Factors Influencing the Delay in Negative Conversion of PCR Swab Test Results in Patients with COVID-19

by Banteng Hanang

Submission date: 29-May-2023 12:12PM (UTC+0700)
Submission ID: 2104305039
File name: ion_of_PCR_Swab_Test_Results_in_Patients_with_COVID-19_2022.docx (86.06K)
Word count: 4040
Character count: 21606

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2022; vol 9 (2) : 199–206

Original Article

Factors Influencing the Delay in Negative Conversion of PCR Swab Test Results in Patients with COVID-19

Fathur Nur Kholis, Banteng Hanang Wibisono, Agus Suryanto, Thomas Handoyo, Farida, Jimmy Tanamas

Division of Pulmonology, Department of Internal Medicine, Faculty of Medicine, Diponegoro University/Dr. Kariadi General Hospital, Semarang, Indonesia

pISSN: 2301-4369 eISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v9i2.755

Accepted: June 22th,2022
Approved: July 21th,2022

Author Affiliation:
Division of Pulmonology, Department of Internal Medicine, Faculty of Medicine, Diponegoro University/ Dokter Kariadi General Hospital, Semarang, Indonesia

Author Correspondence:
Fathur Nur Kholis
Dr. Sutomo Street No. 16 Semarang, Central Java 50244, Indonesia

E-mail Address:
drfnkholis@gmail.com

Abstract

Background : The negative conversion duration of SARS-CoV-2 RNA was related to disease progression, and a prolonged negative conversion could provide early warning signal for poor prognosis in patients with COVID-19. The objectives of this study was to identify the factors influencing the delay in negative conversion of PCR swab test results in patients with COVID-19 as a consideration in determining the COVID-19 prevention policy in the community

Methods : A retrospective cross-sectional study involving 68 patients diagnosed with COVID-19 that was treated in Dr. Kariadi General Hospital Medical Center Semarang from June 1st to December 30th 2020. Negative conversion was evaluated based on the results of the RT-PCR swab test on day 7, 14 and 21.

Results : Mean negative conversion time for all patients was 11.63±5.08 days. Thirty-one factors were evaluated in the initial univariate Cox and Kaplan-Meier analysis. Older age (>59 years), overweight (>25 kg/m^2), fever (>38°C), shortness of breath, diabetes mellitus, neutrophilia, hypoalbuminemia, CRP and antiviral treatment showed significant association with negative conversion time. These factors were then included in a multivariate regression analysis. Hypoalbuminemia or albumin level of <3.0 g/dL was found as an independent factor associated with negative conversion time of viral RNA (HR:1.986; 95%CI:1.098–3.594), and hypoalbuminemia was presumed to cause prolonged viral clearance time in patients with COVID-19.

Conclusion : The factors influencing the prolong in negative conversion of viral RNA in patients with COVID-19 were older age, overweight, fever, shortness of breath, diabetes mellitus, neutrophilia, hypoalbuminemia, CRP and antiviral treatment. Hypoalbuminemia was an independent predictor for prolonged negative conversion of viral RNA in patients with COVID-19.

Keywords : COVID-19, SARS-CoV-2, negative conversion time, RT-PCR.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[1] Hu *et al*. reported that SARS-CoV-2 RNA showed negative conversion on day 14 after the first positive RT-PCR result. Meanwhile, Zhou *et al*. reported that RNA viral load could still be found for a mean duration of 20 days in patients that had recovered from COVID-19, and Ling *et al*. found that viral shedding lasted for a mean duration of 9.5 days. The different results of these previous studies may be influenced by the severity of disease and sampling method. Older age and comorbidity were also reportedly correlated with duration of PCR negative conversion time. The factors influencing the delay in negative conversion of PCR results could provide early warning signal for poor prognosis.[2–4]

Many studies regarding COVID-19 cases were more focused on the epidemiological, clinical, laboratory, and radiologic characteristics to support the development of diagnostic and treatment strategy for patients. Other studies regarding the predictive factors associated with negative conversion time in patient with COVID-19 were very limited.[7] This study goals to identify the factors influencing the duration of PCR negative conversion time

METHODS

A retrospective cross-sectional study involving 68 patients diagnosed with COVID-19 that was treated in Dr. Kariadi General Hospital Medical Center Semarang from June 1st to December 30th 2020. Negative conversion was evaluated based on the RT-PCR swab test results of day 7, 14 and 21. Perdhana's described that the minimum number of samples for research is 30 respondents.[5] Data were collected from patient's medical record in Dr. Kariadi General Hospital, Semarang.

The inclusion criteria were patients with positive COVID-19 diagnosis based on the result of RT-PCR using specimens collected from nasal or throat mucosal swab or bronchial wash. Sixty-eight patients with confirmed diagnosis of COVID-19 were selected as study subjects. The preferred method to detect virus was nucleic acid amplification test such as real-time reverse transcription polymerase chain reaction (rRT-PCR) and sequencing. Samples were confirmed (positive) as SARS-CoV-2 when rRT-PCR showed positive results in a minimum of two target genomes specific for SARS-CoV-2 or positive rRT-PCR for betacoronavirus supported by the result of whole or partial viral genome sequencing compatible with SARS-CoV-2.[6,7]

Negative conversion of viral RNA was the outcome measured in the current study. Univariate Kaplan-Meier analysis and multivariate Cox proportional hazards model analysis analyses were performed to detect the independent factors influencing the duration of RNA negative conversion. The multivariate regression model was performed with the significant factors selected by univariate analysis. The association between independent factors and negative conversion was quantified by hazard ratio (HR), reported with the 95% confidence interval (CI).

Ethical approval was obtained from the The Medical Research Ethics Committee at The Faculty of Medicine Diponegoro University/ Dr. Kariadi General Hospital, Semarang.

RESULTS

Sixty-eight patients that was treated in Dr. Kariadi General Hospital Medical Center Semarang for COVID-19 were included in the current study. All of the respondents were agreed to join in this study. The mean of duration to negative conversion for all subjects were 11.63±5.08 days. The majority of subjects were male (57.4%), and the overall average age was 48 (range 20–85).

Twenty-seven subjects (39.7%) had normal body mass index, while 33 (48.5%) were overweight, 6 (8.8%) were obese, and 1 (2.9%) was underweight. Forty-two (61.8%) subjects had fever (body temperature >38°C). Dry cough, shortness of breath, cold, sore throat, diarrhea, nausea, and vomiting were reported in 29 (57.4%), 34 (50%), 13 (19.1%), 21 (30.9%), 13 (19.1%), and 23 (33.8%) subjects, respectively. Diabetes mellitus, hypertension, cardiovascular disease, malignancy, chronic pulmonary disease, dyslipidemia, kidney failure and liver disease were reported in 17 (25%), 30 (44.1%), 5 (7.4%), 4 (5.9%), 9 (13.2%), 8 (11.8%), 2 (2.9%), and 3 (4.4%) subjects, respectively. Four (5.9%) subjects were reported to have smoking habit.

The mean of white blood cells, platelets, lymphocytes, neutrophils, NLR, ALC, PLR, albumin, CRP and CAR values for all subjects were 10.47±7.79 x103/dL, 278.66±157.98 x103/dL, 14.73±9.28%, 75.66±15.82%, 7.38±6.67%, 1674.02±2450.39, 254.15±183.07, 3.33±0.74, 12.84±12.23, and 3.73±3.77, respectively.

Forty subjects (58.8%) had received antiviral treatments, while antibiotic and steroids were given to 50 (73.5%) subjects (Table 1). Negative conversion status on day 7, 14 dan 21 for all study subjects was presented on Table1.

Thirty-one factors were evaluated in the initial univariate Cox and Kaplan-Meier analysis (Table 1 and 2). Older age (>59 years), overweight (>25 kg/m²), fever (>38C), shortness of breath, diabetes mellitus, neutrophilia, hypoalbuminemia, CRP and antiviral treatment showed significant association with negative conversion duration. These factors were then included in a multivariate regression analysis. Hypoalbuminemia or

TABLE 1
Univariate analysis in 68 subjects with negative conversion

Factors		Patient numbers	Patient with negative conversion			*P value*
			7 days	14 days	21 days	
Total		68	33	25	10	
Gender	Male	39	16	16	7	0.166
	Female	29	17	9	3	
Age	<59 years	39	27	18	3	0.004*
	≥59 years	29	6	7	7	
BMI	<18.5 kg/m^2	1	1	1	–	0.001*
	18.5–24.9 kg/m^2	27	21	5	1	
	25–29.9 kg/m^2	33	7	18	8	
	≥30 kg/m^2	6	4	1	1	
Temperature	<38°C	26	18	6	2	0.014*
	≥38°C	42	15	19	8	
Dry cough	Yes	39	16	17	6	0.331
	No	29	17	8	4	
Shortness of breath	Yes	34	8	17	9	0.000*
	No	34	25	8	1	
Cold	Yes	13	5	5	3	0.309
	No	55	28	20	7	
Sore throat	Yes	21	11	5	5	0.558
	No	47	22	20	5	
Diarrhea	Yes	13	7	3	3	0.758
	No	55	26	22	7	
Nausea, vomiting	Yes	23	9	12	2	0.946
	No	45	24	13	8	
Diabetes Mellitus	Yes	17	2	8	7	0.000*
	No	51	31	17	3	
Hypertension	Yes	30	15	11	4	0.768
	No	38	18	14	6	
Cardiovascular disease	Yes	5	2	3	–	0.745
	No	63	31	22	10	
Malignancy	Yes	4	–	4	–	0.540
	No	64	33	21	10	
Lung disease	Yes	9	5	3	1	0.639
	No	59	28	22	9	
Dyslipidemia	Yes	8	5	2	1	0.526
	No	80	28	23	9	

Factors		Patient numbers	Patient with negative conversion			*P value*
			7 days	14 days	21 days	
Renal failure	Yes	2	–	2	–	0.672
	No	66	33	23	10	
Liver disease	Yes	3	2	–	1	0.860
	No	65	31	25	9	
Smoking habit	Yes	4	–	4	–	0.540
	No	64	33	21	10	
Leukocytes	< 4000	10	4	4	2	0.525
	≥ 4000	58	29	21	8	
Platelets	< 150000	15	6	6	3	0.414
	≥ 150000	53	27	19	7	
Lymphocytes	< 20%	55	28	19	8	0.607
	≥ 20%	13	5	6	2	
Neutrophils	< 70%	15	4	6	5	0.016*
	≥ 70%	53	29	19	5	
NLR	< 3.13	11	5	5	1	0.838
	≥ 3.13	57	28	20	9	
ALC	< 1500	49	22	19	8	0.344
	≥ 1500	19	11	16	2	
PLR	< 200	31	16	10	5	0.922
	≥ 200	37	17	15	5	
Albumin	< 3.0	26	6	14	6	0.004*
	≥ 3.0	42	27	11	4	
CRP	< 10	33	20	10	3	0.050*
	≥ 10	35	13	15	7	
CAR	< 0.25	12	9	2	1	0.084
	≥ 0.25	56	24	23	9	
Antiviral	Yes	40	28	10	2	0.000*
	No	28	5	15	8	
Antibiotic	Yes	50	23	17	10	0.100
	No	18	10	8	–	
Steroid	Yes	50	10	6	4	0.706
	No	18	23	19	6	

*P<0.05; significant. P value from Kaplan Meier analysis.
Abbreviation; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; ACL, absolute neutrophil count; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein; CAR, C-reactive protein/albumin ratio.

albumin level of <3.0 g/dL was found as an independent factor associated with negative conversion time of viral RNA (HR:1.986; 95%CI:1.098–3.594), and hypoalbuminemia was presumed to cause prolonged viral clearance time in patients with COVID-19 (Table 2).

TABLE 2
Univariate and multivariate analysis in 68 subjects with negative conversion

Factors	Univariate analysis		*P value*	Univariate analysis		*P value*
	HR	95%CI		HR	95%CI	
Gender	0.901	0.708 – 1.148	0.400	–	–	–
Age	0.620	0.360 – 1.068	0.085*	0.905	0.487 – 1.681	0.752
BMI	0.718	0.492 – 1.050	0.087*	0.692	0.428 – 1.118	0.133
Temperature	0.680	0.413 – 1.119	0.129*	0.791	0.427 – 1.467	0.457
Dry cough	1.155	0.713 – 1.871	0.558	–	–	–
Cold	1.201	0.655 – 2.204	0.553	–	–	–
Shortness of breath	1.994	1.199 – 3.315	0.008*	1.385	0.791 – 1.425	0.254
Sore throat	1.097	0.652 – 1.846	0.727	–	–	–
Diarrhea	1.058	0.576 – 1.943	0.856	–	–	–
Nausea, vomiting	1.011	0.609 – 1.679	0.967	–	–	–
Diabetes Mellitus	1.986	1.115 – 3.537	0.020*	1.926	0.995 – 3.729	0.520
Hypertension	0.957	0.593 – 1.546	0.859	–	–	–
Cardiovascular disease	0.906	0.362 – 2.268	0.834	–	–	–
Malignancy	1.220	0.440 – 3.382	0.703	–	–	–
Lung disease	0.902	0.447 – 1.820	0.773	–	–	–
Dyslipidemia	0.864	0.413 – 1.808	0.698	–	–	–
Kidney failure	1.209	0.294 – 4.969	0.792	–	–	–
Liver disease	1.060	0.331 – 3.396	0.922	–	–	–
Smoking habit	1.220	0.440 – 3.382	0.703	–	–	–
Leukocytes	1.137	0.580 – 2.225	0.709	–	–	–
Platelets	1.152	0.648 – 2.045	0.630	–	–	–
Lymphocytes	0.910	0.497 – 1.666	0.759	–	–	–
Neutrophils	1.512	0.843 – 2.713	0.166*	1.306	0.683 – 2.498	0.419
NLR	0.959	0.502 – 1.832	0.900	–	–	–
ALC	1.170	0.688 – 1.990	0.562	–	–	–
PLR	0.986	0.611 – 1.589	0.953	–	–	–
Albumin	1.540	0.935 – 2.534	0.090*	1.986	1.098 – 3.594	0.023**
CRP	0.751	0.465 – 1.215	0.244*	0.953	0.561 – 1.619	0.860
CAR	0.704	0.375 – 1.322	0.275	–	–	–
Antiviral	0.519	0.312 – 0.862	0.011*	0.704	0.383 – 1.294	0.258
Antibiotic	1.357	0.778 – 2.368	0.283	–	–	–
Steroid	1.062	0.629 – 1.792	0.823	–	–	–

*P<0.25; significant, P value from univariate cox regression analysis.
**P<0.25; significant, P value from multivariate cox regression analysis.
Abbreviation; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; ACL, absolute neutrophil count; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein; CAR, C-reactive protein/albumin ratio; HR, hazard ratio; 95%CI, confidence interval.

DISCUSSION

This study found that older age (>59 years) was associated with delay in negative conversion time of SARS-CoV-2 RNA was consistent with the results from previous studies. Study by Hu *et al*. in 59 patients that were admitted with a diagnosis of COVID-19 reported that older age (>45 years) was an independent factor associated with delay in negative conversion time of viral RNA.[7] Another study by Zhang *et al*. in 70 patients that were diagnosed with COVID-19 also reported that older age (>50 years) significantly cause a delay in negative conversion time of viral RNA.[10] Elderly patients with COVID-19 reportedly had worse clinical outcome in comparison with younger patients.[9] Older age may also affected the number and function of T cells, resulting in uncontrolled viral replication and excessive host inflammatory response. This age-related disorder may also impair the ability of host cells to eradicate invasive pathogens, thus prolonging viral shedding in the elderly.[7] Comorbidities that came with older age also played a role in causing prolonged negative conversion time. Whilst the severity of disease and comorbidities has no direct influence to PCR conversion time, these may indirectly influence the clearance of viral nucleic acid.[9] Older age was also reportedly associated with the numbers of viral RNA copies in patients with SARS-CoV infection, where increasing age was independently associated with higher viral load.[10]

Obesity was associated with a more severe clinical presentation of COVID-19 and a higher increase of inflammatory markers. This was possibly related to an increase in oxygen demand, thus prolonging the need of supplemental oxygen therapy during hospitalization, delaying viral clearance, and ultimately leading to prolonged hospitalization.[13] Univariate analysis found a significant association between body weight and prolonged negative conversion time of patients with COVID-19, where the negative conversion time will increase with increasing body weight. This result was supported by a previous study by Moriconi *et al*. that reported a longer negative conversion time in obese patients with COVID-19 (body mass index ≥30 kg/m²) in comparison with non-obese patients (19±8 days vs. 13±7 days, p=0.002).[11] Obesity was known to cause disorders on both innate and adaptive immune systems, such as abnormal T cell activity, abnormal natural killer cell activity, disorders of phagocytic function, inhibition of neutrophil chemotaxis, and failure of the complement system.[12] Obesity may also cause hyper-activation of mammalian target of rapamycin (mTOR) signaling, thus prolonging the duration of viral shedding.[13]

This study found that body temperature above 38°C may prolong negative conversion duration, where patients with fever has a significantly longer negative conversion duration, comparison to patients with normal body temperature. This was consistent with previous study by Li *et al*. where body temperature was reportedly found as an independent factor associated with the duration of viral shedding, in which patients with higher body temperature showed longer period of viral shedding (<37.3°C (9 days, IQR 7–11); 37.3–38.5°C (11 days, IQR 7–13); ≥38.5°C (12.5 days, IQR 9–17); p=0.046). The study believed that the higher the body temperature of COVID-19 patients, the longer the patient will show persistent positive nucleic acid test results.[14] A retrospective study in children with COVID-19 also reported the same result, where longer duration of viral shedding was associated with higher body temperature. Fever was a manifestation of inflammatory response elicited by immune response. However, this study did not evaluate the cytokine levels in their subjects, thus the cause-and-effect relationship between longer viral clearance time and fever had not been clearly demonstrated.[15]

Patients with shortness of breath in the study showed statistically longer negative conversion time in comparison with patients without this symptom. A similarly significant association between these two variables was also reported by Hu *et al*., wherein shortness of breath was proven to be an independent predictive factor for prolonged negative conversion time of viral RNA in patients with COVID-19 (HR: 0.290; 95%CI: 0.091–0.919).[7]

Diabetes mellitus (DM) was considered a comorbidity that may increase mortality and morbidity rate in in patients with SARS CoV-2 infection. The study found a significantly longer negative conversion time of SARS-CoV-2 RNA in patients with DM in comparison with those without this comorbidity. A retrospective cohort study in 70 patients diagnosed with COVID-19 reported that DM was an independent predictive factor for prolonged negative conversion time.[10] Another recent study also reported that DM comorbidity in patients with COVID-19 was associated with prolonged viral cleareance.16 Immune system dysregulation caused by diabetes mellitus may play a role in the pathogenesis COVID-19, particularly in prolonging the detection time of SAR-CoV-2 RNA. The mechanism underlying such dysregulation of the immune system in patients with DM were hyperglycemia, inhibition of neutrophil chemotaxis, cytokine dysregulation, and phagocytic cell dysfunction. Diabetic patients also presented with higher risk to develop severe disease, higher mortality rate, and was found to be a risk factor for disease progression.[10]

This study found that increased neutrophil count (>70%) was significantly associated with prolonged negative conversion time of viral RNA. Similar result was also reported by Mo *et al*., where patients with prolonged negative conversion time (>18 days) had a significantly higher neutrophil count (3.94 [2.31–7.75]X10⁹/L), and that neutrophil count was proven to be an independent

predictive factor for prolonged negative conversion time (OR, 0.097; 95%CI:0.015–0.631]; p=0.015).[17] Neutrophil was a widely known marker of systemic inflammation that was found to be a risk factor for the development of ARDS and progression from ARDS to mortality in patients with COVID-19.[20] Neutrophil, a main source of cytokines, would release cytokines and chemokines in a large number to help regulate the immune responses such as antiviral defense, hemopoietic action, angiogenesis or fibrogenesis.[18] Overproduction of neutrophil may contribute to acute lung injury and cytokine storm in COVID-19, thus prolonging the viral clearance time.[19] High neutrophil production was also associated with increased $CD4^+$ lymphocyte ratio. In a previous study, increased $CD4^+$ lymphocyte ratio was associated with a delay in negative conversion up to 24 days, most likely due to dysregulated immune system and prolonged viral clearance time.[19]

Patients with increased C-reactive protein (CRP) level (>10) in this study showed significantly longer negative conversion time of viral RNA in comparison to patients with lower CRP level (<10). A previous study by Moriconi *et al.* also reported the same result, where higher CRP level in obese patients with COVID-19 was associated with longer time for negative result from oropharyngeal or nasal swab test.[11] Study by Gao *et al.* also reported an association between increased CRP level and prolonged viral RNA shedding up to 28 days in patients with COVID-19.[20] Two to ten-fold increase in serum CRP levels above normal value reportedly caused a significantly prolonged duration of viral shedding, and also showed a significant negative correlation with $CD4^+$ T lymphocyte counts, a factor that was known to influence immune response and viral shedding.[21] Analysis conducted with multiple linear regression model by Fu *et al.* found that $CD4^+$ T lymphocyte counts could help predict the duration of viral RNA shedding in stool specimen and lower absolute $CD4^+$ T lymphocyte counts before treatment may prolong the viral clearance time.[8]

Antiviral is useful to increase the duration of conversion in COVID-19 patient. Result from the univariate analysis in the current study indicated that patients receiving antiviral therapy had significantly shorter negative conversion time in comparison with patients that did not receive this therapy. Previous study by Fu *et al.* also reported that the time when antiviral therapy was first initiated was an independent factor associated with SARS-CoV-2 RNA shedding (HR=1.467, 95%CI: 1.187–1.815, p<0.001).[22] The study reported shorter negative conversion time in patients who received antiviral therapy. The limitation of this study are the small number of samples, and patients' data that is till diverse such as smoking habits, patients' comorbidities, and patient's severity of Covid-19.

Hypoalbuminemia was an independent predictor for prolonged negative conversion of viral RNA in patients with COVID-19. Further study is needed with more samples and a more homogenous population.

REFERENCES

1. Chen D, Xu W, Lei Z, Huang Z, Liu J. Recurrence of positive SARS-CoV-2 RNA in COVID-19: A case report. Int J Infect Dis. 2020; 93:297–9.
2. Hu X, Xing Y, Jia J, Ni W, Liang J, Zhao D, *et al*. Factors associated with negative conversion of viral RNA in patients hospitalized with COVID-19. Sci Total Environ [Internet]. 2020;728(175):138812. Available from: https://doi.org/10.1016/j.scitotenv.2020.138812
3. Ling Y, Xu S, Lin Y, Tian D, Zhu Z, Dai F, *et al*. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. Chin Med J. 2020;133(9):1–5.
4. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62.
5. Perdhana L, Shofa C, Yudo MM, Siti N. Peran Gejala Depresi sebagai Faktor Prediktor Kematian dalam Enam Bulan pada Lansia yang Menjalani Hemodialisis. Jurnal Penyakit Dalam Indonesia, 2021. 8(4), 179–186.
6. Zhang F, Hu H, Wang X, Li X, Yang Y, Li L, *et al*. Prediction for the Negative Conversion Probability of Nucleic Acid Testing in Patients with Nonsevere COVID-19 Pneumonia: A Model Based on Retrospective Cohort Study. 2020;1–17.
7. Liu K, Chen, Y., Lin, R., Han, K., 2020. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. J. Infect. https://doi.org/10.1016/j.jinf.2020.03.005 (Epub ahead of print).
8. World Health Organization. Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases. Geneva: World Health Organization; 2020.
9. Direktorat Jenderal Pencegahan dan Pengendalian Penyakit. Pedoman Kesiapsiagaan Menghadapi Coronavirus Disease (COVID-19) Maret 2020. Jakarta: Kementerian Kesehatan Republik Indonesia; 2020.
10. To KK, Tsang OT, Leung WS, Tam AR, Wu TC, Lung DC. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis. 2020 May;20(5):565–574.
11. Moriconi D, Masi S, Rebelos E, Virdis A, Manca ML, De Marco S, Taddei S, Nannipieri M. Obesity prolongs the hospital stay in patients affected by COVID-19, and may impact on SARS-COV-2 shedding. Obes Res Clin Pract. 2020 May-Jun;14(3):205–209.
12. Holly JMP, Biernacka K, Maskell N, Perks CM. Obesity, Diabetes and COVID-19: An Infectious Disease Spreading from the East Collides with the Consequences of an Unhealthy Western Lifestyle. Front Endocrinol (Lausanne). 2020; 11: 1–13.
13. Caci G, Albini A, Malerba M, Noonan DM, Pochetti P, Polosa R. COVID-19 and Obesity: Dangerous Liaisons. J Clin Med. 2020;9(8):2511.
14. Li TZ, Cao ZH, Chen Y, Cai MT, Zhan Y, Xu H. Duration of SARS-CoV-2 RNA shedding and factors associated with prolonged viral shedding in patients with COVID-19. J Med Virol. 2020;(May):1–7.
15. Lu Y, Li Y, Deng W, Liu M, He Y, Huang L, *et al*. Symptomatic Infection is Associated with Prolonged Duration of Viral Shedding in Mild Coronavirus Disease 2019: A Retrospective Study of 110 Children in Wuhan. Pediatr Infect Dis J. 2020;39(7): E95–9.

16. Chen X, Hu W, Ling J, Mo P, Zhang Y, Jiang Q, *et al*. Hypertension and Diabetes Delay the Viral Clearance in COVID-19 Patients. medRxiv [preprint]. 2020;
17. Mo P, Deng L, Liu X, Gao S, Liang K, Luo M, *et al*. Risk factors for delayed negative conversion of SARS-CoV-2 in patients with COVID-19 pneumonia: a retrospective cohort study. Epidemiol Oct. 2020;1–23.
18. Tecchio C, Micheletti A, Cassatella MA. Neutrophil-derived cytokines: Facts beyond expression. Front Immunol. 2014;5(OCT):1–7.
19. Wang H, Zhang Y, Mo P, Liu J, Wang H. Neutrophil to CD4+ lymphocyte ratio as a potential biomarker in predicting virus negative conversion time in COVID-19. Int Immunopharmacol. 2020;(January).
20. Tian D, Wang L, Wang X, Ge Z, Cui S, Xu Y, et Clinical research and factors associated with prolonged duration of viral shedding in patients with COVID-19. 2020;1–16.
21. Gao C, Zhu L, Jin CC, Tong YX, Xiao AT, Zhang S. Proinflammatory cytokines are associated with prolonged viral RNA shedding in COVID-19 patients. Clin Immunol. 0;221(1095).
22. Fu Y, Han P, Zhu R, Bai T, Yi J, Zhao X. Risk factors for viral RNA shedding in COVID-19 patients. Eur Respir J. 2020 Jul 2;56(1):2001190.

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