ORIGINAL ARTICLE

The correlation between viral shedding duration and blood biomarkers in COVID-19-infected patients

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Background: Since December 2019, the world is struggling with an outbreak of coronavirus disease-2019 (COVID-19) infection mostly represented as an acute respiratory distress syndrome and has turned into the most critical health issue worldwide. Limited information is available about the association between dynamic changes in the naso/oropharyngeal viral shedding in infected patients and biomarkers, aiming to be assessed in the current study. **Materials and Methods:** This quasi-cohort study was conducted on 31 patients with moderate severity of COVID-19 manifestations, whose real-time polymerase chain reaction (RT-PCR) test was positive for severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) RNA at baseline. RT-PCR was rechecked for patients every 3–4 days until achieving two negative ones. In parallel, biomarkers, including lymphocyte count, lactate dehydrogenase (LDH), and C-reactive protein (CRP), were assessed every other day, as well. Viral shedding also was assessed. **Results:** Spearman's correlation test revealed a significant direct correlation between the viral shedding from the symptom onset and the time, in which CRP ($P = 0.0015$, $r = 0.54$) and LDH ($P = 0.001$, $r = 0.6207$) return to normal levels after symptom onset, but not for lymphocyte count ($P = 0.068$, $r = 0.34$). **Conclusion:** Based on the current study's findings, the duration of SARS-CoV-2 RNA shedding was directly correlated with the required time for LDH and CRP return to normal levels. Therefore, these factors can be considered the determinants for patients' discharge, isolation, and return to social activities; however, further investigations are required to generalize the outcomes.

Key words: COVID-19, C-reactive protein, lymphocyte count, real-time polymerase chain reaction, virus shedding

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INTRODUCTION

Since December 2019, unknown pneumonia with detrimental effects on human lives and health has sparked in Wuhan, China, which rapidly spread to the other parts of this country and soon throughout the world.[1] Until November 21, over 56 million known cases of COVID-19 have been detected, among which unfortunately 1361847 have died (2.38%). Although the number of affected patients has dramatically declined in China due to the strict and efficient measures launched by the government, other countries, such as the United States, India, Brazil, Europe, and Iran,

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have been affected with an increasing rate of the affected cases.[2]

Most of the patients with COVID-19 experience mild clinical symptoms; however, a small portion of cases may develop severe courses accompanying by acute respiratory distress syndrome, acute kidney injury, multiple organ damage, and disseminated intravascular coagulation.[3]

Based on the phylogenetic analysis, COVID-19 is identified as a distinct clade of betacoronavirus named the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2),[4] similar to the two other viruses leading to fatal outbreaks in the 21st century, SARS-CoV and Middle East respiratory syndrome coronavirus.[5] The fatality of COVID-19 seems to be more than all the estimations, probably because of the high-speed human-to-human transmission of this contagious infection that occurs not only through the respiratory tract as the principal source but also from the fecal–oral origin.[6]

Since the outbreak of COVID-19, quantitative real-time polymerase chain reaction (qRT-PCR) has turned to the primary method for screening and diagnosis of infection.[7]

COVID-19 leads to a pronounced systemic increase in inflammatory mediators and cytokines. Therefore, since the introduction of this infection, alterations in hematological indices, including lymphopenia, thrombocytopenia, elevated C-reactive protein (CRP), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT), have been noted, as well. Nevertheless, there is limited knowledge about the association of changes in the mentioned indices with viral shedding and its severity.[8-10]

On the other hand, taking frequent nasopharyngeal specimens is bothering the patients, and numerous tests are positively false. Besides, due to this instrument's costs and shortage in low-income countries such as Iran, it poses a significant burden on the health-care system. Therefore, the current study assessed the correlation between viral shedding duration with diverse hematological indices.

MATERIALS AND METHODS

Study population

The quasi-cohort study with a single arm has been designed to investigate the association between viral shedding duration using swabs specimens for PCR of COVID-19 with other biomarkers among the patients. In this term, 31 patients with the World Health Organization criteria[11] for COVID-19 infection admitted to the Amin Hospital affiliated at Isfahan University of Medical Sciences affiliated in April/March 2020 were enrolled in the study by convenience sampling method and are being followed for a year.

The Ethics Committee of Isfahan University of Medical Sciences approved the study proposal through code number IR.MUI.MED.REC.1399.184. After that, the study protocol was explained to the eligible patients or their legal guardians, and they were reassured about the confidentiality of personal information, and eventually, written consent for participation in the study was obtained.

Nonpregnant, over 18 years old, positive PCR for COVID-19 patients with high-resolution computed tomography scans (HRCT) compatible with viral pneumonia who met Iran's National guidelines[12] for hospital admission were included in the study. Acquired or congenital immune suppression or administrations of immunosuppressive drugs were determined as the unmet criteria. Those who died during the hospitalization or follow-up period and who did not fulfill the follow-up protocol were excluded from the study. Critical manifestations of COVID 19 were the other criterion for exclusion from the study.

The severity of COVID-19 was graded as follows: mild – mild clinical symptoms, no pneumonia on lung CT; moderate – coughing, fever, oxygen saturation (O_2Sat) 90%–93% at rest, and lung CT with pneumonia; severe – O_2 Sat ≤90% at rest and/or ratio of arterial oxygen partial pressure to fractional inspired oxygen ≤300 mmHg, respiratory distress (respiratory rate >30 min^{-1}); and critical – respiratory failure requiring mechanical ventilation, shock, and/or multiorgan failure and/or admission to the intensive care unit.[12] Mild cases that did not require admission and those who met critical criteria were not included.

Study process

The data of hospitalized patients with a positive result for SARS-CoV-2 nucleic acid from respiratory specimens by RT-PCR analysis whose HRCT was compatible with viral pneumonia were recruited.

Coughing, dyspnea, sputum overproduction, myalgia, headache, diarrhea, nausea, and vomiting with/without fever were the symptoms considered as the clinical presentations for COVID-19. The day of the onset and duration of their symptoms to be improved were recorded in the study checklist.

To understand the viral shedding, the samples were tested by N-gene-specific quantitative RT-PCR assay. A nasopharyngeal and oropharyngeal swab was administered to take respiratory specimens for SARS-CoV-2

Table 1: The demographic and clinical characteristics of the studied population

	n=31, *n* (%)
Age (years)	
Median (range)	46 (23-72)
Mean±SD	44.8 (10.9)
Gender (male)	12 (38.7)
City habitant	26 (83.9)
Traveling history	2 (6.5)
Smoking	
Never smoked	2 (4.5)
Exposure history	26 (83.8)
Current smoker	3 (9.7)
Respiratory rate (bpm)	
Median (range)	20 (11-30)
Mean±SD	20.4 (3.2)
Pulse rate (bpm)	
Median (range)	91 (74-119)
Mean±SD	92.9 (11.9)
Systolic blood pressure (mmHg)	
Median (range)	120 (90-160)
Mean±SD	121.1 (13.9)
Diastolic blood pressure (mmHg)	
Median (range)	80 (60-90)
Mean±SD	75.3 (8.9)
Temperature (°C)	
Median (range)	37 (36.5-39.5)
Mean±SD	37.3 (0.72)

SD=Standard deviation

nucleic acid RT-PCR at baseline and then every 3–4 days until the tests turned negative twice in a row.

In addition, the hematological assessments, including complete blood count (CBC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), LDH, highly sensitive CRP (hs-CRP), and erythrocyte sedimentation rate, were measured at baseline. Then, hs-CRP, LDH, and CBC were repeated every other day until achieving normal entities. Lymphopenia, normal hs-CRP, and LDH were determined as 1500/ml, ≤5 mg/L, and 480 unit/L, respectively. To minimize the bias, RT-PCRs and hematological tests were sent to the referral laboratory of the university.

The patients were released based on the discharge criteria of the Iranian national guidelines for COVID-19 management. Therefore, based on the national guidelines, they were sent to the recovery houses prepared for the patients to stay until the 14th day of COVID-19 symptom onset. To perform the further tests after the hospital discharge, a private hospital-affiliated car was sent to take the patients to the laboratory facilitated with a specific room for taking PCR samples and then return them to the recovery house or their house. Besides, all persons in close touch with the patient were followed for 2 weeks.

Real-time polymerase chain reaction

Nasopharyngeal and oropharyngeal swab specimens were obtained from the patients by a skilled technician. RNA was extracted using a viral RNA isolation kit (ROJE, Iran) according to the manufacturer's instructions. Reverse-transcriptase real-time (rRT-PCR) targeting the N and RdRp genes (Pishtaz Teb kit, Tehran, Iran) was performed. The amplification was performed with a cycle of 15 min at 50°C for reverse transcription, 3 min at 95°C for primary denaturation, followed by 45 cycles at 95°C (15 s) and 55°C (40 s).[7]

Statistical analysis

The obtained data were entered into the Statistical Package for the Social Sciences (SPSS; version 15.0, SPSS Inc., Chicago, IL, USA). The descriptive data were presented in mean, standard deviation, absolute numbers, and percentages. To compare the frequencies between the groups, the Chi-square test was utilized. Shapiro–Wilk test was administered to assess the normality of data distribution. The Spearman's test was used to evaluate the correlation between continuous variables. $P < 0.05$ was considered a significant level.

RESULTS

In the current study, the data of 40 COVID-19 patients were retrieved, among which nine withdrew from the study as they did not refer for further follow-up assessments. Therefore, 31 patients fulfilled the study. The mean age of the studied population was 44.8 ± 10.9 years, among which females were predominant (61.3%). Most of the cases were habitants of Isfahan (83.9%) and did not present a recent traveling history (93.5%). All patients met the criteria for moderate SARS-CoV-2 severity [Table 1].

Table 2 demonstrates the clinical and laboratory findings of the assessed COVID-19 patients. Based on Table 2, the patients were hospitalized within 6.1 ± 3.1 days after the onset of their symptoms. 9 (29%), 5 (16.1%), and 1 (3.2%) of the patients had normal lymphocyte count, LDH, and CRP levels at their symptom onset/admission. PCR tests got negative within 15.2 ± 7 and 21.3 ± 7.6 days after hospital admission and onset of symptoms, respectively. Furthermore, PCR tests got negative within 11.4 ± 7.6, 6.7 ± 6.1, and 6 ± 6.6 days after lymphocyte count, LDH level, and CRP level turning to the normal ranges, respectively.

The detailed information of the studied population is shown in Table 3.

There was a significant direct correlation between the time of PCR test getting negative from the onset of the symptoms and the time, in which CRP ($P = 0.0015$, $r = 0.54$) and LDH ($P = 0.001$, $r = 0.6207$) return to normal levels

Table 2: The periods between clinical and laboratory characteristics

	The normal range at admission, *n* (%)	Normal range after admission/ discharged, *n* (%)	Median (range)	Mean±SD
The duration from the onset of the symptoms to admission (day)			6 (0-14)	6.1±3.1
The duration between lymphocyte return to normal range and admission (day)	9 (29.0)	21 (67.7)	4 (0-10)	3.8±2.9
The duration between lymphocyte return to normal range and symptom onset (day)			10.5 (4-17)	10.0±3.4
The duration between CRP returns to the normal level and admission (day)	1 (3.2)	26 (83.9)	10 (0-22)	11.3±4.1
The duration between CRP returns to the normal level and symptom onset (day)			17 (4-27)	17.6±5.1
The duration between LDH return to normal level and admission (day)	5 (16.1)	19 (61.3)	13 (0-25)	11.7±7.4
The duration between LDH return to the normal level and symptom onset (day)			18 (4-34)	17.6±7.8
The duration between PCR getting negative and admission (day)			16 (7-37)	15.2±7.0
The duration between PCR getting negative and symptom onset (day)			22 (7-44)	21.3±7.6
The duration between PCR getting negative and lymphopenia getting normal (day)		*n*=30	12 (0-30)	11.4±7.6
The duration between PCR getting negative and LDH level getting normal (day)		*n*=20	5 (0-18)	6.7±6.1
The duration between PCR getting negative and CRP getting normal (day)		*n*=23	3 (0-21)	6.0±6.6

PCR=Polymerase chain reaction; LDH=Lactate dehydrogenase; CRP=C-reactive protein; SD=Standard deviation

Table 3: The characteristics of the studied population

ID	Age	Sex	PCRSO[a]	LYSO[b]	CRPSO[c]	LDHSO[d]	PCR-from-LDH[e]	PCR-from-CRP[f]	PCR-from-lymph[g]
1	33	Female	7	7	7	0	7	0	0
2	36	Female	37	7	16	19	18	21	30
3	48	Male	22	4	7	13	9	15	18
4	56	Male	7	4	10	10	−3	−3	3
5	72	Female	10	4	13	10	0	−3	6
6	67	Female	10	7	7	13	−3	3	3
7	45	Female	10	0	10	0	10	0	10
8	31	Male	7	4	10			−3	3
9	36	Male	7	0	10			−3	7
10	48	Male	7	7	10			−3	0
11	46	Female	16	10	16	13	3	0	6
12	40	Female	16	4	13	13	3	3	12
13	57	Female	13	0	13	13	0	0	13
14	37	Female	16	4	13	7	9	3	12
15	30	Female	25	0	22	7	18	3	25
16	35	Female	16	4	7	0	16	9	12
17	54	Female	28	4	16	25	3	12	24
18	51	Female	19	7	0	16	3	19	12
19	54	Male	16	4	7	16	0	9	12
20	55	Female	16	0	13	13	3	3	16
21	48	Male	10	0	10	13	−3	0	10
22	40	Female	22	4	10	13	9	12	18
23	38	Male	10	7	16	16	−6	−6	3
24	43	Female	19	0	16	19	0	3	19
25	48	Female	10	7		0	10		3
26	49	Male	13	4	13			0	9
27	36	Female	13	0	13	0	13	0	13
28	33	Male	16	7	10			6	9
29	52	Male	13	0	10			3	13
30	23	Female	25	4	10	25	0	15	21
31	47	Male	16			19	−3		

[a]PCRSO=The number of days between the PCR test getting negative and the onset of the symptoms; [b]LYSO=The number of days between lymphocyte count returning to normal range and the onset of the symptoms; [c]CRPSO=The number of days between CRP returning to the normal level and the onset of the symptoms; [d]LDHSO=The number of days between LDH returning to the normal level and the onset of the symptoms; [e]PCR-from-LDH=The number of days between PCR test getting negative and LDH returning to the normal level; [f]PCR-from-CRP=The number of days between PCR test getting negative and CRP returning to the normal level; [g]PCR-from-lymph=The number of days between PCR test getting negative and lymphocyte count returning to normal range. PCR=Polymerase chain reaction; LDH=Lactate dehydrogenase; CRP=C-reactive protein

after symptom onset. No other associations were detected between the indices [Table 4].

Further evaluations revealed that the time of PCR getting negative from the onset of the symptoms was not statistically correlated with any of the baselines measured indices ($P > 0.05$), except for hemoglobin, which showed a significant reverse correlation ($P = 0.040$, $r = -0.370$) [Table 5].

DISCUSSION

COVID-19, a highly contagious and easily transmitted infection, has turned into the most critical health emergency worldwide that arose toward the end of 2019.[13] The current schedule for the management of COVID-19 insists on early diagnosis, early isolation, and early treatment. Nevertheless, except for symptomatic control, there is no obvious therapeutic approach for this disease. After appropriate symptomatic management of COVID-19, most of the symptoms would vanish, and the patients rehabilitate successfully. However, a few ones turn to severe or even critical courses.[14] To date, scientists do not have adequate knowledge about the duration of viral shedding, its association with the severity of the disease, and contributing factors. In the current study, we tried to find the contributing factors associated with the duration of SARS-CoV-2 shedding by dynamic observation of the SARS-CoV-2 RNA load.

Our study's first finding revealed that the median time between symptom onset and admission was 6 days, which can be discussed according to two aspects. Primarily, the patients were able to seek medical care promptly, and the second point shows that our patients were referred to the hospitals relatively later than in other communities.[1] Early admission's significance is better clarified by knowing the superior outcome and prognosis of those admitted earlier.[3]

Lymphopenia and elevated levels of LDH and CRP were noted among the majority of the studied patients at admission, findings that are in accordance with most of the previous studies in the literature.[9,10,15] Our study's primary principle was to detect a correlation between viral shedding duration and hematological indices abnormality duration. We found a significant direct moderate correlation between viral shedding duration and required time for the elevated CRP and LDH to get normal, but not for lymphopenia. This correlation probably predicts the COVID-19 infection contagion period or favorable outcomes of this infection. In addition, it primarily limits the requirement for frequent SARS-CoV-2 RNA assessments. On the other hand, this correlation can help early patient discharge, release from isolation, and return to social activities.

To the best of our knowledge, the current study is among the rare ones assessing the correlation between the viral shedding period and the duration of hematological biomarkers change due to SARS-CoV-2 infection. This investigation's significance is better clarified, knowing that viral shedding duration in influenza virus infection was directly associated with infectivity and transmissibility as the

Table 4: The correlation between coronavirus disease-2019-related indices negativity

	LYSO	CRPSO	PCRSO
LYSO	-	r=0.25 P=0.168	r=0.34 P=0.068
CRPSO	-	-	r=0.54 P=0.0015*
LDHSO	r=0.289 P=0.170	r=0.288 P=0.1825	r=0.6207 P=0.001*

*Significant if P<0.05. PCRSO=The number of days between the PCR test getting negative and the onset of the symptoms; LYSO=The number of days between lymphocyte count returning to normal range and the onset of the symptoms; CRPSO=The number of days between CRP returning to the normal level and the onset of the symptoms; LDHSO=The number of days between LDH returning to the normal level and the onset of the symptoms. PCR=Polymerase chain reaction; LDH=Lactate dehydrogenase; CRP=C-reactive protein

Table 5: The correlation between polymerase chain reaction getting negative from the symptom onset and baseline laboratory indices

The baseline indices	Median (range)	Mean±SD	Correlation coefficient with "PCR getting negative duration from symptom onset" (r)	P*
Leukocyte count	6100 (2400-11900)	6461.3 (2409.1)	−0.230	0.210
Lymphocyte count	1312 (713-2215)	1384.1 (462.6)	0.067	0.719
Neutrophil count	4420 (1386-10467)	4669.2 (2241.3)	−0.263	0.151
Neutrophil-to-lymphocyte ration	3.2 (1.1-12.3)	3.7 (2.4)	−0.246	0.181
Hemoglobin	14 (9-17)	13.9 (2.0)	−0.370	0.040*
Platelet× 10^3	217 (122-412)	230.5 (71.5)	−0.077	0.680
ESR	25 (6-82)	33.0 (23.3)	0.012	0.949
CRP	21 (2-130)	30.3 (30.8)	−0.249	0.200
ALT	28 (11-388)	50.6 (81.6)	−0.05	0.796
AST	33 (20-243)	44.2 (45.8)	−0.159	0.457
LDH	544 (303-1007)	562.6 (155.2)	−0.008	0.968

*Significant if P<0.05. SD=Standard deviation; ESR=Erythrocyte sedimentation rate; CRP=C-reactive protein; ALT=Alanine transaminase; LDH=Lactate dehydrogenase; AST=Aspartate transaminases; PCR=Polymerase chain reaction

primary factors associated with the control and prevention of infection.[16] The duration for SARS-CoV-2 RNA to get negative from symptom onset ranged from 7 to 44 days, with a median of 22 and 16 days from symptom onset and admission, respectively. These findings are consistent with the previous studies.[3,17] However, prolonged viral shedding for up to 50 days has been reported, as well.[18]

CRP is one of the most popular determinants of inflammation, which, as a relatively late-onset index, rises within 72 h in response to a systemic inflammatory process in the body. Similar to the other systemic inflammations due to infectious conditions, SARS-CoV-2 leads to CRP rise. The significance of CRP elevation and its intensity is to the extent that numerous scientists have represented it as a predicting factor for COVID-19 infection severity, mortality, and prognosis.[10,19,20] Han *et al*. represented that viral shedding duration was directly associated with CRP levels.[21] Other researchers confirmed this result, but none of them assessed the correlation between SARS-CoV-2 RNA shedding and the required duration for CRP to turn to the normal ranges.[18] Moreover, although Zhang *et al*. confirmed the stand-alone predictive role of CRP for COVID-19 outcomes, they found no correlation between viral shedding duration and CRP time getting negative from the onset time of the symptoms. This may have occurred due to CRP's late response to subsidence;[13] nevertheless, CRP as an available and reliable inflammation-related biomarker can be administered for deciding on both intensive treatments and following-up the discharged COVID-19 patients.

LDH level as a biomarker for cellular turnover is directly associated with SARS-CoV-2 infection, severity, and duration of virus RNA shedding.[15,22,23] Yuan *et al*., in their investigation, represented a direct correlation between LDH level downward trend and COVID-19 shedding duration,[24] which was opposed by Lee.[25] We assume that the decrease in cellular lysis and apoptosis following viral mRNA elimination is associated with less cellular turnover and, in response, leads to a decline in LDH.

Surprisingly, the viral shedding period was not associated with the duration of lymphopenia. Studies have shown that SARS-CoV-2 is approximately 80% similar to SARS-CoV, which invades host cells by binding to the angiotensin-converting enzyme-2 (ACE 2) receptor. This receptor is primarily expressed in the respiratory system. However, ACE 2 receptors are among the surface antigens of lymphocytes, as well, which may cause lymphocyte lysis.[26] Another hypothesis about lymphopenia following COVID-19 infection is the cytokine storm incidence, leading to apoptosis.[27] However, these theories justify lymphopenia due to COVID-19 infection; it is against our findings concerning lacking association between SARS-CoV RNA getting negative and period of lymphopenia from symptom onset. Because it was expected that the number of lymphocytes would increase with the reduction of virus load and reach normal levels.

The novel theory of this investigation and its cohort design is the most notifying strength of the current study; however, we have to confess numerous limitations of this report. The small sample population and single-center evaluation are the two remarkable weak points of this study. Probably, the most important limitation of this study is to suffice to evaluate oropharyngeal or nasopharyngeal swab tests only, while a study represented the continued presence of viral RNA in fecal samples.[28] Therefore, we want to recommend further multicentric studies with large sample populations and precise assessments of both oro- and nasopharyngeal specimens as well as fecal ones.

CONCLUSION

Based on the current study's findings, the duration of SARS-CoV-2 RNA detection was directly correlated with the required time for LDH and CRP return to normal levels. Therefore, we propose this idea that these factors can be considered the determinants for patients' discharge, isolation, and return to social activities; however, further investigations with larger sample populations are required to generalize the outcomes.

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Conflicts of interest
There are no conflicts of interest.

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