fortune Journals

Research Article

FORTUNE JOURNAL OF HEALTH SCIENCES

ISSN: 2644-2906

Polymorphisms in Glutathione S-transferase genes, Development, and Progression of Sepsis

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Abstract

Introduction: Sepsis is an inefficient and deleterious inflammatory response from the host against an infectious agent that can lead to organ dysfunction. The oxidative stress is related to the pathogenesis of several high prevalence diseases. Therefore, a better comprehension of the oxidative regulation during sepsis can lead to new therapeutic perspectives. Glutathione S-transferases (GST) is an important antioxidant enzyme system involved in the mechanism of cellular detoxification. So there has been an increasing interest in the possible pathological implications of the polymorphisms in *GST*.

Methodology: 116 samples from patients admitted in the cardiovascular ICU were analyzed using PCR multiplex and PCR-RFLP techniques to find possible associations between *GSTT1*, *GSTM1* e *GSTP1* polymorphisms and a greater risk of developing sepsis, as well as its worse prognosis.

Results: *GSTM1* and *GSTT1* null genotypes frequency was, respectively, 26.72% and 13.79% while 7.75% of the patients presented nullity for both genes. *GSTP1* genotypic distribution showed a higher percentage for the heterozygous variant genotype. Polymorphisms did not influence the risk of developing sepsis and were also not related to higher APACHE II and SOFA scores.

Conclusions: Despite important studies showed the classes Mu, Pi and Theta polymorphisms effects in the pathogenesis of several diseases, in this study, there has been no significant association between the studied polymorphisms and sepsis, and its worse prognosis.

Keywords: Variant genotypes; GST; Oxidative stress; Sepsis; Prognosis

Introduction

Sepsis is a harmful and inefficient host inflammatory response against an infectious agent that, if left untreated, leads to organ dysfunction. Despite advances in patient care, epidemiological studies suggest that sepsis continues to be a huge burden in all economic regions. However, a change in the allocation of screening, faster administration of antibiotics, and reduction in mortality can be caused by a set of effects generated by better recognition, appropriate treatment, and time trends [1,2]. During infection, the invading microorganisms interact with the host immune system by activating an inflammatory cascade involving cytokines and other mediators, which in turn triggers a potentially fatal systemic response. The effects resulting from this process include vasodilation, increased vascular permeability, cellular hypoxia, myocardial depression, impairments in the coagulation cascade leading to a procoagulant state. During the late phase of sepsis, immunosuppression

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Citation: Natália Brito da Cruz, José Gildo de Moura Monteiro Júnior, Dário Celestino Sobral Filho, Dilênia de Oliveira Cipriano Torres, José Luiz de Lima Filho, Danyelly Bruneska Gondim Martins, Rosângela Ferreira Frade de Araújo. Polymorphisms in Glutathione S-transferase genes, Development, and Progression of Sepsis. Fortune Journal of Health Sciences. 7 (2024): 364-371.

Received: June 19, 2024
Accepted: June 26, 2024
Published: July 03, 2024

Brito da Cruz N, et al., Fortune J Health Sci 2024
DOI:10.26502/fjhs.197

predominates, leading to the Multiple Organ Dysfunction Syndrome and a worsening of the patient's condition. In this context, biomarkers play a significant role in sepsis. They can indicate prognosis, guide antibiotic therapy, assess response to therapy and recovery, predict complications of sepsis and the development of multiple organ dysfunction [3,4,5].

Severity scoring and organ dysfunction systems APACHE II (Acute Physiology and Chronic Health Evaluation) and SOFA (Sequential Organ Failure Assessment) have been widely used in various settings and populations. The purpose of these is to categorize patients according to the degree of commitment that present, and predict the risk of death, from physiological variables and indicating the degree of organ dysfunction. Although these scores were not specifically developed for sepsis, its potential has been extended to patients inwards or in the emergency department with suspected infection. These models are potentially useful to help in decision making, how to determine the need for invasive procedures, special treatments, ICU admissions and evaluate the response to treatment [2,6,7,8,9]. Oxidative stress has been implicated in the pathogenesis of several high-prevalence diseases. There is increasing evidence that the innate immune response can be dramatically influenced by the cellular redox state. Nevertheless, the guidelines for the management of patients with these conditions do not include enhanced antioxidant potential. A better understanding of oxidative regulation during sepsis can lead to new treatments [10,11]. Lorente et al suggest that the determination of total antioxidant capacity during the first week of sepsis can be used as a biomarker of mortality risk [12].

The glutathione S-transferases (GST) are major enzyme systems that are part of a cellular detoxification mechanism. This mechanism protects cells against reactive oxygen metabolites due to the conjugation of glutathione with electrophilic compounds. The GST enzymes present a consistent gene variability and are involved in xenobiotic metabolism including metabolizing environmental carcinogens, reactive oxygen species and chemotherapeutic agents [13]. A growing number of studies indicates that different genotypes of GST could affect the susceptibility, or prognosis of diseases [14,15]. Therefore, this study aimed to evaluate the association between polymorphisms of the glutathione S-transferase and the risk of developing sepsis and a worse prognosis in patients admitted in a Cardiological Hospital.

Methodology

Study Design

Analytical study of the case-control was conducted with samples of 116 adult patients admitted to the ICU of the Cardiological Hospital of Pernambuco (PROCAPE) - Brazil. In the first twenty-four hours of admission, the patients were classified as septic or not, according to previous criteria [16]. Among these patients, 68 had clinical conditions indicative of sepsis and 48 had no sepsis.

Criteria for Inclusion and Exclusion

The inclusion criteria were adult patients with and without sepsis in the ICU with clinical and / or surgical diseases. Exclusion criteria: patients younger than 18, pregnant women, patients who have had previous use of steroids or chemotherapy and patients who died or were discharged within 24 hours after ICU admission.

Clinical and Biochemical Data

The clinical and biochemical data of patients were obtained from medical records and a PROCAPE database (Table 1).

Table 1: Characteristics of 116 patients in intensive care.

Characteristics	All patients
Sex	
Male	65(56.03%)
Female	51(43.96%)
Age (in years)	61.2 ± 16.6
Skin color	
White	46(39.6%)
Mixed	51(43.96%)
Black	19(16.38%)
Origin	
Emergency	96(82.76%)
Wards	16(13.8%)
CTRU [1]	4(3.45%)
APACHE II [2]	
<25 points	70(60.34%)
≥25 points	46(39.65%)
SOFA [3]	
<7 points	52(44.82%)
≥7 points	64(55.17%)
Sepsis	
Yes	68(58.62%)
No	48(41.38%)
Sites of infection	
Respiratory	60(88.24%)
Urinary	3(4.41%)
Cutaneous	2(2.94%)
Cardiac	3(4.41%)
Coronary patient	
Yes	57(49.13%)
No	59(50.86%)
Sepsis/Coronary	
Sepsis and coronary	26(22.41%)
Sepsis and non-coronary	42(36.20%)
No sepsis and coronary	31(26.72%)
No sepsis and non-coronary	17(14.66%)

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Determination of Prognosis Scores

In the first 24 hours of ICU admission, all patients had an APACHE II score calculated. The SOFA score was found from the values of the parameters observed from the 1st to the 5th, 7th, and 14th days of hospitalization.

Ethical Aspects of Research

This work was carried out after the approval of the Ethics Committee of the hospital complex HUOC / PROCAPE under number: 08412412.20000.5192. All patients who agreed to participate in the study signed an informed consent form.

Molecular Analysis

Dna Extraction

DNA was extracted from whole blood cells by the EDTA Wizard® SV Genomic DNA Purification System according to the manufacturer's instructions.

GSTM1 and GSTT1 Polymorphisms

For identification of the GSTM1 and GSTT1 polymorphisms, DNA was amplified by polymerase chain reaction (PCR) multiplex using forward and reverse primers. *GSTM1* (F: 5'- GAA CTC CCT GAA AAG CTA AAG C-3 'and R: 5'- GTT GGG CTC AAA TAT ACG GTG G -3 ') and *GSTT1* (F: 5'- TTC CTT ACT GGT CCT CAC ATC TC -3' and R: 5'-TCA CCG GAT CAT GGC CAG C-3 '), the *ACTB,* b-actin gene (F: 5'-AAG GGT CTG TTC TAG TTG TC - 3 'and R: 5'-AGC TTG GTG ACT GCA TAG AG -3') was used as quality control of extracted DNA. The final volume of the reaction was 12.5 µL using Go-Tac Green Master Mix. The PCR conditions consisted of an initial melting temperature of 94°C (5 min) followed by 35 cycles of melting (94°C, 2 min), annealing (59°C, 1 min) and extension (72°C, 1 min). The final extension step was at 72°C for 10 min. After amplification of the target sequences, the samples were subjected to electrophoresis on 1% agarose gel, the bands were stained with ethidium bromide and then photographed on a UV transilluminator. The presence or absence of amplification products of *GSTT1* (480bp) and *GSTM1* (215pb) indicate, respectively, positivity and nullity of the genes [17].

GSTP1 polymosphism

The extracted DNA was amplified by PCR-RFLP (Restriction Fragment Length Polymorphism) using forward and reverse primers *GSTP1* (F: 5'- GTA GTT TGC CCA AGG TCA AG -3 'and R: 5'- AGC CAC CTG AGG GGT AAG -3 '). The final volume of the reaction was 12.5 µL using Go-Tac Green Master Mix. The cycling parameters included initial denaturation at 94°C for 5 min, followed by 30 cycles of denaturation at 94°C for 1 min, annealing at 59°C for 90s, and extension at 72 °C for 90s. The final polymerization step was at 72°C for 7 min. The PCR products were treated with *Alw*26I restriction enzyme (Fermentas) for 1 hour at 37 °C. After treatment with the enzyme, the samples were subjected to electrophoresis in 1% agarose gel, which was visualized bands 329 and 113pb corresponding to the wild genotype (Ile / Ile), 216pb bands and thick band corresponding bands 107 and 113pb concerning the homozygous variant genotype (Val / Val) and all bands were visualized in the heterozygote variant genotype (Ile / Val) [18]. The bands 107 and 113pb were confirmed on a 10% polyacrylamide gel.

Statistical Analysis

Risk genotypes for sepsis and a worse prognosis were analyzed by the chi-square test and calculating the Odds ratio with 95% confidence interval using GraphPad Prism 5 software.

Results

The characteristics of 116 patients are shown in table 1. Most of the patients included in the study were admitted to PROCAPE in the emergency department and more than 50% of them had SOFA above 7. The main focus of infection in septic patients was the respiratory tract. The analysis of polymorphisms of both *GSTM1* and *GSTT1* showed a

Table 2: Association between GSTP1, GSTT1 and GSTM1 polymorphisms of 116 patients in intensive care and sepsis.

Genotype	With Sepsis	Without Sepsis	X^2	P value	Odds Ratio	CI 95%
GSTP1						
Ile /Val	34	28	0.264	0.607	0.809	0.361 – 1.814
Val/Val	10	4	0.58	0.446	1.667	0.444 – 6.246
Ile/Val+ Val/Val	44	32	0.047	0.826	0.916	0.420 – 1.999
Ile /Ile	24	16	Reference			
GSTT1/ M1						
GSTM1 null	16	15	0.374	0.54	0.761	0.318 – 1.822
GSTT1 null	13	3	2.851	0.091	3.095	0.797 – 12.02
GSTT1/M1 nulls	4	5	0.614	0.433	0.571	0.139 – 2.345
GSTT1/M1 presence	35	25	Reference			

CI: Confidence Interval

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DOI:10.26502/fjhs.197

Table 3: Association between GSTP1, GSTT1 and GSTM1 polymorphisms of 116 patients in intensive care and APACHE II prognostic score

Genotype	APACHE II (≥25)	APACHE II (<25)	X²	P value	Odds Ratio	CI 95%
With Sepsis						
GSTP1						
Ile /Val	18	16	0.008	0.926	0.951	0.333-2.715
Val/Val	6	4	0.097	0.754	1.269	0.283-5.682
Ile/Val+ Val/Val	24	20	0	0.976	1.015	0.374-2.756
Ile /Ile	13	11	Reference			
GSTT1/ M1						
GSTM1 null	8	8	0.447	0.503	0.666	0.202-2.193
GSTT1 null	6	7	0.738	0.39	0.571	0.158-2.062
GSTT1/M1 nulls	2	2	0.148	0.7	0.666	0.083- 5.304
GSTT1/M1 presence	21	14	Reference			
Without Sepsis						
GSTP1						
Ile /Val	7	21	2.406	0.12	5	0.555- 45.04
Val/Val	1	3	1.25	0.263	5	0.239- 104.2
Ile/Val+ Val/Val	8	24	2.462	0.116	5	0.566- 44.11
Ile /Ile	1	15	Reference			
GSTT1/ M1						
GSTM1 null	2	13	0.666	0.414	0.487	0.084 – 2.802
GSTT1 null	0	3	0.916	0.338	0.428	0.019 – 9.457
GSTT1/M1 nulls	1	4	0.037	0.846	0.791	0.073 – 8.523
GSTT1/M1 presence	6	19	Reference			

CI : Confidence Interval

Table 4: Association between GSTP1, GSTT1 e GSTM1 polymorfisms of 116 patients in intensive care and SOFA prognostic score.

Genotype	SOFA (≥7)	SOFA (<7)	X²	P value	Odds Ratio	CI 95%
With Sepsis						
GSTP1						
Ile /Val	24	10	2.533	0.111	2.4	0.808 – 7.128
Val/Val	6	4	0.283	0.594	1.5	0.335 – 6.705
Ile/Val+ Val/Val	30	14	2.174	0.14	2.143	0.771 – 5.951
Ile /Ile	12	12	Reference			
GSTT1/ M1						
GSTM1 null	10	6	0.001	0.98	0.985	0.289 – 3.345
GSTT1 null	8	5	0.007	0.933	0.945	0.254 – 3.508
GSTT1/M1 nulls	2	2	0.25	0.616	0.591	0.074 – 4.715
GSTT1/M1 presence	22	13	Reference			
Without Sepsis						
GSTP1						
Ile /Val	6	22	0.044	0.832	1.182	0.251 – 5.549
Val/Val	1	3	0.078	0.779	1.444	0.108 – 19.23
Ile/Val+ Val/Val	7	25	0.063	0.801	1.213	0.268 – 5.491

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Ile /Ile	3	13	Reference			
GSTT1/ M1						
GSTM1 null	3	12	0.086	0.769	0.791	0.165 – 3.780
GSTT1 null	0	3	0.916	0.338	0.428	0.019 – 9.457
GSTT1/M1 nulls	1	4	0.037	0.846	0.791	0.073 – 8.523
GSTT1/M1 presence	6	19	Reference			

CI= Confidence Interval

percentage of 48.26% of patients with null genotypes. The *GSTM1* gene showed an invalidity rate of 26.72%. 13.79% had genotype *GSTT1* null and 7.75% had both null genes. The genotypic distribution of *GSTP1* showed a higher percentage for the heterozygous variant genotype (53.44% Ile / Val), followed by wild type genotype (34.48% Ile / Ile) and a lower frequency of the homozygous variant genotype (17.75% Val / Val). According to Table 2, there was no association with any of the genotypes alone or in possible combination with the risk of developing sepsis. An association between the individual genotypes and prognostic scores APACHE II and SOFA was investigated. By observing tables 3 and 4, it is found that the association between *GSTM1*, *GSTT1* and *GSTP1* genotypes and prognosis scores were not statistically significant, both in the group with sepsis, as in the control group. These data suggest that there was no influence of the polymorphisms studied in the severity of the condition of patients. There was also no association between polymorphisms of GST and APACHE II and SOFA scores prognostic correlating age and sex of patients (data not shown).

Discussion

In the study by Zaid et al which included 122 Iranian patients with a mean age similar to that found in our study, pneumonia was the most common infection that led to sepsis [5]. Another study with 1,235 patients with a mean age of 65 years in 90 Brazilian ICUs, 71.2% of infected patients had the lung as the focus of infection [19]. Although various types of infections can lead to sepsis, the most common are respiratory, circulatory system and intra-abdominal infections [20]. The *GSTM1* and *GSTT1* genotypes frequency found was similar to those obtained in Brazilian studies, in which the *GSTM1* null genotype had a higher percentage [13,21]. The *GSTP1* genotypes also corroborated the literature data in brazilian studies by Hatagima et al [22] and Lima et al [23], where the heterozygous variant genotype showed a higher frequency.

In recent years there has been increasing interest in the possible pathological implications of polymorphisms in the genes of GST. As the glutathione S-transferases are involved in the processing of reactive oxygen species (ROS), lipid peroxidation products and some metabolites of toxic substances, there are potential links between genetic polymorphisms of these enzymes and pathogenesis of a significant number of chronic diseases. To date studies associating M1, T1 and P1 polymorphisms with sepsis or infectious nature of diseases are scarce. Many studies on the GST polymorphisms have focused on cancers related to tobacco use such as lung, bladder, head, or neck. Studies correlating polymorphisms with asthma and systemic lupus erythematosus, for example, are also found in the literature [24,14]. Human polymorphisms of enzymes involved in the cycle of S-glutathionylation (primarily by GSTP) create a scenario for inter-individual variance in response to oxidative stress has been identified [25]. According to Table 2, there was no association with any of the genotypes alone or in possible combination with the risk of developing sepsis. Hatagima et al [22] analyzed the influence of *GSTP1*, M1 and T1 polymorphisms in susceptibility to oral cancer among Brazilians in Rio de Janeiro. The results did not support the hypothesis that polymorphisms increase the risk of oral cancer. Silva et al [19] in a meta-analysis study found no association between the null polymorphism of the *GSTM1* and *GSTT1* genes and kidney cancer. In contrast, Helzlsouer et al [26] analyzed the association of *GSTM1*, *GSTT1* and *GSTP1* polymorphism and the risk of developing breast cancer. In their results, the *GSTM1* null genotype was associated with a higher risk of developing breast cancer, with a higher prevalence in cases of postmenopausal breast cancer. For *GSTP1*, the data suggested a trend in an increased risk of the variant genotype developing cancer. There was also an increased risk of breast cancer (OR=12.88) for the combination of *GSTM1* and *GSTT1* null genotypes, and *GSTP1* variant genotypes.

Kang et al [27] investigated whether GST genotypes influence genetic susceptibility and the clinical course of disease in muscle-invasive bladder cancer (MIBC) patients in the Korean population. They observed a statistically significant increase of *GSTM1* null genotype in MIBC patients compared to the control group. Individuals with the *GSTT1* null genotype showed an increased predisposition to greater disease progression and cancer-specific death, and to have shorter survival. In the combined analysis, *GSTT1* null genotype was an independent risk factor for disease progression and cancer-specific death regardless of the *GSTM1* genotype. Furthermore, smoking and the *GSTT1* null genotype showed a joint effect, with elevated risks of disease progression and cancer-specific death. On the other hand, Lima et al [23] did not find any association between the

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DOI:10.26502/fjhs.197

GSTM1 and *GSTT1* null genotypes, and the *GSTP1* variant genotype and the risk of diabetic nephropathy. Therefore, the data found in the literature on polymorphisms and associated diseases are conflicting. They have been recognized in the literature an ethnic difference in the frequency distribution of studied polymorphisms and the relevance of environmental factors on the expression of these genotypes [24,27,28]. Bolt & Thier [24] correlated the limited effects of the deletions of *GSTM1* and *GSTT1* in the evolution of diseases with a low penetrance of the genes.

There was also no association between polymorphisms of GST and APACHE II and SOFA scores prognostic. However, other factors are associated with an increased incidence of sepsis, namely: age, sex, race, and comorbidities [29]. Milić et al [7] evaluated the usefulness of APACHE II and SOFA score as the predictors of length of stay (LOS) in various surgical ICUs. Their results suggested that APACHE II and SOFA scoring for predicting LOS varied between different types of surgical ICUs and between times when the scores were calculated. Therefore, they suggested that specialized surgical ICUs should develop and use scores that include specific therapeutic interventions. Procalcitonin (PCT) has been reported in the literature as an important indicator of sepsis [30]. Brunkhorst et al used the PCT, C reactive protein and APACHE II as parameters to evaluate the prognosis of patients with severe pneumonia. In the multivariate analysis of the study, APACHE II was presented as the only statistically significant risk factor for a change in diagnosis. The determination of the PCT showed a slight but limited prognostic value. Within the course of the disease, no survivors had higher levels of PCT. However, there was a large interindividual variation, so need further investigation [31]. Okazaki et al developed a new prognostic score for patients with Acute Heart Failure (AHF) based on APACHE- II. The results showed a more accurate score to predict a worse prognosis in patients with AHF, compared to APACHE II. Probably scores including other parameters may contribute to increased specificity in the diagnosis of patients during sepsis [32].

Although our results suggest no association between polymorphisms of GST and risk of sepsis and a poorer prognosis (based on the interpretation of APACHE II and SOFA) in patients in this condition, we must consider that not always those scores certainly reflect the clinical condition of patients in ICUs. On the other hand, the GST enzymes are part of an integrated protection system. However, it is important to note that the efficiency of this system depends on the combined action of other enzymes, such as γ- glutamylcysteine synthase and glutathione synthase, to provide glutathione as well as carriers to facilitate the elimination of glutathione (GSH) conjugates [33]. Lee et al, for example, found an association between oxidative stress and sepsis when they observed a decrease in Glutathione Peroxidase-3 protein (GPx-3) bioactivity in septic patients [34]. But our study was the first to associate GST polymorphisms and sepsis. Larger studies including other genes involved in antioxidant defense and oxidative stress markers are needed to provide further clarification of the effect of the damage caused by oxidative stress and the clinical condition of patients with sepsis.

Conclusion

The frequency of *GSTM1* and *GSTT1* null genotypes were respectively 26.72% and 13.79%, while 7.75% of patients had nullity for both genes. Already the genotypic distribution of *GSTP1* showed a higher percentage for the heterozygous variant genotype (Ile / Val), corroborating the data found in some Brazilian studies. Although major studies showing the effects of polymorphisms of the Mu, Pi, and Theta classes of GST in the pathogenesis of several human diseases, in this study there was no association between the analyzed polymorphisms and the risk of developing sepsis, or a worse prognosis thereof. However, it is necessary to consider that the GST is part of an integrated network of antioxidant enzymes and widely involved in cellular detoxification processes and the efficiency of this system depends on the combined action of these enzymes.

Acknowledgements

This research was supported by the Research Foundation of the State of Pernambuco – FACEPE (grant #APQ-0996-4.01/08).

Authors Contributions

Natália Brito da Cruz: Investigation, writing - original draft; **José Gildo de Moura Monteiro Júnior**: Investigation and formal analysis; **Dário Celestino Sobral Filho**: Supervision; **Dilênia de Oliveira Cipriano Torres**: Investigation and data Curation; **José Luiz de Lima Filho**: Funding acquisition; **Danyelly Bruneska Gondim Martins**: Resources, methodology and writing - review & editing; **Rosângela Ferreira Frade de Araújo**: Conceptualization, methodology, writing - review & editing, formal analysis and supervision

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