Prevalence, incidence and geographic distribution of familial Mediterranean fever in Turkey: a national cohort study

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Abstract

Objective

This study aimed to analyse the incidence and geographical distribution of Familial Mediterranean Fever (FMF) in Turkey using the electronic medical records database (e-Pulse) of the Ministry of Health.

Method

The study utilised nationwide health data from the e-Pulse, which has been operational since 2016. Patient selection was based on ICD-10 codes for FMF, with a minimum of two recorded codes entered at least 30 days apart. Patients aged ≥50 and those with gout-related ICD-10 codes were excluded. The prevalence and incidence of FMF in 2018 were calculated, taking into account gender, age demographics, and regional distribution.

Results

A total of 160,897 FMF patients were identified from a population of 82,003,882, yielding a prevalence of 139 per 10,000 individuals. The incidence was 2.78 per 10,000. The highest number of records was found among individuals aged 15-19. Geographically, the highest rate of prevalence was found in Ardahan, Bayburt, and Sivas, regions in the North-Eastern part of Turkey. Family records revealed that 11.7% of children under 18 with FMF had at least one parent diagnosed with FMF.

Conclusion

FMF is beyond the definition of a rare disease and a significant health issue in Turkey, with a non-uniform distribution influenced by both genetic and historical factors. The findings of this study highlight the utility of national electronic health records like e-Pulse in conducting large-scale epidemiological research, which could guide future public health strategies for FMF patients.

Key words

familial Mediterranean fever, prevalence, incidence, nationwide study, electronic health records

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Introduction

Familial Mediterranean fever (FMF) is an autosomal recessively inherited autoinflammatory disorder predominantly affecting populations in the Eastern Mediterranean region, including Turks, Armenians, Jews, and North African Arabs, and it is characterised by recurrent episodes of fever and serositis. FMF is caused by mutations in the *MEFV* gene, which encodes the pyrin protein (1). Pyrin is a component of the multiprotein inflammasome complex, which is involved in the proteolytic activation of caspase 1 and then leads to inflammatory attacks through the activation of interleukin-1 beta (IL-1β), and mutations in its carboxy-terminal SPRY domain results in the FMF phenotype associated with increased IL-1β production. Despite its well-documented clinical manifestations and genetic underpinnings, there remains a paucity of comprehensive epidemiological data, particularly concerning the incidence, overall prevalence, and geographical distribution of FMF within Turkey.

The existing literature on FMF has extensively reported its prevalence in various ethnic groups and regions (2-5). A previous field survey study conducted in 46,813 children indicated that the prevalence of FMF in Turkey is approximately 1:1000 (6) with over 100,000 affected individuals, making it one of the countries with the highest number of FMF patients globally. The frequency of FMF patients varies across different regions of Turkey, with higher rates observed in Central and North-Eastern Anatolia, as well as the Black Sea region, while lower rates are reported in the Thrace region (7-12). This suggests underlying genetic diversity and variability of carrier rates in different regions of Turkey. Similar patterns of non-uniform patient distribution are noted in Italy, where FMF is more common in the Southern regions, particularly in Sicily, Calabria, and Apulia, and less frequent in the Northern areas (13). This variation is attributed to the historical migrations and settlements by Greeks, Jews, Christians, Türks, and Arabs in these regions (13). However, no study to date has systematically examined whether FMF is evenly distributed across Turkey for comparative purposes. Additionally, there is a significant gap in national data regarding the incidence rate of FMF patients within Turkey.

The introduction of the e-Pulse electronic health records system by the Ministry of Health in Turkey in 2014 has revolutionized the storage and accessibility of health-related data (14). This comprehensive digital repository presents a unique opportunity to conduct large-scale epidemiological studies. This study aimed to utilize e-Pulse data to examine the prevalence, incidence, and geographical distribution of FMF in Turkey, providing robust national data that can inform healthcare professionals about developing better public health strategies and resource allocation. This study also aimed to compare the current findings with the previous prevalence data to offer a comprehensive overview of FMF's epidemiology both in Turkey and worldwide.

Methods

Turkish Ministry of Health National Electronic Heath Records Database

This nationwide cohort study utilised data from the Turkish Ministry of Health National Electronic Health Records Database, e-Pulse. Since 2014, the Ministry of Health has implemented comprehensive health data depositories that cover the entire country. In 2015, the Ministry established the "e-Pulse" system as a national health records information system, accessible only to authorised individuals and institutions. This system, boasting extensive bandwidth, encompasses the entirety of the country. Turkey operates under a universal system named General Health Insurance (GHI), granting all residents access to medical services without charge through the Social Security Institution (SSI). Therefore, all study data were sourced from the central national database mentioned earlier, overseen by the Turkish Ministry of Health, which employs big data technology to deliver services, with integrated systems such as e-Pulse and the National Healthcare Information System (NHIS). The e-Pulse system

contains clinical records for more than eighty million individuals in Turkey, encompassing demographic details, laboratory results, drug history, and comorbidities. This study was conducted according to the Declaration of Helsinki, and the Ministry of Health Ethical Board approved the study protocol (95741342-020/27112019).

Patient selection

The e-Pulse system has been in use throughout the country since 2016. For the calculation of the prevalence and incidence of FMF, the records of 2018 were taken as the basis, and the accumulated patient load from 2016 and 2017 was removed. A two-stage method was used for the definition of the patients with FMF. In the first stage, individuals who had an ICD 10 code associated with FMF ('E85', 'E85.0', 'E85.1', 'E85.2', 'E85.3', 'E85.4', 'E85.8', 'M85.9') were screened. In the second stage, to prevent a possible incorrect evaluation, those entered twice with at least 30 days of interval were taken and those entered simultaneously with the diagnosis of gout crystal arthropathy, (an ICD- 10 codes of M10.0, M10.1, M10.2 M10.3, M10.4, M10.5, and M10.9) which is especially prevalent in people over the age of 50, as we frequently encounter in clinical practice, were removed in case of a possible incorrect diagnosis.

Calculation of the prevalence and incidence

The number of FMF cases between 1 January 2018 and 31 December 2018 was divided by the number of people residing in the country in the same period was used for the prediction of the disease prevalence.

For the calculation of the incidence rate of FMF, the number of new FMF cases between 1 January 2018 and 31 December 2018 was divided by the number of people residing in the country in the same period. The prevalence and incidence rates of FMF were also analysed for gender and age demographics. Furthermore, the geographical distribution of FMF cases across provinces and regions of Turkey was also assessed.

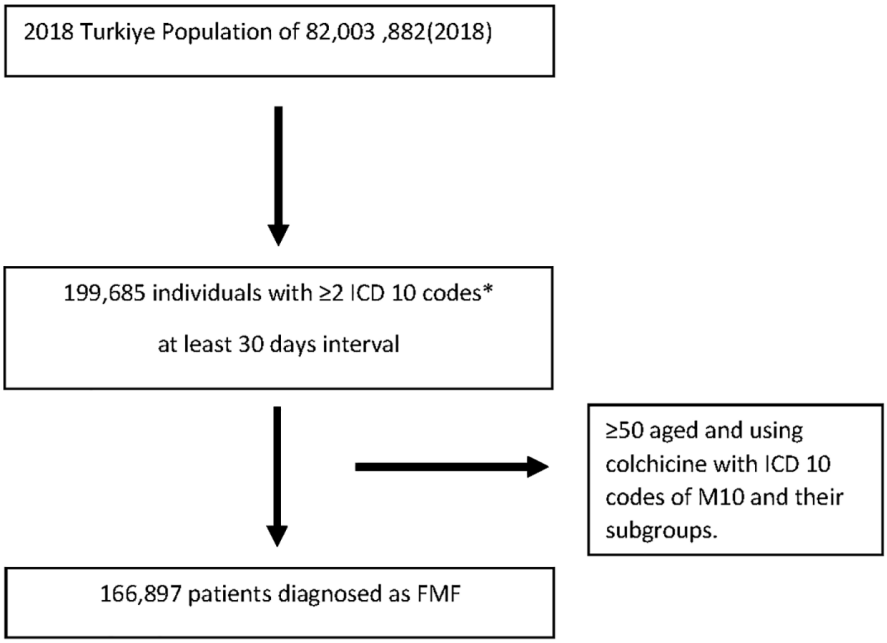

Fig. 1. Flow chart of study design.
*ICD 10 codes include 'E85', 'E85.0', 'E85.1', 'E85.2', 'E85.3', 'E85.4', 'E85.8', 'M85.9'.

Statistical analyses

Statistical analyses were performed with IBM SPSS Statistics v23.0. The population at risk for 2018 was obtained from the Turkish Statistical Institute's address-based Population Registration System. The number of cases between 1 January 2018 and 31 December 2018, as well as the number of newly diagnosed FMF patients between 1 January 2018 and 31 December 2018, were obtained from the e-Pulse database. The quantitative variables were summarised using means and standard deviations, while categorical variables were expressed as frequencies and percentages. The prevalence and incidence rates were calculated per 10,000 individuals, stratified by gender and age groups. Additionally, the geographic distribution of FMF cases was analysed using population-based rates across different provinces.

Results

Identification of the patients with FMF

As of 2018, Turkey's population stands at 82,003,882. Among this population, 199,685 individuals have had at least two ICD-10 codes entered with a 30-day interval for FMF, representing approximately 0,24% of the population. Of these individuals, those patients aged ≥50 and using colchicine and with e-Pulse entries using the ICD-10 codes of M10 and their subgroups were excluded. The remaining 160,897 were accepted as the number of FMF patients in Turkey (Fig. 1). 88,631 of them female (55.1%) and the mean age of the population was 30.7±20.1. There were 67,976 (42.2%) individuals in the paediatric group and 3,889 (2.4%) individuals in the geriatric group. The remaining 89,032 individuals were between the ages of 18 and 64.

Family characteristics

In order to minimise the possibility of missing information about the disease, the family characteristics defined as the current FMF status of the mothers and fathers of individuals were investigated only in the subgroup of patients aged <18. In the analyses performed, 0.9% of the individuals under the age of 18 with FMF had both mothers and fathers diagnosed with FMF. 3.7% had only the father with FMF, while 7.1% had only the mother. For the remaining 88.3% of the parents, there was no e-Pulse entry for FMF.

FMF prevalence

As of 2018, the prevalence rate of FMF was determined to be 139 per 10,000 individuals. Among females, the prevalence was notably higher at 155 per

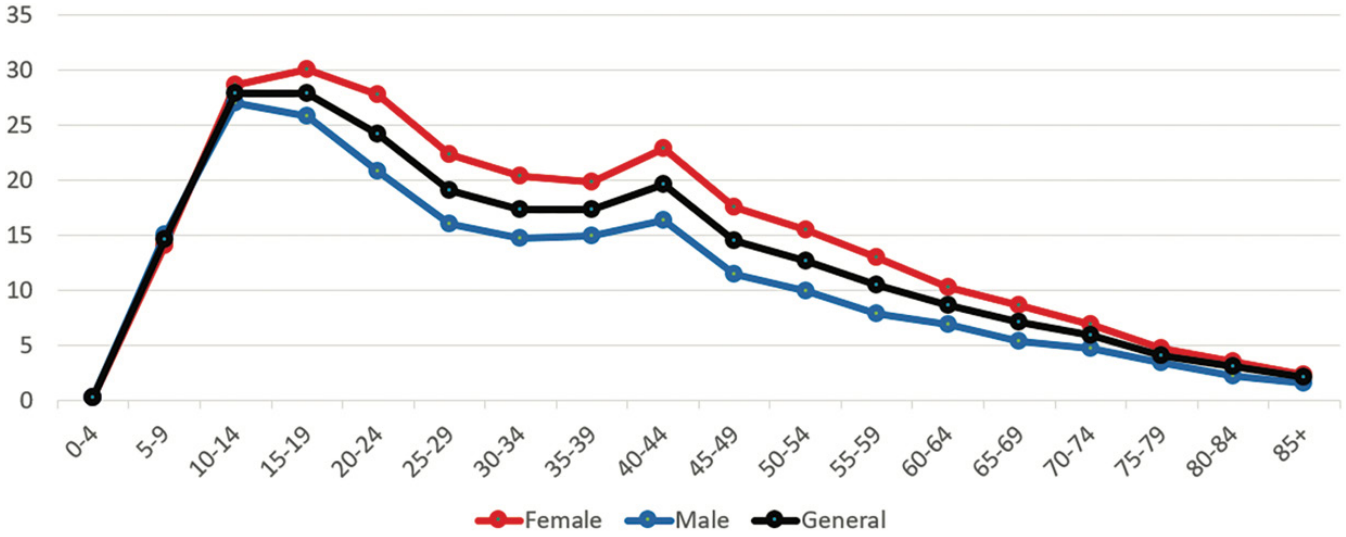

Fig. 2a. Prevalence (../10.000) of FMF patients in terms of age and sex.

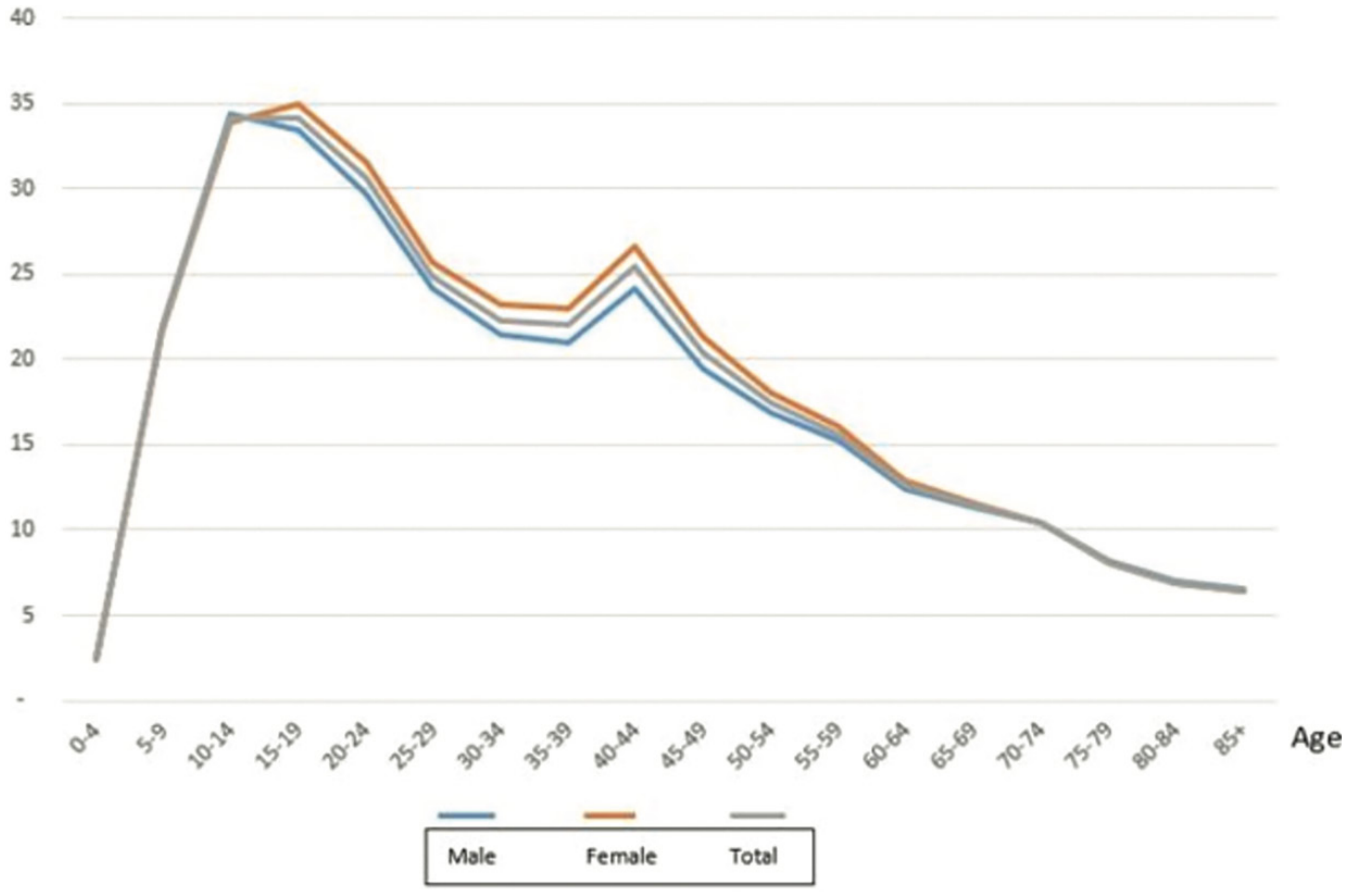

Fig. 2b. Prevalence (../10.000) of FMF patients in terms of age and sex, after being corrected according to the number of individuals applying to the health care facilities.

10,000 patients, while among males, it was lower at 123 per 10,000. Furthermore, the recorded prevalence of FMF peaked within the age range of 15-19 years, which is more prevalent in females within this age group (Fig. 2a). When the prevalence rate was corrected according to the number of individuals applying to the health care facilities, the difference in the prevalence rates between men and women disappeared (Fig. 2b). Based on the number of individuals with FMF per 100,000 people, the most common places of birth for individuals with FMF were Ardahan, Bayburt, and Sivas, respectively. Considering the frequent internal migration within Turkey, the birthplaces of the mothers and fathers of these individuals (independent of their FMF status) were also examined. The numbers of

the patients decreased in the 3 largest cities and the West of Turkey, but there was no change in the ranking of the most prevalent cities for FMF.

FMF incidence

As of 2018, the incidence rate of FMF was identified as 2,78 per 10,000 individuals. Among females, the incidence rate was notably higher at 3,05 per 10,000 individuals, whereas among males, it was lower at 2.52 per 10,000 individuals.

Discussion

FMF is the most common form of the monogenic autoinflammatory disorders, and it is prevalent in Eastern Mediterranean countries. The prevalence rates in this part of the world vary depending on the method and sample size used. In this study, we aimed to use nationwide electronic health records of Turkey, namely e-Pulse, for the prediction of the prevalence and incidence of FMF in Turkey. To improve the accuracy of data, we applied different methods including having at least two entries with 30-day intervals using the ICD-10 codes of FMF, and excluding those patients who were 50 years or older, those with entries using ICD-10 codes of gout (M10 and its subcategories) and using colchicine. Using these records, the prevalence of FMF was estimated to be 139/10,000 individuals, with a gender-specific distribution, of 155/10,000 for females and 123/10,000 for males.

Joint attacks manifesting as red arthritis in FMF may be misdiagnosed as gout by less experienced clinicians, particularly in patients over 50 years of age (15). Thus, those patients aged >50 and using colchicine with the diagnosis of gout (ICD-1O categories of M10 and subcategories) were excluded from this study to mitigate potential confounding factors and thus improve its reliability. The inclusion of these patients would have resulted in a cohort size of 199,685, which would have resulted in an estimated FMF prevalence of approximately 172/10,000.

FMF manifestations usually start during childhood, but it may be diagnosed in different age groups with some delays depending on the awareness among the physicians. This study revealed a significant increase in the prevalence between the ages of 14 and 19, with a similar distribution among men and women, which is compatible with the age of onset and age at the diagnosis of FMF. In paediatric cohorts, the diagnosis of FMF is typically established before the age of 10 years (16, 17). This is because FMF is a monogenic disease that presents in childhood, especially if associated with the severe exon 10 mutations.

The frequency of FMF cases in specific regions has been identified by previous studies investigating the prevalence of FMF in Turkey, particularly in the Eastern Anatolian Region and the Central Black Sea Region (7-11, 18). The number of FMF patients originating from these areas has also increased in our study. FMF patients' birthplaces were mainly located in a geographic area that extends from Ardahan in the East to Sivas in the West, and further North to Sinop and Kastamonu, where a high density of FMF cases' birthplaces were noted. In particular regions, like the Lakes Region, the Inner Aegean Region, and the area surrounding Bitlis, there were measurable increases, compared to other areas. The observed distribution pattern may be explained not only by the genetic characteristics of individuals in these regions but also by historical factors, for instance, the abundance of trade routes in these regions might have made it easy for different ethnic groups to interact. These interactions, along with some currently unknown environmental factors, might have contributed to the geographical distribution of FMF. Supporting this hypothesis, a study conducted in Italy reported a higher prevalence of FMF in the Southern regions of the country, historically characterised by greater military and commercial interactions with other nations, compared to the Northern regions (13). Further research into the geographical distribution of FMF is warranted to elucidate the underlying mechanisms of disease spread, including genetic transmission patterns and potential environmental factors that may influence the expression of the manifestation of FMF.

The limitations of this study are attributable to both the inherent characteristics of the dataset and methodological constraints. Relying on national electronic health records systems requires dependence on the accuracy and consistency of disease classification, with analyses primarily based on the precision of ICD-10 coding. However, the ICD-10 coding system is vulnerable to errors such as misdiagnosis or underdiagnosis in clinical settings, which presents a significant challenge. Several unclassified autoinflammatory syndromes or heterozygote MEFV variant carriers with PFAPA syndrome may have been registered as FMF using the same ICD-10 by physicians. Moreover, this study does not account for patients who have received an FMF diagnosis but remain unreported in the dataset. These factors highlight the need for caution when interpreting the study's findings, as regional variations in healthcare access may significantly impact the reported data. The strong aspect of the study is that it is the first national study conducted in Turkey, where the highest number of FMF patients are found, and that it contains data that can shed light on issues such as the historical spread of the disease and genetic transmission.

In conclusion, this nationwide incidence and prevalence study for FMF is expected to provide data for planning national health policies, which may include allocation of sources depending on the prevalence of the disease within Turkey. It is also expected to be a source for analysis of the historical spread of the disease, including the heterozygous advantage against certain infectious diseases including plague. A recent study has identified the advantage of MEFV carriers to be increased resistance to plague (19). Historical analysis may help explain the geographical differences in the prevalence of FMF in Anatolia as well.

Take home messages

- FMF has shown significant regional variability.
- The prevalence of FMF in Turkey is 139 per 10,000 individuals.

- The use of electronic health records demonstrates its utility for large-scale epidemiological studies.
- There is a need for tailored public health strategies and resource allocation in FMF-endemic regions.

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