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.

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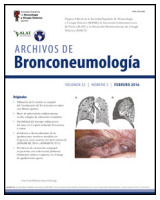

Scientific Letter

Hyperglycemia in Acute Critically Ill COVID-19 Patients

Dear Editor,

Critically ill patients with COVID-19 are at increased risk of complications such as cardiovascular events, coagulation disorders, acute respiratory distress syndrome (ARDS), and nosocomial infections that could contribute to poorer clinical outcomes. It has been reported that the rate of nosocomial infections in critically ill COVID-19 patients ranges from 30 to 50%.[1–3] A variety of factors have been suggested as contributors to this increased risk of developing nosocomial infections: an impaired immune system triggered by SARS-CoV-2 infection, encompassing phenomena such as immune hyper-response and inflammation; the increased risk of ARDS; the need for invasive ventilation; the use of empirical antibiotic therapy; and long ICU stays. Interestingly, recent studies found hyperglycemia to be a risk factor for adverse outcomes and mortality in severe COVID-19,[4,5] but there is still a scarcity of data on the impact of hyperglycemia on the risk of nosocomial infections in critically ill COVID-19 patients. Thus, we aimed to investigate the association between hyperglycemia at ICU admission and the risk of nosocomial bacterial pneumonia in COVID-19 in the ICU setting, along with the risk of in-hospital mortality.

The CIBERESUCICOVID is a prospective, multicenter, and observational study that included consecutive adult patients admitted to 55 Spanish ICUs for severe COVID-19 between 5 February and 21 December 2021. Data was collected as previously described.[6,7] Descriptive statistics were used for the basic features of the study data. Categorical variables were compared using the chi-squared test or Fisher's exact test, whereas continuous variables were compared using the non-parametric Mann–Whitney *U* test. We analyzed the association between hyperglycemia (serum glucose > 126 mg/dL)[8] at ICU admission and nosocomial bacterial pneumonia[9] by means of a mixed-effects multivariable model,[10] defined by a binomial probability distribution and a logit link function, with centers as a random effect. To evaluate the effect of hyperglycemia on in-hospital mortality, a Fine-Gray competing risks model[11] stratified on the centre variable was used, considering discharge from hospital as competing risk for mortality. The study received approval from the Institution's Internal Review Board (Comité Ètic d'Investigació Clínica, registry number HCB/2020/0370) and we obtained informed consent from either patients or their relatives.

During the study period, 6225 patients were admitted to ICU in the 55 Spanish hospitals due to COVID-19. We included 5763 patients in this analysis; of these, 3704 (64%) presented hyperglycemia at ICU admission and 2059 (36%) did not. Baseline characteristics, clinical features, complications, and outcomes of the cohort according to the presence of hyperglycemia at ICU admission are shown in Table 1. Median age was 65 (56–72) years and 71% of patients were male. Hypertension (55%), obesity (43%), diabetes mellitus (33%), and chronic lung disease (16%) were the most frequent comorbidities. Patients were admitted to the ICU after a median of 7[4–9] days from the presentation of symptoms and of 1 (0–3) days from hospital admission. Patients with hyperglycemia were more frequently older and had more comorbidities (33% were diabetic, for example, compared to 9% of those not presenting hyperglycemia), and, overall, they presented more severe COVID-19 at ICU admission, as measured by the APACHE II and SOFA scores. Moreover, patients with hyperglycemia received corticosteroids more frequently and presented significantly more complications, e.g., a need for invasive mechanical ventilation, ARDS, acute renal failure, nosocomial pneumonia, and acute cardiac injury. The lengths of hospital and ICU stays were also significantly longer, and in-hospital, ICU, and 90-day mortality rates were significantly higher in patients with hyperglycemia. As regards the primary outcomes – namely rates of nosocomial bacterial pneumonia and in-hospital mortality, both were significantly higher in patients with hyperglycemia than in those without it (31% vs. 24% and 33% vs. 25%, respectively, both $p < 0.001$). Several variables assessed at ICU admission were associated with an increased risk of developing nosocomial bacterial pneumonia in the multivariable analysis (Table 2, Panel A), notably male gender, older age, administration of antibiotics prior to ICU admission, mechanical ventilation, and corticosteroids, but hyperglycemia was not one of them. However, the factors associated with in-hospital mortality (Table 2, Panel B) did include hyperglycemia at ICU admission.

When we separately analyzed diabetic and non-diabetic patients according to the presence of hyperglycemia at ICU admission, we found that the prevalence of hyperglycemia amongst the former was 86.7%, as against 56.9% in the latter. Furthermore, hyperglycemia did not impact outcomes in patients with diabetes, who, overall, presented poorer outcomes than non-diabetic patients (Supplementary Tables 1 and 2). Moreover, when multivariable analyses of risk factors for bacterial pneumonia and in-hospital mortality were run for both groups separately, hyperglycemia was not found to predict either outcome in diabetic or non-diabetic patients (Supplementary Tables 3 and 4). A receiving operating curve showed a cut-off of 150 mg/dL for hyperglycemia, allowing for a better discrimination of outcomes than 126 mg/dL in the overall cohort (Supplementary Figure 1), although it did not predict bacterial pneumonia in the multivariable analysis (Supplementary table* 5).

The prevalence of hyperglycemia at ICU admission in our cohort was found to be strikingly high, even though only a quarter of the patients were diabetic. Moreover, although a higher percentage

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Table 1
Demographic and clinical characteristics of the study population by hyperglycemia.

Variables	All patients (*N* = 5763)	No hyperglycemia (*N* = 2059)	Hyperglycemia (*N* = 3704)	*p*-Value
Age, median (Q1; Q3), years	63 (54; 71)	61 (51; 69)	65 (56; 72)	**<0.001**
Male sex, *n* (%)	4061 (71)	1420 (69)	2641 (71)	0.058
BMI, median (Q1; Q3), kg/m²	28.8 (26; 32.3)	28.2 (25.6; 31.6)	29.3 (26.1; 32.7)	**<0.001**
BMI, *n* (%)				**<0.001**
Underweight (<18.5 kg/m²)	14 (0.3)	7 (0.4)	7 (0.2)	0.265
Normal weight (≥18.5 to <25 kg/m²)	871 (17)	380 (21)	491 (15)	**<0.001**
Pre-obese (≥25 to <30 kg/m²)	2134 (42)	771 (43)	1363 (42)	0.632
Obese (≥30 kg/m²)	2055 (41)	656 (36)	1399 (43)	**<0.001**
Comorbidities, *n* (%)				
Active smoker	309 (6)	106 (6)	203 (6)	0.466
Hypertension	2904 (50)	863 (42)	2041 (55)	**<0.001**
Diabetes mellitus	1425 (25)	189 (9)	1236 (33)	**<0.001**
Dyslipidemia	1793 (31)	527 (26)	1266 (34)	**<0.001**
Chronic heart disease	734 (13)	206 (10)	528 (14)	**<0.001**
Chronic liver disease	200 (3)	75 (4)	125 (3)	0.595
Chronic lung disease	887 (15)	291 (14)	596 (16)	**0.048**
Chronic renal failure	406 (7)	139 (7)	267 (7)	0.514
Immunosuppression	236 (4)	98 (5)	138 (4)	0.057
Nursing-home, *n* (%)	90 (2)	30 (1)	60 (2)	0.617
Previous 30 days admission, *n* (%)	201 (3)	83 (4)	118 (3)	0.094
Previous antibiotic, *n* (%)	796 (14)	284 (14)	512 (14)	0.942
Days from first symptoms to hospital admission, median (Q1; Q3)	7 (5; 9)	7 (5; 9)	7 (4; 9)	0.741
Days from hospital admission to ICU admission, median (Q1; Q3)	1 (0; 4)	2 (0; 4)	1 (0; 3)	**<0.001**
Symptoms at hospital admission, *n* (%)				
Fever	4813 (84)	1773 (87)	3040 (83)	**<0.001**
Dry cough	3509 (62)	1299 (64)	2210 (60)	**0.019**
Productive cough	736 (13)	281 (14)	455 (12)	0.142
Dyspnoea	4151 (73)	1469 (72)	2682 (73)	0.321
Fatigue	2240 (39)	779 (38)	1461 (40)	0.188
Muscle pain	1533 (27)	588 (29)	945 (26)	**0.018**
Diarrhoea	1229 (22)	436 (21)	793 (22)	0.781
Confusion	260 (5)	69 (3)	191 (5)	**0.001**
Characteristics on ICU admission				
Glasgow Coma Scale, median (Q1; Q3)	15 (15; 15)	15 (15; 15)	15 (14; 15)	**<0.001**
APACHE-II score, median (Q1; Q3)	12 (9; 15)	11 (8; 14)	12 (9; 16)	**<0.001**
SOFA score, median (Q1; Q3)	5 (3; 7)	4 (3; 7)	5 (4; 8)	**<0.001**
Temperature, median (Q1; Q3), ◦C	36.7 (36; 37.5)	36.9 (36.1; 37.7)	36.7 (36; 37.4)	**<0.001**
Respiratory rate, median (Q1; Q3), breaths per min	25 (21; 31)	25 (21; 32)	25 (21; 30)	0.071
Arterial blood gases at ICU admission				
PaO_2/FiO_2 ratio, median (Q1; Q3)	112 (80; 164)	112.9 (78.6; 166)	111.5 (80; 162.3)	0.979
PaO_2/FiO_2 ratio, n (%)				0.995
Severe (<100)	2040 (42)	702 (42)	1338 (42)	–
Moderate (≥100 to <200)	2063 (42)	715 (43)	1348 (42)	–
Mild (≥200 to <300)	556 (11)	190 (11)	366 (11)	–
No ARDS (≥300)	215 (4)	75 (4)	140 (4)	–
pH, median (Q1; Q3)	7.41 (7.34; 7.46)	7.43 (7.36; 7.46)	7.40 (7.32; 7.45)	**<0.001**
$PaCO_2$, median (Q1; Q3), mmHg	39 (34; 47)	38 (33; 45)	40 (34; 48)	**<0.001**
Laboratory findings at ICU admission				
Glucose, median (Q1; Q3), mg/dL	143 (114; 191)	106 (95; 116)	172 (145; 226)	**<0.001**
Hemoglobin, median (Q1; Q3), g/dL	13.2 (12; 14.4)	13.3 (11.9; 14.4)	13.2 (12; 14.3)	0.710
Leucocyte count, median (Q1; Q3), 10^9/L	8.9 (6.4; 12.5)	8.3 (6; 11.6)	9.3 (6.6; 13)	**<0.001**
Lymphocyte count, median (Q1; Q3), 10^9/L	0.69 (0.47; 0.98)	0.76 (0.50; 1.04)	0.63 (0.41; 0.90)	**<0.001**
Neutrophil count, median (Q1; Q3), 10^9/L	7.7 (5.2; 11.1)	6.9 (4.8; 10.1)	8.1 (5.6; 11.6)	**<0.001**
Neutrophil-to-lymphocyte ratio, median (Q1; Q3)	11.2 (6.7; 18.5)	9 (5.5; 15.4)	12.4 (7.8; 20.5)	**<0.001**
Platelet count, median (Q1; Q3), 10^9/L	232 (177; 303)	230 (174; 304)	232 (177; 303)	0.435
D-dimers, median (Q1; Q3), ng/mL	993 (511; 2289)	920 (480; 2139)	1016 (530; 2427)	**0.001**
Ferritin, median (Q1; Q3), ng/mL	1142 (605; 1881)	1143 (626; 1858)	1142 (598; 1888)	0.546
C-reactive protein, median (Q1; Q3), mg/L	130 (62; 221)	132 (61; 226)	128 (63; 220)	0.711
C-reactive protein ≥150 mg/L, n (%)	2365 (43)	863 (44)	1502 (43)	0.328
C-reactive protein-to-lymphocyte ratio, median (Q1; Q3)	183.3 (78;3; 361.6)	169.4 (68.5; 336.7)	192.9 (83.4; 375.4)	**<0.001**
IL-6, median (Q1; Q3), pg/mL	82.2 (27.6; 223.7)	106 (41.4; 277.4)	68.7 (23.7; 202)	**<0.001**
Serum creatinine, median (Q1; Q3), mg/dL	0.83 (0.67; 1.08)	0.80 (0.64; 1.00)	0.86 (0.69; 1.13)	**<0.001**
LDH, median (Q1; Q3), U/L	475 (362; 651)	477 (363; 640)	472 (361; 654)	0.574
Respiratory support at ICU admission, *n* (%)				**<0.001**
Conventional oxygen therapy	409 (7)	209 (10)	200 (5)	**<0.001**
High-flow nasal cannula	1600 (29)	724 (35)	876 (24)	**<0.001**
Non-invasive mechanical ventilation	635 (10)	231 (11)	404 (11)	0.708
Invasive mechanical ventilation	3114 (54)	892 (43)	2222 (60)	**<0.001**
Septic shock at ICU admission, *n* (%)[a]	402 (8)	76 (4)	326 (10)	**<0.001**
Corticosteroids during ICU admission, *n* (%)	4916 (86)	1656 (81)	3260 (89)	**<0.001**
Remdesivir during ICU admission, *n* (%)	871 (15)	334 (16)	537 (15)	0.082
Complications during ICU admission, *n* (%)				
Bacterial pneumonia[b]	1621 (28)	485 (24)	1136 (31)	**<0.001**
Acute renal failure	1841 (32)	556 (27)	1285 (35)	**<0.001**
Liver dysfunction	1744 (30)	633 (31)	1111 (30)	0.542

Table 1 (*Continued*)

Variables	All patients (*N* = 5763)	No hyperglycemia (*N* = 2059)	Hyperglycemia (*N* = 3704)	*p*-Value
Cardiac injury[c]	659 (11)	184 (9)	475 (13)	**<0.001**
Outcomes				
Length of hospital stay, median (Q1; Q3), days				
All patients	24 (15; 40)	23 (15; 39)	24 (15; 41)	0.183
Surviving patients	26 (16; 45)	24 (15; 41)	27 (16; 47.5)	**<0.001**
Length of ICU stay, median (Q1; Q3), days				
All patients	14 (7; 28)	13 (7; 25)	14 (8; 29)	**<0.001**
Surviving patients	13 (7; 28)	12 (6; 23)	14 (7; 30)	**<0.001**
ICU mortality, n (%)	1648 (29)	492 (24)	1156 (31)	**<0.001**
In-hospital mortality, n (%)	1741 (30)	513 (25)	1228 (33)	**<0.001**
90-day mortality, n (%)[d]	1733 (33)	513 (27)	1220 (36)	**<0.001**

Abbreviations: ICU indicates intensive care unit; Q1, first quartile; Q3, third quartile; BMI, body mass index; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; LDH, lactate dehydrogenase. Percentages calculated on non-missing data. *p*-Values marked in bold indicate numbers that are statistically significant on the 95% confidence limit.

[a] Criteria for the Sepsis-3 definition of septic shock include vasopressor treatment and a lactate concentration >2 mmol/L.

[b] Clinically or radiologically diagnosed bacterial pneumonia managed with antimicrobials. Bacteriological confirmation was not required.

[c] Cardiac injury include cardiac arrest, myocardial infarction, endocarditis, myocarditis/pericarditis, cardiomyopathy, heart failure and cardiac ischemia.

[d] Calculated only for patients with 90-day follow-up (1895 in the non-invasive mechanical ventilation group and 3418 in the invasive mechanical ventilation group).

of patients in the hyperglycemia group received systemic corticosteroids, the vast majority of patients only started receiving corticosteroids once they had been admitted to the ICU – i.e., after hyperglycemia was detected. The most likely explanation is the systemic inflammation induced by COVID-19 itself, which has been widely demonstrated in several previous studies.[12] However, we did not assess the percentage of non-diabetic patients who developed, during admission for COVID-19, de novo diabetes that persisted after discharge or until death. This omission prevented us from comparing our results with those of Cromer and colleagues,[13] who recently found that diabetes diagnosed at the presentation of COVID-19 is associated with lower glucose but higher inflammatory markers and a greater likelihood of ICU admission, suggesting that stress hyperglycemia is a significant physiological mechanism. Interestingly, these authors found that 31.2% of their patients were diabetic – in line with our results –, whereas only 13.2% of their patients fulfilled the criteria for newly diagnosed diabetes at some point. Approximately half of these individuals experienced a regression of DM.[13] Remarkably, however, although hyperglycemia was found to be a risk factor for in-hospital mortality in the overall cohort, only non-diabetic patients developed significantly poorer outcomes when presenting hyperglycemia at admission. This finding is crucial to the interpretation of our findings and the subsequent extraction of clinical conclusions, and it also presents the ability to predict mortality more accurately, with a higher cut-off than that of the traditional definition of hyperglycemia (i.e., 150 mg/dL than 126 mg/dL).

Interestingly, while the prevalence of bacterial pneumonia in our cohort was high overall, presentation of hyperglycemia did not predict bacterial pneumonia in the whole cohort or in patients with diabetes, whereas non-diabetic patients with hyperglycemia did have a significantly higher prevalence of bacterial pneumonia than those not presenting hyperglycemia at admission. The higher incidence of bacterial nosocomial pneumonia found in COVID-19 patients compared to other critically ill has mostly been linked to the long duration of invasive mechanical ventilation, the high incidence of ARDS, and immune-suppressive treatment.[14] The non-diabetic patients in our cohort with hyperglycemia had higher rates of invasive mechanical ventilation and immune-suppressive treatment, but not ARDS. While the quality of evidence on the

Table 2
Multivariable models assessing predictors of bacterial pneumonia using mixed-effects regression analysis (Panel A) and predictors of in-hospital mortality using competing risks survival analysis (Panel B).

Panel A		
Variables	OR (95% CI)	*p*-Value
Age (+1 year)[a]	1.01 (1.01 to 1.02)	<0.001
Male sex	0.77 (0.67 to 0.89)	<0.001
Chronic heart disease	1.03 (0.86 to 1.25)	0.728
Chronic liver disease	1.36 (0.97 to 1.89)	0.073
Chronic lung disease	0.91 (0.76 to 1.08)	0.277
Chronic renal failure	0.76 (0.59 to 0.99)	0.041
Immunosuppression	1.50 (1.08 to 2.06)	0.014
Previous 30 days admission	0.95 (0.66 to 1.36)	0.767
Previous antibiotic	0.81 (0.67 to 0.98)	0.027
C-reactive protein at ICU admission (+50 mg/L)[b]	1.02 (1.00 to 1.03)	0.077
Lymphocyte count (+1 × 10^9/L)[a]	0.98 (0.94 to 1.03)	0.435
Platelet count at ICU admission (+50 × 10^9/L)[b]	0.97 (0.94 to 1.00)	0.046
Ferritin at ICU admission (+1000 ng/mL)[c]	1.02 (0.98 to 1.05)	0.295
D-dimers at ICU admission (+1000 ng/mL)[c]	1.00 (1.00 to 1.00)	0.644
LDH at ICU admission (+50 U/L)[b]	1.01 (1.00 to 1.02)	0.045
Hyperglycemia (glucose ≥ 126 mg/dL) at ICU admission	1.13 (0.98 to 1.29)	0.088
Respiratory support at ICU admission		
Conventional oxygen therapy	1.00	–
High-flow nasal cannula	1.44 (1.03 to 2.01)	0.031
Non-invasive mechanical ventilation	2.09 (1.43 to 3.06)	<0.001
Invasive mechanical ventilation	3.46 (2.53 to 4.75)	<0.001
Corticosteroids during ICU admission	1.71 (1.39 to 2.10)	<0.001

Table 2 (*Continued*)

Panel B		
Variables	sHR (95% CI)	*p*-Value
Age (+1 year)[a]	1.06 (1.05 to 1.06)	<0.001
Male sex	0.85 (0.76 to 0.95)	0.005
Chronic heart disease	1.17 (1.03 to 1.34)	0.019
Chronic liver disease	1.07 (0.83 to 1.38)	0.62
Chronic lung disease	1.23 (1.08 to 1.40)	0.002
Chronic renal failure	1.56 (1.32 to 1.85)	<0.001
Immunosuppression	1.60 (1.28 to 2.00)	<0.001
Previous 30 days admission	1.42 (1.13 to 1.78)	0.002
C-reactive protein at ICU admission (+50 mg/L)[b]	1.01 (1.00 to 1.02)	0.062
Lymphocyte count (+1 × 10^9/L)[a]	1.01 (0.98 to 1.03)	0.64
Platelet count at ICU admission (+50 × 10^9/L)[b]	0.93 (0.91 to 0.96)	<0.001
Ferritin at ICU admission (+1000 ng/mL)[c]	1.00 (0.97 to 1.03)	0.96
D-dimers at ICU admission (+1000 ng/mL)[c]	1.00 (1.00 to 1.01)	0.005
LDH at ICU admission (+50 U/L)[b]	1.02 (1.01 to 1.02)	<0.001
Hyperglycemia (glucose ≥ 126 mg/dL) at ICU admission	1.14 (1.03 to 1.27)	0.016
Bacterial pneumonia during ICU admission	1.07 (0.96 to 1.20)	0.20
Respiratory support at ICU admission		
Conventional oxygen therapy	1.00	–
High-flow nasal cannula	0.85 (0.66 to 1.10)	0.22
Non-invasive mechanical ventilation	1.38 (1.04 to 1.82)	0.023
Invasive mechanical ventilation	1.59 (1.25 to 2.03)	<0.001
Corticosteroids during ICU admission	0.79 (0.67 to 0.93)	0.004
Remdesivir during ICU admission	0.82 (0.71 to 0.94)	0.006

Abbreviations: OR indicates odds ratio; CI, confidence interval; ICU, intensive care unit; LDH, lactate dehydrogenase; sHR indicates subdistribution hazard ratio. In Panel A data are shown as estimated ORs (95% CIs) of the explanatory variables in the bacterial pneumonia group and the *p*-value is based on the null hypothesis that all ORs relating to an explanatory variable equal unity (no effect). Area under the ROC curve, AUC = 0.75 (95% CI 0.73–0.76). In Panel B data are shown as estimated sHRs (95% CIs) of the explanatory variables in the in-hospital mortality group and the *p*-value is based on the null hypothesis that all sHRs relating to an explanatory variable equal unity (no effect).

[a] "+1" means a one-unit increase on the scale in the predictor variable (i.e., going from 1 to 2, 2 to 3, etc.).

[b] "+50" means a fifty-unit increase on the scale in the predictor variable (i.e., going from 1 to 50, 50 to 100, etc.).

[c] "+1000" means a one thousand-unit increase on the scale in the predictor variable (i.e., going from 1000 to 2000, 2000 to 3000, etc.).

risk factors for ventilator-associated hospital-acquired pneumonia unrelated to COVID-19 is moderate-good, this is not the case for pneumonia not associated with the use of ventilators.[15] Furthermore, systematic reviews and meta-analyses have consistently found corticosteroids to be a risk factor, along with invasive mechanical ventilation and diabetes, whereas this is not true of hyperglycemia.[14] Further studies are needed to investigate the risk factors for developing nosocomial pneumonia, particularly in non-ventilated critically ill COVID-19 patients.

Our study is limited by the lack of data on antidiabetic therapy, disease baseline control in diabetics (e.g., glycosylated hemoglobin), and the rate of new diagnoses of diabetes during the index episode.

In summary, we found that, overall, patients presenting with hyperglycemia at ICU admission had more aggressive and severe COVID-19 (i.e., less time between hospital and ICU admissions), as well as poorer outcomes, including in-hospital mortality. Hyperglycemia appears to be a better predictor of poor outcomes in non-diabetic than in diabetic patients. Early detection and management of hyperglycemia is required in hospitalized COVID-19 patients.

Authors' contributions

Study concept and design: CC, AM, AT; data collection: CC, AM, AP, TC, AC; statistical analysis: AG; analysis and interpretation of data: CC, AM, JP, TC, AT; drafting of the manuscript: CC, AM, JP, AT; critical revision of the manuscript for important intellectual content: CC, AM, JP, AT; and study supervision: AT. AT had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript. CIBERESUCICOVID consortium participated in data collection.

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Competing interests

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2022.09.001.

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