

A COMPARATIVE STUDY OF INFLAMMATORY MARKERS LEVELS IN PATIENTS OF TUBERCULOSIS AND COVID-TB COINFECTION

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ABSTRACT

Objective: The outbreak of COVID-19 has increased the vulnerability of global population to diseases; above all, the patients suffering from tuberculosis (TB) COVID-19. Both being diseases of the respiratory tract, a coinfection of the two might cause severe implications. The WHO has set a goal of eradicating TB globally by the year 2035 (END-TB program). To achieve this goal, various initiatives are being taken with respect to early diagnosis, screening – research and development of new diagnostic as well as treatment tools. Although, the pandemic largely interrupted these initiatives setting back progress by approximately a decade; it should not be overlooked that COVID-19 has unlocked new doors to research and development in the niche of infectious diseases. This study was aimed at analyzing of inflammatory markers in patients of TB, COVID-19, and COVID-TB coinfection.

Methods: A total of 164 patients aged between 18 years to 85 years were included in this study. Total patients (164) were, then, divided into three groups on the basis of their disease diagnosis. The patient groups are as follows: 57 COVID-19-positive patients, 53 COVID-TB coinfection-positive patients, and 54 TB-positive patients. Serological analysis data of C-reactive protein (CRP), D-dimer, and SGOT were statistically analyzed using one-way ANOVA.

Results: The results of analysis of variance showed significant results for all three inflammatory markers with $p < 0.05$. The levels of CRP, D-dimer, and SGOT underwent the highest increase among COVID-TB coinfection patient.

Conclusion: Through this study, it can be concluded that the addition of inflammatory markers testing in TB patients and diagnostic protocols may prove to be of significant assistance in diagnosis of TB and also to estimate the severity of infection in patients of active TB. It is also noteworthy that the levels of these markers were found to be highest in patients suffering from a coinfection of both the diseases.

Keywords: COVID-19, TB, CRP, D-DIMER.

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INTRODUCTION

Tuberculosis (TB) being the most infectious disease of the past century has affected approximately one-quarter of the total world population and the recent pandemic of COVID-19 has proven to be the most infectious disease seen in the past century [1]. With the stringent social distancing and lockdown norms, the treatment of various diseases was disrupted. Especially, TB treatment protocol which includes repetitive hospital visits and strictly scheduled follow-ups saw a major disruption causing moderate to severe health implications in patients. This has resulted in an increase in vulnerability to TB infection [2].

Both COVID-19 and TB affect the respiratory tract; majorly the lungs.

The decreased health-care access due to lockdowns and social distancing during COVID-19 has worsened the TB burden and vulnerability to TB, also causing aggravated lung damage in patients already suffering from TB. The coinfection of TB and COVID-19 on top of decreased health-care access has led to poor treatment availability and hence, poor prognosis of the patient. There is growing evidence to suggest that previous or current TB infection or disease are associated with poor COVID-19 outcomes, including an approximately two-to-three-fold increase in mortality. It was also observed that the patients with coinfection succumbed to an early death as compared to patients not infected with TB, their possibility of recovery was reduced by 25% and was markedly slow. According to the WHO TB report 2020, to reach the goal of TB elimination by the year 2035, the END TB strategy

outlines interventions to decrease TB-related mortality, morbidity, and transmission. Interventions such as;

- Measuring and appropriately responding to impact of COVID-19 on TB programs and services.
- New preventive, diagnostic, and treatment tools necessary for TB treatment and elimination [3].

However, health organizations such as WHO are aiming to eradicate TB worldwide by the year 2035, and it has proven to be difficult. The COVID-19 pandemic had detrimental effects on ongoing TB elimination efforts, reversing years of global progress for the 1st time in a decade [3]. This has attributed also due to the fact that TB is highly infectious and is usually detected once the infection has set in the body of the patient and has had evident manifestations. Like any other infection, inflammation is invariably seen in patients suffering from TB and COVID-TB coinfection [4]. Inflammatory responses are the primary characteristics of patients with pulmonary TB. Inflammation in TB is caused by sophisticated intracellular survival strategies of tubercle bacilli. TB is a continuum comprising spectrum of lesions as consequences of complex regulation of inflammation.

TB, which is characterized by granulomatous lesions formation and severe inflammatory responses [4]. This study analyzes the inflammatory marker levels in patients of TB, COVID-19, and COVID-TB coinfection.

METHODS

A total of 164 patients aged between 18 years and 85 years were included in this study.

Total patients (164) were then divided into three groups on the basis of their disease diagnosis. The patient groups are as follows: 57 COVID-19-positive patients, 53 COVID-TB coinfection-positive patients, and 54 TB-positive patients.

Inclusion criteria

The following criteria were included in the study:

- Patients who tested positive for COVID-19
- Patients who are diagnosed with TB
- Patients who were diagnosed with COVID-TB coinfection.

Exclusion criteria

The following criteria were excluded from the study:

- Patients who were below 18 years of age
- Patients who were above 80 years of age
- Patients who are suffering from any other inflammatory condition
- Patients who underwent any recent major surgery
- Pregnant woman.

Study design

This was a case-control study.

Collection and analysis of sample

5 mL blood was collected using aseptic technique from antecubital vein in plain vial.

After incubation at 37° C for 15 min in the incubator and centrifugation for 10 min at approximately 3500 pm (revolutions per minute), serum obtained was used for estimation of the three test parameters.

Three test parameters (C-reactive protein [CRP], D-dimer, and SGOT) were analyzed by fully automated analyzer Cobas-6000 and D-dimer by AQT-90.

The data were analyzed statistically by Microsoft Excel and online software Graphpad Prism. Where p<0.05 was considered to be significant.

RESULTS

We have found significant level of D-dimer and CRP in all groups. Tables 1-4 and Figs. 1-3 respectively.

DISCUSSION

The infection of SARS-CoV-2 virus affected persons living with comorbidities the worst especially patients of TB. The coinfection of these diseases (COVID-TB) made the prognosis of the patient much worse. This is in accordance with a study conducted by (Song et al. 2021) [7].

The findings of the present study suggested that testing of inflammatory markers may be of prognostic value in patients of COVID-19, TB, and

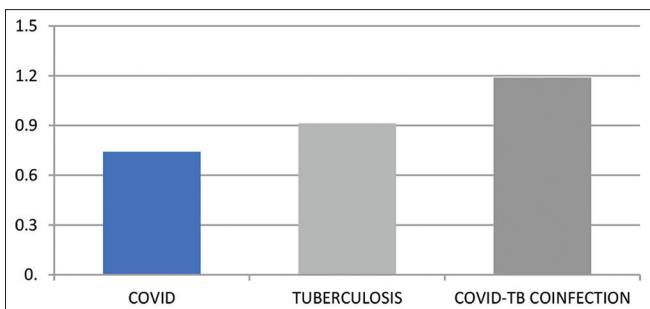


Fig. 1: depicts comparison of mean values of D-dimer across the three patient groups that are COVID-19, COVID-TB coinfection, and tuberculosis

COVID-TB coinfection patients. A similar study by (Raizada et al. 2021) [3] pointed out that the learning gained from treatment, screening, and diagnosis of COVID-19 may prove to be of great importance in developing new therapeutic and diagnostic techniques against the ancient threat of TB that has been prevalent since almost a century.

Singh et al. 2020 [8] also concluded that both COVID-19 and TB have several overlapping symptoms which can cause considerable interference with timely diagnosis of either of these diseases. Our study has yielded results agreeing with Singh et al. 2020. Depicting that, patients of COVID-TB coinfection suffer with more severe symptoms

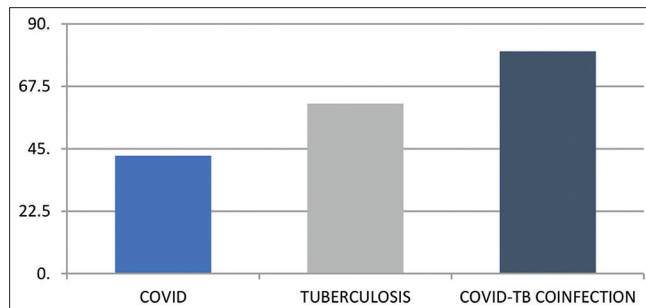


Fig. 2: depicts comparison of mean values of CRP across the three patient groups that are COVID-19, COVID-TB coinfection, and tuberculosis

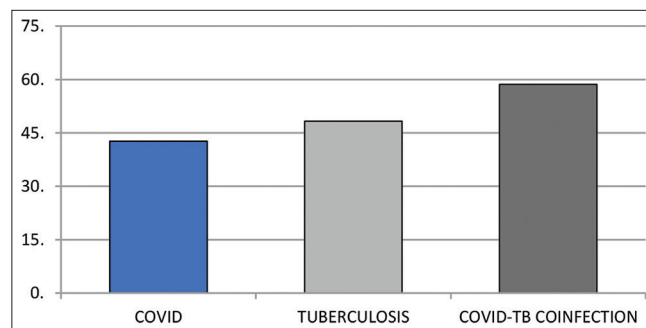


Fig. 3: depicts comparison of mean values of SGOT across the three patient groups that are COVID-19, COVID-TB coinfection, and tuberculosis

Table 1: Comparison of mean values of D-dimer across the three patient groups that are COVID-19, COVID-TB coinfection, and tuberculosis

D-dimer (µg/mL)	
Group	Mean
COVID	0.74
Tuberculosis	0.91
COVID-TB coinfection	1.18

Table 2: Comparison of mean values of CRP across the three patient groups that are COVID-19, COVID-TB coinfection, and tuberculosis

CRP (mg/L)	
Group	Mean
COVID	42.50
Tuberculosis	61.26
COVID-TB coinfection	80.12

CRP: C-reactive protein

Table 3: Comparison of mean values of CRP, D-DIMER and SGOT across the three patient groups that are COVID-19, COVID TB coinfection, and tuberculosis

Parameter	COVID (Mean±SD)	Tuberculosis (Mean±SD)	COVID-TB Coinfection (Mean±SD)	p-value
CRP (mg/L)	42.50±37.44	61.26±32.22	80.12±55.86	<0.05*
D-Dimer (umg/mL)	0.74±0.48	0.91±0.67	1.18±1.05	<0.05*
SGOT (IU/L)	42.64±28.39	48.24±43.71	58.61±44.11	>0.05

Table 4: Comparison of mean values and one-way ANOVA of all test parameters (D-dimer, CRP, and SGOT) across the three patient groups that are COVID-19, COVID-TB coinfection, and tuberculosis

SGOT (IU/L)	
Group	Mean
COVID	42.64
Tuberculosis	48.24
COVID-TB coinfection	58.61

and have poor prognosis as opposed to individuals suffering from either COVID-19 or TB.

Our results showed that the mean value of CRP in COVID-19 patients is 42.50±37.44, in TB patients 61.26±32.22, whereas, in COVID-TB coinfection, it was found to be 80.12±55.86. The analysis of variance also came out to significant with p-value of 0.00005 and f-value of 10.58. These findings point toward the significance of testing CRP in patients of COVID-TB coinfection, TB, and COVID-19. It is stated in a study done by (Zenget *et al.* 2020) [9] which has highlighted that the level of CRP is positively correlated with disease severity and progression. The finding of unpaired t-test done in this study between the patient groups of COVID-TB coinfection and TB came out to be highly significant with p-value of 0.03. These results are also suggestive of using CRP to help with the diagnostic and treatment dilemma in patients of these lung infections.

Similarly, significant results of analysis of variance were found for D-Dimer with p-value of 0.01 and f-value of 4.71. The rise of D-dimer was the highest in COVID-TB coinfection patients with a mean value of 1.18±1.05 followed by TB where a mean value of 0.91±0.6 was observed and the least increase was found in COVID-19 patient group with a mean value of 0.74±0.48. These findings concur with pathophysiological findings stated by Zeng *et al.* 2020 [9] that concluded that immune response-induced cytokine/chemokine release as a result of inflammation caused by infection increases hypercoagulation and fibrin lysis which causes an increased risk of thrombus development and embolism, which can prove to be fatal to the patient.

The result of our study also emphasizes that the patients of COVID-TB coinfection suffer an increased severity of infection, along with a more vigorous lung damage as is depicted by increased inflammation and this phenomenon is reflected in the levels of CRP, IL-6, and D-dimer which were found to the highest in COVID-TB coinfection among all three patient groups.

CONCLUSION

Through this study, it is concluded that the addition of inflammatory markers testing in TB patients and diagnostic protocols may prove to be of significant assistance in diagnosis of TB and also to estimate the severity of infection in patients of active TB. It is also noteworthy that the levels of these markers were found to be highest in patients suffering from a coinfection of both the diseases.

Limitations of the study

One of the limitations of the present study is that details related with onset of TB, the duration of infection was not considered while evaluation of inflammatory markers, which could give more information and correlation between impact of COVID-19 on inflammatory markers in TB patients. Furthermore, larger series of study having a greater number of subjects can more information related with the objectives of the study, it due to financial constraint, limited sample size was considered.

CONFLICTS OF INTEREST

None.

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