

Simple 'Rule-of-6' predicts severe COVID-19 disease

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Dear Editor,

We read with interest the manuscript by Luo *et al* reporting on the prognostic value of the C-reactive protein (CRP) on adverse outcomes in COVID-19 [1]. Accurate triaging, which incorporates biomarkers with enhanced discriminatory capability and is reproducible, is critical in identifying patients at risk of deterioration among the larger population of stable infected individuals early on at presentation in order to prioritise treatment.

We will like to add to the findings by Luo *et al.* by sharing our experience at the National University Health System, Singapore, a 1000-bed tertiary academic medical centre which saw through two waves of COVID-19 patients between February to April 2020, where we adopted a 'Rule-of-6' involving CRP, ferritin and lactate dehydrogenase (LDH) measured in the first 48H of admission which identified patients at risk of disease progression. This was derived from 140 patients which formed a discovery and validation cohort. From the discovery cohort of the first 60 patients (48.3% male, mean age 41.7 years old, range 20–69), 23.3% required supplemental oxygen (to maintain $\text{SaO}_2 > 94\%$), 18.3% ICU care and 13.3% intubation. Patients who deteriorated were older (mean 55.29–58.50 years versus 37.59–39.13 years old respectively, $p < 0.001$; Supplementary Figure 1) but the strongest predictors were early ferritin (mean 663.33+369 in the 'progressors' versus 208.2+239.04 $\mu\text{g/L}$ in stable patients, $p = 0.02$), CRP (mean 71.83+54.65 versus 17.21+24.43 mg/L , $p = 0.01$) and LDH (mean 738.5+398.43 versus 440.19+201.64 U/L , $p < 0.01$). Lymphocyte, monocyte, platelet, polymorphonuclear, white blood cell count and SARS-CoV-2 viral load at presentation were of lesser discriminatory value (Supplementary Figure 1).

Comparatively, the first 48h ferritin and CRP measurements were better predictors of deterioration than age. The ferritin area under receiver operating curve (AUC) for oxygen requirement, ICU and intubation was 0.89, 0.90 and 0.88 respectively (Figure 1B).

Correspondingly, the AUC of CRP for the above severity events were 0.93, 0.93 and 0.88 respectively (Figure 1C). Early 48h LDH (AUC 0.86–0.87) was also a helpful predictor of progression (AUC 0.83–0.85) (Figures 1D). We then identified the following cut-offs in predicting deterioration and ICU admission: CRP > 68 mg/L (in sample AUC 0.93), (ii) ferritin > 532 µg/L (in sample AUC 0.88) and (iii) LDH > 597 (in sample AUC 0.86)

From the above, we derived a 1st 48h ‘Rule-of-6’: using ferritin > 600 µg/L, LDH > 600U/L and CRP > 60 mg/L to aid early identification of COVID patients at risk of disease progression. These were then validated on the discovery cohort of another 80 COVID-19 patients, (mean age 39.86 years old). This ‘Rule-of-6’ demonstrated good performance in identifying patients at risk of deterioration to the ICU, yielding notably high out-of-sample AUCs with the above CRP, ferritin and LDH cut-offs at 0.99, 0.88 and 0.90 respectively.

In summary we improved and validated beyond the CRP test proposed by Luo *et al* in identifying early and high risk COVID-19 patients. This enables burdened healthcare systems to expeditiously differentiate between mild and severe COVID-19 infections, assisting in patient treatment pathway determination, and alleviating equipment and ICU demands more effectively.

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Competing interests

The authors declare that they have no competing interests.

