Original article

Progression to a severe form of COVID-19 among patients with chronic respiratory diseases

Sarah Basin[a,1], Simon Valentin[a,b,1,*], Arnaud Maurac[a], Mathias Poussel[c,d],
Benjamin Pequignot[a], Aurélien Brindel[a], Guillaume Poupet[a], Céline Robert[e], Cédric Baumann[f],
Amandine Luc[f], Julien Soler[a], François Chabot[a,b], Ari Chaouat[a,b]

[a] Université de Lorraine, CHRU-Nancy, Pôle des spécialités médicales/département de pneumologie, F-54000 Nancy, France
[b] Université de Lorraine, Faculté de Médecine de Nancy, Inserm UMR_S1116, Vandœuvre-Lès- Nancy, France
[c] Université de Lorraine, CHRU-Nancy, Department of Pulmonary Function Testing and Exercise Physiology, University Centre of Sports Medicine and Adapted Physical Activity, F-54000 Nancy, France
[d] Université de Lorraine, EA 3450 DevAH-Développement, Adaptation et Handicap, Régulations cardio-respiratoires et de la motricité, Nancy, France
[e] Service de Maladies Infectieuses, Metz Thionville Regional Hospital, Ars-Laquenexy, France
[f] DRCI, Département MPI, Unité de Méthodologie, Data Management et Statistiques, Plateforme d'aide à la recherche clinique, hôpitaux de Brabois, CHRU de Nancy, rue du Morvan, 54511 Vandoeuvre-lès-Nancy, France

ARTICLE INFO

ABSTRACT

Rationale: Viral respiratory infections, including SARS-CoV-2 infection, can trigger respiratory symptoms among patients suffering from chronic respiratory diseases, leading to exacerbations and hospitalizations. Despite the tropism of SARS-CoV-2 into the respiratory tract, chronic respiratory diseases do not seem to be risk factors for severe forms of COVID-19.

Objectives: To assess whether hospitalized patients for COVID-19 with chronic respiratory diseases were at lower risk of developing a severe form than other patients.

Methods: This French study included patients admitted to hospital in COVID-19 ward, suffering from a SARS-CoV-2 infection, diagnosed on RT-PCR or chest computed tomography associated with clinical symptoms, from March 15 to June 30, 2020. Ambulatory patients who were tested in the emergency department and patients with severe hypoxaemia requiring intensive care were not included. All data were collected from electronic medical records up to discharge of the patient.

Main Results: 617 patients were included: 125 with a chronic respiratory disease, mainly chronic obstructive pulmonary disease (45%) and asthma (30%). The percentage of patients scoring 6 or higher on the WHO Clinical Progression Scale during hospital stay was lower in patients with chronic respiratory disease compared to those without chronic respiratory disease (21.6% versus 31.3%, respectively, $p = 0.03$). Among patients with chronic respiratory disease, temperature above 38 °C on admission (OR 16.88 (95% CI 4.01−71.00)), lymphopenia (OR 5.08 (1.25−20.72)), CPAP therapy (OR 4.46 (1.04−19.17)) and age (OR 1.09 (1.02−1.16)) were associated with an increased risk to reach a score of 6 or above.

Conclusions: Hospital admissions in COVID-19 ward of patients suffering from chronic respiratory diseases are at lower risk of developing a severe form of COVID- 19, especially in patients with chronic obstructive pulmonary disease or asthma. Prospective studies would confirm our results and allow to better organize the follow-up of these patients in a pandemic period.

© 2021 SPLF and Elsevier Masson SAS. All rights reserved.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has emerged in Wuhan Province, China, in December 2019 and rapidly spread around the world. France has been experiencing critical circumstances for public health, particularly in the Great East region, which includes the Nancy-Brabois University Hospital and the Metz-Thionville regional Hospital. From March 1st, 2020 to June 2, 2020, 14 416 patients were hospitalized in the Great East region for a Coronavirus Disease 2019 (COVID-19) [1]; the number of patients in intensive care units (ICU) reached a peak on April 3, with 971 hospitalizations, putting a strain on hospitals and health care workers [2].

* Corresponding author at: Département de Pneumologie, Hôpital de Brabois, CHRU Nancy, 54500 Vandœuvre- lès-Nancy, France.
E-mail address: s.valentin@chru-nancy.fr (S. Valentin).
[1] Both authors contributed equally.

SARS-CoV-2 infection has a particular respiratory tropism and may lead to severe viral pneumonia and potentially acute respiratory distress syndrome (ARDS). Thus far, various epidemiological studies have suggested that underlying cardiovascular diseases are a risk factor for critical form of COVID-19 and in-hospital death [3,4]. The underlying pathophysiological mechanisms are currently not fully understood. However, data in the literature on the clinical and epidemiological characteristics of patients with chronic respiratory disease (CRD) affected by severe form of COVID-19 are scarce and controversial. In China, Guan *et al.*, reports 6.1% of severe forms among 1099 hospitalized patients with only 12 patients (1,1%) who had chronic obstructive pulmonary disease (COPD) [5]. In New York, Petrilli *et al.* identified 453 patients with asthma or COPD hospitalized with COVID-19. Asthma or COPD did not appear as a risk factor for a critical illness [6]. Conversely, a recent meta-analysis of 3027 patients showed that smoking patients and patients suffering from respiratory diseases may be at a higher risk of progressing to a severe form of the disease [4]. Also, patients with interstitial lung diseases (ILD) seems to be at increased risk of death from COVID-19 [7].

Viral respiratory infection can trigger respiratory symptoms (dyspnea, cough, sputum) and lead to exacerbations of CRD [8,9]. We hypothesized that patients with chronic respiratory disease mainly consisting of asthma and COPD infected with SARS-CoV-2 do not or less frequently present with an inappropriate inflammatory response that can lead to critical forms of COVID-19 and potentially to death [10,11].

To our knowledge, no study has specifically evaluated the prevalence of critical forms of COVID-19 among patients with CRD (including COPD, asthma, bronchiectasis, ILD, pulmonary arterial hypertension (PAH), cystic fibrosis and obesity hypoventilation syndrome (OHS)) hospitalized for COVID-19. The main objective was to compare the risk of developing a severe form of the disease on COVID-19 ward admission of patients with CRD versus patients without CRD. Secondly, we sought to describe potential risk factors of severe forms of COVID-19 and clinical course of SARS-CoV-2 infection of these patients having CRD.

Material and methods

Study oversight

This multicentric retrospective study was conducted at the Nancy-Brabois university hospital (center 1) and the Metz-Thionville regional hospital (center 2) from March 15, 2020 to June 30, 2020. All patients were first admitted to the emergency department and tested for SARS-CoV-2 infection. In both centers, in case of major hypoxaemia (requirement to $FiO_2 > 50\%$), patients were admitted to ICU. Patients refused to ICU admission and patients with milder hypoxaemia were admitted to dedicated COVID-19 wards and constitutes our study population. Ambulatory patients screened in the emergency department who did not present symptoms requiring hospitalization were not reported in our study.

All adult patients hospitalized in COVID-19 wards to both hospitals during this period with a confirmed diagnosis of SARS-CoV-2 infection with respiratory symptoms were included. Diagnosis of SARS-CoV-2 infection was made by a positive reverse transcriptase polymerase chain reaction (RT-PCR) on nasopharyngeal swab and/or chest computed tomography (CT) with typical abnormalities, as described by the Fleischner Society [12]. Clinical and biological outcomes were monitored up to the discharge of the patient. Patients received written information. All data were collected into an anonymous computerized database registered to the National Commission on Informatics and Liberty (n° 2020PI081). The study design has been registered on *ClinicalTrials* (NCT04407169).

Data collection

Epidemiological, clinical, biological and radiological data were collected from electronic medical records. Background treatments with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB II) were also identified.

Clinical data (body temperature, heart rate, pulse oxygen saturation, arterial blood pressure) were collected on admission to hospital. Time to hospitalization from symptom onset was recorded. In case of a transfer to an intensive care unit during hospitalization, time to invasive ventilation were collected.

Regarding chest computed tomography (CT), the severity of the parenchymal involvement was assessed by a radiologist, according to the percentage of ground-glass extension (less than 25%, 25 to 50%, 50 to 75% and more than 75%) in both centers. Specific treatments implemented during hospitalization were notified (remdesivir, hydroxychloroquine, lopinavir plus ritonavir, steroids, interferon). The in-hospital complications such as bacterial infection or venous thromboembolic disease were collected during the entire hospitalization. In-hospital death, in-ICU death, lengths of stay in ICU and in hospital were assessed at discharge. Specific data about patients with CRD were collected: lung function tests, respiratory treatment (systemic or inhaled corticosteroids, bronchodilators), long-term oxygen therapy, home mechanical ventilation and CPAP therapy. The severity of the disease was assessed by the GOLD classification for COPD and GINA for asthmatic patients. All the definitions used to characterize CRD are available in the online data supplement.

Study outcomes

The primary end point was a score on the World Health Organization Clinical Progression Scale equal or greater than six during hospitalization defining a severe form of COVID-19 [13]. The WHO Clinical Progression Scale provides a harmonized assessment of illness severity, clinical course and progression through the health-care system based on easily obtained data. This scale ranges from zero (uninfected) to ten (dead), a score of six or higher indicates acute respiratory failure requiring mechanical ventilation or high flow oxygen therapy.

Statistical analysis

Categorical variables were described by numbers and percentages, while continuous variables by median and interquartile range [first quartile Q1 - third quartile Q3]. Patients' characteristics were compared between each group (those without any CRD and those with a CRD) using Chi-2 or Fisher's exact test for qualitative variables and Wilcoxon Test for quantitative variables. The characteristics of the patients with CRD associated with severe form of COVID-19 were identified with a bivariate logistic regression model. Variables with a p-value < 0.2 in the bivariable model were eligible for the multivariable model. A stepwise selection procedure was applied to retain significant independent factors. The Kaplan−Meier estimates with 95% confidence intervals (CIs) were calculated to describe survival with the date of admission in the two cohort as the starting point. The significance threshold was set at 5%. Statistical analysis was performed using SAS 9.4 software.

Results

From March 15 to June 30, 2020, 1032 patients were hospitalized in both hospitals in dedicated COVID-19 wards. Finally, 636 patients met our inclusion criteria and 19 refused to participate to the study (Fig. 1). Among the 617 remaining patients, 547 had positive SARS-CoV-2 RT-PCR on nasopharyngeal swab (88.7%) and 70 were diagnosed on the basis of clinical presentation and radiological patterns.
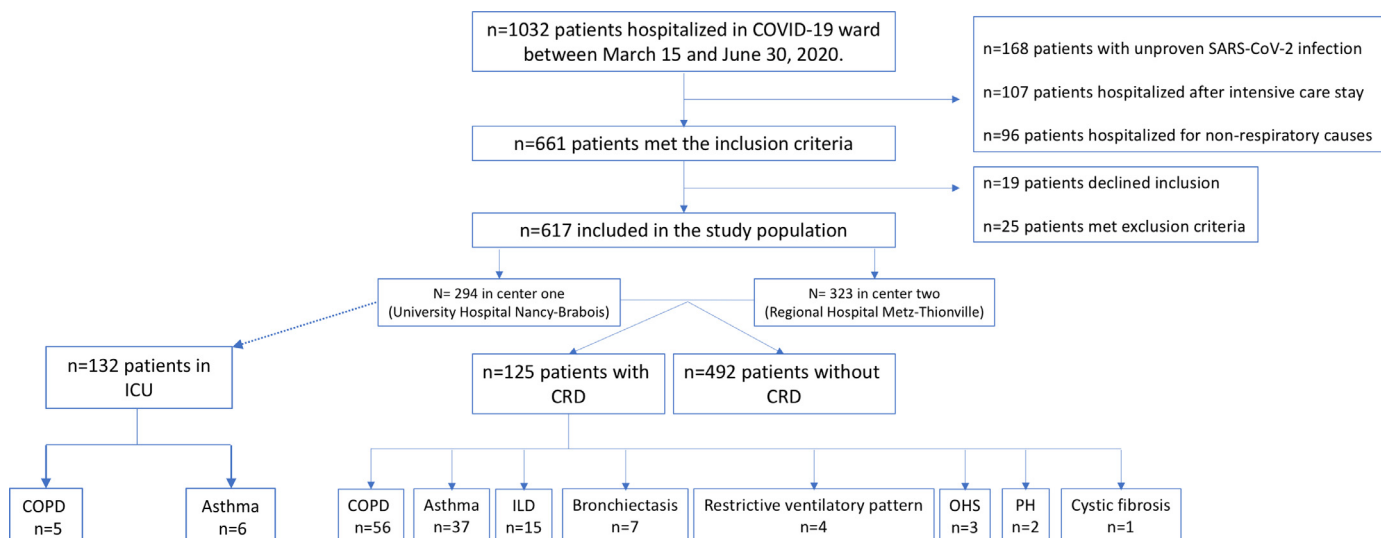
Fig. 1. Flowchart of the study population. COPD: chronic obstructive pulmonary disease; CRD: chronic respiratory disease; ICU: intensive care unit; ILD: interstitial lung disease; OHS: obesity hypoventilation syndrome; PH: pulmonary hypertension; SARS- CoV-2: severe acute respiratory syndrome coronavirus 2.

We identified 125 patients with a chronic respiratory disease, of which the most frequent were COPD (n = 56; 44.8%) and asthma (n = 37; 29.6%). We also reported patients with interstitial lung disease (n = 15; 12%), bronchiectasis (n = 7; 5.6%), OHS (n = 3; 2.4%), PAH (n = 2; 1.6%), cystic fibrosis (n = 1; 0.8%) and other chronic respiratory diseases with restrictive ventilatory pattern (n = 4; 3.2%).

Clinical characteristics

Characteristics of the study population on admission are detailed in Table 1. The median age was 72 (interquartile range (IQR) [58−84] years) years, 330 (53.5%) were men and the median BMI was 26.3 kg/m^2 [23.5−30.9]. The most frequent comorbidities were systemic
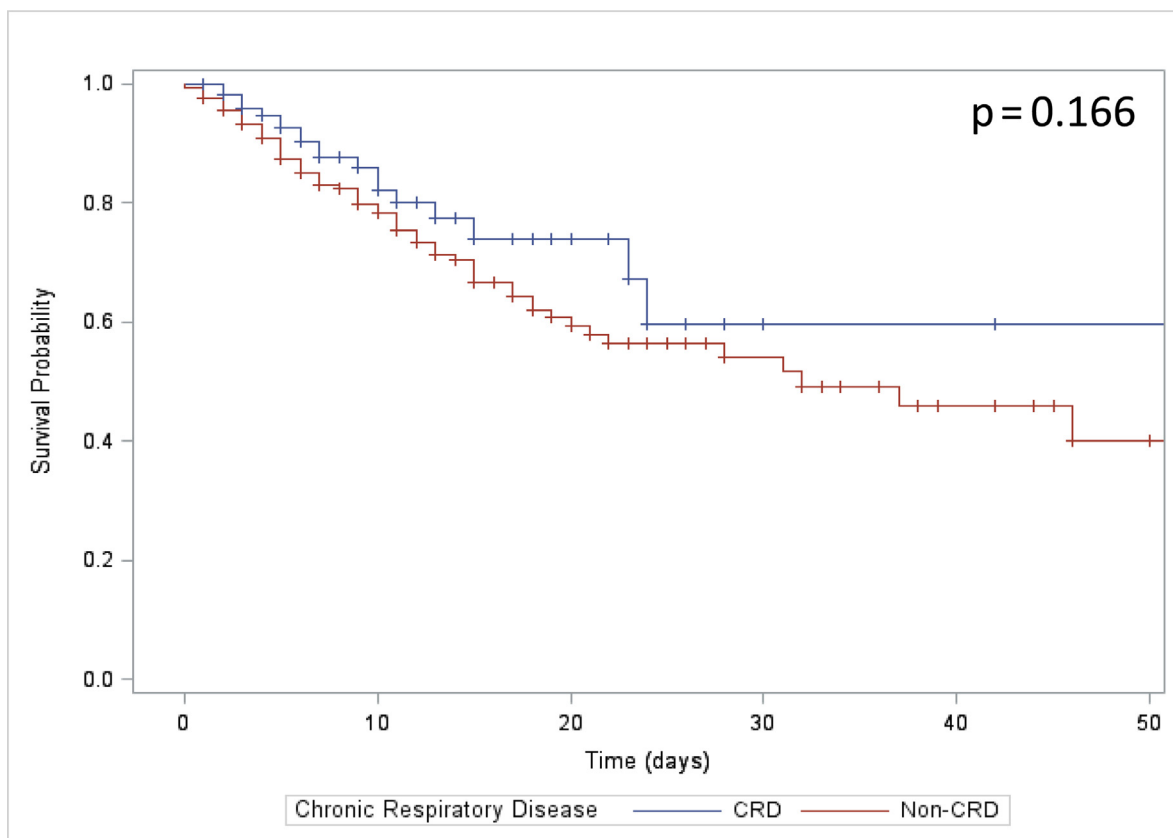

Fig. 2. Comparison of survival rates between patients with chronic respiratory disease and patients without chronic respiratory disease.

Table 1
Characteristics of included patients on admission.

Demographic data	Patients with CRD (n = 125)		Patients without CRD (n = 492)		p
Age, years	n = 125	72 [60−83]	n = 492	71 [58−84]	0.711
Male sex, n (%)	n = 125	65 (52)	n = 492	265 (53.9)	0.709
BMI, kg/m^2	n = 118	26.4 [23.1−30.9]	n = 418	26.3 [23.5−30.9]	0.693
Smoker or ex-smoker, n (%)	n = 103	65 (63.1)	n = 310	127 (41)	<0.0001
Smoking history, pack-years	n = 45	30 [19-50]	n = 87	30 [15−40]	0.203
Comorbidities					
Systemic arterial hypertension, n (%)	n = 125	75 (60)	n = 492	267 (54.3)	0.250
Diabetes mellitus, n (%)		34 (27.2)		111 (22.6)	0.275
Coronary heart disease, n (%)		21 (16.8)		64 (13)	0.272
Neurovascular disease, n (%)		15 (12)		43 (8.8)	0.271
Cancer, n (%)		20 (16)		45 (9.2)	0.026
Chronic renal failure, n (%)		14 (11.2)		46 (9.3)	0.533
Obstructive sleep apnea, n (%)		28 (22.4)		30 (6.1)	<0.0001
Immunodeficiency, n (%)		15 (12)		47 (9.6)	0.421
Routine treatments					
ACE inhibitor, n (%)	n = 125	22 (17.6)	n = 491	81 (16.5)	0.768
ARB, n (%)		24 (19.4)		81 (16.5)	0.450
Immunosuppressant drug, n (%)		12 (9.6)		44 (9)	0.824

Values are expressed as median [IQR] or as number and frequency. n: available data.
BMI: body mass index; ACE inhibitor: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blockers.

hypertension (55.4%), diabetes mellitus (23.5%) and coronary heart disease (13.8%). Obstructive sleep apnea syndrome was reported in 58 (9.4%) patients. Patients with CRD were more frequently smokers or former smokers (63.1% versus 41.0%, p<0.0001). There were no differences between patients with CRD and patients without CRD concerning age, sex and BMI. Vital signs (body temperature, heart rate, arterial blood pressure) were similar between the two groups (Table 2). Patients with CRD had a significantly reduced time period between the onset of symptoms and admission to hospital (median 5 days [3−8] versus 7 days [4−9], p = 0.013). Patients hospitalized in

center two were slightly older (73 years old [60−85] versus 70.5 [55 −83], p = 0.021) and there was a higher percentage of asthmatic patients, among patients with CRD, in center one (38.8% versus 19.0%, p = 0.015). Differences between the two centers are shown in table S1.

Among COPD patients seen in both centers (n = 56), median age was 73.5 [63.5−83.5], with a majority of men (62.5%). Previous lung function tests were available in 32 patients (57%). Median forced expiratory volume in one second (FEV$_1$) was 61.0 [45.5−71.5]% of predicted values. Median forced vital capacity (FVC) was 85 [73−91]%

Table 2
Comparison of clinical features, biological and radiological data on admission between patients with chronic respiratory diseases and patients without chronic respiratory diseases.

Clinical features	Patients with CRD (n = 125)		Patients without CRD (n = 492)		p
Mean arterial blood pressure, mmHg	n = 125	92 [82−100]	n = 489	92 [83−101]	0.832
Heart rate, beats.min^{-1}	n = 125	85 [75−98]	n = 489	84 [73−95]	0.337
Pulse oxygen saturation,%	n = 125	95 [94−97]	n = 490	95 [93−97]	0.598
Body temperature> 38 °C, n (%)	n = 125	31 (24.8)	n = 489	134 (27.4)	0.558
Time since onset of symptoms, days	n = 104	5 [3−8]	n = 429	7 [4−9]	0.013
Biological data					
Leukocytes, G.L^{-1}	n = 125	6.4 [5.1−10.2]	n = 486	6.5 [4.9−9]	0.474
Lymphocytes, G.L^{-1}	n = 117	1.0 [0.6−1.4]	n = 455	0.9 [0.6−1.3]	0.113
CRP, mg.L^{-1}	n = 122	63.5 [23−142]	n = 479	90 [42−146]	0.008
PCT, ng.mL^{-1}	n = 80	0.1 [0.1−0.3]	n = 305	0.2 [0.1−0.4]	0.106
Troponin, pg.mL^{-1}	n = 55	9 [3−30]	n = 215	12 [5.6−40]	0.081
CPK, IU.L^{-1}	n = 24	121 [64.5−191.5]	n = 79	149 [54−502]	0.332
D-Dimers, μg.L^{-1}	n = 35	1146 [628−2060]	n = 138	1363.5 [851−2644]	0.233
LDH, IU.L^{-1}	n = 45	233 [194−302]	n = 164	310 [245−391.5]	0.0003
ASAT, IU.L^{-1}	n = 115	30 [22-52]	n = 457	43 [29−63]	<0.0001
ALAT, IU.L^{-1}	n = 114	22.5 [15−38]	n = 456	28.5 [18−50]	0.003
Creatinine, μmol.L^{-1}	n = 124	73.5 [59−97]	n = 480	79 [60−103.5]	0.427
SOFA score	n = 99	2 [2−3]	n = 380	3 [2−4]	0.039
PaO$_2$ on room air, mmHg	n = 45	63 [59−73]	n = 168	62 [57−69]	0.244
PaCO$_2$ on room air, mmHg	n = 45	36 [32−39]	n = 168	34 [31−36]	0.012
Radiologic data					
CT scan on admission, n (%)	n = 125	96 (76.8)	n = 491	382 (77.8)	0.811
Ground-glass extension	n = 65		n = 301		
<25%, n (%)		41 (63.1)		128 (42.4)	0.002
25−50%, n (%)		17 (26.2)		121 (40.2)	0.034
50−75%, n (%)		6 (9.2)		46 (15)	0.227
>75%, n (%)		1 (1.5)		10 (3.3)	0.445

Values are expressed as median [IQR] or as number and frequency. n: available data. n: population size.
CRP: C-Reactive protein, PCT: procalcitonin, CPK: creatine phosphokinase, LDH: lactate dehydrogenase, ALAT: alanine aminotransferase, ASAT: aspartate aminotransferase.

of predicted values with a median FEV_1/FVC ratio of 60 [45.5−65.5]%. Among them, 4 (12.5%) had mild COPD ($FEV_1 \geq 80\%$ predicted), 19 (59.4%) had moderate COPD ($50\% \leq FEV_1 < 80\%$) and 9 (28.1%) had severe COPD ($FEV_1 < 50\%$). Three patients were treated with long-term oxygen therapy and two were on non-invasive home ventilation (NIV) for chronic respiratory failure. Concerning asthmatic patients, seven patients (18.9%) had lung function data available. Median FEV_1 was 89 [68−108]% of predicted values with a median FEV_1/FVC ratio of 69.5 [58−84]%. None of them were GINA step 5 and none were receiving maintenance systemic corticosteroids nor biologics.

Radiological and laboratory test findings on admission

Overall, chest CT was carried out within the first 48 h of hospitalization in 478 patients (77.6%) (Table 2). The majority (n = 366, 76.6%) had typical bilateral multiple ground glass opacities or consolidations with a standardized evaluation of extension. More patients with CRD had ground-glass extension below 25% (63.1% versus 42.4%; p = 0.002) compared to patients without CRD. Occurrence of pulmonary embolism has not been systematically investigated.

Patients with CRD had a moderate inflammatory syndrome with significantly lower CRP and LDH compared to patients without CRD (CRP: 63.5 mg/L [23−142] versus 90 [42−146], p = 0.008; LDH: 233 UI/L [194−302] versus 311 [245−392], p = 0.0003). However, there was no difference concerning levels of troponin (p = 0.081) nor D-dimers (p = 0.233).

On admission, arterial blood gas while breathing room air was reported in 168 (34%) patients without CRD and 45 (36%) with CRD. While there is no difference concerning hypoxaemia (PaO_2: 63 mmHg [59−73] versus 62 mmHg [57−69], p = 0.244), we found a lower pH (7.4 [7.4−7.5] versus 7.5 [7.4−7.5], p = 0.003) and higher $PaCO_2$ (36 mmHg [32−39] versus 34 mmHg [31−36], p = 0.013) in patients with CRD.

Treatments and complications

Across all patients hospitalized for COVID-19, 115 patients received treatments including lopinavir/ritonavir (n = 48; 7.8%), steroids (n = 41; 6.7%), interferon (n = 11; 1.8%), hydroxychloroquine (n = 9; 1.5%) or remdesivir (n = 6; 1%). Patients with CRD were treated, during hospitalization, more frequently with inhaled corticosteroids (3.2% vs 0.2%; p = 0.007), bronchodilators (40.8% vs 1.2%, p<0.0001) and antibiotics (64.8% vs 52.4%, p = 0.013).

The most frequent in-hospital complications were hepatic cytolysis (ALAT or ASAT > 2 ULN) (60%), acute renal injury (Kidney Disease Improving Global Outcomes stage 1 or higher) (25.8%), bacterial pulmonary infection (8.3%) and venous thromboembolism (4.4%). The only difference between the two groups was a more frequent hepatic cytolysis among patients without CRD (55.6% versus 34.8%, p<0.0001) (data not shown).

Outcomes

The percentage of patients scoring 6 or higher on the WHO Clinical Progression Scale during hospital stay was lower in patients with CRD compared to those without CRD with 27 patients (21.6%) compared to 154 (31.3%), respectively (p = 0.03) (Table 3).

Results of the univariate analysis which determines the relation between reaching a score of 6 or above and covariates among CRD patients are shown in Table 4. Then, a multivariate logistic analysis was performed including all covariates associated with a severe form of COVID-19 among CRD patients in the bivariate analysis (Table 5). Among CRD patients, age, temperature above 38 °C on admission, lymphopenia below 1 G/L and CPAP therapy (*i.e.,* before admission) were independently associated with an increased risk of severe form of COVID-19. The same analysis was performed among patients without CRD, age and fever above 38 °C remained significantly associated in the multivariate analysis. Conversely, in this latter group of patients, lymphopenia on admission was not associated with a risk of progression to a severe form of COVID-19 (data shown in table S2).

Length of hospital stay was similar between the two groups: 8 days [5−12] in patients without CRD versus 8 days [5−13] in patients with CRD, (p = 0.720). Overall, there were no significant difference between patients with and without CRD in mortality rates (Fig. 2). In addition, there was also no differences in mortality rates between patients with and without CRD among patients who developed a severe form of COVID-19 (p = 0.90).

Discussion

In this study, we report baseline characteristics, laboratory and radiological data, and clinical course of adults diagnosed with COVID-19 admitted to two hospitals in the Great East region outside ICU during the first pandemic wave, with a particular focus on patients with CRD. Among hospitalized patients outside ICU, prevalence of severe form of COVID-19 was significantly lower in patients with CRD.

The population in this cohort consisted mostly of men (53.5%), overweight with multiples co-morbidities, especially cardiovascular, in conjunction with previous studies. The age of our population (median 72 years old and 62% of patients older than 65) is slightly higher than that reported in previous studies but the comorbidities identified are similar [5,6,14−16]. Also, the most common laboratory test findings on admission were lymphopenia, hepatic cytolysis, and a moderate inflammatory syndrome. The study of chest CT's showed that extent of ground glass opacification was moderate (below 50%) for the majority of patients (83.3%), especially in patients with CRD.

Median time from symptom onset to hospitalization was significantly lower among patients with CRD. Early hospitalization during SARS-CoV-2 infection in patients with CRD could be explained by faster onset of respiratory symptoms in these patients. However, we cannot exclude that earlier hospitalization in patients with CRD may be due to easier access to care in patients with respiratory vulnerability.

Table 3
Outcomes in patients with chronic respiratory disease and patients without chronic respiratory disease.

Outcomes	Patients with CRD (n = 125)		Patients without CRD (n = 492)		p
WHO scale ≥ 6, n (%)	n = 125	27 (21.6)	n = 492	154 (31.3)	0.033
Length of hospital stay, days	n = 125	8 [5−13]	n = 492	8 [5−12]	0.720
Length of ICU stay, days	n = 11	11 [8−19]	n = 65	11 [4−19]	0.718
In-hospital death, n (%)	n = 125	18 (14.4)	n = 492	93 (18.9)	0.242
In-ICU death, n (%)	n = 125	3 (2.4)	n = 492	16 (3.3)	0.622
Hospital discharge, n (%)	n = 125	77 (61.6)	n = 492	283 (57.5)	0.409

Values are expressed as median [IQR] or as number and frequency. n: available data. n: population size.
ICU: intensive care unit; WHO scale: World health organization progression scale.

Table 4

Univariate analysis of risk factors and severe form of COVID-19 among patients with chronic respiratory disease.

Outcomes	Severe form of COVID-19 ($n = 27$)		Non-severe form of COVID-19 ($n = 98$)		p
Age, years	$n = 27$	75 [63–86]	$n = 98$	70 [54–82]	0.049
Diabetes mellitus, n (%)	$n = 27$	13 (48,1)	$n = 98$	21 (21,4)	0.006
Coronary heart disease, n (%)	$n = 27$	10 (37)	$n = 98$	11 (11.2)	0.003
Long-term oxygen therapy, n (%)	$n = 27$	4 (14.8)	$n = 98$	3 (3.1)	0.039
CPAP, n (%)	$n = 26$	7 (26.9)	$n = 97$	11 (11.3)	0.046
Body temperature > 38 °C, yes	$n = 27$	16 (59.3)	$n = 98$	15 (15.3)	< 0.0001
Pulse oxygen saturation,%	$n = 27$	94 [93–96]	$n = 98$	95 [94–97]	0.008
Leukocytes, $G.L^{-1}$	$n = 27$	5.2 [4–8.8]	$n = 98$	6.8 [5.4–10.4]	0.009
Lymphocytes <1 $G.L^{-1}$, yes	$n = 25$	20 (80)	$n = 92$	40 (43.5)	0.001
Platelets, $G.L^{-1}$	$n = 27$	174 [126–271]	$n = 97$	218 [174–299]	0.017
C-reactive protein, $mg.L^{-1}$	$n = 25$	114 [60–142]	$n = 97$	44 [19-134]	0.029
Troponin, $pg.mL^{-1}$	$n = 11$	16 [9.7–33]	$n = 44$	6.9 [3–23.5]	0.042
ASAT, $IU.L^{-1}$	$n = 25$	43 [27–67]	$n = 90$	27 [21-44]	0.039
Creatinine, $\mu mol.L^{-1}$	$n = 27$	92 [78–142]	$n = 97$	67 [55–90]	0.0005
SOFA score	$n = 23$	3 [2–5]	$n = 76$	2 [1.5–3]	0.015

Values are expressed as median [IQR] or as number and frequency. n: available data. n: population size.
CPAP: continuous positive airway pressure, ASAT: aspartate aminotransferase, SOFA: Sepsis-related Organ Failure Assessment.

Among our study population, 125 patients (20.3%) admitted to COVID-19 ward were affected by a CRD. COPD was the most frequent condition identified with a prevalence of 9.1%, quite similar to the most recent estimated prevalence of COPD in France (8.4%) [17]. Our results are consistent with data from other cohorts of hospitalized patients with COVID-19. In China, the prevalence of COPD among hospitalized COVID-19 patients has ranged from 0 to 10%, in New York City from 2.4 to 14% and in Italy from 5.6 to 9.2% [18]. Asthma was the second most frequent condition reported in our population (5.9%). In previous studies, prevalence of asthma among hospitalized COVID-19 patients range from 0% [19] to 12.5% [20]. In line with our results, a recent French study found a 4.2% rate of asthma among COVID-19 ward hospitalized patients [21]. In 2018 in France, prevalence of asthma was 6.4% among adults [22].

It is then striking that CRD are not over-represented among these patients despite the well-established respiratory tropism of COVID-19, compared to the high prevalence of cardiovascular risk factors (diabetes mellitus, systemic arterial hypertension) [23]. Number of factors could explain this observation. First, due to person-to-person transmission of the virus, physical distancing is essential to avoid infection. Patients with CRD may be more accustomed to distancing measures suggesting that their behavior could have protected them against contamination with SARS-CoV-2. Second, the role of the renin-angiotensin-aldosterone system has been highlighted due to the ability of the virus to establish itself in the host through the use of ACE-2 receptor [24]. In asthmatics, reduced number of ACE-2 gene expression in airway cells may decrease susceptibility to infection [25]. Inhaled corticosteroids use is also associated with a decreased expression of ACE-2 gene in sputum cells [26]. By contrast, Leung et al. [27] demonstrated an up-regulation of ACE-2 in lower airways in COPD and current smokers. In our study, seven (12.5%) patients with COPD were current smokers: smoking status was not associated with a risk of developing a severe form of COVID-19. Third, inhaled treatments could have a protective effect by modifying pulmonary immune response [28]. In vitro, Matsuyama et al. [29] demonstrated the suppression of coronavirus replication by ciclesonide, an inhaled corticosteroid. Budesonide combined with glycopyrronium and formoterol is able to inhibit the production of cytokines in cells exposed to HCoV-229E, another human coronavirus [30]. Whether use of inhaled corticosteroids protects against SARS-CoV-2 infection is still unknown and ongoing clinical trials are evaluating them as a therapeutic intervention [31,32].

Inappropriate inflammatory response seem to be the main cause of acute respiratory distress syndrome, leading to severe form of COVID-19 [33,34]. In our population, patients hospitalized for COVID-19 in dedicated ward with CRD have a significantly lower risk of developing a severe form of COVID-19 than patients without CRD. This observation could reflect that patients with CRD may be more frequently hospitalized than other patients for a pattern of viral pneumonia due to their greater respiratory vulnerability but developing an important inflammatory response less frequently than in other populations. Interestingly, we observed a significant lower inflammatory syndrome and lower lactate dehydrogenase level on admission in patients with CRD, possibly due to lower inflammatory systemic response to the infection or earlier hospitalization. Among them, fever on admission and lymphopenia were associated with higher risk of severe form of COVID-19. However, there were no differences concerning troponin and D-dimers, two major prognostic factors [35,36]. The impact of airway epithelium and alveolar immune cells on the lack of inappropriate inflammatory response to SARS-CoV-2 infection, among patients with CRD remains to be clarified [37]. CPAP therapy was also associated with an increased risk of critical form, possibly due to the association of severe obstructive sleep apnea to metabolic dysfunction, cardiovascular diseases and systemic inflammation [38].

Due to a very heterogeneous study population in terms of CRD, we decided to perform subgroup analyses with a focus on patients with asthma or COPD ($n = 93$). Thus, 20 patients (21.5%) with asthma or COPD had a score greater than or equal to six versus 154 patients (31.3%) without CRD. The full results of this subgroup analysis are available in the supplement (tables S3-S6, figure S2). These results suggest that this group of patients with asthma or COPD follow the same trend as the general study population (*i.e.*, prevalence of severe form of COVID-19 significantly lower in patients with CRD).

Table 5

Multivariate logistic regression analysis among patients with chronic respiratory disease.

	Events /Available obs.	Odds ratio (95% CI)	p
Body temperature > 38 °C, yes	13 / 25	16.88 (4.01–71)	0.0001
Lymphocytes < 1 G/L, yes	18 / 56	5.08 (1.25–20.72)	0.030
Age (per 1 y.o. inc.)	22 / 110	1.09 (1.02–1.16)	0.0071
CPAP therapy, yes	7 / 17	4.46 (1.04–19.17)	0.0443

Events: score of 6 or above on the WHO Clinical Progression Scale; available obs.: available observation. Inc: increment.

Despite the large cohort of patients included from two different centers and the standardized assessment of clinical course by WHO Clinical Progression Scale, our study has limitations. Severe forms of COVID-19 directly admitted to ICU could not be included. There is a possible higher prevalence of CRD patients in ICU but previous studies do not support this assumption [14,39]. Furthermore, our data are retrospective and concerns the first pandemic wave. Since then, management of COVID-19 has evolved with more frequent use of high-flow oxygen therapy, non-invasive ventilation or corticosteroid therapy, that may change the course of the disease [40,41]. It is important to note that most patients with CRD included had, prior to admission, mild to moderate chronic respiratory impairment. However, the most severe patients and in particular patients with severe COPD (FEV_1 <50%) did not develop severe form of COVID-19. Thus, there appears to be no relationship between the severity of the underlying CRD and the risk of developing a severe form of COVID-19. As our population is made up of a large majority of patients with chronic obstructive pulmonary disease and asthma (74.4%), results of our study are relevant to this population. Dedicated studies are needed to assess the risk of progression to severe form of COVID-19 among patients with other CRD.

In conclusion, our study is the first to demonstrate lower prevalence of severe form of COVID-19 among hospitalized patients in COVID-19 ward with CRD. Despite heterogeneous conditions (mainly patients with COPD and asthma), patients hospitalized in COVID-19 ward with CRD seem less likely to develop an inappropriate immune response leading to acute respiratory distress syndrome, directly affecting clinical practices. Age, fever on admission, lymphopenia and CPAP therapy should be systematically kept in mind in patients with CRD since this characteristic could help identify patients at risk of developing a severe form of COVID-19. Further in vitro and in vivo studies are needed to better understand the underlying pathophysiological mechanism of SARS-CoV-2 infection in patients with CRD.

Author's contribution

SB: Conceptualization, – Data curation, – Formal analysis, – Investigation, – Methodology, – Project administration, – Resources, – Software, – Supervision, – Validation, – Visualization, – Writing – original draft, – Writing – review & editing. SV: Conceptualization, – Data curation, – Formal analysis, – Investigation, – Methodology, – Project administration, – Resources, – Software, – Supervision, – Validation, – Visualization, – Writing – original draft, – Writing – review & editing. AM: Conceptualization- Investigation, – Methodology, – Project administration, – Resources,- Visualization, – Writing – original draft, – Writing – review & editing. MP: Conceptualization- Investigation, – Methodology, – Project administration, – Resources,- Visualization, – Writing – original draft, – Writing – review & editing. BP: Conceptualization- Investigation, – Methodology, – Project administration, – Resources,- Visualization, – Writing – original draft, – Writing – review & editing. AB: Conceptualization- Investigation, – Methodology, – Project administration, – Resources,- Visualization, – Writing – original draft, – Writing – review & editing. GP: Conceptualization- Investigation, – Methodology, – Project administration, – Resources,- Visualization, – Writing – original draft, – Writing – review & editing. CR: Conceptualization- Investigation, – Methodology, – Project administration, – Resources,- Visualization, – Writing – original draft, – Writing – review & editing. CB: Conceptualization- Investigation, – Methodology, – Project administration, – Resources,- Visualization, – Writing – original draft, – Writing – review & editing. AL: Conceptualization- Investigation, – Methodology, – Project administration, – Resources,- Visualization, – Writing – original draft, – Writing – review & editing. JS: Conceptualization- Investigation, – Methodology, – Project administration, – Resources,- Visualization, – Writing – original draft, – Writing – review & editing. FC: Conceptualization- Investigation, –

Methodology, – Project administration, – Resources,- Visualization, – Writing – original draft, – Writing – review & editing. AC:Conceptualization, – Data curation, – Formal analysis, – Investigation, – Methodology, – Project administration, – Resources, – Software, – Supervision, – Validation, – Visualization, – Writing – original draft, – Writing – review & editing.

Summary of the "take home" message

COVID-19 ward hospital admission for COVID-19 in patients with chronic respiratory disease (especially chronic obstructive pulmonary disease and asthma) seem to be at reduced risk to develop an acute respiratory distress syndrome than other populations.

Support: none

Declaration of Competing interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.resmer.2021.100880.

References

[1] xxx Communique Coronavirus covid 19 – point de situation en Grand 2021 Est 03 04 20.pdf
[2] xxx 2021 CP_Coronavirus_GrandEst_120420.pdf
[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.
[4] Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. J Infect 2020;81(2) e16-25.
[5] Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708-20.
[6] Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, 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.
[7] Drake TM, Docherty AB, Harrison EM, Quint JK, Adamali H, Agnew S, et al. Outcome of hospitalization for COVID-19 in patients with interstitial lung disease. An International Multicenter Study. Am J Respir Crit Care Med 2020;202(12):1656-65.
[8] Castillo JR, Peters SP, Busse WW. Asthma exacerbations: pathogenesis, prevention, and treatment. J Allergy Clin Immunol Pract 2017;5(4):918-27.
[9] Wedzicha JA, Seemungal TAR. COPD exacerbations: defining their cause and prevention. Lancet 2007;370(9589):786-96.
[10] Blanco-Melo D, Nilsson-Payant BE, Liu W-C, Uhl S, Hoagland D, Møller R, et al. Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. Cell 2020;181(5) 1036−1045.e9.
[11] Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 cytokine storm; what we know so far. Front Immunol 2020;11:1446.
[12] Rubin GD, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, et al. The role of chest imaging in patient management during the COVID-19 pandemic: a multinational consensus statement from the Fleischner Society. Chest 2020;158(1):106-16.
[13] WHO. Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis 2020;20(8) e192-7.
[14] Argenziano MG, Bruce SL, Slater CL, Tiao JR, Baldwin MR, Barr RG, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. BMJ 2020;369:m1996.
[15] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. China. Lancet. 2020;395(10223):497-506.
[16] Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. JAMA 2020;323(14):1335.
[17] Burgel P-R, Laurendeau C, Raherison C, Fuhrman C, Roche N. An attempt at modeling COPD epidemiological trends in France. Respir Res 2018;19(1):130.
[18] Leung JM, Niikura M, Yang CWT, Sin DD. COVID-19 and COPD. Eur Respir J 2020;56(2):2002108.
[19] Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020 NEJMoa2002032.
[20] Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical characteristics of Covid-19 in New York City. N Engl J Med 2020;382(24):2372-4.

[21] Beurnier A, Jutant E-M, Jevnikar M, Boucly A, Pichon J, Preda M, et al. Characteristics and outcomes of asthmatic patients with COVID-19 pneumonia who require hospitalisation. Eur Respirat J 2020;56(5) [cité 13 nov 2020]Disponible sur https://erj.ersjournals.com/content/56/5/2001875.

[22] Raherison-Semjen C, Izadifar A, Russier M, Rolland C, Aubert JP, Sellami R, et al. Prévalence et prise en charge de l'asthme de l'adulte en France en 2018 : enquête ASTHMAPOP. Rev Maladies Respir 2019;36:A7.

[23] Halpin DMG, Faner R, Sibila O, Badia JR, Agusti A. Do chronic respiratory diseases or their treatment affect the risk of SARS-CoV-2 infection? Lancet Respirat Med 2020:S2213260020301673.

[24] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2) 271−280.e8.

[25] Jackson DJ, Busse WW, Bacharier LB, Kattan M, O'Connor GT, Wood RA, et al. Association of respiratory allergy, asthma, and expression of the SARS-CoV-2 receptor ACE2. J Allergy Clin Immunol 2020;146(1) 203−206.e3.

[26] Peters MC, Sajuthi S, Deford P, Christenson S, Rios CL, Montgomery MT, et al. COVID-19-related genes in sputum cells in asthma. Relationship to demographic features and corticosteroids. Am J Respir Crit Care Med. 2020;202(1):83-90.

[27] Leung JM, Yang CX, Tam A, Shaipanich T, Hackett T-L, Singhera GK, et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. Eur Respir J 2020;55(5):2000688.

[28] xxx Inhaled corticosteroids and COVID-19: a systematic review and clinical perspective European Respiratory Society [Internet]. [cité 7 déc 2020]. Disponible sur: https://erj.ersjournals.com/content/early/2020/04/20/13993003.01009-2020

[29] Matsuyama S, Kawase M, Nao N, Shirato K, Ujike M, Kamitani W, et al. The inhaled corticosteroid ciclesonide blocks coronavirus RNA replication by targeting viral NSP15 [Internet]. Microbiology 2020 mars [cité 14 déc 2020]. Disponible sur http://biorxiv.org/lookup/doi/10.1101/2020.03.11.987016.

[30] Yamaya M, Nishimura H, Deng X, Sugawara M, Watanabe O, Nomura K, et al. Inhibitory effects of glycopyrronium, formoterol, and budesonide on coronavirus HCoV-229E replication and cytokine production by primary cultures of human nasal and tracheal epithelial cells. Respir Investig 2020;58 (3):155-68.

[31] xxx. Assistance Publique − Hôpitaux de Paris. Protective role of inhaled steroids for Covid-19 infection [Internet]. clinicaltrials.govsept [cité 30 déc 2020]. Report No.: NCT04331054. Disponible sur: https://clinicaltrials.gov/ct2/show/NCT04331054.

[32] Kim WJ. A trial of ciclesonide to assess the antiviral effect for adults with mild-to-moderate COVID-19. [Internet]. clinicaltrials.govsept [cité 30 déc 2020]. Report No.: NCT04330586. Disponible sur: https://clinicaltrials.gov/ct2/show/NCT04330586.

[33] Blanco-Melo D, Nilsson-Payant BE, Liu W-C, Uhl S, Hoagland D, Møller R, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell 2020;181(5) 1036−1045.e9.

[34] McElvaney OJ, McEvoy NL, McElvaney OF, Carroll TP, Murphy MP, Dunlea DM, et al. Characterization of the inflammatory response to severe COVID-19 illness. Am J Respir Crit Care Med 2020;202(6):812-21.

[35] Mouhat B, Besutti M, Bouiller K, Grillet F, Monnin C, Ecarnot F, et al. Elevated D-dimers and lack of anticoagulation predict PE in severe COVID-19 patients. Eur Respir J 2020;56(4).

[36] Cordeanu E-M, Duthil N, Severac F, Lambach H, Tousch J, Jambert L, et al. Prognostic value of troponin elevation in COVID-19 hospitalized patients. J Clin Med 2020;9(12).

[37] Vareille M, Kieninger E, Edwards MR, Regamey N. The airway epithelium: soldier in the fight against respiratory viruses. Clin Microbiol Rev 2011;24(1):210-29.

[38] Drager LF, McEvoy RD, Barbe F, Lorenzi-Filho G, Redline S. Sleep Apnea and cardiovascular disease: lessons from recent trials and need for team science. Circulation 2017;136(19):1840-50.

[39] Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: early experience and forecast during an emergency response. JAMA 2020;323(16):1545-6.

[40] Patel M, Gangemi A, Marron R, Chowdhury J, Yousef I, Zheng M, et al. Retrospective analysis of high flow nasal therapy in COVID-19-related moderate-to-severe hypoxaemic respiratory failure. BMJ Open Respir Res 2020;7(1).

[41] Collaborative Group RECOVERY, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19 − preliminary report. N Engl J Med 2020.