

Assessment of Deaths with Co-morbidity and COVID-19 in Rural Northern India: A Retrospective Survey using Verbal Autopsy

Richa Panchgaur¹

¹Research Scholar, Department of Statistics, BHU, Email: richa.panchgaur17@bhu.ac.in

Ashish Kumar Verma²

²Research Scholar, Department of Statistics, BHU, Email: ashish.verma17@bhu.ac.in

Sangeeta Kansal³

³Professor, Institute of Medical Science, BHU, Email: sangeeta.kansal1@bhu.ac.in

Alok Kumar^{4*}

⁴Professor, Department of Statistics, BHU, Email: alokkumar@bhu.ac.in

***Corresponding Author:** Alok Kumar

*Professor, Department of Statistics, BHU, Email: alokkumar@bhu.ac.in

Abstract

Objectives: The mortality toll from the Covid 19 epidemic significantly increased, mostly among people who already had co-morbid conditions of some sort. The direct cause of mortality during the pandemic could not be determined since deaths in rural regions were not registered. Our study focuses to identify the cause of death among deceased persons and stratifying them by their comorbidity status.

Study Design: A cross-sectional study was done using the Verbal Autopsy (VA) tool. 143 households from community members where any death occurred were asked to fill out the VA form.

Methods: Stratification was done using the presence or absence of comorbidities, a number of comorbidities, and suspicious corona deaths. With 95% confidence intervals, the relative risk was used to calculate the mortality risk for corona suspected deaths in the years 2020 and 2021.

Results: The rural region of northern India was badly affected by the corona pandemic as the data witnessed that the suspected corona death was 6.63 times higher in people with tuberculosis (95% CI, 0.91-47.83), 2.09 times higher in people with high blood pressure (95% CI, 0.96-4.56) and 5.06 times higher in people with asthma (95% CI, 1.27-20.18). The proportion of men who died from comorbidity (76.1%) was higher than the proportion of women (69.2%).

Conclusion: Among suspected COVID-19 cases, deceased with any comorbidity yield poorer outcomes than those without. Corona symptoms associated with any comorbidity provide poorer outcomes in terms of causalities.

Keywords: COVID-19, Verbal Autopsy, Rural deaths, Co-morbidity, Multimorbidity

INTRODUCTION:

Overall, 458 000 deaths in India had been attributed to COVID-19, as of November 1, 2021¹. Due to incomplete certification of COVID deaths, incorrect attribution of COVID deaths to chronic diseases, and the fact that more than 70% of India's 10 million annual deaths occur in rural areas, frequently without access to medical care^{2,3}, it is widely believed that the reported COVID death totals for the country are underreported⁴. In determining the scope of the pandemic, one worry has been the possibility of underreporting of deaths, particularly in parts of the world with limited COVID-19 testing capability and less effective mechanisms for reporting deaths, as is the situation in many low- and middle-income nations (LMICs)⁵. As a result, it might be challenging to determine the exact causes of mortality in rural locations. To combat these types of situations, an

indirect technique known as Verbal Autopsy (VA) has been employed to determine the cause of death in those nations where the recording of vital events is very low and the percentage of persons who die at home without medical care is high^{6,7,8,9,10,11}.

Numerous variables contributed to mortality, including the deceased's age, the prevalence of comorbid conditions (such as hypertension, heart disease, paralysis, etc), access to medical care, and some degree of habitual smoking and drinking. Multimorbidity (defined as two or more long-term conditions) is highly associated with increasing age. Those persons who were admitted to the hospital with multimorbidity and corona were at higher risk of death¹².

Therefore, this study aims to investigate the mortality in two waves of the pandemic at its peaks and looks into the causes of death among the deceased along with their comorbidities.

METHODS

Rural Survey in Northern India

The rural regions of the Varanasi district of Uttar Pradesh were the location of the VA study. The field interviewers extracted information on the deceased's name, age at death, sex, place of death, date of death, and cause of death from records kept at the Village Administrative Offices in the study district and by asking around among village health nurses and village leaders in the study area. The study's goals were well explained to the informants, and their participation was wholly voluntary. A retrospective study was performed for COVID-19 mortality data from Varanasi city, a district in northern India, between March 1 and April 31, 2021. This study reported fatalities among adults over the age of 15 for the years 2020 and 2021. By removing accidental, suicide, and child fatalities, the overall death toll in these communities in both years was noted. The VA form was used to record the individual death data, and it was used to examine the common health issues among the deceased with complaints made between 10-15 days before death to detect comorbidities and corona suspicion.

Quality assurance and survey approaches

The VA is a methodical retrospective questioning of the family members on the circumstances, events, symptoms, indicators of sickness, and treatment details previous to death to ascertain the underlying cause of death and to categorize the general patterns of mortality. To determine the likely underlying cause of death in this investigation, the VA tool was utilized. To elicit further information, a list of symptoms and indicators was employed as a prompt or a probe. To increase accuracy, the VA report, which was written in the local language, detailed the progression of the signs and symptoms in chronological order, along with any previous occurrences of similar episodes, information about any treatments that were administered, and the name of the hospital or hospitals where the patient was admitted. To write the VA report exactly as the respondent described it, interviewers were given specific instructions. To determine the most likely underlying cause of death, one medical person independently reviewed each VA report.

Statistical Analysis

Statistical analysis was made using SPSS software version 25.0. In the lack of publicly available national data on COVID-19, there was no formal sample size estimate. Continuous variables were exhibited as Mean±S.D whereas categorical variables were given as counts and percentages. Estimates of the Crude Death Rate (CDR) for those older than 15 years, excluding suicides and accidental fatalities, were made for the years 2020 and 2021. The Crude Death Rate (CDR) for those elder than 15 years was calculated for the years 2020 and 2021 as the total number of deaths that occurred during the year, per 1,000 population. By using frequency distribution and relative risk

comparison, the distribution of multimorbidity for the years 2020 and 2021 was evaluated concerning the epidemiological parameters of the dead individual.

RESULTS

Immediate Cause of death in the years 2020 and 2021

A medical professional examined each VA report and then identified the immediate cause of death. Because COVID-19 testing was not conducted, the corona was suspected in deaths that were discovered with symptoms such as fever, exhaustion, breathing difficulties, runny nose, loss of taste and smell, dry cough, sore throat, body pain, vomiting, and diarrhea before 10-15 days of death. Of the 143 cases, 106(74.1%) reported deaths were due to COVID-19(suspected) followed by myocardial infarction 10(6.9%) and cancer 8(5.59%) and any other chronic illness 8(5.5%) (table 1). From the first quarter of 2020 to the fourth quarter of 2021, the second quarter of 2021 witnessed the highest percentage of fatalities with suspected COVID-19 and any type of comorbidity (figure 1). The highest percentage of deaths in the second quartile of 2021 were connected with deceased people who had any associated comorbidity (apart from paralysis), as shown in Figure 1. It is important to note here that the deceased may have more than one co-morbidity and it is included more than once in the line diagram shown (figure 1).

Table 1. Frequency distribution of deceased person according to the immediate cause of death

Immediate Cause of Death	Frequency	Percentage
Communicable disease		
Tuberculosis	1	0.70
Suspected Covid Deaths	106	74.13
Non-Communicable disease		
Myocardial infarction	10	6.99
Cancer	8	5.59
Stroke	4	2.80
Cardiac Arrest	3	2.10
Hypertensive disease	2	1.40
Maternal Death	1	0.70
Any other chronic illness	8	5.59

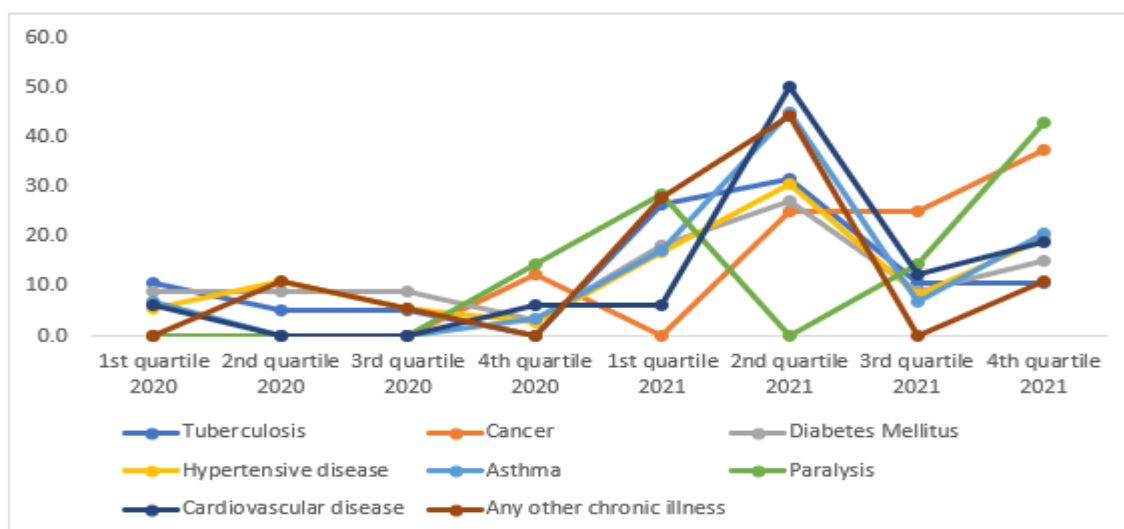


Figure 1. Line diagram showing the percentage of the suspected covid deaths and having other comorbid conditions from the first quartile of 2020 to the 4th quartile of 2021

Demographic and Clinical Traits of Deceased Persons with Suspected Covid-19 Outcomes

Among 106 suspected Covid-19 deceased persons, the mean age was 63.3 years (table 2). Deceased males with any comorbidity were 6.9% more than their counterparts (table 2). Deceased persons of older age (60+) had the highest percent (79.0%) of the presence of comorbidity (table 2). The most common symptom was difficulty in breathing (77.4%) among those deceased who had any comorbidity while this percent was 54.8% less in those who hadn't any comorbidity. Hospitalization was more than two times (68.4%) of those deceased persons who had no comorbidity (31.6%) (table 2).

Deceased Stratified by Number of Comorbidities and COVID-19 Outcomes

In addition, 45 (57.7%) individuals were found to have two or more comorbidities. Older deceased with COVID-19 symptoms were more likely to have two or more comorbidities (59.2%) than those who had no comorbidity (40.8%) (table 3). More than half of the deceased persons had one or two (or more than two) comorbidities with COVID-19 symptoms. Difficulty in breathing (83.3%) was a more likely symptom to occur among deceased persons having one or two (or more than 2) comorbidities.

Relative Risk for Multimorbidity among Suspected Covid Deaths

Table 4 shows that among co-morbidities of deceased persons, a higher frequency of Blood pressure (29.4%) followed by diabetes (28.0%), and asthma (21.7%) were observed. Furthermore, less than three-fourths of the death occurred at home which was 46.8% more than the death that occurred at the hospital (table 4). That indicates that sufficient care for the dead was absent at home, which contributed to their death by depriving them of amenities such as medications and proper care for their needs. Table 4 reveals that suspected corona death occurred in 95.0% of people with tuberculosis ($p < 0.05$), 93.5% of the people with asthma ($p < 0.01$), 85.7% of people with high blood pressure ($p < 0.05$), and 84.8% of those people who were chewing tobacco for the last five years ($p < 0.05$). This may indicate that among the fatalities, smokers and asthmatic patients were particularly at risk during the epidemic. The suspected corona death was 6.63 times higher in people with tuberculosis (95% CI, 0.91-47.83), 5.06 times higher in people with asthma (95% CI, 1.27-20.18), 2.18 times higher for those people who were smoking for last five years (95% CI, 0.81-5.85) and 1.94 times higher for those people who were chewing tobacco for last five years (95% CI, 0.95-3.96) (table 4).

Table 2. Comorbidities among Suspected Covid Deceased Persons

Variables	Total	No Co-morbidity	Presence of Co-morbidity
Age years	63.3±16.4	59.8±18.1	64.5±15.7
Age groups			
18-45	22 (20.8)	10(45.5)	12(54.5)
46-60	22 (20.8)	5(22.7)	17(77.3)
60+	62 (58.5)	13(21.0)	49(79.0)
Gender			
Male	67 (63.2)	16(23.9)	51(76.1)
Female	39 (36.8)	12(30.8)	27(69.2)
Smoking Status			
Never/Don't Know	81 (76.4)	23(28.4)	58(71.6)
Smoking for the last 5 years	25 (23.6)	5(20.0)	20(80.0)
Chewing Tobacco			
Never/Don't Know	67(63.2)	20(29.9)	47(70.1)
Chewing Tobacco for the last 5 years	39 (36.8)	8(20.5)	31(79.5)
Drinking Alcohol			
Never/Don't Know	86 (81.1)	22(25.6)	64(74.4)
Drinking for the last 5 years	20 (18.9)	6(30.0)	14(70.0)

Symptoms			
Fever	78 (73.6)	23(29.5)	55(70.5)
Tiredness	47 (44.3)	13(27.7)	34(72.3)
Running nose	46 (43.4)	12(26.1)	34(73.9)
Cough	66 (62.3)	20(30.3)	46(69.7)
Difficulty in breathing	84 (79.2)	19(22.6)	65(77.4)
Headache	26 (24.5)	6(23.1)	20(76.9)
Vomiting	14 (13.2)	6(42.9)	8(57.1)
Bodypain	52 (49.1)	15(28.8)	37(71.2)
Loss of taste & smell	37 (34.9)	14(37.8)	23(62.2)
Sore throat	47 (44.3)	13(27.7)	34(72.3)
Diarrhea	7 (6.6)	2(28.6)	5(71.4)
Hospitalization	30 (28.3)	11(36.7)	19(63.3)

Table 3. Deceased Persons Stratification by Number of Comorbidities among Suspected Covid Deaths

Variables	Total	1 Co-morbidity	≥2 co-morbidity
Age years	65.3±22.5	63.2±16.4	63.0±21.7
Age groups			
15-45	12 (15.4)	7(58.3)	5(41.7)
46-60	17 (21.8)	6(35.3)	11(64.7)
60+	49 (62.8)	20(40.8)	29(59.2)
Gender			
Male	51 (65.4)	22(43.1)	29(56.9)
Female	27 (34.6)	11(40.7)	16(59.3)
Smoking Status			
Never/Don't Know	58 (74.4)	29(50.0)	29(50.0)
Smoking for the last 5 years	20 (25.6)	4(20.0)	16(80.0)
Chewing Tobacco			
Never/Don't Know	47 (60.3)	23(48.9)	24(51.1)
Chewing Tobacco for the last 5 years	31 (39.7)	10(32.3)	21(67.7)
Drinking Alcohol			
Never/Don't Know	64 (82.1)	31(48.4)	33(51.6)
Drinking for the last 5 years	14 (17.9)	2(14.3)	12(26.7)
Symptoms			
Fever	55 (70.5)	22(40.0)	33(60.0)
Tiredness	34 (43.6)	13(38.2)	21(61.8)
Running nose	34 (43.6)	12(35.3)	22(64.7)
Cough	46 (59.0)	23(50.0)	23(50.0)
Difficulty in breathing	65 (83.3)	30(46.2)	35(53.8)
Headache	20 (25.6)	5(25.0)	15(75.0)
Vomitting	8 (10.3)	2(25.0)	6(75.0)
Bodypain	37 (47.4)	13(35.1)	24(64.9)
Loss of taste & smell	23 (29.5)	10(43.5)	13(56.6)
Sore throat	34 (43.6)	15(44.1)	19(55.9)
Diarrhea	5 (6.4)	1(20.0)	4(80.0)
Hospitalization	19 (24.4)	12(63.2)	7(36.8)

Table 4. Multimorbidity and Relative Risk among Suspected Corona Deaths

Variables	Total deaths	Suspected Corona deaths	RR (95% CI)
Age			
18-60 years	59 (41.3)	44(74.6)	1
>60 years	84 (58.7)	62(73.8)	0.98 (0.72-1.34)
Gender			
Male	81 (56.6)	67(82.7)	1
Female	62 (43.4)	39(62.9)	0.59** (0.42-0.84)
High Blood Pressure			
Yes	42 (29.4)	36(85.7)	2.09* (0.96-4.56)
No	101 (70.6)	70(69.3)	1
Cardiovascular disease			
Yes	21 (14.7)	16(76.2)	1.12 (0.44-2.84)
No	122 (85.3)	90(73.8)	1
Paralysis			
Yes	9 (6.3)	7(77.8)	1.22 (0.26-5.62)
No	134 (93.7)	99(73.9)	1
Diabetes			
Yes	40 (28.0)	33(82.5)	1.64 (0.80-3.40)
No	103 (72.0)	73(70.9)	1
Tuberculosis			
Yes	20 (14.0)	19(95.0)	6.63* (0.91-47.83)
No	123 (86.0)	87(70.7)	1
Cancer			
Yes	12 (8.4)	8(66.7)	0.7 (0.22-2.18)
No	131 (91.6)	98(74.8)	1
Asthma			
Yes	31 (21.7)	29(93.5)	5.06** (1.27-20.18)
No	112 (78.3)	77(68.8)	1
Any other chronic disease			
Yes	28 (19.6)	18(64.3)	0.62 (0.32-1.23)
No	115 (80.4)	88(76.5)	1
Taking medicine regularly			
Yes	91 (63.6)	69(75.8)	1.09 (0.81-1.47)
No	52 (36.4)	37(71.2)	1
Smoking for the last 5 years			
Yes	29 (20.3)	25(86.2)	2.18 (0.81-5.85)
No	114 (79.7)	81(71.1)	1
Chewing tobacco for the last 5 years			
Yes	46 (32.2)	39(84.8)	1.94* (0.95-3.96)
No	97 (67.8)	67(69.1)	1
Drinking for the last 5 years			
Yes	23 (16.1)	20(87.0)	2.33 (0.73-7.38)
No	120 (83.9)	86(71.7)	1
Hospitalization			
No	105 (73.4)	76(72.4)	1
Yes	38 (26.6)	30(78.9)	1.3 (0.66-2.59)
Presence of comorbidity			
Yes	41 (28.7)	28(68.3)	0.75 (0.44-1.30)
No	102 (71.3)	78(76.5)	1

**p<0.01, *p<0.05

DISCUSSION:

The present study shows the data on the cause of death and the presence of comorbidities in dead individuals with COVID-19. More than half of the deceased persons (56.6%) were male than their counterparts. This could be because men engage in more outside activities¹². Other studies have also reported similar findings^{13,14,15}.

The most common symptom observed before 10-15 days of death in a deceased person was breathlessness (58.7%) followed by fever (55.9%) and cough (46.2%). These results concurred with those of earlier research that identified breathing difficulties as the most common symptom^{12,16,17}. Comorbidities were found to enhance the risk of Corona infection¹⁸. Moreover, elderly people who had a long-term, serious sickness or who resided in nursing homes were more likely to get corona infections¹⁸. Furthermore, the elderly with chronic health conditions like diabetes, cardiovascular disease, or lung disease had not only a risk of developing severe illness but also a higher risk of dying from such illnesses¹⁹.

Preliminary findings on 4226 COVID-19 patients in the USA showed increased mortality rates in persons over 85, particularly in those with chronic diseases²⁰. Our study shows that the older population (greater than 60 years age group) shared 61.8 percent of deceased individuals who had one or more comorbidities during their lifespan. According to a prior study, comorbidities were strongly linked to a higher risk of death in men over the age of 50²¹. The risk of contracting COVID-19 infection is higher in people with underlying uncontrolled medical problems such as diabetes, hypertension, lung, liver, and kidney disease, cancer patients receiving chemotherapy, smokers, transplant recipients, and people using steroids persistently¹⁸. The severity of corona disease development is correlated with several comorbidities. Cardiovascular comorbid problems have been linked to several of corona's worse results²². In our study, cardiovascular disease and symptoms of corona affected more than three-quarters of the dead individuals. However, this might be a direct effect of the cardiovascular problem itself or linked to additional comorbidities in addition to a cardiovascular condition²². Our findings showed that individuals with hypertension, tuberculosis, and asthma were more prone to die from COVID-19. According to the results of the previous study, smoking contributes to the progression of illness and has negative effects on COVID-19²³. Our findings discovered comparable characteristics to the earlier study among individuals who had died and had smoked during the preceding five years or more, with a larger percentage (86.2) than those who had not. Similar to smoking, chewing tobacco, and drinking indicated higher percentages of those who were suspected of having corona than those who weren't.

CONCLUSION

The cause of suspected corona deaths was associated with the highest number of fatalities. The death rate for people who had any comorbidities was horrendously high during the second wave of the epidemic. More people died with any comorbidity with corona symptoms than without comorbidities. There was a greater percentage of comorbidity-related deaths among those who died from corona symptoms. To identify those people who have any comorbidity and then provide them with the appropriate care, a risk stratification system is required to combat this sort of pandemic in the future.

DISCLOSURES AND CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The datasets analysed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENTS

Not required.

ETHICS APPROVAL

Participants gave informed consent to participate in the study before taking part.

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AUTHOR CONTRIBUTIONS

AK conceived the study. SK reviewed the VA forms and concluded the cause of death for deceased persons. AKV and RP formed data collection, and data feeding and also conducted the data analysis, and all authors contributed to data interpretation and manuscript writing.

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SUPPLEMENTARY MATERIALS

There are no supplementary materials.

REFERENCES:

1. Lewnard, J. A., Mahmud, A., Narayan, T., Wahl, B., Selvavinayagam, T. S., & Laxminarayan, R. (2022). All-cause mortality during the COVID-19 pandemic in Chennai, India: an observational study. *The Lancet Infectious Diseases*, 22(4), 463-472.
2. Menon, G. R., Singh, L., Sharma, P., Yadav, P., Sharma, S., Kalaskar, S., ... & Jha, P. (2019). National burden estimates of healthy life lost in India, 2017: an analysis using direct mortality data and indirect disability data. *The Lancet Global Health*, 7(12), e1675-e1684.
3. Vital Statistics of India based on the Civil Registration System 2019. New Delhi, India: Office of the Registrar General, 2021 (https://censusindia.gov.in/2011-Common/CRS_2019/CRS_2019_report.pdf)
4. Chatterjee, P. (2020). Is India missing COVID-19 deaths?. *The Lancet*, 396(10252), 657.
5. Mishra D, Baker P, Buckley E, Maida J, Chalkidou K. We must stop flying blind: building on existing systems in low- and middle-income countries to improve the COVID-19 response. Center For Global Development. accessed September 28, 2021. <https://www.cgdev.org/blog/we-must-stop-flying-blind-building-existing-systems-low-and-middle-income-countries-improve>
6. Lulu K, Berhena Y. 2005. The use of simplified verbal autopsy in identifying cause of adult death in predominantly rural population in Ethiopia. *BMC Public Health* 5: 58.
7. Setel PW, Whiting DR, Hemed Y et al. 2006. Validity of verbal autopsy procedures for determining cause of death in Tanzania. *Tropical Medicine and International Health* 11: 681–96.
8. Dongre AR, Singh A, Deshmukh PR et al. 2008. A community based cross sectional study on feasibility of lay interviewers in ascertaining causes of adult deaths by using verbal autopsy in rural Wardha. *Online Journal of Health and Allied Sciences* 7: 1–12
9. Fottrell E, Byass P. 2010. Verbal autopsy: methods in transition. *Epidemiologic Reviews* 32: 38–55.
10. Morris SK, Bassani DG, Kumar R et al. 2010. Factors associated with physician agreement on verbal autopsy of over 27000 childhood deaths in India. *PLoS ONE* 5: 9583.

11. Abbas SM, Alam AY, Majid A. 2011. To determine the probable causes of death in an urban slum community of Pakistan among adults 18 years and above by verbal autopsy. *Journal of Pakistan Medical Association* 61: 235.
12. Agrawal, U., Azcoaga-Lorenzo, A., Fagbamigbe, A. F., Vasileiou, E., Henery, P., Simpson, C. R., ... & McCowan, C. (2022). Association between multimorbidity and mortality in a cohort of patients admitted to hospital with COVID-19 in Scotland. *Journal of the Royal Society of Medicine*, 115(1), 22-30.
13. Kaushal, S. K., Kumar, N., Patel, A. K., & Yadav, M. (2021). Epidemiologic Variables Affecting Deaths among COVID-19 Patients in Second Wave of Pandemic in Bundelkhand Region of Uttar Pradesh: A Cross-sectional Study. *International Journal of Medicine and Public Health*, 11(4).
14. Gupta, N., Agrawal, S., Ish, P., Mishra, S., Gaind, R., Usha, G., ... & Safdarjung Hospital COVID 2019 working group. (2020). Clinical and epidemiologic profile of the initial COVID-19 patients at a tertiary care centre in India. *Monaldi archives for chest disease*, 90(1).
15. Mazumder, A., Arora, M., Bharadiya, V., Berry, P., Agarwal, M., Behera, P., ... & Parameswaran, G. G. (2020). SARS-CoV-2 epidemic in India: epidemiological features and in silico analysis of the effect of interventions. *F1000Research*, 9.
16. Wang, H., Paulson, K. R., Pease, S. A., Watson, S., Comfort, H., Zheng, P., ... & Murray, C. J. (2022). Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020–21. *The Lancet*, 399(10334), 1513-1536.
17. Zhou, F. (2020). Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID19 in Wuhan, China: a retrospective cohort study. *Lancet*, 395(10229), 1054-62.
18. CDC. Coronavirus (COVID-19): symptoms of coronavirus. Centers for Disease Control and Prevention. 2020. [Accessed April 18, 2020, <https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html>].
19. BCCDC. COVID-19 vulnerable populations. British Columbia Centre for Disease Control. 2020. [Accessed April 18, 2020, <http://www.bccdc.ca/health-info/diseases-conditions/covid-19/vulnerable-populations>].
20. CDC COVID-19 Response Team (2020) Severe outcomes among patients with coronavirus disease 2019 (COVID-19) – United States. *Morbidity and Mortality Weekly Report* 69, 343–346.
21. Biswas, M., Rahaman, S., Biswas, T. K., Haque, Z., & Ibrahim, B. (2021). Association of sex, age, and comorbidities with mortality in COVID-19 patients: a systematic review and meta-analysis. *Intervirology*, 64(1), 36-47.
22. Guan, W. J., Liang, W. H., He, J. X., & Zhong, N. S. (2020). Cardiovascular comorbidity and its impact on patients with COVID-19. *European Respiratory Journal*, 55(6).
23. Lacedonia, D., Scioscia, G., Santomasi, C., Fuso, P., Carpagnano, G. E., Portacci, A., ... & Resta, O. (2021). Impact of smoking, COPD and comorbidities on the mortality of COVID-19 patients. *Scientific Reports*, 11(1), 1-9.