Adult-onset Still’s disease and fever of unknown origin in India

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Abstract
Despite an essential differential diagnosis for fever of unknown origin (FUO) in young adults, adult-onset Still’s disease (AOSD) is infrequently considered and remained underdiagnosed in low-middle-income countries. The present study analyzed the clinical, serological, radiological, and pathological characteristics of AOSD presented as FUO in India. A hospital-based retrospective study of patients aged > 13 years admitted with FUO and later diagnosed with AOSD in Postgraduate Institute of Medical Education and Research, Chandigarh (India), was conducted between January 2014 and December 2020. Petersdorf and Beeson’s criteria were used to define FUO. The diagnosis of AOSD was made based on Yamaguchi’s criteria. Twenty-seven patients (median age 26 years, 14 females) were enrolled. All presented with intermittent fever with a median duration of 10 weeks. The typical features of AOSD at admission were arthralgia (n = 24), hepatosplenomegaly (n = 21), spiking fever ≥ 39 °C (n = 19), lymphadenopathy (n = 18), typical rash (n = 17), and sore throat (n = 11). Leukocytosis (n = 25) and neutrophilia (n = 19) were frequent. Hyperferritinemia was universal (range, 700–145,003 ng/ml; ≥ 2000, n = 23). At admission, AOSD was suspected in only nine FUO cases, while tuberculosis (n = 16), undifferentiated connective tissue disorder (n = 14), and lymphoproliferative disorder (n = 11) were common diagnostic possibilities. Crispin et al. clinical scale detected AOSD in only 15 (55.5%) FUO patients. Whole-body imaging (n = 27), including fluorodeoxyglucose positron emission tomography (n = 12), demonstrated reticuloendothelial organ-system involvement and serositis. Seventeen (63%) patients had macrophage activation syndrome at the time of AOSD diagnosis. AOSD FUO presents with typical but nonspecific features; thus, early differentiation from common causes (e.g., tuberculosis, lymphoma) is difficult. Macrophage activation syndrome is common in AOSD with FUO presentation.

Keywords Fever of unknown origin · Pyrexia of unknown origin · Adult-onset Still’s disease · Adults · Macrophage activation syndrome · Diagnosis · India

Introduction
Fever of unknown origin (FUO) commonly refers to persistent fever without an apparent initial cause. The definition of FUO has been evolving based on inpatient or outpatient evaluation, the host’s immune status, and etiological uncertainty after specific investigations or a defined duration of the evaluation [1, 2]. FUO remains one of the knottiest problems in medicine despite extensive and advanced technology. The etiology is a vast undertaking of multiple
infections, non-infectious inflammatory disorders (NIIDs), neoplasms, and miscellaneous disorders [1–4]. The causes mainly depend on geographic location, host age, immune status, and available investigations. Infections remain the most prevalent in low-middle-income countries (LMICs), while the high-income world has recently observed a decrease in infections with a rise in NIIDs in the FUO series [1–5].

Adult-onset Still’s disease (AOSD) is an uncommon NIID; however, it remains a common diagnostic consideration in young adults with FUO [1, 2, 4, 6]. The condition is heterogeneous and usually presents with high-grade fever, arthralgia or arthritis (polyarticular or pauciarticular), skin rash, lymphadenopathy, hepatosplenomegaly, and other systemic features, thus mimicking many common disorders. Moreover, the diagnosis remains clinical and empirical and requires meeting specific inclusion and exclusion criteria with negative evaluation for alternate diagnoses, including infections, NIIDs, and malignancies [7, 8]. Diagnostic testing with specific serological, radiological, and pathological features is not available for AOSD [9, 10].

In LMICs, AOSD often goes undiagnosed or misdiagnosed because of its rarity, a highly variable presentation, similarity with endemic infections (e.g., extrapulmonary tuberculosis, brucellosis, acute rheumatic fever, and enteric fever), and absence of diagnostic testing [2]. However, recent reports draw attention to the possibility that AOSD is a common FUO cause in young adults in LMICs (e.g., India) [2, 4, 6]. Thus, this study aimed to analyze the patients with FUO at presentation and later diagnosed as AOSD for their clinical, serological, radiological, and pathological characteristics.

**Methods**

**Study population**

The case records of all patients above 13 years admitted with FUO and later diagnosed with AOSD in the Department of Internal Medicine (Unit-1), Postgraduate Institute of Medical Education and Research, Chandigarh (India), between January 2014 and December 2019 (six years) were reviewed. Our institute is a 1948-bedded academic hospital that covers a large population of adjoining geographic regions of north India.

**Case definition**

FUO was defined based on Petersdorf and Beeson’s criteria (1961)—fever ≥ 38.3 °C of duration ≥ 3 weeks with no diagnosis after a 1-week inpatient evaluation, which is widely considered a classic definition [11]. According to the standard institutional protocol, FUO evaluation was guided by potentially diagnostic clues, i.e., any localizing clinical, laboratory, or imaging characteristic, potentially leading to a likely diagnosis [2].

The most validated diagnostic tool, Yamaguchi criteria, was used to diagnose AOSD. It consists of four major criteria (intermittent high-grade fever ≥ 39 °C lasting ≥ 1 week, arthralgia ≥ 2 weeks, typical evanescent salmon-pink maculopapular rash, leukocytes ≥ 10,000 per mm³ with ≥ 80% neutrophils), four minor criteria (sore throat, lymphadenopathy or splenomegaly, abnormal liver function tests, negative tests for antinuclear antibody and rheumatoid factor), and exclusion criteria (infection, cancer, and rheumatic disorders) [7]. The diagnosis of AOSD requires at least five features, including at least two major criteria and no exclusion criteria.

The diagnosis of macrophage activation syndrome (MAS) in AOSD was made based on the European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation (EULAR/ACR/PRINTO) criteria 2016. The criteria consist of five characteristic laboratory abnormalities that should not be otherwise explained by the patient’s condition (e.g., concomitant infection) [12]. The diagnosis of MAS requires serum ferritin > 684 ng/ml and two of the following: platelet counts < 181,000 per mm³, aspartate aminotransferase > 48 U/L, triglycerides > 156 mg/dL, and fibrinogen < 3.6 g/L.

**Data collection and analysis**

The patient’s details (e.g., sociodemographic, clinical, laboratory, imaging, pathological, treatment, and outcomes) were collected from the case files of the medical record department of our institution and were documented in the prefilled form. At admission ‘top three’ differential diagnoses (after a detailed clinical history, thorough physical examination, and baseline routine laboratory tests) were noted. A particular emphasis was made on whole-body imaging (fluorodeoxyglucose positron emission tomography with computed tomography [FDG-PET/CT] or contrast-enhanced computed tomography (CECT) thoraco-abdomen) and pathology findings.

A probability of AOSD in the case of FUO at admission was calculated in all patients by applying Crispin et al. clinical scale. It consists of the following five features (points in parentheses): arthritis (10), pharyngitis (7), typical rash (5), splenomegaly (5), and neutrophilia > 9500 per mm³ (18); ≥ 30 points (total 45) can establish AOSD diagnosis without further extensive and costly diagnostic workup [13]. Besides the 2016 EULAR/ACR/PRINTO criteria, the probability of MAS or secondary hemophagocytic lymphohistiocytosis (HLH) was calculated with the HLH-2014 criteria and H-Score at the time of diagnosis of AOSD [12, 14, 15].
The data were fed into Microsoft excel and analyzed using Statistical Package for Social Sciences (SPSS), version 25 for Mac. Discrete variables were described as frequency (n) and percentage (%). Continuous data were recorded as median with interquartile range (IQR) or mean ± standard deviation (SD), depending on the normalcy of data. The Kolmogorov–Smirnov test and visual inspection of quantile–quantile plots checked the normalcy of data.

Results

Baseline characteristics

We enrolled 27 cases (14 females, 13 males). The median age of the patients was 26 years, ranging from 14 to 68 years, with all except one aged ≤ 40 years. All patients presented with intermittent fever with a median duration of 10 weeks (ranging from three weeks to two years, which was high-grade (≥ 39 °C) in 19). The next frequent presenting feature was arthralgia (n = 24) with or without synovitis (i.e., tenderness and/or swelling) (each, n = 12). Knee (n = 23), elbow (n = 21), shoulder (n = 20), wrist (n = 20), ankle (n = 18), hip (n = 18), metacarpophalangeal joints (n = 15), and interphalangeal joints (n = 14) were frequently affected. Both small and large joint involvement (n = 22) was common, and the patients frequently presented with a polyarticular (≥ 4 joints) involvement (n = 21). Seventeen (63%) patients had the typical transient maculopapular rash, which was present over proximal extremities (n = 10), trunk (n = 9), and/or face (n = 8). Sore throat or pharyngitis was documented in 11 cases. Other common systemic manifestations were myalgia (n = 16), involuntary weight loss (n = 15), appetite loss (n = 14), and night sweats (n = 9).

Twenty-one (77.8%) patients had enlargement of the liver and/or spleen (both, n = 13; hepatomegaly alone, n = 5; and splenomegaly alone, n = 3). Peripheral lymphadenopathy (n = 18, 66.6%) involving cervical (n = 13), axillary (n = 13), and/or inguinal (n = 4) groups was typical. Tachycardia was seen in about half (n = 14), and the mean pulse rate was 101.9 ± 14.5 min. Mean systolic and diastolic blood pressure were 105.7 ± 9.8 and 66.4 ± 8.3 mm of Hg, respectively. All patients had anemia which was normocytic normochromic (n = 14) or microcytic hypochromic (n = 13) type. Leukocytosis (n = 25, 92.6%) and neutrophilia (n = 19, 70.4%) were frequent. The prevalence of thrombocytosis (n = 6) and thrombocytopenia (n = 5) was similar and less common. Elevation of lactate dehydrogenase (n = 27, 100%) and liver transaminases (n = 20, 74.1%) was common, but hyperbilirubinemia was not documented. All patients had elevated laboratory markers of inflammation, most notably ferritin (range, 700–145,003 ng/ml; ≥ 2000, n = 23). Markers of coagulation, such as prothrombin time, international normalized ratio, and D-dimer, were invariably elevated (Table 1). Negative testing for rheumatoid factor (n = 27, 100%) and antinuclear antibodies (n = 24, 88.9%) was typical. A tuberculin skin testing (TST) was performed in 21 patients and detected negative in all except 1.

Differential diagnosis of FUO

AOSD was kept in only nine (33.3%) patients as a differential diagnosis for FUO at admission. Tuberculosis (extrapulmonary or disseminated form) (n = 16), undifferentiated connective tissue disorder (n = 14), lymphoproliferative disorder (n = 11), infective endocarditis (n = 4), acute rheumatic fever (n = 4), brucellosis (n = 4), and reactive arthritis (n = 3) were common clinical possibilities. Crispin et al. clinical scale was applied to all cases at baseline, but only 15 (55.5%) patients had ≥ 30 points. All patients had a negative laboratory evaluation for infections such as sterile cultures of blood and/or other body fluids, anti-streptolysin O titer (for acute rheumatic fever), IgM antibodies (for brucellosis,

| Parameter                  | Value                  |
|----------------------------|------------------------|
| Hemoglobin (g/dl)          | 8.5 (± 1.7)            |
| Mean corpuscular volume (fL)| 79.6 (± 7.5)           |
| White blood counts (per mm³)| 18,781.5 (± 6470.0)    |
| Neutrophils (%)            | 83.1 (± 7.1)           |
| Platelet counts (× 10³ per mm³)| 292.1 (± 147.3)   |
| Serum sodium (mmol/l)      | 135.9 (± 3.9)          |
| Serum potassium (mmol/l)   | 4.0 (3.8–4.3)          |
| Blood urea (mg/dl)         | 24.4 (± 10.2)          |
| Serum creatinine (mg/dl)   | 0.5 (0.4–0.6)          |
| Serum bilirubin (mg/dl)    | 0.4 (0.3–0.7)          |
| Aspartate transaminase (U/l)| 79.5 (42.25–171.0)    |
| Alanine transaminase (U/l) | 44.0 (20.5–89.0)       |
| Alkaline phosphatase (U/l) | 164.0 (116.0–236.0)    |
| Total serum protein (g/dl) | 7.0 (± 0.9)            |
| Serum albumin (g/dl)       | 3.0 (± 0.6)            |
| Lactate dehydrogenase (U/l)| 953.5 (637.25–1166.5)  |
| Triglycerides (mg/dl)      | 157.0 (123.0–273.0)    |
| Ferritin (ng/ml)           | 8131 (2000–27,503)     |
| C-reactive protein (mg/l)  | 116 (94.5–165.5)       |
| Erythrocyte sedimentation rate (mm/hr)| 66 (60–70) |
| Procalcitonin (ng/ml)      | 0.6 (0.2–4.4)          |
| Fibrinogen (g/l)           | 4.5 (2.9–5.8)          |
| Prothrombin time (sec)     | 19.0 (18.0–21.25)      |
| International normalization ratio | 1.4 (1.3–1.5)  |
| D-dimer (ng/ml)            | 2131.0 (1344.75–6195.75) |

Values are given in mean (± SD) or median (IQR)
Epstein-Barr virus, and scrub typhus), malaria antigen, and human immunodeficiency virus. However, intravenous broad-spectrum antibiotics were universally prescribed before the diagnosis of AOSD. Five patients also received a trial of empirical anti-tuberculosis therapy.

### Whole-body imaging and pathological findings

A CECT (n = 26) and/or $^{18}$FDG-PET/CT ($n = 12$) was done in all patients. It typically showed hepatosplenomegaly (both, $n = 13$; hepatomegaly alone, $n = 5$; and splenomegaly alone, $n = 3$), lymphadenopathy ($n = 15$; thoracic and/or abdominal), and serositis ($n = 8$; pleural effusion, ascites,

| Case no | Age (years), sex | Lymph nodes | Bone marrow | Spleen | Liver |
|---------|------------------|-------------|-------------|--------|-------|
|         |                  | Cervical (bilateral) | Supraclavicular | Axillary (bilateral) | Thoracic/mediastinal | Abdominal/mesenteric | Inguinal (bilateral) |
| 1       | 24, Female       | 6.6          | 6.6         | 7.2     | 4.2     | 5.4     | 4.5     | 4.1 | 6.2 | –    |
| 2       | 16, Male         | 6.4          | –           | 2.5     | –       | 2.0     | 2.1     | 4.2 | 2.5 | –    |
| 3       | 29, Female       | 9.7          | –           | 10.1    | 7.4     | 8.0     | 6.4     | 4.5 | 8.0 | –    |
| 4       | 36, Male         | 5.5          | 3.0         | 4.7     | 8.0     | 11.4    | –       | 4.5 | 6.0 | 4.4  |
| 5       | 26, Male         | 1.8          | 1.5         | 3.5     | –       | 1.8     | –       | 4.7 | –   | –    |
| 6       | 67, Female       | 1.5          | 3.5         | 6.9     | 9.1     | 5.7     | 1.5     | 5.6 | 4.3 | –    |
| 7       | 23, Male         | 1.6          | –           | –       | 1.5     | 1.5     | –       | 3.4 | –   | –    |
| 8       | 37, Male         | 1.5          | –           | –       | –       | –       | –       | 4.0 | 3.2 | –    |
| 9       | 20, Male         | –            | –           | –       | –       | –       | –       | –   | –   | –    |
| 10      | 31, Female       | 1.6          | –           | –       | –       | 1.5     | –       | –   | 3.1 | –    |
| 11      | 26, Female       | 1.6          | 1.5         | 1.5     | 3.5     | 4.5     | –       | 4.2 | –   | –    |
| 12      | 40, Female       | 6.9          | –           | –       | 1.5     | 5.4     | 4.5     | 6.7 | 4.2 | –    |

**Fig. 1** FDG-PET findings (Case 1, Table 2) showing FDG avid enlarged lymph nodes in bilateral cervical, supraclavicular, axillary, and intrathoracic regions (thin arrows) (a to c), splenomegaly with homogeneously increased FDG uptake (star) (d & e), and diffuse increased FDG uptake in the bone marrow (thick arrow) (a)
and/or pericardial effusion. $^{15}$FDG-PET demonstrated increased FDG avidity in reticuloendothelial organs, particularly in lymph nodes, spleen, and bone marrow (Table 2, Figs. 1, 2, 3). Echocardiography was available in 18 cases and demonstrated abnormalities in three, including pericardial effusion ($n = 3$; mild to moderate in 2, massive in 1) and reduced ejection fraction (ejection fraction 35–40%, $n = 2$; ejection fraction 50%, $n = 1$). All three cases of abnormal echocardiography were detected in patients with MAS.

Lymph node pathology (fine-needle aspiration, $n = 9$; biopsy, $n = 3$; or endobronchial ultrasound-guided transbronchial needle aspiration, $n = 2$) revealed reactive lymphoid hyperplasia ($n = 11$) or normal lymphoid tissue ($n = 4$). Bone marrow examination ($n = 13$) invariably showed a normal-/hypercellular marrow. In addition, hemophagocytosis was detected in five cases. Kidney biopsy was performed in one AOSD patient with persisting nephrotic-range proteinuria and revealed C3 glomerulopathy.

### Treatment and outcome

Combination therapy with nonsteroidal anti-inflammatory drugs (naproxen, $n = 25$; or etoricoxib, $n = 2$), oral steroids (prednisolone, $n = 25$; or dexamethasone, $n = 1$), and/or disease-modifying antirheumatic drugs (methotrexate, $n = 5$; or hydroxychloroquine $n = 3$) was prescribed to all but one (who received only naproxen). The oral steroid was used in a prednisolone-equivalent dose of 0.5–1.0 mg/kg/day. In addition, intravenous pulse-methylprednisolone ($n = 2$) and intravenous immunoglobulin ($n = 2$) were required for treating MAS. Biologics (tumor necrosis factor-α blockers, IL-1 inhibitors, and IL-6 inhibitors) were not used in any patient.

Overall, 17 (63%) patients were diagnosed with MAS based on the 2016 EULAR/ACR/PRINTO criteria, while five (18.5%) patients fulfilled the HLH-2004 criteria. The mean H-score was $173.7 \pm 61.0$ (range 68–309) at the time of diagnosis of AOSD in FUO patients. One patient
died due to MAS. The median hospital stay of the study patients was 11 days (range, 5–35 days).

Discussion

Although AOSD is a rare systemic inflammatory disorder, it remains an essential differential diagnosis for FUO in young adults. Our study is one of the extensive series on AOSD with FUO presentation from LMICs. The report demonstrates that myriad features, albeit typical for AOSD, make an early suspicion and a rapid diagnosis challenging in FUO cases. The diagnosis often requires an extensive evaluation with whole-body imaging and histopathologic examination to exclude infections, malignancies, and other NIIDs. Furthermore, AOSD FUO patients usually have advanced disease with a high incidence of MAS.

Though FUO typically results from an atypical presentation of common diseases, AOSD presented with the usual features in our series. Correlating with the previous series, it remained a disease of young adults with a slight female preponderance [6, 16–18]. High-grade fever, hepatosplenomegaly, lymphadenopathy, arthritis, and skin rash were typical. Laboratory testing almost invariably revealed marked hyperferritinemia (> 2000 ng/ml), neutrophilic leukocytosis, anemia, transaminitis (without hyperbilirubinemia), and coagulopathy. However, these characteristic features are often nonspecific. The possibility of AOSD was considered in only one-third of FUO cases at presentation, while tuberculosis, undifferentiated connective tissue disorder, or lymphoproliferative disorders were considered more frequently. The diagnosis of AOSD remains challenging without high clinical suspicion and a detailed radiological, serological, and pathological evaluation [6–10].

AOSD FUO cases often have hepatosplenomegaly and lymphadenopathy [6, 16, 17]. Moreover, increased FDG activity in the reticuloendothelial organs such as bone marrow, lymph nodes, and spleen is typical on $^{18}$FDG-PET/CT [18–21]. Thus, it can be confused with other common causes of FUO, including hematological malignancies (e.g., lymphoma or leukemia), chronic infections (e.g., extrapulmonary tuberculosis, histoplasmosis, brucellosis, or enteric fever), or other NIIDs (e.g., sarcoidosis) [2, 9, 18, 21–23]. A lymphoproliferative disorder was a common differential diagnosis at admission in our patients. Such cases require invasive diagnostic procedures for detailed histopathological examinations (e.g., lymph node and/or bone marrow biopsy) before initiating steroids which can mask lymphoma or leukemia. Lymph node and bone marrow examinations were frequently performed in our patients and typically yielded normal tissue or reactive hyperplasia, concurring

Fig. 3 FDG-PET findings (Case 3, Table 2) showing increased FDG uptake in the lymph nodes in bilateral cervical, axillary, and intrathoracic regions (thin arrows) (a to c), enlarged spleen (star) (a, f, & g), and bone marrow (thick arrow) (a, g, & h), and mildly FDG avid bilateral pleural thickening (arrowhead) (d & e) and pericardial thickening with moderate pericardial effusion (double vertical arrow) (e)
with previous data [18]. AOSD and coronavirus-associated multisystem inflammatory syndrome in children (MIS-C) or adults (MIS-A) share many clinical and laboratory features; however, cardiovascular and gastrointestinal abnormalities are prominent in the latter [24–26]. Our study was conducted before the pandemic, so MIS-C/A was not among the differentials.

Being the most common cause and a treatable condition, tuberculosis (extrapulmonary or disseminated form) remains a common concern in FUO patients in LMICs [2, 3, 18, 22]. A trial of empirical anti-tuberculosis therapy is frequently given in endemic regions for a delayed or no definitive diagnosis, like in this study [2]. A positive TST has been suggested to have high specificity (up to 90%) for TB in FUO cases and used to decide on empirical anti-tuberculosis therapy [2]. All except 1 had negative TST in our study. Given high-grade fever, neutrophilic leucocytosis, and coagulopathy, antibiotics are commonly prescribed to cover sepsis before diagnosing AOSD in FUO patients. Crispin et al. proposed a clinical scale to differentiate AOSD from other causes of FUO at admission and found a specificity of 98% and sensitivity of 76.9% [13]. However, this score missed about half of the cases in our FUO patients. Though a small single-center study, our report incites further validation of Crispin et al. scale in larger and different populations. We also suggest including essential parameters such as ferritin or glycosylated ferritin, markers of coagulation, or lactate dehydrogenase for further modification and improvement over the current score [13]. A clinical score including readily available investigations may prevent extensive workup (e.g., expensive imaging like PET/CT or invasive studies) to diagnose AOSD in FUO cases.

MAS or secondary HLH is a life-threatening clinical syndrome of pathologic immune dysregulation and extreme inflammation [14, 18, 27]. AOSD is among the common NIIDs associated with MAS [2, 14]. The exact incidence is unknown. It mainly depends on the stage of the disease, the study population, and the criteria used for diagnosing MAS [16]. It has been reported as high as 23% in Asian patients where biological agents are infrequently used [16, 18, 28, 29]. Based on the 2016 EULAR/ACR/PRINTO criteria, MAS was detected in 63% of our patients with FUO. The HLH-2004 criteria were also fulfilled by 19%. The mean H-score of 174 reflected a high probability (54–70%) of secondary HLH at the time of AOSD diagnosis in our FUO cases [15]. Similar to the neoplastic causes of FUO, the presentation as FUO usually reflects a delayed diagnosis and advanced stage of AOSD [2, 5]. MAS may cause systemic complications (e.g., reduced myocardial contractility and massive pericardial effusion in our series) and death [14, 30]. High-dose steroid or intravenous immunoglobulin is required for treating MAS. Given the high morbidity and mortality, immunoglobulin therapy should be considered for secondary HLH or MAS, complicating an FUO case pending a definite diagnosis.

Limitation

Our limitations were single-center data, retrospective design, and a tertiary-care hospital referral bias. The study did not describe the full etiological spectrum of FUO, the prevalence of AOSD, and differentiating features of AOSD from other FUO causes. We could not use Fautrel et al. criteria for AOSD because of the non-availability of glycosylated ferritin [8]. 18FDG-PET/CT was not done in all cases because it was unavailable throughout the study period. The lack of post-discharge outpatient follow-up and long-term data was a limitation of our series, which could help to establish AOSD diagnosis with more certainty and to understand the disease course with initial presentation as FUO.

Conclusion

Though a common cause of FUO in young adults, AOSD is uncommonly considered in LMICs. The patients usually have typical but nonspecific features, thus often mimicking common FUO causes (e.g., extrapulmonary tuberculosis and lymphoma). The incidence of MAS is high in AOSD with FUO presentation. Because extensive investigations are required to reach a diagnosis, novel tools to differentiate AOSD early from other FUO causes are the need of the hour.

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Declarations

Competing interests The authors declare no competing interests.

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval Yes. The Institutional Ethics Committee approved the study (No.: INT/IEC/2021/SPL-1030).

Informed consent Informed consent was waived as the study involved anonymized retrospective patient data.
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