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Characteristics and outcomes of asthmatic patients with COVID-19 pneumonia who require hospitalization

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ABSTRACT

BACKGROUND: Viral respiratory infections are the main causes of asthma exacerbation. The susceptibility of asthmatics to develop an exacerbation when they present with severe pneumonia due to SARS-CoV-2 infection is unknown. The objective of this study was to investigate the characteristics and outcomes of asthmatic patients with COVID-19 pneumonia who required hospitalization during the spring 2020 outbreak in Paris, France.

METHODS: A prospective cohort follow-up was carried out from March 15 to April 15, 2020 in Bicêtre Hospital, University Paris-Saclay, France. All hospitalized patients with a SARS-CoV-2 infection who reported a history of asthma were included.

RESULTS: Among 768 hospitalized patients, 37 (4.8%) reported a history of asthma, which had been previously confirmed by a pulmonologist in 85% of cases. Patients were mainly female (70%), non-smokers (85%), with a median age of 54 years (interquartile range, IQR 42-67). None of them presented with an asthma exacerbation. Twenty-two (59%) had major comorbidities and 31 (84%) had a body mass index $\geq$ 25 kg/m². The most common comorbidities were obesity (36%), hypertension (27%) and diabetes (19%). All patients had a confirmed diagnosis of COVID-19 pneumonia on computed tomography of the chest. Eosinopenia was a typical biologic feature with a median count of 0/mm3 (IQR 0-0). Eleven patients (30%) were admitted in intensive care unit with three death (8.1%) occurring in the context of comorbidities.

CONCLUSION: Asthmatics were not overrepresented among patients with severe pneumonia due to SARS-CoV-2 infection who required hospitalization. Worst outcomes were observed mainly in patients with major comorbidities.

Key words: Asthma; COVID-19, SARS-CoV-2

INTRODUCTION

Viral respiratory infections are the main causes of asthma exacerbations in both adults and children. Coronaviruses are commonly isolated in the respiratory tract of these patients [1]. As the world faces the coronavirus disease 2019 (COVID-19) pandemic due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, concerns have arisen about a possible increased risk of asthma exacerbations. Indeed, SARS-CoV-2 is well known for its respiratory tropism that can lead to severe pneumonia and potentially fatal acute respiratory distress syndrome (ARDS) [2]. However, the prevalence of asthma among inpatients with COVID-19 remains debated. In Wuhan, authors pointed out a rate of 0.9% [3], markedly lower than that in the local population; in another study investigating the clinical characteristics and allergy status of 140 patients infected by SARS-CoV-2 in Wuhan, no patient were reported as being asthmatic [3]. Conversely, other authors found that asthmatics accounted for 12.5% of total COVID-19 inpatients in New York [4]. Beside those conflicting statistics, the characteristics and the outcomes of asthmatic patients infected with SARS-CoV-2 have not yet been described in detail.

In France, the Great Paris region (*Ile-de-France*) has been particularly affected by the epidemic. On March 14, 2020, the Regional Health Agency issued a statement underscoring the rapid spread of SARS-CoV-2 in the region with 376 new daily confirmed cases [5]; the number of regional hospitalizations for COVID-19 eventually reached a peak on April 1st [6]. From March 15, 2020 to April 15, 2020 we carried out a prospective study in Bicêtre Hospital, University Paris-Saclay, France. The objective of this study was to investigate the characteristics and outcomes of asthmatic patients with COVID-19 pneumonia who required hospitalization.

MATERIAL AND METHODS

Patients and study design

A prospective monocentric cohort follow-up was initiated in Bicêtre Hospital, France. All adult patients hospitalized from March 15, 2020 to April 15, 2020 with a diagnosis of SARS-CoV-2 infection and reporting a history of asthma were included. Decision of hospitalization was based on a concerted decision algorithm that has been locally implemented into clinical practice during the French COVID-19 outbreak (supplementary Figure 1) . COVID-19 was first suspected on the basis of compatible symptoms: in suspected cases, both SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) on nasopharyngeal swab and computed tomography (CT) of the chest were systematically performed. Diagnosis was confirmed in the presence of positive SARS-CoV-2 RT-PCR and/or typical CT abnormalities (i.e ground-glass opacities and/or consolidation in the lung periphery) [7]. A random control group of 75 non-asthmatic patients hospitalized for COVID-19 pneumonia in our hospital during the same period has been included and analyzed. Patients received written information about data collection. After inclusion, all data regarding the clinical status, main outcomes, biological and radiological features were recorded in an anymous database registred to the National Commission on Informatics and Liberty (n° 2217978).

Characteristics at diagnosis and outcomes

The following data were collected after patient-centered interviews: comorbid conditions (obesity, hypertension, diabetes, renal failure, coronary heart disease); current smoking status ("non-smokers" referring to both former and never smokers); history of asthma; asthma controller treatment with classification from step 1 to 5 according to the last 2020 Global Initiative for Asthma (GINA) report [8]; when feasable, we also clarified with the patient or

his family whether asthma diagnosis had been confirmed by a pulmonologist or not. In addition, the following laboratory tests were analyzed at admission: SARS-CoV-2 RT-PCR result, blood count, cardiac biomarkers, liver function, arterial blood gas, C-reactive protein (CRP), fibrinogen, D-dimers, creatine phosphokinase (CPK), lactate dehydrogenase (LDH), ferritin. CT of the chest was analyzed by a radiologist and a pulmonologist and the extent of lesions was classified as mild (< 10%), moderate (10-24%), severe (25-49%), very severe (50-74%), and critical (≥ 75%). The following management strategies were detailed: use of systemic corticosteroids (CS), short-acting beta-agonists (SABA), antibiotics, adjustement of asthma controller, oxygen flow, intensive care unit (ICU) admission, and mechanical ventilation requirement. Finally, the main outcomes (mortality, length of ICU stay and total length of hospital stay) were investigated after a one-month follow-up.

Statistical methods

Quantitative data were expressed as median (interquartile range) (IQR, presented as first quartile – third quartile). Qualitative data were expressed as number of occurrence, n (%). In case of missing data, the number of patients with available informations was provided next to each variable. When this number was not specified, data of entire population was available and analyzed. Student's t test or Mann-Whitney U test (if not normally distributed) were used to compare the continuous variables between two groups. Pearson's chi-square ($\chi 2$) test or Fisher's exact tests if appropriate, were used to compare discrete variables between two groups.

RESULTS

Clinical characteristics of patients hospitalized for COVID-19 pneumonia

Among 768 hospitalized COVID-19 patients, 37 (4.8%) reported a history of asthma. Thirty-one asthmatics had positive SARS-CoV-2 RT-PCR on nasopharyngeal swab (84%). The remaining six were diagnosed on the basis of clinical presentation and radiological patterns [7].

Asthmatic patients were mainly female (70%), non-smokers (85%), with a median age of 54 years (42-67) and a median body mass index (BMI) of 28.3 kg/m² (26.8-31.5). In 85% of cases the diagnosis of asthma had been previously confirmed by a pulmonologist. Eleven patients (30%) were GINA step 5, receiving high doses inhaled CS (ICS) with long-acting-beta agonists (LABA), associated with low dose oral CS in one case, and long-term omalizumab therapy in two (**Supplementary Table 1**).Thirty-one asthmatics (84%) had a BMI $\geq$ 25 kg/m². Twenty-two (59%) had at least one major comorbidity. The most common comorbid conditions were obesity (36%), hypertension (27%) and diabetes (19%). Fifteen (41%) had multimorbidities (**Table 1**).

The median time from onset of symptoms to admission in the emergency room was 6 days (3-8). Fifty percent of patients had an initial peripheral oxygen saturation below 95% while breathing room air and 25% had a respiratory rate above 30/min. None of them presented with an asthma exacerbation. Wheezing, mostly reported as mild, was reported at admission in only 6 cases (16%) (**Table 2**).

Non-asthmatic controls are presented in Tables 1 and 2. All differences pointed to worst COVID-19 pneumonia in non-asthmatics, as evidenced by older age, higher male/female gender rate, and a trend to more comorbidities.

Biological findings at inclusion

Laboratory values in the emergency room are summarized in **Table 3**. Among asthmatics, lymphopenia was a frequent finding (median 1,205/mm3, IQR 738-1,476) (**Figure 1A**). Patients also presented with a marked eosinopenia, 78% having a blood eosinophils count equal to zero (**Figure 1B**). N-terminal pro–B-type natriuretic peptide (NT-pro BNP) was measured in 21 patients and normal value (< 300 ng/L) was found in 81% of cases. Of 31 available data, 6 patients (19%) had increased high-sensitive cardiac troponin T (≥ 14 ng/L); however, none of these patients demonstrated consistent evidence of serious myocardial injury. Elevation of D-dimers was commonly observed (median 810 µg/L, IQR 483-1,180), as well as increased CRP levels (median CRP 51 mg/L, IQR 27-116). Arterial blood gas while breathing room air was available in 29 patients : hypoxaemia was a common finding (median arterial partial pressure of oxygen (PaO_2) 68 mmHg, IQR 62-83) with hypocapnia (median arterial partial pressure of carbon dioxide ($PaCO_2$) 34 mmHg, IQR 32-38).

Non-asthmatic controls are presented in **Table 3**. There was a trend for more pronounced lymphopenia and worst CRP, D-dimers, LDH, liver transaminases levels, with more severe hypoxemia.

Radiological findings

All asthmatics underwent a CT of the chest (**Table 4**). Peripheral or mixed ground glass opacities were the most frequent CT patterns (95% of cases), expanding over more than 10 percent of lung parenchyma in 76% of cases. Consolidations were observed in 26 patients (70%) and crazy-paving pattern in 13 patients (35%). In 51% of cases, lesions predominated in inferior lobes. Based on clinical judgement or prediction rules [9], four patients had initial CT pulmonary angiography (CTPA), demonstrating two cases of acute pulmonary embolisms

(PE) at admission. Eight additional CTPA were performed during hospital stays for clinical deterioration, leading to another acute PE diagnosis. In this small cohort of patients, higher inhaled corticosteroid exposure was not associated with higher proportion of severe radiological pneumonia; mild pneumonia tended to be more frequent in asthmatics with higher doses of ICS (**Supplementary Figure 2**).

All non-asthmatic controls had imaging of the chest at admission (66 CT and 9 chest X ray). The results of CT of the chest are presented in **Table 4**. As compared to asthmatics, there was more sereve-to-critical radiological presentation in the non-asthmatics.

Management and outcomes

As shown in **Table 5,** 30 (81%) asthmatics received oxygen with use of high-concentration masks in 10 patients. When nasal oxygen was used, the median oxygen flow-rate was 2 L/min. In two patients, oxygen had to be maintained after discharge. Thirty-one (84%) received at least one antibiotic. SABA as needed was prescribed using a pressurized metered-dose inhaler (p-MDI) with a spacer chamber and previous inhaled treatments were maintained. Five patients received oral CS before admission, one of them in the context of self-medication. Three additional patients received intravenous CS during hospital stay: refractory ARDS was the main cause of CS prescription in two cases and bronchospasm occurring in the context of mechanical ventilation in one case. Eleven patients were admitted in ICU, six of them requiring invasive mechanical ventilation. There was a trend for more aged and comorbid patients among patients admitted in ICU (**Table 6**). A flowchart of the main outcomes is presented in **Figure 2**. As shown in **Figure 3**, asthmatics without multimorbidities were discharged at home earlier.

Two deaths occurred at one-month follow-up and one additional death was later noted, thus leading to a mortality rate of 8.1% in asthmatics (as compared to 14.6% in non-asthmatics, p=0.381). The first patient was a 68 year-old woman treated for asthma by her pulmonologist with fluticasone/salmeterol 500/50 µg daily (medium doses, GINA step 4). She had several comorbidities including obesity (BMI = 31.2 kg/m^2), diabetes, current chemotherapy for ovarian cancer, dyslipidemia and sleep apnea syndrome. At admission, no wheezing was reported, she was eosinopenic ($0/mm^3$), had positive nasal SARS-CoV-2 RT-PCR and presented with mild extent of pulmonary lesions on CT of the chest. Five days after symptoms had started, she was transfered in ICU for acute respiratory failure. No acute PE was detected on CTPA. Due do an extremely poor prognosis, it was decided to restrict advanced life support, including intubation. She died on day 9. The second patient was a 67 year-old

woman with a diagnosis of asthma confirmed by a pulmonologist and treated with inhaled beclometasone/formoterol 200/12 µg daily (low doses, GINA step 3). She also displayed severe obesity (BMI = 43 kg/m²), hypertension, renal failure requiring chronic dialysis and primary biliary cirrhosis. Mild wheezing was noted at admission along with positive nasal SARS-CoV-2 RT-PCR, eosinopenia (0/mm^3) and severe extent of pulmonary lesions on CT of the chest. Ten days after symptoms had started, she was intubated in ICU for acute respiratory failure. She died at day 15 from refractory ARDS. The third patient was a 75 year-old hypertensive and overweight woman (BMI=29.4) treated for asthma with budesonide/formoterol 1200/36 µg daily (high doses, GINA step 5). At admission in the emergency room, no wheezing was reported; she was eosinopenic (0/mm^3), had positive nasal SARS-CoV-2 RT-PCR and presented with very severe extent of radiological lesions (50-75%). She was intubated 4 days later. Bronchospasm occurred during mechanical ventilation and systemic corticosteroids were administrated at day 12. Withdrawal of mechanical ventilation was not possible: she died at day 45 from respiratory failure.

Evolution of asthmatics treated with biologics

Two patients were treated with anti-immunoglobulin E monoclonal antibody (omalizumab) for severe allergic asthma. The first one was a 53 year-old woman treated with budesonide/formoterol 800/12 µg daily, montelukast 10 mg/j and subcutaneous omalizumab at a monthly dose of 300 mg. She had no sign of asthma exacerbation before admission, but took a short course of oral prednisone (40mg/day) during five days as self medication that was stopped at admission. She had positive nasal SARS-CoV-2 RT-PCR, eosinopenia (0/mm^3) and a moderate extent of lesions on CT of the chest. She had no evidence of asthma exacerbation nor respiratory failure, allowing discharge at home on day 5.

The second patient was a 78 year-old overweight woman with severe allergic asthma and allergic bronchopulmonary aspergillosis, treated with budesonide/formoterol 800/12 µg daily, oral prednisone 5 mg/j and subcutaneous omalizumab 300 mg twice monthly. She also suffered from hypothyroidism, lumbar spinal stenosis and depression. Initial presentation included crackles and minor wheezing, with positive nasal SARS-CoV-2 RT-PCR, blood eosinophil count of 50/mm^3 and severe extent of pneumonia on CT at admission (**Figure 4A**). Nine days after the beginning of symptoms, she was admitted in ICU for acute respiratory failure. Oro-tracheal intubation was needed and mechanical ventilation was well tolerated with no evidence of bronchospasm. After 8 days of mechanical ventilation, acute bronchospasm appeared for the first time. *Aspergillus fumigatus* was detected in bronchial secretions. Segmental acute PE was diagnosed 12 days after admission (**Figure 4B**). Other treatments included anticoagulation, bronchodilator nebulizations, intravenous CS and voriconazole. The next omalizumab injection has been administrated as planned, when she was under mechanical ventilation. No adverse events were observed and successful extubation was possible five days later. She was discharged of ICU after 23 days. At day 75, she was well and alive, still undergoing rehabilitation.

DISCUSSION

This prospective monocentric cohort describes clinical, biological and radiological characteristics and outcomes of asthmatics with COVID-19 pneumonia who require hospitalization. During the spring 2020 outbreak, asthmatics accounted for less than 5% of total hospitalized patients in our institution. The most recent data available in France indicate that 6.4% of individuals have a current diagnosis of asthma [10]. In line with previous reports [11], our results suggest that asthmatics were thus not over-represented among COVID-19 inpatients. In addition, no patient was hospitalized for a COVID-19 related asthma exacerbation during the outbreak and very few developed an asthma attack while hospitalized, which is consistent with data recently reported in Strasbourg, France [12]. This contrasts sharply with viral respiratory infections, including other types of coronavirus, being the main causes of asthma exacerbations [1].

Several mechanisms may explain this apparent paradox. First, a lower expression of SARS-CoV-2 cellular receptor angiotensin-converting enzyme-2 (ACE2) has been described in airways cells of patients with respiratory allergy and/or asthma, and it was also found that ACE2 expression was inversely associated with type 2 biomarkers [13]. Of note, severe eosinopenia was a typical biologic feature in our cohort, 78% of hospitalized asthmatics having no detectable blood eosinophils at admission. This finding is unusual in hospitalized asthmatics receiving neither systemic CS nor anti-interleukin 5 (IL-5) therapy. Similar findings were reported in a mostly non-asthmatic COVID-19 population in Wuhan, China, where eosinopenia was described in 53% of hospitalized subjects [14] and in 81% of fatal cases [15]. As suggested by others [16], eosinopenia in COVID-19 may be a marker of more severe disease. In addition, one may speculate that it reflects a down-regulation of type 2 inflammation that might decrease the risk of asthma exacerbation orchestrated by type 2

responses. Of note, it has been recently showed that severe COVID-19 is driven by inappropriate inflammatory response defined by low levels of type I and III interferons juxtaposed to elevated chemokines and high expression of IL-6, supporting the concept that reduced innate antiviral defenses coupled with exuberant proinflammatory cytokine production are the defining and driving features of COVID-19 [17]. Further studies are needed, describing the cytokine profile of asthmatics in response to SARS-CoV-2 infection. Furthermore, there is *in vitro* evidence to support a protective effect of ICS on coronaviruses infections [18]. Indeed, sputum analysis showed that ACE2 expression levels are significantly lower in asthma patients taking ICS than in those not taking ICS, especially when high doses are administrated [19]. Randomized control trials are needed to test the effect of ICS on COVID-19 in both asthmatics and non-asthmatics patients.

We observed a female predominance (70%) in our cohort, whereas previous works demonstrated an increased risk of SARS-CoV-2 infection in males [20]. This might be explained by age-related sex ratio differences, asthma being more prevalent in female adults [21][22]. Moreover, obesity, hypertension and diabetes were the most common comorbidities observed in our cohort of hospitalized asthmatics with COVID-19, which is consistent with earlier research in other patient groups [4][23]. Interestingly, obesity has been associated with asthma in women [24] and severe forms of COVID-19 in both genders [25][26].

Asthmatic patients with COVID-19 pneumonia who required hospitalization presented with radiological characteristics similar to those described previously, with a predominance of peripheral ground glass opacities [27]. Interestingly, three patients had a diagnosis of acute PE (8.1 %) on CTPA at admission or during hospitalization. At the start of the COVID-19 outbreak, the first-line imaging tool in our centre relied on non-contrast CT of the chest [7]. However, more concern has been recently raised about thrombosis and pulmonary embolism

in COVID-19 patients [28], underscoring that this complication may be more prevalent in this patient population.

Asthma therapy was unchanged in all patients, including biologics, as recommended by the French Asthma and Allergy Working Group (G2A) [29]. Interestingly, two patients were on omalizumab therapy prior to COVID-19. In one patient, the planned omalizumab injection has been administrated while she was under mechanical ventilation, experiencing severe bronchospasm and ARDS. No adverse events were observed and successful extubation was possible five days later.

Our study included a control group of COVID-19 pneumonia hospitalized in the same hospital during the same period. As compared to controls, asthmatics were younger, more likely to be female and they tended to be less comorbid, which may explain at least in part, the better outcomes in this population. However, it is interesting to note that mild pneumonia tended to be more frequent in asthmatics with higher doses of ICS (**supplementary Figure 2**). Further studies are needed to investigate the possible positive effect of inhaled corticosteroids on COVID-19 pneumonia as previously showed with dexamethasone in the RECOVERY trial [30]. The ongoing INHASCO trial (NCT04331054) is investigating this research question.

One of the study limitations is the relative small number of asthmatic patients being investigated. However, all patients were identified prospectively by an expert team of asthma specialists in a large University hospital hosting a severe asthma clinic, allowing systematic analysis of relevant information and meticulous follow-up. In a state of emergency, misdiagnoses of both asthma and COVID-19 cannot be excluded. Regarding asthma, it could be underdiagnosed, as diagnosis was based on self-report and pulmonary function tests could not be performed during the outbreak. Asthma might also be overdiagnosed, as previously reported in industrialized countries especially in obese individuals [31]. Nevertheless, asthma

diagnosis had been previously confirmed by a pulmonologist in 85% of cases. A COVID-19 overdiagnosis is also unlikely, with positive SARS-CoV-2 RT-PCR on nasopharyngeal swab in 84% of cases. RT-PCR was negative in only six patients who presented with a high clinical suspiscion of COVID-19 and consistent CT of the chest during the outbreak [7].

In conclusion, our data indicate that asthmatics were not over-represented in a large group of hospitalized pneumonia during the spring 2020 COVID-19 outbreak in Paris, France. In addition, COVID-19 pneumonia was not associated with asthma exacerbation at admission and at one-month follow-up in patients who did not modify their asthma treatment including GINA step 5 (high doses ICS with LABA, low dose oral CS, and long-term omalizumab). Large multicenter cohort studies are needed to confirm these data and explore the reasons why SARS-CoV-2 does not seem to trigger as many asthma exacerbations, as previously seen with other respiratory viruses.

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TABLE

Table 1. Patients characteristics and medical history at inclusion

Patients characteristics	**Asthmatics (n = 37)**	**Controls (n = 75)**	**p-value**
Age (years)	54 (42-67)	60 (52-70)	**0.019**
Gender, male/female	11 (30) / 26 (70)	49 (65) / 26 (35)	**< 0.001**
BMI (kg/m²)	28.3 (26.8-31.5)	28.7 (26.8-31.2) [#]	0.856
Tobacco exposure :			
Current/former smokers	12 (32)	18 (24)	0.343
Never smokers	25 (68)	57 (76)	0.343
Comorbid conditions			
1. Obesity	13 (36)	24/65 (37)	0.901
Class I (30 ≤ BMI < 35)	5	17	
Class II (35 ≤ BMI < 40)	6	4	
Class III (BMI ≥ 40)	2	3	
2. Overweight (25 ≤ BMI < 30)	18 (49)	35/65 (54)	0.613
3. Hypertension	10 (27)	32 (43)	0.161
4. Diabetes	7 (19)	17 (23)	0.834
5. Renal failure	3 (8)	6 (8)	1.000
Dialysis	2	3	
Nephrectomy	1	0	
6. Coronary heart disease	2 (5)	6 (8)	1.000
At least two of the six	15 (41)	35/67 (52)	0.253

Quantitative data are expressed as median (IQR). IQR is presented as first quartile (Q1) – third quartile (Q3). Qualitative data are expressed as number of occurrence, n (% of total). In case of variable with missing data, the number of patients with available information is specified. BMI: body mass index; GINA step refers to the treatment strategy proposed in the 2020 Global Initiative for Asthma report [8]*; IQR: interquartile range.* [#] *65 available data.*

Table 2. Clinical features at presentation in the emergency room

Variable	**Asthmatics (n = 37)**	**Controls (n = 75)**	**p-value**	*Available data, n (asthmatics, controls)*
Time since onset of symptoms, days	6 (3-8)	7 (3-10)	0.239	*37, 75*
Systolic blood pressure, mmHg	132 (123-145)	138 (122-151)	0.457	*36, 73*
Diastolic blood pressure, mmHg	81 (71-89)	79 (69-88)	0.993	*36, 73*
Heart rate, min^{-1}	99 (88-111)	100 (89-109)	0.714	*36, 73*
Temperature, °C	38.1 (37.3-38.7)	38.2 (37.4-38.7)	0.899	*36, 74*
Respiratory rate, min^{-1}	26 (20-30)	28 (20-32)	0.361	*31, 62*
SpO_2 while breathing room air, %	95 (92-97)	93 (89-95)	**0.008**	*35, 71*
Wheezing	6 (16)	2 (3)	**0.015**	*37, 75*
Mild wheezing	5	0		*37, 75*
Severe wheezing	1	2		*37, 75*

Quantitative data are expressed as median (IQR). IQR is presented as first quartile (Q1) – third quartile (Q3). Qualitative data are expressed as number of occurrence, n (% of total). IQR: interquartile range; SpO_2: oxygen peripheral saturation.

Table 3. Laboratory results at diagnosis

Variable	Asthmatics (n = 37)	Controls (n = 75)	p-value	*Available data, n (asthmatics, controls)*
Leucocytes, mm^{-3}	6,990 (5,710-9,020)	6,690 (5,330-9,483)	0.719	*37, 74*
Haemoglobin, g/dL	13.0 (12.3-14.7)	13.5 (12.6-14.6)	0.819	*37, 74*
Platelets, mm^{-3}	213,000 (159,000-239,000)	206,000 (165,000-254,000)	0.699	*37, 74*
Neutrophils, mm^{-3}	5,225 (3,835-6,910)	5,160 (3,815-7,698)	0.883	*36, 74*
Eosinophils, mm^{-3}	0 (0-0)	0 (0-0)	0.254	*36, 74*
Lymphocytes, mm^{-3}	1,205 (738-1,475)	890 (623-1,308)	0.151	*36, 74*
Fibrinogen, g/L	5.2 (4.2-6.2)	6.1 (5.1-7.2)	**0.002**	*35, 73*
D-dimers, µg/L	810 (483-1,180)	1080 (680-1,508)	0.329	*34, 64*
CRP, mg/L	51 (27-116)	86 (51-174)	**0.040**	*37, 75*
LDH, UI/L	283 (235-359)	392 (311-512)	**0.005**	*31, 66*
CPK, UI/L	100 (62-160)	189 (84-390)	0.245	*33, 71*
ASAT, UI/L	38 (25-62)	51 (39-73)	**0.022**	*33, 69*
ALAT, UI/L	30 (23-47)	37 (27-64)	0.058	*34, 71*
Bilirubin, mg/L	6 (4-8)	9 (6-13)	0.157	*34, 71*
Troponin T HS, ng/L	6 (4-13)	12 (8-21)	0.119	*31, 63*
Nt-pro BNP, ng/L	131 (52-214)	230 (54-1,713)	0.745	*21, 44*
Ferritin, ng/mL	632 (460-985)	1,626 (903-3,031)	**0.034**	*8, 15*
PaO_2 in room air, mmHg	68 (62-83)	63 (52-74)	**0.010**	*29, 61*
$PaCO_2$ in room air, mmHg	34 (32-38)	35 (32-38)	0.762	*29, 61*

Data are expressed as median (IQR). IQR is presented as first quartile (Q1) – third quartile (Q3). ALAT: alanine aminotransferase; ASAT: aspartate transaminase ; CPK: creatine phosphokinase; CRP: C-Reactive Protein; IQR: interquartile range; LDH: lactate dehydrogenase; Nt-pro BNP: N-terminal pro–B-type natriuretic peptide; PaCO2: arterial partial pressure of carbon dioxide; PaO2: arterial partial pressure of oxygen; Troponin T HS: high-sensitive cardiac troponin T.

Table 4. Computed of the chest features of COVID-19 pneumonia

Variable	Asthmatics (n = 37)	Controls (n = 75)*	p-value
Ground glass opacities	36 (97)	64 (97)	1.000
Consolidations	26 (70)	56 (85)	0.132
Lower lobes predominance	19 (51)	44 (67)	0.187
Crazy paving	13 (38)	30 (45)	0.453
Topography			
Peripheral	22 (59)	39 (59)	0.971
Central	1 (3)	1 (2)	1.000
Mixed	14 (38)	26 (39)	0.876
Lesion extent			
Mild (< 10 %)	9 (24)	6 (9)	**0.035**
Moderate (10-25 %)	15 (41)	18 (27)	0.166
Severe (25-50 %)	11 (30)	31 (47)	0.088
Very severe (50-75 %)	1 (3)	10 (16)	**0.050**
Critical (> 75 %)	1 (3)	1 (1)	1.000
Mild-to-moderate	24 (65)	24 (36)	**0.005**
Severe-to-critical	13 (35)	42 (64)	**0.005**

*Data are expressed as number of occurrence, n (% of total). * 66 available data*

Table 5. Management of asthmatic patients with COVID-19

Management	
Oxygen	30 (81)
Antibiotic(s)	31 (84)
Azithromycin	16 (52)
IV or oral CS for asthma exacerbation during hospitalization	1 (3)
SABA prescription	31/36 (86)
pMDI + spacer chamber	29/31 (94)
DPI	2/31 (6)
Nebulized	4/31 (13)
Asthma controller treatment adjustment	
Maintenance	33/35 (94)
Stepped-up	1/35 (3)

Quantitative data are expressed as median (IQR). IQR is presented as first quartile (Q1) – third quartile (Q3). Qualitative data are expressed as number of occurrences, n (% of total). In case of variable with missing data, the number of patients with available information is specified. CS: corticosteroids; DPI: dry powder inhaler; IQR: interquartile range; IV: intravenous; pMDI: pressurized metered-dose inhaler; SABA: short-acting bronchodilators.

Table 6. Description of asthmatics admitted or not in ICU

Patients characteristics	ICU (n = 11)	No ICU (n = 26)	p value
Age (years)	61 (50-68)	50 (41-61)	0.162
Gender, male/female	4 (26) / 7 (64)	7 (17) / 19 (73)	0.699
BMI (kg/m²)	29 (28-32)	28 (25-31)	0.144
Tobacco exposure :			
Current/former smokers	3 (27)	9 (35)	1.000
Never smokers	8 (73)	17 (65)	1.000
Asthma management			
No ICS	2 (18)	10 (38)	0.279
Low/medium dose ICS	4 (36)	10 (38)	1.000
High dose ICS	5 (45)	6 (24)	0.244
Biologic therapy (omalizumab)	1 (9)	1 (4)	
Oral corticosteroids	1 (9)	0 (0)	
Comorbid conditions			
1. Obesity (BMI ≥ 30)	5 (45)	8 (31)	0.465
2. Overweight (25 ≤ BMI < 30)	6 (55)	12 (46)	0.728
3. Hypertension	6 (55)	5 (19)	0.051
4. Diabetes	1 (9)	6 (32)	0.649
5. Renal failure	1 (9)	2 (8)	1.000
6. Coronary heart disease	0 (0)	2 (8)	1.000
At least two of the six	7 (64)	8 (31)	0.080

Quantitative data are expressed as median (IQR). IQR is presented as first quartile (Q1) – third quartile (Q3). Qualitative data are expressed as number of occurrences, n (% of total). BMI : body mass index; ICS : inhaled corticosteroids; ICU : intensive care unit.

FIGURES

Figure 1. Blood lymphocyte (A) and eosinophil (B) count at admission

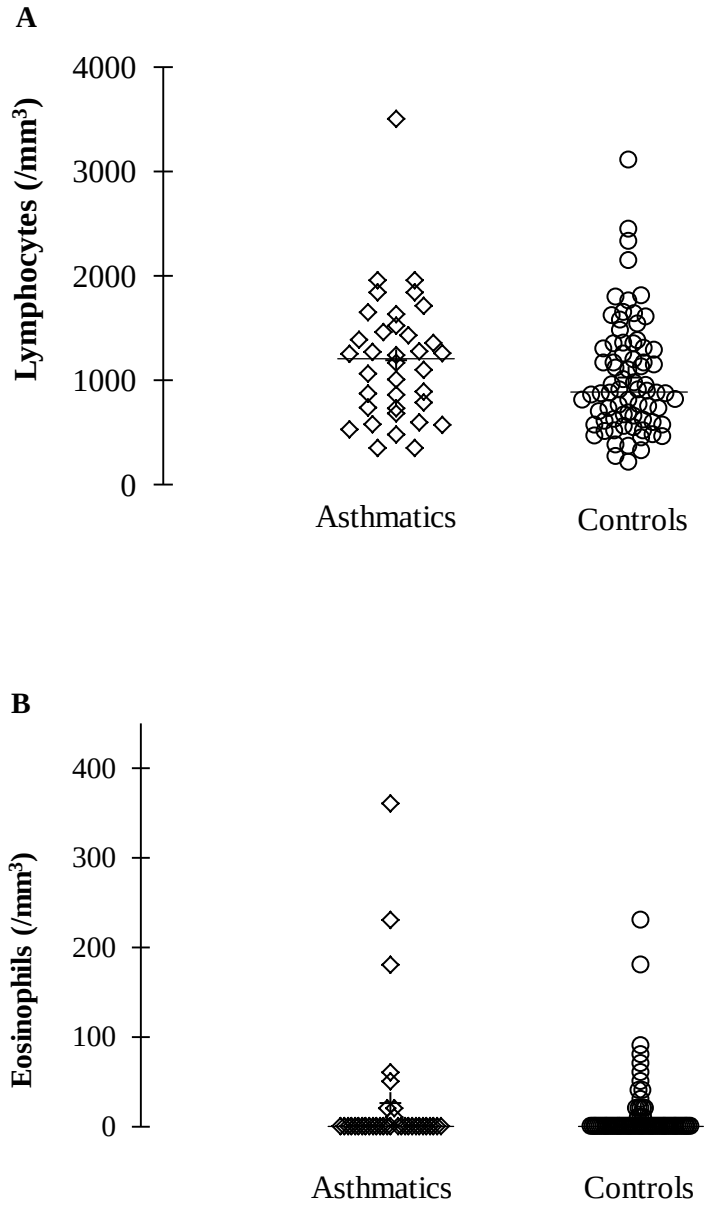
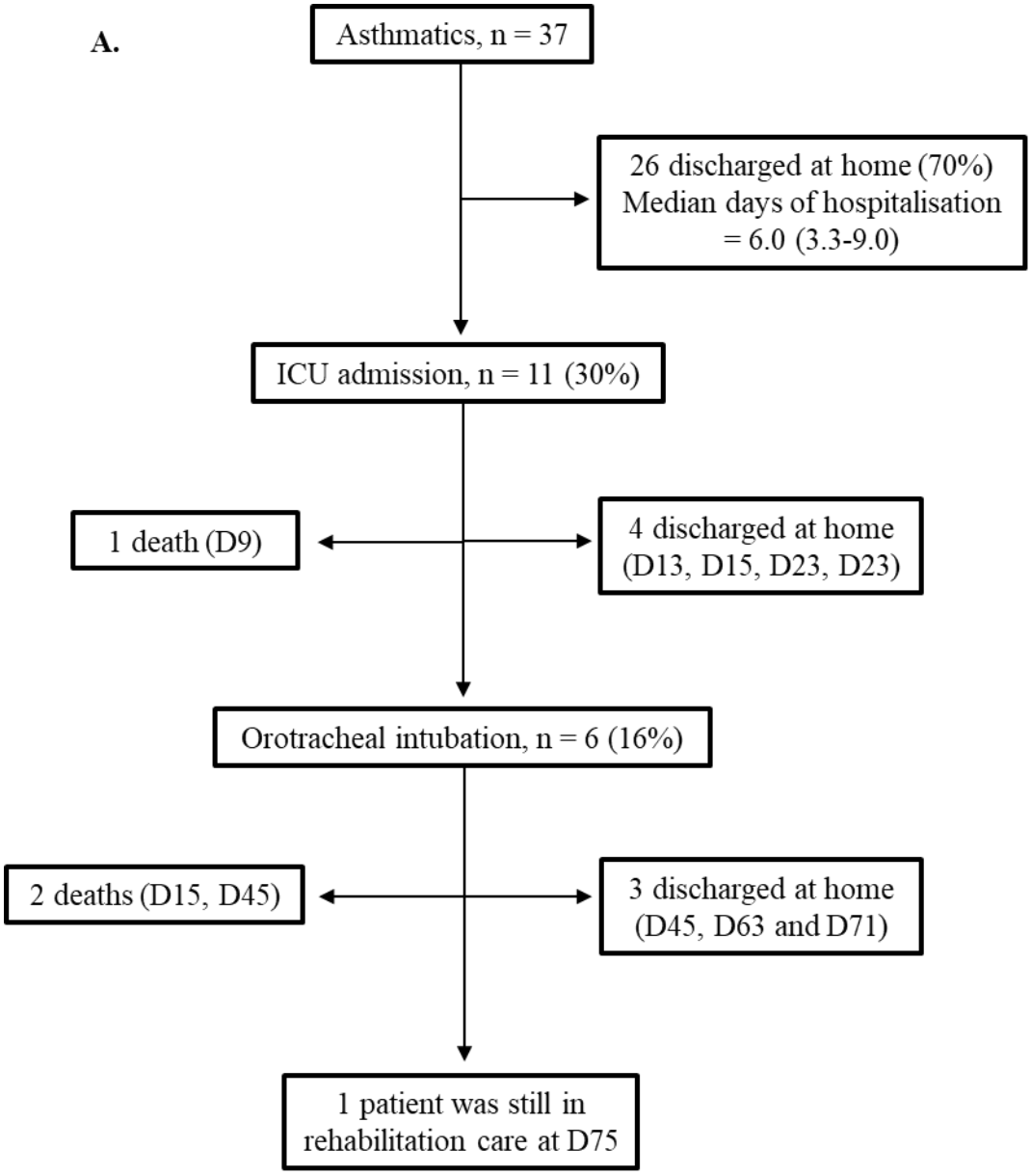


Figure 2. Outcomes of patients with COVID-19 pneumonia



B.

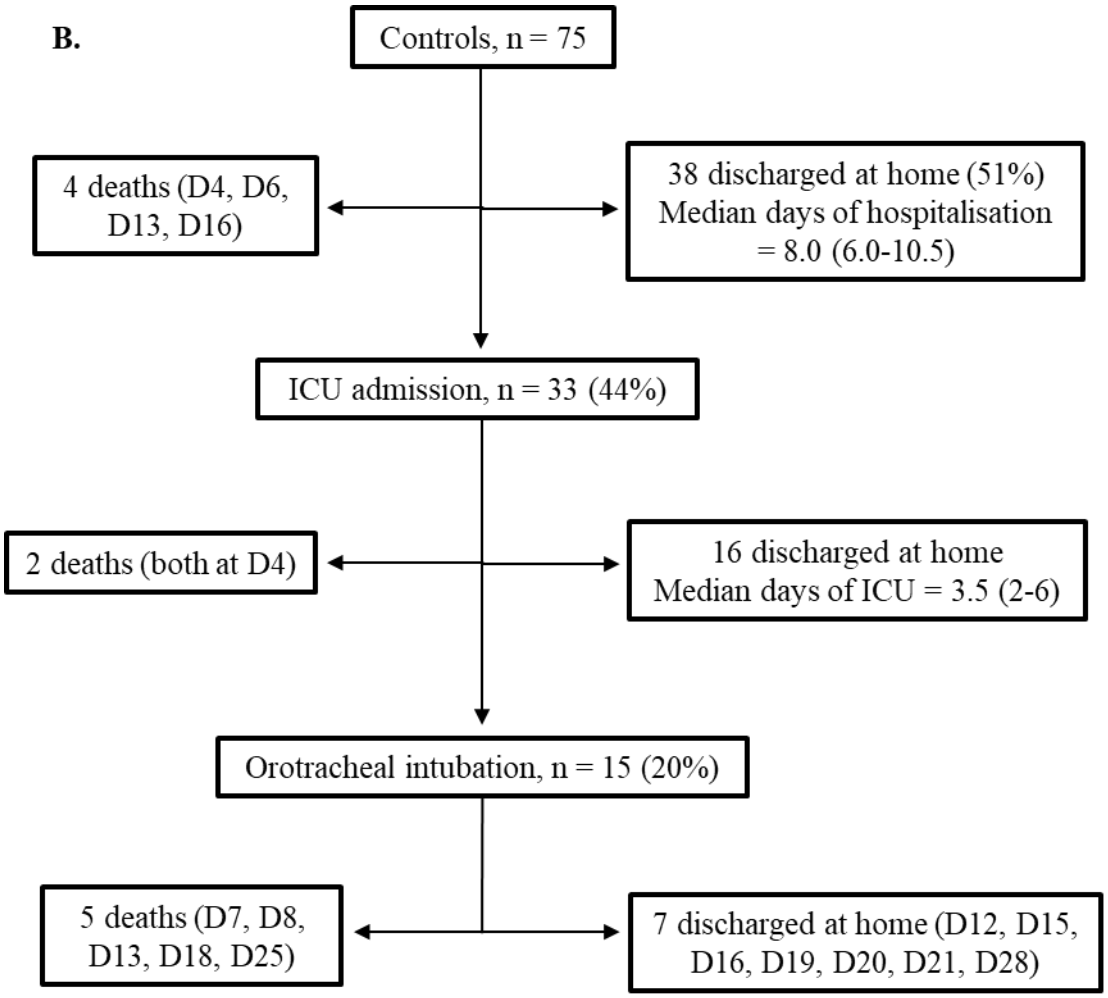

Controls, n = 75
4 deaths (D4, D6, D13, D16)
38 discharged at home (51%)
Median days of hospitalisation = 8.0 (6.0-10.5)
ICU admission, n = 33 (44%)
2 deaths (both at D4)
16 discharged at home
Median days of ICU = 3.5 (2-6)
Orotracheal intubation, n = 15 (20%)
5 deaths (D7, D8, D13, D18, D25)
7 discharged at home (D12, D15, D16, D19, D20, D21, D28)

Figure 3. Proportion of asthmatics discharged at home at 30 days according to the number of their comorbidities

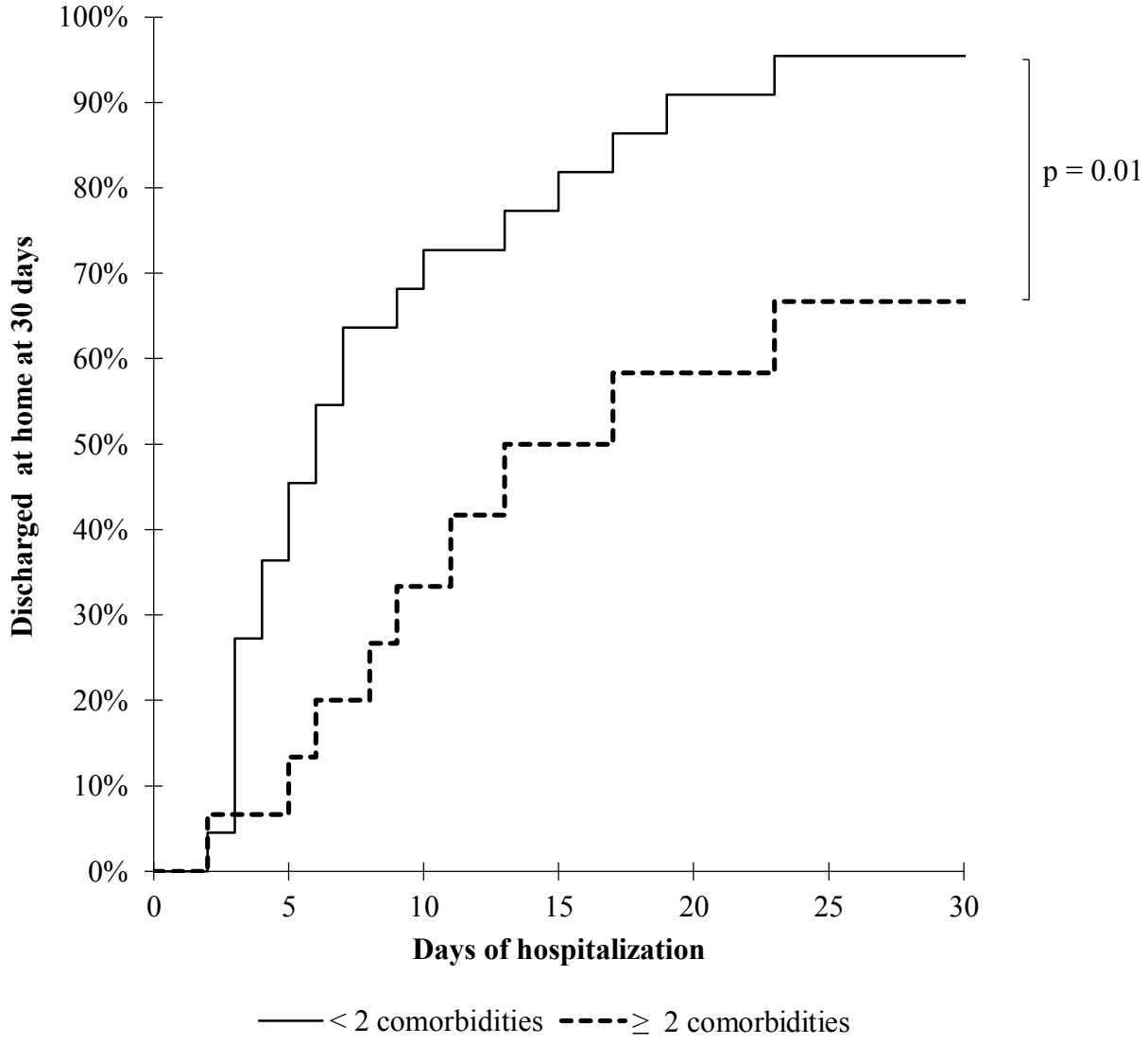
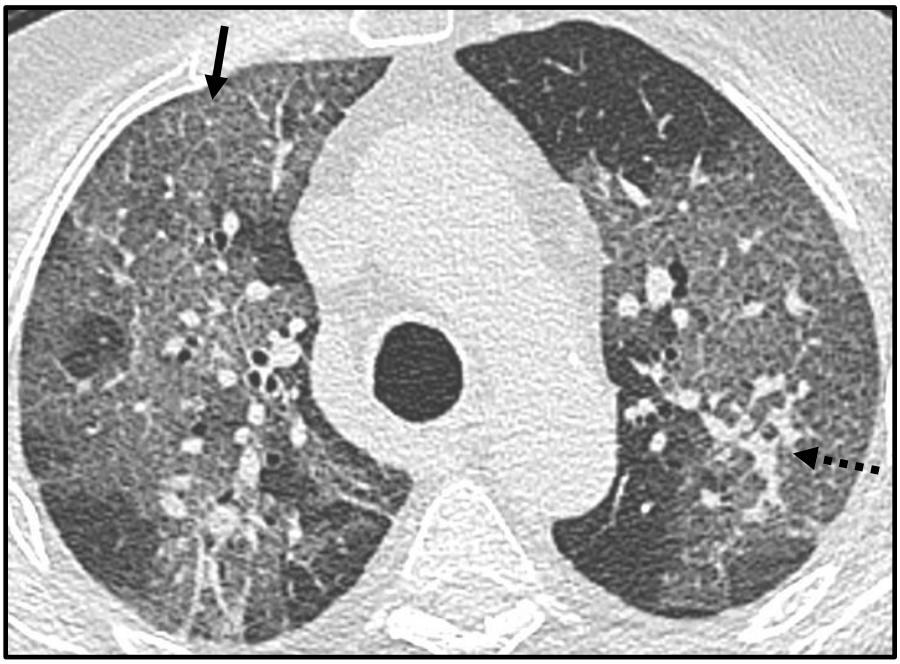
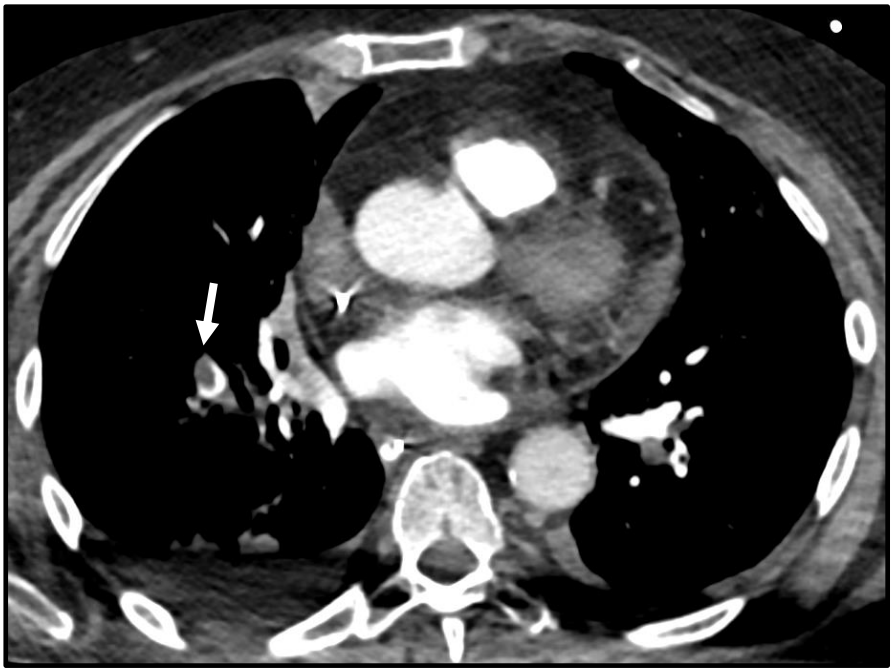


Figure 4. Computed tomography of the chest of the same patient with severe allergic asthma at day 1 (A) and day 12 (B) of hospitalization.

A.



B.

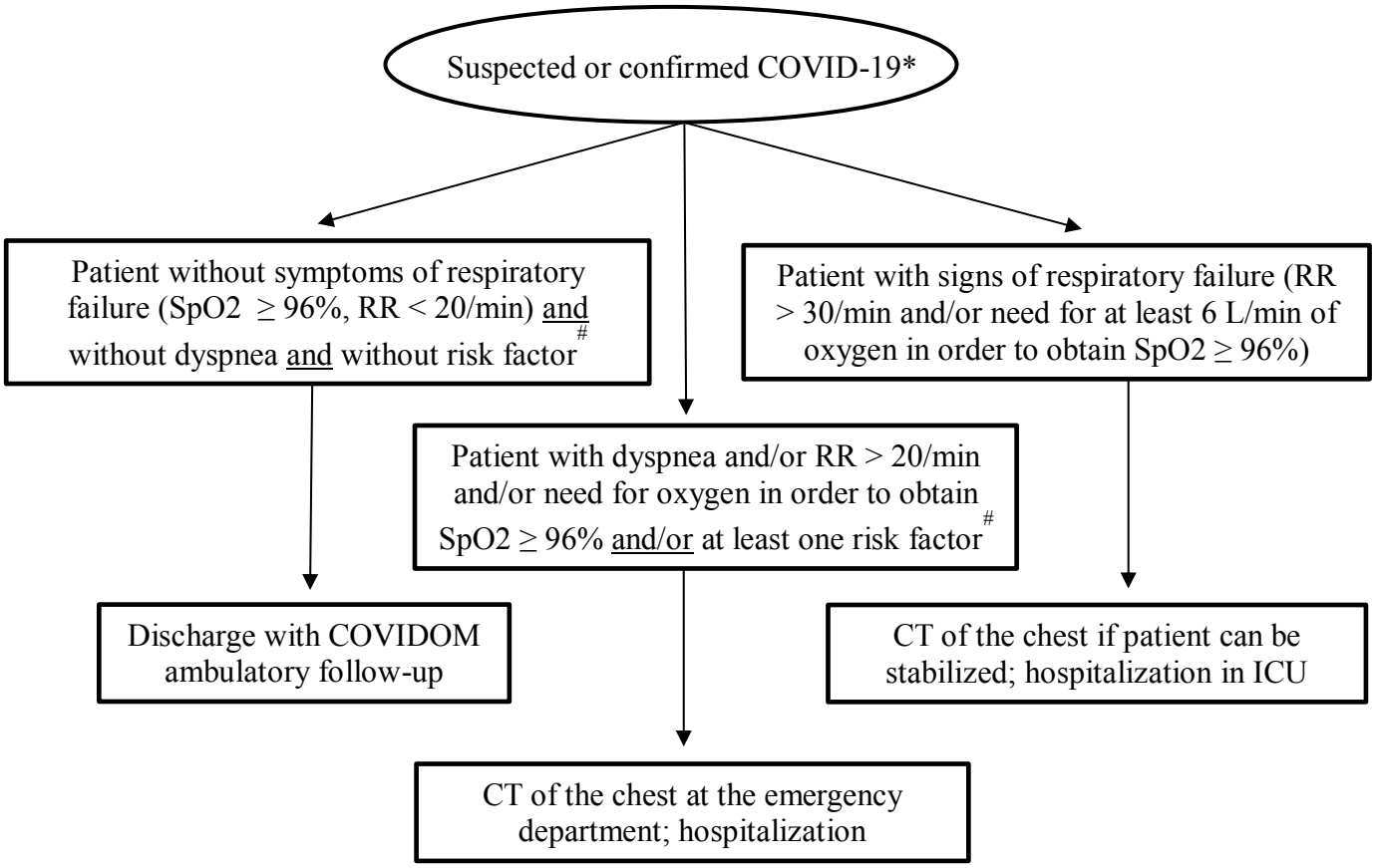


A : Typical extended ground glass opacities with crazy-paving pattern (solid arrow) and nodular consolidations (dashed arrow).

B : Computed tomography with pulmonary angiography revealing acute pulmonary embolism in the right lower lobe pulmonary artery (white arrow).

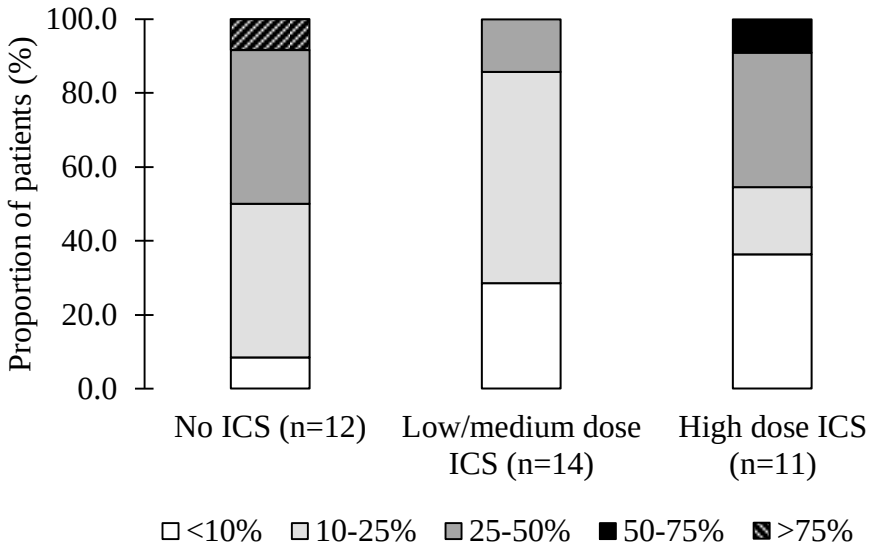
SUPPLEMENTARY DATA

Figure S1. Decision algorithm in Bicêtre Hospital, during the spring 2020 COVID-19 outbreak



*COVIDOM is the French ambulatory follow-up health care program for patients with COVID-19; ICU: intensive care unit; SpO2: oxygen peripheral saturation while breathing room air; RR: respiratory rate; *COVID-19 was highly suspected if symptoms and/or CT-scan were typical; diagnosis was confirmed by positive RT-PCR. #List of risk factors : age > 65 years; obesity; chronic respiratory failure; heart failure; renal failure; cirrhosis; diabetes; immunosuppression/cancer; pregnancy.*

Figure S2. Pneumonia severity according to ICS doses



ICS : inhaled corticosteroids

Table S1. Daily doses of asthma controller at admission

SABA alone	11 (30)
Salbutamol 100 µg p.r.n	9
Terbutaline 500 mg p.r.n	2
LTRA (GINA 2)	1 (2)
Montelukast, 10 mg	1
Medium dose ICS (GINA 2)	1 (2)
Non-extrafine particle beclometasone pMDI, 1000µg	1
Low-dose ICS/LABA (GINA 3)	5 (14)
Fluticasone furoate/vilanterol DPI, 92/22 µg	1
Budesonide/formoterol DPI, 400/12 µg	4
Medium-dose ICS/LABA (GINA 4)	8 (22)
Fluticasone proprionate/salmeterol	3
pMDI, 500/50 µg	1
DPI, 500/100 µg	2
Extrafine particle beclometasone/fomoterol	5
pMDI, 400/24 µg	4
Add-on montelukast, 10 mg	1
DPI, 400/12 µg	1
High-dose ICS/LABA (GINA 5)	11 (30)
Fluticasone proprionate/salmeterol	7
DPI, 1000/100 µg	5
Add-on tiotropium SMI, 5µg	1
DPI, 2000/200 µg	1
pMDI, 1000/100 µg	1
Extrafine particle beclometasone/fomoterol DPI, 800/24 µg	1
Budesonide/formoterol DPI, 1600/48 µg	3
Add-on omalizumab, 300 mg twice monthly	2
Add-on oral CS, 5 mg daily	1

CS: corticosteroids; DPI: dry powder inhaler; LTRA : leukotriene receptor antagonist; pMDI: pressurized metered-dose inhaler; SABA: short-acting bronchodilators.