

# Clonal haematopoiesis and COVID-19: A possible deadly liaison

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## Abstract

We provide evidence for a linear correlation between the frequency of clonal haematopoiesis and COVID-19 mortality rate. We discuss the mechanistic explanations for this association mediated by a pathological inflammatory response. Our hypothesis can be tested in COVID-19-infected patients and eventually lead to new approaches to risk stratification and therapy.

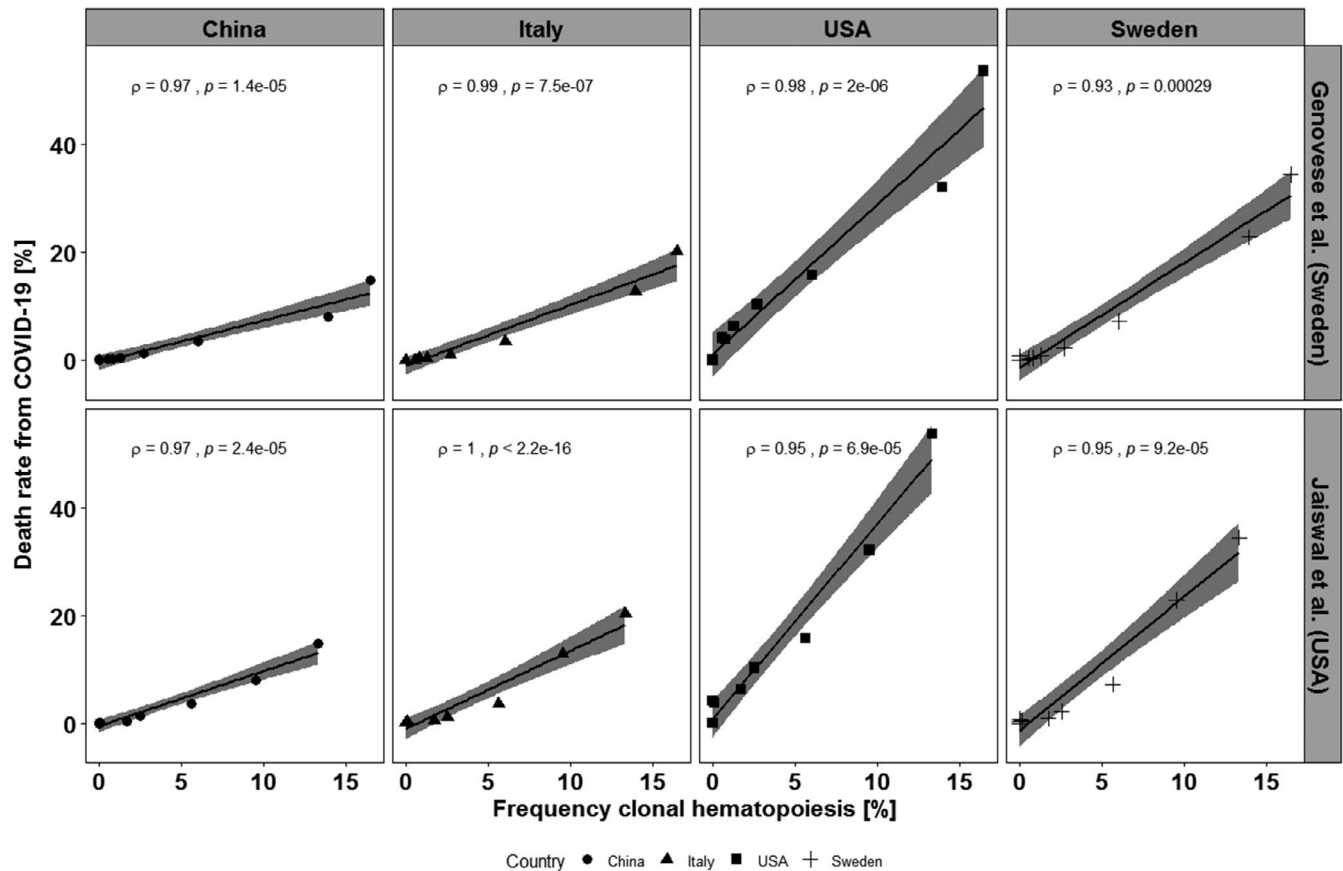
## KEYWORDS

ARDS, clonal haematopoiesis, COVID-19, inflammation, SARS-CoV-2

The recent COVID-19 pandemic due to the newly emerged virus SARS-CoV-2 is challenging the healthcare systems worldwide because of its rapid spread and high mortality rate (Guan et al., 2020; Huang et al., 2020). The latter is particularly prominent among elderly patients. Many possible reasons for that have already been proposed such as high comorbidity, prolonged air pollution exposure and smoking habits. Notably, these possible underlying causes for high mortality rate are not mutually exclusive but a striking unifying feature of most death cases is the development of acute respiratory distress syndrome (ARDS) accompanied by an pathological cytokine storm with central players the lung resident macrophages (Chen et al., 2020; Huang et al., 2020). The proneness to a hyper-inflammatory response in the elderly might not be considered surprising bearing in mind a more pronounced general pro-inflammatory stage in elderly people designated as inflammaging (Franceschi, Garagnani, Parini, Giuliani, & Santoro, 2018). There exist many mechanistic explanations for this age-related skewness of the immune response but in the last several years it becomes more and more evident that at least part of this process is associated with the clonal proliferation of blood cells without overt malignancy (Cook, Luo, & Rauh, 2020; Jaiswal & Ebert, 2019). Two large studies from USA ( $n = 17,182$ ) (Jaiswal et al., 2014) and Sweden ( $n = 12,380$ ) (Genovese et al., 2014) provided data on the frequency of clonal haematopoiesis (CH) in USA and Sweden, respectively. Frequency of CH per each decade of life was estimated as the percentage of patients with verified CH out of the total number of patients within that age group included in the two studies. Therefore, we decided to test whether there was any statistical

association between the age-related increase in the frequency of CH and the age-related increase in mortality of COVID-19-infected patients. We plotted the data from the two largest studies (Genovese et al., 2014; Jaiswal et al., 2014) on CH versus the reported worldwide crude mortality rate from COVID-19 per age group from different countries including China (<https://www.worldometers.info/coronavirus/>) (The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020), Italy (Onder, Rezza, & Brusaferro, 2020), USA (Richardson et al., 2020) and Sweden (<https://www.statista.com/statistics/1107913/number-of-coronavirus-deaths-in-sweden-by-age-groups/>). Of particular interest were the possible correlations between the Genovese et al. (Genovese et al., 2014) and Jaiswal et al. (Jaiswal et al., 2014) CH frequencies and the COVID-19 death rate from Sweden and USA, respectively, because of the matching of populations. We found a perfect linear correlation between each CH data set and the death rate data from all populations (Figure 1), suggesting that the presence of CH may be associated with the risk for fatal outcome in COVID-19-infected patients.

The major criticism for such a hypothesis would be that the age and age-related changes are confounding the association between COVID-19 mortality rate and CH frequency. There is, however, a mounting evidence that CH is more frequently observed in bona fide systemic inflammatory diseases (Arends et al., 2019; Savola et al., 2018). Besides, a recent study showed that CH is associated with the comorbidity status, worse performance status and higher IL-6 serum levels (Cook et al., 2019). Other studies showed that CH might be associated with worse prognosis in cardiovascular



**FIGURE 1** Linear correlation between the frequency of clonal hematopoiesis and worldwide mortality rate from COVID-19-infected patients. Frequency of clonal haematopoiesis per age group was estimated for each decade of life as reported from the two largest studies (Genovese et al., 2014; Jaiswal et al., 2014). The data regarding COVID-19 mortality rate from different countries were obtained as follows: China (<https://www.worldometers.info/coronavirus/>) (The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020), Italy (Onder et al., 2020), USA (Richardson et al., 2020) and Sweden (<https://www.statista.com/statistics/1107913/number-of-coronavirus-deaths-in-sweden-by-age-groups/>) (last accessed on 11 May 2020). The correlation coefficients are from Spearman correlation implemented through R statistical environment (v. 3.6.2)

diseases (Dorsheimer et al., 2019; Jaiswal et al., 2017). Another line of evidence to support our hypothesis comes from mouse models of knockouts of the most frequently affected genes in CH (*Tet2* and *Dnmt3a*). Notably, *Tet2* KO accelerated atherosclerosis development and heart failure and were associated with higher levels of pro-inflammatory cytokines such as IL-6 and IL-1 (Fuster et al., 2017; Sano et al., 2018; Wang et al., 2020). This effect can be attributed to the *Tet2*-dependent gene expression of LPS-induced genes in macrophages (Cull, Snetsinger, Buckstein, Wells, & Rauh, 2017). On the other hand, *Dnmt3a* deletion induces higher level of chemokines and can restrict the antiviral response by the diminished secretion of type I interferons (Li et al., 2016; Sano et al., 2018). Finally, the diseases associated with DNMT3A, TET2 and JAK2 mutations such as myeloproliferative neoplasms, myelodysplastic syndromes and angioimmunoblastic lymphoma are well known for the prominently increased pro-inflammatory cytokines circulation with a direct role in the pathogenesis of those diseases (Feng et al., 2011; Haney et al., 2016; Hermouet, Bigot-Corbel, & Gardie, 2015).

Taken together, we propose that CH in the elderly may be a contributor to the pathogenesis of the cytokine release syndrome associated with higher mortality from COVID-19. This hypothesis could be easily validated through a population genetic study for the presence of CH in COVID-19 severe cases and through challenging of *Tet2/Dnmt3a/Jak2* mutations mouse models with SARS-CoV-2. If the hypothesis holds through, it may be an additional rationale for the use of JAK2 inhibitors in severe COVID-19-infected patients and may help the identification of individuals at particular risk for adverse outcome from SARS-CoV-2 infection.

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VS proposed research, performed the data analysis and wrote the manuscript. MI wrote the manuscript. All authors read and approved the final version of the manuscript.

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