Contents lists available at ScienceDirect

EBioMedicine

Commentary

An epigenetic signature to fight COVID-19

Georges Herbein

Department of Virology, Pathogens & Inflammation EPILAB Laboratory, University of Franche-Comté, COMUE Bourgogne Franche-Comté University, CHRU Besançon, Besançon EA4266, France

ARTICLE INFO

A novel coronavirus, SARS-CoV-2, emerged in China at the end of 2019 and has caused a large global outbreak. Although vaccines are of the utmost importance, mainly in the absence of an effective anti-viral treatment, it is critical to provide patient care as early as possible, especially in hospitals. In such settings, clinical and/or biological scores can be used to assess COVID-19 prognosis. While most individuals will be asymptomatic or experience mild symptoms, COVID-19 can also result in respiratory failure with multiple organ complications such as cerebrovascular accident, myocardial injury, thrombotic events, and hyperinflammation thus causing death in some individuals [1,2]. Several biological and clinical scores have been tested so far to quantify the disease severity and/or clinical outcome [3,4].

Recognizing COVID-19 through the epigenetic lens will result in an improved understanding of disease pathophysiology and better patient management [5]. Based on an epigenome-wide association study (EWAS), the report by Castro de Moura et al. in the April issue of EBioMedicine identifies DNA methylation sites as epigenetic susceptibility loci for respiratory failure in COVID-19 patients [6]. The study ascertains epigenetic biomarkers associated with patients that required hospitalized oxygen therapy versus asymptomatic or pauci-symptomatic patients who were non-hospitalized. In addition, authors define a DNA methylation based signature, named EPICOVID, which could help in assessing disease severity. Patients diagnosed with COVID-19 were considered eligible if they did not possess the following risk factors and/or comorbidities (obesity, diabetes, hypertension, autoimmune disorders, and chronic cardiovascular or lung diseases), smoking habit, or advanced age (> 61 years) thereby restricting the impact of the EPICOVID signature. Moreover, concerning ethnicity and upon referring to the population stratification derived from the Human Origin Project, most of the studied patients were from the West-Eurasia group. In addition, the study looks at only the DNA methylation sites and this reflects limitation; hence, a

broader epigenetic approach including the assessment of histone acetylation, phosphorylation, ubiquitinylation, and sumoylation could have given a broader epigenetic landscape of COVID-19. Even taking into account these biological, clinical, and cohort limitations, the EPICOVID signature could be useful.

It is important to determine whether the EPICOVID signature is specific to COVID-19 and if it allows the discrimination between COVID-19 infection and other respiratory diseases (especially with ARDS), severity outcomes and infections other than SARS-CoV-2. To further demonstrate the specificity of the EPICOVID signature for COVID-19, the authors determined if the identified epigenomic profile was overrepresented in DNA methylation datasets for other respiratory diseases (especially those that involve hyperactivation of the inflammatory cascade) available from the public genomics data repository Gene Expression Omnibus (GEO). They observed that the EPICOVID signature was neither enriched in other respiratory diseases such as tuberculosis, chronic obstructive pulmonary disease, asthma, and other respiratory allergies nor in systemic inflammatory diseases such as rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, Sjögren's syndrome, and inflammatory bowel disease. Concerning viral infections, the EPICOVID signature was not enriched in hepatitis C infection and likewise among HIV-infected individuals. Although other respiratory viral infections, such as influenza and other members of the coronavirus family, were not tested these results further support the specificity of the EPICOVID signature for COVID-19 cases. Finally, since COVID-19 severity is associated with hyperinflammation and immune activation [7], it is important to demonstrate a link between biological parameters including inflammation markers and disease prognosis. The EPICOVID signature is significantly associated with laboratory findings linked to COVID-19 severity such as the levels of proinflammatory cytokine interleukin-6, C-reactive protein, ferritin, fibrinogen and D-dimer, and total lymphocyte count.

Since the EPICOVID signature results from an epigenetic heat map and clustering analysis it would be of great importance if a restricted signature could be derived from those analyses. This might be relevant information for those interested in evaluating the presence/absence of the signature in a patient population to facilitate the analysis at the common hospital laboratory level. Thus, to move from the obtained comprehensive epigenomic signature described in the manuscript by Castro de Moura and colleagues to a more simplified biomarker test, the utilization of additional user-friendly PCR approaches such as some pyrosequencing technology could facilitate the analyses at the common hospital laboratory level. To this end, the

authors selected the top five CpG sites associated with severity according to P-value instead of depending on the comprehensive EPI-COVID signature. In this case, its single differential methylation status was still associated with COVID-19 severity. Thus, a more restricted signature derived from the heat map and clustering analyses might be useful in future prospective multicenter studies and also at the common hospital laboratory level to monitor COVID-19 patients. Besides vaccine and anti-COVID19 treatments, biological tools such as the EPICOVID signature could be considered as crucial assets to fight the disease by allowing a better follow-up of the hospitalized COVID-19 patients and to ultimately participate in curtailing immune activation and organ failure observed in advanced disease.

Declaration of Competing Interest

References

[1] Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA 2020;324:782–93.

[2] Wang T, Du Z, Zhu F, et al. Comorbidities and multi-organ injuries in the treatment of COVID-19. Lancet 2020;395:e52.

[3] Wynants L, Van Calster B, Collins GS, et al. Prediction models for diagnosis and prognosis of COVID-19 infection: systematic review and critical appraisal. BMJ 2020;369:m1328.

[4] Galloway JB, Norton S, Barker RD, et al. A clinical risk score to identify patients with COVID-19 at high risk of critical care admission or death: an observational cohort study. J Infect 2020;81:282–8.

[5] El Baba R, Herbein G. Management of epigenetic networks entailed in coronavirus infections and COVID19. Clin Epigenetics 2020;12:118.

[6] Castro de Moura M, Davalos V, Planas-Serra L, et al. Epigenome-wide association study of COVID-19 severity with respiratory failure. EBioMedicine 2021. doi: 10.1016/j.ebiom.2021.103339.

[7] Shen B, Yi X, Sun Y, et al. Proteomic and metabolomic characterization of COVID-19 patient sera. Cell 2020;182:59–72.