ISSN: 2320-5407

ISSN NO. 2320-5407

International Journal of Advanced Research

Publisher's Name: Jana Publication and Research LLP

www.journalijar.com

REVIEWER'S REPORT

Manuscript No.: IJAR-51855 Date: 27-05-2025

Title: DIFFERENTIAL ANALYSIS OF GENE EXPRESSION IN SEVERELY ILL COVID-19 PATIENTS.

Recommendation:
Accept as it is.....YES.....
Accept after minor revision.....
Accept after major revision .....
Do not accept (*Reasons below*) .....

Rating	Excel.	Good	Fair	Poor
Originality			√	
Techn. Quality			√	
Clarity			√	
Significance		√		

Reviewer's Name: Dr Aamina

Reviewer's Decision about Paper: **Recommended for Publication.**

Comments (*Use additional pages, if required*)
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Reviewer's Comment / Report

1. Relevance and Scientific Merit:
The topic is timely and of significant importance in the ongoing efforts to understand the molecular underpinnings of COVID-19, especially in its severe manifestations. By focusing on transcriptomic changes, the study contributes meaningfully to the growing body of knowledge regarding immune dysregulation in severe SARS-CoV-2 infection.

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2. Abstract:
The abstract is clear, informative, and well-structured. It succinctly summarizes the methodology, including the dataset used (GSE171110), the analysis tool (DESeq2), the number of samples, and key findings. It highlights major differentially expressed pathways and immune components involved, providing a comprehensive snapshot of the study's outcomes. The emphasis on both upregulated inflammatory responses and suppressed adaptive immunity is particularly well-noted, offering a balanced perspective on immune dynamics.

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3. Introduction:
The introduction effectively contextualizes the study, referencing the global burden of COVID-19 and the heterogeneous clinical manifestations of the disease. It identifies a gap in the understanding of molecular mechanisms contributing to disease severity and provides a logical rationale for focusing on transcriptomic profiling. The background discussion on cytokine storms, macrophage activation, and the need for deeper exploration of immune signaling is relevant and well-argued.

4. Methodological Rigor:
The study employs established bioinformatics tools (DESeq2, PCA, heatmaps) and references a publicly available dataset (GSE171110), ensuring reproducibility and transparency. The sample size of 44 severe cases and 10 controls is reasonable for transcriptomic analysis, and the differential gene expression analysis appears robust, identifying a large number of DEGs with biologically meaningful interpretations.

5. Results and Interpretation:
The identification of 737 DEGs, particularly the strong upregulation of pathways involved in inflammation and innate immunity (e.g., Jak-STAT, Toll-like receptor, TNF signaling), is well-supported by existing literature on severe COVID-19. The noted upregulation of MHC class I and suppression of MHC class II genes presents a compelling immunological narrative involving hyperactive cytotoxic responses and impaired helper T-cell function. The disruption in DNA repair pathways and the emphasis on cytokine-related gene expression (e.g., IL-1β, IL-6, IFN-β) further underscores the study's comprehensive molecular insight into severe cases.

6. Theoretical and Clinical Implications:
The findings align with the hypothesis that severe COVID-19 is characterized by exaggerated innate immunity and compromised adaptive responses. The study adds valuable knowledge to the pathophysiological basis of cytokine storm and immune exhaustion in critically ill patients. It also suggests directions for targeted therapeutic interventions aimed at modulating these dysregulated pathways.

7. Structure and Clarity:
The text is coherent and well-organized. Technical terms are appropriately used, and the language remains accessible while retaining scientific precision. The progression from the background to the rationale, and then to the results and implications, is logically sound.

Final Evaluation:
This study provides a rigorous and insightful analysis of gene expression in severely ill COVID-19 patients. By illuminating key pathways and immune components involved in disease progression, it

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contributes to both the academic understanding and potential clinical management of critical COVID-19. The combination of bioinformatics, immunological insight, and clear exposition makes it a valuable addition to current research in the field.