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RESEARCH ARTICLE

The association of glutathione transferase omega polymorphisms with laboratory inflammatory parameters in COVID-19

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Summary

In a view of important functions of glutathione transferase omega (GSTO) class in redox homeostasis and innate immunity, it was proposed that interindividual differences in COVID-19 clinical manifestations might be affected by *GSTO1* (rs4925) and *GSTO2* (rs156697) polymorphisms.

To assess the potential association of these polymorphisms with biochemical, coagulation and inflammatory laboratory parameters in the group of mild and severe COVID-19 patients.

GSTO1 and *GSTO2* single nucleotide polymorphisms were determined by qPCR in 251 samples of COVID-19 patients. Biochemical, coagulation and inflammatory laboratory parameters of COVID-19 participants were procured from routine laboratory practice on the day of admission.

Polymorphisms of *GSTO1* and *GSTO2* affect laboratory biochemical profile of COVID-19 patients. *GSTO1**C allele was associated with increased levels of C-reactive protein (CRP) (p=0.035), interleukin-6 (IL-6) (p=0.047), D-dimer (p=0.014) and lactate dehydrogenase LDH (p=0.002), whereas *GSTO2**G allele was associated with CRP (p=0.033). COVID-19 patients homozygous for variant *GSTO1**A allele and *GSTO2**G had the highest levels of serum Fe (p=0.019, p=0.052, respectively).

Our findings regarding the influence of *GSTO1* and *GSTO2* polymorphisms on inflammation and coagulation parameters might be of clinical importance. In future, these findings could aid in a more personalized approach for better recognition of patients prone to thrombosis and excessive immune response.

Keywords: COVID-19, polymorphisms, inflammation, coagulation, *GSTO1*, *GSTO2*

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INTRODUCTION

Considering diverse variations in severity, duration and outcomes of coronavirus disease 2019 (COVID-19), defining a genetic predisposition, along with clinical and environmental factors, might be an important step in improving the diagnosis and treatment of high-risk individuals. Due to the established role of oxidative distress in the pathophysiology of COVID-19, it has been proposed that inter-individual differences in patients' clinical manifestations might also be affected by variations in genes encoding detoxifying and antioxidant enzymes, glutathione transferases (GSTs) (1). GSTs are a superfamily of enzymes that catalyze the conjugation of glutathione (GSH) to a wide range of chemical carcinogens, drugs and oxidative stress products. Seven cytosolic GST classes have been identified in humans: alpha, mu, pi, sigma, theta, zeta, and omega class (2).

The omega class GST (GSTO) shares only 20% amino acid sequence identity with the other GST classes (3), with a range of catalytic activities that are unrelated to the functions of other GST classes (4). GSTO display a prominent function in redox regulation, glutathionylation/deglutathionylation cycle and innate immune response (3). Glutathionylation/deglutathionylation is thought to be an important regulation mechanism of protein function implicated in the modulation and control of various signaling pathways (5). Monocytes and macrophages are important elements of the innate immune system and the effect of glutathionylation on macrophage function and inflammation has been currently investigated (6–8). GSTO1-1 with its deglutathionylation activity catalyzes the deglutathionylation of cellular proteins and could have and important role in modulating the glutathionylation of intracellular proteins that participate in specific signaling pathways (4). Recent studies have emphasized the role of GSTO1-1 in the pro-inflammatory response of macrophages to bacterial lipopolysaccharide (LPS) that is mediated through Toll like receptor (TLR4) (9). The application of a small molecule inhibitor of GSTO1-1 weakens the inflammatory response to LPS suggesting that the active GSTO1-1 has a pro-inflammatory role. This further implies that the glutathionylation of a key protein has an important role in the TLR4 pro-inflammatory pathway (10). All these findings brought researchers to the conclusion that GSTO1-1 can exert a pro-inflammatory action in innate immunity.

GSTO2-2 has very high dehydroascorbate reductase (DHAR) activity compared to GSTO1-1 (4) with an important role in regeneration of dehydroascorbate (11). DHAR activity makes GSTO2-2 an important participant in the regulation of redox homeostasis and immune system functioning. So far, several studies have reported that a high-dose intravenous vitamin C has positive effects in the treatment of moderate to severe COVID-19 patients due to its potential inhibitory effect on SARS-CoV-2 multiplication (12). Genome-wide association studies (GWAS) recognized the significance of *GSTO2* in pulmonary function, but its precise role and function in the lungs remain unclear (13). Mukherjee B. et al. described 31 polymorphisms in *GSTO1* and 66 polymorphisms of *GSTO2* gene (14). Regarding the functional implication of those genetic variations in *GSTO1* and *GSTO2* genes, the most often investigated are single nucleotide polymorphisms (SNPs) of *GSTO1*, rs 4925 and *GSTO2*, rs 156697 (14). A SNP (NCBI SNP ID: rs4925, 419 C to A) of *GSTO1* was reported at nucleotide 419 causing alanine to aspartate substitution in amino acid 140 (A140D, Ala140Asp) of exon 4. SNP of *GSTO2* was found at nucleotide 424 causing an asparagine to aspartate substitution in amino acid 142 (N142D, Asn142Asp) of exon 4 (NCBI SNP ID: rs156697, 424 A to G) (15). It has been shown that GSTO1 rs4925 polymorphism causes a change primarily in deglutathionylase activity (2,4). Regarding *GSTO2* rs156697 polymorphism, a strong association between variant *GSTO2**G allele and lower *GSTO2* gene expression has been shown (14,16). In our recent study comprising COVID-19 patients and healthy controls, the individuals carrying variant *GSTO1**AA and variant *GSTO2**GG genotypes exhibited higher odds of COVID-19 development, contrary to the ones carrying referent alleles ($p = 0.044$, $p = 0.002$, respectively). These findings have been confirmed by haplotype analysis. Carriers of H2 haplotype (*GSTO1**A and *GSTO2**G variant alleles) were at 2-fold increased risk of COVID-19 development ($p = 0.002$) (17).

Since genetic polymorphisms in glutathione transferase omega genes modify COVID-19 risk, inter-individual differences in COVID-19 clinical presentation might also be affected by *GSTO* genetic profile. In this line, the aim of this study was to assess the potential association of genetic polymorphisms in genes encoding *GSTO1* (rs4925) and *GSTO2* (rs156697), with biochemical, coagulation and inflammatory laboratory parameters in the group of mild and severe COVID-19 patients.

MATERIAL AND METHODS

This case-only study recruited 251 patients from the Institute of Infectious and Tropical Diseases, University Clinical Centre of Serbia, between July 2020 and February 2021, diagnosed with COVID-19 by means of positive RT-PCR test, as previously described by Miljanovic et al. in 2021 (18). All patients were stratified according to the COVID-19 National Guidelines, version 9, into those with mild COVID-19 (Stage I) and severe COVID-19 (Stages II, III and IV). The principles of International Conference on Harmonization (ICH) Good Clinical Practice, the "Declaration of Helsinki," and national and international ethical guidelines were respected throughout this study with the authorization received from the Ethics Commit-

tee of the Clinical Centre of Serbia (566/01 from July 13, 2020 and 608/01 from August 7, 2020). Written informed consent was obtained from all study participants. Clinical, demographic and epidemiological data were collected using RedCap® based questionnaire (https://redcap.med.bg.ac.rs/, AntioxIdentification).

All patients had their laboratory analyses and non-contrast chest CT estimated on the day of admission, on the seventh and on the fourteenth day, consecutively.

All laboratory parameters of COVID-19 participants were procured from routine laboratory practice on the day of admission.

Patients' DNA was extracted from EDTA-anticoagulated peripheral blood obtained from the study participants using PureLink™ Genomic DNA Mini Kit (ThermoFisher Scientific, United States). *GSTO1* (rs4925, ID number: C_11309430_30) and *GSTO2* (rs156697, ID number: C_3223136_1_), polymorphisms were determined by TaqMan Drug Metabolism Genotyping assays (Life Technologies, Applied Biosystems, United States) on the Mastercycler ep realplex platform (Eppendorf, Germany).

Statistical data analysis was performed using IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, United States). The obtained results were presented as frequency, percent and mean ± standard deviation (SD). Based on the normality tests, the differences in continuous data were assessed using an appropriate statistical test. Differences between categorical variables were tested for using a $\chi 2$-test. The risk for COVID-19 development and progression was calculated with adjusted odds ratios (OR) and 95% confidence intervals (CI) using logistic regression analysis. All p-values below 0.05 were considered significant.

RESULTS

Baseline characteristics of 82 mild COVID-19 and 169 severe COVID-19 patients are shown in **Table 1**. As presented, these two groups did not differ significantly in terms of gender, diabetes and obesity (p>0.05), although the patients with severe COVID-19 had higher BMI than those with mild form of the disease (p=0.037). The presence of hypertension was associated with higher odds of severe COVID-19 form (OR=3.15, 95%CI: 1.60-6.21, p=0.001). On the other hand, smoking was associated with decreased odds of severe COVID-19 (OR=0.21, 95%CI: 0.09-0.44, p< 0.001).

The distribution of *GSTO1 (rs4925), GSTO2 (rs156697)* genotypes among mild and severe COVID-19 patients is presented in Table 2. There was a significantly higher number of carriers of at least one variant *GSTO1* allele in the group of mild COVID-19 patients in comparison with the severe COVID-19 group of individuals (57.5% vs. 42.9% respectively, p=0.031).

As for *GSTO2* there was no statistical significance between mild and severe COVID-19 groups in terms of genotypes (p=0.050).

Biochemical parameters, obtained from inspected COVID-19 patients upon their admission to hospital,

Table 1. Baseline characteristics of mild and severe COVID-19 patients

	Mild COVID-19 (n=82)	Severe COVID-19 (n=169)	OR[b] (95%CI)[c]	*p*
Age (years)[a]	45.08 ± 11.10	55.08 ± 11.88	/	< 0.001
Gender, n (%)				
Male	42 (51.2)	94 (55.6)	1.00[d]	
Female	40 (48.8)	75 (44.4)	0.84 (0.49-1.42)	0.512
Hypertension, n (%)[c]				
No	42 (72.4)	55 (45.5)	1.00[b]	
Yes	16 (27.6)	66 (54.5)	3.15 (1.60-6.21)	0.001
Obesity, n (%)[c]				
BMI < 30	50 (64.1)	108 (64.7)	1.00[b]	
BMI > 30	28 (35.9)	59 (35.3)	0.98 (0.56-1.71)	0.931
BMI (kg/m^2)[a]	27.80 ± 5.69	29.31 ± 5.01	/	0.037
Smoking, n (%)[c]				
Never	37 (46.8)	94 (57.7)	1.00[b]	
Former	17 (21.5)	56 (34.4)	1.30 (0.67-2.52)	0.442
Ever	25 (31.6)	13 (8.0)	0.21 (0.09-0.44)	< 0.001
Diabetes[c]				
No	74 (90.2)	150 (88.8)	1.00[b]	
Yes	8 (9.8)	19 (11.2)	1.17 (0.49-2.80)	0.722

n, number of patients in each group, [a]mean ± standard deviation, [b]OR, odds ratio, [c]CI, confidence interval, [d]reference group

Table 2. The distribution of *GSTO1* and *GSTO2* genotypes among mild and severe COVID-19 patients

Genotype	Mild COVID-19 n, %	Severe COVID-19 n, %	*P*
GSTO1 (rs4925)			
CC	34 (42.5)	96 (57.1)	
CA	30 (37.5)	46 (27.4)	
AA	16 (20.0)	26 (15.5)	0.096
CA+AA	46 (57.5)	72 (42.9)	**0.031**
GSTO2 (rs156697)			
AA	30 (36.6)	84 (49.7)	
AG	32 (39.0)	54 (32.0)	
GG	20 (24.4)	31 (18.3)	0.143
AG+GG	52 (63.4)	85 (50.3)	0.050

n, number of patients in each group

with regard to assessed *GSTO1* and *GSTO2* genotypes, are presented in **Table 3**. The COVID-19 patients who were carriers of variant *GSTO1**AA genotype, had decreased levels of lactate dehydrogenase (LDH) (p=0.002) and increased levels of iron (Fe) (p=0.019). The presence of *GSTO2**GG genotype was found to be significantly associated with increased activity of alanine aminotransferase (ALT) (p=0.027). The carriers of variant *GSTO2**GG genotype had increased levels of iron in comparison with the carriers of reference *GSTO2**AA genotype with a clear tendency to significance (p=0.052).

The association of *GSTO1* and *GSTO2* polymorphisms with inflammatory laboratory parameters, are presented in **Figures 1 and 2**. The patients who were carriers of variant *GSTO1**AA genotype had significantly decreased levels of CRP and IL-6 in comparison with the carriers of referent *GSTO1**CC genotype (p=0.035, p=0.047 respectively). As for the *GSTO2* polymorphism, the patients who were carriers of variant *GSTO2**GG genotype had lower CRP values in comparison with the patients with referent *GSTO2* genotype (p=0.033). The association of *GSTO1* and *GSTO2* polymorphisms with D-dimer, as a coagulation laboratory parameter, are presented in **Figures 3 and 4**. COVID-19 patients carriers of variant *GSTO1**AA genotype had significantly lower levels of D-dimer in comparison with carriers of of referent *GSTO1**CC genotype (p=0.033). As for *GSTO2* polymorphisms, no association was found with D-dimer levels.

DISSCUSSION

In a view of important functions of novel glutathione transferase omega class in redox homeostasis and innate immunity, a potential modifying effect of *GSTO1* and *GSTO2* polymorphisms on individual susceptibility towards COVID-19 clinical presentation was suggested. In this study, the inflammatory, coagulation and biochemical laboratory parameters were analyzed in COVID-19 patients stratified according to polymorphic variants in *GSTO* genes. The data obtained showed that *GSTO* polymorphisms were associated with inflammatory parame-

Table 3. The association of GSTO1 and GSTO2 gene polymorphisms with biochemical parameters

Genotype	ALT (U/L)[a]	AST (U/L)[a]	LDH (U/L)[a]	Fe (μmol/L)[a]	TIBC (μmol/L)[a]	Creatinine (μmol/L)[a]
***GSTO1* (rs4925)**						
CC	54.5±39.4	41.1±25.0	315.7±219.8	6.3±4.1	44.3±10.9	95.7±54.0
CA	46.6±25.4	36.5±23.9	267.3±135.2	6.7±5.5	51.6±53.7	83.2±22.6
AA	53.1±21.4	34.1±14.9	222.8±92.9	8.6±5.3	45.2±7.7	81.2±22.7
P	0.158	0.364	0.002	0.019	0.792	0.152
***GSTO2* (rs156697)**						
AA	52.2±39.5	36.9±21.5	295.1±201.7	6.6±4.5	50.3±38.1	91.0±31.1
AG	46.8±21.9	38.8±23.9	296.1±192.5	5.9±4.1	43.1±10.0	94.5±65.7
GG	59.2±30.2	42.6±23.4	245.8±108.8	8.7±5.9	41.0±7.9	80.3±22.4
P	0.027	0.344	0.175	0.052	0.173	0.241

[a]Mean ±SD; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; TIBC, total iron-binding capacity

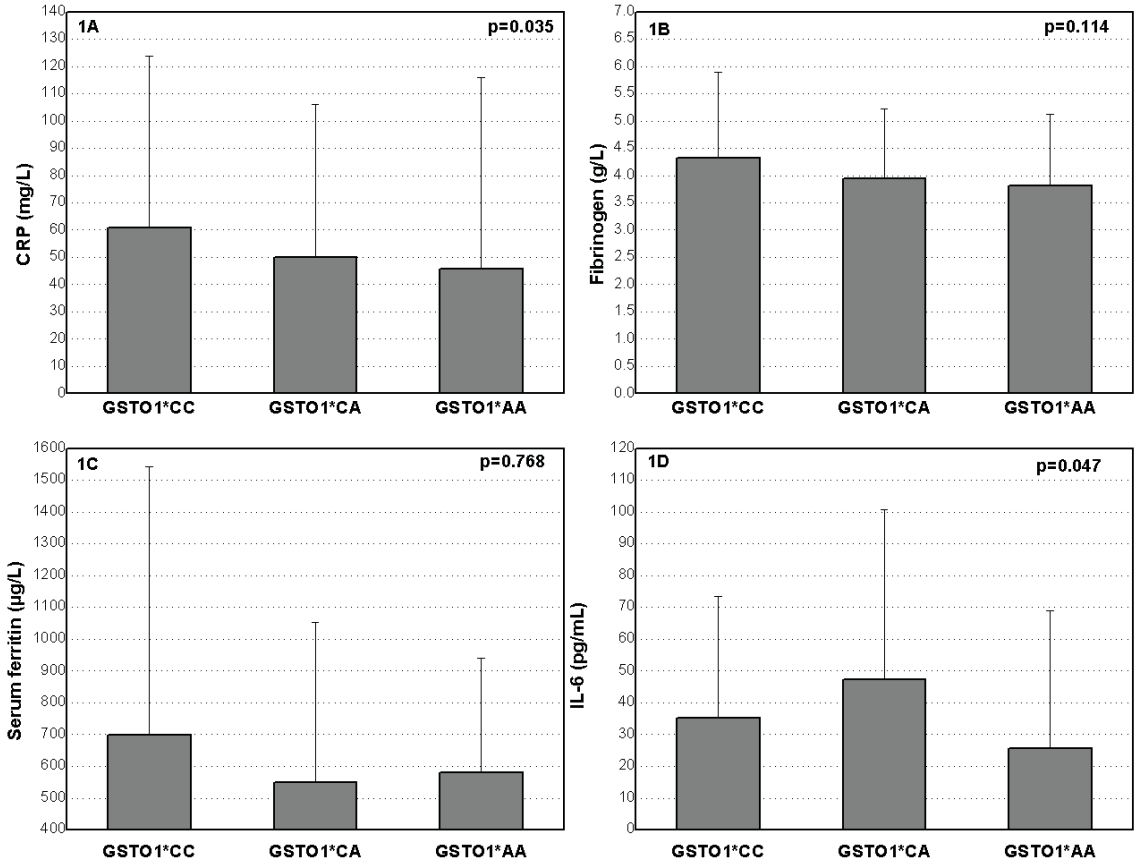

Figure 1. The association of GSTO1 polymorphism with CRP (A), fibrinogen (B), ferritin (C) and IL-6 (D).

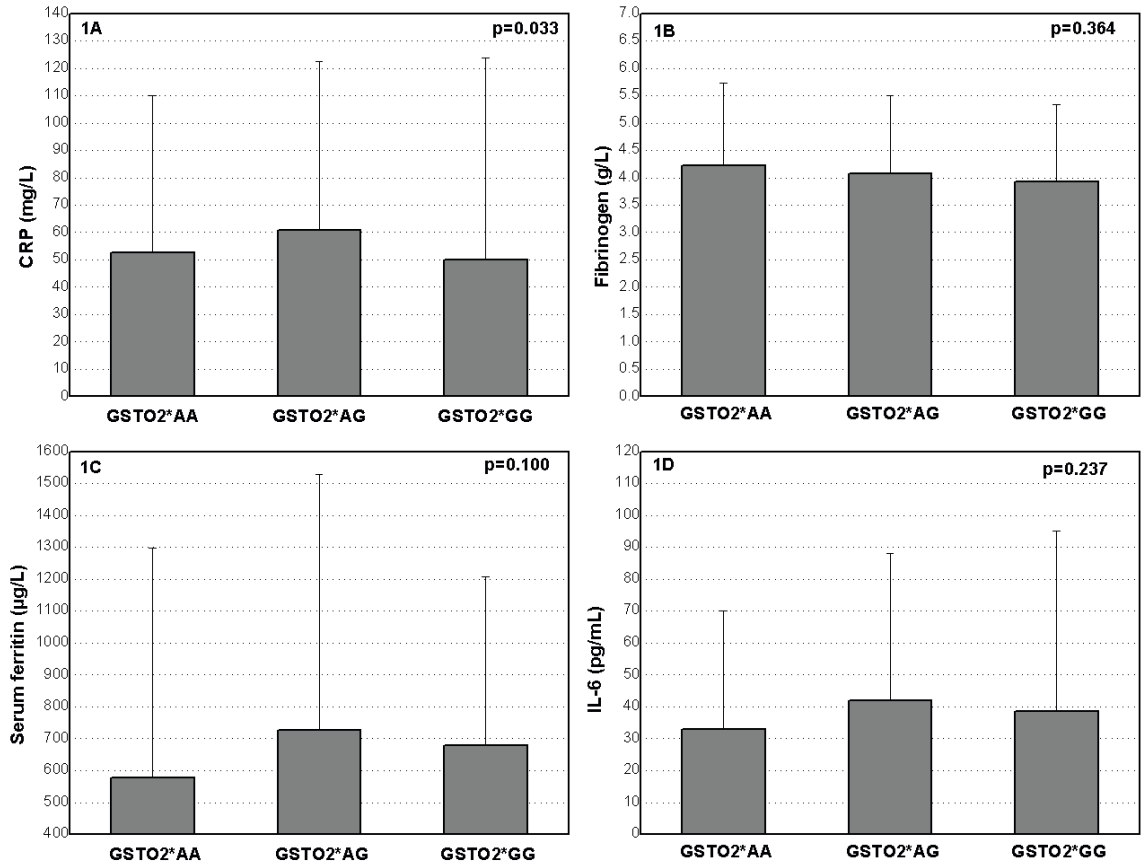

Figure 2. The association of GSTO2 polymorphism with CRP (A), fibrinogen (B), ferritin (C) and IL-6 (D).

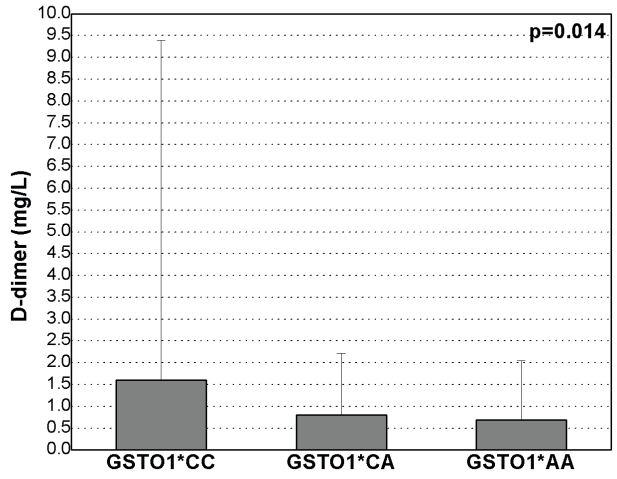

Figure 3. The association of GSTO1 polymorphism with D-dimer.

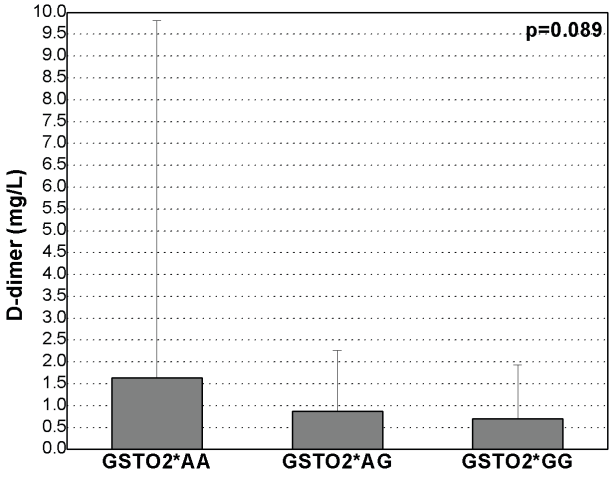

Figure 4. The association of GSTO1 polymorphism with D-dimer.

ters in COVID-19 patients. Indeed, COVID-19 carriers of *GSTO1* referent genotype had significantly higher levels of CRP and IL-6 in comparison to the carriers of at least one variant *GSTO1**A allele. In addition, significant correlations between *GSTO1* polymorphism and serum Fe, D-dimer and LDH were found, whereas *GSTO2* polymorphism was associated with serum Fe level and ALT activity.

It has been well established that patients exhibiting severe form of COVID-19 have significantly lower count of lymphocytes, monocytes and platelets in comparison to the patients with mild COVID-19 (19). Furthermore, significantly increased CRP at admission is frequently associated with severe COVID-19, whereas the predictive value of IL-6 and TNF-α in disease severity and death was assessed in numerous studies (20). In fact, determining the IL-6 level, together with TNF-α, could be considered as a clinical device for identifying patients at increased risk, and those who should be treated with the IL-6R antagonist tocilizumab (21). Furthermore, an increased activity of liver enzymes, alanine ALT and AST, as well as renal parameters, such as blood urea nitrogen and creatinine, along with high D-dimer is characteristic of patients who develop the severe form of the disease represented by multi-organ failure. Additionally, regarding coagulation parameters, patients with severe COVID-19 had statistically significantly higher levels of D-dimer than those with mild to moderate COVID-19. This finding seems important, since increased plasma D-dimer levels, a sensitive fibrin degradation marker indicative of increased coagulation and oxidative distress, also correlate with mortality (22).

Great inter-individual variability among SARS-CoV-2 infected individuals in terms of disease progression and outcome clearly implies a possible effect of host genetic factors (23). Our data suggests that genetic variants in *GSTO1* gene may not only have a modulating effect in the propensity to SARS-CoV-2 infection, but also in determining the intensity of innate immune response. Intriguingly, the novel function of GSTO1-1 in promoting the activation of one of the main innate immune components, NLRP3 inflammasome, has been recently established (24). Namely, it was found that deglutathionylating NIMA related kinase 7 (NEK7) by GSTO1 corresponded to the activation of NLRP3 inflammasome (24,25). This inflammasome is involved in the conversion of pro-IL-1β and pro-IL-18 into mature IL-1β and IL-18 with the consequent release of additional cytokines, such as IL-6 (26). This further implies the importance of the NLRP3 inflammasome in the development of COVID-19 and formation of cytokine storm. In this line, the data on overactivation of NLRP3 inflammasome, as well as its association with acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) in COVID-19 are not unexpected (25–27). In the view of the fact that *GSTO1* polymorphism was proposed to exhibit differential efficiency in activating NLRP3 inflammasome, this potentially contributes to either promoting or attenuating the inflammatory response, as well as to the level of local or systemic tissue injury (24). We found that COVID-19 carriers of referent *GSTO1*CC* genotype had significantly higher levels of LDH, CRP and IL-6 in comparison to the carriers of at least one variant GSTO1*A allele. Since ferritin, CRP and LDH have been shown to be the predictive laboratory biomarkers of COVID-19 severity, it might be speculated that determination of GSTO1 polymorphisms could aid in the identification of high-risk individuals. Moreover, our results are in concordance with findings on the positive correlation between IL-18, CRP, LDH and IL-6, and the inflammasome activation in COVID-19. To date, several FDA-approved therapies that interfere with inflammasome activation signaling have been considered for the treatment of COVID-19, including anakinra, tocilizumab and IFN-β (28).

Interestingly, in our study, COVID-19 patients who were homozygous for variant *GSTO1**A allele and *GSTO2**G had the highest levels of serum Fe. Indeed, our results are in agreement with a recent meta-analysis

on serum levels of Fe metabolism parameters. Namely, in severe COVID-19 patients lower serum Fe levels are related to higher concentrations of hepcidin and ferritin without significant differences in transferrin saturation (29). It is also important to note that increased plasma ferritin stimulates the production of reactive oxygen species further contributing to both dysregulated redox homeostasis and ferroptosis-mediated tissue damage (30,31). In this setting, a possible consequence of *GSTO2* polymorphism is the alteration in its antioxidant activity that may also affect the activity of transcription factor, hypoxia inducible factor alpha, (HIF-1α) important in inducing pro-inflammatory response to COVID-19 (32). In this context, it can be speculated that vitamin C-dependent inhibition of the HIF-1α pathway may provide an additional approach to controlling inflammation (32). Assuming the specific roles of GSTO enzymes in these processes, our results support the hypothesis that GSTO polymorphisms are associated with the propensity for developing severe COVID-19, with special emphasis on the *GSTO1* polymorphism.

Our results on the association between *GSTO1* and *GSTO2* polymorphisms with laboratory parameters of inflammation and coagulation patients may provide some new information in understanding the complex molecular mechanisms in COVID-19, as well as contribute to an early identification of patients who are more prone to a worse course of the disease. Further studies are needed to identify the precise function of *GSTO1* gene variants that may be associated with abnormal immune response in COVID-19 and the potential treatment of GSTO1 inhibitors with anti-inflammatory properties in the patients with the risk of systematic inflammatory response.

Author Contributions

Conceptualization, A.S.-R. and T.S.; methodology, T.D., V.C. and D.J.; software, Z.B.; validation, T.D., V.C. and D.J.; formal analysis, Z.B.; investigation, T.D., V.C. and D.J.; resources, G.S., J.R., I.M., M.A. and M.E.; writing—original draft preparation, A.S.-R., T.S., and T.D.; writing—review and editing, T.S., A.S.-R., M.P.-E., M.M., T.D., V.C., D.J., G.S., J.R., I.M., M.A., M.E. and Z.B.; visualization, T.D., V.C. and D.J.; supervision, A.S.-R. and T.S.; project administration, T.S.; All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

References

1. Coric V, Milosevic I, Djukic T, Bukumiric Z, Savic-Radojevic A, Matic M, et al. GSTP1 and GSTM3 Variant Alleles Affect Susceptibility and Severity of COVID-19. Front Mol Biosci. 2021;8:1169.
2. Whitbread AK, Masoumi A, Tetlow N, Schmuck E, Coggan M, Board PG. Characterization of the omega class of glutathione transferases. Methods Enzymol. 2005;401:78–99.
3. Board PG, Coggan M, Chelvanayagam G, Easteal S, Jermiin LS, Schulte GK, et al. Identification, characterization, and crystal structure of the Omega class glutathione transferases. J Biol Chem. 2000 Aug 11;275(32):24798–806.
4. Menon D, Board PG. A role for glutathione transferase Omega 1 (GSTO1-1) in the glutathionylation cycle. J Biol Chem. 2013 Sep 6;288(36):25769–79.
5. Mieyal JJ, Gallogly MM, Qanungo S, Sabens EA, Shelton MD. Molecular Mechanisms and Clinical Implications of Reversible Protein *S* -Glutathionylation. Antioxid Redox Signal. 2008 Nov;10(11):1941–88.
6. Ullevig S, Kim HS, Asmis R. S-glutathionylation in monocyte and macrophage (dys)function. Int J Mol Sci. 2013 Jul 24;14(8):15212–32.
7. Ullevig SL, Kim HS, Short JD, Tavakoli S, Weintraub ST, Downs K, et al. Protein *S* -Glutathionylation Mediates Macrophage Responses to Metabolic Cues from the Extracellular Environment. Antioxid Redox Signal. 2016 Nov 20;25(15):836–51.
8. Hughes MM, McGettrick AF, O'Neill LAJ. Glutathione and Glutathione Transferase Omega 1 as Key Posttranslational Regulators in Macrophages. Gordon S, editor. Microbiol Spectr. 2017 Feb 24;5(1):5.1.05.
9. Menon D, Coll R, O'Neill LAJ, Board PG. GSTO1-1 modulates metabolism in macrophages activated through the LPS and TLR4 pathway. J Cell Sci. 2015 May 15;128(10):1982–90.
10. Menon D, Innes A, Oakley AJ, Dahlstrom JE, Jensen LM, Brüstle A, et al. GSTO1-1 plays a pro-inflammatory role in models of inflammation, colitis and obesity. Sci Rep. 2017 Dec;7(1):17832.
11. Zhou H, Brock J, Liu D, Board PG, Oakley AJ. Structural Insights into the Dehydroascorbate Reductase Activity of Human Omega-Class Glutathione Transferases. J Mol Biol. 2012 Jul;420(3):190–203.
12. Majidi N, Rabbani F, Gholami S, Gholamalizadeh M, BourBour F, Rastgoo S, et al. The Effect of Vitamin C on Pathological Parameters and Survival Duration of Critically Ill Coronavirus Disease 2019 Patients: A Randomized Clinical Trial. Front Immunol. 2021 Dec 15;12:717816.
13. Wilk JB, Walter RE, Laramie JM, Gottlieb DJ, O'Connor GT. Framingham Heart Study genome-wide association: results for pulmonary function measures. BMC Med Genet. 2007;8(Suppl 1):S8.
14. Mukherjee B, Salavaggione OE, Pelleymounter LL, Moon I, Eckloff BW, Schaid DJ, et al. Glutathione S-transferase omega 1 and omega 2 pharmacogenomics. Drug Metab Dispos Biol Fate Chem. 2006 Jul;34(7):1237–46.
15. Pongstaporn W, Rochanawutanon M, Wilailak S, Linasamita V, Weerakiat S, Petmitr S. Genetic alterations in chromosome 10q24.3 and glutathione S-transferase omega 2 gene polymorphism in ovarian cancer. J Exp Clin Cancer Res CR. 2006 Mar;25(1):107–14.
16. Allen M, Zou F, Chai HS, Younkin CS, Miles R, Nair AA, et al. Glutathione S-transferase omega genes in Alzheimer and Parkinson disease risk, age-at-diagnosis and brain gene expression: an association study with mechanistic implications. Mol Neurodegener. 2012 Dec;7(1):13.

17. Djukic T, Stevanovic G, Coric V, Bukumiric Z, Pljesa-Ercegovac M, Matic M, et al. GSTO1, GSTO2 and ACE2 Polymorphisms Modify Susceptibility to Developing COVID-19. J Pers Med. 2022 Mar 14;12(3):458.
18. Miljanovic D, Milicevic O, Loncar A, Abazovic D, Despot D, Banko A. The First Molecular Characterization of Serbian SARS-CoV-2 Isolates From a Unique Early Second Wave in Europe. Front Microbiol. 2021 Jun 18;12:691154.
19. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med CCLM. 2020 Jun 25;58(7):1021–8.
20. Bivona G, Agnello L, Ciaccio M. Biomarkers for Prognosis and Treatment Response in COVID-19 Patients. Ann Lab Med. 2021 Nov 1;41(6):540–8.
21. Abidi E, El Nekidy WS, Alefishat E, Rahman N, Petroianu GA, El-Lababidi R, et al. Tocilizumab and COVID-19: Timing of Administration and Efficacy. Front Pharmacol. 2022 Feb 18;13:825749.
22. Yu HH, Qin C, Chen M, Wang W, Tian DS. D-dimer level is associated with the severity of COVID-19. Thromb Res. 2020 Nov;195:219–25.
23. Zhang Q, Bastard P, COVID Human Genetic Effort, Karbuz A, Gervais A, Tayoun AA, et al. Human genetic and immunological determinants of critical COVID-19 pneumonia. Nature. 2022 Mar 24;603(7902):587–98.
24. Hughes MM, Hooftman A, Angiari S, Tummala P, Zaslona Z, Runtsch MC, et al. Glutathione Transferase Omega-1 Regulates NLRP3 Inflammasome Activation through NEK7 Deglutathionylation. Cell Rep. 2019 Oct;29(1):151-161.e5.
25. McKee CM, Coll RC. NLRP3 inflammasome priming: A riddle wrapped in a mystery inside an enigma. J Leukoc Biol. 2020 Sep;108(3):937–52.
26. Zhao N, Di B, Xu L li. The NLRP3 inflammasome and COVID-19: Activation, pathogenesis and therapeutic strategies. Cytokine Growth Factor Rev. 2021 Oct;61:2–15.
27. Rodrigues TS, de Sá KSG, Ishimoto AY, Becerra A, Oliveira S, Almeida L, et al. Inflammasomes are activated in response to SARS-CoV-2 infection and are associated with COVID-19 severity in patients. J Exp Med. 2021 Mar 1;218(3):e20201707.
28. Amin S, Aktar S, Rahman MdM, Chowdhury MMH. NLRP3 inflammasome activation in COVID-19: an interlink between risk factors and disease severity. Microbes Infect. 2022 Feb;24(1):104913.
29. Peng D, Gao Y, Zhang L, Liu Z, Wang H, Liu Y. The Relationship Between Hepcidin-Mediated Iron Dysmetabolism and COVID-19 Severity: A Meta-Analysis. Front Public Health. 2022;10:881412.
30. Cavezzi A, Troiani E, Corrao S. COVID-19: Hemoglobin, Iron, and Hypoxia beyond Inflammation. A Narrative Review. Clin Pract. 2020 May 28;10(2):1271.
31. Hirschhorn T, Stockwell BR. The development of the concept of ferroptosis. Free Radic Biol Med. 2019 Mar;133:130–43.
32. Li Y, Schellhorn HE. New developments and novel therapeutic perspectives for vitamin C. J Nutr. 2007 Oct;137(10):2171–84.

POVEZANOST POLIMORFIZMA GLUTATION TRANSFERAZA OMEGA SA LABORATORIJSKIM POKAZATELJIMA ZAPALJENJA U KOVIDU-19

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Sažetak

S obzirom na važnu ulogu koju glutation transferaze klas omega (*GSTO*) imaju u održavanju redoks ravnoteže i u urođenoj imunosti, može se prepostaviti da polimorfizmi gena *GSTO1* (rs4925) i *GSTO2* (rs156697) imaju potencijalni efekat na razlike koje postoje u kliničkim manifestacijama COVID-19.

Da se ispita potencijalna veza između ovih polimorfizama i biohemijskih, koagulacionih i inflamatornih laboratorijskih parametara u grupi pacijenata koji su imali blaži i teži oblik COVID-19.

Polimorfizmi izmene jednog nukleotida *GSTO1* i *GSTO2* su određivani qPCR metodom kod 251 pacijenta obolelog od COVID-19. Biohemijski, koagulacioni i inflamatorni laboratorijski parametri su određivani kod svih pacijenata tokom rutinske analize na prijemu u bolnicu.

Polimorfizmi *GSTO1* i *GSTO2* koreliraju sa biohemijskim laboratorijskim profilom COVID-19 pacijenata. Dobijene su statistički značajno više vrednosti C-reaktivnog proteina (CRP) (p=0,035), interleukina 6 (IL-6) (p=0,047) laktat dehidrogenaze (LDH) (p=0,002) i D-dimera (p=0,014) kod nosilaca referentnog *GSTO1**C alela u poređenju sa vrednostima ovoh parametara kod pacijenata nosilaca varijantnog *GSTO1**A alela. COVID-19 pacijenti nosioci *GSTO-2**G alela imali su značajno niže vrednosti CRP (p=0,033). Pacijenti koji su bili homozigotni nosioci varijantnog *GSTO1**A alela ili varijantnog *GSTO2**G alela su imali značajno više vrednosti serumskog Fe (p=0,019, p=0,052, redom).

Povezanost *GSTO1* i *GSTO2* polimorfizama sa laboratorijskim parametrima inflamacije i koagulacije imaju potencijalni klinički značaj u identifikaciji onih pacijenata koji su skloniji neadekvatnom imunskom odgovoru na prisustvo virusa ili pojavi tromboze.

Ključne reči: COVID-19, polimorfizmi, inflamacija, koagulacija, *GSTO1*, *GSTO2*

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