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DNA and RNA Oxidative Damage and Mortality of Patients With COVID-19

Leonardo Lorente,[1], María M. Martín,[2], Agustín F. González-Rivero,[3], Antonia Pérez-Cejas,[3], Juan J. Cáceres,[4], Alina Perez,[5], Luis Ramos-Gómez,[6], Jordi Solé-Violán,[7], José Alberto Marcos y Ramos,[8], Nazario Ojeda,[9] and Alejandro Jiménez[10]

[1] Intensive Care Unit, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain; [2] Intensive Care Unit, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain; [3] Laboratory Department, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain; [4] Intensive Care Unit, Hospital Insular, Las Palmas de Gran Canaria, Spain; [5] Internal Intensive Care Unit, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain; [6] Intensive Care Unit, Hospital General La Palma, La Palma, Spain; [7] Intensive Care Unit, Hospital Universitario Dr. Negrín, Las Palmas de Gran Canaria, Spain; [8] Intensive Care Unit, Hospital Doctor José Molina Orosa, Lanzarote, Spain; [9] Department of Anesthesiology, Hospital Universitario Dr. Negrín, Las Palmas de Gran Canaria, Spain; [10] Research Unit, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain

ABSTRACT

Background: Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) oxidative damage is associated with mortality of patients with different diseases. However, there are no data about DNA and RNA oxidative damage from coronavirus disease 2019 (COVID-19) patients. Thus, the objective of this study was to explore DNA and RNA oxidative damage in surviving and non-surviving COVID-19 patients.

Materials and Methods: Eight Intensive Care Units from 6 hospitals in the Canary Islands (Spain) participated in this prospective and observational study. We recorded the serum levels at ICU admission of the three guanine oxidized species (OGS) because guanine is the nucleobase that forms the DNA and RNA most prone to oxidation. Survival at 30 days was our end-point study.

Results: Non-surviving (n = 11) compared to surviving patients (n = 42) had higher APACHE-II ($p < 0.001$), SOFA ($p = 0.004$) and serum OGS levels ($p = 0.001$). In logistic regression analyses an association between serum OGS levels and 30-day mortality after controlling for SOFA (OR=2.601; 95% CI=1.305−5.182; $p = 0.007$) or APACHE-II (OR=2.493; 95% CI=1.274−4.879; $p = 0.008$) was found. The area under curve (AUC) for mortality prediction by serum OGS levels was 83% (95% CI=70−92%; $p < 0.001$), by APACHE II was 85% (95% CI=75−96%; $p < 0.001$), and by SOFA was 80% (95% CI=66−94%; $p < 0.001$). No significant differences were found in the AUC between serum OGS levels and SOFA ($p = 0.91$), and serum OGS levels and APACHE-II ($p = 0.64$).

Conclusions: To our knowledge, this is the first study reporting on oxidative DNA and RNA damage in COVID-19 patients, and the main new finding was that serum OGS concentration was associated with mortality.

Key Indexing Terms: DNA and RNA oxidative damage; COVID-19; Patients; Mortality; Prognosis. **[Am J Med Sci 2021;361 (5):585–590.]**

INTRODUCTION

Coronavirus disease 2019 (COVID-19), a disease caused by the new coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an emerging global health threat that was first detected in December 2019 in Wuhan (China). Approximately 66,381,204 confirmed cases and 1,527,390 deaths (2.3%) from COVID-19 as of December 5, 2020.[1] Different factors have been associated with the prognosis of COVID-19 as age, arterial hypertension, cardiovascular diseases, chronic obstructive pulmonary disease (COPD), smoking, diabetes mellitus, cerebrovascular diseases, kidney dysfunction, cardiac injury, liver dysfunction, coagulation alterations or the development of acute respiratory distress syndrome (ARDS).[2–7]

Since COVID-19 was declared as a pandemic disease, a large number of investigations have been carried out to better understand its epidemiology, mechanisms, clinical evolution, and management. Recently, several researchers have suggested the potential role of

oxidative stress on COVID-19 and it has been proposed that oxidative stress in patients with COVID-19 could contribute in the cytokine storm and coagulopathy; in addition, the use of antioxidants agents has been suggested to reduce oxidative stress.[8-14]

Reactive oxygen species (ROS) could damage lipids, proteins, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) during oxidative stress. Adenine, cytosine, guanine, thymine and uracil are the five types of nucleobases that constitute DNA and RNA. Four types of those nucleobases are present in DNA and RNA. In both, DNA and RNA, adenine, cytosine and guanine are present. Furthermore, thymine is present in the DNA and uracil in RNA. As guanine is the nucleobase with the lowest redox potential, it is the most prone to oxidation.[15-18] There are three oxidizied guanine species (OGS): 8-hydroxy-2′-deoxyguanosine (8-OHdG) also named 8-oxo-deoxyguanosine (8-oxo-dG) from DNA, 8-hydroxyguanosine (8-OHG) also named 8-oxo-guanosine (8-oxo-G) from RNA, and 8-hydroxyguanine (8-OHGua) also named 8-oxo-guanine (8-oxo-Gua) from DNA or RNA.

Previously, we found that the oxidative damage of DNA and RNA (assessed by blood concentration of the three oxidizied guanine species) was associated with mortality of patients with spontaneous intracerebral hemorrhage,[19] brain infarction,[20] traumatic brain injury[21] and sepsis.[22] However, there are no data on DNA and RNA oxidative damage of COVID-19 patients. Thus, the objective of this study was to explore DNA and RNA oxidative damage in surviving and non-surviving patients with COVID-19.

METHODS

Design and subjects

Eigth Intensive Care Units from 6 hospitals in the Canary Islands (Spain) participated in the inclusion of patients in this observational and prospective study. The study protocol (code CHUC-2020−26) was approved by the Ethics Committee of each hospital. In the context of the pandemic and that the Spain Government forbid patient visits due to the health outbreak policy, the requirement of written informed consent for patient or family to participate in the study was waived.

Patients with laboratory-confirmed COVID-19 by an assay of real time fluorescence reverse transcription-polymerase chain reaction (RT-PCR) from nasopharyngeal swab sample or a bronchial aspirate admitted to the ICU were included.

Determination of serum concentrations of OGS

Serum samples were collected on admission at ICU and were stored at −80 °C until to the moment of blood determinations. DNA/RNA Oxidative Damage ELISA Kit® (Cayman Chemical Corporation, Ann Arbor, USA) with a detection limit of 0.45 ng/mL was used for the determination of serum OGS concentrations. All determinations were performed blindly to clinical data in the same Laboratory Department.

Variables recorded

The following demographic and clinical data were recorded on admission to the ICU: body max index (BMI), age, sex, chronic renal failure, COPD, smoking, diabetes mellitus, ischemic heart disease, arterial hypertension, steroid agents, solid tumor, hematological tumor, human immunodeficiency virus (HIV), chest radiograpy findings, ARDS,[23] Acute Physiology and Chronic Health Evaluation (APACHE)-II score[24] and Sepsis-related Organ Failure Assessment [SOFA] score.[25] Additionally, the following laboratory data were recorded on admission to the ICU: creatinine, lactic acid, sodium, protein, glucose, albumin, creatine kinase, bilirubin, alanine transaminase, aspartate transaminase, gamma-glutamyl transpeptidase, alkaline phosphatase, lactate dehydrogenase, procalcitonin, ferritin, C-reactive protein, interleukin-6, hemoglobin, hematocrit, white blood cell, lymphocytes, neutrophils, basophils, monocytes, eosinophils, D-dimer, fibrinogen, platelets, activated partial thromboplastin time (aPTT), international normalized ratio (INR), pressure of arterial oxygen (PaO_2) and fraction inspired of oxygen (FIO_2). In addition, the following data regarding ICU treatment were recorded: respiratory support, tocilizumab, hydroxicloroquine, interferon, lopinavir/ritonavir and steroid agents. Finally, survival at 30 days was our end-point study.

Statistical methods

Frequencies (percentages), medians (percentile 25−75), chi-square test and Mann−Whitney U test were used to describe and compare categorical and continuous variables between non-surviving and surviving patient groups. We used receiver operating characteristic analysis to test the ability of serum OGS levels to predict mortality. Kaplan-Meier at 30-day survival curves were conducted using serum OGS concentrations >2 ng/mL and ≤2 ng/mL (cut-off selected by Youden J index). Logistic regression was carried out to determine the association between serum OGS levels and 30-day mortality controlling by SOFA or APACHE-II. As the number of deceased patients was only 11, two models were constructed with only two predictor variables in each model. We used the SPSS 17.0 (SPSS Inc., Chicago, IL, USA) program and $p < 0.05$ as the cut-off of significant differences for the statistical analysis.

RESULTS

Non-surviving patients ($n = 11$) compared to surviving patients ($n = 42$) had higher APACHE-II ($p<0.001$) and SOFA ($p = 0.004$) (Table 1). Additionally, non-surviving patients compared to surviving patients had lower platelet count ($p = 0.02$) and higher serum OGS levels ($p = 0.001$) (Table 2).

We found in logistic regression analyses an association between serum OGS levels and 30-day mortality after controlling for SOFA (OR=2.601; 95% CI=1.305–5.182; $p = 0.007$) or APACHE-II (OR=2.493; 95% CI=1.274–4.879; $p = 0.008$) (Table 3).

The area under curve (AUC) for mortality prediction by serum OGS levels was 83% (95% CI=70–92%; $p<0.001$) (Figure 1), by APACHE II was 85% (95% CI=75–96%; $p<0.001$), and by SOFA was 80% (95% CI=66–94%; $p<0.001$). No significant differences were found in the AUC between serum OGS levels and SOFA ($p = 0.91$), and serum OGS levels and APACHE-II ($p = 0.64$).

Serum OGS levels cut-off of 2 ng/mL showed sensitivity 82% (48%–98%), specificity 83% (69%–93%), positive likelihood ratio 4.9 (2.4–10.2), negative likelihood ratio 0.2 (0.1–0.8), 56% (38%–73%) and negative predictive value 95% (83%–98%) in mortality prediction. In Kaplan-Meier analysis patients with serum OGS levels>2 ngl/mL showed a higher mortality rate (Hazard ratio=23.7; 95% CI=5.9–95.0; $p < 0.001$) (Figure 2).

After Bonferroni correction for multiple comparisons, we have not found any association between serum OGS levels and other variables: sex ($p = 0.20$), COPD ($p = 0.62$), smoking ($p = 0.70$), chronic renal failure ($p = 0.09$), arterial hypertension($p = 0.77$), ischemic heart disease ($p = 0.79$), diabetes mellitus ($p = 0.91$), solid tumor ($p = 0.97$), hematological tumor ($p = 0.14$), steroid agents prior to admission ($p = 0.21$), HIV ($p = 0.84$), chest radiograpy findings ($p = 0.42$), ARDS ($p = 0.93$), respiratory support ($p = 0.54$), tocilizumab ($p = 0.58$), lopinavir/ritonavir ($p = 0.48$), interferon Beta 1-B ($p = 0.33$), hydroxicloroquine ($p = 0.12$), steroid agents in ICU ($p = 0.66$), age ($p = 0.60$), BMI ($p = 0.78$), APACHE-II ($p = 0.70$), SOFA ($p = 0.88$), glucose ($p = 0.88$), lactic acid ($p = 0.15$), sodium ($p = 0.79$), creatine kinase ($p = 0.17$), protein ($p = 0.25$), albumin ($p = 0.65$), creatinine ($p = 0.18$), bilirubin ($p = 0.49$), alanine transaminase ($p = 0.93$), aspartate transaminase ($p = 0.99$), lactate dehydrogenase ($p = 0.66$), gamma-glutamyl transpeptidase ($p = 0.17$), alkaline phosphatase ($p = 0.56$), ferritin ($p = 0.88$), procalcitonin ($p = 0.76$), interleukin-6 ($p = 0.65$), C-reactive protein($p = 0.03$), hemoglobin ($p = 0.83$), white blood cell

TABLE 1. Demographic data, clinical data and treatment of non-surviving and surviving patients.

	Non-survivors ($n = 11$)	Survivors ($n = 42$)	*P* value
Gender female - *n* (%)	7 (63.6)	27 (64.3)	0.99
COPD - *n* (%)	3 (27.3)	5 (11.9)	0.34
Smoking - *n* (%)	2 (18.2)	2 (4.8)	0.19
Chronic renal failure - *n* (%)	0	1 (2.4)	0.99
Arterial hypertension - *n* (%)	6 (54.5)	16 (38.1)	0.49
Ischemic heart disease - *n* (%)	1 (9.1)	1 (2.4)	0.38
Diabetes mellitus - *n* (%)	3 (27.3)	12 (28.6)	0.99
Solid tumor - *n* (%)	0	1 (2.4)	0.99
Hematological tumor - *n* (%)	0	2 (4.8)	0.99
Steroid agents prior to admission - *n* (%)	2 (18.2)	1 (2.4)	0.11
Human Immunodeficiency Virus - *n* (%)	0	1 (2.4)	0.99
Chest radiograpy findings - *n* (%)			0.95
- Consolidation only	1 (9.1)	5 (11.9)	
- Ground glass opacity plus consolidation	6 (54.5)	21 (50.0)	
- Ground glass opacity only	4 (36.4)	16 (38.1)	
ARDS - *n* (%)	9 (81.8)	36 (85.7)	0.67
Age (years) - median (p 25–75)	70 (59–75)	65 (51–70)	0.10
Body max index (kg/m^2) - median (p 25–75)	27.1 (23.0–30.2)	28.1 (24.8–32.4)	0.29
APACHE-II score - median (p 25–75)	18 (16–20)	12 (7–15)	<0.001
SOFA score - median (p 25–75)	8 (5–9)	5 (3–7)	0.004
Respiratory support - *n* (%)			0.30
- Conventional oxygen therapy	0	4 (9.5)	
- High-flow nasal cannula	0	4 (9.5)	
- Non-invasive mechanical ventilation	0	3 (7.1)	
- Invasive mechanical ventilation	11 (100)	31 (73.8)	
Tocilizumab - *n* (%)	6 (54.5)	15 (35.7)	0.31
Lopinavir/Ritonavir - *n* (%)	10 (90.9)	39 (92.9)	0.99
Interferon Beta 1-B - *n* (%)	7 (63.6)	26 (61.9)	0.99
Hydroxychloroquine - *n* (%)	11 (100)	39 (92.9)	0.99
Steroid agents in ICU- *n* (%)	9 (81.8)	31 (73.8)	0.71

COPD = Chronic Obstructive Pulmonary Disease; APACHE = Acute Physiology and Chronic Health Evaluation; SOFA = Sepsis-related Organ Failure Assessment; ARDS = acute respiratory distress syndrome.

TABLE 2. Laboratory data at ICU admission of non-surviving and surviving patients.

	Non-survivors (*n* = 11)	Survivors (*n* = 42)	*P* value
Serum GOS levels (ng/mL) - median (p 25–75)	3.10 (2.30–3.60)	1.25 (0.80–1.83)	0.001
Glucose (g/dL) - median (p 25–75)	160 (135–271)	168 (122–208)	0.46
Lactic acid (mmol/L) - median (p 25–75)	1.60 (1.30–2.20)	1.33 (1.09–1.80)	0.11
Sodium (mEq/L)- median (p 25–75)	140 (135–144)	138 (134–141)	0.20
Creatine kinase (U/L) - median (p 25–75)	200 (50–1467)	152 (43–286)	0.51
Protein (g/L) - median (p 25–75)	6.0 (5.6–7.0)	6.4 (5.8–7.1)	0.60
Albumin (g/L) - median (p 25–75)	3.0 (2.3–3.7)	3.0 (2.6–3.5)	0.94
Creatinine (mg/dl) - median (p 25–75)	1.07 (0.72–1.73)	0.87 (0.68–1.03)	0.23
Total bilirubin (mg/dl) - median (p 25–75)	0.59 (0.35–1.23)	0.62 (0.48–1.20)	0.65
Alanine transaminase (U/L) - median (p 25–75)	34 (14–48)	38 (27–75)	0.14
Aspartate transaminase (U/L) - median (p 25–75)	40 (19–123)	37 (29–77)	0.79
Lactate dehydrogenase (U/L) - median (p 25–75)	418 (263–556)	353 (284–463)	0.58
Gamma-glutamyl transpeptidase (U/L) - median (p 25–75)	84 (33–447)	61 (39–132)	0.91
Alkaline phosphatase (U/L) - median (p 25–75)	67 (41–96)	58 (50–73)	0.99
Ferritin (ng/ml) - median (p 25–75)	1383 (859–2761)	1039 (653–1817)	0.50
Procalcitonin (ng/ml) - median (p 25–75)	0.58 (0.06–0.76)	0.17 (0.08–0.48)	0.49
Interleukin-6 (pg/ml) - median (p 25–75)	61 (24–140)	50 (6–179)	0.77
C-reactive protein (mg/gl) - median (p 25–75)	24 (18–67)	20 (10–76)	0.34
Hemoglobin (g/dL) - median (p 25–75)	12.8 (11.0–15.0)	12.8 (11.7–14.4)	0.95
White blood cell - median*10^3/mm^3 (p 25–75)	7.9 (5.3–13.1)	7.7 (6.0–11.6)	0.95
Neutrophils - median*10^3/mm^3 (p 25–75)	7.4 (4.3–10.4)	7.2 (4.9–10.2)	0.90
Lymphocytes - median*10^3/mm^3 (p 25–75)	0.54 (0.40–1.28)	0.66 (0.50–0.90)	0.44
Eosinophils - median*10^3/mm^3 (p 25–75)	0.02 (0.00–0.02)	0.00 (0.00–0.02)	0.45
Monocytes - median*10^3/mm^3 (p 25–75)	0.46 (0.18–0.58)	0.37 (0.23–0.58)	0.66
Basophils - median*10^3/mm^3 (p 25–75)	0.01 (0.01–0.03)	0.01 (0.00–0.03)	0.69
D-dimer (ng/mL) - median (p 25–75)	3516 (682–21,480)	1102 (744–2202)	0.21
Fibrinogen (mg/dl) - median (p 25–75)	699 (600–910)	711 (506–829)	0.49
Platelets - median*10^3/mm^3 (p 25–75)	158 (108–278)	246 (173–383)	0.02
aPTT (seconds) - median (p 25–75)	30 (23–36)	27 (25–32)	0.52
INR - median (p 25–75)	1.18 (1.02–1.32)	1.17 (1.06–1.36)	0.83
PaO2/FI0_2 ratio - median (p 25–75)	111 (100–140)	133 (103–201)	0.30

OGS = guanine oxidized species; aPTT = Activated partial thromboplastin time; INR = International normalized ratio; PaO_2 = pressure of arterial oxygen; FIO_2 = fraction inspired of oxygen.

TABLE 3. Multiple logistic regression analyses to predict mortality at 30 days.

	Odds Ratio	95% Confidence interval	*P*-value
Model 1:			
SOFA score (points)	1.830	1.199–2.795	0.005
Serum GOS levels (ng/mL)	2.601	1.305–5.182	0.007
Model 2:			
APACHE-II (points)	1.342	1.087–1.657	0.006
Serum GOS levels (ng/mL)	2.493	1.274–4.879	0.008

OGS = guanine oxidized species; SOFA = Sepsis-related Organ Failure Assessment; APACHE = Acute Physiology and Chronic Health Evaluation.

(p = 0.76), neutrophils (p = 0.54), lymphocytes (p = 0.98), eosinophils (p = 0.92), monocytes (p = 0.62), basophils (p = 0.82), D-dimer (p = 0.81), fibrinogen (p = 0.004), platelets (p = 0.21), aPTT (p = 0.41), INR (p = 0.12) and PaO_2/FIO_2 (p = 0.48).

DISCUSSION

To our knowledge, this is the first study reporting DNA and RNA oxidative damage in COVID-19 patients. The main new finding was that serum OGS concentration was associated with mortality. Another interesting finding of our study was that serum OGS concentration showed a similar predictive ability for mortality as SOFA and APACHE-II and could help physicians to estimate the prognosis of these patients.

Recently, different researchers have suggested that oxidative stress in patients with COVID-19 could contribute to cytokine storm and coagulopathy.[8-14] In vitro studies have found that SARS-CoV-1 infection increases the production of ROS in human promonocyte cells[26] and in various mammalian cells.[27] To our knowledge, such observations have not yet been reported in SARS-CoV-2 infection; however, we believe that SARS-CoV-2 infection may similarly lead to increased production of ROS. Regarding cytokine storm and oxidative stress, ROS has

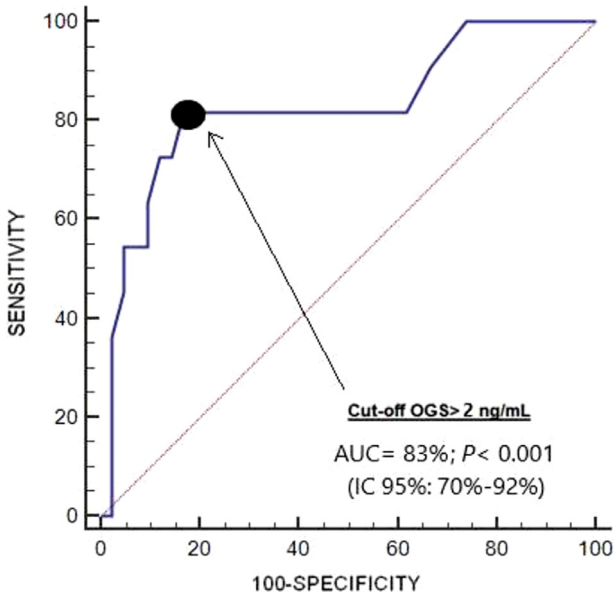

FIGURE 1. Receiver operating characteristic analysis using serum guanine oxidized species (OGS) concentration for prediction of mortality at 30 days.

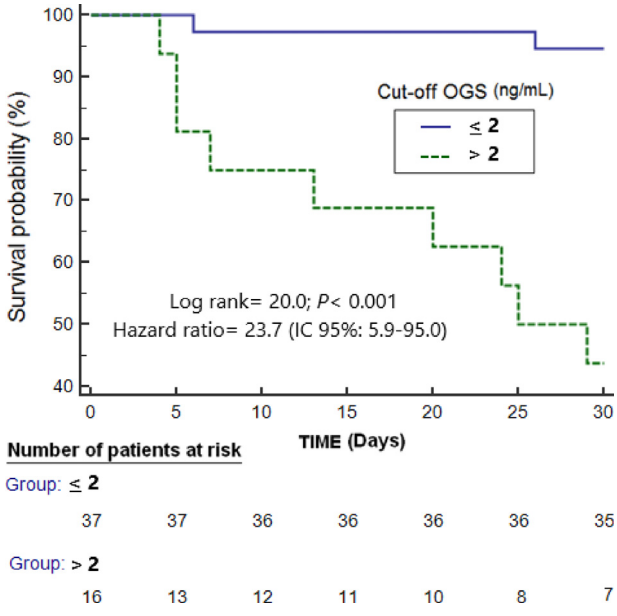

FIGURE 2. Survival curves at 30 days using serum guanine oxidized species (OGS) concentrations lower or equal vs. higher than 2 ng/mL.

been found to activate the nuclear factor kappa B (NF-κB) producing an increase in inflammatory cytokines.[28] In addition, hyperproduction of pro-inflammatory cytokines (such as interleukin-6 and tumor necrosis factor-alpha) has been found in patients with COVID-19 and has been associated with the development of ARDS and multiple organ dysfunction.[2,3] With regard to hematological findings and oxidative stress, hydroxyl radicals (a type of ROS) transform soluble plasma fibrinogen into abnormal fibrin clots (in the form of dense tangled deposits resistant to enzymatic degradation) that cause microthrombosis.[29] In addition, a hypercoagulable state has been found in patients with COVID-19 that could contribute to the development of multiple organ dysfunction.[30]

Besides, our novel findings about higher serum GOS levels in non-surviving than in surviving COVID-19 patients are in line with those found in patients with spontaneous intracerebral hemorrhage,[19] brain infarction,[20] traumatic brain injury[21] and sepsis.[22] We believe that this association between higher serum GOS levels and mortality of COVID-19 patients could be related to higher oxidant state, which could contribute in multiple organ dysfunction and finally the death of patients.

We would like to acknowledge that the main limitation of our study was that the low number of deceased patients prevented the inclusion of more variables in a single regression analysis. However, the strengths of the study were that the association between serum OGS levels and mortality is present in both regression models (controlling for SOFA or APACHE-II), and that is in line with the poor prognosis found in patients with other diseases.[19-22] Therefore, we believe that the new findings of our study could motivate the research to clarify the potential role of oxidative damage on COVID-19 patients, its potential contribution in prognosis, and the possible use of antioxidants agents to reduce oxidative stress.

CONCLUSIONS

As far as we know, this is the first study to report on oxidative DNA and RNA damage in COVID-19 patients, and the main new finding was that serum OGS concentration was associated with mortality.

AUTHOR CONTRIBUTIONS

- LLo conceived, designed and coordinated the study, participated in acquisition and interpretation of data, and drafted the manuscript.
- MMM, JJC, AP, LRG, JSV, JAMR and NO participated in acquisition of data.
- AFGR and APC carried out the determinations of serum GOS concentrations.
- AJ participated in the interpretation of data.

All authors revised the manuscript critically for important intellectual content and made the final approval of the version to be published.

CONFLICTS OF INTEREST

The authors have no financial or other conflicts of interest to disclose.

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collection and analysis, decision to publish, or preparation of the manuscript.

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Corresponding author. Leonardo Lorente, PhD, MD, Intensive Care Unit, Hospital Universitario de Canarias, Ofra, s/n. La Laguna - 38320, Santa Cruz de Tenerife, Spain (E-mail: lorentemartin@msn.com).