

Risk factors for prolonged nucleic acid conversion time in patients with COVID-19

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Introduction

The 2019-nCoV pneumonia epidemic started at the local Seafood Wholesale Market in Wuhan City, Hubei Province, China, in December 2019 and rapidly spread to many countries.^[1] The World Health Organization (WHO) defined the confirmed case as the detection of SARS-CoV-2 nucleic acid material in biological samples, regardless of symptoms and signs. According to the current Coronavirus disease 2019 (COVID-19) diagnostic criteria, the most important criterion in the decision of hospitalization and isolation is the viral nucleic acid test performed with real-time reverse-transcription polymerase chain reaction (rRT-PCR). Factors affecting rRT-PCR test results are sampler, the location of the sample (upper or lower respiratory tract), the time of sampling according to the stage of the disease, and the performance of the diagnostic kit.^[2] rRT-PCR sensitivity was reported as 62% in a study conducted with a large sample size.^[3]

In the presence of computed tomography (CT) findings of viral pneumonia, the suspicion of COVID-19 increases significantly

ABSTRACT

Objectives: The time for PCR positivity to negativity is defined as nucleic acid conversion time (NCT) and is very important in terminating the isolation of patients and determining infectiousness in patients with COVID-19. The aim of this study is to determine the median NCT and to evaluate the clinical and laboratory parameters affecting it in patients with COVID-19.

Methods: This study included 318 patients with mild to moderate COVID-19 diagnosed with PCR positivity retrospectively.

Results: The median NCT was 11 days. Patients were divided into 2 groups as early (<11 days) and late conversion (≥11 days). Older age, sore throat, onset fever, fever 72 h after hospitalization, history of exposure to SARS-CoV-2 virus without a mask, and moderated disease were significantly more common in the late conversion group. In addition, favipiravir use was higher in early conversion group and hydroxychloroquine use was higher in late conversion group. In multivariate analysis, sore throat (OR = 2.570; 95% CI: 1.051–6.284, *P* = 0.039) and hydroxychloroquine use (OR = 3.518, 95% CI: 1.163–10.635, *P* = 0,026) were independent risk factors for late conversion. Favipiravir use (OR = 0.062, 95% CI: 0.021–0.184, *P* = 0.0001) negatively affected the late conversion.

Conclusion: NCT was longer in patients with COVID-19 who had sore throat at admission and were treated with hydroxychloroquine instead of favipiravir.

Keywords: COVID-19, prolonged nucleic acid conversion time, real-time reverse-transcription polymerase chain reaction, SARS-CoV-2

in patients who are clinically compatible with COVID-19, even if RT-PCR is negative.^[1] Although the sensitivity of thorax CT is higher, the gold standard test for the diagnosis of COVID-19 is still rRT-PCR test.

While vaccination continues all over the world, the effect of the vaccine on the mutations that occur in SARS-CoV-2 is not yet known.^[4] Therefore, the most important factor in the fight against COVID-19 is to control the source, that is to isolate the patient.^[5] Nucleic acid conversion time (NCT) is defined as the time from the onset of symptoms to the first negative RT-PCR detection.^[6] Lin *et al.* determined the median duration of conversion as 24 days and reported that the prolonged duration of SARS-CoV-2 negative conversion was independent risk factor for prolonged hospitalization.^[7] NCT is also important in terms of viral transmission.

The aim of this study is to determine the mean NCT in patients hospitalized with mild to moderate COVID-19 and to evaluate the clinical and laboratory parameters affecting this.

Methods

This study retrospectively included 318 young military patients diagnosed with mild to moderate COVID-19 who were hospitalized in Sultan 2. Abdulhamid Han Training and Research Hospital, Istanbul. According to the WHO COVID-19 disease severity classification; mild disease was described as patients who meet the COVID-19 case definition but did not have viral pneumonia or hypoxia. Moderate disease was defined as patients with clinical signs of pneumonia (fever, cough, dyspnea, and rapid breathing) and oxygen saturation with pulse oximeter (SpO_2) $\geq 90\%$ (at room air) but without signs of severe pneumonia (presence of someone in addition to clinical signs of pneumonia: respiratory rate $>30/\text{min}$, severe respiratory distress, or $\text{SpO}_2 < 90\%$, room air).^[8] This study was approved by the Ethics Committee of the Umraniye Training and Research Hospital in Istanbul (approval no. 405, date: Dec 24, 2020).

Although patients with mild-to-moderate COVID-19 were not indicated for hospitalization, since all patients were soldiers, they were hospitalized and treated in the hospital in order to ensure isolation and to prevent transmission in the military unit. Exclusion criteria were being younger than 18-years-old, not having a positive rRT-PCR test, having previous COVID-19, having comorbidity, having severe or critical (acute respiratory distress syndrome, sepsis, septic shock, acute thrombosis) disease according to the WHO disease severity classification.^[8]

The diagnosis of SARS-CoV-2 was confirmed by rRT-PCR with nasal and throat swab samples. Nucleic acid extraction from nasal and throat swabs was performed with the Bio-Speedy[®] nucleic acid extraction kit (Bioeksen Ltd., Turkey) in accordance with the manufacturer's instructions. The presence of SARS-CoV-2 RNA was evaluated by RT-PCR analysis that performed in Rotorgene real-time PCR cyler (Qiagen, Germantown, Maryland, USA) using Bio-Speedy[®] COVID-19 RT-qPCR detection kit. For the evaluation of results, replication curves of the FAM/HEX channels were observed. Human RNase P was used as an internal control to rule out false-negative results for each sample. Non-sigmoidal curves were recorded as negative. In the cases where positive, negative, and internal control values met the appropriate criteria, cycle threshold <38 was assumed positive.

White blood count (WBC), C-reactive protein (CRP), D-dimer, troponin, lymphocyte (%), lymphocyte count, neutrophil (%), neutrophil count, platelet count, ferritin, lactate dehydrogenase (LDH), aspartate transaminase (AST) and alanine transaminase (ALT), symptoms and history of contact without a mask were recorded retrospectively. Neutrophil/Lymphocyte Ratio (NLR) and Platelet/Lymphocyte Ratio (PLR) were calculated.

Chest radiography was performed routinely in all patients on admission. Chest CT was performed in patients who were evaluated to have moderate COVID-19 according to the WHO classification at admission or when there was symptomatic

progression or worsening in laboratory parameters after hospitalization. Laboratory parameters were recorded both on admission to the hospital and on the 8-10th day of treatment. rRT-PCR was taken to evaluate conversion after the 7th day of treatment. Samples were taken at 2-day intervals until the rRT-PCR turned out to be negative. The time between the onset of symptoms and rRT-PCR negativity was recorded as NCT. The patients were divided into two groups as early and late conversion and they were compared in terms of clinical and laboratory parameters.

The patient data collected in the study were analyzed with the IBM Statistical Package for the Social Sciences for Windows 23.0 package program. Frequency and percentage for categorical data and median, minimum and maximum descriptive value for continuous data were used. For comparisons between groups, the Mann-Whitney U-Test was used for the two groups, and the Chi-square Test was used for the comparison of categorical variables. Examination of the factors affecting late conversion was evaluated with Logistic Regression Analysis. Results were considered statistically significant in cases where the $P < 0.05$.

Results

A total of 318 patients were included in the study. The median age of the patients was 24 (interquartile range [IQR] 19–48 years), and all patients were male. The median NCT of the patients in the study was 11 days (IQR 7–26 days). The patients were divided into early NCT (<11 days) and late NCT ($11 \geq$ days) groups according to the conversion time. Patients' symptoms of dyspnea, myalgia, headache, loss of taste and smell, cough, and diarrhea at the hospital admission were similar between the two groups ($P = 1.000, 0.402, 0.180, 0.073, 0.139,$ and 0.088 , respectively). The presence of fever symptoms at admission and at 72 h after hospitalization was more common in the late NCT group ($P = 0.021$ and 0.001). Complaints of sore throat and history of unmasked COVID-19 contact were higher in the late NCT group ($P = 0.041$ and < 0.0001) [Table 1].

There was no difference between early and late NCT groups in terms of WBC, neutrophil (%), neutrophil count, lymphocyte (%), lymphocyte count, platelet count, NLR, PLR, CRP, D-Dimer, troponin, ferritin, LDH, AST and ALT values ($P = 0.871, 0.967, 1.000, 0.778, 0.802, 0.751, 0.883, 0.992, 0.550, 0.552, 0.544, 0.476, 0.715, 0.432$ and 0.407 , respectively). In the late NCT group, compared to early NCT, lung involvement and moderate disease were more common (17.3 vs. 8.1%; $P = 0.030$), and hydroxychloroquine use was higher (69.8 vs. 38.9%; $P < 0.0001$). Favipiravir use was higher in the early NCT group compared to the late NCT group (78.5 vs. 32.5%; $P < 0.0001$). There was no difference between the two groups in terms of antibiotic use (13.4 and 21.3%; $P = 0.066$) [Table 2].

When the factors affecting the conversion time were examined by multivariate analysis, the presence of sore

Table 1: The comparison of the demographic features and symptoms between groups

Parameter <i>n</i> (%) or median (min–max)	All patients (<i>n</i> =318)	Early NCT group (<i>n</i> =149)	Late NCT group (<i>n</i> =169)	<i>P</i> -value
Age	24 (19–48)	24 (19–43)	25 (19–48)	0.024*
Fever (initial)	67 (21.1)	23 (15.4)	44 (26.0)	0.021**
Fever (After 72 h)	121 (38.1)	42 (28.2)	79 (46.7)	0.001**
Dyspnea	12 (3.8)	6 (4.0)	6 (3.6)	1.000**
Myalgia	54 (17.0)	22 (14.8)	32 (18.9)	0.402**
Sore throat	37 (11.6)	11 (7.4)	26 (15.4)	0.041**
Headache	44 (13.8)	16 (10.7)	28 (16.6)	0.180**
Loss of taste and smelling	39 (12.3)	24 (16.1)	15 (8.9)	0.073**
Cough	76 (23.9)	30 (20.1)	46 (27.2)	0.139**
Diarrhea	19 (6.0)	13 (8.7)	6 (3.6)	0.088**
COVID-19 contact without wearing masks	93 (29.2)	28 (18.8)	65 (38.5)	<0.0001**

*Mann Whitney U-Test, **Chi-square Test, NCT: Negative conversion time

Table 2: The comparison of the laboratory parameters, disease severity and treatments between groups

Parameter median (min–max)	All patients (<i>n</i> =318)	Early NCT group (<i>n</i> =149)	Late NCT group (<i>n</i> =169)	<i>P</i> -value
WBC	7.06 (2.86–43.98)	7.28 (2.89–43.98)	6.92 (2.86–13.58)	0.871*
Neutrophil (%)	61.6 (33.4–84.4)	61.8 (34.1–84.4)	61.5 (33.4–81.5)	0.967*
Neutrophil (Count)	4.28 (1.29–13.77)	4.32 (1.31–13.77)	4.27 (1.29–11.07)	1.000*
Lymphocyte (%)	28.5 (5.8–53.9)	28.2 (9.3–53.9)	28.9 (5.8–53.3)	0.778*
Lymphocyte (Count)	1.91 (0.38–4.57)	1.91 (0.80–4.52)	1.91 (0.38–4.57)	0.802*
Platelet (Count)	225 (97–441)	229 (106–441)	223 (97–422)	0.751*
NLR	2.16 (0.63–13.82)	2.18 (0.63–8.44)	2.14 (0.64–13.82)	0.883*
PLR	116.55 (34.93–489.47)	117.01 (60.66–298.87)	116.03 (34.93–489.47)	0.992*
CRP	2.0 (0.35–266.6)	2.0 (0.35–266.6)	2.0 (2.0–105.0)	0.550*
D-dimer	0.11 (0.01–1.88)	0.11 (0.01–1.30)	0.11 (0.01–1.88)	0.522*
Troponin	1.2 (0.1–14.0)	1.4 (0.1–13.9)	1.20 (0.1–14.0)	0.544*
Ferritin	108.51 (7.64–492.5)	102.00 (7.64–492.5)	110.12 (17.65–433.49)	0.476*
LDH	345 (142–952)	350 (186–896)	342 (142–952)	0.715*
AST	20 (10–72)	20 (11–61)	20 (10–72)	0.432*
ALT	25 (3.6–207)	24 (3.6–123)	26 (6–207)	0.407*
Pulmonary involvement	39 (13.1)	11 (8.1)	28 (17.3)	0.030**
Mild Disease	259 (86.9)	125 (91.9)	134 (82.7)	0.030**
Moderate Disease	39 (13.1)	11 (8.1)	28 (17.3)	0.030**
Favipiravir Use	172 (54.1)	117 (78.5)	55 (32.5)	<0.0001**
Hydroxychloroquine Use	176 (55.3)	58 (38.9)	118 (69.8)	<0.0001**
Antibiotic Use	56 (17.6)	20 (13.4)	36 (21.3)	0.066**

*Mann Whitney U-Test, **Chi-square Test, NCT: Negative conversion time, WBC: White blood cell, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, CRP: C-reactive protein, LDH: lactate dehydrogenase, AST: Aspartate transaminase, ALT: alanine transaminase

throat symptom (odds ratio [OR] = 2.570; 95% confidence interval [CI]: 1.051–6.284, $P = 0.039$) and hydroxychloroquine use (OR = 3.518; 95% CI: 1.163–10.635, $P = 0.026$) were independent risk factors increase for late NCT. Favipiravir use (OR: 0.062; 95% CI: 0.021–0.184, $P < 0.0001$) was an independent risk factor reducing the risk of late NCT [Table 3].

Discussion

Since the beginning of the COVID-19 pandemic, the concepts of hospital stay, isolation, and quarantine have

been among the most popular topics.^[9,10] Increased NCT has been reported to be an independent risk factor for prolonged hospitalizations.^[7]

Considering that the incubation period is 1–14 days in international guidelines, the quarantine period after contact with the patient with COVID-19 is specified as 14 days. However, the viral shedding time of a patient with COVID-19 is not known precisely. Although it is accepted as 10 days from the onset of symptoms for mild cases, this period can be extended up to 20 days in severe cases.^[11,12]

Table 3: Factors associated with late NCT

Parameter	Multivariate analysis		
	OR	95% CI	P-value
Age	1.006	0.948–1.068	0.843
Fever (initial)	1.722	0.853–3.478	0.129
Sore throat	2.570	1.051–6.284	0.039
COVID-19 contact	1.419	0.713–2.824	0.319
Pulmonary involvement	1.731	0.707–4.237	0.230
Fever (After 72 h)	1.371	0.777–2.419	0.276
Favipiravir Use	0.062	0.021–0.184	<0.0001
Hydroxychloroquine Use	3.518	1.163–10.635	0.026

NCT: Negative conversion time, OR: Odds ratio, CI: Confidence interval

While the WHO recommends a symptom-based approach for isolation termination, it states that there will not be an isolation termination method that will prevent transmission altogether, and a test-based approach may be appropriate in some cases.^[13] However, no NCT is clearly reported in international guidelines at this time. The median conversion time was determined as 11 days in this study, Eser *et al.* determined this period as 14 days, in line with their international guideline isolation recommendations.^[14] Mo *et al.* reported the median NCT as 18 days in their study, and 19 days in their study by Fu *et al.*^[15,16]

In addition, Zhu *et al.* stated that older age, the presence of comorbidity, and the use of corticosteroids were factors that longer NCT.^[17] In our study, the reason for the lower median NCT was thought to be due to the low mean age of the patients included the exclusion of severe COVID-19 cases, the absence of comorbidities and the absence of steroid use. Wang *et al.* reported that high neutrophil to CD4⁺ lymphocyte ratio (NCD4LR) was associated with prolonged NCT and NCD4LR was superior to NLR in predicting NCT.^[18] NCD4LR was not evaluated in our study; it has been observed that NLR and PLR have no effect on NCT.

Fu *et al.* reported in their study that initiating antiviral therapy > 7 days from the onset of symptoms may be associated with prolonged NCT.^[16] In our study; the duration of treatment initiation was not evaluated. However, the use of favipiravir was higher in the early NCT group. Hydroxychloroquine use was higher in the late NCT group. In the multivariate analysis, hydroxychloroquine was an independent risk factor increasing the risk of late NCT and on the other hand, favipiravir was an independent risk factor decreasing it. Bosaeed *et al.* hypothesized that favipiravir will shorten the NCT in mild COVID-19 patients compared to placebo in a prospective study design, and the study is still ongoing.^[19]

Delayed hospital admissions and severity of the disease were associated with delayed NCT in the study of Smyej *et al.*, but the comparison was not made according to symptoms.^[20] Similarly, in our study, mild disease was more common in the early NCT group and moderate disease was more common

in the late NCT group. Hu *et al.* reported that chest tightness and older age were independent risk factors for NCT.^[21] In our study, although the ages were similar, older age was statistically higher in the late NCT group. However, age was not found as an independent risk factor in multivariate analysis. Dyspnea was an independent risk factor for longer NCT in the study conducted by Wang *et al.*^[18] In our study; dyspnea was similar between the early and late NCT groups.

The relationship between wearing a mask and NCT in the encounter with the virus was investigated by Bennasrallah *et al.* Median NCT was 18 days in those wearing masks and 23 days in those not wearing masks, and the difference between them was statistically significant. It has been stated that the use of masks shortens the conversion time similarly in our study.^[22] Fever and sore throat had no effect on NCT in the study by Eser *et al.*^[14] In our study, on the other hand, initial fever and fever that continued at 72 h after hospitalization were significantly higher in the late NCT group. Sore throat was an independent risk factor for late NCT in multivariate analysis. Unlike our study, Mo *et al.* reported that cough was an independent risk factor for late NCT in their study.^[15] These differences were thought to be due to the different times determined in late and early NCT calculations.

This study has some limitations. The study was designed retrospectively. Since the study only included the military population, all patients in the study were male, and the effect of gender on NCT was not evaluated. Since patients with severe COVID-19, comorbidity and older age were not included in the study; their effect on NCT could not be evaluated.

Conclusion

We calculated the median NCT as 11 days. Older age, sore throat and onset fever at admission, fever 72 h after hospitalization, history of exposure to COVID-19 without a mask and moderate disease were higher in the late NCT group. In addition, favipiravir use was higher in the early NCT group and hydroxychloroquine use was higher in the late NCT group. In the multivariate analysis, sore throat and hydroxychloroquine use were positively correlated for late NCT, while favipiravir use was a negatively correlated independent risk factor for late NCT. If a symptom-based isolation strategy is to be used, it may be necessary to consider extending the isolation periods, especially in patients with sore throat and fever at admission, who still have fever at the 72nd h, and who cannot use favipiravir, as late NCT may occur.

Ethics Approval

This study was approved by the Ethics Committee of the Umraniye Training and Research Hospital in Istanbul (approval no. 405, date: Dec 24, 2020).

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Competing Interest

All authors have no conflicts of interest to declare.

Availability of Data and Material

The dataset is uploaded into the submission system.

Authors Contributions

The Corresponding Author declares that this manuscript is original, has never been published, or under the consideration for publication elsewhere. We also declare that the corresponding author and all of the co-authors have actively participated in this manuscript.

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