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Journal of Infection 82 (2021) e38–e41

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Letter to the Editor

SARS-CoV-2 RNAemia is associated with severe chronic underlying diseases but not with nasopharyngeal viral load

Dear Editor,

The kinetics of the SARS-CoV-2 viral load in respiratory airways and other tissues is of great interest to understand the pathogenesis, course, and the management of COVID-19 patients. Therefore, we read with much interest the systematic literature review recently published in the Journal of Infection by Walsh et al.[1], concluding that viral load in upper respiratory samples peaks around the time of symptoms onset or a few days thereafter, and becomes undetectable about two weeks after symptom onset; moreover, there is evidence of prolonged virus detection in stool samples, with unclear clinical significance. Information regarding the use of other samples to improve patients' management is lacking or inconsistent.[1–3] Thus, the risk factors for bloodstream infection and the clinical meaning of SARS-CoV-2 RNAemia detection has not yet been completely elucidated.

In this regard, we conducted a prospective multicentre cohort study of consecutive COVID-19 adult patients aimed to identify the factors associated with the detection of SARS-CoV-2 RNAemia at hospital admission and if its presence is associated with an unfavourable outcome, defined as intensive care unit (ICU) admission and/or death. Information regarding the study design and the methodology used is provided in the Supplementary Materials file.

Seventy-two patients were included, with a median age of 61 years old. Forty-one (56.9%) were male and 41 (56.9%) had a Charlson comorbidity index ≥3 (Table 1). After their evaluation in the emergency room, sixty-three (87.5%) patients were admitted to the hospital, and nine (12.5%) were managed in an outpatient´setting. SARS-CoV-2 RNAemia was detected in eleven (15.3%) patients, 10 of them admitted to the hospital (Table 1).

Arthro-myalgias were the only symptom more frequently observed in COVID-19 patients with SARS-CoV-2 RNAemia compared to those without RNAemia. SARS-CoV-2 RNAemia was detected more frequently in patients with chronic liver disease (27.3% *vs.* 0.0%, $P=0.001$) and in solid organ transplant (SOT) recipients (36.4% *vs.* 1.6%, $P=0.001$). Fifty-six (77.8%) patients had pneumonia, 49 (87.5%) of them were admitted to the hospital; 20 (35.7%) of the pneumonia cases presented a CURB-65 score ≥2, with no differences between the groups with and without RNAemia (Table 1). Other laboratory analytical and chest X-rays data, and therapy, in patients with and without SARS-CoV-2 RNAemia are detailed in Table 1.

The median viral load in plasma for the 11 patients with SARS-CoV-2 RNAemia was 2.88 Log_{10} copies/mL (IQR, 2.43–4.07) and the median viral load in NP swabs of the 72 patients was 6.98 Log_{10} copies/mL (IQR, 5.15–8.20). There was no significant difference in the viral load in NP swabs between patients with (7.29 Log_{10} copies/mL [IQR, 6.56–8.78]) and without RNAemia (6.64 Log_{10} copies/mL [5.14–7.86], $P=0.262$) (Supplementary Figure 1), and we didn't find a correlation between the viral load in NP and blood samples for the eleven patients with RNAemia (Supplementary Figure 2). Additionally, we found a unique case (1.4%) of co-infection with metapneumovirus and parainfluenza virus 3, both detected in blood of a patient without RNAemia.

As for their clinical outcomes, patients with SARS-CoV-2 RNAemia required more frequently ICU admission (45.50% *vs.* 8.2%, $P=0.005$), showed more frequently acute respiratory distress syndrome (ARDS) (54.5% *vs.* 9.8%, $P=0.01$) and required in more cases invasive mechanical ventilation (36.4% *vs.* 6.6%, $P=0.018$). Mortality (36.4% *vs.* 4.9%, $P=0.007$) and unfavourable outcome (63.6% *vs.* 13.1%, $P=0.001$), were also more frequent in patients with SARS-CoV-2 RNAemia (Table 2).

Results from other studies show discordant rates of SARS-CoV-2 detection in serum, ranging from 10.4% to 74.1%,[2, 4-7] while other authors do not find any patient[8] or report only 1% of RNAemia.[2] Veyer et al. also found higher frequency of SARS-CoV-2 RNAemia in more severely ill patients, however they were included at the time of respiratory deterioration and those with pre-existing unstable chronic disorders were excluded.[6] Most patients presented with chronic underlying diseases (66.7%), a percentage that shows high variability, from the 23.7% reported by Guan et al.[9] to higher percentages (79%) depending on the number and type of the comorbidities considered in each case.[5]

Our results confirm those from Prebensen et al. who did not find an association between the viral load in NP samples and the presence of SARS-CoV-2 RNAemia nor correlation with the viral load in blood.[7] In the present study, the worst clinical evolution and outcome in patients with RNAemia and the lack of correlation between the viral load in NP samples and blood, besides the absence of difference in the NP viral load between patients with and without SARS-CoV-2 RNAemia, support that it is a better indicator of the clinical evolution of COVID-19 patients than NP viral load.

SARS-CoV-2 RNAemia has been shown to be associated with high levels of IL-6 in critically ill COVID-19 patients, and both factors were related to mortality.[4] According to our experience, the levels of D-dimers, which are also used as markers of inflammation, were also higher in patients with SARS-CoV-2 RNAemia. The frequency of patients with elevated levels of AST and LDH, and those with decreased counts of lymphocytes and platelets were in agreement with previous reports,[2, 9, 10] although in our cohort these findings were associated with the presence of SARS-CoV-2 RNAemia.

Regarding the clinical meaning of the SARS-CoV-2 RNAemia, our results agree with those reported by other authors, suggesting an association with underlying diseases and a worst clinical evolution, although without the limitations of including only patients more severely ill, or excluding those with underlying chronic diseases or receiving therapies that may influence the outcome.[5-7] Our results

https://doi.org/10.1016/j.jinf.2020.11.024
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Table 1
Demographics and baseline characteristics of patients with and without SARS-CoV-2 RNAemia.

Variables, *N* (%)	*N* = 72 patients		OR[a]	*P*-value[b]
	With viremia (*N* = 11)	Without viremia (*N* = 61)		
Demographics				
Age (median [IQR])	66 (57–77)	61 (52–75)	[..]	0.531
Male sex	6 (54.5%)	35 (57.4%)	0.891 (0.245–3.241)	1.000
Underlying conditions				
Any underlying chronic disease	8 (72.7%)	40 (65.6%)	1.400 (0.336–5.839)	0.908
Chronic kidney disease	2 (18.2%)	7 (11.5%)	1.714 (0.306–9.599)	0.901
Chronic liver disease	3 (27.3%)	0 (0.0%)	0.116 (0.060–0.222)	0.001
Connective tissue disease	2 (18.2%)	4 (6.4%)	3.167 (0.504–19.883)	0.489
Solid organ transplantation	4 (36.4%)	1 (1.6%)	34.284 (3.346–351.308)	0.001
Charlson index $\geq$ 3	8 (72.7%)	33 (54.1%)	2.236 (0.547–9.354)	0.413
Previous Treatment				
Previous statins	1 (9.1%)	12 (19.7%)	0.408 (0.048–3.507)	0.679
Previous ACEI	1 (9.1%)	12 (19.7%)	0.408 (0.048–3.507)	0.647
Clinical symptoms at diagnosis				
Arthro-myalgias	5 (45.5%)	7 (11.5%)	6.429 (1.547–26.709)	0.019
Weakness	4 (36.4%)	20 (32.8%)	1.171 (0.307–4.473)	1.000
Cough	7 (63.6%)	38 (62.3%)	1.059 (0.279–4.018)	1.000
Dyspnoea	7 (63.6%)	24 (42.9%)	2.233 (0.612–8.890)	0.206
Coryza	0 (0%)	3 (4.9%)	0.841 (0.758–0.932)	1.000
Odynophagia	1 (9.1%)	7 (11.5%)	0.771 (0.085–6.971	1.000
Diarrhoea	4 (36.6%)	12 (19.7%)	2.333 (0.586–9.286)	0.406
Headache	3 (27.3%)	12 (19.7%)	1.531 (0.352–6.656	0.867
Anosmia	1 (9.1%)	11 (18%)	0.455 (0.053–3.929)	0.770
Dysgeusia	1 (9.1%)	9 (14.8%)	0.578 (0.066–5.081)	0.979
Vital signs, exploration, and severity scores at diagnosis				
Temperature (°C, median [IQR])	36.4 (36–37.8)	36.6 (36.1–37.6)	[..]	0.982
SBP < 90 mmHg	0 (0%)	2 (3.3%)	0.843 (0.762–0.933)	1.000
DBP < 60 mmHg	2 (18.2%)	1 (1.6%)	13.333 (1.094–162.532)	0.088
$SatO_2$< 95% at diagnosis	6 (54.5%)	15 (24.6%)	3.680 (0.981–13.806)	0.099
HR $\geq$ 100 bpm (N = 64)	6 (66.7%)	15 (27.3%)	5.333 (1.181–24.085)	0.051
RR $\geq$ 20 bpm(N = 60)	1 (9.1%)	0 (0%)	0.169 (0.096–0.289)	0.409
qSOFA $\geq$ 2	1 (9.1%)	11 (18%)	0.455 (0.053–3.929)	0.770
Chest x-ray findings				
Pneumonia	9 (81.8%)	47 (77%)	1.340 (0.259–6.940)	1.000
Bilateral infiltrates	8 (88.9%)	32 (78.0%)	2.250 (0.248–20.438)	0.665
CURB-65 $\geq$ 2	5 (55.5%)	15 (31.9%)	2.556 (0.681–9.587)	0.291
Laboratory results				
Leucocytes ($x10^3$/μL, median [IQR])	5.22 (3.47–7.06)	7.00 (5.24–9.20)	[..]	0.030
Leucocytes > 11,000 /μL	1 (9.1%)	8 (13.1%)	0.663 (0.074–5.896)	1.000
Neutrophils ($x10^3$/μL, median [IQR])	3.49 (2.96–5.90)	4.79 (3.30–6.88)	[..]	0.348
Neutrophils > 7500 /μL	1 (9.1%)	11 (18.0%)	0.455 (0.053–3.929)	0.677
Lymphocytes (10^3/μL median [IQR])	0.58 (0.39–1.24)	1.36 (0.92–1.80)	[..]	0.002
Lymphocytes < 1000 /μL	7 (63.6%)	18 (29.5%)	4.181 (1.088–16.063)	0.065
Platelets ($x10^3$/μL, median [IQR])	158 (129–201)	248 (175–325)	[..]	0.002
Platelets < 130,000 /μL	3 (27.3%)	4 (6.6%)	5.344 (1.006–28.383)	0.067
Haemoglobin (g/L, median [IQR])	13 (11.2–15.1)	13.8 (12.10–14.8)	[..]	0.191
AST (IU/L, median [IQR]) (N = 63)	37 (26–68)	26 (20–41)	[..]	0.074
AST > 30 IU/L	8 (72.7%)	19 (36.5%)	4.632 (1.095–19.587)	0.063
ALT (IU/L, median [IQR]) (N = 70)	33 (17–40)	23 (17–44)	[..]	0.374
ALT > 40 IU/L	2 (18.2%)	16 (27.1%)	0.597 (0.116–3.067)	0.805
Bilirubin (mg/dL, mean ± SD) (N = 61)	0.59 (0.36–0.68)	0.46 (0.35–0.81)	[..]	0.911
Sodium < 135 mEq/L (N = 71)	2 (18.2%)	4 (6.7%)	3.111 (0.495–19.541)	0.501
Potassium > 5 mEq/L (N = 70)	2 (18.2%)	1 (1.7%)	12.889 (1.057–157.184)	0.095
Creatinine > 1.3 mg/dL (N = 62)	4 (44.4%)	6 (10.7%)	6.667 (1.395–31.849)	0.035
C-reactive protein (mg/L, median [IQR]) (N = 71)	97.9 (33.9–205.0)	44.9 (17.1–98.5)	[..]	0.187
C-reactive protein > 100 mg/L (N = 71)	5 (45.5%)	14 (23.3%)	2.738 (0.725–10.343)	0.249
Ferritin (ng/L, median [IQR]) (N = 63)	625.6 (366.5–1009.2)	442 (191.4–817.3)	[..]	0.275
Ferritin > 1000 ng/mL (N = 63)	2 (20%)	10 (18.9%)	1.075 (0.197–5.858)	1.000
D-dimers (ng/L, median [IQR]) (N = 70)	1430 (770–2620)	620 (380–1140)	[..]	0.043

(*continued on next page*)

Table 1 (*continued*)

Variables, *N* (%)	*N* = 72 patients With viremia (*N* = 11)	Without viremia (*N* = 61)	OR[a]	*P*-value[b]
D-dimers > 600 ng/mL (*N* = 70)	10 (90.9%)	30 (58.8%)	9.667 (1.163–80.337)	0.033
LDH (UI/L, median [IQR]) (*N* = 65)	450 (312–660)	251.5 (213.0–320.5)	[..]	0.001
LDH > 300 UI/L(*N* = 65)	9 (81.8%)	17 (31.5%)	9.794 (1.907–50.302)	0.006
SARS-CoV-2 in nasopharynx Log_{10} copies/mL, median (IQR)	7.3 (6.6–8.8)	6.6 (5.1–7.9)	[..]	0.262
Hospital admission	10 (90.9%)	53 (86.9%)	1.509 (0.170–13.432)	1.000
Treatments				
Antiviral treatment	9 (81.8%)	55 (90.2%)	1.244 (0.339–4.563)	0.772
LPV/r	0 (0%)	5 (8.2%)	0.836 (0.755–0.929)	0.734
Hydroxychloroquine	1 (9.1%)	21 (34.4%)	0.190 (0.023–1.591)	0.186
LPV/*r* + hydroxychloroquine	6 (54.5%)	24 (39.3%)	1.850 (0.508–6.742)	0.542
LPV/*r* + hydroxychloroquine + IFN-β	2 (18.2%)	2 (3.3%)	6.551 (0.818–52.56)	0.204
Remdesivir	0 (0%)	7 (11.5%)	0.831 (0.744–0.921)	0.529
Tocilizumab	3 (27.3%)	4 (6.6%)	5.344 (1.006–28.383)	0.114
Initial antibacterial treatment	5 (45.5%)	25 (41%)	1.200 (0.330–4.367)	1.000

ACEI: angiotensin-converting enzyme inhibitors; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; RR: respiratory rate. AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; LPV/r: lopinavir/ritonavir; IFN-β: beta interferon. [a]Risk estimation from Chi-squared test, Studentś *t*-test and *U*-value from the Mann-Whitneyś test. 95% confidence intervals, according to indication, appear in parentheses. [b]Two-tailed test.

Table 2
Clinical outcomes of patients with and without SARS-CoV-2 RNAemia.

Variables N (%)	*N* = 72 patients With viremia (*N* = 11)	Without viremia (*N* = 61)	OR[a]	*P*-value[b]
ARDS	6 (54.5%)	6 (9.8%)	11.0 (2.563–47.112)	0.001
IMV	4 (36.4%)	4 (6.6%)	8.143 (1.656–40.041)	0.018
Multiple organ failure	1 (9.1%)	0 (0%)	0.141 (0.079–0.250)	0.331
ICU admission	5 (45.5%)	5 (8.2%)	9.33 (2.086–41.765)	0.005
Length of stayDays, median (IQR)	5 (0–19)	6 (2.5–11)	[..]	0.440
Mortality	4 (36.4%)	3 (4.9%)	11.048 (2.039–59.868)	0.007
Unfavourable outcome (ICU admission and/or death)	7 (63.6)	8 (13.1)	11.59 (2.76–48.73)	0.001

ARDS: Acute Respiratory Distress Syndrome; IMV: invasive mechanical ventilation; ICU: Intensive Care Unit. [a]Risk estimation from Chi-squared test, Studentś *t*-test and *U*-value from the Mann-Whitneyś test. 95% confidence intervals, according to indication, appear in parentheses. [b]Two-tailed test.

show that COVD-19 patients with SARS-CoV-2 RNAemia are more likely to develop ARDS than those without RNAemia and show increased needs of ICU admission, in agreement with Prebensen et al.,[7] and invasive mechanical ventilation.

In conclusion, the results of the present study show that the presence of the SARS-CoV-2 RNAemia, at the first evaluation in the emergency room, occurs more frequently in patients with severe underlying chronic diseases, such as chronic liver disease and solid organ transplantation, is not predicted by the viral load in the upper respiratory airways, and it is associated with unfavourable outcome.

Declaration of Competing Interest

None of the study authors have conflicts of interest to declare.

Acknowledgments

Supported by Plan Nacional de $I+D+i$ 2013–2016 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Ministerio de Economía, Industria y Competitividad, Spanish Network for Research in Infectious Diseases (REIPI, RD16/0016/0001, RD16/0016/0005, RD16/0016/0007, RD16/0016/0009, RD16/0016/0010, R D16/0016/0013) cofinanced by European Development Regional Fund “A way to achieve Europe”, Operative program Intelligent Growth 2014–2020. JSC and EC received grants from the Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación, Proyectos de Investigación sobre el SARS-CoV-2 y la enfermedad COVID-19 (COV20/00580; COV20/00370). J.S.C. is a researcher belonging to the program “Nicolás Monardes” (C-0059–2018), Servicio Andaluz de Salud, Junta de Andalucía, Spain.

Ethics approval

The study protocol was approved by the Ethics Committee of Virgen Macarena and Virgen del Rocío University Hospitals (C.I. 0771-N-20) and complied the Declaration of Helsinki.

Consent for publication

All authors have approved the manuscript and its publication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2020.11.024.

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