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ORIGINAL RESEARCH CORONA EXPERIENCE

Comparing critically ill ARDS patients with COVID-19 vs. without COVID-19: A prospective, bivariate and multi-variable analysis of 690 patients

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ABSTRACT

Background & objective: Few studies have directly and prospectively compared ICU patients with acute respiratory distress syndrome (ARDS) caused by COVID-19 vs. other causes. Almost all previously-published studies were retrospective and employed historical non-COVID cases. We aimed to identify and compare patient characteristics and predictors of mortality associated with COVID-related vs. non-CIVID-related ARDS.

Methodology: We performed a prospective cohort study. Consecutive ARDS patients with or without confirmed COVID-19 admitted to an ICU of a major tertiary-care hospital from March-December 2020 were included. A total of 160 patients with ARDS and positive for COVID-19 and 530 ARDS patients without COVID-19 were enrolled. Data were collected and both bivariate and multivariable analyses performed on COVID-19 status, demographics, morphometrics, comorbidities, presenting symptoms, general health status (APACHE-II) on admission, respiratory parameters and laboratory tests at admission, within 24 h of admission, and pre-intubation. The treatment administered and outcomes were also recorded. Data capture was almost 100%.

Results: Numerous clinical differences were detected between 160 patients with COVID-19 vs. 530 patients without COVID-19. Most notably, COVID-19 patients were generally older and heavier, much more frequently presented with fevers/chills, dyspnea, cough, anosmia/ageusia, and sore throat — and had worse outcomes. including over a two-fold rate of mortality and five-fold rate of survivors requiring prolonged supplemental oxygen. The presenting symptom dyad of fevers and/or chills and dyspnea was 93.0% sensitive and 63.4% specific for COVID-related ARDS. A baseline APACHE-II Score ≥ 17 and requiring mechanical ventilation was 94.4% sensitive and 70.5% specific for mortality. All 37 COVID patients with an APACHE-II score > 30 died, vs. survival among non-COVID patients with APACHE-II scores up to 40.

Conclusion: In one of the first large studies to directly compare contemporary populations of COVID-19 and non-COVID ICU patients with ARDS, employing multi-variable analysis, numerous differences in patient characteristics, presentation, and outcomes were detected.

Abbreviations: APACHE-II - Acute Physiologic Assessment and Chronic Health Evaluation 2nd edition; PaO_2 - Partial Pressure of Oxygen; SaO2 - Arterial Oxygen Saturation; BUN - Blood Urea Nitrogen; ALT - Alanine Aminotransferase; AST - Aspartate Aminotransferase; LDH - Lactate Dehydrogenase; NIPPV - Non- Invasive Intermittent Positive Pressure Ventilation; HFNC - High-Flow Nasal Cannula; ECMO - Extra-Corporeal Membrane Oxygenation

Key words: COVID-19; ARDS; Clinical Characteristics; Treatment; Outcomes; Predictors

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1. INTRODUCTION

Starting with the 2003-2004 SARS (severe acute respiratory syndrome) epidemic, a series of viral outbreaks have occurred that have precipitated numerous admissions to intensive care units (ICUs) for acute respiratory distress syndrome.[1] Following the SARS outbreak came the 2017-2018 outbreak of Middle Eastern respiratory syndrome (MERS), during which mortality was as high as 36% overall; even higher among patients admitted to ICUs.[2] Most recently, a pandemic caused by severe acute respiratory syndrome coronovirus-2 (SARS-CoV-2),[3] based upon its morphological similarity to the originally-discovered coronavirus implicated in the 2003-2004 SARS outbreak, has caused a global pandemic that remained classified as such for over two years. As of March 2022, it had caused approximately six million deaths.[4] At that time, roughly 20% of COVID-19-infected patients were hospitalised,[5] among whom 15-20% required ICU care.[1, 6] From 40-96% of COVID patients admitted to ICUs are admitted for respiratory failure caused by severe pneumonia and acute respiratory distress syndrome (ARDS), the latter highly predictive of 28-day mortality.[1]).

Several patient characteristics in COVID patients have been statistically linked to ICU admission, including senior age, male gender, and pre-existing comorbid conditions like obesity, diabetes mellitus, and kidney disease,[7-13] and much the same is true for ARDS in general.[14, 15] However, though studies abound comparing ARDS caused by SARS-CoV-2 against other forms of ARDS, in all but a very few instances, those studies either used historical controls,[16-28] or very small numbers of COVID cases,[20, 29] non-COVID cases,[23, 30-32] or both.[6, 24, 33-36] The few studies that have examined concurrent samples of COVID and non-COVID ARDS cases have generally been highly case specific; for example, the large registry study published by Ruhi-Williams et al., which compared 6040 and 6382 COVID and non-COVID ARDS patients, only evaluated patients requiring extracorporeal membrane oxygenation (ECMO).[37] Similarly, the US national database study reported by Lee et al., with 1940 and 5840 patients, respectively, compared post-operative complications following total joint arthroplasty in COVID and non-COVID ARD survivors.[38] Meanwhile, in one oft-cited paper that combined patients from two randomized controlled trials (RCTs), one RCT only had COVID cases recruited from multiple centers from April through June 2020, while the other RCT only had non-COVID patients recruited from entirely different centers from 2011 through 2017.[39] Moreover, very few of these studies assessed for predictors of mortality.

One exception that appears to have overcome all the above-mentioned shortcomings was a study conducted in India which compared 95 COVID and 117 non-COVID ARDS patients all treated at a single, tertiary-care, academic hospital from March 15 through August 15, 2020 – the first wave of COVID-19 in that area.[40] In this study, logistic regression identified higher APACHE-II scores as predictive of mortality in COVID but not non-COVID patients. However, that there were only 212 patients total might have resulted in inadequate statistical power to detect other predictors either distinct to COVID or shared by both COVID and non-COVID ARDS patients. As one of Saudi Arabia's busiest hospitals and emergency referral centers, we sought to prospectively enroll and compare concurrent cohorts of COVID and non-COVID ARDS patients. Specific objectives were to: (1) characterize ICU ARDS patients with vs. without confirmed COVID-19, with respect to patient characteristics, presentation, treatment, course, and outcomes; (2) identify specific differences between these two patient groups; and (3) identify and compare predictors of mortality.

2. METHODOLOGY

A prospective, observational study was conducted at King Abdulaziz University Hospital, an 850-bed, major tertiary care university hospital in the Saudi city of Jeddah. Enrolled were all ARDS patients admitted to any

ICU bed from 01 March to 31 December, 2020; at least 14 years of age at the time of ICU admission; formally tested for COVID-19 using the real-time polymerase chain reaction (RT-PCR) test, with accessible results; and critically ill with ARDS, defined using the recently validated for COVID Berlin criteria.[41] COVID cases were defined as patients with a clinical presentation of ARDS, using the Berlin criteria, whose RT-PCR test was positive during their ICU admission. Non-COVID cases also met the Berlin criteria for ARDS, but had at least two negative RT-PCR tests. All equivocal tests were repeated. To be included as a non-COVID ARDS case, patients also had to have some other confirmed explanation for their ARDS, including confirmed community-acquired bacterial pneumonia, acute exacerbation of pre-existing chronic lung disease, acutely decompensated heart failure, bacterial sepsis, and influenza, with isolated other diagnoses. Any patient in whom COVID could neither be definitively confirmed nor excluded over the course of observation were excluded from analysis.

2.1. Data collection

Data were collected throughout patients' hospital stays, and included patient demographics (age, sex, nationality); morphometrics (height, weight, body mass index); comorbid conditions (previous renal replacement therapy; chronic cardiovascular or pulmonary disease; chronic renal or hepatic disease; diabetes mellitus; hypertension; other); presenting symptoms (fevers and/or chills; cough; dyspnea; fatigue; musculoskeletal aches/pains; lost smell and/or taste; sore throat; nasal congestion and/or coryza; nausea and/or vomiting; and diarrhea); dates of symptom onset and ICU admission; health status at ICU admission — using the validated and commonly-used *Acute Physiologic Assessment and Chronic Health Evaluation 2nd edition* (APACHE-II) score;[42] measurements of respiratory function at ICU admission (including partial pressure of oxygen (PaO_2); arterial oxygen saturation (SaO_2); partial pressure of carbon dioxide ($PaCO_2$); and serum bicarbonate (HCO_3) level); baseline and daily vital signs, including mean respiratory rate; ICU day #1 measurements (including serum white blood cell, neutrophil, lymphocyte, and platelet counts; serum levels of blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), ferritin, lactate dehydrogenase (LDH), troponin, D-dimer, procalcitonin, and C-reactive protein (CRP); any repeat measurements of the same biomarkers over the next 24 h after ICU admission and prior to intubation (among mechanically-ventilated patients); all treatments for ARDS (including non- invasive intermittent positive pressure ventilation (NIPPV); high-flow nasal cannula (HFNC); mechanical ventilation; prone positioning during mechanical ventilation; extra-corporeal membrane oxygenation (ECMO); tracheostomy; neuromuscular-blocking agents; inhaled pulmonary vasodilators); and all other supportive treatments (including vasopressors, renal-replacement therapy; antimicrobial therapy, and immunomodulatory therapy. Among patients on corticosteroids, type of corticosteroid (e.g., methyl prednisolone), steroid-dosing schedule, and mean cumulative daily dose were recorded.

Data were collected on patient outcomes — including final disposition; e.g., in-hospital mortality, ICU retention, in-hospital transfer, transfer to another hospital, home discharge, need for prolonged supplemental oxygen or mechanical ventilation, need for tracheostomy, venous thrombo-emboli, and barotrauma.

2.2. Data analysis

All data were entered into an electronic database, then imported into SPSS-27. Prior to analysis, the entire database was examined for missing values, which comprised less than 1% of all entries. We also examined for any data clearly entered inaccurately (e.g., outside the range of possibility, like an APACHE-II score > the uppermost limit of 71); in total, only 17 such entries (< 0.01% of all entries) were identified and either corrected (if possible, by reviewing records, 10 entries) or deleted (7 entries). No variable had more than two clearly inaccurate entries out of 690 patients. Then, all continuous variables were examined for normal vs. non-normal distribution using the Wilks-Shapiro test so parametric or non-parametric tests could be used appropriately for inferential analysis. Continuous variables were summarized as means with standard deviations (SD), and categorical variables as percentages with 95% confidence intervals (CI).

Since the primary comparisons were between ICU-ARDS patients with vs. without COVID-19, for bivariate analysis of continuous variables, either Student's t test or the Mann-Whitney U test was used, as appropriate, while Pearson's analysis or Fisher's Exact test was used for categorical variables, as indicated, followed by odds ratios (OR) with 95% CI. For all bivariate tests comparing COVID-19 and non-COVID patients, $P \leq 0.001$ was set as the Bonferroni-adjusted criterion for statistical significance to adjust for multiple comparisons. For multivariable analysis to identify associations with COVID-19 and mortality, hierarchical binary logistic regression analysis was performed, with only independent variables identified as different between COVID and non-COVID patients or between survivors and non-survivors at $P \leq 0.20$ on bivariate analysis entered by forward block entry. Only variables with $P \leq 0.05$ were retained in the ultimate models, from which final odds ratios with CI were generated.

Table 1: Comparing pre-admission clinical status in COVID and non-COVID ICU patients with ARDS

Variable	COVID	non-COVID	OR (95% CI)	Significance[#]
Comorbid conditions				
• Chronic CV or lung disease	30.63%	36.42%	0.77 (0.53-1.13)	P = 0.18
• Chronic kidney of liver disease	11.88%	15.28%	0.75 (0.44-1.27)	P = 0.28
• Renal replacement therapy	10.63%	12.45%	0.84 (0.48-1.47)	P = 0.53
• Diabetes mellitus	56.25%	48.11%	1.39 (0.97-1.98)	P = 0.07
• Hypertension	49.38%	46.04%	1.14 (0.80-1.63)	P = 0.46
• Some other comorbid condition	62.50%	93.02%	0.13 (0.08-0.20)	**P < 0.001**
Presenting symptoms				
• Fevers and/or chills	71.88%	13.96%	16.11 (10.52-24.65)	**P < 0.001**
• Cough	58.75%	11.51%	11.12 (7.35-16.82)	**P < 0.001**
• Shortness of breath	86.25%	28.49%	16.49 (10.04-27.09)	**P < 0.001**
• Fatigue	42.50%	17.36%	3.56 (2.42-5.24)	**P < 0.001**
• Musculoskeletal aches	23.13%	7.74%	3.61 (2.22-5.87)	**P < 0.001**
• Headaches	11.88%	11.13%	1.08 (0.63-1.88)	P = 0.78
• Loss of taste or smell	35.00%	2.08%	25.65 (13.00-50.64)	**P < 0.001**
• Sore throat	29.38%	2.26%	18.12 (9.31-35.26)	**P < 0.001**
• Nasal congestion	20.00%	2.83%	8.65 (4.55-16.46)	**P < 0.001**
• Nausea and/or vomiting	13.13%	15.47%	0.83 (0.50-1.39)	P = 0.50
• Diarrhea	15.00%	7.55%	2.18 (1.27-3.74)	P = 0.004
Number of symptoms, mean	3.06	0.79	NA	**P < 0.001**
Days after symptom onset, mean	8.17	9.34	NA	P = 0.30

CV = cardiovascular; t = Student's t test; χ2 = Pearson chi-square; NA = not applicable; # To compensate for multiple comparisons, only p values < 0.001 considered statistically significant.

3. RESULTS

In total, 690 patients were enrolled, 160 with COVID-19 definitively confirmed and 530 with COVID-19 definitively excluded. Demographically, COVID patients averaged almost five years older and were more likely over 45 y (87.5% vs. 71.3%) than non-COVID patients; in addition, COVID patients were more likely to be male (73.8% vs. 58.9%) and were heavier (mean weight 77.4 kg vs. 72.2 kg) (all P < 0.001). Though COVID patients' BMI was 28.44 kg/m^2 vs. 27.16 kg/m^2 in non-COVID patients, this difference (P = 0.007) failed to meet our Bonferroni-adjusted criterion of P < 0.001 for statistical significance. Not being overweight, obese, or underweight was more common in COVID patients.

Table 1 compares pre-existing health status and presenting symptoms in the two patient groups. For past medical history, the only difference was in health conditions not previously linked to increased COVID risk, which were more common among non-COVID patients (93.0% vs. 62.5%). Similar percentages in the two cohorts had a past history of chronic cardiovascular or lung disease, kidney or liver disease, previous renal replacement therapy (dialysis/transplant), diabetes, and hypertension. Conversely, the two groups were markedly different in presenting symptoms, with vastly-higher percentages of COVID patients reporting fevers and/or chills, cough, dyspnea, loss of taste and/or smell, sore throat, and nasal congestion and/or coryza, and significantly larger percentages reporting fatigue, and musculoskeletal aches and/or pain. One symptom triad – fevers and/or chills, dyspnea, and cough – was 95.3% specific for COVID, though only 45.9% sensitive, while the symptom dyad of fevers/chills and dyspnea was 93.0% specific and 63.4% sensitive. No statistically-significant (P < 0.001) inter-group differences in the percentage with headaches, nausea and/or vomiting, or diarrhea were detected. Though time from symptom onset to ICU admission was one day shorter in COVID patients (8.2 vs. 9.3 days), this difference was non-significant.

Table 2: Comparing admission health status in COVID-19 vs. non-COVID ICU patients with ARDS

Variables	COVID	non-COVID	Significance#
General health status			
APACHE II score, mean	21.14	18.15	**P < 0.001**
PaO_2, mean	53.64	88.88	**P < 0.001**
$PaCO_2$, mean	38.92	40.04	P = 0.43
HCO_3, mean	21.71	22.03	P = 0.79
SaO_2, mean	79.42%	84.82%	P = 0.037
Laboratory results			
WBC count, mean	10.6	11.7	P = 0.038
Lymphocyte count	1.3	2.2	**P < 0.001**
Neutrophil count	11.1	11.3	P = 0.91
Platelet count	253.1	279.0	P = 0.031
BUN	9.9	10.0	P = 0.93
Creatinine	181.3	156.8	P = 0.24
ALT	78.7	64.2	P = 0.51
AST	112.2	72.4	P = 0.17
Troponin	0.36	2.23	**P < 0.001**
D-Dimer	6.8	6.0	P = 0.61
Ferritin	2356	1032	P = 0.013
Procalcitonin	3.7	8.0	P = 0.036
LDH	568.5	362.3	**P < 0.001**
C-reactive protein	130.2	105.4	P = 0.051

BUN = blood urea nitrogen; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; t = Student's t test; χ2 = Pearson chi-square; # To compensate for multiple comparisons, P < 0.001 considered statistically significant.

Table 2 compares the two patient groups' general health status and laboratory results upon ICU admission. The mean APACHE-II score was 3.0 points higher in COVID than non-COVID patients (21.1 vs. 18.1), while their on-admission PaO_2 was lower (53.6 vs. 88.8 mmHg). Among baseline labs, COVID patients averaged fewer lymphocytes ($1.3x10^9$ vs. $2.2x10^9$ cells/L), lower serum troponin (0.36 vs. 2.23 ng/ml), and higher serum LDH (568.5 vs. 362.3 units/L). All the above differences had P < 0.001.

Table 3 compares treatment administered, with COVID patients statistically more likely to receive almost every treatment. However, the two groups did not differ in the need of mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or a tracheostomy. The only laboratory test that differed on the day of intubation was serum LDH, which was higher in COVID patients (757.5 vs. 449.9). Among pre-intubation respiratory parameters, only the PaO_2 level was significantly lower in COVID patients (92.5 vs. 96.6 mmHg).

Among the main outcomes of interest (Table 3), more COVID patients required long-term supplemental oxygen (16.3% vs. 4.5%), suffered barotrauma (5.0% vs. 0.9%) and had higher mortality in hospital (58.8% vs. 25.9%). Mortality rates were higher among COVID patients at all levels of baseline APACHE-II score above 10. No patient out of 37 COVID patients with a baseline APACHE-II score > 30 survived, while survival occurred among non-COVID patients with baseline APACHE-II scores up to 39 (Figure 1).

Table 4 lists the nine patient parameters that, on multivariable analysis, remained in the final model predicting COVID-positivity ($P \leq 0.05$), ranked by the magnitude of the odds ratio (OR), starting with loss of smell or taste (OR = 8.57; 95% CI = 3.35-21.92)) and ending with weight (OR = 1.02; 95% CI = 1.004-1.030) as predictors of COVID-positivity, with 'other co-morbid conditions' the only factor linked to non-COVID status (OR = 0.15 for COVID; 95% CI = 0.07-0.30).

Table 5 lists all parameters that remained in final regression models predicting mortality across the entire sample of 690 ICU ARDS patients, followed by the 530 without and 160 with COVID-19. Interestingly, a positive test for COVID-19 was not significantly predictive of mortality on multi-variable analysis, with an OR = 4.09 (95% CI = 2.82-5.92), but P = 0.072. The baseline APACHE-II score was a significant predictor in all three models, with virtually identical odds ratios (1.15, 1.15, and 1.16, respectively). Mechanical ventilation was a significant predictor in non-COVID and COVID patients when these two patient cohorts were analyzed separately, but fell out of the final model across the entire sample. The only variable statistically predictive of mortality in COVID-ARDS patients was the baseline APACHE-II score and requirement of mechanical ventilation. Among non-COVID-ARDS patients, a low baseline serum platelet count, prior renal replacement therapy, on-admission dyspnea and nasal congestion or coryza also were predictive.

4. DISCUSSION

Debate continues to rage regarding how ARDS caused by SARS-CoV-2 differs, if at all, from previous viral

Table 3: Comparing ICU course and outcomes in COVID-19 vs. non-COVID ICU patients with ARDS

Variable	COVID	non-COVID	OR (95% CI)	Significance#
Treatments provided in the ICU				
NIPPV	15.63%	3.21%	5.59 (2.93-10.65)	**P < 0.001**
Mechanical ventilation (MV)	60.63%	53.40%	1.34 (0.94-1.93)	P = 0.11
ECMO	0.63%	0.00%	1.01 (0.99-1.02)	P = 0.069
High-flow nasal cannula	48.75%	2.26%	41.57 (21.67-79.73)	**P < 0.001**
Tracheostomy	10.00%	6.79%	1.54 (0.83-2.85)	P = 0.17
Prone positioning for MV	61.88%	1.70%	95.52 (45.90-198.77)	**P < 0.001**
Nitrous oxide	4.38%	0.38%	12.16 (2.50-59.13)	**P < 0.001**
Vasopressor(s)	53.75%	28.11%	3.01 (2.09-4.34)	**P < 0.001**
Therapeutic plasma exchange	9.38%	0.75%	13.65 (4.46-41.75)	**P < 0.001**
Remdesivir	9.38%	0.57%	18.36 (5.24-64.28)	**P < 0.001**
Hydroxychloroquine	4.38%	0.19%	24.38 (2.98-199.74)	**P < 0.001**
Anti-bacterial drug(s)	86.25%	64.53%	3.75 (2.27-6.20)	**P < 0.001**
Corticosteroid(s)	85.00%	20.94%	23.22 (14.13-38.16)	**P < 0.001**
IL-6 receptor antagonists	33.13%	0.75%	66.12 (23.43-186.64)	**P < 0.001**
Laboratories on day of intubation				
WBC count, mean	13.9	14.0	NA	P = 0.94
Lymphocyte count	1.6	1.8	NA	P = 0.45
Neutrophil count	12.5	13.5	NA	P = 0.60
Platelet count	267.9	260.2	NA	P = 0.67
BUN	14.4	12.3	NA	P = 0.16
Creatinine	194.3	184.4	NA	P = 0.69
ALT	154.6	53.7	NA	P = 0.06
AST	211.1	96.9	NA	P = 0.20
Troponin	0.84	3.3	NA	P = 0.014
D-Dimer	9.6	9.6	NA	P = 0.99
Ferritin	1949	3357	NA	P = 0.13
Procalcitonin	6.8	18.5	NA	P = 0.008
LDH	757.5	449.9	NA	**P < 0.001**
C-reactive protein	131.2	120.7	NA	P = 0.51
Respiratory parameters on day of intubation				
Respiratory rate, mean	22.6	21.6	NA	P = 0.33
PaO_2	92.5	96.6	NA	**P < 0.001**
Outcomes				
Long-term supplemental O_2	16.25%	4.53%	4.11 (2.29-5.92)	**P < 0.001**
Prolonged MV	9.38%	5.09%	1.94 (1.003-3.74)	P = 0.046
Venous thromboembolism	23.13%	19.25%	1.27 (0.83-1.94)	P = 0.28
Barotrauma	5.00%	0.94%	5.55 (1.79-17.22)	**P < 0.001**
Death	58.75%	25.85%	4.09 (2.82-5.92)	**P < 0.001**

NIPPV = Non-invasive intermittent positive pressure ventilation; ECMO = extracorporeal membrane oxygenation; PaO2 = partial pressure of oxygen; IL-6 = interleukin-6; BUN = blood urea nitrogen; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; MV = mechanical ventilation; t = Student's t test; χ2 = Pearson chi-square; NA = not applicable; # To compensate for multiple comparisons; P < 0.001 considered statistically significant.

Table 4: Clinical differences in COVID-19 and non-COVID ICU patients with ARDS on multi-variable analysis

Variable	Significance	Odds (OR) of COVID
Loss of smell or taste	P < 0.001	8.57 (3.35-21.92)
Shortness of breath	P < 0.001	5.87 (2.94-11.73)
Fevers and/or chills	P < 0.001	4.90 (2.71-8.88)
Long-term supplemental O_2	P < 0.001	4.57 (1.94-10.76)
Age over 45 y	P = 0.009	2.75 (1.28-5.89)
Death	P = 0.004	2.28 (1.30-4.00)
Cough	P = 0.016	2.17 (1.53-4.09)
Weight (Obesity)	P = 0.015	1.02 (1.004-1.03)
Other co-morbid conditions	P < 0.001	0.15 (0.07-0.30)

ARDS = acute respiratory distress syndrome; O2 = oxygen

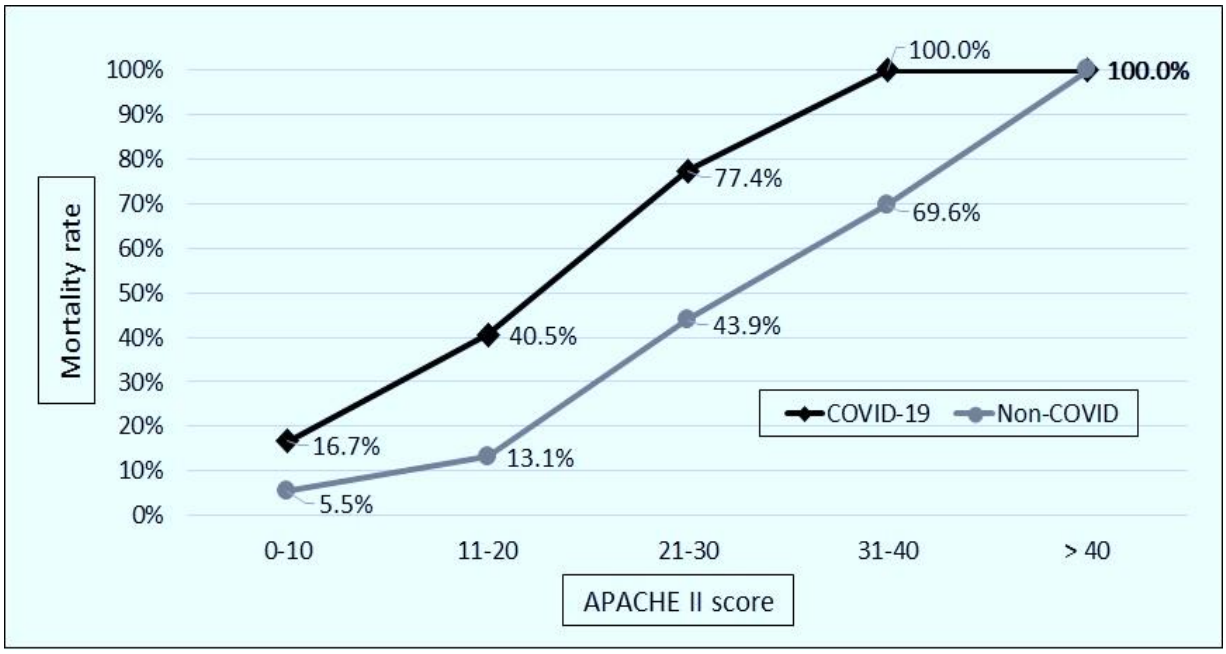
Table 5: Predictors of mortality in COVID and non-COVID ICU patients with ARDS on multi-variable analysis

Predictor	Deceased (n = 231)	Survivor (n = 459)	Significance	Odds ratio (95% CI)
Overall Sample (n = 690)				
APACHE-II score	26.26	15.12	P < 0.001	1.15 (1.12-1.17)*
Pre-existing renal replacement therapy	25.54%	5.23%	P = 0.002	6.21 (3.75-10.31)
Fevers or chills at admission	42.61%	19.83%	P = 0.015	3.00 (2,12-4.26)
Admission blood urea nitrogen (BUN)	11.15	8.11	P = 0.023	1.05 (1.005-1.10)*
Nausea or vomiting at admission	19.13%	12.85%	P = 0.026	1.60 (1.05-2.46)
Admission SaO2	76.47%	87.50%	P = 0.047	1.02 (1.01-1.04)*
Non-COVID Patients (n = 530)				
APACHE-II score	26.36	15.12	P < 0.001	1.15 (1.11-1.18)*
Mechanical ventilation	93.60%	13.60%	P < 0.001	6.31 (3.38-11.76)
Admission platelet count < 150	31.4%	8.7%	P = 0.001	4.44 (2.31-8.55)
Pre-existing renal replacement therapy	31.4%	5.9%	P = 0.001	3.05 (1.55-6.02)
Fevers or chills at admission	24.09%	10.43%	P = 0.020	2.04 (1.03-4.02)
Nasal congestion or coryza	6.57%	1.53%	P = 0.024	5.68 (1.24-26.00)
COVID-19 Patients (n = 160)				
APACHE-II score	26.10	14.09	P < 0.001	1.16 (1.07-1.25)
Mechanical ventilation	86.90%	41.70%	P < 0.001	62.34 (18.75-207.25)

ARDS = acute respiratory distress syndrome; SaO2 = oxygen saturation; BUN = blood urea nitrogen

outbreaks and other causes of ARDS. Such debate includes discussions regarding disease manifestations, which patients are most likely to require intensive care, outcomes, and predictors of mortality. In one meta-analysis, patients with SARS from the 2003-2004 outbreak, with MERS from the 2017-2018 outbreak, and with COVID-19 from the current pandemic were compared and largely perceived to be similar.[2] No study compared any two of these conditions directly; all the SARS, MERS, and COVID samples were drawn from widely disparate locations; and the studies were conducted in three different decades (SARS: 2003-2004;

Figure 1: Mortality rate by APACHE-II score in COVID-19 vs. non-COVID-19 patients



Mortality rates were statistically different (P < 0.001) between COVID and non-COVID patients at all APACHE-II levels except from 0-10 and >40.

MERS: 2017-2018; COVID-19: 2020). In addition, no raw data were collected for multivariable analysis.

In yet another meta-analysis comparing COVID and non-COVID ARDS patients,[43] the focus again was only on outcomes, and only one of the ten analyzed studies directly compared these two patient groups in an ICU setting.[44] Of the remaining nine, five involved retrospective data collection for both COVID and non-COVID cases, six compared COVID patients against non-COVID patients extracted from historical cohorts, two were conducted in emergency departments rather than an ICU, and two studied highly-selective patient populations: one only studying mechanically-ventilated patients, and one only patients undergoing ECMO. A further study only compared 14 COVID patients against seven non-COVID patients with ARDS, and only bronchiolar-lavage specimens were compared. The one study that directly compared COVID and non-COVID ICU ARDS patients only compared 24 COVID against 39 non-COVID patients.[44] Another moderately-large French study that was not included in the previous meta-analysis compared 150 COVID and 233 non-COVID ARDS patients, but again only used historical non-COVID cases.[45]

Conversely, we compared 160 patients with COVID against 530 patients in whom COVID tests were negative, all prospectively-enrolled over the same ten-month period in the same ICU, and all treated for ARDS. In many regards, our sample of 160 COVID patients were highly similar to COVID samples reported by other investigators.[46] For example, in one study of 24 ICU patients drawn from nine Seattle-area hospitals admitted with confirmed SARS-CoV-2 infection and ARDS, 63% of the patients were male (vs. 74% in our sample of COVID patients), their mean age was 64.0 y (vs. 59.4 y), 58% were diabetic (vs. 56%) and, as in our sample, by far the most common symptoms were cough, dyspnea, and fever.[46] In the above-mentioned French study comparing 24 and 39 COVID vs. non-COVID ARDS patients, respectively, the median age of COVID patients was 67 y, 67% were male, mean BMI was 31.0 (vs. 28.4 in our sample), the median duration of symptoms prior to ICU admission was 7 days (vs. 6 days), and 38% (vs. 56%) were diabetic.[44] In a Chinese study of 476 hospitalized COVID-confirmed patients, patients were categorized by disease severity — mild, moderate, severe, and critical — and, whereas the median age among patients with mild symptoms was just 51 y, it increased to 61 and 68 y in those with severe and critical disease, respectively.[13] Similarly, comparing patients with mild vs. critical disease, the percentage who were male increased from 54.0% to 68.6%; the percentages complaining of cough and dyspnea increased from 35.5% and 14.9% to 92.5% and 70.3%; and the percentage who were febrile increased from 82.2% to

97.0%, all numbers consistent with what we observed in our critically-ill COVID patients.

Demographically, our COVID patients were roughly five years older, less than half as likely to be under 45-years-old, and 15% more likely to be male (73.8% vs. 58.9%). Age over 45 y was not only identified as significantly different on bivariate analysis, but also on multivariable analysis, during which the odds of being under 45 y was 2.75 times as great in COVID as non-COVID patients. COVID patients also weighed more (77.4 kg vs. 72.2 kg), and weight itself was retained in our multivariable model (the likelihood of COVID increased by 2% for each kg increase in weight). Nonetheless, at $P < 0.007$, BMI failed to satisfy our strict, Bonferroni-adjusted $P < 0.001$ criterion for statistical significance on bivariate analysis and the percentage of patients considered at least obese was no different in COVID and non-COVID patients (30.4 vs. 25.1, $P = 0.18$).

For pre-existing co-morbidities, the two patient cohorts were similar, with almost half of the patients in both groups having a history of diabetes or hypertension, and a third pre-existing cardiovascular or lung disease. This latter percentage is, admittedly, much lower than the 58% of ICU COVID-ARDS patients reported as having cardiovascular disease alone by Brault et al.44). However, that study was small, with only 24 COVID patients and 39 non-COVID patients; and, as in our study, no statistically-significant difference was detected between COVID and non-COVID patients.

Our COVID patients were much more symptomatic at presentation than our non-COVID patients, in almost all the symptoms recorded, including dyspnea, fevers and/or chills, and cough. In fact, that triad of fevers and/or chills, dyspnea, and cough was 95.3% specific for COVID, though only 45.9% sensitive, while the symptom dyad of fevers/chills and dyspnea was 93.0% sensitive and 63.4% specific. Other symptoms that were appreciably more common in COVID than non-COVID patients were fatigue, musculoskeletal aches or pain, loss of taste or smell, sore throat, and nasal congestion or coryza. Headaches, nausea and/or vomiting, and diarrhea

were uncommon in both of the groups. It must be noted that such differences in symptoms might only pertain to ICU patients, since few differences in the frequency of many of the same symptoms we studied were noted in their study by Shah et al.[47] Nonetheless, on multivariable analysis of our data, of the ten parameters retained as significant predictors of COVID-19, five — loss of smell/taste (OR = 8.57), dyspnea (OR = 5.87), fevers and/or chills (OR = 4.90), sore throat (OR = 2.51), and cough (OR = 2.17) — were presenting symptoms.

In addition to being more symptomatic, our COVID patients' general health status at admission was significantly worse. Their on-admission PaO_2 and their PaO2 receiving supplemental oxygen just prior to intubation was significantly low. However, neither the admission APACHE-II score nor PaO_2 measurement remained as predictors in our final regression model. One difference that must be noted, however, is that every one of the 37 COVID patients whose presenting APACHE-II score exceeded 30 ultimately died, while non-COVID patients survived with admission APACHE-II scores up to 40. On multi-variable analysis, baseline APACHE-II score also remained as one of only two mortality predictors, the other being mechanical ventilation while in the ICU. Combining a baseline APACHE-II score ≥ 17 and mechanical ventilation was 94.4% sensitive and 70.5% specific for mortality. This association, between presenting APACHE-II score and mortality in COVID-19 patients with ARDS, has also been reported by others.[48, 49]

With respect to admission-time laboratory results, only a lower lymphocyte count, lower serum troponin level, and higher serum LDH level were evident in COVID patients. Serum LDH also was statistically higher on the day of intubation. What is interesting here is that both lower lymphocyte counts and elevated LDH have been linked to increased mortality in COVID-19 patients in a recently-published systematic review of the literature,[50] while elevated troponin levels have been linked to myocarditis.[51] However, none of these four inter-group differences detected in laboratory values was retained on multivariable analysis. Serum ferritin, elevated levels of which were found to be predictive of increased mortality in a recently-published meta-analysis of 614 COVID-19 patients,[52] was more than twice as high in our COVID than non-COVID patients ($P = 0.013$); however, large variations in levels prevented this difference from satisfying our stringent criterion for statistical significance.

Where our COVID-19 and non-COVID patients were most different was in modes of treatment, with more COVID-19 patients receiving non-invasive intermittent positive pressure ventilation, and other supportive measures. More of them needed therapeutic plasma exchange, anti-viral drugs and other therapeutic agents. Such is not surprising, however, given the newness of COVID-19 and resulting dearth of data guiding management, its higher mortality rate relative to non-COVID ARDS, and the multiple different mechanisms known to cause ARDS in the absence of COVID-19. Accordingly, treatments commonly used for ARDS in general, like mechanical ventilation and tracheostomy, were no different in the two patient groups.

A markedly-elevated mortality rate was observed in our COVID-19 patients, which is consistent with rates reported elsewhere, including one study in which 96.6% of mechanically-ventilated COVID-19 patients perished.[49] We again point out the limitations of the one recently-published meta-analysis which failed to detect any significant differences in mortality comparing COVID-19 and non-COVID patients with ARDS,[43] limitations which included the inclusion of six (out of ten) studies using historical, rather than contemporary non-COVID cases, five using retrospectively-collected data on COVID-19 patients, two analyzing data from emergency department rather than ICU patients, and two restricting their analysis to just mechanically-ventilated or ECMO patients.

Another difference we detected in an adverse outcome that is not commonly reported was a more than five-fold rate of required supplemental oxygen among COVID survivors, required by 15/66 COVID-19 patients who survived (22.7%) vs. just 16/393 surviving non-COVID patients (4.1%; OR = 6.93, CI = 3.23-14.86). This highlights the potential long-term adverse health consequences of COVID-19, especially among those who develop critical illness, the frequency and severity of which only time will tell.[53]

Interestingly, the only moderately-large prospective study in which data for COVID and non-COVID cases were collected at the same location over the exact same time period, and in which multivariable analysis was performed to identify predictors of mortality found the APACHE-II score to be the only significant predictor, with mechanical ventilation predictive in non-COVID cases.[40] Note that we found both to be predictive of both COVID and non-COVID related ARDS. One potential explanation for this difference is that our study had 160 and 530 COVID and non-COVID cases, respectively, vs. just 95 and 117 in the Indian study.[40] In our study, all 37 COVID patients with a baseline APACHE-II score ≥31 died, while just 39/56 non-COVID patients with an APACHE-II score ≥ 31 died, including one patient with a score of 39 who survived to hospital discharge.

Among our study's strengths are prospective data collection, extensive number of variables examined, and the extremely low rate of missing data, especially among the numerous baseline patient characteristics, measures of health status, and outcomes, where data capture exceeded 99%. It also is, to our knowledge, the largest study reported in which predictors of mortality were compared in concurrently-enrolled cohorts of COVID and non-COVID ARDS patients.

5. LIMITATIONS

Among the weaknesses of our study are the lack of discrimination between pre-admission cardiovascular and pulmonary disease, and between pre-admission renal and hepatic disease, and the lack of imaging data, since chest radiographic findings have been identified as predictors of mortality in COVID patients,[54,55] and may provide further insights into the differences between ARDS caused by COVID vs. no COVID. Some other studies have looked at far more respiratory parameters than we did, like tidal volume, positive end-expiratory pressure (PEEP), the PaO_2/FiO_2 ratio, plateau and driving pressures, and measures of lung compliance.[23, 39] However, some of these other studies specifically examined the impact of respiratory parameters on respiratory outcomes, like transition to pressure support ventilation, rather than survival,[23] and all suffered from the limitations of historical controls. Moreover, respiratory parameters are fluid, typically changing repeatedly, whereas parameters like a patient's baseline or 3-day peak APACHE-II score, SOFA score, and the need for mechanical ventilation are distinct events that are much easier to accurately record. Finally, even if respiratory parameters are important, this does not lessen the predictive importance of such factors as the APACHE-II score, need for mechanical ventilation, and presentation symptoms as early predictors of a patient's course.

6. CONCLUSIONS

Our study directly compared contemporary populations of ICU-COVID-19 and ICU-non-COVID patients with ARDS, employing multi-variable analysis to adjust for potential confounding clinical differences, most notably in patient age, patient weight, the frequency of presenting symptoms, and outcomes, including the rate of mortality and prolonged supplemental oxygen requirement by the survivors. The presenting symptom dyad of fevers and/or chills and dyspnea was 93.0% sensitive and 63.4% specific for ARDS caused by COVID-19. COVID-19 patients requiring mechanical ventilation and a high on-admission APACHE-II were predictive of mortality, with all 37 COVID patients presenting with an APACHE-II score > 30 succumbed to disease.

7. Ethics considerations

All data collection and analysis were performed in accordance with the Declaration of Helsinki and local legislation. The study protocol was approved by the institutional review board at King Abdulaziz University. The requirement for informed consent was waived because of the study's observational design which was approved by the institutional review board at King Abdulaziz University (Ref No 649-20).

8. Availability of data

The data generated during the current study are available from the corresponding author on a reasonable request.

9. Competing interests

None of the authors has any competing interests to declare.

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11. Authors' contributions

HMA and MMA did literature search, study design, supervision of data collection and interpretation. MOA, FYM, SHH, MAJ, HAK, MHA perform data collection. KPW did the formal data analysis. All authors contributed to data interpretation and writing, reviewing, and editing this manuscript.

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