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False-positive typhidot IgM assay in COVID-19 patients: A potential public health problem in tropical countries during COVID-19 endemic phase

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Abstract:

BACKGROUND: Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, reports of false-positive serological test results were reported in COVID-19 patients. Typhidot IgM test is reported in a few studies to give false-positive results in various viral illnesses in the past. The aim of this study was to estimate the typhidot IgM positivity rate in reverse transcription-polymerase chain reaction (RT-PCR)-confirmed COVID-19 patients.

MATERIALS AND METHODS: The present study was a cross-sectional study conducted at a tertiary care hospital. All symptomatic patients having fever that were admitted between April 1, 2021, and July 15, 2021, with a confirmed RT-PCR-positive result for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) were included in the study. Serological testing was done by typhoid IgM/IgG rapid diagnostic test for all SARS-CoV-2 RT-PCR-positive patients. The primary outcome studied was to estimate the typhidot IgM positivity rate among RT-PCR-confirmed COVID-19 patients. The secondary outcome studied was to determine the correlation between SARS-CoV-2 RT PCR cycle threshold (CT) value and typhidot-positive result.

RESULTS: Three hundred and five (17.99%) out of 1695 samples of confirmed COVID-19 patients were positive for typhoid serology by typhidot IgM test. However, upon performing Point-Biserial correlation analysis ($P = 0.832$, $r = 0.021$), no correlation was seen between RT-PCR CT value and typhidot result.

CONCLUSIONS: Typhidot test is a nonspecific diagnostic test for typhoid fever which can be false positive in COVID-19 patients. Hence, physicians should take this into consideration to avoid misdiagnosis and delay in accurate treatment of acute febrile illness cases, especially in the present scenario of COVID-19 endemicity.

Keywords:

Coronavirus disease 2019, enteric fever, false positive, serology, typhidot

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Introduction

Coronavirus disease 2019 (COVID-19) is a viral disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that was first reported in China and subsequently resulted a pandemic.[1] Over the course of next 2 years, the disease caused repeated waves of surged infections causing massive stress on the health-care systems. Owing to the lack of immunity against this novel virus in the communities, protocols for testing, tracing, isolation, and early treatment of COVID-19 patients were set in place to check the spread of transmission of SARS-CoV-2. Many tertiary care hospitals

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were converted into dedicated COVID-19 treatment hospitals.[2]

The clinical course of COVID-19 is highly variable, ranging from asymptomatic infection to severe disease leading to death.[3] A variety of symptoms, ranging from fever, body aches, joint pains, headache, cough, sore throat, running nose, diarrhea, and loss of taste and smell, were reported in the patients.[3] Many of these symptoms are nonspecific and it is challenging to differentiate the patient of COVID-19 from other infections causing acute febrile illness (AFI).[4] The definitive diagnosis of COVID-19 can be made on the basis of reverse transcription-polymerase chain reaction (RT-PCR) test in real-time format. Clinicians often order a spectrum of other tests in these febrile patients to rule out other common causes of AFI such as malaria, dengue, enteric fever, and scrub typhus.[5]

The immunochromatography-based rapid tests act as good screening tests in resource-constraint developing countries such as India.[6] They are rapid, easy to perform, and need minimum infrastructure and manpower. However, one major issue with the use of these tests is their cross-reactivity.[7] Since the beginning of the COVID-19 pandemic, reports of false-positive serological test results were reported in COVID-19 patients.[8-13] Typhidot IgM test is reported in a few studies to give false-positive results in various viral illnesses in the past.[8,14] Keeping in view of these early reports, a study was planned at our institute to estimate the typhidot IgM positivity rate in RT-PCR-confirmed COVID-19 patients and its implications on the public health system.

Materials and Methods

Study setting and design

The present study was a cross-sectional study conducted at a tertiary care hospital from North India between 01 April 2021, and 15 July 2021. The hospital was converted into a dedicated COVID-19 treatment facility during the second wave of the COVID-19 pandemic.

Case definitions

Suspected coronavirus disease 2019 case

A suspected COVID-19 case was defined as any patient who presented with one or more symptoms such as fever, cough, body-aches, running nose, sore throat, loss of taste, loss of smell, diarrhea, and respiratory distress.

Confirmed coronavirus disease 2019 case

A confirmed case of COVID-19 was defined as a case with or without symptoms whose SARS-CoV-2 RT-PCR test was positive. All symptomatic, microbiologically confirmed cases were admitted in the COVID-19 wards and managed as per the National Treatment Protocols, applicable at that particular time. Typhidot IgM results were taken into consideration, since IgM is the acute phase antibody, while IgG levels could be raised owing to the previous exposure in the patient in a tropical country like India.

Inclusion and exclusion criteria and methodology

All suspected cases of COVID-19 infection were admitted in an isolation ward where their specimens were collected for the laboratory diagnosis. Nasopharyngeal and oropharyngeal swabs were collected and transported in viral transport medium under cold chain for performing SARS-CoV-2 RT-PCR testing. Venous blood samples were drawn in Vacutainer and sent to the central laboratory for detecting other causes of AFI. Briefly, 4–5 ml of venous blood was collected in Vacutainer without additives and sent to the microbiology laboratory where serological testing was done by typhoid IgM/IgG rapid diagnostic test. All symptomatic patients having fever that were admitted between 01 April 2021, and 15 July 2021 with a confirmed RT-PCR-positive result for SARS-CoV-2 were included in the study. Any suspected COVID-19 patient whose RT-PCR result came negative was excluded from the study.

Outcome measures studied

The primary outcome studied was to estimate the typhidot IgM positivity rate among RT-PCR-confirmed COVID-19 patients. The secondary outcome studied was to determine the correlation between SARS-CoV-2 RT PCR cycle threshold (CT) value and typhidot-positive result.

Statistical analysis

The data collected during the study included the demographic profile of the patient, namely their age and gender, the results of the SARS-CoV-2 RT-PCR test, presence or absence of symptoms, and the results of serological testing against typhoid fever. For comparison, the data and trends of typhoid serology-positive specimens from the previous years were also collected. The data collected were entered in Microsoft Excel and statistical analysis was performed using SPSS v23 (IBM Corp, Armonk, New York, USA). Point-Biserial correlation analysis was performed to study the correlation between RT-PCR CT value and typhidot result.

Ethical considerations

The study was based on the ethical guidelines as given in the 1964 "Declaration of Helsinki." Further, the study was approved by the Institutional Ethics Committee. Informed consent was obtained from every patients prior to enrollment into the study.

Results

A total of 1695 samples of confirmed COVID-19 patients were received in the laboratory during the study period. The mean age of the patients was 51.5 years (range, 7–92 years). Three hundred and five (17.99%) out of 1695 samples were positive for typhoid serology by typhidot IgM test. Out of 302 patients, 188 were male and 114 were female.

In patients with typhidot-positive results, the SARS-CoV-2 RT-PCR Ct value was 28 (interquartile range [IQR]: 22–32). In patients with typhidot-negative results, the median SARS-CoV-2 RT-PCR CT value was 27 (IQR 21–31) as shown in Figure 1. Upon performing Point-Biserial correlation analysis ($P = 0.832$, $r = 0.021$), no correlation was seen between RT-PCR Ct value and typhidot result.

Discussion

Early case reports have reported cross-reactivity of SARS-CoV-2 antibodies with various other rapid diagnostic tests such as that for dengue and typhoid.[10,11,15] In the present study, 17.99% of the confirmed COVID-19 cases were positive for typhidot IgM test. A detailed review of literature revealed two other studies which have evaluated typhidot results in RT-PCR-confirmed COVID-19 patients.[8,9] In the study by Mustafa *et al*.,[9] the typhidot IgM positive rate among RT-PCR-confirmed COVID-19 patients was 63%, while it was 37.8% in the study by Saxena *et al*.[8] Typhidot test is a nonspecific test with low sensitivity and specificity, but is nevertheless, the most commonly used first-line investigation in AFI patients due to its easy availability, low cost, and quick result.[16,17] Typhidot has been shown to be false positive in patients infected with dengue fever and tuberculosis in the past.[8,14] Therefore, antibody cross-reactivity may be a cause of false-positive typhidot test results in COVID-19.

SARS-CoV-2 RT-PCR Ct value was found to have a positive correlation with typhidot test positivity in a study by Saxena *et al*.[8] However, upon performing Point-Biserail correlation analysis ($P = 0.832$, $r = 0.021$), no correlation was seen between RT-PCR Ct value and typhidot result.

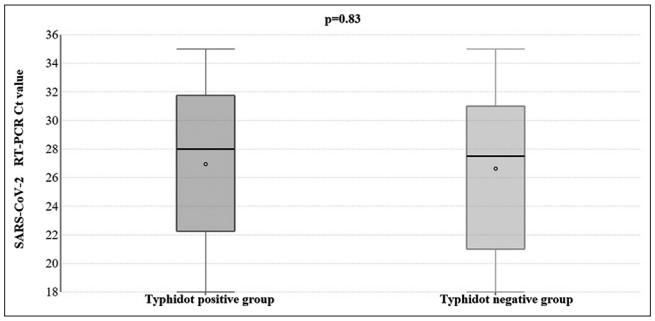

Figure 1: Box plot diagram showing comparison of SARS-CoV-2 reverse transcription-polymerase chain reaction cycle threshold value in typhidot-positive and typhidot-negative group

Comparing the typhidot positivity with non-COVID years of tests done at our hospital, the positivity rate of 17.99% was significantly higher compared to positivity rates in 2018 (12.24%; $P < 0.0001$) and 2019 (7.45%, 0.03). This again points toward the typhidot false positivity in COVID-19 patients.

Ever since the diagnosis of first case of COVID-19, the infection spread at a very rapid rate resulting in strain on the health-care facilities and severely impacting the non-COVID health-care services.[2] The SARS-CoV-2 infection presented an AFI with symptoms like cough, fever, and myalgia that were nonspecific and were commonly seen in other viral infections.[4] This was important from public health point of view, especially in tropical countries like India in which dengue and typhoid fever are endemic diseases.[18] Overlapping clinical features among COVID-19 and other AFIs are a potential source of delay in making the correct diagnosis and subsequent appropriate patient management. Therefore, it presents as a major public health problem in these countries. Moreover, it presents as a potential source of transmission of COVID-19 to non-COVID patients as well as health-care personnel.

With majority of the population getting seroconverted for SARS-CoV-2, COVID-19 is moving toward the endemic stage[19] and the COVID-19 testing has drastically reduced. Therefore, typhidot false positivity has major implications in such COVID-19-infected patients who might be misdiagnosed. At the same time, early treatment of COVID-19 infection is an important prognostic factor for COVID-19 patients.[20] Hence, extreme caution should be taken by physicians when interpreting typhidot-positive results in patients with AFI. In an attempt to contain drug resistance to antimicrobials, the global action plan aims to advocate strict infection control policies, antimicrobial stewardship, and judicious use of antibiotics.[21] The drug of choice for the treatment of enteric fever is a third-generation cephalosporin (ceftriaxone/cefixime) that are considered higher class of antibiotics. Patients treated with antibiotics as a result of false-positive typhidot assay could contribute to the spread of antimicrobial resistance and threaten the containment measures to stop the spread of drug resistance.

A limitation of the study was that blood culture of COVID-19 patients for the isolation of *Salmonella* Typhi was not performed. Culture being the gold standard for establishing the diagnosis of enteric fever[22] could have

assisted in the correlation of typhidot false positivity rate among COVID-19 patients.

Conclusions

Typhidot test is a nonspecific diagnostic test for typhoid fever which can be false positive in COVID-19 patients. Hence, physicians should take this into consideration to avoid misdiagnosis and delay in accurate treatment of AFI cases, especially in the present scenario of COVID-19 endemicity.

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Conflicts of interest
There are no conflicts of interest.

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