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Lymphopenia and lung complications in patients with coronavirus disease-2019 (COVID-19): A retrospective study based on clinical data

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Abstract

A rapid outbreak of novel coronavirus, coronavirus disease-2019 (COVID-19), has made it a global pandemic. This study focused on the possible association between lymphopenia and computed tomography (CT) scan features and COVID-19 patient mortality. The clinical data of 596 COVID-19 patients were collected from February 2020 to September 2020. The patients' serological survey and CT scan features were retrospectively explored. The median age of the patients was 56.7 ± 16.4 years old. Lung involvement was more than 50% in 214 COVID-19 patients (35.9%). The average blood lymphocyte percentage was 20.35 ± 10.16 (normal range, 20%–50%). Although the levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were high in more than 80% of COVID-19 patients; CRP, ESR, and platelet-to-lymphocyte ratio (PLR) may not indicate the in-hospital mortality of COVID-19. Patients with severe lung involvement and lymphopenia were found to be significantly associated with increased odds of death (odds ratio, 9.24; 95% confidence interval, 4.32–19.78). These results indicated that lymphopenia < 20% along with pulmonary involvement >50% impose a multiplicative effect on the risk of mortality. The in-hospital mortality rate of this group was significantly higher than other COVID-19 hospitalized cases. Furthermore, they meaningfully experienced a prolonged stay in the hospital (p = .00). Lymphocyte count less than 20% and chest CT scan findings with more than 50% involvement might be related to the patient's mortality. These could act as laboratory and clinical indicators of disease severity, mortality, and outcome.

KEYWORDS

COVID-19, lung CT scan, lymphopenia, mortality

1 | INTRODUCTION

In December 2019, pneumonia for unknown reasons emerged in Wuhan city, Hubei of China. Chinese scientists extracted novel Coronavirus from patients' specimens and named it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on January 7, 2020, which was formerly called N-COV-2019.[1] The World Health Organization (WHO) finally announced the new coronavirus to be COVID-19 in February 2020.[1] Coronaviruses are a large family of viruses that are well-known to cause a wide variety of clinical

manifestations from the mild common cold to severe forms of respiratory diseases such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS).[2,3] The clinical manifestations of COVID-19 vary from asymptomatic infection, mild forms of upper respiratory tract illness, viral pneumonia, acute respiratory failure, and death.[4,5] The most common clinical features of COVID-19 include fever, dry cough, fatigue, diarrhea, severe muscle pain, and pneumonia that lead to acute respiratory distress syndrome, metabolic acidosis, septic shock, thrombosis, and heart failure, renal failure, and liver disease.[6,7] Although the mild form of COVID-19 can be treated by appropriate medical interventions, the most severe cases, especially the elderly who experience underlying medical conditions, develop severe illness and increase the mortality rate.[8] Older adults with pre-existing medical conditions such as diabetes, asthma, and cardiovascular disease may be more vulnerable to COVID-19.[9] The recognition and discrimination of severe COVID-19, mild infection, and asymptomatic form are clinically vital.[10] The most important laboratory findings in COVID-19 patients are a low concentration of albumin (75.8%), high serum C-reactive protein (CRP) (58.3%), erythrocyte sedimentation rate (ESR) (41.8%), LDH (57%), and lymphopenia (43%).[11] Lymphopenia was detected in severe COVID-19 patients (85%) and suggested as a severity predictor; the average count of lymphocytes of intensive care unit (ICU) —hospitalized patients was $0.81 \times \times 10^9$/L (range, 0.42–1.66). They also reported that low lymphocyte count and poor prognosis were related to aging.[12] Lymphopenia could have occurred in COVID-19 patients via four mechanisms: (a) viral attachment to the cell surface receptor ACE2 infect lymphocytes that lead to lymphocyte death[13]; (b) the possible role of coronavirus in the destruction of lymphoid organs[14]; (c) induction of lymphocyte apoptosis by the production of tumor necrosis factor-α and interleukin-6,[15] and (d) inhibition of lymphocyte production during metabolic acidosis.[16] Although the pathogenesis of COVID-19 remains unclear, lymphopenia was observed in most of the patients.[17] Aging and chronic illness lead to endothelial dysfunction that dismounts cell-cell adhesions, promotes endothelial cell death, extravasation that resulted in lymphopenia.[18] The infection of COVID-19 is diagnosed and confirmed by real-time reverse-transcription polymerase chain reaction (RT-PCR) and gene sequencing of the blood and lung samples. In the early phase of the disease, positive nasopharyngeal RT-PCR results ranged between 30% and 60%.[19] In emergency cases, the low sensitivity of RT-PCR missed diagnoses of COVID-19 patients who failed to receive appropriate medications and upended outside spreading of COVID-19. In contrast with RT-PCR, chest computed tomography (CT) has sufficient sensitivity for atypical radiographic manifestations of COVID-19 cases who are asymptomatic and/or negative on the initial RT-PCR test.[20,21] According to the Chinese reports, chest CT is adequately sensitive (97%) in the early detection of COVID-19 patients compared with RT-PCR.[22] Bilateral lung involvement was observed in 98% of patients and lobular and subsegmental areas of consolidation were considered as the most typical findings of CT.[4] Besides this, several COVID-19 cases demonstrated ground-glass opacities (GGOs) and pulmonary consolidation with round morphology.[23] The main CT findings of COVID-19 pneumonia are the shape of GGO, crazy paving pattern, and consolidation.[24]

Iran is one of the worst affected countries by the coronavirus and Mazandaran province is considered one of the most impacted areas.[25] The paucity of evidence on the relationship between lymphopenia, chest CT examination, and mortality rate in COVID-19 patients made us ascertain this possibility. As Imam Khomeini hospital in Mazandaran was considered as the main referral center for the management of COVID-19 cases, we aimed to retrospect and evaluate the lymphopenia in COVID-19 patients and its association with lung involvement.

2 | METHODS

2.1 | Study design and inclusion patients

This study was approved by the research ethics committee of Mazandaran University of Medical Sciences, Sari, Iran (IR. MAZUMS. REC.1399.7418). All patients who were admitted to Emam Khomeini hospital, Sari, Mazandaran from February 26, 2020, to September 21, 2020, were included. Written informed consent was obtained from all participants with COVID-19 infection. Simple random sampling was used for including patients. The diagnosis, hospitalization, and treatment of patients were performed according to Iran's Ministry of Health and Medical Education guidelines. Iranian guidelines mentioned the laboratory and radiological examinations as a first line of COVID-19 confirmation along with clinical symptoms such as fever, cough, and shortness of breath. The cases without chest CT and laboratory test confirmation were excluded. Assuming 95% confidence level and $p = .7$ (lymphopenia 70%), $d = 0.07$, and Cochran's formula, the sample size was calculated as 596. Clinical outcomes including Complete Blood Count, CRP, and ESR were evaluated within a 7 days monitoring period. All medical data including epidemiological, demographic, laboratory data, and patient's discharge and/or death were extracted via the hospital information system.

2.2 | CT scans

All CT examinations were performed using a multi-detector CT scanner (CT scan) Somatom Emotion Eco (16-slice configuration, Siemens). The supine CT scan was performed and no contrast medium had been administrated. The CT images were observed with both lungs and in parenchymal and mediastinal window settings. Two radiologists appraised the lung scans by the picture archiving and communication system (PACS, INFINITT Healthcare Co., Ltd.). The features of CT imaging were typically focused on unilateral and bilateral GGO, consolidation, and pleural effusion. The pulmonary involvement of COVID-19 patients was categorized into two groups: less than 50% (Figure 1A) and more than 50% involvement (Figure 1B). Clinical data were screened on the date of symptom onset and 7th day and abstracted from the medical records of Imam
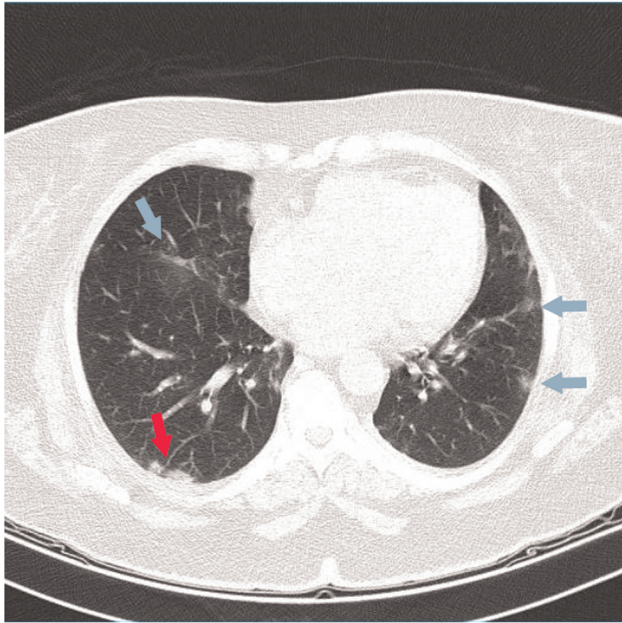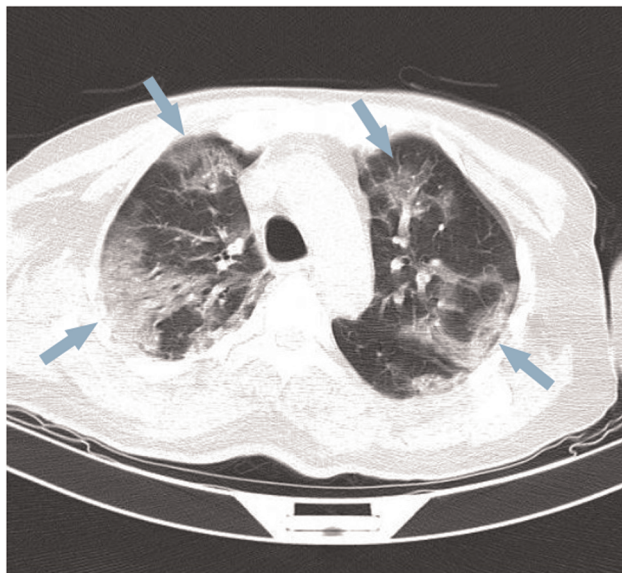
FIGURE 1 (A) A 61-year-old female with COVID-19 pneumonia; Chest computed tomography (CT) shows bilateral ground-glass opacities (blue arrows). The red arrow shows a subpleural pulmonary nodule. (B) This figure demonstrates a 65 years old male with COVID-19. The chest CT scan shows bilateral ground-glass opacities (blue arrows)

Khomeini hospital, Sari, Iran. All data containing age, sex, underlying medical conditions, CT scan results, lymphocyte count, CRP, ESR, Platelet, length of stay (LOS), and mortality were recorded according to the checklist. Data analysis was performed using SPSS, and Mann–Whitney and Kruskal–Wallis tests. The logistic regression model interprets the odds ratio and $p < .05$ was considered as statistically significant.

TABLE 1 Characteristics and clinical data of the included patients

Variable	N (%)/mean ± SD
Sex; N (%)	
Female	296 (49.7)
Male	300 (50.3)
Age (mean ± SD)	56.76 ± 16.47
CT involvement; N (%)	
<5	30 (5)
<25	120 (20.1)
<50	232 (38.9)
<100	214 (35.9)
CRP; N (%)	
Negative	62 (10.4)
Positive	498 (83.6)
ESR; N (%)	
Negative	62 (10.4)
Positive	384 (64.4)
Outcome; N (%)	
Discharge	512 (85.9)
Mortality	84 (14.1)
WBC*1000 (mean ± SD)	6.8 ± 3.5
Platelet *1000 (mean ± SD)	213.4 ± 89.3
Lymphocyte in percent (mean ± SD)	20.35 ± 10.1
Lymphocyte in the count (mean ± SD)	1246.7 ± 709.5
Admission time (mean ± SD)	7.79 ± 4.7

Abbreviations: CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; WBC, white blood cell.

3 | RESULTS

A total of 596 patients were included. The median age was 56.7 ± 16.4 years (range, 18–94 years), and 300 patients (50.3%) were male and 296 patients (49.7%) were female. Based on the CT findings categorization, 214 patients (35.9%) presented >50% lung involvement; 84 deaths occurred (14.09%) and 85.9% of patients were discharged. The mean blood lymphocyte percentage was 20.35 ± 10.16 (Table 1). The mean lymphocyte percentage of COVID-19 patients with >50% lung involvement was significantly lower than that of subjects <50% involvement (median of 17.36 vs. 22.03) ($p = .00$) (Figure 2). All patients were stratified into four groups according to the radiographic and hematological findings: 74 patients (12.4%) with >50% lung involvement and without lymphopenia; 210 patients (35.2%) < 50% lung involvement and without lymphopenia; 140 patients (23.5%) > 50% lung involvement and with lymphopenia,
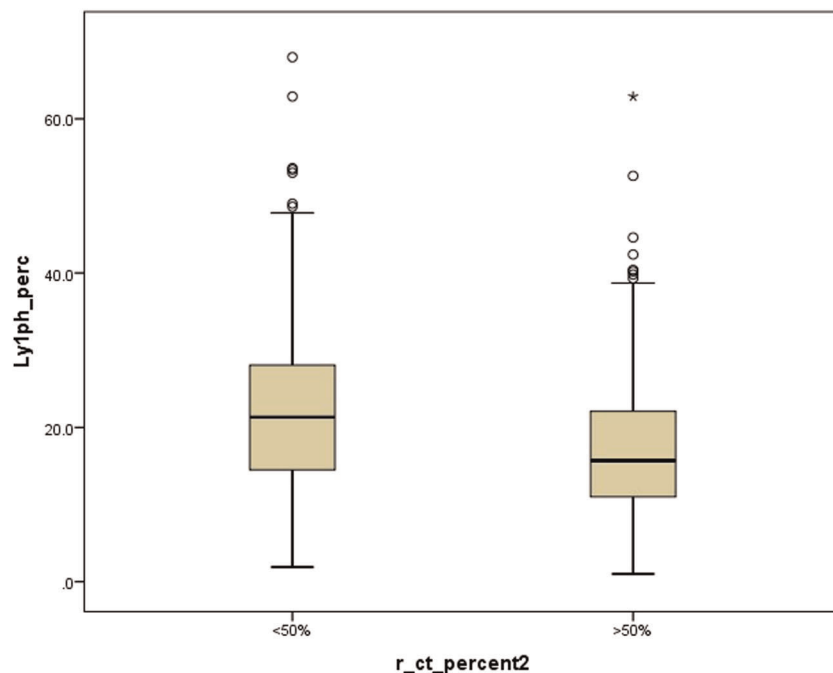
FIGURE 2 Lymphocyte percentage of COVID-19 patients compared to the lung involvement

and 172 patients (28.9%) < 50% lung involvement and with lymphopenia. The mortality was intensely found to be correlated with lung involvement and lymphopenia in COVID-19 patients (Table 2). The mortality rate of patients who presented >50% lung involvement without lymphopenia was higher than patients without lymphopenia and lung involvement (OR, 3.4; 95% CI, 1.3–8.9). Those with lymphopenia but no lung involvement had a 10.5% mortality rate (OR, 3.62; 95% CI, 1.6–8.0). COVID-19 patients with lymphopenia and lung involvement showed the highest mortality rate of 36.6% (OR, 9.2; 95% CI, 4.32–19.78). LOS of patients with lymphopenia and who developed severe lung involvement was strongly correlated with normal lymphocyte count and without pulmonary involvement (p = .000) (Table 3). The LOS of patients with lung involvement and lymphopenia was significantly higher than those with lymphopenia (p = .014). The ESR was above the normal range in 384 (86.1%) patients, of whom 49 patients died. An elevated level of CRP was seen in 498 (88%) COVID-19 patients among whom 76 patients died during the hospitalization period. Therefore, no significant correlation was identified between ESR and CRP levels and in-hospital mortality (p = .11 and p = .56; respectively). The inflammatory marker

TABLE 3 Analysis of length of stay (LOS)[a] for patients with COVID-19

Lymphopenia	Sever lung involvement (>50%)	N (%)	Mean ± SD	p value
No	No	210 (35.2%)	6.7 ± 4.4	.000
No	Yes	74 (12.4%)	8.2 ± 4.5	
Yes	No	172 (28.9%)	7.7 ± 4.3	
Yes	Yes	140 (23.5%)	9.3 ± 5.2	

[a]Inpatient days from admission day to discharge/death.

of platelet-to-lymphocyte ratio (PLR) was also analyzed; the median PLR of all patients was 179.58 (IQR, 127.84–245.68). Of all COVID-19 patients with lung involvement, the mean of PLR in death cases was not significantly associated with the discharged ones (p = .16). A significant correlation was not found between PLR and LOS (p = .062; Spearman correlation coefficient: 0.077).

TABLE 2 Analysis of mortality for patients with COVID-19

Lymphopenia	Sever lung involvement (>50%)	N (%)	Mortality, N (%) No	Yes	OR (CI95%)
No	No	46 (27.5)	43 (93.5)	3 (6.5)	-
No	Yes	23 (13.8)	19 (82.6)	4 (17.4)	3.49 (1.35– 8.96)
Yes	No	57 (34.1)	51 (89.5)	6 (10.5)	3.62 (1.63–8.02)
Yes	Yes	41 (24.6)	26 (63.4)	15 (36.6)	9.24 (5.32–19.78)

4 | DISCUSSION

This study aimed to inquire about the association between lymphopenia and lung involvement in the outcome of hospitalized patients with COVID-19. Here, the lymphocyte percentage was calculated as 20.35 ± 10.16 (normal range, 20%–50%), it was significantly associated with more severe lung involvement ($p = .00$). Lymphopenia was observed in 312 patients (52.3%) and 284 patients lay within the normal range. Of the 596 hospitalized patients, 84 (14%) died and 515 cases were discharged. Though elevated serum sedimentation and CRP levels were seen in more than 80% of patients, we observed that the raised values of CRP and ESR may not a predictable inflammation marker in the outcome of patients with COVID-19 ($p = .56$ and $p = .11$, respectively). Of the 596 patients, 260 (43.6%) showed bilateral ground-glass and consolidative opacities, 253 (42.4%) had bilateral ground-glass opacities, and 50 (8.4%) had bilateral consolidation on chest CT. Although pleural effusion, consolidation, and GGO was seen in COVID-19 cases, 24 patients (4.1%) had exclusively unilateral lung involvement. The bilateral ground-glass opacities and consolidation were the major pulmonary CT findings of COVID-19 patients.

With the same conclusion as ours, other studies reported lymphopenia as a reliable indicator for COVID-19 severity. Tan et al.[14] showed that there is a reverse association between lymphocyte count and COVID-19 severity and its prognosis. Lymphocyte count < 20% was reported in severe clinical illness; lymphopenia at the level <5% was found in patients who died.[14] In another study, lymphopenia at the level of 40% was demonstrated in 191 patients.[26] It was also presented that 48% of included patients experienced underlying non-communicable diseases including hypertension, diabetes, and coronary heart disease.[26] Several symptoms of coronavirus infection were also described in Iranian children and were defined as a less serious disease with a good prognosis.[27] Zheng et al. compared the laboratory features of COVID-19 pneumonia to non-COVID-19 pneumonia. They stated that COVID-19 pneumonia-derived lymphopenia negatively affects the biochemical indicators of organ dysfunction.[28] A study done on 221 hospitalized COVID-19 patients confirmed leukopenia (33%), lymphopenia (73.8%), and more susceptibility to fungal and bacterial infections.[29] Chinese research explained that bilateral pneumonia, shorter duration of onset to admission, lymphopenia, and disease severity are regarded as risk factors of prolonged hospitalization of COVID-19.[30] Lymphopenia may occur along with an increased level of cytokine, disease severity, mortality, and impaired immune response.[31]

Tan et al.[32] showed the inverse relationship between lymphocyte count and disease severity and its prognosis in 92 COVID-19 patients. It was disclosed that LYM% lower than 20% was seen in severe cases and it fell under 5% in dead patients.[32] Comparison of laboratory variations of 88 patients with COVID-19 pneumonia and 22 non-COVID-19 pneumonia cases

revealed that lymphocyte depletion, not neutrophil, and monocyte, inversely affect biochemistry disorder and organ failure.[28] Lymphopenia and augmentation of cytokines are accompanied by increased disease severity, death, and disrupted immune response.[31] Despite that, some studies found higher levels of ESR and CRP as inflammatory indicators in severe patients of COVID-19,[33–35] our results did not show increased ESR and CRP levels in severe cases. It was also shown by Peng et al.[36]

The chest CT scan plays a crucial role in the early diagnosis and evaluation of patients with COVID-19 pneumonia likewise, lymphopenia and thrombocytopenia were the verified markers for disease detection.[37] The sensitivity of chest CT imaging was examined among 1014 patients who had negative RT-PCR.[19] Their results showed high sensitivity of lung CT (75% of the included population were positive for COVID-19) and suggested it to be a reliable detection method in epidemic regions.[19] Subgroup analysis revealed that COVID-19 patients with severe pulmonary lung involvement and lymphopenia had 9.2-fold increased odds of in-hospital mortality. The mortality rate was also calculated in patients with severe lung involvement and patients with lymphopenia, these groups had a mortality rate of 3.4 and 3.6 times greater than those without lung involvement and lymphopenia (Table 3). In other words, the mortality in the case of lymphopenia along with severe lung involvement was deeply different compared with patients with neither lymphopenia nor lung involvement (OR, 9.2; 95% CI, 4.3–19.7) (Table 3). We found that the incremental effect of lymphocyte count and lung involvement tracks the multiplicative model, not the additive model.

Assessment of RT-PCR positive COVID-19 cases showed leukopenia, lymphopenia, and high CRP concentration as hematological and biochemical parameters. The most involved segments were lung segments 6 and 8 with peripheral pulmonary localized lesions.[38] The sensitivity of the CT scan was inspected in mild COVID-19 reaching a high level after 10 days of infection.[39] It was found that the most frequent CT manifestations and clinical features were GGO (86%) and consolidation (62%).[40] Similarly, we found that bilateral distribution of GGO and consolidation are the main pulmonary lesions of COVID-19 patients.

The inflammatory marker of PLR was suggested as a predictive indicator for disease severity and mortality in infectious disease and cancer.[41,42] Rong et al. noted the value of PLR for predicting the clinical outcome of COVID-19 and patients' observation. They found a high PLR is associated with more severity and longer hospitalization.[43] Conversely, our study showed no significance and it was not correlated to mortality ($p = .16$). The PLR was not correlated with the LOS ($p = .06$; $r = .07$). Notably, we found that LOS in patients with lymphopenia and severe lung involvement was remarkably higher than others ($p < .05$). Likewise, a Chinese study represented that bilateral pneumonia in a lung CT scan, a short period from symptoms onset to hospitalization, lymphopenia, and disease severity were the main factors in prolonged LOS (ProLOS).[44]

5 | LIMITATIONS

Limitations of this study include the lack of accessibility to the molecular kit at the beginning of the pandemic. Therefore molecular confirmation of COVID-19 was impossible for all included patients.

6 | CONCLUSION

In summary, while SARS-CoV-2 real-time RT-PCR is considered as a gold standard method,[45] it is accompanied by false-negative results and less than 100% sensitivity.[46] Even though the appropriate period for sampling is the first week after symptom onset, many cases are asymptomatic carriers with pulmonary involvement. COVID-19 pneumonia displays lung involvements and lesions even in asymptomatic patients within 1–3 weeks. Besides this, blood parameters are easily accessible and commonly used everywhere. Relating the valuation of CT scan features with clinical and laboratory outcomes possibly assists the timely diagnosis of COVID-19 pneumonia. It was clarified in our study that lymphopenia < 20% and lung CT involvement > 50% were intensely related to disease severity, mortality, outcome, and prolonged hospitalization.

CONFLICTS OF INTERESTS
The authors declare that there are no conflict of interests.

ETHICS APPROVAL
The study protocol was approved by the Ethics Committee of Mazandaran University of Medical Sciences (IR. MAZUMS. REC.1399.7418).

AUTHOR CONTRIBUTIONS
Ehsan Zaboli: conceptualization, project administration, literature search; Hadi Majidi: data collection; Reza Alizadeh-Navaei: data curation, methodology, data analysis; Akbar Hedayatizadeh-Omran and Hossein Asgarian-Omran: review and editing; Laleh Vahedi Larijani and Vahid Khodaverdi: data collection; OA: writing manuscript, investigation, supervision. All authors reviewed and approved the last version of the article.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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