Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Research Note

N-antigenemia detection by a rapid lateral flow test predicts 90-day mortality in COVID-19: A prospective cohort study

Raquel Almansa 1,2,4, 1, Jose María Eiros 6, #, David de Gonzalo-Calvo 4,13, Tamara Postigo 1, 1, 7, Alicia Ortega 1, 7, Raul Lopez-Izquierdo 8, Anna Moncusí-Moix 4, 13, Clara Gort-Paniello 4, 13, Marta Domínguez-Gil 6, Amanda de la Fuente 1, 7, Laura González-González 1, 4, Tania Luis-García 1, 4, Nadia García-Mateo 1, 7, Ana P. Tedim 1, 7, Fátima Rodríguez-Jara 4, 13, Noelia Jorge 1, 4, Jessica González 13, Gerard Torres 4, 13, Oliver Norberto Gutiérrez-Pérez 9, María José Villegas 9, Sonia Campo 9, Eva Ayllon 9, Tomás Ruiz Albi 10, Julio de Frutos Arribas 10, 3, Ainhoa Arroyo Domingo 10, Jesica Abadia-Otero 11, Julia Gómez Barquero 11, Wysali Trapiello 12, Luis Javier Garcia Frade 9, Luis Inglada 11, Felix del Campo 3, 5, 10, Jesús F. Bermejo-Martin 1, 4, 7, *, 1, Ferran Barbé 4, 13, 1, Antoni Torres 4, 14, 15,

© 2022 European Society of Clinical Microbiology and Infectious Diseases. Published by Elsevier Ltd. All rights reserved.

Abstract

Objectives: To evaluate if the detection of N antigen of SARS-CoV-2 in plasma by a rapid lateral flow test predicts 90-day mortality in COVID-19 patients hospitalized at the wards.

Methods: The presence of N-antigenemia was evaluated in the first 36 hours after hospitalization in 600 unvaccinated COVID-19 patients, by using the Panbio COVID-19 Ag Rapid Test Device from Abbott (Abbott Laboratories Inc., Chicago, IL, USA). The impact of N-antigenemia on 90-day mortality was assessed by multivariable Cox regression analysis.

Results: Prevalence of N-antigenemia at hospitalization was higher in nonsurvivors (69% (82/118) vs. 52% (250/482); p < 0.001) and absence of S1 antibodies (73.4% (240/327) vs. 23.6% (61/259); p < 0.001), absence of anti-SARS-CoV-2 N antibodies (80.7% (264/327) vs. 26.6% (69/259); p < 0.001) and absence of S1 antibodies (73.4% (240/327) vs. 23.6% (61/259); p < 0.001). The patients with N-antigenemia showed more frequently RNAemia (45.7% (148/324) vs. 19.8% (51/257); p < 0.001), absence of anti-SARS-CoV-2 N antibodies (80.7% (264/327) vs. 26.6% (69/259); p < 0.001) and absence of S1 antibodies (73.4% (240/327) vs. 23.6% (61/259); p < 0.001). The patients with antigenemia showed more frequently acute respiratory distress syndrome (30.1% (100/332) vs. 13% (62/475); p < 0.001).

Author information

1 Group for Biomedical Research in Sepsis (BioSepsis), Instituto de Investigación Biomédica de Salamanca, (IBSAL), Gerencia Regional de Salud de Castilla y León, Salamanca, Spain
2 Department of Cellular Biology, Histology and Pharmacology, University of Valladolid, Spain
3 Department of Medicine, Dermatology and Toxicology, School of Medicine, University of Valladolid, Valladolid, Spain
4 Centro de Investigación Biomédica en Red en Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Spain
5 Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Instituto de Salud Carlos III, Madrid, Spain
6 Microbiology Service, Hospital Universitario Río Hortega, Gerencia Regional de Salud de Castilla y León, Valladolid, Spain
7 Research Unit, Hospital Universitario Río Hortega, Gerencia Regional de Salud de Castilla y León, Valladolid, Spain
8 Emergency Medicine Department, Hospital Universitario Río Hortega, Gerencia Regional de Salud de Castilla y León, Valladolid, Spain
9 Hematology Service, Hospital Universitario Río Hortega, Gerencia Regional de Salud de Castilla y León, Valladolid, Spain
10 Pneumology Service, Hospital Universitario Río Hortega, Gerencia Regional de Salud de Castilla y León, Valladolid, Spain
11 Internal Medicine Service, Hospital Universitario Río Hortega, Gerencia Regional de Salud de Castilla y León, Valladolid, Spain
12 Clinical Analysis Service, Hospital Clínico Universitario de Valladolid, Gerencia Regional de Salud de Castilla y León, Valladolid, Spain
13 Translational Research in Respiratory Medicine, University Hospital Arnau de Vilanova and Santa Maria, IRB Lleida, Lleida Spain
14 Department of Pulmonology, Hospital Clinic de Barcelona, Universidad de Barcelona, Institut D’investigacions August Pi i Sunyer (IDIBAPS), Barcelona, Spain
15 Catalan Institution for Research and Advanced Studies, Barcelona, Spain

* Corresponding author. Group for Biomedical Research in Sepsis (BioSepsis), Instituto de Investigación Biomédica de Salamanca, (IBSAL), Gerencia Regional de Salud de Castilla y León, Paseo de San Vicente, 58-182, 37007 Salamanca, Spain.

E-mail address: jbermejo@saludcastillayleon.es (J.F. Bermejo-Martin).

The first authors Raquel Almansa and Jose María Eiros contributed equally to this article.

The senior authors Jesús F. Bermejo-Martin, Ferran Barbé, and Antoni Torres contributed equally to this article.

https://doi.org/10.1016/j.cmi.2022.05.023
1988-743X © 2022 European Society of Clinical Microbiology and Infectious Diseases. Published by Elsevier Ltd. All rights reserved.
Introduction

The presence of SARS-CoV-2 RNA in plasma (RNAemia) is associated to host-dysregulated responses, critical illness, and death in COVID-19 [1–3]. Dissemination of viral components to the blood could reflect severe alveolitis with damage to the alveolar-vascular barrier [4]. In turn, viral components could contribute to induce extra-pulmonary disease by stimulating innate immunity responses and/or mediating endothelial and tissue damage [2,5]. Although current evidence linking SARS-CoV-2 RNAemia with severe disease and poor outcome is solid, the potential influence of antigenemia (the presence of viral antigens in blood) on the prognosis of COVID-19 patients has been poorly explored yet [6,7]. Herein, we evaluated if the detection of N antigen of SARS-CoV-2 in plasma by a rapid lateral flow test predicted 90-day mortality in COVID-19 patients hospitalized at the wards.

Methods

The inclusion criteria was the following: consecutive adult patients with a positive nasopharyngeal swab PCR for SARS-CoV-2 admitted to the wards from 2 July 2020 to 10 March 2021 for whom an informed consent to participate in the study was feasible to obtain from the patient or his/her legal representative in the first 36 hours after admission. The plasma from EDTA blood was obtained in these first 36 hours and stored at –80°C. The exclusion criteria was the following: patients showing concomitant infections at admission, those who had received any dose of a SARS-CoV-2 vaccine, and those for whom informed consent could not be requested/obtained. The study finally involved 600 patients out of the 1333 COVID-19 patients admitted to the participant wards during this period. This was a sub-study of the CIBERES-UCI-COVID project (Clinicaltrials.gov NCT04457505). Approval of the study protocol was obtained from the ethics committees of the participating hospitals. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Samples were processed by the BioSepsis laboratory and by the IRB-Lleida Biobank (B.0000682)/“Plataforma Biobancos PT17/0015/0027”.

N-antigenemia was defined as a positive result for the presence of SARS-CoV-2 in plasma by using the Panbio COVID-19 Ag Rapid Test (Abbott Laboratories Inc., Chicago, IL, USA). Anti-SARS-CoV-2 S1 and N-antibodies were profiled using the SARS-CoV-2 IgG II Quant/SARS-CoV-2 IgG assays on an Alinity platform (Abbott Laboratories Inc.) Viral RNA load in plasma was profiled using droplet digital PCR as previously described [2]. Statistical analysis was performed using IBM SPSS Statistics Version 25.0 (IBM Corp., Armonk, NY, USA). The level of significance was set at p = 0.05. The factors associated to 90-day mortality were identified by multivariable Cox regression analysis. Those variables of the Table 1 yielding p < 0.100 in the univariable analysis were used as adjusting variables.

Results

Patients dying in the first 90 days after hospitalization (19.6%, 118/600) were older than the survivors, presented more frequently hypertension, cardiovascular disease, cerebrovascular disease, atrial fibrillation and renal disease (Table 1). Nonsurvivors arrived to the hospital earlier since the onset of the symptoms and presented with more severe disease, showing slightly higher Sequential Organ Failure Assessment (SOFA) scores. Of the patients, 9.5% (57/600) were transferred to the intensive care unit (ICU) over the course of hospitalization to the wards (Table 1).

The presence of N-antigenemia in the first 36 hours after hospitalization was higher in nonsurvivors (69% [82/118] vs. 52% [250/482]; p < 0.001) who showed also higher viral RNA levels in plasma and lower concentrations of SARS-CoV-2 anti-N and anti-S1 antibodies (Table 1). Interestingly, the patients with N-antigenemia presented earlier at the hospital since disease onset (5 days vs. 6 days in median, p = 0.003), showed with more frequent viral sepsis at hospitalization (63.6% [211/332] vs. 48.1% [129/268]; p < 0.001) (as defined by the SEPSIS-3 consensus [8], along with higher levels of C-reactive protein (CRP) (81 [91] vs. 68 [108] mg/L; p = 0.050). Lactic acid dehydrogenase (LDH) (343 [273] vs. 297 [258] UI/L; p = 0.012), and lower concentrations of lymphocytes (0.8 [0.7] vs. 1.0 [0.7] × 1000 cells/mm3; p < 0.001), monocytes (0.4 [0.4] vs. 0.5 [0.4] cells/mm3; p < 0.001) and platelets (159 [132] 1000 cells × 103/μL; p < 0.001) (values are provided as median [IQR]). Patients with N-antigenemia showed more frequently RNAemia, but were less frequently seropositive for anti-SARS-CoV-2 N and S1 antibodies (see Supplementary material, File 1). Developing ARDS was more common in patients with N-antigenemia (30.1% [100/332] vs. 18.7% [50/268]; p = 0.001). They also suffered more often from nosocomial infections (13.6% [45/331] vs. 7.9% [21/267]; p = 0.026).

The multivariable analysis showed higher odds of 90-day mortality associated with the presence of N-antigenemia, whereas anti-SARS-CoV-2 N antibodies represented a protective factor (Fig. 1 and Supplementary material, File 2). N-antigenemia, or the absence of anti-N antibodies, translated into a significant reduction in survival time (Fig. 1). Other factors independently associated with mortality were age, Sequential Organ Failure Assessment score, hypernatremia, high CRP or neutrophil levels, and developing an acute arrhythmia (Fig. 1 and Supplementary material, File 2).

Discussion

The presence of SARS-CoV-2 N-antigenemia at admission to the hospital wards is a stand-alone predictor of 90-day mortality in
COVID-19. Using either single molecule array, ELISA or CLEIA based tests, other authors had already evidenced the link between anti-SARS-CoV-2 N antigenemia and COVID-19 severity. Perna et al. observed that the serum levels of SARS-CoV-2 N antigen were higher in COVID-19 patients admitted to ICU [7]. Wang et al. found that plasma antigen concentration at COVID-19 diagnosis was associated with ICU admission [9]. As far as we know, our study was the first in demonstrating higher odds of 90-day mortality associated with cases of COVID-19 requiring immediate intubation [6].

### Table 1

Clinical characteristics of the patients

| Clinical characteristics | All cohort | 90-Day mortality | p |
|--------------------------|------------|------------------|---|
| N                        | 600        | 482              | 118 | <0.001 |
| Age, median years (IQR)  | 72.0 (24.0)| 67.5 (23.0)      | 85.0 (10.0) | 0.422 |
| Male, n (%)              | 335 (55.8)| 273 (56.6)       | 62 (52.5) | 0.415 |
| Smoking, n (%)           | 23 (3.8)  | 20 (4.1)         | 3 (2.5)  | 0.032 |

### Comorbidities

- **Hypertension, n (%)**
  - All cohort: 321 (53.5)
  - Survivors: 243 (50.4)
  - Non-survivors: 78 (66.1)
  - p = 0.002
- **Diabetes, n (%)**
  - All cohort: 132 (22.0)
  - Survivors: 103 (21.4)
  - Non-survivors: 29 (24.6)
  - p = 0.451
- **Obesity, n (%)**
  - All cohort: 118 (19.7)
  - Survivors: 102 (21.2)
  - Non-survivors: 16 (13.6)
  - p = 0.063
- **Chronic cardiovascular disease, n (%)**
  - All cohort: 100 (16.7)
  - Survivors: 64 (13.3)
  - Non-survivors: 36 (30.5)
  - p = 0.010
- **Chronic cerebrovascular disease, n (%)**
  - All cohort: 36 (6.0)
  - Survivors: 23 (4.8)
  - Non-survivors: 13 (11.0)
  - p = 0.010
- **Chronic atrial fibrillation, n (%)**
  - All cohort: 73 (12.2)
  - Survivors: 46 (9.5)
  - Non-survivors: 27 (22.9)
  - p = 0.001
- **Chronic renal disease, n (%)**
  - All cohort: 70 (11.7)
  - Survivors: 44 (9.1)
  - Non-survivors: 26 (22.0)
  - p = 0.001
- **Chronic respiratory disease, n (%)**
  - All cohort: 86 (14.3)
  - Survivors: 64 (13.3)
  - Non-survivors: 22 (18.6)
  - p = 0.136
- **Cancer, n (%)**
  - All cohort: 63 (10.5)
  - Survivors: 50 (10.4)
  - Non-survivors: 13 (11.0)
  - p = 0.838

### Status at hospital admission

- **Days since symptoms onset to hospital admission, median years (IQR)**
  - All cohort: 5.0 (6.0)
  - Survivors: 6.0 (5.0)
  - Non-survivors: 3.0 (5.0)
  - p = 0.001
- **SOFA score (IQR)**
  - All cohort: 2.0 (2.0)
  - Survivors: 2.0 (1.0)
  - Non-survivors: 2.5 (3.0)
  - p = 0.001
- **Sepsis, n (%)**
  - All cohort: 340 (56.7)
  - Survivors: 256 (53.1)
  - Non-survivors: 84 (71.2)
  - p = 0.024
- **Bilateral pneumonia in the chest x-ray, n (%)**
  - All cohort: 63 (10.5)
  - Survivors: 50 (10.4)
  - Non-survivors: 13 (11.0)
  - p = 0.838
- **PaO2/FiO2 (mmHg)**
  - All cohort: 70 mmHg
  - Survivors: 70 mmHg
  - Non-survivors: 70 mmHg
  - p = 0.838

### Laboratory parameters at hospital admission

- **Creatinine**
  - All cohort: 0.00 (2.50)
  - Survivors: 0.00 (2.50)
  - Non-survivors: 0.00 (2.50)
  - p = 0.838
- **Bilirubin**
  - All cohort: 0.00 (1.20)
  - Survivors: 0.00 (1.20)
  - Non-survivors: 0.00 (1.20)
  - p = 0.838
- **C-reactive protein**
  - All cohort: 0.00 (0.00)
  - Survivors: 0.00 (0.00)
  - Non-survivors: 0.00 (0.00)
  - p = 0.838
- **Viral RNA load in plasma (copies/mL)**
  - All cohort: 0.00 (0.00)
  - Survivors: 0.00 (0.00)
  - Non-survivors: 0.00 (0.00)
  - p = 0.838

### 90-Day mortality

- **Survivors**
  - Male: 340 (56.7)
  - Survivors: 256 (53.1)
  - Non-survivors: 84 (71.2)
  - p = 0.024
- **Chronic cardiovascular disease, n (%)**
  - All cohort: 100 (16.7)
  - Survivors: 64 (13.3)
  - Non-survivors: 36 (30.5)
  - p = 0.010
- **Chronic cerebrovascular disease, n (%)**
  - All cohort: 36 (6.0)
  - Survivors: 23 (4.8)
  - Non-survivors: 13 (11.0)
  - p = 0.010
- **Chronic respiratory disease, n (%)**
  - All cohort: 86 (14.3)
  - Survivors: 64 (13.3)
  - Non-survivors: 22 (18.6)
  - p = 0.136
- **Cancer, n (%)**
  - All cohort: 63 (10.5)
  - Survivors: 50 (10.4)
  - Non-survivors: 13 (11.0)
  - p = 0.838

### Treatments

- **Remdesivir, n (%)**
  - All cohort: 58 (9.7)
  - Survivors: 51 (10.6)
  - Non-survivors: 7 (5.9)
  - p = 0.126

### Complications

- **ARDS, n (%)**
  - All cohort: 150 (25.0)
  - Survivors: 118 (24.5)
  - Non-survivors: 32 (27.0)
  - p = 0.553
- **Acute renal failure, n (%)**
  - All cohort: 42 (7.0)
  - Survivors: 26 (5.4)
  - Non-survivors: 16 (13.8)
  - p = 0.001
- **Acute arrhythmia, n (%)**
  - All cohort: 43 (7.2)
  - Survivors: 24 (5.0)
  - Non-survivors: 19 (16.1)
  - p = 0.001
- **ICU admission, n (%)**
  - All cohort: 37 (6.3)
  - Survivors: 33 (6.7)
  - Non-survivors: 4 (3.3)
  - p = 0.328
- **Length of hospital stay, median days (IQR)**
  - All cohort: 8.00 (9.00)
  - Survivors: 8.00 (7.00)
  - Non-survivors: 10.50 (11.00)
  - p = 0.001

The continuous variables are represented as median (IQR) and the categorical variables as absolute count (%). The differences between groups were assessed using the chi-squared or Fisher’s Exact Tests for the categorical variables and the Mann-Whitney U test for the continuous variables.

Abbreviations: ARDS, acute respiratory distress syndrome; ALT, alanine aminotransferase; AU: arbitrary units; ICU, intensive care unit; LDH, lactic acid dehydrogenase; MAP, mean arterial pressure; SOFA, Sequential Organ Failure Assessment.

*For those variables with missing values, the sample size is detailed following the superscript letter. Significant p values are highlighted in bold letter.
to N-antigenemia. Antigenemia was accompanied by a number of signatures indicating severity—shorter course of the disease before hospitalization, higher frequency of viral sepsis at admission [10], and ARDS and nosocomial infections over the course of hospitalization, lower platelet, lymphocyte and monocyte counts, along with the activation of the inflammatory response paralleling tissue destruction, denoted by the presence of higher levels of CRP and LDH. Perna et al. had already reported that the concentration of N antigen in serum correlated with CRP levels in COVID-19 patients [7]. Olea et al. found significantly higher serum levels of ferritin, LDH, CRP, and D-dimers in ICU patients with positive SARS-CoV-2 N antigen in plasma [11]. Our results evidenced that patients with N-antigenemia admitted to the wards presented frequently with RNAemia and the absence of anti-SARS-CoV-2 antibodies, as reported also in critically ill COVID-19 patients [12]. This suggested that patients with N-antigenemia have impaired immune responses leading to uncontrolled viral replication. Interestingly, the presence of anti-N antibodies represented a protective factor against mortality.

We did not evaluate whether N-antigenemia responded to the presence of live virus in blood, although mounting evidence supports the infection of distant tissues by SARS-CoV-2 in some patients [13–15]. The results have to be validated also in the current scenario of predominant circulation of Omicron.

In summary, the presence of N-antigenemia or the absence of anti-SARS-CoV-2 N antibodies after hospitalization is associated to increased 90-day mortality in COVID-19. Detection of N-antigenemia by using lateral flow tests is a widely available tool that could contribute to early identify those patients at risk of deterioration. N-antigenemia could represent an important factor to understand the effect of antivirals in this disease.

Transparency declaration

RA, JFBM, JME, and DdGC designed the study. AT coordinated the study implementation. RLI, GT, TRA, JFA, AAD, JA, JGB, LI, FdC, and FB recruited the patients. LGF, ONGP, MJV, SC, AY, FRJ, and JG collected the samples. LGG, TLG, AMM, and CGP collected the clinical data. AdF, NJ, TP, AO, WT, MDG, and RA developed the laboratory works. NGM and APT analyzed the viral load in plasma. RA and JFBM performed the statistical analysis and wrote the manuscript. JFBM and LGG critically revised the data. All the authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflict of interest

The authors declare that they have no conflicts of interest.

Funding

This work was possible thanks to the financial support from Instituto de Salud Carlos III (Subvenciones de concesión directa para proyectos y programas de investigación del virus SARS-CoV-2, causante del COVID-19, FONDO – COVID19, code COV20/00110, Instituto de Salud Carlos III, CIBERES, 06/06/0028) (AT) co-funded by the European Social Fund (ESF) /“A Way to Make Europe”. The work was also supported by Fundació La Marató de TV3 (ajudes Econòmiques a Projectes de Recerca sobre Covid-19 – La Marató 2020, code 202108-30-31) (DdGC, JFBM), in addition by an ESCMID Research Grant 2020 (APT) and finally by Institut Català de la Salut and Gestió de Serveis Sanitaris (project COVIDPONENT) (FB). DdGC, AdF, and APT have received financial support from Instituto de Salud Carlos III (Miguel Servet 2020: CP20/00041/PFIS: FI20/00278/Sara Borrell: CD18/00123), co-funded by the European Social Fund (ESF) /“A way to make Europe” /“Investing in your future”.

Author’s contributions

RA, JFBM, JME, and DdGC designed the study. AT coordinated the study implementation. RLI, GT, TRA, JFA, AAD, JA, JGB, LI, FdC, and FB recruited the patients. LGF, ONGP, MJV, SC, AY, FRJ, and JG collected the samples. LGG, TLG, AMM, and CGP collected the clinical data. AdF, NJ, TP, AO, WT, MDG, and RA developed the laboratory works. NGM and APT analyzed the viral load in plasma. RA and JFBM performed the statistical analysis and wrote the manuscript. JFBM and LGG critically revised the data. All the authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Fig. 1. Left: Forest plot showing the adjusted HR from the Cox multivariate analysis to predict 90-day mortality (see Supplementary material, File 2). Right: Kaplan-Meier curves for 90-day mortality.
Acknowledgements

The authors want to thank Mr. Albert Gabarrus (statistician from Hospital Clinic/IDIBAPS, Barcelona, Spain) for his technical advice with the statistical analysis of this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.05.023.

References

[1] Li H, Gu X, Li H, Gong F, Xu J, Wang Y, et al. Risk factors of viral RNAemia and its association with clinical prognosis among patients with severe COVID-19. Chest 2021;159:1382–6.
[2] Bermejo-Martin JF, Gonzalez-Rivera M, Almansa R, Micheloud D, Tedim AP, Domínguez-Gil M, et al. Viral RNA load in plasma is associated with critical illness and a dysregulated host response in COVID-19. Crit Care 2020;24:691.
[3] Tang K, Wu L, Luo Y, Gong B. Quantitative assessment of SARS-CoV-2 RNAemia and outcome in patients with Coronavirus Disease 2019. J Med Virol 2021;93:3165–75.
[4] McGonagle D, Kearney MF, O’Regan A, O’Donnell JS, Quartuccio L, Watad A, et al. Therapeutic implications of ongoing alveolar viral replication in COVID-19. Lancet Rheumatol 2022;4:e135–44.
[5] Birra D, Benucci M, Landolfi L, Merchianda A, Loi G, Amato P, et al. COVID 19: a clue from innate immunity. Immunol Res 2020;68:161–8.
[6] Ogata AF, Maley AM, Wu C, Gilboa T, Norman M, Lazarovits R, et al. Ultra-sensitive serial profiling of SARS-CoV-2 antigens and antibodies in plasma to understand disease progression in COVID-19 patients with severe disease. Clin Chem 2020;66:1562–72.
[7] Perina F, Bruzzaniti S, Piemonte E, Maddaloni V, Atripaldi I, Sale S, et al. Serum levels of SARS-CoV-2 nucleocapsid antigen associate with inflammatory status and disease severity in COVID-19 patients. Clin Immunol 2021;226:108720.
[8] Singer M, Druschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801–10.
[9] Wang H, Hogan CA, Verghese M, Solis D, Sibai M, Huang C, et al. SARS-CoV-2 nucleocapsid plasma antigen for diagnosis and monitoring of COVID-19. Clin Chem 2021;68:204–13.
[10] Karakike E, Giamarellos-Bourboulis EJ, Kyprianou M, Fleischmann-Struzek C, Pletz MW, Netea MG, et al. Coronavirus Disease 2019 as cause of viral sepsis: a systematic review and meta-analysis. Crit Care Med 2021;49:2042–57.
[11] Oteo B, Albert E, Torres I, Gozalbo-Rovira R, Carbonell N, Ferreres J, et al. SARS-CoV-2 N-antigenemia in critically ill adult COVID-19 patients: frequency and association with inflammatory and tissue-damage biomarkers. J Med Virol 2022;94:222–8.
[12] Martin-Vicente M, Almansa R, Martínez I, Tedim AP, Bustamante E, Tamayo L, et al. Low anti-SARS-CoV-2 S antibody levels predict increased mortality and dissemination of viral components in the blood of critical COVID-19 patients. J Intern Med 2022;291:232–40.
[13] Schurink B, Roos E, Radonic T, Barbe E, Bouman CSC, de Boer HH, et al. Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. Lancet Microbe 2020;1:e290–9.
[14] Dorward DA, Russell CD, Un I, Elshani M, Armstrong SD, Penrice-Randal R, et al. Tissue-specific immunopathology in fatal COVID-19. Am J Respir Crit Care Med 2021;203:192–201.
[15] Recalde-Zamacona B, García-Tobar L, Argüeta A, Álvarez I, Andreea CED, Alonso MF, et al. Histopathological findings in fatal COVID-19 severe acute respiratory syndrome: preliminary experience from a series of 10 Spanish patients. Thorax 2020;75:1116–8.