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# **SARS-CoV-2 pneumonia in hospitalized asthmatic patients did not induce severe exacerbation**

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46 **Abstract**

47

48 Background: Viral infections are known to exacerbate asthma in adults. Previous studies  
49 have found few asthmatics among SARS-CoV-2 pneumonia cases. However, the  
50 relationship between SARS-CoV-2 infection and severe asthma exacerbation is not known.

51

52 Objective: We assessed the frequency of asthma exacerbation in asthmatic patients  
53 hospitalized for SARS-CoV-2 pneumonia and compared symptoms laboratory and  
54 radiological findings in asthmatic and non-asthmatic patients with SARS-CoV-2 pneumonia.

55

56 Methods: We included 106 patients between March 4 and April 6, 2020, who were  
57 hospitalized in the Chest Diseases Department of Strasbourg University Hospital; 23 were  
58 asthmatics. To assess the patients' asthma status, three periods were defined: the last  
59 month before the onset of COVID-19 symptoms (p1), pre-hospitalization (p2) and during  
60 hospitalization (p3). Severe asthma exacerbations were defined according to GINA guidelines  
61 during p1 and p2. During p3, we defined severe asthma deterioration as the onset of  
62 breathlessness and wheezing requiring systemic corticosteroids and inhaled beta-2-agonist.

63

64 Results: We found no significant difference between asthmatics and non-asthmatics in  
65 terms of severity (length of stay, maximal oxygen flow needed, non-invasive ventilation  
66 requirement and ICU transfer). 52.2% of the asthmatic patients were Gina 1. One patient  
67 had a severe exacerbation during p1, two patients during p2, and five patients were  
68 treated with systemic corticosteroids and inhaled beta-2-agonist during p3.

69

70 Conclusion: Our results demonstrate that asthmatic patients appeared not to be at risk for  
71 severe SARS-CoV-2 pneumonia. Moreover, SARS-CoV-2 pneumonia did not induce severe  
72 asthma exacerbation.

73

74 **Highlights box:**

75 1. What is already known about this topic? Asthmatic patients are rare in epidemiological  
76 studies of SARS-CoV-2 pneumonia.

77 2. What does this article add to our knowledge? Being asthmatic is not a risk factor for  
78 severe SARS-CoV-2.

79 3. How does this study impact current management guidelines? SARS-CoV-2 pneumonia  
80 may not induce severe asthma exacerbation.

81

82 **Key words:**

83 Coronavirus, COVID-19, SARS-CoV-2, SARS-CoV-2 pneumonia, asthma, exacerbation,  
84 France, Europe.

85

86 **Abbreviations:**

87 SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

88 COVID-19: Coronavirus Disease 2019

89 ACE2: Angiotensin Converting Enzyme 2

90 qRT-PCR: quantitative real-time Reverse Transcriptase PCR

91 COPD: Chronic Obstructive Pulmonary Disease

92 FEV1: Flow Expiratory Volume in one second

93 FVC: Flow Volume Capacity

94 ICU: Intensive Care Unit

95 BMI: Body Mass Index

96

97 **Introduction**

98

99           At the end of December 2019, Chinese public health authorities reported several  
100 cases of acute respiratory syndrome in Wuhan City, Hubei province in China (1). Since then,  
101 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus  
102 disease 2019 (COVID-19), has spread across the globe, leading to a Public Health Emergency  
103 of International Concern on January 30, 2020, and resulting in a pandemic (2). The most  
104 common symptoms of COVID-19 are fever and respiratory symptoms, including cough, sore  
105 throat and shortness of breath (3). Other noted symptoms include fatigue, myalgia, diarrhea,  
106 abdominal pain, and recently anosmia, dysgeusia (4) and confusion (5). Many patients also  
107 develop lymphopenia and pneumonia with characteristic pulmonary ground glass opacity  
108 changes on chest CT (6,7).

109

110 The pathophysiology mechanisms are not yet well characterized. After inhalation of SARS-  
111 CoV-2 through aerosolized uptake, the virus likely binds to epithelial cells from the nasal  
112 cavity, starts replicating and reach the lower respiratory tract. The main receptor for the  
113 SARS-CoV2 spike is the Angiotensin converting enzyme 2 (ACE2) that is expressed in several  
114 organs such as the lung, heart, kidney, intestine and endothelial cells. For about 20% of the  
115 infected patients, the disease will progress to a pneumoniae through propagation of SARS-  
116 CoV within type II cells through ACE2 and will compromise the alveolo-capilar space. It may  
117 result in a diffuse alveolar damage and fibrosis. A hyperinflammatory syndrome called  
118 “cytokine storm” consisting in fever, cytopenias, hyperferritinaemia, diffuse alveolar damage  
119 and hypercytokinaemia, may occur during this phase. It may lead to multiorgan failure and  
120 high rate of mortality. From an immunologic point of view it is characterized by an increased  
121 interleukin (IL)-2, IL-7, granulocyte-colony stimulating factor, interferon- $\gamma$  inducible protein  
122 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1- $\alpha$ , and  
123 tumour necrosis factor- $\alpha$  (8–11).

124

125 Viral infections exacerbated asthma up to 41% of adult patients. Rhinoviruses (RVs) were the  
126 most frequently detected type of virus. Other respiratory tract viruses, including respiratory  
127 syncytial virus, influenza viruses, coronaviruses, human metapneumoviruses, parainfluenza

128 viruses, adenoviruses, and bocaviruses, have also been detected in patients with asthma  
129 exacerbation (12).

130

131           Until now, coronaviruses seemed to only make a minor contribution to asthma  
132 exacerbation in adults (12). Although the Centers for Disease Control and Prevention stated  
133 that patients with moderate-severe asthma could be at greater risk of more severe COVID-  
134 19 (13), no published data support this statement at this time. However, Zhang *et al*  
135 reported that allergic disease and asthma were not risk factors for SARS-CoV-2 infection in  
136 140 Chinese patients (14).

137

138 The aims of the present study were:

- 139       - to assess the frequency of asthma exacerbation in asthmatic patients hospitalized  
140       for SARS-CoV-2 pneumonia,
- 141       - and to compare the symptoms and, biological and radiological findings in asthmatic  
142       and non-asthmatic patients with SARS-CoV-2 pneumonia.

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144

## 145 **Methods**

146

### 147 **Study design and population**

148

149       This was a monocentric, retrospective, cohort study using clinical, radiological, and  
150       laboratory data obtained from patients hospitalized at the Chest Diseases Department of  
151       Strasbourg University Hospital.

152       The study population consisted of 106 patients with SARS-CoV-2 pneumonia hospitalized  
153       between March 4 and April 6, 2020. Since the outbreak of COVID-19, 60 of 86 beds in  
154       our department have been devoted to the treatment of SARS-CoV-2 pneumonia,  
155       including non-invasive ventilatory support.

156

157       SARS-CoV-2 pneumonia diagnosis was established based on the presence of all the  
158       following:

- 159 - clinical symptoms: fever, asthenia, dyspnea, tachypnea, cough, chest pain and/or  
160 crackles
- 161 - chest CT manifestations indicating SARS-Cov-2 pneumonia according to the  
162 literature: ground glass opacity, bilateral involvement, peripheral distribution,  
163 multilobar involvement, consolidations (15–17). All CT images were acquired using an  
164 80-row CT scanner (Aquilion PRIME SP, Canon Medical Systems) without injection.  
165 Quality of imaging was chosen according to the patient age and BMI. When possible,  
166 patients were instructed to hold their breath and raise their arms above their head to  
167 minimize artefacts. Images were reconstructed with a slice-thickness of 1 mm in the  
168 mediastinal and parenchymal windows and transmitted to post-processing  
169 workstations for multiplanar and maximum intensity projection reconstructions.
- 170 - positive laboratory confirmation of SARS-CoV-2 infection (centralized in Strasbourg  
171 Hospital Viral Laboratory). Quantitative real-time reverse transcriptase PCR (qRT-  
172 PCR) tests for SARS-CoV-2 nucleic acid were performed using nasopharyngeal swabs  
173 (18). The primer and probe sequences target two regions on the RdRp gene and are  
174 specific to SARS-CoV-2. Assay sensitivity is approximately 10 copies/reaction.

175

176 Among the 106 patients with SARS-CoV-2 pneumonia, 23 had a clinical diagnosis of  
177 asthma based on the clinical history recorded by medical staff. All of the clinical data  
178 were verified with the patient's General Practitioner and specialists (allergists,  
179 pulmonologists).

180 Because we are a reference center for asthma, almost all SARS-CoV-2 pneumonia in  
181 asthmatics hospitalized at the emergency room of Strasbourg University Hospital were  
182 referred to our department.

183

184 To assess the patient's asthma status, we defined three periods. The first period was the  
185 last month before the onset of COVID-19 symptoms (p1). The second period was the pre-  
186 hospitalization period between the beginning of the SARS-CoV-2 infection symptoms and  
187 the first day of hospitalization (p2). The third period was during hospitalization (p3).

188 Severe asthma exacerbations were assessed during p1 and p2 periods, and defined as a  
189 deterioration in asthma resulting in hospitalization or emergency room treatment or the  
190 need for oral steroids for more than 3 consecutive days (19)

191 During the hospitalization (p3), we defined symptoms corresponding to asthma as  
192 breathlessness and wheezing requiring systemic corticosteroids and inhaled beta-2-  
193 agonist.

194 This study was performed in accordance with the Declaration of Helsinki and with Good  
195 Clinical Practice guidelines. We received approval from the Clinical Research Ethic  
196 Committee of Strasbourg University Hospital (CE-2020-56). Oral informed consent was  
197 obtained from all patients. All personal data was remained confidential and were  
198 anonymized.

199

#### 200 **Data collection**

201

202 Demographic, clinical, laboratory, and radiological data were recorded during routine  
203 healthcare. All study variables were reported on a standardized data-collection sheet.

204

205 For all patients, the clinical data included the delay before onset of COVID-19 symptoms  
206 and hospitalization; symptoms at admission (e.g., fever, asthenia, anorexia, myalgia,  
207 confusion, odynophagia, nasal obstruction, rhinorrhea, acute anosmia, sneezes,  
208 gastrointestinal symptoms, cough, dyspnea, chest tightness, respiratory frequency,  
209 wheezing and crackles); maximum oxygen flow, non-invasive ventilation need, intensive  
210 care unit transfer for mechanical ventilation or death ; smoking habits (past smoker,  
211 current smoker and the smoking index) ; and health issues such as hypertension, obesity  
212 (defined by BMI  $\geq 30$  kg/m<sup>2</sup>), cardiopathy, diabetes mellitus, chronic renal insufficiency,  
213 lung cancer and obstructive sleep apnea.

214

215 Lung CT images were analyzed and the global percentage of abnormal lung parenchyma  
216 visually estimated and classified by two experienced radiologists into four categories  
217 following the French Society of Thoracic Imaging guidelines (20): absent/minimal (<10%),  
218 moderate (10-25%), extensive (26-50%), severe/critical (>50%).



219

220 Laboratory results comprised neutrophil, lymphocyte, and eosinophil counts, and C-  
221 reactive protein (CRP) level.

222

223 Disease-relevant variables for asthma were age at onset (stratified on “< 18”, “18-50”  
224 and “> 50 years”); eosinophil count before the beginning of COVID-19 infection; allergic  
225 status based on clinical history and/or skin test results; spirometry (FEV1 and FEV1/FVC);  
226 severity of asthma (the number of severe exacerbations during the last 12 months (19),  
227 number of hospitalizations in the intensive care unit, step treatment according to GINA  
228 2019); comorbidities (i.e., gastroesophageal reflux, obstructive sleep apnea,  
229 hyperventilation syndrome, chronic rhinosinusitis with polyposis, anti-inflammatory  
230 drugs hypersensitivity, paradoxical vocal cord motion disorder); asthma control, during  
231 the last 4 weeks before the beginning of SARS-CoV-2 infection based on the GINA  
232 guidelines (well controlled, partly controlled, or uncontrolled) (21).

233

#### 234 **Statistical analysis**

235

236 We summarized continuous measures as medians and interquartile ranges (IQRs) and  
237 categorical variables as frequencies and proportions. We tested comparisons between  
238 asthmatic and non-asthmatic patients using Fisher’s exact or chi-squared tests for  
239 categorical variables and the Wilcoxon rank-sum test for numerical variables. Due to the  
240 absence of randomization and to adjust for possible confounding factors, we performed  
241 multivariable logistic regression analysis using a binomial generalized linear model to  
242 determine the adjusted odds ratio (aOR). Variables with  $p < 0.1$  in the univariate analysis  
243 were selected as independent variables in the multivariate model. To evaluate whether  
244 asthma is associated with and a risk factor for severe COVID-19 outcomes, we used  
245 propensity scores to adjust for confounding variables. The propensity score allows analyzing  
246 an observational nonrandomized study so that it mimics some of the particular  
247 characteristics of a randomized controlled trial as it accounts for systematic differences in  
248 baseline characteristics between asthmatic and non-asthmatic subjects when estimating the  
249 effect of asthma on severe COVID-19 outcomes. Propensity scores were generated by  
250 multiple logistic regression using known risk factors for COVID-19 (age, sex, hypertension,

251 diabetes, BMI  $\geq$  30kg/m<sup>2</sup> and heart failure) as independent variables. Finally, we used a  
252 generalized linear mixed-effect models with subjects as a random effect to evaluate change  
253 in asthma exacerbation (logistic regression) and change in eosinophil counts (Gaussian  
254 regression) during the three different time periods. Statistical analysis were performed using  
255 R software version 3.6.3 (<https://cran.rproject.org>). P < 0.05 was considered significant.

256

257

## 258 **Results**

259

### 260 **Study population**

261

262 A total of 114 patients were hospitalized for suspicion of SARS-CoV-2 pneumonia between  
263 March 4 and April 6, 2020, in a dedicated COVID-19 Unit in the Chest Diseases Department  
264 of Strasbourg University Hospital. Of these patients, 106 were included in the present  
265 study (Figure 1). The clinical characteristics are described in Table I.

266

### 267 **Clinical symptoms and biological and radiological status of all patients**

268

269 The clinical symptoms and biological and radiological status of all patients are described in  
270 Table II. In univariate analysis, dyspnea, chest tightness, and wheezing were significantly  
271 associated with the asthmatic status of the patients. Once adjusted in multivariate  
272 analysis, only chest tightness was more frequent in asthmatic than non-asthmatic patients  
273 (aOR 4.798 [95% CI 1.111-21.783]).

274 Eosinopenia (eosinophil count  $\leq$  0.05g/L) was found in 88.7% of all patients and  
275 lymphopenia (lymphocyte count  $\leq$  1.0g/L) in 60.4% at admission, with no difference  
276 between the two groups.

277 The global severity of lung parenchyma involvement was similar in the two groups. In a  
278 propensity score adjusted analysis, being asthmatic was not a risk factor for having more  
279 involvement of the lung parenchyma (OR 0.904 [95% CI 0.409–1.790], p=0.786).

280

281

282 **Clinical characteristics of asthmatic patients**

283

284 The clinical characteristics of asthmatic patients are described in Table III. We found that  
285 52.2% of the patients were Gina 1 and were not receiving any inhaled corticosteroid, and  
286 39.1% were Gina 4 and 5. Only one patient was treated with biotherapy and oral  
287 corticosteroids. Among asthmatic patients, 63.6% were well-controlled and 23.4% were  
288 partially controlled. Eleven of the 23 asthmatic patients had at least one severe  
289 exacerbation in the previous year, and 68.2% were considered allergic asthma according to  
290 the clinical history. The median eosinophil count before SARS-CoV-2 infection was 0.19  
291 [0,11-0,30] g/L.

292

293 **Patient outcomes**

294

295 Twenty-one patients (19.8%) required ICU management and mechanical ventilation. No  
296 difference was found between the asthmatic and non-asthmatic groups. Eighty of 106  
297 patients had a favorable outcome and were discharged from the hospital. No death was  
298 observed in the asthmatic group. Length of stay ( $p = 0.64$ ), maximal oxygen flow needed  
299 ( $p = 0.83$ ), and the frequency of non-invasive ventilation were similar in the two groups. In  
300 a propensity score adjusted analysis, being asthmatic was not a risk factor for transfer to  
301 the ICU (aOR 1.065 [95% CI 0,272-3,522] ;  $p = 0.92$ ) or for longer length of stay (aOR 1.614  
302 [95% CI 0,586-4.585];  $p = 0.36$ ). The eosinophil counts returned back to normal for 74.5% of  
303 all patients at discharge. In a generalized linear mixed-effect model eosinophil counts  
304 changed significantly over the three time periods ( $p < 0.001$ ), but not asthma ( $p = 0.29$ ).

305

306 **Comparison of asthma exacerbation over time**

307

308 In the first period ( $p_1$ ), only one patient had a severe exacerbation. In the second period  
309 ( $p_2$ ), two patients developed a severe exacerbation. In the third period ( $p_3$ ), five patients  
310 were being treated with systemic corticosteroids because of asthma symptoms. For three  
311 of them, systemic corticosteroids were started only in  $p_3$ . Using exacerbation as a  
312 dependent variable in a generalized linear mixed-effect model, no time-period effect was  
313 found ( $p = 0.09$ , Figure 2).

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**Discussion**

In the eastern part of France, we have been facing a severe COVID-19 epidemic. At the height of the epidemic, Strasbourg University Hospital, had 429 beds in conventional medicine units, and 207 in an ICU devoted to COVID-19. As our department is a reference center for asthma, SARS-CoV-2 pneumonia in asthmatic patients was primarily referred to us. In the same period, we estimated that five patients with a clinical history of asthma had been hospitalized in other medical departments. This could explained why we had a higher prevalence of asthmatics in our population (21.7%) than previous publications (14,22,23). The clinical history of asthma was carefully verified with the patient, the general practitioner, and when possible with the specialist (allergist or pulmonologist). The clinical history was recorded by two different doctors on two different occasions.

We did not observe any increase in severe exacerbation with the development of SARS-CoV-2 pneumonia. This result is not in line with other respiratory viruses. Viral respiratory infections are detected in up to 85% of asthma exacerbations in children and approximately half of exacerbations in adults (12,24,25). During asthma exacerbation in adults, the most frequently detected viruses are rhinoviruses (42.1%), respiratory syncytial virus (13.6%), herpes simplex virus (12.3%), influenza virus (10%), parainfluenzavirus (5.3%), coronaviruses (8.4%), metapneumovirus (5.3%), Bocavirus (6.9%) and adenovirus (3.8%) (26).

Papadoupolos et al noted that reported respiratory infection rates for coronaviruses among children usually range from <1% to 9%, with varied distribution between subtypes, and that, coronavirus infections are often associated with other viruses (12). For adults coming into the emergency department for acute asthma exacerbation, coronaviruses have been found in only 4% of induced sputum samples (27). No data are available on the asthma exacerbation rate and SARS-CoV-1 or Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection. Overall, coronaviruses seem to make a minor contribution to acute asthma exacerbation.

344 In contrast to other respiratory viruses, SARS-CoV-2 may not be a risk factor for severe  
345 asthma exacerbation. Several hypotheses can be raised.  
346 Firstly, SARS-CoV-2 may be a disease mainly of the upper and lower respiratory tract, causing  
347 ENT infection and pulmonary lesions. Angiotensin-converting enzyme 2 (ACE2) has been  
348 shown to be the functional receptor of SARS-CoV-1 (28). This receptor is abundantly  
349 expressed in type I and type II pneumocytes whereas bronchial epithelial cells exhibit only  
350 weak staining (29,30). ACE2 has also been identified as the receptor of novel SARS-CoV-2  
351 (31), indicating that alveolar pneumocytes in the lung could be a possible entry site for SARS-  
352 CoV-2. However, ACE expression is not limited to the lungs, and extrapulmonary spread of  
353 SARS-CoV in ACE2 positive tissues has been observed. The same can be expected for SARS-  
354 CoV-2 (32). This is in accordance with the suggestion that COVID-19 seems to induce a  
355 specific pathology of the alveolo-capillary space leading to severe altered gas exchanges and  
356 pulmonary-specific vasculopathy (33,34). Very recently it has been suggested that ACE2  
357 expression in nasal epithelium was inversely related to allergic sensitization (35).

358

359 The second hypothesis involves the role of eosinophil cells. In our population, 88.7% of  
360 patients had a low eosinophil count at admission. The eosinophil count had returned to  
361 normal at discharge for 74.5% of patients. Fang Liu et al. described similar results with a  
362 low eosinophil count at admission and demonstrated that the increase in eosinophils may  
363 be an indicator of COVID-19 improvement. In their study, during the period of lower  
364 eosinophil count, the SARS-CoV-2 RNA test remained positive, and after the eosinophil  
365 count returned to normal, the SARS-CoV-2 RNA test was negative within 5 days. The  
366 normalization of eosinophil count is also associated with improved symptoms and chest X-  
367 rays (36). However, that previous study included non-asthmatic patients. In our patients,  
368 we did not find any significant difference in eosinophil counts between asthmatic and non-  
369 asthmatic patients.

370 The role of eosinophils in asthma exacerbation is widely published. Since the first paper on  
371 the relationship between eosinophil count and asthma severity (37), several publications  
372 have confirmed a relationship between eosinophil count and frequency of asthma  
373 exacerbation (38). Decreasing the number of eosinophils in eosinophilic asthma is  
374 associated with a reduction in severe exacerbation, use of systemic corticosteroids, or  
375 biotherapy (e.g., anti-IL5 or anti-IL5 receptor) (39,40). In SARS-CoV-2 pneumonia, post-

376 mortem examination did not find any eosinophils in the alveol or in the bronchi and  
377 bronchioles (41).

378 The third hypothesis is on the role of inhaled corticosteroids. In in vitro models, inhaled  
379 corticoids alone or in association with bronchodilators inhibit human coronavirus (HCoV)-  
380 229E replication, partly by inhibiting receptor expression and/or endosomal function and  
381 reducing cytokine production (IL-6, IL-8). This suggests that these drugs modulate infection-  
382 induced inflammation in the airways (42).

383

384 Roughly half of our asthmatic patients (52.2%) had GINA 1 asthma and did not use inhaled  
385 corticosteroids on a regular basis. 63.6% of them were well-controlled. We did not find any  
386 difference between the age of asthmatics and non-asthmatics. Moreover, the classical  
387 factors associated with SARS-CoV-2 pneumonia (hypertension, obesity, diabetes) were found  
388 in both groups. In contrast, the classical factors responsible for uncontrolled asthma, such as  
389 tobacco smoke, obesity and obstructive sleep apnea, were not more frequent in the  
390 asthmatic group. This suggests that the risk factors for hospitalization in our patients were  
391 related more to the risk factors of SARS-CoV-2 pneumonia than to asthma.

392

393 Furthermore, most of our asthmatic patients were considered to have allergic asthma  
394 (68.2%). In adults, the frequency of allergic asthma is approximately 50% (43,44). However,  
395 the diagnosis of clinical allergy was based on a suggestive clinical history. For only a few  
396 patients, skin tests were performed. Further studies showed that pollen may affect the  
397 development and severity of viral infection, decreasing the interferon and pro-inflammatory  
398 chemokine response of airway epithelia to the virus (45). However, only 2 (9.1%) asthmatic  
399 patients had rhino-conjunctivitis before the SARS-CoV-2 pneumonia symptoms, and none of  
400 them required oral corticosteroids for asthma during p1, p2 and p3. Thus, pollen allergy  
401 appeared not to be the reason for asthma exacerbation in our patients.

402

403 The severity and outcome of SARS-CoV-2 pneumonia were similar in the two groups in terms  
404 of lung parenchyma involvement, oxygen flow, frequency of transfer to the intensive care  
405 unit, and duration of hospitalization. This suggests that asthma would not be a risk factor for  
406 the development of severe SARS-CoV-2 pneumonia.

407 Possible limitations of our study could be linked to a monocentric recruitment of patients  
408 and low number of asthmatics included in the study. However, this reflects the findings of  
409 other larger studies (14), demonstrating a low frequency of asthmatic patients with severe  
410 SARS-CoV-2 pneumonia.

411

412

### 413 **Conclusion:**

414

415 Our results demonstrate that asthmatic patients do not experience differences in clinical  
416 symptoms or biological and radiological status in SARS-CoV-2 pneumonia. The published risk  
417 factors associated with SARS-CoV-2 pneumonia (i.e., hypertension, obesity, diabetes) were  
418 found in both asthmatic and non-asthmatic patients. In contrast, we did not find the usual  
419 risk factors responsible for uncontrolled asthma. This suggests that the COVID-19 infection  
420 was the main factor leading to hospitalization. Moreover, in contrast to other viral  
421 respiratory infections, SARS-CoV-2 pneumonia did not appear to induce severe asthma  
422 exacerbation. Larger studies would be desirable to confirm our results and understand the  
423 mechanisms explaining such findings.

424

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426

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433

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435

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558

559 **Tables and figures legends**

560

561

562 **Table I: Clinical characteristics of included patients**

563 Data are given as n (%) or median [interquartile range].

564 \*smoking index = number of cigarettes smoked per day x years of tobacco use

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568 **Table II: Clinical symptoms and biological and radiological status of all**  
569 **patients**

570 Data are given as n (%) or median [interquartile range]. aOR = adjusted odd ratio.

571 model fit : AIC: 104.68

572

573

574 **Table III: Clinical characteristics of asthmatic patients**

575 Data are given as n (%) or median [interquartile range]

576 \*Spirometry data were obtained from the patient's doctors

577 \*\* n=22, for one patient we did not obtain any information since he was immediately  
578 transferred to the ICU. For others, medical information was obtained from patients and  
579 medical report from their GP and specialists.

580 Birch pollen symptoms: rhinitis, conjunctivitis or asthma on March or April. Grass pollen:  
581 symptoms on May and June. House dust: symptoms in contact with domestic dust.

582 \*\*\* positive threshold for skin test: mean diameter of the wheal  $\geq 3$  mm compared to  
583 negative control, n=8

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585


586 **Figure 1. Flow chart of patient inclusion**


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588

589 **Figure 2. Number of patients treated or not with oral corticosteroids during**  
590 **the three periods.**

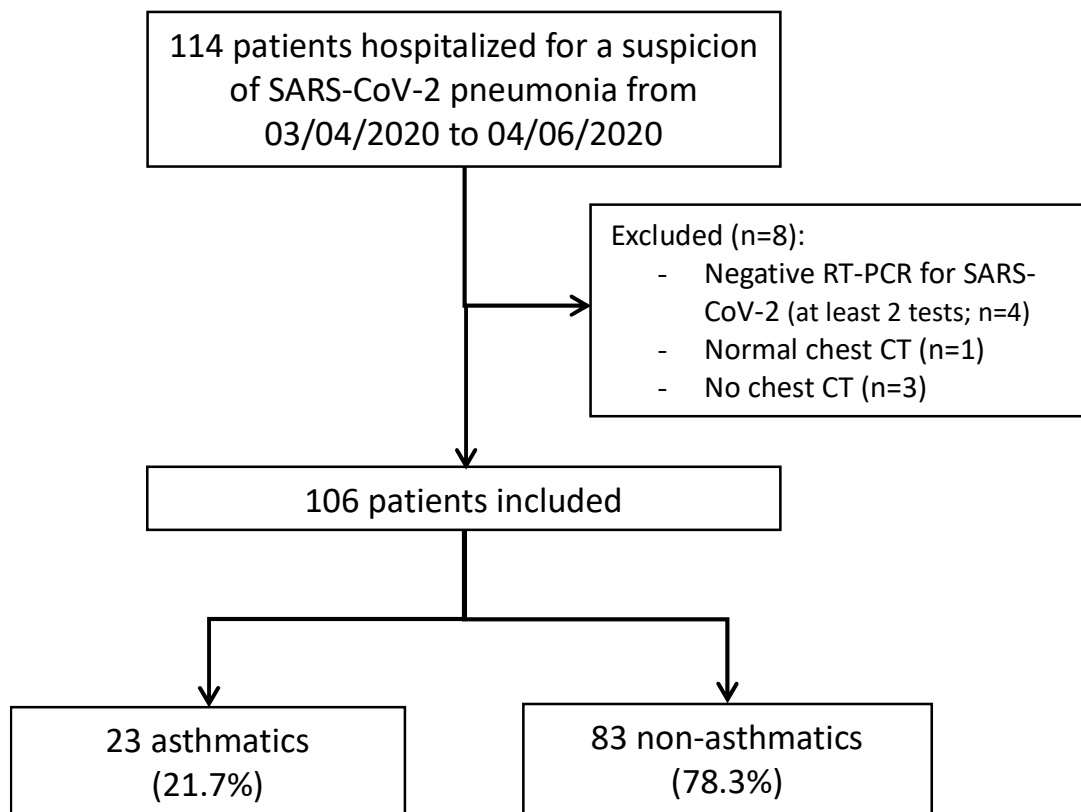
591 p1 (last month before the onset of COVID-19 symptoms) and p2 (pre-hospitalization period):

592 Number of patients with a severe asthma exacerbation; p3 (during hospitalization): Number  
593 of patient treated with oral corticosteroids and beta-2-agonist  ; No treatment with oral

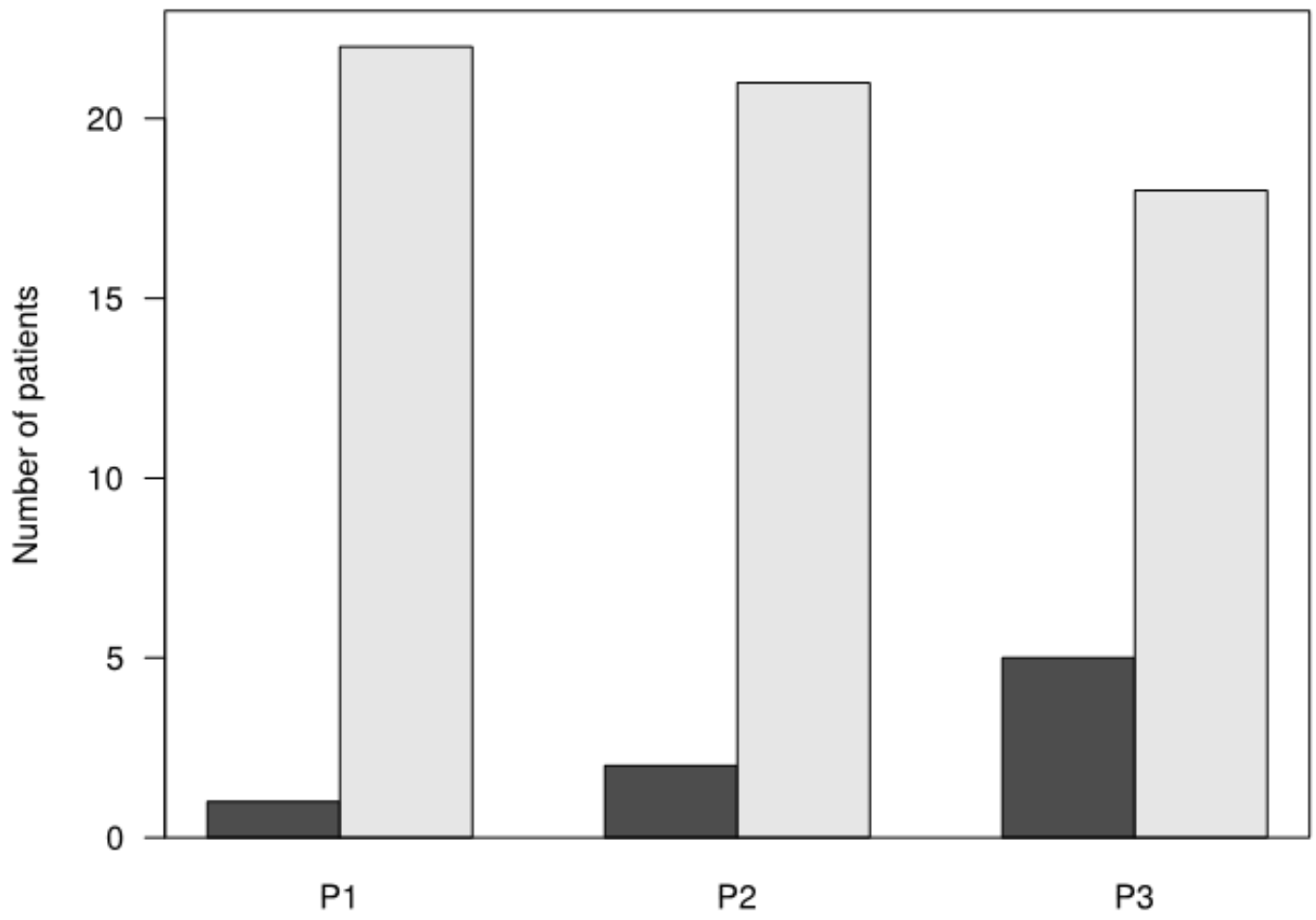
594 corticosteroids, and beta-2-agonist during p1, p2, and p3 

595 No time period effect (p=0.09)

596



**Figure 1. Flow chart of patient inclusion**



**Figure 2. Number of patients treated or not with oral corticosteroids during the three periods.**

	Total n=106	Non-asthmatic patients n=83	Asthmatic patients n=23	p-value
Gender				0.63
Female	40 (37.7)	30 (36.1)	10 (43.5)	
Male	66 (62.3)	53 (63.9)	13 (56.5)	
Age (years)	63.5 [54.2-72.0]	65.0 [56.0-72.0]	59.0 [49.5-9.5]	0.37
Delay between onset of symptoms and hospitalization (days)	7.0 [4.2-10.0]	7.0[4.0-10.0]	7.0 [5.0-9.0]	0.90
Comorbidity				
Obesity (BMI > 30kg/m <sup>2</sup> )	42 (39.6)	33 (39.8)	9 (39.1)	1.00
Hypertension	45 (42.5)	37 (44.6)	8 (34.8)	0.48
Diabetes	23 (21.7)	19 (22.9)	4 (17.4)	0.78
Chronic heart disease	6 (5.7)	5 (6.0)	1 (4.3)	1.00
Chronic renal insufficiency	5 (4.8)	4 (4.9)	1 (4.3)	1.00
Lung cancer	7 (6.6)	6 (7.2)	1 (4.3)	1.00
Obstructive sleep apnea	14 (13.2)	12 (14.5)	2 (8.7)	0.73
Smokers				
Past smokers	33 (31.1)	23 (27.7)	10 (43.5)	0.20
Current smokers	6 (5.7)	5 (6.0)	1 (4.3)	1.00
Smoking index *	0.0 [0.0-20.0]	0.0 [0.0-20.0]	0.0 [0.0-15.0]	0.60

Table I: Clinical characteristics of included patients

	Univariate Analysis				Multivariate Analysis	
	Total n=106	Non- asthmatic patients n=83	Asthmatic patients n=23	p-value	aOR	p-value
<b>Symptoms</b>						
Fever	99 (93.4)	78 (94)	21 (91.3)	0.64		
Asthenia	90 (84.9)	71 (85.5)	19 (82.6)	0.75		
Anorexia	72 (67.9)	54 (65.1)	18 (78.3)	0.31		
Confusion	7 (6.6)	6 (7.2)	1 (4.3)	1.00		
Myalgia	49 (46.2)	37 (44.6)	12 (52.2)	0.64		
Pharyngalgia	5 (4.7)	4 (4.8)	1 (4.3)	1.00		
Nasal Obstruction	10 (9.4)	8 (9.6)	2 (8.7)	1.00		
Acute anosmia	23 (21.7)	16 (19.3)	7 (30.4)	0.26		
Sneezes	8 (7.5)	4 (4.8)	4 (17.4)	0.07		
Rhinorrhea	9 (8.5)	6 (7.2)	3 (13.0)	0.40		
Gastrointestinal symptoms	49 (46.2)	38 (45.8)	11 (47.8)	1.00		
Cough	93 (87.7)	71 (85.5)	22 (95.7)	0.29		
Dyspnea	84 (79.2)	62 (74.7)	22 (95.7)	<b>0.04</b>	5.8 [1.0-109.9]	0.10
Chest tightness	12 (11.3)	5 (6.0)	7 (30.4)	<b>0.004</b>	4.8 [1.1-21.8]	<b>0.04</b>
<b>Pulmonary auscultation</b>						
Wheezing	11 (10.4)	5 (6.0)	6 (26.1)	<b>0.01</b>	2.5 [0.4-12.8]	0.29
Crackles	89 (84.0)	71 (85.5)	18 (78.3)	0.52		
<b>Biology</b>						
Lymphocytes	0.9 [0.7-1.1]	0.9 [0.7-1.1]	1.0 [0.8-1.2]	0.26		
Eosinophils (admission)	0.0 [0.0-0.0]	0.0 [0.0-0.0]	0.0 [0.0-0.0]	0.17		
Eosinophils (discharge)	0.1 [0.0-0.2]	0.1 [0.0-0.2]	0.1 [0.0-0.2]	0.52		
<b>Chest CT</b>						
<10%	14 (13.2)	7 (8.4)	7 (30.4)	<b>0.01</b>		
10-25%	45 (42.5)	38 (45.8)	7 (30.4)	0.24		
25-50%	29 (27.4)	23 (27.7)	6 (26.1)	1.00		
> 50%	18 (17.0)	15 (18.1)	3 (13.0)	0.76		
<b>Ventilation support</b>						
Oxygen therapy	96 (90.6)	73 (88.0)	23 (100)	0.11		
Non-invasive ventilation	15 (14.2)	11 (13.2)	4 (17.4)	0.74		

**Table II: Clinical symptoms and biological and radiological status of all patients**

	Total Asthmatic patients n=23	No exacerbation n=17	Exacerbation n=6
Age at onset			
<18 years	6 (26.1)	4 (23.5)	2 (33.3)
18-50 years	13 (56.5)	10 (58.8)	3 (50.0)
>50 years	4 (17.4)	3 (17.6)	1 (16.7)
Spirometry*			
FEV1 (% predicted)	85.5 [73.3-88.2]	85.5 [82.5-86.8]	78.0 [60.8-88.9]
FEV/FVC (%)	70 [64.3-88.2]	77.1 [68.0-86.1]	67.5 [60.3-73.6]
Allergy (based on clinical history) **	15 (68.2)	11 (68.8)	4 (66.7)
Family atopy **	12 (54.5)	8 (50.0)	4 (66.7)
Positive skin prick test ***	5 / 8	2 / 3	3 / 5
Symptoms to **			
Birch pollen	6 (27.3)	5 (31.3)	1 (16.7)
Grass pollen	6 (27.3)	4 (25.0)	1 (16.7)
Pets (cat or dog)	4 (18.2)	2 (12.5)	2 (33.3)
House dust	11 (50.0)	8 (50.0)	3 (50.0)
Desensitization**	3 (13.6)	3 (18.8)	0 (0.0)
Rhino-conjunctivitis exacerbated (February 2020)**	2 (9.1)	2 (12.5)	0 (0.0)
Severity of asthma			
Exacerbations during the last 12 months	0.5 [0.0-1.0]	0 [0.0-1.0]	1 [0.3-1.0]
Almost one hospitalization in intensive care unit in life	1 (4.3)	0 (0.0)	1 (16.7)
Daily dose of inhaled corticosteroids during the last month	0 [0.0-820.0]	0 [0.0-600.0]	600 [50.0-1210.0]
GINA 1	12 (52.2)	10 (58.8)	2 (33.3)
GINA 2	0 (0.0)	0 (0.0)	0 (0.0)
GINA 3	2 (8.7)	1 (5.9)	1 (16.7)
GINA 4	5 (21.7)	4 (23.5)	1 (16.7)
GINA 5	4 (17.4)	2 (11.8)	2 (33.3)
Comorbidity			
Gastroesophageal reflux	12 (52.2)	8 (47.1)	4 (66.7)
Hyperventilation syndrome	1 (4.4)	0 (0.0)	1 (0.2)
Chronic rhinosinusitis with polyposis	1 (4.4)	0 (0.0)	1 (16.7)
Anti-inflammatory drugs hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)
Paradoxical vocal cord motion disorder	3 (13.0)	2 (11.8)	1 (16.7)
Obesity	9 (39.1)	6 (35.3)	3 (50.0)
Asthma control**			
Well-controlled	14 (63.6)	9 (56.3)	5 (83.3)
Partly controlled	6 (27.3)	6 (37.5)	0 (0.0)
Uncontrolled	2 (9.1)	1 (6.25)	1 (16.7)

**Table III: Clinical characteristics of asthmatic patients**