Phylogeny and Pathogenesis of SARS-CoV-2: A Systematic Study

Larissa Amoroso da Silva[1], Luciana Estevam Simonato[2] and Rogério Rodrigo Ramos[2*]

[1]*Medical Student, Faceres - Medical School of São José do Rio Preto, SP, Brazil*

[2]*PhD, Medical School, Universidade Brasil, Fernandópolis, SP, Brazil*

Abstract: The SARS-CoV-2 is a member of the coronavirus family, they are genetically diverse single-stranded RNA viruses that rapidly evolve and mutate, commonly infecting humans. Due to the current coronavirus outbreak, the present study aimed to carry out an extensive review of the virus evolution, as well as the mechanisms which lead to the development of SARS-CoV-2. For this research, 469 studies were first selected and submitted to eligibility analysis, later, 164 studies were selected for a more careful evaluation and, at the end of this process, 52 studies were chosen to be discussed following the PRISMA guidelines for systematic reviews. Recent studies have shown that SARS-CoV-2 genome and the RaTG13 virus are more than 90% similar to each other, which indicates that the bat genome (Bat-SL-CoVZC45 and Bat-SL-CoVZXC21) and the pangolins genome (pangolin-CoV GD/P1L and pangolin-CoV GD/P2S) share the same human genome ancestry, therefore, these animals are considered responsible for spreading the new virus to humans, this eliminates the theory that SARS-CoV-2 was a lab-made virus. The infection starts when the virus binds itself to the ACE2 cell receptor and proliferates to nasal mucosa epithelial cells and type II pneumocytes, resulting in an increased amount of cytokines (IL-6, IL-10, and TNF-α) and a decreased amount of lymphocytes (CD4 + and CD8 + T cells).

Keywords: Coronavirus, COVID-19, Genome, Severity markers, Pathogenicity, Phylogenesis.

1. INTRODUCTION

Coronaviruses (CoV) are spherical particles ranging from 100nm to 160nm with four structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N). The virus was named because of its crown-like appearance due to the presence of viral spikes (S proteins) on the surface of the cell membrane, similar to a crown of thorns [1-4]. They commonly infect humans, especially the Alpha coronavirus 229E and NL63 and Beta coronavirus OC43 and HKU1. These viruses may cause mild and moderate respiratory infections, similar to a common cold. There are also the SARS-CoV and MERS-CoV, these coronaviruses can cause severe respiratory problems known as severe acute respiratory syndrome and the Middle East respiratory syndrome [5,6].

Coronaviruses are made of a positive single-stranded RNA-binding protein, ranging from 26kb to 32kb, which folds like an oligosaccharide. This protein may explain the unique and complex replication process of the coronavirus [7,8]. It is important to highlight that coronaviruses are widely spread, genetically diverse, and are frequently recombining their genomes, also, the increased interactions between humans and animals contribute to its periodical reappearance [9].

*Address correspondence to this author at the Projected Road F1 s/n, Santa Rita Farm, Medical School, Brazil University, Box: 15613-899, Fernandópolis, Brazil; Tel: 055(17)3465-4200; E-mail: rogerio.enfer@gmail.com

As a result, a new deadly coronavirus agent, SARS-CoV-2, was discovered on December 31st, 2019 in Wuhan, China [10]. The World Health Organization (WHO) has named it as COVID-19, which stands for "Coronavirus Disease 2019" [11]. On 30 January, 2020, the WHO declared a Public Health Emergency of International Concern, the Organization's highest level of alert, as established by the International Health Regulations. On 11 March, 2020, the SARS-CoV-2 was declared a world-class pandemic [12]. In Brazil, until mid-September 2020, there were millions of confirmed cases (4.534.98) and thousands of deaths (136.651) [13] which worsened the economic crisis in Brazil. Given the global pandemic scenario and little consolidated knowledge of the pathogenicity of the virus, the present study conducted a systematic review on the new coronavirus evolution, as well as the mechanisms which lead to the development of SARS-CoV-2.

2. METHODOLOGY

This paper proposes a systematic analysis conducted by collecting electronic scientific articles in the COCHRANE LIBRARY, PUBMED, and VIRTUAL HEALTH LIBRARY (VHL) databases, in addition to ordinances from the Ministry of Health, World Health Organization, Pan American Health Organization, and the National Health Surveillance Agency were searched using the keywords: coronavirus, COVID-19, genome, severity markers, pathogenicity, and phylogenesis, with the interposition of the Boolean operators "OR" and "AND".

E-ISSN: 2308-8044/20

The inclusion criteria were as follows: articles written in English or Portuguese; published within the last five years; fully available for download; they had to describe the phylogenetic properties and aspects of the pathogenesis of the new coronavirus. Then, in the end, 469 papers were submitted to eligibility analysis; 164 of those were selected for careful evaluation and 52 were included and discussed in this study, under the rules PRISMA guidelines (Figure **1**) [14].

One of the researchers (LAS) selected the journals, after this, the abstracts were evaluated, and a new exclusion method was decided by the same researcher. A second researcher (RRR) decided on the conflicting points and made the final decision on choosing the articles. Data extraction was reviewed by both researchers (LAS and LES).

3. LITERATURE REVIEW AND DISCUSSION

A considerable amount of literature has been published on the qualitative and quantitative data of the natural animal reservoir, viral particles, stages of infection, mechanisms of transmission, age group epidemiology, genome, and markers for SARS-CoV-2 (Figure **1**).

3.1. Origins and Viral Pathogenesis

Previous studies revealed that coronaviruses are naturally related to bats, indicating that the SARS-CoV-2 originated by a natural selection process and was transmitted to other animals and humans through the traffic of wild animals in the Huanan street market [15,16].

The infection usually occurs in three main stages. The first stage begins within 1 or 2 days when the virus binds itself to the epithelial cells in the nasal cavity and then replicates through the conductive airways by having a limited innate immune response. During the second stage, the individual is asymptomatic and has a relatively low viral load. In the following days (second phase), the virus spreads in the upper airway, causing a greater innate immune response. In the third stage, the virus infects type II cells causing cell apoptosis, which results in the release of particles, probably a self-replicating pulmonary toxin, that infects adjacent type II cells [17].

The pathological result is diffuse alveolar damage with hyaline membranes rich in fibrin and some multinucleated giant cells. Also, scarring and

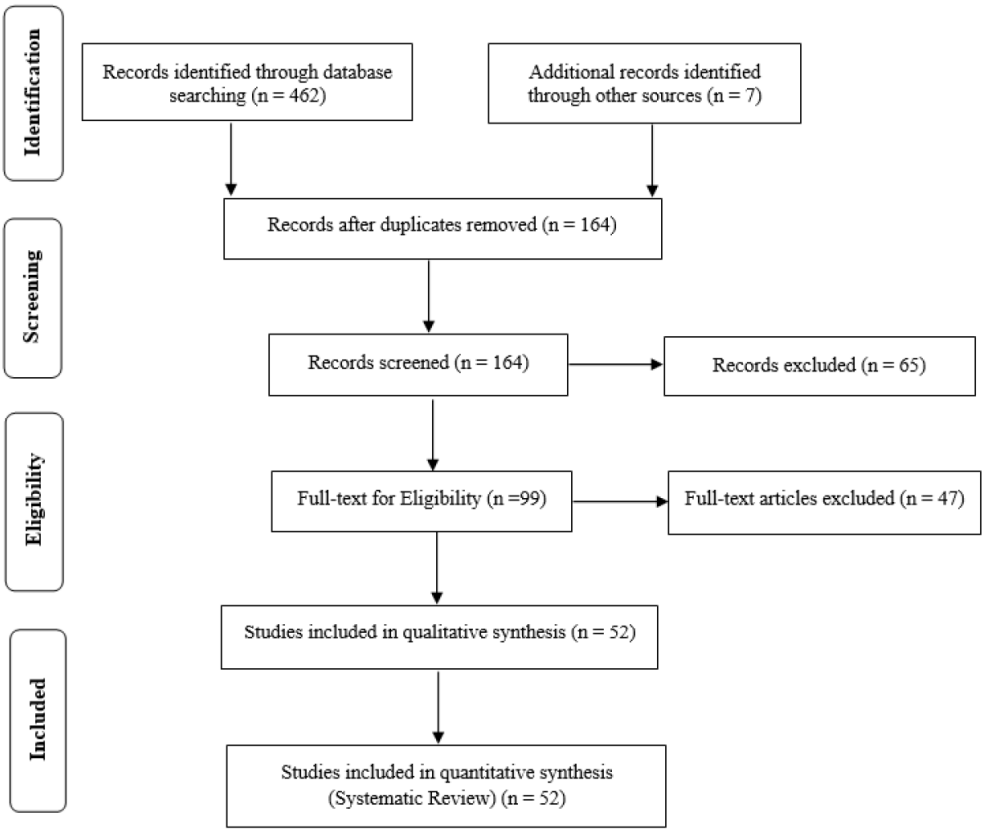

Figure 1: Flowchart.

pulmonary fibrosis are more severe than other acute respiratory distress syndromes (ARDS). The recovery requires a strong, innate, and acquired immune response and epithelial regeneration [17].

3.2. Persistence of the Virus in Body Fluids, Seasonality, and Transmission of SARS-CoV-2

The viral particles of SARS-CoV-2 can survive up to 3 hours in the air, 4 hours on copper, 24 hours on cardboard, and 72 hours on plastics and stainless steel [18]. In this context, it is necessary to consider that people can become infected by touching those surfaces, whether they are at home or even in a hospital and, as a result, they are the source of spreading the virus.

The studies conducted by Kampf *et al.* [19] indicate that the virus can survive on aluminum for 2 to 8 hours; on wood up to 4 days; on glass, metal, and ceramics for 5 days; on latex glove for 8 hours, and on a disposable apron for 2 hours. It is worth mentioning that the survival of the virus in these places depends on the type of surface, temperature, humidity [19].

Another aspect to highlight is the virus incubation period. In a study conducted by Qun *et al.* [20], the authors analyzed data from 425 patients and the findings suggested that the average incubation period is 5.2 days (95% CI, 4.1 to 7.0 days), with 95th percentile of distribution in 12.5 days. At the early stages, the epidemic doubled in size every 7.4 days, with an average serial interval of 7.5 days (95% CI, 5.3 to 19 days), the estimated basic reproductive number was 2.2 (95% CI, 1.4 to 3.9) [20].

Another study analyzed 181 confirmed cases and estimated an average incubation period of 5.1 days (95% CI, 4.5 to 5.8 days), with 97.5% of those patients developing symptoms within 11.5 days (CI, 8.2 to 15.6 days). Therefore, it is suggested that for every 1000 cases, 101 developed symptoms after 14 days of active monitoring or quarantine [21]. It is important to remember that asymptomatic or minimally symptomatic people are potential sources of SARS-CoV-2 [22].

As for the seasonal aspect, it is important to emphasize that the new coronavirus is more active during the winter, according to Dr. McGraw, professor of infectious diseases in the state of Penn, the droplets spread more quickly in cold and dry places [23]. However, Amesh Adalja, an infectious disease specialist, disagrees by arguing that the virus is not seasonal, because the virus's infectivity was not observed in the spring nor the summer [24]. Due to the context, little is known about seasonality, and therefore, it is too early to tell whether the new coronavirus is seasonal or not.

Transmission from animal to human is rare, but, given the circumstance, it is possible to happen. The virus mainly spreads from human to human through respiratory droplets from coughing, sneezing, and talking [25].

SARS-CoV-2 starts when some viral and structural proteins bind to porphyrin, shortly after, the proteins ORF1ab, ORF10 and ORF3a attack the heme on the 1-beta hemoglobin chains causing iron dissociation. Such an attack reduces the amount of hemoglobin, which carries oxygen, making lung cells toxic and inflammatory, causing symptoms such as respiratory distress and ground-glass opacification, and severe acute respiratory syndrome [26,27].

According to Hoffmann *et al.* [28], the binding of SARS-CoV-2 to the cell receptor ACE2 (angiotensin-converting enzyme 2) is activated by the human transmembrane serine protease II (TMPRSS2) on the cell surface. This link is explained by the S1 subunit of the S protein (spike protein) on the surface of host cells. In addition, cleavage of protein S happens on the S1/S2 and S2', resulting in the fusion between viral and cellular membranes. The hypothesis is that the SARS-CoV-2 targets cells depending on the ACE2 receptor and enzymes, which break down amino acids peptide bonds [28].

3.3. Pathogenic Comorbidities and Morbidities for Different Age Groups

The mortality rate of SARS-CoV-2 is higher in older age groups, because of underlying medical conditions [29]. It should be noted that children with hematological tumors are amenable to coronavirus infection due to immunosuppression and special therapeutic characteristics [30].

However, patients in advanced age and with a medical history of comorbidities, cancer, immunosuppression, and/or high ACE2 gene expression are at a greater risk of dying from SARS-CoV-2. Most of the infectivity occurs due to the virus interacting with ACE2, an enzyme highly expressed in human tissues. In China, the mortality rate of patients infected with SARS-CoV-2 is 2.3%, the rate in cancer patients is 28.6%, therefore, they are 3.5 times more likely to need mechanical ventilation or to be admitted

to the Intensive Care Unit, when compared to the general population [31].

Cancer patients have multiple risk factors that increase the chances of infections since they are immunocompromised from underlying malignancy or antineoplastic therapy [32]. A study conducted by Dai *et al.* [33] analyzed 105 cancer patients and 536 cancer-free patients of the same age, who were positive for SARS-CoV-2, the findings indicated that cancer patients have more risks. Also, individuals with hematological, lung, or metastatic cancer (stage IV), have a higher severity rate [33].

3.4. Genome and Severity Markers

When comparing the SARS-CoV-2 genome with typical CoVs, they present at least ten similar open reading frames (ORFs); both SARS-CoV-2 and SARS-CoV use ACE2 to enter the host cell, however, MERS-CoV binds itself to DPP4 [4].

The studies conducted by Guo *et al.* [34] compared the sequencing of the SARS-CoV-2 genome to the RaTG13 and found a 96.2% of similarity, this suggests that the bat genome (Bat-SL-CoVZC45 and Bat-SL-CoVZXC21) [35] and the human genome may share a common ancestor. In addition, by aligning protein sequences and phylogenetic analysis, it was observed similar receptor residues in many species, indicating that there is a possibility of alternative intermediate hosts, such as turtles, pangolins, and snakes. Another important factor is that SARS-CoV-2 ranges from 85.5 to 92.4% of genomic similarity in pangolins (pangolin-CoV GD / P1L and pangolin-CoV GD / P2S), which is sold illegally in China (2,34,36).

The severity of SARS-CoV-2 is related to markers such as high levels of cytokines (IL-6, IL-10, and TNF-α) known as “cytokine storm”, lymphopenia (in CD4 + and CD8 + T cells), and reduced expression of IFN-γ in CD4 + T cells [37].

On a different study, Liu *et al.* [38] analyzed complete blood counts from 12 patients, seven of them were over 60 years and infected with 2019-nCov, six of them had hypoalbuminemia (below 40g/L), lymphopenia (CD4 - 2 patients below 34 counts μ/L), low lymphocytes count (LYM - 6 patients below 1.10×109/L) and neutrophils (NEU - 8 patients below 3.8×109/L), high reactive C protein (CRP - 2 patients below 10mg/L) and lactate dehydrogenase (LDH - all patients above 240 U/L) and low CD8 count (7 patients were below 21 counts t μ/L). In one of these patients, with severe lung disease, a higher viral load was detected. It is, therefore, possible to assume that all the conditions mentioned above contribute to higher pathological severity [3].

Another important factor to highlight was that people with SARS-CoV-2, confirmed by PCR test, presented seroconversion two weeks after being infected. In addition, the ELISA IgA test has sensitivity results when compared to ELISA IgG [39]. So far, coronavirus can be tested by using genetic material (RNA) or virus antigens (RT-PCR - Reverse Transcription - Polymerase Chain Reaction), antibodies such as IgM and IgG, blood, serum, plasma, and/or secretions from the respiratory tracts of nasopharynx and oropharynx [40].

3.5. A Brief Report on Liver Injury

Recent studies have found evidence of SARS-CoV-2 on stool and blood samples, suggesting a possibility of viral exposure in the liver [41]. The expression of ACE2 in the liver (cholangiocytes and hepatocytes) suggests that the SARS-CoV-2 can bind itself directly to cholangiocytes with ACE2 in the liver parenchyma, compromising its function [42]. Therefore, it possible to assume that patients infected with SARS-CoV-2 may also develop liver damage.

Regarding the aspects of liver injury, it is important to highlight that it is a complex disease, with characteristics associated with drug-induced liver injury (DILI) [43] and herb-induced liver injury (HILI) [44]. It is also worth mentioning that these conditionals also have an intrinsic and idiosyncratic background.

The pathogenic aspects related to idiosyncratic liver injury occur regardless of the dose (drugs and herbs) applied, and are very difficult to predict, on the other hand, an intrinsic liver injury does not share these characteristics [45-48]. Chen *et al*. [49] suggest two mechanistic features of idiosyncratic liver damage, the first being inflammation caused by drug-induced cytotoxicity, and the other is the immune response via antigen-presenting cells and / or auxiliary T cells. In addition, other properties and factors may play a fundamental role in different functional pathways, individual susceptibility, and clinical phenotype [49].

Clinically speaking, liver injury can be analyzed by many kinds of biochemical tests. However, it is important to highlight the Roussel Uclaf Causality Assessment Method (RUCAM). Danan and Teschke [43] recommend the use of RUCAM to assess cases of

DILI and HILI. The authors explain that RUCAM takes into account all the essential elements of hepatotoxicity induced by drugs and plants. They also report that this is a well-known and validated method for hepatotoxin chemicals and essential in assessing liver injuries, by quantifying the strength of association between a liver injury and the medication implicated as the cause of the injury.

It is also necessary to consider RUCAM as an assessment tool of liver injury in patients infected with COVID-19, analyzing whether the injury is caused by the virus, other factors, or by potentially hepatotoxic substances. Since acute respiratory syndrome is a serious condition, SARS-CoV-2 may be associated with liver dysregulation and liver injury [44,50-52].

4. CONCLUSION

After genomic comparisons, it is possible to conclude that SARS-CoV-2 is related to the CoV found in bats (CoVZC45 and CoVZXC21) and pangolins (GD/P1L and GD/P2S). Transmission from animal to human is rare, however, it is much more frequent from human to human, it can spread by coughing, sneezing, and talking. The infection starts after the virus binds itself to the ACE2 cell receptor and sequentially proliferates to the nasal cavity epithelial cells and type II pneumocytes, resulting in an increased amount of cytokines (IL-6, IL-10, and TNF-α) and a reduced amount of lymphocytes (CD4 + and CD8 + T cells). The risk of severity is higher in elderly patients and patients presenting a history of comorbidities, cancers, immunosuppression, and/or high ACE2 gene expression.

FUNDING

There was no funding for this study.

ACKNOWLEDGEMENT

We would like to thank our colleagues of Universidade Brasil who contributed to the development of the research.

POTENTIAL CONFLICT OF INTEREST STATEMENT

The authors declare to have no conflict of interest.

REFERENCES

[1] Zheng Y, Shang J, Yang Y, *et al.* Lysosomal proteases are a determinant of coronavirus tropism. J Virol 2018; 92: 1-14. https://doi.org/10.1128/JVI.01504-18

[2] Malik YA. Properties of coronavirus and SARS-CoV-2. Malaysian J Pathol 2020; 42: 3-11. Available from: https://pubmed.ncbi.nlm.nih.gov/32342926/

[3] Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res 2020; 24: 91-8. https://doi.org/10.1016/j.jare.2020.03.005

[4] Xiaowei L, Manman G, Yizhao P, *et al.* Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Analysis 2020; 10: 102-08. https://doi.org/10.1016/j.jpha.2020.03.001

[5] Yang YJ, Hu YW. Molecular epidemiological study of human coronavirus OC43 in Shanghai from 2009-2016. Zhonghua Yu Fang Yi Xue Za Zhi 2018; 52: 55-61. https://doi.org/10.3760/cma.j.issn.0253-9624.2018.01.011

[6] De Sabato L, Lelli D, Faccin F, *et al.* Full genome characterization of two novel Alpha-coronavirus species from Italian bats. Virus Res 2019; 260: 60-6. https://doi.org/10.1016/j.virusres.2018.11.007

[7] Su S, Wong G, Shi W, *et al.* Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends Microbiology 2016; 24: 490-502. https://doi.org/10.1016/j.tim.2016.03.003

[8] Walls AC, Park YJ, M. Tortorici MA, *et al.* Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 2020; 181: 281-92. https://doi.org/10.1016/j.cell.2020.02.058

[9] Zhu N, Zhang D, Wang W, *et al.* A Novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382: 727-33. https://doi.org/10.1056/NEJMoa2001017

[10] Lana RM, Coelho FC, Gomes MFC, *et al.* The novel coronavirus (SARS-CoV-2) emergency and the role of timely and effective national health surveillance. Cad Saude Publica 2020; 36: e00019620. https://doi.org/10.1590/0102-311x00019620

[11] Organização Pan-Americana da Saúde (OPAS). OMS anuncia nome para doença causada por novo coronavírus: COVID-19; OPAS apoia ações de preparo na América Latina e Caribe. February 2020. Available from: https://www.paho.org/

[12] Organização Pan-Americana da Saúde (OPAS). Folha informativa – COVID-19 (doença causada pelo novo coronavírus). April 2020. Available from: https://www.paho.org/

[13] Brasil. Ministério da Saúde. Coronavírus//Brasil. Covid-19 painel coronavírus. Available from: https://covid.saude.gov.br/

[14] Shamseer L, Moher D, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015; 349: g7647. https://doi.org/10.1136/bmj.g7647

[15] Duarte PM. COVID-19: Origem do novo coronavírus. Braz J Hea Rev 2020; 3: 3585-590. https://doi.org/10.34119/bjhrv3n2-187

[16] Agência Nacional de Vigilância Sanitária (ANVISA). Teste para Covid-19: perguntas e respostas. 2020. Available from: http://portal.anvisa.gov.br

[17] Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. ERJ 2020; 55: 2000607. https://doi.org/10.1183/13993003.00607-2020

[18] Doremalen NV, Bushmaker T, Morris DH, *et al.* Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med 2020; 382: 1564-567. https://doi.org/10.1056/NEJMc2004973

[19] Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. J Hosp Infect 2020; 104: 246-51. https://doi.org/10.1016/j.jhin.2020.01.022

[20] Qun L, Xuhua G, Peng W, *et al*. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020; 382: 1199-207. https://doi.org/10.1056/NEJMoa2001316

[21] Lauer SA, Grantz KH, Bi Q, *et al.* The incubation period of coronavirus disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med 2020; 172: 577-82. https://doi.org/10.7326/M20-0504

[22] Rothe C, Schunk M, Sothmann P, *et al*. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. N Engl J Med 2020; 382: 970. https://doi.org/10.1056/NEJMc2001468

[23] Khan S, Ali A, Siddique R, Nabi G. Novel coronavirus is putting the whole world on alert. J Hosp Infect 2020; 104: 252-53. https://doi.org/10.1016/j.jhin.2020.01.019

[24] Huang X, Wei F, Hu L, Wen L, Chen K. Epidemiology and clinical characteristics of COVID-19. Arch Iran Med 2020; 23: 268-71. https://doi.org/10.34172/aim.2020.09

[25] Coronavirus Disease 2019 (COVID-19) Animais e COVID-19. Centers for Disease Control and Prevention. 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/animals.html

[26] Wenzhong L, Hualan L. COVID-19: Attacks the 1-Beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. ChemRxiv 2020; 1-31. https://doi.org/10.26434/chemrxiv.11938173.v6

[27] Huang C, Wang Y, Li X, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506. https://doi.org/10.1016/S0140-6736(20)30183-5

[28] Hoffmann M, Webe HK, Schroeder S, *et al.* SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020; 181: 217-80. https://doi.org/10.1016/j.cell.2020.02.052

[29] Natale F, Ghio D, Tarchi D, Goujon A, Conte A. COVID-19 cases and case fatality rate by age. European Commission 2020; 1-18.

[30] Subspecialty Group of Hematology and Oncology, Society of Pediatrics of Hubei. [Standardized management guideline for pediatric wards of hematology and oncology during the epidemic of coronavirus disease 2019]. Zhongguo Dang Dai Er Ke Za Zhi 2020; 22: 177-82. https://doi.org/10.7499/j.issn.1008-8830.2020.03.001

[31] Gosain R, Abdou Y, Singh A, Rana N, Puzanov I, Ernstoff MS. COVID-19 and cancer: a comprehensive review. Curr Oncol Rep 2020; 22: 53. https://doi.org/10.1007/s11912-020-00934-7

[32] Shamsi HOA, Alhazzani W, Alhuraiji A, *et al.* A practical approach to the management of cancer patients during the novel coronavirus disease 2019 (COVID-19) Pandemic: An International Collaborative Group. The Oncologist 2020; 25: e936-e945. https://doi.org/10.1634/theoncologist.2020-0213

[33] Dai M, Liu D, Liu M, *et al.* Patients with cancer appear more vulnerable to SARS-CoV-2: A Multicenter Study during the COVID-19 Outbreak. Cancer Discov 2020; 10: 783-91. https://doi.org/10.1158/2159-8290.CD-20-0422

[34] Guo YR, Cao QD, Hong ZS, *et al.* The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. Military Med Res 2020; 7: 11. https://doi.org/10.1186/s40779-020-00240-0

[35] Roujian L, Xiang Z, Juan L, *et al*. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020; 395: 565-74. https://doi.org/10.1016/S0140-6736(20)30251-8

[36] Lam TTY, Jia N, Zhang YW, *et al.* Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins. Natura 2020; 583: 282-98. https://doi.org/10.1038/s41586-020-2169-0

[37] Pedersen SF, Ho YC. SARS-CoV-2: a storm is raging. JCI 2020; 130: 2202-05. https://doi.org/10.1172/JCI137647

[38] Liu Y, Yang Y, Zhang C, *et al*. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci 2020; 63: 364-74. https://doi.org/10.1007/s11427-020-1643-8

[39] Okba NMA, Müller MA, Li W, *et al*. Severe acute respiratory syndrome coronavirus 2-specific antibody responses in coronavirus disease patients. Emerg Infect Dis 2020; 26: 1478-88. https://doi.org/10.3201/eid2607.200841

[40] Agência Nacional de Vigilância Sanitária (ANVISA). Nota Técnica GVIMS/GGTES/ANVISA Nº 04/2020. Orientações para serviços de saúde: medidas de prevenção e controle que devem ser adotadas durante a assistência aos casos suspeitos ou confirmados de infecção pelo novo coronavírus (SARS-CoV-2). March 2020. Available from: http://portal.anvisa.gov.br

[41] Yeo C, Kaushal S, Yeo D. Enteric involvement of coronaviruses: is faecal-oral transmission of SARS-CoV-2 possible? Lancet Gastroenterol Hepatol 2020; 5: 335-7. https://doi.org/10.1016/S2468-1253(20)30048-0

[42] Gheblawi M, Wang K, Viveiros A, *et al.* Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: Celebrating the 20th anniversary of the discovery of ACE2. Circ Res 2020; 126: 1456-74. https://doi.org/10.1161/CIRCRESAHA.120.317015

[43] Danan G, Teschke R. RUCAM in Drug and herb induced liver injury: The update. Int J Mol Sci 2016; 17: 14. https://doi.org/10.3390/ijms17010014

[44] Teschke R, Zhu Y, Jing J. Herb-induced liver injury in Asia and current role of RUCAM for causality assessment in 11,160 published cases. J Clin Transl Hepatol 2020; 8: 200-14. https://doi.org/10.14218/JCTH.2020.00009

[45] Danan G, Teschke R. RUCAM in drug and herb induced liver injury: the update. Int J Mol Sci 2015; 17: 14. https://doi.org/10.3390/ijms17010014

[46] Sarges P, Steinberg JM, Lewis JH. Drug-induced liver injury: highlights from a review of the 2015 literature. Drug Saf 2016; 39: 801-21. https://doi.org/10.1007/s40264-016-0427-8

[47] Teschke R, Andrade RJ. Drug, herb, and dietary supplement hepatotoxicity. Int J Mol Sci 2016; 17: 1488. https://doi.org/10.3390/ijms17091488

[48] Teschke R, Larrey D, Melchart D, Danan G. Traditional chinese medicine (TCM) and herbal hepatotoxicity: RUCAM and the role of novel diagnostic biomarkers such as microRNAs. Medicines 2016; 3: 18. https://doi.org/10.3390/medicines3030018

[49] Chen M, Suzuki A, Borlak J, Andrade RJ, Lucena MI. Drug-induced liver injury: Interactions between drug properties and host factors. J Hepatol 2015; 63: 503-14. https://doi.org/10.1016/j.jhep.2015.04.016

[50] Jing J, Wang RL, Zhao XY, *et al*. Association between the concurrence of pre-existing chronic liver disease and worse prognosis in patients with an herb- Polygonum multiflorum thunb. induced liver injury: a case-control study from a specialised liver disease center in China. BMJ Open 2019; 9: e023567. https://doi.org/10.1136/bmjopen-2018-023567

[51] Shen T, Liu Y, Shang J, *et al*. Incidence and etiology of drug-induced liver injury in mainland China. Gastroenterology 2019; 156: 2230-41. https://doi.org/10.1053/j.gastro.2019.02.002

[52] Teschke R. Idiosyncratic DILI: Analysis of 46,266 cases assessed for causality by RUCAM and published from 2014 to early 2019. Front Pharmacol 2019; 10: 730. https://doi.org/10.3389/fphar.2019.00730

Received on 28-08-2020 Accepted on 24-09-2020 Published on 02-10-2020

DOI: https://doi.org/10.12970/2308-8044.2020.08.06