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Original Article

Risk Factors associated with In-Hospital Death in Adult COVID-19 Patients in Karachi, Pakistan: A Retrospective Chart Review

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ABSTRACT

Objective: To identify the risk factors associated with in-hospital mortality of COVID-19 patients in the largest Navy hospitals in Pakistan.

Study Design: Retrospective chart review.

Place and Duration of Study: Department of Medicine, Pakistan Navy Station Shifa Hospital, Karachi Pakistan, from Apr to May 2020.

Methodology: All patients who died in the Intensive care unit of Pakistan Navy Station Shifa Hospital, Karachi during study period, having polymerase chain reaction positive COVID-19 infection were included. The data recorded included basic demographics (age, gender and length of stay in hospital), documentation of co-morbidities (e.g. diabetes mellitus, ischemic heart disease and other medical and surgical problems), need for mechanical ventilation and most probably cause or contributory factor to the death of the patient. Descriptive statistics were used for calculating mean and frequencies. Chi-square test was used to determine the association between variables of the study,

Results: A total of 22 cases were included. There were 21 males. The mean age was 65.7 years. Most 12(56.5%) of the patients were more than 65 years of age. Diabetes Mellitus was the most common risk factor in 15(69%) patients followed by hypertension 13(59%) and ischemic heart disease in 10(45%). The hospital admission ranged from 1 to 19 days with a mean of 7.13 days.

Conclusion: We identified length of stay, mechanical ventilation, age >65 years, pneumonia and DIC are the potential risk factors for in-hospital mortality in severely ill COVID-19 patients. This audit can guide the clinicians working in resource constrained areas, in making decision regarding hospital admission for the high-risk cases.

Keywords: Coronavirus, Complication, Death, Intensive care, Mortality.

How to Cite This Article: *Ahmad I, Rathore FA, Khan MN, Nazir SNB. Risk Factors associated with In-Hospital Death in Adult COVID-19 Patients in Karachi, Pakistan: A Retrospective Chart Review. Pak Armed Forces Med J 2024; 74(Suppl-2): S169-S174.*

DOI: https://doi.org/10.51253/pafmj.v74iSUPPL-2.4652

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INTRODUCTION

The novel coronavirus (COVID-19) originated in December 2019 from Hunan sea food market, China and rapidly spread across the globe in the form of a pandemic affecting more than 200 countries.[1] The World Health Organization (WHO) has reported around 9.4 million cases all around the globe with a death toll more than 484,000.[2] The number of deaths all over the world is unprecedented considering the medical advances of the 21st century.

COVID-19 primarily affects the respiratory system but other organs including cardiovascular, renal, gastrointestinal tract and central nervous system may also be involved.[3,4] Predominant cause of death in COVID-19 documented in the literature is respiratory failure, which may be further complicated by sepsis, Acute respiratory distress syndrome (ARDS), and micro thrombi in pulmonary vasculature. However, death from acute myocardial infarctions, myocarditis, sudden death, strokes, and cytokine release syndromes leading to kidney injury, disseminated intravascular coagulation (DIC) and multi organ dysfunction have also been reported.[5-7]

The case fatality of COVID-19 has been reported to range from 1% to 7% depending upon the population screened. In countries like South Korea and Switzerland, where mass screening was done it was documented as 1%, since mild or asymptomatic cases were also included in the data reporting. However, in countries like Spain and Italy where limited population screening was performed or only people presenting to hospital were screened it was reported as 7%.[8] The official number of confirmed cases in Pakistan is around 198,800 with 4000 deaths (27th June 2020 estimates).[9] There has been an unprecedented number of publications on different aspects of COVID-19 mostly from China, Europe and the USA. There is a paucity of data from the developing countries

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Received: 29 Jun 2020; revision received: 15 Jul 2020; accepted: 01 Sep 2020

including Pakistan which have seen a rapid rise in the number of cases in the last 4 weeks.

The aim of the paper is to provide a mortality audit of COVID-19 related death in one of the largest Navy hospitals in Pakistan and to identify the risk factors for in-hospital mortality in this population of patients. This is part on an ongoing prospective study, and we are reporting the experience of first 08 weeks.

METHODOLOGY

A retrospective chart review of patients admitted to the Intensive care unit (ICU) of PNS Shifa Hospital, Karachi between 1st April - 30th May 2020, for COVID-19 infection was conducted. The study was approved by the hospital ethics review committee (ERC/2020/REHAB/26, June 2020). PNS Shifa is the largest tertiary care hospital in the Sindh province which provides comprehensive medical and surgical services to patients and their family members from the public sector. It is the only Tertiary Care hospital in Karachi for the assessment and management of COVID-19 patients during this pandemic. Due to easy accessibility and a good professional reputation, this hospital is at present managing the bulk load of suspected and confirmed cases of COVID-19. A dedicated COVID-19 clinic has been established for the screening of suspected cases and residents are available in the emergency department round the clock to check, admit and treat suspected or confirmed cases of COVID-19.

Inclusion Criteria: Data from PCR positive cases of covid 19 who expired during hospital stay was included in the study.

Exclusion Criteria: Suspected patients of covid 19 whose diagnosis could not be confirmed on RT PCR were not included in the study.

Only seriously ill patients who were unable to maintain oxygen saturation or rapidly deteriorating were admitted in the ICU. The data collection was performed by the lead author (IA) and was extracted on the pre-designed data extraction sheet. We only included confirmed cases of COVID-19 who expired in the ICU till 30th May 2020. A sample of 22 patients was collected using the convenience sampling technique. Diagnosis was made on Polymerase Chain Reaction (PCR) of the nasopharyngeal swab sample. The national and international guidelines for management of severely ill COVID-19 patients were followed in all cases. The data recorded included basic demographics (age, gender and length of stay in hospital), documentation of co-morbidities (e.g. diabetes mellitus, ischemic heart disease and other medical and surgical problems), need for mechanical ventilation and most probably cause or contributory factor to the death of the patient. Data was computed and analyzed using SPSS 23.0 (IBM, Armonk, NY, USA). Percentages and frequencies were calculated to present a summary of baseline study parameters and Mean+SD were presented for quantitative variables. The chi-square test was used to investigate the level of association among variables. The $p \leq 0.05$ was set as threshold to detect statistical significance.

RESULTS

There were 25 mortalities in the ICU during this time. We identified 22 confirmed cases of COVID-19 who expired in the ICU of PNS Shifa during the study period. Three cases were excluded after a negative PCR test and twenty-two cases were included in the final review (Table-I). There were 21 males and 1 female. The mean age was 65.7±10.25 years with an age range of 50-84 years. Half (12/22) of the patients were above 65 years of age. Diabetes mellitus (DM) was the most common risk factor documented in 15/22(69%) patients followed by hypertension (HTN) in 13(59%) and ischemic heart disease (IHD) in 10(45%). One patient had pre-existing chronic liver disease, and another was a post-operative case who developed COVID-19 related complications during hospital admission and ultimately expired in the ICU. More than one risk factors (any combination of DM, IHD and HTN) was documented in patients 16(72%) and eight patients had three risk factors (Table-I).

The cause of death in Covid-19 was mostly MODS 10(45.45%), followed with ARDS 8(36.36), sudden cardiac death 7(31.81), respiratory failure 6(27.27%) and myocarditis 3(13.63). Table-II presents the association of patient characteristics with COVID-19 cause of death. 8/22 patients died while on ventilator support 10/22 patients did not consented for ventilator support and were either on NIV or oxygen. The hospital admission ranged from 1 to 19 days with a mean of 7.13 days. Statistically significant difference was noted in age classes with ARDS and respiratory failure. Ventilatory status had also significantly association with MODS, sudden cardiac death and respiratory failure. Table-III shows the association of deaths noted in COVID-19 with co-morbidities and complications occurred during the plan of care in hospital. Pneumonia was significantly associated with causes of death including ARDS and MODS in COVID-19. DIC was also significantly associated with ARDS. Postmortem examination was not carried out in any case.

Table-I: Clinical Features and Demographics of Patients Presented in this Case Series (n=22)

S/No	Gender	Age (Years)	Duration of Admission (Days)	Co-morbidities and associated issues	Mechanical Ventilation	Complications	Cause of death
1	Female	68	4	DM, HTN, IHD	Family did not consent for Mechanical Ventilation	Progressive respiratory failure	ARDS/Respiratory failure DNR
2	Male	69	13	DM, HTN	Initially placed on Mechanical Ventilation but then shifted to NIV	Myocarditis with ejection fraction of 40%, DIC, Cytokine storm	Myocarditis and MODS
3	Male	60	5	DM, HTN, IHD, CKD	Yes	Myocarditis, Acute on chronic Renal failure	ARDS
4	Male	66	1	Liver Cirrhosis	No	Nil	Sudden cardiac arrest
5	Male	84	11	Obstructed hernia, HTN	Family did not consent for Mechanical Ventilation	Severe COVID-19 pneumonia with MODS	MODS/DNR
6	Male	76	01	DM, HTN, IHD, Parkinson disease	Family did not consent for Mechanical Ventilation	Respiratory failure and MODS	MODS/DNR
7	Male	80	02	COPD, Bilateral subdural hematoma	Family did not consent for Mechanical Ventilation	Progressive respiratory failure	Progressive respiratory failure/DNR
8	Male	73	01	DM, HTN, IHD	Family did not consent for Mechanical Ventilation	Progressive respiratory failure	Sudden cardiac arrest after admission
9	Male	52	10	HTN, IHD, CVA	Family did not consent for Mechanical Ventilation	COVID-19 pneumonia with ARDS	Sudden cardiac arrest
10	Male	66	19	DM, HTN	Yes	Severe COVID-19 pneumonia, ARDS, Ventilator associated pneumonia, Sepsis and sudden cardiac arrest.	MODS
11	Male	60	3	DM, HTN	Yes	Severe COVID-19 pneumonia, Ventilator associate pneumonia ARDS	MODS
12	Male	55	7	DM, HTN	Yes	Cytokine storm syndrome, Severe COVID-19 pneumonia, ARDS, Acute kidney injury and septic shock	MODS
13	Male	55	4	Nil	Yes	Severe pneumonia and ARDS	MODS
14	Male	58	13	DM	Yes	Severe COVID-19 pneumonia, ARDS, Septic shock, Cytokine storm syndrome	MODS
15	Male	55	9	DM, HTN, IHD	Yes	Severe COVID-19 pneumonia, ARDS, Septic shock, Cytokine storm syndrome	MODS
16	Male	72	01	DM, HTN, IHD	Individual did not consent for mechanical ventilation	Severe COVID-19 pneumonia	Progressive respiratory failure
17	Male	50	09	HTN, IHD	Yes	Severe COVID-19 pneumonia, ARDS, Myocarditis, hypotensive shock, DIC, Acute kidney injury	MODS
18	Male	70	04	DM, HTN	Individual did not consent for mechanical ventilation	Severe COVID-19 pneumonia	Progressive Respiratory failure
19	Male	82	13	DM, IHD	Initially placed on vent and weaned off	Sudden hypotensive shock followed by cardiac arrest	Sudden cardiac arrest
20	Male	61	10	COPD, Fecal peritonitis due to intestinal perforation with Fournier gangrene	Individual did not consent for mechanical ventilation	Fecal peritonitis leading to sepsis and cardiac arrest	Sudden cardiac arrest
21	Male	78	13	DM, IHD	Individual did not consent for mechanical ventilation	Severe COVID-19 pneumonia with MODS	MODS
22	Male	56	04	DM	No		Sudden cardiac arrest

DISCUSSION

Management of COVID-19 is a global health challenge both for the high- and low-income countries. Despite rapid sharing of information, there are still many unanswered questions and lack of clear evidence for many treatments. Although lot of information is now available on the clinical presentation and basic epidemiology of COVID-19, there is still a paucity of COVID-19 mortality data especially from the developing countries. The overall case fatality rate for COVID-19 is reported to be 4.5% but ICU related mortality is remarkably high ranging from 30-70%. Remarkably high mortality rates have been documented in the elderly and patients with

comorbidities.[10-12] Therefore, it becomes imperative to have local data to guide policies and device management strategies to identify high risk patients.

Table-II: Association Between Patient's Characteristics and Cause of Death in COVID-19 (n=22)

	ARDS	Respiratory Failure	Myocarditis	MODS	Sudden Cardiac Death
Age					
50-60	6(75%)	0	3(100%)	6(60%)	2(28.6%)
61-71	2(25%)	2(33.3%)	0	1(10%)	3(42.9%)
>71	0	4(66.7%)	0	3(30%)	2(28.6)
p-value	0.022*	0.036*	0.081	0.161	0.514
Gender					
Male	7(87.5%)	5(83.3%)	3(100%)	10(100%)	7(100%)
Female	1(12.5%)	1(16.7%)	0	0	0
P-value	0.364	0.273	>0.9	>0.9	>0.9
Length of stay					
1-6	2(25%)	6(100%)	2(66.7%)	4(40%)	3(42.9%)
7-12	4(50%)	0	1(33.3%)	3(30%)	2(28.6%)
13-18	1(12.5%)	0	0	2(20%)	1(14.3%)
>18	1(12.5%)	0	0	1(10%)	1(14.3%)
p-value	0.115	0.041*	0.794	0.648	0.505
Mechanical Ventilation					
Family did consent	2(25%)	6(100%)	0	3(30%)	3(42.9%)
Yes	6(75%)	0	2(66.7%)	7(70%)	2(28.6%)
No	0	0	1(33.3%)	0	2(28.6%)
p-value	0.095	0.007*	0.124	0.08*	0.08*

Table-III: Association Between Patients' Complication, Co-morbidity and Cause of Death in COVID-19 (n=22)

	ARDS	Respiratory Failure	Myocarditis	MODS	Sudden Cardiac Death
DM	5(62.5%)	5(83.3%)	2(66.7%)	8(80%)	4(57.1%)
P-value	>0.9	0.616	>0.9	0.630	0.387
HTN	6(75%)	5(83.3%)	2(66.7%)	7(70%)	4(57.1%)
P-value	>0.9	0.616	>0.9	>0.9	0.630
IHD	4(50%)	4(66.7%)	2(66.7%)	4(40%)	3(42.9%)
P-value	>0.9	0.348	0.571	0.691	>0.9
CKD	0	0	1(33.3%)	1(10%)	0
P-value	0	0	0.136	0.455	0
Liver cirrhosis	0	0	0	0	1(14.3%)
P-value	0	0	0	0	0.317
Stroke	1(12.5%)	0	0	0	1(14.3%)
P-value	0.364	0	0	0	>0.9
COPD	0	1(16.7%)	0	0	1(14.3%)
P-value	0	0.481	0	0	>0.9
Pneumonia	8(100%)	4(66.7%)	1(33.3%)	9(90%)	2(28.6%)
P-value	0.018*	>0.9	0.527	0.031*	0.052
DIC	4(50%)	0	1(33.3%)	3(30%)	0
P-value	0.039*	0.266	>0.9	0.624	0

SARS-COV-2 attaches to the host cell through the Angiotensin-converting enzyme 2 (ACE-2) receptor leading to internalization and subsequent replication of the virus. During that phase a dysregulated immune response is generated which leads to hyper inflammation and release of mediators of inflammation including complement and Interleukin-6 (IL-6).[13] This results in a cytokine storm syndrome and MODS leading to death. During the cytokine storm and oxidative stress, a hypercoagulable state occurs in the body with increased risk of venous and arterial embolism. This may be further complicated by development of DIC which is associated with 27 times increased chances of death. A gender difference in COVID-19 related mortality has been reported and males are more severely affected. This is likely related to the higher expression of ACE-2 receptor in males as compared to females and the lack of the protective effect of estrogen and X chromosome.[14]

Table-IV: Comparison of this Series with Selected COVID-19 Mortality Reports from Wuhan, China and Italy

Parameters	Zhou et.al.	Du et.al.	Onder et.al.	Current Series
Number of cases	54	21	355	22
Country	China	China	Italy	Pakistan
World Bank Income Based Classification	Upper-Middle Income Country	Upper-Middle Income Country	High Income Country	Low-Middle Income Country
Centers	Jinyintan Hospital and Wuhan Pulmonary Hospital (Wuhan, China)	Wuhan Pulmonary Hospital (Wuhan, China)	Country level data	PNS Shifa Hospital (Karachi)
Median age (Years)	69	70	79.5	65.72
Gender	38(70%) M	10(47.6%) F	106(30.0%) F	21(95.5%) M
Hypertension	26(48%)	13(61.9)	Nil	13(59%)
Diabetes mellitus	17(31%)	6(28.6)	126(35.5%)	15(68.2%)
Ischemic heart disease	13(24%)	12 (57.1)	117(30%)	10(45.5%)
Chronic obstructive lung disease	4(7%)	Nil	Nil	2(9%)
Chronic kidney disease	2(4%)	1(4.7)	Nil	01(4.5%)
Chronic liver disease	Nil	1(4.7)	Nil	01(4.5%)
Post-operative case	Nil	Nil	Nil	01(4.5%)
Active cancer	Nil	Nil	72(20.3%)	NIL
Stroke	Nil	Nil	34(9.6%)	01

Zhao *et al.* performed a retrospective cohort study of COVID-19 related mortality at 2 different hospitals in Wuhan, China.[15] There are some similarities and differences with our cohort (Table-II). The mean age in our cohort is higher than the mean age reported by Zhao *et al.* (65 years Vs. 54.5 years) Males constitutes the predominate group however we had very few females in our cohort than their group. This could be attributed to less severity of COVID-19 in females, but such low numbers could also represent the attitude of society towards females where males are given priority than females. They reported HTN (19.0%) as the most common risk factor followed by DM (8.2%), and cardiovascular diseases (CVD) in 2.7%. Whereas we documented diabetes mellitus as the most common risk factor in 15(69%), followed by HTN 13(59%) and

IHD in ten patients. We are not sure about the high prevalence of diabetes in our cohort. One explanation can be that due to low level of awareness in the general public , combined with low literacy rates and inadequate follow-up by patients the incidence of uncontrolled DM is higher in Pakistan and might have contributed to a higher number in this study.[16]

Our data has certain similarities and differences with the data reported from other countries (Table-IV). Zhao and Colleagues predicted that age more than 60 years, male gender and any co-morbid including DM, HTN and cerebrovascular disease are risk factors for increased mortality in COVID-19 patients. We also observed higher mortality in males along with an increased prevalence of DM and HTN in our cohort.

Du *et al.* presented the mortality audit of 22 patients from Wuhan, China. They reported HTN in 13(61.9%), DM in 6(28.6%) and IHD in 12(57.1%) patients which is quite similar to our findings.[17]

Onder and colleagues studied the predictors of mortality in a nationwide Italian cohort of 355 patients.[18] The mean age in their report was 79 years as compared to 65.7 years in our cohort. One possible explanation is that the life expectancy of 83 years in Italy is much better than 67.7 years for Pakistan. However, one important finding is the presence of risk factors in large number of their cohort. Eighty-nine (25.1%) had a one disease, 91(25.6%) had 2 diseases, and 172(48.5%) had 3 or more associated diseases. In comparison, patients in our study had two risk factors in 16(72%) and had three risk factors in 8(36%).

Mortality in our case series was predominantly due to MODS in ten cases. Six patients expired due to sudden cardiac death although we cannot comment if it was due to arrhythmias or pulmonary embolism. However, this could represent myocarditis or heart failure which is being identified as an important cause of mortality in COVID-19. Five deaths in our study were due to ARDS. Ruan and colleagues from Wuhan, China reported respiratory failure in 53% of their cohort followed by myocardial damage in 7% and both in 33% cases.[19] The mean duration of admission in our cases was 7 days and 14/22 patients died within ten days.

LIMITATION OF STUDY

Considering the global mortality of COVID-19, this is a relatively small case series. But it adds useful data to the global pool of knowledge being the first attempt of COVID-19 mortality audit from Pakistan. It was a retrospective review and included only risk factors for in-hospital mortality. There is a need for detailed documentation and reporting of the laboratory and radiological parameters in future COVID-19 mortality audits. In addition, this chart review did not document the possible treatment related complications which can be critical in-patient evaluation and outcome.

CONCLUSION

This single center mortality audit suggests that increasing age with the presence of pneumonia, length of stay and DIC are at an increased risk of death. There is also an increased the risk of death for patients who develop ARDS, cardiac injury and acute kidney disease. We hope that this experience of a major tertiary care hospital for COVID-19 related mortality will guide the clinicians in making decision regarding hospital admission for the high-risk cases. This will likely identify cases at higher risk for mortality so that an early and aggressive workup and treatment plan can be instituted, and resources can be prioritized during this global health care crisis. This is especially important for resource constrained areas like Pakistan.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

IA & FAR: Data acquisition, data analysis, critical review, approval of the final version to be published.

MNK & SNBN: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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