Parvovirus B19 infection with rheumatologic manifestations: results from a multicentre Italian study

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Abstract

Objective

To characterise the clinical spectrum of adult parvovirus B19 (B19V) infection referred for rheumatologic evaluation and to identify clinical predictors of arthritis resolution.

Methods

We conducted a multicentre retrospective study across nine Italian rheumatology units during the 2023–2024 post-pandemic resurgence of B19V infection. Clinical, therapeutic, and follow-up data were systematically collected using a standardised REDCap platform.

Results

We enrolled 71 patients (median age 43 years; 72% female), 85% with a confirmed diagnosis. Most reported recent household exposure. Joint involvement was nearly universal (96%), predominantly oligoarticular, and often affected large joints, mimicking early inflammatory arthritis. Fever (65%) and skin manifestations (61%) were frequent. In addition to typical exanthems, 9 patients displayed a distinctive purpuric rash confined to the pretibial region, sparing ankles and feet – a potentially distinctive feature of to B19V infection. Symptom resolution occurred in 87% of cases, usually within one month. Glucocorticoid use was independently associated with – but not proven to cause – faster resolution in Cox regression (HR 0.53; 95% CI: 0.31–0.90; p=0.020), though this finding may reflect indication bias. No other clinical or serological predictors emerged.

Conclusion

This study provides the largest systematically collected multicentre cohort of adults with B19V infection referred to rheumatology during the post-pandemic European outbreak. Our findings expand the clinical spectrum of B19V arthritis and highlight distinctive skin patterns that may aid differential diagnosis during epidemic waves.

Key words

acute viral arthritis, atypical rash, cutaneous vasculitis, infectious mimickers of rheumatologic disease, Parvovirus B19, post-viral arthralgia

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Introduction

Parvovirus B19 (B19V) is a small, non-enveloped DNA virus of the Parvoviridae family, primarily transmitted by respiratory droplets and known for causing erythema infectiosum in children (1-3). In adults, B19V infection may present with arthralgia, arthritis, or rash, occasionally mimicking autoimmune rheumatic disease (4-9). The virus has been implicated in post-viral arthritis, vasculitic eruptions, and transient cytopenia, with symptoms that can overlap with early connective tissue disease (10, 11).

The frequency and clinical spectrum of B19V-related rheumatological manifestations remain incompletely defined, particularly in adults. Most available data derive from small or single-centre case series published before the COVID-19 pandemic (12-18). These studies mainly described classical 'gloves and socks' rashes and self-limiting poly-arthritis, but often lacked standardised data collection and systematic follow-up.

Recently, a marked resurgence of B19V circulation has been reported across Europe, including Italy, France, and the United Kingdom (19-22). The 2023-2024 outbreak provided a unique opportunity to reassess B19V-related manifestations in adults within a modern clinical framework, also considering the post-pandemic epidemiologic context.

This multicentre study fills this gap by systematically characterising the clinical spectrum of adult B19V infection referred to rheumatology clinics during the 2023-2024 outbreak. We sought to describe both typical and atypical articular and cutaneous presentations and to explore clinical factors associated with arthritis resolution, with the goal of improving diagnostic accuracy and recognition of post-viral rheumatic syndromes in real-world practice.

Methods

Main aim and specific objectives

The main aim of this study was to characterise the clinical spectrum of B19V infection in adults referred to rheumatology clinics during the 2023–2024 post-pandemic outbreak in Italy. Specific objectives were to (1) describe the articular and cutaneous manifestations of B19V infection, and (2) explore clinical predictors of arthritis resolution.

Study design and population

We conducted a multicentre, retrospective observational study across nine Rheumatology Units in Italy. The study period spanned from June 15th, 2023 to July 30th, 2024, corresponding to the nationwide increase in B19V circulation reported by the European Centre for Disease Prevention and Control (20).

Eligibility criteria and case definitions

Adult patients (≥18 years) referred for rheumatological symptoms were eligible if they had either (a) a definite diagnosis of B19V infection (based on IgM positivity or detectable DNA) or (b) a probable diagnosis (defined as the presence of fever, rash, arthritis in the context of a documented household exposure to a confirmed case during the 2023-2024 outbreak). This pragmatic classification mirrors the 'confirmed/probable' framework commonly used in infectious disease surveillance, allowing inclusion of clinically and epidemiologically consistent cases when confirmatory testing was unavailable. Alternative infectious or autoimmune causes were excluded according to clinical judgment and routine investigations performed at each centre, based on the individual presentation.

Ethics approval and consent to participate

The study was conducted according to the protocol REUMABANK approved by our local Ethics Committee, in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was collected for each participant.

Data sources and variables collected

Patients were identified through outpatient visits and laboratory records during the epidemic wave, and data were collected using a standardised REDCap survey designed to ensure uniformity across centres.

For each reported case, we systematically collected demographic data,

clinical presentation, treatments, and follow-up outcomes. Physicians could also report atypical clinical features not captured by predefined categories through a free-text field embedded in the survey. Polymerase chain reaction (PCR) testing was performed locally in accredited hospital laboratories using validated commercial assays, without central standardisation. The presence or absence of joint symmetry was not systematically recorded. Joint involvement was classified as oligoarticular (≤4 joints) or polyarticular (>4 joints) based on physician's report. Fever was defined as a body temperature ≥37.8°C. When available, the highest measured temperature was recorded; otherwise, self-reported values documented in clinical records were used. Symptom resolution was reported at the last follow-up visit or based on documented clinical communication. For patients with persistent symptoms, the date of the latest available follow-up was used for censoring.

Statistical analysis

- Descriptive analyses and group comparisons

Normality of data distribution was tested using the Kolmogorov-Smirnov test ($p>0.05$ indicating normal distribution). Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate. Associations between categorical variables were evaluated using Chi-square or Fisher's exact test, while correlations between continuous variables were assessed using Pearson's correlation. Differences in continuous variables between groups were analysed using Student's t-test or the Mann-Whitney U-test, depending on the distribution of data.

- Time-to-resolution analyses

Time to B19V arthritis resolution was analysed using Kaplan-Meier survival curves and log-rank tests for univariate comparisons, and Cox proportional hazards regression for multivariable modelling. Variables were selected based on clinical relevance and potential association with disease resolution. The proportional hazards assumption was assessed using Schoenfeld residuals. Although follow-up was not standardised, the timing of symptom resolution or last clinical contact was available for nearly all patients, and most were followed long enough to observe resolution, allowing a reasonable use of time-to-event analysis.

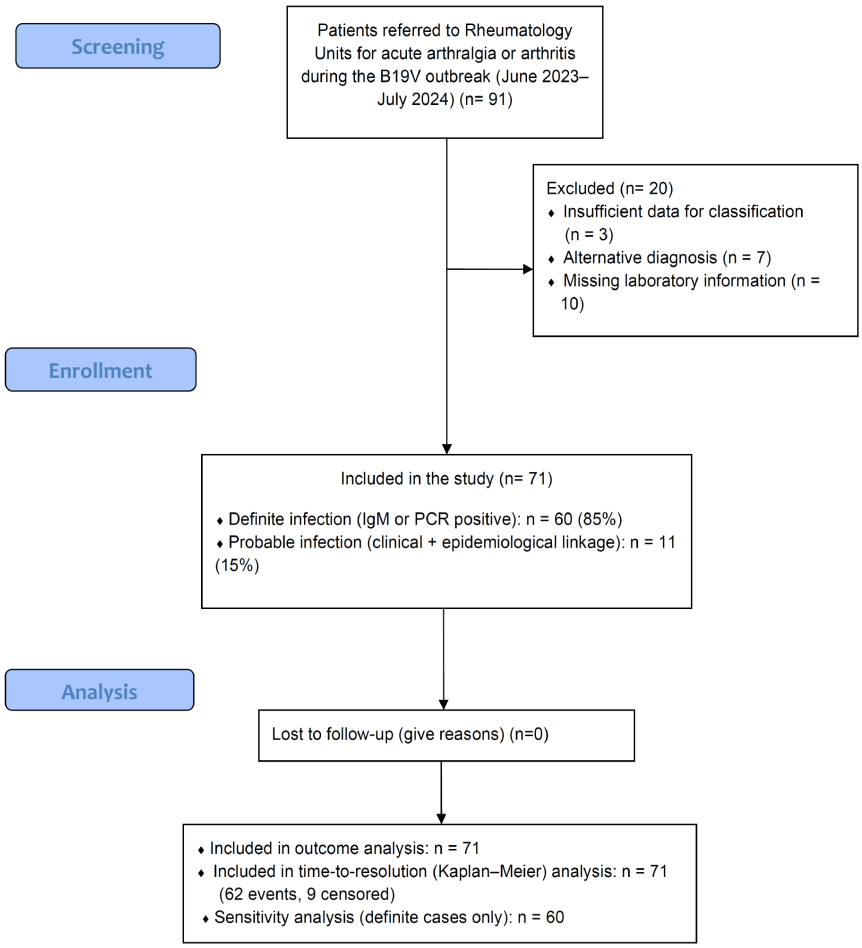

Fig. 1. Flow diagram of patient identification, inclusion, and analysis.

- Predictor analysis and model selection

To explore potential predictors of B19V arthritis resolution, we initially performed a stepwise logistic regression to identify a subset of relevant clinical and serological variables. However, this approach failed to yield a stable or interpretable model, likely due to multicollinearity and limited sample size.

We therefore adopted a two-step alternative approach. First, we used a conditional random forest (cforest) model to explore the overall contribution of clinical and serological variables to outcome prediction. Variables showing non-zero importance were selected for further analysis (23).

We assumed that data were missing at random, based on the clinical context and data collection methods. To minimise potential bias and loss of information, we applied multiple imputation by chained equations (MICE), using predictive mean matching (24). Five imputed datasets were generated and combined using Rubin's rules to obtain pooled estimates (25).

A multivariate logistic regression model was fitted on the imputed datasets, including all variables selected by random forest: glucocorticoid use, symptom onset delay, body mass index (BMI), number of joint sites involved, IgM titre, and glucocorticoid duration. To improve interpretability (26), a reduced model was tested including the three most clinically relevant variables: glucocorticoid use, IgM titre, and number of joints involved. Model comparison using the D1 test (37, 38) showed

no significant loss of fit (p=0.17), supporting the use of the reduced model.

- Sensitivity analyses

To evaluate the robustness of the main findings, all multivariable models were repeated in the subset of patients with definite B19V infection. Analyses were performed in R (v. 4.4.3, RStudio 2024.12.1.563).

Results

Study population and baseline characteristics

A total of 71 patients was enrolled from 9 Italian regions (Veneto, Friuli-Venezia-Giulia, Lombardia, Piemonte, Emilia-Romagna, Marche, Lazio, Puglia, and Sardegna). Figure 1 summarises the selection and classification of patients included in the multicentre cohort, while Figure 2 illustrates the geographical distribution and number of patients per centre, grouped by region. Patients were mostly female (n=51, 72%) with a median (IQR) age of 43 (38.5, 49) years. Most of them (n=60, 85%) had a definite diagnosis, and 53 (75%) had household contact with a confirmed B19V infection. Most of the patients (n=51, 72%) contracted the infection between March and June 2024. Only two patients had a pre-existing rheumatic disease diagnosis: one with psoriatic arthritis (PsA) and one with systemic lupus erythematous (SLE).

Clinical manifestations

The median (IQR) interval between the date of B19V infection onset (fever onset or household contact) and the date of the rheumatic symptoms' onset was 3 (0, 7) days. The most common manifestations at the first evaluation (summarised in Table I) were joint involvement (n = 68, 96%), fever (n=46, 65%), cutaneous (n=43, 61%), headache (n=11, 16%), and haematologic, sore throat and cough (n=10, 14% each). The most involved joints were metacarpophalangeal (n=45, 63%), wrists (n=42, 59%), ankles (n=37, 52%), and knees (n=36, 51%). The number of joint sites involved per patient had a median (IQR) of 3 (2.0, 4.0). Most patients presented with an oligoarticular pattern (n=3, 75%), while 13 (18%) had polyarticular and 2 (3%) monoarticular involvement. The median (IQR) pain NRS was 8.0 (7.0, 8.0). Skin involvement was various, encompassing vascular purpura (n=16, 23%), erythema multiforme (n=15, 21%), gloves and socks (n=14, 20%), and livedo reticularis (n=3, 4%). Among the 16 patients with vascular purpura, 9 (56%) showed a distinctive distribution involving the shins bilaterally, with sparing of the ankles and feet, clearly differing from the classical 'gloves and socks' appearance (Fig. 3). No histologic confirmation was pursued, as the rash was transient and resolved spontaneously without residual changes.

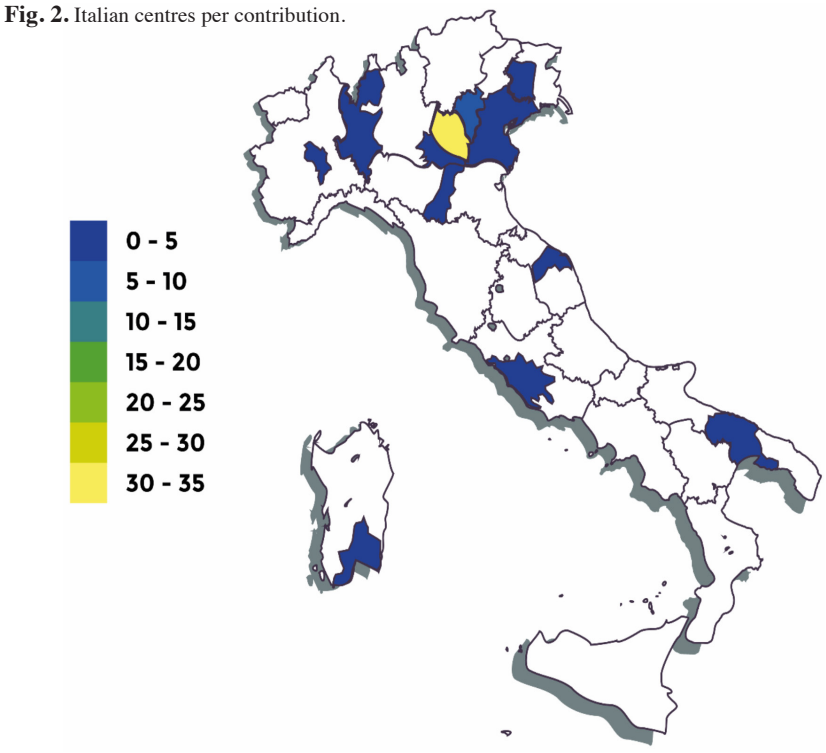

Fig. 2. Italian centres per contribution.

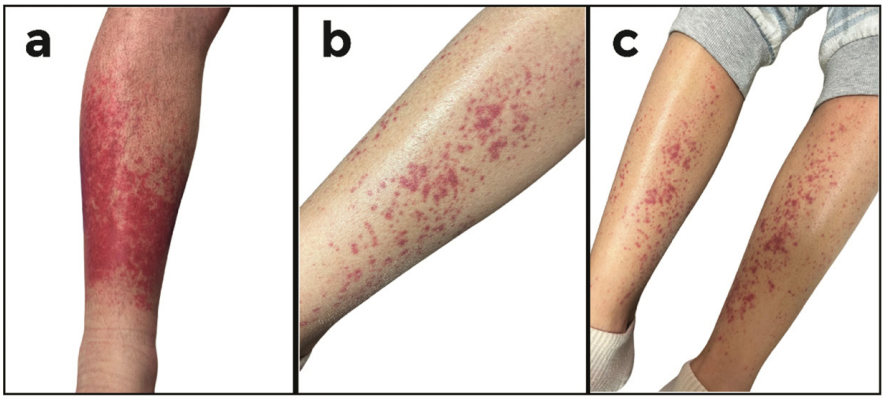

Fig. 3. Bilateral pretibial purpura in adult patients with Parvovirus B19 infection.
A-C: patients with Parvovirus-B19 cutaneous vasculitis involving the shins sparing the ankle and foot.

Treatment and outcomes

Overall, the median (IQR) follow-up was 52.5 (24.5, 85.25) days. In our cohort, 62 patients (87%) achieved symptom resolution during follow-up, mostly within one month (n=46, 65%). The remaining patients developed persistent arthralgia. In a patient with pre-existing PsA, the infection triggered a secondary failure of the current tumour necrosis factor alpha inhibitor treatment. Three patients (4%) were hospitalised due to the consequences of B19V infection, while no deaths were recorded.

Most patients (n=47, 66%) were treated with glucocorticoids (GC) with a median (IQR) starting dose of prednisone 25

Table I. Frequency of clinical manifestations in adults with B19V infection at rheumatologic evaluation. Data are presented as number (%), or median (IQR] when specified.

Manifestation category	Site / Symptoms	All n=71
Joint involvement	Any joint involvement	68 (96)
	Median of joint involvement (IQR]	3.0 [2.0 – 4.0]
	MCP joints	45 (63)
	Wrists	42 (60)
	Ankles	37 (52)
	Knees	36 (51)
	PIP joints	20 (28)
	Shoulders	20 (28)
	Elbows	14 (24)
	MTP joints	12 (24)
	Median of NRS for joint pain (IQR]	8.0 [7.0 – 8.0]
Cutaneous findings	Any skin manifestation	43 (61)
	Vascular purpura	16 (23)
	Gloves and socks syndrome	14 (20)
	Livedo reticularis	3 (4)
Constitutional symptoms	Fever	46 (65)
	Median duration, days (QR]	4.0 [2.0 – 5.0]
	Median temperature, °C (IQR]	38.0 [37.8 – 38.5]
	Headache	11 (16)
	Sore throat	10 (14)
	Cough	10 (14)
	Diarrhoea	5 (7)
	Nausea/vomiting	3 (4)
Other organ involvement	Haematologic abnormalities	10 (14)
	Hepatobiliary	6 (9)
	Ocular symptoms	1 (1)
	Coryza/conjunctivitis	1 (1)
	Cardiovascular	1 (1)

SD: standard deviation; IQR: interquartile range, MCP: metacarpal-phalangeal, MTP: metatarsal-phalangeal, PIP: proximal interphalangeal; NRS: Numeric Rating Scale.

(18.13, 25) mg/day and a median (IQR) duration of 28 (20.5, 38.5) days. The remaining patients were treated with anti-inflammatory drugs (n=27, 38%) or acetaminophen (n=11, 16%). In particular, 9 (90%) patients with haematological manifestations were treated with GC, whereas approximately half of the patients with fever (n=22, 48%) were treated with anti-inflammatory drugs. Baseline characteristics did not significantly differ between patients treated or not treated with GCs, as shown in Supplementary Table S1.

Time-to-resolution analyses

In the Kaplan-Meier analysis (Fig. 4), a borderline difference in time to resolution was observed between patients treated with GC and those not (p=0.051), while no significant differences were found for joint pattern or skin involvement (both p>0.2). In the multivariable Cox model including all three variables, GC use was independently associated with a faster resolution (HR 0.53, 95% CI: 0.31–0.90; p=0.020), whereas joint pattern and skin involvement remained non-significant (both p>0.3). The proportional hazards assumption was tested using Schoenfeld residuals and was not violated (global test p=0.53). Although confidence intervals were relatively narrow, the small number of unresolved cases may limit the precision of hazard estimates.

Predictors of arthritis resolution

In the reduced logistic regression model, none of the included variables showed a significant association. Odds ratios were near 1 with wide confidence intervals: 0.28 [95% CI: 0.03–2.50] for GC use, 1.01 [0.98–1.05] for IgM titre, and 1.01 [0.65–1.58] for joint count. None of the confidence intervals excluded the null value, and the model's overall explanatory power was limited. These analyses are shown in Supplementary Tables S2-4.

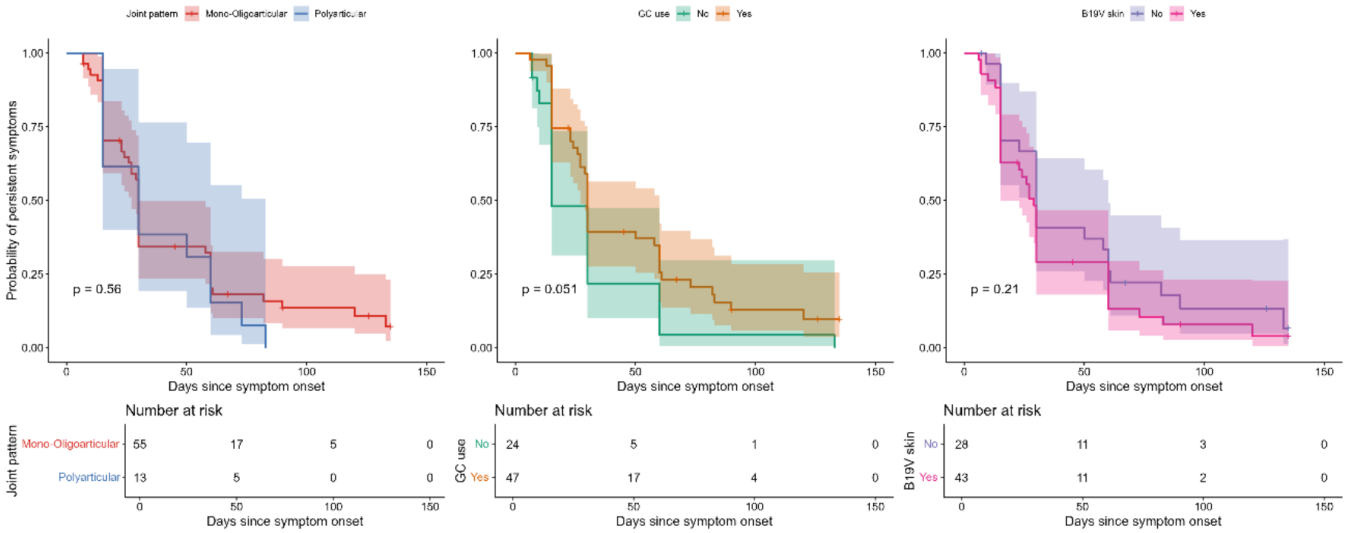

Fig. 4. Kaplan-Meier survival curves with log-ranks tests comparing time to B19V resolution by joint pattern (left), glucocorticoid use (centre) and B19V related skin involvement (right). B19V: Parvovirus B19; GC: glucocorticoid.

Sensitivity analyses

A sensitivity analyses restricted to definite cases yielded similar findings, confirming the robustness of the results.

Discussion

This multicentre study provides the largest systematic description of B19V infection presenting to rheumatology clinics in adults, during the 2023–2024 post-pandemic resurgence.

The clinical spectrum observed in our cohort confirms that B19V remains a relevant cause of acute arthralgia and rash in adults and underscore the diagnostic challenges it poses in routine rheumatology practice.

Most of our B19V patients referred for rheumatological evaluation were women of childbearing age. This likely reflects family-related or work exposure risk rather than a sex-specific susceptibility (27).

Joint manifestations represented the most frequent reason for rheumatologic referral, in line with previous adult cohorts (17, 18). Nevertheless, our findings diverge from classical descriptions of B19V-related arthritis, which typically emphasise acute, symmetric polyarthritis involving the small joints of the hands and feet (9). In our multicentre series, oligoarthritis affecting medium or large joints was by far the most frequent pattern, consistent with recent observations (8, 28). This observation expands the clinical spectrum of adult B19V arthritis and may reflect either a shift in post-pandemic viral epidemiology or improved case recognition by rheumatologists.

Despite some variability in follow-up duration, most patients were observed long enough to allow reliable time-to-event analyses. The 87% resolution rate may slightly underestimate the true recovery rate, yet it aligns with the well-recognised self-limiting course of B19V arthritis (29-31). Neither joint distribution nor concomitant B19V-related skin involvement was associated with a slower resolution, suggesting that these features may not be reliable predictors of a prolonged disease course.

The skin manifestations observed in our cohort expand the classical dermatologic spectrum of B19V infection. More than half of the patients presented with cutaneous involvement, including purpura or petechiae, erythema multiforme and, most frequently, papulopurpuric glove-stocking syndrome (PPGSS). Unlike the classic 'slapped cheek' rash seen in children, adult presentations are often purpuric, either localised or generalised, and can be easily misinterpreted (32, 33). PPGSS, first described by Harms *et al*. in 1990, and subsequently associated with B19V infection by Bagot and Revuz in 1991 (34, 35), remains the most distinctive dermatologic hallmark. However, the emphasis on its typical acral distribution may have led to under recognition of alternative purpuric presentations.

In our cohort, nine patients exhibited a symmetric pretibial purpura pattern without acral involvement, contrasting with the classical glove-and-sock distribution. Similar lesions have been recently described by Torun *et al*. (36). The broader term of 'Parvovirus B19-associated petechial-purpuric eruption (PAPPE)' has been proposed to include these atypical rashes (32), though its heterogeneity may limit its clinical utility. In this context, the distinctive bilateral pretibial distribution could serve as a helpful visual cue for clinicians during outbreaks or in the differential diagnosis of purpuric eruptions. Additionally, about one-in-five patients in our cohort presented with lesions clinically consistent with cutaneous vasculitis, another relatively common mimicker of B19V infection (37).

The apparent association between GC therapy and faster resolution observed in our analyses should be interpreted with caution. This likely reflects indication bias, as GC were prescribed to patients with more severe or systemic presentations rather than conferring a true therapeutic effect. Similar findings have been reported in previous series, where symptom improvement paralleled the self-limiting course of B19V (17, 18, 36, 38). In our cohort, baseline characteristics were broadly comparable between GC-treated and untreated patients, yet the Cox model suggested a faster resolution among those receiving GC, a finding not confirmed in logistic regression. This discrepancy likely reflects the high remission rate and variable follow-up rather than a true treatment effect. Together, these results reinforce the concept that B19V arthritis in adults is predominantly self-limited. Immunopathologic studies further suggest that viral arthritis resolves spontaneously with viral clearance and is not influenced by immunosuppression (10). Therefore, GC should not be used routinely but reserved for selected cases with severe systemic manifestations or diagnostic uncertainty.

Distinguishing post-viral arthritis from early autoimmune rheumatic disease remains a key clinical challenge (8). Both may present with symmetric polyarthritis, transient autoantibody positivity, and elevated inflammatory markers. However, a sudden onset during epidemic periods and resolution within weeks strongly suggest a viral aetiology, whereas persistence beyond three months, recurrence, or progressive serologic changes should raise suspicion for autoimmune disease (4, 39). In our cohort, most patients showed acute oligoarticular involvement and polymorphic rashes, including pretibial purpura, an atypical but distinctive clue. Routine B19V screening is not warranted in all cases of acute arthritis but should be reserved for patients with abrupt symptom onset, documented exposure, or concurrent purpuric or exanthematous rash. IgM serology remains the first-line tool, while PCR used when clinical suspicions persists despite negative serology (3). Interpreting results within their clinical and epidemiologic context is essential to avoid misclassification and unnecessary immunosuppression.

The present cohort was likely facilitated by the unique epidemiologic circumstances of 2023–2024, which saw a marked increase in B19V circulation across Europe following the lifting of COVID-19 containment measures (19, 40, 41). In France, d'Humières *et al*. (20) documented a steep rise in B19V detections, particularly among adults, while Giovanetti *et al*. (19) provided phylogenetic evidence of a single dominant genotype driving the outbreak across Western Europe. In Italy, Tonon *et al*. (42) described the same epidemic

wave through regional surveillance in Veneto, identifying young children as the main reservoir sustaining transmission. Together, these complementary data delineate a coherent picture of a continent-wide post-pandemic rebound. The Italian outbreak thus represents part of this broader European phenomenon, which likely increased population susceptibility and resulted in a higher rate of symptomatic infections in adults, including those previously considered at low risk (19, 43).

The strengths of this study include its multicentre design, the use of standardised data collection, and the inclusion of both typical and atypical clinical features. Limitations include its retrospective nature, the small number of persistent disease, which limits the statical power and of survival analyses. Follow-up duration was heterogeneous across centres, reflecting the real-world setting. However, symptom resolution or last contact was available for nearly all patients, allowing reliable time-to-resolution analysis.

A minority of probable cases were included based on epidemiologic linkage, potentially introducing misclassification bias, although their clinical profiles closely mirrored definite cases. Autoantibody data were not systematically available, precluding evaluation of post-viral autoimmunity.

Conclusion

This multicentre study provides the largest systematic characterisation of adult B19V infection referred to rheumatology. Our findings expand the recognised clinical spectrum, showing that oligoarthritis and atypical rashes, particularly pretibial purpura, are common and may serve as useful diagnostic clues during epidemic periods. The data support a pragmatic diagnostic approach: routine screening is unnecessary in all cases of acute arthritis but should be considered when suggestive features are present, such as sudden onset, known exposure, and concurrent rash. Most cases resolve spontaneously, and GC use, although associated with faster recovery, should be interpreted as observational rather than therapeutic.

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