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ORIGINAL RESEARCH

Predictive factors for therapeutic response and cluster analysis in syndrome of undifferentiated recurrent fever (SURF)

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ABSTRACT

Introduction: Syndrome of undifferentiated recurrent fever (SURF) refers to a group of recurrent fevers without a clear monogenic cause. Clinical spectrum, treatment response predictors and management strategies remain unclear.
Objective: This study aims to longitudinally analyse a homogeneously selected cohort of 101 SURF patients, to identify factors associated with colchicine resistance and to evaluate the efficacy of interleukin-1 (IL-1) inhibitors.
Methods: Patients were enrolled in the Eurofever Registry, carefully excluding those with periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA); familial Mediterranean fever and other known monogenic recurrent fevers. Demographic, clinical and treatment data were analysed to identify predictors of colchicine resistance and define subgroups through cluster analysis.
Results: Common symptoms included fever, arthralgia, abdominal pain and myalgia, with PFAPA-like features (lymphadenopathy, tonsillitis, oral aphthae) observed in one-third of cases, sporadically. Colchicine efficacy, assessed in 77 patients, revealed complete response in the majority of patients (61%). Univariable analysis identified PFAPA-like features, including aphthous stomatitis (p=0.001), cervical lymphadenopathy (p=0.012) and exudative tonsillitis (p=0.004), as associated with colchicine resistance. Multivariable analysis confirmed aphthous stomatitis as an independent predictor of resistance (p=0.014). Tonsillectomy was ineffective. IL-1 inhibitors (anakinra, canakinumab) were beneficial in refractory cases. Cluster analysis revealed three distinct subgroups with varying symptoms and colchicine responses.
Conclusions: These findings provide new insights into SURF, identifying predictors of colchicine resistance and supporting the efficacy of IL-1 blockade. Cluster analysis suggests the heterogeneity within SURF, reinforcing the need for refined diagnostic criteria and personalised treatment strategies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Syndrome of undifferentiated recurrent fever (SURF) is an emerging autoinflammatory condition, still poorly understood.

WHAT THIS STUDY ADDS

⇒ Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis-like features and aphthous stomatitis predict colchicine resistance in SURF.
⇒ Interleukin-1 inhibitors show benefits as a second-line treatment in SURF.
⇒ Cluster analysis revealed three distinct subgroups in our SURF cohort.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study supports SURF's recognition as a distinct clinical entity.

INTRODUCTION

In the era of next-generation sequencing (NGS), a paradox exists with a subset of patients whose symptoms closely resemble familial Mediterranean fever (FMF) but lack known causative mutations. These patients experience recurrent systemic inflammation episodes with fever, mainly associated with abdominal pain and arthralgia, not meeting the criteria to be classified as periodic fever with aphthous stomatitis, pharyngitis and adenopathy (PFAPA) syndrome.[1 2]

This group of patients, first defined as syndrome of undifferentiated recurrent fever (SURF) by Broderick *et al*, has been further discussed in recent reviews.[1 2] NGS studies have been pivotal in identifying undifferentiated recurrent fevers outside known hereditary fevers or PFAPA.[3 4] Approximately 20% of SURF patients present with variants of uncertain significance, although definitive pathogenic mutations cannot be found.[2]

Various groups have addressed the diagnostic challenges in systemic autoinflammatory disease (SAID) patients who lack criteria for monogenic forms. In 2020, Demir *et al*

applied a 16-gene panel to patients with clinical features suggestive of SAIDs but no specific diagnostic markers. Some were diagnosed with monogenic SAIDs, while many were classified as 'undefined SAID', often responding to colchicine or anti-interleukin-1 (IL-1) therapies. These findings highlight shared inflammatory pathways and limitations in current diagnostic criteria.[5]

A study on 39 SURF patients reported fever, arthralgia, abdominal pain and variable colchicine responses.[6] Our previous study confirmed colchicine's effectiveness in a homogeneous SURF cohort.[7]

Data from the Eurofever registry revealed significant heterogeneity among recurrent fever cases without molecular diagnoses. This study identified overlaps between SURF and PFAPA, emphasising the need for refined classification criteria.[8] Similarly, investigations in adult SURF patients showed variability in colchicine responses, underscoring the importance of personalised therapeutic strategies and novel diagnostic markers to distinguish SURF from other autoinflammatory conditions.[9]

The mechanism of SURF remains unclear, but recent studies identified a distinct tonsillar inflammatory signature.[4] The first cytokine analysis in SURF patients revealed a highly inflammatory subset.[10] Our recent work showed minor pyrin inflammasome activation in naïve SURF patients compared with FMF, PFAPA and colchicine-treated SURF. These findings suggest a unique functional mechanism, possibly cytoskeleton-related, as colchicine normalised the response.[11]

Colchicine, used as a continuous therapy, has demonstrated an average 60% efficacy rate, reinforcing its role in long-term management despite the absence of a defined molecular target. IL-1 blockers (anakinra, canakinumab) offer an alternative for colchicine-unresponsive cases.[2 5 6]

Objectives

To study longitudinally a homogeneously selected group of patients with SURF, differentiating their clinical phenotype from other recurrent fevers; to analyse the response to colchicine and to identify potential factors associated with colchicine resistance and to evaluate the response to IL-1 inhibitors.

PATIENTS AND METHODS

Patients with undifferentiated recurrent fevers, followed up at the Istituto Giannina Gaslini in Genoa between 2008 and 2024, were included. The criteria used to define recurrent fever followed the most recent classification criteria for autoinflammatory diseases: evidence of elevation of acute phase reactants (erythrocyte sedimentation rate, C-reactive protein or serum amyloid A) during clinical flares, exclusion of confounding diseases (neoplasms, infections, autoimmune conditions, other inborn errors of immunity), and recurrent disease activity for at least 6 months. Data were collected longitudinally; patients with at least two visits were included. A preliminary study on 43 patients with SURF was extended with additional follow-up.[7 12] Data extraction began in November 2024 and was completed on 31 December 2024. Statistical analysis was conducted in January 2025, and the manuscript was prepared in February 2025.

Exclusion criteria were as follows: (1) follow-up duration shorter than 4 months; (2) alternative diagnosis during follow-up; (3) genetic analysis not performed or unavailable; (4) presence of pathogenic mutations or variants of uncertain significance (VUS) in genes associated with hereditary recurrent fevers (Mediterranean fever gene, mevalonate kinase gene, TNFRSF1A, NLR family pyrin domain containing 3) or other genes of the recurrent fever panel; (5) inflammatory disease progressing to a chronic condition and (6) fulfilment of new PFAPA classification criteria.[7 12]

Demographics, clinical data and treatment response were extracted from records. Following the acquisition of written informed consent, patients were enrolled in the Eurofever registry, approved by the local ethics committee (Comitato Etico Regione Liguria).

Response to treatment was defined as follows: (1) complete (no symptoms or acute phase reactant elevation between episodes), (2) partial (persistence of some symptoms with ≥50% fever episodes reduction) and (3) resistance (minimal/no improvement or worsening).[13]

Statistical analysis

Results were reported as N (%), mean (SD) or median (IQR) depending on the distribution of the variables. Comparisons of colchicine response efficacy categories (complete, partial and ineffective) were performed using the Kruskal-Wallis test or Fisher's exact test. Patients were compared based on anti-IL-1 treatment using Mann-Whitney test or Fisher's exact test. False discovery rate was used to address multiple testing issues. Time to non-response to colchicine treatment was explored using statistical methods for survival analysis. Specifically, Kaplan-Meier curves were estimated, and univariable Cox regression models were used to identify characteristics associated with time to non-response to colchicine treatment. Then, a multivariable model was performed including all the variables showing p value <0.15 in the univariable models. Finally, hierarchical clustering for observations was performed using the complete linkage method, which uses the farthest pair of observations between two groups to determine the proximity of the two groups. Pearson's phi similarity coefficient was used as a similarity measure for binary data. The number of clusters was identified visually on the plotted dendrogram, and clustering adequacy was assessed by the silhouette width.

RESULTS

At the end of enrolment on 1 October 2024, a total of 110 patients were enrolled in the study. Five patients were lost at follow-up (previous visit occurred over 12 months

Table 1 Demographic features of the 101 SURF patients

Demographic features	
Male, N (%)	65 (64.4%)
Family history of recurrent fever, N (%)	19 (18.8%)
European origin, N (%)	99 (98.0%)
Age at onset, median years (IQR)	2.60 (1.00–5.00)
Age at diagnosis, median years (IQR)	6.51 (4.45–10.49)
Age at first visit, median years (IQR)	6.06 (4.26–9.60)
Diagnostic delay, median years (IQR)	2.60 (1.46–4.99)
Duration of follow-up months (IQR)	38.03 (18.67–76.97)
Episode duration (days) (IQR)	4 (3–5)
Number episodes/year (IQR)	12 (12–20)
Regular periodicity, N (%)	63 (62.4%)

N, number of patients; SURF, syndrome of undifferentiated recurrent fever.

earlier), and four patients were excluded because their follow-up period was shorter than 4 months from the enrolment date.

Demographic and clinical characteristics of the cohort

Our cohort consisted predominantly of male subjects and mainly of European origin. Only 18.8% had a family history of recurrent fever. The median age of onset was 2.6 years, with a median age at diagnosis of 6.5 years, revealing a significant diagnostic delay. Regular fever periodicity was observed in 62.4% of patients (table 1). The median number of visits was 6 (IQR 3; 8). 18 patients were studied with a four-gene mini panel for recurrent fevers, 20 patients with NGS analysis and 5 patients with exome sequencing with applied in silico panel for recurrent fevers, while 58 patients with exome sequencing with applied in silico extended panel for autoinflammatory diseases (online supplemental table 1).

The most commonly observed symptoms included fever (100%), arthralgia (72.3%), abdominal pain (65.3%) and myalgia (55.5%). Monoarthritis, generalised lymph node enlargement and oligoarthritis were rare (figure 1).

In terms of symptom frequency patterns, fever was nearly universally persistent during inflammatory episodes, with 94.1% of patients experiencing it 'Always' and a minority (5.9%) 'Sometimes'. Arthralgia and abdominal pain were also prominent, though less consistent, being 'Always' present in 41.6% and 38.6% of patients, respectively, with additional patients reporting them periodically. Myalgia followed a similar trend, affecting one-third of patients continuously. PFAPA-like symptoms, such as cervical lymphadenopathy and aphthous stomatitis, were often intermittent, affecting around one-third of patients 'Sometimes'. Tonsillitis, diarrhoea, vomiting and chest pain occurred less frequently and mainly as periodic issues, while skin rashes, monoarthritis and generalised lymph node enlargement were rare and episodic (figure 1).

Clinical course and response to treatment

The first-line therapy consisted of colchicine, with 84 out of 101 patients receiving it during their follow-up.

Overall colchicine efficacy

Data about overall colchicine efficacy were available for 77 patients. Regarding the other seven patients: in five patients, data on treatment efficacy were missing; in one patient, evaluation was not possible due to family decision to discontinue treatment; and in one case, therapy was discontinued due to drug intolerance. The median duration of treatment was 2.48 years (IQR 1.00; 4.13). The overall response was stratified into complete, partial

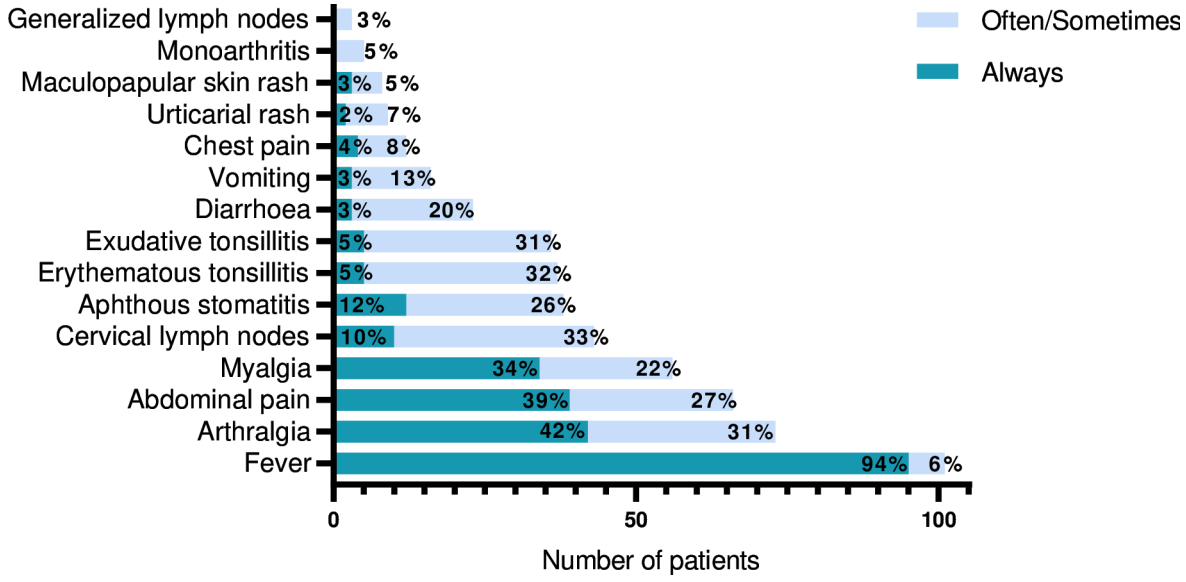

Figure 1 Clinical characteristics of the 101 described patients. The X-axis represents the number of patients. The frequency of each symptom, listed on the Y-axis, is shown as a percentage and stratified in green for symptoms present 'Always' and in light blue for symptoms present 'Often/Sometimes'.

Table 2 Demographic and clinical characteristics of SURF patients treated with colchicine

Variable	Complete efficacy	Partial efficacy	Inefficacy	P value	FDR-adj p value
Number of patients	47	24	6		
Age at onset (years), median (IQR)	3.29 (2.00–6.25)	1.32 (0.50–3.33)	2.04 (0.68–3.41)	0.022	0.183
Age at diagnosis (years), median (IQR)	7.60 (5.80–12.24)	5.23 (3.90–8.72)	5.03 (4.27–6.03)	0.039	0.195
Age at first visit (years), median (IQR)	7.08 (4.92–11.67)	5.13 (3.16–7.80)	4.77 (4.27–5.98)	0.050	0.208
Follow-up (months), median (IQR)	43.13 (20.27–81.90)	52.12 (19.70–89.67)	56.83 (14.63–69.73)	0.976	0.976
Diagnostic delay (years), median (IQR)	3.07 (1.27–5.81)	3.62 (2.04–4.28)	2.41 (1.69–4.42)	0.834	0.907
Episode duration (days), median (IQR)	4.00 (3.00–4.00)	3.75 (3.00–4.50)	4.50 (3.00–5.00)	0.514	0.643
Episodes frequency/year, median (IQR)	12 (10–18)	12 (12–22)	13.5 (10–20)	0.187	0.425
Colchicine duration (years), median (IQR)	2.84 (1.45–4.61)	2.18 (0.91–3.93)	0.46 (0.33–0.88)	0.039	0.195
Gender (male), N (%)	28 (53.8%)	19 (36.5%)	5 (9.6%)	0.210	0.438
Family history, N (%)	8 (66.7%)	3 (25.0%)	1 (8.3%)	0.891	0.928
Irregular periodicity, N (%)	25 (56.8%)	16 (36.4%)	3 (6.8%)	0.584	0.695
Chest pain, N (%)	3 (30.0%)	6 (60.0%)	1 (10.0%)	0.074	0.244
Abdominal pain, N (%)	27 (56.3%)	16 (33.3%)	5 (10.4%)	0.464	0.643
Vomiting, N (%)	7 (53.8%)	4 (30.8%)	2 (15.4%)	0.505	0.643
Diarrhoea, N (%)	10 (55.6%)	5 (27.8%)	3 (16.7%)	0.333	0.550
Enlarged cervical lymph nodes, N (%)	13 (41.9%)	15 (48.4%)	3 (9.7%)	0.013	0.163
Enlarged generalised lymph nodes, N (%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0.078	0.244
Maculopapular rash, N (%)	2 (66.7%)	0 (0.0%)	1 (33.3%)	0.154	0.385
Urticarial rash, N (%)	3 (42.9%)	3 (42.9%)	1 (14.3%)	0.352	0.550
Erythematous tonsillitis, N (%)	15 (53.6%)	10 (35.7%)	3 (10.7%)	0.496	0.643
Exudative tonsillitis, N (%)	9 (34.6%)	14 (53.8%)	3 (11.5%)	0.003	0.075
Oral aphthae, N (%)	15 (48.4%)	12 (38.7%)	4 (12.9%)	0.141	0.385
Arthritis, N (%)	4 (80.0%)	1 (20.0%)	0 (0.0%)	0.773	0.878
Arthralgia, N (%)	33 (55.9%)	21 (35.6%)	5 (8.5%)	0.280	0.538
Myalgia, N (%)	23 (54.8%)	16 (38.1%)	3 (7.1%)	0.348	0.550

FDR-adj, False discovery rate adjustment; N, number of patients; SURF, syndrome of undifferentiated recurrent fever.

and absent (ineffective) (table 2, figure 2A). At the last follow-up, a complete response was observed in 47 patients (61%), a partial response in 24 subjects (31%) and an absent response in 6 patients (8%) (figure 2A).

Efficacy of colchicine over time: 1-year, 2-year and 5-year analyses

In addition to the cumulative efficacy of colchicine therapy over the treatment period, available for the previously mentioned 77 patients, efficacy was also evaluated at 1 year, 2 years and 5 years. Data on colchicine efficacy were available for 66 patients at 1 year, 50 patients at 2 years and 20 patients at 5 years after starting therapy. Colchicine maintained good efficacy over time, particularly during the first 2 years of treatment. The increase in resistance, reaching 20% in the 5-year group, reflects the unchanged number of non-responsive patients. Specifically, the four colchicine-resistant patients exhibited resistance within the first year of therapy. One additional non-responsive patient was excluded from this specific analysis, as 1 year of follow-up had not yet been completed, while another one became resistant only after 15 years of therapy. As a result, despite the apparent unfavourable trend, the number of non-responsive patients remained unchanged (figure 2B).

Colchicine therapy discontinuation

Out of 84 patients treated with colchicine, 40 subjects discontinued the drug during follow-up. The primary reason for discontinuation was clinical improvement or remission (figure 2C). Notably, among the 40 patients reported, (1) 14 discontinued colchicine and later restarted it due to disease relapse. This group (n=14) had a median follow-up duration of 108.52 months (IQR 79.07; 133.5), with a median duration of colchicine therapy of 93.62 (IQR 44.8; 116.73); (2) 26 patients discontinued colchicine without resuming it. Of these, eight—having a median follow-up duration of 49.8 (IQR 18.15; 103.57) and a median colchicine therapy duration of 15.18 months (IQR 4.62; 41.58)—experienced

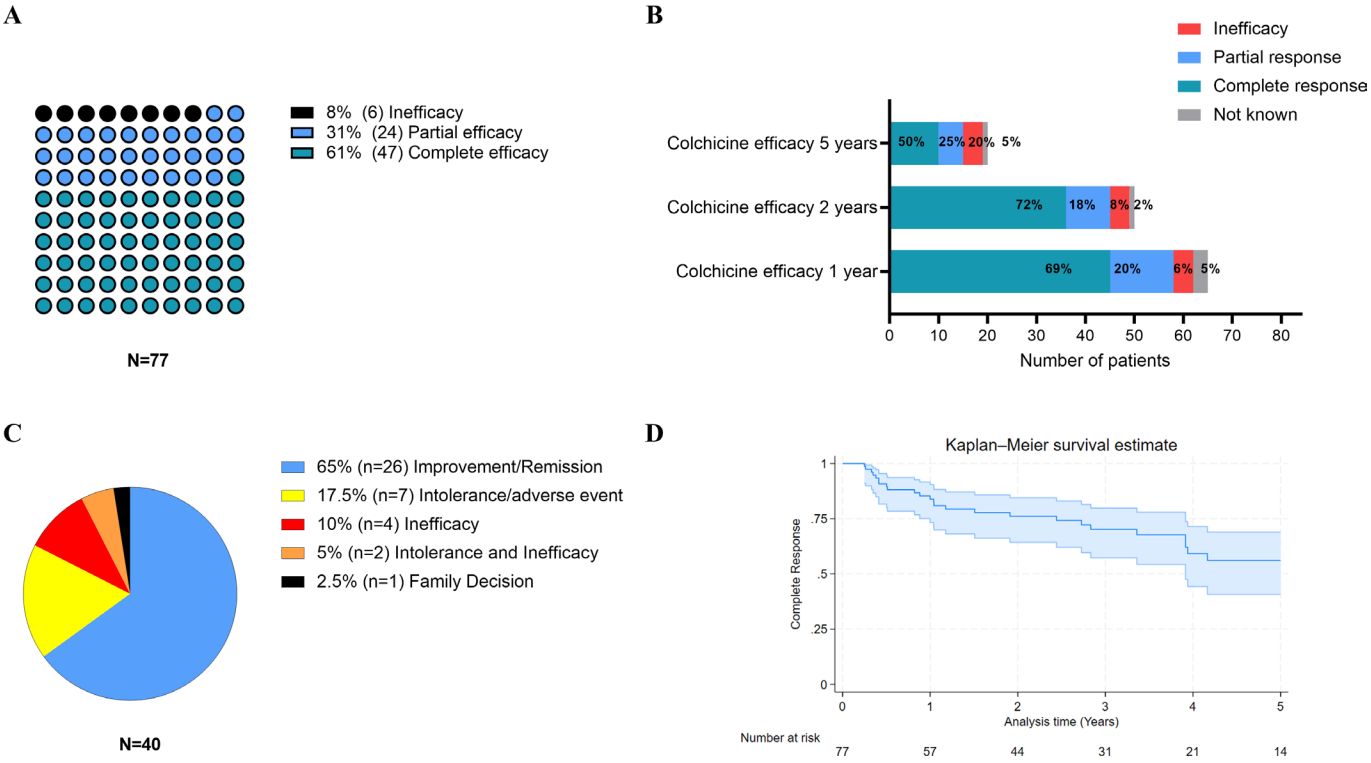

Figure 2 Colchicine treatment in the cohort: (A) Efficacy at last follow-up in 77 SURF patients (complete efficacy in green, partial in blue, inefficacy in black). Data are shown as percentages, with patient numbers in parentheses. (B) Colchicine efficacy observed at 1 year, 2 years and 5 years after treatment initiation, categorised as complete efficacy (green), partial efficacy (blue) and inefficacy (red), with percentages indicated on the bars. (C) Reasons for colchicine discontinuation in the 40 patients who stopped treatment. Data are shown as percentages, with patient numbers in parentheses. (D) Kaplan-Meier survival estimates for complete response to colchicine in the cohort (n=77), showing the probability of achieving and maintaining a complete response over time, with the 95% CI shaded. SURF, syndrome of undifferentiated recurrent fever.

a relapse. 3 patients remained in remission, while data were missing for 15 patients.

Intolerance or adverse events were reported in 17.5% of patients, while inefficacy accounted for 10%. Additionally, 5% of patients discontinued therapy due to a combination of intolerance and inefficacy, while one patient (2.5%) stopped for family decision (figure 2C).

IL-1 blocking therapy

Nine patients were treated with IL-1 blocking therapy due to colchicine inefficacy (n=8) or intolerance (n=1). Specifically, anakinra was administered to seven patients, initially combined with colchicine in six cases. In one patient, anakinra was quickly discontinued due to an adverse event (generalised cutaneous rash) and replaced with canakinumab. Canakinumab was ultimately given to three patients in total, with two of these also receiving colchicine.

With the limitation of the small patients' sample, IL-1 blocking therapy seemed to be effective in our cohort, though with a lower efficacy rate for canakinumab (partial efficacy in two cases—one with canakinumab alone and the other combined with colchicine) compared with anakinra (online supplemental figure 1).

Tonsillectomy

Tonsillectomy was ineffective in 18 cases, partially effective in 1 case, causing a reduction in the frequency and intensity of febrile episodes.

Treatment status at last follow-up

Median follow-up for the cohort (101 patients) was 38.03 months (table 1). Most patients were on colchicine monotherapy. 25 patients discontinued colchicine by the time of follow-up, of whom 12 due to improvement or remission. Smaller subsets were receiving a combination of colchicine and anakinra or treated exclusively with anakinra. Canakinumab was administered alone or in combination with colchicine. Additionally, 17 patients (16.83%) were never treated, possibly due to mild symptoms or alternative management choices (steroids on demand, refusal of treatment). Out of these 17, 9 patients experienced spontaneous remission or improvement without baseline therapy. Finally, data on treatment status were unavailable for two patients (1.98%) (online supplemental figure 2).

Safety and adverse events

Safety was assessed in the longitudinal cohort of 84 patients treated with colchicine and/or IL-1 blocking therapy.

Among 84 colchicine-treated patients, 9 had mild adverse events. Most of these were gastrointestinal (abdominal pain and diarrhoea). Telogen effluvium and mild leucopenia were also reported. In seven out of nine cases, the adverse event led to therapy discontinuation, which was later resumed in one case and permanently discontinued in six cases.

Among the seven patients treated with anakinra, six started the drug concomitantly with colchicine, and one after discontinuing colchicine due to inefficacy. Of these, only one patient, already on colchicine treatment, experienced an adverse event (generalised urticaria) following anakinra administration. Mild injection site reactions during the initial administration of the drug were also reported.

Canakinumab was prescribed to three patients, two of whom were also on concurrent colchicine treatment. No adverse events were reported in these patients (online supplemental table 2).

Predictors for response or resistance to treatment

In this cohort, patients with complete colchicine efficacy exhibited an older median age at disease onset and diagnosis compared with those with partial or no efficacy. Notably, the presence of enlarged cervical lymph nodes was more frequent in the partial efficacy groups (p=0.013), as well as exudative tonsillitis (p=0.003). No significant differences emerged for follow-up duration, diagnostic delay or episode characteristics (table 2).

Significant differences were observed in terms of age at onset (p=0.022), with an older age at onset associated with a better response to colchicine (table 2).

Although colchicine duration showed a trend towards longer use in the groups with complete and partial efficacy compared with the inefficacy group, this difference did not reach statistical significance (p=0.066), possibly due to the relatively small size of non-responder patients. Symptoms such as abdominal pain, vomiting and diarrhoea were more frequent in the complete efficacy group, whereas generalised lymphadenopathies were exclusively observed in the inefficacy group (table 2).

Analysing the efficacy of colchicine during the observation period, a survival analysis was performed to explore the time to non-response. Kaplan-Meier estimates are reported in figure 2D. Specifically, the 25th percentile was found to be 2.44 (95% CI 1.00 to 3.92) while median survival time was not reached before 5 years (figure 2D).

Predictors of colchicine resistance

The group with complete colchicine efficacy was compared with the group with partial efficacy or resistance. In the univariate analysis, longer episode duration (p=0.002), cervical lymphadenopathy (p=0.012), exudative tonsillitis (p=0.004) and oral aphthae (p=0.001) were significantly associated with colchicine partial efficacy or resistance. In the multivariate analysis, the presence of oral aphthae remained significantly associated with reduced colchicine efficacy in our cohort (p=0.014) (table 3, online supplemental figure 3).

A comparison was conducted between patients treated with IL-1 blocking therapy and those who did not receive this treatment. The two groups showed similar median ages at disease onset, age at diagnosis and age at first visit, indicating comparable timelines for the initial progression and identification of the disease.

Urticarial rash was more common in anti-IL-1-treated patients (p=0.032). Age at colchicine start, colchicine duration and temporary colchicine withdrawal rates were consistent across both groups (online supplemental table 3).

Cluster analysis

We identified three patient groups with distinct symptom profiles. The dendrogram and silhouette widths are reported in online supplemental figure 4. Group 1 exhibited mainly gastrointestinal symptoms, with abdominal pain reported by all patients. Group 2 was marked by musculoskeletal involvement, including arthritis, and a higher prevalence of arthralgia and myalgia compared with the other groups. Group 3 was predominantly associated with oral aphthae and minimal gastrointestinal involvement (figure 3A, online supplemental table 4).

The analysis of colchicine therapy response across the groups showed the most favourable response over time in Group 3, a moderate yet positive response in Group 1 and the least favourable response in Group 2 (figure 3B). In Group 3, among the patients for whom data on colchicine response were available, all except one showed a complete response to the drug (online supplemental table 5).

DISCUSSION

This study provides new clinical and therapeutic insights into SURF, including the analysis of symptom frequency during episodes, the identification of predictors of colchicine resistance and a symptom-based cluster analysis revealing distinct clinical subgroups.

SURF represents an emerging clinical entity within the expanding realm of autoinflammatory diseases. With growing interest in SURF, recent studies explored its clinical course and features.[2] However, these analyses often considered small retrospective cohorts or cases included in registries from various centres. This approach presents limitations in accurately analysing the phenotype and therapy response correlation within this patient group.

Our monocentric study is the first on a larger, homogeneously selected and longitudinally observed SURF cohort, excluding PFAPA, FMF and other monogenic SAIDs. Our study cohort of 101 SURF patients, predominantly of European origin, presents a comprehensive view of the demographic and clinical characteristics typical of this syndrome.

With less than 20% of patients having a family history of recurrent fever, the findings suggest that familial

Table 3 Predicting factors of colchicine partial and total inefficacy in our cohort: univariable and multivariable analyses

	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
Age at colchicine start	0.93 (0.83 to 1.03)	0.177	---	---
Male gender	1.81 (0.73 to 4.48)	0.197	---	---
Diagnostic delay (years)	1.03 (0.91 to 1.16)	0.688	---	---
Duration of episodes (days)	1.25 (1.09 to 1.44)	**0.002**	1.11 (0.90 to 1.35)	0.330
Number of episodes/year	1.03 (0.97 to 1.08)	0.351	---	---
Familiarity	1.14 (0.39 to 3.35)	0.807	---	---
Regular pattern	0.62 (0.30 to 1.32)	0.215	---	---
Symptoms				
Chest pain	1.83 (0.78 to 4.30)	0.168	---	---
Abdominal pain	1.35 (0.62 to 2.95)	0.455	---	---
Vomiting	1.35 (0.55 to 3.34)	0.509	---	---
Diarrhoea	1.18 (0.52 to 2.67)	0.689	---	---
Enlarged cervical lymph nodes	2.61 (1.23 to 5.53)	**0.012**	1.62 (0.67 to 3.92)	0.288
Macular rash	1.81 (0.24 to 13.76)	0.565	---	---
Urticarial rash	2.22 (0.76 to 6.47)	0.145	1.77 (0.57 to 5.49)	0.325
Exudative tonsillitis	3.00 (1.43 to 6.30)	**0.004**	1.50 (0.61 to 3.68)	0.380
Erythematous tonsillitis	1.32 (0.63 to 2.77)	0.464	---	---
Oral aphthae	3.80 (1.72 to 8.40)	**0.001**	3.10 (1.26 to 7.61)	**0.014**
Monoarthritis	0.55 (0.07 to 4.04)	0.555	---	---
Arthritis	0.50 (0.07 to 3.69)	0.497	---	---
Arthralgia	2.58 (0.89 to 7.45)	0.080	2.25 (0.75 to 6.75)	0.148
Myalgia	1.73 (0.81 to 3.73)	0.159	---	---

Statistically significant p values are shown in bold.
CI, Confidence Interval; HR, Hazard Ratio.

recurrence is relatively uncommon within this population, confirming the data previously reported.[6–8] The median diagnostic delay was 2.6 years, with a diagnosis often not reached until approximately 6.5 years of age. This delay may reflect the difficulty in distinguishing SURF from other autoinflammatory diseases due to overlapping symptoms, benign course and lack of definitive genetic markers after extensive molecular analysis.

Arthralgia, abdominal pain and myalgia have been confirmed as the predominant symptoms associated with febrile episodes. The typical PFAPA-like manifestations, cervical lymphadenopathy and tonsillitis (erythematous and exudative) appeared sporadically in about one-third of the cohort. The presence of these symptoms in some SURF patients could lead to misdiagnosis as PFAPA syndrome. However, our study highlights not only the reduced frequency of PFAPA-like symptoms in our cohort, but also their sporadic occurrence during episodes in SURF patients. More specifically, unlike PFAPA, patients with SURF experience tonsillitis, cervical lymphadenopathy and oral aphthae only occasionally, reflecting a less typical presentation. Additionally, many SURF patients present only one of these symptoms rather than a combination of them. Differentiating SURF from PFAPA is essential due to their different treatment responses: SURF patients respond well to colchicine and poorly to tonsillectomy, while PFAPA patients exhibit an excellent response to tonsillectomy with a lower rate of response to colchicine, especially concerning the complete response.[2 7 14–16] Colchicine was the main long-term treatment, primarily used as monotherapy for its favourable efficacy. Nearly half of the cohort remained on colchicine alone at the last follow-up, achieving significant symptom control.

Interestingly, we identified the above-mentioned PFAPA-like symptoms and longer fever episodes as univariate factors related to colchicine resistance, while the multivariate analysis confirmed aphthous stomatitis as resistance-related in our cohort. In contrast to PFAPA,[15 16] tonsillectomy proved ineffective in our SURF cohort.

IL-1 blocking therapy showed potential benefits in colchicine-unresponsive or intolerant cases. In the absence of intolerance, IL-1 blocking therapy (anakinra or canakinumab) was initiated in combination with colchicine. Regardless of this combination and considering the limited sample size, anakinra seems to have a higher

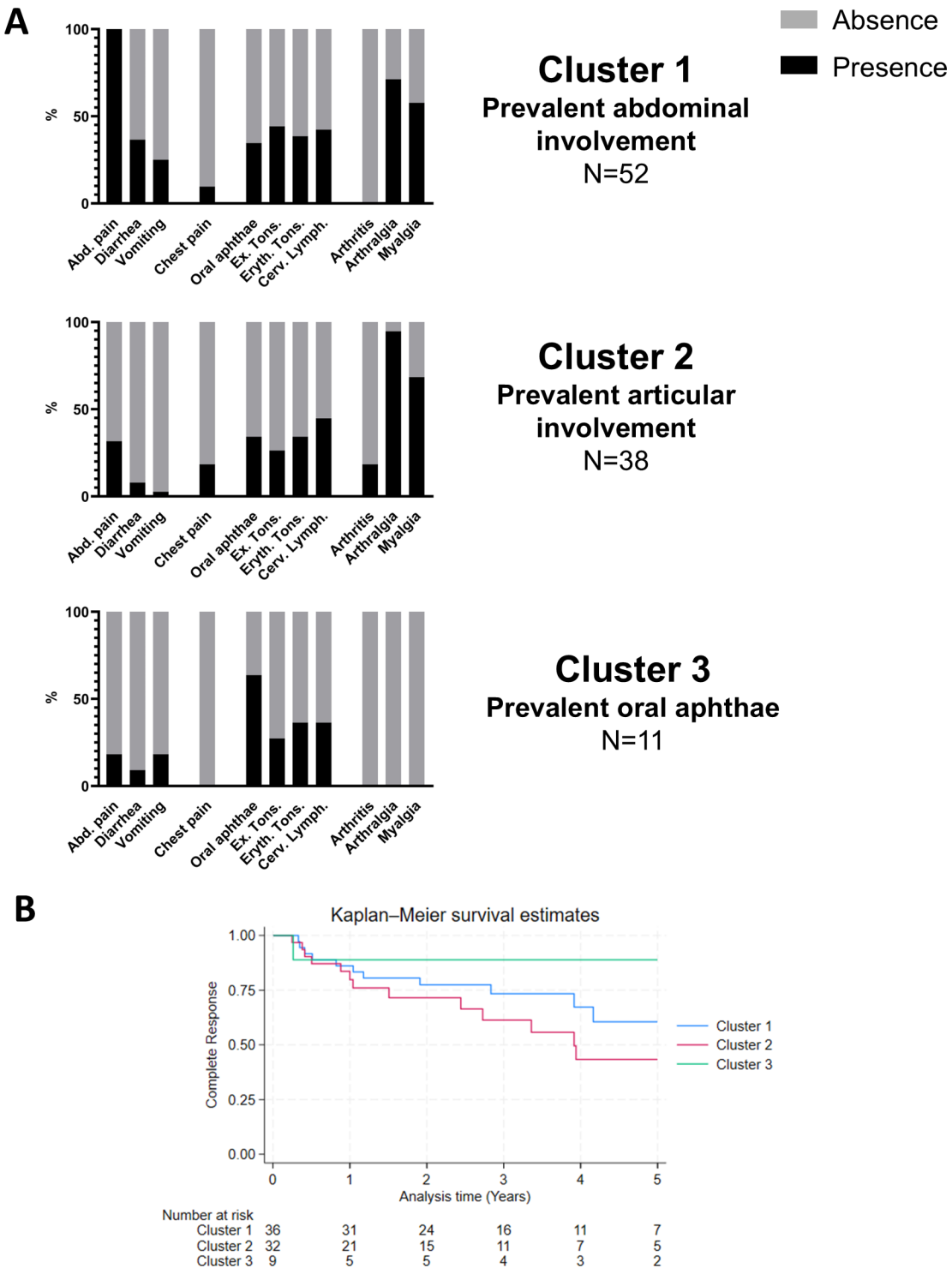

Figure 3 Cluster analysis in the SURF cohort. (A) Histograms showing symptom frequency across three clusters, with black indicating presence and grey absence. Clinical features and patient numbers are listed. (B) Kaplan-Meier survival estimates for complete colchicine response across clusters, showing a trend for better response in Cluster 3, followed by Cluster 1 and Cluster 2 (p=0.1096). Abd, abdominal; Cerv. Lymph, cervical lymph nodes; Eryth, erythematous; Ex, exudative; SURF, syndrome of undifferentiated recurrent fever.

rate of complete efficacy compared with canakinumab. Previous studies have demonstrated the efficacy of anakinra in patients with undifferentiated SAIDs, although data remain limited to small cohorts.[2 6 17] Canakinumab has only recently been described in a cohort of patients with SURF, proving effective either as monotherapy or, in cases of partial response, in combination with on-demand anakinra.[10] Additional data on its efficacy and safety are available in cohorts of patients with undifferentiated autoinflammatory disease; however, their symptomatology differs from the definition of SURF.[18] Nine patients showed spontaneous remission; larger cohorts

are needed to identify predictive factors. Additionally, these patients should be monitored over time to assess whether they might require treatment in the future. The observed treatment discontinuation rate due to clinical remission or intolerance also highlights colchicine's dual role in both effective management and the importance of monitoring for adverse effects, such as gastrointestinal issues, which led some patients to stop treatment.

Interestingly, the cluster analysis performed in our cohort identified three distinct patient groups, each exhibiting unique clinical characteristics and showing a different trend of response to colchicine therapy. The group that showed the most favourable response to colchicine was characterised by oral aphthae as the dominant symptom. This result may appear contradictory to the multivariable analysis findings; however, a closer examination of the data reveals that, within this group, all but one patient achieved a complete response to colchicine. In contrast, patients with oral aphthae in other clinical subgroups had a significantly lower rate of complete response. This finding suggests the existence of a subset of patients, primarily presenting with oral aphthae as the predominant clinical manifestation associated with fever, who may particularly benefit from colchicine treatment. Moreover, the group with predominant gastrointestinal involvement responded well to colchicine, whereas the musculoskeletal-dominant group showed a less favourable response.

In conclusion, our study offers key clinical and therapeutic insights on SURF. Familial recurrence is uncommon, and diagnosis is often delayed. PFAPA-like symptoms are present in the cohort, but with a low frequency compared with the total number of episodes. Colchicine is effective for most patients, though some show resistance, particularly those with PFAPA-like symptoms. IL-1 blocking therapies demonstrate promise in colchicine-resistant cases. Notably, the clustering analysis revealed distinct patients' subgroups with varying responses to treatment, emphasising the potential for personalised therapeutic strategies. However, our study has limitations: while the single-centre design allows for accurate and homogeneous patient selection, it also poses a constraint due to the small size of some comparison groups, including the anti-IL-1-treated group, and reproducibility of the results in other centres. In addition, genetic testing was not uniform across the cohort: 18% of patients underwent a limited four-gene panel, while the others received broader testing, which may have influenced the homogeneity of genetic characterisation within the cohort. Due to the large debate on the possible pathogenic contributing role of some VUS, such as E148Q for MEFV or R92Q for TNFRSF1A, patients carrying these variants were excluded from the study, in order to avoid any confounding factor. This choice does not reflect what happens in the daily clinical practice. Interestingly, in a recent study, the group of patients bearing the R92Q variant of the TNFRSF1A gene displayed a high degree of clinical similarity with SURF patients rather than TRAPS and PFAPA.[19]

Upon confirmation of these findings in larger multicentre cohorts, it may be necessary to define the clinical criteria for SURF suspect. This would allow for more precise targeting of therapeutic interventions and optimising management strategies.

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