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ORIGINAL RESEARCH

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Prevalence of indeterminate tuberculosis interferon-gamma release assays in COVID-19 patients: Systematic review and meta-analysis

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Abstract

Background and Aims: The reliability of interferon-gamma-release-assays (IGRAs) for tuberculosis (TB) testing in coronavirus disease 2019 (COVID-19) patients is unknown. This study aimed to systematically review the prevalence of indeterminate TB-IGRA following SARS-CoV-2 infection or vaccination and to review associated factors.

Methods: This systematic literature review was guided according to the PRISMA guidelines by searching PubMed, Scopus, Web of Science, Clinicalkey, and Cochrane Library. Studies reporting results of TB-IGRA tests (QuantiFERON [QFT]-TB, T-SPOT.TB) in COVID-19 patients or vaccines were included. The random effects model was used to assess the prevalence of indeterminate IGRA results. Heterogeneity was evaluated using the T^2 and 95% predictive interval.

Results: Of the 273 citations screened, 12 articles were included in the final analysis including a total of 2107 patients. The overall pooled effect size proportion of indeterminate QFT-TB results, estimated in eight studies using the QFT-TB Plus assay, was 0.26 (95% CI: 0.205–0.324, $T^2 = 0.158$). The mean true effect size was 0.26 (95% predictive interval: [0.110–0.500]). A subgroup analysis was not undertaken due to the small number of studies. Indeterminate QFT-TB rates were associated with COVID-19 severity, steroid treatment, inflammation-related parameters, neutrophilia, and lymphopenia.

Conclusion: Indeterminate QFT-TB results in COVID-19 patients occur in almost one-quarter of tests performed. Further studies are needed to assess associated factors.

KEYWORDS

latent tuberculosis, QuantiFERON, SARS-CoV-2, T cell response

1 | INTRODUCTION

According to the World Health Organization (WHO), latent tuberculosis (TB) infection (LTBI) affects about one-third of the world's population.[1] Patients at a high risk of developing TB have to be identified before prescribing corticosteroids or immunosuppressants. This will enable effective preventative therapy and avoid the risk of a TB outbreak.

The coronavirus disease 2019 (COVID-19) has affected over 757 million individuals worldwide, as reported by the WHO.[2] Corticosteroids and immunomodulatory drugs such as tocilizumab, an interleukin [IL]-6 receptor antagonist, may be used in critically ill patients with a risk of activation of LTBI. Conversely, TB is reported to be associated with increased susceptibility to COVID-19, and worse prognosis in patients with both diseases.[3]

Since LTBI is the most important source of new TB cases,[4] the accurate diagnosis of LTBI is extremely important. Unlike active TB, LTBI is clinically asymptomatic[5] with negative mycobacterial cultures.[5,6] Thus, the reliability of screening tests is a crucial determinant in patient management. The diagnosis of LTBI relies mainly on interferon-gamma (IFN-ɣ) release after T-cell stimulation by specific antigens. The immuno-diagnostic arsenal includes the tuberculin skin test (TST) and IFN-ɣ release assays (IGRAs), with the latter showing greater specificity compared to TST.[6,7] IGRAs measure the production of IFN-ɣ in response to stimulation with specific *Mycobacterium tuberculosis* antigens (ESAT-6 and CFP-10) in peripheral blood samples.[6] The results are compared to negative and positive control (phytohaemagglutinin, PHA). Globally, a test is called "indeterminate" and cannot be interpreted when there is a reaction in the presence of negative control or when there is no reaction in the presence of positive control.[8]

Several factors have been reported to be associated with IGRAs indeterminate results including active inflammation, immunocompromising conditions, and administration of immunosuppressive drugs.[9] Recently, there has been emerging data indicating an increase in indeterminate IGRA results among patients with COVID-19.[10–12] While insights have been gained into the impact of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on innate, humoral, and cellular immune responses,[13] the effects of aberrant immune responses in COVID-19 on screening for LTBI remain unclear.

This meta-analysis aimed to assess the prevalence of indeterminate TB-IGRA following SARS-CoV-2 infection or vaccination and to review associated factors.

Key points

- Coronavirus disease 2019 (COVID-19) is known to impact the host's cellular immune response. The reliability of interferon-gamma-release-assays (IGRAs) for tuberculosis (TB) testing in context of COVID-19 is unknown.
- Physicians should take in account that indeterminate QuantiFERON-TB results occur in 26% of COVID-19 patients. Associated factors with indeterminate results include COVID-19 severity, mortality, corticosteroids use, high levels of inflammation-related parameters, neutrophilia, and lymphopenia.

2 | METHODS

This systematic review and meta-analysis were performed within the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA) statement.[14] Ethical approval was not required, since this research was a systematic review of published articles.

2.1 | Data sources and search strategy

The following databases were screened for every article published until November 21, 2022 without language restriction: Pubmed, Scopus (containing the Embase database), Web of Science, Clinicalkey, and Cochrane Library.

The search was implemented using the following combination of terms: ("Latent Tuberculosis" OR "Tuberculin Test" [Mesh] OR "Interferon-gamma Release Tests" [Mesh]) AND ("indeterminate") AND ("COVID-19" [Mesh] OR "SARS-CoV-2" [Mesh] OR "COVID-19 Vaccines" [Mesh] OR "ChAdOx1 nCoV-19" [Mesh] OR "pediatric multisystem inflammatory disease, COVID-19 related" [Supplementary Concept] OR "adult multisystem inflammatory disease, COVID-19 related" [Supplementary Concept] OR "2019-nCoV Vaccine mRNA-1273" [Mesh] OR "post-acute COVID-19 syndrome" [Supplementary Concept] OR "BNT162 Vaccine" [Mesh] OR "COVID-19 vaccine booster shot" [Supplementary Concept] OR "Ad26COVS1" [Mesh] OR "Gam-COVID-Vac vaccine" [Supplementary Concept] OR "heterologous prime-boost COVID-19 vaccination" [Supplementary Concept]). A manual complementary search using the commercial IGRA tests ("QFT-TB" OR "T-SPOT-TB") was also performed. To maximize the search for other relevant studies, we manually screened the references of the retrieved articles, reviews, guidelines, and conferences.

2.2 | Eligibility criteria

The inclusion criteria were studies (1) case-control or cohort studies including patients diagnosed with a SARS-CoV-2 infection or vaccinated for COVID-19, (2) screened for LTBI by IGRA or tuberculin tests, with (3) no restrictions regarding study country or LTBI's incidence. We excluded case reports, reviews or comments, guidelines, and studies that did not report their detailed results of the tuberculin test or IGRA screening for LTBI (including a statement about indeterminate test results or low mitogen response).

2.3 | Selection process

Two reviewers (B. T. A. and B. S. M.) screened independently each record (title/abstract) to identify potentially relevant studies. When both agreed that a citation met the eligibility criteria, each report retrieved was individually reviewed in the full text to match the inclusion and exclusion criteria by the same two investigators. If there was a disagreement, the document was evaluated by a third investigator (M. I.) to reach a consensus.

2.4 | Data extraction

Two coauthors (M. S. and J. A.) independently extracted the studies' eligibility and data using a standardized procedure. Any disagreement between data collectors was resolved by a third investigator's assessment (M. I.). The following variables were collected:

- Study and population: year of publication, study design, study period, study location (country/region), ethical statement and patient's consent, selection criteria, sample size, age, sex ratio, concomitant use of steroid treatment, and other potential immunocompromising conditions.
- Latent TB infection diagnosis: type of IGRA test performed, definition, and number of positive/negative/indeterminate results.
- SARS Cov-2 infection: diagnosis test performed, disease severity (mild/moderate vs. severe/critical), outcomes, and biological data including neutrophils, lymphocytes counts, and inflammation-related parameters (C reactive protein [CRP], tumor necrosis factor [TNF]-α, D-dimer, fibrinogen, ferritin, procalcitonin, and IL-6 levels…).

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

2.5 | Study risk of bias assessment

Assessment of the quality of the selected studies was performed independently by the two investigators (B. T. A. and B. S. M.). A third investigator (M. I.) was consulted if there was a disagreement. The Newcastle–Ottawa scale (NOS) was applied to evaluate the quality of the included studies.[15] Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

The NOS scale checklist contained three domains: selection of study groups, comparability of groups, and ascertainment of exposure in case-control studies or assessment of outcomes in cohort studies. We considered a study to be of good quality if its NOS score was seven or more (out of a maximum possible score of nine).

2.6 | Statistical analysis

The primary outcome was the prevalence of indeterminate IGRA results among COVID-19 patients which was defined as the number of indeterminate test results divided by the total number of valid test results. We used the "Comprehensive Meta-Analysis Version 4" software[16] and the random-effects model for the analysis. The heterogeneity of the true effect size was determined using the Q-test and the T^2. The Q-statistic serves as a test of the null hypothesis that all studies within the analysis share a common effect size. If all studies were to possess the same true effect size, the expected value of Q would be equivalent to the degrees of freedom (the number of studies minus one).

The secondary outcome was to identify the associated factors with an indeterminate IGRA test result in COVID-19 patients.

The Estmeansd package (https://github.com/stmcg/estmeansd) was used for estimating the sample mean and standard deviation from reported quantiles.

The significance level was set at 0.05. p Values below 0.05 were considered significant.

3 | RESULTS

3.1 | Study selection

The search yielded 273 citations in all databases. After removing duplicate records and screening the titles and abstracts, 17 articles were retained for a full-text assessment. Disagreements were resolved through minor discussion and arbitration by the third investigator. Based on the eligibility criteria, 12 studies were included in the systematic review.[10–12,17–25] The screening flowchart demonstrated the study selection process in Figure 1. Studies characteristics are detailed in Table 1.

Four studies were of good quality,[10,11,21,22] three studies were of fair quality,[12,17,18] and five studies were of poor quality.[19,20,23–25]

3.2 | Epidemiological data

The 12 selected studies described 2107 patients with COVID-19 (63.4% were male with an average mean age ranging from 47 to 68.6 years), and 141 healthcare workers who received two doses of COVID-19 vaccination. All studies were conducted between 2020 and 2022. Two studies were performed in a high TB incidence country (India),[21,24] 10 studies in intermediate/low TBC incidence countries (Italy,[18,20,22,25] Spain,[10,19,23] United States,[11] Turkey[12]), and Japan.[17] The BCG vaccination was reported in two studies[21,24] (80% and 48.2%, respectively).

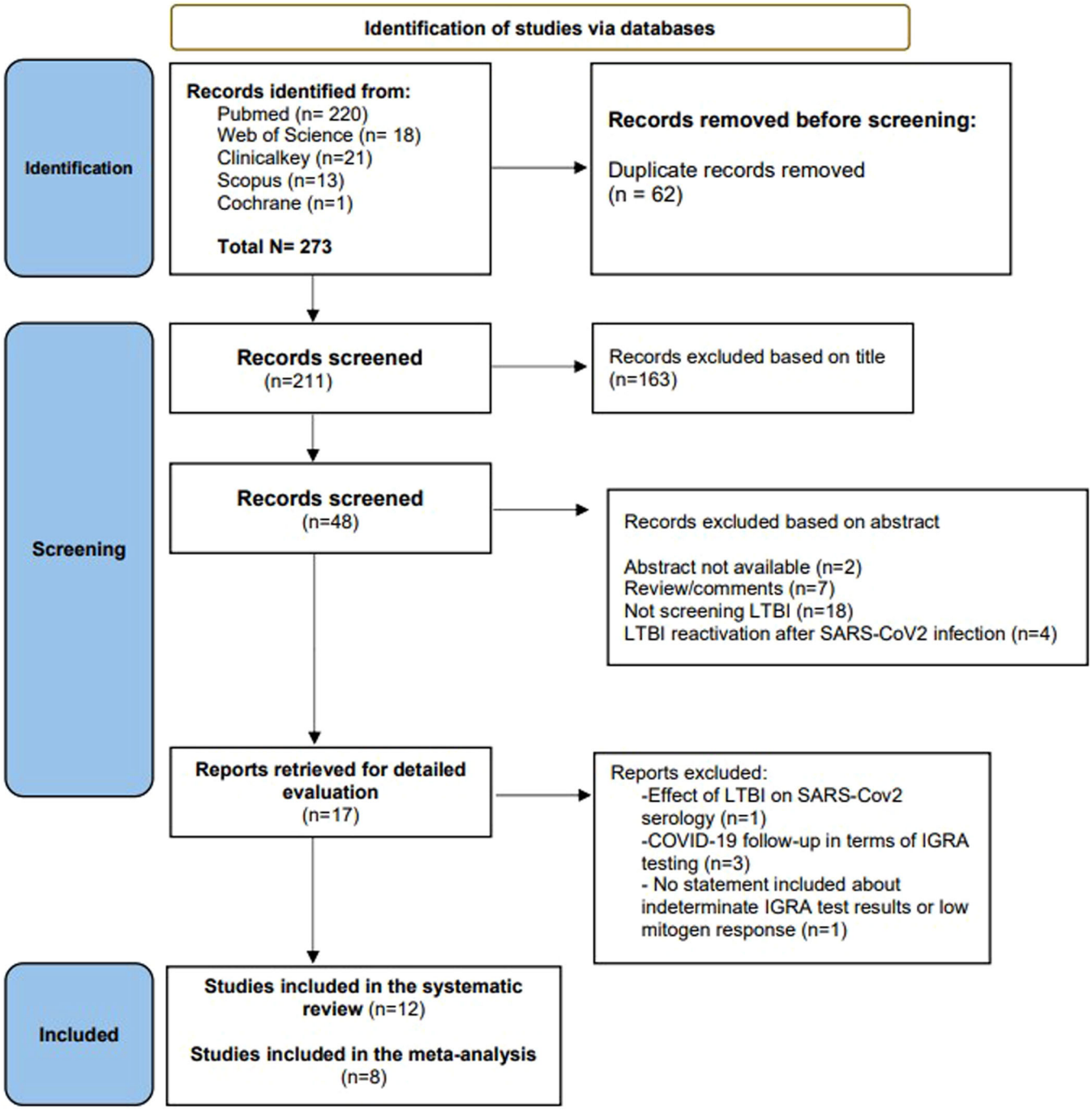

FIGURE 1 Flow chart outlining the selection of articles included in the review. LTBI, latent tuberculosis infection.

3.3 | IGRAs results

3.3.1 | Type of IGRAs

All included studies used the QFT-TB test. The QFT-TB Plus kit was used in 10/12 studies (83.3%) corresponding to 1993 patients (94.6%),[10–12,17–20,22,23,25] and the QFT-TB GIT kit in 2/12 studies (16.6%) corresponding to 114 patients (5.4%).[21,24] No data was retrieved on TB-SPOT or tuberculin test. Only one study was retrieved on COVID-19 vaccines in healthcare workers.[17]

3.3.2 | Definition of indeterminate results of IGRAs

A definition of indeterminate results was mentioned in 8/12 studies (66.6%).[11,12,17–20,25] An indeterminate result was defined according to the manufacturers' definition in six studies,[11,12,17,18,22,25] and as (Nil [baseline] >8.0 IU/mL) or [nil ≤8.0 IU/mL and mitogen-nil <0.5 IU/mL] in two studies.[19,20]

The term "low response to the mitogen" was used in two other studies.[10,24] Palacios-Gutiérrez et al. defined "a low IFN-ɣ response to PHA" as an IFN-ɣ concentration ≥0.5 IU/mL and less than 50%

TABLE 1 Characteristics of included studies sorted by year of publication.

References	Location	Study design	Study period	Ethics	Consent	Inclusion criteria	Non inclusion criteria	SARS-Cov-2 diagnosis test	Number of Covid-19 patients or vaccinated participants	Control group	Looking for vaccination	Other tests
Chen et al.[17]	Japan (Taiwan)	Prospective	January 2021 to November 2021	NR	Yes	Healthcare workers in four hospitals with available baseline IGRA results who had received two doses of COVID-19 vaccination.	Participants who received vaccines other than those for COVID-19 during the study period	NA	141	No	COVID-19 vaccination (n = 141): -ChAdOx1 vaccine: n = 95 -mRNA-1273 vaccine: n = 31 -Heterologous vaccination (ChAdOx1/mRNA-1273 prime-boost vaccination): n = 15	No
Cortes et al.[12]	USA (Florida)	Retrospective	October 13, 2020 to September 20, 2021	Exempted by a local institutional review board	No	Hospitalized patients with COVID-19 pneumonia who had undergone QFT-Plus testing.	Patients with negative PCR and/or antigen test results for SARS-CoV-2 on nasopharyngeal swabs	RT-PCR for SARS-CoV-2	495	Yes (pre-COVID-19 pandemic cohort: hospitalized patients between October 13, 2018 and September 20, 2019 with QFT-Plus test)	Yes (COVID-19 vaccines)	CRP, D-dimer, ferritin, fibrinogen, interleukin 6, LDH, activated partial thromboplastin time, international normalized ratio, creatinine, lymphocytes, platelet, and neutrophils absolute counts, procalcitonin,

(Continues)

TABLE 1 (Continued)

References	Location	Study design	Study period	Ethics	Consent	Inclusion criteria	Non inclusion criteria	SARS-Cov-2 diagnosis test	Number of Covid-19 patients or vaccinated participants	Control group	Looking for vaccination	Other tests
												prothrombin time, and prothrombin time
Granozzi et al.[18]	Italy (Bologna)	Retrospective	October 1, to November 25, 2020	Yes	No	Hospitalized patients with severe COVID-19 who were eligible for immunosuppressive therapies.	Subjects with incomplete clinical and laboratory data	RT-PCR for SARS-CoV-2	268	No	No	Lymphocytes, IL-6 levels, ferritin, and LDH
Imeneo et al.[20]	Italy (Roma)	Retrospective, observational	March to May 2020 and September to December 2020	Yes	No	1. Patients hospitalized at the infectious diseases ward due to SARS-CoV-2 infection. 2. QFT-Plus assay performed during hospitalization within 30 days from the first positive NPhS.	NR	RT-PCR for SARS-CoV-2	420	No	No	Neutrophils (N), lymphocytes (L), N/L ratio, CRP, IL-6, TNF-α, D-dimer, fibrinogen, and ferritin
Palacios-Gutiérrez et al.[10]	Spain (Asturias)	Prospective, observational, comparative (two groups)	July 2016 to October 2021	Yes	Yes	1. QFT-TB requests from 36,709 patients conducted during the study period. 2. All charts of patients hospitalized with clinical or radiological evidence of pneumonia, and/or acute respiratory distress for 2 weeks in March 2020.	NR	RT-PCR for SARS-CoV-2	57	33	Flu vaccine	Leukocytes, lymphocytes, ASAT, ALAT, LDH, CRP, procalcitonin, D-dimer, fibrinogen, ferritin

TABLE 1 (Continued)

References	Location	Study design	Study period	Ethics	Consent	Inclusion criteria	Non inclusion criteria	SARS-Cov-2 diagnosis test	Number of Covid-19 patients or vaccinated participants	Control group	Looking for vaccination	Other tests
Rajamanickam et al.[21]	India (Chennai)	Prospective, comparative (four groups)	July to September 2020	Yes	Yes	Elderly persons (60–80 years), living in hotspots for SARS-CoV-2 infection in Chennai, India. Group 1: individuals with LTBI (confirmed by IGRA). Group 2: individuals with LTBI without seropositive SARS-CoV-2 infection. Group 3: individuals negative for LTBI and seropositive for SARS-CoV-2. Group 4: individuals negative for both LTBI and SARS-CoV-2.	Individuals diagnosed with tuberculosis (TB) during the previous 6 months or currently on anti-TB treatment, HIV or malignancy	SARS-CoV-2 specific IgG antibody	74	Two groups: (n = 24) with LTBI, (n = 20) negative for LTBI	BCG vaccine	Red blood cells, hematocrit, hemoglobin, platelets, leukocytes, lymphocytes, neutrophils, monocytes, basophils, eosinophils, proinflammatory cytokines (IFNɣ, IL-2, TNF-α, IL-17A, IL-1α, IL-1β, Il-6, IL-10, IL-A12), anti-inflammatory cytokines (IL-4, IL-5, IL-13), chemokines (CCL1, CCL2, CCL3, CCL4, CCL11, CXCL1, CXCL2, CXCL9, CXCL10, CXCL11)
Petrone et al.[22]	Italy (Roma)	Prospective, comparative (four groups: Covid-19, TB-Covid-19, LTBI-Covid-19, Non-Covid-19)	April to December 2020	Yes	Yes	1. Covid-19 patients: positive NPhS for SARS-CoV-2. 2. Pulmonary TB based on a positive *Mycobacterium* culture from respiratory samples, or extrapulmonary	HIV	SARS-CoV-2 IgG serology	Covid-19 (n = 63) TB-Covid-19 (n = 10) LTBI-Covid-19 (n = 11)	8	No	Lymphocytes, CD4-S

(Continues)

TABLE 1 (Continued)

References	Location	Study design	Study period	Ethics	Consent	Inclusion criteria	Non inclusion criteria	SARS-Cov-2 diagnosis test	Number of Covid-19 patients or vaccinated participants	Control group	Looking for vaccination	Other tests
						TB based on positive *Mycobacterium*-specific molecular testing. 3. LTBI diagnosis: positive score to QFT-Plus test or by the presence of radiological apical scars indicative of previous TB exposure, after excluding TB disease. 4. No-Covid-19: healthy donors or bacterial pneumonia or echinococcosis and scored negative for SARS-CoV-2 IgG serology.						
Gupta et al.[24]	India (New Delhi)	Prospective, comparative (three groups)	NR	Yes	Yes	Group A: asymptomatic or mildly symptomatic cases admitted in a particular male ward on 3 consecutive days with a COVID-19 positive test report RT-PCR	Malignancy, chronic renal failure, cardio-myopathy, chronic respiratory failure with preexisting dyspnea, inflammatory diseases like rheumatoid arthritis, inflammatory	RT-PCR for SARS-CoV-2	40	Healthy volun-teers (n = 20)	BCG vaccine	Widal test, D-dimer, ferritin, triacylglycerol, hemoglobin, hematocrit, differential leukocyte counts, absolute neutrophil counts, lymphocytes, monocytes, platelet count

TABLE 1 (Continued)

References	Location	Study design	Study period	Ethics	Consent	Inclusion criteria	Non inclusion criteria	SARS-Cov-2 diagnosis test	Number of Covid-19 patients or vaccinated participants	Control group	Looking for vaccination	Other tests
						from the oro-nasopharyngeal swab. Group S: severely ill COVID-19-positive cases admitted to the intensive care unit. Group H: 20 healthy male volunteers working as healthcare workers at LN hospital with a COVID-19-negative RT-PCR.	bowel disease, or patients on long-term immuno-suppressants					
Ward et al.[11]	USA (North Carolina)	Retrospective observa-tional	March to July 2020	NR	NR	-Outpatients and inpatients, aged 18 years or older, treated in the UNC healthcare system with a positive COVID-19 nasopharyngeal or tracheal aspirate sample using FDA-approved (EUA) SARS-CoV-2 PCR assays. -A positive SARS-CoV-2 PCR test within 10 days of their QFT-TB Gold Plus test.	Patients that tested positive for *Mycobacterium* tuberculosis antigen response with the QFT-TB Gold Plus assay were excluded.	RT-PCR for SARS-CoV-2	48	Healthy subjects ($n = 75$),	No	Lymphocytes (L), neutrophil (N), N/L ratio, CRP, total bilirubin, LDH, IL-6, TNF-α, IL-2R, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12, and IL-13

(Continues)

TABLE 1 (Continued)

References	Location	Study design	Study period	Ethics	Consent	Inclusion criteria	Non inclusion criteria	SARS-Cov-2 diagnosis test	Number of Covid-19 patients or vaccinated participants	Control group	Looking for vaccination	Other tests
Sánchez-Martínez et al.[23]	Spain	Prospective	March to May 2020	Yes	Yes, verbal	Patients with SARS CoV-2 infection who met clinical (on the COVID-19 severity scales), radiological (new onset or progression of the initial pulmonary infiltrates), and biological (IL-6 > 40 pg/mL) criteria for treatment with tocilizumab.	NR	RT-PCR for SARS-CoV-2	190	No	No	CD4 and CD8 lymphocyte counts
Solanich et al.[19]	Spain (Barcelona)	Retrospective	March to April 2020	Yes	Yes	All hospitalized patients with COVID-19.	NR	RT-PCR for SARS-CoV-2	96	No	No	Leukocytes, neutrophils, lymphocytes, ferritin, LDH, CRP, IL-6, troponin, D-dimer
Torre et al.[25]	Italy (Milan)	Retrospective	March 1 to May 15, 2020	No ethical clearance required	No	Patients with severe COVID-19 admitted to five hospitals in the Milan area.	NR	NR	335	No	No	Total lymphocyte count, HIV infection

Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; CRP, C reactive protein; COVID-19, coronavirus disease 2019; IGRA, interferon-gamma-release-assays; LDH, lactate dehydrogenase; LTBI, latent tuberculosis infection; NA, non applicable; NPhS, nasopharyngeal swab; NR, not reported; QFT, QuantiFERON®; RT-PCR, real-time reverse transcriptase-polymerase chain reaction; TB, tuberculosis infection; TNF-α, tumor necrosis factor alpha.

below the average values and "a very low IFN-ɣ response to PHA" for an IFN-ɣ concentration <0.5 IU/mL in the mitogen tube without mentioning the term "indeterminate."[10]

3.3.3 | Prevalence of indeterminate QuantiFERON results in COVID-19 patients

The prevalence of indeterminate QFT-TB results among COVID-19 patients was mentioned in nine studies and varied from 7.14% to 64.58% (Table 2).[10–12,18–20,22,23,25] For the meta-analysis, the prevalence of indeterminate QFT-TB results was retrieved from eight studies and ranged from 7.14% to 40.33%.[10,12,18–20,22,23,25] We excluded the study of Ward et al. from the metanalysis because the prevalence of indeterminate QFT-TB results was not calculated among all valid results (authors excluded patients with a positive QFT-TB resulting in a high rate of indeterminate results [64.58%]).[11]

The overall pooled effect size (equivalent to the pooled proportion of indeterminate QFT-TB Plus results) was 0.26 (95% confidence interval: 0.205−0.324, $T^2 = 0.158$) for QFT-TB Plus. The mean of true effect size was 0.26 (95% prediction interval: 0.11−0.5) (Figure 2). The *Q*-value was 53,956 with 7 degrees of freedom and a *p*-value < 0.001. A subgroup analysis was not undertaken due to the small number of studies.

Indeterminate results were due to a lack of response in the mitogen in five studies.[10,11,18,19,24] Five other studies did not report whether their indeterminate results were due to a low mitogen response or an increased baseline response in the Nil tube.[12,20,22,23,25] Rajamanickam et al. reported a global increase in baseline (nil tube).

Three studies reported an increase in the indeterminate QFT-test rates during the COVID-19 pandemic compared to the pre-pandemic period in the same region[10–12] (from 1.4%, 8.7%, and 19.4% before the pandemic to 4.2%, 15.5%, and 28.1%, respectively). The results of indeterminate QFT results in COVID-19 patients and mean values of IFN-ɣ production for Nil, TB1, TB2, and mitogen tubes of the QFT assay were summarized in Table 3. The delay between a positive SARS-CoV-2 test and a QFT-TB test, mentioned in five studies, varied between 24 h and 30 days.[11,18–20,24] QFT-TB test was retested in patients with low/very low response to mitogen in three studies[10,23,24] corresponding to 107 patients. The delay in obtaining an interpretable QFT-TB test result ranged from 3 days to 8 weeks.[10,23,24]

3.4 | Associated factors to indeterminate QuantiFERON results

Additional information on immunocompromising factors potentially influencing IGRA results was noted in seven studies.[10–12,18–20,25] The significantly-associated factors with indeterminate QFT-TB results in each study were presented in Table 2.

3.4.1 | Clinical data

- Severity of COVID-19 disease: Nine studies with 1698 (80.6%) COVID-19 patients provided information on the severity of the COVID-19 disease.[10–12,18–20,22–24] QFT-TB indeterminate results in severe COVID-19 reported in four studies,[12,18–20] ranged from 26.5% to 52.5%. Nine studies with 1949 COVID-19 patients

TABLE 2 Significant factors associated with an indeterminate QuantiFERON TB result or a low mitogen response in included papers.

Epidemiological factors	- Male sex (Cortes et al.[12]; Imeneo et al.[20]) - Age >65 years (Imeneo et al.[20])
Clinical factors	- Comorbidities: patients with chronic kidney disease, lung disease, diabetes mellitus, transplant recipients including solid-organ transplant (Cortes et al.[12]), Charlson comorbidity index (Imeneo et al.[20]). - Steroid treatment before QFT testing (Solanich et al.[19]; Granozzi et al.[18]) (the longer the duration of corticosteroid therapy before the QFT testing, the higher the probability of having an indeterminate result [Granozzi et al.[18]]). - Immunosuppressive drugs (Ward et al.[11]). - Disease severity (Solanich et al.[19]; Granozzi et al.[18]). - Need for intensive care unit (Cortes et al.[12]; Granozzi et al.[18]; Imeneo et al.[20]). - Mortality (Torre et al.[25]; Solanich et al.[19]; Ward et al.[11]; Granozzi et al.[18]; Imeneo et al.[20]). - Abnormal radiological findings (Palacios-Gutiérrez et al.[10]).
Laboratory findings	- High neutrophils count (Ward et al.[11]; Cortes et al.[12]; Imeneo et al.[20]). - Low lymphocyte count (Torre et al.[25]; Cortes et al.[12]; Granozzi et al.[18]; Imeneo et al.[20]). - High neutrophil/lymphocyte ratio (Ward et al.[11]; Imeneo et al.[20]). - High Inflammation-related parameters including LDH (Solanich et al.[19]; Cortes et al.[12]; Granozzi et al.[18]), ferritin (Cortes et al.[12]; Granozzi et al.[18]; Imeneo et al.[20]), CRP (Cortes et al.[12]; Imeneo et al.[20]), D-dimer (Cortes et al.[12]; Imeneo et al.[20]), fibrinogen (Cortes et al.[12]; Imeneo et al.[20]), and IL-6 (Cortes et al.[12]) levels. - Low TNF-alpha level (Imeneo et al.[20]). - Low T cells (CD3+) including low CD4+ and CD8+ cells count with high CD4/CD8 ratio (Imeneo et al.[20]). - Low NK cells (CD3- CD16+CD56+) (Imeneo et al.[20]).

Abbreviations: CRP, C reactive protein; IL-6, interleukin 6; LDH, lactate dehydrogenase; NK, natural killer cells; QFT, QuantiFERON®; TNF, tumor necrosis factor.

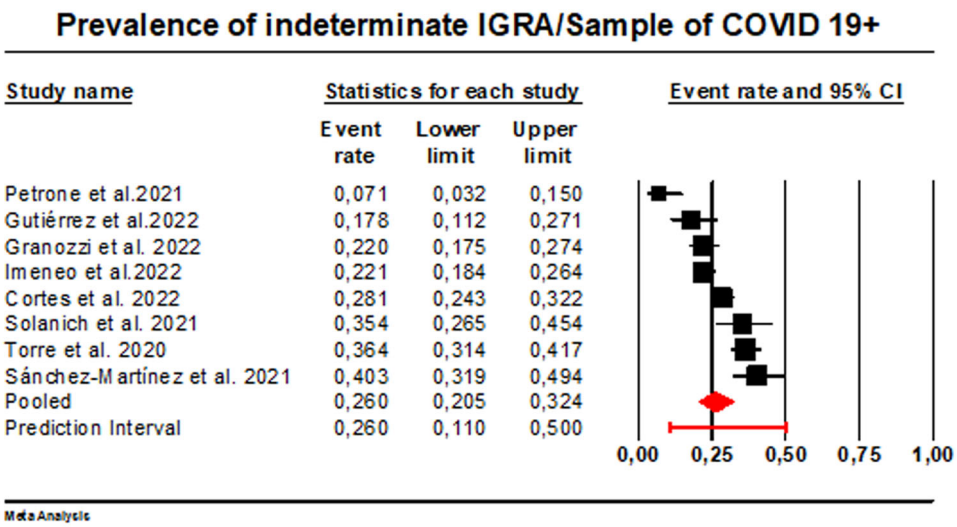

FIGURE 2 Prevalence of indeterminate QuantiFERON-TB test results in COVID-19 patients. COVID-19: coronavirus disease 2019; IGRA: interferon-gamma-release-assays.

provided information on survival.[10–12,18–20,23–25] QFT-Plus indeterminate results were associated with mortality in five studies,[11,18–20,25] and ranged from 32% to 64.7%.

- Immunosuppressive treatment.

Corticosteroid use before the QFT-assay was reported in seven studies,[10,11,18–20,22,24] and ranged from 13.7% to 81.9%. Steroid treatment was a significant predictor factor for an indeterminate result or a decreased response in mitogen in three studies.[11,18,19] Interestingly, three studies showed that even among patients who did not receive prior corticosteroid therapy, a considerable proportion had an indeterminate result (14.7% and 16.7%)[18,19] or a significant decrease in mitogen response on QFT assay.[11] Notably, COVID-19 patients had a significantly low mitogen response compared to controls even when QFT results were interpretable in three studies[10,11,24] (Table 3). Anti-IL-6 receptor monoclonal antibodies (anti-IL-6–R) use was reported in two studies studies[19,20] with no significant association with indeterminate IGRA test results.

3.4.2 | Biological data

Nine studies among 12 with 1975 (93.7%) COVID-19 patients provided data about laboratory test results (Table 2).

- Inflammation-related parameters, assessed in six studies,[10,12,18–20,24] were reported to be high in patients with indeterminate QFT-TB test results including D-dimer,[12,18–20] CRP,[12,20] lactate dehydrogenase (LDH),[12,18,19] procalcitonin,[12] fibrinogen,[12,20] ferritin,[12,18,20] neutrophils count,[11,12,20] and IL-6.[12]
- Total lymphocyte count was assessed in 10 studies.[10–12,18–22,24,25] There was a significant association between lymphopenia and indeterminate QFT-TB results or a low response to mitogen in seven studies.[10,12,18–20,24,25] Lymphocyte count ranged from 640 to 1050 cells/μL in patients with indeterminate QFT-TB results.[10,12,18–20,24,25] A high neutrophil/lymphocyte ratio (NLR) was associated with indeterminate results in two studies.[11,20] An increased CD4/CD8 ratio and reduced T-cells counts were found to be independent predictors of indeterminate QFT-TB test results in one study.[20]

Levels of pro and anti-inflammatory cytokines were assessed in six studies corresponding to 1278 patients.[11,12,18–21] COVID-19 patients exhibited high levels of proinflammatory cytokines (IFNγ, IL-2, TNF-α, IL-17A, IL-1β, IL-6, and IL-12).[11,21] Cortes et al. found a significant association between high IL-6 levels and indeterminate QFT-TB results[12] while IL-6 levels were similar between indeterminate and determinate QFT-TB results in the study of Ward et al.[11]

4 | DISCUSSION

SARS-CoV-2 has developed several mechanisms to alter the host's immune response. Due to the potential impact of various immune dysregulation factors on QFT-TB assay performance, the accuracy of QFT-TB results in COVID-19 patients may also be compromised. However, little is known regarding the reliability of QFT-TB testing in COVID-19 patients.

The main finding of this work was the occurrence of indeterminate QFT results in 26% of COVID-19 patients, suggesting that nearly a quarter of performed QFT tests will not yield a conclusive result mainly because of low mitogen response. Associated factors with QFT-TB indeterminate results included COVID-19 severity, mortality, corticosteroids use, high levels of inflammation-related parameters (D-dimer, LDH, and fibrinogen) as well as the presence of neutrophilia and lymphopenia.

TABLE 3 QuantiFERON-TB test results in all included papers sorted by year of publication.

References (study)	IGRA method	Positive results *N* (%)		Negative results *N* (%)		Indeterminate results *N* (%)		Nil tube[a]		Tb1 tube[a]		Tb2 tube[a]		Mitogen tube[a]	
		Covid-19 patients	Control group	Covid-19 patients	Control group	Covid-19 patients	Control group	Covid-19 patients	Control group	Covid-19 patients	Control group	Covid-19 patients	Control group	Covid-19 patients	Control group
Chen et al.[17]	QFT-Plus	7 (4.96%)	-	134 (95%)	-	NR	-	NR	-	NR	-	NR	-	NR	-
Cortes et al.[12]	QFT-Plus	-	-	356 (71.9%)	245 (80.6%)	139 (28%) ***p* = 0.006**	59 (19.4%)	NR	NR	NR	NR	NR	NR	NR	NR
Granozzi et al.[18]	QFT-Plus	10 (3.7%)	-	199 (74.2%)	-	59 (22%)	-	NR	-	NR	-	NR	-	NR	-
Imeneo et al.[20]	QFT-Plus	35 (8%)	-	292 (70%)	-	93 (22.1%)	-	NR	-	0.106 (0.055–0.249)	-	0.103 (0.057–0.2-46)	-	3.920 (0.980–10,000)	-
Gutiérrez et al.[10]	QFT-Plus	NR	NR	NR	NR	16 (28%)	NR	0.124 [0.106]	0.297 [0.754]	0.512 [1.26]	0.979 [2.25]	0.557 [1.38]	0.985 [2.27]	3.35 [2.80] ***p* = 0.03**	5.04 [2.80]
Rajamanickam et al.[21]	-QFT-GIT-Luminex[b]	NR	NR	NR	NR	NR	NR	42.1[b] ***p* < 0.05**	21.06[b]	121.9[b] ***p* < 0.05**	76.6[b]	-	-	NR	NR
Petrone et al.[22]	QFT-Plus	14 (16.6%)	0	64 (76%)	8 (100%)	6 (7.14%)	0	NR	NR	NR	NR	NR	NR	NR	NR
Gupta et al.[24]	QFT-GIT	13 (32.5%)	10 (50%)	NR	NR	NR	NR	NR	NR	1.03 [1.39] ***p* = 0.001**	4.32 [5.65]	-	-	5.08 [4.23] ***p* < 0.001**	14.29 [3.51]
Ward et al.[11]	QFT-Plus	0	0	17 (35.42%)	73 (97.33%)	31 (64.58%)	2 (2.67%)	NR	NR	NR	NR	NR	NR	1.29 ***p* < 0.001**	7.87
Sánchez-Martínez et al.[23]	QFT-Plus	4 (3.4%)	-	67 (56.3%)	-	48 (40.3%)	-	NR	-	NR	-	NR	-	NR	-
Solanich et al.[19]	QFT-Plus	8 (8.3%)	-	54 (56.3%)	-	34 (35.4%)	-	NR	-	NR	-	NR	-	NR	-
Torre et al.[25]	QFT-Plus	19 (5.7%)	-	194 (57.9%)	-	122 (36.4%)	-	NR	-	NR	-	NR	-	NR	-

Note: *p* values below the level of significance (0.05) are mentioned in bold.

Abbreviations: IGRA, interferon-gamma release assay; NR, not reported; QFT-GIT, QuantiFERON TB gold in tube; QFT-Plus®, QuantiFERON® TB gold plus.

[a]Results are expressed in median (interquartile range) or mean [SD].

[b]In this study,[21] cytokine levels were measured by Luminex in the supernatant obtained from incubation of whole blood with media alone (unstimulated) or a cocktail of TB antigens (ESAT-6, CFP-10, TB 7.7 [TB Ag]) or mitogen (PHA) for 18 h, according to the manufacturer's instructions using the QFT-GIT kit (Qiagen®).

4.1 | Prevalence of indeterminate IGRAs results

The analysis of indeterminate IGRA results has often been overlooked in the literature, with such results either being excluded from prior systematic literature reviews or only included in limited subgroup analyses.[26] Indeterminate rates of QFT-TB results among COVID-19 patients seem to be high compared to rates reported in other conditions. The estimated prevalence of indeterminate results based on IGRAs tests (QFT/T-SPOT) using the random effects meta-analysis varied between 4% in children and adolescents,[26] 7% in HIV-infected adults,[27] and 9% (95% CI: 8%–10%) in liver or renal transplant candidates.[28]

Two commercial IGRAs are currently available: the QFT-TB Gold Plus assay and the T-SPOT.TB assay. In our study, only studies using QFT assay were retrieved. Compared to the QFT-GIT, the QFT-Plus contains two *Mycobacterium*-antigen tubes (TB1 and TB2) with additional short peptides that elicit CD8 antigen-specific T-cell responses in addition to CD4 responses. The latter test was designed to enhance the identification of LTBI, particularly among immunocompromised patients.[29] In our study, the prevalence of indeterminate QFT-TB results among COVID-19 patients was assessed only in studies using QFT-TB-Plus assay. Besides, no retrieved studies used TST or T-SPOT.TB.

4.2 | Associated factors with indeterminate IGRAs results

To optimize the use of IGRAs in clinical practice, it is important to determine the factors that contribute to indeterminate results. The current meta-analysis did not achieve a sufficient sample size to identify the predictive factors of indeterminate QFT in COVID-19 patients. Therefore, associated factors with an indeterminate QFT-TB, determined through a narrative review, included: COVID-19 severity, steroid treatment, inflammation-related parameters, neutrophilia, and lymphopenia.

Several immunocompromising conditions, such as HIV infection,[30] advanced liver disease,[31] malnutrition, a low albumin level,[32,33] helminth infection,[34] and corticosteroid use[8,35,36] have been reported to be associated with indeterminate IGRA results. Since corticosteroids and other immunosuppressive therapies could be prescribed in COVID-19 patients, it is plausible to speculate that the elevated rates of indeterminate results may be related to their use. However, it is worthwhile to mention that in our study, even in patients who did not use immunosuppressive medications before QFT-TB testing, 14.7%–16.7% had indeterminate results or a significant decrease in mitogen response.[18,19] On the other hand, our results showed that COVID-19 patients had a significantly low mitogen response compared to controls even when QFT results were interpretable. This may suggest the significant implication of SARS-CoV-2 infection as a determining factor in such results.

Concerning the SARS-CoV-2 infection, most included studies were conducted in hospitalized patients in the early inflammatory phase of COVID-19. Patients in this phase exhibit high plasma levels of proinflammatory cytokines (IL-1b, IL-2, IL-4, IL-7, MCP-1, GCSF, MIP-1A, TNF-α, IFN-ɣ, and IP-10).[37] However, this "cytokine storm" does not seem to affect the accuracy of the QFT-TB test since the majority of the indeterminate results were caused by a low mitogen response rather than a high concentration of IFN-γ in the nil tube.

While impaired IFN-I/III signatures have been associated with a chronic viral load and inflammatory disturbance with a worse COVID-19 prognosis,[38–40] there are contradictory findings regarding the role of type II interferons, such as IFN-ɣ, in COVID-19. Several studies have reported that elevated levels of IFN-ɣ are associated with a more severe disease outcome.[37,39,41] Other researchers suggest that COVID-19 may lead to lymphopenia and suppression of T-cell IFN-ɣ production.[41] IFN-ɣ is known to promote the differentiation of undifferentiated CD4-positive T helper cells into differentiated Th1 cells while inhibiting the differentiation of Th2 cells. The impaired ability to produce IFN-ɣ may have altered the development of an effective Th1 immune response. This could be supported by the fact that decreased IFN-ɣ responses or indeterminate results were associated with COVID-19 severity parameters including mortality, need for intensive care unit, elevated levels of inflammatory markers (IL-6, CRP, procalcitonin, neutrophilia, LDH, ferritin, fibrinogen, and D-dimer). We found that an indeterminate QFT-TB result or a low response to mitogen was associated with lymphopenia. Similar to our findings, lymphopenia was reported to be an independent factor affecting indeterminate results of the QFT-TB assays in Korean patients with rheumatic diseases.[33] Reduced lymphocyte counts are associated with higher rates of indeterminate IGRA results, likely due to decreased production of IFN-ɣ in response to mitogen stimulation. Interestingly, we noticed that COVID-19 patients were lymphopenic regardless of whether their QFT-TB results were interpretable or not. This suggests that lymphopenia alone does not explain the indeterminate results. A tendency toward an exhausted phenotype of T lymphocytes expressing PD-1 was reported in COVID-19 patients.[39,42]

Also, we found a correlation between neutrophilia and increased NLR with indeterminate results. The NLR, an inflammatory marker, has been linked to negative outcomes in patients with COVID-19,[43] inflammatory diseases,[44–46] and tumors.[47,48] It has been also identified as an independent predictor for an indeterminate QFT result.[49]

4.3 | Other diagnostic tests for assessing LTBI

We did not retrieve any study using TST or T-SPOT.TB. Compared to the QFT-TB assay, a normalized number of peripheral blood mononuclear cells is used in T-SPOT.TB. This was designed to overcome immune deficiency induced by lymphopenia such as in HIV patients.[50] However, we speculate that the latter test may also be affected in COVID-19 patients since lymphopenia alone does not fully account for the high rates of indeterminate results in COVID-19 patients. As mentioned above, T lymphocytes of COVID-19 patients have an exhausted phenotype with low IFN-ɣ production.[39,42]

The diagnosis contribution of T-SPOT.TB and TST versus QFT-TB to reduce the occurrence of indeterminate results in COVID-19 patients remained to be determined.

4.4 | Impact of COVID-19 vaccines on IGRAs results

It is recommended to perform TB testing using either TST or IGRA regardless of the timing of COVID-19 vaccination.[51] However, we retrieved one study showing that COVID-19 vaccines affected mostly nil and mitogen-nil values for more than 11 weeks.[17] Further studies assessing IGRAs after COVID-19 vaccines are needed to establish reliable conclusions.

4.5 | Implications of the results for practice

To avoid indeterminate IGRA results in COVID-19 patients, timing would be the key. Based on our results, a QFT-TB test could be performed within 6–8 weeks of a SARS-CoV-2 positive test.[23,24]

To the best of the authors' knowledge, this systematic review is the first to examine the incidence of indeterminate QFT-TB results in the context of SARS-CoV-2 infection or vaccination. Moreover, we conducted a narrative review of the associated factors.

There are some limitations to our meta-analysis. First, our study comprised observational studies resulting in low-level-evidence.[52] The pooled studies showed a marked heterogeneity, which may have affected the accuracy of the estimated prevalence of indeterminate QFT in SARS-CoV-2 patients. Several factors, such as non-randomized patient selection, various patient screening techniques, and low quality in some of the studies could have contributed to this heterogeneity. Besides, studies were performed in countries with low and high TB burdens. Analysis according to TB incidence and BCG vaccination was not performed. Likewise, BCG vaccination status was not mentioned in all studies. Additionally, the current study did not find any data on the use of the T-SPOT.TB or TST tests in COVID-19 patients.

In conclusion, the systematic review and meta-analysis highlights that there is a high prevalence of indeterminate QFT-TB results (26%) in COVID-19 patients which may limit the clinical utility of the test in this particular situation. Clinical and biological factors associated with indeterminate results included disease severity, corticosteroid use before the QFT assay, and increased inflammation-related parameters including neutrophilia and lymphopenia.

AUTHOR CONTRIBUTIONS

Aicha Ben Tekaya: Methodology; writing—original draft. **Ameni Jerbi**: Writing—original draft; writing—review and editing. **Mouna Ben Sassi**: Methodology. **Salma Mokaddem**: Writing—original draft. **Ines Mahmoud**: Supervision; validation; writing—review and editing. **Chedli Dziri**: Software; validation. **Leila Abdelmoula**: Supervision; validation. All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials. [Ameni Jerbi] had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

The lead author Ameni Jerbi affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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REFERENCES

1. Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent *Mycobacterium tuberculosis* infection. *N Engl J Med*. 2015;372(22):2127-2135.
2. WHO. Weekly epidemiological Updates on COVID-19. https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19—22-february-2023
3. Aggarwal AN, Agarwal R, Dhooria S, Prasad KT, Sehgal IS, Muthu V. Active pulmonary tuberculosis and coronavirus disease 2019: a systematic review and meta-analysis. *PLoS One*. 2021;16(10 October):0259006. doi:10.1371/journal.pone.0259006
4. Gong W, Wu X. Differential diagnosis of latent tuberculosis infection and active tuberculosis: a key to a successful tuberculosis control strategy. *Front Microbiol*. 2021;12(October):1-23.
5. Alebouyeh S, Weinrick B, Achkar JM, García MJ, Prados-Rosales R. Feasibility of novel approaches to detect viable *Mycobacterium tuberculosis* within the spectrum of the tuberculosis disease. *Front Med*. 2022;9(August):1-11.
6. Haas MK, Belknap RW. Diagnostic tests for latent tuberculosis infection. *Clin Chest Med*. 2019;40(4):829-837. doi:10.1016/j.ccm.2019.07.007
7. Lalvani A, Pareek M. A 100 year update on diagnosis of tuberculosis infection. *Br Med Bull*. 2010;93(1):69-84.
8. Shafeque A, Bigio J, Hogan CA, Pai M, Banaei N. Fourth-generation quanti FERON-TB gold plus: what is the evidence? *J Clin Microbiol*. 2020;58(9):1-8.
9. Redelman-Sidi G, Sepkowitz KA. IFN-γ release assays in the diagnosis of latent tuberculosis infection among immunocompromised adults. *Am J Respir Crit Care Med*. 2013;188(4):422-431.
10. Palacios-Gutiérrez JJ, Rodríguez-Guardado A, Arias-Guillén M, et al. Clinical and epidemiological correlates of low IFN-gamma responses in mitogen tube of QuantiFERON assay in tuberculosis infection screening during the COVID-19 pandemic: a population-based marker of COVID-19 mortality? *Arch Bronconeumol*. 2022;58(January):649-659.
11. Ward JD, Cornaby C, Schmitz JL. Indeterminate QuantiFERON gold plus results reveal deficient interferon gamma responses in severely ill COVID-19 patients. *J Clin Microbiol*. 2021;59(10):1-10.

12. Cortes MP, Schultz CS, Isha S, et al. The pitfalls of mining for QuantiFERON gold in severely ill patients with COVID-19. *Mayo Clin Proc. Innovations, Qual Outcomes*. 2022;6(5):409-419. doi:10.1016/j.mayocpiqo.2022.06.004
13. Ni L, Cheng ML, Feng Y, et al. Impaired cellular immunity to SARS-CoV-2 in severe COVID-19 patients. *Front Immunol*. 2021;12(February):1-10.
14. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
15. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of non-randomized studies in meta-analyses 2013. 2021.
16. Borenstein M, Hedges LE, Higgins JPT, Rothstein HR Comprehensive meta-analysis version 4. Biostat Inc. 2022. www.Meta-Analysis.com
17. Chen NY, Liu ZH, Kao SW, et al. Changes in interferon-γ release assay readout after COVID-19 vaccination: a prospective cohort study. *Int J Infect Dis*. 2022;122(January):537-542.
18. Granozzi B, Bisognin F, Tadolini M, et al. IGRA test for TB in COVID-19: role of corticosteroids. *Int J Tuberc Lung Dis*. 2022;26(11):1088-1091.
19. Solanich X, Fernández-Huerta M, Basaez C, et al. Clinical significance of indeterminate quantiferon-tb gold plus assay results in hospitalized covid-19 patients with severe hyperinflammatory syndrome. *J Clin Med*. 2021;10(5):918.
20. Imeneo A, Alessio G, Di Lorenzo A, et al. In patients with severe COVID-19, the profound decrease in the peripheral blood T-cell subsets is correlated with an increase of QuantiFERON-TB gold plus indeterminate rates and reflecting a reduced interferon-gamma production. *Life*. 2022;12(2):244.
21. Rajamanickam A, Pavan Kumar N, Chandrasekaran P, et al. Effect of SARS-CoV-2 seropositivity on antigen—specific cytokine and chemokine responses in latent tuberculosis. *Cytokine*. 2022;150:155785.
22. Petrone L, Petruccioli E, Vanini V, et al. Coinfection of tuberculosis and COVID-19 limits the ability to in vitro respond to SARS-CoV-2. *Int J Infect Dis*. 2021;113:S82-S87.
23. Sánchez-Martínez F, Arenas-Miras M, Neus Jové-Caballé HK-F. Influence of cytokine release syndrome in severe COVID-19 patients treated with tocilizumab over the quantiferon TB gold plus results. *Cartas científicas/Arch Bronconeumol*. 2021;57(S2):45-63.
24. Gupta A, Sural S, Gupta A, et al. Positive QuantiFERON test and the severity of COVID-19 disease: a prospective study. *Indian J Tuberc*. 2021;68:474-480.
25. Torre A, Aliberti S, Castellotti PF, et al. Preliminary observations on IGRA testing for TB infection in patients with severe COVID-19 eligible for immunosuppressive therapy. *Respir Med*. 2020;175(January):106204.
26. Meier NR, Volken T, Geiger M, Heininger U, Tebruegge M, Ritz N. Risk factors for indeterminate interferon-gamma release assay for the diagnosis of tuberculosis in children—a systematic review and meta-analysis. *Front Pediatr*. 2019;7(May):208.
27. Zhen-Yu Huo LP. Accuracy of the interferon-γ release assay for the diagnosis of active tuberculosis among HIV-seropositive individuals: a systematic review and meta-analysis. *BMC Infect Dis*. 2016;22(16)350.
28. Rahimifard N, Mahmoudi S, Mamishi S, Pourakbari B. Prevalence of latent tuberculosis infection in transplant candidates: a systematic review and meta-analysis. *Microb Pathog*. 2018;125:401-410.
29. Chiacchio T, Petruccioli E, Vanini V, et al. Characterization of QuantiFERON-TB-Plus results in latent tuberculosis infected patients with or without immune-mediated inflammatory diseases. *J Infect*. 2019;79(1):15-23. doi:10.1016/j.jinf.2019.04.010
30. Haustein T, Ridout DA, Hartley JC, et al. The likelihood of an indeterminate test result from a whole-blood interferon-γ release assay for the diagnosis of mycobacterium tuberculosis infection in children correlates with age and immune status. *Pediatr Infect Dis J*. 2009;28(8):669-673.
31. Cholongitas E, Marelli L, Shusang V, et al. A systematic review of the performance of the model for end-stage liver disease (MELD) in the setting of liver transplantation. *Liver Transpl*. 2006;12(7):1049-1061.
32. Kim KH, Kang JM, Ahn JG. Low-dose steroids are associated with indeterminate QuantiFERON-TB Gold In-Tube assay results in immunocompetent children. *Sci Rep*. 2021;11:6468.
33. Ahn SS, Kim HW, Park Y. Frequency and factors of indeterminate QuantiFERON-TB Gold In-Tube and QuantiFERON-TB Gold PLUS test results in rheumatic diseases. *J Clin Med*. 2021;10(19):4357.
34. Thomas TA, Mondal D, Noor Z, et al. Malnutrition and helminth infection affect performance of an interferon γ-release assay. *Pediatrics*. 2010;126(6):e1522-e1529.
35. Kim SH, Jo KW, Shim TS. Quantiferon-tb gold plus versus quantiferon-tb gold in-tube test for diagnosing tuberculosis infection. *Korean J Intern Med*. 2020;35(2):383-391.
36. Park CH, Park JH, Jung YS. Impact of immunosuppressive therapy on the performance of latent tuberculosis screening tests in patients with inflammatory bowel disease: a systematic review and meta-analysis. *J Pers Med*. 2022;12(3):507.
37. Chen Y, Wang J, Liu C, et al IP-10 and MCP-1 as biomarkers associated with disease severity of COVID-19. *Molecular Medicine [Internet]*. 2020;26(1):97. doi:10.1186/s10020-020-00230-x
38. Hadjadj J, Yatim N, Barnabei L, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science*. 2020;369:718-724.
39. Nicolas V, Britton GJ, Gruber C. Immunology of COVID-19: current state of the science. *Immunity*. 2020;52(6):910-941.
40. Carvalho T, Krammer F, Iwasaki A. The first 12 months of COVID-19: a timeline of immunological insights. *Nat Rev Immunol*. 2021;21(4):245-256.
41. Remy KE, Mazer M, Striker DA, et al. Severe immunosuppression and not a cytokine storm characterizes COVID-19 infections. *JCI Insight*. 2020;5(17):15-18.
42. Mahmoodpoor A, Hosseini M, Soltani-Zangbar S, Sanaie S. Reduction and exhausted features of T lymphocytes under serological changes, and prognostic factors in COVID-19 progression. *Mol Immunol*. 2020;138(January):121-127.
43. Simadibrata DM, Calvin J, Wijaya AD, Ibrahim NAA. Neutrophil-to-lymphocyte ratio on admission to predict the severity and mortality of COVID-19 patients: a meta-analysis. *Am J Emerg Med*. 2021;42(January):60-69.
44. Lee YH, Song GG. Neutrophil-to-lymphocyte ratio, mean platelet volume and platelet-to-lymphocyte ratio in Behçet's disease and their correlation with disease activity: a meta-analysis. *Int J Rheumatic Diseases*. 2018;21(12):2180-2187.
45. Wang L, Wang C, Jia X, Yang M, Yu J. Relationship between neutrophil-to-lymphocyte ratio and systemic lupus erythematosus: a meta-analysis. *Clinics*. 2020;75:e1450.
46. Karageorgiou V, Milas GP, Michopoulos I. Neutrophil-to-lymphocyte ratio in schizophrenia: a systematic review and meta-analysis. *Schizophrenia Res*. 2019;206:4-12. doi:10.1016/j.schres.2018.12.017
47. Templeton AJ, McNamara MG, Šeruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *JNCI: J Natl Cancer Institute*. 2014;106(6):1-11.
48. Liu D, Heij LR, Czigany Z, et al The prognostic value of neutrophil-to-lymphocyte ratio in cholangiocarcinoma: a systematic review and meta-analysis. *Scientific Reports [Internet]*. 2022;12(1):1-12. doi:10.1038/s41598-022-16727-w
49. Woo KS, Kim BG, Choi JL, Kim BR, Kim KH. Neutrophil-to-lymphocyte ratio is associated with impaired interferon-gamma release to phytohemagglutinin. *PLoS One*. 2015;10(5):e0125794.

50. Huo Zyu, Peng L. Accuracy of the interferon-γ release assay for the diagnosis of active tuberculosis among HIV-seropositive individuals: a systematic review and meta-analysis. *BMC Infec Dis [Internet]*. 2016;16(1):350. doi:10.1186/s12879-016-1687-8
51. CDC. Guidelines for using the QuantiFERON®-TB gold test for detecting *Mycobacterium tuberculosis* infection, United States. 2023. https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a4.htm
52. HAS/Service des bonnes pratiques professionnelles. Level of evidence and grade of recommendation of recommendations for good practice—state of the art. 2013. https://www.has-sante.fr/jcms/c_1600564/fr/niveau-de-preuve-et-gradation-des-recommandations-de-bonne-pratique-etat-des-lieux

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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