Characteristics and outcome of critically ill patients with coronavirus disease-2019 (COVID-19) pneumonia admitted to a tertiary care center in the United Arab Emirates during the first wave of the SARS-CoV-2 pandemic. A retrospective analysis

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Abstract

Background
The aim of this study was to describe the clinical characteristics and outcome of patients with coronavirus disease-2019 (COVID-19) pneumonia admitted to an intensive care unit (ICU) of a tertiary care center in the United Arab Emirates (UAE) and to identify early risk factors for in-hospital mortality in these patients.

Methods
A total of 371 adult patients (>18 years) admitted to the ICU of Al Ain Hospital between March 16 and July 19, 2020 with SARS-CoV-2 infection confirmed using real-time reverse transcription polymerase chain reaction (rt-PCR) on nasopharyngeal swabs were included.

Results
The mean patient age was 53 years (standard deviation = 13). Patients were mostly male (n = 314 [84.6%]) and of South Asian origin (n = 231 [62.3%]). Invasive mechanical ventilation was required in 182 (49.1%) patients for a median of 11 days (25–75% interquartile range: 6–17). During the ICU stay, renal replacement therapy was required in 87 (23.5%) and vasopressor therapy in 190 (51.2%) patients. ICU and hospital lengths of stay were 9 (IQ: 5–17) and 18 (IQ: 13–29) days, respectively and ICU and hospital mortality rates were both 20.2%. In a multivariable analysis with in-hospital mortality as the dependent variable, greater Acute Physiology and Chronic Health Evaluation II score on ICU admission, diarrhea prior to hospital admission, greater, admission from hospital ward, and higher lactate
dehydrogenase levels and neutrophil:lymphocyte ratio on admission to the ICU were independently associated with higher risk of in-hospital mortality.

**Conclusion**
In this cohort of patients admitted to the ICU of a tertiary hospital in the UAE, COVID-19 pneumonia was associated with high morbidity and mortality rates. Identifying patients at high risk of death may help detect future therapeutic targets.

**Introduction**
As the health burden from coronavirus disease-2019 (COVID-19) due to the novel SARS-CoV-2 continues to rise, the world’s governments, institutions, and agencies are still working toward understanding who is most at risk of severe complications and death [1]. The subset of patients who require admission to the intensive care unit (ICU) has been reported to be at particular risk of developing major complications with a high mortality rate [2–20]. The characteristics and outcomes of these patients have been reported in several studies from China [10, 21–24], Europe [2, 3, 5, 9, 11, 14, 17–20], and North America [4, 6, 7, 25]; however, similar data from other geographic regions are scarce. Such data are important to understand the disease burden worldwide. Indeed, the COVID-19 epidemic has affected countries around the globe to different extents. Notably, most of the large published ICU cohorts have included patients from countries that were overwhelmed during the early months of the epidemic and may not be representative of critically ill patients with severe SARS-CoV-2 infections worldwide [2–7, 9–11, 14, 17, 18, 21–25].

The United Arab Emirates (UAE) is known for its diverse population with hundreds of nationalities within its borders, creating considerable challenges in terms of cultural diversity. Nonetheless, access to healthcare services is regarded as adequate and healthcare infrastructure is considered better than in other Middle Eastern countries. The UAE has experienced relatively low COVID-19 mortality per capita [26]; its experience may provide valuable insight for other countries to prepare for future waves of the pandemic.

The aim of this study was, therefore, to describe the clinical characteristics and outcomes of critically ill patients with COVID-19 pneumonia admitted to a tertiary care center in the UAE during the first wave of the pandemic. We also evaluated the risk factors for in-hospital mortality that may help is early risk stratification of these patients. Our hypothesis was that severe COVID-19 would be associated with high morbidity and mortality rates in the ICU and that parameters of tissue inflammation on admission to the ICU would play an important role in determining the COVID-19-associated risk of death.

**Methods**
The study was approved by the institutional review board of the Department of Health, Abu Dhabi (PO box 5674, Abu Dhabi, UAE, application number: DOH/CVDC/2020/1669), which waived informed consent due to the retrospective nature of data collection. Source data were accessed by the attending physicians (KI and HB). Data were anonymously recorded prior to further handling and analysis. All adult patients (>18 years) admitted to the ICU of Al Aín Hospital between March 16 and July 19, 2020, with SARS-CoV-2 infection confirmed using real-time reverse transcription polymerase chain reaction (rt-PCR) on nasopharyngeal swabs.
and radiologic evidence of respiratory infections were considered for inclusion in the study. Patients with incomplete records were excluded from the analysis. Follow-up was completed until death or hospital discharge, whichever occurred first. Preliminary results on the potential impact of camostat mesylate therapy on outcome in this cohort were recently published [27].

Patient records were reviewed by the attending physicians (HB and KI). Demographic data, referring facility, preexisting comorbid conditions, and the initial manifestations of COVID-19 prior to hospital admission were recorded. Laboratory parameters and therapeutic interventions on admission to the ICU were retrieved electronically from the local patient data management system (Cerner corp, North Kansas City, Missouri, USA) and recorded. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was calculated from the data obtained within 24 hours of admission to the ICU [28]. Data were then anonymously recorded for further handling and analysis.

**Standard of care**

Al Ain Hospital is a tertiary care hospital located in Abu Dhabi, the capital of the UAE, which was devoted to the isolation and treatment of patients with suspected or confirmed SARS-CoV-2 infections during the study period. The ICU of Al Ain Hospital is an interdisciplinary ICU with a normal capacity of 23 beds. During the study period, the capacity of the ICU was extended to 96 beds, fully equipped with advanced organ support therapies, including, but not limited to, invasive mechanical ventilation and renal replacement therapy. Intensivists were available 24-h/day with a background in anesthesiology and intensive care and qualified according to local regulations. The medical staff, including attending physicians, nursing staff, and physiotherapists, performed daily patient rounds. Standard ICU management followed the Standard Operating Procedures of the Al Ain Hospital and was in accordance with international guidelines [29]. Patients were isolated in single rooms and received medical care with a 1:1 nurse:patient ratio. Infection control measures were implemented and monitored by the department of infection control of Al Ain Hospital. Admission to the ICU was at the discretion of the attending physician. Antiviral and adjunctive therapies were prescribed at the discretion of the attending physician. Invasive mechanical ventilation was performed using lung protective ventilation settings [30].

**Outcome parameters**

The primary outcome parameter was in-hospital mortality. Secondary outcome parameters included death in the ICU, ICU and hospital lengths of stay, and use of mechanical ventilation, renal replacement therapy or vasopressor therapy during the ICU stay.

**Statistical analysis**

All data were processed and analyzed in Al Ain Hospital, in collaboration with Jena University Hospital, Jena, Germany. Data were analyzed using IBM® SPSS® Statistics software, v.21 for Windows (IBM, Somers, NY, USA). Data are summarized using means with standard deviation, medians and interquartile ranges (IQ), or numbers and percentages. Difference testing between groups was performed using Student's t test, Mann–Whitney test, Chi-square test or Fisher’s exact test, as appropriate. The Kolmogorov–Smirnov test was used to verify whether there were significant deviations from the normality assumption of continuous variables.

To determine independent risk factors for in-hospital death, we performed a multivariable logistic regression analysis with in-hospital death as the dependent variable. Covariates to be included in the final model were based on a univariate logistic regression analysis (p<0.2) of demographic variables (age, sex, and ethnicity), referring facility, initial symptoms prior to
ICU admission, comorbid conditions, need for mechanical ventilation on admission to the ICU, inflammatory parameters, D-dimer levels, laboratory parameters of organ function, and complete blood count blood picture (the neutrophil:lymphocyte ratio [NLR] was included instead of the individual counts) on admission to the ICU. Colinearity between variables was ruled out before covariates were introduced in the model. Goodness of fit was tested using a Hosmer and Lemeshow test, and odds ratios (OR) with 95% confidence intervals (CIs) were computed. To reduce the number of variables included in the multivariable model, a forward stepwise approach was used with an inclusion criteria of \( p < 0.2 \) and exclusion at \( p > 0.1 \). Secondary outcome parameters were assessed using descriptive statistics and compared between survivors and non-survivors.

Receiver operator characteristic (ROC) curves and the areas under the curves (AUC) were computed to determine the value of the independent risk factors for discriminating between survivors and non-survivors. The best cut-off point was defined using the Youden index, and sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were calculated.

All reported \( p \) values are two-sided and a \( p \) value < 0.05 was considered to indicate statistical significance.

### Results

#### Characteristics of the study group

During the study period, 5021 patients were admitted to Al Ain Hospital with confirmed SARS-CoV-2 infection. Of 378 patients who required admission to the ICU, 371 patients had documented COVID-19 pneumonia and constituted the study group (Fig 1). Seven patients were excluded due to incomplete records, in which the diagnosis of pneumonia was not established. The characteristics of the study group are presented in Table 1. The mean age was 53 years (SD = 13); the majority were male (84.6%) and of south Asian origin (62.3%). The most common comorbid conditions were diabetes mellitus (44.2%), systemic hypertension (43.1%), and cardiovascular disease (17.0). About half of the patients (52%) were referred from another hospital, and 40% were admitted to the ICU directly from the emergency department of our hospital. The symptoms most commonly reported prior to hospital admission were cough (79.8%), fever (77.6%), dyspnea (77.4%), malaise (49.6%), and headache (32.1%). South Asian patients were more commonly younger males, had less comorbid, had lower APACHE II score on admission to the ICU, and greater BMI than Arabs (S1 Table).

#### Diagnostic procedures, therapeutic interventions, and antimicrobial therapy

All patients had pulmonary infiltrates in chest x ray examinations. Lung computed tomography (CT) scan was performed in 262 patients and revealed bilateral peripheral ground glass opacities in 254 (96.9%) patients. On the day of admission to the ICU, 54 patients (14.5%) required invasive mechanical ventilation and 21 patients (5.7%) required renal replacement therapy. Anticoagulation using therapeutic dose of enoxaparin sodium (1mg/kg bid) was given in 318 (85.7%) patients; prophylactic anticoagulation (enoxaparin sodium at 0.4 IU/d) was given in 53 (14.3%) patients. Favipiravir was used in 91.6% of patients (n = 340) and camostat in 38% (n = 141). Immunomodulatory therapy using tocilizumab was administered in 143 (38.5%) patients and steroids were given in 62 (16.7%) patients (dexamethasone in 41 (11.1%) patients). Additional antibiotic therapy was given in 270 (72.8%) patients: piperacillin and
tazobactam in 124 (33.4%), and doxycycline in 106 (28.6%) patients. Hydroxychloroquine was given to 227 (61.2%) patients.

Morbidity and mortality
During the ICU stay, renal replacement therapy was required in 87 (23.5%) patients and vasopressor therapy in 190 (51.2%). Invasive mechanical ventilation was required in 182 (49.1%) patients for a median of 11 days (IQ: 6–17). The ICU and hospital lengths of stay were 9 (IQ: 5–17) and 18 (IQ: 13–29) days, respectively, and ICU and hospital mortality rates were both 20.2% (n = 75).

Hospital non-survivors were older, more commonly referred from the hospital ward and other hospitals, more likely to have ischemic heart disease and chronic renal disease, less likely to complain of malaise and headache as the initial symptoms of COVID 19 disease, and had greater APACHE II score than survivors (Table 1). On admission to the ICU, inflammatory parameters, D-dimer levels, direct bilirubin, serum creatinine, urea, and alkaline phosphatase concentrations, neutrophil count, and NLR were higher in non-survivors than in survivors, whereas serum albumin, red blood cell count, hemoglobin, hematocrit, and lymphocyte count were lower in non-survivors than in survivors (Table 2). The ICU length of stay was longer (12 (6–23) vs. 8 (5–16), days, p = 0.035) and hospital length of stay shorter (14 (7–24) vs. 18 (13–29), days, p = 0.001) in non-survivors than in survivors. Non-survivors more commonly required invasive mechanical ventilation (98.7 vs. 37.8%, p<0.001), renal replacement therapy (57.3 vs. 14.9%, p<0.001), and vasopressor therapy (98.7 vs. 39.2%, p<0.001) than did survivors.
Risk factors for in-hospital mortality

In a multivariable analysis with in-hospital mortality as the dependent variable, admission from hospital ward (OR: 3.55, 95% CI: 1.26–10.03, p = 0.017), greater APACHE II score on ICU admission (OR:1.13, 95% CI: 1.08–1.18, p<0.001), diarrhea prior to hospital admission (OR: 3.71, 95% CI: 1.10–12.57, p = 0.017), higher NLR (OR: 1.04, 95% CI: 1.01–1.18, 0.027.
p = 0.017), and higher LDH (OR: 1.01, 95% CI: 1.01–1.02, p = 0.026) were independently associated with a higher risk of in-hospital mortality (Table 3 and S3A–S3C Table).

The APACHE II score had the highest AUC in discriminating non-survivors from survivors (AUC = 0.77; 95% CI: 0.71–0.84, p<0.001), followed by the NLR (AUC = 0.69; 95% CI: 0.61–0.76, p<0.001), and LDH value (AUC = 0.66; 95% CI: 0.59–0.73, p<0.001) (Fig 2). The best cut-off point for the APACHE II score was 15 points with a sensitivity of 61%, specificity of 83%, NPV 89%, and PPV 50%. The best cut-off point for the NLR was 12 with sensitivity of 65%, specificity 59%, NPV 87%, and PPV 45%. LDH levels higher than 462 IU/L discriminated between non-survivors and survivors with a sensitivity of 61%, specificity 66%, NPV 87%, and PPV 31%.

Discussion

The main findings in this cohort of patients with severe COVID-19 pneumonia admitted to the ICU of a tertiary hospital in the UAE during the first wave of the epidemic were that: 1) patients were most commonly middle age males with preexisting comorbid conditions; 2)
Table 3. Summary of logistic regression analysis with in-hospital death as the dependent variable.

|                                | OR (95% CI)   | p value |
|--------------------------------|---------------|---------|
| APACHE II (per point)          | 1.13 (1.08–1.18) | <0.001  |
| Source of admission            |               |         |
| • Primary admission            | R             | NA      |
| • Other hospital, same city    | 1.56 (0.47–5.16) | 0.465   |
| • Other hospital, another city | 0.76 (0.36–1.64) | 0.490   |
| • Hospital ward                | 3.55 (1.26–10.03) | 0.017   |
| Initial symptoms               |               |         |
| • Diarrhea                     | 3.71 (1.10–12.57) | 0.035   |
| Laboratory parameters on ICU admission |         |         |
| • Neutrophil:lymphocyte ratio  | 1.04 (1.01–1.18) | 0.017   |
| • Lactate dehydrogenase (per IU/L) | 1.01 (1.01–1.02) | 0.026   |

APACHE: acute physiology and chronic health evaluation, CI: Confidence interval, ICU: intensive care unit, OR: odds ratio.

*Forward stepwise approach, excluding 8 patients with missing values.

The presented values are those resulting from the last step of the respective models. Covariate inclusion was based on a univariate logistic regression analysis (p<0.2) within the categories demographic variables (age, sex, and ethnicity), comorbid conditions, the need for mechanical ventilation on admission to the ICU, the initial symptoms prior to ICU admission, inflammatory parameters, D-dimer levels, and laboratory parameters of organ function on admission to the ICU. The neutrophil:lymphocyte ratio was included instead of the individual counts. Hosmer & Lemeshow goodness of fit Chi square: 7.36, p = 0.460.

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**Fig 2. Receiver operator characteristic (ROC) curves.** Receiver operator characteristic (ROC) curves for discriminating between hospital survivors and non-survivors. Values represent those measured on admission to the intensive care unit. APACHE = acute physiology and chronic health evaluation; NLR = neutrophil:lymphocyte ratio; LDH = lactate dehydrogenase.

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COVID-19 was associated with high morbidity and mortality rates; 3) admission from the hospital ward, greater APACHE II score on ICU admission, the occurrence of diarrhea prior to hospital admission, greater NLR, and higher LDH were independently associated with a higher risk of in-hospital mortality; and 4) the APACHE II score had the highest AUC for discriminating non-survivors from survivors, followed by NLR, and LDH.

Patients in our cohort were predominantly middle age males, reflecting the demography of patients who may be at a higher risk of developing severe COVID-19 in our community. Previous large cohorts of COVID-19 patients admitted to the ICU have also shown a high prevalence of male patients [2–5, 17, 18]; however, the mean age reported in these studies was markedly higher than that reported in our study. The relatively high prevalence of preexisting comorbid conditions in our patients may explain in part the increased likelihood of developing severe COVID-19 despite the younger age. Nonetheless, age was not identified as a risk factor for in-hospital death in the multivariable analysis after adjustment for other possible confounders, probably due to the inclusion of APACHE II score in the model, which considers age as an essential component.

Although COVID-19 was associated with a high mortality rate of around 20% in our cohort, this rate was significantly lower than that reported for critically ill COVID-19 patients in previous international cohorts. In a meta-analysis, including literature published on MEDLINE, EMBASE, PubMed, and Cochrane databases up to May 31, 2020, combined ICU mortality was 41.6% [12]. However, most of the studies published to-date have included patients from Asian [10, 15, 21–24], European [2, 3, 5, 9, 11, 14, 16–20], and North American [4, 6, 7, 25] ICUs. Moreover, the healthcare systems in these regions were often overwhelmed in the early months of the epidemic, which may have negatively influenced outcomes in these cohorts. Indeed, the meta-analysis by Armstrong et al. showed that combined ICU mortality in the included studies decreased from 59.5 to 41.6% as the epidemic progressed. We may also speculate that the mortality rate was relatively low in our unit because of the younger age of the patients admitted to our ICU. Indeed, survivors in our study were significantly younger than non-survivors.

We also found that the occurrence of diarrhea prior to hospital admission was independently associated with a high risk of in-hospital death. In a meta-analysis including a total of 4805 patients with COVID-19, 7.4% of the patients had reported diarrhea and a total of 12% had reported gastrointestinal symptoms [31]. The high prevalence of gastrointestinal manifestations may be explained, at least in part, by the high expression of angiotensin-converting enzyme 2 receptors along the epithelial lining of the gut, which act as host-cell receptors for SARS-CoV-2 [32]. An association between SARS-CoV-2 infections and gastrointestinal disorders was confirmed by El Moheb et al. [33], who found a higher rate of gastrointestinal complications in critically ill patients with COVID-19, including mesenteric ischemia, compared with propensity score–matched patients without COVID-19, suggesting a distinct phenotype for COVID-19 compared with conventional acute respiratory distress syndrome (ARDS). Previous studies have also demonstrated that COVID-19-associated digestive symptoms may be associated with poor outcome [34]. In a meta-analysis by Mao et al., patients with gastrointestinal symptoms had an increased risk of ARDS and liver injury; however, the pooled rates of discharge, length of hospital stay, and mortality were similar in patients with and without gastrointestinal symptoms [35]. The lack of routine adjustment for possible confounders in the studies included in this analysis [35] and the marked heterogeneity among the studies may have masked a possible association between gastrointestinal symptoms and mortality.

Patients were either admitted directly to the ICU from our emergency department, from the emergency departments of other hospitals, or from the hospital ward. Admissions from the hospital ward represent, therefore, patients who spend several days in the hospital prior to
ICU admission. We may assume that these patients may have been more liable to hospital acquired complications, are at a more advanced stage throughout the disease trajectory, and have already received available therapies without initial success. We may also assume that early intensive care management may be associated with improved outcome in these patients. The admission/discharge policies and abundant availability of ICU resources, together with the local cultural values, have probably lead to systematic referral of severely ill patients to the ICU, irrespective of the possible outcome. This may explain the higher risk of death in patients referred from the hospital ward compared to primary ICU admissions in our cohort.

Although the APACHE II score was relatively low in our cohort, it had the highest AUC for discriminating non-survivors from survivors. The best cut-off point for the APACHE II score was only 15 points. Our findings are in agreement with those of Zou et al. who showed that an APACHE II score with a cut-off point of 17 was a more effective clinical tool to predict hospital mortality in patients with COVID-19 disease than the Sequential Organ Failure Assessment (SOFA) and CURB-65 scores [36]. Low APACHE II scores on admission to the ICU have consistently been reported in COVID-19 patients [9, 11, 13, 23, 25, 36], probably due to the pre-dominance of respiratory failure, with minimal impairment of other physiologic parameters in the early phase of the disease process. In agreement with earlier studies [37, 38], we found that the NLR was a good predictor of mortality in patients with COVID-19. SARS-CoV-2 infection may be associated with both excessive inflammation [39] and immune suppression [40]. Accordingly, the lymphocyte count decreases progressively, whereas the neutrophil count increases in patients with severe COVID-19 [37, 38]. Indeed, a pooled analysis of 10 studies, including 2967 COVID-19 patients, found that an elevated NLR had both sensitivity and specificity of 0.83 for discriminating between survivors and non-survivors [41]. The elevation of NLR in ICU patients compared patients with milder disease forms may be explained by the time lag between the onset of the disease and ICU admission, enabling NLR to reach higher levels than those reported in patients hospitalized with mild disease progression. Elevated LDH levels were independently associated with a higher risk of in-hospital death in our study. LDH is an intracellular enzyme in the glycolytic pathway, which catalyzes the interconversion of pyruvate and lactate [42]. Since LDH is present in lung tissue, patients with severe COVID-19 infection can be expected to release greater amounts of LDH into the circulation [43, 44]. Elevated LDH levels may also be associated with multiple organ dysfunction and subsequently poor outcome [43]. In a pooled analysis of 9 studies including 1532 COVID-19 patients, Henry et al. found that elevated LDH levels, measured at the earliest possible time after hospital admission, were associated with a 6-fold increase in the odds of developing severe disease and a 16-fold increase in the odds of mortality in these patients [43]. The presence of a high LDH value on admission to the ICU may, therefore, be a potential marker of poor prognosis in critically ill patients with COVID-19.

Survivors may be more likely to stay for a short period of time in the ICU as they are less sick than non-survivors and are, hence, more likely to spend more time in the hospital ward after discharge from the ICU. This may explain the shorter ICU and longer hospital LOS in survivors than no-survivors in our cohort. As expected, invasive mechanical ventilation, the need for hemodialysis, and vasopressor therapy were more prevalent in non-survivors than survivors, which reflect the degree of organ dysfunction/failure and its relation to outcome in these patients.

Our study has some limitations including that it was retrospective and the multivariable analysis is limited by the variables included in the analysis, so that the possible effect of unmeasured confounders cannot be excluded. Our cohort may also not be representative of all critically ill patients admitted to ICUs in the UAE during the first wave of the epidemic. Indeed, our patients included different ethnic groups, but were mainly of Asian origin.
Conclusion

In this cohort of patients admitted to the ICU of a tertiary hospital in the UAE, COVID-19 pneumonia was associated with high morbidity and mortality rates. Admission from the hospital ward, greater APACHE II score on ICU admission, diarrhea prior to hospital admission, greater NLR, and higher LDH value were independently associated with a higher risk of in-hospital mortality.

Supporting information

S1 Table. Anonymized data set of the 371 patients included in the study. Age and ethnicity were masked by the authors to avoid patients’ identification. (XLS)

S2 Table. Characteristics of the two major ethnic groups included in the study. (DOCX)

S3 Table. A. Variables retained in the predictive equation throughout the various steps of the multivariable modeling. B. Variable not retained in the predictive equation throughout the various steps of the multivariable modeling. C. Hosmer & Lemeshow goodness of fit test throughout the consecutive steps of the multivariable model. (DOCX)

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References
1. Roser M, Ritchie H, Ortiz-Ospina E, & Hasell J. Coronavirus (COVID-19) deaths—statistics and research. Our World in Data. https://ourworldindata.org/covid-deaths 2020.

2. Grimaldi D, Aissaoui N, Blonz G, Carbutti G, Courcelle R, Gaudry S, et al. Characteristics and outcomes of acute respiratory distress syndrome related to COVID-19 in Belgian and French intensive care units according to antiviral strategies: the COVADIS multicentre observational study. Ann Intensive Care 2020; 10(1):1345–55. https://doi.org/10.1001/jamaime.2020.3539 PMID: 3267669

3. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani 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(10):1345–55. https://doi.org/10.1001/jamainternmed.2020.00751-y PMID: 33025225

4. Flythe JE, Assimon MM, Tugman MJ, Chang EH, Gupta S, Shah J, et al. Characteristics and Outcomes of Individuals With Pre-existing Kidney Disease and COVID-19 Admitted to Intensive Care Units in the United States. Am J Kidney Dis 2020. https://doi.org/10.1053/j.ajkd.2020.09.003 PMID: 33011244

5. Dennis JM, Mateen BA, Sonabend R, Thomas NJ, Patel KA, Hattersley AT, et al. Type 2 Diabetes and COVID-19-Related Mortality in the Critical Care Setting: A National Cohort Study in England, March-July 2020. Diabetes Care 2020.

6. Auld SC, Cardi-Scheible M, Blum JM, Robichaux C, Kraft C, Jacob JT, et al. ICU and Ventilator Mortality Among Critically Ill Adults With Coronavirus Disease 2019. Crit Care Med 2020; 48(9):e799–e804. https://doi.org/10.1097/CCM.0000000000004457 PMID: 32452888

7. Arvinte C, Singh M, Marik PE. Serum Levels of Vitamin C and Vitamin D in a Cohort of Critically Ill COVID-19 Patients of a North American Community Hospital Intensive Care Unit in May 2020: A Pilot Study. Med Drug Discov 2020; 8:100064. https://doi.org/10.1016/j.medidd.2020.100064 PMID: 32964205

8. Klein SJ, Bellmann R, Dejaco H, Eschertzhuber S, Fries D, Furtwangler w, et al. Structured ICU resource management in a pandemic is associated with favorable outcome in critically ill COVID19 patients. Wien Klin Wochenschr 2020.

9. Richards-Belle A, Orzechowska I, Gould DW, Thomas K, Doidge JC, Mouncey PR, et al. COVID-19 in critical care: epidemiology of the first epidemic wave across England, Wales and Northern Ireland. Intensive Care Med 2020; 46(11):2035–47. https://doi.org/10.1007/s00134-020-06267-0 PMID: 33034689

10. Zhang H, Zhang Y, Wu J, Li Y, Zhou X, Li X, et al. Risks and features of secondary infections in severe and critical ill COVID-19 patients. Emerg Microbes Infect 2020; 9(1):1958–64. https://doi.org/10.1080/22221751.2020.1812437 PMID: 32815458

11. Wendel Garcia PD, Fumeaux T, Guerci P, Heuberger DM, Montomoli J, Roche-Campo F, et al. Prognostic factors associated with mortality risk and disease progression in 639 critically ill patients with COVID-19 in Europe: Initial report of the international RISC-19-ICU prospective observational cohort. EClinicalMedicine 2020; 25:100449. https://doi.org/10.1016/j.eclinm.2020.100449 PMID: 32838231

12. Armstrong RA, Kane AD, Cook TM. Outcomes from intensive care in patients with COVID-19: a systematic review and meta-analysis of observational studies. Anaesthesia 2020; 75(10):1340–9. https://doi.org/10.1111/anae.15201 PMID: 32602561

13. 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(4):487–9. https://doi.org/10.1016/j.accp m.2020.07.001 PMID: 32654909

14. Martin-Villares C, Perez Molina-Ramirez C, Bartolome-Benito M, Bernal-Sprekelsen M, Group COEC. Outcome of 1890 tracheostomies for critical COVID-19 patients: a national cohort study in Spain. Eur Arch Otorhinolaryngol 2020. https://doi.org/10.1007/s00405-020-06220-3 PMID: 32749607

15. Liu X, Zheng X, Liu B, Wu M, Zhang Z, Zhang G, et al. Serum IgM against SARS-CoV-2 correlates with in-hospital mortality in severe/critical patients with COVID-19 in Wuhan, China. Aging (Albany NY) 2020; 12(13):12342–40. https://doi.org/10.18632/aging.103417 PMID: 32628642

16. Kristinsdottir LB, Blindal AT, Thomar KM, Kristjansson M, Karason S, et al. Nationwide Incidence and Outcomes of Patients With Coronavirus Disease 2019 Requiring Intensive Care in Iceland. Crit Care Med 2020; 48(11):e102–e5. https://doi.org/10.1097/CCM.0000000000004582 PMID: 32796182
17. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabirini L, Castelli A, 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(16):1574–81. https://doi.org/10.1001/jama.2020.5394 PMID: 32250385

18. Lechien JR, Chiesa-Estomba CM, Place S, Van Laethem Y, Cabaraux P, Mat Q, et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. J Intern Med 2020; 288(3):335–44. https://doi.org/10.1111/joim.13088 PMID: 32352202

19. Popov GT, Baymakova M, Vaseva V, Kundra Zhiev T, Mutaichiyski V. Clinical Characteristics of Hospitalized Patients with COVID-19 in Sofia, Bulgaria. Vector Borne Zoonotic Dis 2020; 20(12):910–5. https://doi.org/10.1089/vbz.2020.2679 PMID: 33054699

20. Gudbjartsson DF, Helgason A, Jonsson H, Magnusson OT, Melsted P, Norddahl GL, et al. Spread of SARS-CoV-2 in the Icelandic Population. N Engl J Med 2020; 382(24):2302–15. https://doi.org/10.1056/NEJMoa2006100 PMID: 32289214

21. Chen H, Wang J, Su N, Bao X, Li Y, Jin J. Simplified immune-dysregulation index: a novel marker predicts 28-day mortality of intensive care patients with COVID-19. Intensive Care Med 2020; 46(8):1645–7. https://doi.org/10.1007/s00134-020-06114-2 PMID: 32435824

22. Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. J Transl Med 2020; 18(1):206. https://doi.org/10.1186/s12967-020-02374-0 PMID: 32434518

23. Qian SZ, Hong WD, Lingjie M, Shenfeng L, Zhendong F, Pan JY. Clinical Characteristics and Outcomes of Severe and Critical Patients With 2019 Novel Coronavirus Disease (COVID-19) in Wenzhou: A Retrospective Study. Front Med (Lausanne) 2020; 7:552002. https://doi.org/10.3389/fmed.2020.552002 PMID: 33015108

24. Zhou W, Qin X, Hu X, Lu Y, Pan J. Prognosis models for severe and critical COVID-19 based on the Charlson and Elixhauser comorbidity indices. Int J Med Sci 2020; 17(15):2257–63. https://doi.org/10.7150/ijms.50007 PMID: 32922189

25. Mitra AR, Fergusson NA, Lloyd-Smith E, Wormsbecker A, Foster D, Karpov A, et al. Baseline characteristics and outcomes of patients with COVID-19 admitted to intensive care units in Vancouver, Canada: a case series. CMAJ 2020; 192(26):E694–E701. https://doi.org/10.1503/cmaj.200794 PMID: 32461326

26. Organization WH. COVID-19 Weekly Epidemiological Update as of 6 December 2020. https://www.who.int/publications/m/item/weekly-epidemiological-update-8-december-2020. 2020.

27. Sakr Y, Bensasi H, Taha A, Bauer M, Ismail K, Belhaj G, et al. Camostat mesylate therapy in critically ill patients with COVID-19 pneumonia. Intensive Care Medicine 2021. https://doi.org/10.1007/s00134-021-06395-1 PMID: 33846824
37. Yan X, Li F, Wang X, Yan J, Zhu F, Tang S, et al. Neutrophil to lymphocyte ratio as prognostic and predictive factor in patients with coronavirus disease 2019: A retrospective cross-sectional study. J Med Virol 2020; 92(11):2573–81. https://doi.org/10.1002/jmv.26061 PMID: 32458459

38. Cheng B, Hu J, Zuo X, Chen J, Li X, Chen Y, et al. Predictors of progression from moderate to severe coronavirus disease 2019: a retrospective cohort. Clin Microbiol Infect 2020; 26(10):1400–5. https://doi.org/10.1016/j.cmi.2020.06.033 PMID: 32622952

39. Mangalmurti N, Hunter CA. Cytokine Storms: Understanding COVID-19. Immunity 2020; 53(1):19–25. https://doi.org/10.1016/j.immuni.2020.06.017 PMID: 32610079

40. Zhang X, Tan Y, Ling Y, Lu G, Liu F, Yi Z, et al. Viral and host factors related to the clinical outcome of COVID-19. Nature 2020; 583(7816):437–40. https://doi.org/10.1038/s41586-020-2355-0 PMID: 32434211

41. Li X, Liu C, Mao Z, Xiao M, Wang L, Qi S, et al. Predictive values of neutrophil-to-lymphocyte ratio on disease severity and mortality in COVID-19 patients: a systematic review and meta-analysis. Crit Care 2020; 24(1):647. https://doi.org/10.1186/s13054-020-03374-8 PMID: 33198786

42. Jialal I, Sokoll LJ. Clinical utility of lactate dehydrogenase: a historical perspective. Am J Clin Pathol 2015; 143(2):158–9. https://doi.org/10.1016/j.ajcp.2014.10.005 PMID: 25596240

43. Henry BM, Aggarwal G, Wong J, Benoit S, Vikse J, Plebani M, et al. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: A pooled analysis. Am J Emerg Med 2020; 38(9):1722–6. https://doi.org/10.1016/j.ajem.2020.05.073 PMID: 32738466

44. Hsu PP, Sabatini DM. Cancer cell metabolism: Warburg and beyond. Cell 2008; 134(5):703–7. https://doi.org/10.1016/j.cell.2008.08.021 PMID: 18775299