COVID19: uncovering interindividual variability for tailoring appropriate therapeutic interventions

COVID19: a variabilidade individual da resposta imunoinflamatória

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Article Summary Line: Covid19 severity should account for the diversity of human individual immunoinflammatory responses with individualized therapeutics for better outcomes.

ABSTRACT

The severity of SARS-CoV2 infection, Covid19 disease, should account for the diversity of human individual immunoinflammatory responses. Serum immunological markers during Covid19 illness may lead to individualized therapeutics with better outcomes. Efficient treatment for Covid19 may require: 1) early disease detection, 2) combined drug therapy for 3) targeting the virus replication cycle, and 4) individualized drug treatment for specific immunoinflammatory human profile responses administered in a 5) timely manner. Covid19 is unlikely to be the last emergent human disease with fast pandemic potential. Gathering knowledge on the individual human host profiles of immunoinflammatory responses is an opportunity that could lead us to understand individual differences in response to infection at the individual and population level, paving the way to faster, more efficient strategies to tackle upcoming infectious diseases. This is a position paper based on an integrative non-exhaustive literature revision.

Keywords: COVID-19, Severe Acute respiratory syndrome, Immunoinflammatory response, Cytokine storm, SARS-CoV2, Treatment outcome.

RESUMO

A diversidade das respostas imunoinflamatórias individuais humanas muito provavelmente tem papel na gravidade da doença Covid19 causada pela infecção pelo vírus SARS-CoV2. Marcadores imunológicos séricos durante a Covid19 podem guiar a escolha de terapias individualizadas com melhores resultados. O tratamento eficiente para Covid19 pode exigir: 1) detecção precoce da doença, 2) terapia medicamentosa combinada com alvo ao 3) ciclo de replicação do vírus e 4) terapia anti-inflamatória individualizada para perfis de respostas imunoinflamatórias humanas, administradas em tempo hábil. É improvável que a Covid19 seja a última doença humana emergente com potencial de alastramento veloz pandêmico. Reunir conhecimento sobre perfis de respostas imunoinflamatórias individuais dos hospedeiros humanos é uma oportunidade ímpar que pode nos levar a entender as diferenças dessas respostas entre indivíduos, abrindo caminho para estratégias terapêuticas mais rápidas e eficientes no combate à futuras epidemias.

Palavras-chave: COVID-19, Síndrome respiratória aguda grave, Resposta imunoinflamatória, Modelo iceberg de doença, Resultado do tratamento.

We are all different - We are 7.8 billion humans[1]. Even though we share 99.9% of our genetic composition in 3 billion DNA base pairs, none of us are alike. The 0.1% that separates each one of us humans holds an incredible individual variability which can be seen in the shapes of our faces, the color of our eyes, and, among other traits, the way we respond to infection. Not only our genetics but also the way we live, work, eat, exercise, and think are epigenetic factors that add to our human individuality. Nonetheless, when we talk about emerging pathogens and the pathogenesis of infectious diseases, it seems we aim at pathogen variation. Oddly, we disregard individual human genetics and

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https://doi.org/10.11606/issn.2176-7262.rmrp.2022.180873

epigenetic variations in response to infection when we observe human populations and their cohorts diversely impacted by a given infectious disease. Unique human host variations to pathogen infection are likely to lead to different immune responses, disease phenotypes, and outcomes.

The iceberg. In the early 1960's John Murray Last, an Australian doctor, while working as a postgraduate in the London Hospital, UK, observed what he called 'subclinical diseases' and created the strong metaphorical image of 'disease as iceberg' watching that only a fraction of patients showed symptoms in a given exposed population[2] (Fig. 1) (Last 1963). In the visible tip part of the iceberg, a few individuals present moderate to severe symptoms, while for some individuals, in fact, in most of the affected population, mild or no symptoms prevail (Fig. 1). Data from the SARS-CoV2 epidemics in Ribeirão Preto, São Paulo, followed this distribution (Martinez et al., 2021). Positivity for the virologic test (RT-PCR) was 0.11% to 2.37% of the human population would be cumulatively infected with SARS-CoV2 by mid-June 2020 (Martinez et al., 2021). The local COVID-19 fatality rate was estimated to be 0.37%, or four deaths per 1,000 individuals infected (Martinez et al., 2021). It seemed that only 11.78% of SARS-CoV2 infection cases were reported to the epidemiological surveillance system. This means that, roughly, for every case reported, there were 8.5 asymptomatic or subclinical non-reported patients (Martinez et al., 2021).

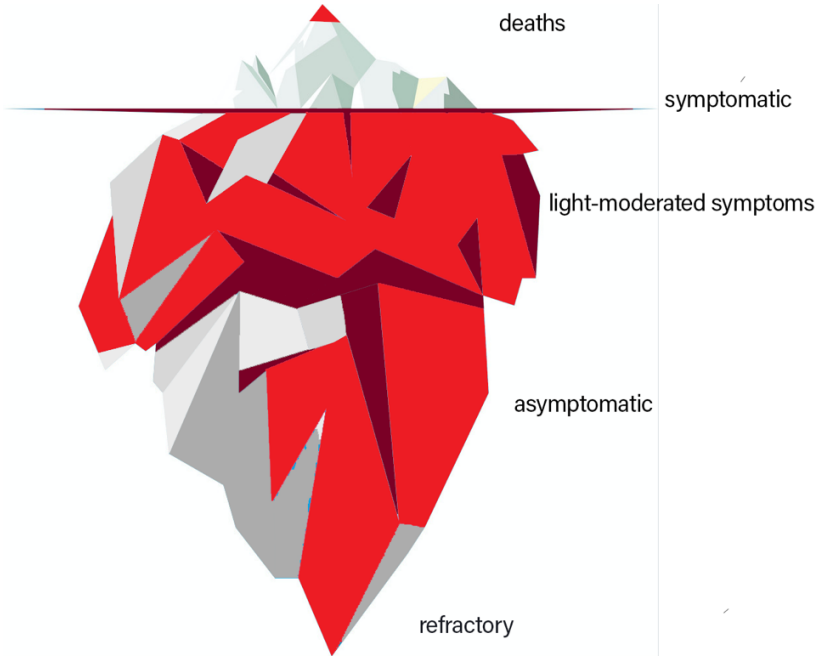

Figure 1: Covid19 infections in a given exposed population seen as an iceberg. Some individuals, in fact, the majority of the population, present mild symptoms or are asymptomatic. Very few have moderate to severe symptoms. In fact, when analyzing accurate data during the SARS-CoV2 epidemics in Ribeirão Preto, São Paulo State, Brazil, in 2020, Martinez et al. observed deaths to occur for 4 in every 1,000 infected individuals (0.4%) with SARS-CoV2 while the ratio symptomatic/ light to moderated symptoms or asymptomatic was 1:8.5 (Martinez et al., 2021). These actual data match well with our iceberg image metaphor where the visible part floating on top of the surface would represent 10% of total SARS-CoV2 symptomatic cases with 0.4% deaths at the tip of the iceberg while most, or approximately 85-90% of low and asymptomatic cases remain invisible underneath the surface. Individuals refractory to infection are also expected. Source: The Authors after Last, 1963 and Martinez et al., 2021.

A highly individualized response to infection. In 2015, Casanova referred to the human host response variability on infection as "interindividual variability"[3], and we will, in this paper, call it 'individuality'. When we analyze numbers for Covid19, the disease caused by the **s**evere **a**cute **r**espiratory **s**yndrome by number **2 co**rona**v**irus - SARS-CoV2, the number of severe cases seem to follow the iceberg model of disease with the number of deaths on its tip (Fig. 1) (Table 1).

Table 1

Percentages of confirmed cases and deaths per country by Covid19 in descending order of % deaths in the total population for the 30 most-affected countries by January 12, 2021. Sources: [4,5,6]

Country	confirmed cases	% confirmed cases who have died	number of deaths	deaths per million people	cases per million people	Population	% of confirmed cases in the total population	% of deaths in the total population
Belgium	665,223	3.02	20,122	845	57398.2	11589623	5.74	0.1736
Italy	2,289,021	3.46	79,203	579	3992.0	60461826	3.79	0.1310
UK	3,127,643	2.62	82,096	631	4493.0	67886011	4.61	0.1209
Peru	1,035,184	3.70	38,280	208	7142.0	32971854	3.14	0.1161
USA	22,620,330	1.66	376,295	357	6454.0	331002651.00	6.83	0.1137
Spain	2,111,782	2.48	52,275	585	5262.0	46754778	4.52	0.1118
France	2,845,030	2.40	68,198	453	2988.0	65273511	4.36	0.1045
Mexico	1,541,633	8.72	134,368	133	11956.9	128932753	1.20	0.1042
Argentina	1,730,921	2.58	44,654	988.0	38298.3	45195774.00	3.83	0.0988
Brazil	8,131,612	2.50	203,580	207	4146.0	212559417	3.83	0.0958
Colombia	1,801,903	2.58	46,451	915.5	35514.1	50737681.00	3.55	0.0916
Chile	645,892	2.66	17,162	184	9654.0	19116201	3.38	0.0898
Poland	1,395,779	2.26	31,593	834.8	36879.9	37846611.00	3.69	0.0835
Netherlands	890,566	1.40	12,512	730.2	51973.9	17134872.00	5.20	0.0730
Iran	1,299,022	4.34	56,360	109	2309.0	83992949	1.55	0.0671
South Africa	1,246,643	2.69	33,579	566.2	21019.6	59308690	2.10	0.0566
Germany	1,947,660	2.15	41,917	107	23246.2	83783942	2.32	0.0500
Ukraine	1,160,243	1.80	20,915	478.2	26529.7	43733762.00	2.65	0.0478
Canada	672,931	2.54	17,096	224	2741.0	37742154	1.78	0.0453
Russia	3,412,390	1.81	61,908	424.2	3669.0	145934462.00	2.34	0.0424
Turkey	2,336,476	0.98	22,981	272.5	27703.4	84339067	2.77	0.0272
Saudi Arabia	363,949	1.73	6,295	180.8	3872.0	34813871	1.05	0.0181
India	10,479,179	1.44	151327.00	109.7	7593.6	1380004385	0.76	0.0110
Indonesia	846,765	2.91	24,645	90.1	3095.8	273523615.00	0.31	0.0090
Pakistan	506,701	2.12	10,717	48.5	2293.9	220892340	0.23	0.0049
Bangladesh	524,020	1.49	7,819	47.5	3181.9	164689383	0.32	0.0047
China	97,001	4.94	4,793	3.3	67.4	1439323776	0.01	0.0003

The number of individuals who have died from Covid19 showed to be 0.17% (Belgium) to 0.0003 (China) in the total population[4,5,6] (Table 1, up to January 12, 2021). Positive cases for SARS-CoV2 (through rapid immunochromatography for IgM and IgG antibodies and antigens by polymerase chain reaction-PCR) (Table 1) can be considered a proxy of individuals having moderate to severe symptoms, seeking testing in hospitals and health care units and being statistically registered. Asymptomatic individuals, even if positive for SARS-CoV2, would remain unregistered. Active field-testing studies in 120 cities in Brazil corresponding to 32.7% of the total Brazilian population (or 68.6 million individuals) have demonstrated average percentages of 3% of infected individuals sometimes completely asymptomatic (EPICOVID19 - Universidade de Pelotas, June 11, 2020)[7]. This 3% average of positive individuals for SARS-CoV2 hides highly variable positivity numbers for different Brazilian cities. While for some Southern Brazilian cities, tests showed SARS-CoV2 positivity of around 0.5%, for the Northern city of Boa Vista, positivity was 25% (data of June 11, 2020)[7]. Even though 0.5 to 3% average seem small, they challenge even the most prepared health systems in any country since Covid19 is a fast-spreading contagion causing the acute respiratory syndrome, which requires complex treatment

involving intensive care units, ventilators, and other special equipment, high use of disposable consumables and highly skilled personnel. Some patients require intensive care for weeks, and approximately 1 to 16% of those symptomatic individuals will not recover[4] (Table 1).

Highly variable individual immunoinflammatory responses. When we look retrospectively at a newly emerging pathogen such as SARS-CoV2, individual exacerbated immunoinflammatory responses, in an attempt to overcome the pathogen invasion, seem to be linked to the most symptomatic and severe Covid19 cases[8,9]. These immunoinflammatory responses are likely to vary in individual fashion during Covid19 time progression and are strongly linked to disease outcomes. As for other diseases, age, hypertension, diabetes, obesity, immunosuppression, and chronic illnesses are considered risk factors for the development of severe Covid19[10,11]. Nonetheless, severe presentation for Covid19 has also been observed in healthy individuals. Therefore, comorbidities and risk groups alone cannot entirely explain severe Covid19 clinic presentation segmentation in a given population[12]. The involvement of genetically linked immunoinflammatory individual profiles is likely to add to Covid19 severity[13].

Out of control. The storm. Severe Covid19 cases present a 'cytokine storm'. Cytokines are molecules regulating inflammatory response, B-cell differentiation, and antibody production. The term 'cytokine storm' was first used in 1993 on a paper on graft-versus-host disease[14]. The cytokine storm phenomenon was previously applied for the avian H5N1 influenza virus, cytomegalovirus, Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis, group A streptococcus, smallpox virus, and for the previous severe acute respiratory syndrome coronavirus (SARS-CoV)[15]. Unregulated immunoinflammation is also a central pathological process in several infectious diseases such as hemorrhagic dengue[16] and severe malaria[17]. Cytokine storm was revived for Covid19 since its striking immunoinflammatory cellular and molecular processes seem to be strongly linked with death outcomes (Fig. 2).

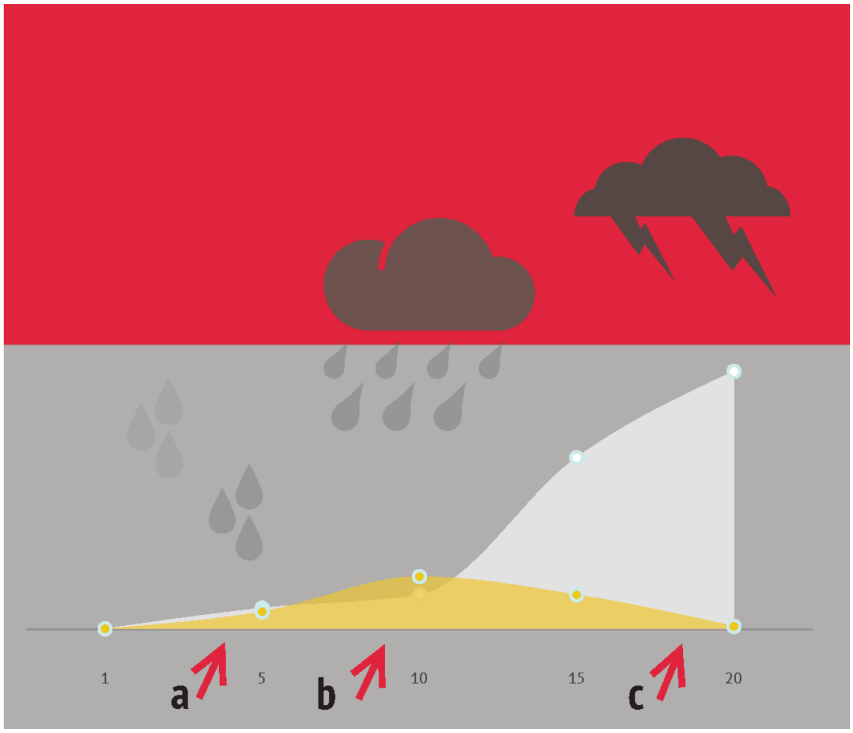

Figure 2: The Covid19 storm. The x-axis is time in days, and the y-axis is the amount of immunoinflammatory response by the host, normal in yellow and abnormal in light gray. Red arrows represent possible times for drug intervention: a) early (possibly using antivirals), b) symptomatic (probably using anti-inflammatory drugs), and c) storm (probably using MAbs and corticosteroids). See the text for the explanation on the suggested times. Source: The Authors.

When compared with mild Covid19 cases, severe Covid19 cases have exhibited increased plasma levels of cytokine molecules related to inflammation, such as IL2, IL6, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNFα, indicating unregulated immunoinflammation is also a pathological process for serious Covid19[18,19]. Patient data suggest that excessive cytokine release, the so-called cytokine storm induced by SARS-CoV-2 infection, is related to Covid19 pathogenesis, such as lung tissue injury[20] and other tissue injuries like heart and kidney[21,22].

Suggested intervention points for therapeutics. Studies have shown that the median time from symptoms onset to hospital discharge for those patients needing hospitalization was 22 days (interquartile range-IQR 18-25), while the median time to death was 18.5 days (IQR 15-22)[22]. The onset of inflammation for Covid19 happened around the 7th day after symptoms started[21,22] and coincided with dyspnea. Thus, a plausible first intervention point would be at day 5 before inflammation escalates and a cytokine storm is established (point a in Fig. 2). Sepsis and acute respiratory distress syndrome-ARDS were observed on days 9 and 10, respectively[21,22,] which would suggest a second intervention point around the 10th day after the onset of symptoms (point b in Fig. 2). Acute heart and kidney injuries were registered on day 15[21,22]. Therefore, a third intervention point and a third line of therapeutics should be considered on day 15 (point c in Fig. 2). Symptomatic Covid19 after day 15 is of poor prognosis[21].

Genetically-linked immunoinflammatory individual profiles. Multiple host genes ought to be involved in Covid19 physiopathology[13] and immunoinflammatory profiles. Immunoinflammatory data such as serum levels of d-dimer, high-sensitivity cardiac troponin I, serum ferritin, lactate dehydrogenase, and interleukin-6 (IL-6)[22] might enable separate individuals into groups, take this knowledge to clinics, and maximize its use in therapeutics.

Proposing immunoinflammatory profiles for covid19 cases. Rationale-based clinical therapeutic strategies can be built for groups of patients at a higher risk of pathological inflammation driving Covid19 severe pathological presentations[9]. Three major human immune profile groups for Covid19 can be suggested, which can be applied to other cytokine storm prone-diseases: 1) individuals who probably will not develop a cytokine storm, 2) those who potentially will make a storm, and 3) those who will most likely make a storm. These three major immune profile groups could be separated on: **1)** nucleocytes/ monocytes ratio (8), **2)** IL-6 levels, and **3)** immunoinflammatory factors' levels, e.g., tumor necrosis factor (TNF-a), interferon-gamma (IFN-c), tumor growth factor-beta (TGF-b), and interleukins such as IL-10, IL-2, IL-4, and IL-5[8,16,22]. More specific laboratory indicators of factors present in the blood serum will help better outcome predictions using fast, practical screening, and specific therapeutical approaches. If we could know more about the specific immune and inflammatory responses of each individual, we would be in a better position to understand real risk groups and provide better therapeutics. Possible suitable times for drug intervention in Covid19 are represented by red arrows in Figure 2: point a) early (probably using antivirals), point b) symptomatic (probably using anti-inflammatory drugs), and point c) during the storm (probably using MAbs and corticosteroids) (Fig. 2).

Concluding thoughts. This is a time to learn. SARS-CoV-2 is an emerging infectious disease, a high contagion, easily transmitted by air and fomites. The severity of some Covid19 cases requires hospitalization with complex, expensive intensive care treatments. Spilling over sylvatic cycles (Fig. 3), Covid19 is unlikely to be the last emergent human infectious disease. If we knew more about Covid19 individual immune and inflammatory responses, we would be in a better position to talk about risk groups. This understanding will also provide opportunities for highly focused individual-centered therapeutics.

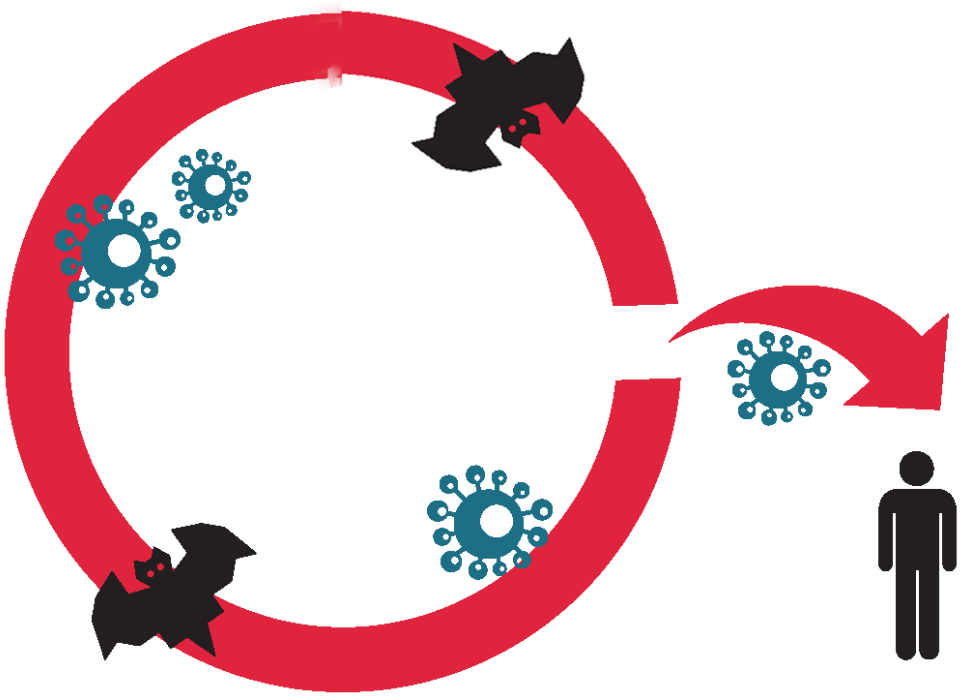

Figure 3: Simplified representation of SARS-CoV-2 spilling over its natural cycle among bats to reach humans. Source: The Authors.

Take-home message. To gather knowledge on individual human host immune and inflammatory profiles and responses to infectious diseases using Covid19 as a model is an opportunity to learn that could lead to faster, more efficient ways to tackle ever-challenging human emerging diseases.

REFERENCES

1. United Nations [homepage on the Internet]. Geneva: Department of Economic and Social Affairs. Population Dynamics.; c2020 [cited 2020 August 7]. Available from https://population.un.org/wpp/Download/Standard/Population/
2. Last JM. The iceberg "completing the clinical picture" in general practice. The Lancet 1963; 282 (7297): 28–31.
3. Martinez, EZ et al. Prevalence of virological and serological markers of SARS-CoV-2 infection in the population of Ribeirão Preto, Southeast Brazil: an epidemiological survey. Revista da Sociedade Brasileira de Medicina Tropical [online]. 2021, v. 54 [Accessed 17 November 2021] , e0210-2021. Epub 02 July 2021. ISSN 1678-9849. https://doi.org/10.1590/0037-8682-0210-2021.
4. Casanova JL. Human genetic basis of interindividual variability in the course of infection. Proc Natl Acad Sci USA. 2015;112(51):E7118–E7127.
5. Coronavirus Resource Center [homepage on the Internet]. Baltimore: Johns Hopkins University; c2020 [cited 2020 September 22]. Available from https://coronavirus.jhu.edu/map.html
6. Covid19-coronavirus-infographic-datapack [homepage on the Internet]. London: Information is beautiful; c2020 [cited 2020 August 29]. Available from https://informationisbeautiful.net/visualizations/Covid19-coronavirus-infographic-datapack/
7. Population by country [homepage on the Internet]. Delaware: Worldometers info; c2020 [cited 2020 August 29]. Available from https://www.worldometers.info/world-population/population-by-country/
8. EPICOVID-19 [homepage on the Internet]. Pelotas: University of Pelotas; c2020 [cited 2020 June 11]. Available from http://epidemio-ufpel.org.br/uploads/downloads/19c528cc30e4e5a90d9f71e56f8808ec.pdf.
9. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of Covid19: immunity, inflammation and intervention [published online ahead of print, 2020 Apr 28]. Nat Rev Immunol. 2020;1–12.
10. Merad M, Martin JC. Pathological inflammation in patients with Covid19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20,355–362.

11. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with Covid19 in China: a nationwide analysis [published online ahead of print March 26, 2020]. Eur Respir J. 2020; https://doi.org/10.1183/13993003.00547-2020.

12. Li X, Xu S, Yu M, Yu M, Wang K, Tao Y, et al. Risk factors for severity and mortality in adult Covid19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146(1):110–118. doi:10.1016/j.jaci.2020.04.006

13. Wu C, Chen X, Cai Y, Xia, Zhou X, Xu S, et al. Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934–943.

14. Debnath M, Banerjee M, Berk M. Genetic gateways to COVID-19 infection: Implications for risk, severity, and outcomes. The FASEB Journal. 2020;34:8787–8795.

15. Ferrara JL, Abhyankar S, Gilliland DG. Cytokine storm of graft-versus-host disease: a critical effector role for interleukin-1. Transplant Proc. 1993; 25(1 Pt 2):1216–7.

16. Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. Microbiol Mol Biol Rev. 2012; 76(1):16–32.

17. Sierra B, Perez AB, Vogt K, Garcia G, Schmolke K, Aguirre E, et al. Secondary heterologous dengue infection risk: Disequilibrium between immune regulation and inflammation? Cellular Immunology. 2010; 262 (2): 134–140.

18. Penha-Gonçalves C. Genetics of Malaria Inflammatory Responses: A Pathogenesis Perspective. Front Immunol. 2019;10:1771.

19. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020;395:497–506.

20. 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):507–513.

21. Xiong Y, Liu Y, Cao L, Wang D, Guo M, Jiang A, et al. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. Emerging Microbes & Infections. 2020;9:761–770.

22. Polak SB, Van Gool IC, Cohen D, Thüsen JH, Paassen J. A systematic review of pathological findings in Covid19: a pathophysiological timeline and possible mechanisms of disease progression. Modern Pathol. 2020;33:2128–2138.

23. Zhou F, Ting Yu, Ronghui Du, Guohui Fan, Ying Liu, Zhibo Liu, et al. Clinical course and risk factors for mortality of adult inpatients with Covid19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395:1054–62.

Manuscript writing and editions, data analyses, article submission **MGRF**
Manuscript writing and editions, bibliographic search, data analyses **CMC**
Data analyses, brainstorming **LFD**
Original insight and concept, data analyses **LEC**
Manuscript writing, ideas, data analyses **JK**

Financial support and Disclaimers:
No financial support and no other interests to disclaim.

Acknowledgments:
Hugo Cabrera for English revision and critics.

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Editor:
Prof. Dr. Paulo Henrique Manso

Received: feb 01, 2021
Approved: nov 24, 2021