipyrone, Propyphenazone, acetic derivatives, such as Diclofenac, Indomethacin, ASA; [3]Indomethacin, Celecoxib, Flurbiprofen, Ibuprofen, Meloxicam, Piroxicam, Tenoxicam, Naproxen, Aceclofenac, Diclofenac, Ketorolac, Dexketoprofen; [4]Simvastatin, Rosuvastatin, Cerivastatin, Simvastatin, Atorvastatin; [5]Prednisone, Dexamethasone, Methylprednisolone; [6]Prednisone±Dexamethasone; [7]Prednisone, Dexamethasone; [8]oral conjugated equine oestrogen plus medroxyprogesterone acetate.

ADEs in the identified RCTs were secondary endpoints, which are often collected and assessed with less rigour compared to the primary endpoints (35). However, "adverse effect" or "drug toxicity" were indexed in the databases and mentioned in the title or abstract when the authors of those studies dedicated their substantive discussions to the ADEs themselves, indicating their clinical significance. This usually occurs when the authors consider the examined ADEs to be either serious or clinically important (36). Therefore, our set of variant-drug pairs associated with MIADEs can be more accurate than a list of genomic variants associated with ADEs.

Study limitations. First, our searches were limited to English articles, possibly introducing language bias. However, most relevant trials are in English, and non-English studies are prone to lower methodological quality (37). Second, chemotherapy-based studies were excluded when we generated the set of variant–drug pairs significantly associated with MIADEs. However, this was inevitable due to the complexity of their combination designs and concerns about interactions.

Conclusion

To date, this study is the first to explore the pharmacogenomics of ADEs without restrictions on patient characteristics, interventions, follow-up periods or outcome types. Through extensive searches across major databases and in a reproducible manner, this study identified variant-drug pairs associated with MIADEs, which have substantial impacts on morbidity and mortality as well as pharmacogenomic testing practices. Additional replication is required in light of the observed heterogeneity and inconsistent findings across the studies. It is imperative to improve indexing and standardise definitions of the seriousness of ADE in the literature. While this systematic review identified gaps and areas in knowledge that require further research, research that discusses the progress made in addressing those gaps can be valuable.

Supplementary Material

Available at: https://doi.org/10.6084/m9.figshare.25869532.v1

Data Availability Statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Conflicts of Interest

The Authors declare that they have no conflicts of interest that are directly relevant to the content of this study.

Authors' Contributions

KM, MW, and LJ conceptualised the study and designed the research. KM and LJ conducted the research and graphical overviews. MW performed the statistical analysis and generated the graphs.

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