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Clinical Outcomes and Severity of Acute Respiratory Distress Syndrome in 1154 COVID-19 Patients: An Experience Multicenter Retrospective Cohort Study

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Abstract: Background: Acute Respiratory Distress Syndrome (ARDS) is caused by non-cardiogenic pulmonary edema and occurs in critically ill patients. It is one of the fatal complications observed among severe COVID-19 cases managed in intensive care units (ICU). Supportive lung-protective ventilation and prone positioning remain the mainstay interventions. Purpose: We describe the severity of ARDS, clinical outcomes, and management of ICU patients with laboratory-confirmed COVID-19 infection in multiple Saudi hospitals. Methods: A multicenter retrospective cohort study was conducted of critically ill patients who were admitted to the ICU with COVID-19 and developed ARDS. Results: During our study, 1154 patients experienced ARDS: 591 (51.2%) with severe, 415 (36.0%) with moderate, and 148 (12.8%) with mild ARDS. The mean sequential organ failure assessment (SOFA) score was significantly higher in severe ARDS with COVID-19 (6 ± 5, $p = 0.006$). Kaplan–Meier survival analysis showed COVID-19 patients with mild ARDS had a significantly higher survival rate compared to COVID-19 patients who experienced severe ARDS ($p = 0.023$). Conclusion: ARDS is a challenging condition complicating COVID-19 infection. It carries significant morbidity and results in elevated mortality. ARDS requires protective mechanical ventilation and other critical care supportive measures. The severity of ARDS is associated significantly with the rate of death among the patients.

Keywords: COVID-19; Acute Respiratory Distress Syndrome; ARDS; outcome; mortality; survival; risk factors

1. Introduction

COVID-19 disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which originated in China, has caused a global outbreak that has affected more than 70 million people worldwide [1]. SARS-CoV-2 associated pneumonia can be acquired in the community or in individuals with comorbidities [2,3]. The severity and mortality are particularly high in these patients [4]. Given the high mortality rates, the complexity of the care given to patients with COVID-19-associated respiratory distress syndrome (CARDS) has increased significantly worldwide. CARDS is ARDS due to SARS-CoV-2, and therefore follows the same characteristics of ARDS based on the Berlin definition [5]. Patients who are suffering hypoxemia are classified as mild ($PaO_2/FIO_2 \leq 300$ mm Hg), moderate ($PaO_2/FIO_2 \leq 200$ mm Hg), or severe ($PaO_2/FIO_2 \leq 100$ mm Hg) [5] ARDS. The increasing number of reports on this condition globally has helped us to understand the respiratory mechanics and ventilatory management, targeted to optimize the care for these patients [6–11]. Due to the increasing number of patients with COVID-19, hospitals had to work under tremendous pressure and often with limited resources to provide the best possible care to these individuals. The observations of heterogeneity in the clinical course and the various features of CARDS have led to the development of different management strategies [12–14].

The severity of the SARS-CoV-2 infection depends on the nature of the virus and the lack of effective therapy [15–18]. In addition, individuals with CARDS have higher mortality due to refractory hypoxemia, septic shock, and multi-organ failure [19]. In a recent study, it has been demonstrated that the two most common comorbidities in COVID-19 cases was hypertension (severe 33.4 vs. 21.6% non-severe) followed by diabetes (severe 14.4% vs 9% non-severe) [20]. However, when it came to severe cases, it was estimated that CARDS occurred at a high incidence rate of 41.1% vs. 3% in non-severe cases. Acute kidney injury and shock in these severe cases were higher as well at 16.4% vs. 2.2% non-severe, and 19.9% vs. 4.1% in non-severe cases, respectively. The mortality rate was high at 30.3% in these severe cases [20].

Some of the studies suggest that about 20% of patients with SARS-CoV-2 experience high disease severity and require hospitalization [21,22]. Among the hospitalized patients, it is seen that over a quarter percentile [26%] eventually end up in the intensive care unit (ICU) [23]. Evidence on the efficacy of prone positioning while on a ventilator [14], pharmacological interventions with pulmonary vasodilators [24], and neuromuscular blocking agents [25–27] for COVID-19 patients with ARDS is limited, and is based on anecdotal observations and data on the outcomes are conflicting. For those who fail these interventions, extracorporeal membrane oxygenation (ECMO) is suggested as a rescue strategy (27). Therefore, observational studies are a reasonable alternative to randomized clinical trials. Hence, this study aims to investigate the clinical characteristics and outcomes of COVID-19 patients with ARDS in Saudi Arabia.

2. Methods

2.1. Study Design

A multicenter, retrospective, cohort study was conducted and included patients who had positive tests by reverse transcriptase–polymerase chain reaction (RT-PCR) for SARS-CoV-2 during 2020 from ICUs in Saudi Arabia. The diagnosis was confirmed, and severity was determined using the Berlin definition [5]. This study obtained an ethical clearance from the Institutional Review Board "REDACTED". The study was performed in accordance with the Declaration of Helsinki. Unique patient codes were issued to each study participant to maintain anonymity and confidentiality throughout the study.

2.2. Population

A total of 1154 COVID-19 positive case who developed ARDS were included following the inclusion criteria. The following inclusion criteria were utilized: an ICU patient with confirmed SARS-CoV-2 infection, potentially requiring mechanical ventilation support, has respiratory arrest, organ failure, or potentially requiring continuous renal replacement therapy (CRRT), and has an acidosis and decreased level of consciousness. As this was a retrospective study, no informed consent was deemed necessary, and data were de-identified for the use of this publication.

2.3. Data Collection

Clinical data were collected utilizing standardized data collection forms [Microsoft Word and Excel forms (Microsoft Corp., Redmond, WA, USA)] following ICU admission. The recorded data included the following: age, sex, smoking status, medical comorbidities, and mode of respiratory support (invasive mechanical ventilation, non-invasive mechanical ventilation, and oxygen mask), the use of extracorporeal membrane oxygenation (ECMO), and prone positioning. The number of patients who died, had been discharged, and were still admitted in the ICU as of the end of the study period, were recorded, and the ICU length of stay was also determined.

2.4. Statistical Analysis

Descriptive variables were expressed as a percentage, mean and standard deviation (SD), or median and interquartile range (IQR), as appropriate. Variables across groups using Kruskal–Wallis or one-way Analysis of Variance (ANOVA) for numerical and categorical variables were compared. We assessed the relationship between ARDS severity and discontinuation from mechanical ventilation, ICU discharge, and mortality on day 28. Time to event curves were plotted using the Kaplan–Meier method and analyzed with the log-rank test and univariable Cox regression analysis. The chi-square test was used to determine the association of concomitant medication, heart failure, and liver failure with the course of ARDS severity in COVID-19 positive patients. Lastly, a one-way ANOVA was used to compare the transaminase levels among mild, moderate, and severe ARDS.

3. Results

The data from a total of 1154 COVID-19 positive patients who developed ARDS shows a resulting high prevalence rate of 78.5% where patients had a mean age of 55.9 ± 15.1 years and a mean body mass index (BMI) of 30.1 ± 6.8 kg/m2. In relation to ARDS, 591 (51.2%) had severe, 415 (36.0%) had moderate, and 148 (12.8%) had mild ARDS. Socio-demographic characteristics of the study population are shown in Table 1, including sex, nationality, and smoking habit; neither of them showed a significant difference in relation to the severity of ARDS. Most patients, 847 (73.4%) were males and half of them, 576 (49.9%) were Saudi nationals. All participants were critically ill; 111 (9.6%) of them had co-existing bronchial asthma and 92 (8%) had chronic kidney disease (CKD), with a significant association between severity of ARDS and the co-existence of bronchial asthma and CKD (*p*-values = 0.006 and 0.027, respectively). The mean sequential organ failure assessment (SOFA) score was significantly higher in COVID-19 patients with severe ARDS (6 ± 5, *p*-value 0.006) compared to mild and moderate ARDS cases.

Table 1. Baseline characteristics (*n* = 1154).

Characteristics	Mild ARDS (*n* = 148)	Moderate ARDS (*n* = 415)	Severe ARDS (*n* = 591)	*p*-Value
Gender [a]				
Male	110 (74.3)	302 (72.8)	435 (73.6)	0.922
Female	38 (25.7)	113 (27.2)	156 (26.4)	
Nationality [a]				
Saudi	78 (52.7)	204 (49.1)	294 (49.7)	0.755
Non-Saudi	70 (47.3)	211 (50.8)	297 (50.2)	
Age [b]	57 ± 23	55 ± 21.1	55 ± 21.8	0.896
BMI [b]	28.4 ± 7.7	29.4 ± 8.3	29.3 ± 7.2	0.36
Smoking [a]				
Smokers	25 (16.9)	57 (13.7)	76 (12.8)	0.443
Non-smokers	123 (83.1)	358 (86.3)	515 (87.1)	
Coexisting bronchial asthma [a]	6 (4)	34 (8.2)	71 (12)	0.006 *
Coexisting CKD [a]	20 (13.5)	31 (7.5)	41 (6.9)	0.027 *
ICU Inflammatory markers				
1st week				
ESR (mm/hour) [b]	49.62 ± 30.63	47.34 ± 42.67	49.36 ± 49.86	0.898
CRP (mg/L) [b]	133.01 ± 219.67	127.30 ± 130.59	154.56 ± 262.44	0.282
Ferritin (µg/L) [b]	1073.3 ± 1112.8	$1567.6 \pm 35.09.5$	1061.1 ± 1621.3	0.044 *
4th week				
ESR (mm/hour) [b]	65.0 ± 444.1	62.5 ± 48.4	62.6 ± 49.5	0.205
CRP (mg/L) [b]	110.9 ± 89.7	76.1 ± 68.1	67.1 ± 54.7	0.323
Ferritin (µg/L) [b]	7458.6 ± 1458.8	1079.7 ± 1338.8	1033.6 ± 1960.9	0.005 *
SOFA [b]	5 ± 3	5 ± 3	6 ± 4	0.006 *

Data are presented as number (%), mean $\pm$ SD or median (IQR). ARDS acute respiratory distress syndrome, BMI body mass index, CKD chronic kidney disease, CRP C-reactive protein, ICU intensive care unit, IQR interquartile range, ESR erythrocyte sedimentation rate, SOFA sequential organ failure assessment, SD standard deviation. [a] Kruskal—Wallis test was used to compare between mild ARDs, moderate ARDS, and severe ARDS groups. [b] One-way Analysis of Variance (ANOVA) test was used to compare between mild ARDs, moderate ARDS and severe ARDS groups. * Represents significant differences.

In Table 2, non-invasive respiratory support of high-flow nasal cannula (HFNC) was needed for 219 (37%) of the severe ARDS patients, which was more than the mild and moderate ARDS groups. Similarly, bilevel positive airway pressure (BiPAP) was needed more in severe cases of ARDS (*n* = 96, 16.2%) when compared to mild and moderate cases. Further, invasive mechanical endotracheal tube (ETT) ventilation was needed by a total of 642 (55.6%) patients, the majority of them suffering from severe ARDS (*n* = 346, 58.5%).

Table 2. Interventions during ICU stay (*n* = 1154).

Intervention	Mild ARDS (*n* = 148)	Moderate ARDS (*n* = 415)	Severe ARDS (*n* = 591)	*p-Value*
IMV(ETT) [a]	77 (52)	219 (52.8)	346 (58.5)	0.123
ECMO [a]	5 (3.4)	23 (5.5)	34 (5.7)	0.742
HFNC [a]	38 (25.7)	132 (31.8)	219 (37)	0.089
BiPAP (NIV) [a]	12 (8.1)	53 (12.8)	96 (16.2)	0.113
Paralysis infusion [a]	47 (31.7)	154 (37.1)	283 (47.9)	0.0001 *
Inhaled nitric oxide [a]	1 (0.7)	15 (3.6)	41 (6.9)	0.007 *
Prone positioning [a]	28 (18.9)	101 (24.3)	177 (29.9)	0.040 *
HFOV [a]	2 (1.3)	4 (1)	5 (0.8)	0.39
Steroids use [a]				
Dexamethasone	17 (11.5)	61 (14.7)	133 (22.5)	0.318
Methylprednisolone	20 (13.5)	56 (13.5)	159 (26.9)	

Data are presented as number (%). ARDS acute respiratory distress syndrome, BiPAP bilevel positive airway pressure, ECMO extracorporeal membrane oxygenation, ETT Endotracheal tube, HFNC High-flow nasal cannula, HFOV high frequency oscillatory ventilation, IMV invasive mechanical ventilation, NIV Non-invasive ventilation. [a] One-way Analysis of Variance (ANOVA) test was used to compare between mild ARDs, moderate ARDS, and severe ARDS groups. * Represents significant differences.

Table 3 shows some patients that developed medical complications including pulmonary embolism, deep vein thrombosis, and stroke which were observed more in the severe ARDS group, compared to mild and moderate ARDS cases. A longer length of stay in the ICU was observed among patients with severe ARDS, compared to mild and moderate cases. The overall ICU mortality in COVID-19 complicated with ARDS was 488 (42.3%); 273 (46.2%) mortalities were in the severe ARDS group, 169 (40.7%) in the moderate group, and 46 (31.1%) in the mild ARDS group were observed. In the same table, more than half of the patients who received steroid therapy (*n* = 446, 65.5%) were from the severe ARDS group.

Table 3. Overall patients' outcomes (*n* = 1154).

Characteristics	Mild ARDS (*n* = 148)	Moderate ARDS (*n* = 415)	Severe ARDS (*n* = 591)	*p-Value*
Length of stay in ICU [a]				
>28 days	8 (5.4)	44 (10.6)	57 (9.6)	0.174
≤28 days	140 (94.6)	371 (89.4)	534 (90.3)	
Length of stay in ICU [b]	8.0 (6.8–10.1)	9.0 (8.1–14.2)	10.0 (8.3–14.7)	0.672
Positive respiratory culture [a]	18 (12.2)	68 (16.4)	96 (16.2)	0.434
Candidiasis [a]				
Culture positive candidiasis	5 (3.4)	14 (3.4)	10 (1.7)	0.189
Culture negative candidiasis	143 (96.6)	401 (96.6)	581 (98.3)	
Complication of PE [a]	2 (1.3)	9 (2.2)	19 (1.5)	0.35
Complication of DVT [a]	4 (2.7)	10 (2.4)	13 (2.2)	0.93
Complication of stroke [a]	7 (4.7)	9 (2.2)	9 (1.5)	0.057
Complication of Pneumothorax [a]	9 (6.1)	24 (5.8)	41 (6.9)	0.751
Duration of MV [b]	9.12 ± 11.36	12.67 ± 18.19	9.46 ± 13.02	0.009 *
Overall ICU mortality [a]				
Survived	102 (68.9)	246 (59.3)	318 (53.8)	0.003 *
Non-survived	46 (31.1)	169 (40.7)	273 (46.2)	

Data are presented as number (%), mean ± SD or median (IQR). ARDS acute respiratory distress syndrome, DVT deep vein thrombosis, ICU intensive care unit, IQR interquartile range, PE pulmonary embolism, MV mechanical ventilation, SD standard deviation. [a] Kruskal—Wallis test was used to compare between mild ARDs, moderate ARDS, and severe ARDS groups. [b] One-way Analysis of Variance (ANOVA) test was used to compare between mild ARDs, moderate ARDS, and severe ARDS groups. * Represents significant differences.

Multiple logistic regression analysis is shown in Table 4 and revealed: (a) males infected with COVID-19 were more likely than COVID-19 females to develop ARDS (OR 1.165, 95% CI 0.871–1.557; *p* = 0.303). (b) COVID-19 patients of an older age [≥60 years old]

were significantly more likely to develop ARDS (OR 0.987, 95% CI 0.978–0.995; *p* = 0.002). (c) COVID-19 patients who required high frequency oscillatory ventilation (HFOV) (OR 2.311, 95% CI 1.692–3.155; *p* = 0.0001), or invasive mechanical ventilation (IMV) (OR 1.660, 95% CI 1.291–2.133; *p* = 0.0001) were significantly more likely to develop ARDS. Survival analysis applying the Kaplan—Meier curve revealed COVID-19 patients with mild ARDS to have a significantly higher survival rate, compared to those who suffered severe ARDS, *p*-value 0.03. Figure 1.

Table 4. Multiple logistic regression comparing the presence of ARDS predicted by demographic and clinical characteristics of patients (*n* = 1154).

Characteristics	OR	95% CI	*p-Value*
Gender *Males* vs. *females to develop ARDS*	1.165	(0.871–1.557)	0.303
Age *Developing ARDS in relation to age*	0.987	(0.978–0.995)	0.002 *
HFOV *Those needing HFOV* vs. *those who did not need*	2.311	(1.692–3.155)	0.0001 *
NIV (BiPAP) Those needing NIV vs. *those who did not need*	1.002	(0.700–1.436)	0.99
Number of days in the hospital before ICU *Developing ARDS with each day in ICU*	1.006	(0.996–1.016)	0.265
IMV(ETT) *Those needing IMV* vs. *those who did not need*	1.66	(1.291–2.133)	0.0001 *
BMI *Developing ARDS with each* kg/m^2 *increase in BMI*	1.003	(0.983–1.022)	0.785

Data are presented as odds ratio (OR). ARDS acute respiratory distress syndrome, BiPAP bilevel positive airway pressure, BMI body mass index, CI confidence interval, ETT Endotracheal tube, HFOV high frequency oscillatory ventilation, IMV invasive mechanical ventilation, NIV Non-invasive ventilation. * Represents significant differences.
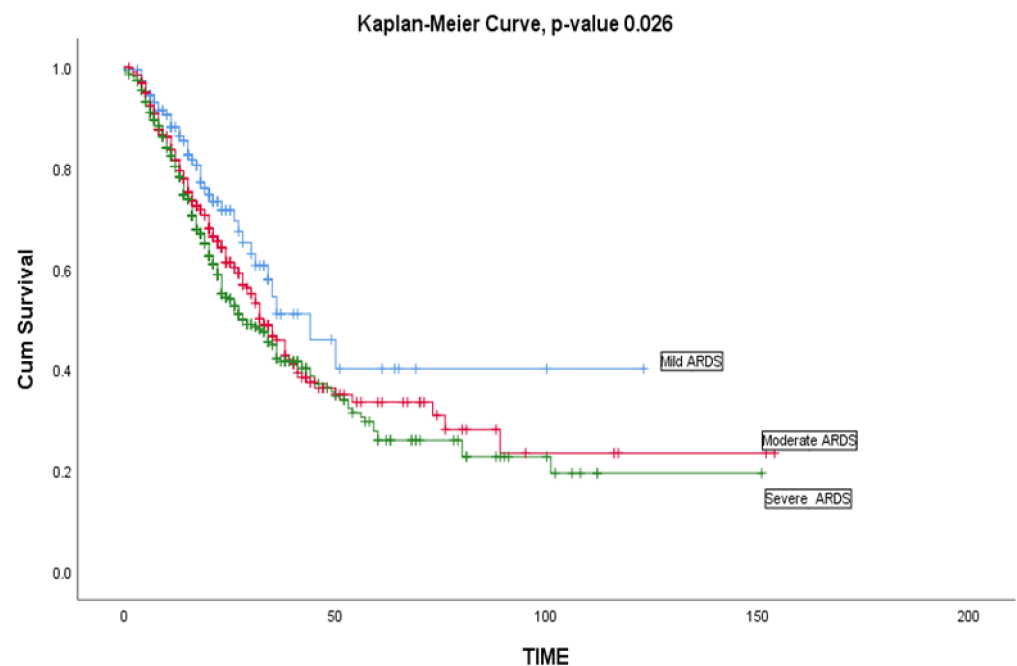

Figure 1. Kaplan—Meier curve survival of critically ill patients with COVID-19 infection based on ARDS severity (mild ARDS, moderate ARDS, and severe ARDS) (*n* = 1154).

Multiple chi-square tests shown in Table 5 revealed a significant association between favipiravir and severity of ARDS (p = < 0.00001, 95% CI). A significant association was also seen between Toclizumab and course of severity of ARDS in COVID-19 positive patients (p = 0.049, 95% CI). Furthermore, the association of heart failure and chronic liver disease with the course of severity of ARDS did not show any significance (Table 6). Comparing the liver enzymes Aspartate transaminase (AST) and Alanine transaminase (ALT) (maximum levels shown in Table 7) using a one-way ANOVA showed there was no significant difference between the mild, moderate, and severe ARDS in COVID-19 positive patient groups (see Tables 8 and 9, respectively).

Table 5. Association [a] between medications and the course of ARDS severity (n = 1154).

Characteristics	Mild ARDS (%)	Moderate ARDS (%)	Severe ARDS (%)	*p*-Value
Favipiravir				
Yes	26 (17.6%)	69 (16.6%)	187 (31.6%)	<0.00001
No	122 (82.4%)	346 (83.4%)	404 (68.4%)	
Remdesivir				
Yes	2 (1.4%)	5 (1.2%)	4 (0.7%)	0.7346
No	146 (98.6%)	410 (98.8%)	587 (99.3%)	
Ribavirin				
Yes	24 (16.2%)	68 (16.4%)	117 (19.8%)	0.3128
No	124 (83.8%)	347 (83.6%)	474 (80.2%)	
Tamiflu				
Yes	32 (21.6%)	107 (25.8%)	125 (21.2%)	0.210
No	116 (78.4%)	308 (74.2%)	466 (78.8%)	
Toclizumab				
Yes	37 (25.0%)	130 (31.3%)	208 (35.2%)	0.049
No	111 (75.0%)	285 (68.7%)	383 (64.8%)	

Data are presented as number (%). ARDS acute respiratory distress syndrome. [a] Chi-square test (95% CI).

Table 6. Association between comorbidities and the course of ARDS severity (n = 1154).

Characteristics	Mild ARDS (%)	Moderate ARDS (%)	Severe ARDS (%)	*p*-Value
Heart failure				
Yes	11 (14.9%)	18 (4.3%)	28 (4.7%)	
No	137 (85.1%)	397 (95.7%)	563 (95.3%)	[a] 0.372
Chronic liver disease				
Yes	3 (2.0%)	4 (1.00%)	14 (2.4%)	
No	145 (98.0%)	411 (99.00%)	577 (97.6%)	[a] 0.096

Data are presented as number (%). ARDS acute respiratory distress syndrome. [a] Chi-square test.

Table 7. Highest levels of AST and ALT enzyme (n = 1154).

Enzyme	Median	Maximum	Mean	Std. Deviation
AST	48.00 with ICR (46.22)	5156.00	92.86	251.44
ALT	38.00 with ICR (39.00)	3097.00	69.16	171.52

No data on troponin enzyme. Data are presented as number (%). AST Aspartate transaminase. ALT Alanine transaminase.

Table 8. Comparing levels of AST enzyme per ASDS status (n = 1154).

AST Enzyme	Mean	SD	F [a]	*p*-Value
Mild ARDS	93.49	190.94		
Moderate ARDS	101.62	332.91	1.117	0.328
Severe ARDS	78.54	172.89		

ARDS acute respiratory distress syndrome. [a] One-way Analysis of Variance (ANOVA) (95% CI). SD, standard deviation.

Table 9. Comparing levels of ALT enzyme per ARDS status (*n* = 1154).

AST Enzyme	Mean	SD	F [a]	*p*-Value
Mild ARDS	69.83	180.42		
Moderate ARDS	75.74	211.82	0.477	0.620
Severe ARDS	64.78	142.52		

ARDS acute respiratory distress syndrome. [a] One-way Analysis of Variance (ANOVA) (95% CI). SD, standard deviation.

4. Discussion

The aim of our study was to assess the characteristics and outcomes of ADRS associated with COVID-19 in Saudi hospitals at the time of ICU admission. Our results showed that many patients were males (*n* = 847, 73.4%) and half of them were Saudi nationals (*n* = 576, 49.9%) with a mean age of 55.9 ± 15.1 years and a mean body mass index (BMI) of 30.1 ± 6.8 kg/m^2. All participants were critically ill. In our study, the male gender predominated the development of ARDS in SARS-CoV-2 patients. Similar findings were suggested in most of the reports from South Korea and Iceland [26,28]. Males infected with COVID-19 were associated with more than a twofold higher risk of suffering ARDS compared to females [29].

In addition, patients with severe ARDS requiring mechanical ventilation are predisposed to acute kidney injury owing to the presence of acute lung injury in them [25,30]. In COVID-19 patients, acute kidney injuries are common clinical presentations affecting approximately 20–40% of patients admitted to ICU [31,32] and about 20% of patients admitted to an ICU with COVID-19 require renal replacement therapy at a median of 15 days from illness onset [33].

The risk factors and clinical characteristics associated with clinical outcomes in COVID-19 pneumonia patients who developed ARDS after admission were reported in this study. The presence of any coexisting illness was more common among patients with severe disease than among those with non-severe disease (38.7% vs. 21.0%) that was reported in China [2]. Consistent with previous reports, we found the development of ARDS in SARS-CoV-2 patients was high in the presence of comorbidities such as bronchial asthma and chronic kidney disease [34,35]. Patients with a predisposition to smoking were surprisingly found to be able to reduce the severity of CARDS owing to the inflection of the innate macrophage responses by nicotine which is an active component of cigarettes [36]. However, in our study it was found that smoking had no significant correlation with the severity of CARDS.

The management of CARDS is highly modulated by the severity of the condition. During the COVID-19 pandemic, in patients with moderate to severe CARDS, oxygenation was provided by the high-flow nasal cannula O$_2$ method (HFNO) [37]. The advantage of this method is that it provides the patients with higher inspired oxygenation levels while it can also provide larger lung volume through the production of a low level of continuous positive airway pressure (CPAP) [38]. A retrospective study on 104 COVID-19 patients with moderate to severe hypoxemia showed that more than half (64%) of them were treated using the HFNO method and avoided the need for mechanical ventilation, thereby reducing the mortality in that group to 2.9% when compared to the 14.4% mortality in the group that required intubation [39]. However, in a multicenter trial on the use of HFNO therapy on ARDS patients, it was seen that although the method reduced the 90-day mortality of patients by 50%, it made no difference in the need for mechanical ventilation [40].

Continuous positive airway pressure (CPAP) or non-invasive positive pressure ventilation (NIPPV) methods have gained prominence during the COVID pandemic, especially in places where there has been a lack of proper ICU infrastructure [41]. All these non-invasive (NIV) methods have been shown to have a significant risk of failure in a global LUNGSAFE study [42]. It is seen that 22.2% of mild ARDS patients, 42% of moderate ARDS, and 47% of severe ARDS patients failed when the abovementioned non-invasive methods were used.

Based on the Berlin definition, stages of mild, moderate, and severe ARDS were associated with increased mortality and increased median duration of mechanical ventilation in

the survivors [5]. In severe CARDS patients, invasive respiratory support—which includes endotracheal intubation and mechanical ventilation—is often recommended for patients with persistent respiratory distress or worsening of respiratory hypoxemia ($SpO_2 < 92\%$, which is similar to the respiratory management seen in the usual ARDS patients [43–45]. The main objective of mechanical ventilation is focused on the strategy to prevent atelectasis-recruitment and tidal-inflation stress, which can lead to ventilation-induced lung injury [46]. The most important measure is the use of low-tidal volumes to minimize atelectasis [47].

In our cohort study, about ($n = 642$, 56%) of patients initially received non-invasive methods of respiratory support, and ($n = 669$, 58%) of patients received invasive mechanical ventilation, which was less than that reported in observational studies from China [2], New York [48], Washington state [49], and Italy [50] (67%, 79%, 71%, and 88%), respectively. Our study demonstrated the SOFA score at admission. The results found a total SOFA score of 6 ± 4 with a mortality rate of 46% for severe ARDS patients and a SOFA score of 5 ± 3 for both mild and moderate cases with a mortality rate of 41 % and 31%, respectively. When compared with other studies, the United Arab Emirates reported a SOFA score of ICU patients of 4 (3–7) with a mortality rate of 22% [51]. In the European study of COVID-19, ICU group patients had a SOFA score of 5 (3–8) [52]. In a Spanish study, critically ill patients had a SOFA score of 5 (3–7), and the overall mortality rate was 31% [53]. A SOFA score of 4 (2–8) at admission was reported in a prospective multicenter study of COVID-19 critical care patients that was conducted in China [54].

Corticosteroids have significant anti-inflammatory and antifibrotic properties in relieving pulmonary and systemic injury in ARDS patients [55]. Several studies have found that corticosteroids can improve the clinical condition of patients suffering from severe acute respiratory syndrome [56,57]. One large randomized controlled trial from the United Kingdom (RECOVERY) showed that treating COVID-19 patients with intravenous corticosteroids (dexamethasone) for 10 days improved the survival [58]. The incidence of death was higher in the control group (41.4%) when compared to patients receiving dexamethasone (29.3%) among patients who were undergoing invasive mechanical ventilation. Among patients who received oxygen with no invasive mechanical ventilation, the death rate among the control group (26.2%) was again higher when compared to the dexamethasone group (23.3%). However, further trials need to be run to see if these results can be replicated and a further understanding of the side effects of corticosteroid use needs to be investigated. In addition, the effectiveness of corticosteroids in viral ARDS remains controversial [59,60]. Since the syndrome's first clinical diagnosis, corticosteroids have been the most used drugs [61]. Clinicians commonly used adjunctive corticosteroids to decrease hyperinflammation in COVID-19 patients, particularly those with critical disease [2,62]. Our results showed that severe ARDS patients received corticosteroids at ($n = 292$, 65.5%), which is higher than what was reported in a European study, where only 46% of the severe ARDS patients received corticosteroids [52].

In our study, the incidence rate of pneumothorax has been found to vary between 5.8% and 7% in patients with mild to severe ARDS due to COVID-19. The pneumothorax incidence rate from our study is in line with the Özdemir et al. study that reported a 7.5% incidence among patients in the ICU who underwent intubation following the diagnosis of COVID-19 pneumonia [40,63], and is less than the incidence of pneumothorax of 10% that was reported in a Chinese study. We report a higher incidence rate of spontaneous pneumothorax (6.9%) in severe SARS-CoV-2 patients treated due to ARDS compared to the rates reported by one study in Hong Kong (1.3%) [64].

Venous thromboembolism is common in patients receiving COVID-19 treatment for ARDS, and it is associated with a high mortality rate [65]. Patients with COVID-19 manifest a hypercoagulable state, often resulting in deep vein thrombosis or pulmonary embolism [66]. Our results outline that the occurrence of pulmonary embolisms varies from 1.4% to 3.2 % depending on the severity of ARDS. One prospective cohort reported only 1.3% of pulmonary embolisms in critically ill patients [67], which is in contrast to the high prevalence of pulmonary embolisms reported (16.7%) in a cohort of patients admitted to the

ICU for hypoxemic acute respiratory failure due to COVID-19 [66]. Pulmonary embolism occurrence in COVID-19 patients who suffered ARDS when matched with non-COVID-19 patients who never experienced ARDS was observed to be high (11.7% vs. 2.1%, $p < 0.008$) despite prophylactic anticoagulation [66].

The Kaplan—Meier median duration of survival was 9 days. The observed median length of stay was 8 days for mild ARDS cases, 9 days for moderate ARDS cases, and 10 days for severe ARDS cases. Survival analysis applying the Kaplan—Meier curve revealed COVID-19 patients with mild ARDS have a significantly higher survival rate compared to those with severe ARDS, (p-value 0.023) which is consistent with an American study [68].

The severity of CARDS patients varies greatly, with no standardized effective therapies [69,70]. Unfortunately, during the period of this study, no definite drug was available for CARDS that was capable of reducing either short-term or long-term mortality [71]. Thus, apart from corticosteroids, the study examined the association of some concomitant medications used for the treatment of COVID-19 with the course of severity of ARDS. Only Favipiravir and Tocilizumab showed a significant association with the course of severity of ARDS in COVID-19 positive patients. Though not directly used for CARDS management, favipiravir was reported to show a higher viral clearance in a preliminary double-blinded randomized controlled trial with 57 hospitalized COVID-19 patients, where assessment of chest X-rays showed remarkable improvement of pneumonia patients receiving Favipiravir [72]. Similarly, the efficacy of Tocilizumab was demonstrated through several studies on COVID-19 positive patients with ARDS. A study on 79 patients with severe COVID-19 pneumonia and worsening acute respiratory failure (ARF), showed that Tocilizumab treatment may be effective in COVID-19 patients with severe respiratory impairment receiving non-invasive ventilation [70]. In yet another study, Tocilizumab for the treatment of mechanically ventilated patients with COVID-19, included 154 patients, and showed an association of Tocilizumab with a lower mortality despite higher superinfection occurrence. Furthermore, as COVID-19 causes severe respiratory and multiorgan failure, including liver damage and elevated transaminase levels, this study examined the association of heart failure and liver damage to the course of severity of ARDS in COVID-19 positive patients. There was no significant association of neither heart failure nor liver damage with the severity of ARDS in COVID-19 positive patients. Though there are multiple studies suggesting patients with heart failure (HF) are at a higher risk of severe disease and mortality with COVID-19 [73], reports on the association of heart failure to the severity of ARDS in COVID-19 positive patients are limited. Additionally, liver-related comorbidities were not common among the patients with COVID-19 pneumonia and their frequency was about 3% [74]. Very low expression of the ACE2 receptor in hepatocytes and bile duct epithelium [75,76] possibly explain the small influence of viral infection in the liver [77]. Lastly, comparing the transaminase levels among mild, moderate, and severe ARDS patients with COVID-19 showed no significance. Analogous results were reported through a meta-analysis of 60 studies that concluded in critically ill and fatal cases, no difference was found in the prevalence of elevated ALT or AST [78].

This study has several strengths. First, our study represents one of the largest multicenter retrospective cohorts of patients with COVID-19 associated critical illness reported in Saudi Arabia. Second, our findings mirror the ongoing outbreak of COVID-19 in Saudi Arabia in addition to the data being collected using a large Ministry of Health electronic health record system. Lastly, data analyses were conducted with near-complete data.

5. Limitations

Though the present study was a multicenter study that included a large cohort, the retrospective nature of the study stalls the possibility of differences in the quality of care affecting the patients' recovery which rises as a limitation of the study. As the ventilation management was not standardized, it could lead to data variability. Furthermore, analyzing vaccination history of the patient could have added insight on their immunity and resistance

to severity of the disease. In addition, comparing COVID-19 ARDS with concurrent non-COVID-19 ARDS could have provided broader insights to CARDS management.

6. Conclusions

The study results revealed that ARDS is a challenging critical care condition complicating COVID-19 at a high rate, resulting in significant morbidity and mortality. ARDS requires protective mechanical ventilation and other critical care supportive measures. The severity of ARDS is associated significantly with the mortality rate among COVID-19 critically ill patients.

References

1. *WHO Coronavirus Disease (COVID-19) Dashboard*; World Health Organization: Geneva, Switzerland, 2020. Available online: https://covid19.who.int/ (accessed on 1 June 2021).
2. Zhu, N.; Zhang, D.; Wang, W.; Li, X.; Yang, B.; Song, J.; Zhao, X.; Huang, B.; Shi, W.; Lu, R.; et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N. Engl. J. Med.* **2020**, *382*, 727–733. [CrossRef] [PubMed]
3. Guan, W.-J.; Ni, Z.-Y.; Hu, Y.; Liang, W.-H.; Ou, C.-Q.; He, J.-X.; Liu, L.; Shan, H.; Lei, C.-L.; Hui, D.S.C. Clinical characteristics of coronavirus disease 2019 in China. *N. Engl. J. Med.* **2020**, *382*, 1708–1720. [CrossRef] [PubMed]
4. Domecq, J.P.; Lal, A.; Sheldrick, C.R.; Kumar, V.K.; Boman, K.; Bolesta, S.; Bansal, V.; Harhay, M.O.; Garcia, M.A.; Kaufman, M.; et al. Outcomes of Patients with Coronavirus Disease 2019 Receiving Organ Support Therapies: The International Viral Infection and Respiratory Illness Universal Study Registry. *Crit. Care Med.* **2021**, *49*, 437–448. [CrossRef] [PubMed]
5. Ranieri, V.M.; Rubenfeld, G.D.; Thompson, B.T.; Ferguson, N.D.; Caldwell, E.; Fan, E.; Camporota, L.; Slutsky, A.S. Acute respiratory distress syndrome: The Berlin Definition. *JAMA* **2012**, *307*, 2526–2533.
6. Shrestha, G.S.; Khanal, S.; Sharma, S.; Nepal, G. COVID-19: Current Understanding of Pathophysiology. *J. Nepal Health Res. Counc.* **2020**, *18*, 351–359. [CrossRef]
7. Zambon, M.; Vincent, J.L. Mortality rates for patients with acute lung injury/ARDS have decreased over time. *Chest* **2008**, *133*, 1120–1127. [CrossRef]
8. Sedhai, Y.R.; Yuan, M.; Ketcham, S.W.; Co, I.; Claar, D.D.; McSparron, J.I.; Prescott, H.C.; Sjoding, M.W. Validating Measures of Disease Severity in Acute Respiratory Distress Syndrome. *Ann. Am. Thorac Soc.* **2021**, *18*, 1211–1218. [CrossRef]
9. Gajic, O.; Dabbagh, O.; Park, P.K.; Adesanya, A.; Chang, S.Y.; Hou, P.; Anderson, H., 3rd; Hoth, J.J.; Mikkelsen, M.E.; Gentile, N.T.; et al. Early identification of patients at risk of acute lung injury: Evaluation of lung injury prediction score in a multicenter cohort study. *Am. J. Respir. Crit. Care Med.* **2011**, *183*, 462–470. [CrossRef]
10. Sharma, N.S.; Lal, C.V.; Li, J.D.; Lou, X.Y.; Viera, L.; Abdallah, T.; King, R.W.; Sethi, J.; Kanagarajah, P.; Restrepo-Jaramillo, R.; et al. The neutrophil chemoattractant peptide proline-glycine-proline is associated with acute respiratory distress syndrome. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2018**, *315*, L653–L661. [CrossRef]

11. Huang, D.; Ma, H.; Xiao, Z.; Blaivas, M.; Chen, Y.; Wen, J.; Guo, W.; Liang, J.; Liao, X.; Wang, Z.; et al. Diagnostic value of cardiopulmonary ultrasound in elderly patients with acute respiratory distress syndrome. *BMC Pulm. Med.* **2018**, *18*, 136. [CrossRef]

12. Cherian, S.V.; Kumar, A.; Akasapu, K.; Ashton, R.W.; Aparnath, M.; Malhotra, A. Salvage therapies for refractory hypoxemia in ARDS. *Respir. Med.* **2018**, *141*, 150–158. [CrossRef]

13. Pan, C.; Chen, L.; Lu, C.; Zhang, W.; Xia, J.A.; Sklar, M.C.; Du, B.; Brochard, L.; Qiu, H. Lung Recruitability in COVID-19-associated acute respiratory distress syndrome: A Single-Center Observational Study. *Am. J. Respir. Crit. Care Med.* **2020**, *201*, 1294–1297. [CrossRef]

14. Gupta, A.; Madhavan, M.V.; Sehgal, K.; Nair, N.; Mahajan, S.; Sehrawat, T.S.; Bikdeli, B.; Ahluwalia, N.; Ausiello, J.C.; Wan, E.Y.; et al. Extrapulmonary manifestations of COVID-19. *Nat. Med.* **2020**, *26*, 1017–1032. [CrossRef]

15. Al Mutair, A.; Al Mutairi, A.; Alhumaid, S.; Maaz Abdullah, S.; Zia Zaidi, A.R.; Rabaan, A.A.; Al-Omari, A. Examining and investigating the impact of demographic characteristics and chronic diseases on mortality of COVID-19: Retrospective study. *PLoS ONE* **2021**, *16*, e0257131. [CrossRef]

16. Al Mutair, A.; Al Mutairi, A.; Zaidi, A.R.Z.; Salih, S.; Alhumaid, S.; Rabaan, A.A.; Al-Omari, A. Clinical Predictors of COVID-19 Mortality Among Patients in Intensive Care Units: A Retrospective Study. *Int. J. Gen. Med.* **2021**, *14*, 3719–3728. [CrossRef]

17. Almoosa, Z.; Saad, M.; Qara, S.; Mustafa, M.; Mansour, A.; Alshab, D.; Alhashem, J.; ALKhawajah, S.; Alkhalifah, S.; ALmarzooq, M.; et al. Favipiravir versus standard of care in patients with severe COVID-19 infections: A retrospective comparative study. *J. Infect Public Health* **2021**, *14*, 1247–1253. [CrossRef]

18. Alhumaid, S.; Al Mutair, A.; Al Alawi, Z.; Al Salman, K.; Al Dossary, N.; Omar, A.; Alismail, M.; Al Ghazal, A.M.; Jubarah, M.B.; Al Shaikh, H. Clinical features and prognostic factors of intensive and non-intensive 1014 COVID-19 patients: An experience cohort from Alahsa, Saudi Arabia. *Eur. J. Med. Res.* **2021**, *26*, 47. [CrossRef]

19. Sun, P.; Qie, S.; Liu, Z.; Ren, J.; Li, K.; Xi, J. Clinical characteristics of hospitalized patients with SARS-CoV-2 infection: A single arm meta-analysis. *J. Med. Virol.* **2020**, *92*, 612–617. [CrossRef]

20. Wang, Z.; Deng, H.; Ou, C.; Liang, J.; Wang, Y.; Jiang, M.; Li, S. Clinical symptoms, comorbidities and complications in severe and non-severe patients with COVID-19: A systematic review and meta-analysis without cases duplication. *Medicine* **2020**, *99*, e23327. [CrossRef]

21. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **2020**, *395*, 497–506. [CrossRef]

22. Young, B.E.; Ong, S.W.X.; Kalimuddin, S.; Low, J.G.; Tan, S.Y.; Loh, J.; Ng, O.T.; Marimuthu, K.; Ang, L.W.; Mak, T.M.; et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. *JAMA* **2020**, *323*, 1488–1494. [CrossRef]

23. Wang, D.; Hu, B.; Hu, C.; Zhu, F.; Liu, X.; Zhang, J.; Wang, B.; Xiang, H.; Cheng, Z.; Xiong, Y.; et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* **2020**, *323*, 1061–1069. [CrossRef]

24. Alhazzani, W.; Møller, M.H.; Arabi, Y.M.; Loeb, M.; Gong, M.N.; Fan, E.; Oczkowski, S.; Levy, M.M.; Derde, L.; Dzierba, A.; et al. Surviving Sepsis Campaign: Guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med.* **2020**, *46*, 854–887. [CrossRef]

25. Coronavirus Disease-19: The First 7755 Cases in the Republic of Korea. *Osong Public Health Res. Perspect.* **2020**, *11*, 85–90, Erratum in *Osong Public Health Res. Perspect.* **2020**, *11*, 146. [CrossRef]

26. Gudbjartsson, D.F.; Helgason, A.; Jonsson, H.; Magnusson, O.T.; Melsted, P.; Norddahl, G.L.; Saemundsdottir, J.; Sigurdsson, A.; Sulem, P.; Agustsdottir, A.B.; et al. Spread of SARS-CoV-2 in the Icelandic Population. *N. Engl. J. Med.* **2020**, *382*, 2302–2315. [CrossRef]

27. Henry, B.M. COVID-19, ECMO, and lymphopenia: A word of caution. *Lancet Respir. Med.* **2020**, *8*, e24. [CrossRef]

28. Coronavirus Disease-19: Summary of 2370 Contact Investigations of the First 30 Cases in the Republic of Korea. *Osong Public Health Res. Perspect.* **2020**, *11*, 81–84. [CrossRef]

29. Hoste, E.A.; Bagshaw, S.M.; Bellomo, R.; Cely, C.M.; Colman, R.; Cruz, D.N.; Edipidis, K.; Forni, L.G.; Gomersall, C.D.; Govil, D.; et al. Epidemiology of acute kidney injury in critically ill patients: The multinational AKI-EPI study. *Intensive Care Med.* **2015**, *41*, 1411–1423. [CrossRef]

30. Hirsch, J.S.; Ng, J.H.; Ross, D.W.; Sharma, P.; Shah, H.H.; Barnett, R.L.; Hazzan, A.D.; Fishbane, S.; Jhaveri, K.D. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int.* **2020**, *98*, 209–218. [CrossRef]

31. Zahid, U.; Ramachandran, P.; Spitalewitz, S.; Alasadi, L.; Chakraborti, A.; Azhar, M.; Mikhalina, G.; Sherazi, A.; Narh, J.T.; Khattar, P. Acute kidney injury in COVID-19 patients: An inner city hospital experience and policy implications. *Am. J. Nephrol.* **2020**, *51*, 786–796. [CrossRef]

32. Richardson, S.; Hirsch, J.S.; Narasimhan, M.; Crawford, J.M.; McGinn, T.; Davidson, K.W.; Barnaby, D.P.; Becker, L.B.; Chelico, J.D.; Cohen, S.L. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* **2020**, *323*, 2052–2059. [CrossRef] [PubMed]

33. Zhou, F.; Yu, T.; Du, R.; Fan, G.; Liu, Y.; Liu, Z.; Xiang, J.; Wang, Y.; Song, B.; Gu, X. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet* **2020**, *395*, 1054–1062. [CrossRef]

34. Xu, W.; Sun, N.-N.; Gao, H.-N.; Chen, Z.-Y.; Yang, Y.; Ju, B.; Tang, L.-L. Risk factors analysis of COVID-19 patients with ARDS and prediction based on machine learning. *Sci. Rep.* **2021**, *11*, 2933. [CrossRef] [PubMed]

35. Sanyaolu, A.; Okorie, C.; Marinkovic, A.; Patidar, R.; Younis, K.; Desai, P.; Hosein, Z.; Padda, I.; Mangat, J.; Altaf, M. Comorbidity and its impact on patients with COVID-19. *SN Compr. Clin. Med.* **2020**, *2*, 1069–1076. [CrossRef]

36. Kloc, M.; Ghobrial, R.M.; Kubiak, J.Z. How nicotine can inhibit cytokine storm in the lungs and prevent or lessen the severity of COVID-19 infection? *Immunol. Lett.* **2020**, *224*, 28–29. [CrossRef]

37. Wang, K.; Zhao, W.; Li, J.; Shu, W.; Duan, J. The experience of high-flow nasal cannula in hospitalized patients with 2019 novel coronavirus-infected pneumonia in two hospitals of Chongqing, China. *Ann. Intensive Care* **2020**, *10*, 37. [CrossRef]

38. Nishimura, M. High-flow nasal cannula oxygen therapy in adults. *J. Intensive Care* **2015**, *3*, 15. [CrossRef]

39. Patel, M.; Gangemi, A.; Marron, R.; Chowdhury, J.; Yousef, I.; Zheng, M.; Mills, N.; Tragesser, L.; Giurintano, J.; Gupta, R.; et al. Retrospective analysis of high flow nasal therapy in COVID-19-related moderate-to-severe hypoxaemic respiratory failure. *BMJ Open Respir. Res.* **2020**, *7*, e000650. [CrossRef]

40. Frat, J.-P.; Thille, A.W.; Mercat, A.; Girault, C.; Ragot, S.; Perbet, S.; Prat, G.; Boulain, T.; Morawiec, E.; Cottereau, A. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N. Engl. J. Med.* **2015**, *372*, 2185–2196. [CrossRef]

41. Winck, J.C.; Ambrosino, N. COVID-19 pandemic and non invasive respiratory management: Every Goliath needs a David. An evidence based evaluation of problems. *Pulmonology* **2020**, *26*, 213–220. [CrossRef]

42. Bellani, G.; Laffey, J.G.; Pham, T.; Madotto, F.; Fan, E.; Brochard, L.; Esteban, A.; Gattinoni, L.; Bumbasirevic, V.; Piquilloud, L.; et al. Noninvasive Ventilation of Patients with Acute Respiratory Distress Syndrome. Insights from the LUNG SAFE Study. *Am. J. Respir. Crit. Care Med.* **2017**, *195*, 67–77. [CrossRef]

43. Bhimraj, A.; Morgan, R.L.; Shumaker, A.H.; Lavergne, V.; Baden, L.; Cheng, V.C.; Edwards, K.M.; Gandhi, R.; Muller, W.J.; O'Horo, J.C.; et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. *Clin. Infect. Dis.* **2020**, ciaa478. [CrossRef]

44. Papazian, L.; Aubron, C.; Brochard, L.; Chiche, J.-D.; Combes, A.; Dreyfuss, D.; Forel, J.-M.; Guérin, C.; Jaber, S.; Mekontso-Dessap, A.; et al. Formal guidelines: Management of acute respiratory distress syndrome. *Ann. Intensive Care* **2019**, *9*, 69. [CrossRef]

45. Rhodes, A.; Evans, L.E.; Alhazzani, W.; Levy, M.M.; Antonelli, M.; Ferrer, R.; Kumar, A.; Sevransky, J.E.; Sprung, C.L.; Nunnally, M.E.; et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit. Care Med.* **2017**, *45*, 486–552. [CrossRef]

46. Beitler, J.R.; Malhotra, A.; Thompson, B.T. Ventilator-induced Lung Injury. *Clin. Chest Med.* **2016**, *37*, 633–646. [CrossRef]

47. Brower, R.G.; Matthay, M.A.; Morris, A.; Schoenfeld, D.; Thompson, B.T.; Wheeler, A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N. Engl. J. Med.* **2000**, *342*, 1301–1308.

48. Cummings, M.J.; Baldwin, M.R.; Abrams, D.; Jacobson, S.D.; Meyer, B.J.; Balough, E.M.; Aaron, J.G.; Claassen, J.; Rabbani, L.E.; Hastie, J.; et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: A prospective cohort study. *Lancet* **2020**, *395*, 1763–1770. [CrossRef]

49. Arentz, M.; Yim, E.; Klaff, L.; Lokhandwala, S.; Riedo, F.X.; Chong, M.; Lee, M. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *JAMA* **2020**, *323*, 1612–1614. [CrossRef]

50. Grasselli, G.; Zangrillo, A.; Zanella, A.; Antonelli, M.; Cabrini, L.; Castelli, A.; Cereda, D.; Coluccello, A.; Foti, G.; Fumagalli, R.; et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA* **2020**, *323*, 1574–1581. [CrossRef]

51. Nadeem, A.; Hamed, F.; Saleh, K.; Abduljawad, B.; Mallat, J. ICU outcomes of COVID-19 critically ill patients: An international comparative study. *Anaesth. Crit. Care Pain Med.* **2020**, *39*, 487–489. [CrossRef]

52. COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: A prospective cohort study. *Intensive Care Med.* **2021**, *47*, 60–73. [CrossRef]

53. Ferrando, C.; Mellado-Artigas, R.; Gea, A.; Arruti, E.; Aldecoa, C.; Bordell, A.; Adalia, R.; Zattera, L.; Ramasco, F.; Monedero, P.; et al. Patient characteristics, clinical course and factors associated to ICU mortality in critically ill patients infected with SARS-CoV-2 in Spain: A prospective, cohort, multicentre study. *Rev. Esp. Anestesiol. Reanim.* **2020**, *67*, 425–437. [CrossRef]

54. Yu, Y.; Xu, D.; Fu, S.; Zhang, J.; Yang, X.; Xu, L.; Xu, J.; Wu, Y.; Huang, C.; Ouyang, Y.; et al. Patients with COVID-19 in 19 ICUs in Wuhan, China: A cross-sectional study. *Crit. Care* **2020**, *24*, 219. [CrossRef]

55. Rhen, T.; Cidlowski, J.A. Antiinflammatory action of glucocorticoids—New mechanisms for old drugs. *N. Engl. J. Med.* **2005**, *353*, 1711–1723. [CrossRef]

56. Peiris, J.S.; Chu, C.M.; Cheng, V.C.; Chan, K.S.; Hung, I.F.; Poon, L.L.; Law, K.I.; Tang, B.S.; Hon, T.Y.; Chan, C.S.; et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: A prospective study. *Lancet* **2003**, *361*, 1767–1772. [CrossRef]

57. Zhao, Z.; Zhang, F.; Xu, M.; Huang, K.; Zhong, W.; Cai, W.; Yin, Z.; Huang, S.; Deng, Z.; Wei, M.; et al. Description and clinical treatment of an early outbreak of severe acute respiratory syndrome (SARS) in Guangzhou, PR China. *J. Med. Microbiol.* **2003**, *52*, 715–720. [CrossRef]

58. Horby, P.; Lim, W.S.; Emberson, J.R.; Mafham, M.; Bell, J.L.; Linsell, L.; Staplin, N.; Brightling, C.; Ustianowski, A.; Elmahi, E.; et al. Dexamethasone in Hospitalized Patients with Covid-19. *N. Engl. J. Med.* **2021**, *384*, 693–704.

59.	Villar, J.; Confalonieri, M.; Pastores, S.M.; Meduri, G.U. Rationale for Prolonged Corticosteroid Treatment in the Acute Respiratory Distress Syndrome Caused by Coronavirus Disease 2019. *Crit. Care Explor.* **2020**, *2*, e0111. [CrossRef]

60.	Russell, C.D.; Millar, J.E.; Baillie, J.K. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* **2020**, *395*, 473–475. [CrossRef]

61.	Ashbaugh, D.G.; Bigelow, D.B.; Petty, T.L.; Levine, B.E. Acute respiratory distress in adults. *Lancet* **1967**, *2*, 319–323. [CrossRef]

62.	Wu, C.; Chen, X.; Cai, Y.; Xia, J.; Zhou, X.; Xu, S.; Huang, H.; Zhang, L.; Du, C.; Zhang, Y.; 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*, 934–943. [CrossRef] [PubMed]

63.	Özdemir, S.; Bilgi, D.Ö.; Köse, S.; Oya, G. Pneumothorax in patients with coronavirus disease 2019 pneumonia with invasive mechanical ventilation. *Interact. Cardiovasc. Thorac. Surg.* **2021**, *32*, 351–355. [CrossRef] [PubMed]

64.	Wang, X.-H.; Duan, J.; Han, X.; Liu, X.; Zhou, J.; Wang, X.; Zhu, L.; Mou, H.; Guo, S. High incidence and mortality of pneumothorax in critically Ill patients with COVID-19. *Heart Lung* **2021**, *50*, 37–43. [CrossRef] [PubMed]

65.	Sihoe, A.D.; Wong, R.H.; Lee, A.T.; Lau, L.S.; Leung, N.Y.; Law, K.I.; Yim, A.P. Severe acute respiratory syndrome complicated by spontaneous pneumothorax. *Chest* **2004**, *125*, 2345–2351. [CrossRef]

66.	Llitjos, J.F.; Leclerc, M.; Chochois, C.; Monsallier, J.M.; Ramakers, M.; Auvray, M.; Merouani, K. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J. Thromb. Haemost.* **2020**, *18*, 1743–1746. [CrossRef]

67.	Helms, J.; Tacquard, C.; Severac, F.; Leonard-Lorant, I.; Ohana, M.; Delabranche, X.; Merdji, H.; Clere-Jehl, R.; Schenck, M.; Fagot Gandet, F.; et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: A multicenter prospective cohort study. *Intensive Care Med.* **2020**, *46*, 1089–1098. [CrossRef]

68.	Lim, W.; Meade, M.; Lauzier, F.; Zarychanski, R.; Mehta, S.; Lamontagne, F.; Dodek, P.; McIntyre, L.; Hall, R.; Heels-Ansdell, D.; et al. Failure of anticoagulant thromboprophylaxis: Risk factors in medical-surgical critically ill patients*. *Crit. Care Med.* **2015**, *43*, 401–410. [CrossRef]

69.	Grasselli, G.; Greco, M.; Zanella, A.; Albano, G.; Antonelli, M.; Bellani, G.; Bonanomi, E.; Cabrini, L.; Carlesso, E.; Castelli, G.; et al. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. *JAMA Intern. Med.* **2020**, *180*, 1345–1355. [CrossRef]

70.	Menzella, F.; Fontana, M.; Salvarani, C.; Massari, M.; Ruggiero, P.; Scelfo, C.; Barbieri, C.; Castagnetti, C.; Catellani, C.; Gibellini, G.; et al. Efficacy of tocilizumab in patients with COVID-19 ARDS undergoing noninvasive ventilation. *Crit. Care* **2020**, *24*, 589. [CrossRef]

71.	Matera, M.G.; Rogliani, P.; Calzetta, L.; Cazzola, M. Pharmacological management of COVID-19 patients with ARDS (CARDS): A narrative review. *Respir. Med.* **2020**, *171*, 106114. [CrossRef]

72.	Rahman, S.M.A.; Kabir, A.; Abdullah, A.B.M.; Alam, M.B.; Azad, K.A.K.; Miah, M.T.; Mowla, S.G.M.; Deb, S.R.; Amin, M.R.; Asaduzzaman, M.; et al. Safety and efficacy of favipiravir for the management of COVID-19 patients: A preliminary randomized control trial. *Clin. Infect. Pract.* **2022**, *15*, 100145. [CrossRef]

73.	Zhang, Y.; Coats, A.J.S.; Zheng, Z.; Adamo, M.; Ambrosio, G.; Anker, S.D.; Butler, J.; Xu, D.; Mao, J.; Khan, M.S.; et al. Management of heart failure patients with COVID-19: A joint position paper of the Chinese Heart Failure Association & National Heart Failure Committee and the Heart Failure Association of the European Society of Cardiology. *Eur. J. Heart Fail.* **2020**, *22*, 941–956.

74.	Mantovani, A.; Beatrice, G.; Dalbeni, A. Coronavirus disease 2019 and prevalence of chronic liver disease: A meta-analysis. *Liver Int.* **2020**, *40*, 1316–1320. [CrossRef]

75.	Hamming, I.; Timens, W.; Bulthuis, M.L.C.; Lely, A.T.; Navis, G.J.; van Goor, H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J. Pathol.* **2004**, *203*, 631–637. [CrossRef]

76.	Bahardoust, M.; Heiat, M.; Khodabandeh, M.; Karbasi, A.; Bagheri-Hosseinabadi, Z.; Ataee, M.H.; Seidalian, N.; Babazadeh, A.; Agah, S.; Abyazi, M.A. Predictors for the severe coronavirus disease 2019 (COVID-19) infection in patients with underlying liver disease: A retrospective analytical study in Iran. *Sci. Rep.* **2021**, *11*, 3066. [CrossRef]

77.	Grace, J.A.; Herath, C.B.; Mak, K.Y.; Burrell, L.M.; Angus, P.W. Update on new aspects of the renin-angiotensin system in liver disease: Clinical implications and new therapeutic options. *Clin. Sci.* **2012**, *123*, 225–239. [CrossRef]

78.	Li, G.; Yang, Y.; Gao, D.; Xu, Y.; Gu, J.; Liu, P. Is liver involvement overestimated in COVID-19 patients? A meta-analysis. *Int. J. Med. Sci.* **2021**, *18*, 1285–1296. [CrossRef]