

Clinical Analysis on Diagnostic Accuracy of Bosch Vivalytic SARS- CoV-2 Point-of-Care Test and Evaluation of Cycle Threshold at Admission for COVID-19 Risk Assessment

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Abstract

Background Point-of-care (POC) polymerase chain reaction (PCR) tests have the ability to improve testing efficiency in the Coronavirus disease 2019 (COVID-19) pandemic. However, real-world data on POC tests is scarce.

Objective To evaluate the efficiency of a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) POC test in a clinical setting and examine the prognostic value of on admission cycle threshold (CT) on length of hospital stay (LOS) in COVID-19 patients.

Methods Patients hospitalised between January and May 2021 were included in this prospective cohort study. Patients' nasopharyngeal swabs were tested for SARS-CoV-2 with Allplex™ 2019-nCoV (Seegene Inc.) real-time (RT) PCR assay and novel POC test (Bosch Vivalytic SARS-CoV-2 [Bosch]) as well as the SARS-CoV-2 Rapid Antigen Test (Roche) accordingly. Clinical sensitivity and specificity as well as inter- and intra-assay variability were analysed.

Results 120 patients met the inclusion criteria with 46 (38%) having definite COVID-19 diagnose by RT-PCR. Bosch Vivalytic SARS-CoV-2 POC had a sensitivity of 88% and specificity of 96%. The inter- and intra- assay variability was below 15%.

CT Value at baseline was lower in patients with LOS ≥ 10 days when compared to patients with LOS < 10 days (27.82 (± 4.648) vs. 36.2 (25.9 - 39.18); $p=0.0191$). There was a negative correlation of CT at admission and LOS ($r[44]_s = -0.31$; $p=0.038$)

Conclusion Our data indicate that POC testing with Bosch Vivalytic SARS-CoV-2 is a valid strategy to identify COVID-19 patients and decrease turnaround time to definite COVID-19 diagnosis. Also our data suggests at admission CT as promising marker for length of hospital stay and possibly severity of disease in COVID-19 patients.

Contribution To The Field

Coronavirus disease 2019 (COVID-19) is a rapidly spreading global pandemic with increased burden on healthcare. Often, centralised laboratory polymerase chain reaction (PCR) testing leads to long severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test turnaround times, which in return result in poor patient flow and nosocomial transmission. Point-of-care (POC) PCR tests have the ability to improve testing efficiency by reducing steps between sample collection and results, ultimately contributing to better COVID-19 containment. Numerous assays are suggested for use in clinical practice. However, with some of them just recently released data on their clinical performance is limited. We provide prospective real world data supporting the accuracy and reliability of a new rapid PCR point of care test (Bosch Vivalytic SARS-CoV-2) in a comparative analysis with an antigen test and an extern laboratory. Also our data suggests at admission POC Cycle threshold (CT) as promising marker for length of hospital stay

and possibly severity of disease in COVID-19 patients. Furthermore our data emphasise the increased risk for long-term health effects of COVID-19 patients and the consecutive need for individual follow-up.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with the resulting COVID-19 pandemic has presented hospitals with considerable challenges.(1) These are partly aggravated by long COVID-19 test turnaround times, associated with centralised laboratory PCR testing, resulting in poor patient flow and nosocomial transmission. (2, 3) Standard real-time (RT) - polymerase chain reaction (PCR) for COVID-19 is the gold standard but requires specialized materials, equipment, personnel and transportation to a centralized laboratory. (4) Point-of-care (POC) PCR tests have the ability to improve testing efficiency by reducing steps between sample collection and results, ultimately contributing to better COVID-19 containment.(3) Numerous assays are suggested for use in clinical practice. However, with some of them just recently released data on their clinical performance is limited. (5) We compare in a prospective clinical setting Bosch Vivalytic SARS-CoV-2 test for Bosch Vivalytic One with a centralised laboratory PCR test and an established COVID-19 ELISA Elecsys Anti-SARS-CoV-2 assay (Roche).

Current data point towards a plausible positive correlation between the amount of detected virus measured by the proxy PCR cycle threshold (CT) value and the severity of disease. (6) Previous evidence from influenza suggests that the higher the initial viral load, the worse the clinical development. (7) However, firm conclusion on the relationship between initial CT value and individual prognosis is still missing and data for the most part limited to nasopharyngeal viral load samples processed through external laboratories. (8) Whether CT values derived from POC testing could yield similar results is yet to be established. Different scoring systems have been suggested for COVID-19 risk-assessment, with several of them being derived from established assays. (9, 10) Although being influenced by comorbidities and patient characteristics, Length of hospital stay (LOS) has been shown to be a rational choice to measure severity of disease and level of care needed in hospitalized patient. (11, 12) Therefore, we strive to evaluate cycle threshold (CT) in POC reverse-PCR tests in confirmed COVID-19 patients as possible marker for LOS and severity of disease.

Such early indicators providing insight into potential disease progression are critical in order to properly select patients requiring special care, especially when exponentially increasing numbers of infections occur in a short time interval and hospitals become overcrowded.

Not only the heterogeneous clinical presentations of COVID-19 poses a challenge for attending physicians but also the prevalence of a variety of late-effects. (13) Divided into two different entities, "post acute COVID-19" where symptoms extend beyond 3 weeks and "chronic COVID-19" where symptoms extend beyond 12 weeks, long COVID-19 is estimated to affect up to 80%. (14, 15) However, real-world data for hospitalized patients and long COVID-19 is limited.

Methods

2.1 Study design

We here report data from an investigator-initiated, single-center, prospective registry study to evaluate Vivalytic™ SARS-CoV-2 Multiplex POC (Bosch) COVID-19 test in clinical practice and to evaluate CT value at admission for risk stratification in hospitalized patients conducted at the Severinenklösterchen Hospital – University of Cologne.

The protocol of this study conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional ethical committee of the Ärztekammer Nordrhein (20211001).

2.2. Study population

All-comers admitted to the hospital over 18 years were eligible for inclusion.

The decision to perform a PCR-test for SARS-CoV-2 was made independently of study inclusion by the treating physician and patients were asked to participate before the test results were available.

Written informed consent was obtained from all patients prior to study inclusion.

Patients with a positive PCR-test for SARS-CoV-2 were finally allocated to the “positive” group, patients with a negative PCR-test for SARS-CoV-2 to the control group (Figure 1). Every patient was then tested 2 additional times using Vivalytic SARS-CoV-2 Test (Bosch), and SARS-CoV-2 Rapid Antigen Test (Rosche) respectively. All nasopharyngeal swabs were taken from nurses or trained personnel.

2.3. Study plan

Patient admitted to hospital between January and May 2021 were randomly asked to participate in the study. If patients had agreed to participate, overall characteristics such as sex, age and medical history were recorded.

To characterize the severity of the course of disease in COVID-19 patients were divided according to the length of stay (LOS) in: patients hospitalized for longer or shorter than 10 days .

All clinical data gathered during this period was obtained from the electronic patient file. During follow-up no interventions were applied for the purpose of this study and all therapeutic and diagnostic procedures were applied as part of standard care at the discretion of the treating physicians. Finally, participants were contacted by phone and asked about the course of disease using a standardized questionnaire after 3 month. Herein, the patients were asked to rank their current physical fitness on a scale from 0–100% in relation to the COVID-19 disease.

2.4 Measurements

SARS-CoV-2 testing using Allplex™ 2019-nCoV Assay (Seegene, Seoul, Korea: polymerase chain reaction assay (PCR) targeting envelope protein- (E-), RNA-dependent RNA polymerase- (RdRP-), and N- genes) was performed by an external laboratory with Applied Biosystems™ 7500 Real-Time PCR System according to the manufacturer guidelines.

For analysis with Bosch Vivalytic SARS-CoV-2 assay (Bosch Healthcare Solutions GmbH, Waiblingen, Germany) using the Vivalytic SARS-CoV-2 analyzer samples were collected in a guanidine thiocyanate-based medium eNAT® (COPAN Diagnostics Inc.; Murrieta, USA), stabilizing the viral RNA and completely inactivating the microbial viability. Vivalytic SARS-CoV-2 analyzer is a portable device and works fully automatically.

Roche SARS-CoV-2 Rapid Antigen Test is an immunochromatographic assay for qualitative detection of SARS-CoV-2 infection in nasopharyngeal swabs. The presence of viral antigens in sufficient concentration enables binding to specific mouse monoclonal anti-SARS-CoV-2 antibodies, which is then reflected by the appearance of a visual indication after clinical specimen is collected and then deposited in a pre-filled extraction buffer container with the solution being put on the test sample according to manufacturer guidelines.

Inter-assay variability was performed conducting repetitive tests on four samples throughout three days. Intra-assay variability was performed conducting four consecutive assays in one run. Both times we were using inactivated whole pathogen sample: AMPLIRUN® TOTAL SARS-CoV-2 RNA Control (Viracell SA, Granada, Spain).

2.5. Statistic

Continuous patient data were compared using a Mann–Whitney U-test or unpaired T-test. Categorical differences between patient groups were compared using Fisher's exact test. Continuous variables are presented as mean \pm standard deviation (SD) if found to follow a Gaussian distribution according to the D'Agostino-Pearson omnibus normality test or as median \pm lower and upper quartiles if found to follow a non-Gaussian distribution. Categorical patient characteristics are presented as percentages. Spearman nonparametric correlation was used to evaluate the measures the degree to which LOS and CT value at admission move in relation to each other.

Descriptive analyses were performed using Graph Pad Prism Version 9.0 (Prism 9 for Mac OS X; GraphPad Software, Inc., La Jolla, CA).

Results

3.1 Baseline characteristics

We included 120 patients hospitalized between January and May 2021 in this prospective cohort study. Of those 46 (38%) patients were tested positive for COVID-19 infection via the extern laboratory. The COVID-19 positive group was younger when compared to the negative control group (55.5 [38.5 - 65.75] years vs. 63.05 [\pm 17.41] years; $p=0.007$).

Patients with COVID-19 disease had higher levels of LDH (362.3 [\pm 136.1] U/l vs. 236 [203.3 – 301]; $p=0.014$) and CRP (5.96 [\pm 5.348] mg/dl vs. 0.4 [0.4 - 2.7] mg/dl; $p< 0.001$) when compared to the control group. If the cut-off for a normal value for LDH was considered to be 250 U/l, an increased level of LDH at baseline had a sensitivity of 75% and a specificity of 53.5% (PPV 50%; NPV 77.5%) for COVID-19 diagnosis. There was no difference with anamnesis for coronary artery disease (8 [17.4%] patients vs. 15 [20.3%] patients; $p=0.495$), hypertension (18 [39.1%] patients vs. 36 [48.6%] patients; $p=0.349$) or pulmonary disease (9 [19.5%] patients vs. 25 [33.9%] patients; $p=0.101$). Symptoms of COVID-19 patients included dyspnea (39.1%), cough (30.4%), fatigue (37%), gastrointestinal complaints (17.4% [Abdominal pain, diarrhea and anosmia]), fever (41.3) and chest pain (8.7%). The majority of COVID-19 patients were affected by the virus variant B1.1.7 (31 [67.4%] of all included COVID-19 patients. (Table 1)

Table 1
Patients baseline characteristics at admission.

Variable	COVID-19 n=46		Non-COVID-19 n=74		P- Value
Age (years)	55.5	38.5 - 65.75	63.05	± 17.41	0.006
Sex (female)	15	(33.3%)	39	(52.7%)	0.057
C-reactive protein (mg/dl)	5.96	(±5.348)	0.4	(0.4 - 2.7)	< 0.001
Hemoglobine /g/dl)	13.46	(±2.068)	12.79	(±2.164)	0.094
Leukocytes (Tsd/ul)	6.75	(4.575 - 9.85)	7.9	(6.15 - 10.2)	0.169
Platlets (Tsd/ul)	217.5	(179 - 261.8)	258.5	(195.3 - 310.3)	0.116
Lactate dehydrogenase (U/l)	362.3	(±136.1)	236	203.3 - 301	0.014
Aspartate Aminotransferase (U/l)	38	(26.5 – 55)	24	17 - 31.25	0.614
CAD*	8	(17.4%)	15	(20.3%)	0.495
Hypertension	18	(39.1%)	36	(48.6%)	0.349
Pulmonary disease	9	(19.5%)	25	(33.9%)	0.101
Length of Stay (days)	9.5	(4.75 - 15.25)			

*CAD=Coronary Artery Disease; Continuous variables are presented as mean ± standard deviation (SD) if found to follow a Gaussian distribution according to the D'Agosstino-Pearson omnibus normality test. or as median ± lower and upper quartiles if found to follow a non-Gaussian distribution.

3.2 Bosch Vivalytic SARS-CoV-2 assay precision

Inter- and Intra-assay coefficients of variability for Vivalytic™ SARS-CoV-2 Multiplex analyzer were below 15%. (Table 2A and B)

In relation to the results of the established extern laboratory PCR test, the POC test had a test-sensitivity for SARS-CoV-2 infection of 88% with a specificity of 96%. The positive predictive value was 90% and the negative predictive value 95%.

The antigen-test had a sensitivity for COVID-19 infection of 65% with a specificity of 100%. The positive predictive value was 100% and the negative predictive value 88%.

Table 2
Inter- (A) and intra- (B) test variability for different test samples L1-L4 and T1-T4

A	Ct-Wert	Ct-Wert	Ct-Wert	Mittelwert	SD	VK	VK%
L1	31.9	31	33	31.97	1.00	0.03	3.1
L2	30.5	31.8	31.9	31.4	0.78	0.02	2.5
L3	31.7	34.9	31.5	32.7	1.91	0.06	5.8
L4	33.7	38.3	36.7	36.23	2.33	0.06	6.4

B	Ct-Wert	Ct-Wert	Mittelwert	SD	VK	Vk%
T1	34.1	33	33.55	0.78	0.02	2.32
T2	32.6	31.9	32.25	0.49	0.02	1.52
T3	38.1	31.5	34.8	4.67	0.13	13.41
T4	35.4	36.7	36.05	0.92	0.03	2.55

3.3. Length of stay

Patients with positive SARS-CoV-2 test had an overall length of hospital stay of 9.5 (4.75 - 15.25) days. To quantify severity of disease we divided COVID-19 patients into two groups of patients with LOS ≥ 10 d (21 ± 17 days) and patients with LOS < 10 d (4.7 ± 2.7 days).

Patients with LOS < 10 d had significant lower CT values at admission when compared to patients with LOS ≥ 10 d (36.2 [25.9 - 39.18] vs. 27.82 [± 4.648]; $p=0.0191$). (Figure 2)

Patients with a LOS < 10 days were younger (45.6 ± 14 years vs. 62.4 [± 62.4] years; $P=0.001$) and had higher levels of haemoglobin (13.6 (± 1.7) g/dl vs. 11.9 (± 2.3) g/dl; $p=0.007$) when compared to patients with a LOS > 10 days. There was a negative correlation of CT at admission and LOS ($r[44]_s = -0.31$; $p=0.038$). There was no statistical significant difference between both groups regarding other baseline characteristics collected. 15 (75%) patients in the group with LOS < 10 days were affected by the virus variant B1.1.7 and 16 (61.5%) patients in the group with LOS ≥ 10 days ($p=0.4834$). (Table 3)

Table 3

Baseline characteristics at admission in patients hospitalized with COVID-19 disease with length of hospital stay (LOS) above or below 10 days respectively.

Variable	LOS <10d n=23		LOS ≥10d n=23		P-Value
LOS*	4.7	(±2.7)	21	(±17)	
Age (years)	45.6	(±14)	62.4	(±62.4)	0.001
Sex (female)	7	(30.4%)	8	(34.8%)	0.753
C-reactive protein (mg/dl)	3.6	(0.4-7.6)	7.7	(±6.3)	0.051
Haemoglobine (g/dl)	13.6	(±1.7)	11.9	(±2.3)	0.007
Leukocytes (Tsd/ul)	7.5	(±4)	7.4	(4.9-10)	0.628
Platlets (Tsd/ul)	209	(173-257)	233	(181 - 282)	0.652
Lactate dehydrogenase (U/l)	330	(258-469)	377	(230-447)	0.989
Aspartate Aminotransferase (U/l)	38	(16-38)	46	(±30)	0.941
CAD**	2	(9%)	6	(25%)	0.119
Hypertension	7	(29%)	11	(48%)	0.567
Pulmonary disease	4	(17%)	5	(22%)	0.710
Virus Variant B1.1.7	15	(65%)	11	(48%)	0.234
POC-CT*** at admission	36.2	(25.9 - 39.18)	27.82	(±4.648)	0.019
Vital parameters at admission					
Mean Pressure (mmHg)	94.5	(81-105)	90	(87 - 94)	0.616
Temperature	37.6	(36.8-38.5)	37.4	(36.5-38.1)	0.410
Respiratory Rate (per min.)	18.3	(±4.8)	17.6	(±3.2)	0.530
Heart Rate (Beats/minute)	87.7	(±15.1)	92.4	(±18.7)	0.367
Saturation at admission (%)	96	(94.8 - 98)	95.5	(89.5-96.3)	0.127
* LOS=Length of stay; **CAD_ Coronary Artery Disease; ***CT=Cycle Threshold only CT values of the Point-of Care test (LOS <10d n=20 and LOS ≥10d n=20); Continuous variables are presented as mean ± standard deviation (SD) if found to follow a Gaussian distribution according to the D'Agosstino-Pearson omnibus normality test. or as median ± lower and upper quartiles if found to follow a non-Gaussian distribution.					

3.4 Outcome

Of 46 patients tested positive, 22 completed the follow-up and 5 COVID-19 patients died.

At three month after hospital discharge 15 (68%) COVID-19 patients had persistent depreciation of Quality of life incidental with COVID-19 disease (80 [70 – 90] % of the normal physical capacity).

Discussion

In this single centre prospective cohort study we evaluate real-world diagnostic accuracy of point-of-care testing using Bosch Vivalytic SARS-CoV-2 test for Bosch Vivalytic One by comparing sensitivity and specificity to an established extern laboratory as well as a commercially available antigen test.

Our prospective and comparative evaluation shows that Bosch Vivalytic SARS-CoV-2 POC test is a valid strategy for COVID-19 detection with the potential to increase door-to-diagnosis allowing earlier detection of COVID-19 positive patients. (3, 17) With its advertised turnaround time of approximately 39 minutes it exceeds those of established extern laboratories using RT-PCT by far. (5) The agreement of the POC test and RT-PCR is good with robust inter- and intra-assay reliability and good detection of positive samples. However, recently published data indicates that in the very early phase of the infection with high CT values, in which the RT-PCR can already detect the infection, the antigen level is not high enough for the POC test, necessitating repeated testing. (18, 19)

While RT-PCR should still be the gold standard, POC testing could help with patient triage and improve patient flow dynamics. (20) Antigen detection alone proved to be too uncertain for definite COVID-19 diagnosis in line with other publications. (21)

The prognostic value of Cycle Threshold in COVID-19 patients has been suggested by several studies. (22) Prospective data as well as data depending on CT values acquired using POC tests however is missing. Our data shows that on admission POC CT values are lower in patients with prolonged length of hospital stay in COVID-19 patients and that CT value at admission correlates with LOS. Nevertheless, variability of CT values of up to 8 cycles were observed for the same specimen material tested in different laboratory in a recent publication. (23) Therefore, risk assessment using CT values should be only considered if tests are acquired from only one single laboratory using the same assay.

Nevertheless, through their easier implementation, cost effectiveness and accuracy POC COVID-19 test could help monitoring epidemiological features of the COVID-19 pandemic through testing of large cohorts. (24)

Long-term health effects of COVID-19 called Long-COVID or COVID long-haulers are challenging for clinicians through their heterogeneity. (13) It is vital to understand the percentage of patients suffering from long-term effects. Our data shows, that up to 68% of discharged patients experience a COVID-19 related decrease in quality of life at three month after hospital discharge. This is in line with several other studies and the recommendation for Patients discharged after COVID-19 hospitalization to follow-up with their primary care physician on a regular basis maybe even through telemedicine visits. (25, 26)

Our data depicts the third wave of COVID-19 pandemic in Germany early 2021 with SARS-CoV-2 Variant B.1.1.7 being the predominantly detected variant. (27) This mutant strain prompted border closures, lockdowns and new restrictions ultimately cumulating in further deaths and economic loss. However, with a large proportion of the elderly being already inoculated following the guidelines of the Standing Committee on Vaccination (STIKO) we report COVID-19 patients to be younger than regular hospital all-comers forming our control group. (28) This all-the more emphasises the need for rapid inoculation to protect patients.

Several routine laboratory markers have been suggested in COVID-19 diagnostic algorithm. (29) In a recent meta-analysis Lactate dehydrogenase (LDH) has been suggested as cost-effective biomarker in patients with COVID-19. (30) An important variable in our study is that two distinct patient groups were analysed one composed out of regular all-comers and one of COVID-19 patients. In our prospective data elevated LDH was a distinct feature of COVID-19 patients when compared to the control group. However, LDH was not associated with LOS. Larger clinical trials are needed to confirm the value of LDH at baseline for COVID-19 diagnosis.

Limitations

POC PCR is a qualitative not quantitative measurement and it is not possible to quantify the virus load via CT values. CT values vary in-between different assays. We used only a single. negative RT-PCR to confirm the absence of COVID-19 infection, risking missing infection. A lot of patients were lost to follow-up. We did not assess quality of life at the time point of inclusion. The fact, that patients with LOS >10 days were younger could possibly diminish the interpretability of our data.

Conclusion

This data from a single centre provides prospective and comparative data indicating, that POC testing using Bosch Vivalytic SARS-CoV-2 is a valid strategy to identify COVID-19 patients and decrease turnaround time during COVID-19 pandemic. Also our data suggests at admission CT as promising marker for length of hospital stay and possibly severity of disease in COVID-19 patients. Our data emphasise the increased risk for long-term health effects of COVID-19 patients and the consecutive need for individual follow-up.

Declarations

Ethics approval, accordance and consent to participate:

The protocol of this study conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional ethical committee of the Ärztekammer Nordrhein (20211001). Written informed consent was obtained from all patients prior to study inclusion.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there is no conflict of interest'.

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This work was not funded.

Authors' contributions

LH, IA, and NE designed the study. LH and NE collected the data. NE and LH analysed the data. LH, NE and IA wrote the manuscript. US, NG, DD, US, CB and MO reviewed and corrected the paper. All authors contributed to the article and approved the submitted version.

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Figures

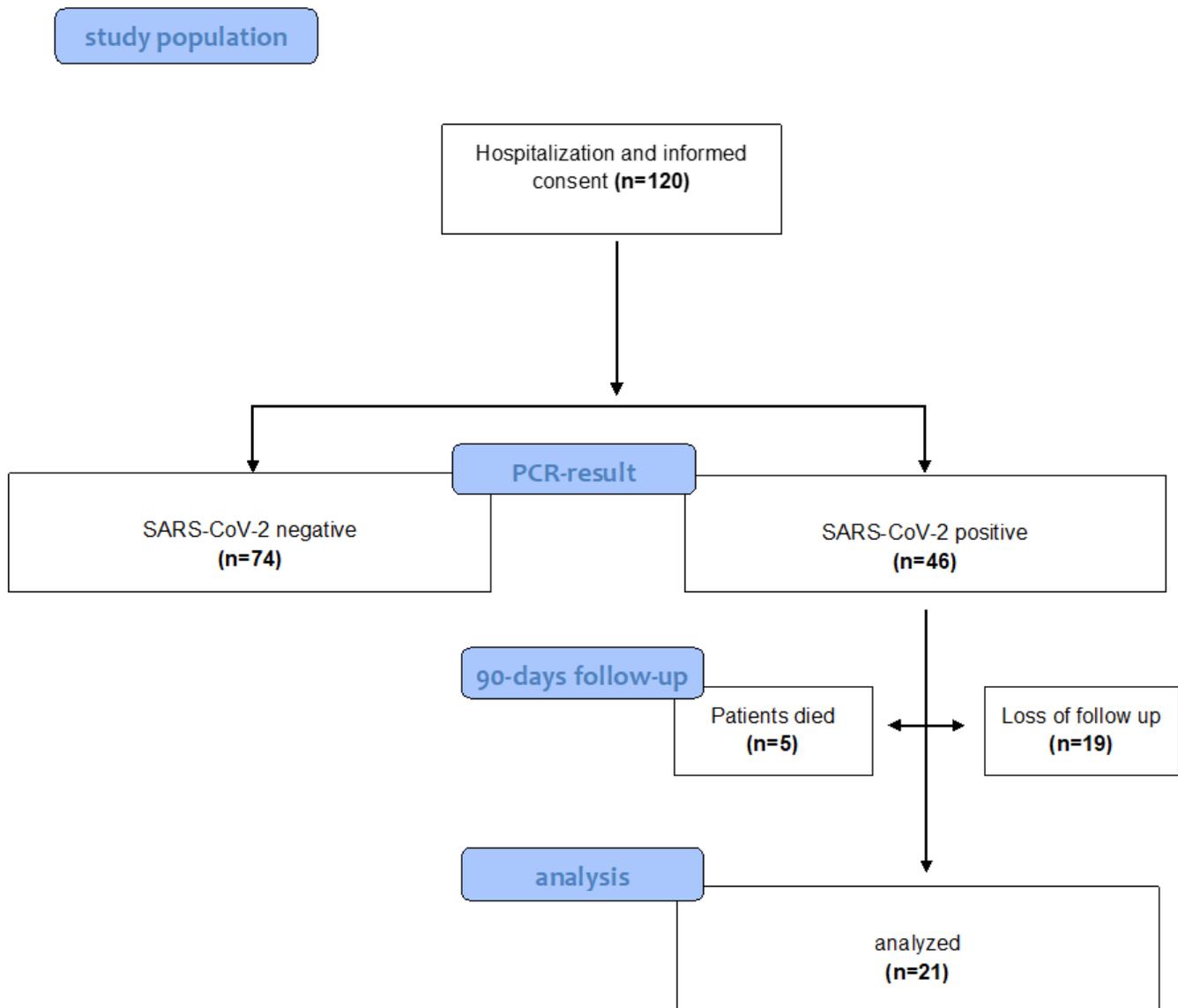


Figure 1

Schematic representation of the allocation to the positive or negative group of the 120 participants. 19 participants of the SARS-CoV-positive cohort were lost to follow-up and 5 participants died. The flow diagram is based on the template of the CONSORT flow diagram. (16)

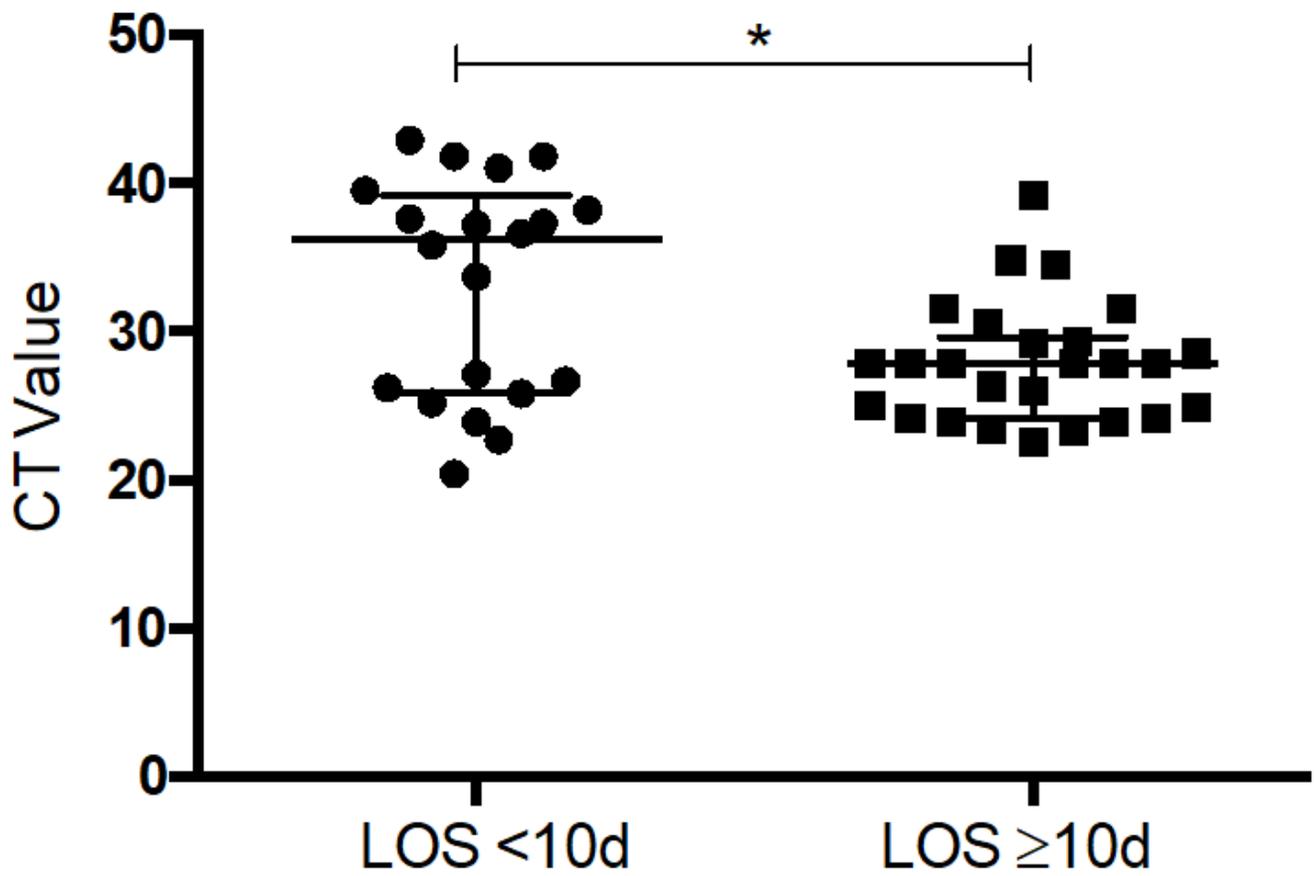


Figure 2

Point-of-Care Cycle- threshold (CT) Value at admission in patients with confirmed diagnose of COVID-19 and length of hospital stay (LOS) above (≥ 10 days) or below (LOS <10d) ten days respectively. Data are presented as scatter block with Interquartile Range.