Tom Schoenmakers*, Mathie P.G. Leers, Ruben Deneer, Frank van Rosmalen, Stefan H.M. Gorissen, Wilhelmine P.H.G. Verboeket-van de Venne, Una Vojinovic, Walther N.K.A. van Mook, Petra F.G. Wolffs, Bas C.T. van Bussel and Inge H.M. van Loo, on behalf of the CoLaIC-consortium

The CoLab score is associated with SARS-CoV-2 viral load during admission in individuals admitted to the intensive care unit: the CoLaIC cohort study

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Abstract

Objectives: The present study examines the temporal association between the changes in SARS-CoV-2 viral load during infection and whether the CoLab-score can facilitate de-isolation.

Methods: Nasal swabs and blood samples were collected from ICU-admitted SARS-CoV-2 positive patients at Maastricht UMC+ from March 25, 2020 to October 1, 2021. The CoLab-score was calculated based on 10 blood parameters and age and can range from −43 to 6. Three mixed effects analyses compared patient categories based on initial PCR Ct values (low; Ct≤20, mid; 20>Ct≤30, high; Ct>30), serial PCR Ct values to CoLab-scores over time, and the association between within-patient delta Ct values and CoLab-scores.

Results: In 324 patients, the median Ct was 33, and the median CoLab-score was −1.78. Mid (n=110) and low (n=41) Ct-categories had higher CoLab-scores over time (+0.60 points, 95 % CI; 0.04–1.17, and +0.28 points, 95 % CI −0.49 to 1.04) compared to the high Ct (n=87) category. Over time, higher serial Ct values were associated with lower serial CoLab-scores, decreasing by −0.07 points (95 % CI; −0.11 to −0.02) per day. Increasing delta Ct values were associated with a decreasing delta CoLab-score of −0.12 (95 % CI; −0.23; −0.01).

Conclusions: The study found an association between lower viral load on admission and reduced CoLab-score. Additionally, a decrease in viral load over time was associated

Bas C.T. van Bussel and Inge H.M. van Loo share last authorship.

***Corresponding author: Tom Schoenmakers**, Department of Clinical Chemistry and Hematology, Zuyderland Medical Center, Sittard-Geleen, Dr. H. van der Hoffplein 1, 6162 BG Sittard-Geleen/Heerlen, The Netherlands; School of Nutrition and Translational Research in Metabolism (NUTRIM), University of Maastricht, Maastricht, The Netherlands; and Department of Intensive Care Medicine, Maastricht University Medical Center +, Maastricht, The Netherlands, E-mail: t.schoenmakers@zuyderland.nl. https://orcid.org/0000-0002-1576-7832

Mathie P.G. Leers, Department of Clinical Chemistry & Hematology, Zuyderland Medical Center, Sittard-Geleen/Heerlen, The Netherlands; School of Nutrition and Translational Research in Metabolism (NUTRIM), University of Maastricht, Maastricht, The Netherlands; and Faculty of Science, Environmental Sciences, Open Universiteit, Heerlen, The Netherlands. https://orcid.org/0000-0001-5186-5600

Ruben Deneer, Department of Clinical Chemistry & Hematology, Zuyderland Medical Center, Sittard-Geleen/Heerlen, The Netherlands; and Faculty of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands. https://orcid.org/0000-0002-6011-7783

Frank van Rosmalen, Department of Intensive Care Medicine, Maastricht University Medical Center +, Maastricht, The Netherlands; and Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, The Netherlands. https://orcid.org/0000-0002-9522-3711

Stefan H.M. Gorissen, Zuyderland Academy, Zuyderland Medical Center, Sittard-Geleen/Heerlen, The Netherlands. https://orcid.org/0000-0003-3737-9053

Wilhelmine P.H.G. Verboeket-van de Venne, Department of Clinical Chemistry & Hematology, Zuyderland Medical Center, Sittard-Geleen/Heerlen, The Netherlands. https://orcid.org/0000-0003-4980-0116

Una Vojinovic, Department of Medical Microbiology, Infectious Diseases and Infection Prevention, Maastricht University Medical Center +, Maastricht, The Netherlands

Walther N.K.A. van Mook, Department of Intensive Care Medicine, Maastricht University Medical Center +, Maastricht, The Netherlands; and School of Health Professions Education (SHE), Maastricht University, Maastricht, The Netherlands. https://orcid.org/0000-0003-2398-8878

Petra F.G. Wolffs and Inge H.M. van Loo, Department of Medical Microbiology, Infectious Diseases and Infection Prevention, Maastricht University Medical Center +, Maastricht, The Netherlands; and Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, The Netherlands. https://orcid.org/0000-0002-5326-3985 (P.F. Wolffs). https://orcid.org/0000-0002-5960-4357 (I.H. van Loo)

Bas C.T. van Bussel, Department of Intensive Care Medicine, Maastricht University Medical Center +, Maastricht, The Netherlands; Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, The Netherlands; and Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, The Netherlands. https://orcid.org/0000-0003-1621-7848

with a decrease in CoLab-score. Therefore, the CoLab-score may make patient de-isolation an option based on the CoLab-score.

Keywords: COVID-19; SARS-CoV-2; RT-PCR; cycle threshold; linear mixed-effects models

Introduction

The effective isolation and de-isolation of patients were crucial components of infection prevention in the healthcare sector during the 2019 Coronavirus disease (COVID-19) pandemic. Prolonged periods of isolation can negatively impact mental health and place additional strain on the healthcare system [1, 2]. Therefore, it is essential to develop strategies for safe and reliable de-isolation. Although polymerase chain reaction (PCR) is the current standard diagnostic method, it may detect non-infectious viral RNA remnants. It is important to detect and exclude the presence of infectious viral particles to determine if a patient is no longer infectious and can be de-isolated. However, viral culture, the gold standard for establishing infectiousness, is unsuitable for widespread use due to the need for specialised facilities and personnel, long throughput times, and high costs [3]. Several studies have found that a higher viral load is associated with a lower cycle threshold (Ct) value in PCR tests [4, 5]. However, it has been observed that some patients and healthcare workers who have recovered from COVID-19 symptoms may continue to test positive for a prolonged period [6, 7]. While a higher culturable viral load typically corresponds to a lower Ct value, PCR tests detect all genetic material and do not differentiate between active and inactive viral particles [4, 5, 8]. This suggests that PCR is not ideal for assessing viral infectivity in individuals with confirmed SARS-CoV-2 infection. Nonetheless, due to its ease of use in routine diagnostic workflows and the urgency of the COVID-19 pandemic, PCR tests were used as a proxy for viral shedding and infectiousness.

The CoLab-score is a potential alternative method for determining and evaluating the infectivity of COVID-19 patients [9, 10]. It is based on standard hemocytometric and biochemical blood markers involved with the host response to the viral infection. Unlike PCR, which measures both intact and non-intact viral particles, monitoring the host response may provide information about infectivity. Previous research has utilised the CoLab-score to exclude COVID-19 when the score falls below a certain threshold (~−6) for patients presenting at the emergency department (ED). The CoLab-score demonstrated a negative predictive value of 99.5 % and a sensitivity of 96.9 % in ruling out SARS-CoV-2 infection in COVID-19 suspected ED patients [9, 10]. The score was subsequently implemented in the EDs of two large Dutch teaching hospitals, and it was used to rule out COVID-19 in healthcare workers who presented with COVID-19-related symptoms [10]. Recently, our group observed that the CoLab-score decreased over time in patients admitted to the ICU with COVID-19 [11].

The present study aims to examine the validity of the association between the serially measured, semi-quantified viral load of SARS-CoV-2, determined using PCR, and the CoLab-scores in individuals admitted to the intensive care unit (ICU) to guide de-isolation based on the CoLab-score.

Materials and methods

Patient cohort

The Maastricht Intensive Care COVID (MaastrICCht) cohort has been described extensively elsewhere [12–16]. This comprehensive prospective cohort study was conducted in patients admitted to the ICU of Maastricht University Medical Centre+ (MUMC+), a tertiary care university teaching hospital in the southern part of The Netherlands [12].

The cohort included all patients with respiratory insufficiency requiring mechanical ventilation and at least one PCR positive for SARS-CoV-2 and/or CO-RADS score of 4–5 scored by a radiologist (i.e., a chest computed tomography scan strongly suggestive of SARS-CoV-2 infection) [17]. Patients diagnosed in another hospital and transferred to MUMC+ were not retested by PCR due to scarce PCR testing resources, particularly at the beginning of the pandemic [18]. Patients were followed daily from intubation until discharge from the ICU. For the present study, patients were included from March 25th, 2020, the inception of the cohort, until October 1st, 2021. ICU survival and mortality were classified as patients who did not die during their ICU stay (survivors) or patients who died during their ICU stay (non-survivors). The Institutional Review Board (Medical Ethics Review Committee (METC) 2020-1565/300523) of the Maastricht UMC+ approved the study, which was performed following the Declaration of Helsinki. During the pandemic, the board of directors of Maastricht UMC+ adopted a policy to inform patients and ask their consent to use the collected data and stored left-over serum samples for COVID-19 research purposes. This study was registered in the International Clinical Trials Registry Platform (registration number NL8613).

CoLab-score

The CoLab-score includes, in addition to patient age (in years), 10 blood parameters of which 9 were measured in blood samples daily drawn and analysed according to the study protocol; leukocytes ($*10^9$/L), eosinophilic granulocytes ($*10^9$/L), basophilic granulocytes ($*10^9$/L), bilirubin (μmol/L), lactate dehydrogenase (LD) (U/L), alkaline phosphatase (ALP) (U/L), gamma-glutamyltransferase (γGT) (U/L), albumin (g/L) and c-reactive protein (CRP) (mg/L) concentrations [12].

The erythrocyte concentration, also required for the Colab-score, was not routinely measured. However, other erythrocyte-related variables were measured, i.e., haemoglobin (Hb)

concentration (mmol/L) and hematocrit (Hct) (L/L). Therefore, we imputed erythrocyte concentrations according to the formula '*erythrocytes=0.0011 – Hb*0.0380 + Hct*0.1211*' (established by a generalised least squares (GLS) regression model using an external dataset [19]). Using the estimated erythrocyte concentrations, the other nine laboratory variables, and age, the CoLab-score was calculated daily for the entire cohort.

SARS-CoV-2 polymerase chain reaction testing

Within the cohort, multiple SARS-CoV-2 PCRs were performed in the patients to test for infectiousness. These samples were analysed according to the following protocol [20]:

Following the manufacturer's instructions, RNA extraction was primarily carried out using the Chemagic Viral DNA/RNA 300 Kit H96 kit (Perkin Elmer, Waltham, Massachusetts, USA), resulting in elution with 100 µL of elution buffer. A smaller proportion of the extractions were performed using the MagNA Pure 96 DNA (Roche Diagnostics GmbH, Mannheim, Germany) and Viral NA Small Volume Kit (Roche Diagnostics, Basel, Switzerland), also by the manufacturer's guidelines, and yielded eluates of 100 µL (comprising 50 µL of elution buffer and 50 µL of water).

Both extraction methodologies consistently produced RNA concentrations of high similarity, thereby resulting in comparable viral loads and limits of detection (2 log 10 viral copies/mL). All RT-qPCR data was produced on Quantstudio 5 systems (Thermo Fisher, Waltham, Massachusetts, USA). Amplification was conducted via multiplex PCR, including the E gene target20, the N1 target21, and mCMV-ie as an internal control. The multiplex PCR employed primer concentrations of 400 nM and probe concentrations of 200 nM for both the E and N1 targets, while the internal control utilised 300 nM primer concentrations (sense: 5′-CAACATTGACCACGCACTAGATG-3′; antisense: 5′-TTAAACTCCCCAGGCAATGAA-3′) and 200 nM probe concentrations (5′-CTTGGCCCATGCGGCACG-3′). The assay composition was 5 µL of TaqPath 1-Step RT-qPCR Master Mix (Thermo Fisher), 10 µL RNA eluate, and 5 µL primer/probe mix. Cycling conditions were 2 min at 25 °C, 15 min at 50 °C, 2 min at 95 °C followed by 42 cycles of 3 s at 95 °C and 30 s at 60 °C.

The MaastrICCht cohort is a clinical study by design, and PCR testing was done clinically based on the available resources, which were strained particularly at the beginning of the pandemic, and the need for testing, as assessed by the acting physician [18]. When the testing capacity increased during later phases of the pandemic, PCR tests during ICU admission were ordered clinically to diagnose if a patient could still be infectious (which was the assumption at the time). In patients transferred from other hospitals to our hospital, PCR tests were not repeated due to a scarcity of resources. Also, supplementing the locally generated data with PCR test results from the referring hospitals was not done, as a direct comparison of absolute PCR Ct values between centres is not possible [21]. Taken together, the cohort includes patients with serial PCR tests done in one hospital, the Maastricht UMC+.

Statistical analyses

Data were expressed as median and interquartile range (IQR), or percentage, when appropriate. After analysing missing data, the variables were imputed via multiple imputation chained equations with a decision tree algorithm (CART in the R MICE packages) [22].

The first analysis evaluated the association between the admission PCR value and the CoLab-score. The second analysis evaluated the association between the serial PCR values and the serial CoLab-score. The third analysis evaluated the association between the slope of the PCR values and the slope of the CoLab-scores per individual.

First, the cohort was categorised according to the first (i.e. admission) PCR as follows: low PCR Ct values (below or equal to 20; i.e. high viral load), middle PCR Ct values (between 20 and 30 and equal to 30; i.e. medium viral load) and high PCR Ct values (above 30; i.e. low viral load). Due to the repeated measures design, we used linear mixed-effects models to investigate the association between the PCR Ct values and the CoLab-score. First, we fitted a model including only the categorical PCR Ct value on admission as a predictor and subsequently, we added time and the interaction between time and categorical PCR Ct value on admission to the model. Time was in days since intubation.

Second, all Ct and CoLab-measurement pairs (i.e. days where both a PCR test was performed and a CoLab-score was determined) were used to establish the longitudinal association between PCR and CoLab-scores. We fitted two mixed effect models, one including only the Ct value as a covariate and a second adjusting for time since intubation (also including an interaction between time and Ct value).

Third, the changes in patients over time were investigated as follows. Per the patient, the difference (delta) between the outermost Ct values in time, which had corresponding CoLab-scores, and the CoLab-score was calculated. The resulting deltas of both values were used in a linear regression model to investigate the association between changes in PCR values and changes in CoLab-score over time.

Statistical software: We used R (version: 4.1.2) package nlme (version: 3.1). Effect estimates β with their 95 % confidence interval (95 % CI) were reported with p-values. A two-sided p-value <0.05 and $p_{interaction}$<0.10 were considered statistically significant.

Results

Of the total cohort of 324 patients, we analysed 306 patients (Figure 1, Table 1), 221 of whom were male (72.2 %). The remaining 18 patients were excluded because the PCR was measured in another hospital, after which they were referred to our center (Figure 1). The median age was 64 years (IQR 57, 71), with a median BMI of 28.0 (IQR 25.32, 31.61) kg/m^2. The median length of ICU stay was 14 days (IQR 8, 23); 193 (63.1 %) patients survived the ICU stay. The low (n=41 patients), middle (n=110 patients), and high (n=87 patients) admission PCR categories showed statistically significant (p=0.018) differences in ICU mortality, with the low admission Ct group having 21 survivors (51 %), the middle admission Ct group having 77 survivors (70 %), and the high admission Ct group having 66 survivors (76 %). There were also differences in the serial CoLab-scores and Ct values. The median serial CoLab-score was −1.02 (IQR −5.96, 0.55) in the low admission Ct group (high viral load), −1.70 (IQR −5.83, 0.52) in the middle admission Ct group, and −2.28 (IQR −6.76, 0.01) in the high admission Ct group (low viral load). The

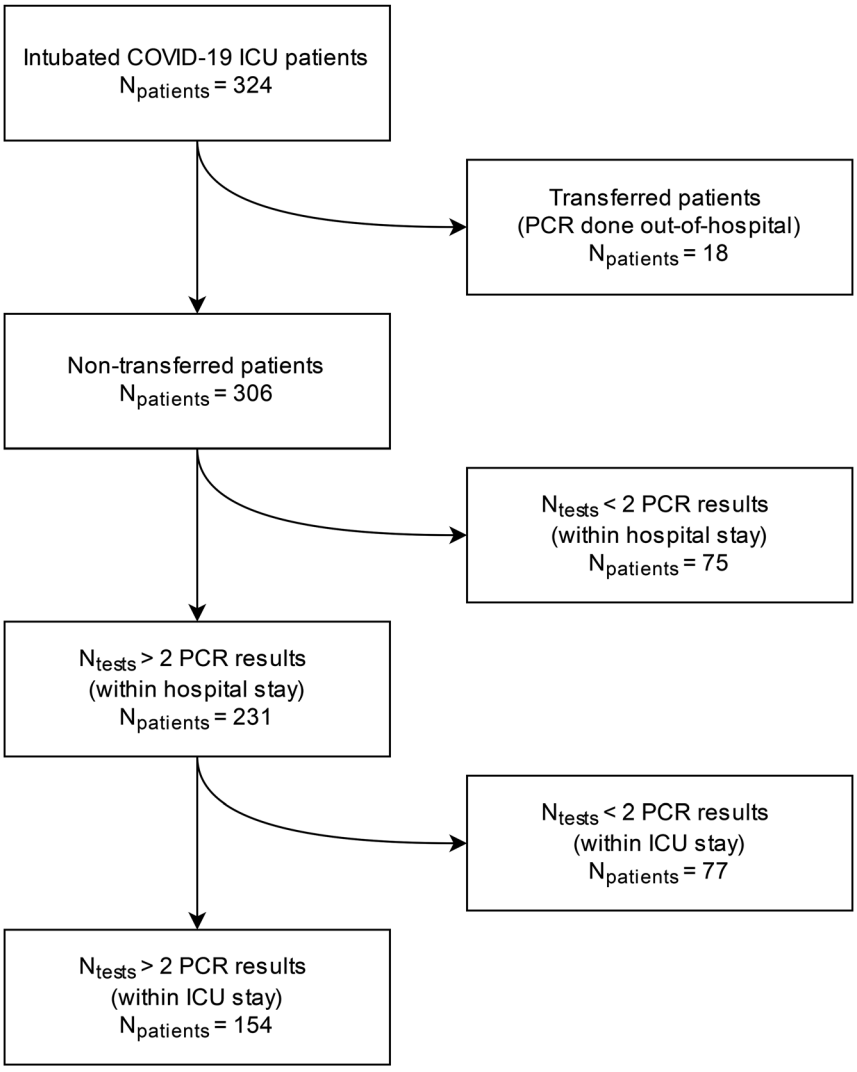

Figure 1: Cohort inclusion scheme. Inclusion flowchart of the cohort.

median serial Ct value was 28 (IQR 20, 36) in the low admission Ct group, 31 (IQR 25, 38) in the middle admission Ct group, and 37 (IQR 32, 45) in the high admission Ct group (Table 1).

When we investigated the association between the admission Ct categories and the average CoLab-score during ICU stay, the results showed that relative to the high Ct category (i.e. low viral load), the middle Ct category (i.e. medium viral load) on average had a higher CoLab-score of 0.60 points (95 % CI 0.04 to 1.17) and the low Ct category (i.e. high viral load) had a higher CoLab-score of 0.28 points (95 % CI −0.49 to 1.04) (Table 2 Model 1). Adding time and the interaction term between time and Ct categories decreased −0.30 (95 % CI −0.35 to −0.25), indicating that the CoLab-score in *all* Ct categories decreased comparably over time (Table 2).

When we investigated the temporal association between Ct values and CoLab scores, the results showed that per 1 Ct value increase (i.e., lower viral load), the CoLab-score was 0.07 points lower (95 % CI −0.11 to 0.03) on average. Adding time in days and the interaction term between time and Ct categories resulted in a statistically significant interaction with time ($P_{interaction}$=0.089), indicating that the CoLab-score decreased slightly slower over time with increased Ct (Table 3).

Furthermore, we investigated the longitudinal trends in Ct values and CoLab-scores during ICU stay for the three categories of admission Ct value using the delta's as determinant (delta Ct) and outcome (delta CoLab) using linear regression. The association was −0.12 (95 % CI −0.23; −0.01), suggesting an increasing Ct value was associated with a decreasing CoLab-score (Table 4).

Additionally, we investigated the slopes for Ct value and CoLab-scores per patient estimated by linear regression, which showed that if the slope of the Ct increased by 1 point, the slope of the CoLab-score decreased by −0.07 points (95 %

Table 1: Cohort characteristics.

	Level	Overall	Low admission cycle threshold (Ct)	Middle admission cycle threshold (Ct)	High admission cycle threshold (Ct)	p-Value
Patients, n		306	41	110	87	
Sex, n (%), male	Male	221 (72.2)	29 (70.7)	82 (74.5)	64 (73.6)	0.894
ICU mortality, n (%)	Survivor	193 (63.1)	21 (51.2)	77 (70.0)	66 (75.9)	**0.018**
	Non-survivor	113 (36.9)	20 (48.8)	33 (30.0)	21 (24.1)	
BMI (median [interquartile range (IQR)])		28.01 [25.32, 31.61]	27.11 [24.97, 30.25]	28.08 [25.88, 32.20]	28.04 [25.34, 31.22]	0.289
Age (median [IQR])		64.00 [57.00, 71.00]	65.00 [61.00, 70.00]	64.00 [57.00, 71.75]	62.00 [53.00, 70.00]	0.155
ICU length of stay in days (median [IQR])		14.00 [8.00, 23.00]	14.00 [11.00, 27.00]	16.00 [9.00, 31.00]	14.00 [7.50, 25.00]	0.345
APACHE II (median [IQR])		15.00 [12.00, 18.00]	16.00 [13.00, 18.00]	14.00 [11.00, 17.00]	14.00 [12.00, 16.25]	0.057
Diabetes, n (%), yes		65 (21.2)	5 (12.2)	28 (25.5)	17 (19.5)	0.188
Chronic kidney disease, n (%), yes		9 (2.9)	1 (2.4)	4 (3.6)	2 (2.3)	0.840
Malignancy, n (%), yes		25 (8.2)	5 (12.2)	10 (9.1)	4 (4.6)	0.282
Liver disease, n (%), yes		4 (1.3)	0 (0.0)	3 (2.7)	0 (0.0)	0.171
Immunosuppression, n (%), yes		24 (7.8)	6 (14.6)	9 (8.2)	4 (4.6)	0.147
Patients, n		306	41	110	87	
n (serial measurements)		6,279	1,021	2,984	2,274	
Serial CoLab-score, median [IQR]		−1.78 [−6.18, 0.34]	−1.02 [−5.96, 0.55]	−1.70 [−5.83, 0.52]	−2.28 [−6.76, 0.01]	**<0.001**
Serial cycle threshold values, median [IQR]		33.00 [26.00, 45.00]	28.00 [20.00, 36.00]	31.00 [25.00, 38.00]	37.00 [32.00, 45.00]	**<0.001**

ICU, intensive care unit; BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II. Bold values represent significant values.

Table 2: Admission polymerase chain reaction analysis.

Variables	Model 1: $Y_{CoLab\ score}$			Model 2: $Y_{CoLab\ score}$		
	Estimates	Confidence interval	p-Value	Estimates	Confidence interval	p-Value
Low cycle threshold	0.28	−0.49 to 1.04	0.474	0.01	−0.92 to 0.93	0.984
Middle cycle threshold	0.60	0.04–1.17	**0.037**	0.63	−0.06 to 1.31	0.073
High cycle threshold reference	−0.89	−1.32 to −0.46	**<0.001**	0.50	−0.01 to 1.02	0.054
Time (per day)[a]				−0.30	−0.35 to −0.25	**<0.001**
Interaction: time and low cycle threshold				0.06	−0.04 to 0.15	0.233
Interaction: time and middle cycle threshold				−0.00	−0.07 to 0.07	0.973
n	306 Patients			306 Patients		
Observations	5,673			5,673		
Marginal R^2/conditional R^2	0.004/0.286			0.398/0.734		

[a]Time is measured in days since intubation. Bold values represent significant values.

Table 3: Serial cycle threshold analysis.

Determinants	Model 1: $Y_{CoLab\ score}$			Model 2: $Y_{CoLab\ score}$		
	Estimates	Confidence interval	p-Value	Estimates	Confidence interval	p-Value
(Intercept)	1.21	0.01–2.42	**0.049**	1.54	0.05–3.02	**0.044**
Serial cycle threshold	−0.07	−0.11 to −0.03	**<0.001**	−0.05	−0.10 to 0.00	0.056
Time (per day)[a]				−0.30	−0.40 to −0.19	**<0.001**
Interaction: time and serial cycle threshold				0.00	−0.00 to 0.01	**0.089**
n	306 Patients			306 Patients		
Observations	765			765		
Marginal R^2/conditional R^2	0.028/0.049			0.311/0.666		

[a]Time is measured in days since intubation. Bold values represent significant values.

Table 4: Delta cycle threshold analysis.

Predictors	Model 1: $Y_{\Delta\ CoLab}$		
	Estimates	Confidence interval	p-Value
(Intercept)	−3.04	−4.33 to −1.75	**<0.001**
Delta cycle threshold	−0.12	−0.23 to −0.01	**0.036**
Observations		154	
R^2/R^2 adjusted		0.029/0.022	

Bold values represent significant values.

CI −0.11; −0.02) (Table S1). This approach was chosen to confirm the results found in Table 4 in all patients with two PCR measurements, as the PCR results might have been outside the time frame where the CoLab-score was calculated (Figure 2).

Discussion

The present study examining the validity of the association between serially measured SARS-CoV-2 PCRs and the CoLab-scores in individuals admitted to the ICU has three main findings. First, when comparing the high Ct category (low viral load) to the middle and low Ct categories (higher viral loads), the CoLab-score at ICU admission is lower in the group with lower viral loads. Second, we observed a longitudinal association between serially measured Ct values and serially determined CoLab-scores, indicating that per 1 Ct value increase, the CoLab-score was 0.07 points lower, albeit not statistically significant after adjusting for time. Third, as this longitudinal association includes both differences between patients and within-patient changes, we investigated the within-patient changes in detail. Patients with increasing delta Ct had decreasing delta CoLab-scores, as observed in the main and additional analyses (Table 4, Table S1). These results suggest that decreasing CoLab-score over time is associated with an increasing Ct value (semi-quantified viral load). The latter is also associated with viral culture, the gold standard to determine COVID-19 infectivity [4, 5].

Several studies have been performed to link SARS-CoV-2 PCR results to the results of SARS-CoV-2 viral culture [4, 5]. Singanayagam et al. reported in patients with mild symptoms and a high Ct value (Ct>35) that there was a likelihood of 8 % (5/60) of having culturable viral particles [5]. No viral particles were cultured after 10 days within their cohort of mild COVID-19 patients. Kampen et al. showed a probability

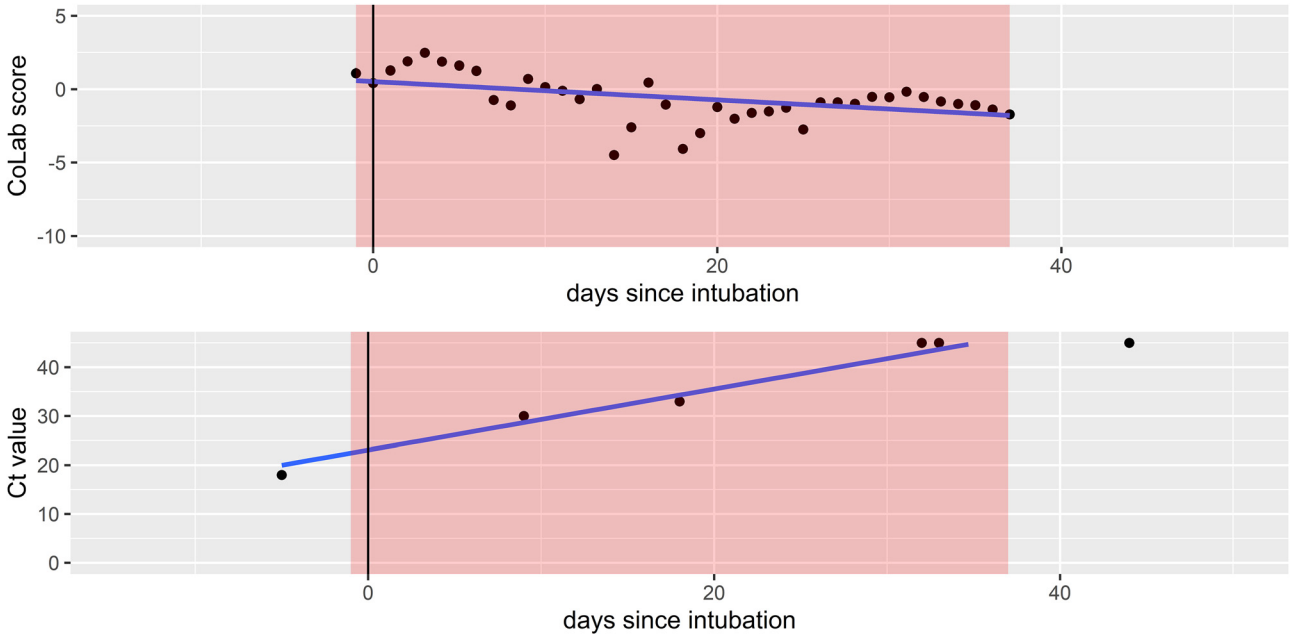

Figure 2: Example patient. Shown here is a scatter plot of one patient in the cohort. Time is plotted on the X-axis for both panels. The upper panel visualises the CoLab-score on the Y-axis, while the lower panel visualises the Ct value on the Y-axis. The red panel indicates the time when the CoLab-score was calculated. The utmost Ct values and their corresponding (on the same day) CoLab-scores within this red panel were used for the delta-delta analysis (Table 4). The slope of the linear regression line illustrated in blue was used for the slope analysis. The latter was done for patients with one or no Ct value in the red panel but outside this range (PCR measured before and after ICU stay and intubation period).

for a positive culture of less than 5 % (1/20) in patients with a low viral load o (<6.63 $\log_{10}$ RNA copies/mL) [4]. The detection of sub-genomic RNA by PCR possibly remained longer than the culturability of the SARS-CoV-2 virus and was found to be a poor predictor of culture-positive virus (37.5 % positive predictive value). Due to this predictability, the SARS-CoV-2 PCR proved a poorly applicable parameter for minimising isolation time for affected individuals as it remained longer positive than the culturable virus.

Previous studies established the ability of the CoLab-score to exclude SARS-CoV-2 infection in patients presenting to the emergency department and health care workers [9, 10]. Furthermore, within these cross-sectional studies, it was established that below a specific threshold, the likelihood of a positive PCR and, thus, infectious SARS-CoV-2 was negligible (negative predictive value of 99.5 %). In addition, it was also observed that within an ICU cohort, the CoLab-scores had trajectories with a negative slope [11]. Combining the latter results with results described in the current study indicates that a decreasing CoLab-score is associated with a decreasing viral load (as indicated by an increasing PCR Ct value), with the CoLab-score being linked to a higher probability of viral shedding when compared with PCR [4, 5]. This study indicates that the CoLab-score can assess infectivity by monitoring the host response to SARS-CoV-2.

A limitation of the present study is the infrequency of the PCR measurements during ICU admission, which were done based on clinical care and restrained due to scarce pandemic resources (Figure 1). Nevertheless, in-depth analyses using all available data were performed. For example, for the delta Ct to delta CoLab-score, which required at least two measurements of the PCR and CoLab-score at the same time points, we missed several patients, and this was overcome by the use of the slope method, which allowed all patients with two measurements to be included in the analyses (Supplementary 1). Although this minimised selection bias, there seems to be informative censoring about survival status. The survival rate in the category with low Ct value at admission was lower (51.2 %) than in the middle (70.0 %) and high category (75.9 %). The overall Ct value was lower, and the overall CoLab-score was higher in the low Ct group (Table 1). Thus, this may have led to an underestimation of the current results. The generalisability of this single-center study is thus somewhat limited.

During the course of this cohort, new treatment regimens changed as evidence accumulated in a way that dexamethasone [23] followed by tocilizumab [24] became the standard of care. Within the cohort, these drugs have been studied more extensively [15]. When we adjusted the serial Ct models for the use of dexamethasone, tocilizumab, and their combination (Supplementary Table 2), the results were similar with a negative association between serial measured Ct values and serially determined CoLab score (Table 3, model 1). In the adjusted model (Supplementary Table 2, model 1) an increase of 1 Ct lowered the CoLab-score by 0.06 points, which is similar to the 0.07 decrease found in the unadjusted model (Table 3, model 1).

The vaccination status of patients was not reliably registered in the hospital medical files. To address this limitation an additional sensitivity analysis was performed to gauge the impact of the vaccination on the associations presented in this study, which is shown in Supplementary Table 3. These results suggest that the association between serial Ct and serial CoLab score is not altered before or after the start of the vaccination program in The Netherlands.

Strengths of this study include the daily prospective measurements of the biochemical and hemocytometric blood tests (of which a daily CoLab-score could be calculated), vital signs, and clinical scores. The longitudinal nature of the study allowed the analysis of between- and within-patient variations. Another strength is the use of mixed-effects models, which enabled the nested analysis of the measurements per patient.

A recommendation for a future study would be to assess the association between PCR and CoLab-scores within a cohort with both frequent determinations of the CoLab-score and PCR measurements. In such a design, the more frequent measurements would enable the investigation of fluctuation over time. Furthermore, including a measure of viral viability in the study would enable the investigation of infectivity related to the PCR and CoLab-score. Such a measure could potentially be a test regarding antigen detection of SARS-CoV-2 nucleocapsid protein, which can be measured in blood serum in a quantitative manner [25]. Another method to detect viable SARS-CoV-2 would be using viability PCR. The viability PCR employs propidium monoazide to bind to free or damaged RNA selectively, enabling exclusive amplification of intact viral particles [19, 26]. These two methods or their combination would potentially enable a more accurate measurement of viable viral load in patients and are being considered for an upcoming prospective study as outlined in the overarching study protocol [19]. In addition, a multicentre design could increase generalisability.

In conclusion, there is an association between lower viral load (increasing Ct values) on admission and reduced CoLab-scores. Next to this, a decrease in viral load over time was associated with a decrease in CoLab-score. The CoLab-score, which can be easily calculated from routinely measured blood parameters, could provide temporal monitoring information about SARS-CoV-2 infection and contribute to de-isolation decision making.

Collaborators

The members of the Dutch CoLaIC consortium are: Stephanie Ament (MUMC+, Maastricht); M. Sesmu Arbous (LUMC, Leiden); Otto Bekers (MUMC+, Maastricht); Miranda van Berckel (Radboud UMC, Nijmegen); Arjan-Kars Boer (Catharina Hospital, Eindhoven), Dirk W. van Dam (Zuyderland MC, Sittard-Geleen/Heerlen); Ruben Deneer (Catharina Hospital, Eindhoven); William P.T.*M. van* Doorn (MUMC+, Maastricht); Tom P. Dormans (Zuyderland MC, Sittard-Geleen/Heerlen); Silvia M.M.A. Evers (Maastricht University, Maastricht); Tim Frenzel (Radboud UMC, Nijmegen); Madeleen Bosma (LUMC, Leiden); Judith Gillis (LUMC, Leiden); Iwan C.C van der Horst (MUMC+, Maastricht); W. Nadia H. Koek (Medical Center Leeuwarden); Kitty Linssen (Zuyderland MC, Sittard-Geleen); Steven J.R. Meex (MUMC+, Maastricht); Guy J.M. Mostard (Zuyderland MC, Sittard-Geleen/Heerlen); Remy L.M. Mostard (Zuyderland MC, Sittard-Geleen/Heerlen); Luuk C. Otterspoor (Catharina Hospital, Eindhoven); Natal A.W. van Riel (Technical University, Eindhoven), Frans Stals (Zuyderland MC, Sittard-Geleen/Heerlen); Harro van Westreenen (Zuyderland MC, Heerlen); Albert Wolthuis (Certe, Leeuwarden); Meta van der Woude (patient expert); Ghislaine van Mastrigt (Maastricht University, Maastricht); Andrea Peeters (Maastricht University, Maastricht).

Research ethics: The Institutional Review Board (Medical Ethics Review Committee (METC) 2020-1565/300523) of the Maastricht UMC+ approved the study, which was performed following the Declaration of Helsinki. During the pandemic, the board of directors of Maastricht UMC+ adopted a policy to inform patients and ask their consent to use the collected data and stored left-over serum samples for COVID-19 research purposes. This study was registered in the International Clinical Trials Registry Platform (registration number NL8613).

Informed consent: Informed consent was obtained from all individuals included in this study, or their legal guardians or wards.

Author contributions: The authors have accepted responsibility for the entire content of this manuscript and approved its submission. Tom Schoenmakers: Methodology, Software, Formal analysis, Visualization, Writing – Original Draft, Writing – Review & Editing. Mathie P.G. Leers: Conceptualization, Writing – Review & Editing, Supervision, Funding acquisition. Stefan H.M. Gorissen: Conceptualization, Writing – Review & Editing, Project administration, Funding acquisition. Inge H.M. van Loo: Conceptualization, Methodology, Writing – Review & Editing, Funding acquisition. Una Voijnovic: Writing – Review & Editing. Frank van Rosmalen: Software, Resources, Data Curation, Writing – Review & Editing, Funding acquisition. Ruben Deneer: Software, Formal analysis, Writing – Review & Editing. Wilhelmine P.H.G. Verboeket-van de Venne: Conceptualization, Writing – Review & Editing, Funding acquisition. Petra F.G. Wolffs: Conceptualization, Methodology, Writing – Review & Editing, Supervision, Funding acquisition. Walther N.K.A. van Mook: Conceptualization, Writing – Review & Editing, Supervision, Funding acquisition. Bas C.T. van Bussel: Conceptualization, Methodology, Writing – Review & Editing, Supervision, Funding acquisition.

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