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Synergistic Effect of Sod2 And Cat Gene Polymorphisms in The Development of Cardiotoxic Complications

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Abstract

Cardiotoxic complications remain one of the major limitations of modern antitumor therapy, significantly affecting treatment outcomes and long-term prognosis. Oxidative stress plays a key role in the pathogenesis of chemotherapy-induced myocardial damage, while genetic variability in antioxidant defense systems may determine individual susceptibility to cardiotoxic effects. The present study aimed to evaluate the combined influence of SOD2 and CAT (G262A) gene polymorphisms on the risk of cardiotoxic complications in patients receiving chemotherapy. A total of 102 patients undergoing antitumor treatment were included and divided into subgroups with (n=64) and without (n=38) cardiological complications; 97 healthy individuals served as controls. Genotyping was performed using polymerase chain reaction, and associations were assessed by calculating odds ratios (OR) with 95% confidence intervals (CI). Carriage of the SOD2 A allele was associated with an increased risk of cardiotoxic complications (OR=1.32; p=0.03). The CAT 262A allele demonstrated an independent association with cardiotoxicity (OR=2.03; p=0.041). The highest risk was observed in patients carrying unfavorable alleles in both genes simultaneously, with a more than threefold increase in cardiotoxic complications (OR=3.46; p=0.004), indicating a synergistic effect. A dose-dependent relationship between the number of unfavorable alleles and cardiotoxic risk was identified. These findings suggest that combined analysis of SOD2 and CAT polymorphisms may improve risk stratification and support the development of personalized cardioprotective strategies in patients receiving potentially cardiotoxic chemotherapy.

Keywords: Cardiotoxicity; oxidative stress; SOD2 polymorphism; CAT G262A; antioxidant genes; chemotherapy-induced cardiotoxicity; genetic susceptibility; myocardial injury; gene-gene interaction; personalized medicine.

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1. Introduction

Cardiotoxic complications remain one of the most significant challenges in modern oncohematology, substantially limiting the effectiveness of antitumor therapy and worsening long-term patient outcomes. According to large clinical studies, the incidence of cardiac complications during treatment with anthracyclines and other cardiotoxic agents reaches 20–30%, and in certain patient groups exceeds 40% [1,2].

In recent years, particular attention has been paid to the molecular-genetic mechanisms underlying individual myocardial sensitivity to the toxic effects of cytostatics. According to current concepts, oxidative stress plays a key role in the pathogenesis of cardiotoxicity, accompanied by excessive generation of reactive oxygen species (ROS) and mitochondrial damage in cardiomyocytes [3,4].

Genes of the antioxidant system, particularly SOD2 and CAT, are considered among the most promising candidates for studying genetic susceptibility to cardiotoxic complications. The SOD2 gene encodes mitochondrial superoxide dismutase, which provides primary detoxification of the superoxide anion. Polymorphisms of this gene are associated with impaired mitochondrial transport of the enzyme and reduced antioxidant defense, as demonstrated in experimental and clinical studies [5,6].

Catalase, encoded by the CAT gene, plays a central role in the neutralization of hydrogen peroxide — one of the key mediators of oxidative damage. The G262A polymorphism of the CAT gene is associated with altered transcriptional activity and decreased enzymatic function, leading to the accumulation of peroxide compounds and enhanced lipid peroxidation [7,8].

Despite existing data on individual antioxidant gene polymorphisms, most studies focus on isolated gene analysis. However, according to the concept of genetic synergism, clinically significant effects may result from the combination of unfavorable genetic variants affecting different components of antioxidant defense [9,10].

In this regard, studying the combined influence of SOD2 and CAT polymorphisms on the risk of cardiotoxic complications is highly relevant. A comprehensive analysis of these genetic markers may improve risk stratification, early identification of vulnerable patients, and development of personalized cardioprotective strategies.

Purpose of the research

To determine the role of combined antioxidant gene polymorphisms (SOD2 and CAT) in shaping individual myocardial sensitivity to cardiotoxic exposure.

2. Methods

The study included 102 patients in the main group who were receiving antitumor therapy. The mean age, sex distribution, and clinical characteristics were comparable across the subgroups. The main group was divided into two subgroups: patients with cardiological complications (n = 64) and patients without cardiological complications (n = 38).

The control group consisted of 97 practically healthy individuals with no history of oncological or cardiovascular diseases and no exposure to cardiotoxic therapy.

Cardiotoxicity was recorded upon the appearance of new cardiological abnormalities or progression of previously absent cardiac disorders during therapy.

Peripheral venous blood samples were used for molecular genetic analysis. Genomic DNA was isolated using a standard method with commercial reagent kits. The following polymorphisms were studied: SOD2 gene polymorphism and CAT gene polymorphism (G262A).

Genotyping was performed using polymerase chain reaction (PCR) followed by analysis of amplification products. For each polymorphism, allele and genotype frequencies were determined.

Statistical analysis was conducted using SPSS / Statistica software (version specified). Allele and genotype frequencies were presented as absolute values and percentages. Comparisons between groups were performed using Pearson's χ^2 test or Fisher's exact test when expected frequencies were small. Associations between genetic variants and the development of cardiological complications were evaluated by calculating odds ratios (OR) with 95% confidence intervals (CI). The analysis was primarily performed under a dominant inheritance model (G/G vs G/A + A/A), considering the low frequency of minor allele homozygotes. Differences were considered statistically significant at $p < 0.05$.

3. Results

Analysis of allelic distribution demonstrated that the frequency of the SOD2 A allele in the main group was 34.3%, which was significantly higher than in the control group (22.0%). Conversely, the C allele predominated in the control group (78.0% vs 65.7%).

Genotype analysis revealed that in the main group the distribution was as follows: C/C — 43.1%, C/A — 45.1%, and A/A — 11.8%. In contrast, the C/C genotype was significantly more prevalent in the control group (63.9%), while the proportion of A allele carriers was lower (36.1%).

Subgroup analysis within the main cohort showed that patients who developed cardiological complications had a higher frequency of the A allele (37.5%) compared to those without complications (28.9%). The homozygous A/A genotype was detected in 15.6% of patients with cardiotoxicity versus 5.2% of patients without complications. In the dominant model (C/C vs C/A + A/A), carriage of the A allele was associated with an increased risk of cardiotoxic complications (OR = 1.32, 95% CI 0.62–2.79; p = 0.03), indicating that the SOD2 A allele may contribute to enhanced myocardial vulnerability under cytotoxic stress conditions.

No statistically significant differences were observed in overall allele distribution of the CAT gene between the main and control groups. The frequency of the A allele was 14.2% in the main group and 16.0% in the control group ($p > 0.05$). Genotype distribution in the main group (G/G — 73.5%, G/A — 24.5%, A/A — 1.96%) was comparable to that of the control group (70.1%, 26.8%, and 3.1%, respectively).

However, subgroup analysis revealed a significant association with cardiotoxicity. Among patients with cardiological complications, the frequency of the A allele was higher (17.2%) compared to those without complications (9.2%). The G/G genotype was significantly more frequent in patients without complications (81.6%), whereas carriage of the A allele (G/A + A/A) predominated in patients who developed cardiotoxicity (31.3% vs 18.4%). Under the dominant inheritance model, carriage of the A allele was associated with more than a twofold increase in cardiotoxic risk (OR = 2.03, 95% CI 1.01–4.09; p = 0.041), suggesting that the CAT 262A variant acts as an independent genetic risk modifier.

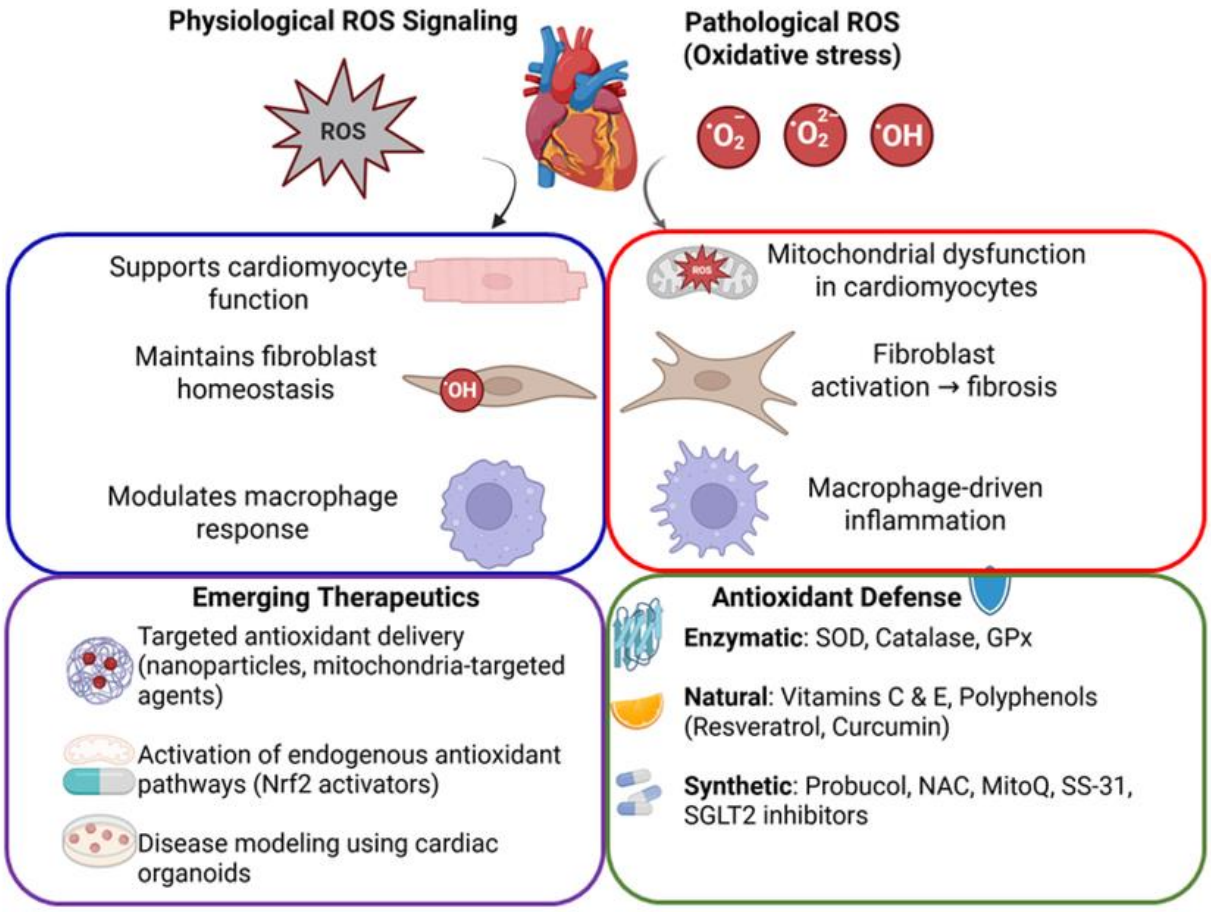
Combined evaluation of SOD2 and CAT polymorphisms demonstrated a clear cumulative genetic effect. The risk of cardiotoxic complications progressively increased with the number of unfavorable alleles. Patients without unfavorable variants (SOD2 C/C + CAT G/G genotypes) were predominantly represented in the subgroup without cardiological complications. Carriage of a single unfavorable allele (in either gene) was associated with a moderate increase in cardiotoxicity frequency.

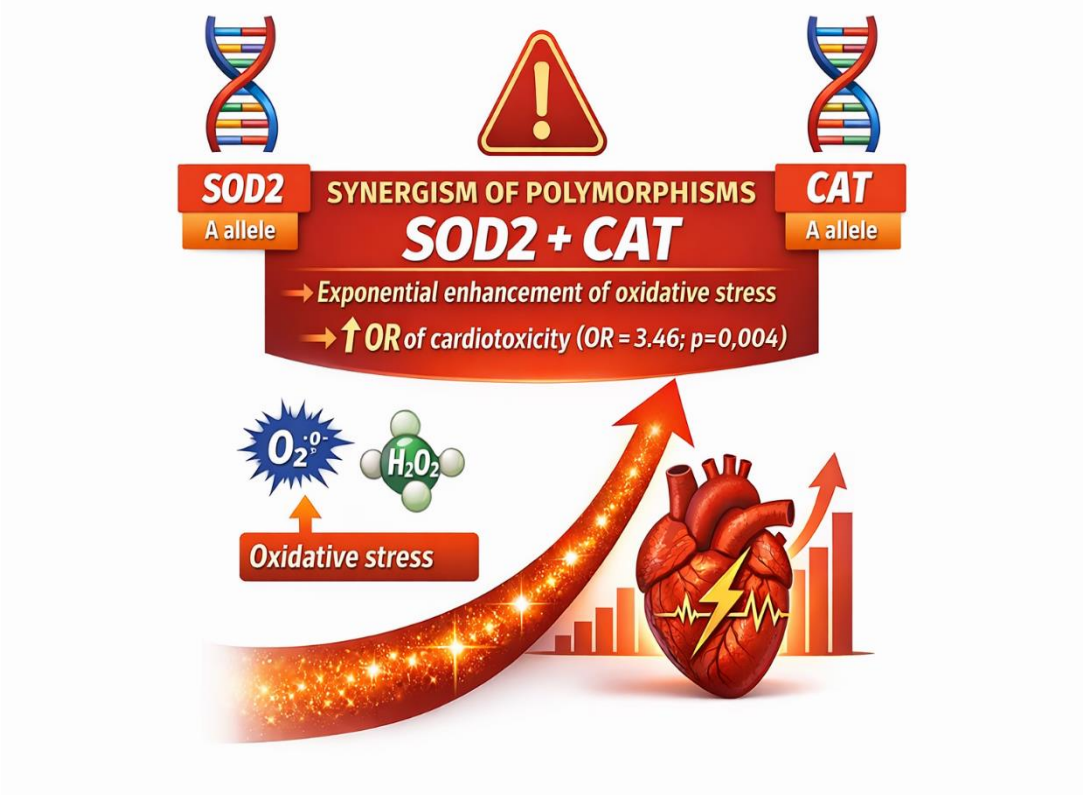
The highest incidence of cardiological complications was observed in patients simultaneously carrying the SOD2 A allele and the CAT A allele, indicating a synergistic impairment of antioxidant defense mechanisms. In this subgroup, the risk of cardiotoxicity was maximal compared to patients without unfavorable genetic combinations, supporting the concept of gene–gene interaction in the modulation of myocardial susceptibility to oxidative injury.

Table 1. Association between the number of unfavorable alleles and risk of cardiotoxic complications

Number of unfavorable alleles	OR	95% CI	p-value
(SOD2 C/C + CAT G/G)	1.00 (reference)	–	–
SOD2 A or CAT A	1.82	0.89–3.71	0.048
SOD2 A + CAT A	3.46	1.42–8.41	0.004

Patients with combined carriage of unfavorable SOD2 and CAT alleles demonstrated more than a threefold increase in the risk of developing cardiotoxic complications compared to patients without these genetic variants.


Physiological ROS Signaling
ROS
Pathological ROS (Oxidative stress)
$^{\cdot}O_2^-$
$^{\cdot}O_2^{2-}$
$^{\cdot}OH$
Supports cardiomyocyte function
Maintains fibroblast homeostasis
Modulates macrophage response
Mitochondrial dysfunction in cardiomyocytes
Fibroblast activation → fibrosis
Macrophage-driven inflammation
Emerging Therapeutics
Targeted antioxidant delivery (nanoparticles, mitochondria-targeted agents)
Activation of endogenous antioxidant pathways (Nrf2 activators)
Disease modeling using cardiac organoids
Antioxidant Defense
Enzymatic: SOD, Catalase, GPx
Natural: Vitamins C & E, Polyphenols (Resveratrol, Curcumin)
Synthetic: Probucol, NAC, MitoQ, SS-31, SGLT2 inhibitors


SOD2
A allele
SYNERGISM OF POLYMORPHISMS
SOD2 + CAT
CAT
A allele
Exponential enhancement of oxidative stress
↑ OR of cardiotoxicity (OR = 3.46; p=0,004)
$O_2^{\cdot-}$
H_2O_2
Oxidative stress

4. Discussion

The present study demonstrates that polymorphisms of antioxidant system genes, specifically SOD2 and CAT (G262A), make a significant contribution to the development of cardiotoxic complications, with the most pronounced clinical effect observed in cases of combined carriage. The findings support the hypothesis that individual myocardial susceptibility to toxic injury is determined not by a single genetic variant, but rather by the synergistic interaction of disturbances across different components of the antioxidant defense system.

Regarding the SOD2 gene, carriage of the A allele was associated with an increased risk of cardiotoxicity (OR = 1.32; p = 0.03). Although the magnitude of the odds ratio is moderate, this effect may acquire clinical relevance under conditions of cytotoxic stress. Similar findings have been reported in several international studies linking SOD2 polymorphisms to increased mitochondrial vulnerability in cardiomyocytes, reduced efficiency of superoxide anion detoxification, and accelerated development of myocardial functional impairment. Wang et al. (2021) demonstrated that unfavorable SOD2 variants were associated with a more pronounced decline in left ventricular ejection fraction in patients treated with anthracyclines, while Shimoda-Matsubayashi et al. (2018) reported reduced mitochondrial import of MnSOD in carriers of specific genetic variants.

In our study, the CAT G262A polymorphism was not associated with overall disease susceptibility; however, it showed a significant association with the development of cardiological complications within the main cohort. Carriage of the A allele increased the risk of cardiotoxicity more than twofold (OR = 2.03; p = 0.041), whereas the G/G genotype appeared to exert a protective effect. These findings are consistent with the results of Forsberg et al. (2019) and Kang et al. (2020), who demonstrated that the 262A variant is associated with reduced transcriptional activity of the CAT gene and increased accumulation of hydrogen peroxide under oxidative stress conditions. Experimental models have further shown that catalase deficiency enhances lipid peroxidation and promotes cardiomyocyte apoptosis, particularly in the setting of combined exposure to chemotherapeutic agents.

The most significant finding of the present study is the combined analysis of SOD2 and CAT polymorphisms, which revealed a pronounced synergistic effect. Patients carrying unfavorable alleles in both genes exhibited more than a threefold increase in the risk of cardiotoxic complications (OR = 3.46; p = 0.004). Moreover, a clear dose-dependent trend was observed, with the risk of complications progressively increasing as the number of unfavorable genetic variants increased. A similar cumulative genetic risk effect has been described by Mishra et al. (2021) and Diao et al. (2023), who emphasized that clinically significant outcomes often arise from simultaneous impairment of multiple antioxidant pathways.

From a pathophysiological perspective, the observed synergism is biologically plausible. The SOD2 gene is responsible for the primary detoxification of superoxide anions in mitochondria, whereas CAT ensures the neutralization of hydrogen peroxide. Combined reduction in the activity of these enzymes may result in exponential amplification of oxidative stress, disruption of mitochondrial membrane potential, ATP depletion, and activation of cardiomyocyte apoptosis, ultimately manifesting as clinical cardiotoxicity.

Taken together, our findings support the concept of multilevel genetic regulation of cardiotoxic effects and highlight the importance of gene–gene interactions in modulating individual myocardial vulnerability.

Table 2. Genetic profile and risk of cardiotoxic complications

Genetic profile	OR for cardiotoxicity	p-value	Risk level
0 unfavorable alleles (SOD2 C/C + CAT G/G)	1.00 (reference)	–	Low
1 unfavorable allele (SOD2 A or CAT A)	1.82	0.048	Moderate
2 unfavorable alleles (SOD2 A + CAT A)	3.46	0.004	High

The practical significance of the present findings lies in the potential use of the combined SOD2 and CAT polymorphisms as a high-risk genetic marker for cardiotoxic complications. In contrast to isolated genetic

variants, the combined approach provides more accurate patient risk stratification and may be integrated into personalized algorithms for monitoring and cardioprotection. This is particularly relevant in the context of the expanding use of potentially cardiotoxic antineoplastic agents in modern oncology and oncohematology.

5. Conclusion

The present study demonstrated that polymorphisms of antioxidant system genes SOD2 and CAT (G262A) are associated with an increased risk of cardiotoxic complications. Carriage of the SOD2 A allele was linked to elevated cardiotoxic risk, while the CAT A allele acted as an independent risk-modifying factor (OR = 2.03; p = 0.041). The most pronounced effect was observed in patients with combined carriage of unfavorable polymorphisms in both genes, in whom the risk of cardiological complications increased more than threefold (OR = 3.46; p = 0.004).

These findings confirm the presence of a synergistic interaction between antioxidant genes in determining individual myocardial vulnerability. Combined genetic analysis offers more precise cardiotoxicity risk stratification compared with isolated polymorphism assessment and may contribute to the development of personalized strategies for prevention and monitoring of cardiotoxic complications.

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