Original Article

Asthma and COPD Are Not Risk Factors for ICU Stay and Death in Case of SARS-CoV2 Infection

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What is already known about this topic? Asthmatics and patients with chronic obstructive pulmonary disease (COPD) are at risk of more severe outcomes with common cold virus infections. Prior studies have suggested that allergic diseases, asthma, and COPD may not be risk factors for severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection.

What does this article add to our knowledge? The strength of this study is the characterization of obstructive disease according to lung function testing. In our study, asthma, COPD, and treatment with inhaled corticosteroid (ICS) or oral corticosteroid were not risk factors for admission to the intensive care unit or mortality.

How does this study impact current management guidelines? Our results confirm the recommendations that patients with obstructive airway disease should not decrease the dose of ICS during SARS-CoV2 infection. Asthma and COPD treatments should be pursued and adapted to ensure optimal control of the lung disease throughout the pandemic, potentially reducing the risk of severe coronavirus disease 2019.

BACKGROUND: Asthmatics and patients with chronic obstructive pulmonary disease (COPD) have more severe outcomes with viral infections than people without obstructive disease.

OBJECTIVE: To evaluate if obstructive diseases are risk factors for intensive care unit (ICU) stay and death due to coronavirus disease 2019 (COVID19).

METHODS: We collected data from the electronic medical record from 596 adult patients hospitalized in University Hospital of Liege between March 18 and April 17, 2020, for severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection. We classified patients into 3 groups according to the underlying respiratory disease, present before the COVID19 pandemic.

RESULTS: Among patients requiring hospitalization for COVID19, asthma and COPD accounted for 9.6% and 7.7%, respectively. The proportions of asthmatics, patients with COPD, and patients without obstructive airway disease hospitalized in the ICU were 17.5%, 19.6%, and 14%, respectively. One-third of patients with COPD died during hospitalization, whereas only 7.0% of asthmatics and 13.6% of patients without airway obstruction died due to SARS-CoV2. The multivariate analysis showed that asthma, COPD, inhaled corticosteroid treatment, and oral corticosteroid treatment were not independent risk factors for ICU admission or death. Male gender (odds ratio [OR]: 1.9; 95% confidence interval [CI]: 1.1-3.2) and obesity (OR: 8.5; 95% CI: 5.1-14.1) were predictors of ICU admission, whereas male gender (OR 1.9; 95% CI: 1.1-3.2), older age (OR: 1.9; 95% CI: 1.6-2.3), cardiopathy (OR: 1.8; 95% CI: 1.1-3.1), and immunosuppressive diseases (OR: 3.6; 95% CI: 1.5-8.4) were independent predictors of death.

CONCLUSION: Asthma and COPD are not risk factors for ICU admission and death related to SARS-CoV2 infection. © 2020 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). (J Allergy Clin Immunol Pract 2020;■:■-■)

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Asthmatics and patients with chronic obstructive pulmonary disease (COPD) are at risk of more severe outcomes with common cold virus infections than are people without obstructive lung disease.[1,2] This seems to be partly due to a deficient and delayed innate antiviral immune response in these patients. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) is a new virus that appeared in China in the end of 2019 and is responsible for coronavirus disease 2019 (COVID19). At the beginning of the COVID19 pandemic, respiratory physicians were worried about the vulnerability of patients exhibiting chronic obstructive airway disease in case of SARS-CoV2 infection. It seemed inevitable that patients with airway obstruction were at risk of severe COVID19. In the first publications from Wuhan in China,[3] the prevalence of obstructive diseases in patients with COVID19 was surprisingly lower than that reported in the general population. The authors concluded that allergic diseases, asthma, and COPD were not risk factors for SARS-CoV2 infection. However, they found that older age, high number of comorbidities, and more prominent laboratory abnormalities were associated with severity of disease. It was suggested that chronic pulmonary disease was underdiagnosed in the first studies or that there was a possible protective effect of inhaled corticosteroids (ICS).[4]

Some authors hypothesize that type 2 inflammation may suppress antiviral immunity in the lung[5] and may increase susceptibility to severe COVID19. Suppressing type 2 inflammation with the use of topical steroids might thus restore local antiviral immunity.

Moreover, it has been shown that poor asthma control was a risk factor for greater virus-induced exacerbations severity.[6] Like

H5N1 and H7N9,[7] SARS-CoV2 is responsible for severe lymphopenia. SARS-CoV2-infected patients also presented with eosinopenia, extensive highly hypoxemic interstitial pneumonia, in the most severe cases diffuse lung tissue damage, a cytokine storm leading to acute respiratory distress syndrome requiring intensive care unit (ICU) stay, and mechanical ventilation.

International guidelines currently recommend the use of the same maintenance medication during the pandemic, including a regular treatment with ICS in asthmatics[8-10] or in patients with COPD[11] who are frequent exacerbators with forced expiratory volume in 1 second (FEV$_1$) lower than 50%. Corticosteroids are immunosuppressive drugs and could be deleterious during viral infection. Dong et al,[12] however, previously confirmed the safety of ICS use in patients with COPD.

In our study, we collected data from patients who were hospitalized due to COVID19 and classified them according to their lung status either in a nonobstructive group or in an asthma or COPD group. The aim of the study was to determine if patients with asthma or COPD are at risk of experiencing an ICU admission and death as compared with nonobstructive patients.

METHODS

We collected data from the electronic medical record from 596 adult patients who were hospitalized in University Hospital of Liege between March 18 and April 17, 2020, for COVID19.

Demographic characteristics, maintenance treatments, and comorbidities at baseline were extracted. Subjects were characterized as atopic if they had at least 1 positive specific IgE test (0.35 kU/L; Phadia, Groot-Bijgaarden, Belgium) for at least 1 common aeroallergen (cat, dog, house dust mites, grass pollen, tree pollen, and a mixture of molds). Chronic renal failure was defined as a permanent reduction in glomerular filtration rate <60 mL/min/1.73 m^2. Cardiopathy involved ischemic cardiomyopathy, hypertensive cardiomyopathy, chronic heart failure, cardiomegaly, cardiac hypertrophy, and congestive heart failure. Emphysema and bronchiectasis were defined based on chest computed tomography (CT) according to current guidelines[13,14] and according to lung function testing for emphysema. Immunosuppressive diseases recorded among hospitalized patients were grafts, history of splenectomy, and HIV infection.

We classified patients into 3 groups according to the underlying respiratory disease that was present before COVID19. The diagnosis was done by a pulmonologist according to lung function tests, bronchodilation test, and methacholine concentration provoking a 20% fall in FEV$_1$ if necessary as previously described.[15,16] We distinguished one group with asthmatics, a second group with patients suffering from COPD, and a third group with all patients without a history of obstructive pulmonary disease. The latest lung function tests performed over the last 3 years were reported in patients with asthma and COPD. Symptoms at admission such as dyspnea, chest pain, rhinorrhea, pharyngeal pain, nonproductive and productive cough, diarrhea, headache, myalgia, fever, nausea, and vomiting were extracted. Ambient air oxygen saturation was measured, blood sampling was taken at hospital admission, and chest CT scan was performed.

We reported the number of cycles of polymerase chain reaction (PCR) COVID19 (gene E and gene open reading frame 1ab [ORF1ab]) at baseline. We used a real-time RT-PCR test intended for the qualitative detection of nucleic acids from SARS-CoV2 in

TABLE I. Demographic, treatment, and functional characteristics and comorbidities of patients hospitalized for SARS-CoV2 infection according to the presence or absence of asthma and COPD

	No obstruction (N = 493)		Asthma (N = 57)		COPD (N = 46)		
	N	Value	N	Value	N	Value	P value
Female gender	493	249 (50%)	57	32 (56%)	46	21 (46%)	.56
Age (y)	493	58 ± 19	57	53 ± 18	46	74 ± 10	<.0001
BMI (kg/m^2)	243	27.8 ± 5.8	32	28.6 ± 7.5	37	27.9 ± 5.4	.80
Smoking status	411		57		46		<.0001
Nonsmoker		268 (65%)		41 (72%)		3 (7%)	
Ex-smoker		102 (25%)		13 (23%)		37 (80%)	
Smoker		41 (10%)		3 (5%)		6 (13%)	
Anxiolytics	480	38 (8%)	56	2 (4%)	41	13 (32%)	<.0001
Aspirin	480	96 (20%)	56	7 (12%)	41	20 (49%)	<.0001
Azithromycin	485	0 (0%)	56	0 (0%)	42	3 (7%)	<.0001
ICS	493	0 (0%)	57	40 (70%)	46	16 (35%)	<.0001
Low dose		0		3		6	
Moderate dose		0		17		7	
High dose		0		20		3	
OCS (dose, mg)	493	20 (4%) (16 mg)	57	2 (3%) (4 mg)	46	1 (2%) (4 mg)	.81
Post-BD FEV$_1$, % pred	0	–	57	88 (70-101)	46	64 (53-72)	<.0001
Post-BD FEV$_1$/FVC (%)	0	–	57	69 (63-87)	46	58 (52-68)	.0062
FVC, % pred	0	–	57	89 (80-99)	46	80 (68-92)	.041
TLC, % pred	0	–	30	95 (88-106)	22	100 (93-112)	.41
RV/TLC, % pred	0	–	27	37 (27-45)	18	53 (49-58)	.0002
FRC, % pred	0	–	28	105 (91-134)	15	121 (104-147)	.27
RV, % pred	0	–	29	96 (80-125)	20	120 (97-150)	.066
DLCO,% pred	0	–	30	80 (68-87)	25	47 (32-64)	.0003
KCO, % pred	0	–	29	91 (76-102)	24	72 (56-91)	.023
sGaw, % pred	0	–	19	60 (42-72)	7	40 (34-66)	.15
Atopy	484	105 (22%)	56	35 (62%)	46	14 (30%)	<.0001
Emphysema	350	35 (10%)	56	7 (15%)	46	28 (61%)	<.0001
Bronchiectasis	493	15 (3%)	56	4 (7%)	46	4 (9%)	.067
Cardiopathy	493	88 (18%)	56	8 (14%)	46	20 (43%)	<.0001
Diabetes	493	90 (18%)	56	11 (20%)	46	13 (28%)	.26
History of cancer	493	53 (11%)	56	3 (5%)	46	14 (30%)	.0007
Immunosuppressive disease	493	28 (6%)	57	0 (0%)	46	4 (9%)	.11
Hypertension	493	198 (40%)	56	19 (34%)	46	29 (63%)	.0053
Dyslipidemia	493	109 (22%)	56	12 (21%)	46	16 (35%)	.14
Obesity	493	89 (18%)	56	12 (21%)	46	14 (30%)	.12
CRF	493	32 (7%)	56	2 (4%)	46	8 (17%)	.012
GOR	479	65 (14%)	56	7 (12%)	41	16 (39%)	<.0001

BD, Bronchodilation; *BMI*, body mass index; *COPD*, chronic obstructive pulmonary disease; *CRF*, chronic renal failure; *DLCO*, diffusing capacity of the lungs for carbon monoxide; *FEV$_1$*, forced expiratory volume in 1 second; *FRC*, functional residual capacity; *FVC*, forced vital capacity; *GOR*, gastroesophageal reflux; *ICS*, inhaled corticosteroid; *IQR*, interquartile range; *KCO*, carbon monoxide transfer coefficient; *OCS*, oral corticosteroid; *RV*, residual volume; *SARS-CoV2*, severe acute respiratory syndrome coronavirus 2; *SD*, standard deviation; *sGaw*, specific conductance; *TLC*, total lung capacity.
Values are n (%) and P value χ^2 test for contingency tables, or mean ± SD and P value analysis of variance, or median (IQR) and P value Kruskal-Wallis test.

nasopharyngeal swab samples collected (Cobas SARS-CoV2 assay for use on the Cobas 6800/8800 systems). We detected specific nucleic acid sequences from the nonstructural ORF1ab in the genome of the SARS-CoV2 virus in the carboxyfluorescein channel and the conserved sequences in the structural envelope (E) gene to provide a high degree of robustness.

A "COVID working group" constituted in the University Hospital of Liege at the beginning of the pandemic decided to treat all hospitalized patients tested positive to COVID19 with hydroxychloroquine for 5 days (400 mg on day 1 and 200 mg from day 2 to day 5) and doxycycline 200 mg per day for 5 days, but this was not part of a clinical trial.

Statistical analysis

The results were expressed as mean ± standard deviation for continuous variables; median (interquartile range) was preferred for skewed distributions. For categorical variables, the number of observations and percentages are given in each category. For continuous variables, comparisons between different subgroups were performed with the analysis of variance method or using Kruskal-

TABLE II. Percentage of patients reporting symptoms at admission when hospitalized for SARS-CoV2 infection according to the presence or absence of asthma and COPD

	No obstruction	Asthma	COPD	*P* value
N	245	30	9	
Fever	163 (67%)	20 (67%)	6 (67%)	.99
Headache	156 (64%)	21 (70%)	1 (11%)	.0040
Nonproductive cough	150 (61%)	21 (70%)	4 (44%)	.36
Myalgia	152 (62%)	17 (57%)	2 (22%)	.052
Dyspnea	116 (47%)	15 (50%)	6 (67%)	.51
Chest pain	78 (32%)	10 (33%)	2 (22%)	.81
Diarrhea	74 (30%)	10 (33%)	2 (22%)	.81
Nausea	74 (30%)	7 (23%)	0 (0%)	.11
Rhinorrhea	54 (22%)	7 (23%)	0 (0%)	.28
Pharyngeal pain	52 (21%)	6 (20%)	0 (0%)	.30
Productive cough	50 (20%)	4 (13%)	3 (33%)	.40
Vomiting	23 (9%)	1 (3%)	0 (0%)	.35

COPD, Chronic obstructive pulmonary disease; *SARS-CoV2*, severe acute respiratory syndrome coronavirus 2.
Values are n (%) and *P* value χ^2 test for contingency tables.

Wallis tests for skewed distributions. The χ^2 test for contingency tables was used for categorical variables. Variables associated with ICU admission and death were identified by binary logistic regression. For each variable, results were presented as odds ratios (OR), their 95% confidence intervals (95% CI), and *P* values of simple logistic regression models and logistic regression models adjusted for age and gender. Multiple regression models were built for each outcome (ICU stay and death) including age, gender, asthma, COPD, and the other comorbidities with *P* < .10 in the models adjusted for age and gender. Because atopy is highly correlated with asthma, this variable was not included in the multiple model predicting ICU stay. Final multiple models obtained by stepwise selection (with age, gender, asthma, and COPD forced to be included) were presented in the results. In all the regression models, skewed continuous variables were log-transformed or expressed as ordered qualitative variables.

A *P* value <.05 was considered as statistically significant. Missing values were not replaced. Statistical analysis was performed using SAS (version 9.4) software (Cary, NC).

RESULTS
Demographic characteristics

Among the 596 patients requiring hospitalization for COVID19, asthma and COPD accounted for 9.6% (N = 57) and 7.7% (N = 46), respectively. Not surprisingly, asthmatic patients were more often atopic than COPD and non-obstructive ones (Table I). Patients with COPD were older, more often current or ex-smokers with higher rates of emphysema. Regarding comorbidities, patients with COPD had more often hypertension, gastroesophageal reflux, cardiopathy, chronic renal failure, and a cancer history. Patients with chronic airway obstructive diseases were more often treated with anxiolytics before admission. Seventy percent of asthmatics were treated with ICS, and half of them received high doses of ICS ($\geq$1000 µg of beclomethasone equivalent per day). One-third of patients with COPD were treated with ICS with 19% of them receiving high doses and 44% moderate doses of ICS.

Three percent of patients with asthma and 2% of patients with COPD received chronic oral corticosteroid (OCS) with a median dose of 4 mg per day, whereas 4% of the nonobstructive patients were treated with chronic OCS with a median dose of 16 mg per day.

Symptoms at admission and SARS-COV2 PCR

Fever, headache, nonproductive cough, and myalgia were the most common symptoms at admission (Table II). Patients with COPD had less headache than asthmatics and non-obstructive patients. Other symptoms were similar between the subgroups.

The numbers of cycles of positive PCR for COVID19 gene E and gene ORF1ab were similar between the groups (Table III).

Risk factors for intensive care unit stay

The proportions of asthmatics (N = 10 of 57), patients with COPD (N = 9 of 46), and patients without obstructive airway disease (N = 69 of 493) hospitalized in the ICU were 17.5%, 19.6%, and 14%, respectively (Table IV).

We searched for risk factors of being hospitalized in the ICU for the whole population (Table V). The regression analysis showed that male gender and older age increased the risk of ICU stay. Independently from age and gender, atopy, obesity, diabetes, high baseline C-reactive protein (CRP), D-dimers, and fibrinogen levels were associated with a risk of ICU stay (Table V). Moreover, higher white blood cell and neutrophil counts, lower blood eosinophil and lymphocyte counts, lower glomerular filtration rate, higher creatinine and urea levels, lower concentration of albumin and higher procalcitonin, lactate dehydrogenase (LDH) and creatinine kinase (CK) levels were associated with a higher risk of ICU stay independently of age or gender.

The multivariate analysis confirmed that male gender and obesity were risk factors for hospitalization in the ICU (Table V). Men had 1.9 times (95% CI: 1.1-3.2) more risk of ICU stay, and obesity increased 8.5 times (95% CI: 5.1-14.1) the risk of ICU stay. Interestingly, neither asthma or COPD nor ICS and OCS treatments were significant risk factors for ICU admission.

Risk factors for death due to COVID19

One-third of patients with COPD hospitalized for SARS-CoV2 infection died during hospitalization (34.8%, N = 16 of 46), whereas only 7.0% of asthmatics (N = 4 of 57) and 13.6% (N = 67 of 493) of patients without obstructive airway disease died due to COVID19 (Table IV). The regression analysis revealed that male gender and older age increased the risk of death and that, independently of age and gender, cardiopathy, diabetes, immunosuppressive disease, obesity, and chronic renal failure were predictors of death in hospitalized patients (Table VI). Higher baseline CRP levels increased the risk of death. The level of LDH was higher and the value of albumin was lower at admission to the hospital in patients who died of SARS-CoV2 infection. Patients dying of COVID19 had also a significantly lower number of cycles of PCR gene E and ORF1ab, suggesting a higher viral load (Figure 1). Moreover, higher levels of white blood cells, neutrophils, urea, procalcitonin, and CK and lower levels of eosinophils, monocytes, red blood cells, hemoglobin, and total proteins were predictors of death.

The multivariate analysis confirmed that male gender, older age, cardiopathy, and immunosuppressive disease were predictors

TABLE III. Blood tests and chest CT scan results at admission to the hospital

	No obstruction (N = 493)		Asthma (N = 57)		COPD (N = 46)		
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	P value
White blood cells (/mm^3)	323	6370 (4650-8230)	31	6280 (5080-9830)	43	6080 (4620-9960)	.83
Lymphocytes (/mm^3)	322	890 (650-1250)	31	1060 (700-1370)	42	1000 (630-1280)	.39
Neutrophils (/mm^3)	322	4755 (3180-6580)	31	4520 (3200-7050)	42	4170 (2630-6670)	.92
Eosinophils (/mm^3)	322	10 (0-30)	31	10 (0-50)	42	10 (0-60)	.42
Basophils (/mm^3)	322	20 (10-30)	31	20 (10-30)	42	20 (10-30)	.71
Monocytes (/mm^3)	322	390 (250-560)	31	450 (300-630)	42	430 (240-820)	.47
Platelets (/mm^3)	323	197 (159-264)	30	194 (167-269)	43	179 (151-315)	.92
Red blood cells (10^6/mm^3)	318	4.6 (4.1-4.9)	30	4.8 (4.3-5.3)	40	4.2 (3.8-4.7)	.026
Hemoglobin (g/dL)	323	13.5 (12.2-14.8)	30	14.0 (12.2-15.1)	43	12.6 (11.1-14.3)	.078
GFR (mL/min/1.73 m^2)	319	72 (51-90)	30	67 (49-89)	43	61 (46-82)	.29
Creatinine (mg/dL)	320	0.95 (0.76-1.3)	30	1.0 (0.69-1.4)	43	1.0 (0.75-1.5)	.56
Urea (mg/dL)	320	40 (29-59)	29	49 (27-64)	42	51 (32-74)	.06
Albumin (g/L)	290	38 (35-41)	29	40 (37-42)	36	37 (33-41)	.14
Total proteins (g/L)	300	69 (64-74)	30	70 (66-76)	37	67 (63-70)	.12
Bicarbonates (mmol/L)	280	24 (22-26)	27	25 (22-26)	34	26 (22-29)	.04
CRP (mg/L)	323	76 (28-152)	31	60 (10-117)	43	55 (15-111)	.11
D-dimers (µg/L)	249	826 (486-1644)	24	582 (460-1140)	28	947 (494-1996)	.29
Fibrinogen (g/L)	290	5.1 (4.2-6.5)	25	4.9 (4.4-6.0)	33	4.3 (3.8-5.5)	.018
Procalcitonin (µg/L)	250	0.10 (0.05-0.24)	25	0.08 (0.02-0.45)	27	0.07 (0.04-0.40)	.90
LDH (U/L)	299	332 (250-446)	29	356 (266-503)	35	279 (216-383)	.10
CK (UI/L)	292	134 (67-298)	27	115 (63-323)	32	106 (55-553)	.88
PCR COVID gene E positif	493	493 (100%)	57	56 (98.2%)	46	45 (97.8%)	
No. of cycles	241	27 (22-32)	31	29 (21-33)	25	24 (22-31)	.71
PCR COVID ORF1ab positif	493	493 (100%)	57	56 (98.2%)	46	45 (97.8%)	
No. of cycles	240	27 (21-31)	31	28 (21-31)	25	24 (22-30)	.77

CK, Creatinine kinase; *COPD*, chronic obstructive pulmonary disease; *COVID*, coronavirus disease; *CRP*, C reactive protein; *CT*, computed tomography; *GFR*, glomerular filtration rate; *IQR*, interquartile range; *LDH*, lactate dehydrogenase; *ORF*, open reading frame; *PCR*, polymerase chain reaction.
Number of cycles <19: very high positive, 19-25: high positive, 26-33: moderate positive, >33: low positive.
Values are median (IQR) and *P* values of the Kruskal-Wallis test, or n (%).

TABLE IV. Deterioration and death rate of patients hospitalized for SARS-CoV2 infection according to the presence or absence of asthma and COPD

	No obstruction	Asthma	COPD
N	493	57	46
ICU, n (%)	69 (14.0)	10 (17.5)	9 (19.6)
Mechanical ventilation days (range)	12 (10-18)	12 (9-23)	17 (9-24)
Death, n (%)	67 (13.6)	4 (7.0)	16 (34.8)

COPD, Chronic obstructive pulmonary disease; *ICU*, intensive care unit; *SARS-CoV2*, severe acute respiratory syndrome coronavirus 2.

of death in patients hospitalized due to COVID19 infection. COPD was a predictor of death in the univariate but not in the age- and gender-adjusted models nor in the multivariate analysis, suggesting that this risk is probably linked to the higher rate of comorbidities recorded in this subpopulation and to the older age of this subgroup. As for ICU admission, neither asthma nor ICS and OCS treatments were significant risk factors for mortality.

DISCUSSION

ICU stay was necessary in one-fifth of asthmatics and patients with COPD hospitalized due to SARS-CoV2 infection. Predictors of hospitalization in the ICU were gender and obesity. The presence of high baseline CRP levels increased the risk of ICU admission. Asthma, COPD, ICS treatment, and chronic OCS requirement were not identified as significant risk factors for ICU admission or mortality. The multivariate analysis showed that male gender, older age, cardiopathy, and immunosuppressive disease were independent predictors of death in patients hospitalized for SARS-CoV2 infection.

In the previous reports on COVID19, the prevalence of asthma in patients with SARS-CoV2 infection was surprisingly low.[3,17] However, most of the first reports combined asthmatics and patients with COPD in a "chronic obstructive respiratory diseases" group, and it has been suggested that chronic pulmonary diseases were underdiagnosed in the first studies.[18] The proportion of asthmatics and patients with COPD hospitalized in the CHU of Liege due to COVID19 is similar to the one reported by Richardson et al[19] and close to the percentage of patients suffering from these diseases in the general population.[20,21] This suggests that asthma and COPD are not risk factors for hospitalization due to SARS-CoV2 infection. One hypothesis is that asthmatics and patients with COPD were more compliant to their treatment[22] and respected social distancing during the pandemic because they were afraid of having severe pulmonary infection. A protective role of inhalation therapy by ICS has also been proposed as a possible explanation. Moreover, Peters et al[4] found that there were no significant differences in

TABLE V. Factors associated with intensive care unit stay due to SARS-CoV2 infection: results of the logistic regression analysis

		Simple logistic regression			Logistic regression adjusted for age and gender			Multiple logistic regression final model (N = 595)	
	N	OR (95% CI)	*P* value	N	OR (95% CI)	*P* value		OR (95% CI)	*P* value
Male gender	596	2.0 (1.2-0.3.2)	**.0041**	—	—	—		1.9 (1.1-3.2)	**.013**
Age (by 10 y)	596	1.2 (1.04-1.3)	**.0093**	—	—	—		1.1 (0.96-1.3)	.17
BMI (kg/m^2)	312	1.1 (1.1-1.2)	**<.0001**	312	1.1 (1.1-1.2)	**<.0001**		—	—
Smoker or ex-smoker	514	1.8 (1.1-2.9)	**.017**	514	1.5 (0.90-2.5)	.12		—	—
Atopy	586	2.1 (1.3-3.4)	**.0021**	586	2.4 (1.5-3.9)	**.0005**		—	—
Emphysema	452	0.72 (0.36-1.4)	.34	452	0.66 (0.32-1.3)	.24		—	—
Bronchiectasis	595	0.86 (0.25-3.0)	.81	595	0.61 (0.17-2.1)	.44		—	—
Cardiopathy	595	1.3 (0.73-2.2)	.41	595	0.94 (0.53-1.7)	.84		—	—
Diabetes	595	2.3 (1.4-3.8)	**.0013**	595	2.1 (1.2-3.5)	**.0060**		—	—
History of cancer	595	1.7 (0.91-3.1)	.099	595	1.3 (0.69-2.5)	.40		—	—
Immunosuppressive disease	596	0.82 (0.28-2.4)	.71	596	0.73 (0.25-2.1)	.57		—	—
Hypertension	595	1.9 (1.2-3.0)	**.0070**	595	1.3 (0.98-2.7)	.061		—	—
Dyslipidemia	595	1.9 (1.2-3.2)	**.0083**	595	1.6 (0.92-2.6)	.10		—	—
Obesity	595	9.0 (4.5-15)	**<.0001**	595	8.5 (5.1-14)	**<.0001**		8.5 (5.1-14.1)	**<.0001**
CRF	595	0.96 (0.39-2.3)	.92	595	0.82 (0.33-2.0)	.68		—	—
GOR	576	1.9 (1.04-3.4)	.036	576	1.6 (0.85-2.9)	.15		—	—
Asthma	596	1.3 (0.61-2.6)	.53	596	1.4 (0.69-3.0)	.33		1.4 (0.64-3.2)	.39
COPD	596	1.4 (0.67-3.1)	.34	596	1.1 (0.52-2.5)	.74		0.94 (0.39-2.2)	.89
Anxiolytics	577	1.4 (0.64-2.9)	.41	577	1.1 (0.48-2.4)	.86			
Aspirin	577	2.4 (1.5-4.1)	**.0007**	577	1.9 (1.1-3.5)	**.030**			
Azithromycin	583	13 (1.2-150)	**.035**	583	13 (1.1-152)	**.041**			
ICS	596	1.9 (0.91-3.8)	.088	596	1.8 (0.85-3.7)	.13			
OCS	596	2.1 (0.81-5.5)	.13	596	2.1 (0.80-5.6)	.13			
Blood test at admission									
White blood cells (/mm^3)*	397	2.9 (1.7-4.8)	**<.0001**	397	2.9 (1.7-4.8)	**<.0001**			
Lymphocytes (/mm^3)*	395	0.64 (0.41-0.99)	**.047**	395	0.60 (0.38-0.96)	**.031**			
Neutrophils (/mm^3)*	395	2.9 (1.8-4.5)	**<.0001**	395	2.9 (1.9-4.6)	**<.0001**			
Eosinophils (/mm^3)*	395	0.91 (0.87-0.96)	**.0001**	395	0.91 (0.87-0.96)	**.0002**			
Basophils (/mm^3)*	395	0.99 (0.92-1.1)	.70	395	0.99 (0.92-1.1)	.77			
Monocytes (/mm^3)*	395	1.02 (0.87-1.2)	.83	395	1.02 (0.87-1.2)	.80			
Platelets (/mm^3)*	396	0.77 (0.46-1.3)	.31	396	0.78 (0.46-1.3)	.34			
Red blood cells (10^6/mm^3)	388	1.4 (0.997-2.0)	.052	388	1.3 (0.91-1.8)	.46			
Hemoglobin (g/dL)	396	1.1 (1.02-1.3)	**.024**	396	1.1 (0.99-1.3)	.086			
GFR (mL/min/1.73 m^2)	392	0.99 (0.98-0.99)	**.0057**	392	0.98 (0.97-0.99)	**.0001**			
Creatinine (mg/dL)*	393	1.9 (1.2-3.1)	**.011**	393	2.1 (1.3-3.6)	**.0042**			
Urea (mg/dL)*	391	1.9 (1.2-2.9)	**.0027**	391	2.7 (1.7-4.3)	**<.0001**			
Albumin (g/L)	355	0.92 (0.88-0.97)	**.0022**	355	0.90 (0.86-0.95)	**.0002**			
Total proteins (g/L)	367	0.98 (0.95-1.01)	.15	367	0.97 (0.94-1.001)	.057			
Bicarbonates (mmol/L)	341	0.97 (0.91-1.04)	.34	341	0.97 (0.91-1.04)	.39			
CRP (mg/L)†	397	2.1 (1.7-2.8)	**<.0001**	397	2.2 (1.7-2.9)	**<.0001**			
D-dimers (µg/L)*	301	1.6 (1.2-2.0)	**.0009**	301	1.7 (1.3-2.3)	**.0002**			
Fibrinogen (g/L)	348	1.5 (1.3-1.7)	**<.0001**	348	1.4 (1.2-1.7)	**<.0001**			
Procalcitonin (µg/L)*	302	1.6 (1.3-1.9)	**<.0001**	302	1.8 (1.4-2.2)	**<.0001**			
LDH (U/L)*	363	15 (7.4-30)	**<.0001**	363	17 (8.1-34)	**<.0001**			
CK (UI/L)*	351	1.5 (1.2-1.9)	**.0003**	351	1.5 (1.2-1.9)	**.0003**			

BMI, Body mass index; *CI*, confidence interval; *CK*, creatinine kinase; *COPD*, chronic obstructive pulmonary disease; *CRF*, chronic renal failure; *CRP*, C-reactive protein; *GFR*, glomerular filtration rate; *GOR*, gastroesophageal reflux; *ICS*, inhaled corticosteroid; *LDH*, lactate dehydrogenase; *OCS*, oral corticosteroid; *OR*, odds ratio; *SARS-CoV2*, severe acute respiratory syndrome coronavirus 2.

Bold *P*-values are considered as significant.

*Log-transformed.

†CRP: 0 if ≤25.6, 1 if >25.6 and ≤71.6, 2 if >71.6 and ≤148.7, and 3 if >148.7 and ≤500.

TABLE VI. Factors associated with death during hospital admission due to SARS-CoV2 infection: results of the logistic regression analysis

|	N	Simple logistic regression OR (95% CI)	P value	N	Logistic regression adjusted for age and gender OR (95% CI)	P value	Multiple logistic regression final model (N = 595) OR (95% CI)	P value
Male gender	596	2.2 (1.4-3.5)	**.0013**	—	—	—	1.9 (1.1-3.2)	**.016**
Age (by 10 y)	596	1.9 (1.6-2.3)	**<.0001**	—	—	—	1.9 (1.6-2.3)	**<.0001**
BMI (kg/m^2)	312	1.0 (0.96-1.05)	.98	312	1.0 (0.97-1.1)	.47	—	—
Smoker or ex-smoker	514	2.3 (1.4-3.7)	**.0008**	514	1.4 (0.81-2.3)	.24	—	—
Atopy	586	1.03 (0.61-1.7)	.91	586	1.2 (0.68-2.1)	.53	—	—
Emphysema	452	1.7 (0.96-3.1)	.068	452	1.3 (0.68-2.3)	.46	—	—
Bronchiectasis	595	4.1 (1.47-9.7)	**.0016**	595	1.9 (0.73-4.7)	.20	—	—
Cardiopathy	595	3.6 (2.2-5.8)	**<.0001**	595	1.9 (1.1-3.2)	**.018**	1.8 (1.05-3.1)	**.033**
Diabetes	595	2.3 (1.4-3.9)	**.0011**	595	1.8 (1.1-3.1)	**.031**	—	—
History of cancer	595	3.2 (1.8-5.7)	**<.0001**	595	1.7 (0.94-3.2)	.078	—	—
Immunosuppressive disease	596	3.4 (1.6-7.2)	**.0020**	596	3.8 (1.6-8.6)	**.0017**	3.6 (1.5-8.4)	**.0031**
Hypertension	595	2.9 (1.8-4.6)	**<.0001**	595	1.4 (0.80-2.3)	.25	—	—
Dyslipidemia	595	2.9 (1.8-4.6)	**<.0001**	595	1.4 (0.86-2.4)	.17	—	—
Obesity	595	2.0 (1.2-3.3)	**.0078**	595	1.8 (1.1-3.2)	**.029**	—	—
CRF	595	3.7 (1.9-7.3)	**.0002**	595	2.5 (1.2-5.3)	**.014**	—	—
GOR	576	1.8 (1.004-3.2)	**.048**	576	0.86 (0.45-1.7)	.66	—	—
Asthma	596	0.41 (0.15-1.2)	.098	596	0.59 (0.20-1.8)	.35	0.74 (0.24-2.3)	.59
COPD	596	3.6 (1.9-6.9)	**<.0001**	596	1.9 (0.95-3.8)	.071	1.6 (0.80-3.3)	.18
Anxiolytics	577	2.8 (1.4-5.3)	**.0020**	577	1.1 (0.56-2.4)	.70		
Aspirin	577	3.2 (1.9-5.2)	**<.0001**	577	0.97 (0.54-1.7)	.93		
Azithromycin	583	—	—	583	—	—		
ICS	596	1.7 (0.79-3.4)	.18	596	1.4 (0.62-3.0)	.44		
OCS	596	2.1 (0.82-5.6)	.12	596	2.5 (0.88-7.2)	.085		
Blood test at admission								
White blood cells (/mm^3)*	397	2.1 (1.3-3.4)	**.0041**	397	2.1 (1.2-3.5)	**.0062**		
Lymphocytes (/mm^3)*	395	0.60 (0.38-0.94)	**.027**	395	0.74 (0.47-1.2)	.20		
Neutrophils (/mm^3)*	395	2.1 (1.4-3.3)	**.0006**	395	2.1 (1.3-3.4)	**.0013**		
Eosinophils (/mm^3)*	395	0.95 (0.91-0.99)	**.028**	395	0.94 (0.90-0.99)	**.024**		
Basophils (/mm^3)*	395	0.94 (0.88-1.003)	.060	395	0.94 (0.88-1.004)	.067		
Monocytes (/mm^3)*	395	0.78 (0.65-0.93)	**.0060**	395	0.74 (0.60-0.90)	**.0034**		
Platelets (/mm^3)*	396	0.65 (0.39-1.1)	.11	396	0.78 (0.45-1.3)	.37		
Red blood cells (10^6/mm^3)	388	0.49 (0.35-0.68)	**<.0001**	388	0.48 (0.34-0.70)	**.0001**		
Hemoglobin (g/dL)	396	0.82 (0.73-0.92)	**.0008**	396	0.81 (0.72-0.92)	**.0009**		
GFR (mL/min/1.73 m^2)	392	0.99 (0.98-1.000)	**.039**	392	1.0 (0.99-1.008)	.83		
Creatinine (mg/dL)*	393	1.8 (1.1-3.0)	**.017**	393	1.3 (0.75-2.3)	.34		
Urea (mg/dL)*	391	3.1 (2.0-4.9)	**<.0001**	391	2.2 (1.3-3.6)	**.0026**		
Albumin (g/L)	355	0.84 (0.79-0.89)	**<.0001**	355	0.85 (0.80-0.90)	**<.0001**		
Total proteins (g/L)	367	0.94 (0.91-0.97)	**<.0001**	367	0.95 (0.92-0.98)	**.0018**		
Bicarbonates (mmol/L)	341	0.95 (0.88-1.01)	.12	341	0.95 (0.89-1.02)	.19		
CRP (mg/L)†	397	1.9 (1.5-2.4)	**<.0001**	397	1.9 (1.4-2.4)	**<.0001**		
D-dimers (μg/L)*	301	1.6 (1.2-2.1)	**.0012**	301	1.3 (0.97-1.8)	.072		
Fibrinogen (g/L)	348	1.1 (0.92-1.3)	.36	348	1.1 (0.94-1.3)	.22		
Procalcitonin (μg/L)*	302	1.7 (1.3-2.0)	**<.0001**	302	1.5 (1.2-1.9)	**.0002**		
LDH (U/L)*	363	3.0 (1.7-5.2)	**<.0001**	363	3.1 (1.7-5.6)	**.0002**		
CK (UI/L)*	351	1.4 (1.1-1.7)	**.0040**	351	1.3 (1.02-1.7)	**.032**		

BMI, Body mass index; *CI*, confidence interval; *CK*, creatinine kinase; *COPD*, chronic obstructive pulmonary disease; *CRF*, chronic renal failure; *CRP*, C-reactive protein; *GFR*, glomerular filtration rate; *GOR*, gastroesophageal reflux; *ICS*, inhaled corticosteroid; *LDH*, lactate dehydrogenase; *OCS*, oral corticosteroid; *OR*, odds ratio; *SARS-CoV2*, severe acute respiratory syndrome coronavirus 2.
Bold *P*-values are considered as significant.
*Log-transformed.
†CRP: 0 if ≤25.6, 1 if >25.6 and ≤71.6, 2 if >71.6 and ≤148.7, and 3 if >148.7 and ≤500.
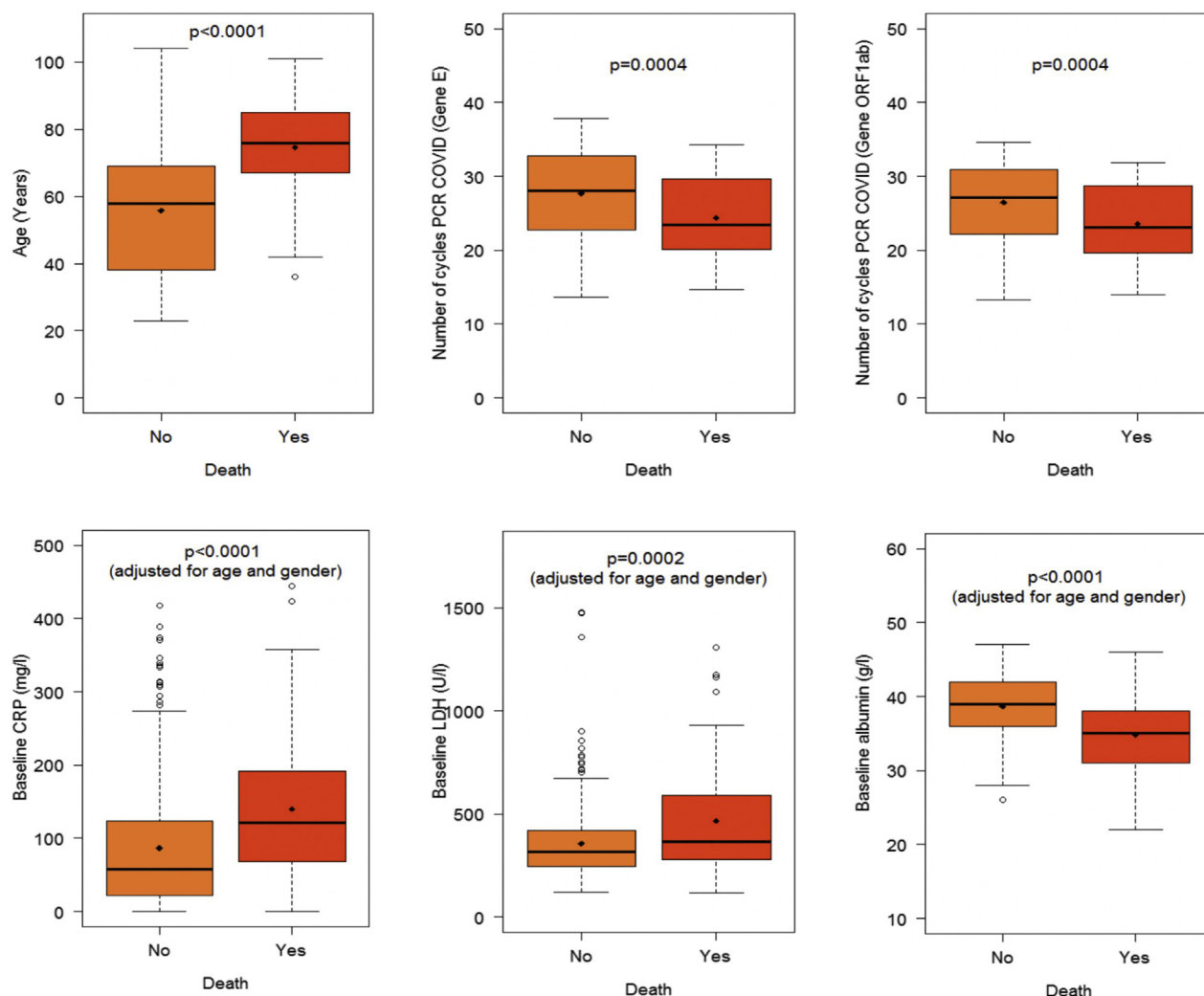
FIGURE 1. Comparison of clinical parameters in patients who died during SARS-CoV2 infection as compared with patients who survived. *COVID19*, Coronavirus disease 2019; *CRP*, C-reactive protein; *LDH*, lactate dehydrogenase; *ORF*, open reading frame; *PCR*, polymerase chain reaction.

gene expression of angiotensin converting enzyme 2 (ACE2) in sputum between patients with asthma and healthy subjects, suggesting that patients with asthma might not be at increased risk of COVID19. However, we have to recognize that hospitalized asthmatics in our series are not representative of the general population of asthmatics seen in our hospital[15] because the mean post-bronchodilation FEV$_1$/forced vital capacity ratio was below 70%, thereby indicating fixed airway obstruction. It would therefore suggest that fixed airway obstruction in asthma may be a risk factor to be hospitalized. However, among the 226 severe asthmatics treated with anti-IgE, anti-IL5, and anti-IL5R in the Asthma Clinic of the CHU of Liege, only 4 presented a SARS-CoV2 infection and none of them were admitted to the hospital due to COVID19 (unpublished data).

We found that one-fifth of asthmatics and patients with COPD who were hospitalized due to COVID19 required a stay in the ICU. Previous studies have suggested that patients suffering from airway obstructive disease had a deficient and delayed innate antiviral immune response.[1,2] In a meta-analysis, Lippi and Henry[23] reported that COPD was associated with

severe coronavirus disease with an OR of 5.69. In another study, the prevalence of COPD was higher in the nonsurvivors.[24] This paper has however been retracted. In our population, COPD was a predictor of death during hospitalization in the univariate but not in the multivariate analysis, suggesting that this risk is probably linked to the higher rate of comorbidities recorded in this subpopulation and to the older age of this subgroup. Cardiopathy is indeed frequently associated with COPD and has emerged as a key comorbidity to predict death after COVID19.

In our study, we confirm that older age and high number of comorbidities are associated with more severe infections.[3] Male gender and the presence of obesity were indeed predictors of ICU stay, whereas male gender, older age, cardiopathy, and immunosuppressive disease were associated with death during hospitalization. Male gender and a history of diabetes mellitus have been found to be associated with an elevated ACE2, a receptor for SARS-CoV2 to enter host target cells.[4] In the report of Li et al,[17] patients with older age and hypertension were significantly associated with severe COVID19 on admission. Mehra et al[25] found that underlying cardiovascular disease was

associated with increased risk of in-hospital death among patients hospitalized with COVID19. We also found that high baseline CRP levels at hospital admission were predictors of ICU stay or death. We found higher fibrinogen and D-dimers levels in patients who stayed in the ICU. This is not surprising as a high incidence of thromboembolic events has been reported in such patients, and this suggests an important role of SARS-Cov2-induced endothelial activation.[26]

We did not find a higher risk of severe infections in patients treated with ICS or OCS. It has been previously shown that type 2 inflammation may suppress antiviral immunity in the lung[5] and may increase susceptibility to severe COVID19. Our group also previously found that allergic asthma was characterized by impaired spontaneous release of IFN-gamma that correlated with the magnitude of eosinophilic inflammation.[27] Suppressing type 2 inflammation using local corticosteroids may thus restore antiviral immunity. Moreover, it has been recently suggested that ICS is dose-dependently associated with reduced ACE2 mRNA expression. This observation was, however, not confirmed in a study looking at bronchial brushes.[28] This suggests that patients with obstructive airway disease should not decrease the dose of ICS during SARS-CoV2 infection as recommended by most of the current international guidelines.[8-10] Asthma and COPD treatments should be pursued and adapted to ensure optimal control of the lung disease throughout the epidemic, thus potentially reducing the risk of severe COVID19 disease.

We also looked at intubation length according to airway status and did not find that asthma prolonged intubation as compared with nonobstructive patients. However, we found similar intubation length to the one reported by Mahdavinia et al[29] and a prolonged intubation in patients with COPD.

Data related to smoking and risk of SARS-CoV2 infection have been somewhat contradictory despite the fact that the association between smoking and an increased risk of respiratory diseases is clear. Recent publications suggested that smoking upregulates the ACE2 receptor, which could increase the susceptibility to the infection.[30] The proportion of current smokers in our patients hospitalized for COVID19 was lower than that in the general population in Belgium. In addition, smoking was not a risk factor for ICU stay or death in our study. It might be that smoking is protective against COVID19 by damaging cells that are entrance gate to the virus such as pneumocytes type 2 expressing ACE2.

CONCLUSION

Asthma and COPD are not risk factors for ICU stay and death due to SARS-CoV2 infection. Independent predictors of hospitalization in the ICU were male gender and obesity. Male gender, older age, cardiopathy, and immunosuppressive disease were independent predictors of death due to COVID19.

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