Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Inflammation and hypercoagulopathy are predominant risk factors of severity in COVID-19 patients with diabetes mellitus: Summary of a meta-analysis

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Dear Editor,

With COVID-19 still ravaging populations across the world, search for clinico-pathological factors and conditions that can predict possibility of a patient leading to more severe form of disease has acquired prime importance. A detailed review by Zaki et al. [1] published in this journal identified co-morbid conditions like diabetes mellitus (DM), hypertension and obesity having significant correlation with severity of COVID-19 with DM alone contributing to 10–40% cases of severity and mortality. Though several meta-analysis efforts have indisputably established the association of DM with poor prognosis [2–4], widely varied observed risk/odds ratio of 1.5–3.64 [5] has prompted significant research efforts to identify predominant risk factors of worse outcome in COVID-19 patients with DM.

Retrospective studies involving COVID-19 patients with DM [6–8] showed association of worst outcome with decrease in lymphocyte count and increase in C-Reactive Protein (CRP), Interleukin-6 (IL-6) and Interleukin-10 (IL-10). Association of coagulation parameters (D-dimer and prothrombin time) along with other cardiac, hepatic and renal parameters with mortality or severity in DM patients were found in some studies [7,8], whereas a logistic regression analysis on 74 COVID-19 patients showed significant contribution only from decreased lymphocyte count and elevated pancreatic enzyme serum Amyloid A level [8]. This heterogeneity in risk factors could possibly be due to different intensity and duration of DM in the subjects.

In this correspondence, we present results of a meta-analysis of 12 clinical studies, from China, France, Italy and USA, selected through literature search covering 1015 DM and 3026 non-DM COVID-19 patients with 42% and 44% patients having severe COVID-19 respectively (Supplementary Table S1). Meta-analysis using random-effects model shows risk ratio of severe COVID-19 in DM patients to be 1.52 (95% CI: 1.25–1.85, $p < 0.0001$) over non-DM patients (Supplementary Fig. S1). The summarized risk ratio manifested considerable heterogeneity ($I^2 = 84\%$), source of which was investigated using a meta-regression of the risk ratio with ratio of means of laboratory parameters between DM and non-DM groups in three categories: (i) immune cell counts including leucocytes, lymphocytes, and neutrophils, (ii) inflammation markers including procalcitonin and CRP and (iii) coagulation parameters including D-dimer, prothrombin time (PT) and activated partial thromboplastin time (APTT). Other parameters such as monocyte and platelet counts, glycated haemoglobin (HbA1c), IL-6 and ferritin levels were excluded from analysis due to infrequent ($\leq$50%) reporting in selected studies.

Meta-regression carried out using a mixed-effects model with parameters in each individual category as moderators, showed only three parameters – decrease in lymphocyte count and increase in levels of D-dimer and CRP in DM patients to be associated with statistically significant contribution to risk ratio (Fig. 1). All other parameters had insignificant contribution (Supplementary Table S2). Observed asymmetry in funnel plot for log risk ratio (Supplementary Fig. S2) and Egger's test p-value (<0.01) indicate presence of small-study effects.

The findings that inflammation, manifested by lymphopenia and increase in serum CRP level is a risk factor for progression to severe COVID-19 illness, is commensurate with maximum loss of lymphocytes observed in DM patients compared to non-DM severe COVID-19 patients [9,10] indicating the hyperinflammatory state of infection in presence of DM.

Increased levels of D-dimer, a biomarker for hypercoagulability, was found elevated in both DM and non-DM COVID-19 patients [11] and was also assessed as a predictor of mortality [12]. Hypercoagulability is observed in COVID-19 patients due to enhancement of pro-thrombotic function caused by down-regulation of ACE2 and elevation of pro-inflammatory cytokines [13]. Association between hyperglycaemia and increased risk of venous thrombosis was observed in a case-control study [14] and it is likely that this synergy of pro-thrombotic forces of COVID-19 and DM tilts the balance towards exacerbation of the illness [15,16].

Importance of our finding of inflammation and hypercoagulopathy as predominant risk factors of COVID-19 severity is multifarious. Firstly, in addition to IL-6 and IL-10 as predictors for severity in COVID-19 infection [17,18], lymphocyte count, CRP and D-dimer levels could be assessed to predict worse outcome of COVID-19 patients with DM. Secondly, as suggested by Ceriello [19], interventions to reduce hyperglycaemia or potential use of heparin may alter the prothrombic state of a COVID-19 patient, thereby reducing the chance of worse outcome. Future clinical research on COVID-19 patients with DM will be crucial to validate these hypotheses.

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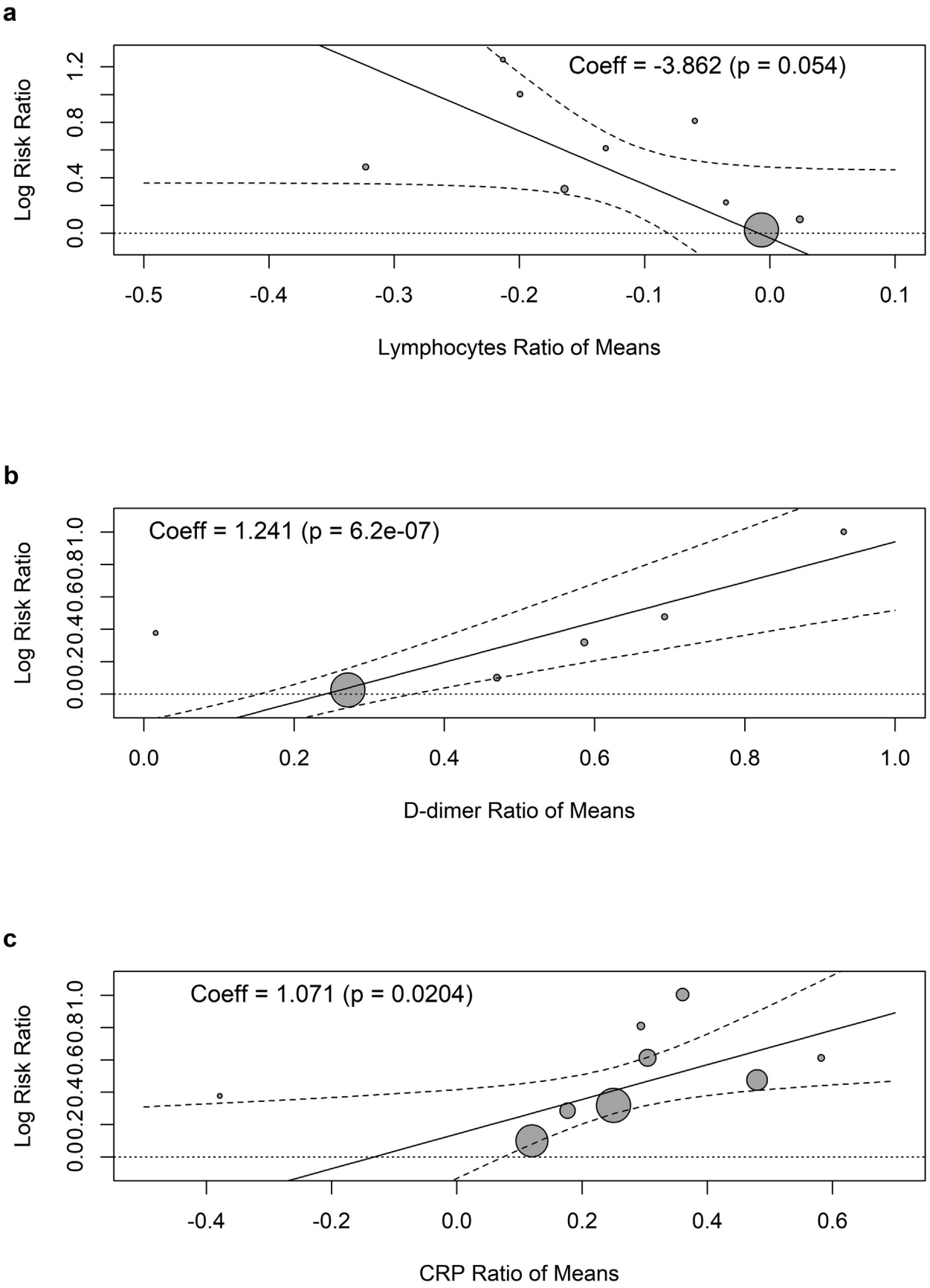

Fig. 1. Bubble plot for meta-regression of log risk ratio of severe COVID-19 infection in diabetic patients against ratio of means between severe and non-severe patient groups for on-admission laboratory parameters: (a) Lymphocyte count, (b) D-dimer level and (c) C-Reactive Protein (CRP).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2021.02.021.

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