Comparison of Predictors of Mortality between Young and Elder Covid-19 Patients Admitted in Covid-19 Designated Tertiary Care Hospital

Sonal Shah[1], Manisha Kapdi[2], Jyoti Vora[3], Kuldeep Joshi[4], Pratik Patel[5], Sandip Malhan[6]

[1]Associate Professor, Community Medicine Department, [2]Associate professor, Department of Anaesthesia & Critical Care, [3]Associate Professor, Department of General Medicine, [5]Dean, Smt. NHL Municipal Medical College, Ahmedabad, Gujarat, India

[4] Chief Resident Medical Officer (RMO), SVP Institute of Medical Sciences & Research, Ahmedabad, Gujarat, India

[6]Superintendent, SVP Institute of Medical Sciences & Research & Professor, Department of General Medicine, Smt. NHL Municipal Medical College, Ahmedabad, Gujarat, India

Correspondence : Dr. Manisha Kapdi, Email: manisha_kapdi@yahoo.com

Abstract:

Introduction: The outbreak of Covid-19 has led to a health emergency and economic crisis worldwide. Mortality in productive age further worsens the crisis, so it is important to understand reasons for death in productive age group. **Objective:** To identify predictors of mortality and to compare the intensity of rise in inflammatory markers amongst young Covid-19 deceased in comparison with elder Covid-19 deceased. **Method:** Record based study was conducted among all Covid-19 infected patients (n=3131, 209 deceased and 2922 recovered patients) admitted in tertiary care hospital. Clinic-epidemiological markers of younger (18-45 years) deceased were compared with elder deceased (>45 years). Mann–Whitney test and the Chi-square test for significance were used. Bivariate multiple logistic regression was used to identify predictors of mortality among younger and elder Covid-19 patients. **Results:** Case Fatality Rate (CFR) in Covid-19 infected patients was 2.4% and 9.7% amongst younger and elder group respectively. (Odds Ratio:8.83, 95% Confidence Interval 5.9-13.2; p <0.001). Biomarkers were raised and similar in both groups except Neutrophil Lymphocyte Ratio (NLR) was significantly higher in elder deceased while Lactate Dehydrogenate (LDH) was significantly higher in younger deceased. **Conclusion:** Males had higher CFR than females after 45 years of age, which was due to co-morbidity. Reaching late to the health care facility and high LDH were predictors in younger decedent, while male gender, co morbidities and high NLR were more important predictors in elder group. **Recommendation:** Monitoring Covid-19 patients by measuring Oxygen saturation with oxymeter after 6 meter walk test may detect hypoxia early and help patient to reach health facility timely.

Key words: Bio markers, Covid-19, Female Case fatality, Predictors, Young Covid-19 deceased

Introduction:

In 21st century, combination of modern technology and medicine started conquering health problems step by step by identifying promising solutions. COVID-19 patients who are aged, hypertensive or diabetic, are more likely to develop a more severe course and progression of the disease. [1] About 15.1% deaths are below 45 years age group. Although case fatality rate in this productive age group is less, deaths amongst young and healthy

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people contribute far more quality-adjusted life-years lost than deaths in elderly individuals with pre-existing morbidity.[2,3] The single death of person in productive age group can have deep impact in the family as well as nation.

Premature deaths and hospitalization adversely affect economic growth and development.[4] Gujarat, reported more than 90000 Covid-19 cases and 3000 Covid-19 deaths.[5] Marked shift in lifestyle, urbanization, and oil and sugar rich dietary habits have pushed ethnic Gujarati people to the forefront as contributors to Cardio Vascular Disease (CVD) risk factors.[6] Prevalence of Diabetes Mellitus (DM), in Gujarat is 9.8%.[7] The knowledge of reasons of Covid-19 mortality rates amongst young adults can help in guiding different management strategies for the pandemic.

Objectives:

Primary objective

- To identify predictors of mortality amongst young in comparison with elder Covid-19 deceased.

Secondary objectives

- To evaluate clinical status on admission in young decedents
- To compare commonest complications and the intensity of rise in inflammatory markers of amongst young Covid-19 decedents in comparison with elder Covid-19 decedents.
- To identify risk factors and their association with Covid-19 mortality amongst young patients in comparison with elder deceased

Method:

Study design-Record based study was carried out after getting clearance from Institutional Review Board(IRB). IRB approved to study records of patients aged 18 years and above.

Study setting- Information was taken from hospital records of Covid-19 positive patients admitted in Covid-19 designated 1200 bedded tertiary care hospital run by the Ahemedabad Municipal Corporation.

Study duration- Records of all Covid-19 positive patients admitted between 17th March 2020 (first reported case) and 15th June 2020 were included.

Inclusion Criteria-Records of all Covid-19 positive patients aged 18 years and above admitted in hospital during study period. Patient with Covid-19 infection diagnosed and managed as per the guideline issued by Indian Council of Medical Research(ICMR) guideline.[8] As per the guideline patient with positive report by RTPCR/ Rapid Antigen testing was considered as Covid-19 infected patient irrespective of patient tested positive before (outside hospital laboratory) or after hospitalization.

Exclusion criteria-Patients who were discharged or expired after 15th June 2020 and voluntarily transferred to private hospitals were excluded from the study.

Total 5441 patient were admitted having Covid-19 infection. After applying exclusion criteria, total sample size of Covid-19 positive admitted patients was 3131(2922 recovered and 209 deceased).

The hospital has electronic record keeping system. Information from record of each study subject was taken after taking permission of concerned authority. Swab Positivity Rate (SPR) was calculated as percentage of nasopharyngeal swab tested positive by RTPCR test out of total nasopharyngeal swab examined. Complications were identified from the clinical and laboratory records. Intensity of inflammatory markers in decedents was evaluated.

Defining young and elder group-

Interest of currents study is to identify factors associated with death in young Covid-19 patients in comparison with recovered young as well as decedent elder Covid-19 patients. Lack of literature regarding cut off age defining young Indian Covid-19 patients, cut off age was decided from based on data from current study. From the records included for the study, it was found that an average age of recovered patients was (41.6 years, SD 17.2) which falls in class interval of 40 to 45 years age group.

Hence, 45 years of age was kept as cutoff to group young and elder patients. To identify reasons for death in young patients, deceased aged 45 years or less (younger) were compared with deceased aged more than 45 years (elder).Out of total (209),29 deceased were below 45 years of age.

Swab Positivity Rate (SPR) was calculated as percentage of nasopharyngeal swabs tested positive by RTPCR test out of total nasopharyngeal swabs examined. Low Oxygen saturation (SpO2) at the time of admission was taken as indicator of hypoxia. Patients who needed invasive oxygen therapy (BiPAP, Hi flow nasal oxygen, invasive ventilator) were categorized as severely hypoxic.

Analysis-

To avoid confounding, parameters in both groups were calculated taking subset/s of mortality as numerator and subset/s of recovered Covid-19 as denominator in respective groups.

Quality check of records- Hospital has electronic record system maintained by IT department. Each patient is given unique identity number. System identifies this number and clinical and laboratory records are linked from the source of data generation. At the time of death or discharge all such records are reviewed by treating consultant while making discharge or death summary.This minimizes errors in record keeping.

Statistical analysis-

SPSS software version20 was used for statistical analysis. Descriptive statistics included frequency analysis (percentages) for categorical variables and mean ± Standard Deviation (SD) or median for continuous variables. Kolmogrov- Sminov test for normality was applied to each variable before applying statistical test. Based on this comparison between recovered and deceased was determined by Mann–Whitney U-test (continuous variables) and the Chi-square test (categorical variables). Parameters in the group of decedents aged <45 years and above 45 years were calculated and compared taking subset/s of mortality as numerator and subset/s of recovered Covid-19 as denominator in respective groups. Predictors were identified by finding association of risk factors with death using binary multiple logistic regressions in both groups separately. The statistical inference was made at significance level of 0.05 (two-tailed).

Results:

With pandemic alert, the city started RT-PCR testing of individuals returning from foreign countries in the hospital since 6th February 2020. The first reported case having Covid-19infection in the city as well as of hospital was reported on 17th March. On 28th March 2020 the first case (deceased afterward) without any history of positive contact of traveler from affected country (suspected probable indigenous) was reported. Out of total 3131 Covid-19 positive patients, 771 (24.6%) gave history of contact with positive person. Total 93 patients were frontline workers (health care workers, police, volunteer) during Corona pandemic that contracted infection during their Covid-19 duty out of which 4 sacrificed their lives.

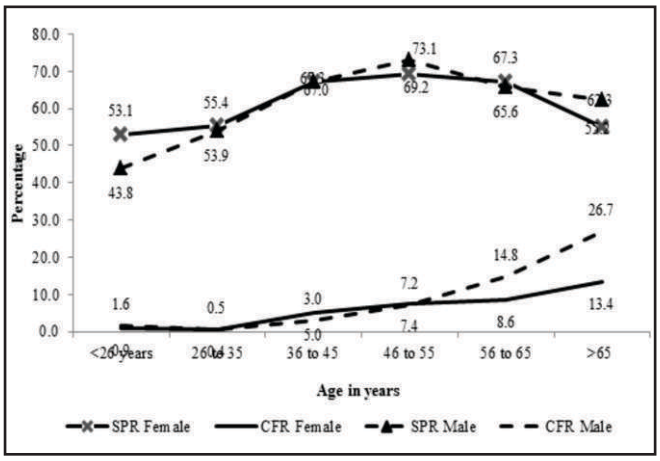
Epidemiological scenario-

Swab Positivity Rate (SPR) was calculated as percentage of nasopharyngeal swab tested positive by RTPCR test out of total nasopharyngeal swab examined. Rapid antigen testing was not introduced during study period. As depicted in(Figure 1), Swab Positivity Rate(SPR) was lowest below 25 years age group (43.2%) afterwards it was increasing in successive age group reaching to the peak 71.7% (46 to 55 years) then after SPR was reduced to 60% in >65 years age. Similar trend was seen in both sexes. The Case Fatality Rate (CFR) was increasing with age. CFR doubled every 10 years increase in age after 35 years (Graph-1). Overall CFR (6.7%) was comparable with WHO report (6.4 %).[9] Deceased patients were significantly older (59.4 years,SD-15.02) than the recovered (41.6 years, SD 17.2) group (p<0.001).

Covid-19 infected patients with age >45 years were associated with 8.83 folds significantly increased risk of mortality as compared to patients with age <45 years (unadjusted OR 8.83 : 95% CI 5.9-13.2; p < 0.001). Although CFR in young infected was

lower, their absence has severe consequences for surviving family members and may curtail overall development of their children.

Figure 1: Age & Sexwise Swab Positivity (SPR) and Case Fatality Rate (CFR)



Female patients were 38.8%(n=1214) of total Covid-19 positives admissions and 28%(n=59) of total deaths. There was no significant difference in swab positivity between male & female but overall females (4.9%) had lower CFR than males (7.8%). Although females are contributing 28% of total death, deceased females were 6 years younger than deceased male.

The female survivor (average age-40.3 years ,SD-17.9) and deceased female (54.8 years,SD-14.9) were significantly younger than male survivor(42.5 years ,SD-16.7)(p<0.001) and deceased males(61.3 years,SD-14.8)(p<0.001).

Clinical scenario:-

Proportions of asymptomatic patients were 13.1% (n=226) and 8.8% (n=124) in young and elder group of patients, respectively. Amongst all symptomatic, top four common symptoms was fever, dry cough, breathlessness, weakness (diarrhea in few cases) in both the groups.

Median duration between onset of symptom and reaching first health facility in recovered and deceased patients were between three days and five days respectively. Mean (SD) duration of breathlessness in recovered and expired patients were 0.81 day (1.2 days) and 2.3 day (2.7 days) respectively. It was statistically significant (p<0.001). Nearly 85% of deceased had SPO_2 level below 90%. These findings indicate that fever was usually an ignored symptom to seek health facility while difficulty in breathing was the main reason to reach to the hospital. Deceased admitted with poor general condition were45%, among them five had Diabetic Ketoacidosis on admission.

'The presence of co morbidities is associated with poorer outcomes in Community Aquired Pneumonia' which holds true for Covid-19, too. More than half of elderly(n=756,54%) and 196 younger (14%) Covid-19 positive patients had at least one co morbidity, out of these 10.2%(n=20) younger and 161 elder deceased (21.3%) expired (table 1). Absolute number of Covid-19 positive patient suffering from Chronic Kidney Disease (CKD), Ischemic Heart Disease (IHD) and Cerebro-Vascular Stroke (CVS) were less but case fatality rate was high.(Table 1).

Case Fatality Rate (CFR) in younger and elder decedents without any co morbidity was 0.6% and 2.9% respectively. Hypertension (5.4% of young, 31.3% elder) followed by Diabetes type 2 (3.5% of young, 23% elder) were the commonest co morbidity in both younger and elder group CFR was highest in younger decedents with Diabetes Mellitus (18%) followed by those with history of Ischemic heart disease (IHD) (15.4%) whereas amongst elder decedent CFR was highest with Chronic Kidney Disease (CKD) (50%) followed by IHD(32.5%).All younger patients with Chronic Kidney Diseases were recovered.

Chest X ray revealed 173 (84.3%) deceased had bilateral Mid Zone or Lower zone pneumonia. A study from China reported 80% of Covid-19 patient had ground glass opacity. Bilateral Xray changes were seen in 73.2% deceased among them 71·5% required O2 therapy. [10]

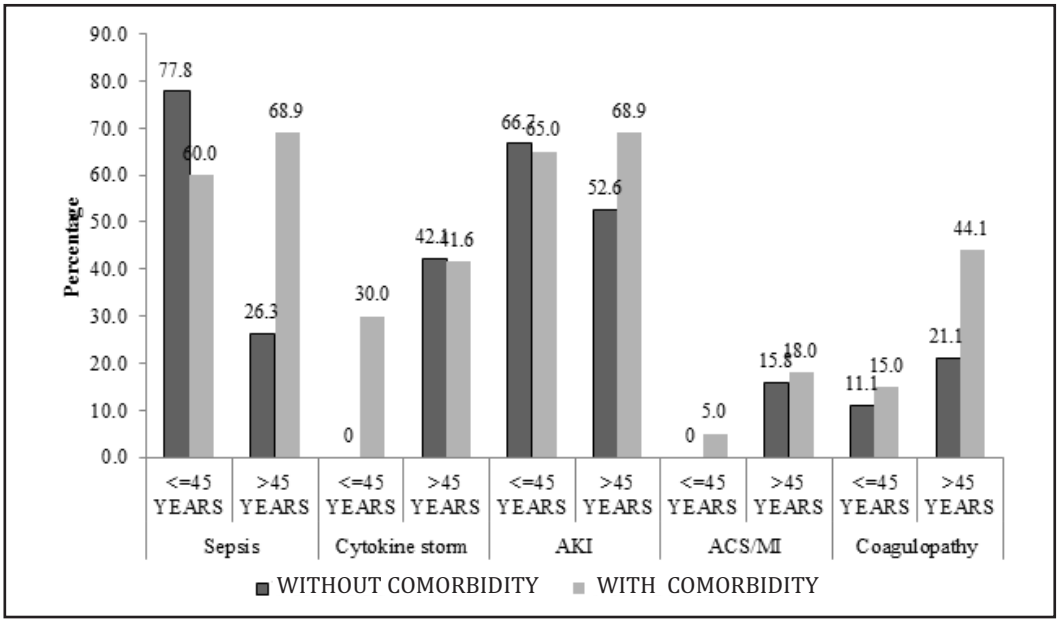
High Flow Nasal Oxygenation and Bi PAP were means of Non Invasive Ventilation to postpone intubation. Out of total patients put on ventilator (n=213), only 13 recovered out of these 4 were

Table 1: Comparison of case fatality specific to existing co morbidity between young and elderly group

Sr. No.	Co morbid status	≤45 years frequency		>45 years frequency		Total frequency		CFR (%)		
		R**	D*	R**	D*	R*	*D*	<=45 year	>45 year	Total
1	Chronic Kidney Disease	3	0	13	13	16	13	0.0	50.0	44.8
2	Ischemic Heart Disease	11	2	78	37	89	39	15.4	32.2	30.5
3	Diabetes Mellitus	50	11	297	101	347	112	18.0	25.4	14.4
4	Hypertension	86	7	429	112	515	119	7.5	20.7	18.8
5	Chronic Lung Disease	22	1	23	5	45	6	4.3	17.9	11.8
6	Miscellaneous	33	2	57	26	90	28	5.7	31.3	23.7
7	No Co-morbidity	1480	9	570	19	2050	28	0.6	3.2	1.3
8	1 Co-morbidity	140	6	328	49	468	55	4.1	13.0	10.5
9	2 Co-morbidity	33	10	212	57	248	67	23.3	21.2	21.5
10	>=3 Co-morbidity	3	4	55	55	58	57	57.1	50.0	50.4
Total		1699	29	1226	**180**	**2925**	**209**	**1.7**	**12.8**	**6.7**

**R- Recovered *D- Deceased

Figure 2: Complications in Decedents



*AKI- Acute Kidney Injury, ACS-Acute Coronary Syndrome, MI- Myocardial Infarction

Table 2: Comparison of association of risk factors with Covid-19 mortality between young and elder deceased

Risk factors	Adjusted Odds Ratio (Confidence interval)	
	Age 45 years & less	Age > 45 years
Gender= Male (Female- Ref)	0.45 (0.1-2.5)	2.02 (1.1-3.6)
On admission low Oxygen saturation (Room air &Non invasive Oxygen Ref)	2586.7 (400.9-16690.3)	238.8 (133.3-426.7)
Hypertension (Non hypertensive- ref)	0.8 (0.1-6.3)	3.6 (0.9-2.7)
Diabetes Mallitus (Ref-Non diabetic)	4.96 (0.6-86.7)	1.6 (0.9-2.7)
Comorbidity (Ref- no comorbidity)	11.4 (1.5-86.7)	13.1 (6.99-24.4)

younger survivors. All deceased except two were intubated as resort to improve their Oxygenation.

Complications- The commonest complication was Septicemia (n= 146, 71·2%) out of them 76 (37% of total) developed Cytokine storm. Excessive production of pro inflammatory cytokines aggravates Acute Respiratory Distress Syndrom (ARDS) and widespread tissue damage resulting in multi-organ failure and death.

Complication in younger deceased without co morbidity were related to septicemia, coagulopathy and acute hepatic and renal injury secondary to septicemia.(Figure 2). Younger deceased with co morbidity had both septicemia and micro thrombus related of complications but lesser extent for thrombotic complications as compared to elder deceased (irrespective of type & number of co morbidity).

Apart from ARDS, Acute Kidney Injury and Disseminated intravascular coagulation were the last events before death and all deceased could not survived more than 3 days after developing them. Two deceased collapsed suddenly in the high dependency unit. Of these two, one younger decedent collapsed due to severe cytokine crises (20 years age) and the other elder decedent succumbed due to Cardiogenic shock.

Association of risk factor with Covid-19 mortality

To identify independent association of risk factor with Covid-19 mortality binary multiple logistic regressions in both groups was used separately in both the groups.Patients who needed invasive oxygen therapy (BiPAP, Hi flow nasal oxygen, invasive ventilator) were categorized as severely hypoxic. At the time of admission, patients with severe hypoxia were compared with patients who could maintain oxygen saturation more than 95% at room air or low pressure non invasive oxygen mask.

Considering Hypertension and Diabetes important risk factors and contributors in causation of CKD, IHD and CV stroke hence in each group binary logistic regression was applied using five variables-gender, status of Oxygen saturation (SpO2) on admission along with Hypertension and Diabetes. (Table 2).

Since number of patient maintained SpO2 on room air were very less as compared to patients required non invasive oxygen in both groups of deceased, odds ratio came too high for condition of admission.

Discussion:

Covid-19 deceased age was 9–10 years lower (59.4 years,SD-15.02) than Covid-19 deceased from

Wuhan (deceased-70.2±7.7 years Survivor-56.0±13.5 years) in non white decedents from USA (median 72 years).[10,11] In present study one or more comorbidities was reported 86.2% decedent which was higher than United States and China (three fourths of decedents). Our study 53.6% deceased had Diabetes while USA (39.5%) and China reported (28.6%).[11,12]

Case Fatality Rate (CFR) in COVID-19 infected patients was 2.4% and 9.7% amongst younger and elder group respectively. Systemic review & meta-analysis reported 15.4-folds significantly increased risk of mortality in COVID-19 infection amongst patients with age ≥50 years as compared to patients with age <50 years. [13]

The average duration between breathlessness and admission was 3.1 days in young decedents as compared to elder deceased (>45 years) 2.1 days. 60% of younger deceased as compared to 54% elder deceased had O_2 saturation <85% or came with oxygen support on admission. None of younger deceased had stable condition on admission and 15 had to put on ventilator within 24 hours of admission, where as recovered patient in same age group only 1.6% needed non invasive oxygen support on admission. This indicates that younger decedent reached late to the health care facility may be due to happy hypoxia.

In present study, the median durations between onset of symptoms and reaching first health care facility among recovered and deceased patients were three days and five days, respectively. These averages were less than reported by Wuhan city was (mean±SD =9.7±4.3).[11] This may be due to negligence of symptoms or rapid worsening of condition due to higher prevalence of co morbidities in the population in present study.

Complications:

In COVID-19 infection, patients developed complication related to Septicemia or thrombo-embolism. [14]

Myocardial injury, Coagulopathy and Acute coronary syndrome occurred in 36.1% ,19·5% and 16% of deceased respectively. Myocardial injury in COVID-19 infection is due to Septicemia and Hypoxemia. [15,16]

In-hospital mortality was significantly higher in patients with myocardial injury than in patients without myocardial injury (14 (60.9%) vs. 8 (25.8%), P=0.013).[13]

Biomarkers in COVID-19 deceased patients-

Biomarkers in decedents were studied to facilitate selecting treatment modalities. Acute Respiratory Distress Syndrome (ARDS) was observed in all decedents. Hadith Rastad et al reported, $PaO_2 \geqslant 80$mm/Hg in deceased patient was the only factor that was associated with patients' survival. [11]

Neutrophil : Lymphocyte Ratio (NLR) was 5 or more in 97 deceased out of these patients 88 had lymphocyte count five or less. Biomarkers were raised and similar in both groups except Neutrophil Lymphocyte Ratio (NLR) was significantly higher in elder decedent while LDH was significantly higher in younger decedents.(table-3)Increase or decrease of Lactate Dehydrogenate (LDH) was indicative of radiographic progress or improvement.[17]

Therefore, in younger patients especially without co morbidity anti inflammatory agents might play major role rather than thrombolytic therapy to improve CFR. Henrery et al in his met analysis observed that NLR >=2.48 is the predictive prognostic biomarker of poor out come due to sepsis.[14,18]C Reactive Protein (CRP) was progressively raised after 3rd median day of admission in majority of decedents.

Comparison of predictors of Mortality between young and elder Covid-19 deceased patients

Gender difference:

Gender difference in younger age group CFR was similar (Female-1.8, Male-1.6, p=0.9) whereas in elder age group males hadabout twice the risk of death from COVID-19(CFR =female- 9.2, Male-14.9, p<0.001) (Table 3). Findings of Covid-19 associated data from 45 countries revealed higher risk of death

Table 3: Comparison in intensity of biomarkers between young and elderly deceased

Sr. No.	Biomarkers	45 years & less			above 45 years			P * value
		N	Mean	SD	N	Mean	SD	
1	C Reactive Protein (mg/L)	19	50.1	78.7	121	63.4	100.5	0.92
2	PaO2(mm/Hg)	15	73.7	24.7	67	72.4	28.3	0.88
3	PaCO2 (mm/Hg)	10	56.3	19.4	43	59.6	21.3	0.65
4	HbA1c (%)	25	7	2	180	6.8	1.9	0.68
5	Neutrophil LymphocyteRatio	15	13.2	8.4	88	22.6	21.8	0.04
6	D dimer(mg/ml)	11	3.5	1.2	86	3.3	1.2	0.36
7	Platelets(no./cmm)	2	86.5	19.1	17	146.8	89.1	0.23
8	Ferritin(ng/ml)	9	1152.8	617.1	62	1223	909.7	0.93
9	Lactate Dehydrogenate (unit/l)	7	1158.9	709.1	56	850	825.2	0.04
10	Polymerase Chain Reaction (ng/ml)	7	4.5	6.9	31	8.2	28.9	0.68

* Mann Whitney U test

COVID-19 infection for men is significantly higher than that of women particularly in older individuals.[19]

In younger group co morbidity was significantly high(Chi Square =6.9,d.f=1,p<0.01) in females (76.9%) than males(56.3%), whereas in elder group co morbidity was significantly high(Chi Square =14.2,d.f=1,p<0.001) in males (91.1%) than females (84.4%). It indicates that gender difference in CFR in our study may be due to co morbidity rather than gender itself. Men and women have the same susceptibility; men may be more prone to have higher severity and mortality independent of age and susceptibility, leading to a range of hypotheses, from lifestyles to differences in chromosomal structure.[20-22]

Conclusion:

Male gender, Hypertension and Neutrophil Lymphocyte Ratio (NLR) were more important predictors in elder group. Whereas in younger age group, gender did not have any influence in mortality but Diabetics had 5 times higher risk of mortality and LDH was significantly raised as compared to elder age group. Overall an older age was non modifiable risk factor for worst outcome in patients with COVID-19 whereas gender difference in CFR was due to presence of co morbidities.

Recommendation: Monitoring Covid-19 patients by measuring O2 saturation with oxymeter after 6 meter walk test may detect hypoxia early and help patient to reach health facility timely.

Study Limitation:

1. Various inflammatory and immune markers in decedents were not carried out for all patients. Therefore our conclusion based on available biomarkers was limited to few patients instead of total study population.

2. Patients with moderate to severe illness were admitted in the hospital hence inference made from

hospital based study may not fully represent community scenario.

Declaration:

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Conflict of Interest: Nil

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