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MEFV Genetic Variants and Acute Abdominal Presentations in Adults Undergoing Genetic Testing for Familial Mediterranean Fever: A Retrospective Single-Center Study

İbrahim Çakır

opdricakir@gmail.com

University of Health Sciences

Turan Pehlivan

University of Health Sciences

Leyli Şentürk

University of Health Sciences

Erkan Yavuz

University of Health Sciences

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Abstract

Background

Familial Mediterranean fever (FMF) is an inherited autoinflammatory disease characterized by recurrent attacks of fever and serosal inflammation. The relationship between *MEFV* genetic characteristics and acute abdominal outcomes remains incompletely defined. This study aimed to evaluate the associations between *MEFV* variants and emergency department presentations, abdominal computed tomography (CT) abnormalities, and surgical intervention in adults with detected MEFV variants.

Methods

This retrospective single-center study included 171 adults with at least one detected MEFV variant who underwent MEFV testing between January 1, 2021 and December 31, 2024. Demographic characteristics, *MEFV* variant number and type, zygosity, ACMG classification, emergency department presentations for abdominal pain, abdominal CT findings, and surgical intervention were retrospectively assessed. Group comparisons used parametric, nonparametric, and exact tests as appropriate ($p < 0.05$).

Results

Among 171 patients, 66.7% were female; mean age was 37.99 ± 14.13 years. One *MEFV* variant was detected in 129 patients (75.4%), two variants in 41 (24.0%), and four variants in one patient (0.6%). M694V was the most frequent single variant. Sixty-five patients (38.0%) presented to the emergency department with abdominal pain during the study period. Fourteen patients (8.2%) had abdominal CT abnormalities. All patients with CT abnormalities presented to the emergency department, versus 32.5% of those without ($p = 0.001$). Surgical intervention was performed in four patients (2.3%). Surgery was more frequent with CT abnormalities (14.3% vs 1.3%; $p = 0.025$). All four patients who underwent surgery had an emergency department presentation ($p = 0.005$), and the number of emergency department visits was higher in the surgical group ($p = 0.028$). Specific *MEFV* variants were not significantly associated with emergency department presentation or surgical intervention.

Conclusions

Specific *MEFV* variants and the number of detected variants were not significantly associated with emergency department utilization or surgical intervention in this cohort. In contrast, abdominal CT abnormalities were associated with emergency department presentations and were associated with a higher frequency of surgical intervention. Larger prospective studies are warranted.

Background

Familial Mediterranean fever (FMF) is an inherited autoinflammatory disease characterized by recurrent, self-limited episodes of fever and serosal inflammation, most commonly involving the peritoneum, pleura, and joints. The disease predominantly affects populations originating from the Mediterranean region, including Turkish, Armenian, Arab, and Jewish populations [1–6]. The clinical manifestations of FMF are highly heterogeneous, and the frequency and severity of attacks may vary considerably among patients.

FMF is primarily associated with pathogenic variants in the *MEFV* gene, which encodes pyrin, a key component of the inflammasome pathway. The *MEFV* gene contains numerous variants with variable clinical significance [7]. Several studies have demonstrated associations between specific *MEFV* variants and clinical phenotypes, particularly the M694V variant, although genotype–phenotype relationships are not absolute and may be influenced by ethnic background, modifier genes, and environmental factors [8–11].

Acute abdominal attacks are among the most characteristic manifestations of FMF and may clinically resemble surgical emergencies such as acute appendicitis, cholecystitis, or other causes of acute abdomen. This overlap may lead to emergency surgical evaluation and, in some patients, operative intervention [12–15]. The problem is clinically important because recurrent inflammatory attacks can produce substantial emergency department utilization and repeated abdominal imaging, while distinguishing an FMF attack from a true surgical condition may be challenging during an acute presentation.

Current management recommendations emphasize colchicine as the cornerstone of FMF treatment and recommend individualized assessment of disease activity, treatment response, and complications [16, 17]. However, the relationship between specific *MEFV* genetic characteristics and acute abdominal presentations requiring emergency department evaluation or surgical assessment remains incompletely defined.

Therefore, the present study aimed to investigate the associations between *MEFV* genetic characteristics and acute abdominal clinical outcomes in adults with detected MEFV variants. We specifically evaluated the relationships of *MEFV* variant number, individual variants, zygosity, and ACMG classification with emergency department presentations for abdominal pain, abdominal CT abnormalities, and surgical intervention.

Methods

Study Design and Setting

This retrospective single-center observational study was conducted at the Medical Genetics Outpatient Clinic of Bağcılar Training and Research Hospital, University of Health Sciences, Istanbul, Türkiye.

Adult patients who underwent *MEFV* genetic testing between January 1, 2021 and December 31, 2024 were retrospectively evaluated. During this period, 239 patients aged 18–75 years underwent *MEFV* testing. Among these patients, 68 (28.5%) had no detected MEFV variant and were excluded; the remaining 171 patients, in whom at least one MEFV variant was detected, formed the study cohort (Fig. 1). Clinical FMF diagnostic criteria were not applied as an inclusion criterion; all included patients carried at least one MEFV variant.

Clinical data were obtained retrospectively from the hospital information system, medical records, and Medical Genetics outpatient clinic records. The study is reported in accordance with the STROBE guidelines for observational studies.

Patient Selection

Patients aged 18–75 years with complete clinical and genetic records were eligible for inclusion. Patients younger than 18 years or older than 75 years, deceased patients, and patients with incomplete clinical or genetic data were excluded.

Patients had been referred to the Medical Genetics outpatient clinic for various clinical indications, including unexplained arthritis, abdominal pain, chest pain, amyloid deposition, and a family history suggestive of FMF.

Genetic Analysis

MEFV variants were evaluated using either gene sequencing or targeted mutation analysis. Gene sequencing was performed in 151 patients (88.3%), whereas targeted mutation analysis was performed in 20 patients (11.7%).

The following genetic characteristics were evaluated: variant type, exon, protein change, zygosity, ACMG classification, and the number of detected variants. Patients were categorized according to the presence of one, two, or four detected variants.

Clinical Outcomes

Emergency Department Presentations

Emergency department presentations for abdominal pain occurring between January 1, 2021 and December 31, 2024 were recorded. Both the presence of an emergency department presentation and the total number of presentations were evaluated.

Abdominal CT Findings

Abdominal CT findings documented during evaluation of abdominal symptoms were recorded. Patients with abdominal CT abnormalities were identified by retrospective screening of the hospital information system; the total number of patients who underwent abdominal CT (including those with normal findings) was not recorded. CT abnormalities included findings such as acute appendicitis, enterocolitis, acute pancreatitis, intra-abdominal fluid, intra-abdominal contamination, and acute cholecystitis.

Surgical Evaluation and Intervention

Emergency surgical evaluation and actual surgical intervention were evaluated separately.

Emergency surgical evaluation was defined as assessment by the surgical team because of an acute abdominal presentation. Surgical intervention was defined as an operative procedure performed during the study period. All operations were performed after an emergency department presentation; none were elective.

Statistical Analysis

Statistical analyses were performed using NCSS 2020 Statistical Software (NCSS LLC, Kaysville, UT, USA).

Descriptive statistics included mean, standard deviation, median, minimum–maximum values, frequencies, and percentages. Normality was assessed using the Shapiro–Wilk test and boxplot evaluation. Normally distributed continuous variables were compared using Student's *t* test, whereas non-normally distributed variables were compared using the Mann–Whitney *U* test. Categorical variables were compared using Pearson's chi-square test, Fisher's exact test, or Fisher–Freeman–Halton test, as appropriate. A p value < 0.05 was considered statistically significant. No adjustment for multiple comparisons was made; the analyses are therefore exploratory. Individual variants (in single-variant patients) and the three most frequent two-variant combinations were each compared with all remaining patients in the same group; Pearson’s chi-square test was used when all expected counts were ≥ 5 and Fisher’s exact test otherwise.

Ethics

The study was approved by the Bağcılar Training and Research Hospital Non-Interventional Clinical Research Ethics Committee on October 22, 2024 (decision no. 2024/10/03/081). The study was also reviewed and approved by the Education and Planning Board of the University of Health Sciences Bağcılar Health Application and Research Center on October 4, 2024. All patients had signed the hospital’s general consent form at presentation. The institutional ethics committee confirmed that this general consent was sufficient for the retrospective use of clinical and genetic data in the present study. The study was conducted in accordance with the Declaration of Helsinki.

Results

Patient Characteristics

A total of 171 patients were included. The cohort consisted of 114 women (66.7%) and 57 men (33.3%). The mean age was 37.99 ± 14.13 years, with a median age of 37 years (range, 18–75 years) (Table 1).

Table 1
Demographic, genetic, and clinical characteristics of the study cohort (n = 171)

Characteristic	Statistic	Value
Age, years	Mean ± SD	37.99 ± 14.13
Age, years	Median (range)	37 (18–75)
Female sex	n (%)	114 (66.7)
Male sex	n (%)	57 (33.3)
One detected MEFV variant	n (%)	129 (75.4)
Two detected MEFV variants	n (%)	41 (24.0)
Four detected MEFV variants	n (%)	1 (0.6)
ED presentation for abdominal pain	n (%)	65 (38.0)
ED visits	Mean ± SD	3.03 ± 2.96
ED visits	Median (range)	2 (1–22)
Abdominal CT abnormalities	n (%)	14 (8.2)
No CT abnormality	n (%)	157 (91.8)
Surgical intervention	n (%)	4 (2.3)
No surgical intervention	n (%)	167 (97.7)

One *MEFV* variant was detected in 129 patients (75.4%), two variants in 41 patients (24.0%), and four variants in one patient (0.6%).

Abdominal CT abnormalities were documented in 14 patients (8.2%), whereas 157 patients (91.8%) had no documented CT abnormality (normal CT or no CT performed).

Sixty-five patients (38.0%) had at least one emergency department presentation for abdominal pain during the study period, whereas 106 patients (62.0%) did not. The mean number of emergency department visits was 3.03 ± 2.96, with a median of 2 (range, 1–22).

Four patients (2.3%) underwent surgical intervention, whereas 167 (97.7%) did not.

MEFV Genetic Characteristics

M694V was the most frequent single *MEFV* variant, followed by R202Q, E148Q, V726A, and other less frequent variants (Table 3).

Among patients with two detected variants, M694V + R202Q was the most frequent combination (12 of 41 patients; Table 3).

Emergency Department Presentations and CT Findings

A significant association was observed between abdominal CT abnormalities and emergency department presentation.

All 14 patients with CT abnormalities had presented to the emergency department with abdominal pain. Among the 157 patients without CT abnormalities, 51 (32.5%) had an emergency department presentation, whereas 106 (67.5%) had no emergency department presentation (p = 0.001) (Table 2).

Table 2
Associations between CT findings, emergency department presentation, and surgical intervention

Comparison	Outcome	Group 1	Group 2	p value
CT abnormality vs no CT abnormality	ED presentation	14/14 (100%)	51/157 (32.5%)	0.001
CT abnormality vs no CT abnormality	No ED presentation	0/14 (0%)	106/157 (67.5%)	—
Surgery by CT status	Surgery performed	2/14 (14.3%)	2/157 (1.3%)	0.025
Surgery by CT status	No surgery	12/14 (85.7%)	155/157 (98.7%)	—
ED presentation by surgery status	ED presentation	4/4 (100%)	61/167 (36.5%)	0.005
ED presentation by surgery status	No ED presentation	0/4 (0%)	106/167 (63.5%)	—
ED visits by surgery status	Mean ± SD	4.50 ± 1.29	2.93 ± 3.02	0.028
ED visits by surgery status	Median (range)	4.5 (3–6)	2 (1–22)	—
Single-variant subgroup by CT status	Pathogenic classification	82/117 (70.1%)	4/12 (33.3%)	0.020
Single-variant subgroup by CT status	VUS classification	35/117 (29.9%)	8/12 (66.7%)	—

Table 3
Distribution of MEFV variants in the study cohort

Genotype / variant	Protein change	cDNA	n (%)
Single variant (n = 129)			
M694V	p.Met694Val	c.2080A > G	45 (34.9)
R202Q	p.Arg202Gln	c.605G > A	23 (17.8)
E148Q	p.Glu148Gln	c.442G > C	21 (16.3)
M680I	p.Met680Ile	c.2040G > C	16 (12.4)
V726A	p.Val726Ala	c.2177T > C	12 (9.3)
A744S	p.Ala744Ser	c.2230G > T	6 (4.7)
Other*			6 (4.7)
Two variants (n = 41)			
M694V + R202Q			12 (29.3)
E148Q + R202Q			7 (17.1)
V726A + R202Q			3 (7.3)
M694V + V726A			3 (7.3)
Other combinations			16 (39.0)
Four variants (n = 1)			
p.Ala457Val, p.Arg408Gln, p.Pro369Ser, p.Glu148Gln			1 (100)

*Other single variants: p.Lys695Arg (n = 2), p.Met694Ile, p.Arg761His, p.Gly304Arg, and p.Asp510Asn (n = 1 each).

Surgical Intervention and Emergency Surgical Evaluation

Four patients underwent surgical intervention during the study period.

Among the 14 patients with CT abnormalities, 12 underwent emergency surgical evaluation, whereas 2 ultimately underwent surgical intervention.

Surgical intervention occurred in 2 of 14 patients (14.3%) with CT abnormalities and in 2 of 157 patients (1.3%) without CT abnormalities ($p = 0.025$).

The four surgical procedures consisted of two appendectomies, one cholecystectomy, and one oophorectomy. All four were emergency operations performed after an emergency department presentation.

MEFV Variant Number and Clinical Findings

The number of detected *MEFV* variants was not significantly associated with emergency department presentation or surgical intervention (p = 0.299 and p = 0.263, respectively; Table 4).

Table 4
Number of detected MEFV variants and clinical outcomes

Outcome, n (%)	One variant (n = 129)	Two variants (n = 41)	Four variants (n = 1)	p value
CT abnormality	12 (9.3)	1 (2.4)	1 (100)	0.021a; 0.193b
ED presentation	51 (39.5)	13 (31.7)	1 (100)	0.299a
Surgical intervention	2 (1.6)	2 (4.9)	0 (0)	0.263a

ED, emergency department. aFisher–Freeman–Halton test across the three groups. bFisher's exact test, one versus two variants.

The number of detected variants differed significantly across the three groups with respect to CT abnormalities (Fisher–Freeman–Halton p = 0.021; Table 4); however, the difference between patients with one and two variants was not significant (12 of 129 [9.3%] vs 1 of 41 [2.4%]; p = 0.193). However, the subgroup with four detected variants consisted of only one patient.

Specific MEFV Variants and Emergency Department Presentation

No statistically significant association was identified between the major individual *MEFV* variants and emergency department presentation (Table 5).

Table 5
Individual MEFV variants and clinical outcomes in patients with a single detected variant

Variant	n	CT abnormality, n (%)	p	ED presentation, n (%)	p	Surgery, n (%)	p
M694V	45	4 (8.9)	1.000	19 (42.2)	0.648	2 (4.4)	0.120
R202Q	23	5 (21.7)	0.039	11 (47.8)	0.370	0 (0)	1.000
E148Q	21	3 (14.3)	0.412	10 (47.6)	0.408	0 (0)	1.000
M680I	16	0 (0)	0.360	3 (18.8)	0.069	0 (0)	1.000
V726A	12	0 (0)	0.602	4 (33.3)	0.763	0 (0)	1.000
A744S	6	0 (0)	1.000	2 (33.3)	1.000	0 (0)	1.000
Other	6	0 (0)	1.000	2 (33.3)	1.000	0 (0)	1.000

Single-variant patients (n = 129). Each variant was compared with all other single-variant patients; Pearson's chi-square test when all expected counts were ≥ 5, otherwise Fisher's exact test. p values are unadjusted.

For example, among patients with a single detected variant, M694V was present in 26 of 78 patients (33.3%) without emergency department presentation and in 19 of 51 patients (37.3%) with emergency department presentation (*p* = 0.648).

Similarly, no significant associations were observed for R202Q, E148Q, V726A, or other evaluated variants. Likewise, no individual variant or two-variant combination was significantly associated with surgical intervention (all p > 0.05; Table 5).

Specific MEFV Variants and CT Findings

Among patients with a single detected variant, p.Arg202Gln (R202Q) was more frequent in those with CT abnormalities (5 of 23 [21.7%] vs 7 of 106 [6.6%]; Fisher's exact p = 0.039; Table 5). This difference did not remain significant after Bonferroni correction for the six variants tested (adjusted p = 0.23). No other individual variant was significantly associated with CT abnormalities, and no two-variant combination was associated with CT abnormalities (all p > 0.05).

Emergency Department Presentation According to Surgical Intervention

A significant association was observed between surgical intervention and emergency department presentation.

Among the 167 patients who did not undergo surgery, 106 (63.5%) had no emergency department presentation and 61 (36.5%) had at least one presentation. All four patients who underwent surgery had an emergency department presentation (*p* = 0.005).

The mean number of emergency department visits was 2.93 ± 3.02 among patients who did not undergo surgery and 4.50 ± 1.29 among those who underwent surgery. The corresponding medians were 2 (range, 1–22) and 4.5 (range, 3–6), respectively (p = 0.028).

Zygosity and ACMG Classification

No significant associations were observed between zygosity and CT abnormalities, emergency department presentation, or surgical intervention.

Among patients with a single detected variant, ACMG classification differed according to CT findings. In patients without CT abnormalities, 82 (70.1%) variants were classified as pathogenic and 35 (29.9%) as variants of uncertain significance (VUS). Among patients with CT abnormalities, 4 (33.3%) were classified as pathogenic and 8 (66.7%) as VUS (p = 0.020).

This subgroup finding should be interpreted cautiously because of the small number of patients with CT abnormalities.

Discussion

The present study evaluated the relationship between *MEFV* genetic characteristics and acute abdominal clinical outcomes in adults with detected MEFV variants. The principal finding was that individual *MEFV* variants and the number of detected variants were not significantly associated with emergency department utilization or surgical intervention. In contrast, abdominal CT abnormalities were associated with emergency department presentation and were also associated with a higher frequency of surgical intervention. These findings suggest that, in patients presenting with acute abdominal symptoms, the immediate clinical and radiologic findings may be more informative for surgical decision-making than the presence of a specific *MEFV* variant alone.

The genetic characteristics of our cohort were broadly consistent with the known molecular epidemiology of FMF in Türkiye. M694V was the most frequently identified single variant in our cohort, followed by R202Q and E148Q. The high frequency of M694V is consistent with previous studies demonstrating its prominent role among Turkish patients with FMF [8, 9, 18]. However, despite its relatively high frequency in our cohort, M694V was not significantly associated with emergency department presentation or abdominal CT abnormalities. In contrast, the R202Q variant, classified as a variant of uncertain significance, was more frequent among single-variant patients with CT abnormalities (21.7% vs 6.6%; unadjusted p = 0.039), but this did not remain significant after correction for multiple comparisons and should be regarded as hypothesis-generating.

Previous studies have demonstrated that genotype–phenotype correlations in FMF are complex. Although M694V, particularly in homozygous or compound heterozygous states, has frequently been associated with a more severe disease phenotype, these associations are not uniformly observed across all clinical manifestations [7–11].

The relationship between the number of detected *MEFV* variants and abdominal CT abnormalities requires cautious interpretation. A statistically significant association was observed across the three groups ($p = 0.021$) but not when patients with one and two variants were compared ($p = 0.193$); however, the subgroup containing four detected variants included only one patient. Therefore, this finding should be regarded as exploratory rather than as evidence of a clinically meaningful dose-response relationship.

One of the most notable findings was the association between abdominal CT abnormalities and emergency department presentation. All patients with CT abnormalities had presented to the emergency department with abdominal symptoms, compared with approximately one-third of patients without CT abnormalities. However, this association must be interpreted cautiously: patients with CT abnormalities were identified through the hospital information system, and CT was generally obtained during emergency evaluation, so the finding is largely expected from the way the cohort was assembled. Previous literature has emphasized that FMF can mimic an acute surgical abdomen and may lead to repeated emergency assessments [12–15].

The association between CT abnormalities and surgical intervention was also statistically significant. Surgical intervention occurred in 2 of 14 patients with CT abnormalities compared with 2 of 157 patients without CT abnormalities. Nevertheless, only four patients in the entire cohort underwent surgery. Therefore, this association should be interpreted as exploratory rather than as evidence that CT abnormalities independently predict the need for surgery.

An important distinction in our cohort was made between emergency surgical evaluation and actual surgical intervention. Among the patients with CT abnormalities, 12 underwent emergency surgical evaluation, whereas only 2 ultimately underwent an operative procedure. This distinction is clinically relevant in FMF because acute abdominal symptoms may appropriately prompt surgical assessment even when surgery is ultimately not required. Previous studies have similarly highlighted the diagnostic challenge created by FMF attacks that resemble surgical abdominal emergencies [11–15].

Patients who underwent surgical intervention also had more frequent emergency department presentations and a higher number of emergency visits. All four patients who underwent surgery had at least one emergency department presentation, and the median number of visits was higher in the surgical group. However, because the surgical subgroup was very small, these findings should not be interpreted as demonstrating a causal relationship between recurrent emergency department use and surgery. Moreover, because all operations followed an emergency department presentation, the association between surgery and emergency department presentation is inherent to the definition of the surgical group.

The analysis of ACMG classification provided another potentially relevant observation. Among patients with a single detected *MEFV* variant, the distribution of pathogenic variants and variants of uncertain significance differed between patients with and without CT abnormalities. However, this subgroup analysis included relatively few patients with CT abnormalities, and the biological interpretation of an association between a VUS classification and CT findings is uncertain. All eight VUS variants in the CT-

abnormality group were p.Arg202Gln (n = 5) or p.Glu148Gln (n = 3), so this finding largely reflects the R202Q result and is unlikely to reflect an effect of ACMG classification itself. Therefore, this result should be considered hypothesis-generating.

From a surgical perspective, our findings support an approach in which genetic information is considered as part of the patient's overall clinical context rather than being used as a direct indication for operative management. In an adult with FMF presenting with acute abdominal pain, the decision to perform emergency surgery should remain based on the clinical examination, laboratory findings, imaging findings, disease history, and evolution of symptoms.

The current EULAR recommendations emphasize individualized assessment and management of FMF, with colchicine remaining the cornerstone of treatment [16, 17]. Our findings complement this clinical framework by suggesting that genetic characteristics alone may have limited ability to identify patients who will present to the emergency department or undergo surgical intervention.

This study has several limitations. First, its retrospective, single-center design limits generalizability and introduces the possibility of incomplete or inconsistently documented clinical information. Second, the numbers of patients with CT abnormalities and, particularly, surgical intervention were small, limiting the statistical power of subgroup analyses. Third, the subgroup with four detected variants consisted of only one patient, making the corresponding association with CT findings particularly unstable. Fourth, the study did not include standardized prospective measurements of FMF disease activity, inflammatory markers, colchicine adherence, or treatment response. Fifth, patients with CT abnormalities were identified by screening the hospital information system, and the number of patients who underwent CT with normal findings, or who did not undergo CT, could not be determined; the group without documented CT abnormalities is therefore heterogeneous, and the association between CT abnormalities and emergency department presentation is partly inherent to how the cohort was assembled. Sixth, only patients in whom an MEFV variant was detected were included; patients tested without a detected variant were excluded, so the findings cannot be generalized to variant-negative patients and no comparison with them was possible, and clinical FMF diagnostic criteria were not applied. Seventh, no adjustment for multiple comparisons was made. Finally, because surgical intervention occurred in only four patients, the surgical findings should be considered exploratory.

Despite these limitations, the study has several strengths. It evaluates genetic characteristics together with clinically relevant acute abdominal outcomes in a relatively well-defined cohort of adults with detected MEFV variants. In addition, the analysis distinguishes emergency department presentation, radiologic abnormalities, emergency surgical evaluation, and actual surgical intervention rather than treating these outcomes as a single composite event.

Conclusions

In conclusion, specific *MEFV* variants and the number of detected variants were not significantly associated with emergency department utilization or surgical intervention in this retrospective cohort. In

contrast, abdominal CT abnormalities were associated with emergency department presentations and were associated with a higher frequency of surgical intervention. These findings suggest that acute clinical and radiologic characteristics may be more relevant than individual *MEFV* variants when evaluating adults with MEFV variants who present with acute abdominal symptoms. Larger prospective multicenter studies are warranted to determine whether genetic characteristics, disease activity, treatment factors, and imaging findings can be integrated into a clinically useful approach for distinguishing FMF attacks from true surgical abdominal pathology.

Declarations

Ethics approval and consent to participate

The study was approved by the Bağcılar Training and Research Hospital Non-Interventional Clinical Research Ethics Committee on October 22, 2024 (decision no. 2024/10/03/081). The study was also reviewed and approved by the Education and Planning Board of the University of Health Sciences Bağcılar Health Application and Research Center on October 4, 2024. All patients had signed the hospital's general consent form at presentation, and the institutional ethics committee confirmed that this general consent was sufficient for the retrospective use of clinical and genetic data. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available because they contain patient-level clinical and genetic information but are available from the corresponding author on reasonable request, subject to institutional and ethical restrictions.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

İÇ: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – Original Draft, Writing – Review & Editing.

TP: Data curation, Investigation, Writing – Review & Editing.

LŞ: Investigation, Data validation, Resources, Writing – Review & Editing.

EY: Supervision, Conceptualization, Project administration, Writing – Review & Editing.

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Artificial intelligence (Claude Sonnet 5.5, Anthropic) was used solely for language editing. The authors reviewed all text and take full responsibility for the content of the manuscript.

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Figures

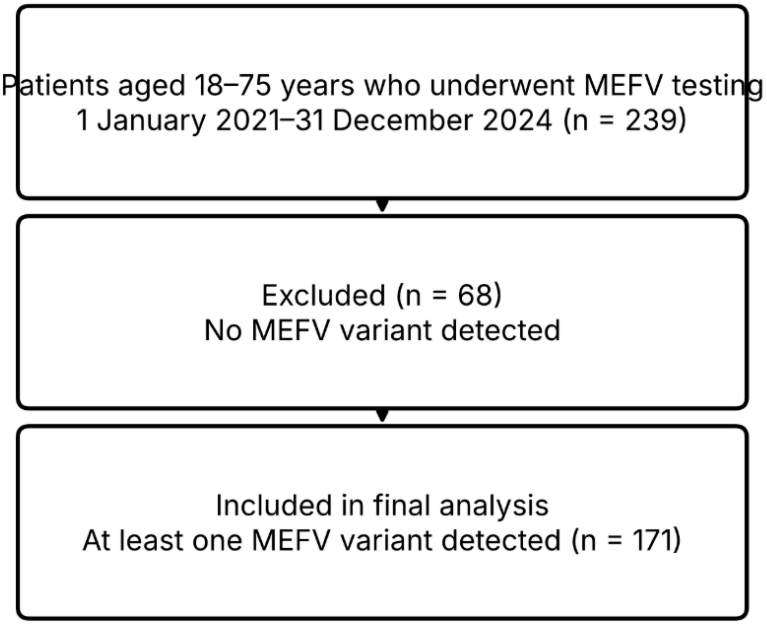


Figure 1

Flow diagram of patient selection.