

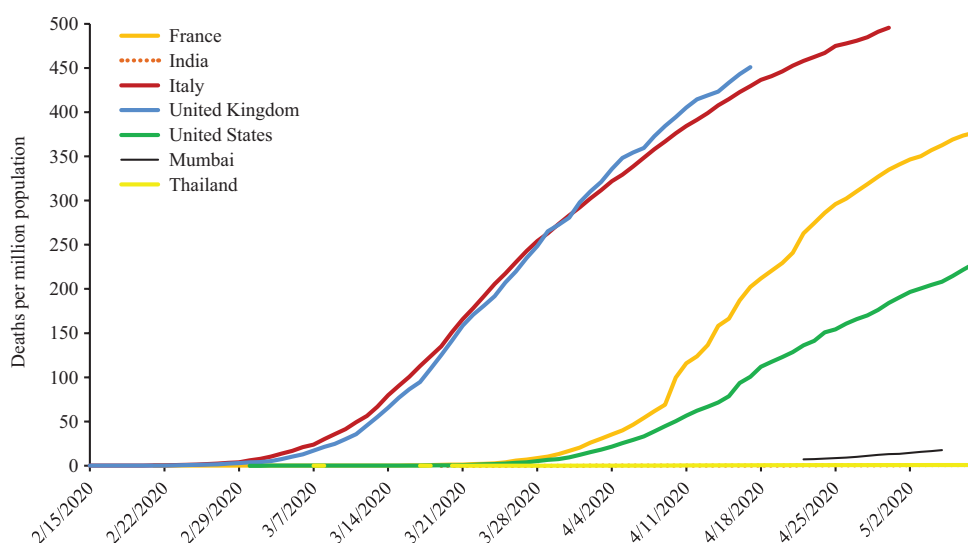


## Viewpoint

### Geographical & seasonal variation in COVID-19 related mortality

The difference in COVID-19 related mortality between India (5 per million population) and many developed countries such as Italy, France, United Kingdom and the United States (200-400 per million population) was striking<sup>1,2</sup> (Figure). While the number of cases is dependent on the number of tests performed and hence unreliable for comparison, the number of deaths can be more reliably compared between countries despite concerns about underreporting in some locations. In Mumbai, India, where the number of cases was highest in India and all deaths were documented, the COVID-19 mortality was 14 per million population<sup>1,2</sup>. The all-cause mortality in Mumbai was reduced by 20 per cent in March 2020 compared with March 2019 and was also reduced compared with January and February 2020, indicating that the low COVID-19 related mortality was true<sup>2,3</sup>.

Studies from China<sup>4</sup>, the United States<sup>5</sup> and Europe<sup>6</sup> indicate that venous thromboembolism (VTE) in major organ microcirculation is an important cause of poor gaseous exchange and death in COVID-19 patients, and D-dimer is an important predictor of mortality<sup>7</sup>. In the current context, we were reminded of the astute observation on venous thrombosis in the 17<sup>th</sup> edition of Bailey and Love's Short Practice of Surgery<sup>8</sup>, "virtually unknown in Singapore and is believed to occur more frequently with the arrival of snow and ice". This observation on the lower incidence of VTE in warmer climates is well supported by a meta-analysis<sup>9</sup> indicating greater predisposition to VTE in winter compared with summer and also in higher latitudes compared with closer to equator<sup>10</sup>. This seasonal and geographic variation in VTE could



**Figure.** Time trends of COVID-19 deaths per million population in various locations. *Source:* Refs 1, 2.

have the biological underpinning of variation in antiphospholipid antibodies (aPL), predisposing to VTE in colder climate<sup>11</sup>. In a randomized study from India evaluating peri-operative VTE prophylaxis, the incidence of VTE in the control arm was reported to be low<sup>12</sup>. The reduced predisposition to VTE in tropical countries is also seen in other contexts such as thrombotic complications of tamoxifen<sup>13</sup>. At our tertiary cancer centre at Mumbai, where annually about 20,000 women are on tamoxifen, the incidence of new VTE in such patients is <5 per annum (unpublished data). Identical observations have been reported from another cancer centre in India<sup>14</sup>.

The aPLs have been found to be associated with COVID-19 related morbidity<sup>15,16</sup>. These studies have reported the presence of anticardiolipin IgA, anti- $\beta$ 2-glycoprotein IgA and IgG and lupus anticoagulant associated with clinical thrombosis in some patients. These studies are not definitive because aPL can be present in other acute illnesses<sup>17</sup>. However, the association of thrombotic phenomenon with severe illness in COVID-19 combined with the presence of these antibodies in some of the patients point towards a pathogenetic association. The role of aPLs in inducing the macrophage activation syndrome-like state associated with possible immunothrombosis in the pulmonary vasculature in COVID-19 patients<sup>18</sup> remains to be elucidated. The geographic variation in COVID-19 mortality could be explained, at least in part, by the seasonal variation in aPL and the consequent propensity to VTE, further accentuated by COVID-19-induced increase in aPL. It may not be too optimistic to expect the seasonal variation in aPL and VTE to reduce mortality as we move closer to summer. Germline genetic associations of variation in aPL antibody prevalence in countries with low versus high COVID-19 population mortality could also be explored<sup>19</sup>. The striking geographic differences in mortality provide a unique opportunity for gaining insights into the pathophysiology of COVID-19 and possible solutions. It is likely that other differences such as those in age, comorbidity burden and other as yet unknown factors could account for the difference in population-level mortality between India and Western countries. Moreover, long-term data, when available, will allow more definitive conclusions about the final toll of this infection in various populations and account for possible differences in the stage of epidemic curve.

The lower population-level mortality from COVID-19 in India could form the basis of reducing the widespread anxiety related to this disease and for undertaking nuanced social-distancing measures and personal protective measures without enforcing strict lockdowns.

**Conflicts of Interest:** None.

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