

# Temporal immunological marker risk model for predicting severity of COVID-19 outcomes: early risers, late bloomers and general giants

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## Introduction

Treatment strategies for severe COVID-19 presentations have improved. However, predicting severity early remains a challenge, as the onset of deterioration is highly variable and difficult to recognise. Patients showing late deterioration are particularly affected by limited treatment options.

## Objectives

- To temporally compare immunological ‘phenotypes’ of severe and non-severe COVID-19 presentations.
- To create a clinical tool to help clinicians stratify high-risk subgroups.

## Methods

A literature search for temporally-mapped immunological markers showing differences between mild and severe COVID-19 patients was conducted on the PubMed database and results were pooled. Post-analysis, the biomarkers were split into three categories, according to when significant differences between mild and severe cases arose post-disease onset: ‘early risers’ (<7 days), ‘late bloomers’ (>7 days) and ‘general giants’ (whole disease course).

## Results and discussion

The early risers chosen were IL-6, aspartate aminotransferase (AST) and creatine kinase-MB (CK-MB). For late bloomers, serum D-dimer, cardiac troponin and serum creatinine were selected. For general giants, neutrophils, lymphocyte count and serum ferritin were predictive (Fig 1).

IL-6 was significantly raised in severe versus mild COVID-19 patients, likely due to its role in cytokine storms, a key contributor to multi-organ failure and acute respiratory distress. Further, IL-6 levels correlate to pre-existing risk factors of severe disease, eg hypertension.<sup>1–3</sup>

AST levels also demonstrated a high correlation to COVID-19 mortality risk and strongly predicted systemic inflammation, and liver injury via direct viral invasion of cholangiocytes.<sup>4,5</sup>

Interestingly, CK-MB rose early in the disease course before returning to normal range, though levels were still higher in severe patients than mild ( $p < 0.05$ ).<sup>4</sup> CK-MB is a known predictor of cardiac damage through direct invasion of cardiomyocytes via ACE2 receptor.<sup>6</sup>

The late bloomers, D-dimer, troponin and creatinine were all markedly increased in severe patients from day 7 onwards and were associated with coagulopathy, cardiac disease and renal impairment respectively. Subsequently, these patients had poorer outcomes with higher mortality rates.<sup>1,4,7–9</sup>

For general giants, severe cases presented with higher neutrophil and lower lymphocyte counts compared to mild, confirming the potential of neutrophil-lymphocyte ratio as a predictor of disease severity (Fig 2).<sup>1,2,4,7,10</sup>

High serum ferritin levels were associated with development of ARDS and cytokine storm, suggesting this marker may indicate a transition towards hyper-inflammatory state in severe COVID-19 cases.<sup>1</sup>

## Conclusion

Our study compiles key immunological markers and their temporal importance in COVID-19 disease progression. A comprehensive timescale of these markers can alert clinicians to potential deterioration in advance, and guide management and treatment options. Used in conjunction with patient characteristics and presentation, our study provides an efficient and simple method of streamlining risk stratification. ■

## Conflicts of interest

None declared.

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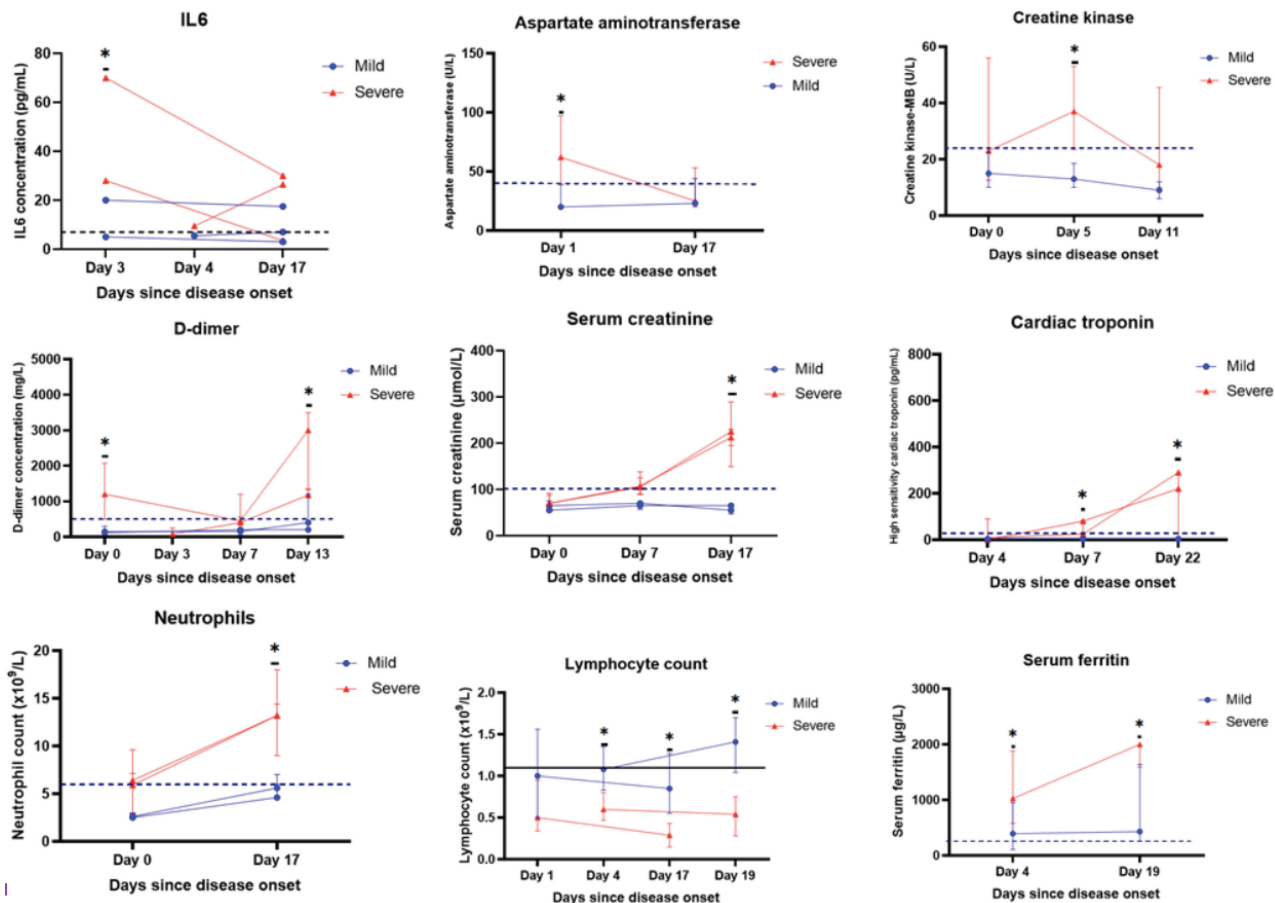


Fig 1. Line graph summarising predictors through disease course.\* Statistically significant (p<0.05) points are shown by the asterisk. The normal range upper limit of each parameter is represented by the dashed blue line. The black solid line represents the lower limit of the lymphocyte count.<sup>1-5,7-10</sup>

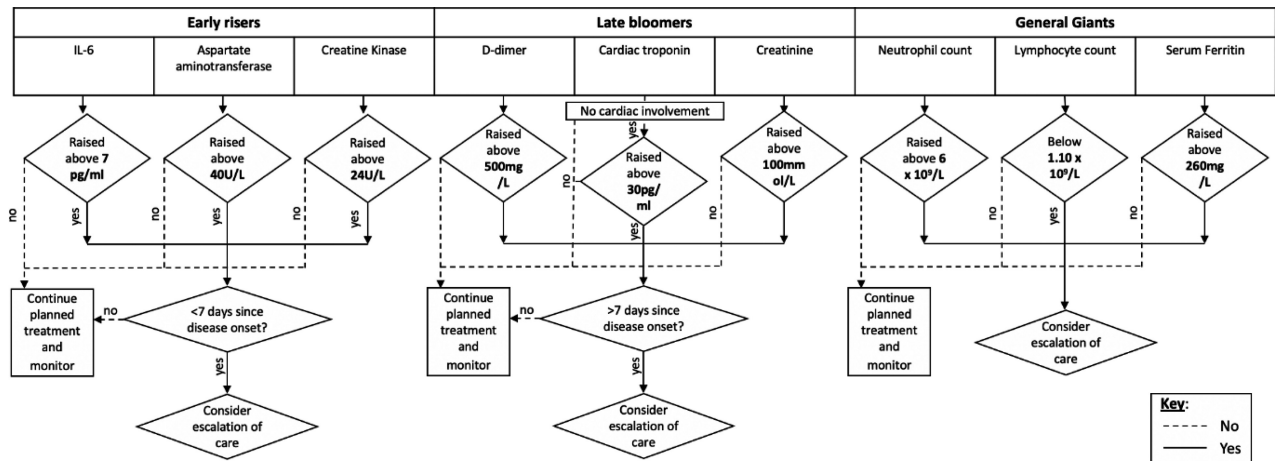


Fig 2. Example flowchart as a clinical tool to distinguish severe COVID-19 cases.

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