# SARS-CoV-2, a possible new oncovirus?

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## Abstract

CA 72-4 is a tumor marker associated with gastrointestinal, lung and ovarian tumors. The analysis of tumor markers is not usual in COVID-19, since there is no established relationship between SARS-CoV-2 infection and the development of tumors, but data suggest that 15 percent of all human cancers worldwide may be attributed to viruses. Changes in Ca 72-4 levels were observed in individuals with COVID-19, suggesting a possible oncogenic characteristic of the virus, requiring further attention and investigation.

**Background:** Since the arrival of a new type of coronavirus in December 2019 in Wuhan, China, the world has undergone changes due to the pandemic impact caused by the virus. SARS-CoV-2 is mainly related to lung involvement, but gastrointestinal complaints, such as vomiting and diarrhea, have also been reported.
**Methods:** We brought a series of cases of patients seen in Brazil, infected by SARS-CoV-2, who had high levels of CA 72.4 during the course of the infection, suggesting a possible oncogenic characteristic of the virus under study.

**Results:** The described group showed relevant variations in the levels of the tumor marker CA 74-2 after infection by the SARS-CoV-2 virus. The minor variation of the tumor marker was 4% and the highest observed, 7146%.

**Conclusions:** Considering that some viruses can induce the tumor process, the analysis of tumor markers after viral infection can be a useful tool in assessing the possible impact on post-pandemic global health scenario.

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## Background

In December 2019, in the Chinese province of Wuhan, a new type of coronavirus was identified in patients, characterized by a picture of atypical pneumonia composed of fever, dry cough and progressive dyspnoea.[1] In addition to respiratory symptoms, gastrointestinal complaints such as vomiting and diarrhea have also been reported with high frequency.[2] Quickly, this coronavirus has spread around the world, leading to a high impact pandemic worldwide.[3] It is known that SARS-CoV-2 enters cells through the angiotensin-converting enzyme receptor 2 (ACE2). Its expression was mainly mapped to the luminal surface of differentiated epithelial cells of the small intestine and is responsible for the key regulation of homeostasis of the intestinal microbiota.[4] A regulated intestine, among its functions, is to secrete mucus in order to lubricate and protect epithelial surfaces.[5] Mucus is composed of water, inorganic salts, immunoglobulins, proteins and mucins. Mucins are the most abundant macromolecules in mucus and are responsible for the biochemical and biophysical properties of mucus. The genes that code for the protein component of mucin are referred to as MUCs. MUC1 is a membrane-bound mucin, highly expressed in the apical membranes of the bronchial epithelium and in the gastrointestinal tract, including the colon. MUC5AC is a secretory mucin and is expressed mainly in the gastric and tracheobronchial lining.[6] Under tumor conditions, glycosylated mucins are aberrantly overexpressed by tumors and secreted in the circulation of cancer patients, serving as a tumor marker. CA 72.4, also known as TAG-72, is a glycoprotein complex with mucinic properties and is strongly used as a tumor marker to control remission and recurrence of gastrointestinal tract carcinomas.[7] The present study presents a case series approach of patients infected with COVID-19 who presented high levels of marked CA 72.4 during the course of the infection. The aim of the study is to highlight the possibility that the SARS-CoV-2 virus has an oncogenic potential.

## Methods

We retrospectively evaluated all analyzes of laboratory tests in our health service, carried out from October 10 to November 20, 2020, in search of the investigation of tumor biomarker CA 72.4 during infection by COVID-19.

Eleven patients (from a dataset of 37 subjects) met the inclusion criteria, which were standardized for individuals with no previous history of gastrointestinal pathologies or malignancies. Of the patients evaluated, six were male and five were female. The average age was 42 years, ranging from 22 to 58 years. All patients tested positive for the real-time polymerase chain reaction (RT-PCR) test using a nasopharyngeal swab sample. During the course of the infection, laboratory tests were collected, among them, the tumor marker CA 72-4, which showed a significant change (upper limit of the normal range 6.9 U/mL). The most frequent gastrointestinal symptoms were abdominal pain, diarrhea, nausea, vomiting and lack of appetite. The laboratory data regarding the alteration of CA 72-4 can be seen in **Table 1.**

**Table 1.** Laboratory data of Ca 72-4 in patients infected with SARS-CoV-2. The upper limit of the normal range for CA 72-4 is 6.9 U/mL.

| Pacient | Gender | Age | CA-72.4 (U/mL) |
|---|---|---|---|
| 1. 1. | M | 39 | 87,1 |
| 1. 2. | M | 41 | 186,0 |
| 1. 3. | M | 39 | 87,1 |
| 1. 4. | M | 58 | 11,4 |
| 1. 5. | M | 48 | 31,3 |
| 1. 6. | M | 51 | 23,9 |
| 1. 7. | F | 39 | 7,2 |
| 1. 8. | F | 36 | 500,0 |
| 1. 9. | F | 33 | 278,0 |
| 1. 10. | F | 55 | 7,3 |
| 1. 11. | F | 25 | 17,10 |

## Results

Changes in the levels of the tumor marker CA 74-2 occurred regardless of the gender of the patients, as can be seen in figure 1. The standard deviation of all patients was 154,97 and the mean was 112,4 U/mL, much higher value than the appropriate value for the marker (table 2), with the higher variation reaching 500 U/mL (figure 2) representing 7146% of the normal level of CA 72-4 (figure 3).

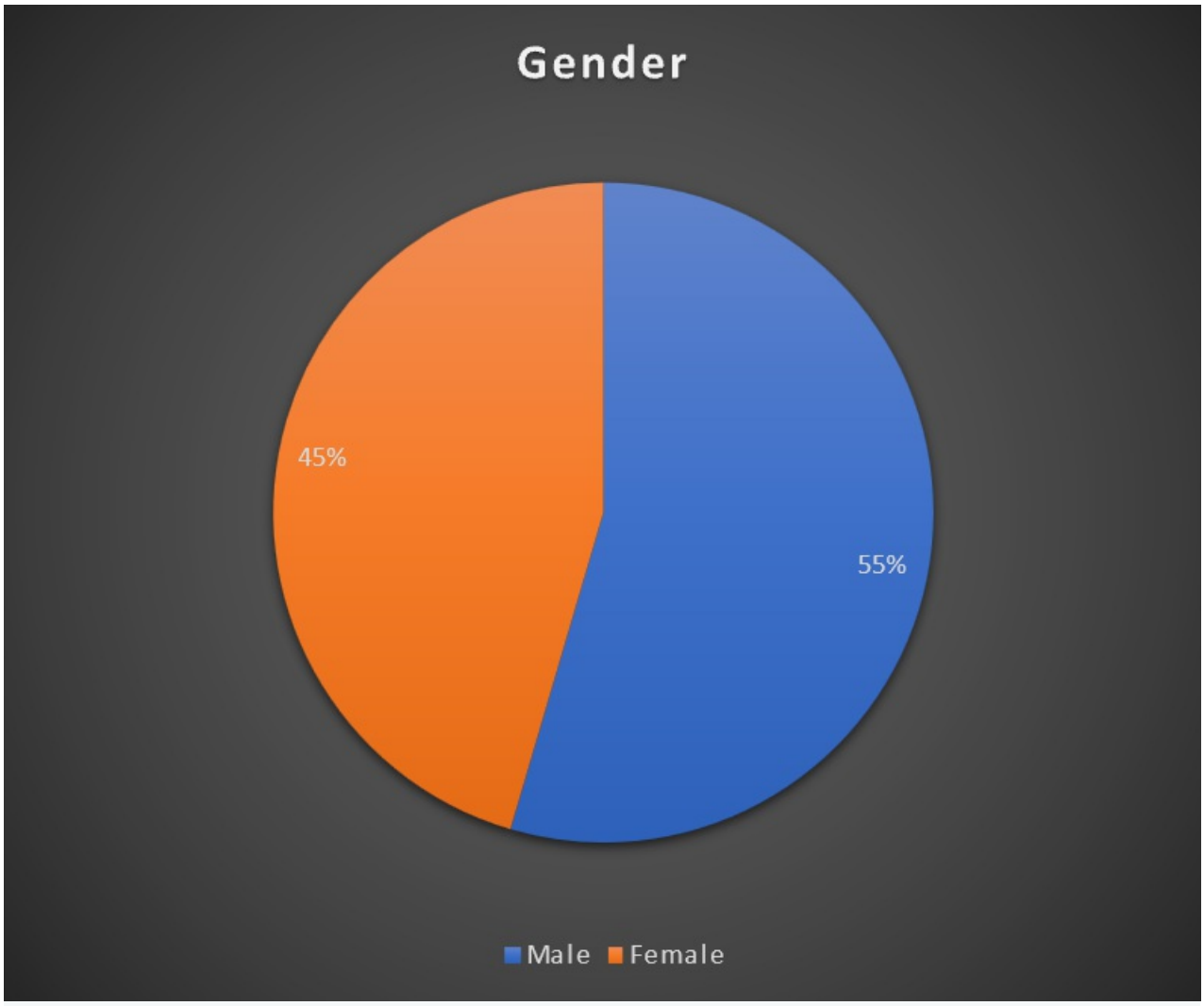


**Figure 1.** Representation by gender, female (orange) and male (blue), of patients who showed changes in the biochemical levels of Ca72.4

| Patient | Gender | Age | CA-72.4 (U/mL) | % related to 6.9 | Is above 6.9? |
|---|---|---|---|---|---|
| 1. | Male | 39 | 87,1 | 1162% | Yes |
| 2. | Male | 41 | 186 | 2596% | Yes |
| 3. | Male | 39 | 87,1 | 1162% | Yes |
| 4. | Male | 58 | 11,4 | 65% | Yes |
| 5. | Male | 48 | 31,3 | 354% | Yes |
| 6. | Male | 51 | 23,9 | 246% | Yes |
| 7. | Female | 39 | 7,2 | 4% | Yes |
| 8. | Female | 36 | 500 | 7146% | Yes |
| 9. | Female | 33 | 278 | 3929% | Yes |
| 10. | Female | 55 | 7,3 | 6% | Yes |
| 11. | Female | 25 | 17,1 | 148% | Yes |
| **Mean** | | **42,18** | **112,4** | **1529%** | |
| **St. Dev** | | **9,877** | **154,97** | **2246%** | |

**Table 2.** Analysis of patient data included in the study, with the variation (%) of CA 74-2 levels from the reference value (6.9 U / mL)

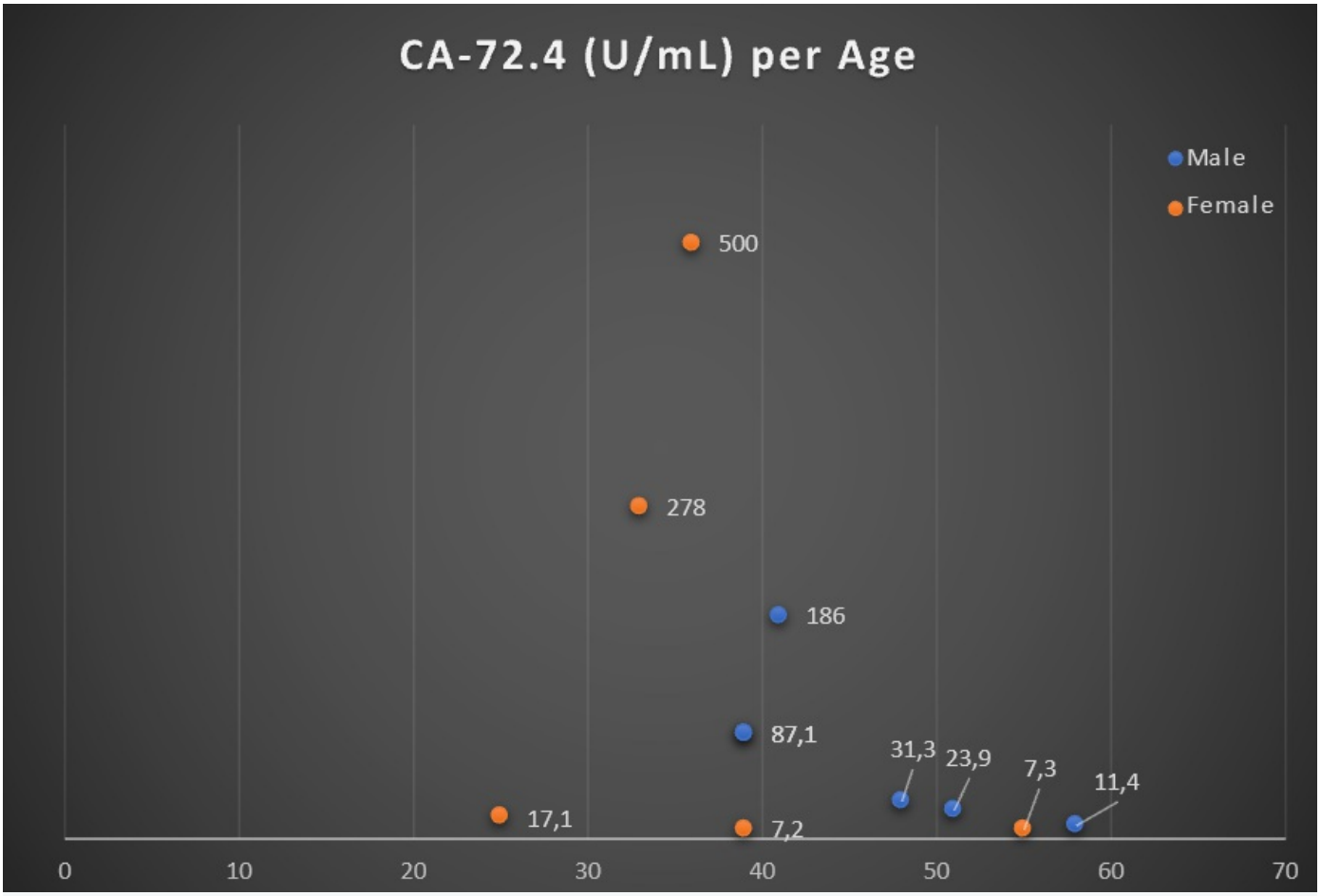


**Figure 2.** Representation of Ca 72.4 levels in U/mL, in patients described by female and male gender according to age group

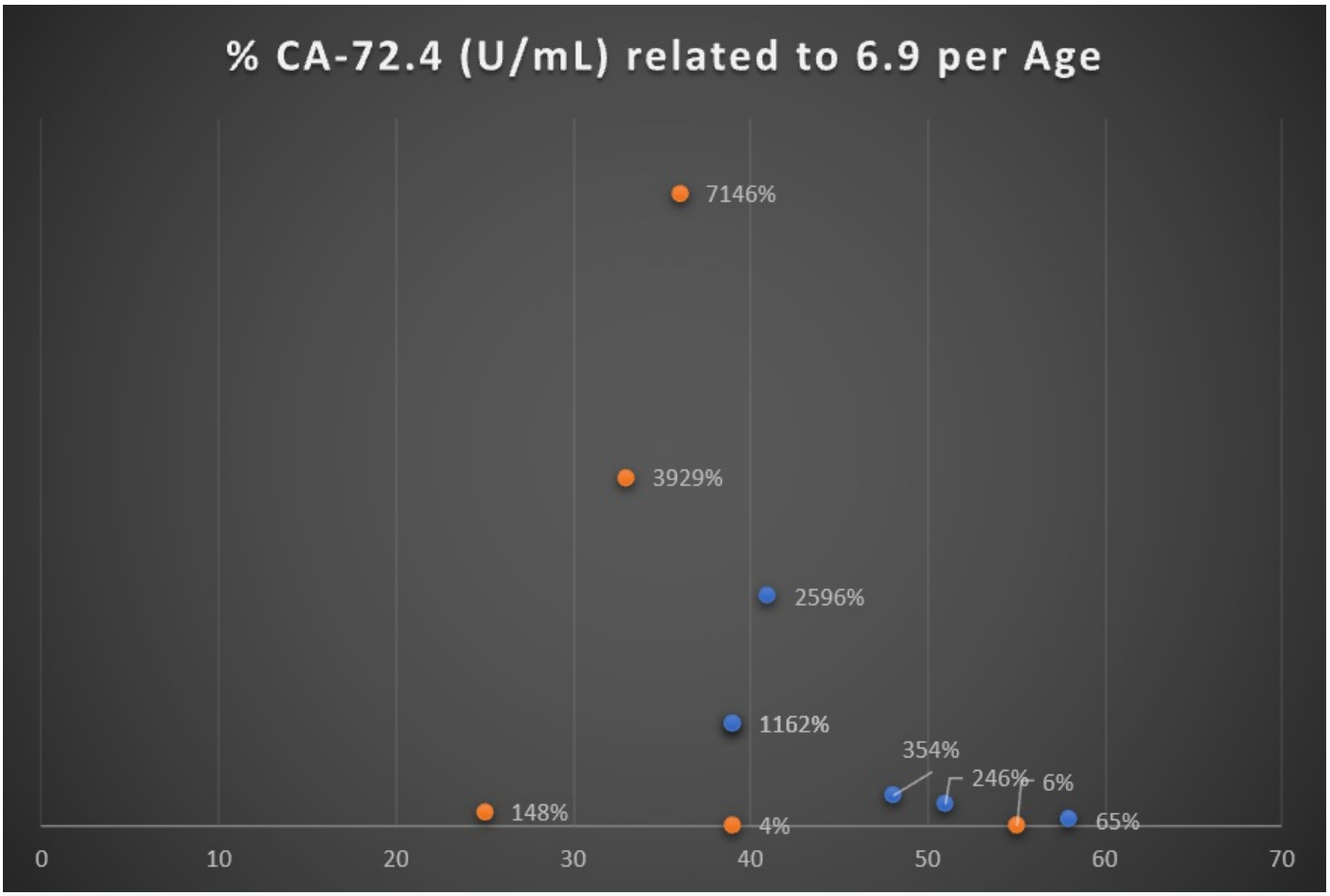


**Figure 3.** Representation of the percentage of variation, in relation to the normal value of the CA 72.4 marker

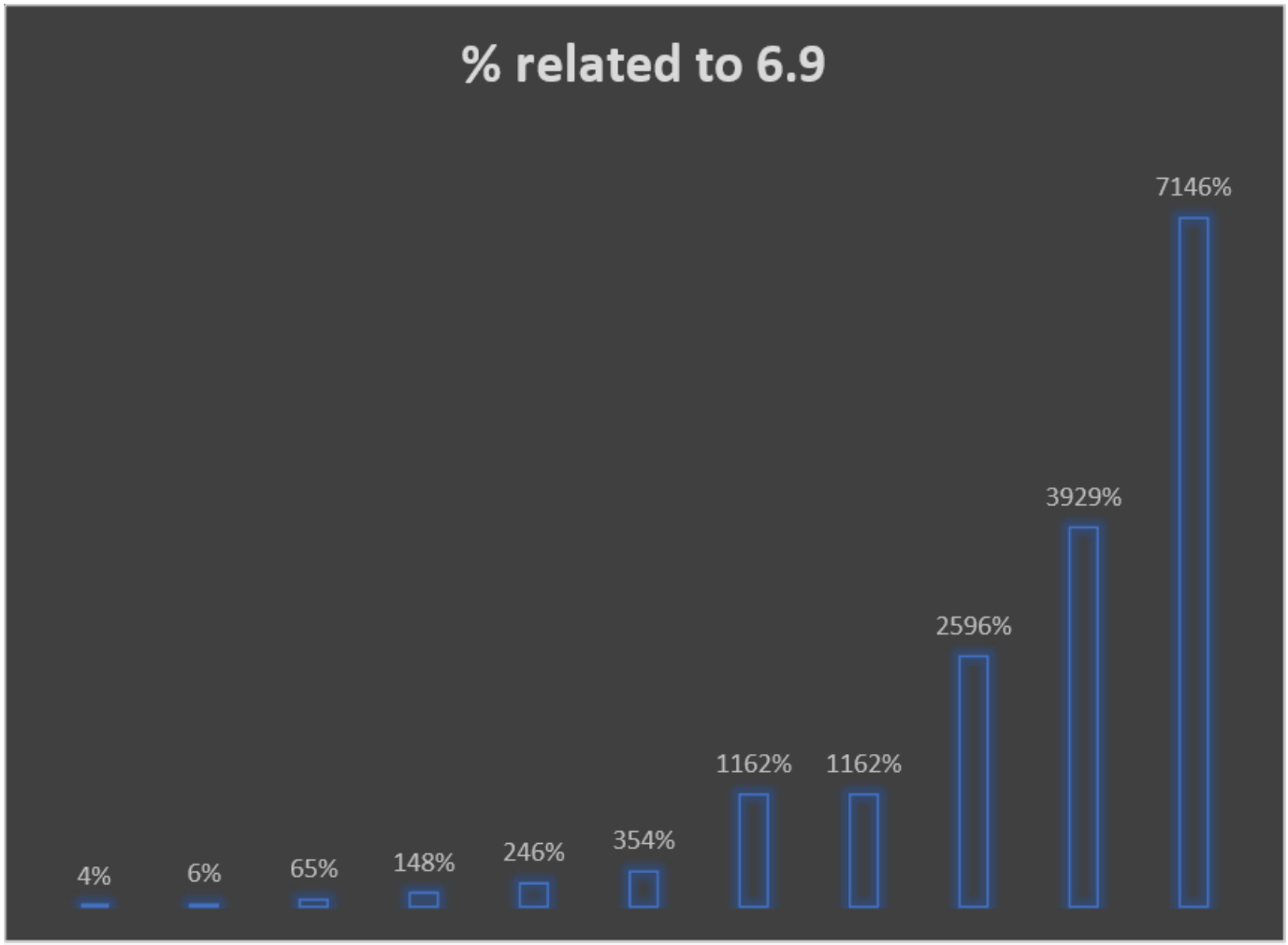


**Figure 4.** Description of the range of variations observed in the study patients

## Discussion

Control of the pandemic has become a global emergency since the outbreak in China began, and with the advancement of the new coronavirus pandemic, there was an opening to elucidate greater opportunities to explore new insights into COVID-19 laboratory variations. Common laboratory biomarkers have been used to better track the disease and are also useful to assist in clinical management and prevention of serious complications. Some of these biological markers used to assess viral infection are hematological (lymphocyte count, neutrophil count), inflammatory (C-reactive protein, erythrocyte sedimentation rate, procalcitonin), immunological and biochemical (D-dimer, troponin, creatine kinase, aspartate aminotransferase).[8]

All of these markers are usually altered in the clinical picture of COVID-19, but other markers are gaining attention, mainly because they present many unspecific changes. The analysis of tumor markers is not usual in COVID-19, since there is no relationship studied, until now, of how the analysis of these markers can be useful in the clinical case of the disease. In the year 2020, in an analysis made by Wenju Lu et al.[9] an alteration of the mucin proteins, MUC5AC AND MUC1, was observed in the airway mucus of a patient with COVID-19 in critical condition. Mucins, under tumor conditions, are hyperstimulated and secreted into the circulation, being detected by antibodies in patient sera, serving as a tumor

marker.[10]

## Conclusions

In the present study, we brought a case series of eight patients, who were infected with SARS-CoV-2 and had a high level of tumor marker CA 72-4. The link between viral infections and cancer began in 1900, when scientists discovered that a virus in a tumor found in a chicken could be transmitted to other chickens.[11] From this, the concept of oncovirus was created, that is, viruses that have the ability to induce the development of some tumor. Considering that ACE2 as the gateway to SARS-CoV-2, we elucidate the hypothesis of ACE2 interaction with the virus, providing a negative impact on the control of intestinal microbiota, leading to alteration of intestinal mucins, through cellular hyperexpression, which would respond to the present increase in tumor marker CA 72-4 in patients infected with the SARS-CoV-2 virus. To date, there are seven known oncoviruses, would SARS-CoV-2 be a possible candidate to qualify as the eighth on the list?

## Declarations

### Competing interests

The authors declare no conflict of interest.

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### Authors' Contributions

R.S, Knack interpreted the results and researched; T.Z, Hanada wrote the manuscript and researched; R.K Silvestre designed and analyzed; S. Dana performed the statistical analysis; G.L, Afonso reviewed the data; T.O, Omena reviewed the content; R.E.S, Knack reviewed the content.

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