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ORIGINAL ARTICLE

The Pitfalls of Mining for QuantiFERON Gold in Severely Ill Patients With COVID-19

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Abstract

Objective: To assess the proportion of indeterminate QuantiFERON-TB Gold Plus (QFT-Plus) results in patients admitted for severe coronavirus disease 2019 (COVID-19) pneumonia and evaluate the factors associated with indeterminate QFT-Plus results.

Patients and Methods: Data on COVID-19 admissions at Mayo Clinic in Florida were extracted between October 13, 2020, and September 20, 2021, and data from a prepandemic cohort were extracted between October 13, 2018, and September 20, 2019. A secondary analysis of the COVID-19 cohort was performed using gradient boosting modeling to generate variable importance and SHapley Additive exPlanations plots.

Results: Our findings demonstrated more indeterminate QFT-Plus test results in patients hospitalized for severe COVID-19 infection than in patients without COVID-19 (139 of 495, 28.1%). The factors associated with indeterminate QFT-Plus test results included elevated levels of C-reactive protein, ferritin, lactate dehydrogenase and interleukin-6 and included lower levels of leukocyte, lymphocyte, and platelet counts.

Conclusion: The patients with severe COVID-19 had a higher likelihood of indeterminate QFT-Plus results, which were associated with elevated levels of inflammatory markers consistent with severe infection. Interferon-gamma release assay screening tests are likely confounded by COVID-19 infection itself, limiting the screening ability for latent tuberculosis infection reactivation. Indeterminate QFT-Plus results may also require follow-up QFT-Plus testing after patient recovery from COVID-19, increasing the cost and complexity of medical decision making and management. Additional risk assessments may be needed in this patient population for screening for latent tuberculosis infection in patients with severe COVID-19.

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Patients with coronavirus disease 2019 (COVID-19) present with a wide range of clinical symptoms and disease severity, which is classified as mild, moderate, severe, and critical.[1] Most patients with mild disease do not require hospitalization, whereas patients with moderate-to-severe disease often require hospitalization and treatment. Immunosuppressive drugs, such as corticosteroids and tocilizumab, have demonstrated benefits in patients with moderate-to-severe COVID-19 by decreasing the hyperinflammatory response.[2-4] Reactivation of latent infections, such as tuberculosis, is a potential complication of immunosuppressive therapy.[5] Interferon-gamma release assays (IGRAs), such as QuantiFERON-TB Gold Plus (QFT-Plus), are widely used to screen for latent tuberculosis infection (LTBI).[6] QuantiFERON-TB Gold Plus testing has been used to screen patients with COVID-19 for LTBI before initiation of immunosuppressant drugs[7] according to prepandemic guidelines from the Centers for Disease Control and Prevention and Infectious Diseases Society of America.[8]

QuantiFERON-TB Gold Plus tests are used to determine whether a patient has a cell-mediated immune response after stimulation by *Mycobacterium tuberculosis* antigens. The test reports a positive, negative, or indeterminate result based on the response to tubercular

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antigens. An increased rate of indeterminate QFT-Plus test results among patients with COVID-19 has been demonstrated in several studies over the course of the pandemic.[9,10] Multiple factors have been considered as potential links between indeterminate QFT-Plus test results and COVID-19 infections. Lymphocytopenia, which is a common finding in patients with severe COVID-19, was found to be associated with a higher incidence of indeterminate QFT-Plus test results in a study conducted by Torre et al.[10] The study by Torre et al[10] also reported higher mortality rates in patients with indeterminate QFT-Plus test results.

QuantiFERON-TB Gold Plus testing was performed at Mayo Clinic in Florida, per protocol, before initiation of immunosuppressive therapy for moderate-to-severe COVID-19 infections. This study aimed to analyze the prevalence of indeterminate QFT-Plus test results in patients hospitalized for COVID-19, determine possible associations between indeterminate QFT-Plus test results and other common laboratory assays, and explore factors associated with indeterminate QFT-Plus test results, including underlying comorbidities and clinical outcomes.

MATERIALS AND METHODS

Patient Identification

This retrospective study was deemed exempt by the local institutional review board (#21-009658). Data on patients with COVID-19 pneumonia who had undergone QFT-Plus testing while hospitalized at Mayo Clinic in Florida between October 13, 2020, and September 20, 2021, were extracted from their electronic health records. The variables of interest included demographics, comorbidities, length of hospital stay, mortality, and laboratory assays performed during the hospitalizations, including inflammatory markers and QuantiFERON-TB Gold Plus results. Patients with negative polymerase chain reaction and/or antigen test results for severe acute respiratory syndrome coronavirus 2 on nasopharyngeal swabs during the same admission were excluded. Similarly, data on QFT-Plus tests were acquired for a prepandemic, hospitalized comparison cohort between October 13, 2018, and September 20, 2019.

IGRA Testing

In our hospital, IGRA testing was performed using QuantiFERON-TB Gold Plus tests (QIAGEN). The QFT-Plus assay consists of 4 components: a TB1 refers to the tuberculosis testing tube which contains mycobacterial polypeptides stimulating mainly CD4+ T-helper lymphocytes; TB2 refers to the tuberculosis testing tube which contains peptides that stimulate CD4+ and CD8+ T cells; a mitogen tube containing phytohemagglutinin, which serves as a positive control for assessing overall cell-mediated immunity; and a Nil tube, which is devoid of any immunostimulants and serves as a negative control (QIAGEN QuantiFERON-TB Gold Plus).[11] The result was interpreted as positive, negative, or indeterminate per the manufacturer's instruction.

Statistical Analyses

To determine whether the pre-COVID-19 QFT-Plus test results were significantly different from the COVID-19 QFT-Plus test results, we compared the rates of indeterminate results using the chi-square analysis. Patient characteristics and baseline comorbidities were compared between the cohort with indeterminate results and that with negative QFT-Plus test results. Similarly, for each laboratory assay, the measurement closest to that at the time of admission was compared and stratified by QFT-Plus test results. Laboratory assay results below the lower limit of detection were imputed to equal half the lower limit. Values greater than the upper limit were Winsorized at the upper limit. Standardized differences were used to identify significant differences (absolute value greater than 10%).

In a secondary exploratory analysis, we generated a gradient boosting machine (GBM) model to predict the QFT-Plus test results (indeterminate vs negative) by tuning multiple hyperparameters (eg, number of trees, interaction depth, sample rate, and learning rate). The final model was determined by identifying the highest mean area under the curve across 5-fold cross-validation. Before GBM modeling, missing data were imputed using the missForest imputation algorithm.[12] To provide interpretability, the underlying model was then used to generate variable importance and SHAP plots. Variable importance plots are

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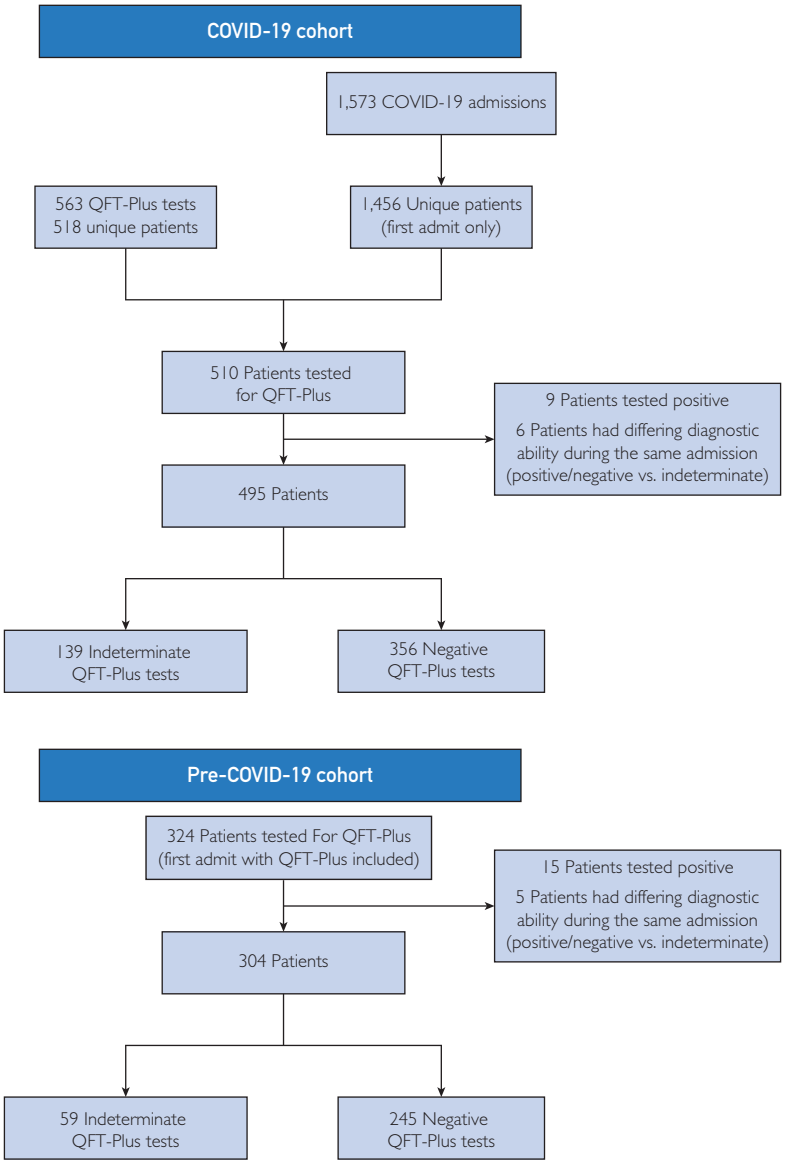

FIGURE 1. A consort diagram depicting the inclusion or exclusion criteria and classifications of test results for the coronavirus disease 2019 and precoronavirus disease 2019 cohorts. COVID-19, coronavirus disease 2019; QFT, QuantiFERON-TB.

used to identify variables that have the most influence on a model's predictive ability, and SHAP plots are used to identify both influence and the directional relationship between a value and a prediction.[13] Lastly, we generated partial dependence plots to determine the nonlinear relationships between laboratory assays and the likelihood of indeterminate QFT-Plus test results.

Conducting the exploratory analysis using GBM modeling allowed us to further explore feature importance and nonlinear relationships between assays and indeterminate test results. Interpretation of the SHAP and variable importance plots allowed us to discern that several assays were strongly related to indeterminate results. The results of this study highlight which assays should be considered

TABLE 1. Cohort Overview in Patients With Coronavirus Disease 2019 With QuantiFERON-TB Gold Plus Results[a,b]

Characteristics and comorbidities	Indeterminate (N=139)	Negative (N=356)	Total (N=495)	Standardized difference[c]
Age (y)	61 (24-93)	61 (21-98)	61 (21-98)	6.7%
Sex (male)	96 (69.1%)	221 (62.1%)	317 (64.0%)	**14.7%**
Race				**11.0%**
American Indian or Alaskan Native	0 (0.0%)	1 (0.3%)	1 (0.2%)	
Asian	9 (6.5%)	22 (6.2%)	31 (6.3%)	
Black or African American	10 (7.2%)	30 (8.4%)	40 (8.1%)	
White	113 (81.3%)	290 (81.5%)	403 (81.4%)	
Other or unknown	7 (5.0%)	13 (3.7%)	20 (4.0%)	
Ethnicity				8.1%
Hispanic	11 (7.9%)	21 (5.9%)	32 (6.5%)	
Non-Hispanic	125 (89.9%)	328 (92.1%)	453 (91.5%)	
Unknown	3 (2.2%)	7 (2.0%)	10 (2.0%)	
Chronic kidney disease	12 (8.6%)	14 (3.9%)	26 (5.3%)	**19.5%**
Chronic lung disease	118 (84.9%)	266 (74.7%)	384 (77.6%)	**25.5%**
Congenital heart disease	1 (0.7%)	3 (0.8%)	4 (0.8%)	1.4%
Congestive heart failure	12 (8.6%)	33 (9.3%)	45 (9.1%)	2.2%
Coronary artery disease	28 (20.1%)	65 (18.3%)	93 (18.8%)	4.8%
Diabetes mellitus	27 (19.4%)	88 (24.7%)	115 (23.2%)	**12.8%**
Hypertension	68 (48.9%)	183 (51.4%)	251 (50.7%)	5.0%
Immunosuppression[d]	21 (15.1%)	47 (13.2%)	68 (13.7%)	5.5%
COVID-19 risk score[e]	4 (1-9)	3 (0-10)	3 (0-10)	6.6%
End-stage renal disease	11 (7.9%)	20 (5.6%)	31 (6.3%)	9.1%
Breakthrough case	14 (10.1%)	26 (7.3%)	40 (8.1%)	9.8%
Monoclonal antibodies	5 (3.6%)	11 (3.1%)	16 (3.2%)	2.8%
Dialysis	3 (2.2%)	7 (2.0%)	10 (2.0%)	1.4%
Transplant recipients[f]	21 (15.1%)	37 (10.4%)	58 (11.7%)	**14.2%**
Solid organ transplant	12 (8.6%)	21 (5.9%)	33 (6.7%)	**10.5%**
Vaccination status				**11.8%**
Unvaccinated	118 (84.9%)	306 (86.0%)	424 (85.7%)	
Partially vaccinated	7 (5.0%)	24 (6.7%)	31 (6.3%)	
Breakthrough	14 (10.1%)	26 (7.3%)	40 (8.1%)	
Vaccination type at first shot				**22.8%**
N-Miss	118	306	424	
Johnson & Johnson	2 (9.5%)	2 (4.0%)	4 (5.6%)	
Moderna	7 (33.3%)	19 (38.0%)	26 (36.6%)	
Pfizer	12 (57.1%)	29 (58.0%)	41 (57.7%)	
Reason for testing				2.7%
N-Miss	53	156	209	
Asymptomatic	3 (3.5%)	8 (4.0%)	11 (3.8%)	
Symptomatic	83 (96.5%)	192 (96.0%)	275 (96.2%)	
ICU care	73 (52.5%)	148 (41.6%)	221 (44.6%)	**22.1%**

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TABLE 1. Continued

Characteristics and comorbidities	Indeterminate (N=139)	Negative (N=356)	Total (N=495)	Standardized difference[c]
Reason for testing, continued				
Mechanical ventilation	22 (15.8%)	44 (12.4%)	66 (13.3%)	10.0%
Length of stay (d)	8 (2-114)	7 (1-193)	7 (1-193)	7.7%
Mortality	25 (18.0%)	59 (16.6%)	84 (17.0%)	3.7%

Bold indicates significant standardized differences.
[a]COVID-19, coronavirus disease 2019; ICU, intensive care unit.
[b]Categorical data are shown as count (percentage). Numeric data are represented as median (range).
[c]Standardized difference = difference in proportions divided by standard error; imbalance defined as absolute value greater than 10%.
[d]Immunosuppression status was attributed to patients with the following criteria: diagnosed with HIV infection, actively receiving chemotherapy, receiving immunosuppressive medications, or diagnosed with iatrogenic immunosuppression.
[e]COVID-19 complication risk score from Halalau et al.[14]
[f]Transplant status overall and solid organ transplant specifically was analyzed separately because our medical center is a large transplant center.

while identifying whether a patient may return an indeterminate result via QFT-Plus testing.

RESULTS

Between October 13, 2020, and September 20, 2021, 1456 unique patients with COVID-19 were admitted at Mayo Clinic in Florida. Of them, 510 patients underwent QuantiFERON Gold testing during their hospitalization. Fifteen patients were excluded because of either a positive QFT-Plus test result or multiple tests with different results (ie, positive or negative vs indeterminate), due to small sample size. This resulted in a final cohort of 495 patients (139 with an indeterminate QFT-Plus test result and 356 with a negative QFT-Plus test result; Figure 1). The median age of patients in our COVID-19 cohort was 61 years (range, 21-98 years), 64% were men, 81.4% were White, 91.5% were non-Hispanic or Latino, 85.7% were unvaccinated, and 8.1% had breakthrough infections (Table 1).[15]

The prepandemic group included 324 patients hospitalized between October 13, 2018, and September 20, 2019, who had undergone a QFT-Plus test during their admission. Of them, 20 patients were excluded because of either a positive QFT-Plus test result or multiple tests with different results. This resulted in a final cohort of 304 patients in the pre-COVID-19 cohort (59 with an indeterminate result and 245 with a negative result). The COVID-19 group had a higher rate of indeterminate QFT-Plus test results than the prepandemic cohort (28.1% vs 19.4%, respectively; P=.006).

The characteristics and comorbidities of patients with COVID-19 varied across QFT-Plus subgroups; higher indeterminate result rates were noted among men and patients with chronic kidney disease, lung disease, diabetes, and status after transplantation (Table 1). When clinical outcomes were analyzed, the proportion of patients who needed intensive care was higher in the indeterminate QFT-Plus test result group; however, no differences were seen in the need for mechanical ventilation, length of stay, or mortality.

A comparative analysis of laboratory parameters of the patients with COVID-19 at admission, stratified by QFT-Plus test results, revealed a significantly higher level of inflammatory laboratory assays, including C-reactive protein (CRP), -dimer, ferritin, fibrinogen, interleukin 6, and lactate dehydrogenase (LDH), in those with an indeterminate QFT-Plus test result than in those with a negative result (Table 2). The indeterminate QFT-Plus test result subgroup also demonstrated a higher absolute neutrophilia count and a lower absolute lymphocyte count than the negative test result subgroup. The feature importance of the GBM model is shown in the SHAP and variable importance plots in Figure 2. Directionality and trends are shown in both SHAP and partial dependence plots (Figure 3).

DISCUSSION

Our study demonstrated a higher incidence of indeterminate QFT-Plus test results in our patients with COVID-19 (28.1%) than in our pre-COVID-19 cohort (19.4%). Although

TABLE 2. Laboratory Assays of Patients With Coronavirus Disease 2019 With QuantiFERON-TB Gold Plus Results[a]

Labs	Indeterminate (N=139)	Negative (N=356)	Total (N=495)	*P* value[b]
Activated partial thromboplastin time (seconds)				.22
N	94	267	361	
Median (range)	30.0 (19.0-86.0)	30.0 (19.0-177.0)	30.0 (19.0-177.0)	
C-reactive protein (mg/dL)				**<.001**
N	138	355	493	
Median (range)	92.3 (1.5-400.0)	54.4 (1.5-400.0)	67.0 (1.5-400.0)	
Creatinine (mg/dL)				.24
N	133	341	474	
Median (range)	1.0 (0.4-20.3)	0.9 (0.3-8.8)	0.9 (0.3-20.3)	
D-dimer (mg/L FEU)				**.024**
N	138	354	492	
Median (range)	916.5 (110.0-42000.0)	735.5 (110.0-42000.0)	776.5 (110.0-42000.0)	
Ferritin (ng/mL)				**<.001**
N	134	348	482	
Median (range)	782.5 (25.0-6918.0)	549.5 (33.0-30714.0)	610.0 (25.0-30714.0)	
Fibrinogen (mg/dL)				**.014**
N	111	303	414	
Median (range)	632.0 (175.0-1000.0)	559.0 (111.0-1000.0)	571.5 (111.0-1000.0)	
Interleukin 6 (pg/mL)				**.001**
N	131	340	471	
Median (range)	68.0 (1.0-3096.0)	38.0 (1.0-3543.0)	44.0 (1.0-3543.0)	
International normalized ratio				**.003**
N	132	345	477	
Median (range)	1.2 (0.9-16.0)	1.2 (0.9-3.8)	1.2 (0.9-16.0)	
Lactate dehydrogenase (U/L)				**<.001**
N	137	349	486	
Median (range)	392.0 (87.0-1206.0)	339.0 (103.0-25000.0)	357.0 (87.0-25000.0)	
Lymphocytes, absolute (10^3 cells/μL)				**<.001**
N	133	331	464	
Median (range)	0.7 (0.1-3.1)	0.8 (0.0-81.3)	0.8 (0.0-81.3)	
Mean platelet volume (femtoliters)				.51
N	138	345	483	
Median (range)	10.2 (8.5-13.0)	10.2 (7.9-14.2)	10.2 (7.9-14.2)	
Neutrophils, percentage (%)				**<.001**
N	133	331	464	
Median (range)	83.9 (45.0-94.6)	78.2 (4.8-95.7)	79.7 (4.8-95.7)	
Neutrophils, absolute (cells/μL)				**<.001**
N	133	331	464	
Median (range)	7.2 (0.5-32.9)	5.0 (0.3-23.0)	5.3 (0.3-32.9)	
Platelet count (platelets per microliter)				**<.001**
N	139	347	486	
Median (range)	261.0 (25.0-793.0)	211.0 (23.0-899.0)	219.5 (23.0-899.0)	
Procalcitonin (ng/mL)				**.009**
N	138	349	487	
Median (range)	0.2 (0.0-81.5)	0.1 (0.0-43.3)	0.2 (0.0-81.5)	
Prothrombin time (seconds)				**.004**

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TABLE 2. Continued

Labs	Indeterminate (N=139)	Negative (N=356)	Total (N=495)	*P* value[b]
Prothrombin time (seconds), continued				
N	132	345	477	
Median (range)	13.3 (10.2-185.9)	12.8 (10.4-42.7)	12.9 (10.2-185.9)	

Bold indicates significant standardized differences.
[a]Laboratory assays at the ordering time closest to QuantiFERON-TB. Laboratory assays below the lower limit of detection were imputed to equal half the lower limit. Values greater than the upper limit were Winsorized at the upper limit.
[b]*P* values arise from Kruskal-Wallis rank sum tests.

previous studies (Solanich et al[7] and Torre et al[10]) have similarly demonstrated a higher incidence of indeterminate QFT-Plus test results in patients with COVID-19, our study is strengthened by the number of patients tested (510) and the fact that all QFT-Plus tests were performed before initiation of immunosuppressive therapies. Furthermore, we analyzed comorbid conditions and their association with indeterminate QFT-Plus test results and found that patients with chronic kidney disease, chronic lung disease, diabetes, and history organ transplantation had a higher incidence of indeterminate QFT-Plus test results.

Previous studies have found increased length of stay, intensive care utilization, and mortality among patients with COVID-19 with indeterminate QFT-Plus test results compared to COVID-19 positive patients with negative results.[7,15] Our study found a significant association between indeterminate QFT-Plus test results and intensive care utilization but did not demonstrate a significant difference in the length of stay or in-hospital mortality between the 2 groups in our patient population. The reason for these differences remains unclear but may reflect changes in therapeutics and preventive measures throughout the evolving pandemic.

All QFT-Plus tests in our COVID-19 cohort were performed before initiation of immunosuppressive therapies, which further supports the hypothesis that immune dysregulation, caused by severe COVID-19, impacts indeterminate QFT-Plus test results. Although some of the cited studies were conducted using previous commercially available IGRAs, the results can be extrapolated to ours.

Patients with COVID-19 with indeterminate QFT-Plus test results were characterized by neutrophilia, lymphopenia, and higher levels of inflammatory markers, such as CRP, D-dimer, ferritin, fibrinogen, LDH, and interleukin 6, compared with those with negative results. The marked increase in the levels of the inflammatory marker indicates an associated hyperinflammatory response of COVID-19 inversely associated with reduction in interferon-gamma secretion from T cells. These findings are supported by Ward et al,[9] who observed that peripheral T cells in severely ill patients with COVID-19 were unable to produce measurable interferon-gamma when stimulated with mitogen interferon control even after excluding patients who had been treated with immunosuppressive drugs or had pre-existing immunosuppressive comorbidities. A similar impression was made by Huang et al[16] in their study focusing on critically ill patients before the pandemic.

Limitations

There are several limitations to our study. First, this was a retrospective cross-sectional analysis of patients from a single institution, which may have limited its generalizability. Additionally, prepandemic patient demographics and clinical characteristics were not extracted because of the study design because our prepandemic cohort included a heterogeneous pool of diagnoses in comparison with the COVID-19 cohort.

The modeling limitation includes some missing assay data, primarily for patients with negative QFT-Plus test results. Patients with positive QFT-Plus test results were excluded from the analysis because of the small sample size. Additionally, because the use of GBM was exploratory, we did not split our data into a test set and training set for

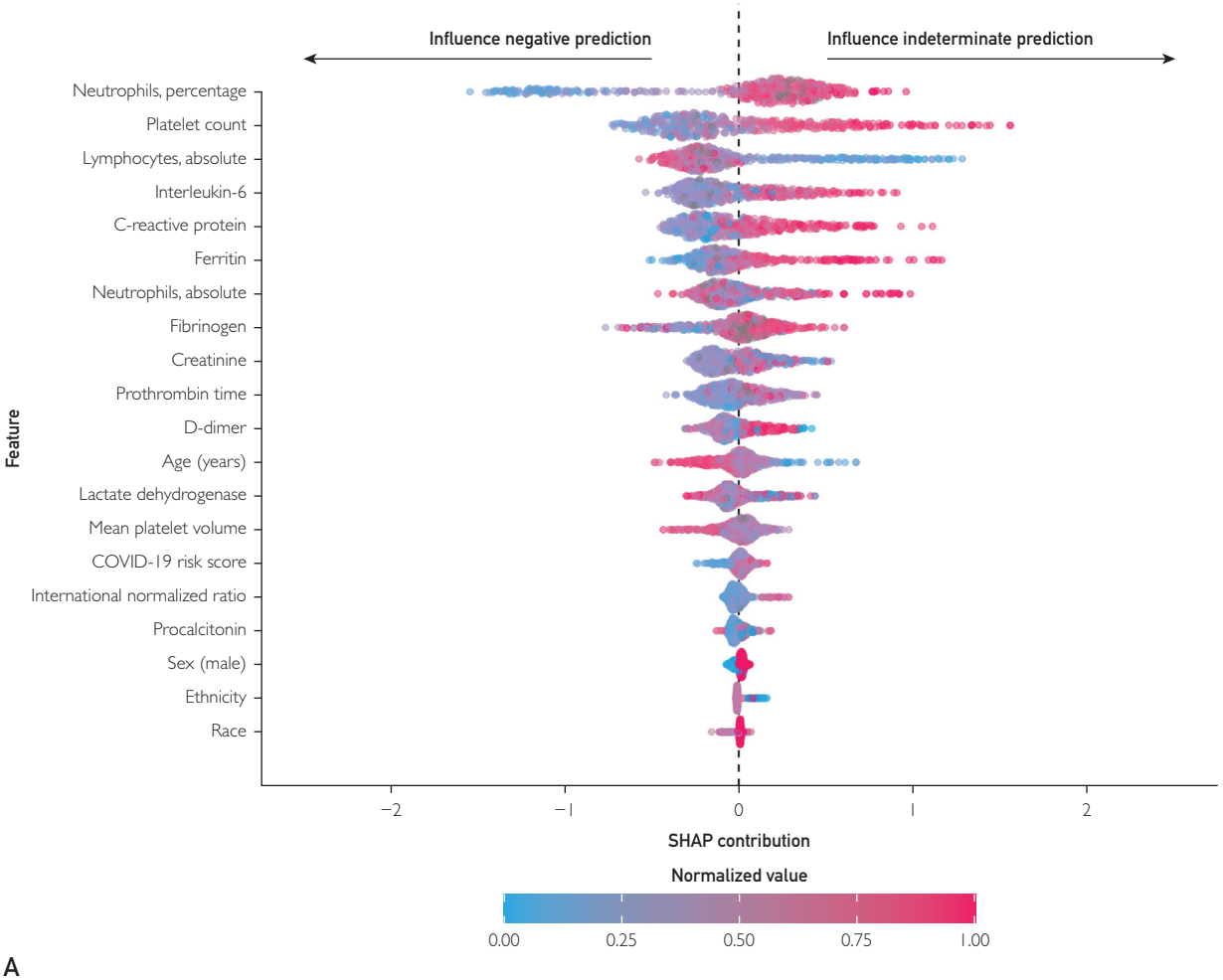

FIGURE 2. SHAP plots (A) and variable importance plot (B) results from the gradient boosting machine. SHAP plots are used to identify feature importance and are ordered from highest to lowest in terms of importance. Points are placed on the X-axis, which identifies the SHAP contribution on the continuum from a negative prediction (left) to an indeterminate prediction (right). Points are colored based on the normalized value for each variable. Variable importance is another mechanism to rank how influential a variable is in model prediction. In this presentation, variables are colored to represent the level of importance and ordered to match the SHAP feature importance. COVID-19, coronavirus disease 2019; SHAP, SHapley Additive exPlanations.

model validation, and further study is needed to validate this model.

Additionally, the QFT-Plus test results were collected once per patient and not repeated. It remains unclear whether serial testing would yield alternate results, particularly if performed under similar clinical circumstances because data on this topic are limited. Lastly, factors external to the patient, such as specimen handling and processing, were not evaluated.

CONCLUSION

The patients with COVID-19 had a higher prevalence of indeterminate QFT-Plus test results than the pre-COVID-19 cohort. Indeterminate QFT-Plus test results were associated with higher levels of inflammatory markers,

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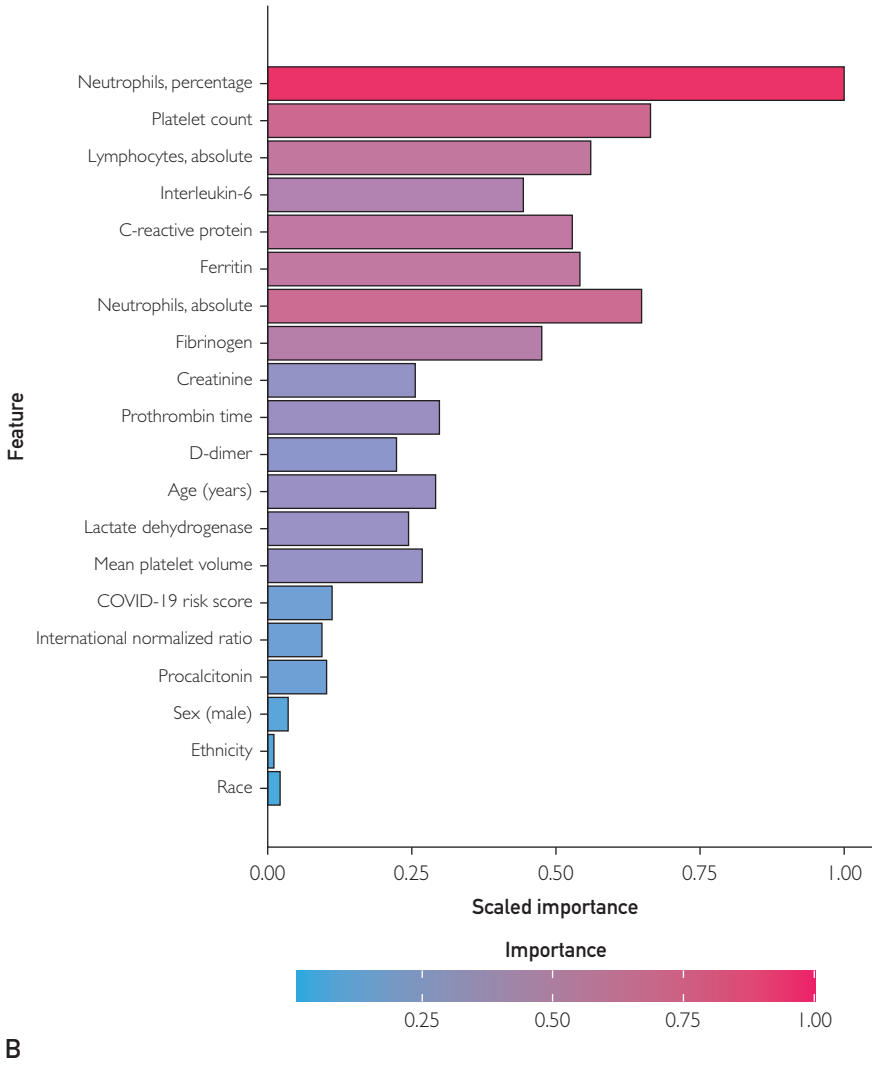

FIGURE 2. Continued

including CRP, LDH, prothrombin time, fibrinogen, neutrophils, and interferon, as well as low levels of white blood cells and lymphocytes. This study demonstrates that QFT-Plus testing has important limitations in screening for LTBI in patients hospitalized for COVID-19. Indeterminate results complicate medical decision making while considering the need for immunosuppressive therapy for severe COVID-19 vs the risk of reactivation of latent tuberculosis. Patients with indeterminate QFT-Plus test results may also require follow-up testing after recovery from COVID-19, increasing the cost and complexity of care. Future studies are required to longitudinally evaluate the conversion of an initial indeterminate result to a determinate one and follow-up patients clinically for the risk of requiring LTBI therapy. Clinicians should consider incorporating other risk assessment strategies for screening for latent tuberculosis in patients with COVID-19 with indeterminate IGRA results.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

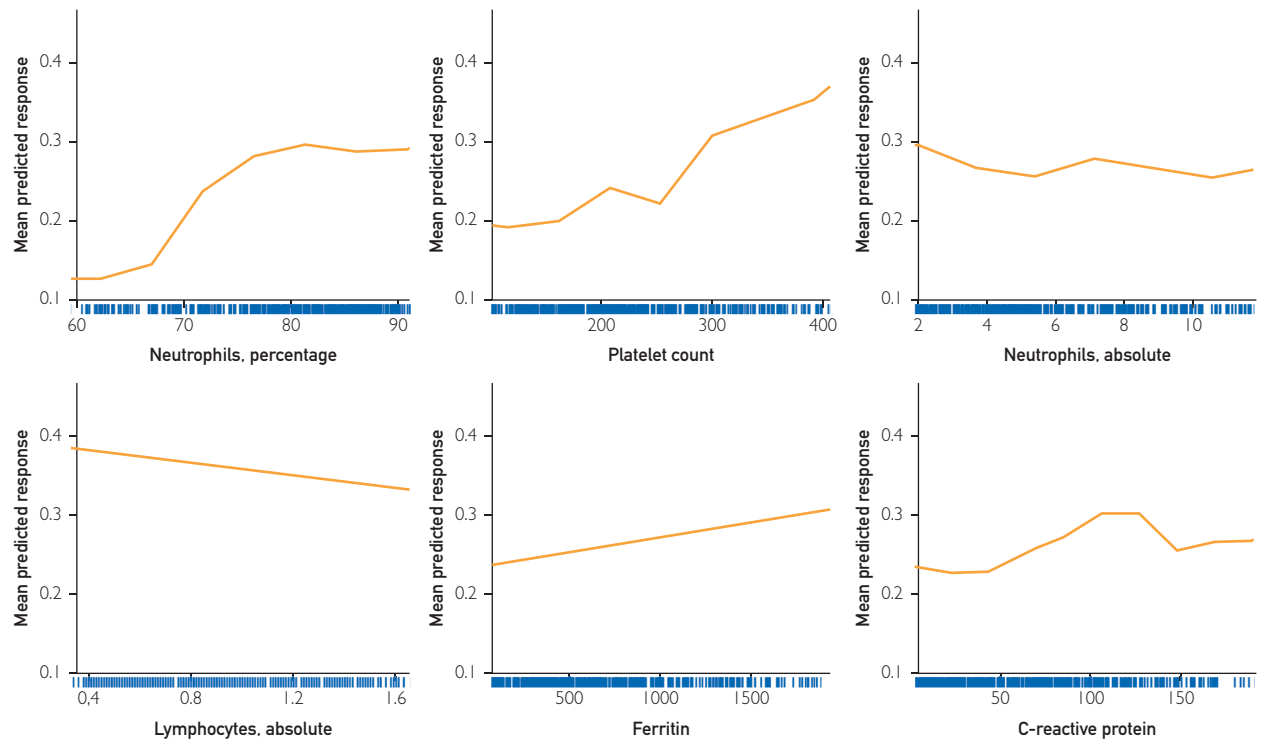

FIGURE 3. Partial dependence plots are generated using the gradient boosting machine for variables of clinical interest. The Y-axis represents the mean predicted response from laboratory values across from the 10th to 90th percentile after accounting for other variables in the model. The dashed lines along the X-axis represent the individual observations.

Abbreviations and Acronyms: **CRP,** C-reactive protein; **COVID-19,** coronavirus disease 2019; **GBM,** gradient boosting machine; **IGRA,** interferon-gamma release assay; **LDH,** lactate dehydrogenase; **LTBI,** latent tuberculosis infection; **QFT-Plus,** QuantiFERON-TB Gold Plus; **SHAP,** SHapley Additive exPlanations

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