Short Communication

Dzemaal Elezagic*, Wibke Johannis, Volker Burst, Florian Klein and Thomas Streichert

Venous blood gas analysis in patients with COVID-19 symptoms in the early assessment of virus positivity

<https://doi.org/10.1515/labmed-2020-0126>

Received October 27, 2020; accepted December 14, 2020;

published online December 25, 2020

Abstract

Objectives: Coronavirus disease 2019 (COVID-19) is currently a worldwide major health threat. Recognizing hypoxia in patients early on can have a considerable effect on therapy success and survival rate.

Methods: We collected data using a standard blood gas analyzer from 50 patients and analyzed measurements of partial pressure of carbon dioxide- $p\text{CO}_2$, partial pressure of oxygen- $p\text{O}_2$ and oxygen saturation- sO_2 , bicarbonate concentrations- HCO_3^- as well as ionized calcium concentrations. We further examined PCR test results for SARS-CoV-2 of the patients and analyzed differences between patients tested positive and those tested negative for the virus.

Results: Venous $p\text{CO}_2$ was significantly higher whereas $p\text{O}_2$ and sO_2 were significantly lower in patients who tested positive for SARS-CoV-2. The pH, and ionized calcium

concentrations of patients tested positive for the virus were significantly lower than in those tested negative.

Conclusions: Symptomatic SARS-CoV-2-positive patients upon admission to the emergency room exhibit lower venous blood levels of oxygen, pH, and calcium and higher levels of carbon dioxide compared to symptomatic SARS-CoV-2-negative patients. This blood gas analysis constellation could help in identifying SARS-CoV-2-positive patients more rapidly and identifying early signs of hypoxia.

Keywords: blood gas analysis; COVID-19; silent hypoxia.

Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) is the virus strain causing coronavirus disease 2019 (COVID-19), which was officially declared as a pandemic on 11 March 2020 [1]. Over 200 countries have reported cases of the disease, with over 1.3 million deaths to date, as of 20.11.2020 (World Health Organization). Although the transmissibility and case fatality rate vary between countries, the median reproduction number (R_0) reported is 5.7, whereas the case fatality rate ranges from 7.2% in Italy to 0.7% in South Korea. These values are expected to change in the future, because the pandemic is still ongoing [2]. Several risk factors are associated with COVID-19 complications as older age, pre-existing respiratory and cardiovascular diseases, as well as hypertension, diabetes and obesity. Most patients present with symptoms such as fever, cough, sore throat, dyspnea and fatigue or muscle pain. Respiratory failure is the most common cause of death, followed by septic shock, organ failure and cardiac arrest [1].

As a major health threat, COVID-19 is currently the leading focus of research worldwide. A substantial amount of data describe laboratory abnormalities in patients with COVID-19, identifying hematological, biochemical and immunological parameters allowing prediction of disease progression, level of severity and mortality [1, 3–5]. Most of this data, however, compares parameters between COVID-19 patients and healthy individuals, limiting its practicality in a

***Corresponding author: Dzemaal Elezagic**, Faculty of Medicine and University Hospital Cologne, Institute for Clinical Chemistry, University of Cologne, 50931 Cologne, Germany, Phone: +49 221 478 5293; E-mail: dzemaal.elezagic@uk-koeln.de

Wibke Johannis and Thomas Streichert, Faculty of Medicine and University Hospital Cologne, Institute for Clinical Chemistry, University of Cologne, Cologne, Germany

Volker Burst, Emergency Department, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany; Department II of Internal Medicine and Center for Molecular Medicine Cologne, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

Florian Klein, Laboratory of Experimental Immunology, Institute of Virology, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany; German Center for Infection Research, Partner Site Bonn-Cologne, Cologne, Germany; Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany; and Faculty of Medicine, University of Cologne, Cologne, Germany

hospital setting. In such a setting, especially during a pandemic, rapid and efficient screening of patients is crucial. Another difficulty is “silent hypoxia”, a condition seen in many patients that end up developing respiratory failure. These patients have hypoxia but without any signs of respiratory distress, making early detection of hypoxia a crucial step in order to initialize an adequate therapy as soon as possible [6].

In order to speed up the triage process and distinguish hypoxemic patients early on, we here investigate differences in the venous blood gas and electrolyte analysis of patients immediately upon admission to the emergency department, who later tested negative or positive for the SARS-CoV-2 virus. We collected data from 50 patients, of whom 29 later tested negative, and 21 positive for SARS-CoV-2 (Table 1). There were no significant differences in mean age and presence of risk factors for COVID-19-associated complications between the two study groups. Apart from a higher percentage of females in the positively-tested study group, the gender distribution proved to be fairly homogenous. The negatively-tested group follow-up diagnoses included (in decreasing prevalence) other non-respiratory infectious diseases, bacterial or atypical respiratory infections, cardiovascular diseases or neurological diseases.

Venous blood gas measurements (partial pressure of carbon dioxide- $p\text{CO}_2$, partial pressure of oxygen- $p\text{O}_2$ and oxygen saturation- sO_2) were collected from a total of 48 patients, of whom 28 tested negative and 20 tested positive for SARS-CoV-2 (Figure 1). The venous $p\text{CO}_2$ was significantly higher whereas $p\text{O}_2$ and sO_2 were significantly lower in patients who tested positive for the virus (Figure 1).

Table 1: An overview of differences between the SARS-CoV-2 negatively-tested and positively-tested group.

SARS-CoV-2 status	Number of patients	Mean age	Gender distribution	Risk factors
Negative	29	55.9	55.2% male 44.8% female	1.48
Positive	21	58.14	38.1% male 61.9% female	1.38
Statistical significance	–	0.76	0.27	0.78

Presence of individual risk factors (obesity, D. mellitus, cardiovascular disease, respiratory disease, hypertension) was added up for each patient and then averaged to obtain the shown values. Statistical analysis of the data was performed using GraphPad Prism, Version 8.0. Normality test was performed using Shapiro–Wilk test, the p-value for age differences was determined using the t-test with Welch’s correction, the p-value for gender distribution using the two-sided Fisher’s exact test and since the data were not normally distributed, the p-value for risk factors was determined using the Mann–Whitney test.

Figure 1: Graphs depicting mean and range of venous blood gas data of patients tested negative and those tested positive for SARS-CoV-2.

$p\text{CO}_2$ -partial pressure of carbon dioxide, $p\text{O}_2$ -partial pressure of oxygen, sO_2 -oxygen saturation, * $p \leq 0.05$, ** $p \leq 0.01$. Eligible patients were adults admitted to the Emergency Department in the Cologne University Hospital during March and April 2020 with COVID-19 typical symptoms. All patients received a routine venous blood gas analysis upon admission using ABL 800 FLEX blood gas analyzer (Radiometer, Germany). The only exclusion criteria was previous SARS-CoV-2-positivity prior to admission. Testing for the SARS-CoV-2 virus was conducted in the Institute of Virology in the Cologne University Hospital using a standard PCR test. Since data were obtained retrospectively, informed patient consent to review medical records was not required by the Ethics Committee of the University of Cologne. Statistical analysis of the data was performed using GraphPad Prism, Version 8.0. Normality test was performed using Shapiro–Wilk test, the p-values were determined using the t-test with Welch’s correction. Since data for $p\text{O}_2$ were not normally distributed, the p-value was determined using the Mann–Whitney test.

We further collected pH measurements, bicarbonate concentrations- HCO_3^- and ionized Calcium concentrations- Ca^{++} ($n=50$, 29 negative and 21 positive for SARS-CoV-2) (Figure 2). The pH of patients tested positive for the virus was significantly lower than in those tested negative. Although bicarbonate concentration differences were not statistically significant, there is an increasing tendency in positively tested patients. Ionized calcium concentrations in patients tested positive for SARS-CoV-2 were significantly lower than in patients tested negative for the virus.

COVID-19, the currently largest health threat in the world leads to acute respiratory distress syndrome (ARDS) and in an estimated 3.6% of patients to death. Most common symptoms include fever, cough, and fatigue, followed by increased sputum production, shortness of breath, and myalgia [7]. An especially challenging aspect of the disease management in a clinical setting is “silent hypoxia”, in which patients with no or few symptoms of respiratory distress rapidly develop respiratory failure [6, 8]. We have therefore investigated differences between

Figure 2: Graphs depicting mean and range of pH, bicarbonate concentration (HCO_3^-) and ionized calcium concentration (Ca^{++}) data of patients tested negative and those tested positive for SARS-CoV-2. * $p \leq 0.05$, ns-not statistically significant. All patients received a routine venous blood gas analysis upon admission using ABL 800 FLEX blood gas analyzer (Radiometer, Germany). The only exclusion criteria was previous SARS-CoV-2-positivity prior to admission. Testing for the SARS-CoV-2 virus was conducted in the Institute of Virology in the Cologne University Hospital using a standard PCR test. Since data were obtained retrospectively, informed patient consent to review medical records was not required by the Ethics Committee of the University of Cologne. Statistical analysis of the data was performed using GraphPad Prism, Version 8.0. Normality test was performed using Shapiro–Wilk test, the p-values were determined using the t-test with Welch’s correction.

venous blood gas and electrolyte levels of patients admitted to the emergency department in order to speed up the triage process and detect hypoxia early on in the disease onset.

Although blood gas analysis in our study was conducted using venous blood, patients tested positive for the virus exhibited statistically significant lower pO_2 and sO_2 levels and higher pCO_2 levels in comparison to patients tested negative. Analogous findings were previously described using arterial blood, which is routinely used for blood gas analysis [9]. Significant differences between blood gas analyses of SARS-CoV-2 positive and SARS-CoV-2 negative patients in venous blood reveal a faster, more practical way of screening patients for hypoxia as well as a solid assessment of potential positivity for the virus and complications risk.

A helpful tool against silent hypoxia, which has gotten increasing attention during the COVID-19 pandemic, is pulse oximetry. Originally developed to monitor oxygen saturation (sO_2) during anesthesia, pulse oximetry is still widely used today in operation rooms, intensive care units and emergency departments [10]. Using pulse oximeters, sO_2 can easily be monitored not only in hospitalized patients, but also in SARS-CoV-2-positive patients discharged from the emergency department, identifying the need for hospitalization before

worsening of symptoms [11]. Moreover, sO_2 readings can accurately be performed using smartphones, identifying need for hospitalization even faster [12]. Blood gas analysis could be a valuable addition to pulse oximeter data, especially with the potential of smartphones, providing a rapid flow of information from the patients to the physicians thereby reducing unnecessary visits to the emergency department.

Along with blood gas levels, pH, bicarbonate and electrolyte levels are also essential diagnostic tools in a standard blood gas analyzer. The increased pCO_2 levels of patients later tested positive for SARS-CoV-2 prompted us to investigate the pH levels of these patients. Patients that tested positive for the virus indeed show lower pH levels. It is postulated that the acidosis is caused by hypercapnia and organ hypoperfusion in COVID-19 patients. Moreover, lower pH levels have also been linked to low survival rates of infected patients [13].

Lower levels of calcium, sodium and potassium are associated with the severity of COVID-19 [14]. Additionally, low levels of calcium predict whether infected patients will be hospitalized [15]. Since SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2), it reduces ACE2 expression, and increases angiotensin II levels. This is thought to be one of the mechanisms behind increased electrolyte excretion by the kidneys [14]. Although the differences between sodium and potassium levels in our study were not statistically significant due to a limited patient number, we could see significantly lower calcium levels in patients who tested positive for SARS-CoV-2 than in symptomatic patients who tested negative for the virus. Calcium is therefore not only a good predictor of disease severity and need for hospitalization but it could also serve as an additional parameter in assessing positivity for the virus.

The major drawback of this study is the low patient number, thereby not allowing the calculation of diagnostic specificity and sensitivity. Receiver Operating Characteristics (ROC) curves of all parameters yielded appropriate areas under the curve of only two parameters, namely pCO_2 and HCO_3^- (Supplementary Material). Larger studies are therefore needed before the findings can be generalized to a wider population and cut-off values can be reported for identifying positive patients. Moreover, the use of venous blood is only of limited value in blood gas analysis, although faster and less invasive in a clinical setting. Another limitation of this study is that this particular parameter constellation is not specific for COVID-19. Although similar constellations can appear in other respiratory diseases and viral infections, rapidly identifying risk factors for virus positivity during the COVID-19 pandemic could nonetheless be useful for preliminary patient assessment.

Taken together, we here show that symptomatic patients upon admission to the emergency room and later tested positive for SARS-CoV-2 exhibit lower venous blood levels of oxygen, pH, and calcium and higher levels of carbon dioxide compared to symptomatic patients later tested negative for the virus. This blood gas analysis constellation, upon an unknown infection status, could help in identifying SARS-CoV-2-positive patients more rapidly and identifying first signs of silent hypoxia that leads to respiratory failure.

Acknowledgments: We would like to thank Dr. Hildegard Christ from the Institute of Medical Statistics and Computational Biology in the University of Cologne for her outstanding help with the analysis of ROC curves.

Research funding: None declared.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The local Institutional Review Board deemed the study exempt from review.

References

1. Baj J, Karakula-Juchnowicz H, Teresinski G, Buszewicz G, Ciesielka M, Sitarz E, et al. COVID-19: specific and non-specific clinical manifestations and symptoms: the current state of knowledge. *J Clin Med* 2020;9. <https://doi.org/10.3390/jcm9061753>.
2. Baek WK, Sohn SY, Mahgoub A, Hage R. A comprehensive review of severe acute respiratory syndrome coronavirus 2. *Cureus* 2020;12: e7943.
3. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. *Clin Chem Lab Med* 2020;58:1131–4.
4. Cecconi M, Piovani D, Brunetta E, Aghemo A, Greco M, Ciccarelli M, et al. Early predictors of clinical deterioration in a cohort of 239 patients hospitalized for covid-19 infection in Lombardy, Italy. *J Clin Med* 2020;9. <https://doi.org/10.3390/jcm9051548>.
5. Ferrari D, Cabitza F, Carobene A, Locatelli M. Routine blood tests as an active surveillance to monitor COVID-19 prevalence. A retrospective study. *Acta Biomed* 2020;91:e2020009.
6. Tobin MJ, Laghi F, Jubran A. Why COVID-19 silent hypoxemia is baffling to physicians. *Am J Respir Crit Care Med* 2020;202: 356–60.
7. Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and meta-analysis. *J Infect* 2020;80: 656–65.
8. Ottestad W, Seim M, Maehlen JO. COVID-19 with silent hypoxemia. *Tidsskr Nor Lægeforen* 2020;7:140.
9. Geier MR, Geier DA. Respiratory conditions in coronavirus disease 2019 (COVID-19): important considerations regarding novel treatment strategies to reduce mortality. *Med Hypotheses* 2020; 140:109760.
10. Michard F, Shelley K, L'Her E. COVID-19: pulse oximeters in the spotlight. *J Clin Monit Comput* 2020. <https://doi.org/10.1007/s10877-020-00550-7>. [Epub ahead of print].
11. Shah S, Majmudar K, Stein A, Gupta N, Suppes S, Karamanis M, et al. Novel use of home pulse oximetry monitoring in COVID-19 patients discharged from the emergency department identifies need for hospitalization. *Acad Emerg Med* 2020;27: 681–92.
12. Teo J. Early detection of silent hypoxia in covid-19 pneumonia using smartphone pulse oximetry. *J Med Syst* 2020;44:134.
13. Skevaki C, Fragkou PC, Cheng C, Xie M, Renz H. Laboratory characteristics of patients infected with the novel SARS-CoV-2 virus. *J Infect* 2020;81:205–12.
14. Lippi G, South AM, Henry BM. Electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). *Ann Clin Biochem* 2020;57:262–5.
15. Di Filippo L, Formenti AM, Rovere-Querini P, Carlucci M, Conte C, Ciceri F, et al. Hypocalcemia is highly prevalent and predicts hospitalization in patients with COVID-19. *Endocrine* 2020;68: 475–8.

Supplementary Material: The online version of this article offers supplementary material (<https://doi.org/10.1515/labmed-2020-0126>).