In conclusion, the SARS-CoV-2 infection induced lymphopenia but increased HFLs. The HFLs level might be correlated with disease severity in patients with COVID-19. Given that HFLs can be conveniently counted by a haematology analyser, it might be a useful parameter for clinical monitoring and mechanism studies of COVID-19. Studies based on larger samples are warranted to confirm our present finding.

## Acknowledgements

We appreciate all the colleagues who worked in the front-line or as medical logistics support staff during the SARS-CoV-2 outbreak.

## Conflicts of interest

The authors do not have any conflict of interest to declare.

## Author contributions

Zhao Wang and Zhaoming Tang conceived the study and wrote the paper. Yu He and Huaqing Shu analysed the data and wrote the paper. Ping Wang, Hui Xing and Xiaoqian Zeng collected the data. All authors contributed to critical revision and final approval of the manuscript to be published.

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**Keywords:** high fluorescent lymphocytes, coronavirus disease 2019, circulating plasma cells, B cells, lymphocytes

First published online 8 June 2020
doi: 10.1111/bjh.16867

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# Molecular mechanisms for thrombosis risk in Black people: a role in excess mortality from COVID-19

We read with interest your recent article by Fogarty *et al.*,[1] in particular their conclusion that differences in thrombotic risk may contribute to ethnic disparities in mortality from coronavirus disease 2019 (COVID-19). This is especially important in the UK, where age-sex adjusted hospital death rates for COVID-19 are 2·17-times higher for people with ethnicity recorded as Black compared to those recorded as White, and 1·95 higher for those recorded as Asian.[2] This excess mortality persists after adjustment for deprivation, body mass index (BMI), smoking and comorbidities,[2] and

despite correction for region, rural or urban living, deprivation, household composition, socioeconomic status and health.[3] Similar data from the USA show that in 14 States, African-Americans represent 33% of hospitalisations for COVID-19, despite only making up 14% of the catchment population.[4] Black ethnicity is a construct incorporating diverse populations of African descent. Studies from several communities labelled as 'Black', in particular African-Americans, imply a common increase in thrombotic risk, which may contribute to unexplained ethnic disparities in the UK and USA in COVID-19.

Fogarty *et al.*[1] propose that COVID-19 causes pulmonary intravascular coagulopathy. Our own study of patients hospitalised with COVID-19 found raised D-dimer levels and a high associated rate of venous thromboembolism (VTE; 7·7%).[5] Another study of intensive care patients with COVID-19 also found raised D-dimer levels, without disseminated intravascular coagulation, and reported a 16·7% rate of pulmonary embolism (PE).[6] Patients with COVID-19 acute respiratory distress syndrome (ARDS) had a sixfold increase in PE rates compared with matched patients with non-COVID-19 ARDS. The authors similarly concluded that thrombosis risk is not entirely explained by respiratory failure or critical illness *per se*, and may be associated with abnormal pulmonary microvascular thrombosis. Von Willebrand factor (VWF) and Factor VIII were also elevated in patients with COVID-19.[6] A proposed model of pulmonary intravascular coagulopathy could depend on endothelial release of VWF, which mediates platelet aggregation, and prevents breakdown of circulating pro-thrombotic factor VIII.

The Fogarty *et al.*[1] article refers to increased thrombosis risk in African-Americans, who have a 67–104% higher age-sex adjusted rate of VTE than White Americans.[7–9] Higher VTE risk in African-Americans is contributed to by BMI, hypertension, diabetes, kidney disease, anti-coagulation status and socioeconomic factors.[7–9] Increased D-dimer levels have been demonstrated in African-Americans without VTE,[10] which persist despite controlling for age, sex, VTE risk factors, medications and lifestyle.[11] This suggests that African-Americans might have higher baseline clot formation and breakdown, even in the absence of detected VTE.

African-Americans also have higher circulating levels of VWF, Factor VIII and fibrinogen.[10,12] Factor VIII and VWF are reported in covariate analyses to independently confer risk of VTE in African-Americans,[7,9] irrespective of ABO type, Factor VIII levels, hypertension, renal disease, recent surgery, diabetes, annual household income or alcohol use.[13] Higher circulating VWF levels may be due to increased baseline production by endothelium, or reduced clearance. Along with elevated Factor VIII and D-dimer levels, these findings may imply that increased endothelial activation of the clotting cascade acts as a common pathway for VTE risk factors that are already known to occur at greater prevalence in African-Americans. Alternatively, differences in endothelial regulation of clot formation and breakdown may represent a distinct risk factor that is more common in this ethnic group, due to genetics or unrecognised environmental factors.

Similar trends have been reported for Black people in the UK. One British centre described higher Factor VIII levels in Black patients with deep vein thrombosis (DVT) compared to White patients with DVT.[14] Thrombin generation was increased in Black people with or without DVT compared to White people,[14] suggesting that in both the UK and USA, some Black populations have higher thrombotic risk.

If Black ethnicity and COVID-19 are both associated with increased VTE, Black people with COVID-19 may suffer from a combined thrombotic risk, which contributes to excess mortality. For Black people in the UK and USA, thrombotic risk would be one of multiple interacting biological and socioeconomic variables causing increased death from COVID-19. Interaction between Black ethnicity, thrombotic risk and mortality from COVID-19 could be mediated by traditional VTE risk factors such as BMI, diabetes and cardiovascular disease. Increased Factor VIII and VWF in some Black populations also imply a molecular mechanism for this. If COVID-19 does cause pulmonary intravascular coagulopathy with microvascular thrombosis, then VTE risk in Black people may confer increased vulnerability to COVID-19, even in the absence of detectable macrovascular thrombi such as PE.

Thrombotic risk may not account for increased deaths from COVID-19 in British Asians. Excess mortality seems to particularly affect people from Pakistani, Bangladeshi and Indian backgrounds, even after correction for age, geography and socioeconomic variables.[3] This current data do not appear to show significantly increased mortality in the British Chinese community, once corrected for age. Fogarty *et al.*[1] discuss differences in coagulopathy between Caucasian and Chinese patients with COVID-19, and mention the lower rate of VTE in Chinese people in general, but there are limited data in South Asians regarding relative VTE risk. One large study reported reduced incidence of DVT in British Indians compared to White people,[15] but there are no data on differences in clotting factors, including VWF and Factor VIII.

Studies of ethnic disparities in outcomes from COVID-19 rely on crude distinctions between 'Black', 'Asian' and 'White'.[2] This obscures ethnic variation within these groups, and specific subpopulations may have unique risk factors for both thrombosis and COVID-19. It is disappointing that there are little data on thrombotic risk in ethnic minority communities in countries outside the USA, given the extensive data on VTE in African-Americans. For COVID-19, research should prioritise multivariate analysis of risk factors for mortality in specific ethnic subgroups, with consideration of both socioeconomic and biological factors, particularly clotting factor levels. Investigations as to whether VWF and Factor VIII levels might independently correlate with outcome in COVID-19 are also urgently required. If certain ethnicities are at increased risk of thrombosis, this may have implications for thromboprophylaxis in COVID-19, such as

full dose anti-coagulation for inpatients, or anti-platelet agents if not admitted to hospital.

## Acknowledgement

Roshan Ramasamy wrote the letter. Kate Milne, Deanne Bell, Simon Stoneham and Timothy Chevassut reviewed and revised the letter.

## Competing interests

There are no competing interests.

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**Keywords:** thrombosis, coagulation, COVID-19, ethnicity, SARS-CoV-2

First published online 8 June 2020
doi: 10.1111/bjh.16869

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# Interleukin-1 blockade with anakinra in acute leukaemia patients with severe COVID-19 pneumonia appears safe and may result in clinical improvement

As of 17 May 2020 the number of patients infected by coronavirus disease 2019 (COVID-19) worldwide has exceeded 4·5 million.[1] A subgroup of patients with COVID-19 pneumonia develop a hyperinflammatory syndrome which has a similar cytokine release profile to secondary haemophagocytic lymphohistiocytosis (HLH).[2] Immunomodulatory drugs are hypothesised to abrogate the dysfunctional immune response in hyperinflammatory COVID-19 and are currently being