Original Article

Diagnostic value of HRCT-Thorax for pandemic COVID-19 pneumonia in Pakistan

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Abstract

Background: In the scenario of, inadequate testing, the low sensitivity of the COVID-19-PCR test, limited availability of testing kits, and low detection rate, we aimed to investigate the usefulness of high-resolution computed tomography of chest (HRCT) for diagnosing pandemic coronavirus (COVID-19) pneumonia.

Objective: To determine the diagnostic efficacy of HRCT thorax in Covid-19 pandemic pneumonia.

Materials and Methods: This prospective, cross-sectional study was conducted in the Pulmonology–OPD of Gulab Devi Teaching Hospital, Lahore-Pakistan from 01-04-2020 to 15-07-2020.   121 patients with dry cough, fever, and dyspnea of sudden onset were included while patients with Bronchial Asthma, ILD, Tuberculosis, Bronchiectasis, COPD, and overt heart failure were excluded. Patients were investigated with chest x-ray, HRCT, COVID-PCR, and hematological tests. HRCT films were evaluated by a qualified and experienced radiologist. Findings were summarized, organized and statistical analysis was done by using SPSS-26 software to make an inference.

Results: Five patients were diagnosed as non-covid. Out of 116-diagnosed covid-19 patients, 38(32.75%) showed sub-pleural consolidation, 19(16.37%) consolidation with air-bronchogram, 29(25.0%) crazy paving sign, one pleural effusion (0.86%) and 18 cases (15.51%) displayed reticulations. 11cases(9.48%) had isolated ground glass appearances, while all categories showed it to variable extent. 65 patients (56.03%) were PCR-positive while 51(43.96) patients with positive-HRCT findings for COVID-19 pneumonia had negative nasopharyngeal-PCR. HRCT-Thorax revealed sensitivity: 97.41 %, specificity: 80%, PPV: 99.12%, NPV: 57.14%, and diagnostic accuracy of 96.69% for COVID-19 pneumonia.

Conclusion: HRCT-Thorax, having high sensitivity and adequate specificity, can provide foundations for evidence-based early diagnosis and quantification of coronavirus pneumonia. It can be tremendously useful for decision making in   PCR-negative patients and anticipating respiratory improvement or decline by serial scans.

Keywords: Corona Virus Pneumonia-HRCT Thorax-High sensitivity, Diagnostic value.

Introduction

The first case of coronavirus pneumonia was noticed in Wuhan, China in December 2019 and was later on recognized as coronavirus disease 2019 (COVID-19).[1] This epidemic spread worldwide like wildfire. WHO (World Health Organization) declared it as a Public Health Emergency of International Concern (PHEIC).[2] This disease is highly contagious and the number of cases multiplied rapidly over the globe. Current literature suggests that one infected patient may lead to more than two new patients.[3] Some-times, the disease is too drastic to be controlled and the outcome is a disaster only.

This disease has challenged almost all fields of medicine and has affected not only the public rather very senior health care providers and eminent figures from the society have been lost to this lethal disease. At the mid of July, we are having 255,769 confirmed cases and 5,386 mortalities in the country, indicating the load and damage caused by this fatal disorder. The presentation of COVID-19 disease ranges from mild to an extensive disease requiring mechanical ventilation. Early diagnosis is crucial for the good management and effective control to preclude further dissemination.

Usually patient presents with fever, dry cough, shortness of breath, and body aches and pains. The severity and acuteness of the symptoms, coupled with the propensity for an abrupt decline in respiratory function, necessitates the need to measure the magnitude of pulmonary involvement. Nasopharyngeal-PCR is the gold standard for diagnosis but its availability and sensitivity are quite low, around 60%. About 30-40% of cases are missed by this technique due to a high false-negative rate.[4] Furthermore, this test is not capable of calculating the magnitude and expected respiratory decline in patients. Chest X-ray PA view is limited in its ability to detect the early involvement of lung with COVID-19 infection.[5] In contrast, HRCT-Thorax has been reported as a good tool for evidence-based diagnosis in the current epidemic, providing immediate results with high sensitivity and adequate specificity for COVID-19 pneumonia and the extent of pulmonary disease.[6-7] HRCT-thorax can play a pivotal role by identifying the early phase lung infection and have been recommended as major evidence for clinical diagnosis in China.[8]

Current researchers have reported the sensitivity of HRCT for COVID-19 infection more than 90% as compared to PCR around 60-70%. According to WHO, HRCT can be very useful in determining the diagnosis, progression, and severity of the COVID-19 disease.[9-10] The use of HRCT in Pakistan is very limited due to profound fear, contagiousness & inadequate understanding and is tried only in selected cases.[11-12] The Chinese literature is rich in evidence, advocating the use of HRCT-thorax while the European, British and American radiological societies which were not recommending this modality in the beginning, are changing their statements about the use of HRCT.[13-15] Radiological Society of Pakistan has also suggested, the appropriate use of CT scan in selected patients as a tool to triage, in the background of increased incidence of COVID-19 symptomatic patients.[16]

Materials and Methods

This prospective study was conducted in Pulmonology-OPD of Gulab Devi Teaching Hospital, Lahore. (A 1500 bed-tertiary care hospital in the capital city of Punjab province). Ethical approval was obtained from the IRB of the hospital vide: No. Admin/GDEC/20/325. After informed consent, 121 OPD patients, from 1st April 2020 to 15 July 2020 with a presumptive clinical diagnosis of COVID-19 infection were included. History of dry cough, fever, and shortness of breath of sudden onset were the main complaints while patients with Bronchial Asthma, ILD, Tuberculosis, Bronchiectasis, COPD, and overt heart failure were excluded. All patients underwent routine hematological tests including white blood cell count, lymphocyte count, and hypersensitive C-reactive protein tests. The patients were subjected to an X-ray chest PA view, HRCT thorax, ECG, and echocardiography. The x-ray chest (CXR) & HRCT images were evaluated by a qualified radiologist with 20 years of experience at least. CXR was analyzed for haze and ill-defined consolidations with bilateral involvement. HRCT films were evaluated for radiological morphology and distribution patterns. ECG & Echocardiography explored cardiac status. All patients underwent the COVID-19 PCR-test by nasopharyngeal sample. Imaging findings, demographic and clinical data of the 121 patients were recorded on a preformed form. Sensitivity, specificity, and diagnostic accuracy were calculated by considering nasopharyngeal-PCR as a gold standard. Diagnostic yield was calculated on clinical, PCR, and HRCT grounds independently. Data was organized, summarized, tabulated and bio-statistical analysis was

done to conclude. For statistical analysis, SPSS-26 software was utilized. Quantitative data were described by $\pm$ SD and categorical variables were expressed by frequency (percentage). Fissure exact test was used for comparison and a *p-value < 0.05* was considered as significant.

Results

This study included 121 patients age 18 to 67 years. The mean age was 42.64 years $\pm$ SD 17.62. Male gender was noted in 67 patients while 54 patients were female, male to female ratio was 1.2. All patients had contact history from their familial clusters. Patients presented with typical respiratory complaints (Table-I). 56 cases (46.28%) were above the age of 50 years, obesity was found in 13 cases (10.74%), Cigarette smoking 39 (32.23%) and Diabetes Mellitus (DM) was found in 39 cases (32.23%). 79 patients (65.28%) had elevated levels of CRP with mean 8.7 $\pm$ SD 6.2 mg/dl. Only 65 patients (53.71%) were positive for COVID-19 PCR-Test. HRCT findings were consistent with COVID-19 in 113 patients while it was unremarkable for 03 patients.

Five patients, diagnosed as Non-COVID-19, consisted of ABPA (Allergic Broncho-pulmonary Aspergillosis) and Bacterial pneumonia two cases each and one case was diagnosed NSIP by correlation with clinicopathological data.

Table 1: Frequency of symptoms in 121 Patients

Nos	Clinical feature	No. of cases	Percentage
1.	High-grade fever	96	79.33
2.	Dry cough	67	55.37
3.	Shortness of breath	109	90.08
4.	Muscle pain and weakness	99	81.81
5.	Vague Chest pain	34	28.09
6.	Flu-like symptoms	21	17.35
7.	No symptoms	12	9.91

The radiological morphology and radiographic appearance are described by Figure 1 and Figure 2. Not even a single case of cavitation or pneumothorax was found in 116 cases. Disease distribution pattern is depicted in Table 2.

Table 2: Frequency of symptoms in 121 Patients

Nos.	Pattern of distribution	No. of cases	Percentage
1.	Unilateral	00	00
2.	Bilateral	121	100
3.	Predominant right lung	57	47.10
4.	Predominant left lung	38	31.40
5.	Symmetrical bilateral	26	21.48
6.	Upper part predominant	26	21.48
7.	Lower part predominant	95	78.51
8.	Central lesions	35	28.93
9.	Peripheral lesions	86	71.07
10.	Scattered lesions	11	9.09

n = 121
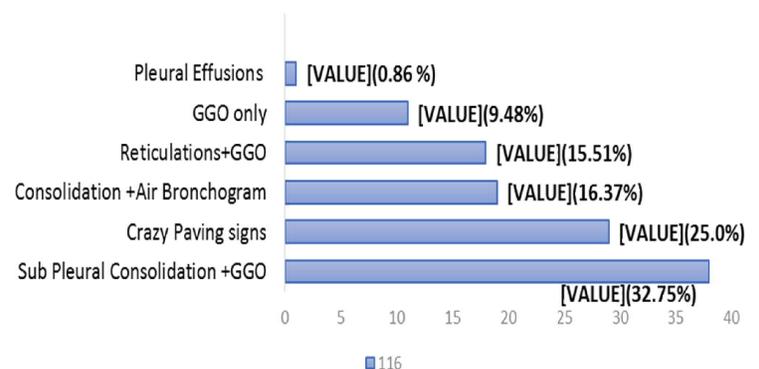
Figure 1: HRCT-morphology of 116 COVID-19 patients.
(GGO: Ground Glass Opacity)

Pleural Effusions [VALUE](0.86 %)
GGO only [VALUE](9.48%)
Reticulations+GGO [VALUE](15.51%)
Consolidation +Air Bronchogram [VALUE](16.37%)
Crazy Paving signs [VALUE](25.0%)
Sub Pleural Consolidation +GGO [VALUE](32.75%)
116

Figure 2: Common Radiological Morphologies in COVID-19 Pulmonary Infection
*A: Patchy ill-defined consolidations, B: Bilateral haze, C: Bilateral Reticulations, D: Diffused GGO (coronal scan), E: Multifocal GGO, F: Basal GGO, G: Focal GGO, H & I: multifocal sub-pleural consolidation, J: Crazy paving sign, K&L: Peripheral multi-focal consolidations + Reticulations, M&N: Peripheral consolidation, O: Consolidation with air-bronchogram, P: Reticulations with minimal GGO.

Calculations:

1. Total number of included patients= 121
2. Number of cases diagnosed as non-COVID = 05
3. Clinically proven cases of COVID-19= 116
4. A number of Covid-19 cases were indicated by CXR. = 86
5. Number of cases diagnosed by nasopharyngeal-PCR = 65
6. Number of cases diagnosed on HRCT findings = 113

The sensitivity of PCR = 65/116 X100 =56.03%
The sensitivity of CXR = 86/116 x 100 =74.13 %
The sensitivity of HRCT = 113/116 x 100 = 97.41%
Considering PCR as gold standard diagnostic test, TP=65, FN=51, TN=05, FP = 00
The calculated efficacy result is shown in Table 3. Similarly, if HRCT is considered a new diagnostic test for COVID-19 pneumonia, we have TP=113, FN = 03, TN = 04, FP=1, the calculated efficacy is depicted in Table 3.
TP: True positive, FP: False positive, TN: True Negative, FN: False Negative.

Table 3: Diagnostic Efficacy of PCR & HRCT for COVID-19 Pneumonia

Biostatistics for the efficacy of PCR		
Statistic	**Value**	**95% Confidence interval**
Sensitivity	56.03%	46.52% to 65.24%
Specificity	100.00%	47.82% to 100.00%
PPV	100.00%	
NPV	8.93%	7.39% to 10.75%
Diagnostic Accuracy	57.85%	48.54% to 66.77%
Biostatistics for the efficacy of HRCT-Thorax		
Sensitivity	97.41%	92.63% to 99.46%
Specificity	80.00%	28.36% to 99.49%
PPV	99.12%	95.14% to 99.85%
NPV	57.14%	28.66% to 81.57%
Diagnostic Accuracy	96.69%	91.75% to 99.09%

PPV: Positive predictive value and NPV: Negative predictive value.
The Fisher Exact Test statistic values = 0.0006 which is < 0.05.

Discussion

This study showed that the age range of 121 patients was from 18 to 67 years with a mean age of 42.64 years (± SD 17.62) which is comparable with the report of Qiongjie Hu and co-authors about Chinese population, with mean age 39.2 years $\pm$ SD 9.6.[17] We had 67 male (55.37%) and 54 female (44.62%) patients and male to female ratio was 1.2. The male gender preponderance is in agreement with the published studies of Badawi A, Ryoo SG and Channappanavar R, and co-authors.[18-19] This reduced susceptibility of females to COVID-19 infection could be due to the protection from X chromosome and sex hormones, providing innate and adaptive immunity.[20]

In this study, 46.28% of patients found above the age of 50 years, shows that this age can be a relative risk factor for the disease. Similarly, 39 cases (32.23%) with Cigarette smoking, 39 cases (32.23%) with Diabetes Mellitus (DM), and 13cases (10.74%) with Obesity were identified as co-morbidities (39+39+13=91) which is a significant number. Current literature has described the comorbidity induced increased risk of disease and mortality in viral pneumonia.[21-22]

Out of 116, only 65patients (56.03%) were diagnosed with COVID-19 infection by PCR while 51 cases (43.96%) were not identified by the gold standard test. It means, if the PCR test report is negative, nobody can claim with confidence that patient is COVID-19 free, because of poor sensitivity and a high false-negative rate of the test. The availability, virus specificity, quality of the testing kits, and under-testing due to resource limitations may be responsible factors for disease multiplication & dissemination in the community. But the good news here is that the virulence of virus in Pakistani population appears to be relatively weak because the number of patients with severe disease is low while we have abundant patients with mild to moderate, COVID-19 pneumonia.

It is also worth mentioning that not every patient requires mechanical ventilation on the first day of infection. It takes adequate time for transition from mild to severe COVID disease. The track of transition from mild to severe disease can be blocked by early diagnosis and prompt management. Because this virus is highly contagious a very much unpredictable in behavior, its control needs early diagnosis for timely isolation or quarantine. In these circumstances,

there is an urgent need for some alternative high sensitivity test, capable of capturing the disease untimely, for achieving good control in population.

On the other hand, 87/116 patients were identified by x-ray chest (CXR) with a sensitivity of 75.0%. Although diagnostic yield is better than that of the gold standard (PCR) 25.0% patients were missed, while abnormal findings were noted on HRCT images of the same patients which are in agreement with the report of Van der Bruggen-Bogaarts BA1, Van der Bruggen HM.[23]

The current study showed that HRCT thorax diagnosed viral pneumonia in 113 out of 116 cases with a sensitivity of 97.41%. Although it furnishes specific signs regarding COVID-19 pneumonia, it is not considered as specific as PCR, but according to the principles of differential diagnosis, we should always think about common issues. In the current on-going epidemic milieu, COVID-19 infection is the commonest issue, so HRCT can be utilized with confidence for its diagnosis.

This study exhibited that both lungs were affected in 100% cases, the predominant affected part was the lower zone in 78.51 % of patients. GGO was the earliest and the commonest (82.75% cases) sign on HRCT. Out of 96 cases, 11 cases (11.45%) showed isolated GGO scattered in lung fields, 38/96 cases (39.58%) were associated with consolidation, and 29/96 cases (30.20%) were part of the crazy paving sign. Modern literature shows that in COVID-19 pneumonia, type II alveolar epithelial cell injury, proteinaceous exudate, focal hyperplasia of pneumocytes and patchy inflammatory cellular infiltration, contribute to this GGO.[24-26]

Consolidation was noted in 57cases, 38/57 cases (66.67%) showed sub-pleural, multifocal consolidation, and 19/57 cases (33.33%) were associated with the air-bronchogram sign. All cases displayed GGO to a variable extent. These findings are very much comparable with the published report of Cheng Z, Lu Y and co-authors.[27]

When septal thickening occurs in addition to GGO, crazy paving appearance is manifested on HRCT which is found in moderate to severe COVID-19 Pneumonia. This study communicated 29 cases (25.0%) with this morphology while X. He, J. Zheng Dr., and co-workers have also described 25.0% of patients with the crazy paving sign.[28] These patients pose a practical challenge because of having a potential of transition into serious disease and anticipated mechanical ventilation, in the future. Many precious lives have been lost to this pattern.[29]

We found only one case of pleural effusion in this study which was bilateral and cardiogenic, secondary to coronary bypass surgery with superimposed COVID-19 infection. Otherwise, pleural effusion is not a common sign of this disease. But Huang *et al.* reported that pleural effusion may be noted in severe COVID-19 pneumonia.[30]

This study displayed the efficacy of HRCT-thorax as sensitivity: 97.41 %, specificity: 80%, PPV: 99.12 %, NPV: 57.14%, diagnostic accuracy: 96.69 % for pulmonary Covid-19 disease. The detailed efficacy of COVID-PCR is described in table-III. The *p-value* of 0.0006 is < 0.05 and is highly significant, showing a remarkable difference between the diagnostic potential of the two modalities. This value indicates that HRCT has excellent capabilities of diagnosing COVID-19 pulmonary disease in an epidemic.

According to the current literature, the sensitivity of PCR is as low as 60%.[31] False-negative results can create the risk of inadvertent contamination of non-COVID-19 patients, wards, and the community. Lower respiratory symptoms require tracheal aspirates or BAL (broncho-alveolar lavage) for maximum diagnostic yield but there is a very high risk of aerosolization & disease transmission to healthcare workers during these procedures.[32] While HRCT is free of such drawbacks and was widely used in China as a diagnostic tool for COVID-19 pulmonary disease. HRCT can give rapid and valuable information for triaging isolation, and treatment procedures. It also determines the extent of lung involvement and is of tremendous help in anticipating the risk of rapid respiratory decline. No doubt, performing HRCT for every respiratory patient is neither cost-effective nor long-term sustainable. But this modality can be used during an epidemic, especially where high sensitivity reliable laboratory testing tool for COVID-19 is not available.

In summary, HRCT features of COVID-19 pneumonia include ground-glass opacity, multi-focal, sub-pleural & basal consolidation, and crazy paving sign. Reticulation is found in patients with 2-3 weeks of history. We hope, the current study findings can facilitate early identification and good management of symptomatic and suspected COVID-19 pneumonia cases by adequate use of HRCT thorax, under adequate biosafety measures.

Limitations

The main limitation of our study is that it is a single-center study performed on limited sample size (121), so the study may not reflect a full range of radiological morphology and distribution pattern of COVID-19 pulmonary disease. To additionally elucidate, a study with larger sample size or preferably, a multi-center study can further explore the radiological behavior of the disease. The 15.51% cases with reticulations found in the current study need further interpretation by a longitudinal study whether these reticulations are going to resolve completely or going to develop into a new cluster of ILD in the community.

Conclusion

HRCT thorax, having excellent sensitivity and significant specificity for COVID-19 pulmonary infection, is a superb modality. It can play a positive role in early detection, quantification, and management of pulmonary coronavirus disease during a pandemic. If available, can be used with confidence for a re-evaluation of PCR-negative suspect for decision making about treatment and anticipating the risk of respiratory decline.

Acknowledgements

References

1.   Chen N, Zhou M, Dong X, Qu JM, Gong FY, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study;2020, Lancet, 395(10223):507-513.
2.   World Health Organization, 2020. Novel Coronavirus (2019-nCoV) Situation Report -1. Available at: https://www.who.int/emergencies/ diseases/novel-coronavirus-2019/situation-reports. Accessed June 5, 2020.
3.   Wu JT, Leung K, Leung GM, Now casting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study;2020, Lancet, 395(10225): 689-697.
4.   Kanne JP. Chest CT findings in 2019 novel coronavirus (2019-nCoV) infections from Wuhan, China: key points for the radiologist. Radiology. 2020 Feb 4:200241. DOI:10.1148/radiol.2020200241. [Epub ahead of print] Link, Google Scholar
5.   Wong HYF, Lam HYS, Fong AH, et al. Frequency and Distribution of Chest Radiographic Findings in Patients Positive

for   COVID-19.   Radiology.   2020;296(2):   E72-E78. DOI:10.1148/radiol.2020201160
6.   Harrison X. Bai*, Ben Hsieh*, Zeng Xiong, Kasey Halsey, Ji Whae Choi, Thi My Linh Tran, et al, Performance of radiologists in differentiating COVID19 from viral pneumonia on chest CT; 2020, RadiologyVol. 296, No. 2; 200823.
7.   Pan Y, Guan H. Imaging changes in patients with 2019-nCov.   Eur   Radiol.   2020;30(7):3612-3613. DOI:10.1007/s00330-020-06713-z
8.   Ming-Yen Ng, Elaine YP Lee, Jin Yang, Fangfang Yang, Xia Li, Hongxia Wang et al. Imaging profile of the COVID-19 infection: Radiologic findings and literature review. Radiology: Cardiothoracic   Imaging;   2020;2(1):e200034. DOI:10.1148/ryct.2020200034 Link, Google Scholar
9.   WHO. Coronavirus disease 2019 (COVID-19) situation report - 32. (accessed Feb 22, 2020). Available online: https://www.who.int/emergencies/diseases/novelcoronavirus-2019/situation-reports/
10. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases; Radiology Vol. 296, No. 2. 2020;200642.doi: 10.1148/radiol.2020200642
11. National Institute of Health Islamabad Pakistan [Internet]. National Institute of Health Islamabad [cited 2020 Apr 21]. Available from: https://www.nih.org.pk/, www.nih.org.pk › novel-coronavirus-2019-ncov.
12. Salehi S, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus disease 2019 (COVID-19): asystematic review of imaging findings in 919 patients. AJR Am J Roentgenol 2020:1-7. DOI: 10.2214/AJR.20.23034.
13. Rubin GD, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, et al. The role of chest imaging in patient management during the COVID-19 pandemic: a multinational consensus statement from the Fleischner Society. Chest 2020. DOI: 10.1016/j.chest.2020.04.003.
14. BSTI. Covid-19: BSTI /BSGAR decision tool for chest imaging in patients undergoing CT for acute surgical abdomen [Internet] The British Society of Thoracic Imaging 2020 [cited 2020 Apr 21].   Available   from: https://www.bsti.org.uk/media/resources/files/BSGAR_BSTI_joint_decision_tool_for_CT_v1_FINAL_25.03.20_CM7VQla.pdf
15. NHS   England.Minimum   operating   standards: Novel Coronavirus (COVID-19) Patient Pathway [Internet] V 2.2 2020 February   20   [cited   2020   Apr   21].   Available   from: https://www.england.nhs.uk/wp-content/uploads/2020/02/coronavirus-patient-pathway.pdf.
16. Aman Nawaz Khan, Najam Ud Din, Ummara Siddique Umer, COVID-19 National Pakistan Guidelines: Radiological Society of Pakistan (RSP) Recommendations Regarding Utilisation of Chest Imaging; May 2020, Volume 70, Issue 5
17. 17. Qiongjie Hu1, Hanxiong Guan1, Ziyan Sun, Lu Huang, Chong Chen, Tao Ai et al. Early CT features and temporal lung changes in COVID-19 pneumonia in Wuhan, China, FULL LENGTH   ARTICLE/   VOLUME128,   109017,   JULY   01, 2020.DOI:https://doi.org/10.1016/j.ejrad.2020.109017
18. Badawi A, Ryoo SG. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. Int J Infect Dis. 2016; 49:129–133. [PMC free article] [PubMed] [Google Scholar]
19. Channappanavar R, Fett C, Mack M, Ten Eyck PP, Meyerholz DK, Perlman S. Sex-based differences in susceptibility to severe acute respiratory syndrome coronavirus infection. J Immunol. 2017; 198:4046–4053. [PMC free article] [PubMed] [Google Scholar]
20. Jaillon S, Berthenet K, Garlanda C. Sexual dimorphism in innate immunity. Clin Rev Allergy Immunol. 2019;56:308–321. [PubMed] [Google Scholar]

21. Wang XF, Shi GC, Wan HY. Clinical features of three avian influenza H7N9 virus-infected patients in Shanghai. Clin Respir J. 2014; 8:410–416. [PMC free article] [PubMed] [Google Scholar]

22. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schønheyder HC, Sørensen HT. Diabetes, glycemic control, and risk of hospitalization with pneumonia: a population-based case-control study. Diabetes Care. 2008;31(8):1541-1545. DOI:10.2337/dc08-0138

23. van der Bruggen-Bogaarts BA1, van der Bruggen HM, van Waes PF, Lammers JW. A comparative study Chest. 1996 Mar; 109(3).

24. Koo HJ, Lim S, Choe J, Choi SH, Sung H, Do KH, Radiographic and CT Features of Viral Pneumonia; (2018). Radiographics, 38(3): 719-739.

25. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome; (2020), Lancet Respir Med, 2020 Feb 18. PII: S2213-2600(20)30076-X. DOI: 10.1016/S2213-2600(20)30076-X. [Epub ahead of print].

26. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao et al. Pulmonary Pathology of Early Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients with Lung Cancer; (2020). J Thorac Oncol, 2020 Feb 28. PII: S1556-0864(20)30132-5. DOI: 10.1016/j.jtho.2020.02.010. [Epub ahead of print]

27. Zenghui Cheng1, Yong Lu1, Qiqi Cao1, Le Qin1, Zilai Pan1 et al. Clinical features and chest CT manifestations of coronavirus disease 2019 (COVID-19) in a single-center study in Shanghai, China.; American Journal of Roentgenology. 2020; 215: 121-126. 10.2214/AJR.20.22959

28. He X, Zheng J, Ren J, Zheng G, Liu L. Chest high-resolution computed tomography imaging findings of coronavirus disease 2019 (Covid-19) pneumonia. Int J Radiat Res. 2020; 18 (2) :343-349, URL: http://ijrr.com/article-1-2926-en.html

29. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster; (2020) Lancet, 395(10223): 514-523.

30. Huang C, Wang Y, Li X. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 DOI: 10.1016/S0140-6736(20)30183-5. published online Jan 24. DOI

31. Yicheng Fang, Huangqi Zhang, Jicheng Xie, Minjie Lin, Lingjun Ying, Peipei Pang, et al. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. Radiology 2020; RadiologyVol. 296, No. 2, 200432.

32. Roman Woelfel, View ORCID ProfileVictor Max Corman, Wolfgang Guggemos, Michael Seilmaier, Sabine Zange, Marcel A MuellerWoelfel et al. Clinical presentation and virological assessment of hospitalized cases of coronavirus disease 2019 in a travel-associated transmission cluster.; medRxiv 2020.03.05.20030502; DOI: https://doi.org/10.1101/2020.03.05.20030502