Original Article

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Public Health Section

Diurnal Variation in the Mortality of Patients with COVID-19 Pneumonia: A Retrospective Study

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ABSTRACT

Introduction: Coronavirus Disease 2019 (COVID-19), the new contagious novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), pandemic in 2020-21 has had a devastating impact on human race. The most common cause of death among hospitalised patient was COVID-19 pneumonia or lung injury. Various studies have shown diurnal variation in human mortality due to all causes with or without intervention.

Aim: To identify existence of diurnal variations for mortality among the hospitalised patients with COVID-19 pneumonia.

Materials and Methods: This hospital-record based, retrospective study was conducted in a tertiary referral centre of north-east India (Assam Medical College, Dibrugarh, Assam, India) which was a dedicated COVID-19 hospital during the pandemic. The study was conducted from September 2021 to December 2021 and the data was collected and recorded from the Cadaver slips issued to families of patient dying of COVID-19 pneumonia during the period January 2021 to August 2021. The data were generated by plotting the number of deaths of COVID-19 cases for each two hour interval as a percent of the mean number of deaths per two-hour interval and as a percentage of cumulative deaths per two-hour interval on a 24 hour scale. The deaths were sub grouped according to gender, age, and reported co-morbid causes of death along with pneumonia. Comparisons of data i.e., mean deaths/2 hour interval (mean±SD) were performed by one-way Analysis of Variance (ANOVA), followed by Bartlett's test for equal variances. The p-value <0.05 was considered as statistically significant.

Results: Total 743 deaths, with 537 males and 206 females were included in the study. Mean age of the deaths was 56.01 years. There was rise of deaths during 4 PM-6 PM (16:00-18:00) interval for all deaths due to COVID-19 pneumonia. The increase in deaths during this period mainly accounted for males equal or above 65 years and females below age 65 years. However, the deaths of females equal or above the age of 65 years did not show significant diurnal variation. Only 26.51% (n=197) of pneumonia deaths were without co-morbidity.

Conclusion: There exists a diurnal variation in mortality among COVID-19 pneumonia patients with evening rise of deaths. Diurnal variation is significantly more among males rather than females above 65 years.

Keywords: Circadian rhythm, Coronavirus disease 2019, Severe acute respiratory syndrome coronavirus 2, Time of death

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) pandemic in 2020-21 had a devastating impact on human race resulting in large numbers of death in a very short period of time. The most common cause of death among hospitalised patient was COVID-19 pneumonia [1,2]. Age ≥65 years, existing co-morbidities, increased blood pressure, increased White Blood Cell (WBC) count, elevation in levels of cardiac troponin, myoglobin, creatinine, D dimer and IL-2R, IL-6 were associated with death in COVID-19 pneumonia, whereas Partial pressure of O_2 (PaO_2) ≥80 mmHg was the only protective factor [3-5].

Mortality and morbidity due to cardiovascular events, hypertensive diseases and asthma show an increase in morning hours [6,7]. Human mortality due to all causes show diurnal variation with maximum death during 6 AM-8 AM interval, one of the probable reason being circadian rhythm [8]. Circadian rhythms have been observed in several human organs [9]. In healthy individuals increase in airway resistance, and decrease in peak respiratory flow, Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF) and FEV1/FVC values are seen in morning hours, Adrenocorticotropic Hormone (ACTH) secretion and levels of cytokines and cytokine receptors also show diurnal variation. These variations have profound impact on disease processes [10-13].

Chronic Obstructive Airways Diseases (COPD) and asthma which involves lung, show severity during morning hours due to exacerbation of the physiological variations in various lung parameters [14] and since the major organ involved in COVID-19 pneumonia was lung, it was imperative to expect that the diurnal variation of lung parameters must have affected mortality due to the disease. Thus, in the present study, we sought to identify existence of diurnal variations for mortality among the hospitalised patients with COVID-19 pneumonia.

MATERIALS AND METHODS

This hospital-record based, retrospective study was conducted in a tertiary referral centre of north-east India (Assam Medical College, Dibrugarh, Assam, India) which was a dedicated COVID-19 hospital during the pandemic. The study was conducted from September 2021 to December 2021 and the data was collected and recorded from the Cadaver slips issued to families of patient dying of COVID-19 pneumonia during the period January 2021 to August 2021.

Ethical clearance was taken from the Institutional Ethics Committee (vide letter no EC 8393 dated 22nd September 2021). Due permission from the hospital authority was taken to access the data available in the Medical Record Department.

Inclusion and Exclusion criteria: Deaths due to COVID-19 pneumonia with or without co-morbid conditions were included in the study. COVID-19 pneumonia deaths associated with accidents, pregnancy and poisoning were excluded from the study.

All deaths occurring during the study period, where COVID-19 pneumonia was the primary cause of death were selected. Total 743 deaths were included as per the inclusion and exclusion criteria.

COVID-19 positive cases: As per hospital protocol COVID-19 positive was defined as all cases showing positive Rapid Antigen Test (RAT) and or Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test for COVID-19 done under supervision of the Department of Microbiology of the Institute [15].

COVID-19 pneumonia: It was defined as patients with clinical symptom of pneumonia and bilateral ground glass opacity with peripheral distribution and lower lobe preference on chest X-ray [16].

Data Collection

Information regarding time of death, sex, age, and associated co-morbidity was entered in Excel sheet. The deaths were sub grouped according to gender, age, and reported co-morbid conditions along with pneumonia. The time of the day was represented in 24 hour format e.g., 10:00 AM was represented as 10:00 and 2:00 PM as 14:00. The 24 hour format of the day was divided into 12 temporal groups, each group of 2 hour duration. The data were generated by plotting the number of deaths of COVID-19 pneumonia for each 2 hour interval as a percent of the mean number of deaths per 2 hour interval and as a percentage of cumulative deaths per 2 hour interval on a 24 hour scale.

STATISTICAL ANALYSIS

Comparisons of mean deaths/2 hour interval (mean±SD) were performed by one-way Analysis of Variance (ANOVA), followed by Bartlett's test for equal variances. The temporal distribution of percentage mean death/2 hr interval for total COVID-19 pneumonia related deaths of various subgroups were statistically analysed by two-way ANOVA, followed by Bonferroni post-tests for equal variances. GraphPad Prism-5 software (Graph Pad Software Inc., CA, USA) was used for statistical analysis. The p-value <0.05 was considered as statistically significant. Statistically analysed report of percentage cumulative death of COVID-19 pneumonia cases with respect to gender-cum-age was performed for the linear fitting by the multiple-data fit mode using OriginPro 8 statistical software.

RESULTS

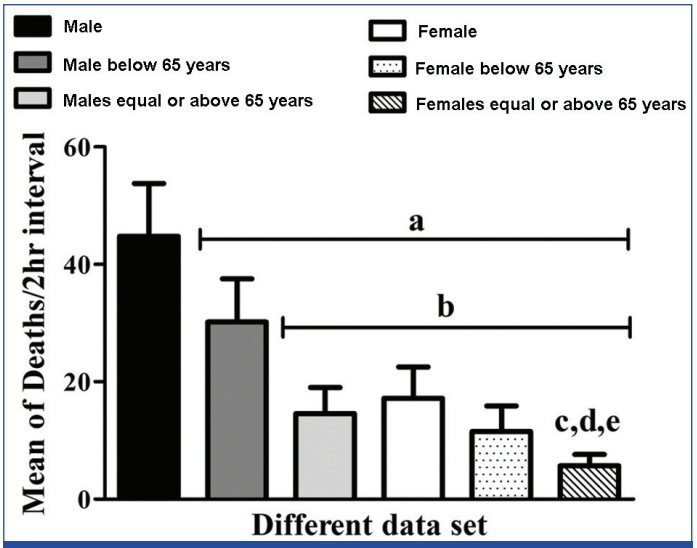
Total 743 cadavers, with 537 males and 206 females had COVID-19 pneumonia as primary cause of death. Mean age of the deaths was 56.01 years [Table Fig-1]. Mean number of deaths/2 hours interval for 12 (N) different time points among different subgroups showed that deaths among males and males below 65 years were significantly more in comparison to the other subgroups [Table Fig-2,3].

Subgroups	Mean±SD	N
Total death	56.01±15.01	743
Male	56.59±14.61	537
Male below 65 years	48.75±10.11	362
Males equal or above 65 years	72.82±7.22	175
Female	55.88±16.08	206
Female below 65 years	47.07±11.15	138
Females equal or above 65 years	73.76±7.23	68

[Table/Fig-1]: Average age of patients dying due to COVID-19 pneumonia.

Subgroups	No. of death/2 hour interval Mean±SD
Total death	61.92±12.75
Male	44.75±9.05[a]
Male below 65 years	30.17±7.38[a,b]
Males equal or above 65 years	14.58±4.44[a,b,c]
Female	17.17±5.36[a,b,c]
Female below 65 years	11.50±4.38[a,b,c]
Females equal or above 65 years	5.67±1.97[a,b,c,d,e,f]

[Table/Fig-2]: Mean of number of deaths/2 hour interval for different time points for COVID-19 pneumonia deaths of various subgroups (N=12).
Statistically significant changes among the subgroups obtained from the above mentioned tests were designated by the superscripts, [a]depicts significant (p-value <0.05) different from total death subgroup; [b]shows significant (p-value <0.05) different from male subgroup; [c] illustrates significant (p-value <0.05) different from male below 65 years subgroup; [d] depicts significant (p-value <0.05) different from Males equal or above 65 years subgroup; [e] shows significant (p-value <0.05) different from female subgroup; [f] illustrates significant (p-value <0.05) different from female below 65 years subgroup.
Statistically analysis was performed by one-way ANOVA, followed by Bartlett's test for equal variances. The p-value less than 0.05 was considered as statistically significant



[Table/Fig-3]: Shows the mean deaths/2 hour interval (Mean±SD) of various subgroups i.e., male, male below 65 year, males equal or above 65 years, female, female below 65 year and females equal or above 65 years. Comparisons of data i.e., Mean deaths/2 hour interval (Mean±SD) were performed by one-way ANOVA, followed by Bartlett's test for equal variances. The p-value less than 0.05 was considered as statistically significant. Statistically significant changes among the subgroups obtained from the above mentioned tests were designated by the superscripts ([a,b,c,d,e]).

On temporal distribution of total COVID-19 pneumonia deaths at two hours interval, mortality during the 4 PM-6 PM (16:00-18:00) interval was maximum, and was minimum during 8 AM-10 AM (08:00 to 10:00) [Table Fig-4,5]. All other subgroups except females equal or above 65 years of age also showed diurnal variations. The overall effect of time of day was significant for temporal concentrations in deaths of the males and females under 65 years of age. The temporal distribution of percentage mean death/2 hr interval for 743 COVID-19-related deaths of various subgroups has been depicted in [Table Fig-6].

Furthermore, such gender and/or age related variation in the pattern COVID-19 deaths was also supported by the statistical analysis of the percentage cumulative death/2 hour interval of gender and/or gender-cum-age, respectively [Table Fig-7-9].

COVID-19 pneumonia deaths were commonly associated with co-morbid conditions. Only 197 (26.51%) of COVID-19 pneumonia cases had no associated co-morbidity. Hypertension, diabetes, both diabetes and hypertension, diabetes associated with other clinical conditions, hypertension associated with other clinical conditions, both diabetes and hypertension associated with other clinical conditions and other clinical conditions alone were seen in decreasing order of prevalence among these deaths [Table Fig-10].

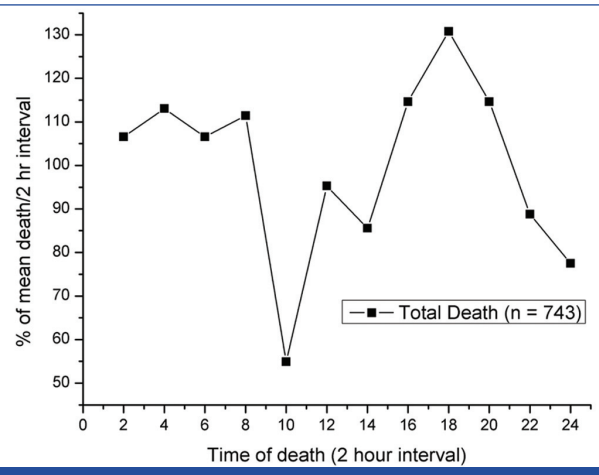
Other clinical conditions included dyselectrolytemia, alcohol withdrawal, metabolic encephalopathy, hypothyroidism, Space occupying lesion of Brain, chronic kidney disease, chronic liver disease, rheumatic heart disease, post mitral valve regurgitation, hyperkalaemia, cerebrovascular accidents, COPD, hypoxic encephalopathy, seizure, pulmonary TB, respiratory failure, decompensated chronic liver disease, renal cell carcinoma, hepatic encephalopathy, asthma, bronchial asthma, congenital heart disease, cardiac disease, shock, hepatic parenchymal disease, liver failure, acute liver failure, metabolic encephalopathy, acute pancreatitis, coagulopathy, acute hepatitis, oesophageal varices, Intestinal perforation, depression, schizophrenia, acute abdominal perforation, TB, carcinoma, anaemia, obstructive hydrocephalus, hepatic encephalopathy, Acute respiratory failure.

DISCUSSION

In the present study, 72.3% of deaths were among males, the excess in deaths were seen irrespective of age above and below 65 years. Asirvatham ES et al., also had observed more deaths among males (71.4%) [17]. Priya S et al., reported that when compared to females, males had 2.03 times higher risk of dying which was statistically

Subgroups	Number of death/2 hour interval												Total
	0 to <2	2 to <4	4 to <6	6 to <8	8 to <10	10 to <12	12 to <14	14 to <16	16 to <18	18 to <20	20 to <22	22 to <24	
Total death	66	70	66	69	34	59	53	71	81	71	55	48	743
Male	51	53	50	47	27	40	42	55	53	50	36	33	537
Male below 65 year	33	35	36	35	16	27	33	37	28	39	24	19	362
Males equal or above 65 years	18	18	14	12	11	13	9	18	25	11	12	14	175
Female	15	17	16	22	7	19	11	16	28	21	19	15	206
Female below 65 year	12	13	12	12	3	13	7	10	21	14	13	8	138
Females equal or above 65 years	3	4	4	10	4	6	4	6	7	7	6	7	68

[Table/Fig-4]: The temporal distribution COVID-19 pneumonia deaths at 2 hour interval over 24 hours duration of the day.
Each column represents deaths occurring during that 2 hour interval of the day



[Table/Fig-5]: The temporal distribution for total COVID-19 pneumonia related deaths (n=743).
The X-axis is successive 2 hour intervals throughout the day. The Y-axis is the percent of mean death rate per 2 hour interval

significant [18]. In a study from China, men were 2.4 times more vulnerable for death even though they were equally susceptible as women [19]. COVID-19 virus targets the respiratory system and mainly invades alveolar epithelial cells resulting in respiratory symptoms. Three major risk factors for COVID-19 mortality were sex (male), age (≥60), and severe pneumonia [20]. Decreased mortality among females is probably due to down regulation of Angiotensin II Receptor Type 1 (ATR1) and regulation of rennin activity by estrogen, due to the protective effect of X chromosome and sex hormones [21] and due to difference in response to virus and in innate or adaptive immunity [22]. The higher mortality among men could be due to the behavioural risk factors such as smoking, and alcohol consumption in India [23].

Age was considered as one of the most important factors for hospitalisation and mortality in COVID-19 infection [18]. In the present study the mean age of the dead patients was 56.01 year (SD-15.01). In a study from Madurai in the state of Tamil Nadu in India, the risk of death was observed to have increased with increase

Subgroups	Percentage of mean death/2 hour interval											
	0 to <2	2 to <4	4 to <6	6 to <8	8 to <10	10 to <12	12 to <14	14 to <16	16 to <18	18 to <20	20 to <22	22 to <24
Total death	106.59	113.05	106.59	111.43	54.91	95.28	85.59	114.66	130.81	114.66	88.82	77.52
Male	82.36	85.59	80.75	75.90	43.60	64.60	67.83	88.82	85.59^{aa}	80.75	58.14	53.29
Male below 65 year	53.29^{aaa}	56.52^{aaa}	58.14^{aa}	56.52^{aaa}	25.84	43.60^{aaa}	53.29	59.75^{aaa}	45.22$^{aaa, b}$	62.98^{aaa}	38.76^{aa}	30.68^{aa}
Males equal or above 65 years	29.07$^{aaa, bbb}$	29.07$^{aaa, bbb}$	22.61$^{aaa, bbb}$	19.38$^{aaa, bbb, c}$	17.76^{a}	20.99$^{aaa, bb}$	14.53$^{aaa, bbb,c}$	29.07$^{aaa, bbb}$	40.37$^{aaa, bb}$	17.76$^{aaa, bbb, cc}$	19.38$^{aaa, b}$	22.61^{aaa}
Female	24.22$^{aaa, bbb}$	27.45$^{aaa, bbb}$	25.84$^{aaa, bbb}$	35.53$^{aaa, b}$	11.30^{aa}	30.68^{aaa}	17.76$^{aaa, bb}$	25.84$^{aaa, bbb}$	45.22$^{aaa, b}$	33.91$^{aaa, bb}$	30.68^{aaa}	24.22^{aaa}
Female below 65 year	19.38$^{aaa, bbb}$	20.99$^{aaa, bbb}$	19.38$^{aaa, bbb, c}$	19.38$^{aaa, bbb, c}$	4.84$^{aa, b}$	20.99$^{aaa, bb}$	11.30$^{aaa, bbb,c}$	16.15$^{aaa, bbb, cc}$	33.91$^{aaa, bbb}$	22.61$^{aaa, bbb ,c}$	20.99$^{aaa, b}$	12.92^{aaa}
Females equal or above 65 years	4.84$^{aaa, bbb, cc}$	6.46$^{aaa, bbb, cc}$	6.46$^{aaa, bbb, ccc}$	16.15$^{aaa, bbb, c}$	6.46$^{aa, b}$	9.69$^{aaa, bbb}$	6.46^{aaa,bbb,cc}	9.69$^{aaa, bbb, cc}$	11.30$^{aaa, bbb}$	11.30$^{aaa, bbb, ccc}$	9.69$^{aaa, bb}$	11.30$^{aaa, b}$

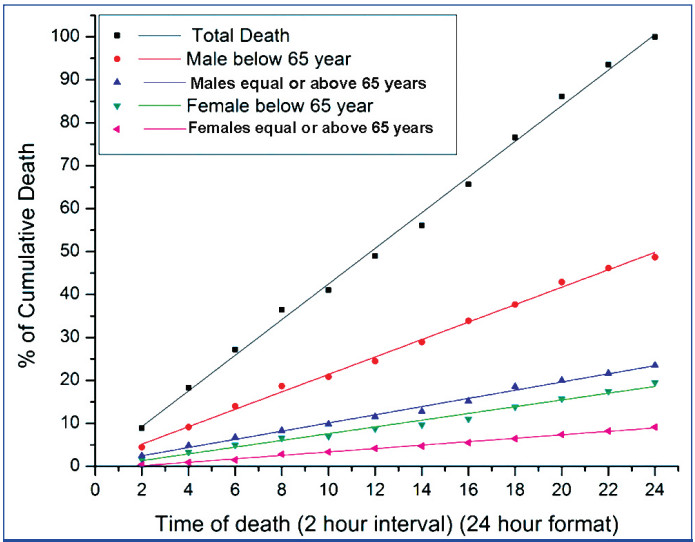
[Table/Fig-6]: The temporal distribution of percentage mean death/2 hr interval for 743 COVID-19-related deaths of various subgroups.
Data was repersented as % Mean death/2 hour interval. (% Mean death/2 hour interval=[{Death in given 2 hr/Mean of death in 24 hr}×100]). Statistically analysis was performed by two-way ANOVA, followed by Bonferroni posttests for equal variances. The p-value less than 0.05 was considered as statistically significant. Statistically significant changes among the subgroups obtained from the above mentioned tests were designated by the superscripts ^{a} (p-value <0.05), ^{aa} (p<0.01) and ^{aaa}(p-value <0.001) depicts significant different from total death subgroup; ^{b} (p-value <0.05), ^{bb} (p-value <0.01) and ^{bbb} (p-value <0.001) shows significant different from male subgroup; ^{c} (p-value <0.05), ^{cc} (p-value <0.01) and ^{ccc} (p-value <0.001) illustrates significant different from male below 65 years subgroup

Subgroups	% Cumulative death/2 hour interval											
	0 to <2	2 to <4	4 to <6	6 to <8	8 to <10	10 to <12	12 to <14	14 to <16	16 to <18	18 to <20	20 to <22	22 to <24
Total death	8.88	18.30	27.19	36.47	41.05	48.99	56.12	65.68	76.58	86.14	93.54	100.00
Male	6.86	14.00	20.73	27.05	30.69	36.07	41.72	49.13	56.26	62.99	67.83	72.27
Male below 65 year	4.44	9.15	14.00	18.71	20.86	24.50	28.94	33.92	37.69	42.93	46.16	48.72
Males equal or above 65 years	2.42	4.85	6.73	8.34	9.83	11.57	12.79	15.21	18.57	20.05	21.67	23.55
Female	2.02	4.31	6.46	9.42	10.36	12.92	14.40	16.55	20.32	23.15	25.71	27.73
Female below 65 year	1.62	3.36	4.98	6.59	7.00	8.75	9.69	11.04	13.86	15.75	17.50	18.57
Females equal or above 65 years	0.40	0.94	1.48	2.83	3.36	4.17	4.71	5.52	6.46	7.40	8.21	9.15

[Table/Fig-7]: Demonstrate the percentage cumulative death/2 hour interval for total, male, male below 65 year, male above 65 year, female below 65 year, and female above 65 year.
(% Cumulative death/2 hour interval) nth hr = {A(n-1)+An} where fraction of total death (A) = [{Death in given 2 hr/total death (i.e. 743)} x 100], and n =1, 2, 3, ……12

Subgroups	Degree of freedom	Residual sum of squares	Equation: y=a+b*x				
			Intercept		Slope		Statistics
			Value	Standard error	Value	Standard error	Adj. R-Square
Total	10	31.9154	0.966	1.09951	4.1497	0.0747	0.9965
Male	10	14.3317	1.7296	0.7368	2.9805	0.0501	0.9969
Male below 65	10	7.4747	1.1093	0.5321	2.0301	0.0362	0.9965
Males equal or above 65 years	10	3.2659	0.5649	0.35172	0.9539	0.0239	0.9931
Female	10	5.9370	-0.7086	0.47422	1.1672	0.0322	0.9917
Female below 65	10	5.3341	-0.2304	0.4495	0.7847	0.0305	0.9836
Females equal or above 65 years	10	0.37981	-0.6342	0.11994	0.3991	0.0082	0.9954

[Table/Fig-8]: Statistically analysed report of percentage cumulative death of COVID-19 pneumonia cases with respect to gender-cum-age.
The equation y=a+b*x is called the slope-intercept form of the equation of the line. It requires the slope value 'b' and the y-intercept a of the line. Analysis was performed for the linear fitting by the multiple-data fit mode using OriginPro 8 statistical software.



[Table/Fig-9]: Depicts the percentage cumulative death/2 hour interval of various subgroups i.e., total, male below 65 year, male above 65 year, female below 65 year and female above 65 year. Statistical parameters are compiled in [Table/Fig-3].

Co-morbid conditions	Numbers	Percentage
Pneumonia deaths associated with co-morbid conditions	546	73.49%
COVID-19 pneumonia deaths not associated with any co-morbid condtions	197	26.51%
Hypertension alone as a co-morbid condition	246	33.11%
Diabetes alone as a co-morbid condition	236	31.76%
Other associated clinical conditions	387	52.09%
Hypertension and Diabetes both present as a co-morbid condition	126	16.96%
Hypertension and Diabetes along with other clinical conditions	134	18.03%
Hypertension with other clinical conditions	127	17.09%
Hypertension, diabetes along with other clinical conditions	66	8.88%

[Table/Fig-10]: The co-morbid conditions associated with COVID-19 pneumonia deaths.
All the deaths were due to COVID-19 pneumonia (Total deaths 743, 100%), Hypertension was the single most common co-morbid condition associated with these deaths. Some of the cases had more then one associated co-morbidity

of age compared to the death among 18-29 years, the highest risk being among the age group ≥70 years [18], whereas in a study from Chennai, Tamil Nadu, mean age of the deceased was 62.5 years without a significant difference between male and female [17]. In a study from China 83.8% of deaths were in the age range ≥65 years [19]. The increasing death rate with age was expected due to the higher prevalence of co-morbidities, and less responsive innate and adaptive immune system among the elderly [24,25]. In the present study, more numbers of deaths were observed in age group below 65 years, both in males and females, which is younger than that observed by others authors, the difference may be because of the study setting.

In the present study, diurnal variation in mortality was observed among the COVID-19 pneumonia deaths. Mortality during the 4 P.M.-6 P.M. (16:00-18:00) interval was high in comparison to morning hours. The peak was mainly due to the significantly more deaths among the males and females under 65 years of age rather than females above 65 years. Human mortality due to all causes have shown a peak at 6 AM-8 AM ($p<0.001$) [8], diseases such as asthma, myocardial infarction, stroke, and ventricular arrhythmia also show a peak in mortality during morning hours of 6 AM-12 PM [6,7]. A common explanation for the peak is the presence of a circadian rhythm in a proarrhythmic trigger, a morning surge in sympathetic drive, β-adrenergic stimulation, delayed after depolarisations, and re-entry [26]. Unlike the deaths due to the asthma, myocardial infarction, stroke, and ventricular arrhythmia, in the present study there was evening rise of mortality due to COVID-19 pneumonia, which suggests that increase in deaths due to COVID-19 pneumonia during evening hours is not due to circadian rhythm in proarrhythmic triggers.

Changes of airway caliber, airway resistance, respiratory symptoms, mucus secretion and immune-inflammatory responses during different period of day results in variation in exacerbation, frequency and occurrence of chronic obstructive pulmonary diseases and asthma [9,14]. Clock gene expression is rhythmic in the lung. Circadian rhythm within the lung is important for the immunologic control of acute lung infection and in development of chronic lung disease. Circadian rhythms is observed to be associated with susceptibility and severity of disease after infection, it also modifies its clinical presentation [27].

Alteration of the clock impedes the initial recognition of pathogens by lung innate defenses and negatively affects neutrophil function [10]. Intra nasal inoculation of the influenza virus in mice just before the onset of their "active phase/lights off" shows significantly higher mortality and morbidity than during "rest phase/light on", and has shown more lung injury irrespective of the rate of viral replication or viral burden [28].

Some viral infections exploit host susceptibility during the rest phase by disrupting epigenetic mechanisms, affecting the circadian clock of the host and altering the potency of the pathogenicity and the host immunity [29] some viruses either reprogram cellular metabolism or exploit host circadian variation for replication kinetics [30]. Immune response and functions of T and B lymphocytes also show circadian rhythm. Melatonin suppression is associated with increased levels of specific antibodies. High levels of IL-10, an anti-inflammatory cytokine, are seen during daytime, whereas high levels of inflammatory cytokines (TNF, IL-1, and IL-6) and cytokine receptors are seen during the nighttime [13]. One of the common cause of death in COVID-19 (SARS-CoV-2) was reported to be COVID-19 Pneumonia. Mal-adjusted immune responses against SARS-CoV-2 was said to be responsible for the immunopathology

of the disease [1]. Cellular entry of the SARS-CoV-2, triggers an inflammatory response by recruiting T-helper cells that produce interferon (IFN)-gamma (IFN-γ), interleukin (IL)-2, and IL12. The injured alveolar cells also release interferons, cytokines, and other intracellular components. The subsequent recruitment of other inflammatory cells leads to the development of a 'cytokine storm' which can precipitate the organ damage and multi-organ failure seen in severe disease. Tumour Necrosis Factor (TNF)-α and IL-1β are proinflammatory cytokines that cause an increase in vascular permeability, and induce recruitment of more immune cells, including neutrophils and monocytes. IL-8 recruits neutrophils, and other chemokines attract monocytes, increases vascular permeability causing leakage of fluid into the interstitial space and alveoli, resulting in interstitial and pulmonary oedema [31]. Organ damage was mainly attributed to secretion of IL1β, IL-6, and TNF-α [24]. The elevated inflammatory mediators the blood IL-6 level was highly correlated with the disease mortality when COVID-19 survivors and non survivors were compared [5]. In the present study, the diurnal variation shown in mortality of COVID-19 pneumonia patients (evening rise) does not coincide with the physiological increase in airway resistance, and other variations in physiological functions of the lung. The evening increase in the mortality among COVID-19 pneumonia patients may have been due to the time of infection, alteration of the host circadian rhythm or abnormal immune response to the infection.

In a study from south India co-morbidities such as diabetes, hypertension and Coronary Artery Disease (CAD) were found among 62%, 49.2% and 17.5% of the deaths, respectively. The co-existence of diabetes and hypertension or diabetes, hypertension and CAD were found in 36.6% and 8.7% of the individuals respectively [17]. In the present study, 546 (73.49%) of patients dying due to COVID-19 pneumonia had associated co-morbidity. Among the co-morbidities, hypertension and diabetes were the most common. Priya S et al., reported that COVID-19 patients had atleast 3 times greater risk of mortality when they had atleast one of these co-morbidity. The mortality risk was highest among those patients who had diabetes, hypertension and heart disease as co-morbidities in combination [18]. In the present study, diabetes was associated in only 31.76% which was much less than the findings from studies from south India [17]. The difference was probably due to selection of deaths due to COVID-19 pneumonia only rather than deaths due to all causes.

Limitation(s)

As this was a hospital record based study from a single centre, findings may not represent the deaths due to COVID-19 pneumonia at community level. It also does not reflect human intervention related reasons of death such as delay in care, deaths during shift change, death due to non availability of ICU beds, interruption of oxygen supply.

CONCLUSION(S)

There exists a diurnal variation in mortality among COVID-19 Pneumonia patients during evening hours which is significantly more in males age ≥65 years and below the age of 65 years and insignificant in females above 65 years. The evening increase in the mortality among COVID-19 pneumonia patients may have been due to the time of infection, alteration of the host circadian rhythm or abnormal immune response to the infection. Further studies involving multiple centres must be carried out to validate the results of this study.

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