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Original Article

Tuberculin Skin Test as a Diagnostic Tool for Sarcoid Uveitis: A Retrospective Analysis at Ramathibodi Hospital, Thailand

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Abstract

Background: Sarcoid uveitis is rarely diagnosed in tuberculosis-endemic countries like Thailand, despite similar clinical presentations to tuberculous uveitis. Differentiating between the 2 conditions is challenging.

Objectives: To identify the diagnostic value of the tuberculin skin test (TST) for diagnosing sarcoid uveitis and use high-resolution computed tomography (HRCT) chest as a gold standard.

Methods: A retrospective review of medical records was conducted for patients who visited the uveitis clinic between January 2006 and December 2021. The inclusion criteria is the patients who underwent both TST and HRCT as part of the diagnostic workup. TST result < 10 mm, which excluded tuberculous uveitis, was strongly considered for diagnosing sarcoid uveitis, with HRCT finding serving as the gold standard due to the limitation of performing tissue biopsy.

Results: The study included 48 uveitis patients, with 19 (39.6%) showing sarcoidosis on HRCT. Among these, 18 (94.7%) had TST < 10 mm, while 1 (5.3%) had TST ≥ 10 mm. In contrast, of those in the non-sarcoidosis group, 13 (44.8%) had TST < 10 mm and 16 (55.2%) had TST ≥ 10 mm. Statistical analysis revealed a significant association between TST and HRCT ($P < .001$). The TST's sensitivity, specificity, positive predictive value, and negative predictive value for sarcoid uveitis was 94.7%, 55.2%, 58.1%, and 94.1%, respectively.

Conclusions: This study suggested that TST is a potential noninvasive adjunctive diagnostic tool for sarcoid uveitis. Using TST as a screening tool, due to its high sensitivity, could improve early detection and appropriate management of patients, leading to better clinical outcomes.

Keywords: Sarcoid uveitis, Noninvasive tool, Tuberculin skin test, High-resolution computed tomography chest, Tuberculous uveitis

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Introduction

Sarcoidosis is a multisystem inflammatory disease that can affect various organs in the body with unknown etiology characterized by the presence of noncaseating granulomas in the affected organs. Sarcoidosis affects people worldwide. The incidence of sarcoidosis can vary across the world. Sarcoidosis is generally more common in the western countries rather than the eastern countries. For example, the annual incidence of sarcoidosis in African-Americans is as high as 30-70 per 100 000 population, followed by the Europeans is 10-20 per 100 000 population, but as low as 1-3 per 100 000 population

among Asians and Hispanics.[1-11] However, in the recent years, there has been an increase in incidences among Asian countries like India,[2] Japan,[3] and Korea.[4] It is important to note that accurate data on the global incidence for sarcoidosis are limited due to variations in diagnostic practices, underreporting, and regional differences in disease awareness.

The most affected sites are the lungs and intrathoracic lymph nodes (more than 90% of patients.)[5-12] Including the eyes, sarcoidosis uveitis, also known as ocular sarcoidosis, is a specific manifestation of sarcoidosis that primarily affects the intraocular tissue. A recent retrospective series reported that uveitis was the first presentation of sarcoidosis in 80% of presumed or biopsy-proven cases.[13] Patients with sarcoidosis uveitis can present with blurred vision, redness, floater, or discomfort. Clinical manifestations are acute or chronic granulomatous uveitis, which can be any type of uveitis (anterior, intermediate, posterior, or panuveitis). Typical biomicroscopic findings include mutton-fat keratic precipitates, Koeppe and Busacca iris nodules at the pupil margin and in the iris stroma, respectively, and white clumps of cells (snowball) in the anterior vitreous. Moreover, typical radiological findings are bilateral hilar lymphadenopathy, or parenchymal lung changes consistent with sarcoidosis. Definite diagnosis requires the presence of noncaseating granuloma or only minimal amount of focal necrosis from biopsy tissue. A combination of clinical, radiological, and histopathological criteria is used to diagnose sarcoidosis. However, biopsy procedures such as diagnostic pars plana vitrectomy (PPV), transbronchial lymph node and lung biopsies are invasive procedures.[14, 15]

Clinical, radiological, and histopathological similarities with tuberculosis (TB) make the differential diagnosis of 2 conditions difficult especially in countries with endemic area of TB including Thailand.

In Thailand, sarcoid uveitis has rarely been diagnosed. It is not known whether the rarity of sarcoid uveitis in Thailand is genuine or whether sarcoid uveitis in this area remains underdiagnosed. However, a recent retrospective cohort study from Siriraj Hospital[16] showed an increase in diagnosis of sarcoidosis in Thailand. The study found that from 2005 to 2018, 89 confirmed cases of sarcoidosis were identified. Most patients had intrathoracic disease (81 cases [91%]). Sarcoid uveitis was the most common extrathoracic disease (35 cases [39.3%]), which is far higher than previous reports from Europe and North America.[6, 7, 17, 18] It may be the clue that the actual number of sarcoid uveitis is higher than we expected. So, we need to know what the noninvasive diagnostic tools to differentiate sarcoid uveitis from tuberculous uveitis.

Tuberculin skin test (TST), also known as the Mantoux test, is primarily used to diagnose TB infection. This test is cost-effective and feasible in almost every hospital. It involves injecting a small amount of purified protein derivative (PPD) 0.1 mL, a substance derived from *Mycobacterium tuberculosis* (MTB), into the skin and then measures the reaction at the injection site after 48-72 hours. The test measures the immune response to the PPD antigen, which can indicate previous exposure to TB. So, we can use TST as a tool to exclude TB infection.

The aim of this study was to evaluate sensitivity, specificity, positive predictive value, and negative predictive value of TST as a diagnostic tool to diagnose sarcoid uveitis. We used high-resolution computed tomography (HRCT) of the chest as a gold standard. Indicative findings of sarcoid uveitis from chest HRCT such as bilateral hilar lymphadenopathy, mediastinal lymphadenopathy, lung parenchymal involvement of micronodules with a perilymphatic distribution.[2, 19]

Methods

Data Source

All data were kept confidential in our database. We retrospectively reviewed the electronic medical records of 1628 subjects who were diagnosed with uveitis at Faculty of Medicine Ramathibodi Hospital, Bangkok, Thailand between January 2006 and December 2021.

Subject Selection

In this study, we aimed to assess the diagnostic utility of TST compared to HRCT of the chest as a noninvasive tool for identifying sarcoid uveitis. Patients may or may not have undergone a biopsy.

Besides the performed TST and HRCT, inclusion criteria consisted of clinical signs corresponding with sarcoidosis uveitis following the International Workshop on Ocular Sarcoidosis (IWOS)[15] by 2 of the following: mutton-fat keratic precipitates (large and small) and/or iris nodules at pupillary margin (Koeppe) or in stroma (Busacca), trabecular meshwork nodules and/or tent-shaped peripheral anterior synechia, snowballs/string of pearls vitreous opacities, multiple chorioretinal peripheral lesions (active and atrophic), nodular and/or segmental periphlebitis (candle wax drippings) and/or macroaneurysm in an inflamed eye, optic disc nodule(s)/granuloma(s) and/or solitary choroidal nodule, or bilaterality (assessed by ophthalmological examination including ocular imaging showing subclinical inflammation). Exclusion criteria consisted of HIV infected patients, immunocompromised patients or on immunosuppressive drugs, and concurrent active pulmonary or other TB disease.

Interpretation

TST results were considered positive for the diagnosis of sarcoid uveitis if the induration diameter measured less than 10 mm (negative results for tuberculosis infection). Cut point of 10 mm in the endemic area where TB is common, including Thailand according to the Centers for Disease Control and Prevention guideline. In this study, interpretation was performed in an ophthalmology outpatient department at 48-72 hours after the PPD injection. Chest HRCT findings indicative of sarcoidosis[2, 19] included bilateral hilar lymphadenopathy, mediastinal lymphadenopathy, lung parenchymal involvement of micronodules with a perilymphatic distribution were used as a gold standard.

A standardized case record form was used to record demographics and disease characteristics. Analyses were performed using Stata software, version 17 (StataCorp. Version 17. College Station, TX: StataCorp LLC; 2021). The mean (SD), median, and range were used for descriptive statistics. The chi-squared test was used to analyze the statistics. *P* values < .001 were considered statistically significant. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated by using Stata software.

Results

Demographic Data and Clinical Characteristics

From 2006 to 2021, a total of 48 patients with uveitis met the inclusion criteria. There were 23 (48%) men and 25 (52%) women. The mean (SD) age at presentation was 48.2 (16.0) years (range 10-77 years). Most cases (43.75%) were in the middle-age range of 40-59 years. In terms of laterality, bilateral involvement (29 patients [60.4%]) was more

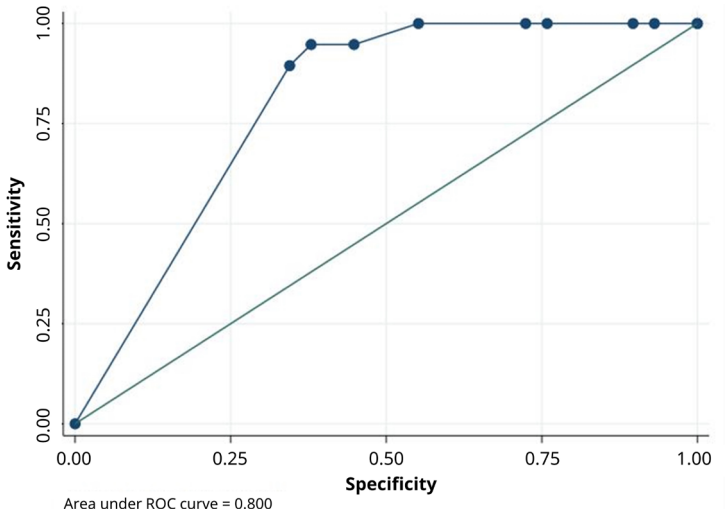
common than unilateral involvement (19 patients [39.6%]). Anatomically, panuveitis was the most common type of uveitis, seen in 34 cases (70.8%), followed by posterior uveitis 7 cases (14.6%), anterior uveitis 6 cases (12.5%), and intermediate uveitis 1 cases (2.1%).

The study included 48 uveitis patients, with 19 (39.6%) showing findings consistent with sarcoidosis on HRCT chest. Among patients diagnosed with sarcoid uveitis based on chest HRCT, 18 (94.7%) exhibited TST < 10 mm, while 1 (5.3%) showed TST ≥ 10 mm. In contrast, of those in the non-sarcoid uveitis on chest HRCT, 13 (44.8%) displayed TST < 10 mm, while 16 (55.2%) had TST ≥ 10 mm (Table 1). Statistical analysis demonstrated a significant association between TST results and chest HRCT findings ($P < .001$). The sensitivity, specificity, positive predictive value, and negative predictive value of TST for sarcoid uveitis, using chest HRCT as the gold standard, were 94.7%, 55.2%, 58.1%, and 94.1%, respectively, and the areas under the receiver operating characteristic curve (AUC) was 0.800 (95% CI 0.698-0.903) (Figure 1).

Table 1. The Results of Tuberculin Skin Test as a Diagnostic Tool for Sarcoid Uveitis

Value	No. of Patients		
	Sarcoid Uveitis	Non-Sarcoid Uveitis	Total
< 10 mm (positive diagnostic test for sarcoid uveitis)	18	13	31
≥ 10 mm (negative diagnostic test for sarcoid uveitis)	1	16	17
Total	19	29	48

Figure 1. Areas Under the Receiver Operating Characteristic Curve Plotted to Determine the Diagnostic Values of Tuberculin Skin Test



A total of 48 patients with uveitis met the inclusion criteria. The number of sarcoid uveitis was 19 cases (definite 5 case, presumed 14 cases). The most common cause of non-sarcoid uveitis was tuberculous uveitis 18 cases, followed by 5 cases of Vogt-Koyanagi-Harada disease, 1 case of systemic lupus erythematosus, 1 case of Behcet's disease, 1 case of granulomatosis with polyangiitis, 1 case of Sjögren's syndrome, and 2 cases of idiopathic uveitis (Table 2).

Definite Sarcoid Uveitis

A 28-year-old male with bilateral granulomatous anterior uveitis, TST 0 mm, chest HRCT showed bilateral hilar lymphadenopathy, peribronchovascular nodularity (Figure 2A). Transbronchial needle aspiration (TBNA) detected nonnecrotizing granulomatous inflammation with Schaumann bodies.

A 31-year-old female with bilateral panuveitis, TST 0 mm, chest HRCT showed extensive small pulmonary nodules in both lungs with multifocal patchy ground-glass opacities in both upper lobes with extensive lymphadenopathy (Figure 2B). Cervical lymph node biopsy detected nonnecrotizing granulomatous lymphadenitis.

A 61-year-old female with bilateral panuveitis, TST 0 mm, chest HRCT showed bilateral hilar lymphadenopathy, multiple nodular and patchy ground-glass opacities at right upper lobe and right lower lobe (Figure 2C). TBNA detected nonnecrotizing granulomatous inflammation.

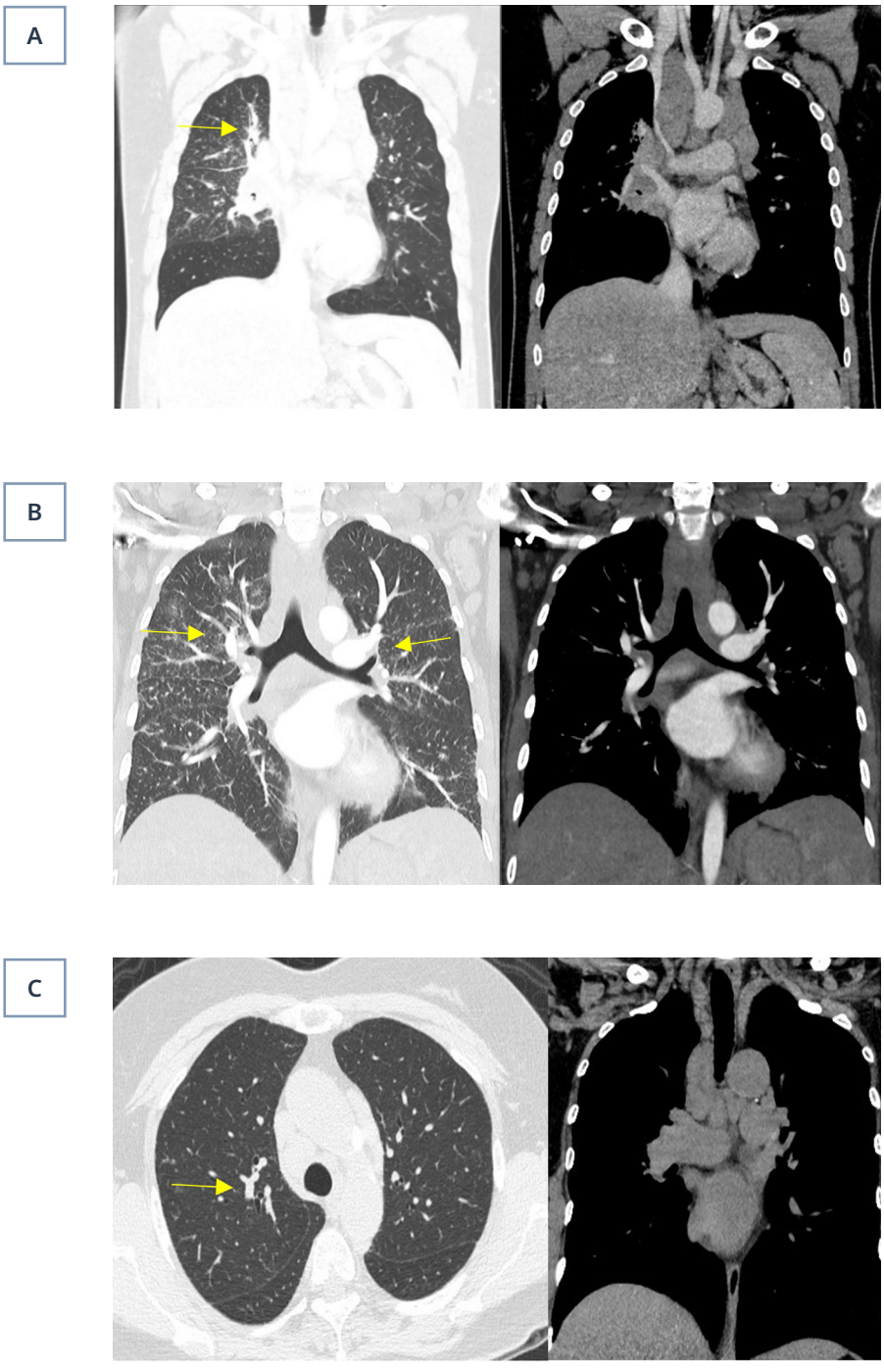
Presumed Sarcoid Uveitis

A 54-year-old male with right multifocal choroiditis with snowball and snowbank (Figure 3A), TST 5 mm, chest HRCT showed bilateral calcified hilar lymphadenopathy with '1-2-3 sign', peribronchovascular patchy ground-glass opacities both lungs (Figure 3B). TBNA detected no evidence of granuloma or carcinoma was seen.

Table 2. Causes of Uveitis

Cause	No. (%)
Sarcoid uveitis	19 (39.6)
Non-sarcoid uveitis	
Tuberculous uveitis	18 (37.5)
Vogt-Koyanagi-Harada disease	5 (10.4)
Systemic lupus erythematosus	1 (2.1)
Behcet's disease	1 (2.1)
Granulomatosis with polyangiitis	1 (2.1)
Sjögren's syndrome	1 (2.1)
Idiopathic	2 (4.1)

Figure 2. High-Resolution Computed Tomography of the Chest in Definite Sarcoid Uveitis

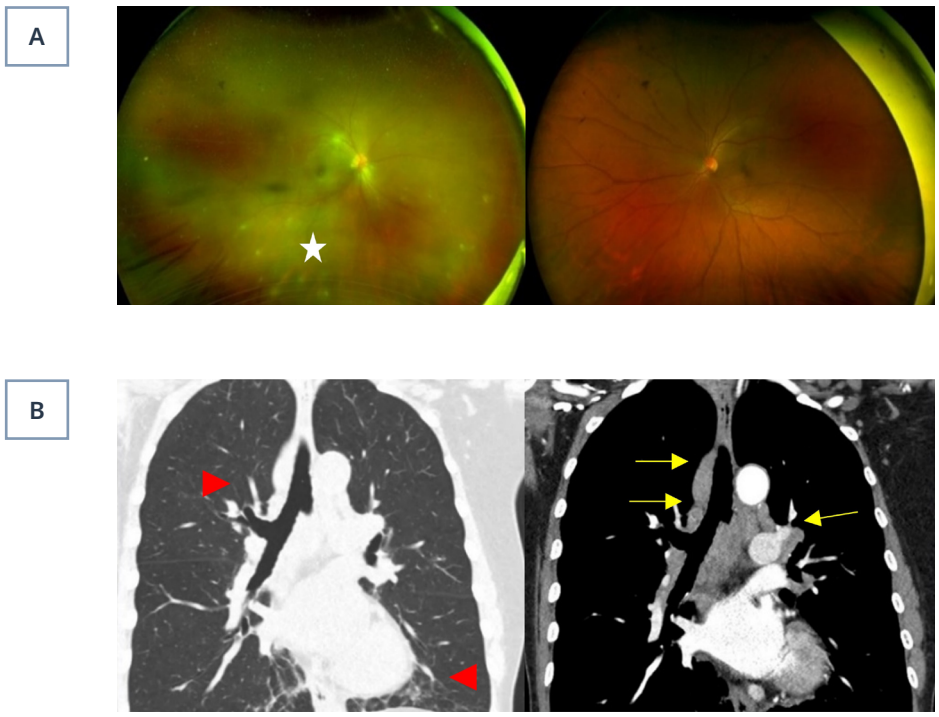


A, Bilateral hilar lymphadenopathy with peribronchovascular nodularity (arrow).

B, Extensive small pulmonary nodules with multifocal patchy ground-glass opacities in both upper lobes with extensive lymphadenopathy (arrow).

C, Bilateral hilar lymphadenopathy with ground-glass opacities at right upper lobe and right lower lobe (arrow).

Figure 3. Ultra-Widefield Fundus Camera of Right Eye and High-Resolution Computed Tomography of the Chest in Presumed Sarcoid Uveitis



A, Ultra-widefield fundus camera of right eye showed multifocal choroiditis with snowball and snowbank (star).

B, Chest HRCT showed bilateral calcified hilar lymphadenopathy with '1-2-3 sign' (arrow), peribronchovascular patchy ground-glass opacities both Lungs (arrow head).

Discussion

This study showed that TST had high sensitivity and negative predictive value which can be used as a screening tool to rule out sarcoid uveitis. Contrastingly TST had low specificity and positive predictive value which are not specific to sarcoid uveitis.

Sarcoidosis is a granulomatous disease that can sometimes resemble TB clinically, radiologically, and histologically. Therefore, it is important to rule out active TB infection, as it can present with similar symptoms and findings. The TST can help determine if a person has been exposed to TB in the past by measuring the immune response to TB antigens. This study chose TST as a study test due to feasibility, cost-effectiveness, and safety.

HRCT of the chest in which thin-slice chest images are obtained and post-processed in a high-spatial-frequency reconstruction algorithm. This technique is performed to visualize small structures of the lung and detect enlarged lymph nodes, which can be suggestive of various conditions, including sarcoidosis. That otherwise may be difficult to assess on a conventional chest imaging.[20]

To the diagnosis of sarcoid uveitis, both the TST and chest HRCT can be helpful. The diagnosis of sarcoid uveitis is typically based on a combination of clinical evaluation, ocular examination, imaging studies, laboratory tests (eg, serum ACE), and sometimes

a biopsy of affected tissues. The histopathological finding of sarcoidosis is the presence of noncaseating granulomas. These granulomas tend to be most prevalent around the bronchovascular area and the fibrous septate containing pulmonary veins.[21] While caseating granulomas are usually found in ocular tuberculosis, in conjunction with positive culture for MTB such as polymerase chain reaction (PCR) for MTB.[22]

In our study, there was a limitation in tissue biopsy for some patients. Tissue biopsy was attempted to confirm diagnosis as definite sarcoidosis uveitis in only 5 patients. The other 14 patients were diagnosed as presumed sarcoidosis uveitis. According to the revised the IWOS criteria[15] in 2017, ocular sarcoidosis was determined as definite, presumed, and probable.

Due to the retrospective nature of the study, it was not feasible to conduct TST or chest HRCT in all patients exhibiting clinical features consistent with sarcoid uveitis. Consequently, the number of patients included in this study is likely underestimated. Nonetheless, further prospective studies with larger sample sizes and extended follow-up periods are warranted to validate the utility of TST and HRCT of the chest. Additionally, it's important to acknowledge limitations associated with TST, such as the potential for false-positive results due to previous Bacillus Calmette-Guérin (BCG) vaccination or nontuberculous mycobacterial infections. Therefore, if feasible, the use of interferon-gamma release assay might be considered as an alternative to TST. For cases of highly suspected sarcoidosis uveitis with a positive TST, we recommend obtaining a tissue biopsy that presents pathological evidence of noncaseating granulomas to prevent missing a diagnosis of sarcoid uveitis.

However, the prevalence of the disease in the tested population has a significant impact on the positive and negative predictive values. This study conducted in Thailand, where sarcoidosis has a low prevalence. As the prevalence of the disease decreases, the positive predictive value experiences a decline, indicating a lower probability of correctly identifying true positive cases. Conversely, the negative predictive value shows an upward trend, suggesting a higher likelihood of correctly identifying true negative cases. These findings underscore the critical role that disease prevalence plays in determining the accuracy and reliability of predictive values in diagnostic testing.

The results of this present study correlate with a prior study[23] which suggested that TST may be a useful tool for diagnosing sarcoid uveitis. However, the diagnosis and management of sarcoid uveitis would typically involve a multidisciplinary approach, including ophthalmologists, pulmonologists, and other relevant specialists. The diagnosis may be based on a combination of clinical evaluation, medical history, imaging tests (such as chest x-ray or CT scan), laboratory investigations (such as TST, QuantiFERON TB, serum lysozyme or serum ACE), and sometimes a biopsy of affected tissues.[24-27]

Conclusions

This study suggested that the TST may be a potential noninvasive adjunctive tool for sarcoid uveitis. TST < 10 mm showed a significant association with the presence of sarcoidosis on chest HRCT. Using TST as a screening tool, due to its high sensitivity, could improve early detection and appropriate management of patients, leading to better clinical outcomes. Specifically, highly suspected sarcoidosis uveitis with common ocular signs includes mutton-fat keratic precipitates, iris nodules and snowballs/string of pearls vitreous opacities.

Additional Information

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Ethics Approval: This retrospective cross-sectional study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (MURA2022/290 on 9 May 2022), which waived the need for written informed consent from the subjects.

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Author Contributions:
Conceptualization: All authors
Formal Analysis: All authors
Methodology: All authors
Visualization: Salinthip Chimdist
Writing – Original Draft: Salinthip Chimdist
Writing – Review & Editing: All authors

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