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Drug-gene interactions in older patients with coronary artery disease

Shizhao Zhang[1,2†], Chao Lv[1,2†], Lisha Dong[1,2], Yangxun Wu[1,2] and Tong Yin[1,2*]

Abstract

Background Older patients with coronary artery disease (CAD) are particularly vulnerable to the efficacy and adverse drug reactions, and may therefore particularly benefit from personalized medication. Drug–gene interactions (DGIs) occur when an individual's genotype affects the pharmacokinetics and/or pharmacodynamics of a victim drug.

Objectives This study aimed to investigate the impact of cardiovascular-related DGIs on the clinical efficacy and safety outcomes in older patients with CAD.

Methods Hospitalized older patients (≥ 65 years old) with CAD were consecutively recruited from August 2018 to May 2022. Eligible patients were genotyped for the actionable pharmacogenetic variants of CYP2C9, CYP2C19, CYP2D6, CYP3A5, and SLCO1B1, which had clinical annotations or implementation guidelines for cardiovascular drugs. Allele frequencies and DGIs were determined in the cohort for the 5 actionable PGx genes and the prescribed cardiovascular drugs. All patients were followed up for at least 1 year. The influence of DGIs on the cardiovascular drug-related efficacy outcomes (all-cause mortality and/or major cardiovascular events, MACEs) and drug response phenotypes of "drug-stop" and "dose-decrease" were evaluated.

Results A total of 1,017 eligible older patients with CAD were included, among whom 63.2% were male, with an average age of 80.8 years old, and 87.6% were administrated with polypharmacy (≥ 5 medications). After genotyping, we found that 96.0% of the older patients with CAD patients had at least one allele of the 5 pharmacogenes associated with a therapeutic change, indicating a need for a therapeutic change in a mean of 1.32 drugs of the 19 cardiovascular-related drugs. We also identified that 79.5% of the patients had at least one DGI (range 0–6). The median follow-up interval was 39 months. Independent of age, negative association could be found between the number of DGIs and all-cause mortality (adjusted HR: 0.84, 95% CI: 0.73–0.96, $P=0.008$), and MACEs (adjusted HR: 0.84, 95% CI: 0.72–0.98, $P=0.023$), but positive association could be found between the number of DGIs and drug response phenotypes (adjusted OR: 1.24, 95% CI: 1.05–1.45, $P=0.011$) in the elderly patients with CAD.

Conclusions The association between cardiovascular DGIs and the clinical outcomes emphasized the necessity for the integration of genetic and clinical data to enhance the optimization of cardiovascular polypharmacy in older

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patients with CAD. The causal relationship between DGIs and the clinical outcomes should be established in the large scale prospectively designed cohort study.

Keywords Older patients, Coronary artery disease, Drug-gene interactions, Pharmacogenomics

Introduction

As the top-ranked cause of disability-adjusted life-years among older patients worldwide, coronary artery disease (CAD) is the leading cause of mortality and morbidity, especially among older adults [1, 2]. For all patients with CAD, evidence-based use of optimal medical therapy, including antiplatelet drugs, statin, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, and beta-blockers is recommended. However, cardiovascular pharmacotherapy in older patients with CAD is complicated by the age-related modification of the pharmacokinetic and pharmacodynamic properties [3]. Additionally, with the acquired multimorbidity and advancing age, polypharmacy and adverse drug reactions (ADRs) accumulated [4]. Polypharmacy increases the risk of ADRs and drug interactions, which in turn can lead to increased morbidity-mortality and healthcare costs [5]. Older patients are particularly vulnerable to the efficacy and ADRs of medications and may therefore particularly benefit from individualized treatment [6]. Pharmacogenetic biomarkers are increasingly used for individually optimized drug therapy. Compared to age and drug-drug interactions (DDIs), actionable drug-gene interactions (DGIs) could cause a larger effect on pharmacokinetic exposure and confer more chance for personalized medication [7, 8]. Moreover, the assessment of how DDIs are affected by DGIs is an important area to have a fuller understanding of potential adverse clinical consequences [9]. Assuming additive effects of age and genotype, different priorities should be considered for drugs when administrated to older patients. Given the broad relevance of pharmacogenetics to areas including thrombosis and coagulation, hyperlipidemia, and interventional cardiology et al. [10–12], older patients with CAD might particularly benefit from pharmacogenomic diagnostics. Several pilot studies implicated the feasibility of pharmacogenetic testing for the reduction of hospital admissions in older patients [13, 14]. However, whether the pharmacogenetic testing could improve the clinical favourable outcomes remains uncertain. In the present study, we aimed to investigate the impact of drug- and gene-based pharmacokinetic interactions on clinical outcomes in older patients with CAD.

Methods

Participants and clinical characteristics

Hospitalized patients with CAD were consecutively recruited from August 2018 to May 2022 in the Department of Cardiology, General Hospital of the Chinese People's Liberation Army. Patients were eligible for inclusion in the current study if they were older than 65 years and were discharged with more than 2 prescriptions. Exclusion criteria included patients with severe diseases and expected life expectancy < 12 months, severe hepatic and renal insufficiency (Child-Pugh class C liver disease or K/DOQI Stage 5 chronic kidney disease), history of organ transplant, invasive solid tumours, or hematologic malignancies. Patient demographic information and medical history were collected from the Electronic Medical Record (EMR) system. CAD was defined as stable coronary artery disease (SCAD, including stable angina, previous myocardial infarction and ischemic cardiomyopathy) and acute coronary syndrome (ACS, including unstable angina and acute myocardial infarction). The diagnosis of CAD was reached according to the positive diagnostic procedures including stress tests, computed tomography, radionuclide imaging, and coronary angiography, et al. The diagnosis of CAD was qualified according to the consensus of two experienced physicians. Comorbidities were further subdivided into cardiovascular and non-cardiovascular conditions. Pre-existing cardiovascular multimorbidity includes heart failure, hypertension, diabetes mellitus, stroke, and atrial fibrillation. Pre-existing non-cardiovascular multimorbidity includes chronic obstructive pulmonary disease, hepatic and renal insufficiency, peptic ulcer disease, connective tissue disease, dementia and any canner. Baseline use of drugs for cardiovascular conditions was collected. This included antiplatelet agents, oral anticoagulation agents, lipid-lowering agents, beta-blockers, calcium channel blockers, diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and oral antidiabetic agents. Additionally, the use of proton pump inhibitors and psychotropic agents was collected at baseline, but no information on other drugs was available.

Participants were followed up for incident events for at least 1 year. The Morisky Medication Adherence Scale-8 items [15] was used to evaluate the medication adherence of each patient during follow-ups. The full score of the scale is 8 points, with a score < 6 as low compliance, a score ≤ 6 as < 8 as medium compliance, and a score of 8 as high compliance. Accordingly, patients with low compliance during follow-ups were not included for the analysis in the study. The study complied with the Declaration of Helsinki and was approved by the ethics committee of the People's Liberation Army General Hospital. All patients signed informed consent forms.

Identification of actionable genetic variants

Participants were genotyped using the MassARRY platform (Agena Bioscience, San Diego, CA, USA), with the inclusion of the following actionable pharmacogenetic variants including CYP2C9*2 (rs1799853), CYP2C9*3 (rs1057910), CYP2C19*2 (rs4244285), CYP2C19*3 (rs4986893), CYP2C19*17 (rs12248560), CYP2D6*10 (rs1065852), CYP3A5*3 (rs776746), and SLCO1B1*5 (rs4149056), all of which had the clinical annotation from Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB) and/or implementation guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC) for the cardiovascular drugs [16, 17]. Allele frequency was calculated and compared with the frequency in the East Asian population reported in the 1,000 Genomes Project [18].

Assessment of drug-gene interactions and drug-drug interactions

Drug-gene interaction (DGI) is defined as an individual's genetic phenotype that affects the patient's ability to clear a drug [19]. For pharmacokinetic DGIs, substrate drugs were available in the clinical annotations from the PharmGKB for the above genotyped pharmacogenes (Table S1). we identified and counted the total number of unique DGIs, and the numbers of interactions per patient and gene were determined. Information about DGIs of clinical recommendations was collected from corresponding CPIC [17] or Dutch Pharmacogenetics Working Group (DPWG) guidelines [20]. DGIs not mentioned in pharmacogenomics guidelines were considered to need to be applied under clinician monitoring.

Drug-drug interactions (DDIs) were defined as the individual's regimen affecting that individual's ability to clear another drug [19]. For pharmacokinetic DDIs, substrates, inhibitors and inducers were available from Flockhart Table [21]. The drugs involved in this study are summarized in Table S2.

Clinical outcomes

The primary outcome was defined as all-cause mortality. The secondary outcome was defined as the major adverse cardiovascular events (MACEs) including a composite of cardiovascular mortality, nonfatal myocardial infarction, stent thrombosis, nonfatal stroke, and unplanned revascularization. Drug response phenotypes defined as "drug-stop" or "dose-decrease" were also evaluated. "Drug-stop" after only one prescription was considered to avoid ADRs, lack of therapeutic efficacy, or both, while "dose-decrease" similarly indicated ADRs-related intolerance or extreme efficacy. There may be other reasons why people stop their drugs that may not reflect drug efficacy or tolerance, such as being unable to obtain the medication prescription from local pharmacies or not following medical advice. We excluded these conditions when counting the drug response phenotypes.

Statistical analysis

Continuous variables with a normal distribution were summarized as the mean ± standard deviation. Categorical clinical variables were presented as group numbers (percentages). Integer count variables were presented as median [interquartile range (IQR) /range] for numbers of comorbidities, drugs and DGIs. Multivariable Cox regression was applied to test whether the number of DGIs was associated with efficacy outcomes, and drug response phenotypes during follow-ups. Efficacy outcomes based on time to the first event were evaluated by comparing Kaplan–Meier-based cumulative incidence rates with the log-rank test. In sensitivity analyses, the relationship between the number of DGIs and clinical outcomes within the follow-up interval of 1 year, 2 years, 3 years and all relevant analyses were analyzed. All multivariate analyses were adjusted for age, sex, number of comorbidities, coexisting diseases (myocardial infarction, heart failure, hepatic and renal insufficiency), number of drugs, and number of DDIs. All data analyses were conducted with SPSS 26.0 (IBM, Armonk, NY, USA). The P value was used to test for the significance threshold ($P<0.05$).

Results

Participants characteristics

A total of 1,017 eligible older patients with CAD were included in the present study (Fig. 1). Baseline clinical characteristics are shown in Table 1. In the cohort, 63.2% were male, mean age was 80.81 ± 5.18 years old (range 65–102). The most common cardiovascular comorbidity was hypertension (79.3%), followed by diabetes (40.8%) and stroke (19.3%). Non-cardiovascular comorbidities were found in 29.3% of patients. The median numbers of the Charlson comorbidity index were 4 (IQR 3–5, range 2–13). 87.6% of the patients were administrated with ≥5 medications. The most commonly used cardiovascular medications were lipid-lowering agents (91.3%), followed by antiplatelet agents (90.1%) and antihypertensives (89.5%). The median number of drugs per patient was 6 (IQR 5–8, range 2–13), with cardiovascular drugs of 5 (IQR 5–7, range 1–11), and non-cardiovascular drugs of 1(IQR 0–1, range 0–7). All participants were followed up for incident events for at least 1 year, and the median follow-up interval was 39 months.

Pharmacogenetic genotypes and phenotypes

The pharmacogenetic allelic characteristics in older patients with CAD for the 5 actionable pharmacogenes are depicted in Fig. 2 (Tables S2 and S3). A total of 95.1% of the older patients with CAD had at least one

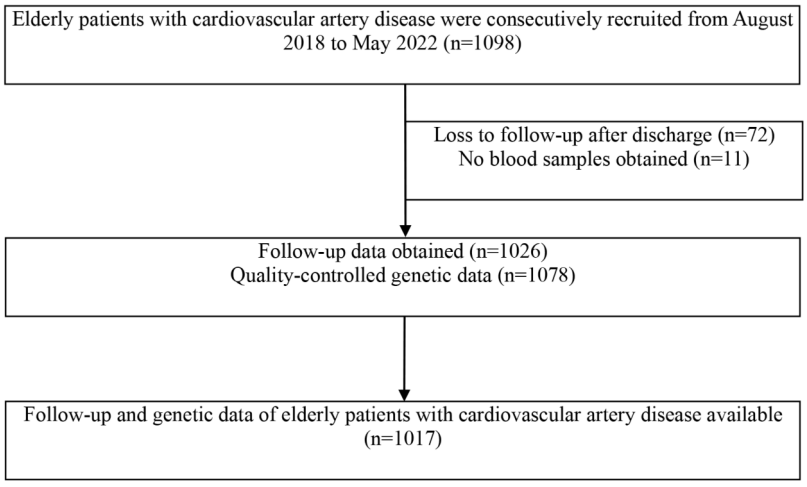

Fig. 1 Study flow chart

actionable genotype (range 0–7), and the median number of actionable genotypes per patient was 3. The most common actionable allele was CYP3A5*3 (72.2%), followed by CYP2D6*10 (51.1%). The least actionable allele was CYP2C9*3 (4.3%) (Fig. 2A). The allele frequencies of the actionable genotypes were comparable with the frequencies described for the East Asian population in the 1,000 Genomes Project.

In the cohort, the phenotype information was correlated with the genotype characterization. The vast majority of the older patients with CAD presented a normal metabolic status for the genes of CYP2C9 and SLCO1B1 with low variability. For the CYP3A5*3 as the most common actionable allele, 52.3% of the patients presented a poor metabolizer and 39.8% an intermediate metabolizer. In the case of the CYP2C19 gene which was tested for 3 phenotypic varieties, 1.6% of the cohort presented a rapid metabolizer, 11.9% a poor metabolizer, and 47.6% an intermediate metabolizer. As for the CYP2D6 gene, 28.9% of the patients present an intermediate metabolizer (Fig. 2B, Table S4).

Distribution and the therapeutic impact of drug-gene interactions

In the cohort, 19 prescribed cardiovascular drugs were found related to the 5 actionable pharmacogenes. A total of 74.0% of the patients had at least one DGI (range 0–5), and the median number of DGI per patient was 1 (Fig. 3A). The most common DGI involved with CYP3A5 (n=617, 45.8%), followed by CYP2C19 (n=366, 27.2%), SLCO1B1 (n=220, 16.4%), CYP2D6 (n=125, 9.3%) and CYP2C9 (n=18, 1.3%) (Fig. 3B, Table S5). The transfer of the DGIs to the clinical implementation is depicted in Fig. 3C. The older patients with CAD would benefit from a therapeutical change in a mean (min-max) of 1.32 drugs (0–5). The patients prescribed with clopidogrel could benefit the most from the implementation, with 59.9% (n=366) of the older patients with CAD needing the altered prescription (Fig. 3C, Table S5). In addition to the cardiovascular drugs, 58.4% (n=594) of the patients were administrated with the proton pump inhibitor at discharge to reduce antiplatelet agents induced gastrointestinal bleeding adverse events, among whom 4.4% (n=26) patients processed DGI between omeprazole and CYP2C19, and 55.6% (n=330) patients had DGI between rabeprazole and CYP2C19.

Associations between drug-gene interactions and clinical outcomes

The primary efficacy outcomes of all-cause mortality occurred in 220 (21.6%) patients, with MACEs in 172 (16.9%), and the drug response phenotypes in 142 (14.0%) during the follow-ups. The number of cardiovascular-related DGIs was independently associated with all-cause mortality (adjusted HR: 0.84, 95% CI: 0.73–0.96, P=0.008), MACEs (adjusted HR: 0.84, 95% CI: 0.72–0.98, P=0.023), and the drug response phenotypes (adjusted OR: 1.24, 95% CI: 1.05–1.45, P=0.011). When the DGIs were divided by the therapeutic impact, only the number of cardiovascular DGIs related to decreased efficacy was independently associated with all-cause mortality, MACEs, and drug response phenotypes (Table 2). When we divided the follow-up intervals according to years, the independent association between the number of cardiovascular DGIs related to decreased efficacy and the outcomes of all-cause mortality and MACEs could still be observed. It is worth noting that the correlation was more favourable with the prolonged follow-up intervals (Fig. 4). Kaplan-Meier survival analysis showed that patients with decreased efficacy-related cardiovascular DGIs had a significantly lower risk of all-cause mortality (18.5% vs. 27.1%, adjusted HR: 0.66, 95% CI: 0.50–0.88,

Table 1 Clinical characteristics of the cohort

Characteristics	*n* = 1017
Demographics	
Age (years, mean ± SD)	80.81 ± 5.18
Male/Female, n (%)	643 (63.2%)
BMI (kg/m^2, mean ± SD)	24.30 ± 3.52
Comorbidities, median (IQR, range)	
Comorbidities	3 (2–4, 2–9)
Cardiovascular multimorbidity	3 (2–4, 1–7)
Non-cardiovascular multimorbidity	0 (0–1, 0–4)
Charlson comorbidity index	4 (3–5, 2–13)
Stable coronary artery disease, n (%)	292 (28.7%)
Unstable angina, n (%)	575 (56.5%)
Myocardial infarction, n (%)	150 (14.8%)
Heart failure, n (%)	88 (8.7%)
Hypertension, n (%)	806 (79.3%)
Diabetes mellitus, n (%)	415 (40.8%)
Stroke, n (%)	196 (19.3%)
Atrial fibrillation, n (%)	157 (15.4%)
Hepatic and renal insufficiency, n (%)	148 (14.6%)
Drugs at discharge	
Number of drugs/patients, median (IQR, range)	6 (5–8, 2–13)
Number of cardiovascular drugs/patients, median (IQR, range)	5 (5–7, 1–11)
Number of non-cardiovascular drugs/patients, median (IQR, range)	1 (0–1, 0–7)
Antiplatelet agents, n (%)	916 (90.1%)
Oral anticoagulation agents, n (%)	120 (11.8%)
Statin, n (%)	929 (91.3%)
Calcium channel blockers	431 (42.4%)
Beta-blockers	613 (60.3%)
ARB	289 (28.4%)
ACEI	40 (3.9%)
Oral antidiabetic agents, n (%)	203 (20.0%)
Proton pump inhibitors, n (%)	594 (58.4%)
Psychotropic agents, n (%)	62 (6.1%)

BMI, body mass index; IQR, interquartile range, ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

P=0.004), and the tendency for the lower risk of MACEs (15.4% vs. 19.5%, adjusted HR: 0.83, 95% CI: 0.60–1.15, *P*=0.254) (Fig. 5).

Discussion

The present study mainly found that cardiovascular-related DGIs commonly occurred in older patients with CAD. Importantly, independent of age, comorbidities, hepatic and renal function, and DDIs, cardiovascular-related DGIs were associated with all-cause mortality and MACEs, as well as drug response. The findings suggested that integrating clinical and genetic data, especially the implementation of DGI assessment could improve the optimization of medicine in older patients with CAD. As we know, the clinical implications of DGIs have not been evaluated in such patients.

Polypharmacy is common, and often appropriate, given the need to treat multiple, complex, chronic conditions including CAD, even at the cost of the increased healthcare costs, adverse drug events, and drug interactions. In the present older patients, 87.6% of the patients were administrated with ≥5 medications. The proportion was much higher than that reported in the community-dwelling adults ≥65 years with the proportion of 30–50% [5]. The higher proportion of the present cohort might be attributed to the higher prevalence of polypharmacy in the patients with CAD, and the higher average age (81 years old) of the included older patients, who will receive more medication during their remaining lifespan due to the co-mortalities.

With more drugs being used and prescribed in patients with CAD and many related to pharmacogenetic recommendations, older patients may be an ideal group to be evaluated with multiple DGIs [22]. Therefore, the panel-based pharmacogenetic test could provide an opportunity for the personalized prescribing of a wide variety of medications in older patients [23]. Overall, around 30% of the drug response variability has been attributed to

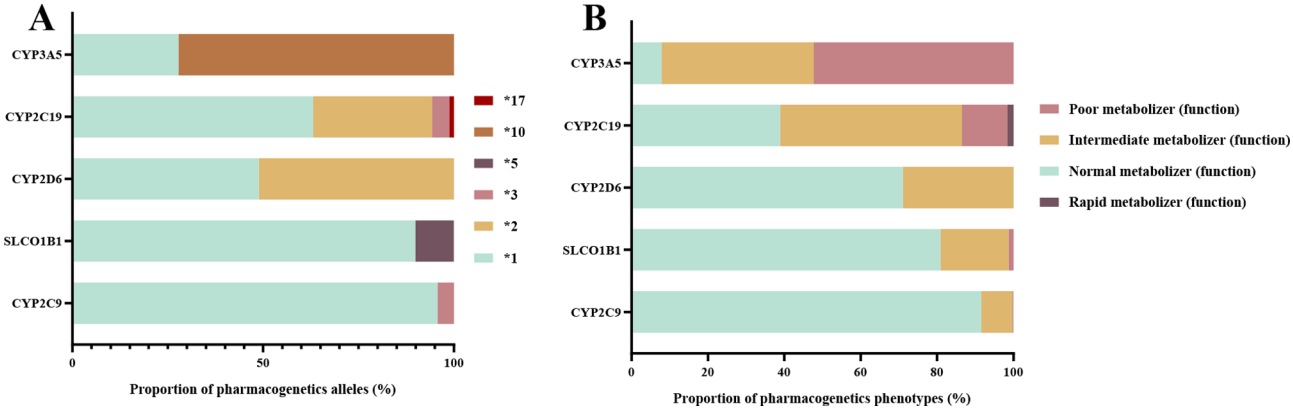

Fig. 2 Pharmacogenetic genotype and phenotype of the cohort for the 5 actionable pharmacogenes. This figure shows (**A**) the proportion of pharmacogenetics alleles, (**B**) the proportion of pharmacogenetics phenotypes

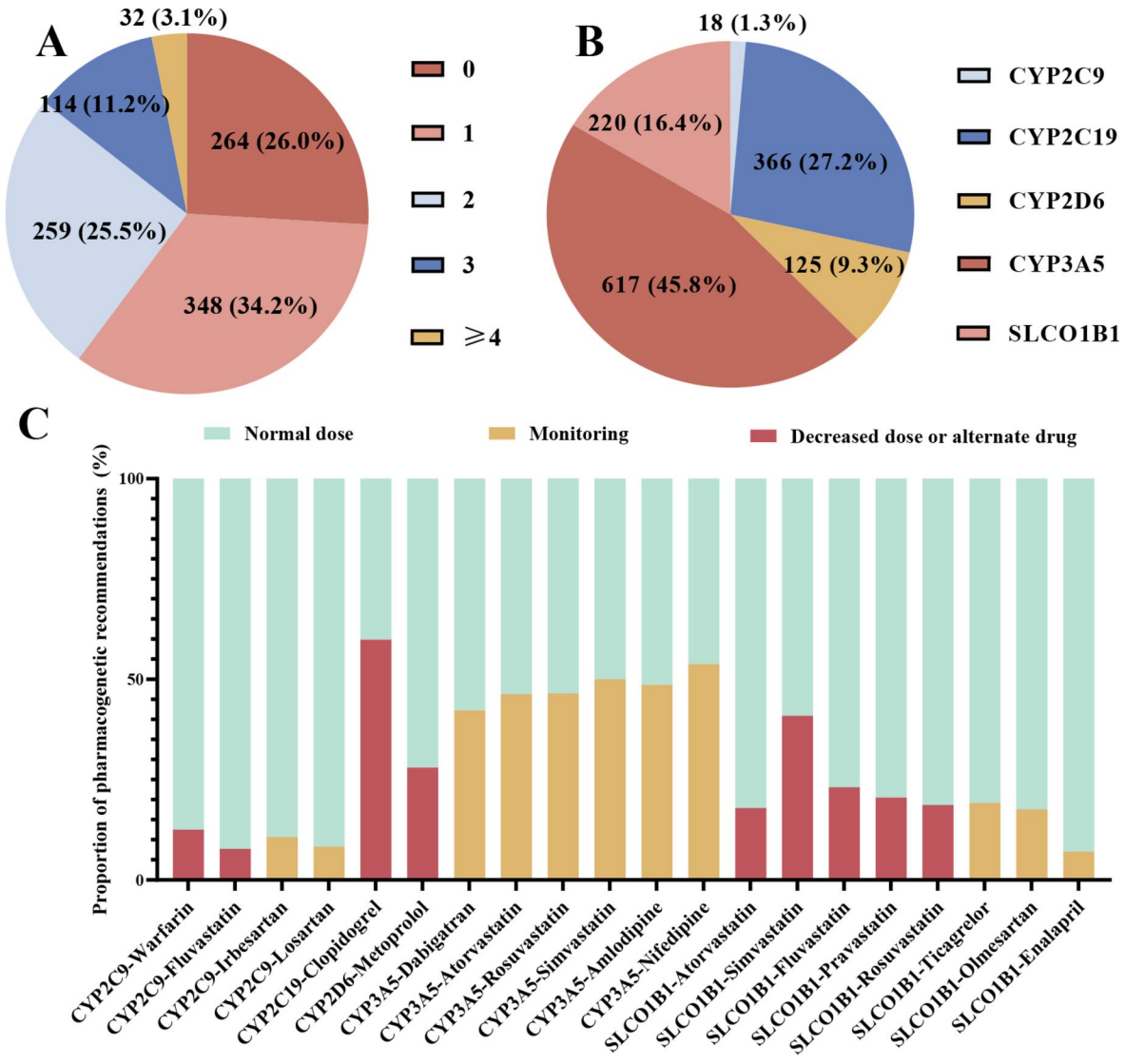

Fig. 3 Drug-gene interactions. This figure shows (**A**) the number (%) of drug-gene interactions per patient, (**B**) the percentage of drug-gene interactions mediated per metabolic enzyme/transporter, and (**C**) therapeutical recommendations in older patients with coronary artery disease for drugs associated with drug-gene interactions according to CPIC or DPWG guidelines. drug-gene interactions not mentioned in pharmacogenomics guidelines were considered to need to be applied under clinician monitoring. CPIC, Clinical Pharmacogenetics Implementation Consortium; DPWG, Dutch Pharmacogenetics Working Group

genetic factors, and the variations in cytochrome P450 (CYP) genes alone have been estimated to be relevant for 10–20% of all drug therapies [3]. Notably, of the 57 CYP enzymes encoded in the human genome, four (CYP2C9, CYP2C19, CYP2D6 and CYP3A5) are responsible for the metabolism of the commonly prescribed drugs in patients with CAD, including the agents of antiplatelet, anticoagulation, and antihypertension [24]. In the present older patients with CAD, we evaluated the DGIs from the 8 clinical annotated variants in the four CYP enzymes and the variant of the transporter SLOC1B1 weakening the metabolism of lipid-lowering agents of statins. As a whole, 95.1% of the older patients with CAD had at least one actionable genotype in the 5 pharmacogenes, which is comparable with the frequency of the 14 CPIC pharmacogenes known to influence human drug response in the UK biobank [25]. Nowadays, genotyping platforms allow for the simultaneous characterization of multiple pharmacogenes [26], and the panel-based pharmacogenetic results might maximize the implementation of clinically relevant DGIs [27].

In the present study, 74.0% of the older patients with CAD had at least 1 DGI according to the interaction between the cardiovascular drugs at discharge and the 8 genotypes of the 5 analyzed pharmacogenes. The higher prevalence of DGIs compared with the previous studies derived from the different sources of criteria or guidelines (including CPIC guidelines, PharmGKB, or DPWG

Table 2 Associations between cardiovascular drug-gene interactions and clinical outcomes in multivariable analysis

	All-cause mortality		Major adverse cardiovascular events		Drug-stop or dose-decrease	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.08 (1.05–1.11)	< 0.001	1.00 (0.97–1.04)	0.862	1.02 (0.92–1.06)	0.281
Male	0.80 (0.58–1.08)	0.145	0.92 (0.66–1.29)	0.638	0.99 (0.68–1.45)	0.965
Number of comorbidities	1.14 (1.02–1.27)	0.017	1.03 (0.90–1.17)	0.705	0.90 (0.75–1.08)	0.259
Myocardial infarction	1.75 (1.24–2.46)	0.001	1.70 (1.15–2.51)	0.008	0.80 (0.45–1.43)	0.462
Heart failure	1.63 (1.10–2.42)	0.016	2.12 (1.34–3.35)	0.001	1.10 (0.50–2.40)	0.810
Hepatic and renal insufficiency	2.58 (1.85–3.60)	< 0.001	1.79 (1.18–2.72)	0.007	1.04 (0.52–2.06)	0.911
Number of drugs	0.97 (0.90–1.05)	0.443	1.00 (0.91–1.09)	0.931	1.16 (1.05–1.28)	0.005
Number of cardiovascular DDIs	1.08 (0.97–1.19)	0.175	1.03 (0.89–1.18)	0.714	1.06 (0.91–1.23)	0.462
Number of cardiovascular DGIs	0.84 (0.73–0.96)	0.008	0.84 (0.72–0.98)	0.023	1.24 (1.05–1.45)	0.011
Number of cardiovascular DGIs related to decreased efficacy	0.77 (0.65–0.90)	0.002	0.83 (0.69–0.99)	0.049	1.24 (1.02–1.50)	0.030
Number of cardiovascular DGIs related to increased efficacy	1.00 (0.80–1.25)	0.994	0.85 (0.65–1.13)	0.264	1.23 (0.94–1.63)	0.134

Multivariable Cox and logistic regression adjusted by age, sex, number of comorbidities, coexisting diseases (myocardial infarction, heart failure, hepatic and renal insufficiency), number of drugs and number of CDDIs. CDDIs, cardiovascular drug-drug interactions; CDGIs, cardiovascular drug-gene interactions

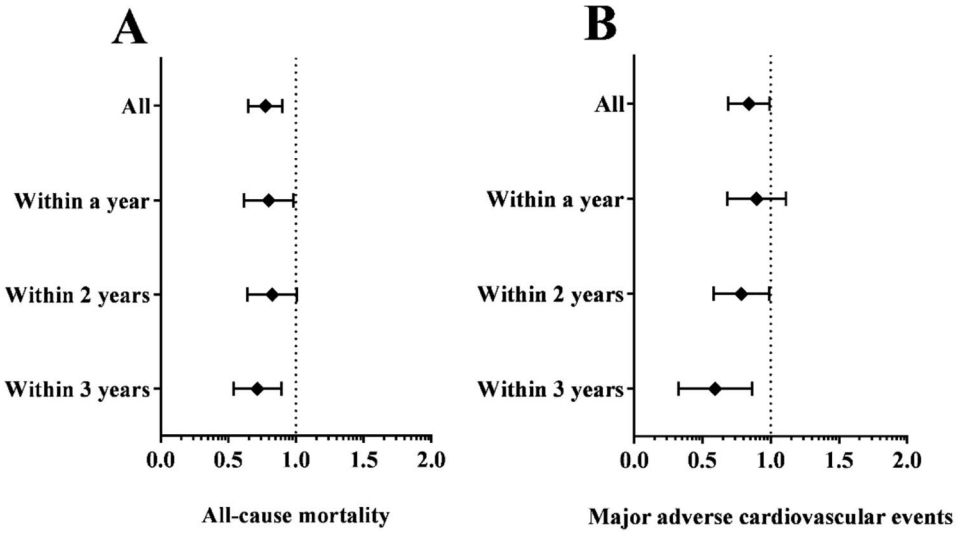

Fig. 4 Forest plot of correlations between the number of cardiovascular drug-gene interactions related decreased efficacy and efficacy outcomes in different periods. Multivariable cox regression adjusted by age, sex, number of comorbidities, coexisting diseases (myocardial infarction, heart failure, hepatic and renal insufficiency), number of drugs

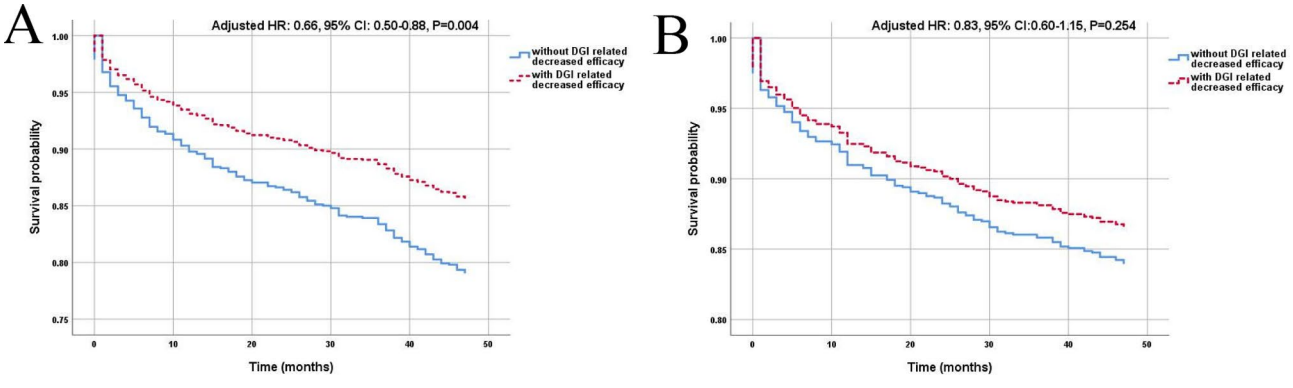

Fig. 5 Kaplan-Meier survival curves for (**A**) all-cause mortality (**B**) major adverse cardiovascular events in patients with or without cardiovascular drug-gene interactions related decreased efficacy

guidelines) for the assessment of DGIs [26]. An investigation in the Netherlands found DGIs according to DPWG guidelines in 23.6% of all new prescriptions for 45 drugs. More importantly, these DGIs would result in 5.4% of new prescriptions being dose-adjusted or switched to other drugs.

The present study found that cardiovascular DGIs were negatively associated with the risk of all-cause mortality and MACEs, independently of clinical baseline characteristics and DDIs. However, when the DGIs were subgrouped according to the alteration of the cardiovascular drug efficacy, the negative association attributed mainly to the DGIs related to the decreased drug efficacy. The paradox of the association between DGIs-related drug efficacy declines and better clinical outcomes in older patients with CAD might be explained that increased cardiovascular medication efficacy may not be the best choice for older patients. For example, intensive blood pressure treatment may not be appropriate for all older patients with hypertension [28, 29], which could increase the risk of hypotension [30] and renal failure [31]. In patients>65 years of age after percutaneous coronary intervention, short or standard dual antiplatelet therapy was non-inferior to prolonged or intensive dual antiplatelet therapy on the compositive endpoints of ischemic and bleeding outcomes [32]. Thus, cardiovascular DGI-related decreased efficacy may prevent the harms of intensive cardiovascular therapy in older patients with CAD.

We referred to two drug response phenotypes which relied on drug prescribing behaviours rather than measured effects of each drug [33, 34]. The two phenotypes were "drug-stop" and "dose-decrease", which was considered to be a surrogate for an intolerable side effect, and lack of extreme therapeutic efficacy. In the present study, a positive association was found between the number of cardiovascular DGIs and the risk of "drug-stop" and "dose-decrease" phenotypes. As the most plausible mechanism for the drug response phenotypes was the alteration of drug metabolism or transport, therefore the pharmacogenetic variant's alteration or DGI could in turn lead to differences in clinical scenarios, such as increased or decreased efficacy or experience of side effects [35]. Thus, early identification of DGIs may facilitate the subsequent personalized decisions to change prescriptions in older patients with CAD.

Limitations

Several limitations should be mentioned for this study. First, this was an observational cohort study, which cannot establish the causality between the DGIs and the clinical outcomes. Therefore, we acknowledged that the results from the study could be spurious or chance findings caused by the relatively small sample size, which hampers the demonstration of significant differences in the subgroup analyses. Secondly, not all ADRs were collected in the current study, we defined drug response phenotypes to reflect the risk of ADRs. Thirdly only 14 patients had drug-drug-gene interactions, and the role of drug-drug-gene interactions in the clinical outcome of older patients with CAD was not evaluated in the present study. Fourthly, the data on medications reported in the present study did not include over-the-counter medications and supplements such as vitamins, minerals and Chinese herbs. The burden of DGIs in the present study only accounts for CAD-indicated/relevant therapies and may be underestimated for the influence of non-cardiovascular drugs. Fifthly, a total of 12 patients diagnosed with dementia were included in the study. As the cognitive assessment was not routinely performed for the patients recruited from the Department of Cardiology in our hospital, the baseline variables on the mental or cognitive function in these elderly patients with CAD were not available. In the future study in the elderly patients with polypharmacy, we would consider the enrichment of mental or cognitive variables in the baseline and the follow up intervals. Finally, the clinical utility of the pharmacogenetics panel to guide older patients with CAD based on a pre-emptive genotyping strategy should be investigated in future intervention studies.

Conclusions

Actionable pharmacogenetic variants and DGIs commonly occur in older patients with CAD, and panel-based pharmacogenetic testing might be appreciated to identify DGIs. The association between DGIs and clinical outcomes emphasized the necessity for the integration of genetic and clinical data to enhance the optimization of cardiovascular medicines in older patients with CAD.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-024-05471-7.

Supplementary Material 1

Author contributions

TY: study concept and design and critical revision of the manuscript for important intellectual content. SZ, LD and YW: acquisition of data. CL: genotyping for enrolled patients. SZ and TY: analysis and interpretation of data. SZ and TY: drafting of the manuscript. All authors contributed to the article and approved the submitted version.

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Data availability
Upon a reasonable request, the corresponding author will make the datasets used in this study public.

Declarations

Ethics approval and consent to participate
The study complied with the Declaration of Helsinki and was approved by the ethics committee of the People's Liberation Army General Hospital (S2021-664-02). All patients signed informed consent forms.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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