



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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



## Virology

## Duration of SARS-CoV-2 viremia and its correlation to mortality and inflammatory parameters in patients hospitalized for COVID-19: a cohort study

Karl Hagman<sup>a,b,\*</sup>, Magnus Hedenstierna<sup>a</sup>, Johan Rudling<sup>a</sup>, Patrik Gille-Johnson<sup>a</sup>, Berit Hammas<sup>c</sup>, Malin Grabbe<sup>c</sup>, Jan Jakobsson<sup>b,d</sup>, Joakim Dillner<sup>e</sup>, Johan Ursing<sup>a,b</sup><sup>a</sup> Department of Infectious Diseases, Danderyd Hospital, Stockholm, Sweden<sup>b</sup> Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden<sup>c</sup> Department of Microbiology, Karolinska University Hospital, Stockholm Sweden<sup>d</sup> Department of Anesthesia and Intensive Care, Danderyd Hospital, Stockholm, Sweden<sup>e</sup> Karolinska University Laboratory, Stockholm, Sweden

## ARTICLE INFO

## Article history:

Received 21 September 2021

Revised in revised form 6 November 2021

Accepted 10 November 2021

Available online 17 November 2021

## Keywords:

SARS-CoV-2

COVID-19

viremia

RNAemia

mortality

## ABSTRACT

SARS-CoV-2 viremia at admission is associated with high risk for mortality. However, longitudinal data on viremia duration are limited. Viremic patients hospitalized for COVID-19 were included in a cohort. Time to serum viral clearance and the effect of viremia duration on the odds of mortality were calculated. One hundred and twenty-one viremic patients were included. Median age was 62 (IQR 52–71) years and 68% were males. The total in-hospital mortality of the cohort was 33%. Median time from admission to serum viral clearance was 7 (95% CI 6–8) days. Duration of viremia showed a relative risk ratio of 1.40 (95% CI 1.02–1.92) for the odds of mortality in an adjusted multinomial logistic regression. Serum viral clearance coincided with defervescence and decreasing C-reactive protein. Median time to serum viral clearance was 7 days after admission. The odds of mortality increased with 40% for each additional day of viremia.

© 2021 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

## 1. Introduction

Presence of *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) RNA in blood is a predictor for progression to critical disease and death in patients hospitalized for coronavirus disease 2019 (COVID-19) (Fajnzylber et al., 2020; Hagman et al., 2020; Hogan et al., 2020; Jacobs et al., 2021; Li et al., 2021; Prebensen et al., 2020; Ram-Mohan et al., 2021). In line with this, SARS-CoV-2 RNA in serum was more common in severely ill patients, and those aged more than 60 years (Hagman et al., 2020; Veyer et al., 2020). The frequency of SARS-CoV-2 RNA in blood depends on the sampled populations and the PCR method used. Six percent (6/102) of COVID-19 patients presenting at an emergency department had positive plasma samples (Nijhuis et al., 2020). Forty-seven percent (58/123) of consecutively hospitalized patients had at least 1 positive plasma sample (Prebensen et al., 2020). With an ultra-sensitive method, up to 88% of critically ill patients were positive (Veyer et al., 2020).

The role of SARS-CoV-2 RNA in blood in the pathology of COVID-19 is largely unknown, and both viremia and RNAemia have been used to denote this finding. Multiple organ dysfunction is a common feature of severe COVID-19 and viral RNA has been demonstrated in the kidneys, liver, heart, and brain as well as the airways (Puelles et al., 2020; Richards-Belle et al., 2020). Autopsy data have demonstrated sub-genomic RNA indicative of replicating virus in non-airway tissues (Hanley et al., 2020). Moreover, SARS-CoV-2 virions have been visualized in blood plasma (Jacobs et al., 2021). Prolonged shedding of infectious virus has been shown in critically ill patients compared to patients with mild disease (Walsh et al., 2020). Available data thus suggest that SARS-CoV-2 RNA in the blood may represent viremia and could indicate uncontrolled viral replication (Jacobs and Mellors, 2020). However, SARS-CoV-2 has not yet, to our knowledge, been cultured from blood.

Longitudinal data on viremia are limited. A cohort of 27 viremic patients showed that 52% (14/27) had undetectable serum SARS-CoV-2 RNA 10 days after symptom onset (Ram-Mohan et al., 2021). Viremia was no longer detected 3 weeks after symptom onset in 8 patients in a small cohort (Colagrossi et al., 2021). Moreover, viremia lasted longer in 10 hospitalized patients with critical disease

Summary: The odds of mortality increased 40% for each day of viremia in patients hospitalized for COVID-19.

\* Corresponding author. Tel.: +46739592027

E-mail address: [karl.hagman@ki.se](mailto:karl.hagman@ki.se) (K. Hagman).

<https://doi.org/10.1016/j.diagmicrobio.2021.115595>

0732-8893/© 2021 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

compared to 10 patients with moderate/severe disease (van Riel et al., 2021). Two other case series (n = 6) described patients recovering quickly after serum viral clearance, while 1 patient with more severe disease had prolonged viremia (Kodama et al., 2020; Tan et al., 2020). We hypothesized that duration of viremia correlates to COVID-19 severity. This study thus aimed to describe the association of viremia duration and mortality, and the correlation of serum viral clearance to fever and relevant laboratory parameters, in hospitalized patients with SARS-CoV-2 viremia.

## 2. Methods

### 2.1. Study design, setting, and population

This cohort study was conducted at a 500-bed, tertiary care hospital in Danderyd, Stockholm, Sweden. Patients aged  $\geq 18$  years, diagnosed with COVID-19 from airway samples, with at least 1 positive serum SARS-CoV-2 RT-PCR were eligible for inclusion. The study period was April 1 to September 5, 2020.

During the study period a phase 1/2 convalescent plasma study for hospitalized patients, and a study investigating inhaled nitric oxide for mechanically ventilated patients was conducted. Hospitalized COVID-19 patients routinely received prophylaxis for thromboembolism during the study period. Corticosteroid treatment was given routinely from June 18 to patients requiring oxygen therapy. Remdesivir treatment was given to moderately/critically ill patients with viremia from June 29. No other COVID-19 specific treatments were used. A proportion of the data (61/439 analyzed serum samples) was previously published in an article regarding viremia at admission as a predictor for mortality (Hagman et al., 2020).

### 2.2. Serum sampling

The beginning of the study period coincided with the first peak of the COVID-19 epidemic. During this period patients were admitted to different wards throughout the hospital. There were no particular criteria for admission to the department of infectious diseases. During this period, only more severely ill patients admitted to the department of infectious diseases were tested for SARS-CoV-2 RNA in serum, at the discretion of the treating physician. From May 10, patients treated for COVID-19 at the department of infectious diseases, and the ICU were routinely tested for SARS-CoV-2 in serum every 1 to 3 days until serum viral clearance. Sampling at other wards was done sporadically throughout the study period.

Serum viral clearance was defined as 2 consecutive negative serum samples or 1 negative serum sample when no more sampling was done. The timepoint for serum viral clearance was subsequently defined as the day after the last positive serum sample as the interval between samplings could vary by a number of days. Duration of viremia was defined as the number of days from admission to serum viral clearance.

### 2.3. Data collection

Data collection was retrospective. RT-PCR results were collected from the microbiological laboratory at Karolinska University Hospital. Patient characteristics and outcome data were collected from electronic medical records. Laboratory sampling was irregular at non-ICU wards, but daily and extensive at the ICU. Therefore, only peak body temperature and C-reactive protein (CRP) were recorded serially 7 days before and after serum viral clearance for patients clearing virus whilst on a regular ward. For patients admitted to the ICU at time of serum viral clearance, daily peak body temperature, CRP, procalcitonin (PCT), fibrin d-dimer, estimated, relative Glomerular Filtration Rate (eGFR), Troponin T, and alanine aminotransferase (ALT)

were recorded serially 7 days before and after viral clearance in serum.

### 2.4. RT-PCR-analyses

SARS-CoV-2 RNA RT-PCR analyses were performed at the Karolinska University Laboratory using normal routine practices. Serum samples were analysed using either of 2 methods with similar sensitivity and specificity in in-house assessments (Hagman et al., 2020). One method utilized the fully automated cobas 6800 instruments (Roche Molecular Diagnostics, Pleasanton, CA), targeting the *Envelope* (E) and *Open Reading Frame* (ORF) 1 genes (Roche, 2020). The other method was an in-house test with RNA-extraction (MagNA Pure 96, Roche Diagnostics or MGISP-960, MGI Tech) followed by a modified version (unpublished) of the Drosten protocols for RT-PCR analysis, targeting the *Envelope* (E), and *RNA-dependent RNA polymerase* (RdRp) genes (Corman et al., 2020). Amplification of at least 1 gene was considered a positive test. For the diagnostic airway samples, the GeneXpert system (Cepheid, Sunnyvale, CA) was used in addition to the 2 previously described methods (Xpert, 2020).

### 2.5. Statistics

Continuous variables are presented as medians and interquartile ranges (IQR). The duration of viremia was described using a Kaplan-Meier estimate, including time from admission to serum viral clearance. Data was censored the day after the last SARS-CoV-2 RNA positive serum sample if serum viral clearance was not observed before death or discharge.

Multinomial logistic regression was applied to estimate the effect of covariates on the odds of dying or being discharged compared to continued hospitalization. The analysis was restricted to patients with viremia in a first serum sample collected within 3 days of admission to avoid overestimation of the viremia duration. A cluster-robust variance estimator was used to allow for the dependence between the repeated measures on individual patients. The results are presented as relative risk ratios (RRR) with 95% confidence intervals (CI). Variables indicating disease severity, comorbidities, immunosuppression, and treatments were included in the univariable analysis. Variables with  $P$ -values  $< 0.1$  in univariable regression models were included in the final multivariable regression. The analyses were also performed with time for serum viral clearance defined as the day for the first negative serum sample and with viremia duration defined as number of days from first to last positive serum sample.

Trends for laboratory samples and peak body temperature were analysed by median regression, using a piecewise linear function of time to allow different time trends before and after serum viral clearance. The model included individual fixed effects to capture the between-subject variability. To estimate standard errors, we used standard nonparametric bootstrap (reps = 100). Cycle threshold (CT) values were recorded for the serum samples and analysed separately for each targeted gene and method.

Statistical analyses were performed with STATA version 15.1 (StataCorp, TX). A  $P$  value of  $< 0.05$  was considered significant.

### 2.6. Ethics

The study was approved by the Swedish Ethical Review Authority (Registration number 2020-01770). Informed consent was waived.

## 3. Results

A total of 1363 patients were diagnosed with COVID-19 at Danderyd Hospital during the study period. Thirty-one percent (417/1363) were tested for SARS-CoV-2 RNA in serum and 29% (121/417) of them were positive in at least 1 sample and included in the cohort

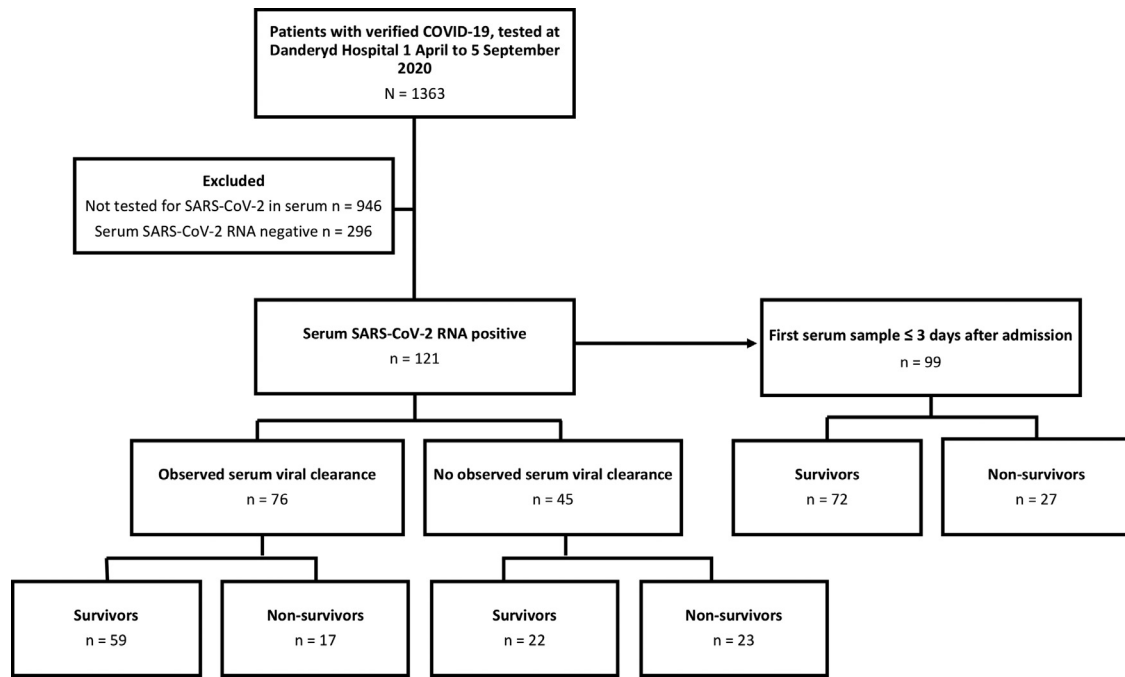


Fig. 1. Flowchart for study population. Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

(Fig. 1). Twenty-four percent (99/417) were positive in a sample collected within 3 days of hospital admission and included in the multinomial regression. Their baseline characteristics are shown in Supplementary Table 1. The total in-hospital mortality in the cohort was 40/121 (33%). Baseline characteristics for the patients in the cohort are shown in Table 1.

The median time to first serum sample was 1 (IQR 1–2) day after admission, corresponding to 9 (IQR 8–12) days after symptom onset. A total of 439 serum samples were included with a median of 3 (IQR 2–5) serum samples per patient resulting in a median of 2 (IQR 1–3) positive and 1 (IQR 0–2) negative RT-PCR test results. The median time from last positive serum sample to the first negative sample in patients with observed serum viral clearance was 3 (IQR 1–3) days.

Serum viral clearance was observed in 76/121 (63%) patients during hospitalization. Serum viral clearance was not observed in 45/121 (37%) patients of whom 23/45 died without clearing virus during hospitalization and 22/45 were discharged without a negative test. In-hospital deaths occurred in 17/76 (22%) patients with observed serum viral clearance.

### 3.1. Duration of viremia

The Kaplan-Meier estimate for median time from hospital admission to serum viral clearance was 7 (95% CI 6–8) days, corresponding to 15 (95% CI 14–16) days after symptom onset (Fig. 2). The maximal duration of confirmed viremia was 11 days in a patient who subsequently died.

In the multinomial logistic regression, duration of viremia had a RRR of 1.16 (95% CI 1.01–1.34,  $P = 0.03$ ) for a patient dying compared to continued hospitalization in the univariable analysis (Supplementary table 2). Viremia duration remained significantly associated with mortality, with a RRR of 1.40 (95% CI 1.02–1.92,  $P = 0.04$ ) after adjustment for baseline variables (Table 2).

The results were consistent in sensitivity analyses where serum viral clearance was defined as the day of the first negative serum sample, and viremia duration defined as number of days from first to last positive serum sample (Supplementary table 3 and 4).

### 3.2. Clinical and laboratory characteristics before and after serum viral clearance

Daily median peak body temperatures and CRP values 7 days before and after confirmed serum viral clearance ( $n = 76$ ) are shown in Fig. 3. The median body temperature declined continuously with 0.2 (95% CI 0.2–0.3) degrees per day during viremia, and 0.2 (95% CI 0.1–0.2) degrees per day after serum viral clearance, a non-significant difference ( $P = 0.14$ ). However, defervescence coincided with serum viral clearance. The median CRP increased by 7 (95% CI 0.7–14) mg/L per day during viremia and decreased by 17 (95% CI 10–24) mg/L per day after serum viral clearance ( $P < 0.01$ ).

For patients in ICU at time for serum viral clearance, daily median PCT, Fibrin D-dimer, eGFR, Troponin T, and ALT did not have a clinically significant correlation to serum viral clearance (Supplementary fig. 1 and 2).

### 3.3. CT values

The median CT value in RT-PCR positive serum samples was 34.2 (IQR 32.5–35.3) for the E-gene and 34.3 (IQR 32.8–35.4) for the RdRp-gene, analysed with the in-house assay. The median CT values were 36.2 (IQR 34.9–37.9) for the E-gene and 32.5 (IQR 31.6–35.1) for the ORF1-gene, analysed with the cobas-assay.

The daily median CT values for the in-house E-gene analyses increased by 0.7 (95% CI 0.5–0.8) per day ( $P < 0.01$ ) during the 7 days before serum viral clearance (Supplementary fig. 3). The corresponding increase for the RdRp-gene was 0.4 (95% CI -0.01 – 0.8) per day ( $P = 0.07$ ). Due to insufficient number of positive analyses performed with the cobas-assay ( $n = 46$ ), no further analysis of the CT values was performed for this assay.

## 4. Discussion

We investigated time to serum viral clearance in a cohort of 121 viremic adults hospitalized for COVID-19. Median time to serum viral clearance was 7 days after admission, corresponding to 15 days after symptom onset. The odds of mortality increased with 40% for each

**Table 1**  
Demographics, clinical characteristics at admission, and outcome data.

Variable	Full cohort (n = 121)	Survivors (n = 81)	Non-survivors (n = 40)	Complete data (%)
Age, y	62 (52–71)	58 (50–68)	69 (60–81)	121 (100)
Sex Female: Male	39:82 (32:68)	27:54 (33:67)	12:28 (30:70)	121 (100)
Any comorbidity	84 (69)	56 (69)	28 (70)	121 (100)
Pulmonary disease	16 (13)	11 (14)	5 (13)	121 (100)
Cardiovascular disease	30 (25)	16 (20)	14 (35)	121 (100)
Hypertension	55 (45)	35 (43)	20 (50)	121 (100)
Diabetes mellitus	30 (25)	15 (19)	15 (38)	121 (100)
Liver Disease	0 (0)	0 (0)	0 (0)	121 (100)
Chronic Renal Disease	11 (9)	5 (6)	6 (15)	121 (100)
Malignancy	6 (5)	3 (4)	3 (8)	121 (100)
Immunosuppression	8 (7)	6 (7)	2 (5)	121 (100)
Body Mass Index, kg/m <sup>2</sup>	27 (24–31)	27 (25–31)	27 (24–30)	110 (91)
Symptom duration at admission, d	7 (6–10)	7 (7–10)	7 (4–8)	121 (100)
D from admission to first serum sample	1 (1–2)	1 (1–2)	2 (1–4)	121 (100)
Number of serum samples	3 (2–5)	3 (2–5)	3 (2–4)	121 (100)
Body temperature, °C	39 (38–40)	39 (38–40)	39 (39–40)	121 (100)
Oxygen demand, L/min	4 (2–10)	4 (1–6)	6 (2–12)	121 (100)
C-reactive protein, mg/L	129 (75–201)	129 (81–198)	129 (63–201)	120 (99)
Procalcitonin, µg/L	0.3 (0.2–1)	0.3 (0.2–1)	0.3 (0.2–1)	87 (72)
Neutrophil count, x 10 <sup>9</sup> /L	5.6 (4.1–8.0)	5.3 (3.3–7.8)	5.9 (4.9–8.7)	118 (98)
Lymphocyte count, x 10 <sup>9</sup> /L	0.8 (0.6–1.1)	0.8 (0.6–1)	0.8 (0.5–1)	118 (98)
Neutrophil/Lymphocyte ratio	7 (4–11)	7 (4–10)	8 (6–15)	118 (98)
eGFR, mL/min/1.7m <sup>2</sup>	68 (54–84)	73 (58–86)	61 (49–78)	117 (97)
Fibrin D-dimer, mg/L	1.1 (0.7–1.9)	1.0 (0.7–1.6)	1.4 (0.8–4)	87 (72)
Troponin T, ng/L	11.5 (8–22)	9 (8–20)	16 (12–27)	98 (81)
ALT, µkat/L	0.7 (0.5–1.1)	0.7 (0.5–1.1)	0.6 (0.5–1.1)	96 (79)
Radiological signs of pneumonia	86 (99)	54 (100)	32 (97)	87 (72)
Remdesivir treatment	5 (4)	3 (4)	2 (5)	121 (100)
Corticosteroid treatment <sup>a</sup>	22 (18)	15 (19)	7 (18)	121 (100)
Convalescent plasma treatment	40 (33)	30 (37)	10 (25)	121 (100)
HFNO/NIV <sup>b</sup>	26 (21)	15 (19)	11 (28)	121 (100)
Mechanical ventilation <sup>b</sup>	41 (34)	18 (22)	23 (58)	121 (100)
ICU-care	46 (38)	23 (28)	23 (58)	121 (100)
In-hospital mortality	40 (33)	0 (0)	40 (100)	121 (100)

Data are median (IQR) or no. (%).

<sup>a</sup> Equivalent of  $\geq 20$  mg prednisolone for  $\geq 3$  days, initiated before viral clearance

<sup>b</sup> Highest need of respiratory support during hospitalization

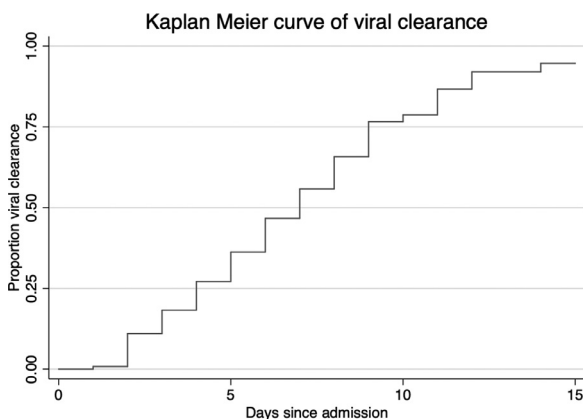
eGFR = estimated glomerular filtration rate; ALT = alanine aminotransferase; HFNO = high flow nasal oxygen; NIV = non-invasive ventilation; ICU = intensive care unit.

additional day of viremia. The results support recent studies showing that viremia at admission is a predictor of mortality in COVID-19 and the hypothesis that poor viral control contributes to disease severity (Hagman et al., 2020; Prebensen et al., 2020; Veyer et al., 2020). The maximal measured duration of viremia was 11 days in a patient that subsequently died. This is consistent with studies that showed a maximal duration of viremia of 10 days and a viremia half-life of

approximately 3 days (Hogan et al., 2020; Prebensen et al., 2020; Tan et al., 2020). Two outliers with  $\geq 30$  days from symptom onset to serum viral clearance were both B-cell depleted by rituximab treatment. The long duration of symptoms and viremia are in line with previous case reports and highlight the importance of a functional B-cell response for viral control (Hueso et al., 2020; Tepasse et al., 2020).

It is unclear whether detectable SARS-CoV-2 RNA in blood represents a systemic infection with replicating virus, spill-over from high viral loads in other organs, or leakage from damaged tissues. However, the principle finding of an increased odds for dying for each additional day of viremia is in line with previously described prolonged viral shedding in patients that die versus survive in ICUs, patients that are severely ill compared to mildly ill, and studies correlating high viral load in blood and nasopharyngeal samples at admission to mortality (Bermejo-Martin et al., 2020; Bitker et al., 2020; Magleby et al., 2020; Pujadas et al., 2020; Ram-Mohan et al., 2021; Wang et al., 2020). Prolonged shedding of infectious virus in critically ill patients and signs of replicating virus in multiple organs of non-survivors suggest that viremia represents replicating virus (Hanley et al., 2020; Walsh et al., 2020). Furthermore, decreasing viral load and daily peak body temperature over time, as well as the decrease in CRP coinciding with viral clearance, are consistent with gradual viral control. Available data thus suggest that poor viral control is a contributing factor for progression to critical disease and mortality in COVID-19.

Detection of viremia upon admission identifies a population with high risk of critical disease (Hagman et al., 2020). This study showed that following viremic patients with repeated serum samplings



**Fig. 2.** Kaplan-Meier failure curve of time from admission to serum viral clearance. Serum viral clearance was defined as the day after the last positive serum *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) sample. The Kaplan-Meier failure function was censored the day after the last positive serum SARS-CoV-2 sample was detected if serum viral clearance was not observed before death or discharge.

**Table 2**  
Adjusted multinomial logistic regression models.

Variable	Death		Discharge	
	RRR <sup>a</sup> (95% CI)	P value	RRR <sup>a</sup> (95% CI)	P value
Viremia duration, d	1.40 (1.02–1.92)	0.04	1.00 (0.90–1.12)	0.96
Age, y	1.13 (1.03–1.23)	<0.01	1.01 (0.98–1.04)	0.66
Male gender	0.58 (0.06–5.56)	0.64	0.63 (0.32–1.23)	0.18
Chronic kidney disease	4.73 (0.30–74.9)	0.27	8.38 (2.23–31.4)	< 0.01
Malignancy	3.24 (0.20–53.2)	0.41	0.26 (0.07–0.92)	0.04
Cardiovascular disease	0.36 (0.04–3.28)	0.37	1.61 (0.75–3.45)	0.22
Oxygen demand <sup>b</sup> , L/min	0.97 (0.79–1.18)	0.76	0.92 (0.87–0.98)	< 0.01
eGFR <sup>b</sup> , mL/min/1.7m <sup>2</sup>	1.01 (0.95–1.08)	0.67	1.03 (1.01–1.05)	< 0.01
ALT <sup>b</sup> , $\mu$ kat/L	1.00 (0.14–7.08)	0.99	1.73 (0.84–3.55)	0.13
C-reactive protein <sup>b</sup> , mg/L	1.00 (0.99–1.01)	0.62	1.00 (0.99–1.00)	0.11
Fibrin D-dimer <sup>b</sup> , mg/L	1.03 (0.95–1.13)	0.46	0.91 (0.73–1.14)	0.42
Symptom duration <sup>b</sup> , d	0.91 (0.78–1.06)	0.23	1.03 (0.97–1.09)	0.36
Convalescent plasma treatment	0.22 (0.03–1.48)	0.12	1.30 (0.70–2.42)	0.41

<sup>a</sup> Compared to continued hospitalization<sup>b</sup> At admission

RRR = relative risk ratio; CI = confidence interval; eGFR = estimated glomerular filtration rate; ALT = alanine aminotransferase.

enables a continuous risk assessment. Increasing CRP in patients who have cleared virus in serum signals an alternate cause such as secondary infection or thromboembolism.

This study showed an association between viremia duration and mortality. However, prospective studies are needed to investigate if shortening of viremia duration can reduce mortality. If so, novel inhibitors of viral replication may have a role later in the course of severe COVID-19, even though remdesivir was not effective in this sub-group (Beigel et al., 2020).

#### 4.1. Strengths and limitations

This is, to our knowledge, the largest study analysing viremia duration in patients with COVID-19. Though all patients tested for serum SARS-CoV-2 RNA at Danderyd Hospital were included in this study, the policy for ordering a test varied over time, possibly affecting the generalizability of the study.

Moreover, serum samplings were not structured for all patients, affecting the calculated time until serum viral clearance. The timing of serum viral clearance was defined as the day after the last positive serum sample, probably leading to an underestimation of the true duration of viremia. However, the main result was consistent even though alternate definitions of timepoint for serum viral clearance were used.

#### 5. Conclusion

Serum SARS-CoV-2 viral clearance occurred a median of 7 days after admission, corresponding to a median of 15 days after symptom onset in a cohort of 121 hospitalized, viremic patients. The odds of mortality increased with each additional day of viremia.

#### Authors' contributions

*Karl Hagman*: Conceptualization, Methodology, Data Curation, Investigation, Formal Analysis, Visualization, Writing - Original Draft, Writing - Review & Editing. *Magnus Hedenstierna*: Conceptualization, Methodology, Data Curation, Investigation, Formal Analysis, Writing - Review & Editing. *Johan Rudling*: Data Curation, Writing - Review & Editing. *Patrik Gille-Johnson*: Conceptualization, Methodology, Investigation, Formal Analysis, Writing - Review & Editing. *Berit Hammas*: Data Curation, Investigation, Formal Analysis, Writing - Review & Editing. *Malin Grabbe*: Data Curation, Investigation, Formal Analysis, Writing - Review & Editing. *Jan Jakobsson*: Conceptualization, Methodology, Writing - Review & Editing. *Joakim Dillner*: Investigation, Formal Analysis, Writing - Review & Editing. *Johan Ursing*: Conceptualization, Methodology, Data Curation, Investigation, Formal Analysis, Writing - Original Draft, Writing - Review & Editing.

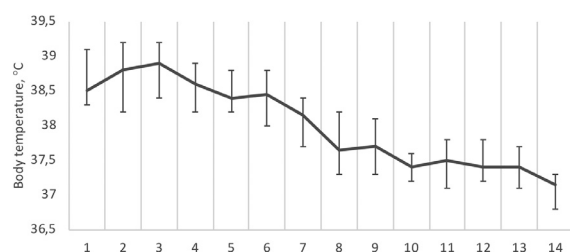
#### Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. J.U. has a position as clinical researcher funded by The Stockholm County Council (SLL20160597). No funding source was involved in the planning, implementation, or reporting of the study.

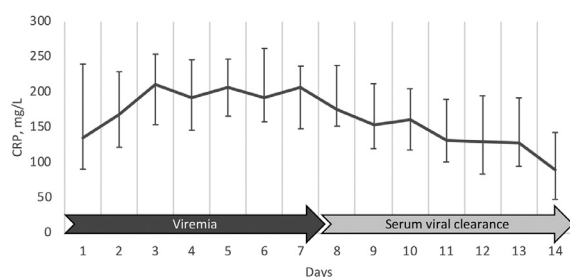
#### Acknowledgments

The main results from this study were presented at the ECCMID-conference 2021.

A. Peak body temperature



B. C-reactive protein



**Fig. 3.** Daily median (95% confidence interval) peak body temperature and C-reactive protein (CRP) 7 days before and after serum viral clearance (n = 76). Serum viral clearance was defined as the day after the last positive serum *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) sample.

## Declaration of competing interest

Declaration of competing interest: J.J. reports personal fees from consulting as a safety physician for Astra Zeneca, outside of the submitted work. No other author reports any conflicts of interest.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.diagmicrobio.2021.115595.

## References

- Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of covid-19 - final report. *N Engl J Med* 2020;383(19):1813–26.
- Bermejo-Martin JF, Gonzalez-Rivera M, Almansa R, Micheloud D, Tedim AP, Dominguez-Gil M, et al. Viral RNA load in plasma is associated with critical illness and a dysregulated host response in COVID-19. *Crit Care* 2020;24(1):691.
- Bitker L, Dhelft F, Chauvelot L, Frobert E, Folliet L, Mezidi M, et al. Protracted viral shedding and viral load are associated with ICU mortality in Covid-19 patients with acute respiratory failure. *Ann Intensive Care* 2020;10(1):167.
- Cepheid. Xpert Xpress SARS-CoV-2 assay CE-IVD ENGLISH package insert 302-3787 rev. A; 2020. Available at: <https://www.cepheid.com/Package%20Insert%20Files/Xpress-SARS-CoV-2/Xpert%20Xpress%20SARS-CoV-2%20Assay%20CE-IVD%20ENGLISH%20Package%20Insert%20302-3787%20Rev.%20A.pdf>. Accessed October 2, 2020.
- Colagrossi L, Antonello M, Renica S, Merli M, Matarazzo E, Travi G, et al. SARS-CoV-2 RNA in plasma samples of COVID-19 affected individuals: a cross-sectional proof-of-concept study. *BMC Infect Dis* 2021;21(1):184.
- Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro Surveill* 2020;25(3):2000045.
- Fajnzylber J, Regan J, Coxen K, Corry H, Wong C, Rosenthal A, et al. SARS-CoV-2 viral load is associated with increased disease severity and mortality. *Nat Commun* 2020;11(1):5493.
- Hagman K, Hedenstierna M, Gille-Johnson P, Hammam B, Grabbe M, Dillner J, et al. Severe acute respiratory syndrome coronavirus 2 RNA in serum as predictor of severe outcome in coronavirus disease 2019: a retrospective cohort study. *Clin Infect Dis* 2020;73(9):e2995–3001.
- Hanley B, Naresh KN, Roufosse C, Nicholson AG, Weir J, Cooke GS, et al. Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: a post-mortem study. *Lancet Microbe* 2020;1(6):e245–e53.
- Hogan CA, Stevens BA, Sahoo MK, Huang C, Garamani N, Gombar S, et al. High Frequency of SARS-CoV-2 RNAemia and association with severe disease. *Clin Infect Dis* 2020;72(9):e291–e5.
- Hueso T, Poudroux C, Péré H, Beaumont A-L, Raillon L-A, Ader F, et al. Convalescent plasma therapy for B-cell-depleted patients with protracted COVID-19. *Blood* 2020;136(20):2290–5.
- Jacobs JL, Bain W, Naqvi A, Staines B, Castanha PMS, Yang H, et al. SARS-CoV-2 viremia is associated with COVID-19 severity and predicts clinical outcomes. *Clin Infect Dis* 2021.
- Jacobs JL, Mellors JW. Detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA in blood of patients with coronavirus disease 2019 (COVID-19): what does it mean?. *Clin Infect Dis* 2020;73(9):e2898–900.
- Kodama T, Kouzaki Y, Kawano S, Obinata H, Taniguchi H, Sasaki H, et al. Serial serum SARS-CoV-2 RNA results in two COVID-19 cases with severe respiratory failure. *J Infect Chemother* 2020;26(11):1220–3.
- Li Y, Schneider AM, Mehta A, Sade-Feldman M, Kays KR, Gentili M, et al. SARS-CoV-2 viremia is associated with distinct proteomic pathways and predicts COVID-19 outcomes. *J Clin Invest* 2021;131(13).
- Magleby R, Westblade LF, Trzebucki A, Simon MS, Rajan M, Park J, et al. Impact of severe acute respiratory syndrome coronavirus 2 viral load on risk of intubation and mortality among hospitalized patients with coronavirus disease 2019. *Clin Infect Dis* 2020.
- Nijhuis RHT, Russcher A, de Jong GJ, Jong E, Herder GJM, Remijn JA, et al. Low prevalence of SARS-CoV-2 in plasma of COVID-19 patients presenting to the emergency department. *J Clin Virol* 2020;133: 104655.
- Prebensen C, Myhre PL, Jonassen C, Rangberg A, Blomfeldt A, Svensson M, et al. Severe acute respiratory syndrome coronavirus 2 RNA in plasma is associated with intensive care unit admission and mortality in patients hospitalized with coronavirus disease 2019. *Clin Infect Dis* 2020;73(3):e799–802.
- Puelles VG, Lütgehetmann M, Lindenmeyer MT, Spherhake JP, Wong MN, Allweiss L, et al. Multiorgan and renal tropism of SARS-CoV-2. *N Engl J Med* 2020;383(6):590–2.
- Pujadas E, Chaudhry F, McBride R, Richter F, Zhao S, Wajnberg A, et al. SARS-CoV-2 viral load predicts COVID-19 mortality. *Lancet Respir Med* 2020;8(9):e70.
- Ram-Mohan N, Kim D, Zudock EJ, Hashemi MM, Tjandra KC, Rogers AJ, et al. SARS-CoV-2 RNAemia predicts clinical deterioration and extrapulmonary complications from COVID-19. *Clin Infect Dis* 2021.
- Richards-Belle A, Orzechowska I, Gould DW, Thomas K, Doidge JC, Mouncey PR, et al. COVID-19 in critical care: epidemiology of the first epidemic wave across England, Wales and Northern Ireland. *Intensive Care Med* 2020;46(11):2035–47.
- Roche. cobas® SARS-CoV-2, qualitative assay for use on the cobas® 6800/8800 systems. Version 1; 2020. Available at: [https://www.who.int/diagnostics\\_laboratory/eul\\_0504-046-00\\_cobas\\_sars\\_cov2\\_qualitative\\_assay\\_ifu.pdf?ua=1](https://www.who.int/diagnostics_laboratory/eul_0504-046-00_cobas_sars_cov2_qualitative_assay_ifu.pdf?ua=1). Accessed October 2, 2020.
- Tan C, Li S, Liang Y, Chen M, Liu J. SARS-CoV-2 viremia may predict rapid deterioration of COVID-19 patients. *Braz J Infect Dis* 2020;24(6):565–9.
- Tepasse PR, Hafezi W, Lutz M, Kuhn J, Wilms C, Wiewrodt R, et al. Persisting SARS-CoV-2 viraemia after rituximab therapy: two cases with fatal outcome and a review of the literature. *Br J Haematol* 2020;190(2):185–8.
- van Riel D, Embregts CWE, Sips GJ, van den Akker JPC, Endeman H, van Nood E, et al. Temporal kinetics of RNAemia and associated systemic cytokines in hospitalized COVID-19 patients. *mSphere* 2021;6(3) e0031121.
- Veyer D, Kernéis S, Poulet G, Wack M, Robillard N, Taly V, et al. Highly sensitive quantification of plasma severe acute respiratory syndrome coronavirus 2 RNA sheds light on its potential clinical value. *Clin Infect Dis* 2020;73(9):e2890–7.
- Walsh KA, Spillane S, Comber L, Cardwell K, Harrington P, Connell J, et al. The duration of infectiousness of individuals infected with SARS-CoV-2. *J Infect* 2020;81(6):847–56.
- Wang Y, Zhang L, Sang L, Ye F, Ruan S, Zhong B, et al. Kinetics of viral load and antibody response in relation to COVID-19 severity. *J Clin Invest* 2020;130(10):5235–44.