



Risk Factors and Mortality in Elderly ARDS COVID-19 Compared to Patients without COVID-19

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During the last few decades, due to the increase in elderly patients among the general population, the number of patients aged over 80 years admitted in intensive care significantly incremented [1]. Bagshaw et al. recently showed that elderly patients represented one in every four admissions to intensive care [2]. Pneumonia and sepsis have been reported as the two most common risk factors for acute respiratory distress syndrome (ARDS) [3].

The current incidence and mortality for ARDS are quite variable among countries. For example, in the United States, the incidence of ARDS was significantly higher compared to Europe, where it was found to reach up to 58 cases per 100.000 persons-years [3]. Moreover, the incidence increased with age, with up to 306 cases per 100.000 person-years for patients aged between 75 and 84 years [3].

Concerning critically ill patients with community pneumonia, an age over 80 years was an independent risk factor for death, both at 30 days (OR = 2.54 (1.2–5.3)) and at 1 year (OR = 3.47 (1.9–6.0)) [4]. Similarly, the mortality in ARDS increases up to 60% for patients up to 85 years, with a hazard ratio of 2.5 for hospital deaths [3,5]. Although previous data reported that after intensive care admission, young and older patients received different intensities of treatment in terms of mechanical ventilation, vasopressor infusion, and renal replacement therapy, more recently, studies found that the number of treatments for patients aged 80 years has increased [1,6,7].

In addition, elderly patients with ARDS presented a higher duration of mechanical ventilation and length of stay in intensive care [5]. The prediction of mechanical ventilation duration could affect both clinical management and intensive care resource utilization. Additionally, comorbidities, such as the presence of chronic respiratory disease, heart failure, cerebrovascular diseases, malnutrition, and end-stage renal failure, affected the duration of mechanical ventilation and the final outcome [8–10]. Unfortunately, an accurate prediction of mechanical ventilation is quite difficult for critical care physicians according to clinical data at admission. A possible solution may be the application of a machine learning technique according to the clinical features of ARDS evaluated in the first days of intensive care admission [11].

Since the first cases of coronavirus disease 2019 (COVID-19) reported in Wuhan, China, more than 416 million cases with 5.8 million deaths have been reported around the world [12,13]. Typically, COVID-19 can range from an asymptomatic infection to a severe form of ARDS. Unfortunately, other than vaccination as the most useful preventive measure, there are only a few available therapeutic treatments. Among these, invasive and noninvasive mechanical ventilation remain the most powerful symptomatic treatment [14].

Based on the first report in hospitalized patients from China, age was associated with death, similar to previous data from SARS and MERS infection [15–18]. Elderly patients, in addition to presenting more chronic diseases, could have a lower efficacy to respond to



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Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). virus infection. In the largest cohort of hospitalized patients with COVID-19, the increased age was an independent risk factor for mortality, with odds risk approximately doubling for an age between 65 and 79 years compared to 50 and 64 years [19]. A systematic review showed that mortality from COVID-19 was independently associated with the patient's age and older patients were more likely to be admitted to intensive care and develop ARDS [20]. Patients aged 70 years represented up to 28 of the total COVID-19 critically ill patients admitted to intensive care [21]. The factors independently associated with intensive care admission included age, the presence of immunosuppression, and diabetes [22].

The mortality for elderly patients admitted to intensive care ranged between 75 and 85%, significantly higher compared to that previously reported in non-COVID-19 patients [23–25]. Comparing ARDS in COVID-19 and not COVID-19, it was shown that COVID-19 patients presented a higher lung gas volume with lower extension of lung disease but a higher impairment in oxygenation [26]. By analyzing two cohorts of patients older than 80 years, it was found that COVID-19 patients presented a slightly lower age and SOFA, while being more likely to receive invasive mechanical ventilation and had a worse outcome, 38 vs. 57% [27]. Furthermore, there were no differences in the use of vasoactive drugs or renal replacement therapy. Regarding the hospital mortality, it was associated with age, race, immunosuppression, renal disease, neurologic disorders, and diabetes. The presence of at least three of these medical conditions was associated with a higher risk for intensive care admission and death [22].

In two studies that compared the outcomes, COVID-19 had significantly higher lethality compared to patients with influenza [28,29]. In particular, the mortality was 67% in patients aged 70–89 years with a severe case of COVID-19, compared to 45% in the influenza group for similar ages [28].

These data suggest that ARDS, due to COVID-19, in addition to age, comorbidities, the severity of infection, the disease progression, and inflammatory trajectory, could lead to a worse outcome compared to patients without COVID-19.

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References

- 1. Nguyen, Y.-L.; Angus, D.C.; Boumendil, A.; Guidet, B. The challenge of admitting the very elderly to intensive care. *Ann. Intensive Care* 2011, *1*, 29. [CrossRef] [PubMed]
- 2. Bagshaw, S.M.; Webb, S.A.R.; Delaney, A.; George, C.; Pilcher, D.; Hart, G.K.; Bellomo, R. Very old patients admitted to intensive care in Australia and New Zealand: A multi-centre cohort analysis. *Crit. Care* **2009**, *13*, R45. [CrossRef]
- Rubenfeld, G.D.; Caldwell, E.; Peabody, E.; Weaver, J.; Martin, D.P.; Neff, M.; Stern, E.J.; Hudson, L.D. Incidence and outcomes of acute lung injury. N. Engl. J. Med. 2005, 353, 1685–1693. [CrossRef]
- Sligl, W.I.; Eurich, D.T.; Marrie, T.J.; Majumdar, S.R. Age still matters: Prognosticating short- and long-term mortality for critically ill patients with pneumonia. *Crit. Care Med.* 2010, *38*, 2126–2132. [CrossRef]
- Ely, E.W.; Wheeler, A.P.; Thompson, B.T.; Ancukiewicz, M.; Steinberg, K.P.; Bernard, G.R. Recovery rate and prognosis in older persons who develop acute lung injury and the acute respiratory distress syndrome. *Ann. Intern. Med.* 2002, *136*, 25–36. [CrossRef] [PubMed]
- 6. Guidet, B.; Vallet, H.; Boddaert, J.; de Lange, D.W.; Morandi, A.; Leblanc, G.; Artigas, A.; Flaatten, H. Caring for the critically ill patients over 80: A narrative review. *Ann. Intensive Care* **2018**, *8*, 114. [CrossRef] [PubMed]
- Guidet, B.; de Lange, D.W.; Boumendil, A.; Leaver, S.; Watson, X.; Boulanger, C.; Szczeklik, W.; Artigas, A.; Morandi, A.; Andersen, F.; et al. The contribution of frailty, cognition, activity of daily life and comorbidities on outcome in acutely admitted patients over 80 years in European ICUs: The VIP2 study. *Intensive Care Med.* 2020, *46*, 57–69. [CrossRef] [PubMed]
- Huang, H.-Y.; Huang, C.-Y.; Li, L.-F. Prolonged Mechanical Ventilation: Outcomes and Management. J. Clin. Med. 2022, 11, 2451. [CrossRef]
- Wozniak, H.; Dos Santos Rocha, A.; Beckmann, T.S.; Larpin, C.; Buetti, N.; Quintard, H.; Pugin, J.; Heidegger, C.P. Hypophosphatemia on ICU Admission Is Associated with an Increased Length of Stay in the ICU and Time under Mechanical Ventilation. *J. Clin. Med.* 2022, *11*, 581. [CrossRef]
- Kim, B.K.; Kim, C.Y.; Kim, S.; Kim, Y.J.; Lee, S.H.; Kim, J.H. Associations between Phosphate Concentrations and Hospital Mortality in Critically Ill Patients Receiving Mechanical Ventilation. J. Clin. Med. 2022, 11, 1897. [CrossRef]

- 11. Sayed, M.; Riaño, D.; Villar, J. Predicting Duration of Mechanical Ventilation in Acute Respiratory Distress Syndrome Using Supervised Machine Learning. *J. Clin. Med.* **2021**, *10*, 3824. [CrossRef] [PubMed]
- 12. World Health Organization. WHO Coronavirus-19 Dashboard. Available online: https://covid19.who.int/ (accessed on 21 August 2022).
- Oliaei, S.; SeyedAlinaghi, S.; Mehrtak, M.; Karimi, A.; Noori, T.; Mirzapour, P.; Shojaei, A.; MohsseniPour, M.; Mirghaderi, S.P.; Alilou, S.; et al. The effects of hyperbaric oxygen therapy (HBOT) on coronavirus disease-2019 (COVID-19): A systematic review. *Eur. J. Med. Res.* 2021, 26, 96. [CrossRef] [PubMed]
- Gattinoni, L.; Gattarello, S.; Steinberg, I.; Busana, M.; Palermo, P.; Lazzari, S.; Romitti, F.; Quintel, M.; Meissner, K.; Marini, J.J.; et al. COVID-19 pneumonia: Pathophysiology and management. *Eur. Respir. Rev. Off. J. Eur. Respir. Soc.* 2021, 30, 210138. [CrossRef]
- Zhou, F.; Yu, T.; Du, R.; Fan, G.; Liu, Y.; Liu, Z.; Xiang, J.; Wang, Y.; Song, B.; Gu, X.; et al. 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]
- 16. Yang, X.; Yu, Y.; Xu, J.; Shu, H.; Xia, J.; Liu, H.; Wu, Y.; Zhang, L.; Yu, Z.; Fang, M.; et al. Clinical Course and outcomes of critically ill patients with COVID-19 in Wuhan China. *Lancet Respir Med.* **2020**, *8*, 475–481. [CrossRef]
- Choi, K.W.; Chau, T.N.; Tsang, O.; Tso, E.; Chiu, M.C.; Tong, W.L.; Lee, P.O.; Ng, T.K.; Ng, W.F.; Lee, K.C.; et al. Outcomes and prognostic factors in 267 patients with severe acute respiratory syndrome in Hong Kong. *Ann. Intern. Med.* 2003, 139, 715–723. [CrossRef]
- 18. Hong, K.-H.; Choi, J.-P.; Hong, S.-H.; Lee, J.; Kwon, J.-S.; Kim, S.-M.; Park, S.Y.; Rhee, J.-Y.; Kim, B.-N.; Choi, H.J.; et al. Predictors of mortality in Middle East respiratory syndrome (MERS). *Thorax* **2018**, *73*, 286–289. [CrossRef]
- 19. Sundaram, S.S.; Melquist, S.; Kalgotra, P.; Srinivasan, S.; Parasa, S.; Desai, M.; Sharma, P. Impact of age, sex, race, and regionality on major clinical outcomes of COVID-19 in hospitalized patients in the United States. *BMC Infect. Dis.* **2022**, *22*, 659. [CrossRef]
- Dadras, O.; SeyedAlinaghi, S.; Karimi, A.; Shamsabadi, A.; Qaderi, K.; Ramezani, M.; Mirghaderi, S.P.; Mahdiabadi, S.; Vahedi, F.; Saeidi, S.; et al. COVID-19 mortality and its predictors in the elderly: A systematic review. *Health Sci. Reports* 2022, *5*, e657. [CrossRef]
- 21. Dres, M.; Hajage, D.; Lebbah, S.; Kimmoun, A.; Pham, T.; Schmidt, M.; Combes, A.; Mercat, A.; Guidet, B.; Demoule, A. Characteristics, Management and Prognosis of Elderly Patients with COVID-19 Admitted in the ICU During the First Wave: Insights from the COVID-ICU Study. *EuropePMC* 2020, *11*, 77. [CrossRef]
- Kim, L.; Garg, S.; O'Halloran, A.; Whitaker, M.; Pham, H.; Anderson, E.J.; Armistead, I.; Bennett, N.M.; Billing, L.; Como-Sabetti, K.; et al. Risk Factors for Intensive Care Unit Admission and In-hospital Mortality Among Hospitalized Adults Identified through the US Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET). *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* 2021, 72, e206–e214. [CrossRef] [PubMed]
- Lim, Z.J.; Subramaniam, A.; Ponnapa Reddy, M.; Blecher, G.; Kadam, U.; Afroz, A.; Billah, B.; Ashwin, S.; Kubicki, M.; Bilotta, F.; et al. Case Fatality Rates for Patients with COVID-19 Requiring Invasive Mechanical Ventilation. A Meta-Analysis. *Am. J. Respir. Crit. Care Med.* 2021, 203, 54–66. [CrossRef] [PubMed]
- 24. Eachempati, S.R.; Hydo, L.J.; Shou, J.; Barie, P.S. Outcomes of acute respiratory distress syndrome (ARDS) in elderly patients. *J. Trauma* **2007**, *63*, 344–350. [CrossRef]
- Kao, K.-C.; Hsieh, M.-J.; Lin, S.-W.; Chuang, L.-P.; Chang, C.-H.; Hu, H.-C.; Wang, C.-H.; Li, L.-F.; Huang, C.-C.; Wu, H.-P. Survival predictors in elderly patients with acute respiratory distress syndrome: A prospective observational cohort study. *Sci. Rep.* 2018, *8*, 13459. [CrossRef]
- Chiumello, D.; Busana, M.; Coppola, S.; Romitti, F.; Formenti, P.; Bonifazi, M.; Pozzi, T.; Palumbo, M.M.; Cressoni, M.; Herrmann, P.; et al. Physiological and quantitative CT-scan characterization of COVID-19 and typical ARDS: A matched cohort study. *Intensive Care Med.* 2020, *46*, 2187–2196. [CrossRef]
- Guidet, B.; Jung, C.; Flaatten, H.; Fjølner, J.; Artigas, A.; Pinto, B.B.; Schefold, J.C.; Beil, M.; Sigal, S.; van Heerden, P.V.; et al. Increased 30-day mortality in very old ICU patients with COVID-19 compared to patients with respiratory failure without COVID-19. *Intensive Care Med.* 2022, 48, 435–447. [CrossRef] [PubMed]
- Ludwig, M.; Jacob, J.; Basedow, F.; Andersohn, F.; Walker, J. Clinical outcomes and characteristics of patients hospitalized for Influenza or COVID-19 in Germany. Int. J. Infect. Dis. Off. Publ. Int. Soc. Infect. Dis. 2021, 103, 316–322. [CrossRef]
- Hernández-Cárdenas, C.; Lugo-Goytia, G.; Hernández-García, D.; Pérez-Padilla, R. Comparison of the clinical characteristics and mortality in acute respiratory distress syndrome due to COVID-19 versus due to Influenza A-H1N1pdm09. *Med. Intensiva* 2021. *Online ahead of print*. [CrossRef]