PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Validating a clinical laboratory parameters-based de-isolation algorithm for COVID-19 patients in the intensive care unit using viability- PCR: the CoLaIC multicentre cohort study protocol
AUTHORS	Schoenmakers, Tom; van Bussel, Bas; Gorissen, Stefan H.M.; van Loo, Inge; van Rosmalen, Frank; Verboeket-van de Venne, Wilhelmine P.H.G.; Wolffs, Petra F.G.; Van Mook, WN; Leers, Mathie; Consortium, CoLaIC

VERSION 1 – REVIEW

REVIEWER	Weiss, Luisa University College Dublin, School of Biomolecular and Biomedical Science
REVIEW RETURNED	18-Dec-2022

GENERAL COMMENTS	In the presented study protocol, the authors aim to asses the use of a blood-parameter based algorithm to determine when a patient in intensive care diagnosed with COVID-19 is no longer infectious and can be safely released from isolation. This is a timely study as earlier release from isolation not only increases the patient's quality of life, it may also decrease the workload of health care workers. The authors present a well-designed study comprising of three different parts which will be assessed in three different patient cohorts. This approach allows thorough evaluation of the algorithm. Specifically interesting is the validation of the authors algorithm across all current variants of concern as this might facilitate generalisation of this test for all current and potentially future variants. Below are some suggestions the authors might consider when revising the manuscript. 1. Assessment of the impact of combining a viability PCR with the CoLab algorithm score to determine when a patient is no longer infectious is an interesting approach. Can the authors comment on the feasibility of implementing a viability PCR test in a routine clinical laboratory. 2. The authors aim to assess if the development of the CoLab score differs in immunocompromised patients. Male gender is associated with more severe outcomes and a higher fatality rate. The authors should consider assessing potential effects of sex on the CoLab cut-off value. 3. The authors state that consent to participate in the study will be obtained by the next of kin if the patient is unable to communicate. Will the patients consent be retrospectively obtained should the patient become able to?

REVIEWER	Batistela, Cristiane Polytechnic School of University of São Paulo, Electrical Engineering
REVIEW RETURNED	29-Dec-2022

GENERAL COMMENTS	Many studies on covid-19 have been carried out in the last year. The work may consider more references, including on the protocols.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
1. Assessment of the impact of combining a viability PCR with the CoLab algorithm score to determine when a patient is no longer infectious is an interesting approach. Can the authors comment on the feasibility of implementing a viability PCR test in a routine clinical laboratory.
The feasibility of implementation is important when introducing additional diagnostics and upon re-reading the manuscript this was not fully clear.
The implementation of the viability PCR in the routine diagnostics would add some processing time to the existing SARS-CoV-2 PCR protocols. However, the added value of the viability PCR would be the determination of complete virus particles. As such it would only be necessary to run this viability PCR for patients suspected of being virus-free.
This implementation of the viability PCR will also be evaluated, and a revised implementation strategy (for future implementation) will also be done based on this evaluation. So the viability PCR, replacing the routine diagnostic PCR, can be implemented in an intelligent way to optimise resources.
For clarification, we have added the following sentence “The implementation of the viability PCR in the routine diagnostics would add some processing time to the existing SARS-CoV-2 PCR protocols. The v-PCR method is currently not (yet) automated and might as such not fit in every COVID-19 diagnostic workflow. However, the added value of the v-PCR would be the determination of complete virus particles. ” at the viability PCR section in the manuscript.

2. The authors aim to assess if the development of the CoLab score differs in immunocompromised patients. Male gender is associated with more severe outcomes and a higher fatality rate. The authors should consider assessing potential effects of sex on the CoLab cut-off value.
We thank the reviewer for this suggestion. Indeed we aimed to investigate immunocompromised patients. We will add other subgroup analyses as well. We are aware that male gender has worse outcome on the ICU1. We feel that assessing potential effects of sex should be investigated as suggested by the reviewer. We have modified the manuscript accordingly at Statistical analysis section that now runs as follows:
“ For the local cohort, a prospective serially collected dataset of 390 COVID-19 positive patients admitted to the ICU of MUMC+ is available. This also includes a subset of immunocompromised patients (n=60). Adding interaction terms with immunocompromised groups to the mixed models will test whether the development of the CoLab score over time differs for these patients compared to non-immunocompromised patients. A similar approach will be taken to investigate whether results for sex differ.”
1Meijs, D.A.M., van Bussel, B.C.T., Stessel, B. et al. Better COVID-19 Intensive Care Unit survival in females, independent of age, disease severity, comorbidities, and treatment. Sci Rep 12, 734 (2022). https://doi.org/10.1038/s41598-021-04531-x

3. The authors state that consent to participate in the study will be obtained by the next of kin if the patient is unable to communicate. Will the patients consent be retrospectively obtained should the patient become able to?
We fully agree that this aspect could be elaborated more in the manuscript. The text has been revised as follows:
“If the patient is not able to communicate him/herself, e.g., due to ICU treatment, the next of kin will be approached. Patients will be asked for consent later, when the patient has recovered. ”
Reviewer 2:
Many studies on covid-19 have been carried out in the last year. The work may consider more references, including on the protocols.

We agree with the reviewer that some references can be considered. We have added several of these relevant de-isolation protocol papers to the main manuscript.

“Several study protocols described methods to determine if COVID-19-infected patients can be de-isolated: based on clinical signs1, using RT-PCR-2, or with rapid antigen tests3. ”

1: Kang SW, Park H, Kim JY, Park S, Lim SY, Lee S, Bae JY, Kim J, Bae S, Jung J, Kim MJ, Chong YP, Lee SO, Choi SH, Kim YS, Yun SC, Park MS, Kim SH. Clinical scoring system to predict viable viral shedding in patients with COVID-19. J Clin Virol. 2022 Dec;157:105319. doi: 10.1016/j.jcv.2022.105319. Epub 2022 Oct 4. PMID: 36223658; PMCID: PMC9529675.
2: Alshukairi AN, Al-Omari A, Al Hroub MK, Al-Tawfiq JA, Qutub M, Shaikh S, Allali K, Saeedi MF, Alosaimi RS, Alamoudi E, Hefni LK, El-Saed A, Alhamlan FS, Dada A, Wali GY. De-isolation of vaccinated COVID-19 health care workers using rapid antigen detection test. J Infect Public Health. 2022 Aug;15(8):902-905. doi: 10.1016/j.jiph.2022.06.020. Epub 2022 Jul 7. PMID: 35868074; PMCID: PMC9259551.
3: Syue LS, Hung YP, Li CW, Tsai CS, Chen PL, Li MC, Lee NY, Ko WC. De-isolation criterion of real-time PCR test in patients with COVID-19: Two or three consecutive negative nasopharyngeal swabs? J Microbiol Immunol Infect. 2021 Feb;54(1):136-138. doi: 10.1016/j.jmii.2020.08.014. Epub 2020 Aug 19. PMID: 32861625; PMCID: PMC7437530.

VERSION 2 – REVIEW

REVIEWER	Weiss, Luisa University College Dublin, School of Biomolecular and Biomedical Science
REVIEW RETURNED	10-Feb-2023

GENERAL COMMENTS	The authors have addressed all comments appropriately. I recommend acceptance of the manuscript.