

Risk factors for SARS-CoV-2 detection in blood of critically ill patients.

Niccolò Buetti^{1*}, Juliette Patrier^{2*}, Quentin Le Hingrat³, Ambre Loidice¹, Lila Bouadma^{1,2}, Benoit Visseaux³, Jean-François Timsit^{1,2}

- 1) University of Paris, INSERM, IAME, Team DeSCID, Paris, France
- 2) Medical and Infectious Diseases ICU (MI2), Bichat-Claude Bernard Hospital, AP-HP, 75018, Paris, France
- 3) Paris University, AP-HP, Hôpital Bichat-Claude-Bernard, IAME, Inserm, Laboratoire de virologie, 46 rue Henri-Huchard 75018 Paris, France

***equal contribution.**

Corresponding author: Niccolò Buetti, MD, MSc. Rue Henri Huchard, Faculté de médecine, INSERM, IAME, Team Descid, 75018 Paris. 0033782436010. Email: niccolo.buetti@gmail.com.

Dear Editor,

Data on detection of SARS-CoV-2 viral RNA within COVID-19 patients' blood are scarce [1-3]. The recently published article by Veyer *et al.* described plasma SARS-CoV-2 viral load in 58 non-critically and critically ill patients [4]. In their multivariate analysis the authors showed that SARS-CoV-2 RNAemia was strongly associated with the clinical class, with higher level RNAemia among critically ill patients. However, to date, risk factors for detectable SARS-CoV-2 RNAemia in critically ill patients remain unknown. Therefore, we conducted a similar study using prospectively collected data at the Bichat University Hospital, France, in order to identify risk factors for SARS-CoV-2 detection in blood in critically ill intubated patients. All included patients had a SARS-CoV-2 positive nasopharyngeal swab before intensive care (ICU) admission. During the ICU stay, all patients underwent a regularly monitoring of SARS-CoV-2 RNAemia. All blood specimens were sent to the virology laboratory and used for RNA extraction, using MagnaPure Large Volume Total NA kit (Roche), and amplification by real time polymerase chain reaction (RT-PCR) techniques using RealStar SARS-CoV-2 RT-PCR RUO assay (Altona). Of note, such RT-PCR assay presents a low limit of detection at 625 copies/mL [5], probably slightly higher than droplet PCR assay used by Veber *et al.* In order to identify risk factors for SARS-CoV-2 detection in blood, we used univariable and multivariable mixed-effect logistic models for clustered data (PROC GLIMMIX of SAS) and we adjusted for the time between symptoms' onset and date of sampling. This model takes into account the clustering effect of multiple sampling per patient.

From March to April 2020, in 42 patients 81 blood samples for SARS-CoV-2 detection were collected; 30 samples (37%) were positive. Thirty-four (81%) patients were male and the median age was 58 (IQR: 46; 67); 22 (52%) had a cardiovascular comorbidity and eight (19%) were immunosuppressed. Twenty-two (52%) and 18 (43%) patients received corticosteroids and lopinavir/ritonavir. The median time to negativity (*i.e.*, time between onset of symptoms and viral clearance process from blood) was 17 days (IQR: 12; 21). Using univariable mixed-effect models after adjusting for the time interval between onset of symptoms and date of sampling, we showed that immunosuppression (OR 12.16, 95% CI 1.74-84.93, $p=0.013$) and chronic renal failure (OR 5.98,

95% CI 1.14-31.35, $p=0.035$) increased the risk for SARS-CoV-2 detection in blood (Table). Interestingly, SARS-CoV-2 detection in blood was not associated with 6-week mortality. In the multivariable analysis, immunosuppression significantly increased the risk for SARS-CoV-2 detection in blood (OR 8.95, 95% CI 1.17; 68.38, $p=0.035$, Table).

Veyer *et al.* showed that SARS-CoV-2 RNAemia was strongly correlated with disease severity [4]. With our data and using classical RT-PCR, we observed that especially immunosuppressed critically ill patients tended to be viremic with SARS-CoV-2. In contrast to Veyer *et al.*, we did not observe any association with mortality. Further larger multicentric cohorts are urgently needed to investigate risk factors for RNAemia using classical and ultrasensitive RT-PCR methods in severe and non-severe COVID-19 patients.

Accepted Manuscript

Funding:

NB is currently receiving a postdoc Mobility grant from the Swiss National Science Foundation (grant number: P400PM_183865) and a grant from the Bangerter-Rhyner Foundation.

Potential conflict of interest:

JFT received fees for lectures to Gilead, 3M, MSD, Pfizer, and Biomerieux. JFT received research grants from Astellas, 3M, MSD, and Pfizer. JFT participated to advisory boards of 3M, MSD, Biomerieux, Paratek, Medimmune, Gilead, Bayer Pharma, Nabriva, and Pfizer. BV reports grants, personal fees for lectures and travel accommodations from Qiagen. BV received personal fees for lecture and travel accommodations from BioMérieux. BV received personal fees for lectures from Hologic. BV received grants, personal fees, and non-financial support from Qiagen, and received personal fees from Gilead. All other authors have disclosed that they do not have conflict of interest.

Accepted Manuscript

Accepted Manuscript

References

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **2020**; 395(10223): 497-506.
2. Chen X, Zhao B, Qu Y, et al. Detectable serum SARS-CoV-2 viral load (RNAemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **2020**.
3. Chen W, Lan Y, Yuan X, et al. Detectable 2019-nCoV viral RNA in blood is a strong indicator for the further clinical severity. *Emerging microbes & infections* **2020**; 9(1): 469-73.
4. Veyer D, Kerneis S, Poulet G, et al. Highly sensitive quantification of plasma SARS-CoV-2 RNA sheds light on its potential clinical value. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **2020**.
5. Visseaux B, Le Hingrat Q, Collin G, et al. Evaluation of the RealStar(R) SARS-CoV-2 RT-PCR kit RUO performances and limit of detection. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology* **2020**; 129: 104520.

Accepted Manuscript

Table: Risk factors for SARS-CoV-2 detection in blood in critically ill patients.

Variable	OR	95% CI	p-value	OR	95% CI	p-value
	Univariable*			Multivariable*		
Age	1.02	[0.96 ; 1.08]	0.46			
Gender (Male)	1.32	[0.08 ; 3.74]	0.53			
Comorbidities :						
Diabetes mellitus	0.59	[0.12 ; 2.83]	0.50			
Chronic respiratory failure	3.57	[0.77 ; 16.66]	0.10			
Chronic renal failure	5.98	[1.14 ; 31.35]	0.035	4.07	[0.67; 24.86]	0.12
Immunosuppression	12.16	[1.74 ; 84.93]	0.013	8.95	[1.17; 68.38]	0.035
SOFA at ICU admission	1.18	[0.94 ; 1.47]	0.15			
Treatment:						
Corticosteroids	1.80	[0.44 ; 7.33]	0.40			
Tocilizumab	0.63	[0.04 ; 0.12]	0.74			
Ritonavir / Lopinavir	1.06	[0.24 ; 4.55]	0.94			
Hydrochloroquine	1.99	[0.27 ; 14.92]	0.49			
Mortality at 6 week	0.67	[0.16 ; 2.88]	0.58			

Legend. *Adjustment for the time interval between onset of symptoms and date of sampling. OR: Odds ratio. CI: Confidence interval. SOFA: Sequential organ failure assessment score. ICU: Intensive care unit. A sensitivity analysis forcing the variables "SOFA" and "chronic respiratory failure" in the multivariable analysis showed similar results (OR for immunosuppression 8.35, 95% CI 0.89- 78.29, p=0.063).