ORIGINAL ARTICLE

Eastern Journal of Medicine

East J Med 28(4): 653-659, 2023
DOI: 10.5505/ejm.2023.69320

Anatomical and Stereological Examination of Infected Lung Area Volumes in CT Images of COVID-19 Positive Patients by Age and Gender

Necat Koyun[1*], Veysel Akyol[1], Sadi Elasan[2], Cemil Göya[3], Gizem Gizli[4]

[1]*Department of Anatomy, Faculty of Medicine, Van Yüzüncü Yıl University, Van, Turkey*
[2]*Department of Biostatistics, Faculty of Medicine, Van Yüzüncü Yıl University, Van, Turkey*
[3]*Department of Radiology, Faculty of Medicine, Van Yüzüncü Yıl University, Van, Turkey*
[4]*Department of Emergency, Faculty of Medicine, Van Yüzüncü Yıl University, Van, Turkey*

ABSTRACT

SARS-CoV-2 (COVID-19), a previously unidentified type of coronavirus in humans, causes respiratory tract infection. The infection is transmitted by droplets and leads to several serious diseases characterized by acute respiratory distress syndrome (ARDS). We aimed to examine the changes in the volumes of lung regions infected with COVID-19, a new and highly pathogenic strain, according to age and gender.

After obtaining ethical permission, 6700 patients who applied with positive COVID-19 test were selected between 01/03/2020 and 01/03/2021. Patients with asthma, bronchiectasis, obstructive pulmonary disease, pleurisy, allergic lung disease, lung tumor, and smokers were excluded from the study. After the excluded patients, computed tomography images of a total of 407 COVID-19-positive patients, 188 women, and 219 men, were obtained retrospectively. From the images taken, 2 to 10- decade groups of male and female patients between the ages of 10 and 100 were formed for the study. Images were skipped at certain intervals from the lung CT images for each patient in the groups. By applying stereological methods to the images, the total volume of the lung and the volumes of the infected lung regions were calculated.

In the analysis of the infected COVID-19 lung volume/total lung volume (%) ratio by gender and decades, there was a statistically significant difference according to gender in the 2nd, 6th, and 9th decades [(p=0.002), (p=0.001) and (p=0.032)] was observed. In the comparison of the infected COVID-19 lung volume/total lung volume ratio by decades, a statistically significant difference was observed in both genders (p=0.001).

Further studies and medical research are needed to better understand age- and sex-specific differences for effective intervention.

Keywords: COVID-19, lung, infected volume, stereology

Introduction

Coronaviruses are enveloped RNA viruses that can spread between humans, other mammals, and birds. It mainly causes respiratory-related symptoms. It is transmitted easily and quickly through respiratory droplets. Infection can cause a range of clinical conditions, from asymptomatic viral carriers/spreaders to severe diseases characterized by acute respiratory distress syndrome (ARDS) (1,2). Sometimes it also causes hepatic, neurological, and enteric symptoms. Six types of coronavirus were known to cause diseases in humans, up to SARS‐CoV2 (COVID-19), which was first seen in December 2019 and caused the pandemic (3). Among these species, HKU1, OC43, 229E, and NL63 cause mild symptoms similar to the common cold. Other SARS‐CoV (severe acute respiratory syndrome‐ coronavirus) and MERS‐CoV (Middle East respiratory syndrome‐coronavirus) coronaviruses cause more severe and potentially fatal illnesses (4). General histopathological findings such as diffuse alveolar damage in the lung, necrotizing bronchitis/bronchiolitis, and interstitial inflammation are observed in viral infections (5,6). Clinically, the symptoms of COVID-19 are nonspecific, fever, cough, shortness of breath, anosmia, and fatigue. But some patients are asymptomatic throughout the course of the disease. Nasopharyngeal and upper respiratory tract specimens are the first choice for diagnostic testing (7). Classical CT imaging of viral pneumonia also provides a highly accurate diagnosis of COVID-19. COVID-19 is visualized as multifocal

***Corresponding Author:** Necat Koyun, Department of Anatomy, Faculty of Medicine, Van Yüzüncü Yıl University, Van, Turkey
E-mail: veysel-akyol@hotmail.com
Necat Koyun: 0000-0002-6626-0302, **Veysel Akyol:** 0000-0002-6355-441X, **Sadi Elasan:** 0000-0002-3149-6462, **Cemil Göya:** 0000-0003-4792-8722, **Gizem Gizli:** 0000-0001-9141-6121
.**Received:** 10.07.2023, **Accepted:** 14.09.2023

bilateral peripheral ground glass among chest CT patterns. Lung segmental irregular consolidation areas are usually seen in the subpleural and lower lung lobes and posterior segments (8,9,10,11,12,13,14). Stereology is a method that reveals the properties of the three-dimensional structure by applying various mathematical operations on two-dimensional sections obtained from three-dimensional samples. It is used in medicine to calculate the volume or cell density of a region or structure. Moreover, it reduces human error by about 5%. Therefore, it is used in scientific studies (15,16).

Materials and Methods

Obtaining, Exclusion Criteria and Grouping of Data: Computerized tomography images were obtained from Van Yüzüncü Yıl University Faculty of Medicine, Dursun Odabaş Medical Center, Radiology Department retrospectively the electronic environment. Patients with a history of asthma, bronchiectasis, obstructive pulmonary disease, pleurisy, allergic lung diseases, lung tumors, and smokers, among the patients to whom the images belonged, were not included in the study. Then, a total of 407 patients, 188 women, and 219 men, were divided into two groups by gender. Each group obtained was divided into 2 to 10 decades, in the range of 10 to 100 years old.

Making Volume Measurements: Approximately, 10 images were obtained from each patient by skipping images from CT images at certain intervals. Total lung volumes were measured with a dotted area measurement ruler on the images obtained (Figure 1). The volume of infected lung regions was then measured in the same images (Figure 2).

Infected lung volume and total lung volumes of each patient in their groups were calculated. Then, the infected lung volume and total lung volumes were proportioned between them, and the average was calculated (Table 1).

Statistical Analysis: Data obtained from decades were subjected to statistical analysis (Table 2,3). Sample size of the retrospective study; Calculated using the G*Power statistical program (ver.3.1.9.7)*. According to this; in one-way ANOVA experimental design; By distributing the 407 samples according to the groups, the Power (power of the test) was found to be 0.99 when the Effect size was 0.5 and the Type-1 error (α) was 0.05. Kolmogorov-Smirnov ($n>50$) and Skewness-Kurtosis tests were used to check whether the volumes in the study were normally distributed, and parametric tests were applied because the measurements were normally distributed. Descriptive statistics for continuous variables in the study; expressed as mean, standard deviation, number (n) and percentage (%). "Independent T" and "one-way ANOVA" tests were used to compare volume measurements according to gender and decades. Statistical significance level was taken as $p<0.05$ in calculations and SPSS (IBM SPSS for Windows, ver.26) statistical package program was used for analysis.

Results

General descriptive statistics of the volumes of total lung and Covid-19 infected lung regions by gender and decades are given. Accordingly, 188 women and 219 men were included in the study (Table 2). The mean values of the total lung volume and the infected COVID-19 lung volumes in each decade and their standard mean were determined (Table 2).

In Table 3; the comparison results of the COVID-19 infected lung volume/Total lung volume (%) of measurements by gender and decades are given. According to these results; in the 2nd decade, a statistically significant difference was observed in the ratio of COVID-19 infected lung volume/total lung volume according to gender ($p=0.002$). In other words; The COVID-19 infected lung volume/total lung volume ratio varied by gender in the 2nd decade.

Similarly; in the 6th decade, a statistically significant difference was observed in the ratio of COVID-19 infected lung volume/total lung volume according to gender ($p=0.001$). According to this; the ratio of COVID-19 infected lung volume/total lung volume varied by sex in the 6th decade.

Again; in the 9th decade, a statistically significant difference was observed in the COVID-19 infected lung volume/total lung volume ratio according to gender ($p=0.032$). According to this; the COVID-19 infected lung volume/total lung volume ratio varied by gender in the 9th decade.

Despite that; in other decades, no statistically significant difference was observed in the ratio of COVID-19 infected lung volume/total lung volume by gender ($p>0.05$).

In addition, in table 3; the groups that make a difference in the comparison of the COVID-19 infected lung volume/total lung volume ratio by decades are indicated with lowercase letters. According to this; A statistically significant difference was observed in the ratio of COVID-19 infected lung volume/total lung volume in men compared to decades ($p=0.001$). In this context; while the 6th, 7th, 8th, 9th and 10th decades in men were found to be similar with the highest values, the 3rd and 5th decades were similar among themselves, and a difference

Table 1. Averages of the Ratios of Infected COVID-19 Lung Volume to Whole Lung Volume

Infected COVID-19 lung volume / Total lung volume (%)	Gender	
	Female (n:188)	Male (n:219)
	Mean	Mean
2.Decade	23,0	59,3
3.Decade	42,4	42,6
4.Decade	59,1	50,2
5.Decade	53,4	46,7
6.Decade	54,2	71,4
7.Decade	65,2	65,8
8.Decade	66,1	65,7
9.Decade	70,1	63,4
10.Decade	69,6	70,6

Table 2. General Descriptive Statistics of Total Lung Volume and Infected COVID-19 Lung Volumes By Gender and Decades

		Gender			
		Female (n:188)		Male (n:219)	
		Mean	SD	Mean	SD
Total lung volume (cm^3)	2.Decade	2196,6	667,1	1407,7	359,7
	3.Decade	2235,1	795,2	1875,8	577,6
	4.Decade	2407,2	2195,5	1463,3	528,9
	5.Decade	1994,6	453,9	1404,8	407,8
	6.Decade	1972,7	545,3	1718,5	367,9
	7.Decade	2309,1	405,4	1518,5	213,6
	8.Decade	2686,8	710,2	1244,2	248,6
	9.Decade	2315,8	624,6	1366,5	191,0
	10.Decade	2083,8	565,5	1270,4	210,7
Infected COVID-19 lung Volume (cm^3)	2.Decade	544,8	886,1	790,1	344,6
	3.Decade	923,2	572,1	707,9	304,6
	4.Decade	1413,0	1814,5	688,6	256,2
	5.Decade	1073,6	497,4	611,7	163,2
	6.Decade	1065,8	500,5	1207,6	305,0
	7.Decade	1495,7	468,6	996,7	268,3
	8.Decade	1760,7	561,1	817,4	203,8
	9.Decade	1618,9	526,9	860,8	170,1
	10.Decade	1455,5	558,1	881,4	151,2

SD: Standard Deviation

was observed in the 4^{th} decade. On the other hand, patients in the 2^{nd} decade were found to be different from all other decades by taking the lowest value.

Again; a statistically significant difference was observed in the ratio of COVID-19 infected lung volume/total lung volume in women compared to decades (p=0.001). According to this; In women, the 7^{th}, 8^{th}, 9^{th} and 10^{th} decades were found to be similar with the highest values, while the 3^{th}, 4^{th}, 5^{th} and 6^{th} decades were similar among themselves. On the other hand, patients in the 2^{th} decades were found to be different from all other decades by taking the lowest value. When the rates of total lung volume and infected COVID-19 lung volume in both sexes were examined, it was found that there was a similarity in the 3^{th}, 7^{th}, 8^{th}, and 10^{th} decades (Figure 3).

Table 3. Comparison of Infected COVID-19 Lung Volume/Total Lung Volume (%) Ratio by Gender and Decades

		Gender				
		Female (n:188)		Male (n:219)		*p.
		Mean	Std. Dev.	Mean	Std. Dev.	
Infected COVID-19 lung volume/Total lung Volume (%)	2.Decade	23,0 c	27,6	59,3 b	26,1	,002
	3.Decade	42,4 b	23,8	42,6 d	23,7	,981
	4.Decade	59,1 b	27,5	50,2 c	17,3	,218
	5.Decade	53,4 b	20,2	46,7 d	18,6	,235
	6.Decade	54,2 b	23,4	71,4 a	15,9	,001
	7.Decade	65,2 a	17,4	65,8 a	15,2	,867
	8.Decade	66,1 a	13,5	65,7 a	10,4	,924
	9.Decade	70,1 a	12,4	63,4 a	11,7	,032
	10.Decade	69,6 a	25,1	70,6 a	13,6	,923
	**p.	,001		,001		

* Significance levels according to Independent T-test results →
** Significance levels according to one-way ANOVA test results ↓
a,b,c: Shows the difference between groups (Duncan post-hoc test)

Discussion

In the diagnosis of COVID-19, testing is done on respiratory samples using reverse transcription polymerase chain reaction (RT-PCR) (17,18). Conditions such as sample collection, transport, and diagnostic kit performance vary the sensitivity of RT-PCR from 60% to 71% (19). In a study conducted on 1014 patients in Wuhan, China, the sensitivity of chest CT in the detection of COVID-19 pneumonia was 97%, the specificity was 25%, and the accuracy was 68% (20). CT scan showed superior sensitivity to RT-PCR in patients at the early stage of COVID-19 infection. Moreover, it was found that the RT-PCR test confirmed the false negative cases it gave (21,22).

Since our study is retrospective, the patients with a positive RT-PCR test and a corresponding CT image were obtained. This means that the detection of COVID-19 pneumonia has very high accuracy in terms of ground glass appearance in both RT-PCR tests and CT imaging of our study.

It has been observed that studies examining the volume, density, and mass changes caused by COVID-19 in the lung are limited (23). However, there are many segmental studies.

Many segmental studies have observed sub-segmental patchy consolidations of the lung in those infected with COVID-19 compared to controls. In addition, bilateral, multifocal, peripheral, and nonspecific distributions of ground glass opacity (GGO) of the lung have been shown to have a high frequency (24). Our research was conducted on the volumetric detection of COVID-19-infected shadows in the total lung, not the segmental lung. In volumetric calculations, areas of the lung with bilateral, multifocal, peripheral, and nonspecific distributions of ground glass opacity (GGO) were calculated.

Understanding the extent to which epidemics affect both sexes differently is an important step in assessing the primary and secondary effects on individuals and communities in a health emergency (25).

Females are known to have a stronger immune response to viral infections than males (26). In parallel, in a study of 44,672 confirmed cases from the onset of COVID-19 in China to February 11, 2020, 51.4% of patients were male (27). Our study, which was conducted on 407 patients, supported this study with the results of 46.19% female and 53.81% male patients.

In terms of the rate of spread, a study was conducted in cases with positive diagnoses from the onset of COVID-19 until April 28, 2020, using China's national COVID-19 surveillance database. In the study, a total of 82858 positive COVID-19 cases, of which 41580 were female and 41278 were male, were examined. The overall rate of spread was found to be higher in women than in men. However, female cases aged 10-39 years were found to be significantly lower than male cases. The rate of spread in female cases was found to be significant between the ages of 50-69 (28).

In the United States, the Maine Centers for Disease Control and Prevention (CDC) enrolled 614 contacts with symptom monitoring between May 14, 2020, and June 26, 2020. Of these individuals, it was observed that 190 people developed COVID-19 infection. It was reported that 52.1% of the patients were female and 47.9% were male (29). On the contrary, in our

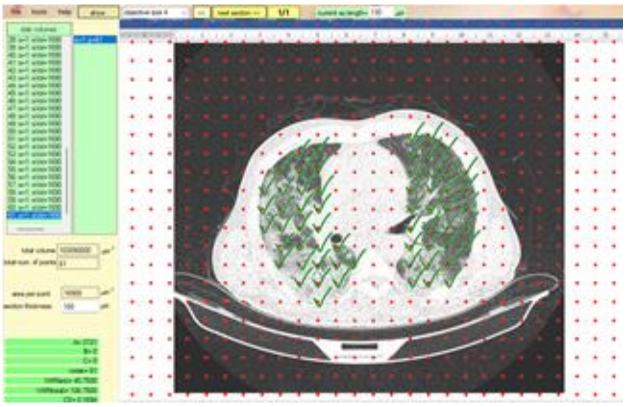

Fig. 1. Total Lung Volume Measurement With Dotted Measurement Ruler On The Lung CT Image

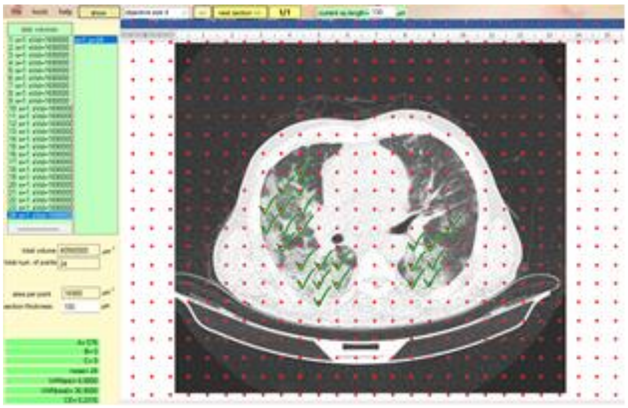

Fig. 2. Volume Measurement of Infected COVID-19 Lung With Dotted Measurement Ruler On The Lung CT Image

study, it was determined that 46.19% were female patients and 53.81% were male patients.

A study was conducted with data obtained using the System (TESSy) database developed at the European Center for Disease Prevention and Control (ECDC). When all of the positively diagnosed cases in the study were examined, it was found that the population aged 35-65 represented 50 percent of all cases. The age group of 75+ accounts for 20 percent of all cases. Men have been found to have a higher incidence of positive cases than women aged 55 to 80 (30).

The effect of Gender on COVID-19 infection and deaths in Germany was examined.

Considering the sex ratios of infection, it has been determined that the risk of infection is higher among women between the ages of 10 and 49. Men, on the other hand, have been found to be at higher risk of infection, usually from the age of 50 (except 70-79 years old) (31).

Data on COVID-19 cases by gender and age from ten European countries were analyzed. It has been observed that the number of women diagnosed with COVID-19 is higher than men. The highest rate of

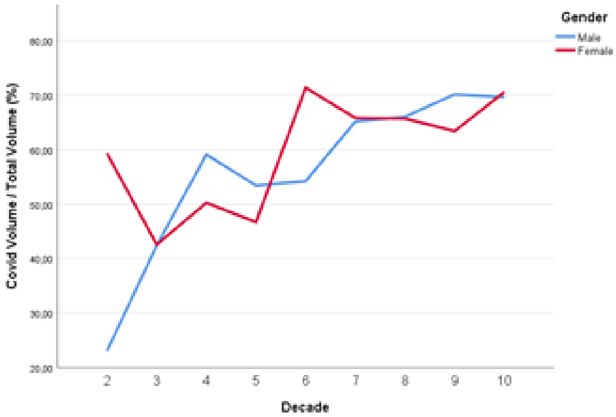

Fig. 3. Infected COVID-19 Lung Volume/Total Lung Volume By Decades

cases in women diagnosed with COVID-19 was observed at the age of 20-29 (3th decade), while the highest rate in men was observed at the age of 70-79 (8th decade). The age at which both sexes were close to each other in terms of ratio was found to be 60-69 (7th decade) (32). When these results were compared with our study, the highest incidence was seen in 50-59 (6th decade) women and 80-89 (9th decade) cases in men. However, similarly, the age at which the two sexes were closest to each other in terms of ratio was found to be 60-69 (7th decade).

We think that it would be beneficial to identify resistant age groups with studies based on other cities or countries, similar to our study. In addition, our study or studies similar to ours should be supported by microanatomical studies. Because it will be more beneficial for resistant age groups to take the lead in the fight against infection in future COVID-19 family infections.

Conflict of Interest: The authors declare that they have no competing interests

Informed Consent: The study was carried out in accordance with the ethical principles and the Helsinki Declaration. The study protocol was approved by the ethics committee of Van Yüzüncü Yıl University Non-invasive Clinical Research Ethics Committee (No:2021/04-10).

References

1. Wu F, Zhao S, Yu B et al. A new coronavirus associated with human respiratory disease in China. Nature 2020; 579: 265–269. https://doi.org/10.1038/s41586-020-2008-3
2. Zhu N, Zhang D, Wang W et al. A novel Coronavirus from patients with pneumonia in China, 2019. NEJM 2020; 382: 727-733. https://doi.org/10.1056/NEJMoa2001017
3. Su S, Wong G, Shi W et al. Epidemiology, genetic recombination, and pathogenesis of

coronaviruses. Trends Microbiol 2016; 24 (6): 490-502.

4. Zhong NS, Zheng BJ, Li YM et al. Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. Lancet 2003; 362: 1353-1358.
5. Strano AJ. Light microscopy of selected viral diseases (morphology of viral inclusion bodies). Pathol Annu. 1976; 11: 53-75. PMID: 188006
6. Burke AP, Aubry MC. Viral pneumonias. In: Burke AP, Aubry MC, Maleszewski JJ, Alexiev BA, Tavora FR editors. Practical Thoracic Pathology. Philadelphia, PA: Wolters Kluwer; 2016: 174-80.
7. Centers for Disease Control. Interim guidelines for collecting, handling, and testing clinical specimens from persons for coronavirus disease 2019 (COVID-19).
8. Ng MY, Lee EYP, Yang J et al. Imaging Profile of the COVID-19 Infection: Radiologic Findings and Literature Review. Radiol Cardiothorac Imaging 2020; 2 (1): e200034.
9. Bernheim A, Mei X, Huang M et al. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. Radiology 2020 Feb 20:200463 [Epub ahead of print].
10. Song F, Shi N, Shan F et al. Emerging 2019 Novel Coronavirus (2019-nCoV) Pneumonia. Radiology 2020; 295 (1): 210–217.
11. Bai HX, Hsieh B, Xiong Z et al. Performance of radiologists in differentiating COVID-19 from viral pneumonia on chest CT. Radiology 2020 Mar 10: 200823 [Epub ahead of print].
12. Pan F, Ye T, Sun P et al. Time Course of Lung Changes On Chest CT During Recovery From 2019 Novel Coronavirus (COVID-19) Pneumonia. Radiology 2020 Feb 13:200370 [Epub ahead of print].
13. Pan Y, Guan H, Zhou S et al. Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China. European Radiology 2020; 30: 3306–3309.
14. Chung M, Bernheim A, Mei X et al. CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). Radiology 2020; 295 (1): 202–207.
15. Weibel ER. Stereological Principles for Morphometry in Electron Microscopic Cytology. International Review of Cytology 1969; 26: 235-302.
16. Kaplan S, Canan S, Aslan H, Sahin B. A simple technique to measure the movements of the microscope stage along the x and y axea for stereological methods. J Microsc 2001; 203 (3): 321-325.
17. Centers for Disease Control and Prevention (CDC) (2020). 2019 Novel Coronavirus (2019-nCoV) Situation Summary [online]. Website https://stacks.cdc.gov/view/cdc/84806/cdc_84806_DS1.pdf [30 Ocak 2020].
18. Centers for Disease Control and Prevention (DCD) (2020). Real-Time RT-PCR Panel for Detection 2019-nCoV [online]. Website https://stacks.cdc.gov/view/cdc/84525 [1 Şubat 2020].
19. Caruso D, Zerunian M, Polici M et al. Chest CT Features of COVID-19 in Rome, Italy. Radiology 2020; 296: 79–85.
20. Ai T, Yang Z, Hou H et al. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology 2020; 296 (2): 32-40.
21. Fang Y, Zhang H, Xie J et al. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. Radiology. 2020; 296 (2): 115-117.
22. Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for Typical 2019-nCoV Pneumonia: Relationship to Negative RT-PCR Testing. Radiology. 2020; 296 (2): 41-45.
23. Feng Shi, Ying Wei, Liming Xia et al. Lung volume reduction and infection localization revealed in Big data CT imaging of COVID-19. International Journal of Infectious Diseases 2021; 102: 316-318.
24. Xu X, Yu C, Qu J et al. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2 European Journal of Nuclear Medicine and Molecular Imaging 2020; 47: 1275–1280.
25. Wenham C, Smith J, Morgan R. Gender and COVID-19 Working Group. COVID-19: the gendered impacts of the outbreak. Lancet 2020; 395: 846–848.
26. Bartz D, Chitnis T, Kaiser UB et al. Clinical Advances in Sex- and Gender-Informed Medicine to Improve the Health of All: A Review. JAMA Internal Medicine 2020; 180: 574–83.
27. The Novel Coronavirus Pneumonia Emergency R esponse Epidemiology Team. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China. Chinese Journal of Epidemiology 2020; 41 (02): 145-151.
28. Qian J, Zhao L, Ze Ye, Jun Li X, Li Liu Y. Age-dependent Gender Differences in COVID-19 in Mainland China: Comparative Study. Clinical Infectious Diseases 2020; 71 (9): 2488–2494.
29. Krueger A, Gunn JKL, Watson J et al. Characteristics and outcomes of contacts of COVID-19 patients monitored using an automated symptom monitoring tool – maine. Morbidity and Mortality Weekly Report 2020; 69 (31): 1026–1030.
30. Goujon A, Natale F, Ghio D, Conte A, Dijkstra L. Age, gender, and territory of COVID-19 infections and fatalities. Luxembourg: Publications Office of the European Union, 2020.

31. Doerre A, Doblhammer G. The influence of gender on COVID-19 infections and mortality in Germany: Insights from age- and gender-specific modeling of contact rates, infections, and deaths in the early phase of the pandemic. PLoS ONE 2022; 17 (5): e0268119.

32. Sobotka T, Brzozowska Z, Muttarak R, Zeman K, Lego Vd. This article is a preprint and has not been peer-reviewed [what does this mean?]. It reports new medical research that has yet to be evaluated and so should not be used to guide clinical practice. MedRxiv The preprınt serve for health scıences 2020.