Wiener klinische Wochenschrift
The Central European Journal of Medicine

A retrospective comparison between influenza and COVID-19-associated ARDS in a Croatian tertiary care center

Branimir Gjurašin · Marija Santini · Vladimir Krajinović · Neven Papić · Anita Atelj · Viktor Kotarski · Juraj Krznarić · Martina Vargović · Marko Kutleša

Summary

Background Since the beginning of the Corona virus disease 2019 (COVID-19) pandemic the new Severe acute respiratory syndrome coronoavirus 2 (SARS-CoV-2) virus has been repeatedly compared to the influenza virus; however, the comparison of invasively mechanically ventilated patients with acute respiratory distress syndrome (ARDS) caused by these viruses is very scarce. The purpose of this study was to compare clinical course and laboratory parameters between the most severely ill flu and COVID 19 patients treated with invasive mechanical ventilation (IMV).

Methods The study was conducted at the intensive care unit (ICU) of the tertiary care hospital in Zagreb, Croatia in the period between November 2018 and July 2020. Investigation included 72 adult patients requiring IMV due to influenza or SARS-CoV-2 virus infection and 42 patients had influenza and 30 had SARS-CoV-2 virus infection and the comparison between two etiological groups was conducted.

Results Invasively mechanically ventilated patients with COVID 19 and influenza differ in certain aspects. COVID 19 patients are older, male, have lower C-reactive protein (CRP) levels and have less need for extracorporeal membrane oxygenation (ECMO) support. In other measured variables, including mortality, the difference between influenza or SARS-CoV-2 etiology was not significant.

Conclusion High mortality of IMV patients with influenza and COVID 19 with 55% and 63%, respectively, challenges and urges medical and especially ICU community to expand our quest for further treatments,

B. Gjurašin, MD · V. Krajinović, MD, PhD · A. Atelj, MD ·
V. Kotarski, MD · J. Krznarić, MD · M. Vargović, MD
Department of Intensive Care Medicine and
Neuroinfectology, University Hospital for Infectious
Diseases "Dr. Fran Mihaljević", Mirogojska 8, 10000 Zagreb,
Croatia

B. Gjurašin, MD
brangjur@gmail.com

V. Krajinović, MD, PhD
vkrajinovic74@gmail.com

A. Atelj, MD
atelj.anita@gmail.com

V. Kotarski, MD
viktor.kotarski@gmail.com

J. Krznarić, MD
juraj.krznaric@hotmail.com

M. Vargović, MD
martina.varg@gmail.com

assistant professor M. Santini, MD, PhD · N. Papić, MD,
PhD · assistant professor M. Kutleša, MD, PhD (✉)
University of Zagreb—School of Medicine, Department of
Intensive Care Medicine and Neuroinfectology, University
Hospital for Infectious Diseases "Dr. Fran Mihaljević",
Zagreb, Croatia
marko.kutlescha@gmail.com

assistant professor M. Santini, MD, PhD
marijasantini.ms@gmail.com

N. Papić, MD, PhD
papic.neven@gmail.com

especially since ECMO use that is scarcely required in COVID 19 patients probably has limited impact in reducing mortality in COVID 19 patients.

Keywords Severe acute respiratory syndrome coronavirus 2 · Intensive care unit · Acute respiratory distress syndrome · Extracorporeal membrane oxygenation

Introduction

Since the beginning of the COVID-19 pandemics the new SARS-CoV-2 virus has been repeatedly compared to influenza virus; however, the comparison of invasively mechanically ventilated patients with acute respiratory distress syndrome (ARDS) caused by these viruses is very scarce, limited to a single short report [1].

The 2018/2019 flu epidemic in Croatia was one of the most severe ever recorded. Our tertiary hospital intensive care unit (ICU) at the University Hospital for Infectious Diseases in Zagreb, Croatia was overwhelmed with patients with severe flu during the 2018/2019 epidemic and was similarly burdened this year during the first wave of COVID 19 epidemic. In both epidemics our ICU capacity needed to be expanded for additional beds and in both circumstances maximum occupancy at one point was 22 patients, all on invasive mechanical ventilation (IMV) simultaneously. The predominant, almost exclusive flu serotype at our ICU during the 2018/2019 epidemic was H1N1, the pandemic virus that emerged in 2009.

The mortality of COVID 19 patients who require IMV is high, even up to 92% [2]. Flu mortality in the same population of patients was determined to be somewhat lower by some reports [3]; however, it is well known that the severity of flu depends on the serotype of influenza involved and on the comorbidities of the patients. Furthermore, in patients with severe H1N1 flu that require IMV, mortality can be high and in some studies it was reported to range from 50% up to a staggering 77% [4, 5]. Our tertiary care center is a respiratory extracorporeal membrane oxygenation (rECMO) referral center for Croatia and we tend to admit patients who are considered for rECMO treatment due to acute respiratory failure (ARF), mostly ARDS.

The purpose of this study was to compare clinical course and laboratory parameters between the most severely ill flu and COVID 19 patients treated with IMV. Furthermore, comparison of survivors and nonsurvivors in both groups was analyzed. The study was conducted at a single center during epidemic conditions with a high influx of patients in a short period of time.

Methods

Patients

All adult patients treated with IMV during the 2018/2019 flu epidemic and the 2020 COVID 19 pandemic were retrospectively identified from the electronic database and analyzed. The study was conducted at the ICU of the tertiary care hospital in Zagreb, Croatia in the period between November 2018 and July 2020.

Influenza and COVID 19 infections were confirmed by real-time polymerase chain reaction (RT-PCR) from a nasal swab, bronchoalveolar lavage or tracheal aspirate specimen. Blood cultures and tracheal aspirate cultures were obtained prior to antimicrobial treatment.

All the patients in the influenza group were treated equally and received antiviral treatment with oseltamivir in the dose of 150 mg twice daily and none of them received flu vaccination prior to admission. Empirical antimicrobial treatment consisted of ceftriaxone (1×2 g intravenously) and azithromycin (1×500 mg intravenously) and was terminated after 10 days and 3 days, respectively. Steroids were administered at low dose (2×100 mg of hydrocortisone intravenously) for patients in shock.

The COVID 19 group was empirically treated with ceftriaxone (1×2 g intravenously) and azithromycin (1×500 mg intravenously). Antimicrobial treatment was de-escalated after COVID 19 was diagnosed and hydroxychloroquine was commenced (2×400 mg on the first day and 2×200 mg following 4 days). All patients received methylprednisolone 1 mg/kg for 5–7 days. Tocilizumab was administered in 3 patients.

ARDS was defined by the Berlin definition published in JAMA in 2012 by Ranieri.

Acute renal failure was defined as stage 3 according to KDIGO (Kidney disease. Improving gloal outcome) criteria.

Lung protective IMV was provided according to the ARDS guidelines with low tidal volume ventilation and with a plateau pressure of < 30 cmH$_2$O. Positive end expiratory pressure (PEEP) was titrated to achieve the best static lung compliance and minimal driving pressure. Muscle paralysis, if administered as continuous infusion lasted up to 48 h. Sedation and analgesia did not differ between the groups.

All ECMO circuits in our patients were venovenous.

Data

Data were acquired retrospectively from the ICU patient database. Variables included in the analysis were age, gender, mortality, etiology, presence of diabetes mellitus, arterial hypertension, chronic obstructive lung disease, rECMO support, lactate dehydrogenase, creatine kinase, acute physiology and chronic health evaluation II score (APACHE II score), duration of me-

Table 1 Variables analyzed in patients on invasive mechanical ventilation according to etiology

	Influenza (42 pts.)	COVID 19 (30 pts.)	*p*-value
Nonsurvivors	23 (55%)	19 (63%)	0.63[a]
Age (years)	55 (45–63)	70 (56–75)	*<0.001*[b]
Sex (female, *n*)	22 (52%)	8 (27%)	*0.03*[a]
APACHE (Acute Physiology and Chronic Health Evaluation) II	18 (14–28)	16.5 (12–26)	0.49[b]
Mechanical ventilation (days)	13 (7–25.5)	17 (13–26)	0.18[b]
Intensive care unit stay (days)	16 (8–31.5)	20 (13–30)	0.29[b]
Respiratory extracorporeal membrane oxygenation	18 (43%)	3 (10%)	*0.003*[a]
Muscle paralysis	22 (52%)	17 (57%)	0.81[a]
Arterial hypertension	13 (31%)	15 (50%)	0.14[a]
Chronic obstructive pulmonary disease	5 (12%)	3 (10%)	1.0[a]
Diabetes mellitus	9 (21%)	7 (23%)	1.0[a]
Acute renal failure	25 (60%)	13 (43%)	0.23[a]
Nosocomial sepsis	19 (45%)	9 (30%)	0.23[a]
Lactate (mmol/L)	1.45 (1.26–1.65)	1.62 (1.29–3.11)	0.15[b]
C-reactive Protein (mg/L)	194 (132.8–319.7)	164.05 (123.8–235.5)	*<0.001*[b]
Lactate dehydrogenase (U/L)	643 (431.5–977.5)	570.5 (465–702)	0.36[b]
Creatine kinase (U/L)	391 (119–1400)	179.5 (111–448)	0.15[b]
Leukocytes (10^9/L)	6.8 (3.45–15.5)	10.4 (8.6–13.4)	0.49[b]

Data are counts (%) or median (lower and upper quartile)
[a]Fisher's two tailed exact test
[b]Mann-Whitney test

chanical ventilation, duration of ICU stay, occurrence of acute renal failure, C-reactive protein level.

Statistics

Continuous variables were presented as the median, the 25th and the 75th percentile. Categorical variables were presented as frequencies and percentages.

Univariate analysis tested the statistical significance of the difference in outcome variables between the groups with the Fisher's two-tailed exact test for categorical and with the Mann-Whitney test for continuous variables. Both tests were used due to nonparametrical distribution of the data.

P-values of less than 0.05 were considered to indicate a statistical significance in all statistical tests.

For statistical analysis SAS software for Windows, version 9.3. SAS Institute Inc. (Cary, NC, USA) was used.

Results

The investigation included 72 adult patients requiring IMV due to influenza or SARS-CoV-2 virus infections of whom 42 patients had influenza (40 H1N1 and 2 influenza B) and 30 had SARS-CoV-2 virus infection. The results for measured variables in IMV patients are presented according to the etiology (Table 1). In both etiology groups 8 ICU patients were omitted from this study because they did not require IMV but were treated with other respiratory support and all survived. Despite its proven efficacy, proning was scarce and was not statistically different between the two groups. In COVID 19 patients we proned only 5 patients due to preserved lung compliance and sufficiency of IMV to provide satisfactory gas exchange without proning. We used proning in 7 influenza patients but influenza patients were frequently too sick at admission for a prone trial and needed rECMO urgently.

All laboratory variables were measured on admission. It is important to notice that none of the patients had bacterial superinfections at admission in samples (blood cultures, tracheal aspirate cultures) taken prior to antimicrobial treatment. Viral pneumonia was the sole cause for ICU admission and IMV.

The incidence of acute renal failure indicates that the multiorgan failure was common in both groups. Principal cause of death in many patients was refractory shock. Septic shock was confirmed in 12 patients with influenza and in 5 with COVID 19. In 4 influenza patients sudden refractory ventricular fibrillation occurred with a fatal outcome and clinically inapparent myocarditis is a probable cause of this phenomenon. Despite comprehensive work-up in the remaining patients the etiology of shock was not elucidated; however, the clinical presentation of shock is compatible with cytokine release syndrome or septic shock with negative blood cultures. All patients died in the ICU.

In COVID 19 patients cardiac arrythmias with hydroxychloquine as the possible culprit were not noticed.

Tocilizumab was administered to only 3 patients because indication for treatment could not be attained due to unavailability of ferritin and IL-6 blood

Table 2 Variables according to outcome in invasively mechanically ventilated influenza patients

	Survivors (19 pts.)	Nonsurvivors (23 pts.)	P
Age (years)	54 (47–58)	58 (44–68)	0.48[a]
Sex (female)	12 (63%)	10 (43%)	0.23[b]
APACHE (Acute Physiology and Chronic Health Evaluation) II	16 (14–18)	20 (16–29)	0.10
Mechanical ventilation (days)	14 (10–29)	11 (7–22)	0.38
Intensive care unit stay (days)	20 (8–43)	12.5 (8–27)	0.32
Respiratory extracorporeal membrane oxygenation	6 (32%)	12 (52%)	0.22
Chronic obstructive pulmonary disease	0 (0%)	5 (22%)	0.05
Diabetes mellitus	0 (0%)	9 (30%)	0.002
Acute renal failure	7 (37%)	18 (78%)	0.01
Nosocomial sepsis	7 (37%)	12 (52%)	0.37
Lactate (mmol/L)	1.47 (1.35–1.71)	2.1 (1.00–5.20)	0.20
C-reactive protein (mg/L)	217.3 (119.8–316.1)	191.4 (142.7–323.3)	0.93
Lactate dehydrogenase (U/L)	519 (404–732)	694 (490–960)	0.28
Creatine kinase (U/L)	391 (107–1348)	421.5 (138–1452)	0.65
Leukocytes (10^9/L)	6.5 (2.8–12.4)	8.4 (4.4–15.4)	0.37

Data are counts (%) or median (lower and upper quartile)
[a]Fisher's two tailed exact test
[b]Mann-Whitney test

Table 3 Variables according to outcome in invasively mechanically ventilated COVID 19 patients

	Survivors (11 pts.)	Nonsurvivors (19 pts.)	P
Age (years)	71 (49–75)	70 (59–76)	0.79[a]
Sex (female)	3 (27%)	5 (26%)	1.00[b]
APACHE (Acute Physiology and Chronic Health Evaluation) II	13 (11–20)	18 (14–30)	0.03
Mechanical ventilation (days)	18 (13–28)	16 (9–26)	0.25
Intensive care unit (days)	30 (23–31)	16 (9–26)	0.01
Respiratory extracorporeal membrane oxygenation	0 (0%)	3 (16%)	0.28
Chronic obstructive pulmonary disease	1 (9%)	2 (10%)	1.00
Diabetes mellitus	2 (18%)	5 (26%)	1.00
Acute renal failure	2 (18%)	11 (58%)	0.06
Nosocomial sepsis	4 (36%)	5 (26%)	0.69
Lactate (mmol/L)	1.64 (0.955–1.905)	1.435 (1.26–1.5)	0.58
C-reactive protein (mg/L)	166.2 (123.8–244.2)	162 (109–211.8)	0.64
Lactate dehydrogenase (U/L)	530 (314–608)	620 (526–731)	0.14
Creatine kinase (U/L)	183 (76–940)	176 (117–448)	1.00
Leukocytes (10^9/L)	9.9 (7.1–11.3)	10.4 (8.9–16.8)	0.74

Data are counts (%) or median (lower and upper quartile)
[a]Fisher's two tailed exact test
[b]Mann-Whitney test

levels for the first couple of weeks of the epidemic. Of these 3 patients 2 survived.

Comparisons of survivors and nonsurvivors according to etiology are presented in Tables 2 and 3. Weaning from rECMO was possible in an additional 4 nonsurviving patients with influenza who later died in the ICU.

As expected, COPD, diabetes mellitus and acute renal failure were significantly more frequent in influenza patients who died, than in influenza survivors. These variables were not associated with mortality in COVID 19 patients. The small sample size together with severe illness in all patients at admission are probably responsible for such data; however, in acute renal failure there was a clear trend towards significance ($p = 0.06$), as 2 (18%) and 11 (53%) patients had acute renal failure in survivor and nonsurvivor groups, respectively.

Discussion

Our study revealed that the most severely ill patients with COVID 19 and influenza differed in certain aspects. The COVID 19 patients tended to be older, male, have lower CRP levels and have less need for rECMO support. In other measured variables, in-

cluding mortality, the difference between influenza or SARS-CoV-2 etiology was not significant.

In our opinion the most important finding of the study is significantly less rECMO support in patients with severe COVID 19 infection. It could be argued that this finding reflects different ARDS pathogenesis with lung compliance preserved more frequently in COVID 19 ARDS, despite similar severity prior to IMV [6]; however, in a small fraction of patients with COVID 19 ARDS the disease progresses and compliance is reduced. Those patients, 3 of them, we treated with venovenous ECMO that commenced afer IMV lasted for >7 days, and that fact further predisposed patients for adverse outcome of rECMO. The results were disappointing and all 3 patients died. Ideal ECMO timing in COVID 19 ARDS remains to be determined and probably depends on our knowledge about the pathogenesis of this disease. It seems that COVID 19 ARDS can have more than one phase of escalation, this might be due to the hyperinflammatory response to SARS-CoV-2 that can have more than one wave of progression [7, 8]. At this level of current knowledge, it could be suggested that rECMO in COVID 19 will not have the role it had during the H1N1 pandemic; however, a recent publication found that rECMO can be used in COVID 19 patients with

results comparable to other ARDS etiologies but in that cohort patients were younger with average age of 49 years and were treated with early rECMO [9].

Since 2009 and H1N1 pandemic our rECMO center treated 197 ARDS patients with venovenous ECMO with 51% survival; however, the 2018/2019 flu season was severe in Croatia, surge of patients in a need of rECMO or IMV had unfavorable effect on survival, probably due to higher incidence of nosocomial sepsis as a consequence of intense work load.

We found that the age is significantly different between the influenza and COVID 19 groups. Besides the fact that the severe form of flu is less age discriminative, older age reduces the chance for ICU survival regardless of the reason for admission, and especially if prolonged IMV is required [10]. Higher CRP in the influenza group might not only be due to the severity of the inflammatory response induced by the virus, but also to the age of the patients, since younger individuals certainly have more robust immune system; however, this difference in CRP levels at admission is not to be relied upon for clinical decision making or for etiology assumption. Predominance of males has been consistent throughout the COVID 19 data from different studies [11].

The mortality of IMV patients with severe influenza and COVID 19 in our study was high at 55% and 63%, respectively. Other studies reported high mortality as well [2]; however, the reasons for such adverse outcomes still needs to be elucidated. It could be due to the fact that both diseases are recent and thus our knowledge of their optimal treatment is still deficient. H1N1 primary pneumonia has been with us since 2009, prior to that primary influenza pneumonia was a rarity. Of course, COVID 19 is a completely new disease caused by the newly emerged virus. Furthermore, the range of mortality in IMV COVID 19 patients reported from different studies is substantial [2, 12]. Explanation for such difference in mortality across the studies remains to be determined. One of the reasons could be due to methodological bias in different studies. For example, our center is a tertiary center and rECMO referral center, consequently we admit patients who are under consideration for rECMO and thus many have the most severe form of ARF with frequent and expected poor outcome. Furthermore, contraindications for IMV treatment vary across the nations and health systems with possible effect on the outcome of all patients requiring IMV.

The limitations of our study are relevant and include a small number of patients and the retrospective as well as observational nature of the study. Consequently, the inference of the results is restricted due to possible confounder variables. Missing data about mechanical ventilation parameters is unfavorable; however, it is a single center study, so the ICU care was consistent regardless of the etiology. Furthermore, it is one of the first studies to compare these two different viruses with respect to their most severe presentations and indicates that rECMO use in COVID 19 should be addressed promptly to avoid unnecessary harm and cost. Hopefully, further studies will address this and other issues in order to elucidate if there are any more hidden differences between these two entities that could affect the ICU treatment approach, apart from the antiviral medications.

High mortality of IMV patients with influenza and COVID 19 challenges and urges the medical and especially the ICU community to expand our quest for further treatments, especially antiviral drugs, immunomodulatory medications or procedures and the least detrimental respiratory support in order to enhance chances for survival of our patients. Furthermore, it seems prudent to expand influenza vaccination to include a higher proportion of a certain population in order to avoid overlapping of the two epidemics and thus avoid deleterious effects on providing the optimal ICU care.

References

1. Lee J, Lee YH, Chang HH, Choi SH, et al. Comparison of short-term mortality between mechanically ventilated patients with COVID-19 and influenza in a setting of sustainable healthcare system. J Infect. 2020; https://doi.org/10.1016/j.jinf.2020.05.005.
2. Hua J, Qian C, Luo Z, et al. Invasive mechanical ventilation in COVID-19 patient management: the experience with 469 patients in Wuhan. Crit Care. 2020;24(1):348. https://doi.org/10.1186/s13054-020-03044-9.
3. Dominguez-Cherit G, De la Torre A, Rishu A, et al. Influenza A (H1N1pdm09)-related critical illness and mortality in Mexico and Canada, 2014. Crit Care Med. 2016;44:1861–70.
4. Teke T, Coskun R, Sungur M, et al. 2009 H1N1 influenza and experience in three critical care units. Int J Med Sci. 2011;8:270–7.
5. Tanna K, Vegad MM, Soni ST, et al. Patients with swine flu on mechanical ventilator and its outcome at Civil Hospital, Ahmedabad. Int J Med Sci Public Health. 2015;4:1383–7.
6. Polak SB, Van Gool IC, Cohen D, et al. A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. Mod Pathol. 2020; https://doi.org/10.1038/s41379-020-0603-3.
7. Pelaia C, Tinello C, Vatrella A, et al. Lung under attack by COVID-19-induced cytokine storm: pathogenic mechanisms and therapeutic implications. Ther Adv Respir Dis. 2020;14:1753466620933508.
8. Mahmudpour M, Roozbeh J, Keshavarz M, et al. COVID-19 cytokine storm: The anger of inflammation. Cytokine. 2020; https://doi.org/10.1016/j.cyto.2020.155151.
9. Schmidt M, Hajage D, Lebreton G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. Lancet Respir Med. 2020; https://doi.org/10.1016/S2213-2600(20)30328-3.
10. Ishiguro T, Kagiyama N, Uozumi R, et al. Risk factors for the severity and mortality of pneumococcal pneumonia:

importance of premorbid patients' performance status. J Infect Chemother. 2016;22:685–91.

11. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020;369:m1966.

12. Auld SC, Caridi-Scheible M, Blum JM, et al. ICU and ventilator mortality among critically ill adults with Coronavirus disease 2019. Crit Care Med. 2020; https://doi.org/10.1097/CCM.0000000000004457.