Exposure to sulfur mustard increases the risk for mortality in patients with COVID-19 infection: A cohort study

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ARTICLE INFO

ABSTRACT

Objective: This study aims to assess the prognosis of inpatients with COVID-19 infection who have a history of sulfur mustard exposure.
Methods: We started a cohort study in October 2020 and ended in May 2021 on inpatients with COVID-19 infection who had been admitted to university healthcare centers. The analytic sample included 960 inpatients having COVID-19 infection (192 with; and 768 without sulfur mustard exposure). The exposed patients were male war veterans, and the unexposed patients were male individually age-matched people. All patients had a positive RT-PCR test and a positive chest CT for COVID-19. The outcome was death within 28 days of admission, and the predictors were clinical features recorded at patients' bedsides.
Results: There was a significantly higher prevalence for asthma ($p = 0.026$) and pulmonary disease other than asthma ($p < 0.001$) in patients with the exposure. Sulfur mustard exposure was associated with increased risk for mortality of COVID-19 [hazard ratio (95% CI) = 1.92 (1.14,3.24), $p = 0.013$]. Early intubation signified a poor prognosis [hazard = 7.34 (4.65,11.58), $p < 0.001$]. However, individuals with higher PaO2 [hazard = 0.97 (0.95,0.98), $p < 0.001$], or people undergoing O2 therapy early upon admission [hazard = 0.58 (0.38,0.89), $p = 0.011$] showed lower risks for mortality. Individuals with asthma were at higher risk for mortality [hazard = 3.76 (1.69,8.36), $p = 0.001$].
Conclusion: Individuals with COVID-19 infection and sulfur mustard exposure should be considered high-risk patients and that, healthcare settings should be ready to provide critical care for them, including O_2 therapy. They are more likely to have asthma or other pulmonary diseases.

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1. Introduction

As of 25 May 2021, there has been about 3.5 million death caused by the global pandemic of COVID-19 according to the World Health Organization dashboard for Coronavirus. The infection manifests within an average of 11.5 days from exposure in 97.5% of symptomatic people [1]. Early in the course of COVID-19, typical findings on chest computerized tomography (CT) include ground-glass opacities with bilateral peripheral involvement in multiple lobes and consolidation [2]. The disease is commonly diagnosed using reverse transcription-polymerase chain reaction (RT-PCR) test with 20% to 67% false-negative based on time since exposure as reported in the literature [3]. In patients with clinical suspicion of COVID-19, the negative test result should be interpreted with other clinical and paraclinical evidence [3]. Overall, inpatient mortality is 15–20%, and 40% of hospitalized patients require intensive care [1].

Meanwhile, reports from different populations show variability in mortality rates. Hospital mortality is estimated to be less than 5% for individuals younger than 40 years, 35% for patients aged 70 to 79 years, and more than 60% for people 80 to 89 years of age [4]. Concerning sex, a similar mortality pattern was reported in Europe, while a study carried out in the US showed that male sex was independently associated with death, hospitalization, and intensive care unit admissions [5,6]. Individuals undergoing kidney transplants or dialysis; and patients with cancer, diabetes, and neurologic or cardiovascular diseases are suggested to be at increased risk for mortality [7-11].

People exposed to chemical weapons experience severe acute and chronic health problems. Sulfur Mustard (SM) is a chemical agent which was commonly used by Iraq in the 1980s as a weapon against Iran. It is believed that thousands of unprotected people living in Iran, Iraq, and Syria have been exposed to SM [12,13]. Late in the course of

the disease, SM exposure (SME) is associated with pulmonary complications (Mustard lung) such as asthma, emphysema, chronic bronchitis, obliterative bronchiolitis syndrome, chronic obstructive pulmonary disease, and tracheobronchomalacia [14-19]. Other long-term effects of SME include cancer, hematologic, immunological, neuropsychiatric, and reproductive problems [12,20-22]. Patients experience eye and skin complications [23,24] and also social isolation [15].

In an observational study, about 34,000 patients who had sustained SME during the Iran-Iraq war of 1980–1988 were screened for the complications of the exposure [25]. Overall, 23 to 37% had mild, 1.5% to 4.5% had moderate, and 0.023–1.0% had severe health problems. In a cross-sectional study of 197 veterans with SME, asthma was diagnosed in 21 (10.65%), chronic bronchitis in 116 (58.88%), bronchiectasis in 17 (8.62%), airway narrowing in 19 (9.64%), and pulmonary fibrosis in 24 (12.18%) patients [26]. It was concluded that SM is associated with developing a series of chronic destructive pulmonary sequelae in the long term.

In another cross-sectional study of chronic SME complications, patients commonly complained of cough and dyspnea [27]. They had wheezing and coarse rale in chest auscultation. However, in about one-third of patients, clinical examination and radiographic findings were not conclusive for pulmonary complications of SME. Meanwhile, spirometry showed an obstructive pattern, and the pulmonary function test implied normal or restrictive patterns. Bronchospasms typically followed lung infections, asthma, environmental allergens, and cold air [26,27].

Overall, SME seems to increase the rates of pulmonary problems that are risk factors of COVID-19 mortality. Also, SME might be an independent risk factor for the mortality of COVID-19. There is no quantitative study in the literature to deal with the effects of coexisting SME and COVID-19 on patients' mortality. The aim of conducting this study was to assess the prognosis of inpatients with a history of SME who have COVID-19 infection and thereby, enable the triage officer to rapidly evaluate the necessity of more critical care for the patient.

2. Methods

2.1. Design and setting

We carried out a study to assess the risk for mortality of COVID-19 among patients with a history of SME. Our cohort study started in October 2020 and ended in May 2021. The target population was people with COVID-19 infection who were admitted to university healthcare centers. Patients were managed according to the instructions given by World Health Organization on COVID-19 [28]. This research was conducted by a Research Center affiliated with a University of Medical Sciences. Ethics approval was obtained from the Institutional Review Boards of the University of Medical Sciences with the ethics code of IR. SBMU.RETECH.REC.1399.499. At the admission time, written consents were taken from all participants or their companions.

2.2. Eligibility

We included all people who were hospitalized with a diagnosis of COVID-19 infection. All consecutive patients were evaluated for COVID-19 and monitored for progressive signs of respiratory failure and shock. Acute respiratory distress syndrome was diagnosed based on the Berlin definition [29]. We used pharmacological prophylaxis to prevent thromboembolism when not contraindicated. The complications associated with critical care, such as ventilator-associated pneumonia and catheter-related bloodstream infection, were prevented according to the standard practice. The registration process was online using a single electronic form. Patients were considered as having the new coronavirus infection if they had a positive RT-PCR test plus a positive chest CT finding for COVID-19. The RT-PCR result was reported based on testing collected specimens from the upper respiratory tract.

Radiologists or pulmonologists read CT images who considered the presence of ground-glass opacities with multifocal distribution and a progressive evolution towards organizing pneumonia as supportive of the diagnosis [30]. Both RT-PCR test results and CT findings were recorded as binary values. All patients with SME were identified by general practitioners. They were responsible for admission and were not involved in treatment or outcome assessment. They recognized SME by interviewing patients or their companions, reviewing patients' medical history, and assessing their medical documents regarding SME. All SME patients had been previously registered officially in an organization and had a specific ID card. They had their diagnosis of SME confirmed by a special commission consisting of a pulmonologist, a dermatologist, a neurologist, and an ophthalmologist that collectively decided on SME. Meanwhile, data on the dose of SME were not available, and therefore, we were not able to record the amount of exposure for each patient.

2.3. Outcome and predictors

The outcome was death within 28 days of admission. Because there is still no definitive cure for COVID-19 infection, we considered that the predictive effect of the interventions is small compared with the other predictors. Most of the data were collected early in admission and later reviewing patients' medical records. All potential predictors were recorded at the patients' bedside. Collected data were recorded in a Microsoft Excel spreadsheet. For resolving the imbalance in exposure to SM we carried out random sampling of Non-SME. Predictors with a less than 1% frequency for at least one of its levels were considered highly imbalanced and were excluded from further analysis. There were no missing data for the outcome variable. We used the random forest for initial feature selection because of its good performance, low overfitting, easy interpretability, and robustness to the presence of correlated features [31].

2.4. Modeling

Results are presented as mean (SD) for continuous variables and as absolute numbers (percentages) for categorical data. The means of the continuous variables were compared using independent t-tests. Either a χ^2 test or Fisher exact test was used for testing differences among the groups for categorical variables. For statistical analyses, p-values less than 0.05 were considered significant. The survival curves for two groups of patients (SM and non-SM) were constructed with the Kaplan-Meier method and were compared with the log-rank test. We used the Cox proportional-hazards model to investigate the association between the survival time of patients and predictors (including SME). We used R software version 4.0.2 for data analysis and visualization. R is a free software environment, and it is well known for its statistical and machine learning libraries and graphics. We used a variety of R packages for the analysis. All the packages were downloaded from the Comprehensive R Archive Network (https://cran.r-project.org/), the official R package repository, or the GitHub (https://github.com/) website.

3. Results

3.1. Sample

All the patients with SME were male war veterans. Therefore, to eliminate any possible confounding effect of sex we included male inpatients with a positive RT-PCR test and a positive chest CT for COVID-19. The total number of patients was 67,871 of which 192 had SME. Because of severe imbalance in exposure variable, we randomly under-sampled the Non-SME group to provide a 1:4 ratio of SME: Non-SME patients in the final sample. However, to cancel out possible age confounding effect, each Non-SME patient was randomly selected as an individually age-matched to 4 SME patients. At the end of the process, the analytic sample included 960 patients (192 SME and 768

age- and sex-matched Non-SME patients) and had 49 missing data. The missing data included respiratory rate (46, 4.8%) and O2 therapy at admission (3, 0.3%). The missing data were imputed using predictive mean matching. We excluded highly imbalanced predictors from the analysis,
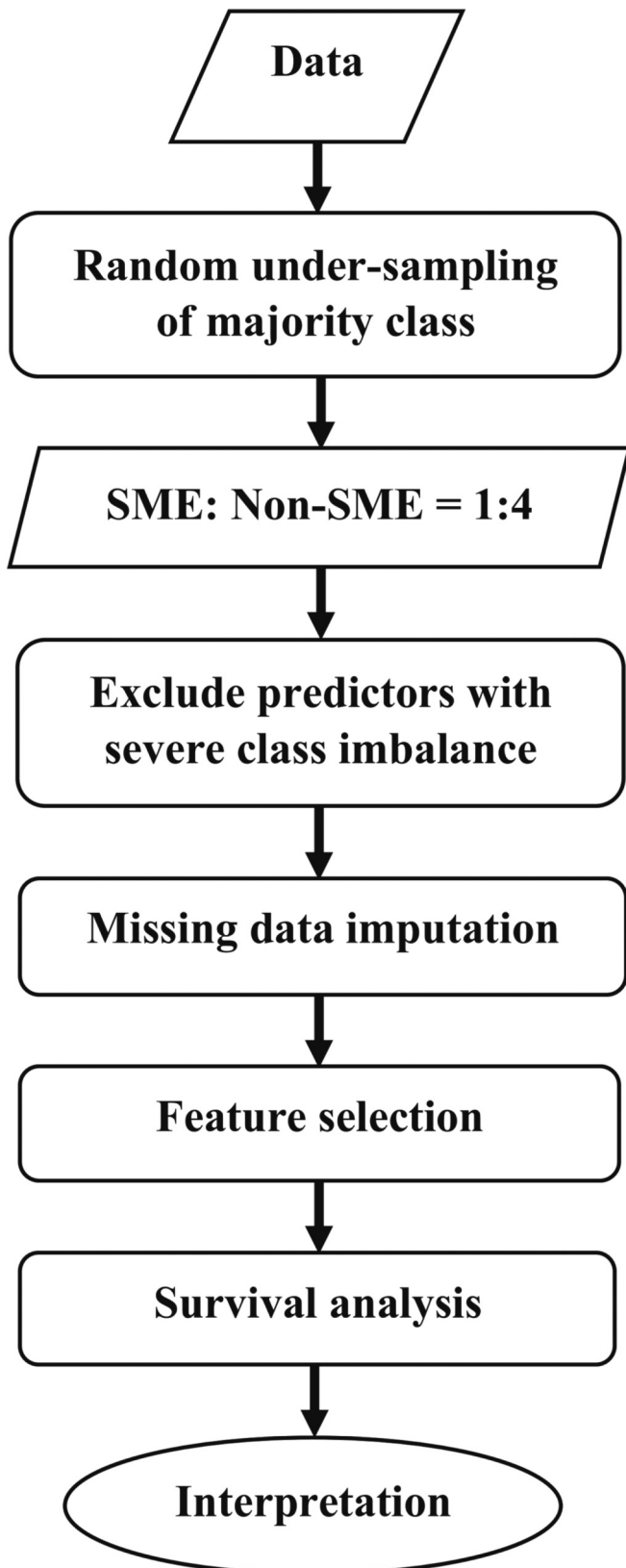
including seizure, paresis, plegia, dermatologic and hematologic problems, liver diseases, HIV/AIDS, chemotherapy or immune deficiency, and dialysis. Fig. 1 shows the flow of data in the study, and Fig. 2 illustrates initial variable importance for predicting mortality, estimated with random forest technique. Based on the selected features, Table 1 shows the characteristics of the two groups of patients. The percentages of intubation, history of kidney disease or pulmonary disease other than asthma, SME, age, asthma, and the percentage of patients with respiratory rate > 28 were significantly higher among deceased patients. Also, the mean PaO2 at admission was lower in the deceased group. In addition, comparisons of Non-SME and SME groups showed that both asthma and pulmonary disease other than asthma were significantly higher in SME groups. The higher percentage of O2 therapy early at admission for SME groups could be attributed to the fact that SME patients are rapidly recognized and treated as people with a high risk for mortality.

3.2. Survival analysis

The median hospital stay was 6 days for both Non-SME and SME groups (W = 72,908, p = 0.811). The maximum hospital stays were

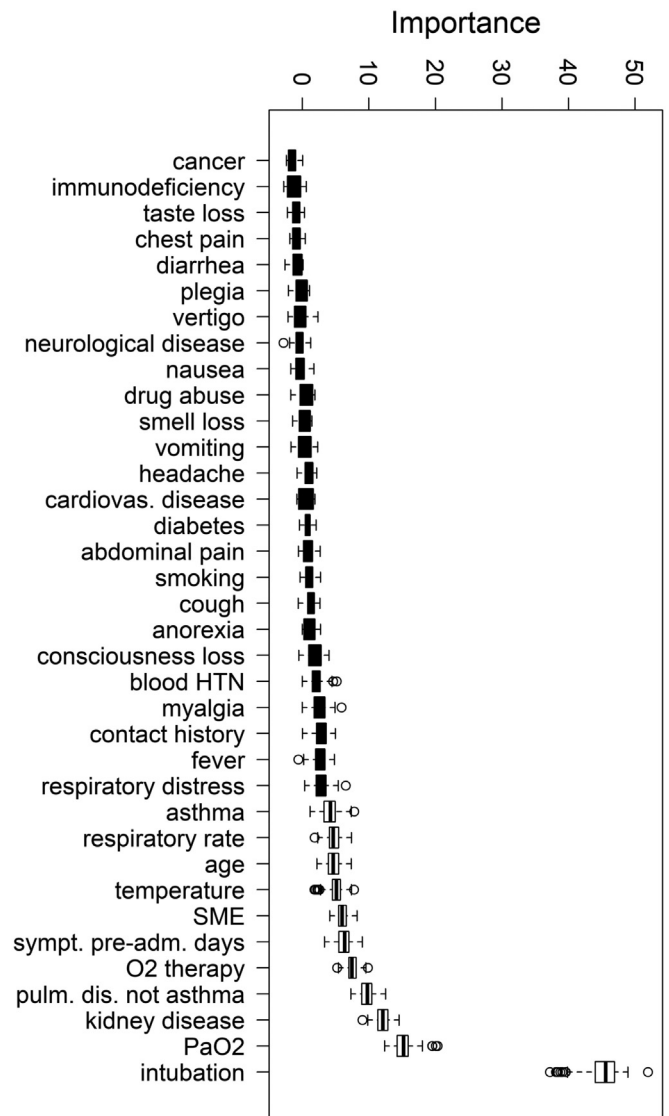**Fig. 1.** Data flow chart of the study. SME: Sulfur Mustard Exposure.

Fig. 2. Variable importance for predicting mortality rate. The white boxplots represent confirmed variables. PaO2: Partial Pressure of Oxygen; SME: Sulfur Mustard Exposure.

Table 1

Patients' characteristics in alive and dead groups. Categorical variables were compared with χ2, and continuous variables were compared with *t*-test for independent samples

Feature	Group			Group		
	Alive (*n* = 836)	Dead (*n* = 124)	*p*	Non-SME (*n* = 768)	SME (*n* = 192)	*p*
Intubation (%)	14 (1.7)	46 (37.1)	<0.001*	49 (6.4)	11 (5.7)	0.868
Mean (SD) PaO$_2$ mmHg	90 (6.3)	84.4 (10.7)	<0.001*	89.4 (6.8)	88.5 (8.7)	0.173
Kidney disease (%)	21 (2.5)	10 (8.1)	0.003*	24 (3.1)	7 (3.6)	0.891
Pulmonary disease other than asthma (%)	47 (5.6)	19 (15.3)	<0.001*	18 (2.3)	48 (25.0)	<0.001*
O$_2$ therapy early at admission (%)	444 (53.3)	69 (55.6)	0.695	388 (50.7)	125 (65.1)	<0.001*
Mean(SD) Symptomatic Days Before Admission	6 (3.8)	5.8 (4.4)	0.618	5.9 (3.7)	6.4 (4.4)	0.106
SME (%)	157 (18.8)	35 (28.2)	0.020*	–	–	–
Mean (SD) Temperature (°C)	37.2 (0.7)	37.3 (0.7)	0.138	37.2 (0.7)	37.1 (0.8)	0.191
Mean (SD) Age (year)	56.8 (6.5)	58.3 (7.9)	0.045*	57.0 (6.7)	57 (6.7)	≈1.000
Respiratory Rate (%)						
14–18	201 (24.0)	35 (28.2)	<0.001*	193 (25.1)	43 (22.4)	0.208
18–22	471 (56.3)	53 (42.7)		424 (55.2)	100 (52.1)	
22–28	141 (16.9)	24 (19.4)		127 (16.5)	38 (19.8)	
>28	23 (2.8)	12 (9.7)		24 (3.1)	11 (5.7)	
Asthma (%)	16 (1.9)	7 (5.6)	0.026*	12 (1.6)	11 (5.7)	0.001*

PaO2: Partial Pressure of Oxygen; SME: Sulfur Mustard Exposure.

 * Significant at *p* < 0.05.

54 and 23 for Non-SME and SME patients, respectively. Fig. 3 illustrates Kaplan-Meier curves for survival probability. Early at admission, the two curves are parallel; however, they separate gradually with a steeper decline in the SME group. The log-rank test for comparing the survival distributions of the two groups showed a statistically significant difference between the two groups; χ2(1) = 7.8, *p* = 0.005. The Cox proportional-hazards model significantly predicted the risk of mortality; Wald χ2(10) = 118.6, *p* < 0.001. Table 2 shows the results of the Cox proportional-hazards regression. Intubation, PaO2, history of kidney disease, O2 therapy early at admission, previous exposure to SM, and asthma significantly affected the survival of patients admitted with COVID-19. Patients with exposure to SM were at almost two times higher risk for mortality.

4. Discussion

We conducted the current study to investigate the effects of exposure to SM on the risk of mortality among inpatients with COVID-19 infection. The infection was confirmed with both RT-PCR test and positive chest CT findings for COVID-19. Clinical features on admission significantly affected the death risk of the patients. Our results showed that SME is associated with a nearly two-fold increased risk for mortality. Patients with SME showed accelerated mortality within three weeks of admission compared with well-matched Non-SME people. In addition, early intubation signifies a poor prognosis. However, individuals with higher PaO2 or people undergoing O2 therapy early upon admission showed lower risks for mortality.

Our data suggest that the percentage of patients with SME who have received O2 therapy at admission was significantly higher than the Non-SME group. Patients with SME have likely been triaged correctly as requiring critical care services and consequently have been admitted to hospital and received O2. This also might lower the risk of mortality for the SME group than what has been previously thought. Also, our results implied there is a significantly higher prevalence of asthma and pulmonary disease other than asthma in patients with SME and that individuals with asthma are at higher risk for mortality. These findings

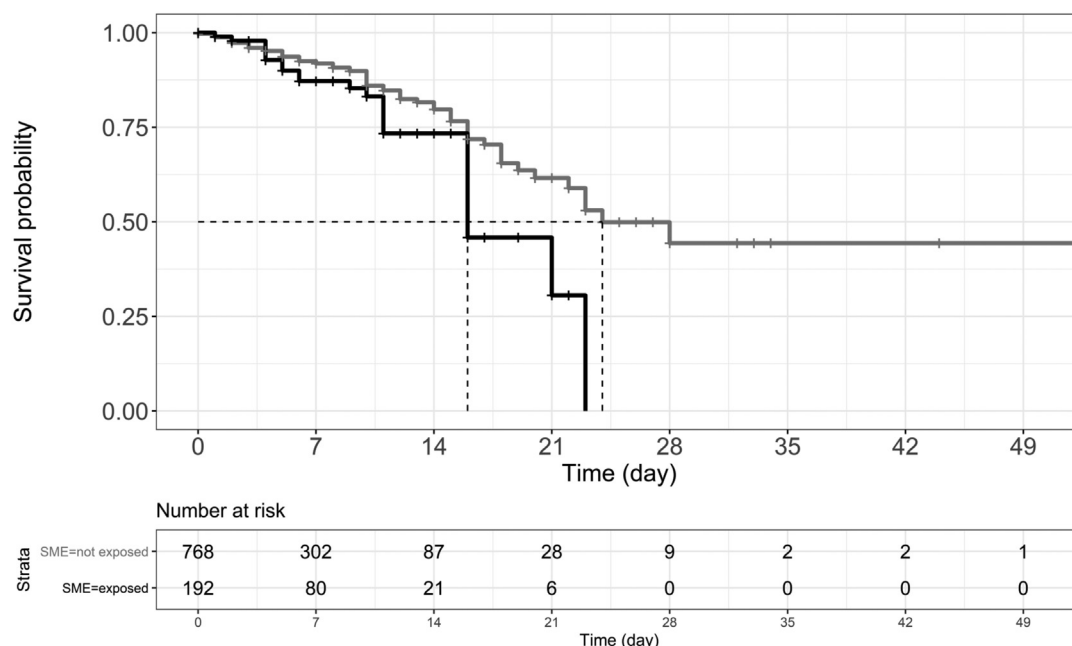| Strata								
Number at risk								
SME=not exposed	768	302	87	28	9	2	2	1
SME=exposed	192	80	21	6	0	0	0	0
Time (day)	0	7	14	21	28	35	42	49

Fig. 3. Kaplan-Meier curve of survival probability for Non-SME and SME patients. The dashed lines represent median survival. SME: Sulfur Mustard Exposure.

Table 2
Cox proportional-hazards regression for the survival data

Feature	Hazard	95% CI		p
		Lower Limit	Upper Limit	
Intubation	7.34	4.65	11.58	<0.001*
PaO$_2$ mmHg	0.97	0.95	0.98	<0.001*
Kidney disease	2.83	1.37	5.85	0.004*
Pulmonary disease other than asthma	0.66	0.33	1.33	0.253
O$_2$ therapy early at admission	0.58	0.38	0.89	0.011*
Symptomatic Days Before Admission	1.00	0.95	1.05	0.940
SME	1.92	1.14	3.24	0.013*
Temperature (°C)	0.99	0.76	1.29	0.934
Age	1.02	1.00	1.05	0.062
Respiratory Rate	1.01	0.80	1.28	0.919
Asthma	3.76	1.69	8.36	0.001*

PaO2: Partial Pressure of Oxygen; SME: Sulfur Mustard Exposure.

* Significant at p < 0.05.

show that people with SME should be considered as high-risk patients and a more serious clinical approach should be planned for them. Our results are consistent with some findings reported in the literature regarding the impacts of SME on respiratory health.

SM [bis-(2-chloroethyl) sulfide] is a vesicating electrophilic alkylating agent that has mutagenic, cytotoxic, and carcinogenic effects on living tissues causing significant morbidity [32]. The mortality rate is 2% to 3% with lethal exposure of approximately 100 mg/kg or 5 to 7 mL. Death is usually from pulmonary complications. The mechanism for late pulmonary complications of SME is still unknown [33]. However, the pulmonary renin-angiotensin system has been suggested as an underlying process of lung damage through engaging in inflammatory and fibrotic responses. Variable concentrations of angiotensin-converting enzyme (ACE) have been reported to be associated with the severity of chronic respiratory problems following SME. A study on 208 patients with previous SME suggested that genotypes of ACE are associated with specific percentages of FEV1 [33]. Researchers studying COVID-19 proposed a possible role for ACE in the pathogenesis of the infection. Hypoxia-induced increase in ACE2 expression in type II AEC, angiotensin II receptor blockers, and ACE inhibitors are believed to affect the course of acute respiratory distress syndrome and the risk for mortality in COVID-19 [34-36].

Our results showed that 5.7% of patients with SME and 1.2% without SME had asthma. Also, 25.0% of SME and 2.3% of Non-SME group had non-asthma pulmonary disease. Bronchitis was the most commonly reported pulmonary disease for our SME sample. However, due to inconsistent recording of verbal data, we were not able to estimate its prevalence among our patients.

To our knowledge, this is the only cohort study describing the effect of SME on mortality of COVID-19. We selected strict inclusion criteria (positive RT-PCR test result plus CT findings). This allowed us to be more confident regarding the diagnosis of COVID-19 infection. We assessed a large number of predictors including clinical manifestations and comorbidities. Our analyses were straightforward, and the model incorporated features that are quickly obtained by interview or physical examination upon admission of patients.

4.1. Limitations

Our study is limited in several ways. We did not include lab tests in our predictor list and did not perform spirometry or pulmonary function test. Recording binary variables prevented errors in data entry and led to a bit of ease in filling forms, but we lost information by not recording details of the medical history for each patient. We also lacked data on the quantity of exposure and, therefore, were not able to

quantitatively describe the relationship between the extent of exposure and mortality. The pathophysiologic bases of the findings can be investigated in further and more basic biomedical research.

5. Conclusion

In conclusion, the current study showed that patients with SME have an increased risk of mortality from COVID-19. They should be considered high-risk patients, and the healthcare setting should be ready to provide more intensive care for them. Specifically, patients with SME are more likely to have asthma or pulmonary disease other than asthma. Also, we recommend O2 therapy early at admission, particularly for patients with SME.

Credit author statement

PK and **MF** conceived the original idea, conceptualized the study, and helped with developing protocols. They also supervised the research and guided the administrative processes. **LK** contributed to the design of the study, formulated the theoretical framework, analyzed the data, and developed the models. **ML** assisted with literature review and designing the study and interpretation of the results. All the authors discussed the results and participated in drafting and its final approval.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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