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COVID-19 severity determinants – modulating effect of environmental factors.

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Abstract

The new coronavirus that appeared in 2019 (SARS-CoV-2) caused the COVID-19 pandemic, which is responsible for over a million confirmed deaths in 2020, making it the most important event of the 21st century thus far and making SARS-CoV-2 the most scientifically studied virus. Most of those infected with the SARS-COV-2 virus (about 80%) recover quickly from the disease, showing minimal signs of inflammation, mostly similar to the common cold. We analyzed the possible explanations of this observation and demonstrated the association of relative humidity, temperature and IgG N-glycosylation with COVID-19 severity.

Keywords: *SARS-CoV-2, pandemic, humidity, temperature, glycans*

Introduction

The coronavirus is one of the major pathogens responsible for respiratory infections. Seven known coronaviruses cause disease in humans. SARS-CoV and MERS-CoV viruses cause the so-called severe acute respiratory syndrome (SARS), while four other coronaviruses that cause human diseases (HCoV-OC43, HCoV-229E, HCoV-NL63 and HCoV-HKU1) lead to mild upper respiratory tract infections, against which most adults have antibodies [1, 2]. The new coronavirus that appeared in 2019 (SARS-CoV-2) caused the COVID-19 pandemic, responsible for over a million confirmed deaths in 2020, making it the most important event of the 21st century thus far and making SARS-CoV-2 the most scientifically studied virus. The genome of the SARS-CoV-2 virus is composed of a single-stranded (positive-sense) ribonucleic acid (RNA) molecule and contains 29,903 nucleotides [3]. Using a special spike-like glycoprotein on its surface, the SARS-CoV-2 virus binds itself to angiotensin-converting enzyme (ACE2) to enter human cells, mainly in the respiratory system, where it successfully uses the cell structures to produce a new generation of viruses [4]. The clinical presentation of patients infected with the SARS-COV-2 is diverse and the symptoms that may occur include: fever, fatigue, dry cough, muscle pain and dyspnea (difficulty breathing), while the less common symptoms include: diarrhea and nausea, headache, hemoptysis (coughing up blood), productive cough and chest pain [5-7]. However, most patients infected with SARS-COV-2 (about 80%) recover quickly from the disease and show minimal signs of inflammation, mostly similar to the common cold. Many factors have been proposed as clinical predictors of disease progression including obesity, diabetes, hypertension, kidney, previous cardiovascular disease and age [8, 9].

Mucosal barrier

Epidemiological data from several sources show that transmission of SARS-CoV-2 is more efficient in cold and dry climate than in warm and humid locations [10, 11]. The majority of respiratory viruses demonstrate seasonality in their epidemiologic peaks, which suggests an important role of the environment for viral transmission [12]. Possible explanations for this phenomenon include indoor crowding in the cold months, effects of temperature and humidity on stability of viral particles and inactivation of the mucosal barrier of the respiratory tract. If the mucosal barriers dry-out, they cannot perform their protective functions [13]. It is, therefore, necessary to stay well hydrated to maintain the structural integrity and enable the constant flow of mucins that carry viruses and other pathogens out of

the airways [14]. Animal studies of influenza mortality demonstrated that increasing relative humidity from 20% to 50% significantly decreased mortality [15]. Another study examining this topic found that indoor relative humidity of over 40% significantly reduces the infectivity of aerosolized influenza virus particles [16]. These findings demonstrate the important role of relative humidity on viral transmissibility, which can be attributed to either their inactivation or to the preserved integrity of the mucosal barrier.

IgG N-glycome

IgG is the key effector of acquired humoral immunity. Synthesized by B-lymphocytes, IgG binds to its specific antigen and clears it out of our system by activating other immune cells. IgG glycome composition is an essential component of the immune system that regulates inflammation at multiple levels. Its role as both a biomarker and a functional effector of inflammation that contributes to the development of different inflammatory diseases has been established in the literature [17-19]. Therefore, our international group of authors analyzed the total IgG N-glycome composition of three COVID-19 patient cohorts from Spain, Italy and Portugal. 167 patients with mild and 166 patients with severe COVID-19 were included. Disease severity was defined in regard to intensive care unit admission and the need for mechanical ventilation. The results demonstrated a significant difference in the IgG glycome composition in severe and mild COVID-19 patients. A consistent decrease in the level of bisecting N-acetylglucosamine (GlcNAc) in severe cases was observed in all cohorts (meta-analysis effect = - 0.34; adjusted meta-analysis p= 0.009). Galactosylation was also consistently decreased in severe cases in all three cohorts, but the statistical significance of this difference was observed only for monogalactosylation in the Barcelona cohort. Consistent changes in the levels of sialylated and fucosylated IgG glycan structures between mild and severe COVID-19 cases were not detected.

Despite the small size of each cohort, the decreased level of bisecting GlcNAc in severe patients was statistically significant even after adjusting for multiple testing (adjusted meta-analysis p = 0.009). Higher levels of bisecting GlcNAc on IgG are often associated with increased FcγRIII binding and enhanced antibody-dependent cell cytotoxicity (ADCC), explaining more pro-inflammatory effector functions of IgGs [20-21].

The cross-sectional design of this study did not allow us to distinguish whether the observed associations reflected a pre-existing risk factor or rapid changes in IgG glycosylation that occurred during the natural course of the disease. This question will be addressed in future studies. The observed differences are not large enough to suggest the use of IgG glycome as a predictor of COVID-19 severity, but it is intriguing to hypothesize that changes in the IgG glycome that lead to the loss of its immunosuppressive potential may be one of the molecular mechanisms behind environmental risk factors for severe COVID-19. We do, however, know that age and adiposity are the main environmental factors that drive the decrease in IgG glycosylation implicating that the observed changes may be individual and partially depending on these and other factors [22-23]. IgG glycome composition is strongly associated with age, so it is very hard to exclude confounding factors with some other age-related changes, but the fact that people with severe COVID-19 had “older” IgG glycome composition suggests the need for further research in this direction.

Seasonality of SARS-CoV-2

Aiming to evaluate the seasonal nature of COVID-19, we evaluated the disease course in 6,914 individuals from nine cohorts admitted to hospitals in Europe and China from the beginning of the pandemic until July 2020. To avoid sampling bias, all hospitalizations that resulted in either death or medical discharge were included in the analysis. Patients with confirmed diagnosis of COVID-19 by polymerase chain reaction testing of a nasopharyngeal sample and/or a clinically/radiologically diagnosis of COVID-19 at the time of admission were included. Patients were not followed after discharge, but COVID-19 related early readmissions were considered as part of the COVID-19 course.

A meta-analysis of the effect of admission date on the mortality was performed and demonstrated a weighted average decrease in mortality odds across all studied hospitals of 1.9% per day. The most significant change was observed in Barcelona, where mortality odds decreased by 4.1% per day ($p < 0.001$).

Our model included age as a co-variate, so this change is unlikely to be accounted for by a change in the age of patients. To further confirm that age was not underlying the observed changes, we analyzed the age of patients admitted to hospitals in different periods and demonstrated that change in the age of patients was not a factor that could explain the observed decrease in mortality. The decrease in lengths of hospitalization was also statistically significant. The odds to need intensive care decreased in all hospitals in Europe and were individually statistically significant in all hospitals besides Bergamo, Helsinki, and Zagreb. A meta-analysis of European hospitals estimated that the odds to need intensive care decreased by 2.2% per day of change in the admission date and the odds to need mechanical ventilation decreased 2.1% per day of change in the admission date. Additionally,

we correlated the observed changes with local ambient temperature. To evaluate whether the temperature change may have been responsible for the observed changes in disease severity, we modeled mortality with the ambient temperature instead of the admission date. The results suggest a strong effect of ambient temperature on the mortality risk (OR = 0.854 per 1°C; CI = 0.773–0.944; p = 0.007).

The main limitation of this study is sampling bias. By focusing on the individual progression of the disease in already hospitalized patients, we excluded effects of the unknown number of true infections on national mortality rates, and we still cannot exclude the possibility that some other unidentified external factors (including confinement and social distancing, improvement and compliance of prevention and environmental hygiene protocols, and even decreased air pollution, which could have progressively affected the severity of patients arriving to the hospital) were affecting the composition of hospitalized patient cohorts and contributing to the decreased COVID-19 severity and mortality. Nevertheless, the data suggest that, in addition to affecting viral transmission, environmental factors also play an important role in already infected patients.

Conclusion

The COVID-19 pandemic has upended all areas of life and stopped the way of life as we knew it. During the course of the past year, we embraced a much different lifestyle than what we were used to in order to reduce the spread of the virus and save as many lives as possible. The immense effort put into SARS-CoV-2 research resulted in the fastest vaccine development, emphasizing the value of science in our society. There are high hopes for a return to our lives as they were before the pandemic, but caution is still prudent until the majority of our population is vaccinated and/or recovered. With winter nearing its end and warm spring and summer weather approaching, we could expect a decrease in both patient count and symptom severity.

Note:

COVID-19 severity determinants – modulating effect of environmental factors is an excerpt from the texts prepared for: Journal of Global Health, scientific journal (Lauc G, Markotić A, Gornik I, Primorac D. Fighting COVID-19 with water. J Glob Health. 2020 Jun;10(1):010344. doi: 10.7189/jogh.10.010344.); Frontiers in medicine, scientific journal (Kifer D, Bugada D, Villar-Garcia J, Gudelj I, Menni C, Sudre C, Vučković F, Ugrina I, Lorini LF, Posso M, Bettinelli S, Ughi N, Maloberti A, Epis O, Giannattasio C, Rossetti C, Kalogjera L, Peršec J, Ollivere L, Ollivere BJ, Yan H, Cai T, Aithal GP, Steves CJ, Kantele A, Kajova M, Vapalahti O, Sajantila A, Wojtowicz R, Wierzba W, Krol Z, Zaczynski A, Zycinska K, Postula M, Lukšić I, Čivljak R, Markotić A, Brachmann J, Markl A, Mahnkopf C, Murray B, Ourselin S, Valdes AM, Horcajada JP, Castells X, Pascual J, Allegri M, Primorac D, Spector TD, Barrios C, Lauc G.. Effects of Environmental Factors on Severity and Mortality of COVID-19. Front Med (Lausanne). 2021 Jan 20;7:607786. doi: 10.3389/fmed.2020.607786.); and Glycobiology, scientific journal (Petrović T, Alves I, Bugada D, Pascual J, Vučković F, Skelin A, Gaifem J, Villar-Garcia J, Vicente MM, Fernandes Â, Dias AM, Kurolt IC, Markotić A, Primorac D, Soares A, Malheiro L, Trbojević-Akmačić I, Abreu M, Sarmento E Castro R, Bettinelli S, Callegaro A, Arosio M, Sangiorgio L, Lorini LF, Castells X, Horcajada JP, Pinho SS, Allegri M, Barrios C, Lauc G.. Composition of the immunoglobulin G glycome associates with the severity of COVID-19. Glycobiology. 2020 Nov 10:cwaa102. doi: 10.1093/glycob/cwaa102.) in which the environmental factors and IgG glycome compositions in COVID-19 patients were studied and presented in full.

References

[1] He, F., Deng, Y., Li, W.. Coronavirus Disease 2019 (COVID-19): What we know? J Med Virol. 2020;14;jmv.25766. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25766

[2] Gorse, G.J., Patel, G.B., Vitale, J.N., O'Connor, T.Z. Prevalence of Antibodies to Four Human Coronaviruses Is Lower in Nasal Secretions than in Serum. Clin Vaccine Immunol. 2010;17(12):1875–80.

[3] Wu, F., Zhao, S., Yu, B., Chen, Y.M., Wang, W., Song, Z.G., et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265–9.

[4] Gurwitz, D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res. 2020;ddr.21656. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/ddr.21656

[5] Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061.

[6] Guan, W., Ni, Z., Hu, Y., Liang, W., Ou, C., He, J., et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;NEJMoa2002032.

[7] Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–13.

[8] Sehra, S.T., Salciccioli, J.D., Wiebe, D.J., Fundin, S., Baker, J.F. Maximum Daily Temperature, Precipitation, Ultraviolet Light, and Rates of Transmission of Severe Acute Respiratory Syndrome Coronavirus 2 in the United States, Clinical Infectious Diseases. 2020;71(9): 2482–2487

[9] Williamson, E., Walker, A. J., Bhaskaran, K. J., Bacon, S., Bates, C., Morton, C. E., Curtis, H. J., Mehrkar, A., et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. MedRxiv, 2020.05.06.20092999. https://doi.org/10.1101/2020.05.06.20092999

[10] Wang, J., Tang, K., Feng, K., Lv, W. High temperature and high humidity reduce the transmission of COVID-19. SSRN Electron J. doi: 10.2139/ssrn.3551767

[11] Araujo, M.B., Naimi, B. Spread of SARS-CoV-2 Coronavirus likely to be constrained by climate. medRxiv 2020.03.12.20034728; doi: https://doi.org/10.1101/2020.03.12.20034728

[12] Moriyama, M., Hugentobler, W.J., Iwasaki, A..Seasonality of respiratory viral infections. Annu Rev Virol. 2020;7(1):83-101.

[13] Pflüger, R., Feist, W., Tietjen, A., Neher, A.Physiological impairments at low indoor air humidity. Gefahrst Reinhalt Luft. 2013;73:107-8.

[14] Wheeler, K.M., Cárcamo-Oyarce, G., Turner, B.S., Dellos-Nolan, S., Co, J.Y., Lehoux, S., et al. Mucin glycans attenuate the virulence of Pseudomonas aeruginosa in infection. Nat Microbiol. 2019;4:2146-54.

[15] Kudo, E., Song, E., Yockey, L.J., Rakib, T., Wong, P.W., Homer, R.J., et al. Low ambient humidity impairs barrier function and innate resistance against influenza infection. PNAS. 2019;116(22):10905-10910.

[16] Noti, J.D., Blachere, F.M., McMillen, C.M., Lindsley, W.G., Kashon, M.L., Slaughter, D.R., et al. High humidity leads to loss of infectious influenza virus from simulated coughs. PLoS One. 2013;8:e57485. 10.1371/journal.pone.0057485

[17] Lauc, G., Pezer, M., Rudan, I., Campbell, H. Mechanisms of disease: The human N-glycome. Biochimica et Biophysica Acta - General Subjects. 2016;1860(8):1574–1582.

[18] Nimmerjahn, F., Ravetch, J. V. Anti-inflammatory actions of intravenous immunoglobulin. Annu Rev Immunol. 2008;26:513–533.

[19] Seeling, M., Brückner, C., Nimmerjahn, F. Differential antibody glycosylation in autoimmunity: Sweet biomarker or modulator of disease activity? Nature Reviews Rheumatology. 2017;13(10):621–630.

[20] Irvine, E. B., Alter, G. Understanding the role of antibody glycosylation through the lens of severe viral and bacterial diseases. Glycobiology. 2020;30(4), 241–253.

[21] Um ana, P., Jean-Mairet, J., Moudry, R., Amstutz, H., Bailey, J. E. Engineered glycoforms of an antineuroblastoma IgG1 with optimized antibody-dependent cellular cytotoxic activity. Nat Biotechnol. 1999;17(2):176–180.

[22] Krištić, J., Vučković, F., Menni, C., Klarić, L., Keser, T., Beceheli, I., Pučić-Baković, M., et al. Glycans are a novel biomarker of chronological and biological ages. Journals of Gerontology - Series A Biological Sciences and Medical Sciences. 2014;69(7):779–789.

[23] Russell, A. C., Kepka, A., Trbojević-Akmačić, I., Ugrina, I., Song, M., Hui, J., Hunter, M., et al. Increased central adiposity is associated with pro-inflammatory immunoglobulin G N-glycans. Immunobiology. 2019:224(1);110–115.