Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Available online at www.sciencedirect.com

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Original article

Risk factors for transfer from Respiratory Intermediate Care Unit to Intensive Care Unit in COVID-19

Enrico Buonamico [a,1], *Vitaliano Nicola Quaranta* [b,1], *Esterina Boniello* [a], *Michela Dimitri* [a], *Valentina Di Lecce* [a,*], *Luciana Labate* [a], *Paola Pierucci* [a], *Elena Capozza* [a], *Giovanna Elisiana Carpagnano* [a], *Onofrio Resta* [a]

[a] *Institute of Respiratory Disease, Department of Basic Medical Science, Neuroscience, and Sense Organs, University of Bari "Aldo Moro", Piazza Giulio Cesare 11, 70125, Bari, Italy*

[b] *Pneumology Department, "Di Venere" Hospital, Via Ospedale Di Venere 1, 70131, Bari, Italy*

ARTICLE INFO

Article history:
Received 28 December 2020
Received in revised form
5 May 2021
Accepted 6 May 2021
Available online 1 June 2021

Keywords:
COVID-19
COVID-19 management Italy
COVID-19 ICU transfer risk factors
Respiratory intermediate care unit

ABSTRACT

Background: Patients hospitalized for COVID-19-related pneumonia often need several degrees of ventilatory support, which are performed between Respiratory Intermediate Care Units (RICUs) and Intensive Care Units (ICUs), and which depend on the severity of acute respiratory distress syndrome. There is no firm consensus on transfer predictors from the RICU to the ICU.

Methods: In this retrospective observational single center study, we evaluated 96 COVID-19 patients referred to the RICU for acute respiratory failure (ARF) according to their transferal to the ICU or their stay at the RICU. We compared demographic data, baseline laboratory profile, and final clinical outcomes to identify early risk factors for transfer.

Results: The best predictors for transfer to the ICU were elevated C-reactive protein and lymphopenia. The mortality rate was lower in the RICU than in the ICU, where transferred patients who died were mostly younger men and with less comorbidities than those in the RICU.

Conclusions: Few inflammatory markers can predict the need for transfer from the RICU to the ICU. Due to the ongoing COVID-19 pandemic, we urge better clinical stratification by early and meaningful profiles in patients admitted to the RICU who are at risk of transferal to the ICU.

Abbreviations: COVID-19, coronavirus disease; RICU, Respiratory Intermediate Care Units; ICU, Intensive Care Unit; IQR, interquartile range; HR, hazard ratio; BMI, body mass index; CCI, Charlson comorbidity index; COPD, Chronic obstructive pulmonary disease; LDH, Lactate dehydrogenase; CRP, C-reactive protein; PaO2/FiO2 ratio, arterial oxygen partial pressure to fractional inspired oxygen; HFNC, high-flow nasal cannula; CPAP, continuous positive airway pressure; BPAP, bilevel positive airway pressure; IMV, invasive mechanical ventilation.

* *Corresponding author*. Piazza Giulio Cesare 11, 70125, Bari, Italy
E-mail address: valentina.dilecce@policlinico.ba.it (V. Di Lecce).

[1] Enrico Buonamico and Vitaliano Nicola Quaranta contributed equally.

https://doi.org/10.1016/j.resinv.2021.05.002

1. Introduction

The World Health Organization (WHO) declared coronavirus disease (COVID-19) to be a public health emergency of international concern [1], and that a novel coronavirus (severe acute respiratory syndrome coronavirus 2) was confirmed as responsible for the COVID-19 pandemic [2]. The clinical spectrum of COVID-19 infection is wide, encompassing asymptomatic infection, mild upper respiratory tract illness, and severe pneumonia with acute respiratory failure (ARF) [3]. In Italy, Non-invasive ventilation is often delivered in the setting of Respiratory Intermediate Care Units (RICUs) lead by pneumologists. However, many patients are at risk of transferal to the Intensive Care Unit (ICU) due to the progressive worsening of respiratory failure. In China, RICUs are not widespread; thus, among hospitalized patients with COVID-19, the percentage of those who required the ICU has varied from 5% to 32% [4].

Aim of this study was to evaluate predictive factors of transfer to ICU or of permanence in RICU, in a population of 96 COVID-19 patients admitted to RICU for Acute Respiratory Failure.

2. Materials and methods

2.1. Population

This is a retrospective observational single center study. We obtained the medical records and compiled data from 96 hospitalized adult inpatients that were in our RICU of Teaching Hospital "Policlinico" of Bari from March 11, 2020 to May 31, 2020. COVID-19 was diagnosed on the basis of the WHO interim guidelines [5]. Only laboratory-confirmed cases were hospitalized in our RICU and included in the analysis, all of which were affected by ARF.

2.2. Data collection

Demographic data, medical history, comorbidities and the Charlson Comorbidity Index (CCI; in order to better evaluate the comorbidity burden in each patient), laboratory findings, and respiratory parameters were collected within the first 12 h following intermediate RICU admission. In addition, we reported patients' clinical outcomes that were evaluated as "survived," "deceased in RICU," "transferred to ICU," and "deceased in ICU". The samples were collected according to the Strengthening the Reporting of Observational Studies in Epidemiology Statement [6]. The study was approved by the Institutional Review Board of Policlinico of Bari (Ethical Committee number: 6380; Approval date: May 12, 2020). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

2.3. Statistical analysis

We verified the distribution normality of continuous variables using the Kolmogorov-Smirnov test.

Asymmetrical continuous variables were compared using the Mann-Whitney *U* test, and variables that showed normal distribution were compared using the Student T-test for independent variables.

Nominal variables were compared with the Fisher Chi-square test and Mantel-Haenszel test.

Univariate and multivariate logistic regression analyses relative to the probability of transfer to the ICU were performed. Survival analysis was performed by Cox regression.

For all statistical analyses performed in this study, we assumed a significance level of $p < 0.05$.

Data are described as mean ± standard deviation for parametric variables, and with median and interquartile range (IQR) for non-parametric variables. Categorical variables are indicated with numbers (%).

3. Results

Demographic and clinical characteristics of the study population are reported in Table 1. Among the 96 patients, 29 (30.2%) were transferred to the ICU. Forty-five patients (46.9%) died, of whom 23 (51.1%) died in the RICU and 22 (48.9%) died in the ICU. A lower arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2) ratio at admission is a predictor of mortality, as evidenced by the Cox survival analysis (hazard ratio [HR] 0.996 [0.992–0.999]; $p = 0.017$).

3.1. Probability of transfer to ICU

Factors linked to ICU transfer, obtained by univariate logistic regression, are shown in Table 2. Twenty-nine patients (30.2%) were transferred to the ICU. Using univariate linear regression analysis, we verified that age was not a predictive parameter of transfer to the ICU. Female sex was a protective parameter against transfer to the ICU, underlining once again the role of sexes in COVID-19 pathogenesis and evolution. Patients transferred to the ICU had 6.012 times the probability of death (2,237–16,161; $p = 0.000$). The PaO2/FiO2 ratio was not significant in predicting the probability of transfer to the ICU. Patients with the ICU as their final unit, compared to those remaining in the RICU, showed comparable levels of D-dimer (1447.27 ± 1104.86 vs. 2777.37 ± 4305.14; $p = 0{,}156$). Moreover, it was non-significant in the binomial logistic regression test on the probability of having the ICU as the final unit. Parameters that significantly predicted transfer to the ICU as obtained with univariate analysis were male sex, lymphopenia, and high C-reactive protein (CRP). These were tested with a multivariate model, underlining the importance of lymphopenia, which gets close to statistical significance, and of high CRP (Table 3).

3.2. Subgroup analysis: comparison between deceased and surviving patients transferred to ICU and deceased and surviving patients not transferred to ICU

Out of 29 patients who were transferred to the ICU, 22 (75.9%),died. When comparing the patients who died with

Table 1 – Demographic and clinical characteristics of the study population.

Parameter	Population (n = 96)
Age	
M ± SD	69.65 ± 14.33
median (IQR 25–75)	66.00 (57.00–88.00)
Female Sex (%)	28.9
BMI	
M ± SD	27.98 ± 5.00
median (IQR)	27.68 (23.89–31.25)
Smoking habit (%)	
Never smokers	36.1
Ex-smokers	42.3
Current smokers	3.1
CCI	
M ± SD	4.25 ± 2.66
median (IQR)	4.00 (2.00–6.00)
Asthma (%)	17.5
COPD (%)	17.5
Hypertension (%)	70.1
Renal Failure (%)	44.3
Congestive heart failure (%)	22.7
Chronic ischemic heart failure (%)	27.8
Neurological comorbidities (%)	17.6
Number of peripheral lymphocyte cells	
M ± SD	928.39 ± 637.35
median (IQR)	783.24 (629.18–1039.88)
LDH	
M ± SD	332.20 ± 113.31
median (IQR)	342.00 (245.00–396.00)
CRP	
M ± SD	116.74 ± 79.99
median (IQR)	106.00 (69.30–167.00)
D-dimer	
M ± SD	2448.33 ± 3811.22
median (IQR)	947.00 (581.00–2280.00)
PaO2/FiO2 ratio at admission	
M ± SD	209.58 ± 94.00
median (IQR)	198.00 (123.00–273.00)
Respiratory support at admission (%)	
Low flow oxygen	9.3
HNFC	3.1
CPAP	38.1
BPAP	36.1
IMV through tracheostomy	7.2
Treatment	
enoxaparin (%)	81%
azithromycin (%)	80%
lopinavir/ritonavir (%)	38%
hydroxychloroquine (%)	74%
tocilizumab (%)	6%
corticosteroids (%)	25%
Total Days of Hospitalization in RICU	
M ± SD	10.68 ± 8.94
median (IQR)	10,00 (4,00–19.00)
Exitus (%)	46.4

M, mean; SD, standard deviation; IQR, interquartile range; BMI, body mass index; CCI, Charlson comorbidity index; COPD, Chronic obstructive pulmonary disease; LDH, Lactate dehydrogenase; CRP, C-reactive protein; PaO2/FiO2 ratio, arterial oxygen partial pressure to fractional inspired oxygen; HFNC, high-flow nasal cannula; CPAP, continuous positive airway pressure; BPAP, bilevel positive airway pressure; IMV, invasive mechanical ventilation; RICU, Respiratory Intermediate Care Units.

Table 2 – Univariate Logistic Regression for the probability of having ICU as final unit.

Parameter	O.R.	CI 95%	P
Age	0.987	0.957–1.018	0.410
Female sex	0.259	0.089–0.921	**0.036**
BMI	0.903	0.795–1.025	0.114
CCI	0.880	0.739–1.048	0.880
PaO2/FiO2 ratio	0.997	0.992–1.002	0.227
Lymphocytes	0.998	0.997–1.000	**0.038**
CRP	1.007	1.001–1.013	**0.018**

OR, odds ratio; CI, confidence interval; PaO2/FiO2 ratio, arterial oxygen partial pressure to fractional inspired oxygen; CRP, C-reactive protein. Statistically significant results are highlighted in bold.

Table 3 – Multivariate Logistic Regression for the probability of having ICU as final unit.

Parameter	O.R.	CI 95%	P
Female sex	0.316	0.091–1.004	0.071
Lymphocytes	0.998	0.997–1.000	0.054
CRP	1.007	1.001–1.013	**0.034**

OR, odds ratio; CI, confidence interval; CRP, C-reactive protein. Statistically significant results are highlighted in bold.

those who survived among the 29 patients, we found age and CCI to be determining factors (Table 4). No specific comorbidity was associated with death, suggesting that it is a high comorbidity burden and not a specific comorbidity that is associated with death in the ICU. All other parameters, such as PaO2/FiO2 ratio ($p = 0.134$), were not significant. Among patients not transferred to the ICU (n = 67), 23 (34.3%) died. Older age and higher CCI were associated with death. Regarding comorbidity, deceased patients had significantly higher prevalence of chronic obstructive pulmonary disease, hypertension, renal failure, neurological comorbidities, congestive heart failure, and chronic ischemic heart failure. Low blood lymphocyte count and higher D-dimer values were associated with death (Table 4). Again, no difference emerged between the subgroups regarding the PaO2/FiO2 ratio. While the comparison between the median ages of the patients transferred and not transferred to the ICU were not significantly different (69 [61–75] vs. 69 [57.75–85]; $p = 0.53$), the comparison between the median ages of patients transferred to the ICU versus patients who died in the RICU were significantly different (69 [61–75] vs. 85 [80–88]; $p = 0.0002$). In a similar way, comparison of CCIs between those who were transferred and those who were not transferred to the ICU were not significantly different (4 [2–7] vs. 4 [2–5]; $p = 0.28$), while the comparison of CCIs between patients transferred to the ICU versus patients who died in the RICU were significantly different (4 [2–5] vs. 7 [6–9]; $p < 0.0001$).

3.3. *Sub-population analysis: comparison between deceased patients previously transferred to the ICU and deceased patients not transferred to the ICU*

Patients who died after being transferred to the ICU had younger ages, a lower median comorbidity number, lower D-dimer values, and lower prevalence of the female sex (Table 5).

Table 4 – Comparison of subpopulation (transferred to ICU and not transferred to ICU) between deceased and survived.

Subpopulation	Parameters	Deceased	Survived	P
	Numerosity	7	22	
Transferred to ICU (n = 29)	Age median (IQR)	72.0 (64.7–76.7)	60 (57.0–65.0)	0.024
	CCI median (IQR)	4.0 (2.7–5.2)	2.0 (2.0–3.0)	0.028
Not transferred to ICU (n = 67)	Numerosity	23	44	
	Age median (IQR)	84.0 (77.5–89.0)	61.0 (55.2–76.2)	0.000
	CCI median (IQR)	7.0 (5.0–9.0)	3.0 (1.0–5.0)	0.000
	Lymphocytes median (IQR)	727.7 (482.4–915.2)	852.3 (647.8–1217.2)	0.028
	D-dimer median (IQR)	1607.0 (888.0–5617.5)	1100.5 (530.0–2792.5)	0.039
	COPD %	47,6	5	0.000
	Hypertension	95.5	58.5	0.001
	Renal failure	81.8	31.7	0.000
	Neurologic comorbidity	38.1	2.4	0.000
	Congestive heart disease	57.1	11.9	0.000
	Chronic ischemic heart disease	61.9	14.3	0.000

IQR, interquartile range; ICU, Intensive Care Unit; CCI, Charlson comorbidity index; COPD, Chronic obstructive pulmonary disease.

Table 5 – Comparison between patients deceased in ICU and deceased not transferred to ICU.

	Transferred to ICU (n = 22)	Not transferred to ICU (n = 23)	P
Age median (IQR)	72.0 (64.5–75.0)	84.0 (77.5–89.0)	0.000
CCI median (IQR)	4 (2.5–5.5)	70 (5.0–9.0)	0.000
D-dimer median (IQR)	947.0 (637.5–2020)	1067.0 (888.0–5617.5)	0.043
Female sex %	13.6	43.5	0.029

IQR, interquartile range; ICU, Intensive Care Unit; CCI, Charlson comorbidity index.

4. Discussion

The aim of our study was to identify ICU transfer prognostic factors in patients hospitalized in the RICU for COVID-19-related ARF. Moreover, we wanted to compare causes of death between patients transferred to the ICU versus patients not transferred to the ICU.

We found that only high CRP and low blood lymphocyte count were predictive factors for transfer to the ICU, while female sex showed a protective role against transfer to the ICU. Conversely, laboratory parameters of disease severity, such as CRP and lymphocyte count, worked as risk factors from the baseline, suffering less variability until any improvement in clinical conditions. Patients transferred to the ICU suffer higher mortality than the others. Indeed, they were 6.012 times more likely to die. We further observed that among the deceased patients, those who died in the ICU had a lower median age, lower median comorbidity number, and lower D-dimer mean values, but, unexpectedly, not a significantly different baseline PaO2/FiO2 ratio, showing similar respiratory conditions at admission.

Another interesting finding is that median age and CCI are similar in patients transferred and patients not transferred to the ICU. However, considering patients who died in the RICU as the most severe patients in this group, and comparing them with the patients transferred to the ICU, median age and CCI became significantly different. The explanation of these findings is linked to the emergency condition of the COVID-19 pandemic: ICU beds were reserved, in case of similar critical conditions, for younger patients with less comorbidities. For this reason, severe patients who remained in the RICU and died were older and were affected by a higher comorbidity burden.

Our results regarding the PaO2/FiO2 ratio may sound unexpected. Indeed, the PaO2/FiO2 ratio is the main determinant for acute respiratory distress syndrome (ARDS) severity [7] and has already been shown to be associated with the risk of mortality. In an observational, prospective, multicenter study conducted by Santus et al. on 412 COVID-19 patients, a moderate-to-severe impairment in PaO2/FiO2 was independently associated with a significant increase in risk of in-hospital mortality, along with age >65 years and the presence of respiratory failure at admission [8]. The evidence, in our population, of no significant difference in the baseline PaO2/FiO2 ratio between patients transferred and not transferred to the ICU, may be explained by a high variability of respiratory values in the first few hospitalization days of COVID-19 patients. In our experience, the PaO2/FiO2 ratio in some patients suffered rapid falls from the baseline, needing sudden patient's intubation and transfer to the ICU.

Several studies since the start of the pandemic outbreak tried to describe factors associated with poor outcome and, in particular, ICU transfer, showing different results depending on many reasons, linked to geographical and logistic factors, and nonetheless linked to the phase of the pandemic during which the study was conducted. In an early Chinese paper by Chen et al. considering patients hospitalized between late January 2020 and the first days of February 2020, factors independently associated with ICU transfer were CD4 T cell count and older age, which are coherent to a phase of the

epidemic characterized by a small number of hospitalized patients [9]. In contrast, in our study, patients hospitalized at a later phase and older age were not linked with ICU transfer, while the evidence of a lower median age in patients died who in the ICU, when compared with those in the RICU suggests that, on the contrary, in our region's situation of March–May, transfer to the ICU was reserved for younger severe patients, a normal solution in case of shortage of ICU beds. A research letter by Barnett et al. focused the attention on the predictive value of baseline factors associated with transfer to the ICU, but, differently from our study, proposed a Modified Early Warning Score for risk assessment, which is based on clinical parameters rather than anamnestic and laboratory findings [10].

Other studies aimed to find poor outcome predictors, but considered death together with ICU transfer, thus leading to consider also older age as a predictor, like in a single-center French study by Allenbach et al. [11], and coexisting coronary heart disease, as found in a single-center Italian study by Cecconi et al. The latter also considered low PaO2/FiO2 ratio as a predictor, while in the former, arterial blood gas analysis values were not taken into account. Both of the aforementioned studies found lymphopenia and high PCR as poor outcome predictors. A study by Cheng et al. describes a machine learning-based risk prioritization tool to predict ICU transfer in a 24-h span and considers respiratory rate as the most important predictor of ICU transfer, with PCR and lymphopenia among the top-five most important factors [12].

The higher mortality rate of patients transferred to the ICU may be explained by common ICU mortality risks, such as intubation and antibiotic-resistant bacterial super-infections. Another possible explanation is a more powerful cytokine storm in some younger patients, which is associated with high mortality risk; however, further research needs to be conducted in order to deepen our knowledge of mortality causes in younger COVID-19 patients. In our sample, patients who died in the ICU showed a lower prevalence of the female sex when compared to patients who died outside the ICU. This evidence may be explained by the older age of women in our population, which, once again, is a factor related with non-transferal to the ICU in severe COVID-19 patients.

Finally, the data relating to pharmacological treatments used in our population were affected by the time during which the study was carried out. In particular, there was a wider use of hydroxychloroquine and anti-retroviral therapies, as suggested by the Chinese official guidelines and recommendations published in that period [13], compared to corticosteroids. In fact, while the use of hydroxychloroquine and antiretrovirals was subsequently reconsidered in large international trials [14,15], the role of dexamethasone in reducing 28-d mortality in COVID-19 patients also receiving respiratory support was highlighted in the RECOVERY trial at a later time [16]. Conversely, anticoagulant therapy did not experience this two-phase trend, since early evidence of D-dimer increase in a high percentage of COVID-19 patients suggested the presence of pulmonary embolism, which was later also described in autopsies [17]. In our population, 81% of the patients underwent anticoagulant therapy with enoxaparin. The importance of COVID-19 vascular involvement and the potential role of anticoagulant and antiplatelet drugs has been underlined in several studies [18,19], and at the time of writing, anticoagulants are still a cornerstone of COVID-19 treatment protocols [20].

5. Conclusions

Our study confirms that predictors of transfer to the ICU from the RICU (high baseline CRP and lymphopenia) are related more to inflammatory status that influences disease severity rather than to age and comorbidities. Patients who were transferred to the ICU suffered a significantly higher mortality than those who remained in the RICU, and patients who died in the ICU were mostly younger men with fewer comorbidities compared to those who died in the RICU. The PaO2/FiO2 ratio is the most important marker of ARDS, but in baseline is not a good predictor of transfer to the ICU. This is likely because of the trend of COVID-19 patients that suffer sudden worsening in respiratory failure. More studies need to be conducted on COVID-19 patients in order to identify risk factors for severe disease and for transfer to ICU as early and as precisely as possible, in the urgency of a pandemic that, after more than 12 m from the very beginning, still puts health systems all over the world to the test.

Conflict of Interest

The authors have no conflicts of interest.

REFERENCES

[1] World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. 2020. https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020.

[2] Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet 2020;395:15–8. https://doi.org/10.1016/S0140-6736(20)30185-9.

[3] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, 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(10229):1054–62. https://doi.org/10.1016/S0140-6736(20)30566-3.

[4] Guan W, Ni Z, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708–20. https://doi.org/10.1056/NEJMoa2002032.

[5] World Health Organization. Public health surveillance for COVID-19; interim guidance. 2020. https://www.who.int/publications/i/item/who-2019-nCoV-surveillanceguidance-2020.8.

[6] Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453–7. https://doi.org/10.1016/S0140-6736(07)61602-X.

[7] ARDS Definition Task Force, Ranieri MV, Rubenfeld GD, Thompson TB, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome. The berlin definition. J Am Med Assoc 2012;307:2526–33. https://doi.org/10.1001/jama.2012.5669.
[8] Santus P, Radovanovic D, Saderi L, Marino P, Cogliati C, De Filippis G, et al. Severity of respiratory failure at admission and in-hospital mortality in patients with COVID-19: a prospective observational multicentre study. BMJ Open 2020;10:e043651. https://doi.org/10.1136/bmjopen-2020-043651.
[9] Chen J, Qi T, Liu L, Ling Y, Qian Z, Li T, et al. Clinical progression of patients with COVID-19 in Shanghai, China. J Infect 2020 May;80(5):e1–6. https://doi.org/10.1016/j.jinf.2020.03.004.
[10] Barnett WR, Radhakrishnan M, Macko J, Hinch BT, Altorok N, Assaly R. Initial MEWS score to predict ICU admission or transfer of hospitalized patients with COVID-19: a retrospective study. S0163-4453 J Infect 2020 Sep 2;(20). https://doi.org/10.1016/j.jinf.2020.08.047. 30583-1.
[11] Allenbach Y, Saadoun D, Maalouf G, Vieira M, Hellio A, Boddaert J, et al. Development of a multivariate prediction model of intensive care unit transfer or death: a French prospective cohort study of hospitalized COVID-19 patients. PloS One 2020;15(10):e0240711. https://doi.org/10.1371/journal.pone.0240711.
[12] Cheng F-Y, Joshi H, Tandon P, Freeman R, Reich DL, Mazumdar M, et al. Using machine learning to predict ICU transfer in hospitalized COVID-19 patients. J Clin Med 2020 Jun 1;9(6):1668. https://doi.org/10.3390/jcm9061668.
[13] Gautret P, Lagier J, Parola P, Hoang VT. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;(January). https://doi.org/10.1016/j.ijantimicag.2020.105949.
[14] RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2020;19(20):1–8. https://doi.org/10.1016/S0140-6736(20)32013-4.
[15] The RECOVERY Collaborative Group. Effect of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med 2020;383(21):2030–40. https://doi.org/10.1056/nejmoa2022926.
[16] The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19 — preliminary report. N Engl J Med 2020:1–11. https://doi.org/10.1056/nejmoa2021436.
[17] Borczuk AC, Salvatore SP, Seshan SV, et al. COVID-19 pulmonary pathology: a multi-institutional autopsy cohort from Italy and New York City. Mod Pathol 2020. https://doi.org/10.1038/s41379-020-00661-1.
[18] Viecca M, Radovanovic D, Battista G, Santus P. Enhanced platelet inhibition treatment improves hypoxemia in patients with severe COVID-19 and hypercoagulability. A case control, proof of concept study. Pharmacol Res 2020;158(January). https://doi.org/10.1016/j.phrs.2020.104950.
[19] Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemostasis 2020;18(5):1094–9. https://doi.org/10.1111/jth.14817.
[20] Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. Blood Adv 2021;5(3):872–88. https://doi.org/10.1182/bloodadvances.2020003763.