ORIGINAL ARTICLE

COVID-19 Inside Out: In-hospital Outcomes at a Public Sector Tertiary Care Hospital in Karachi

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ABSTRACT

Objective: To present in-hospital COVID-19 mortality and the associated factors at a public sector tertiary care hospital in Karachi

Methodology: The current prospective, observational study was conducted at Jinnah Postgraduate Medical Center, Karachi, Pakistan from June 1 to August 30, 2021 with the approval of the hospital ethics committee. Data was collected prospectively from patients' medical record files. COVID-19 infection positive cases were diagnosed according to the guidelines of the WHO on laboratory investigation of real time polymerase chain reaction tests on a nasopharyngeal or oropharyngeal swab.

Result: Total 143 patients were enrolled in the study with median (IQR) age of 58 (48–69). The majority of the patients were males (n=96, 67.13%) and had moderate to severe disease (n=128, 89.51%). During their hospital stay, patients developed the following complications; pneumonia (n=99, 69.23%), ARDS (n=19, 13.28%), sepsis (n=11, 7.69%), septic shock (n=5, 3.49%) and pedal edema (n=2, 1.39%). As many as 104 (72.72%), 69 (48.25%), and 42(29.37%) patients required pharmatherapy, non-invasive ventilation, and mechanical ventilation respectively. While 54 (37.76%) patients died during their hospital stay. On multivariable model, pneumonia, use of non-invasive ventilation, and mechanical ventilation, were identified as independent predictors of mortality.

Conclusion: Most of the patients in our study had moderate to severe disease. Therefore, the study indicates that timely presentation to the hospital is of great importance to avoid adverse events which are significantly associated with mortality.

Keywords: COVID-19 infection, in-hospital outcomes, mortality, SARS-CoV-2, Karachi, Pakistan

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INTRODUCTION

In December 2019, the world came across a new challenge for which it was unprepared. China officially declared that a respiratory illness caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2), had begun in the city of Wuhan with an estimated average incubation period of 5.1 days[1,2]. The virus was spreading so dramatically that within a span of a few weeks, it had spread across the world and affected more than 210 countries with a mortality rate of 2.85% when it was declared a global pandemic by the Word health Organization (WHO) on March 11, 2020[4,3].

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After the 1918 Influenza pandemic, COVID-19 brought the biggest crises for public health[5]. Although the clinical spectrum of the disease is quite broad, the commonest presentation is flu-like illness. New emerging variants such as alpha, beta, and delta were associated with new waves of COVID-19 across the world[6]. In spring 2020, the first COVID-19 wave occurred which was at its peak in the summer season in Pakistan. Then the second wave emerged in fall 2020 and its intensity was decreased in early 2021[7]. A third wave started with the emergence of a new variant B.1.1.7 from the United Kingdom, detected in Pakistan on 27th January, 2021, leading to 100 deaths per day across the country[8].

Pakistan being a middle-income country with an estimated population of 197 million and having a weaker healthcare system, has been at risk of higher transmission of COVID-19[9]. Moreover, the failure to achieve distancing because of social and economic

barriers has been encouraging further waves of infection. Therefore, it is of immense importance to examine possible factors at all levels that could worsen the patient outcome, so that it can be managed at the earliest in order to sustain the smooth functioning of healthcare systems in our local settings. We aim to present in-hospital Covid-19 mortality and the associated factors at a public sector tertiary care hospital.

METHODOLOGY

The current prospective, observational study took place at Jinnah Postgraduate Medical Center, Karachi, Pakistan. The study was conducted from June 1 to August 30, 2021. The Institutional Review Board of JPMC approved this study by certifying it with IRB certificate No. F.2-81/2020-GENL/42869/JPMC. Each COVID-19 positive case was diagnosed according to the guidelines of WHO on laboratory investigation of real time polymerase chain reaction test on a nasopharyngeal or oropharyngeal swab. Records of all admitted patients were reviewed.

Patients' age, gender, comorbidities, presenting symptoms, diseases severity as assessed by Wang criteria, laboratory investigations including haemoglobin, total leukocytes count (TLC), lymphocytes, neutrophils, total bilirubin, urea, creatinine, sodium, potassium, c-reactive protein (CRP), prothrombin time (PT), international normalized ratio (INR), ferritin, d-dimer, procalcitonin levels, other events during hospitalization such as development of pneumonia, sepsis ARDS, septic shock, requirement of non-invasive ventilation (NIV), and mechanical ventilation (MV) were recorded.

The collected data was entered into SPSS version 21 for statistical analysis. Categorical variables were summarized as frequency and percentage. Numerical variables were presented as median with inter-quartile range (IQR) after assessing the assumption of normality with Shapiro-Wilk test. Chi-square or Fisher-Exact test was applied to compare categorical variables among survivors and non-survivors whereas Mann-Whitney U-test was applied to compare numerical variables. Univariable odds ratio with 95% confidence interval were computed using binary logistic regression to assess significant factors associated with mortality. Variables with p-value<0.25 on univariate model were taken as candidates to build the final regression model. A p-value of 0.05 was taken as statistically significant and <0.01 is highly significant on final regression model.

RESULTS

Total 143 patients were made part of the study with median (IQR) age of 58 (48–69). Most of the patients were males (n=96, 67.13%), non-smokers (n=123, 86.01%) and had moderate to severe disease (n=128, 89.51%). The most frequently observed comorbidity was hypertension (n=70, 48.95%), followed by diabetes (n=59, 41.25%), ischemic heart disease (n=20, 13.98%), chronic obstructive pulmonary disease (n=8, 5.59%), chronic kidney disease (n=5, 3.49%), chronic liver disease (n=3, 2.09%), and malignancy (n=1, 0.69%). Presenting features included fever (n=124, 86.71%), dyspnea (n=99, 69.23%), cough (n=92, 64.34%), fatigue (n=36, 25.17%), myalgia (n=35, 24.47%), diarrhoea (n=22, 15.38%), headache (n=11, 7.69%), sore throat (n=10, 6.99%), chest pain (n=5, 3.49%), haemoptysis (n=4, 2.79%) and rhinorrhea (n=3, 2.09%). During their hospital stay, patients developed the following complications: pneumonia (n=99, 69.23%), ARDS (n=19, 13.28%), sepsis (n=11, 7.69%), septic shock (n=5, 3.49%), and pedal edema (n=2, 1.39%). As many as 104 (72.72%), 69 (48.25%), and 42 (29.37%) patients require pharmatherapy, non-invasive ventilation, and mechanical ventilation respectively. While 54 (37.76%) patients died during their hospital stay, 89 (62.24%) were survivors and were discharged alive.

Table 1 presents the comparison of patients' characteristics among COVID-19 survivors and non-survivors. Survivors were significantly younger than non-survivors (p<0.001). Frequency of diabetes (p=0.007) and hypertension (p=0.009), moderate to severe illness (p=0.001), pharmatherapy (p=<0.001), sepsis (p<0.001), septic shock (p<0.01), ARDS (p<0.01), use of NIV (p<0.001), and the use of MV (p<0.001) were significantly higher in non-survivors than in survivors.

Table 2 shows the comparison of patients' presenting vitals and laboratory investigations among alive and dead patients. Respiratory rate (p=0.001), TLC (p=0.005), lymphocytes count (p=0.003), neutrophils count (p<0.001), urea (p<0.001), creatinine (p=0.002), INR (p=0.021), ferritin levels (p=0.008), d dimer (p=0.006) and procalcitonin levels (p=0.003) were significantly different among alive discharged and non-survivors.

Table 3 presents uniavriable and multivariable association of variables with mortality. On univariables model, advanced age (OR=1.06, 95% CI: 1.03 - 1.09), presence of diabetes (OR=2.57, 95% CI: 1.29 - 5.19) and hypertension (OR=2.50, 95% CI: 1.25 - 5.01), increasing TLC (OR=1.09, 95% CI: 1.03 - 1.16), neutrophils (OR=1.07, 95% CI: 1.02 - 1.12), ferritin levels (OR=1.01, 95% CI: 1 - 1.01), use of NIV (OR=241.81, 95% CI: 31.09 - 1880-28) and MV (OR=124.86, 95% CI: 26.96 - 572.92) were associated with increased risk of mortality. On multivariable model, when effects were adjusted for other covariates,

Table 1: Comparison of Patients' Characteristics Among COVID-19 Survivors and Non-survivors

Variables	Alive n (%)	Dead n (%)	p-value
Socio-demographics			
Age#	54 (45 - 61)	65 (54.5 - 73)	**<0.001
Male gender	63 (65.6)	33 (34.4)	0.232
Smoking	10 (50)	10 (50)	0.224
Comorbidity			
Diabetes	29 (49.2)	30 (50.8)	**0.007
Hypertension	36 (51.4)	34 (48.6)	**0.009
IHD	10 (50)	10 (50)	0.224
CKD	2 (40)	3 (60)	†0.366
Malignancy	0 (0)	1 (100)	†0.378
COPD	4 (50)	4 (50)	†0.476
CLD	2 (66.7)	1 (33.3)	†1.000
Presenting features			
Fever	77 (62.1)	47 (37.9)	0.929
Myalgia	23 (65.7)	12 (34.3)	0.625
Fatigue	24 (66.7)	12 (33.3)	0.526
Cough	60 (65.2)	32 (34.8)	0.324
Haemoptysis	4 (100)	0 (0)	†0.297
Headache	6 (54.5)	5 (45.5)	†0.748
Dyspnea	59 (59.6)	40 (40.4)	0.328
Chest Pain	3 (60)	2 (40)	†1.000
Mild illness	15 (100)	0 (0)	**0.001
In-hospital events			
Pharmatherapy	50 (48.1)	54(51.9)	**<0.001
Pneumonia	66 (66.7)	33(33.3)	0.135
Sepsis	0 (0)	11(100)	†**<0.001
Septic shock	0 (0)	5(100)	†**<0.007
ARDS	0 (0)	19(100)	†**<0.001
Use of NIV	16 (23.2)	53(76.8)	**<0.001
Use of MV	2 (4.8)	40(95.2)	**<0.001

CKD: chronic kidney disease, CLD: chronic liver disease, COPD: chronic obstructive pulmonary disease IHD: ischemic heart disease NIV: non-invasive ventilation, MV: mechanical ventilation, #: Age is expressed as median (inter-quartile range), †Fisher-Exact test was reported, **Significant at p<0.01

use of NIV (aOR=1276.53, 95% CI: 15.63-104227.54) and (94.25, 95 CI: 6.44-1378.66) were associated with odds of mortality.

Table 2: Comparison of Vitals and Laboratory Investigations Among Alive and Dead Patients

Variables	Alive Median (IQR)	Death Median (IQR)	p-value
Systolic blood pressure	130 (120-140)	130 (109-140)	0.366
Diastolic blood pressure	80 (74-90)	80 (66.8-90)	0.090
Respiratory rate	22 (20-25)	28 (21.8-32)	**0.001
Pulse rate	96 (89-104)	98.5 (78.8-110)	0.633
Haemoglobin	12.2 (11.15-13.6)	12.3 (10.3-13.8)	0.525
platelets	209 (153-310)	214.5 (127.5-288)	0.376
TLC	10 (7.3-14.1)	13.2 (8.7-22.1)	**0.005
Lymphocytes	15 (9.3-19)	10 (5.5-17)	**0.003
Neutrophils	79 (73.9-85.5)	87.5 (80-91.3)	**<0.001
Total bilirubin	0.52 (0.41-0.7)	0.5 (0.4-0.8)	0.332
Urea	42 (26.5-51.5)	58.5 (37-103.8)	**<0.001
Creatinine	0.89 (0.74-1)	1 (0.8-2.2)	**0.002
Sodium	136 (133-138)	137 (134-140)	0.079
Potassium	3.9 (3.6-4.3)	3.8 (3.5-4)	0.144
CRP	61 (14.8-119)	94.5 (26.8-175)	0.050
PT	10.7 (10.3-12)	10.7 (10.3-11.9)	0.925
INR	0.93 (0.9-1.01)	0.955 (0.9-1)	*0.021
Ferritin	577 (331.5-1135)	792 (577-1365.75)	**0.008
D dimer	0.3 (0.3-0.7)	0.6 (0.3-2.8)	**0.006
Procalcitonin	0.19 (0.12-0.36)	0.7 (0.2-0.7)	**0.003

CRP: C-reactive protein, TLC: total leukocytes count, PT: Prothrombin time, INR: international normalized ratio, *Significant at p<0.05, **Significant at p<0.01

DISCUSSION

We aimed to ascertain the in-hospital COVID-19 patients' mortality and its associated factors. We observed that around 40% of the patients were non-survivors. A similar mortality rate (39%) was reported in another Pakistani study[10]. In-hospital death rates of 47%, 40.8% and 48.6% were reported from other parts of the world[11-13]. However, a meta-analysis showed a lower in-hospital mortality rate of 24.3%[14]. In our study, most of the admitted patients were male and majority was admitted in hospital in a moderate to severe condition. In contrast to our findings, another Pakistani study reported a higher proportion of mild disease cases than moderate to severe. However, that study was conducted in one of the biggest free of cost hospitals in Karachi which is easily accessible to patients. Otherwise in our society, usually health seeking behaviour of people is casual with the assumption that they were safe from COVID-19 which was also reported in a survey conducted in Karachi[15].

Predominance of males among infected patients has also been documented in other studies[16,17]. The most plausible explanation for this is simple that males spend more time outdoors than females in our society hence are more exposed and vulnerable to infections. However, mortality rate among males and females was not significant in the current investigation which is in line with the findings of many other studies[10,16,17]. However, there are some studies that report higher mortality risk in males than females[11,18]. The difference in males and females mortality rates could be due to higher smoking rate among males which has overall influence on the immune system response.

Table 3: Univariable and Multivariable Predictors of Mortality

Variables	OR (95% CI)	p-value	aOR (95% CI)	p-value
Age (in years)	1.06 (1.03 - 1.09)	**<0.001	1.04 (0.96-1.13)	0.306
Male gender	0.65 (0.32 - 1.32)	0.234	-	-
Smoking	1.79 (0.69 - 4.64)	0.228	-	-
Diabetes	2.57 (1.29 - 5.19)	**0.007	0.17 (0.01-2.06)	0.162
Hypertension	2.50 (1.25 - 5.01)	*0.010	6.83 (0.62-75.14)	0.116
IHD	1.79 (0.69 - 4.64)	0.228	-	-
Systolic blood pressure	0.99 (0.98 - 1.01)	0.241	1.01 (0.95-1.07)	0.684
Diastolic blood pressure	0.984 (0.96 - 1.01))	0.167	0.91 (0.82-1.02)	0.103
Respiratory rate	0.996 (0.98 - 1.01)	0.600	-	-
Platelets	0.99 (0.99 - 1)	0.135	1 (0.99-1.01)	0.847
TLC	1.09 (1.03 - 1.16)	**0.003	1.03 (0.91-1.16)	0.677
Neutrophils	1.07 (1.02 - 1.12)	**0.003	1 (0.97-1.03)	0.980
Urea	1.01 (1 - 1.02)	**0.004	1.01 (0.99-1.04)	0.345
Creatinine	1.01 (0.99 - 1.03)	0.242	1.01 (0.91-1.12)	0.880
CRP	1 (1 - 1.01)	0.053	1 (0.99-1.01)	0.896
Ferritin	1.01 (1 - 1.01)	*0.032	1 (1-1)	0.769
Use of NIV	241.81 (31.09 - 1880-28)	**<0.001	1276.53 (15.63-104227.54)	**0.001
Use of MV	124.86 (26.96 - 572.92)	**<0.001	94.25 (6.44-1378.66)	**0.001
Pneumonia	0.55 (0.27 - 1.13)	0.103	0.02 (0-0.33)	**0.007

*Significant at p<0.05, **Significant at p<0.01

In our study, increasing age was observed to be linked with increased mortality risk. Increasing age is a consistent factors that has been reported globally as predictor of death for COVID-19 infection[10,16]. In our study, hypertension was the most frequent comorbity and was also linked with higher death risk in univariate analysis. Hypertension was also seen as COVID-19 mortality predictor in other studies[19]. Moreover, hypertension is a well-known factor for increased risk of all-cause mortality regardless of age and gender[20]. In present study, diabetic patients were more likely to be non-survivors but there was no association when sample was adjusted for other covariates which could be due to low sample size. However, various studies report that diabetes could worsen the patients' outcome and prolong the recovery time and even cause mortality[21-23].

We found that neutrophils' counts, urea, creatinine, ferritin levels, CRP levels, d-dimer, and procalcitonin were significantly higher among non-survivors. Wu et al, in their study, also reported higher neutrophils, d-dimer, ferritin levels, and CRP levels among non survivors[24]. Almazeedi et al and Giacomelli et al also reported higher levels of CRP and d-dimer in their studies[16,25]. It is also noticeable that non-survivors in our study developed acute ARDS, sepsis, septic shock which is in line with other studies[11,16]. Interestingly, pneumonia was associated with less risk of mortality in our study which may be taken as patients who were developing pneumonia were surviving, as compared to patients who were developing any other complications.

The current study presented an experience of public sector tertiary care hospital in Karachi. In our study, antibiotics' impact on mortality was not studied which could further guide the clinicians in management of COVID-19 cases. Secondly, being a single center study, the sample size was not sufficiently large. It might be possible to obtain more possible associated factors with larger sample size. Therefore, a study with larger sample size may be conducted as pandemic is not over yet, to further strengthen the findings.

CONCLUSION

Most of the patients in our study had moderate to severe disease. Thus the study indicates that timely presentation to the hospital is of great importance to avoid adverse events which are significantly associated with mortality.

Conflict of Interest: The authors declare that they have no conflict of interest.

Authors' Contribution: SA proposed study concept and critically revised initial draft, NS prepared study protocol and helped in data collection, BH and NA wrote initial manuscript draft and collected data, SJ performed data entry and data analysis. All authors have proofread and approved the manuscript.

REFERENCES

1. WHO. Timeline: WHO's COVID-19 response. 2019 [Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline/#].
2. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med. 2020;172(9):577–82. doi: 10.7326/M20-0504.
3. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta Biomed. 2020;91(1):157–160. doi: 10.23750/abm.v91i1.9397.
4. Coronavirus Worldwide Graphs. Worldometer. 2020. https://www.worldometers.info/coronavirus/worldwide-graphs/
5. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus Disease 2019 (COVID-19): a review. JAMA. 2020;323(18):1824–36.
6. Karim SSA, Karim QA. Omicron SARS-CoV-2 variant: a new chapter in the COVID-19 pandemic. Lancet. 2021;398(10317):2126-2128.
7. Ejaz M, Syed MA. COVID-19 third wave: a challenge for overburdened and underdeveloped healthcare system of Pakistan. Turk J of Med Sci. 2021;51:2789-91.
8. Kamran K, Ali A. Challenges and Strategies for Pakistan in the Third Wave of COVID-19: A Mini Review. Front Pub Health. 2021;9:690820.
9. Raza, Sohail R, Rasheed MA, Rashid MK. Transmission potential and severity of COVID-19 in Pakistan. Preprints.2020. 2020040004. DOI:10.20944/preprints 202004.0004.v1
10. Sarfaraz S, Shaikh Q, Saleem SG, Rahim A, Herekar FF, Junejo S, et.al. Determinants of in-hospital mortality in COVID-19; a prospective cohort study from Pakistan. PLoS One. 2021;16(5):e0251754.
11. Rieg S, von Cube M, Kalbhenn J, Utzolino S, Pernice K, Bechet L, et.al. COVID UKF Study Group. COVID-19 in-hospital mortality and mode of death in a dynamic and non-restricted tertiary care model in Germany. PLoS One. 2020;15(11):e0242127.
12. Baqui P, Bica I, Marra V, Ercole A, van der Schaar M, et.al. Ethnic and regional variations in hospital mortality from COVID-19 in Brazil: a cross-sectional observational study. Lancet Glob Health. 2020;8:e1018–e26.
13. Bonetti G, Manelli F, Patroni A, Bettinardi A, Borrelli G, Fiordalisi G, et al. Laboratory predictors of death from coronavirus disease 2019 (COVID-19) in the area of Valcamonica, Italy. Clin Chem Lab Med. 2020; 58:1100–5. doi: 10.1515/cclm-2020-0459.
14. Mesas AE, Cavero-Redondo I, Álvarez-Bueno C, Sarriá Cabrera MA, Maffei de Andrade S, et.al. Predictors of in-hospital COVID-19 mortality: A comprehensive systematic review and meta-analysis exploring differences by age, sex and health conditions. PLoS One. 2020;15(11): e0241742.
15. Casual attitude towards Covid-19 in Pakistan remains cause for concern: study. Dawn. 2020. Availeable at https://www.dawn.com/news/1571872
16. Giacomelli A, Ridolfo AL, Milazzo L, Oreni L, Bernacchia D, Siano M, et al. 30-day mortality in patients hospitalized with COVID-19 during the first wave of the Italian epidemic: A prospective cohort study. Pharmacol Res. 2020;158:104931.
17. Alkundi A, Mahmoud I, Musa A, Naveed S, Alshawaf M. Clinical characteristics and outcomes of COVID-19 hospitalized patients with diabetes in UK: A retrospective single centre study. Diabetes Res Clin Pract . 2020 Jul;165:108263. doi: 10.1016/j.diabres. 2020.108263.
18. Nguyen NT, Chinn J, De Ferrante M, Kirby KA, Hohmann SF, Amin A. Male gender is a predictor of higher mortality in hospitalized adults with COVID-19. PLoS One. 2021;16(7):e0254066.
19. Iþýk F, Çap M, Akyüz A, Bilge Ö, Aslan B, Ýnci Ü, et.al. The effect of resistant hypertension on in-hospital mortality in patients hospitalized with COVID-19. J Hum Hypertens. 2022;36(9):846-851. doi: 10.1038/s41371-021-00591-8.
20. Rodilla E, Saura A, Jiménez I, Mendizábal A, Pineda-Cantero A, Lorenzo-Hernández et.al. Association of Hypertension with All-Cause Mortality among Hospitalized Patients with COVID-19. J Clin Med. 2020;9(10):3136.
21. Eastin C, Eastin T. Clinical Characteristics of Coronavirus Disease 2019 in China: Guan W, Ni Z, Hu Y, et al. N Engl J Med. 2020 Feb 28 [Online ahead of print] DOI: 10.1056/NEJMoa2002032. J Emerg Med. 2020;58(4):711–2.
22. Wang L, He W, Yu X, Hu D, Bao M, Liu H.et.al. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. J Infect. 2020;80(6):639-645.
23. Carrasco-Sánchez FJ, López-Carmona MD, Martínez-Marcos FJ, Pérez-Belmonte LM, Hidalgo-Jiménez A, Buonaiuto V, et al. Admission hyperglycaemia as a predictor of mortality in patients hospitalized with COVID-19 regardless of diabetes status: data from the Spanish SEMI-COVID-19 Registry. Ann Med. 2021; 53(1):103-116.
24. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934-943.
25. Almazeedi S, Al-Youha S, Jamal MH, Al-Haddad M, Al-Muhaini A, Al-Ghimlas F, et al. Characteristics, risk factors and outcomes among the first consecutive 1096 patients diagnosed with COVID-19 in Kuwait. EClinical Med. 2020;24:100448. doi: 10.1016/j.eclinm.2020. 100448