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Research Article

COMPARATIVE ANALYSIS OF THE FREQUENCY OF RS1801133 POLYMORPHISM OF THE MTHFR GENE IN THE GROUP OF PATIENTS WITH POSTCOVID COMPLICATIONS OF MAXILLOFACIAL AREA

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ABSTRACT

In the article of genetic studies of patients with post-covid maxillofacial complications. The condition after COVID-19 is considered a life-threatening disease, ranging from mild symptoms to serious complications. Candidiasis is the most common type of superficial purulent infection. The Candida species is a frequent inhabitant of the oral mucosa, but its growth is inhibited by other organisms in the body, which prevents any pathological change in the mucous membrane of this fungus. Candida albicans is the most common yeast, followed by Candida glabrata, Candida krusei, Candida tropicalis and Candida stellatoidea. According to this systematic review, 57 cases of oral candidiasis and one case of retinitis candidiasis were reported in patients undergoing treatment for COVID-19. Single-cell RNA-seq analysis of angiotensin-converting enzyme II (ACE2) expression and serologic examination of samples indicates that ACE2 may be the cellular receptor for SARS-CoV-2, suggesting that ACE2-expressing cells are likely to be the main target cell type that vulnerable to SARS-CoV-2 infection. As a rule, there is a high expression of ACE2 r on the epithelial cells of the oral mucosa, enrichment is enriched in epithelial cells of the tongue. There were few reports prior to this study.

KEYWORDS

Post-covid maxillofacial complications, COVID-19, oral mucosa, Candida.

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INTRODUCTION

Mucormycosis is an angioinvasive infection characterized by tissue necrosis and blood vessel infarction [1]. Mucormycosis is caused by saprophytic fungi belonging to the order Mucorales [2,3]. Compared to global data, the incidence of mucormycosis in India has been estimated to be 70 times higher than the COVID-19 pandemic originated [4,5]. A multicountry study of mucormycosis associated with COVID-19 found that 53% of cases occur in India, followed by the United States of America (10%), Pakistan (6.3%), France (5%), Mexico (5%) , Iran (5%) and Russia (2.5%) [6]. During this pandemic, the number of cases of mucormycosis in India increased significantly (> 40,000 cases), prompting the Indian health authorities to declare mucormycosis a notifiable disease [7]. The situation is exacerbated by the limited availability of first-line antifungals such as liposomal amphotericin or amphotericin B deoxycholate. Whereas, the European Confederation for Medical Mycology (ECMM) and the International Society for Human and Animal Mycology (ISHAM) have proposed guidelines for the treatment of mucormycosis in low to moderate income level [7]; in addition, they also offered global guidelines for the management of mucormycosis [8]. Prior to the COVID-19 pandemic, diabetes mellitus was considered the most frequent risk factor for mucormycosis in India, followed by hematologic malignancies and solid organ transplant recipients [4,5]. Mucormycosis has also been reported in patients without any disease [4,5]. A multicenter study in India identified diabetes, inappropriate steroid therapy (6 mg dexamethasone daily for 7-10 days is recommended; higher dose and longer duration of treatment are considered impractical) and COVID-19 virus as risk factors for increased incidence of mucormycosis during the first wave COVID-19 in 2020 [9]. During this outbreak, the most common manifestation was rhino-orbital-cerebral mucormycosis (ROCM), followed by pulmonary mucormycosis [6,9].

An ecological study of the ecology of Mucorales in Indian soils has shown a high prevalence of clinically significant Mucorales [2]. Mucorales spores are also widespread in indoor and outdoor air in the same country [10]. Patients become infected by inhalation, ingestion, or traumatic contamination of environmental spores. The causes of this CAM outbreak can be multifactorial. In addition to environmental factors, uncontrolled diabetes mellitus, inappropriate steroid therapy, increased iron accumulation and damage caused by the COVID-19 virus may be the cause of this outbreak [9,11-13]. This review attempts to elucidate the interaction of risk factors or possible pathogenic mechanisms in the onset of CAM.

Humans contract mucormycosis by inhalation, ingestion, or traumatic inoculation of environmental mucorales sporangiospores [2,3]. Mucorales are ubiquitous; however, the number of spores is higher in tropical countries [2.14]. Spores of Mucorales have been isolated from indoor and outdoor air in Europe [10,14]. Rhizopus arrhizus, the main pathogenic species, is also the predominant species isolated from the environment [2,4,14,15]. The number of CAM cases is very high in Europe compared to the rest of the world during this COVID-19 pandemic [6,11], and this high number may be due to the high environmental burden of pathogenic Mucorales spores. The study reported the isolation of rare species such as Apophysomyces variabilis and Rhizopus homothallicus in the Indian environment [2]. Infections caused by these rare species are also widespread in India [4,5]. Rhizopus homothallicus was isolated from clinical

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specimens in many centers even during the current outbreak, in addition to the usual species, R. arrhizus (unpublished data). During this outbreak, systematic environmental research is needed; further comparison of ecological and clinical isolates may provide a plausible explanation for the emergence of SAMs. The high burden of CAM cases in India may also be related to the emergence of virulent strains of the order Mucorales. Genome analysis of Mucorales isolated prior to COVID-19 and the pandemic, as well as in vivo animal experiments, may reveal a possible role for Mucorales virulence factors in the onset of CAM.

Host factors are likely to play a more important role in increasing the burden of CAM cases. Patients with diabetes mellitus and hematologic malignancies, as well as transplant recipients, were at high risk of contracting mucormycosis in the pre-COVID-19 era [5,16,17]. By comparison, patients with diabetes mellitus and inadequately high doses of corticosteroids are at increased risk of contracting mucormycosis during the COVID-19 pandemic [6,9,11,14]. Hyperglycemia in COVID-19 patients can be caused by four reasons: (a) pre-existing diabetes mellitus, (b) damage to COVID-19 pancreatic beta cells, leading to decreased insulin production [13,15], (c) corticosteroid therapy [1.12] and (d) increased cortisol levels associated with stress [3,4]. Hyperglycemia and treatment with glucocorticoids impair phagocytic functions without stopping the germination and growth of spores and leading to the progression of the disease [5,16]. receptors have been found in patients with COVID-19 [14]. Thus, these factors

In addition, patients with diabetes mellitus and COVID-19 have elevated ferritin levels, such as preexisting endothelial damage and upregulation of endothelial receptors (hyperferritinemia), resulting in altered iron homeostasis [17]. In addition, endothelial glucocorticoid therapy, hyperglycemia-related complications such as damage and overexpression of endothelial receptors have been observed in COVID-19 hyperferritinemia and immune dysfunction of innate immune cells, likely to homeostasis [15]. In addition, endothelial damage and increased endothelial expression.

Thus, the factors mentioned above, such as preexisting endothelial damage, contribute to the pathogenesis of CAM and upregulation of endothelial receptors, glucocorticoid therapy, complications associated with hyperglycemia such as hyperferritinemia, and immune dysfunction of innate immunity.

COVID-19 turns a blind eye to the angiotensin-converting enzyme 2 (ACE2) receptor on endothelial cells, followed by internalization of viral particles leading to coagulation, endotheliitis and internalization of viral particles, resulting in coagulation, endotheliitis and endothelial cell death. In addition to the ACE2 receptor, glucose regulates protein cell death. In addition to the ACE2 receptor, glucose-regulated protein 78 (GRP78) 78 (GRP78) acts as a coreceptor for the recognition of the SARS-CoV-2 spike protein and acts as a coreceptor for the recognition of SARS-CoV-2. protein spike and increases the internalization of the virus. GRP78 is a 78 kDa heat shock protein, also known as heat shock protein A5 (HSPA5). GRP78, 78 kDa, also known as heat shock protein A5 (HSPA5). GRP78 is a molecular chaperone localized in the endoplasmic reticulum (ER), has a significant molecular chaperone localized in the endoplasmic reticulum (ER), and plays an important role in the regulation of the unfolded protein response (UPR), protein stability, the role of calcium homeostasis in the regulation of unfolded protein response (UPR), protein stability, calcium homeostasis and autophagy. Elevated serum GRP78 levels have

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been observed in autophagic patients. Elevated serum GRP78 levels have been observed in patients with COVID-19 infections compared to healthy controls. Hence, suppression of COVID-19 infections versus healthy controls. Therefore, inhibition of the GRP78 receptor GRP78 can reduce the internalization of SARS-CoV-2 by decreasing the receptor, it can reduce the internalization of SARS-CoV-2 by reducing the expression of ACE2 receptors, which will further lead to a decrease in viral binding and infection of the ACE2 receptors, which in further leads to a decrease in the binding of the virus and the severity of the infection [8]. severity. Like the ACE2 receptor, GRP78 also mediates the endothelial cell barrier. Like the ACE2 receptor, GRP78 also mediates endothelial cell barrier disruption and inflammation.

The aim of this work is to study the features of genetic studies in the diagnosis and prognosis of patients with postcoid complications of the maxillofacial region.

From 2020 to 2021, we carried out a comprehensive examination and treatment of 118 patients with COVID-19 and its purulent-necrotic complications in the maxillofacial area, who were being treated at the post-COVID center of the Multidisciplinary Clinic of the Tashkent Medical Academy.

All patients were divided into three groups (Figure 1).

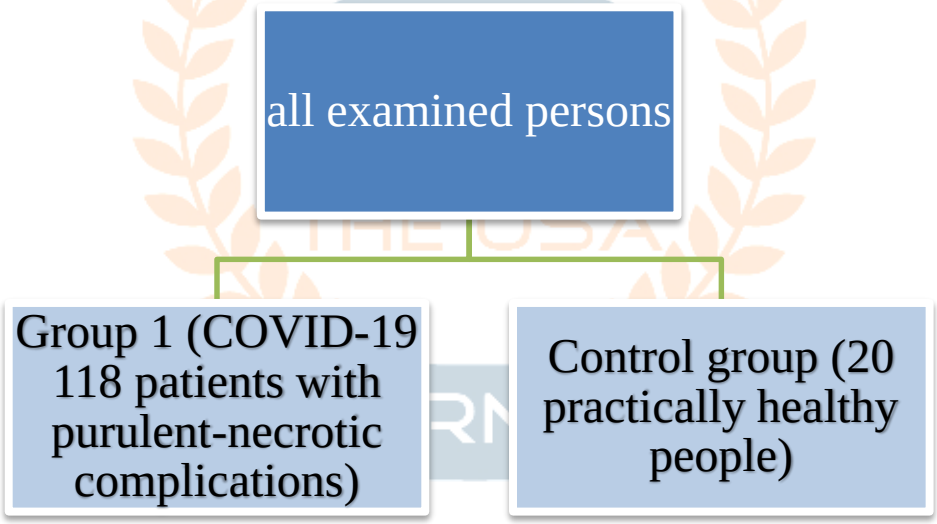

Figure 1. Distribution of groups.

Molecular genetic studies were performed in the Hematology Department of the TMA Multidisciplinary Clinic.

This part of the work consisted of several stages:

1. Blood sampling (Figure 2).
2. Isolation of DNA from peripheral blood lymphocytes.
3. Carrying out PCR.
4. Carrying out electrophoresis and visualization of results.

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Figure 2. Blood sampling

In the course of the work, 4 polymorphic variants of genes were investigated (table 1).

Table 1

List of studied gene polymorphisms

Gene (abbreviation)	Localization	Polymorphism	A source
MTHFR	1p36.22, 677 C>T	rs1801133	Morrison N.A. et all. 1992
MTHFR	1p36.22, 1298 A>C	rs1801131	Braun N. et all 1996
MTR	1q43, 2756 A>G	rs1805087	Um J.Y., et all. 2004; 50: 647-650.40
MTR	5p15.31, 66 A>G	rs1801394	Vincenti V. et all. 1996

RESULTS AND DISCUSSION

In patients with postcoid complications of the PMO, the unfavorable C allele of the rs1801133 677C> T polymorphism in the MTHFR gene occurs slightly more often than in healthy individuals. There is a high frequency of occurrence of this allele with a predominance of the homozygous T / T variant, especially at stage 3 of the course of the disease (from 2.3 to 5.3 times). At the same time, the differences between 1 and the control sample were noted at the level of the trend, and the trend had a borderline level of statistical significance. These data allow us to conclude that the C allele and the T / T genotype of the rs1801133 677C> T polymorphism in the MTHFR gene, associated with a decrease in MTHFR production, have an insignificant predisposing effect on the development and clinical course of postcoid complications of MCL. Since this polymorphism is located in the promoter region of the gene and belongs to functional polymorphisms, it can be argued that its presence affects the rate of expression of the

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gene encoded by MTHFR. The pattern of the inflammatory response gene is capable of modifying the implementation of the immune and inflammatory response in the direction of an inappropriate hyperinflammatory response, leading to the progression and development of a more severe degree of postcoid complications of MCL. According to the odds ratio, the risk of postcoid complications of MCL in carriers of this genotype is increased by 1.17 times ($\chi 2$ = 3.423; P = 0.068; RR = 5.271; OR = 5.902; 95% CI: 3.166 - 8.774).

Summarizing the obtained results, we can conclude that there are insignificant differences in the frequency of detection of allelic and genotypic variants of the rs1801131 polymorphic locus in the MTHFR gene in 1 and the control group. In patients with postcoid complications of MCL, compared with the control group, there is a slight tendency to an increase in the frequency of the C / C genotype. According to the odds ratio, the risk of postcoid complications of MCL in carriers of this genotype increased by 1.17 times ($\chi 2$ = 0.017; P = 0.898; RR = 1.171; OR = 1.176; 95% CI: 0.238 - 5.762).

Thus, we have found that in patients with postcoid complications of the PMO, the unfavorable G allele of the 66A> G rs1801394 polymorphism in the MTR gene is more common than in healthy individuals. There is a high frequency of occurrence of this allele with a predominance of the homozygous variant G / G (from 2.3 to 7.02 times). At the same time, the differences between group 1 and the control sample were noted at the level of the trend, and the trend had a borderline level of statistical significance. These data allow us to conclude that the G allele and the G / G genotype of the 66A> G rs1801394 polymorphism in the MTR gene have a predisposing effect on the risk of development and severe clinical course of postcoid complications of MCL. Since this polymorphism is located in the promoter region of the gene and refers to functional polymorphisms. The presence of the G allele in patients with postcoid complications of the PMO is accompanied by a decrease in the production of the MTR gene in the presence of the G / G genotype. The pattern of the inflammatory response gene is capable of modifying the implementation of the immune and inflammatory response in the direction of an inadequate hyperinflammatory response, leading to the progression and development of a more severe form of postcoid complications of MCL.

The MTHFR gene is located in the promoter region of chromosome 1 at locus 1q36-22 and has 5 exons and 4 introns []. Several polymorphisms are found in the gene, the most famous of which are the transition - at the C \ T point 677 (rs1801133). This polymorphism plays an important role in inflammatory and infectious diseases [].

This part of the work is devoted to the study of the distribution frequencies of the rs1801133 polymorphism of the MTHFR gene, as well as to the analysis of the contribution of this polymorphism to the formation, development and clinical course of postcoid complications of MCL.

The study of the frequencies of detection of alleles and genotypes of 677C> T polymorphism in the MTHFR gene showed the presence of differences in their distribution between the main and control groups (Table 2).

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Table 2

Frequency of distribution of alleles and genotypes of rs1801133 polymorphism (gene localization on chromosome lp36.22) 677C> T in the MTHFR gene in patient and control groups

Num	Group	Allele frequency				Genotype distribution frequency					
		C		T		C /C		C /T		T /T	
		n	%	n	%	n	%	n	%	n	%
1	Main group (n = 70)	105	75	35	25	45	64,29	16	22,86	9	12,86
2	Control group (n = 41)	72	87,8	10	12,2	31	75,61	9	21,95	1	2,44

In the course of the study, it was possible to establish the frequency of detection of the C allele, which was 3.0 times higher than the frequency of detection of the T allele in the main group and 7.19 times in the control group. The C \ C genotype in the main group, in comparison with the C \ T and T \ T genotypes, was detected more often by 2.8 and 4.9 times, respectively, and in the population sample by 3.4 and 30.9 times, respectively (diagram 1).

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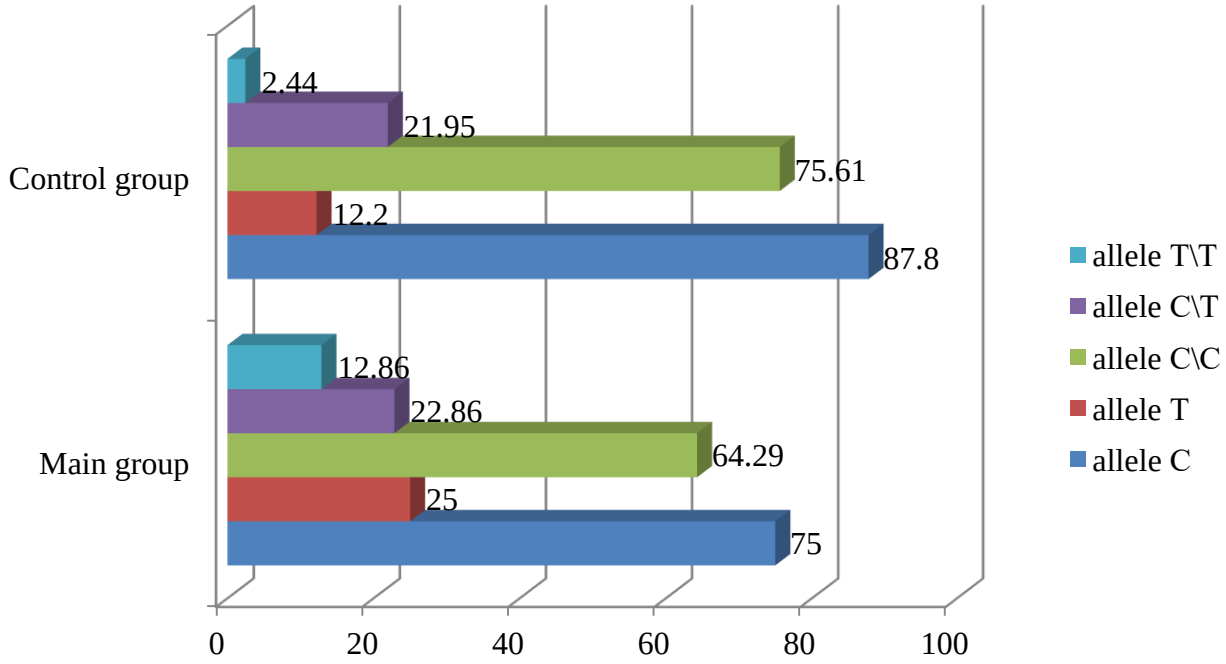

Diagram. 1.

Frequency of distribution of alleles and genotypes rs1801133 (gene localization on chromosome lp36.22) 677C> T in the MTHFR gene in patient and control groups

The results of a comparative analysis of the frequencies of detection of alleles and genotypes of the rs1801133 677C> T polymorphism in the MTHFR gene in group 1 of patients with postcoid complications of the PMO and in the population sample are presented in Table 3.

Table 3

Differences in the frequency of allelic and genotypic variants of the rs1801133 677C> T polymorphism in the MTHFR gene in patient groups

Alleles and genotypes	Number of examined alleles and genotypes				Xi2	p	RR	95%CI	OR	95%CI
	Main group		Control group							
	n	%	n	%						
C	105	75	72	87,8	5,25	0,02	0,85	0,579 - 1,259	0,42	0,197 - 0,881

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T	35	25	10	12,2	5,25	0,02	1,17	0,38 - 3,612	2,40	1,135 - 5,077
C /C	45	64,29	31	75,61	1,536	0,219	0,85	0,49 - 1,473	0,581	0,246 - 1,371
C /T	16	22,86	9	21,95	0,012	0,916	1,041	0,539 - 2,011	1,053	0,418 - 2,653
T /T	9	12,86	1	2,44	3,423	0,068	5,271	3,166 - 8,774	5,902	0,9 - 38,706

Allele C among practically healthy people in the control group in the study group 2 than in group 1 met with a slightly higher frequency (1.17). Allele T among patients with postcoid complications of PMO in the study group 1 than in the control group met a slightly higher frequency (2.04). It was possible to note only a slight prevalence of the frequency of detection of the genotype T 1 group among patients with postcoid complications of the PMO. There was also a slightly more significant, but still statistically insignificant, 0.9 times, excess of the frequency of genotype C, among patients with postcoid complications of PCO, relative to the frequency of detection of this genotype in the control sample ($\chi 2 = 5.25$; $p = 0$, 02; RR = 0.85; OR = 0.42; 95% CI: 0.579 - 1.259). The frequency of detecting the C / C genotype of the rs1801133 677C> T polymorphism in the MTHFR gene, by 1.17 times, prevailed in the control group, relative to its values in group 1 of patients with postcoid complications of PMO ($\chi 2 = 1.536$; $p = 0.219$; RR = 0, 85; OR = 0.581; 95% CI: 0.49 - 1.473). The frequency of occurrence of the C / T genotype was slightly higher among patients with postcoid complications of PMO compared to the control group, amounting to 1.04 and 22.86%, respectively ($\chi 2 = 0.012$; $p = 0.916$; RR = 1.041; OR = 1.053; 95% CI : 0.539 - 2.011). The frequency of detection of the Gln / Gln genotype was 3.23% among patients with postcoid complications of the PMO, which was statistically significant, 5.27 times higher than in the population sample, where its occurrence was at the level of 8.4% ($\chi 2 = 3.423$; $p = 0.068$; RR = 5.271; OR = 5.902; 95% CI: 3.166 - 8.774) (Table 3).

Thus, we have established that the unfavorable allele C of the rs1801133 677C> T polymorphism in the MTHFR gene occurs insignificantly more often in patients with postcoid complications of BLO than in healthy individuals. There is a high frequency of occurrence of this allele with a predominance of the homozygous T / T variant, especially at stage 3 of the course of the disease (from 2.3 to 5.3 times). At the same time, the differences between 1 and the control sample were noted at the level of the trend, and the trend had a borderline level of statistical significance. These data allow us to conclude that the C allele and the T / T genotype of the rs1801133 677C> T polymorphism in the MTHFR gene, associated with a decrease in MTHFR production, have an insignificant predisposing effect on the development and clinical course of postcoid complications of MCL. Since this polymorphism is located in the promoter region of the gene and belongs to functional polymorphisms, it can be argued that its presence affects the rate of expression of the gene encoded by MTHFR. The pattern of the inflammatory response gene is capable of modifying

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the implementation of the immune and inflammatory response in the direction of an inappropriate hyperinflammatory response, leading to the progression and development of a more severe degree of postcoid complications of MCL. According to the odds ratio, the risk of postcoid complications of MCL in carriers of this genotype is increased by 1.17 times ($\chi 2$ = 3.423; P = 0.068; RR = 5.271; OR = 5.902; 95% CI: 3.166 - 8.774).

CONCLUSION

Thus, our data confirm the complexity of the genetic mechanism for the development of polyposis processes in patients with postcoid complications of PCO and indicate the need and importance of understanding complex gene interactions in the analysis of the development and clinical stage of the studied pathology. Analyzing the prevalence of genotypic variants of this polymorphism, we revealed a direct association of the T / T monogenotype of the 677C> T rs1801133 polymorphism in the MTHFR gene, the C / C monogenotype of the 66A> G rs1801394 polymorphism in the MTR gene with the development of postcoid complications of the PLC.

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