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Factors Associated with Early and Late COVID-19 Related Deaths in Riyadh city, Saudi Arabia: A Prospective Cohort study

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***Abstract*---**Background: COVID-19 is a contagious viral disease affecting the respiratory system leading to severe acute respiratory distress syndrome (ARDS) and can progress to respiratory failure and death. Objective: To evaluate factors associated with early versus late COVID-19 related deaths for patients who were admitted to the intensive care unit (ICU). Methods: We prospectively followed up all critically ill cases with a confirmed diagnosis of COVID-19 who progressed to death at the adult ICU in Prince Mohammed bin Abdul-Aziz hospital in Riyadh, from January to December, 2020. We analyzed demographic characteristics, presenting symptoms and signs before and after admission, associated comorbidities, the use of mechanical ventilation and admission-death duration. A subsample of 160 cases were divided into two groups according to the admission to death duration, Group 1 < 14 days (n = 71) and group 2 > 14 days (n = 89). Results: A total of 160 deaths underwent detailed analysis. The population's median age was 60.4 years. There was significantly more deaths occurred in males 123/160 (77.5%) compared to females

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37/160 (22.5%) (P < 0.001). There was significantly higher mortality cases in the age group of 60-69 years occurring in group 2 compared to group 1. All possible risk factors were analyzed by the univariate model, persistent dry cough, preexisting lung disease and prolonged ARDS were selected for multivariable logistic regression model. Persistent dry cough and prolonged ARDS were associated with increased likelihood of mortality with an adjusted odd ratios (AOR) = 6.9 and 2.5 respectively. Conclusions: Preexisting lung disease in males aged 60-69 years were strongly associated with COVID-19 related deaths. However, persistent dry cough and prolonged ARDS were more likely to be associated with late deaths regardless of the use of mechanical ventilation.

***Keywords*---**COVID-19, pandemic, risk factors, mortality, health policy, comorbidity, gender.

Introduction

Coronaviruses (COVS), a large family of single-stranded RNA viruses, can infect animals and humans, causing respiratory, gastrointestinal, hepatic, and neurologic diseases (1). In late December 2019, many local health authorities reported clusters of patients with virus-infected pneumonia of unknown origin (2). These cases had a history of exposure to a large seafood market in Wuhan, China. Later in February, it was confirmed the infection was caused by a contagious novel coronavirus (sars-cov-2) COVID-19, spreading through the droplet route and close contact causing acute severe respiratory distress syndrome (ARDS) (3, 4). So far, this disease outbreak spread from Wuhan, China to more than166 countries worldwide. Patients infected with COVID-19 had a wide range of clinical manifestations ranging from asymptomatic to mild and moderate symptoms to severe respiratory distress. The common presenting symptoms were primarily fever, fatigue, dry cough, dyspnea with or without nasal congestion, runny nose, and loss of taste (5). The majority of patients with mild to moderate symptoms have a favorable prognosis and does not require hospital admission, but needed isolation or self-quarantine. However, critically ill patient with respiratory distress requires hospital admission, isolation and advanced care including admission to the ICU, mechanical ventilation and hemodynamic support (5, 6). The overall case fatality rate (CFR) of COVID-19 has been estimated to range from 0.001% to 10 % and can be as high as 28% among hospitalized and critically ill patients aged 20 to ≥ 80 years (5-7). Epidemiological studies have shown that about 15% to 20% of symptomatic moderate cases required hospitalization and 3% to 5% of severe cases required admission to critical care units (8-9). The ICU COVID-19 related mortality is based on the number of deaths relative to the number of cases admitted to the ICU, which is estimated to range from 50% to 65% (8-10). Furthermore, patients requiring mechanical ventilation the mortality rates substantially increase to 97% (9-11). Recent report have shown that the COVID-19 ARDS mortality rates of 50% to 65% is substantially higher than ARDS mortality rates of 35% to 46% from other causes (12). Several studies have reported the clinical characteristics and risk factors associated with mortality in patients with COVID-19 infection with varying results (7-12). No study compared factors associated with early versus late COVID-19 related deaths. This study aims to evaluate factors associated with early versus late COVID-19 related deaths for patients who were admitted to the adult ICU.

Materials and Methods

After obtaining institutional review board (IRB) # 20-266 approval, we prospectively followed up all critically ill cases with confirmed diagnosis of COVID-19 who were admitted to the hospital adult ICU at Prince Mohammed bin Abdul-Aziz hospital (PMAH) in Riyadh, Saudi Arabia from January 1, 2020, till December 30, 2020. We collected data for all symptomatic cases who deteriorated and progressed to death. Data privacy and confidentiality were maintained throughout the study. We are defining COVID-19 related deaths as; those occurring independently from preexisting diseases that may have caused death. Acute kidney injury was diagnosed according to the KDIGO clinical practice guidelines and acute respiratory distress syndrome (ARDS) was diagnosed according to the Berlin Definition (14, 15). Fever was defined as axillary temperature of ≥37·5°C. A confirmed COVID-19 diagnosis was made via reverse transcriptase-polymerase chain reaction (RT-PCR) test from a nasopharyngeal swab. We included adult patients aged > 18 years. We excluded cases with mild/moderate disease or those who survived, pregnant women, and children aged < 18 years. We analyzed all included cases' demographic characteristics, presenting symptoms and signs before and after admission, associated and number of comorbidities, the need for mechanical ventilation, and admission-death duration. A total of 2,000 symptomatic critically ill cases were admitted to the ICU during the study period of which 500 cases died during admission. A subsample of 160 cases with complete data underwent detailed analysis. The mortality cases were divided into two groups according to admission to death duration period. Group 1 < 14 days (n = 71) and group 2 > 14 days (n = 89).

Statistical analysis

Statistical analysis was done via SPSS software (Statistical Package for the Social Sciences, version 25, SPSS Inc, Chicago, Illinois, USA). Continues data presented as mean/median. Student's t test was used to compare means, Mann-Whitney U test used to compare median and chi-square ($\chi 2$) or Fisher exact tests were used to compare dichotomous variables. Conditional logistic regression analysis was used to estimate separately each risk factor associated with mortality. Results were presented by odds ratios (OD) including 95% confidence interval and determination of significance for each group. P values of less than 0.05 were considered to indicate statistical significance.

Results

In this prospective cohort study there was a total of 5,000 symptomatic adult patients with a confirmed diagnosis of COVID-19 throughout the period from January till December 2020. Of which, 500 of these patients died and 4,500 patients survived and recovered during the study period. The overall case-fatality rate (CFR) was10%. A total of 2,000 critically ill cases were admitted to the ICU during the study period of which 500 cases died during admission, making the

ICU mortality rate 25%. A total of 160 deaths underwent detailed analysis and evaluation for the associated risk factors for early versus late deaths. The median admission to death duration was 17 days ranging from 1 day to 315 days. Group 1; 71 patients (44.4%) died within the first 14 days, and Group 2; 89 patients (55.6%) died 14 days after admission. There were significantly more patients that survived > 14 day, P = 0.001. The study population's median age was 60.4 years (30 – 90 years). There were significantly higher mortality cases in the age group 60-69 years in group 2 compared to group 1 (Table 1). There was a significantly higher mortality cases in the age group ≥ 80 years occurred in group 1 compared to group 2 (Table 1) and (Fig 2). The gender related deaths were significantly higher in males 123/160 (77.5%) than females 37/160 (22.5%) (P < 0.001). There was also a higher mortality rate, 116/160 (72.5%) occurring in non-Saudi nationals (Filipino, Pakistani, Syrian, Bangladeshi, Egyptian, Indian, Yemeni, Sudanese, Nepalese, Jordanian, Thailand, and Lebanese) compared to Saudi nationals 44 /160 (27.5%) (P < 0.001). Comorbidities were absent in 29 cases (18%) and present in 131/160 cases (82%) of which 37 cases (45.6%) had one, 40 cases (25%) had two and 18 cases (11.3%) had three comorbidities (Table 2). There were no significant differences between both groups with regards to number and individual comorbidities (Table 2). Hypertension was the most common comorbidity followed by diabetes mellitus (DM) and obesity (Fig 1). The most common presenting symptoms on admission were dyspnea 151/160 (94.4 %), dry cough 140/160 (87.5%) and fever 139/160 (86.9%). There were significantly more patients who presented with persistent cough in group 2, 86/89 (96.6%) versus 57/71 in group 1 (76.1%) P = 0.001. There were no significant differences with regards to dyspnea and fever between both groups (Table 2). Morbidities that developed after infection are shown in Table 3. There were significantly more lung diseases and ARDS cases occurring in group 2 compared to group 1 (Table 3). A total of 148/160 patients (92.5%) needed mechanical ventilation, while 12/160 patients (7.5%) needed high oxygen concentration mask. No patients required a tracheostomy (Table 1). The number of patients on mechanical ventilation was significantly higher for group 2 compared to group 1 89/89 (100%) versus 53/71 (83%) (P< 0.001) (Table 1). Several risk factors were identified for mortality using univariate and multivariate logistic regression analysis with outcomes being binary as 0 = < 14 days and 1 = > 14 days. All possible risk factors were analyzed by the univariate model. Persistent dry cough, preexisting lung disease and ARDS were selected for multivariable logistic regression model (Tables 3 and 4). Multivariable analyses found persistent dry cough and ARDS to be strongly associated with late deaths with an adjusted odd ratios (AOR) of 6.9 and 2.5 respectively (Table 5).

Discussion

To the best of our knowledge, this is the first prospective Cohort study in Saudi Arabia to evaluate the association of risk factors, comorbidities and clinical manifestations for COVID-19 related deaths. Our study showed that the median age of our cohort population was 60.4 years (30 – 90 years). This was lower than other similar studies in the United States and Italy, where the median age was 80.5 years (31-103 years) and 71years (64-78 years) respectively (16, 17). In this study, the highest death rates occurred in the age group of 60-69 years (27.5%), followed by 50-59 years (22.5%), 40-49 years (16.3%), 70-79 years, ≥80 years

(13.8%), and 30-39 years (8.1%). These differences could be attributed to population density for the age group (60-69 years) 1,212,881 is higher than the age group (70-79 years) 460, 914 and more than the total of age group >80 years 204,485 according vital statistics in Saudi Arabia (18). Our study showed that there were significantly higher death rates occurring in males compared to female patients with a ratio of 3.4:1. Our findings were consistent with several other studies (9-13). Data from the Ministry of Health's surveillance in Chile, they evaluated the fatality risk by age and gender among 444,921 COVID-19 cases. They found the highest risk occurred in males aged 70–79 years (29.5%), followed by aged ≥ 80 years (29.2%) (19). Furthermore, female deaths commonly occurred at age ≥ 80 years (44.4%) (6, 8-9). The proportion of male versus female CFR was higher than 50% across all age groups (19). Our study showed that the overall CFR was 10%. The majority of deaths occurred in non-Saudi nationals which was significantly higher than those of Saudi nationals 27.5% (P< 0.001). This observation is in agreement with an epidemiological study done by Ahmed et al in Saudi Arabia (20). The high death rates among the non-Saudi nationals could be attributed to workforce's largest population. Subsequently, they were exposed more and became vulnerable to COVID-19 infections. The most common presenting clinical symptoms found in our study population were dyspnea (94.4%) followed by dry cough (87.5%) and fever (76.1). Ahmed et al, reported in an epidemiological study that common presenting symptoms were fever and cough that occurred in 85.2% and 85% respectively among 240,474 screened patients with confirmed COVID-19 in Saudi Arabia (20). Likewise, a systematic review and meta-analysis of 148 studies from nine countries revealed that fever and cough were the most prevalent presenting symptoms, occurring in 78% and 57% of patients respectively (21). In our cohort series, we found that 82% of deaths occurred in cases with one or more comorbidities and 18% occurred in patients with no coexisting morbidities. In agreement with previous studies, we found the most common associated comorbidity were hypertension 83%, DM 81%, obesity 47% cardiac disease 32% and cancer 23% (11-13). However, we found that only preexisting chronic lung disease was strongly associated with a poor prognosis. Those cases in our study with preexisting lung disease (57.5%) further progressed to COVID-19 related ARDS. Subsequently, prolonged ARDS can progress to lung fibrosis and death due to respiratory failure. We found that 93% of our mortality cases required mechanical ventilation making the death rate 30%. Our overall ICU mortality rate was 25%, which is substantially lower than the 50–97% reported in the literature (7-11). These data indicate that learning curve of our clinical management for dealing with critically ill COVID-19 patients with ARDS can improve clinical outcomes and minimizing the death rates. Respiratory failure was the most common cause of death among our patients (61%) followed by respiratory failure alongside with cardiac failure (33%), myocardial damage and circulatory failure (6%) (12). Furthermore, patients who had a persistent dry cough and prolonged ARDS for more than14 days were associated with 7 times and 2.5 times increases death likely (Adjusted OR = 6.9, 95% CI: 1.9-25.3) and (Adjusted OR= 2.5, 95% CI: 1.3-5.0) respectively.

Conclusion and Limitations

In conclusion, preexisting lung disease in male patients aged 60-69 years was strongly associated with COVID-19 related deaths. However, persistent dry cough and prolonged ARDS were more likely to be associated with late deaths regardless of receiving mechanical ventilation. This report has several limitations. This was an observational study conducted at a single medical center thus limiting the generalizability of our results. Additionally, this study did not have a comparable control arm to compare our mortality with survival rates to evaluate the impact of intervention and available treatments. This study was conducted before the discovery and implementation of the COVID-19 vaccine discovery and implementation.

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