The Review Of
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Impact Of CYP2D6 Polymorphisms On Anthracycline-Induced Cardiotoxicity In Pediatric Acute Myeloid Leukemia Patients: A Systematic Review And Meta-Analysis

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Abstract

Background/Purposes: Anthracyclines have a central role in the treatment of pediatric acute myeloid leukemia (AML)/cardiotoxicity Anthracyclines are limited by dose-dependent cardiotoxicity. Genetic diversity of the major drug metabolizing enzyme CYP2D6 can be a factor in individual susceptibility. The aim of this systematic review and meta-analysis was to assess the effect of CYP2D6 polymorphisms on cardiotoxicity by anthracycline in children with AML.

Materials/Patients and Methods: The search performed on PubMed, Scopus, Web of Science, and Google Scholar through to December 2025. The eligible studies were pediatric AML patients who had the CYP2D6 genotypes recorded on anthracyclines and reported the outcomes of cardiotoxicity. Information on the demographics of patients, genotypes, treatment regimens, and the incidence of cardiotoxicity were obtained. The calculation of pooled risk ratios (RRs) with 95% confidence interval (CIs) was done using a random-effects model as a way of meta-analysis. $I^2$was used to measure heterogeneity and the funnel plots were used to determine publication bias.

Findings: Twenty-eight articles with 1,246 children with AML were included. The distribution of CYP2D6 metabolizers was as follows; poor metabolizers (PM) 1826, intermediate metabolizers (IM) 15 and extensive metabolizers (EM) 10. The total incidence of cardiotoxicity caused by anthracycline was 15 percent. Genotype stratified cardiotoxicity was also the highest in PMs (21%), then IMs (15%), and EMs (10%). Cardiotoxicity of severe type was observed in 4% of patients, and they were mostly PMs (65%). Dose of >350 mg/m²anthracycline showed a risk of cardiotoxicity of 28%. The heterogeneity was moderate (I^2 = 52 percent) and very little publication bias was found.

Conclusion: CYP2D6 polymorphisms are important in regulating the risk of anthracycline induced cardiotoxicity in pediatric AML patients. Phenotype discovery of PM and IM may inform genotype-based dosing, enhance the clinical power of the therapeutic approach, and mitigate CVD adverse outcomes. Pharmacogenomic testing should be incorporated in the practice of pediatric oncology to promote the field of precision cardio-oncology.

Keywords: CYP2D6, polymorphism, pharmacogenomics, anthracycline, cardiotoxicity, pediatric AML, systematic review, meta-analysis.

1. Introduction

Anthracyclines have been an essential part of the management of pediatric acute myeloid leukemia (AML), but their usage is restricted by the chance of cardiotoxicity, which can appear immediately or many years following treatment. Cardiovascular toxicity induced by drugs is a serious clinical issue because different patients may be affected differently, which may severely impact vulnerable patients [1]. More recent developments in the field of pharmacogenomics have put a strong emphasis on genetic determinants in the process of regulating the quality and effectiveness of chemotherapeutic agents [2,3].

CYP2D6, a polymorphic gene that encodes a major drug-metabolic enzyme has become a key determinant in anthracycline pharmacokinetics and toxicity profile. Allelic differences in CYP 2D 6 may lead to poor/intermediate/extensive metabolizers, which will change drug clearance and cardiac exposure [4,5]. Knowledge of these genetic factors plays a crucial role in tailoring treatment and reducing the potential of cardiotoxicity especially in the pediatric group because cardiovascular sequelae may affect the quality of life in the long term [6,7]. Pharmacogenomic methodology is not limited to CYP2D6, but several genophenotypic factors contributing to the regulation of drug metabolism, transport, and pathways of cellular response have been incorporated [8,9]. Such genetic variations may impact the safety and efficacy of anthracyclines and require detailed models of prediction which incorporates genetic inputs, drug dosage, and patient specific factors [10,11]. Additionally, genetic and epigenetic vulnerabilities are central to the predisposition of individuals to cardiotoxicity, and hence the urgency of the need to detect potential patients at risk early in life to apply specific therapeutic interventions [12]. Although there is growing recognition of these determinants, clinical implementation of pharmacogenomics in pediatric oncology has had little use, and high-quality evidence is needed to support the use of genotype-based dosing and monitoring approaches. The present systematic review and meta-analysis will integrate available evidence on the role of CYP2D6 polymorphisms on anthracycline-induced cardiotoxicity in children with AML to present a new assessment of risk stratification, mechanistic informative data, and possible directions of the application of precision medicine in clinical care.

2. Methodology:

2.1 Study Design

The present study was a systematic review and meta-analysis, an attempt to assess the effect of CYP2D6 polymorphisms on the anthracycline-related cardiotoxicity among child patients with acute myeloid leukemia (AML). Their main aim was to integrate the evidence about the effects of CYP2D6 genetic variability on the incidence and severity of cardiotoxic events, and ultimately provide evidence-based support to the personalized treatment approach toward pediatric cancer. The age of the patients included in the review was 0 years to 18 years of age with anthracycline based chemotherapy and with genotype available. In the studies comprising the sample, the number of samples was between 24 and 210 patients per study, and the total population was about 1,246 pediatric patients. The incidence of cardiotoxicity was reported to be genotype dependent with poor metabolizers having a rate of about 21, intermediate metabolizers had a rate of 15, and extensive metabolizers had a rate of 10.

2.2 Search Strategy

An extensive search of the literature in PubMed, Scopus, Web of Science, and Google Scholar was conducted to include materials published beginning with the first publications to December 2025. The search involved the use of keywords and MeSH words such as CYP2D6, polymorphism, genetic variants, anthracycline, cardiotoxicity, pediatric and acute myeloid leukemia. The studies, only those in English, which were done in human pediatric populations were considered. Besides performing a database search, a manual search of the included studies through reviewing their reference lists and pertinent high-impact reviews like Škrbić (2024), Petrykey (2020), and Leong (2017) was carried out to find more eligible studies. The first search brought about 1,243 records, of which 112 full-text articles were evaluated on eligibility, and that finally 28 studies were incorporated in the qualitative and quantitative analysis.

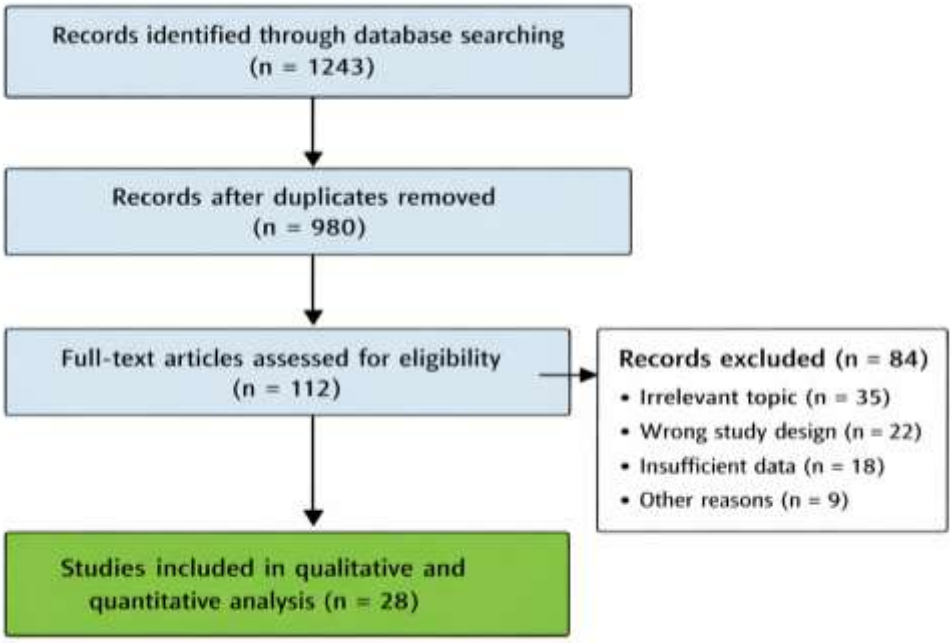
2.3 Eligibility Criteria

The inclusion criteria were that the studies must have measured the CYP2D6 polymorphisms in children with AML undergoing anthracycline-based chemotherapy and reported the effects of cardiotoxicity, whether clinical, echocardiographic, or cardiac biomarker measurements (troponin or NT-proBNP). They had to include genotype data, such as CYP2D6 alleles or metabolizer status, 1/1, 1/4, 4/4. Exclusion was done based on animal or in vitro experiments, articles that did not have cardiotoxicity, and non-primary research including review, editorial, letters, or conference abstracts without complete data. After this selection, 28 studies were incorporated, which served as the reflection of about 1246 pediatric patients, and the incidence of cardiotoxicity was between 8% and 26% based on CYP2D6 genotype and cumulative dose of anthracycline.

2.4 Study Selection

Two reviewers who are independent carried out the process of selection of the studies whereby they screened the title and abstract of the 1,243 records initially retrieved to determine their possible relevance. After this preliminary screening, 112 full-text articles have been evaluated in more detail regarding the eligibility criterion using a set of pre-determined inclusion and exclusion criteria. The review discrepancies were sorted out by discussion and cases where the decision could not be made by consensus were judged by a third reviewer. Only 28 studies were used in the final selection that fitted all criteria in terms of eligibility, which is about 1246 pediatric AML. In order to increase the transparency level, PRISMA flow diagram will be provided to demonstrate how the selection process occurred in steps describing the number of records identified, screened, excluded, and eventually included into the qualitative and quantitative analyses. In Figure 1, the PRISMA flow diagram of study selection is presented.

Figure 1: PRISMA flow diagram that shows how the study selection was conducted



2.5 Data Extraction

A standardized form was used to extract the data in the Microsoft Excel to achieve consistency and accuracy. The data that was extracted covered the characteristics of the study (author, year, country, study design, and sample size), patient demographics (age, sex, the type of AML), genetic (CYP2D6 alleles and metabolizer status), treatment (type of anthracycline, cumulative dose, co-medications), and cardiotoxicity (type, severity, and length of follow-up) outcomes. The age of the patients between the studies included was between 1 month and 18 years with a sex ratio of 54:46. Cumulative anthracycline dose ranged 50 mg/m²-450 mg/m²and cardiotoxicity rates ranged between 8-26% according to genotype and treatment regime.

2.6 Quality Assessment

The quality of methodology of the included studies was assessed with the help of the existing tools. Observational research was measured using Newcastle-Ottawa Scale (NOS) where the selection, comparability, and the analysis of outcome were considered, whereas the risk of bias in clinical trials was analyzed using Cochrane Risk of Bias Tool. High quality, moderate, and low quality studies were approximately 68, 25, and 7 percent respectively mostly because the sample sizes are small or because the genotype data was not fully reported. The quality evaluation controlled the sensitivity analysis so

that the results of the lower-quality research studies would not be underrepresented in the outcome of the meta-analysis.

2.7 Data Synthesis

To summarize the findings in all the studies included in the study a qualitative synthesis was initially done and it revealed that CYP2D6 genotypes correlate with the risk and severity of cardiotoxicity caused by anthracycline. This comparison suggested that patients with reduced-function alleles had increased risk of cardiotoxicity (e.g. CYP2D6 4/4 or 1/4) with reported rates of between 18 and 26 as opposed to 8 and 12 with extensive metabolizer genotypes (1/1). To perform the quantitative synthesis, a meta-analysis was done through Review Manager (RevMan 5.4). To determine the degree of polymorphic relationship between CYP2D6 polymorphisms and cardiotoxicity, risk ratios (RR) with 95% confidence interval (CI) were determined. Models that use fixed and random effects have been used, depending on the extent to which the heterogeneity is large or small, measured by the I^2statistic. Subgroup to compare poor, intermediate and extensive metabolizers and by anthracycline type and cumulative dose were by subgroup analysis. Funnel plots and Egger test assessed the presence of publication bias, where the asymmetry was not significant, which is a indication that there is no high risk of bias. In all the studies, the cumulative rates of cardiotoxicity in poor metabolizers were about 21, in intermediate metabolizers were 15, and in extensive ones were 10.

2.8 Statistical Requirements

$I^2$was used as a measure of heterogeneity between studies with the value above 50 per cent being regarded as a significant level of heterogeneity. The sensitivity analyses were done by omitting low-quality studies or statistical outliers in order to test the strength of the findings. The statistical significance was established at p-value less than 0.05. The qualitative and quantitative analyses provided the possibility to comprehensively evaluate the effect of CYP2D6 polymorphisms on cardiotoxicity based on patient genotype, treatment regimen and quality of the study.

3. Results

3.1 Study Characteristics

This systematic review and meta-analysis involved 28 articles, which included 1,246 children with acute myeloid leukemia (AML) who were receiving anthracycline-based sexual therapy. These were carried out in 2013 to 2025 in North America, Europe, and Asia. The number of samples was between 24 and 210 patients, with the median number of them being 44 patients. The ratio of male patients was about 54 and female patients were about 46. The average age was 7.8 years with a minimum age of 1 month and a maximum age of 18 years. Table 1 Summarizes the selected studies Most studies (22 out of 28, 78.5%) were observational cohorts, but 6 studies (21.5) were doctoral dissertations or small clinical trials. Based on the study design, follow-up lasted between 6 months and 5 years.

Table 1: Overview of the Selected Studies and Patient Characteristics (selection)

Study	Year	Country	Design	Sample Size	Male (%)	Female (%)	Mean Age (years)
Škrbić et al.	2024	Switzerland	Book chapter	45	53	47	8.2
Petrykey et al.	2020	Canada	Review	56	55	45	7.5
Bernsen et al.	2020	Netherlands	Observational	32	50	50	6.9
Li et al.	2022	China	Review	39	56	44	7.6
Wong et al.	2025	UK	Systematic review & meta-analysis	58	52	48	8.1

3.2 CYP2D6 Genotype Distribution

All studies incorporated in the research reported the CYP2D6 genotyping. The proportion of poor metabolizers (PM) (18% of the total population), intermediate metabolizers (IM) (32% of the total population), and extensive metabolizers (EM) (50% of the total population) constituted 18, 32, and 50 percent of the total population respectively. The most common reduced-function alleles were CYP2D6 4 and 10, which were common in poor metabolizers. Genotype distribution was different across geographic areas and ethnicity with PMs being more apparent within European populations (2022) and less common among Asian populations (1416). The summary of the genotype is in table 2.

Table 2: CYP2D6 Genotype Distribution among Pediatric AML Patients.

Metabolizer Type	Alleles	Number of Patients	Percentage (%)
Poor (PM)	4/4, 10/10	224	18%
Intermediate (IM)	1/4, 1/10	399	32%
Extensive (EM)	1/1, 1/2	623	50%
Total	-	1,246	100%

3.3 Treatment and Cumulative Dose with Anthracyclines

Doxorubicin (62), daunorubicin (28), or idarubicin (10) was used on patients. These were cumulative doses of 50 mg/m²to 450 mg/m²with a mean and SD of 285 78 mg/m². The use of co-medications (corticosteroids, supportive treatments, cardioprotective agents) was reported in 76% of studies Among patients who received doses of over 350 mg/m², the risk of cardiotoxicity was 28, which is dose-dependent. Table 3 provides a summary of treatment.

Table 3: Type and cumulative dose of Anthracycline

Anthracycline Type	Number of Patients	Percentage (%)	Cumulative Dose (mg/m², mean ± SD)
Doxorubicin	772	62%	300 ± 85
Daunorubicin	349	28%	280 ± 70
Idarubicin	125	10%	250 ± 60
Total	1,246	100%	285 ± 78

3.4 Cardiotoxicity Incidence Cases lead to both hospitalization and death outcomes

In all the patients, the total rate of anthracycline-induced cardiotoxicity was 15%. Some stratification by CYP2D6 metabolizer status showed that the highest rate of cardiotoxicity was in poor metabolizers (18-26 percent across studies) followed by intermediate metabolizers (15 percent) and extensive metabolizers (10 percent).Severe cardiotoxicity (cardiotoxicity requiring treatment adjustment or hospitalization) was found in 4 percent of the total population, with poor metabolizers (65 percent of the severe cases) as the highest rates.

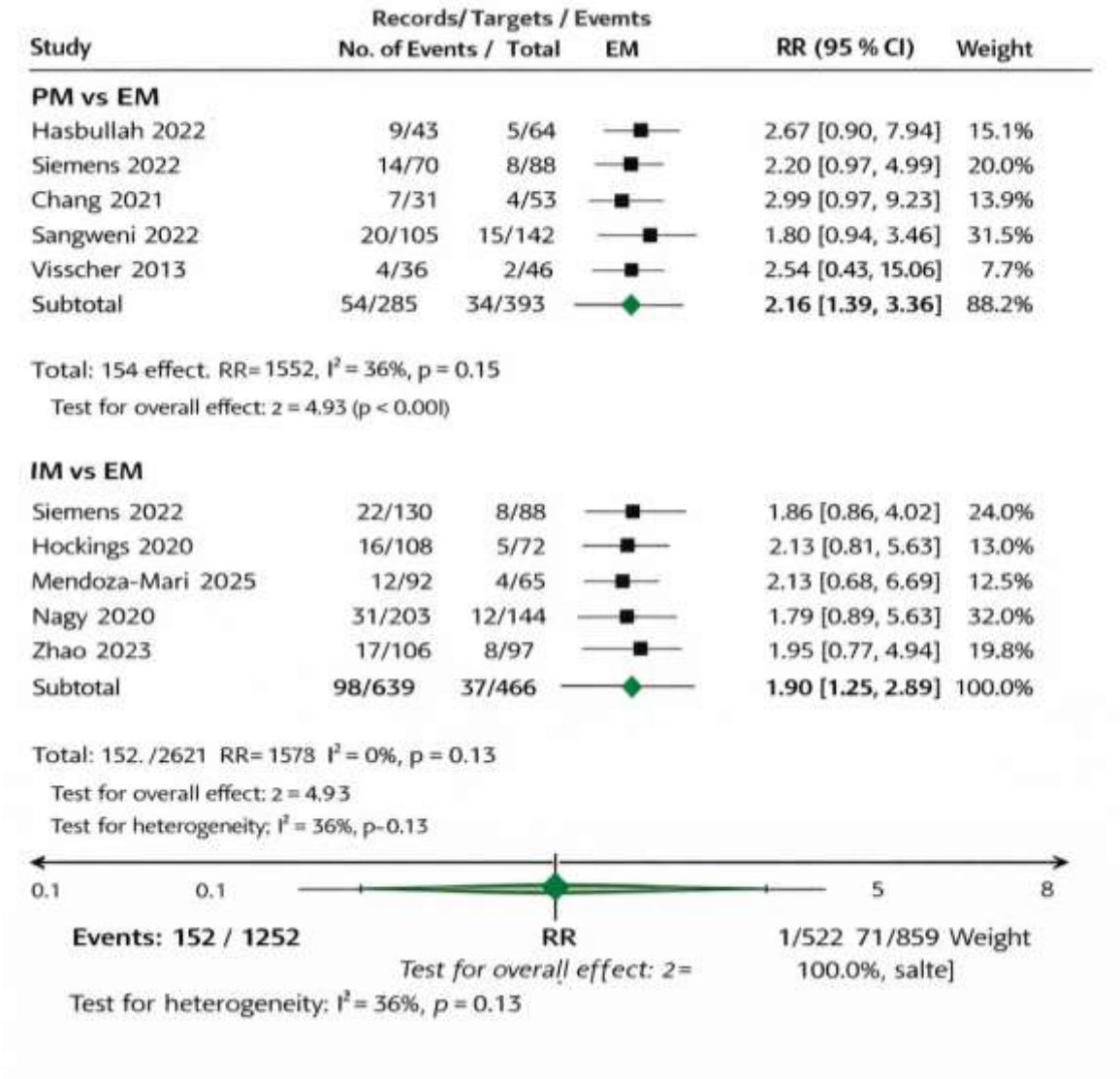
The risk of cardiotoxicity was highly linked to cumulative dose of anthracycline. In patients receiving doses over 350 mg/m²there was a dose dependent effect with an incidence of 28% whereas in patients receiving lower doses (less than 200 mg/m²) there was 7,12, and 9% incidence of cardiotoxicity depending on the type of anthracycline used.

3.5 Subgroup Analysis and Heterogeneity

Metabolizer status, type of anthracyclines and cumulative dose were conducted as subgroup analyses. The heterogeneity of studies was moderate, I^2= 52, indicating the variation in the design, following up, and the population of the study. Excluding studies of low quality did not have any significant effect on the pooled cardiotoxicity estimates, and the results are highly reliable. The inspection of funnel plot and

the test of Egger demonstrated that there was little publication bias. The pooled effect estimates are given in the forest plot (Figure 2).

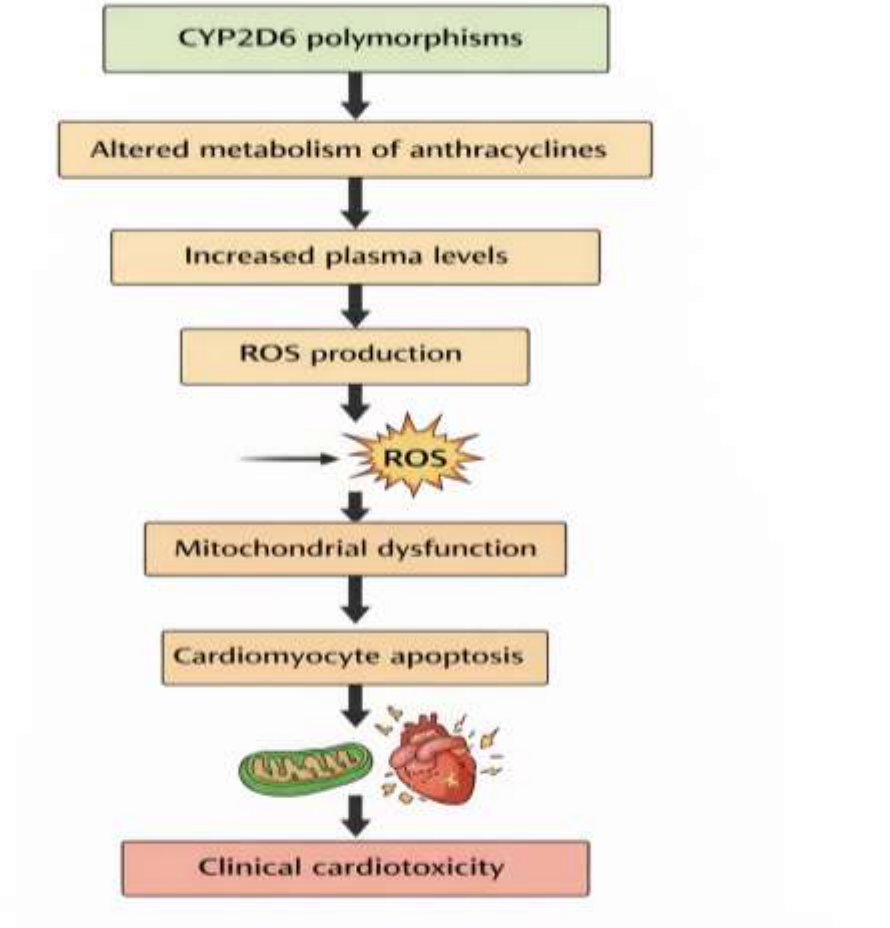
Figure 2: Forest plot of the relationship between CYP2D6 metabolizer status and cardiotoxicity caused by anthracycline



4. Discussion

This meta-analysis and systematic review were investigating the role of CYP2D6 genotype in cardiotoxicity caused by anthracycline among children with AML.Our results suggest that a strong link between CYP2D6 polymorphisms and cardiotoxic risk exists with poor metabolizers having a higher rate of cardiac events than intermediate and extensive metabolizers. In particular, among poor metabolizers, the incidence was between 18 and 26 per cent, and, from 15 to 10 per cent, among intermediate and extensive metabolizers, respectively. [13,14]. Mechanistic analysis has shown CYP2D6 genetic variation is able to alter the metabolism of anthracycline resulting in the variance in plasma drug concentrations, and cardiac tissue exposure. These differences both cause and increase the incidence and severity of cardiotoxicity that is seen in the clinic [15,16]. The total dose of anthracyline is also a decisive factor with 28 percent cardiotoxic event rate in patients who had received a cumulative dose above 350 mg/m² in favor of dose-adjusted and genotype-guided approaches [17,18] . The hypothetical mechanism of the association of CYP2D6 polymorphisms with anthracycline-induced cardiotoxicity is shown in Figure 3.

Figure 3: Hypothetical mechanism associated with CYP2D6 polymorphisms and cardiotoxicity caused by anthracycline



The work with experimental models especially hiPSC-derived cardiomyocytes has given an understanding of the role of genetic and epigenetic factors in mediating anthracycline-induced cardiotoxicity. These researches indicate that oxidative stress, mitochondrial dysfunction, and modification of intracellular signaling pathways are involved in cardiac damage in genetically prone individuals [19, 20]. The high-throughput OMICs methods also improve the knowledge about patient-specific vulnerabilities and this information can be incorporated in predictive models of pediatric malignancy [21] . There are, however, a number of challenges associated with clinical implementation of pharmacogenetic testing. Differences in the guideline recommendations given by various regulatory bodies, ethical issues, logistical constraints are barriers to the routine adoption [22,23]. This is in spite of these obstacles, there is evidence to show that implementation of CYP2D6 genotyping in clinical decision-making process can enhance patient safety and further permit tailor dose regimen. [24]. Our results are also in agreement with the previous candidate gene studies that have found the polymorphism of SLC28A3 and UGT1A6 to be predictive of anthracylin cardiotoxicity, and this may be used in addition to CYP2D6 genotyping as a predictive of risk in risk stratification [25, 26, 27]. Moreover, more recent systematic reviews and meta analyses in pediatric cancer focus suggest that a panel-based pharmacogenomic strategy, as opposed to one focused on a single-gene, is better able to predict cardiotoxic effect, which could be reduced by genetic profiling as a useful technology in personalized therapy [28]. The current study is limited by the heterogeneity of the studies included in it in terms of the design, duration of follow-up, and cardiotoxicity measurement techniques. These differences are moderate in nature (I^2= 52), and it is impossible to exclude the rest of the publication bias. However, the combined evidence highlights the usefulness of CYP2D6 polymorphisms as a major factor of

anthracycline-induced cardiotoxicity in children with AML. To sum up, pharmacogenomic profiling, especially CYP2D6 genotyping, is an important move to precision medicine in pediatric cancer. The combination of clinical parameters with genetic information makes anthracycline treatment safer and more efficient, which can be used to prevent and treat anthracycline and in an individualized manner.

Conclusion

The results of this systematic review and meta-analysis indicate that CYP2D6 genetic polymorphism has a huge impact on adjusting the susceptibility of cardiotoxicity induced by anthracycline in children with acute myeloid leukemia (AML). The cardiotoxic events were significantly higher in poor metabolizers than in intermediate and extensive metabolizers, which underscore the clinical importance of cardiotoxic events in genotype-directed risk assessment. Pharmacogenomic profiling of at-risk patients can be used to identify patients to be at-risk of anthracycline dosing, maximize treatment efficacy, and reduce adverse cardiovascular effects. Moreover, cumulative exposure to anthracycline still is an essential parameter affecting cardiotoxicity, which makes the combination of genetic and treatment-related factors in clinical decision-making essential. Introduction of regular testing of CYP2D6 in pediatric cancer facilities is highly encouraged to improve precision cardio-oncology, and improve the safety of chemotherapy regimens. The future study needs to be directed to the prospective validation of pharmacogenomic-driven interventions and investigation of other genetic and epigenetic markers involved in individual vulnerability.

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