ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 19(6): 739-744 (2023)

BIOINFORMATION
Discovery at the interface of physical and biological sciences
BIOMEDICAL INFORMATICS
www.bioinformation.net
Volume 19(6)
Research Article

Received June 1, 2023; Revised June 30, 2023; Accepted June 30, 2023, Published June 30, 2023
DOI: 10.6026/97320630019739

Edited by P Kangueane
Citation: Siva *et al.* Bioinformation 19(6): 739-744 (2023)

Assessment of segmental lung involvement in covid-19 patients using biochemical parameters

T. Siva[1], Yuvaraj Maria Francis[2], PK Sankaran[3,*], CP Kirthika[1], Vinoth Kumar Kalidoss[4], R Sarah[5], K Hemanth[3] & Madhan Krishnan[6]

[1]Department of Anatomy, Sri Ramachandra Institute of Higher Education and Research, Chennai- 600 116, India; [2]Department of Anatomy, Saveetha Medical College, Saveetha institute of medical and technical sciences, Thandalam, Chennai- 602 105, India; [3]Department of Anatomy, All India Institute of Medical Sciences (AIIMS) Mangalagiri, Andhra Pradesh- 522 503, India; [4]Department of community & Family Medicine, All India Institute of Medical Sciences (AIIMS) Mangalagiri, Andhra Pradesh- 522 503, India; [5]Department of Anatomy, All India Institute of Medical Sciences (AIIMS) Madurai, Tamil Nadu – 625 008, India; [6]Research, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam-603103, Tamilnadu, India; *Corresponding Author

Authors contact:
PK Sankaran - E-mail: drpks@live.com
T Siva - E-mail: siva17187@gmail.com
Yuvaraj Maria Francis - E-mail: sujinalways@gmail.com
CP Kirthika - E-mail: cpkirthika@gmail.com
K Vinoth Kumar - E-mail: vinob4u@gmail.com
R Sarah - E-mail: drsarahsenthilkumar@gmail.com

ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 19(6): 739-744 (2023)

K Hemanth - E-mail: hemanth.kommuri@gmail.com
Madhan Krishnan - E-mail: kmadhan91@gmail.com

Abstract:
This study is to investigate the segmental involvement of lung in COVID-19 individuals using high resolution computed tomography (HRCT) and to correlate with serum inflammatory markers. Retrospective study done in 100 COVID 19 RTPCR positive patients with radiological images were collected and analyzed for lobar involvement, bronchopulmonary segments in 3D and CT Scores and it was compared with serum inflammatory markers (SIM). Variables like gender, involvement of segments and co-morbid conditions were summarized as frequency and percentage. Sub group analysis was done using independent t test, Chi-Square. Findings revealed that males were commonly affected than females with the mean age 57.47 ± 13.0. Lower lobes and posterior basal segment of both the lungs were affected with preponderance on the left side. Additionally, SIM were up regulated in the COVID-19 individuals. Serum IL-6, D-dimer and Ferritin showed upsurge in right lung and CRP and LDH elevated in left lung in the COVID-19 and it was statistically correlated with CT severity score. Chest HRCT and biochemical parameters individually and in combination help in identifying the COVID 19 severity among individuals for preventing or reducing the mortality rate in adults.

Key words: COVID 19, HRCT, ground glass opacity, IL-6, D-dimer, ferritin, CRP and LDH

Background:
COVID-19 is a very contagious respiratory disease which is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV -2) with the mean incubation period of 4 to 5 days and spreads via respiratory droplets. After being declared as a pandemic by World Health Organization (WHO) on march 11th 2020, death to case ratio in this disease is 2.8% as of October 2020 as per John Hopkins University statistics, though number varies by region to region and so far there is more than 6 million deaths recorded worldwide. The common symptoms of this disease include fever, sore throat, dry cough, fatigue, shortness of breath, loss of taste sensation or smell, while its complications include pneumonia, viral sepsis, acute respiratory distress syndrome, kidney failure and cytokine release syndrome indicating a multi-organ failure in body, thus emerging as a serious threat to mankind. There are no specific treatments available to treat this infection and mostly it is self-limiting in most of the patients except in some individuals it may undergo complications involving lower respiratory tract infection, myocarditis, thromboembolic events *etc.* Standard method of diagnosis is by Real Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) supported by thorax CT scan and chest X-ray **[1, 2 & 3]**. Other available laboratory investigations to assess the severity of this disease include serum biomarkers like C-reactive protein (CRP), Lactate dehydrogenase (LDH), D-Dimer, and ferritin. For better understanding of the disease severity, chest X-ray findings in COVID-19 are classified by British Society of Thoracic Imaging (BSTI) and Chest CT scan findings are classified as per CORADS classification **[4, 6].** The most common finding observed in the X-ray and Computed Tomography of patients infected with COVID-19 is the peripheral ground glass opacity and consolidation involving right lower lobe and left lower lobe **[7, 8]**. There were studies done to correlate the clinical profile severity with the radiological findings and they found to correlate, but there are no detailed studies on exploring the lobar and segmental involvement of specific bronchopulmonary segments and its comparison with biochemical parameters. Therefore this study was done to assess the segmental lung involvement in COVID-19 patients using CT scan and to correlate them with the biochemical parameters.

Materials and methods:

Ethical Approval:
This retrospective cross-sectional study was done from May 2021 to December 2021 academic year after getting institutional ethical committee approval (Approval No: AIIMS/MG/IEC/2020-21/77).

Study Design and Data Set:
This was a retrospective cross sectional study done in 100 COVID-19 RT-PCR positive patients with radiological findings at AIIMS Mangalagiri, An Institute of National Importance under Ministry of Health and Family Welfare and Sri Ramachandra Institute of Higher Education and Research, Porur, Chennai- The patients with incomplete biochemical reports, without radiological findings and RT-PCR negative CT scan suggestive of COVID 19 were excluded from the study. Radiological images and Biochemical parameters of patients were collected and analyzed for lobar involvement, bronchopulmonary segments in 3D and CT scores. If multiple CT are taken only the images with maximum severity is included in the study for analyzing involved lobes and segments, the prevalence of upper, middle and lower lobes and pattern of distribution whether axial or diffuse were noted. These radiological parameters were compared with complete blood count, C-Reactive protein, LDH, Ferritin, D-Dimer, Urea, Creatinine, Prothrombin time, and Interleukin-6 whichever available in the patient records. If multiple times the biochemical parameters were undertaken, then the data nearest to the CT images were noted. The continuous variables like age, C-reactive protein, LDH, Ferritin, D-Dimer, Urea, Creatinine, Prothrombin time, and Interleukin-6 were summarized as mean and standard deviation.

Statistical Analysis:
Categorical variables like gender, involvement of segments and co-morbid conditions were summarized as frequency and percentage. Sub group analysis was done using independent t-test, ANOVA or Chi-Square. P-value less than 0.05 were considered as statistically significant.

ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 19(6): 739-744 (2023)

Results:

There was significant difference noted between the right and left lungs, while based on the lobes there was only nominal difference noted in the COVID 19 cases. The most commonly affected segments were located primarily in the lower lobes than middle and upper lobes. Additionally, in this study left lower segments were chiefly affected than right, followed by upper and middle lobe segments and the findings were expressed in **Figure 1**. **Table 5 and Figure 2** depict the comparison between right and left lung involvement and inflammatory markers. There is no statistical significant difference found between the mean inflammatory markers and the lobes involvement. The posterior segment of the left lower (82.5%) was commonly involved in the study participants followed by superior segment of left lower lobe (81.4%). The left lower medial and anterior segments showed least involvement **Figure 3.**

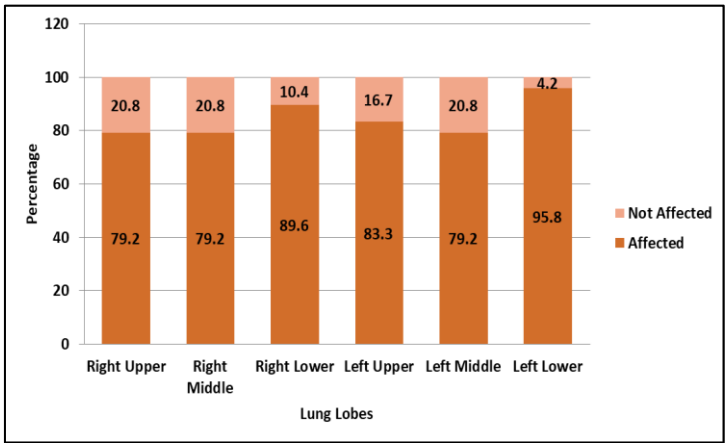

Figure 1: Involvement of lung segment (lobes) among the COVID-19 Patients

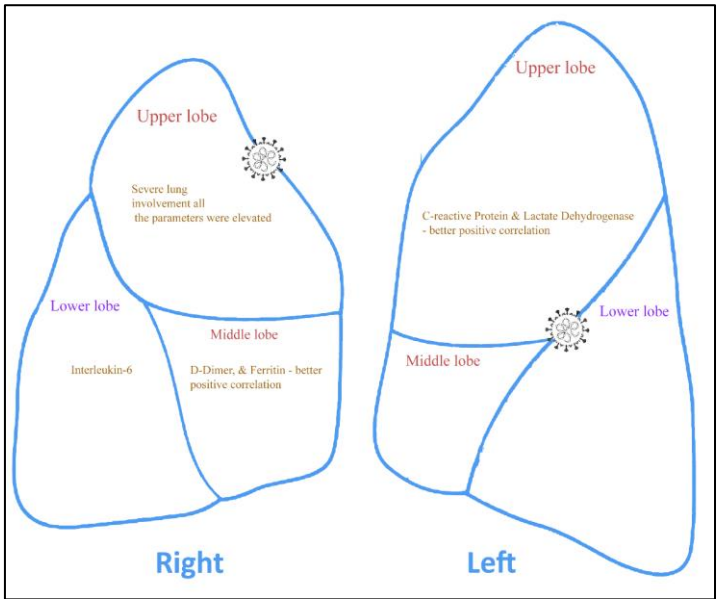

Figure 2: Shows the correlation of inflammatory markers with Lungs affected with COVID-19

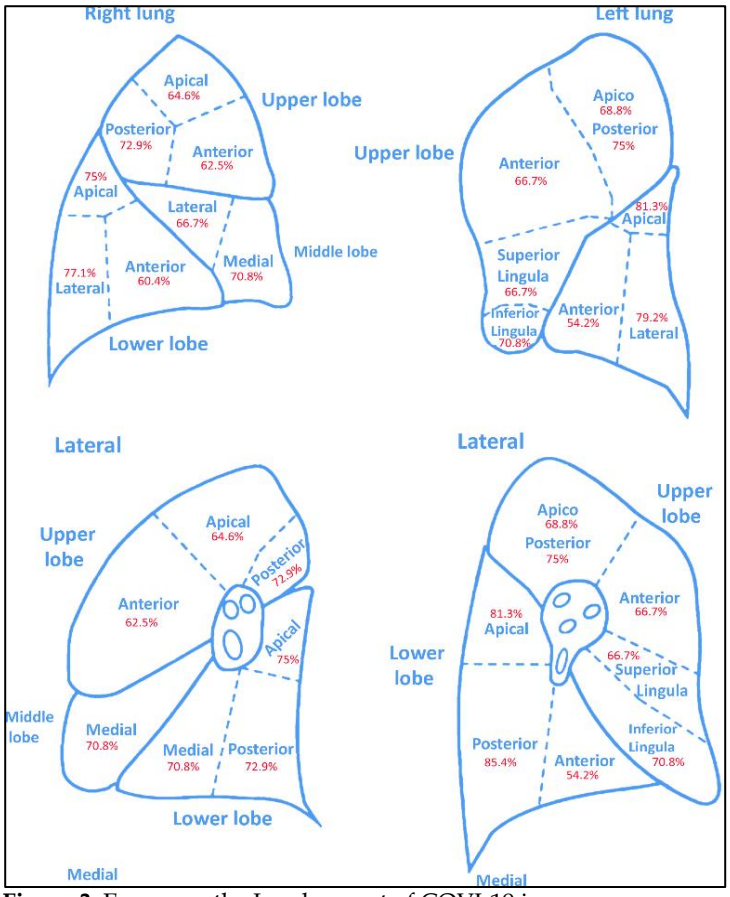

Figure 3: Expresses the Involvement of COVI-19 in Bronchopulmonary segments of Lung (Percentage)

Discussion:

HRCT imaging has an essential role in diagnosis especially in assessing the severity and monitoring of care in patients with COVID-19 pneumonia over chest X-ray. The peripheral ground glass opacity (GGO) followed by consolidation is the most common finding in COVID-19 pneumonia and in this study all the CT images showed peripheral GGO which is due to accumulation of exudative fluid in the alveolar space**.** The other findings like cavitation, bronchiectasis, bronchial wall thickening, crazy paving and sub-pleural bands are uncommon findings seen in COVID-19 pneumonia **[9].** In this study majority of patients were moderately affected with mean age of 57.47 ± 13.0 years with male preponderance. This was corroborated by the study conducted by Orlacchio *et al.* where the mean age was 57± 17 years **[10].** This was supported by the review conducted by Abate *et al* where it was observed that the prevalence of COVID-19 was higher among men than women **[11].** The males have higher chances of infection due to Y chromosomes have high viral load level, lower CD4+ T cells and IFN **[12].** The most commonly affected regions are the lower lobes of both the lungs with the major involvement with left lung. Similarly, the findings of this study correlated with Lomoro *et al.* observed in the COVID-19 in Italian population **[13].** However, much evidence suggests that the left lung is less likely to be affected

than the right lower lobe **[14].** Haseli *et al.* found that the more frequently, both the left lower lobe (85.7%) and the right lower lobe (87.3%) were affected **[7].** The reason for involvement in right side may be due to the fact that right main bronchus is wider, shorter and more vertical in direction and enters root an inch higher than left bronchus and this exposes the right lung point of early contact for pathogens than that of the left lung. Also, the differences in the perfusion gradient between apical and basilar portions, central and peripheral areas and the longer distance and slower blood flow in the lung periphery makes lower lobes of lungs more prone for infection. The slow blood flow and greater transit time increases the interaction between virus and peripheral lung, making it deposit in the pulmonary vascular bed **[15].** In this study the lower posterior basal segment is most commonly affected in both the lungs with 76% on right side and 74% on left side. Followed by commonly involved segments in both lungs are the posterior segment in the upper lobe, the superior basal segment, and the lateral basal segment. There is a good growing body of evidence in the literature which revealed similar segmental lung involvement, primarily affecting the lower lobe and peripheral opacity, which was consistent with the study done by Yang *et al.* observed that posterior basal segments of right and left lung were commonly involved in COVID-19 **[16].** Similarly, Khan *et al.* observed that the posterior basal regions of the lower lobes of both the right and left lungs were frequently affected, followed by the posterior segments of the upper lobe of the right lung **[17].** Zayed *et al.* observed that right lung with its lateral segment was commonly affected in COVID-19 patients **[18].** In individuals with COVID-19, several laboratory markers, such as lymphocyte count, CRP, LDH, D-Dimer, and fibrinogen, have been reported to change more often **[19].** Hence it is prudent to assess the inflammatory markers and correlate it with grades of severity of COVID which will further improvise the diagnostic patterns and enhance the treatment care among the patients. For all laboratory tests, a higher proportion of damaged lung is associated with a positive result of up regulation in the inflammatory markers. The strongest link is found between lymphocytopenia, increased D-Dimer levels, and increased lung damage on a chest CT scan **[20].** Similarly, we found a positive correlation that existed among the D-Dimer and IL-6 levels. Snijders *et al.* highlighted that D-dimer levels were significantly elevated in patients with severe community-acquired pneumonia, and D-dimer levels within the normal range indicated a low risk of complications **[20].** Recent studies documenting laboratory changes in patients with confirmed COVID-19 have found that elevated D-dimer levels may be associated with COVID-19 disease progression. The level of D-dimer in COVID-19 patients admitted to the ICU was found to be significantly higher **[21].** We found that the IL-6 levels involving right upper, middle and lower segment (0.7, 0.6 and 0.7 respectively) were strongly correlating with the severity of the COVID-19. Talwar *et al.* found that IL-6 levels can be correlated with computed tomography (CT) severity scores. Patients with elevated IL-6 levels, the majority (91.11%) had CT severity scores of >17, indicating severe COVID-19, 5% had CT severity scores of 8-17, and only 3.8% had CT severity less than 7, indicating patients with mild CT severity **[22].** Similarly, Coomes *et al.* suggested that pro-inflammatory cytokines like IL-6 contribute for the acute lung injury seen in COVID-19. Thus, blocking this IL-6 pathway could be the key to reduce COVID-19 lung injury **[23].** Positive correlation was also found in ferritin, LDH and CRP inflammatory markers. This was supported by the study conducted by Kaftan *et al* where they observed that CRP, LDH, ferritin, and D-Dimer levels increased significantly in those who tested COVID-19 positive with RT-PCR compared to those who tested negative **[24].** In our study, the D-dimer levels involving right upper and lower segment (0.5 and 0.5 respectively) were moderately correlating with the severity of the COVID-19. Similarly, Ferritin levels of both lungs were moderately correlated with the severity of the COVID 19 in this study. A study conducted by Ferrari *et al.* in Italy found that CRP and LDH levels were significantly higher in COVID-19 positive patients, suggesting that inflammatory tests could be used instead of RT-PCR to identify COVID-19 positive patients **[25].** According to the findings of the multivariate logistic regression analysis done by Huang *et al*, CRP, LDH, and ferritin are associated with an increased risk of COVID-19 infection **[26].** We found that in our patients, lower lobes on both sides were found to be more frequently involved. We also observed that the most predominant segment which was affected was left lower posterior segment (85.4%). This was corroborated by the study conducted by Haseli *et al.* where they had found that lower lobes on both sides were found to be more frequently involved **[7].**The posterior segment of the left lower lobe (82.5%) had the most involvement, followed by the superior segment of the right lower lobe (77.8%) and the lateral segment of the left lower lobe (76.2%). The least reported finding (17.5%) was medial segment involvement of the right middle lobe. In our study we, found that left lower medial and anterior segments were least affected. Similarly, Sultan *et al.* noticed that the lower lobe was more commonly involved (17.7%) than the middle lobe/lingula (8.3%) and upper lobe (3.1%) in the majority of cases (70.8%). Changes in the unilateral involvement were greater on the right (68.8%) than the left (31.2%) side **[27].** Also, Chung *et al* found that at the time of the initial CT, 14 of the 21 patients (67%) had involvement of the right upper lobe, 12 (57%) of the right middle lobe, 16 (76%) of the right lower lobe, 14 (67%) of the left upper lobe, and 14 (67%) of the left lower lobe **[28-29].**

Table1: Demographic details of study participants in severity wise:

Items	Sub-Group	Mild	Moderate	Severe	P-value
Age	Mean ± SD Years	53.5± 15.3	57.47±13.0	62.67±13.0	0.050
Gender	Male	16(32.0)	24(48.0)	10(20.0)	0.196
	Female	18(39.1)	14(30.4)	14(30.4)	
Total		34(35.4)	38(39.6)	24(25.0)	96(100)

P-value < 0.005 was considered as statistically significant

Majority of the study participants had moderate COVID-19 (39.6%) followed by mild (35.4%) and severe (25%). The mean age was mild, moderate and severe grades of COVID are 53.5± 15.3, 57.47±13.0 and 62.67±13.0 years respectively Table 1. The difference of the age of the participants among the severity of the COVID is statistically significant (p = 0.050).

The difference in the gender of the participants among the severity-wise of the COVID is not statistically significant (p= 0.196). About 48% of the males were moderately affected, while 40% of the females were affected mildly.

Table 2: Comparison of Severity of COVID with Lung lobes involvement among the COVID-19 patients

Severity	Right Upper	Right Middle	Right Lower	Left Upper	Left Middle	Left Lower
Mild	41.2%	52.9%	70.6%	64.7%	47.1%	88.2%
Moderate	100%	89.5%	100%	89.5%	95%	100%
Severe	100%	100%	100%	100%	100%	100%

The Table 2 depicts the percentage severity of COVID-19 with the various lobes of the lungs. In severe cases almost all the lobes were affected, while in the moderate cases lower segments of both the lungs were fully affected and in mild stage lungs were affected partially.

Table 3: Correlation of Inflammatory markers with CT Severity Score

Inflammatory markers	CRP	Ferritin	LDH	D- Dimer	IL-6	CT severity
CRP mg/dl	1	.279**	.264**	.251*	.211*	.390**
Ferritin ng/ml		1	0.146	.410**	.284**	.470**
LDH U/l			1	.368**	.394**	.441**
D-Dimer mg/dl				1	.691**	.643**
IL- 6 pg/dl					1	.776**
CT severity						1

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

CRP-C-reactive protein, LDH- Lactate dehydrogenase, IL-6- Interleukin-6

The Table 3 expresses the correlation of inflammatory markers with CT severity score. In the present study all the serum inflammatory markers were up regulated in the COVID-19 cases. Among the biomarkers, IL-6 showed strong positive correlation (0.77), whereas D-dimer, LDH and ferritin showed moderate correlation and CRP showed weak correlation in COVID-19 individuals.

Table 4: Correlation of Inflammatory markers with Lung Lobes wise CT score

Lung lobes	**CRP** mg/dl	**Ferritin** ng/ml	**LDH** U/l	**D-Dimer** mg/dl	**IL-6** pg/dl
Right Upper	.355**	.358**	.501**	.559**	.700**
Right Middle	.270**	.399**	.427**	.649**	.650**
Right Lower	.287**	.330**	.360**	.543**	.741**
Left Upper	.371**	.445**	.375**	.355**	.485**
Left Middle	.317**	.272**	.320**	.528**	.719**
Left Lower	.275**	.432**	.367**	.529**	.593**
Left Lung	.345**	.441**	.396**	.531**	.655**
Right Lung	.331**	.385**	.452**	.621**	.775**

Table 4 shows that the lobe wise correlation of inflammatory markers. IL-6, D-Dimer, Ferritin showed better positive correlation in patients with right lung involvement than left lung involvement, whereas CRP and LDH showed better positive correlation in patients with left lung involvement. Among the inflammatory markers IL-6 showed higher correlation with the involved lobes. Strong positive correlation was found between in IL-6 and involvement of right upper (0.700), right lower (0.741) and left middle (0.719) lobes.

Table 5: Comparison of Inflammatory markers with Lung involvement in COVID 19 individuals

	RU (n=76)		**RM (n=76)**		**RL (n=86)**		**p-value**	**LU (n=80)**		**LM (n=76)**		**LL (n=92)**		**p-value**
	Mean	SD	Mean	SD	Mean	SD		Mean	SD	Mean	SD	Mean	SD	
CRP mg/dl	9.3	8.0	8.3	8.3	8.4	8.0	0.932	8.8	8.1	8.8	8.1	8.0	7.9	0.965
Ferritin ng/ml	410.7	366.6	404.7	390.2	372.6	360.7	0.763	396.6	379.1	408.7	374.1	375.8	363.0	0.919
LDH U/l	397.4	258.7	385.6	256.8	379.1	249.1	0.937	392.3	252.5	394.1	260.7	370.4	243.2	0.819
D-Dimer mg/dl	1.3	1.0	1.3	1.0	1.2	1.0	0.982	1.2	1.0	1.3	1.0	1.1	1.0	0.910
IL-6 pg/dl	41.3	18.6	39.9	19.3	38.5	19.1	0.947	38.8	19.4	40.7	18.9	37.2	19.1	0.973
CT Severity	20.5	7.9	20.0	8.4	18.8	8.9	0.571	19.4	8.9	20.3	8.1	17.9	9.2	0.507

* = *p*-value < 0.005 was considered as statistically significant.

RU-Right upper lobe, RM-Right middle lobe, RL-Right lower lobe, LU- Left upper lobe, LM-Left middle lobe, LL-Left lower lobe.

Conclusion:

To conclude, before proceeding to definitive diagnosis by RT-PCR, a combination of routine laboratory biomarkers (CRP, LDH, Ferritin and D-Dimer) can be used to predict the diagnosis of COVID-19 with acceptable sensitivity and specificity. This aids in the early diagnosis of new cases, which can be extremely beneficial to the patient as well as the larger public health surveillance and response systems

Funding: Self-funding

Conflict of interest: Authors declare no competing interest and all authors have read and agreed to the published this manuscript.

References:

[1] COVID-19 Dashboard by the Center for Systems Science and Engineering at Johns Hopkins University (JHU)" 2020.

[2] Dey A *et al. Infection*. 2023 1-16. [PMID: 36906872]

[3] https://www.who.int/emergencies/diseases/novel-coronavirus-2019

[4] Hare S *et al. Clin Radiol*. 2020 **75**:399e404. [PMID: 32321645]

[5] https://www. england.nhs.uk/coronavirus/

[6] Zhang C *et al.International Journal of Antimicrobial Agents.* 2020 **55**: 105954. [PMID: 32234467]

[7] Haseli S *et al. Arch Acad Emerg Med.* 2020 **8**:e55. [PMID: 32440666]
[8] Rousan LA *et al. BMC Pulm Med.* 2020 **20**:245.
[9] Garg M *et al. Indian J Med Res.* 2021 **153**:86. [PMID: 33402610]
[10] Orlacchio A S *et al. Medicine (Baltimore).* 2021 **100**:e25310. [PMID: 33832103]
[11] Abate BB *et al. BMJ Open.*2020 **10**:e040129. [PMID 33028563]
[12] Conti P *et al. J Biol Regul Homeost Agents.* 2020 **34**: 339. [PMID 32253888]
[13] Lomoro P *et al. Eur J Radiol Open***.**2020 **7**:100231. [PMID: 32289051]
[14] Li K *et al. Invest Radiol.* 2020 **55**:327. [PMID: 32118615]
[15] Nemec *SF et al. AJR Am J Roentgenol.* 2013 **200**:712. [PMID: 23521438]
[16] Yang R *et al. Radiol Cardiothorac Imaging.* 2020 **2**:e200047. [PMID: 33778560]
[17] Khan MS *et al. Cureus.* 2021 **13**:e15849. [PMID: 34322339]
[18] Zayed NE *et al. Egypt J Bronchol.* 2021 **15**:13.
[19] Tang N *et al. J Thromb Haemost***.** 2020 **18**:844. [PMID: 32073213]
[20] Snijders D *et al. Eur J Intern Med.*2020 **23**:436. [PMID: 22726372]
[21] Huang C *et al. Lancet*. 2020 **395**:497–506. [PMID: 31986264]
[22] Talwar D *et al. Indian J Crit Care Med.* 2022 **26**:39. [PMID: 35110842]
[23] Coomes *EA et al. Rev Med Virol.* 2020 **30**:e2141. [PMID: 32845568]
[24] Kaftan A *et al. Acta Inform Med.* 2021 **29**:45. [PMID: 34012213]
[25] Ferrari D *et al. Clin Chem Lab Med.*2020 **58**: 1095. [PMID: 32301746]
[26] Huang I *et al. Ther Adv Respir Dis.* 2019 **14**: 1753466620937175. [PMID: 32615866]
[27] Sultan OM *et al. Curr Med Imaging.* 2021 **17**:775. [PMID: 33357198]
[28] Chung M *et al. Radiology.* 2020 **295**:202-207. [PMID: 32017661]
[29] Sathish T & Chandrasekaran ND. *J Diabetes*. 2021 **13**:521. [PMID: 33559395]

Reader comments from Clarivate Inc. Raffaella Bosurgi:

"Also, Chung et al found that at the time of the initial CT, 14 of the 21 patients (67%) had involvement of the right upper lobe, 12 (57) of the right middle lobe, 16 (76%) of the right lower lobe, 14 (67%) of the left upper lobe, and 14 (67%) of the left lower lobe [28-29]".

"Reference 29 above is not by Chung *et al.* "

Reply from authors

"Reference 28 above is by Chung *et al.* "as cited correctly including reference 28 [28-29] and reference 29 is an erratum so as to read as follows

"Also, Chung et al found that at the time of the initial CT, 14 of the 21 patients (67%) had involvement of the right upper lobe, 12 (57) of the right middle lobe, 16 (76%) of the right lower lobe, 14 (67%) of the left upper lobe, and 14 (67%) of the left lower lobe **[28]**".