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ECONOMIC EVALUATION OF PHARMACOGENETIC-GUIDED PRESCRIBING IN PRECISION MEDICINE FOR CARDIOVASCULAR DISEASES: AN EVIDENCE SYNTHESIS FROM ASIAN COUNTRIES

Via Dolorosa Halilintar[1], Lonah[2], Pujiyanto[3]*

[1] School of Public Health, University of Indonesia
[2] Department of Pharmacology, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia
[3] Department of Administration and Health Policy, School of Public Health, University of Indonesia

**Corresponding author:*
vd.halilintar@gmail.com/
via.dolorosa@ui.ac.id

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ABSTRACT

Precision medicine, particularly pharmacogenetic-guided approaches, has emerged as a promising tool to optimize treatment strategies for cardiovascular disease. However, the economic evaluation of these approaches in Asian populations remains underexplored. This review study aimed to synthesize evidence on the implementation, methodology, research gaps, and limitations of pharmacogenetic-guided precision medicine in cardiovascular disease among the Asian population. A comprehensive search of electronic databases (Pubmed, Embase, Google Scholar and Cochrane Library) was conducted to identify relevant studies. The data were extracted and synthesized to address the study objectives A total of 12 studies were included in the analysis. Economic evaluation studies of pharmacogenetic-guided precision medicine in cardiovascular disease management in Asian countries are still limited, with precision medicine interventions often requiring high resources. The sampling process remains a challenge in conducting economic evaluation studies, and there are limitations in obtaining clinical outcome descriptions from real-world evidence, as most studies rely on literature reviews or modeling-based approaches. Furthermore, most studies use a provider or healthcare cost perspective, limiting the comprehensiveness of cost information. This evidence synthesis highlights the potential for pharmacogenetic-guided precision medicine in cardiovascular disease management among the Asian population, as well as the current challenges and limitations in conducting economic evaluations. Further research is needed to address these issues, develop more robust sampling strategies, obtain real-world clinical outcome data, and provide comprehensive cost information to inform clinical practice and healthcare policy in the region.

Keywords: *Precision medicine, Pharmacogenetics, Cardiovascular disease, Economic evaluation, Asian population.*

INTRODUCTION

Alteration in environment, technology and lifestyle have changed the pattern of disease from infectious disease to non-communicable disease.[1]

Cardiovascular disease (CVD) stands as the primary cause of mortality worldwide, responsible for 30% of deaths globally. Key CVDs encompass coronary or ischemic heart disease, stroke, hypertension, heart failure, and rheumatic heart disease. Despite a decrease in CVD death rates in the US and other developed nations, there has been a rising trend in developing countries, including many in Asia.[2] CVD held the grim distinction of being the most frequent cause of death in Asia in 2019, accounting for approximately 10.8 million lives lost, or about 35% of all deaths in the area. Almost 39% of these deaths from CVD occurred prematurely, defined as those happening to individuals below 70 years of age. This rate of premature deaths was considerably more than those recorded in the United States (23%), Europe (22%), and the global average (34%). The vast majority of these CVD deaths (87%) were due to ischemic heart disease (IHD) (47%) or stroke (40%). [3]

Research into pharmacogenetic or pharmacogenomic differences in Asian populations is growing, suggesting that genetic variations can lead to varying drug reactions or metabolism changes tied to race or ethnicity. These differences, seen more or less frequently in Asians compared to other groups, typically involve previously recognized variants.[4] Increasing evidence indicates that genetic variations in the Asian population, exemplified by the presence of the CYP2C19 allele, are associated with a higher risk of cardiovascular or bleeding events. This raises significant concerns about the impact of such genetic variations on the pharmacokinetic properties of drugs, potentially affecting their efficacy and safety in this population. This underscores the need for careful pharmacogenetic considerations in the medical treatment of Asian individuals. [5]

Precision medicine (PM) is an evolving medical strategy that categorizes patients according to their unique phenotypes and genotypes, which includes molecular profiling, medical imaging, and lifestyle data. The objective of PM is to make more precise predictions about disease susceptibility and to provide timely, personalized prevention or treatment strategies.[6] PM, a potential solution for challenges in cardiovascular disease (CVD) treatment, personalizes care based on genetics, environment, and lifestyle. Pharmacogenomics (PGx), a key element of this approach, uses genetic information to optimize drug therapy, reducing guesswork.[7] Through years of pharmacogenetic research, connections between genetics and the safety and efficacy of various treatments have been established. These findings are now being incorporated into clinical practice. In the last decade, pharmacogenetic testing has made its way into clinical practice, providing guidance for certain cardiovascular treatments. [8]

Over the past few decades, there have been significant advancements in the discovery of pharmacogenetics (PGx) associations. However, the integration of these findings into clinical practice has been slower. Factors such as cost and reimbursement problems, educational and awareness hurdles, and technical challenges have acted as barriers, slowing the adoption of PGx discoveries in clinical settings.[9] Interestingly, numerous systematic reviews suggest that pharmacogenetic (PGx) tests not only yield satisfactory clinical results, but their implementation is predominantly

considered a cost-efficient or cost-saving approach. [10–12]

Therefore, we are conducting a synthesis of evidence drawn from various studies and best practices within an Asian context. Our aim is to identify, analyze, and compare economic evaluations of precision medicine strategies, with a particular focus on the integration of pharmacogenomics. This endeavor will yield insights into the potential economic benefits and challenges of implementing such strategies within healthcare systems across diverse Asian countries. Ultimately, our findings will inform decision-making processes related to the allocation of healthcare resources for Precision Medicine.

METHODS

Search Strategy

We conducted a literature search using the Medline (via PubMed), EMBASE, Google Scholar, and Cochrane Review databases. We limited the publication timeframe to the period between 2013 and 2023 to provide the most current context for the information we aim to synthesize.

The key definitions included in this review study are "Economic Evaluation," "Pharmacogenomic in Precision Medicine Practices," and "Asian Population". The term "Economic Evaluation" implies that the articles fitting into the inclusion criteria must employ a full economic study in the form of Cost-Benefit Analysis, Cost-Effectiveness Analysis, or Cost-Utility Analysis. The study must use genomic-based interventions that have comparisons with universal care or standard treatment. The population used refers to studies conducted and/or published in Asian countries. The selection of literature with the PICOS Framework can be seen in Table 1.

Table 1. PICOS Criteria for study selection

Criteria	Description
Population (P)	Adult patients (18 years and older) of Asian descent with diagnosed cardiovascular disease (CVD) or at risk of developing CVD.
Intervention (I)	Pharmacogenetic-guided precision medicine for the prevention or treatment of cardiovascular disease.
Comparator (C)	Patients receiving standard care for cardiovascular disease (e.g., treatment based on clinical guidelines without consideration of patients' genetic information or universal care).
Outcomes (O)	Primary outcome: Cost-effectiveness from various cost perspectives (e.g., payer, societal, provider) considering metrics such as cost per QALY gained, ICER. Secondary outcomes: Clinical effectiveness, patient-related outcomes (e.g., adherence, satisfaction, quality of life). In addition, the study should provide cost perspective information.
Study design (S)	Economic evaluations, randomized controlled trials, non-randomized controlled trials, cohort studies, case-control studies, model-based studies (e.g., decision-analytical models, Markov models) with sensitivity analysis included. Additionally, model-based studies like decision-analytical models and Markov models will be included. The included studies should incorporate sensitivity analyses to assess the robustness of their findings. Studies conducted from 2013-2023. Exclude: case reports, editorials, commentaries, studies without a comparator group.

Table 2. Keyword structure, strategy and result

No.	Query	Results
#27	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit' OR 'cost utility' OR 'cost consequences' OR 'economic outcome') AND ('genetic test' OR 'genotype test' OR 'pharmacogenetic test' OR 'pharmacogenomics test') AND 'asian'	6

No.	Query	Results
#26	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit' OR 'cost utility' OR 'cost consequences' OR 'economic outcome') AND ('genetic test' OR 'genotype test' OR 'cyp450 guided' OR 'pharmacogenetic test' OR 'pharmacogenomics test')	238
#25	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit' OR 'cost utility' OR 'cost consequences' OR 'economic outcome') AND ('genetic test' OR 'genotype test' OR 'cyp450 guided' OR 'pharmacogenetic test' OR 'pharmacogenomics test') AND ('cardiovascular event*' OR 'cardiovascular disease') AND ('asian' OR 'asian people' OR 'asian population')	0
#24	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit' OR 'cost consequences') AND 'cyp450 guided'	0
#23	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit' OR 'cost consequences') AND 'cyp450 test'	3
#22	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit' OR 'cost consequences') AND 'cyp450'	39
#21	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit' OR 'cost consequences') AND 'cyp guided'	0
#20	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit' OR 'cost consequences') AND 'cyp guided' AND 'cardiovascular'	0
#19	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit' OR 'cost consequences') AND 'genotype guided' AND 'cardiovascular'	35
#18	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit' OR 'cost consequences') AND 'genetic guided' AND 'cardiovascular'	3
#17	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit' OR 'cost consequences') AND 'pharmacogenomic' AND 'cardiovascular'	27
#16	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit' OR 'cost consequences') AND 'pharmacogenomic' AND 'asian'	11
#15	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit') AND 'pharmacogenomic' AND 'asian'	11
#14	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit') AND 'pharmacogenomic' AND 'cardiovascular'	27
#13	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit') AND 'genetic screening' AND 'cardiovascular'	212
#12	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit') AND 'cyp2c19 guided' AND 'cardiovascular'	7
#11	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit') AND 'genetic guided' AND 'cardiovascular disease'	1
#10	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit') AND 'precision medicine' AND 'cardiovascular disease'	31
#9	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit') AND 'personalized medicine' AND 'cardiovascular disease'	121
#8	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit') AND 'genotype guided' AND 'asian'	10
#7	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit') AND 'genotype guided' AND 'hypercholesterolemia'	1
#6	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit') AND 'genotype guided' AND 'stroke'	35
#5	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit') AND 'genotype guided' AND 'cardiovascular disease'	9
#4	('economic evaluation' OR 'cost effectiveness' OR 'cost benefit') AND 'genotype guided'	140
#3	('cost consequence analysis' OR 'cost utility analysis') AND 'pharmacogenetic testing'	19
#2	('cost-effectiveness' OR 'cost effective') AND ('genetic guided test' OR 'genetic testing' OR 'genetic screening') AND ('cardiovascular disease' OR 'heart disease') AND ('asian population' OR 'asians' OR 'asia')	2
#1	('economic evaluation'/exp OR 'economic evaluation' OR 'cost-effectiveness'/exp OR 'cost-effectiveness' OR 'cost-utility'/exp OR 'cost-utility' OR 'cost-benefit'/exp OR 'cost-benefit' OR 'cost consequences analysis') AND ('genetic guided test' OR 'genetic testing'/exp OR 'genetic testing' OR 'genetic screening'/exp OR 'genetic screening') AND ('cardiovascular disease'/exp OR 'cardiovascular disease' OR 'heart disease'/exp OR 'heart disease') AND ('asian population' OR 'asians'/exp OR 'asians' OR 'asia'/exp OR 'asia')	25
	Total	1013

Eligibility Criteria

Our research was conducted with a stringent selection process to ensure the accuracy and relevance of the included studies. The first of these criteria was the necessity for original data. The exclusion of studies without original data was important to us as we wanted to base our research on primary, novel findings rather than reiterative or secondary information. Additionally, we only considered full-text publications. This allowed us to obtain a comprehensive understanding of the methodologies and results of each study, which can often be missing in summaries or abstracts.

Secondly, we avoided certain types of academic content, such as comments, letters to the editor, descriptive studies, case reports, or conference papers. The rationale for this was to maintain a high standard of data rigor and depth, as these types of documents often lack the comprehensive, empirical evidence necessary for our

review. We also focused on studies that used Asian populations to ensure the cultural and genetic relevance of our research, hence studies using non-Asian populations were excluded.

Our third set of exclusion criteria pertained to the type of information provided in the studies. Those that only offered clinical consequences were removed, as our analysis required both clinical and economic data. Studies lacking information on health outcomes or intervention costs were also removed, as these elements are integral for a comprehensive economic evaluation. The focus was on net economic benefit, accounting for both costs and benefits, rather than just gross economic benefit. Lastly, to ensure precise interpretation and understanding, we only included studies that were published in English, minimizing the risk of misinterpretations that could occur during translation

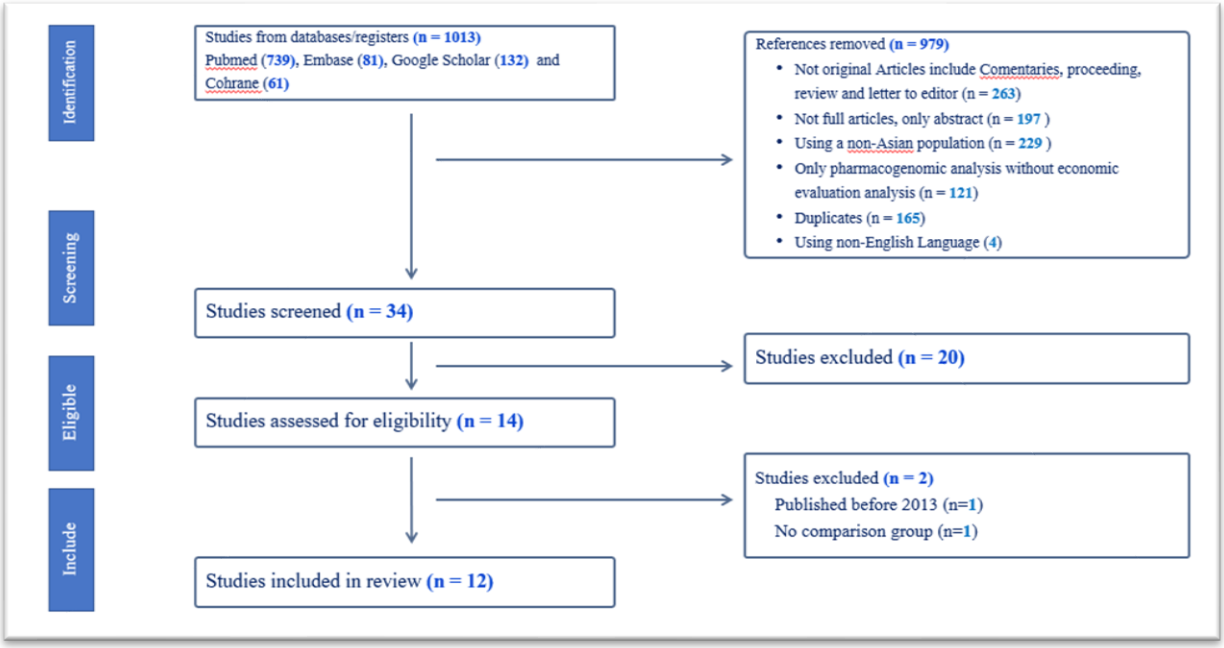

Figure 1. Flow PRISMA Diagram depicting the phases of study selection.

Data Extraction

Data extraction will be documented in MS Word, with Mendeley serving as the reference management tool to keep track of references. The first reviewer (VDH) will conduct the initial review, followed by an independent review by the second reviewer (LN). The third author (PJ) will review the information that has been extracted. Any discrepancies arising during the screening processes will be resolved through discussion.

We extracted pertinent characteristics from all the reviewed studies, including the country or region of origin, the base year for cost determination, year of publication, and the study population. These characteristics provide essential context for understanding the settings and demographics under consideration in each study, and they help to identify any potential regional or temporal trends that may influence the outcomes.

Methodological characteristics, such as the type of economic evaluation, study

design, perspective, time horizon, and effectiveness measures, were also obtained. These elements are crucial in understanding the structure and scope of the studies, as well as the metrics used for evaluating outcomes. Further, we recorded information regarding cost, discount rate, and sources used for estimating effectiveness and resource utilization. The results of the studies were summarized based on the economic evaluation results provided by the original authors, offering a clear snapshot of each study's conclusions.

Data Synthesis

After data extraction, which includes identifying the type of economic evaluation study, the intervention and comparator used, the cost perspective, clinical and economic consequences, and study limitations, a comprehensive analysis is initiated.

This analysis begins with categorizing the extracted data based on the types of economic evaluation studies, such as cost-effectiveness, cost-utility, or cost-benefit analyses. Then, the specific interventions and comparators in each study are examined to understand the different pharmacogenomic strategies used in precision medicine for cardiovascular diseases. The cost perspectives adopted in these studies are also considered, as they can influence the comprehensiveness of cost data included. Synthesis of clinical and economic consequences helps to gauge the overall impact of the interventions, including their potential benefits and drawbacks. Lastly, evaluating the limitations of each study aids in understanding the potential sources of bias and uncertainty in the data, as well as areas where further research may be needed.

The second part of data synthesis involves comparing and contrasting the data within and across the categories formed. This step is crucial in discerning patterns, trends, or discrepancies in the findings. For instance, a comparison of economic evaluations could reveal which pharmacogenomic strategies are consistently found to be cost-effective. Similarly, an examination of the clinical and economic consequences could identify which interventions offer the best balance between clinical outcomes and costs. Furthermore, understanding the limitations of the studies could shed light on the reliability of the findings and the areas where more robust evidence is needed. The ultimate goal of this data synthesis process is to provide an evidence-based assessment of the economic value of pharmacogenomics in precision medicine for cardiovascular diseases in Asian countries.

Reporting Quality Assessment

The reporting quality of each study was examined utilizing the CHEERS 2022 statement, a recognized benchmark for assessing the comprehensiveness of economic evaluations in health strategies .[13] This tool, featuring a 27-item checklist, outlines the minimum information that should be reported in such studies. Each study included in the review underwent careful evaluation against these rigorous criteria.

A three-tiered scoring system was applied to each checklist item for rating the reporting quality. A score of 1 was assigned for full compliance with an item, 0.5 for partial compliance, and 0 for failure to report or provide minimal information. This scoring system enabled a nuanced assessment of the reporting quality. A percentage score was then computed by summing the individual scores and dividing this by the total possible score. Studies with

a score of 75% or higher were deemed high quality, those scoring between 50% and 74% were considered medium quality, and those scoring less than 50% were categorized as low quality.[14]

RESULTS AND DISCUSSION

Upon utilizing the predetermined inclusion and exclusion criteria, 12 articles were acquired, providing valuable insights into the economic evaluation of precision medicine for cardiovascular diseases (CVD) within Asian countries.

Table 3. Summary of study characteristics (n=12)

Study Characteristics	n	%
Year		
2013-2018	5	41.7
2019-2023	7	58.3
Country		
China	1	8.3
Hongkong	3	25
Qatar	2	16.7
Singapore	2	16.7
South Korea	1	8.3
Thailand	3	25
Disease		
Acute Coronary Syndrome	4	33.3
Atrial Fibrilation	3	25
Ischemic Stroke	2	16.7
Operative Procedure	3	25
Type of Economic Evaluation		
Cost Benefit Analysis (CBA)	2	16.7
Cost Effectiveness Analysis (CEA)	9	75
Cost Utility Analysis (CUA)	1	8.3
Cost Perspective		
Healthcare/Provider	9	75
Societal	3	25
Study Design		
Model-Based	4	33.3
Cohort-Based	8	66.7
Time Horizon		
No statement	1	8.3
1 year	2	16.7
30 years	2	16.7
Lifetime	7	58.3

Notably, seven of these studies were conducted within the last five years, while the remaining five spanned the period from 2013 to 2018. The countries most represented in these studies were Hong Kong and Thailand, each contributing three articles. In addition, Qatar and Singapore each contributed two articles, with China and South Korea each offering one.

Considering the specific types of cardiovascular diseases or issues, the treatment of Acute Coronary Syndrome was the most frequently studied subject in economic evaluations using a precision medicine approach. The subsequent CVD issues addressed include the management of Atrial Fibrillation and treatment for operative studies. Cost-effectiveness analysis emerged as the most commonly used study type, followed by cost-benefit analysis and cost-utility analysis.

The majority of studies adopted the perspective of the healthcare provider when considering costs, whereas a minority used the societal perspective (9 vs 3 studies). Regarding the types of studies used, most employed a cohort-based approach, including those that were hypothetical in nature, while the remainder utilized studies involving modeling, either through decision-analytical models or specifically using Markov models. A significant majority of studies used a lifetime time horizon in their studies.

Quality of Reporting

Applying the established cut-off criteria, and utilizing the CHEERS 2022 guidelines, it was determined that out of the 12 eligible studies, eight were classified as high-quality in terms of their reporting. The remaining studies were distributed between medium and low quality categories, with three studies falling into the medium quality reporting category, and one study deemed to have low-quality reporting.

Intervention Outcomes: Clinical and Economical Consequences

In the realm of cardiovascular intervention, it has been found that the precision medicine (PM) approach,

specifically tailoring regimens with pharmacogenomic-pharmacogenetic guidance, offers superior benefits compared to standard or universal care.

Studies utilizing Cost-Effectiveness Analysis (CEA) and Cost-Utility Analysis (CUA) indicate that preliminary screening for the management of cardiovascular disease (CVD) issues leads to better clinical outcomes. This includes improved prognosis rates and the prevention of unwanted deterioration and complications.

Turning to cost outcomes, while there were additional costs associated with PGx, these studies indicated cost-saving benefits due to improved treatment outcomes. This result also points to the potential for cost avoidance, in the form of costs prevented.

Table 4. Reporting Quality Appraisal (CHEERS, 2022)

Ref ID	Reference(S)	Score Awarded (Max Score)							Reporting Quality
		Title, Abstract and Introduction (3)	Methods (17)	Results (4)	Discussion (1)	Funding & Conflict of Interest (2)	Sum of Scores	% Item Scores (Total/27 x100%)	
#4	15	3	16	4	1	1	25	92.6	High
#6	16	2.5	15.5	4	1	1	24	88.9	High
#8	17	3	16	4	1	2	26	96.3	High
#10	18	3	11	3	1	2	20	74,1	Medium
#17	19	3	15.5	4	1	1	24.5	90.7	High
#18	20	2.5	12.5	3	1	0	19	70.3	Medium
#19	21	3	15	4	1	1	24	88.9	High
#30	22	3	16	4	1	2	26	96.3	High
#33	23	3	12	3	1	2	21	77,8	Medium
#34	24	3	16	4	1	2	26	96.3	High
#35	25	2.5	10.5	2	1	0	15	55.6	Low
#39	26	3	15	4	1	1	24	88.4	High

The utility derived, whether in the form of Quality Adjusted Life Years (QALY), survival, or life-years gain, was found to be superior in groups receiving pharmacogenomics (PGx) as compared to those receiving standard therapy.

by reducing the probability of comorbidities occurring. The Incremental Cost-Effectiveness Ratio (ICER) required for additional QALY (ICER/QALY) in the PGx intervention group was also found to be superior when compared to the control group. Studies utilizing Cost-Benefit Analysis (CBA) illustrated that investment in PGx results in greater returns in the form of net benefit, a more favorable benefit-to-cost ratio, and an improved return on investment. Monetary benefits were also evident through productivity gains for patients benefiting from PGx intervention

Sensitivity Analysis

Out of the twelve studies encompassed within this review, eleven implemented a sensitivity analysis as an integral component of their economic evaluation sequence. This is a crucial aspect

of such studies, as it explores the impact of changes or uncertainties in the input parameters on the results of the study.

These eleven articles incorporated both one-way sensitivity analysis and probabilistic sensitivity analysis. The one-way sensitivity analysis, also known as a univariate sensitivity analysis, involves the alteration of a single parameter while keeping all others constant. In addition, these articles also carried out a probabilistic sensitivity analysis. This type of analysis provides a more comprehensive picture of uncertainty by simultaneously varying all parameters within their respective distributions, often using Monte Carlo simulations.

These studies proposed several scenarios which might occur if there were changes or uncertainties in the parameters used. By doing so, they were able to assess the robustness of their findings and provide insights into the impact of potential variability in the key parameters.

Economic Evaluation Study of Precision Medicine in CVD

Housing approximately 60% of the global populace, Asia stands as the world's most densely populated continent. The vast and heterogeneous population, distinguished by unique sociocultural, environmental, and biological attributes, leads to a substantial extent of genetic heterogeneity. This genetic variance not only provides an abundant resource for studying human biology but also presents challenges in medical research and clinical care [27]. Population-specific genetic variants can profoundly influence disease predisposition, pharmacological response, and treatment outcomes, thus underscoring the imperative of exploring this genetic heterogeneity.

Pharmacogenetics emerges as a noteworthy research domain highlighting the importance of comprehending genetic diversity within Asian populations. The goal of pharmacogenetic studies is to elucidate how genetic variance influences drug response and the potential for adverse reactions. It is becoming progressively evident that certain adverse drug reactions (ADRs) or anticipated alterations in drug metabolism due to genetic variability can be linked to Asian or other racial/ethnic backgrounds [4]. Such research endeavors can facilitate the advancement of personalized medicine strategies, optimizing drug effectiveness, and reducing the likelihood of adverse reactions based on individual genetic make-up [28]. Particularly in relation to cardiovascular diseases, a primary health concern in many Asian countries, pharmacogenetic research can be instrumental in customizing treatment regimens to assure optimal patient outcomes.

One notable example of genetic polymorphism, or genetic abnormality, is the presence of the CYP2C19 allele. This polymorphism is prevalent in approximately 30% of the Asian population, and it carries significant implications for drug metabolism and therapeutic efficacy. The CYP2C19 gene is involved in the metabolism of a substantial portion of clinically used drugs, and variations in this gene can lead to altered drug responses.Medications affected by this polymorphism span various therapeutic classes, including proton-pump inhibitors (PPIs), certain antipsychotics, and anticoagulants such as clopidogrel [29].

Pharmacogenomics screening enables healthcare providers to tailor cardiovascular treatments to individual genetic profiles. This approach can be

particularly beneficial when dealing with genetic variations that influence drug metabolism or response, such as those seen in the CYP2C19 gene. For instance, patients with specific genetic variations that affect drug metabolism can be identified through pharmacogenomic testing. The results of these tests can then guide adjustments in their treatment regimens - this could mean altering drug dosages, choosing different therapeutic agents, or predicting the risk of adverse drug reactions.[30]

The implementation of precision medicine in healthcare settings presents substantial challenges, particularly concerning human resources and funding. A multidisciplinary team of specialists is necessary, including geneticists, bioinformaticians, clinicians, and health economists. There is a shortage of such professionals. Furthermore, financial constraints pose a significant challenge, particularlu in Low-Middle Income Countries. The expenses related to genomic testing, data analysis, data storage, and necessary infrastructure development can limit the reach of precision medicine, especially in resource-constrained settings.[8]

In this review, we encountered challenges in identifying studies that met the predetermined inclusion criteria. Our findings indicate that economic evaluations or Health Technology Assessment (HTA) studies on the practice of precision medicine for cardiovascular treatment in Asian countries are not yet widely employed. The majority of articles obtained were from high-income or fiscally capable countries, such as Singapore, Hong Kong, South Korea, and China. This situation may be related to the availability of resources, both in terms of personnel and funding, to support HTA studies [31].

In addition to fiscal capacity, the maturity and experience of HTA boards can also influence this landscape. HITAP (Health Intervention and Technology Assessment Program), situated under Thailand's Ministry of Public Health, serves as a leading institution for HTA studies in Asia. HITAP has an established reputation for producing a substantial quantity and quality of HTA studies (World Health Organization. 2021).

Furthermore, In this review, 11 out of 12 studies employed interventions with anticoagulant medications such as Warfarin, Clopidogrel, or Ticagrelor. This is understandable given that anticoagulants are among the most commonly used drug classes in the management of cardiovascular disease conditions [33]. Notably, as mentioned earlier in this subsection, approximately 30% of the Asian population possess polymorphisms in the CYP2C19 allele, which influence the performance of anticoagulants [29]

In this study, we also present an evaluation of study quality based on the CHEERS 2022 checklist. Using this guideline, we found that most articles, with our predefined key interventions, have met the required quality standards. There was one article ranked low due to the absence of a comparator and a comprehensive cost-outcome analysis

Outcome Assessment

The article search results revealed that the majority of the studies employed disease transition probability data derived from modelling or literature adjustments. This condition suggests that the evaluation results may not be fully generalizable as real-world evidence. Nevertheless, such a methodology is frequently utilized in economic evaluation studies or Health Technology Assessment (HTA) as an

alternative when actual clinical data are difficult to obtain. Similar review studies conducted by Zhu et al (2020)[12] and Chen et al (2022)[6] also provided information regarding these limitations.

Consistently, all studies demonstrated that precision medicine practices in cardiovascular disease treatment yield superior health outcomes. Adverse conditions such as bleeding, stroke, or even death have a lower probability with the application of precision medicine [9]. The results of pharmacogenomics (PGx) examinations within precision medicine can assist clinicians in designing regimens tailored to the individual needs of patients. Improved clinical outcomes ultimately yield greater utilities in the form of Quality Adjusted Life Years (QALY), survival, and Life-Years Gained (LYG).

Furthermore, concerning cost outcomes, the recommended cost perspective in economic evaluation studies employs a societal perspective. This perspective can accommodate non-medical cost outcomes, such as costs resulting from job loss or reduced productivity at work. This perspective is considered more comprehensive as it can explain cost consequences more thoroughly. In this review, the majority of articles used the healthcare or provider perspective, which typically occurs when studies only use secondary data, and hence, patient cost information cannot be obtained.

Sensitivity Analysis Appraisal

The results of the sensitivity analysis, a critical component of this systematic review, are expected to illuminate the robustness of the economic evaluations carried out in the selected studies [35]. This analysis will explore how modifying key parameters in the economic models affects the cost-effectiveness of the pharmacogenomics approach in precision medicine for cardiovascular diseases. We anticipate identifying which parameters—such as costs, effectiveness measures, or discount rates—most significantly impact the final cost-effectiveness results. This insight will be instrumental in pinpointing potential areas for future research and informing the optimal allocation of health resources in the context of precision medicine for cardiovascular diseases in Asian countries.

Moreover, the sensitivity analysis in the studies also had underscore the factors that may yield divergent conclusions regarding the cost-effectiveness of the pharmacogenomics approach, potentially due to variations in healthcare system structures, pricing, or clinical practice across different Asian countries [5]. Ultimately, the sensitivity analysis will not only bolster our confidence in the study findings but also provide valuable insights that can shape health policy decisions concerning the integration of pharmacogenomics in treating cardiovascular diseases.

STUDY LIMITATIONS

A key limitation of this review may lie in the potential for publication and language bias, as studies with significant findings are more likely to be published and those in languages other than English may be overlooked. Furthermore, the inherent heterogeneity in study design, quality, and methods of economic evaluation may present challenges in data synthesis. Variations in healthcare systems, costs, and policies across Asian countries could also affect the transferability of findings. Finally, the rapid evolution of precision medicine and pharmacogenomics might

mean that the findings of this review quickly become outdated as new research and technologies emerge.

CONCLUSION

The findings of this review highlight that Health Technology Assessment (HTA) studies evaluating the application of Precision Medicine (PM) in Cardiovascular Diseases (CVD) are still limited in number. Therefore, we recommend conducting more similar studies across diverse nations. This variability in outcomes can offer valuable insights into the financial implications if PM interventions are integrated into national health insurance remuneration schemes.

In addition to the quantity of studies, this review underscores the need for a robust methodology in executing HTA studies. This includes striving for data collection that can deliver real-world evidence. The input parameters in the analysis also need to be carefully considered to provide comprehensive information about the interventions' consequences. Given the inherent uncertainty in economic evaluation studies, the necessity for sensitivity analysis in every HTA or Economic Evaluation study is emphasized.

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