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# Combination method for the diagnosis of Tuberculous lymphadenitis in high burden settings

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## Abstract

**Background:** India reports the highest number of extrapulmonary tuberculosis (EPTB) cases globally, most of which are lymph node TB (LNTB). In high tuberculosis (TB) burden countries rapid diagnosis is very important. Fine needle aspirate cytology (FNAC) diagnosis can be made with features of caseous necrosis with/without epithelioid granulomas. However, bacteriological confirmation is essential. This study was performed to evaluate the performance of the diagnostic tests available namely FNAC, GeneXpert (GX) and Ziehl Neelsen stain (ZN) stain at resource restricted settings, for LNTB.

**Methods:** FNAC samples from affected lymph nodes were collected from 100 consenting patients with clinically suspected LNTB. FNA material was analyzed by cytomorphology, ZN and GX. If no Mycobacterium tuberculosis (MTB) was detected, repeat aspirate was cultured on Lowenstein Jensen medium. Descriptive statistical analysis was performed.

**Results:** Out of 100 cases, 73% showed cytological features consistent with TB. The most common cytomorphological pattern was epithelioid cell granulomas with caseous necrosis (59%). Caseous necrosis only pattern was seen in 14%. MTB was detected in 34% by ZN and 60% by GX. Overall, the combination of FNAC, ZN, GX detected 85% of LNTB.

**Conclusions:** A combination of FNAC, ZN and GX is a practical tool that can improve and quicken the diagnosis of LNTB in resource restricted high-burden settings.

**Keywords:** FNAC, GeneXpert, ZN stain, Extrapulmonary tuberculosis, Tuberculous lymphadenitis

## Introduction

Tuberculosis (TB) is an old disease; Genus Mycobacterium had originated more than 150 million years ago (Hayman 1984; Daniel 2006). Egyptian mummies had skeletal abnormalities characteristic of TB and their ancient art depicted Pott's deformities (Cave 1939; Morse et al. 1964). Even after so many years, TB is still a major global health problem.

World Health Organization (WHO) declared TB as the leading cause of death from a single infectious agent and one of the top ten causes of death worldwide (Global tuberculosis report 2020. 2020). According to the WHO global TB report 2020, globally an estimated 10 million people developed TB and 1.4 million died (Plan and to End TB, 2018–2022. 2019, United Nations; 2020).

Currently, India is at the first position among the eight counties carrying a high burden of Mycobacterium tuberculosis (MTB) in the world (World Health Organization. 2016). India accounts for 36% of global TB deaths among Human immunodeficiency virus (HIV)-negative people, and for 31% of the combined total number of TB

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deaths in HIV-negative and HIV-positive people (Global tuberculosis report 2020. 2020).

WHO has classified TB based on anatomical site of disease as Pulmonary Tuberculosis (PTB) and extrapulmonary tuberculosis (EPTB) (World 2013). EPTB is an equally important manifestation of TB which remains undiagnosed due to diagnostic challenges in developing countries. EPTB most frequently manifests as peripheral lymphadenopathy and it can involve any organ of the body including brain, skin, soft tissues, small and large intestine, appendix and genitourinary tract (World 2013).

EPTB represented 16% of the 7.1 million incident cases in 2019 (Global tuberculosis report 2020. 2020). Lymph node TB (LNTB, also called TB lymphadenitis) is the most common form of EPTB in India, accounting for around 35% of EPTB cases. The estimated incidence of TB in India was 2.1 million cases in 2019, out of which 385,254 people have EPTB (Global tuberculosis report 2020. 2020; Central TB division. 2020).

Cytology and conventional smear microscopy for acid fast bacilli (AFB) are used as the initial diagnostic tools for LNTB in resource poor settings. Fine needle aspiration cytology (FNAC) is a simple and rapid diagnostic technique (Corbett et al. 2003) but r cytomorphological features of LNTB can overlap with few other lesions other than TB (Sarfaraz et al. 2018). Conventional smear microscopy for AFB lacks sensitivity due to the paucibacillary nature of fine needle aspirates (FNA) (Tadesse et al. 2015; Shetty et al. 2020). Isolation of the organism in EPTB by culture remains a gold standard, but it has major limitation of turnaround time of 2–4 weeks leading to a delay in the commencement of anti-tuberculosis treatment (ATT). Considering these limitations, more rapid and reliable methods were needed.

In December 2010, WHO introduced the use of the GeneXpert MTB-RIF for detecting TB (Dewan et al. 2015). In India, it was adopted by Revised National TB Control Programme (RNTCP) in 2012 and the first pilot project was started in Maharashtra state, India (Pamra et al. 1987). The GeneXpert MTB-RIF is a real-time nucleic acid amplification test (NAAT) that simultaneously detects the DNA of MTB and the rpoB mutation associated with rifampicin resistance. It requires minimal technical expertise and has a turnaround time of less than 2 h (World Health Organization 2011). It can be readily performed on the aspirated samples for detection of MTB and helps in ruling out other cytomorphological mimics. GeneXpert MTB-RIF can detect as low bacterial load as 100–130 bacilli per ml of sample makes it ideal for paucibacillary tuberculosis. GeneXpert MTB-RIF is at par with culture which demands 100 bacilli per ml of sample (Manju and Madhusudhan 2020).

Nowadays, Xpert MTB/RIF assay is the most commonly used rapid diagnostic test worldwide. (Global tuberculosis report 2020. 2020). WHO recommends the use of Xpert MTB/RIF to improve the diagnosis of TB and rifampicin resistance in patients with various forms of EPTB (WHO consolidated guidelines on tuberculosis 2020).

WHO defines a bacteriologically confirmed case of TB as one from whom a biological specimen is positive by smear microscopy, culture or WHO-recommended rapid diagnostic test, such as the GeneXpert MTB-RIF assay (Global tuberculosis report 2020. 2020). The diagnostic accuracy of GeneXpert MTB-RIF for pulmonary TB has been reported high but the diagnostic performance-related data for lymph node specimens from high TB burden regions are limited.

More studies are needed in settings with high EPTB burden. We aimed to correlate the different cytomorphological patterns in a clinically suspected case of LNTB with GX and ZN. We tried to suggest the best possible combination of tests that will maximize the detectability in resource limited settings.

## Material and methods

The present prospective study was carried out in the department of pathology (Mumbai, India) over a period of one year. One hundred FNAC cases with clinical suspicion of LNTB and MTB detected either on GX, ZN smear or culture was taken up for the study. The scope of this study was not restricted by age or sex. Informed consent was obtained from the patients. All the necessary details such as age, sex, relevant history, group of lymph nodes involved, type of aspirate obtained on FNAC were noted.

This study was approved by the ethical committee. Only the approved personnel were involved in the collection of aspiration samples, compilation of the clinical data, and analysis of the aspiration samples.

### Sample collection and processing

Samples were collected from the enlarged superficial lymph nodes using 22–23 gauge needle and 10 ml plastic syringe with a detachable syringe holder.

### Preparation of Study samples

In each case, one part of the aspirated material was put in a sterile container with normal saline for GeneXpert and the other part was smeared on 2–3 slides and fixed in 95% ethyl alcohol for staining with Papanicolaou stain. In addition, one air-dried smear was stained by the Ziehl–Neelsen stain to indicate the acid fast bacilli (AFB). If both the GX and ZN were negative for MTB, a repeat

aspirate was collected in a sterile container for MTB culture.

### Cytological diagnosis

Papanicolaou (PAP) stained FNA smears were examined microscopically by two experienced pathologists. They were categorized into four cytomorphological patterns, a modification of the categories suggested by Das et al. (Das et al. 1990) namely; Pattern A: Cases showing caseous necrosis with epithelioid cell granulomas, Pattern B: Only epithelioid cell granuloma, Pattern C: Only caseous necrosis and Pattern D: Acute suppuration. FNA smears were considered as cytomorphologically suggestive of TB if cytology showed caseous necrosis with or without epithelioid granuloma. i.e. Pattern A and C.

### GeneXpert MTB-RIF

An equal volume of sample reagent was added into sample (1:1 ratio) and mixed well twice during the 15 min incubation time at room temperature. Two milliliters of the mixture was transferred in to test cartridge. The test cartridge was loaded into the Gene Xpert machine (Cepheid, USA). MTB positivity and its rifampicin resistance were determined within two hours.

### Ziehl Neelsen (ZN) smears microscopy

The second air dried FNA smear was stained with ZN staining procedure; the stained smears were examined under the oil immersion (100X) objective of a light microscope. A minimum of 100 fields of the stained smear were scanned to declare as negative.

### Mycobacterial culture

The samples which were negative for GX and ZN, a repeat aspiration was done and was outsourced for MTB culture by Lowenstein Jensen medium.

### Statistical analysis

The obtained parameters were evaluated using descriptive statistical analysis and presented in terms of percentage.

## Result

A total of 100 FNAC cases with clinical suspicion of TB and MTB detected either on GX, ZN smear or culture was taken up for the study. The age group of patients ranged from 6 to 73 years. Maximum cases (59%) were in their second to fourth decades of life, with male-to-female ratio of 1:2.7 and mean age of 26.3 years [Table 1].

Out of 100 cases of LNTB, 73 cases (73%) were cytologically suggestive of TB; 34 cases (34%) showed ZN positivity whereas 66 cases (66%) were ZN negative; sixty cases (60%) showed GX positivity and 40 cases (40%) were GX negative [Table 2].

**Table 1** Distribution of demographic and clinical characteristics

| Categories | n (%) |
|---|---|
| **Age (years)** | |
| ≤ 15 | 17 (17) |
| 16 to 30 | 59 (59) |
| 31 to 45 | 19 (19) |
| > 45 | 5 (5) |
| **Sex** | |
| Male | 27 (27) |
| Female | 73 (73) |
| **Anatomical site** | |
| Cervical | 89 (89) |
| Axillary | 10 (10) |
| Inguinal | 1(1) |
| **Size (cm)** | |
| ≤ 2 | 29 (29) |
| 2.1 to 4 | 59 (59) |
| 4.1 to 6 | 10 (10) |
| > 6 | 2 (2) |
| **Aspirate appearance** | |
| Purulent | 49 (49) |
| Hemorrhagic | 44 (44) |
| Caseous | 7 (7) |

**Table 2** TBLN positivity by different diagnostic methods

| Methods | Positive | Negative |
|---|---|---|
| FNAC | **73 (73%)** | **27 (27%)** |
| ZN | **34 (34%)** | **66 (66%)** |
| GeneXpert MTB-RIF | **60 (60%)** | **40 (40%)** |

The cervical region was the most common site of involvement (89%), followed by axillary (10%) and inguinal lymph node (1%). None of the cases presented with generalized lymphadenopathy. In our study, majority (85%) had single palpable lymph node followed by multiple unilateral lymphadenopathies (10%) and multiple bilateral lymphadenopathies in (5%) cases. Discharging skin sinuses were seen in association with matted lymph node in 10 cases (10%). The size of the involved lymph nodes varied from 1 to 9 cm; size range of 2.1 to 4 cm was the most common (59%). Grossly purulent material was aspirated in 49% cases, caseous or cheesy material in 7% cases, and hemorrhagic aspirate in 44% cases [Table 1].

The 100 cases of LNTB were grouped into four patterns based on cytomorphology. Cases showing epithelioid granulomas with caseous necrosis (Pattern A) constituted the predominant pattern with 59% cases, followed

by caseous necrosis only without epithelioid granulomas (Pattern C) 14% cases, epithelioid granuloma without necrosis (Pattern B) in 22% of the cases and 5% cases of non-caseating non-granulomatous pattern (Pattern D) which showed presence of abundant viable and degenerated polymorphs [Fig. 1; Table 3].

Overall, AFB smear positivity was seen in 34% cases, and out of that maximum positivity was present in Pattern D (100%) and least (9.1%) in Pattern B. GX positivity was seen in 60% cases, and out of that maximum GX positivity was seen in Pattern D (100%) and least (31.8%)", i.e., seven of 22 cases in Pattern B [Table 3].

Tubercle bacilli were demonstrated by ZN smear and/or GX and/or culture in the four FNAC cytomorphological categories as shown in Table 3. GX could not detect MTB in 40% of LNTB cases, which were detected on smear (1%) and culture (39%). GX detected MTB in 27% cases which were missed by AFB smear; out of which majority showed Pattern A (20%), followed by Pattern B (5%), and Pattern C (2%). Thus, in comparison to ZN smear, GX increased the MTB bacilli yield by 27%. Five among 60 (8.3%) MTB detected samples in GX had rifampicin resistance. Out of the 27 cases with cytomorphological that were not suggestive of TB, seven cases were MTB positive on both ZN stain and GX; two were positive on GX alone. Rest of the cases (Dewan et al. 2015) was MTB positive on culture. So overall, 85% of the cases of LNTB patients were identified by the combination of FNAC, ZN smear and GX.

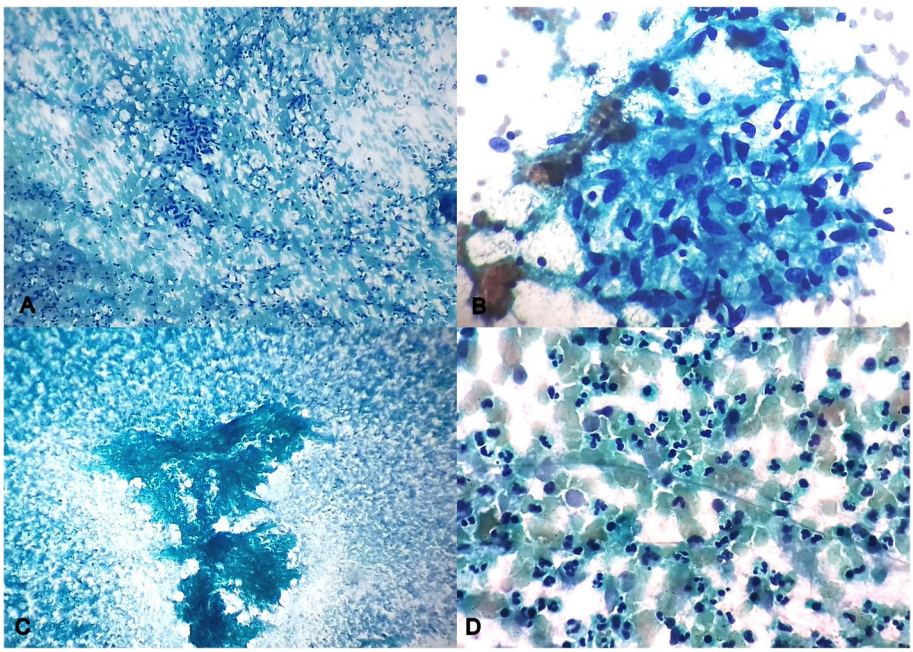


**Fig. 1** Photomicrograph showing **A**) Epithelioid cell granuloma admixed with lymphocytes, and caseous necrosis (Papanicolaou stain, 40x); **B**) Only epithelioid cell granuloma (Papanicolaou stain, 10x); **C**) Only caseous necrosis (Papanicolaou stain, 10x); **D**) acute suppuration (Papanicolaou stain, 40x)

**Table 3** Distribution of cases demonstrating positivity by ZN and/or GeneXpert MTB-RIF (GX) and/or culture according to cytomorphological patterns ($n = 100$)

| Methods | Cytomorphological patterns | | | | Total n (%) |
|---|---|---|---|---|---|
| | Pattern A | Pattern B | Pattern C | Pattern D | |
| **Only ZN positive (1)** | 1 | - | - | - | 1 (1) |
| **Only GX positive (27)** | 20 | 5 | 2 | - | 27 (27) |
| **ZN + GX positive (33)** | 14 | 2 | 12 | 5 | 33 (33) |
| **Culture positive (39)** | 24 | 15 | - | - | 39 (39) |

The majority of the aspirates were purulent (49%). Xpert MTB/RIF showed the highest detection rate of caseous (71.4%) and purulent (71.4%) aspirate, but low number of LNTB cases was identified from the hemorrhagic type of aspirate (45.5%). MTB was detected in 25% of hemorrhagic aspirates by ZN. Hemorrhagic aspirate showed Patterns A (50%) and B (50%). Patterns A (75.5%) was predominantly seen in purulent aspirate followed by, Patterns C (14.3%) and Patterns D (10.2%). Caseous aspirate only showed Patterns C (100%) on cytology [Table 4].

In the present study seven known cases of HIV were also included. Out of these, four cases (57.1%) showed Patterns D pattern and three cases (42.9%) showed Patterns C. GX positivity was seen in all the cases and ZN smear positivity in five cases.

## Discussion

Tuberculous lymphadenitis (LNTB) is the most common form of EPTB (Tadesse et al. 2015). It can be cured with a timely diagnosis and correct treatment. However, it remains a diagnostic and therapeutic challenging entity because it mimics other pathologic conditions. Obtaining tissue specimens for microbiological diagnosis is difficult and yields inconsistent laboratory findings.

There are various tests available for the diagnosis of LNTB namely; FNAC, AFB detection by smear, GX, culture. Each test has its own advantages and disadvantages. Culture is considered to be the gold standard test but, it is very time-consuming. If the patient is on anti-tuberculosis treatment the result may be negative because culture detects only live bacteria. AFB detection by microscopy is difficult due to sparse number of MTB bacilli in aspirates. FNAC is cheap, inexpensive and a quick test; epithelioid cell granulomas and caseous necrosis are highly suggestive of TB in India where TB is endemic. GeneXpert MTB-RIF can provide results within few hours and it can detect MTB as well as Rifampicin resistance.

LNTB can present at any age. In our study, cases belonged to the age range of 6–73 years. Majority of patients (59%) were in their second to fourth decades of life after which a declining trend was observed which was analogous with the findings of Ahmad et al. and Hemalatha et al. (Ahmad et al. 2005; Hemalatha et al. 2014) Male- to-female ratio of 1:2.7 which was also noted by Purohit et al. (Purohit et al. 2009) and Gupta et al. (Gupta et al. 2015). While Rajsekaran et al. (Rajsekaran et al. 2001) and Ahmad et al. (Ahmad et al. 2005) noted male predominance. The high incidence in females can be attributed to the poor nutritional status and overall lower standard of living in the socio-economically weaker sections of developing countries.

MTB usually gains access to the cervical lymph nodes through the tonsillar lymphoid tissue. This justifies the reason for the cervical lymph nodes (89%) being most commonly involved and inguinal lymph nodes (1%) being least commonly involved. Similar findings were also seen in most of the recently published studies by Nidhi et al., Chand et al., Bezabih et al. and Sharma et al. (Nidhi et al. 2011; Chand et al. 2014; Bezabih et al. 2002; Sharma et al. 2010). Single lymphadenopathy was the most common presentation (85%), which corroborated with the results reported by Paliwal et al. (Nidhi et al. 2011) and Chand et al. (Chand et al. 2014). However, Aggarwal et al. (Aggarwal et al. 2001), Gupta et al. (Gupta et al. 2015) and Ahmad et al. (Ahmad et al. 2005) reported multiple unilateral lymph node involvement as the most common presentation.

In the present study, gross appearance of the aspirate was mostly purulent (49%) and hemorrhagic (44%) whereas caseous aspirate was least common (7%). In other studies, hemorrhagic aspirate was the most common and caseous the least common (Hemalatha et al. 2014; Masilamani et al. 2015). Most common cytomorphological pattern in our study was epithelioid granulomas with caseous necrosis in 59% cases. Gosavi et al. (Gosavi et al. 2017) (60%) and Gupta et al. (Gupta et al. 2015) (52.5%) also reported epithelioid granulomas with caseous necrosis as the most common cytomorphological pattern. However Paliwal et al. (Nidhi et al. 2011) (39.2%) reported necrosis only without epithelioid granuloma as the most common cytomorphological pattern. Chand et al. (Chand et al. 2014) observed reported caseous necrotic material with epithelioid cell granulomas and giant cells as the most common cytological pattern. Blood tinged aspirate was predominantly seen in Patterns A and B. Purulent and caseous aspirate were seen predominantly in Patterns C and D. These findings could also be considered similar to

**Table 4** Detection of TBLN in association with aspirate types using ZN, GeneXpert MTB-RIF and cytolomorphological patterns

| Aspirate type | n | ZN stain | | GeneXpert MTB-RIF | | Cytomorphological patterns | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Positive n (%) | Negative n (%) | Positive n (%) | Negative n (%) | CN + ECG n (%) | ECG n (%) | CN n (%) | AS n (%) |
| **Purulent** | 49 | 19 (38.8) | 30 (61.2) | 35 (71.4) | 14 (28.6) | 37 (75.5) | - | 7 (14.3) | 5 (10.2) |
| **Hemorrhagic** | 44 | 11 (25) | 33 (75) | 20 (45.5) | 24 (54.5) | 22 (50) | 22 (50) | - | - |
| **Caseous** | 7 | 4 (57.1) | 3 (42.9) | 5 (71.4) | 2 (40) | - | - | 7 (100) | - |

studies by Hemalatha et al. (Hemalatha et al. 2014) and Masilamani et al. (Masilamani et al. 2015).

Ziehl Neelsen staining for AFB is a simple, quick and affordable method. In our study, overall AFB positivity was seen in 34% of the cases, out of which the maximum positivity of AFB (57.1%) was observed in caseous aspirates followed by purulent aspirate (38.8%) and least in hemorrhagic (25%). It is analogous to the findings of Nidhi et al. (Nidhi et al. 2011) and Fanny et al. (Fanny et al. 2012). The reason may be increased bacillary load in the aspirates showing purulent or necrotic material. Based on the cytology pattern, maximum positivity was seen in smears revealing acute suppurative pattern (100%) and least in epithelioid granuloma only pattern (9.1%). Gosavi et al. (Gosavi et al. 2017) observed an AFB positivity of 75%; Pattern A most commonly showed AFB positivity (51.5%). Gupta et al. (Gupta et al. 2015) reported overall AFB positivity of 65% with maximum positivity (75%) in acute suppurative and with or without epithelioid granulomas. Aggarwal et al. (Aggarwal et al. 2001) reported AFB positivity in 19.6% among 138 cases with maximum AFB positivity in caseous necrosis only pattern. According to Fantahun et al. (Fantahun et al. 2019) and Iwnetu et al. (Iwnetu et al. 2009), the explanation for low positive rate in ZN is because the detection rate is greater than 5,000 organisms/ml of sample, however very low bacilli is retrieved in a FNA sample. Tadesse et al. (Shetty et al. 2020) had higher AFB detection rate on ZN smear. The uneven distribution of bacilli during the smear making in FNA or excessively bloody aspirate may be causing the discrepancy. The quality of the aspirate, the smearing method used, and the scanty bacilli found in the FNA could be the main factor for decreased AFB detectability with ZN stain.

Xpert MTB/RIF assay positivity rate was 60%. Twenty seven samples were detected in Xpert MTB/RIF assay but negative in ZN. Out of this majority had a Pattern A (21%) and a hemorrhagic aspirate (20.5%). Thus, in comparison to smear, GX increased the MTB bacilli yield by 27%. This might be due to early stage of the disease and low bacterial load. Fantahun et al. (Fantahun et al. 2019) observed Xpert MTB/RIF positivity as 20% and 68.4% in hemorrhagic and caseous/purulent aspirates respectively. Manju et al. (Manju and Madhusudhan 2020) study had Xpert MTB/RIF positive rate of 79.89% despite inclusion of only non-caseous or non-purulent material for Xpert MTB/RIF. This relative higher yield may be due to microscopic necrosis which grossly doesn't look like pus or may be due to more number of needle strokes or repeat sampling.

## Conclusion

The detectability of LNTB with combination of FNAC, ZN smear and GX is very high (85%). Therefore, they may be employed for better and quicker diagnosis of clinically presumptive LNTB patients in resource restricted settings with high EPTB burden.

#### Abbreviations

AFB: Acid fast bacilli; ATT: Anti-tuberculosis treatment; EPTB: Extrapulmonary tuberculosis; FNAC: Fine needle aspirate cytology; GX: Genexpert; HIV: Human immunodeficiency virus; LNTB: Lymph node TB; MTB: Mycobacterium tuberculosis; NAAT: Nucleic acid amplification test; PAP: Papanicolaou; PTB: Pulmonary Tuberculosis; RNTCP: Revised National TB Control Programme; TB: Tuberculosis; WHO: World Health Organization; ZN: Ziehl Neelsen.

#### Authors' contributions

All authors have contributed towards the conception and development of survey, data collection, data analysis and interpretation, and preparation and critical revision of this manuscript. The author(s) read and approved the final manuscript.

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#### Availability of data and materials

Available.

### Declarations

#### Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

#### Consent for publication

Informed consent was obtained from all individuals included in the study.

#### Competing interests

The authors declare that they have no competing interests.

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## Publisher's Note