INPLASY PROTOCOL

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None declared.

Protocol for systematic search and reanalysis of transcriptomic biomarkers of severity in COVID-19

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Review question / Objective: **Mass vaccination has significantly reduced the incidence of severe COVID-19, but as immunity declines with time, the emergence of new strains may lead to more severe infections. Moreover, those with co-morbidities, the elderly, the immunocompromised and the unvaccinated remain susceptible to severe COVID-19. There remains an unmet need for reliable disease prognostic biomarkers to both triage COVID-19 cases at risk of disease progression at presentation, as well as for early detection of increasing trend of severe COVID-19 from either waning immunity or more pathogenic VOCs. We performed a systematic search to identify publicly available transcriptomic datasets from whole blood or peripheral blood mononuclear cells in patients with mild vs severe acute COVID-19, with the goal of reanalaysing these datasets to identify consistently expressed early prognostic biomarkers that reliably differentiate severe and mild COVID-19 patients.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 November 2022 and was last updated on 09 November 2022 (registration number INPLASY2022110038).

INTRODUCTION

Review question / Objective: **Mass vaccination has significantly reduced the incidence of severe COVID-19, but as immunity declines with time, the emergence of new strains may lead to more severe infections. Moreover, those with co-morbidities, the elderly, the immunocompromised and the unvaccinated remain susceptible to severe COVID-19. There remains an unmet need for reliable disease prognostic biomarkers to both triage COVID-19 cases at risk of disease progression at presentation, as well as for early detection of increasing trend of severe COVID-19 from either waning immunity or more pathogenic**

VOCs. We performed a systematic search to identify publicly available transcriptomic datasets from whole blood or peripheral blood mononuclear cells in patients with mild vs severe acute COVID-19, with the goal of reanalaysing these datasets to identify consistently expressed early prognostic biomarkers that reliably differentiate severe and mild COVID-19 patients.

Rationale: Transcriptomic analyses have revealed widespread dysregulation of innate and adaptive immunity in severe COVID-19, including prominent neutrophil hyperactivation, production of monocytes with immunosuppressive characteristics and a marked decrease in T cells transcripts in the peripheral blood. However, these gene expression signatures have not been systematically analysed across multiple cohorts, and so it remains unknown which of these gene sets are more broadly generalizable and which of these transcripts are most suitable for early prognosis of severe COVID-19.

Condition being studied: Patients with SARS-CoV-2 infection can experience a range of clinical manifestations, from no symptoms to critical illness. SpO2 measurement using pulse oximetry is a key parameter for defining illness severity. Severe illness is identified in individuals who have SpO2 50%. These patients may experience rapid clinical deterioration, and immediate oxygen therapy using a nasal cannula or a high-flow oxygen device is recommended. Critical illness is identified in individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction. It is typically characterized by the acute respiratory distress syndrome, virus-induced distributive (septic) shock, cardiac shock, an exaggerated inflammatory response, thrombotic disease, and/or exacerbation of underlying comorbidities.

METHODS

Search strategy: Searches were conducted using the keywords "covid AND SARS AND transcriptomic* AND immune" on PubMed, Web of Science, Scopus, and Gene Expression Omnibus (GEO).

Participant or population: Patients with acute mild/moderate vs severe/critical COVID-19

Intervention: Not applicable.

Comparator: Not applicable.

Study designs to be included: Partek® Genomics Suite® 7.21.1119 was used to analyse the fold changes, p-value and adjusted p-values between the mild vs severe COVID-19 patients in the different databases.

Eligibility criteria: Studies that performed whole-transcriptome analysis on whole blood or PMBCs in severe and mild acute COVID-19 patients were selected for further analysis.

Information sources: Searching PubMed, Web of Science, Scopus, and Gene Expression Omnibus (GEO) databases, and forward and backward reference searching.

Main outcome(s): Identification of unique publicly available whole-transcriptome analysis on whole blood or PMBCs in severe and mild acute COVID-19 patients which can be reanalyzed.

Quality assessment / Risk of bias analysis: Risk of bias for observational studies was assessed in accordance with GRADE guidelines, which takes into account method issues such as: (i) Failure to develop and apply appropriate eligibility criteria; (ii) Flawed measurement of both exposure and outcome; (iii) Failure to adequately control confounding; and (iv) Incomplete follow-up.

Strategy of data synthesis: We used a multi-cohort analysis framework to evaluate the common genes which were differentially expressed in severe compared to mild acute COVID-19. A database app was made using Streamlit (https://www.streamlit.io), which converts python codes into an interactive web tool. The

online app is deployed at https://kuanrongchan-covid19-severity-app-t7l38g.streamlitapp.com/ and GitHub codes to build the web tool can be accessed at https://github.com/kuanrongchan/COVID19-severity.

Subgroup analysis: Nil.

Sensitivity analysis: NA.

Language restriction: English.

Country(ies) involved: Singapore.

Other relevant information: Nil.

Keywords: COVID-19, transcriptomics, biomarkers, pathogenesis, meta-analysis.

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