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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Letter to Editor

Linking hydroxychloroquine to hemolysis in a 'suspected' glucose-6-phosphate dehydrogenase deficient patient with COVID-19 infection – a critical appraisal

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We read the recent letter by De Franceschi et al. [1] attributing acute intravascular hemolysis in a patient with COVID-19 infection to intake of hydroxychloroquine (HCQ). We would like to highlight some inconsistencies and a lack of clarity in the report. Moreover, we would like to do a thorough literature review on the existing controversy [2] on whether hemolysis is induced by chloroquine (CQ) or HCQ in G6PD-deficient patients to which the authors were relied on.

Since the authors themselves stated in the manuscript that the index patient was a 'suspected' case of G6PD-deficiency, and not confirmed, we think it is exploratory to put a title that denoted G6PD-deficiency. The testing for G6PD deficiency is fairly common and nowadays feasible even during episodes of acute hemolysis and it was surprising why the test couldn't be done to confirm the authors' suspicions. The inconsistency in the report is visible even in the discussion part. The authors were cautioning about the pro-hemolytic effects of CQ-HCQ during the introduction, and at the same time highlighting the lack of conclusive data for the same in the concluding paragraph; by citing supporting literature. Of these three literature references, two [3,4] are proofs against pro-hemolytic effects of CQ-HCQ, and the third one was literature on primaquine, an 8-aminoquinoline (unlike CQ-HCQ which are 4-aminoquinolines).

It must be considered that CQ-and HCQ are not novel drugs but have been used for the treatment of multiple infectious and inflammatory disorders for more than 50 years. Hemolysis due to administration of CQ-HCQ in patients with G6PD-deficiency has not been conclusively proven in any of the large trials using CQ and HCQ [3–5]. The belief of 'antimalarials' causing hemolysis, unfortunately, became engraved in the minds of clinicians by the well-founded evidence on hemolysis by primaquine. A seminal study by Youngster et al. [3] refuted such claims and categorically suggested the lack of evidence of CQ (thus its hydroxy derivative, HCQ) causing hemolysis in patients with G6PD-deficiency. A recent meta-analysis of clinical trials in CQ+/- primaquine, did not demonstrate a significant drop in hemoglobin from baseline in G6PD-deficients on CQ monotherapy [5]. No incidents of hemolysis were observed in 11 G6PD-deficient patients even after >700 months of HCQ exposure as per the largest US study that examined the occurrence of hemolysis with hydroxychloroquine [4].

The trend of major hemolytic parameters was lacking in the text, except for the peripheral smear findings. It should also be considered that, sometimes, a 1-2 g/dL drop in hemoglobin can occur in the first few days of admission after hydration with IV fluids, blood draws etc. As per the graph, one can observe an initial dip of hemoglobin from 15.0g/dL to 12.5g/dL at 48 hrs that normalized to 14.5g/dL within a day, which raises suspicion on the actual course of hemolysis. Moreover, a high D-dimer level seen in this patient can be considered an indirect indicator of the severity of COVID-19 infection in the patient [6]. There is emerging evidence on the complement-mediated pro-coagulated state, a pre-requisite for the atypical hemolytic-uremic syndrome (aHUS), in patients with COVID-19 [7]. This also warrants further clarity, and the need to exclude other possible causes of hemolysis in a patient with severe COVID-19 infection, such as disseminated intravascular coagulation (DIC). Apart from this, COVID-19 infection poses an important confounding factor here, since the infections are the most common trigger for hemolysis in G6PD-deficiency [4]. In a similar report by Beauverd *et al.*, [8] hemolysis was observed even before starting hydroxychloroquine, in a G6PD-deficient COVID-19 patient [9].

Lastly, the contribution of lopinavir in the hemolytic peripheral smear picture should also be considered. Lopinavir is known to cause eryptosis (erythrocyte apoptosis characterized by erythrocyte membrane changes) and this may be aggravated in the context of G6PD-deficiency [10].

In summary, the authors did not establish G6PD-deficiency in the index patient and thus attributing the hemolysis to HCQ, should be considered exploratory. The presence of confounding factors like COVID-19 infection, suspected DIC with high D-dimer, concurrent administration of lopinavir, along with lack of robust supporting evidence preclude establishing hydroxychloroquine as the sole cause for hemolysis in the patient. To conclude, linking CQ-HCQ with hemolysis in G6PD-deficient subjects based on the present report with above-mentioned confounding factors and inconsistencies is against the established scientific evidence [3–5].

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Declaration of Competing Interest

We declare no competing interests.

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