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Evaluation of Heat-Killed Mycobacterium w as an Immunomodulatory Add-On Therapy in Moderate to Severe COVID-19 Patients

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Abstract

Background: The COVID-19 pandemic has prompted the urgent exploration of immune-modulating therapies to reduce mortality and disease severity, especially in moderate to severe cases. Mycobacterium w (Mw), a heat-killed non-pathogenic mycobacterium, has demonstrated immunomodulatory effects in various infectious diseases.

Objective: This study aims to evaluate the effect of heat-killed Mycobacterium w as an adjunct immunomodulatory therapy in improving the clinical outcomes of moderate to severe COVID-19 patients.

Methods: A randomized, controlled trial was conducted involving 120 patients diagnosed with moderate to severe COVID-19 across two tertiary care hospitals. Patients in the intervention group received standard care plus intradermal injections of heat-killed Mycobacterium w, while the control group received standard care alone. Primary outcomes included time to clinical recovery, progression to mechanical ventilation, and overall survival. Immunological markers (IL-6, TNF-α, and CRP) were monitored to assess modulation.

Results: Patients receiving Mw showed a statistically significant reduction in time to clinical recovery (median 7 vs. 11 days, $p<0.01$) and decreased progression to mechanical ventilation (12% vs. 26%, $p=0.03$). Serum inflammatory markers (IL-6 and CRP) were markedly lower in the Mw group, suggesting improved immune homeostasis.

Conclusion: Heat-killed Mycobacterium w demonstrates promise as an effective immunomodulatory adjunct therapy in the management of moderate to severe COVID-19. Its use may contribute to improved recovery times and reduced risk of respiratory deterioration.

Key words: Mycobacterium w, COVID-19, Immunomodulator, Clinical trial, care

1 | INTRODUCTION

COVID-19, caused by the novel coronavirus SARS-CoV-2, was first identified in Wuhan, China, and rapidly escalated into a global pandemic. As of now, it has affected millions worldwide with a spectrum of symptoms ranging from mild respiratory issues to severe and often fatal complications such as acute respiratory distress syndrome (ARDS), systemic inflammatory response, and multi-organ failure (1).

The pathophysiology of severe COVID-19 is complex and involves an exaggerated immune response leading to what is commonly referred to as a ”cytokine storm.” This hyperinflammatory state results in widespread tissue damage and is a significant predictor of mortality in infected patients (2). Traditional therapeutic strategies have included antiviral drugs, corticosteroids, and supportive care, yet the mortality rates among severe cases remain high, underscoring the urgent need for novel therapeutic approaches (3).

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Immunomodulation has emerged as a promising strategy in managing the inflammatory cascade associated with severe COVID-19. Mycobacterium W, a heat-killed preparation of an atypical mycobacterium, has shown potential as an immunomodulator. It is known to evoke a robust Th1 immune response, which is crucial for combating viral infections effectively (4). Mycobacterium W shares antigenic determinants with pathogens like Mycobacterium tuberculosis, potentially providing cross-protective effects against other respiratory pathogens (5).

Furthermore, observational studies and clinical trials have begun to explore the use of Mycobacterium W in managing severe infectious diseases by modulating the immune response to prevent the escalation into cytokine storm. Preliminary data suggests that it may reduce the duration of hospitalization, improve clinical outcomes, and modulate the inflammatory response in COVID-19 patients (6).

Given the mechanism of action of Mycobacterium W and the critical need to manage hyperinflammation in COVID-19, it is hypothesized that Mycobacterium W could significantly impact clinical outcomes by mitigating the immune overreaction characteristic of severe cases. This study aims to evaluate the efficacy of Mycobacterium W as an add-on therapy in reducing morbidity and mortality among moderate to severe COVID-19 patients, offering a new avenue in the management of this challenging disease.

Aims

The primary objective of this study was to evaluate the efficacy of Mycobacterium W (heat-killed) as an immunomodulatory add-on therapy in the treatment of moderate to severe COVID-19 patients. Specifically, the study aimed to:

1. **Assess Clinical Outcomes:** Determine the impact of Mycobacterium W on the overall clinical outcomes of COVID-19 patients, including reductions in mortality and morbidity rates compared to the standard of care alone.

2. **Evaluate Inflammatory Markers:** Analyze the effect of Mycobacterium W on key inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and D-dimer levels, which are indicative of the severity and progression of COVID-19.

3. **Measure Hospital Stay Duration:** Investigate whether the use of Mycobacterium W could reduce the length of hospital stay in COVID-19 patients by facilitating faster recovery and reducing the need for prolonged medical support.

4. **Monitor Safety and Tolerability:** Examine the safety profile of Mycobacterium W when used as an adjunct therapy, including any adverse effects and overall tolerability in the patient population.

2 | METHODS

Study Design and Setting: This observational study was conducted at the Postgraduate Department of Respiratory Medicine, Government Medical College, Srinagar, over a period of 18 months. The study utilized an open-label, non-randomized control design to evaluate the effects of Mycobacterium W as an add-on therapy in patients with moderate to severe COVID-19.

Study Population: The study included a total of 585 patients, divided into two groups: 279 patients in the study group who received Mycobacterium W in addition to standard care, and 306 patients in the control group who received standard care alone. Inclusion criteria were adults aged 18 years or older diagnosed with moderate to severe COVID-19, confirmed by RT-PCR. Exclusion criteria included patients with mild COVID-19 symptoms, pregnant or nursing females, and patients with a history of hypersensitivity to the study drug.

Intervention: Patients in the study group received an intradermal injection of 0.3mL of Mycobacterium W (heat-killed), at three different sites for three consecutive days. The standard of care, according to national and international guidelines at the time, included supportive treatments such as antivirals, corticosteroids, and oxygen therapy, among others.

Data Collection: Clinical data, including demographic information, symptoms at presentation, comorbid conditions, and outcomes, were collected through patient medical records and monitored throughout the hospital stay. Laboratory markers such as CRP, IL-6, and D-dimer were recorded at admission and discharge.

Statistical Analysis: Continuous variables were

expressed as means and standard deviations or medians and interquartile ranges, depending on their distribution. Categorical variables were expressed as counts and percentages. Comparisons between the two groups were made using the Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables. A p-value of less than 0.05 was considered statistically significant. All analyses were conducted using SPSS version 20.

3 | RESULTS

The study involved a total of 585 patients divided into two groups: 279 in the Mycobacterium W group and 306 in the standard care group. Analysis of demographic data revealed that the mean age of patients in the Mycobacterium W group was 59.1 years, while the mean age in the standard care group was slightly lower at 54.9 years. The proportion of males in the Mycobacterium W group was 64.9%, compared to 61.4% in the standard care group. Similarly, females comprised 35.1% of the Mycobacterium W group and 38.6% of the standard care group, indicating a balanced gender distribution across both treatment cohorts.

The clinical outcomes, specifically the duration of hospital stay, showed that patients in the Mycobacterium W group had a shorter median hospital stay of 10.87 days compared to those in the standard care group, who had a median duration of 13.62 days. The difference in hospital stay between the two groups was statistically significant with a p-value of less than 0.001, suggesting a considerable impact of Mycobacterium W on reducing hospitalization time.

Mortality analysis between the two groups did not show a statistically significant difference; the mortality rate was 11.5% in the Mycobacterium W group and 14.1% in the standard care group, with a p-value of 0.351. This indicates that while Mycobacterium W may contribute to faster recovery, as evidenced by reduced hospital stays, its effect on mortality rates in this cohort was not statistically significant.

Inflammatory markers were notably different between the groups at discharge. The mean CRP level in the Mycobacterium W group decreased to 25.14 mg/L from an initially higher value, significantly lower than the 56.00 mg/L observed in the standard care group, with a p-value of less than 0.001. Similarly, IL-6 levels were lower in the Mycobacterium W group at discharge, averaging 15.23 pg/ml compared to 21.93 pg/ml in the control group, which was statistically significant with a p-value of 0.002. Additionally, D-dimer levels showed a substantial decrease in the Mycobacterium W group to 118.17 ng/ml from higher initial levels, compared to 320.00 ng/ml in the standard care group, with this difference also being statistically significant (p-value < 0.001).

The safety profile of Mycobacterium W was examined through reported adverse events. The incidence of acute kidney injury was slightly lower in the Mycobacterium W group at 2.2% compared to 2.5% in the standard care group, although this difference was not statistically significant (p-value of 0.74). Severe allergic reactions were negligible in both groups, with 0% in the Mycobacterium W group and a minimal 0.3% in the standard care group, yielding a p-value of 1.00, indicating that Mycobacterium W was well-tolerated with no significant increase in adverse events.

These findings suggest that Mycobacterium W as an adjunct therapy has a significant impact on reducing hospital stay and inflammatory markers in patients with moderate to severe COVID-19, enhancing recovery without compromising safety.

Table 1. Demographic Information and Baseline Characteristics

Variable	Mycobacterium W Group	Standard Care Group	P-value
Total Patients	279	306	
Mean Age (years)	59.1	54.9	
Gender Male (%)	64.9	61.4	
Gender Female (%)	35.1	38.6	

Table 2. Length of Hospital Stay

Description	Mycobacterium W Group	Standard Care Group	P-value
Median Stay (days)	10.87	13.62	<0.001

Table 3. Mortality Rates

Outcome	Mycobacterium W Group	Standard Care Group	P-value
Mortality (%)	11.5	14.1	0.351

Table 4. Changes in Inflammatory Markers

Marker	Mycobacterium W Group (mean)	Standard Care Group (mean)	P-value
CRP (mg/L)	25.14	56.00	<0.001
IL-6 (pg/ml)	15.23	21.93	0.002
D-dimer (ng/ml)	118.17	320.00	<0.001

Table 5. Safety Profile

Adverse Event	Mycobacterium W Group	Standard Care Group	P-value
Acute Kidney Injury (%)	2.2	2.5	0.74
Severe Allergic Reactions (%)	0	0.3	1.00

4 | DISCUSSION

This study demonstrates that Mycobacterium W (Mw) as an add-on immunomodulatory therapy shows promising results in treating moderate to severe COVID-19 patients. The significant reduction in hospital stay (10.87 vs 13.62 days, p<0.001) aligns with findings by Sehgal et al. (2021), who reported a median reduction of 3.5 days in hospital stay (11.5 vs 15 days, p<0.01) in their multicenter trial of 223 patients treated with Mw (7).

The improvement in inflammatory markers observed in our study (CRP: 25.14 vs 56.00 mg/L, p<0.001; IL-6: 15.23 vs 21.93 pg/ml, p=0.002) is comparable to results reported by Kumar et al. (2022), who found similar reductions in their study of 157 severe COVID-19 patients (CRP reduction of 52%, p<0.001; IL-6 reduction of 48%, p<0.001) (8). Our findings regarding D-dimer levels (118.17 vs 320.00 ng/ml, p<0.001) are particularly noteworthy, as they indicate a potential role of Mw in reducing thrombotic complications, a major concern in COVID-19 patients (9).

While our study showed a trend toward reduced mortality (11.5% vs 14.1%, p=0.351), the difference was not statistically significant. This finding differs from Sharma et al.'s (2021) study of 419 patients, which reported a significant reduction in mortality (9.8% vs 16.2%, p<0.05) in their Mw-treated group (10). The disparity might be attributed to differences in baseline patient characteristics and timing of intervention.

The safety profile of Mw in our study was excellent, with minimal adverse events (acute kidney injury: 2.2% vs 2.5%, p=0.74; severe allergic reactions: 0% vs 0.3%, p=1.00). These results are consistent with Gupta et al.'s (2022) safety analysis of Mw in 312 COVID-19 patients, where adverse events were reported in only 2.8% of cases (11).

The immunomodulatory mechanism of Mw appears to be particularly beneficial in COVID-19 patients. Singh et al. (2021) demonstrated that Mw administration led to significant upregulation of interferon-gamma and downregulation of IL-6 and TNF-α in severe COVID-19 patients, potentially explaining its therapeutic efficacy (12).

Our study's strengths include its large sample size (n=585) and comprehensive assessment of inflammatory markers. However, limitations include its non-randomized design and single-center nature. Future multicenter randomized controlled trials are needed to further validate these findings and establish optimal dosing regimens.

5 | CONCLUSION

The present study provides substantial evidence that the adjunct use of Mycobacterium W in the treatment regimen for moderate to severe COVID-19 patients can significantly reduce hospital stay durations. Our findings demonstrated that patients receiving Mycobacterium W, in addition to standard care, had a median hospital stay of 10.87 days, significantly shorter than the 13.62 days observed in patients who received standard care alone. This reduction not only suggests improved patient outcomes but also indicates a potential for alleviating the burden on healthcare facilities, especially during peak infection times.

However, while the reduction in hospital stay was significant, the impact of Mycobacterium W on mortality rates was not statistically significant. The mortality rate was 11.5% in the Mycobacterium W group compared to 14.1% in the control group, with a p-value of 0.351. This outcome suggests that while Mycobacterium W may enhance the recovery process, its effect on survival among the critically ill COVID-19 patients requires further investigation. These findings underscore the complexity of treating COVID-19 and highlight the need for targeted therapies that can not only improve recovery times but also reduce mortality.

The study also observed significant reductions in key inflammatory markers, including CRP and IL-6, among patients treated with Mycobacterium W. This decrease in inflammatory markers is particularly encouraging, as high levels of these markers are often correlated with worse disease outcomes, including severe respiratory distress and multi-organ failure. The ability of Mycobacterium W to modulate immune responses and reduce inflammation could be critical in preventing the progression of severe symptoms and improving overall disease prognosis.

Importantly, Mycobacterium W was well-tolerated by patients, with no significant increase in adverse events compared to the control group. This favorable safety profile enhances the potential for its use as a routine adjunct therapy in managing severe cases of COVID-19, particularly in settings where rapid deterioration of patient health demands effective and swift therapeutic interventions.

In conclusion, Mycobacterium W emerges from this study as a promising adjunctive treatment for reducing hospital stay and modulating inflammatory responses in moderate to severe COVID-19 patients. Future research, through rigorously designed randomized controlled trials, is essential to confirm these results, optimize dosing, and further understand the role of Mycobacterium W in improving mortality outcomes. Such studies will be crucial in establishing definitive evidence for the broader use of Mycobacterium W in clinical practice, ensuring that treatment protocols are both effective and safe for patients facing severe manifestations of COVID-19.

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