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ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2024;13(2):250-8

# Course of COVID-19 in patients carrying different MEFV mutations of familial Mediterranean fever

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Received 17 November 2023; Accepted 15 February 2024
Available online 30 April 2024 with doi: 10.5455/medscience.2023.11.217



**Abstract**

Familial Mediterranean fever (FMF) is a genetic auto-inflammatory disease. Mutations in the Mediterranean fever (MEFV) gene cause inappropriate immune system triggering, leading to inflammatory episodes in the peritoneum, pleura, and joints. In the severe Coronavirus disease-19 (COVID-19) picture, the hyperimmune response and inflammatory process develop with exacerbation of the clinical condition. FMF disease, the drugs used in its treatment, and the possible effects of different genetic MEFV mutations on the course of COVID-19 arouse interest. In this study, 158 FMF patients with different MEFV gene mutations were evaluated using an online survey method in terms of COVID-19 course, hospitalization, additional comorbidities, and COVID-19 vaccination status. Participants were asked 21 questions and the data provided were compared between FMF MEFV gene mutations. 104 out of 158 cases did not get COVID-19. 9 of 54 cases who got COVID-19 were hospitalized. No statistically significant difference was found between MEFV gene mutations when evaluated and compared in terms of susceptibility to COVID-19, vaccination status, and presence of additional chronic diseases and comorbidities. The present study provides guidance on the role of FMF genetic mutations in the course of COVID-19. Our study may suggest that FMF MEFV gene mutations do not have a protective role against COVID-19. The results also may suggest that, as an inverse effect, MEFV gene mutations do not increase the risk of hyper-immune response and severe acute respiratory syndrome (SARS), which play a role in the severe course of COVID-19.

**Keywords:** Familial Mediterranean fever, Coronavirus disease-19, vaccines, Mediterranean fever gene

## Introduction

Familial Mediterranean fever (FMF) is a genetic auto-inflammatory disease presenting with intermittent fever, abdominal pain, chest and back pain, skin rashes, serositis, and arthritis attacks [1-3]. It is especially common in Turkish, Arab, Jewish, and Armenian communities living around the Mediterranean Region [1-3]. Its prevalence in these populations has been found to be 1-5/10,000 [4]. The disease (FMF) is mostly inherited with autosomal recessive mutations in the Mediterranean fever (MEFV) gene [1,2,4]. Autosomal dominant and double heterozygous mutations in trans position progress with a more dominant clinic [1]. The Tel Hashomer criteria generally form the basis of the FMF clinical diagnosis. These criteria contain 3 major (recurrent febrile episodes with serositis; AA type amyloidosis; favorable response to colchicine) and 3 minor criteria (FMF in first-degree relatives; erysipelas like erythema; recurrent febrile episodes). It needs 2 major or 1 major plus 2 minor criteria for diagnosis of FMF [5].

The MEFV gene is located at the 16p13.3 locus and consists of 10 exons and 781 codons [1-3]. There are 393 identified mutations in the MEFV gene listed in InFevers [6]. Most of these mutations are in exon 10, located between amino acids 680 and 761 [1-3,6]. It is stated that the most frequently observed mutations are M694V, V726A, M694I and M680I mutations seen in exon 10 and E148Q observed in exon 2 [1].

The MEFV gene encodes the 86 kDa pyrin (marenostrin, TRIM20) protein found in immune-related cells (neutrophils, eosinophils, monocytes, dendritic cells and synovial fibroblasts). Different forms of pyrin proteins produced as a result of mutations in the MEFV gene cause inappropriate triggering of

**CITATION**
Demir B, Karahan D. Course of COVID-19 in patients carrying different MEFV mutations of familial mediterranean fever. Med Science. 2024;13(2):250-8.

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DOI: 10.5455/medscience.2023.11.217

neutrophil activation of the immune system and uncontrolled release of interleukin-1 (IL1), interferon, and tumor necrosis factor-alpha (TNF alpha), leading to inflammatory episodes in the peritoneum, pleura, and joints [2,4].

Coronaviruses are enveloped, positive, single-stranded RNA viruses with ~30 kb of genetic material. Severe Acute Respiratory Syndrome-Cov-2 (SARS-CoV-2) is classified as a beta coronavirus subtype [7]. The disease caused by SARS-CoV-2 was named Coronavirus disease (COVID-19) by World Health Organization (WHO). Symptoms of patients infected with SARS-CoV-2 range from minimal symptoms to severe respiratory failure that can progress to multi-organ failure [7]. It is stated that genetic variability causes different results in protection from COVID-19 infection or in the severe occurrence of infection [8]. In the severe COVID-19 picture, the hyperimmune response and inflammatory process, which is defined as a cytokine storm, develops and the clinic worsens [9]. The pyrin protein has an N-terminal pyrin domain (PYD) that is frequently found in innate immune pathogen sensors such as NLRP1, NLRP3, and AIM2, which induce inflammatory responses [10]. It is stated that when SARS-CoV-2 enters the cell, a cytokine storm may develop with the triggering of the nod-like receptor pyrin domain (NLRP), which contains the pyrin domain-containing protein 3 (NLRP3) inflammasome, which is a part of the genetic immune system, through immunological mechanisms [9,11]. The development of genetic pyrin inflammatory process disorders and immune system defects seen in FMF raises the question of evaluation in terms of COVID-19 susceptibility and severity [9]. It has been suggested that FMF-associated MEFV mutations are advantageous against some infections such as tuberculosis and plague [12].

The COVID-19 pandemic has progressed in the form of peaks and remissions with the vaccination process and mutations in the virus in the approximately 3-year period. Based on whether the genetic variability of FMF patients would protect against COVID-19, our study aimed to evaluate the course of COVID-19 in FMF patients carrying different MEFV gene mutations. We evaluated the relationship between different gene mutations with COVID-19 and the severity of the disease. And again, we aimed to examine the immune status of FMF patients with different variations before and after COVID-19 vaccination.

## Material and Methods

The study was prepared on the basis of evaluating the answers given by the participants to the online questionnaire form on the internet. Ethical approval for the study was obtained from the ethics committee of Malatya Turgut Özal University with the date 20.10.2022 and the number 2022/163. 158 people diagnosed with FMF were included in the study.

Participants were asked 21 questions in the study. The first questions were about demographic characteristics. Other questions were made in the form of multiple choice and fill-in-the-blank questions including whether to get COVID-19, the number of having COVID-19, whether to receive treatment in the hospital or in the intensive care unit, whether the COVID-19 vaccine was performed, FMF gene analysis results, presence of additional diseases, colchicine use and medications used (Table 1). Before the start of the survey, the statement that the participants had given written voluntary consent for the use of data by participating in the survey was obtained before the first question.

**Table 1.** Survey questionnaire

| | |
|---|---|
| 1. | Age |
| 2. | Gender |
| 3. | Diagnosed with FMF (Familial Mediterranean fever)? |
| 4. | Having another FMF patient in the family |
| 5. | Number of people with FMF in the family, if any have FMF |
| 6. | Having an FMF gene test |
| 7. | MEFV gene results |
| 8. | Heterozygous-Homozygous? |
| 9. | Using Colchicine regularly |
| 10. | Daily dose of Colchicine take |
| 11. | Having any known chronic diseases other than FMF. If yes, existing chronic diseases |
| 12. | Medications chronically used for these diseases |
| 13. | Having COVID-19 |
| 14. | Number of having COVID-19 |
| 15. | Hospitalization due to COVID-19? |
| 16. | Number of days staying in the hospital |
| 17. | Admission to the Intensive Care Unit due to COVID-19? |
| 18. | Number of days in the Intensive care unit |
| 19. | Having COVID-19 vaccine |
| 20. | Number of doses of vaccination |
| 21. | Types of vaccines administered |

The inclusion criteria for the study were:

1. Being over the age of 18,
2. Being under follow-up and treatment with a diagnosis of FMF.

The diagnosis of COVID-19 was confirmed by the reverse transcriptase PCR (RT-PCR) method, by taking nasopharyngeal swabs from patients with symptoms.

The exclusion criteria for the study were:

1. Being under the age of 18,
2. Not being diagnosed with FMF,
3. Not having a gene test result,
4. Use of immunosuppressants and steroids for any reason before the onset of COVID-19.

DOI: 10.5455/medscience.2023.11.217

The following gene mutations of E148Q, P369S, H478Y, F479L, S675N, G678E, M680L, M694L, M694V, M680IGgtA, M680IGgtC, T681I, I692del, M694I, K695R, K695M, R717S, I720M, V722M, V726A, A744S, R761H were included to questionnaire. According to InFevers, mutations E148Q, P369S, H478Y, G678E, T681I, K695R, I720M, V722M, A744S are classified as uncertain significance (VUS); F479L, M680L, M694L, I692del, R761H are likely pathogenic; S675N is likely benign; M680IGgtA, M680IGgtC, M694V, M694I, V726A are pathogenic; R717S, K695M are classified as unsolved [6].

The data provided were compared between FMF MEFV gene mutations. Gene mutations were compared in terms of having COVID-19, hospitalization, intensive care hospitalization, chronic additional co-morbidities, and vaccination status.

Statistical analysis: The analysis of the data was carried out by SPSS (Statistical Program in Social Sciences) 26.0 program. The significance level (p) for the comparison tests of the data was taken as equal or less than 0.05. The chi-square ($\chi 2$) test was performed in categorical data analysis by creating cross tables. Number and percentage were used for the descriptive values of the data.

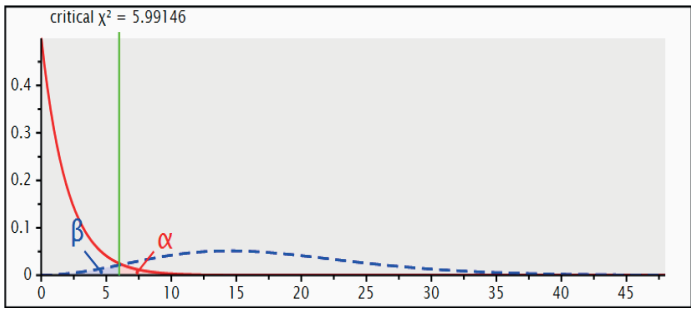
The sample of this study was determined by power analysis. According to the calculation made using the G*power 3.1 program; the sample size was determined to be at least 171, with an effect size of 0.3, a margin of error of 0.05, a confidence level of 0.95, and a universe representation power of 0.95 [13].

**G*power program output**

***$\chi^2$ tests-Goodness-of-fit tests: Contingency tables***

Analysis: A priori: Compute required sample size

| | | | |
|---|---|---|---|
| Input: | Effect size w | = | 0.3 |
| | α err prob | = | 0.05 |
| | Power (1-β err prob) | = | 0.95 |
| | Df | = | 2 |
| Output: | Noncentrality parameter λ | = | 15.4800000 |
| | Critical $\chi^2$ | = | 5.9914645 |
| | Total sample size | = | 171 |
| | Actual power | = | 0.9504692 |




## Results

A hundred fifty-eight people diagnosed with FMF were included in the study. The number of female participants was 91, and the male was 67. The age range of the study population is predominantly under 65 years of age. There were only 3 cases over the age of 65. Age distribution and demographic data are shown in Table 2.

**Table 2.** Demographic data

| Variable | Group | Frequency | Percent (%) |
|---|---|---|---|
| **Age** | **18-25 age** | 35 | 22.2 |
| | **26-35 age** | 34 | 21.5 |
| | **36-45 age** | 51 | 32.3 |
| | **46-55 age** | 24 | 15.2 |
| | **56-65 age** | 11 | 7.0 |
| | **>65 age** | 3 | 1.9 |
| **Gender** | **Female** | 91 | 57.6 |
| | **Male** | 67 | 42.4 |
| **Non-FMF disease** | **Yes** | 51 | 32.3 |
| | **No** | 107 | 67.7 |
| **Getting COVID-19** | **Yes** | 54 | 34.2 |
| | **No** | 104 | 65.8 |
| **Number of being COVID-19** | **0** | 104 | 65.8 |
| | **1** | 46 | 29.1 |
| | **2** | 5 | 3.2 |
| | **3** | 3 | 1.9 |
| **Hospitalization due to COVID-19** | **Yes** | 9 | 5.7 |
| | **No** | 149 | 94.3 |
| **Length of hospital stay** | **0** | 150 | 94.9 |
| | **4** | 5 | 3.2 |
| | **5** | 3 | 1.9 |
| **Intensive care due to COVID-19** | **No** | **158** | **100.0** |

A hundred-four out of 158 cases did not have COVID-19, and 54 people did. Of the 54 people, 46 declared that they had COVID-19 once, 5 of them twice, and 3 of them 3 times. Only 9 of these 54 people were hospitalized. The hospitalized cases were discharged from the hospital in good health without the need for intensive care follow-up.

We included the 22 FMF gene mutations in our study survey and asked the participants to share their gene analyses with us. Since FMF patients can carry more than one gene mutation at the same time, participants were asked to mark all mutations they carry in

DOI: 10.5455/medscience.2023.11.217

the survey. All gene analysis results of the participants are shown in Table 3.

All gene analyses were evaluated and compared in terms of susceptibility and resistance to COVID-19. A statistically significant result could not be achieved (Table 4).

No statistically significant difference was found between E148Q, P369S, H478Y, S675N, M680L, M694L, M694V, M680IGgtA, M680IGgtC, T681I, I692del, M694I, K695R, K695M, R717S, I720M, V722M, V726A, A744S, R761H genetic mutations and the risk of having COVID-19 (p>0.05).

When we examine whether the presence of additional chronic diseases in FMF patients poses a risk for having COVID-19, no significant difference was found in risk in all gene mutations (Table 5).

**Table 3.** FMF gene analyses

| Variable | Group | Frequency | Percent (%) |
|---|---|---|---|
| **FMF family history** | **Yes** | 103 | 65.2 |
| | **No** | 55 | 34.8 |
| **Gene testing** | **Yes** | 158 | 100.0 |
| **E148Q** | **(+)** | 6 | 3.8 |
| | **(-)** | 152 | 96.2 |
| **P369S** | **(+)** | 3 | 1.9 |
| | **(-)** | 155 | 98.1 |
| **H478Y** | **(-)** | 158 | 100.0 |
| **F479L** | **(+)** | 1 | 0.6 |
| | **(-)** | 157 | 99.4 |
| **S675N** | **(-)** | 158 | 100.0 |
| **G678E** | **(-)** | 158 | 100.0 |
| **M680L** | **(-)** | 158 | 100.0 |
| **M680IGgtA** | **(+)** | 6 | 3.8 |
| | **(-)** | 152 | 96.2 |
| **M694L** | **(+)** | 2 | 1.3 |
| | **(-)** | 156 | 98.7 |
| **M694V** | **(+)** | 22 | 13.9 |
| | **(-)** | 136 | 86.1 |
| **M680IGgtC** | **(+)** | 1 | 0.6 |
| | **(-)** | 157 | 99.4 |
| **T681I** | **(-)** | 158 | 100.0 |
| **I692del** | **(-)** | 158 | 100.0 |
| **M694I** | **(+)** | 2 | 1.3 |
| | **(-)** | 156 | 98.7 |
| **K695R** | **(-)** | 158 | 100.0 |
| **K695M** | **(-)** | 158 | 100.0 |
| **R717S** | **(-)** | 158 | 100.0 |
| **I720M** | **(-)** | 158 | 100.0 |
| **V722M** | **(-)** | 158 | 100.0 |
| **V726A** | **(+)** | 6 | 3.8 |
| | **(-)** | 152 | 96.2 |
| **A744S** | **(+)** | 1 | 0.6 |
| | **(-)** | 157 | 99.4 |
| **R761H** | **(-)** | 158 | 100.0 |
| **Gene result** | **Heterozygous** | 128 | 81.0 |
| | **Homozygous** | 30 | 19.0 |
| **Total** | | 158 | 100.0 |

DOI: 10.5455/medscience.2023.11.217

**Table 4.** Comparison of genes according to COVID-19 status

| Gene | COVID-19 | n/% | Getting COVID-19 | | Total | Test | p value |
|---|---|---|---|---|---|---|---|
| | | | Yes | No | | | |
| **1. E148Q** | (+) | **n** | 5 | 1 | 6 | 4.620 | 1.000 |
| | | **%** | 9 | 1 | 4 | | |
| | (-) | **n** | 49 | 103 | 152 | | |
| | | **%** | 91 | 99 | 96 | | |
| **2. P369S** | (+) | **n** | 3 | 0 | 3 | 3.285 | 1.000 |
| | | **%** | 6 | 0 | 2 | | |
| | (-) | **n** | 51 | 104 | 155 | | |
| | | **%** | 94 | 100 | 98 | | |
| | | **%** | 100 | 100 | 100 | | |
| **3. F479L** | (-) | **n** | 1 | 0 | 1 | 0.112 | 1.000 |
| | | **%** | 2 | 0 | 1 | | |
| | (+) | **n** | 53 | 104 | 157 | | |
| | | **%** | 98 | 100 | 99 | | |
| | | **%** | 100 | 100 | 100 | | |
| **4. M680IGgtA** | (+) | **n** | 6 | 0 | 6 | 9.163 | 1.000 |
| | | **%** | 11 | 0 | 4 | | |
| | (-) | **n** | 48 | 104 | 152 | | |
| | | **%** | 89 | 100 | 96 | | |
| **5. M694L** | (+) | **n** | 2 | 0 | 2 | 1.501 | 1.000 |
| | | **%** | 4 | 0 | 1 | | |
| | (-) | **n** | 52 | 104 | 156 | | |
| | | **%** | 96 | 100 | 99 | | |
| **6. M694V** | (+) | **n** | 20 | 2 | 22 | 33.695 | 1.000 |
| | | **%** | 37 | 2 | 14 | | |
| | (-) | **n** | 34 | 102 | 136 | | |
| | | **%** | 63 | 98 | 86 | | |
| **7. M680IGgtC** | (+) | **n** | 1 | 0 | 1 | 0.112 | 1.000 |
| | | **%** | 2 | 0 | 1 | | |
| | (-) | **n** | 53 | 104 | 157 | | |
| | | **%** | 98 | 100 | 99 | | |
| | | **%** | 100 | 100 | 100 | | |
| **8. M694I** | (+) | **n** | 2 | 0 | 2 | 1.501 | 1.000 |
| | | **%** | 4 | 0 | 1 | | |
| | (-) | **n** | 52 | 104 | 156 | | |
| | | **%** | 96 | 100 | 99 | | |
| | | **%** | 100 | 100 | 100 | | |
| **9. V726A** | (-) | **n** | 4 | 2 | 6 | 1.618 | 1.000 |
| | | **%** | 7 | 2 | 4 | | |
| | (+) | **n** | 50 | 102 | 152 | | |
| | | **%** | 93 | 98 | 96 | | |
| **10. A744S** | (-) | **n** | 1 | 0 | 1 | 0.112 | 1.000 |
| | | **%** | 2 | 0 | 1 | | |
| | (+) | **n** | 53 | 104 | 157 | | |
| | | **%** | 98 | 100 | 99 | | |
| **Total** | | **n** | 54 | 104 | | 158 | |
| | | **%** | 100 | 100 | | 100 | |

n: number of samples, %: percent, p: Chi-square Test value ($\chi 2$), *p<0.05; There is a statistically significant difference between the groups
Genes with too little data to calculate are excluded from the table in order to avoid information confusion

DOI: 10.5455/medscience.2023.11.217

**Table 5.** Comparison of gene mutations in terms of COVID-19 risk by non-FMF disease presence

| Gene mutation | COVID-19 | n/% | Non-FMF disease | | Total | Test | p value |
|---|---|---|---|---|---|---|---|
| | | | Yes | No | | | |
| **1. E148Q** | (+) | **n** | 2 | 4 | 6 | 0.000 | 1.000 |
| | | **%** | 4 | 4 | 4 | | |
| | (-) | **n** | 49 | 103 | 152 | | |
| | | **%** | 96 | 96 | 96 | | |
| **2. P369S** | (+) | **n** | 3 | 0 | 3 | 3.647 | 1.000 |
| | | **%** | 6 | 0 | 2 | | |
| | (-) | **n** | 48 | 107 | 155 | | |
| | | **%** | 94 | 100 | 98 | | |
| **3. F479L** | (-) | **n** | 0 | 1 | 1 | 0.000 | 1.000 |
| | | **%** | 0 | 1 | 1 | | |
| | (+) | **n** | 51 | 106 | 157 | | |
| | | **%** | 100 | 99 | 99 | | |
| | | **%** | 100 | 100 | 100 | | |
| **4. M680IGgtA** | (+) | **n** | 1 | 5 | 6 | 0.151 | 1.000 |
| | | **%** | 2 | 5 | 4 | | |
| | (-) | **n** | 50 | 102 | 152 | | |
| | | **%** | 98 | 95 | 96 | | |
| **5. M694L** | (+) | **n** | 1 | 1 | 2 | 0.000 | 1.000 |
| | | **%** | 2 | 1 | 1 | | |
| | (-) | **n** | 50 | 106 | 156 | | |
| | | **%** | 98 | 99 | 99 | | |
| **6. M694V** | (+) | **n** | 7 | 15 | 22 | 0.000 | 1.000 |
| | | **%** | 14 | 14 | 14 | | |
| | (-) | **n** | 44 | 92 | 136 | | |
| | | **%** | 86 | 86 | 86 | | |
| **7. M680IGgtC** | (+) | **n** | 0 | 1 | 1 | 0.000 | 1.000 |
| | | **%** | 0 | 1 | 1 | | |
| | (-) | **n** | 51 | 106 | 157 | | |
| | | **%** | 100 | 99 | 99 | | |
| | | **%** | 100 | 100 | 100 | | |
| **8. M694I** | (+) | **n** | 1 | 1 | 2 | 0.000 | 1.000 |
| | | **%** | 2 | 1 | 1 | | |
| | (-) | **n** | 50 | 106 | 156 | | |
| | | **%** | 98 | 99 | 99 | | |
| | | **%** | 100 | 100 | 100 | | |
| **9. V726A** | (-) | **n** | 2 | 4 | 6 | 0.000 | 1.000 |
| | | **%** | 4 | 4 | 4 | | |
| | (+) | **n** | 49 | 103 | 152 | | |
| | | **%** | 96 | 96 | 96 | | |
| **10. A744S** | (-) | **n** | 1 | 0 | 1 | 0.145 | 1.000 |
| | | **%** | 2 | 0 | 1 | | |
| | (+) | **n** | 50 | 107 | 157 | | |
| | | **%** | 98 | 100 | 99 | | |
| **Total** | | **n** | 51 | 107 | | 158 | |
| | | **%** | 100 | 100 | | 100 | |

n: number of samples, %: percent, p: Chi-square Test value ($\chi 2$), *p<0.05; There is a statistically significant difference between the groups
Genes with too little data to calculate are excluded from the table in order to avoid information confusion

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No statistically significant difference was found between E148Q, P369S, H478Y, S675N, M680L, M694L, M694V, M680IGgtA, M680IGgtC, T681I, I692del, M694I, K695R, K695M, R717S, I720M, V722M, V726A, A744S, R761H genetic mutations and the risk of having COVID-19 in terms of non-FMF disease status ($p>0.05$).

The COVID-19 pandemic has been going on for about 3 years and multiple vaccine forms have been developed against the disease. Comparative results were examined in terms of whether vaccination had an effect on immunity in FMF patients and no significant results were obtained (Table 6).

**Table 6.** Comparison of gene mutations by COVID-19 vaccination status

| Gene mutation | COVID-19 | n/% | COVID-19 vaccination status | | Total | Test | p value |
|---|---|---|---|---|---|---|---|
| | | | Yes | No | | | |
| **1. E148Q** | (+) | **n** | 4 | 2 | 6 | 0.114 | 1.000 |
| | | **%** | 3 | 6 | 4 | | |
| | (-) | **n** | 123 | 29 | 152 | | |
| | | **%** | 97 | 94 | 96 | | |
| **2. P369S** | (+) | **n** | 3 | 0 | 3 | 0.017 | 1.000 |
| | | **%** | 2 | 0 | 2 | | |
| | (-) | **n** | 124 | 31 | 155 | | |
| | | **%** | 98 | 100 | 98 | | |
| **3. F479L** | (-) | **n** | 1 | 0 | 1 | 0.000 | 1.000 |
| | | **%** | 1 | 0 | 1 | | |
| | (+) | **n** | 126 | 31 | 157 | | |
| | | **%** | 99 | 100 | 99 | | |
| **4. M680IGgtA** | (+) | **n** | 3 | 3 | 6 | 1.922 | 1.000 |
| | | **%** | 2 | 10 | 4 | | |
| | (-) | **n** | 124 | 28 | 152 | | |
| | | **%** | 98 | 90 | 96 | | |
| **5. M694L** | (+) | **n** | 2 | 0 | 2 | 0.000 | 1.000 |
| | | **%** | 2 | 0 | 1 | | |
| | (-) | **n** | 125 | 31 | 156 | | |
| | | **%** | 98 | 100 | 99 | | |
| **6. M694V** | (+) | **n** | 18 | 4 | 22 | 0.000 | 1.000 |
| | | **%** | 14 | 13 | 14 | | |
| | (-) | **n** | 109 | 27 | 136 | | |
| | | **%** | 86 | 87 | 86 | | |
| **7. M680IGgtC** | (+) | **n** | 0 | 1 | 1 | 0.589 | 1.000 |
| | | **%** | 0 | 3 | 1 | | |
| | (-) | **n** | 127 | 30 | 157 | | |
| | | **%** | 100 | 97 | 99 | | |
| **8. M694I** | (+) | **n** | 2 | 0 | 2 | 0.000 | 1.000 |
| | | **%** | 2 | 0 | 1 | | |
| | (-) | **n** | 125 | 31 | 156 | | |
| | | **%** | 98 | 100 | 99 | | |
| **9. V726A** | (-) | **n** | 5 | 1 | 6 | 0.000 | 1.000 |
| | | **%** | 4 | 3 | 4 | | |
| | (+) | **n** | 122 | 30 | 152 | | |
| | | **%** | 96 | 97 | 96 | | |
| **10. A744S** | (-) | **n** | 1 | 0 | 1 | 0.000 | 1.000 |
| | | **%** | 1 | 0 | 1 | | |
| | (+) | **n** | 126 | 31 | 157 | | |
| | | **%** | 99 | 100 | 99 | | |
| **Total** | | **n** | 127 | 31 | | 158 | |
| | | **%** | 100 | 100 | | 100 | |

n: number of samples, %: percent, p: Chi-square Test value ($\chi 2$), *$p<0.05$; There is a statistically significant difference between the groups
Genes with too little data to calculate are excluded from the table in order to avoid information confusion

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No statistically significant difference was found between E148Q, P369S, H478Y, S675N, M680L, M694L, M694V, M680IGgtA, M680IGgtC, T681I, I692del, M694I, K695R, K695M, R717S, I720M, V722M, V726A, A744S, R761H genetic mutations and the risk of having COVID-19 in terms of vaccination status ($p>0.05$).

## Discussion

Co-morbidities such as advanced age, obesity, hypertension, diabetes mellitus, chronic lung or kidney disease, and cardiovascular disease have been identified as risk factors for worse consequences in COVID-19 [14]. Preliminary results of the COLCORONA trial (Colchicine Coronavirus SARS-CoV2 Trial) indicate that colchicine reduces the combined rate of death or hospitalization in non-hospitalized patients with COVID-19 [15]. Although 51 of the 158 patients in our study had chronic co-morbidities other than FMF, no complications developed in these patients, either during their hospitalization or during their COVID-19 period.

Accumulated data on rheumatic diseases have shown that especially those with moderate/high disease activity are at risk for severe COVID-19 [16]. A study from Spain stated that risk factors for COVID-19-related hospitalization in patients with inflammatory rheumatic diseases are increasing age and systemic autoimmune conditions [17]. The incidence and severity of SARS-CoV-2 infection in FMF are intriguing. Gunendi et al. [11] and Guler et al. [18] stated in their studies that FMF-related characteristics were not associated with worse COVID-19 consequences and were not a risk factor. Guler et al. stated that not using colchicine is a risk factor for hospitalization and oxygen support [18]. Bourguiba et al. found similar incidence rates of COVID-19 in FMF patients (8%) and the general population (11%) in a French endemic region [19]. They also reported that FMF patients with severe SARS-CoV-2 infection had known risk factors such as increasing age, obesity, and hypertension [19]. According to these results, our study is similar to them, with a low hospitalization, and no need for intensive care unit in FMF patients. Based on both these studies and our study, FMF is probably not a risk factor for severe COVID-19.

Theoretically, colchicine could reduce the hospitalization and mortality of COVID-19 by targeting intersecting pathways in the SARS-CoV-2-induced inflammatory cascade [20]. There is limited information on COVID-19 outcomes in FMF patients [21]. Colchicine is a synthetic drug used successfully in the treatment of FMF. Colchicine inhibits microtubule formation and prevents neutrophils from taking the virus into the cell. It also has an antiviral effect with this mechanism [22]. Colchicine can also inhibit NLRP3 inflammation, which can be activated by SARS-CoV-2 and possibly associated with hyperinflammation in COVID-19 [23]. According to this theoretical knowledge, colchicine may be beneficial in the treatment of COVID-19. Scarsi et al. showed that colchicine treatment is associated with better survival in patients with COVID-19 pneumonia in their controlled studies [24]. Drosos et al. in their review reported that colchicine is promising as an effective, safe and easy-to-use drug in reducing the risk of severe COVID-19 [25]. The majority of the participants in our study had a history of colchicine intake, albeit irregularly (103 patients were using colchicine regularly and 55 patients were using it irregularly). Based on this, we think that these patients received the necessary treatment for COVID-19 without being aware of it, with the use of colchicine. In other words, patients were treating themselves for COVID-19 at the same time as the medication they took for their chronic illnesses. Although there are positive studies on colchicine mentioned above, it should be taken into consideration that these studies were observational studies. Despite colchicine has promising benefits, this benefit awaits to be proven by randomized controlled trials.

Patients with FMF have an intense biologic inflammatory syndrome during attacks and a chronic subclinical inflammatory syndrome characterized by cytokine activation and TH1 polarization between attacks. Moreover, even asymptomatic heterozygous carrier mutations of MEFV have been reported to have increased C-reactive protein, serum amyloid-A protein, and mRNAs for TNF, IL1, IL6, and IL18 cytokines, as well as TH1 polarization of the inflammatory process [26]. More than 300 sequence variants exist for MEFV, and the large number of MEFV mutations observed in ethnic groups perhaps points to an advantage that helps these carriers survive better than non-carriers. This presumed advantage has been claimed to be effective against diseases such as tuberculosis, smallpox, cholera, plague, typhus, and malaria, which are now well-treated [27]. Marinelli et al. reported that although prospective randomized controlled trials are needed, they can cautiously state that innate FMF immune system dysfunction does not appear to be a risk factor for the development of severe COVID-19, and FMF patients are not at higher risk for COVID-19 [28].

According to the MEFV gene analysis results of the participants included in our study, no gene defects were found that could be considered as risky for COVID-19. Most of the FMF patients included in our study had more than one gene defect. It was thought that the presence of such a large number of gene combinations created difficulties in obtaining isolated results. Therefore, clearer results can be obtained with observational studies to be performed with isolated or multiple combination studies.

Partially small number of cases, survey-style study design, and the lack of homogeneous distribution of gene mutations can be stated as the limitations of our study. Since the study was carried out in the form of a survey, there may be a lack of inclusion of severe and mortal COVID-19 cases in the study. Among the MEFV gene mutations compared in the study, there are mutations defined as unsolved, benign, likely benign, or VUS according to InFevers. Although cases under follow-up and treatment with the diagnosis of FMF were included in the survey, this heterogeneity of mutations creates confusion. In fact, there are still unclear points in the relationship between the diagnosis of FMF and

DOI: 10.5455/medscience.2023.11.217

disease-causing gene mutations. Again, there are handicaps such as the inability to differentiate syndromes overlapping with FMF, such as Pyrin-associated Autoinflammation with Neutrophilic Dermatosis (PAAND) and Pyrin-associated Dominant Disease (PAD) in the questionnaire study. However, from a general point of view, our study provides information about the attitude of MEFV mutations associated with FMF against COVID-19.

## Conclusion

In conclusion, the results of our study may suggest that FMF MEFV gene mutations do not have a protective role against COVID-19. No differentiation was observed between MEFV gene mutations in terms of having COVID-19, COVID-19 status associated with vaccination, and COVID-19 status associated with additional chronic diseases. Supporting our study with further studies will provide important results in better analysis of COVID-19 and other Coronavirus infections in terms of their association with FMF.

**Conflict of Interests**
*The authors declare that there is no conflict of interest in the study.*

**Financial Disclosure**
*The authors declare that they have received no financial support for the study.*

**Ethical Approval**
*Ethical approval for the study was obtained from the non- interventional ethics committee of Malatya Turgut Özal University with the date 20.10.2022 and the number 2022/163.*

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