# Incidence and course of COVID-19 hospitalizations among patients with familial Mediterranean fever

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**Abbreviations:** CI, confidence interval; COVID-19, coronavirus disease 2019; EMR, electronic medical record; FMF, familial Mediterranean fever; HMO, health management organization; IL, interleukin; NLRP3, NLR Pyrin domain containing 3; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SOC, standard of care.

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The data that support the findings of this study can be made available through contact with the corresponding author, Eldad Ben-Chetrit (E-mail: eldad@hadassah.org.il), upon reasonable request

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Ethical approval and waiver of informed consent was sought and given by the Hadassah Medical Center Ethics Committee (0089-21-HMO)

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## Abstract

**Objectives:** To evaluate the incidence of hospitalization for COVID-19 in patients with familial Mediterranean fever (FMF), as compared to the general population, and to compare the disease course between FMF inpatients, and age, sex, ethnicity, and comorbidity-matched non-FMF COVID-19 inpatients.

**Methods:** We used electronic medical records (EMR) to obtain data about the total number of the insured population and the number of FMF patients in the two largest health management organizations (HMOs) in Jerusalem, Clalit and Meuhedet. The total number of COVID-19 inpatients at the Hadassah Medical Center, including those with FMF, for the period between the 1 February 2020, and the 10 March 2021 was retrieved from the EMR of Hadassah. COVID-19 course was compared between the FMF inpatient group and age, sex, ethnicity, and comorbidity-matched non-FMF COVID-19 inpatients. Each FMF inpatient was matched with 2 non-FMF controls.

**Results:** We found no statistically significant difference in the odds of hospitalization for COVID-19 between FMF patients and the non-FMF population (0.46% vs. 0.41%; p= 0.73). Furthermore, we found similar disease

severity and therapeutic approach in FMF COVID-19 inpatients and matched non-FMF COVID-19 inpatients.

**Conclusions:** Neither FMF, nor baseline colchicine therapy appear to affect the incidence of hospitalization for COVID-19 or the disease course, in terms of severity and therapeutic approach.

**Key messages:**

- Several studies have suggested colchicine as a potential therapeutic option in coronavirus disease 2019 (COVID-19).
- Neither baseline familial Mediterranean fever (FMF), nor colchicine therapy provide protection against hospitalization for COVID-19.
- The severity of COVID-19 appears to be similar in FMF inpatients and matched control inpatients.

## Introduction

Coronavirus disease 2019 (COVID-19), caused by infection with the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), is an event of

pandemic proportions, affecting every facet of modern life. In most cases, COVID-19 is a mild-to-moderate illness, characterized by fever, cough, and malaise. However, in certain cases, the disease takes a more ominous course, necessitating hospitalization, respiratory support, and is potentially lethal. Whether or not patients with pre-existing autoinflammatory rheumatic diseases are at an increased risk of SARS-CoV-2 infection or of severe COVID-19 remains unknown.

When SARS-CoV-2 enters the cell, the NLR Pyrin domain containing 3 (NLRP3) inflammasome is triggered via immunological mechanisms. The elevated presence of NLRP3-induced pro-inflammatory cytokines (Interleukin (IL)-1, IL-1β) in the serum of SARS-CoV-2-infected patients supports a hypothesis of innate immunity involvement in the pathogenesis and evolution of the disease[1].

Familial Mediterranean fever (FMF) is an autoinflammatory hereditary disease characterized by recurrent attacks of fever and serositis, commonly lasting 1-3 days. Its pathogenesis involves defects in the innate immune system, namely

enhancement of the proinflammatory effects of the Pyrin inflammasome[2]. Severe COVID-19 induces an intense inflammatory response known as 'cytokine storm'[1], raising the question of the susceptibility and severity of SARS-CoV-2 infection in patients with *a priori* innate immunity disorders, such as those with FMF.

Colchicine is the drug of choice for FMF treatment since 1972. It prevents acute attacks and fends off the development of amyloidosis[3]. Its anti-inflammatory mechanism is mediated by inhibition of microtubule polymerization. Microtubules play an important role in cell migration, signal transduction, and gene expression. Colchicine acts on NLRP3 and probably on the Pyrin protein, resulting in inhibition of pathways involved in cellular inflammatory signaling[4]. Since it is thought that one of the important pathogenic mechanisms of COVID-19 is through the activation of NLRP3 inflammasome, there is a rationale for considering colchicine use in this disease.

Several recent reviews have discussed the role of colchicine in preventing COVID-19 complications[5-7]. However, clinical studies evaluating colchicine use

in SARS-CoV-2-infected patients have produced conflicting results[8-10]. Thus, studying the prevalence and the course of COVID-19 among FMF patients who are already treated with colchicine may shed light on the real-life interactions between SARS-CoV-2 infection, FMF and colchicine.

## Patients and methods

**Study population.** The two largest health management organizations (HMOs) in the greater Jerusalem area, Clalit and Meuhedet were queried for their total number of insured patients and the total number of patients with an active diagnosis of FMF. The query was for the time between 1 February 2020 and 10 March 2021.

The Hadassah Medical Center electronic medical record (EMR) was then queried for the total number of Clalit and Meuhedet patients hospitalized due to COVID-19 over the same period. Patients with a concurrent diagnosis of FMF, at the time of COVID-19 hospitalization, were located. Each hospitalized patient with FMF and COVID-19 was matched with 2 control inpatients diagnosed with COVID-19 but not with FMF. The matching attempted to account for age, sex,

ethnicity, and major comorbidities. Data regarding COVID-19 duration, severity, imaging results, treatment, and vaccination status was retrospectively sought from the EMR. Patient characteristics, including active medications, were likewise mined from the EMR.

This is a convenient sample and no power calculation was used, however statistical analyses were adjusted for the power available.

Ethical approval and waiver of informed consent was sought and given by the Hadassah Medical Center Ethics Committee (0089-21-HMO).

## Statistical analysis

The appropriate use of statistical tests was determined by the nature of the variables and the sample size. The relation between categorial independent variables and the dichotomous outcome variable was determined using the Fisher's exact test when applied to the hospitalized patient groups, and by the chi-square test in the assessment of the odds of COVID-19 hospitalization in FMF patients. The relation between the dichotomous independent variables and non-normally distributed outcome variables was examined using the Man

Whitney (Wilcoxon) Test. The cutoff for statistical significance was pre-determined at p=0.05.

## Results

750,008 persons (398,745 persons from the Clalit HMO and 351,263 from the Meuhedet HMO) were identified as HMO participants in the Jerusalem region at the beginning of February 2020. 1014 persons from of the Clalit cohort and 960 persons from the Meuhedet cohort had an active FMF diagnosis. Over the period between 1st of February 2020 and 10th of March 2021, 2068 persons insured by Clalit and 982 insured by Meuhedet were hospitalized in the Hadassah Medical Center COVID-19 wards. In this combined cohort (N = 3,050), 9 patients (0.3%) had a diagnosis of FMF.

We initially probed these numbers to ascertain whether there was a significant difference in the odds of COVID-19 hospitalization in FMF patients. Out of a total of 750,008 persons from both HMOs, 748,034 did not have a diagnosis of FMF (99.7%) and 1974 did (0.3%). Of patients not suffering from FMF, 3041 (0.41%) were hospitalized in Hadassah. Of the 1974 patients with FMF, 9

(0.46%) were hospitalized in Hadassah. No difference in odds was detected between suffering from FMF and being hospitalized in our center due to COVID-19 (p=0.73) (Figure 1). We then sought to characterize the disease course in FMF patients and to detect any differences between FMF patients and a matched COVID-19 inpatient cohort.

Twelve FMF patients were hospitalized in the Hadassah COVID-19 wards in the relevant period; 9 patient from the cohort and 3 additional patients from other HMOs. Twenty- four non-FMF COVID-19 inpatients matched as best possible were used as a control cohort. The groups were similar in age, gender, ethnicity, and major comorbidities. All patients were hospitalized between June of 2020 and March of 2021. Most patients (26/36, 72%) were hospitalized in the 6 months between August 2020 and January 2021. The diagnosis of amyloidosis was more prevalent in the FMF group, as expected. Table 1A summarizes the baseline characteristics of the two cohorts.

Both cohorts were assessed for the prevalence of fever and respiratory symptoms (including cough and shortness of breath) during the disease, length

of stay, the presence or absence of pulmonary infiltrates on imaging, treatment for COVID-19 with dexamethasone or an equivalent steroid dose or antiviral therapies, degree of oxygen support, and mortality (Table 1B). No differences were apparent in terms of the odds of respiratory symptoms (Odds ratio (OR) 1.2, p= 0.73), fever (OR 1.7, p=0.86), infiltrates on imaging (OR 1.6, p= 0.67), need for oxygen support (OR 0.6, p= 0.36), and need for augmented oxygen supply (≥ 5 liters/min) (OR 3.7, p= 0.97). Furthermore, there was no statistically significant difference in the need for corticosteroids (OR 2.3, p= 0.94) and antivirals (OR 0.6, p=0.46), or in the duration of hospital stay (5 days vs 7 days, p= 0.65) between the two groups.

Of all patients treated with COVID-19 specific medications, one patient from the FMF group and four patients from the control group were treated with Remdesivir. One patient from each group was treated with Favipiravir. One control patient was treated with Bamlanivimab.

3 patients in the FMF group were being concurrently treated with anti-cytokine medications, 2 with Adalimumab and 1 with Anakinra. No patients in the control group were under anti-cytokine treatment at admission.

## Discussion

Analysis of COVID-19 disease mechanisms suggests a central role for the hyper-activation of the innate immune system in patients, with sinister outcomes[11]. Theoretically, colchicine, by targeting intersecting pathways in the SARS-CoV-2-induced inflammatory cascade, may reduce COVID-19 hospitalization and mortality[6]. Ongoing prospective clinical studies aim to evaluate efficacy of the drug in COVID-19[7].

Preliminary results of the COLCORONA study suggest that colchicine reduces the composite rate of death or hospitalization among non-hospitalized patients with COVID-19[12]. In a randomised double-blinded, placebo-controlled clinical trial, the addition of colchicine to the standard of care (SOC) in moderate-severe COVID-19 patients resulted in a reduced length of supplemental oxygen therapy and hospitalisation[8]. Furthermore, an Italian study compared 122

hospitalized patients who received colchicine plus SOC with 140 hospitalized patients receiving SOC alone. The former group had a significantly better survival rate[13]. Finally, the GREECO-19 study, a prospective, randomized, open label, controlled study, suggested through its preliminary results that COVID-19 patients receiving colchicine on top of SOC had a longer time to clinical deterioration, with no major differences in C-reactive protein and high-sensitivity cardiac troponin levels[9].

Colchicine has also been suggested to protect against the acquisition of SARS-CoV-2 infection, but this has not been adequately demonstrated. In a large retrospective study, Gendelman et al. were unable to demonstrate COVID-19 prevention by colchicine[14]. Moreover, Bourguiba et al conducted a survey regarding SARS-CoV-2 infection in a cohort of 342 FMF patients receiving long-term colchicine in a French endemic area. Overall, 27 FMF patients (7.8%) contracted COVID-19. All but one of the FMF COVID-19 patients were taking daily colchicine, and four were receiving an IL-1 inhibitor. Seven of the 27 (25.9%) COVID-19 patients were admitted to the hospital, and six (22.2%) required oxygen therapy. The risk of severe or life-threatening COVID-19 in this

cohort was similar to that of the general population. Severe disease was mainly present in those with comorbidities[15]. It is worth mentioning that anakinra (IL-1 receptor antagonist), a drug commonly used in resistant FMF, was found to reduce both the need for invasive ventilation and mortality among patients with severe COVID-19[16].

In a previous study, it was shown by Park et al that FMF patients had genetic advantages in Yersinia infection[2] . Stella et al proposed that Pyrin may have evolved to combat pathogens, including viral infections[1] . Whether these speculations are practically relevant to COVID-19 remains a matter of debate.

Our cohort was composed of a unique Arab and Jewish population and drawn from the 2 biggest HMOs in the Jerusalem area, serving over 750,000 persons. We found no statistically significant difference in the odds of hospitalization for COVID-19 between FMF patients and the non-FMF population. We also found a similar disease course between FMF COVID-19 inpatients and well-matched COVID-19 hospitalized controls.

All of the FMF inpatients in our cohort, except for one, were adherent to colchicine therapy. This was confirmed through a combination of direct questioning and revision of the documented recent purchases from the pharmacies.

It is noteworthy that almost all (14/15) of the severe COVID-19 patients (FMF and control inpatients) had at least one comorbidity, including hypertension, diabetes mellitus, chronic renal failure, and kidney transplantation. The only mortality case in our cohort occurred in an FMF COVID-19 kidney transplant patient with multiple comorbidities, receiving anakinra in addition to colchicine. Four patients, two from each group, contracted severe COVID-19 at least 2 weeks after receiving the second dose of the Pfizer BNT162b2 mRNA vaccine; all of these were patients who had received a kidney transplant and were taking immunosuppressive medications. This is in line with studies suggesting diminished vaccine-induced protection in immunosuppressed patients and organ transplantees[17-19].

Our results suggest that neither a background FMF, nor baseline colchicine therapy provide protection against COVID-19 infection or hospitalization. The disease course, in terms of severity and treatment, was similar in FMF inpatients when compared to age, sex, ethnicity, and comorbidity-matched non-FMF COVID-19 inpatients.

It is interesting to note that while comorbidities and chronic immunosuppression were relatively common in our cohort, a protracted, life-threatening disease course was rare.

Our study has several limitations. Firstly, the number of FMF COVID-19 inpatients in our tertiary care center during the study period was low; this is due to the fact that FMF is a relatively rare disease. Secondly, the disease course was charted only for hospitalized FMF patients and may not necessarily be generalizable to outpatients. Our relatively youthful cohort may also not be indicative of the disease course in more elderly patients. Finally, we had access to only two of the four large Israeli HMOs. While these represent a majority of

the patients in the Jerusalem area, resultant skewing of the patient population may have occurred.

Still, our work remains one of a few studies evaluating COVID-19 prevalence and course in an FMF population in an endemic area. Further studies are required to better define the interaction between COVID-19, FMF, and colchicine.

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## Figures

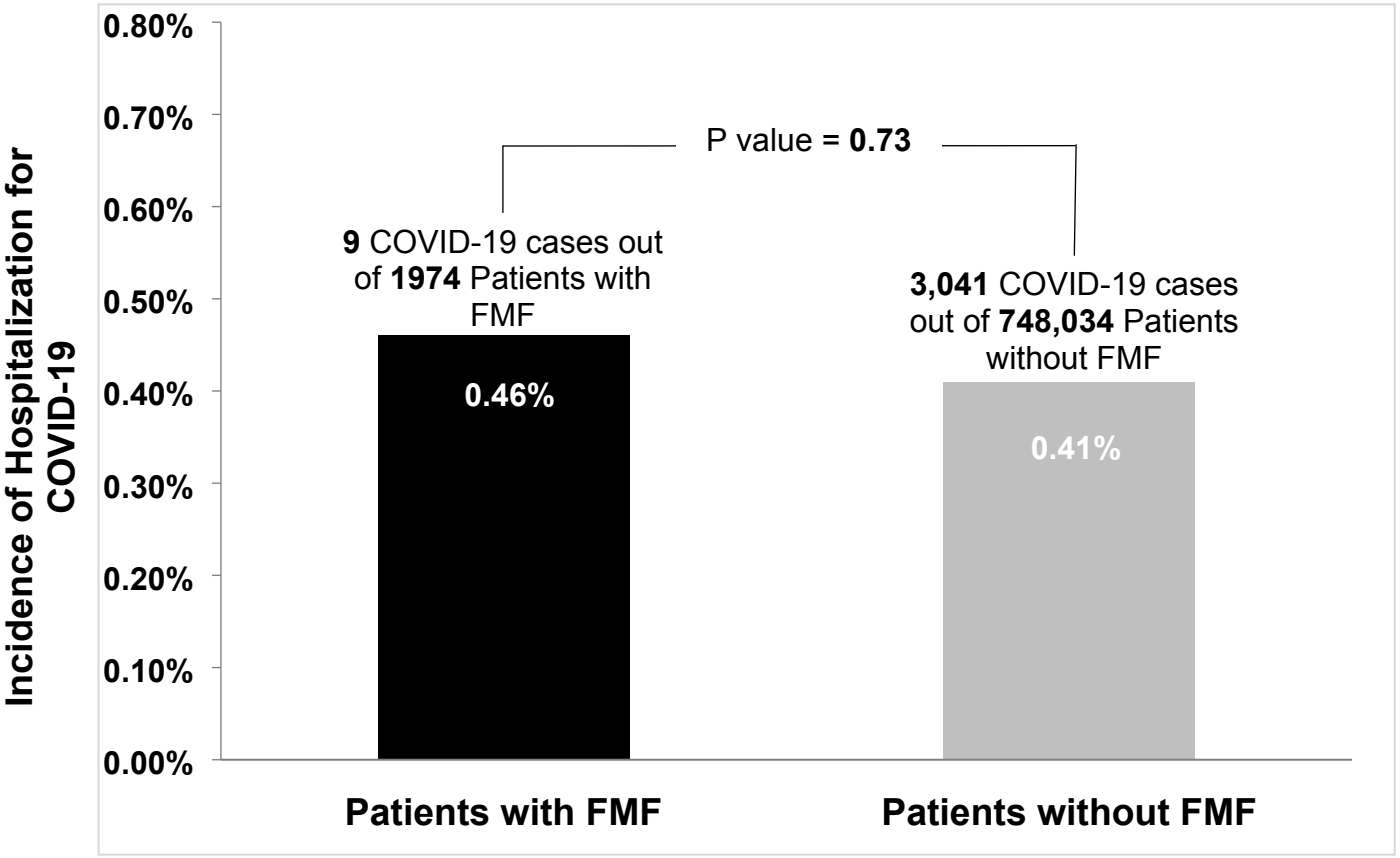


**Figure 1: Incidence of hospitalization for COVID-19 among patients with and without FMF**. The data was obtained from two HMOs and covered 750,008 insured patients in the Jerusalem district.

**Abbreviations:** COVID-19, coronavirus disease 2019; FMF, familial Mediterranean fever; HMO, health management organization.

| | | |
|---|---|---|
| **Age groups (years)** | | |
| 15 – 35 | 3 (25.0) | 3 (12.5) |
| 36 – 55 | 5 (41.7) | 13 (54.2) |
| 56 – 75 | 4 (33.3) | 8 (33.3) |
| **Sex** | | |
| Female | 2 (16.7) | 6 (25.0) |
| Male | 10 (83.3) | 18 (75.0) |
| **Underlying medical conditions** | | |
| Ischemic heart disease | 1 (8.3) | 2 (8.3) |
| Hypertension | 2 (12.5) | 8 (33.3) |
| Diabetes mellitus | 4 (33.3) | 6 (25.0) |
| Chronic lung disease | 0 (0.0) | 1 (4.2) |
| Chronic kidney disease | 6 (50.0) | 12 (50.0) |
| Renal transplantation | 5 (41.7) | 10 (41.7) |
| Chronic liver disease | 1 (8.3) | 3 (12.5) |
| **Colchicine treatment** | 11 (91.7) | 0 (0.0) |

Table 1A: Basic characteristics of FMF patients vs. Matched control patients.

Abbreviation: FMF: Familial Mediterranean fever

| Parameter | N (%) FMF (N=12) | Control (N=24) | OR (95% CI) | p Value |
|---|---|---|---|---|
| Fever | 8 (66.7) | 13 (54.2) | 1.7 (0.4, 7.2) | 0.86 |
| Respiratory Symptoms | 8 (66.7) | 15 (62.5) | 1.2 (0.3, 5.2) | 0.73 |
| Pulmonary infiltrates [a] | 3 (25.0) | 4 (17.4) | 1.6 (0.3, 8.6) | 0.67 |
| Dexamethasone | 7 (58.3) | 9 (37.5) | 2.3 (0.6, 9.6) | 0.94 |
| Antiviral therapy | 2 (16.7) | 6 (25.0) | 0.6 (0.1, 3.5) | 0.46 |
| Any oxygen support | 4 (33.3) | 11 (45.8) | 0.6 (0.1, 2.5) | 0.36 |
| Significant oxygen support [b] | 3 (25.0) | 2 (8.3) | 3.7 (0.5, 25.8) | 0.97 |
| Mechanical ventilation | 1 (8.3) | 0 (0.0) | - | - |
| Mortality | 1 (8.3) | 0 (0.0) | - | - |
| | **Median (range)** | | | |
| Length of Stay (days) | 7 (2,12) | 5 (1,13) | - | 0.65 |

[a] Either on Chest X-ray or on computed tomography scan, [b] Includes either face mask with or without reservoir, high-flow nasal cannula or non-invasive ventilation.

**Table 1B: Clinical presentation, required treatment and outcomes of COVID-19 in patients with FMF vs. Matched controls.**

**Abbreviations:** CI, confidence interval; FMF, familial Mediterranean fever; OR, odds ratio.