



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

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Poor outcome of SARS-CoV-2 infection in patients with severe asthma on biologic therapy

Katrien Eger^{a,*}, Simone Hashimoto^a, Gert Jan Braunstahl^b, Anneke ten Brinke^c, Kornelis W. Patberg^d, Annelies Beukert^e, Frank Smeenk^f, Simone van der Sar-van der Brugge^g, Els J.M. Weersink^a, Elisabeth H. Bel^a

^a Dept. Respiratory Medicine, Amsterdam University Medical Center, University of Amsterdam, Meibergdreef 9, 1105, AZ, Amsterdam, the Netherlands

^b Department of Pulmonology, Franciscus Gasthuis & Vlietland, Kleiweg 500, 3045, PM, Rotterdam, the Netherlands

^c Department of Pulmonology, Medical Centre Leeuwarden, Henri Dunantweg 2, 8934, AD, Leeuwarden, the Netherlands

^d Department of Pulmonology, Isala Klinieken, Dokter van Heesweg 2, 8025, AB, Zwolle, the Netherlands

^e Department of Pulmonology, Martini Ziekenhuis, Van Swietenplein 1, 9728, NT, Groningen, the Netherlands

^f Department of Pulmonology Catharina Ziekenhuis, Michelangelolaan 2, 5623, EJ, Eindhoven, the Netherlands

^g Dept of Respiratory Medicine, Amphia Hospital, Molengracht 21, 4818, CK, Breda, the Netherlands

ARTICLE INFO

Keywords:
Biologics
COVID-19
SARS-CoV-2
Severe asthma

ABSTRACT

Background: It is unclear whether asthma and asthma medications increase or decrease the risk of severe COVID-19, and this is particularly true for patients with severe asthma receiving biologics.

Objectives: The aim of this study was to assess incidence and disease course of COVID-19 in patients with severe asthma on biologic therapy (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab), as compared with COVID-19 data from the general Dutch population.

Methods: COVID-19 cases were identified through a prospective ongoing survey between March 17 and April 30, 2020 among all severe asthma specialists from 15 hospitals of the Dutch Severe Asthma Registry RAPSODI. From these cases, data was collected on patient characteristics, including co-morbidities, COVID-19 disease progression and asthma exacerbations. Findings were then compared with COVID-19 data from the general Dutch population.

Results: Of 634 severe asthma patients who received biologic therapy in RAPSODI, 9 (1.4%) were diagnosed with COVID-19. Seven patients (1.1%) required hospitalization for oxygen therapy, of which 5 were admitted to the intensive care for intubation and mechanical ventilation. One patient died (0.16%). All intubated patients had ≥ 1 co-morbidities. Odds (95%CI) for COVID-19 related hospitalization and intubations were 14 (6.6–29.5) and 41 (16.9–98.5) times higher, respectively, compared to the Dutch population. One patient presented with an asthma exacerbation.

Conclusion: Patients with severe asthma using biologic therapy showed to have a more severe course of COVID-19 compared to the general population. This may be due to co-morbidities, the severity of asthmatic airway inflammation, the use of biologics, or a combination of these.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic is an ongoing

crisis, and currently, second waves are a major concern in many parts of the world [1]. From the earliest observations it has appeared that the course of COVID-19 is heterogeneous, varying from asymptomatic

Abbreviations: COVID-19, corona virus disease 2019; IL, interleukin; OCS, oral corticosteroids; R_{α} , receptor alpha; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

* Corresponding author. Amsterdam UMC, University of Amsterdam Dept. of Respiratory Medicine F5-260, Meibergdreef 9, 1105, AZ, Amsterdam, the Netherlands.

E-mail addresses: k.a.eger@amsterdamumc.nl (K. Eger), s.hashimoto@amsterdamumc.nl (S. Hashimoto), g.braunstahl@franciscus.nl (G.J. Braunstahl), a.ten.brinke@mcl.nl (A. Brinke), k.w.patberg@isala.nl (K.W. Patberg), a.beukert@mzh.nl (A. Beukert), frank.smeenk@catharinaziekenhuis.nl (F. Smeenk), svandersar@amphia.nl (S. van der Sar-van der Brugge), e.j.weersink@amsterdamumc.nl (E.J.M. Weersink), e.h.bel@amsterdamumc.nl (E.H. Bel).

<https://doi.org/10.1016/j.rmed.2020.106287>

Received 19 October 2020; Received in revised form 4 December 2020; Accepted 9 December 2020

Available online 24 December 2020

0954-6111/© 2020 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

infection to severe pneumonia in 20% of cases including 5% developing critical disease [2]. Several risk factors for poor outcome of COVID-19 have been identified, including older age, diabetes, cardiovascular disease and obesity [3–5]. Since the outbreak there has been much debate about the extent to which asthma is a risk factor for susceptibility to SARS-CoV-2 infection or severe disease progression of COVID-19, and results of studies addressing these issues vary substantially [6–12]. Recent large studies and meta-analyses however suggest that asthma patients in general may not be at risk for severe COVID-19, which may be due to a potential protective effect of type 2 inflammation [13–17].

In most studies COVID-19 asthmatics had mild to moderate disease, and only a few reports have been published on patients with severe asthma and COVID-19 [15,18–22,38]. A growing number of these patients with severe asthma use monoclonal antibodies targeting immune globulin E (IgE), IL-5, IL-5 receptor alpha (R α) or IL-4R α [23]. Currently, it is unknown whether severe asthma patients who use biologics have increased susceptibility to SARS-CoV-2 infection, or increased risk of a more severe course of COVID-19. Neither is it known whether SARS-CoV-2 infection is a trigger of acute asthma exacerbations in these patients. In the present study we aimed to explore; (1) the incidence of COVID-19 cases in patients with severe asthma on biologic therapy included in the Dutch Severe Asthma Registry RAPSODI; (2) the frequency of asthma exacerbations at COVID-19 diagnosis; (3) the proportion of these COVID-19 positive patients needing hospitalization or ventilatory support; and (4) the incidences of (severe) COVID-19 and COVID-19 related death compared to the RAPSODI population not on biologic treatment and the general Dutch population.

2. Methods

This was a prospective study in which data on COVID-19 were collected from patients included in the Dutch Severe Asthma Registry RAPSODI (Registry of Adult Patients with Severe asthma for Optimal Disease management) as from May 2016. These patients were all diagnosed with severe asthma according ERS/ATS guidelines and included in the registry after having provided informed consent. There were no exclusion criteria for enrollment in the registry. COVID-19 cases were identified through a prospective ongoing survey between March 17th and April 30th, 2020 among all severe asthma specialist at the 15 RAPSODI hospitals. A COVID-19 diagnosis was defined as a positive PCR for SARS-CoV-2, typical symptoms <10 days after contact with a confirmed case, or typical symptoms with positive SARS-CoV-2 serology results afterwards. Patient characteristics including co-morbidities, as well as the course of COVID-19 from patients diagnosed with COVID-19 were collected. Information on COVID-19 in the Dutch population in the period March 1st, 2020 and April 30, 2020 was derived from the Dutch National Institute for Public Health and the Environment and the Statistics Netherlands' database [24–26]. Consent for participation in this study was obtained from all COVID-19 patients. Ethical approval for the study was obtained under nr W20_155 # 20.169.

2.1. Analysis

First we collected all cases of COVID-19 between March 1st' 2020 and April 30th' 2020 among patients included in RAPSODI who were treated with biologics and calculated the incidence of COVID-19 in this population. Then we assessed the proportion of these COVID-19 patients who presented with an asthma exacerbation, were admitted to the hospital, were intubated and died. Finally, we compared the incidence rates of confirmed COVID-19 cases, hospitalizations, intubations and mortality with the RAPSODI population not treated with biologics and the general Dutch population, and calculated odds ratio's. We expected only small numbers of COVID-19 cases in our study population and therefore did not plan a regression analysis for adjusting for confounders. P values < 0.05 were considered statistically significant.

3. Results

3.1. COVID-19 incidence

At the start of the COVID-19 pandemic in the Netherlands, on March 1st' 2020, the RAPSODI database contained data from 707 well-characterized patients of which 634 were treated with a biologic for asthma (19% omalizumab, 39% mepolizumab, 16% reslizumab, 19% benralizumab, 7% dupilumab) and were frequently monitored. Nine of these 634 severe asthma patients in the RAPSODI database (1.42%) were diagnosed with COVID-19, of which eight were laboratory confirmed (1.26%). Characteristics of these 9 patients are summarized in the upper panel of Table 1. Most of them were treated with an anti-IL-5 biologic (mepolizumab, reslizumab, benralizumab). Co-morbidities known to increase the risk for severe COVID-19, such as obesity, diabetes or cardiovascular disease, were present in two-thirds of cases.

3.2. COVID-19 disease course

Seven out of nine COVID-19 patients were hospitalized because of hypoxemia, requiring oxygen therapy by nasal canula or non-rebreather mask, five of these (71%) were admitted to the intensive care unit for intubation and mechanical ventilation, and one patient died (14%), as shown in the lower panel of Table 1. None of the patients received Continuous Positive Airway Pressure (CPAP), Non-Invasive Ventilation (NIV), or Extracorporeal Life Support (ECLS). Asthma symptoms (wheeze) at COVID-19 diagnosis were observed in one patient.

3.3. COVID-19 incidences compared to patients in RAPSODI not treated with biologics and the general Dutch population

Only 1 of the 73 (1.73%) patients included in RAPSODI who were not treated with biologics was diagnosed with COVID-19, which made any comparisons with the patients on biologic therapy trivial. This patient was a 50 year old male, who used maintenance prednisolone (10 mg/day), had a normal BMI and no other relevant co-morbidities. He was hospitalized for 3 days because of an ongoing exacerbation asthma. The positive PCR for SARS-CoV-2 infection was quite unexpected since he had no other symptoms typical for COVID-19.

Compared to the general Dutch population the incidence of COVID-19, hospitalization or intubation for COVID-19, and COVID-19 related mortality were higher in the RAPSODI population on biologic therapy (Table 2), with corresponding odds ratio's for contracting COVID-19 of 4.6 (95% confidence interval (CI) 2.3–9.2, p value < 0.0001), for hospitalization of 14.0 (95% CI 6.6–29.5, p value < 0.0001), for intubation of 40.8 (16.9–98.5, p value < 0.0001), and for mortality of 5.0 (95% CI 0.7–35.8, p value 0.106).

4. Discussion

This study shows that the incidence of COVID-19 in 634 Dutch patients with severe asthma on biologic therapy was relatively high, and that the outcome of COVID-19 in these patients was poor. Compared to the general Dutch population with COVID-19 odds for hospitalization and intubations were 14 times and 41 times higher, respectively. A trend for a 5 times increased odds for mortality was also observed. Factors contributing to the increased severity of COVID-19 in these patients could not be determined due to the relative small number of cases, but comorbidities like obesity, severity of asthma, and the use of biologic therapy may all have played a role.

Our study is amongst the largest of 6 published reports on patients with severe asthma treated with biologics and shows the worst outcome of COVID-19. The other studies in asthma patients on biologic treatment reported cases of COVID-19, but out of a total of 19 confirmed COVID-19 patients admitted to the hospital, only 2 were intubated, and 2 died [15, 18–22]. Compared to these other studies, the COVID-19 cases in our

Table 1
Clinical characteristics, treatments and outcomes in patients with severe asthma and COVID-19.

Patient	1	2	3	4	5	6	7	8	9
Age category	60–65	55–60	55–60	55–60	60–65	55–60	45–50	65–70	45–50
Gender (m/f)	m	f	m	m	f	m	f	f	m
BMI	32	30	25	27	44	41	34	38	25
Asthma characteristics and treatment									
Asthma phenotype	early onset allergic eosinophilic	allergic	early onset allergic eosinophilic	late onset allergic eosinophilic	late onset non-allergic eosinophilic	early onset allergic eosinophilic	late onset non-allergic eosinophilic	early onset allergic eosinophilic	late onset non-allergic eosinophilic
ACQ-6 <1.5*	no	not known	yes	yes	yes	yes	no	yes	yes
FEV ₁ (%pred)*	97%	not known	87%	73%	75%	78%	72%	113%	61%
Biologic	omalizumab	omalizumab	dupilumab	mepolizumab	mepolizumab	mepolizumab	reslizumab	benralizumab	benralizumab
OCS (mg/day)	5	0	0	0	0	0	7.5	0	12.5
Co-morbidities									
Known risk factors for severe COVID-19	obesity diabetes CVD	obesity diabetes	none	none	obesity	obesity diabetes	obesity	obesity	none
COVID-19 diagnosis, treatment and outcome									
SARS-CoV2 confirmed	PCR	PCR	no	serology	PCR	PCR	PCR	PCR	PCR
Asthma exacerbation [#]	yes	no	no	no	no	no	no	no	no
OCS burst at start symptoms	yes	yes	no	no	no	no	yes	yes	yes
Admission to hospital for oxygen therapy	yes	yes	no	no	yes	yes	yes	yes	yes
Admission to ICU for intubation	yes	yes	no	no	yes	yes	no	yes	no
Days hospital admission	56	22	n/a	n/a	58	19	5	84	4
Days ICU admission	44	15	n/a	n/a	48	15	n/a	44	n/a
Death	no	no	no	no	no	yes	no	no	no

Legend to Table 1: *Most recent FEV₁ or ACQ-6 score before COVID-19 infection; [#] Asthma exacerbation defined as wheezing, night time awakening, relieve of symptoms by bronchodilation. Abbreviations: ACQ-6, asthma control questionnaire – 6 item score, BMI, body mass index; CVD, cardiovascular disease; ICU, intensive care unit; OCS, oral corticosteroids.

Table 2
Incidences of COVID-19, hospitalization, intubation and death.

	RAPSODI population age range 19–89yr n = 634	Dutch population age category 20–90yr n = 13,363,687	Dutch population age category 45–65yr n = 4,840,946
COVID-19 cases* - %	1.26%	0.28%	0.28%
hospitalization for COVID-19 - %	1.10%	0.08%	0.07%
intubation for COVID-19 - %	0.79%	0.02%	n/a
COVID-19 related deaths - %	0.16%	0.03%	0.006%

Legend to Table 2: RAPSODI is the Dutch Severe Asthma Registry. *Only laboratory confirmed cases were considered for comparison with the general Dutch population. Abbreviations: n/a, not available.

study were clearly more severe. We can only speculate about the causes for this higher incidence of severe cases, but one important difference was the relatively high proportion of patients in the RAPSODI population who had adult-onset asthma, were non-atopic and had been previously on chronic oral corticosteroid treatment [27].

A higher incidence of severe COVID-19 cases in our patients was however confirmed by the results from a study in unselected COVID-19 patients in one of the 15 RAPSODI hospitals in the same period [28]. In this study 198 COVID-19 patients were hospitalized because of hypoxemia, of which 75 (38%) were intubated, much less than the 71% of intubated cases among our RAPSODI patients. Based on these comparisons, we could be certain that the incidence of severe COVID-19 in the RAPSODI population was higher than expected from other studies in severe asthma patients treated with biologics or unselected COVID-19 patients.

A possible explanation for the higher incidence of severe COVID-19 cases amongst the RAPSODI patients may be the relatively high prevalence of obesity as compared to the general population (30% vs 15%)

[29], which is a known risk factor for severe COVID-19 and commonly seen in patients with severe asthma as a result of frequent OCS use [30]. Other reports have also suggested that co-morbidities may play an important role in severe COVID-19 progression in patients with asthma [7,9].

Still, it cannot be excluded that the use of biologics itself has contributed to a more severe course of COVID-19 in our patients. All currently available biologics for severe asthma are known to block different pathways involved in type 2 inflammation. At present, the role of type 2 immune responses, and in particular that of eosinophils in antiviral defense against SARS-CoV-2 has not yet been elucidated [31,32]. There is some evidence that type 2 inflammation can reduce susceptibility to infection with SARS-CoV-2 and mitigate the course of COVID-19. One hypothesis is that this occurs by decreasing expression levels of the angiotensin-converting enzyme-2 (ACE-2) receptor used by SARS-CoV-2 to enter cells. Studies have shown that ACE2 receptor levels are negatively associated with Th2-gene expression, allergen exposure and interleukin (IL)-13 [33,34]. Another hypothesis is that a type 2 inflammatory milieu inhibits interferon responses, thereby preventing the hyper-inflammatory state observed in severe COVID-19 cases [17,35]. Thus, since asthma biologics block type 2 pathways, it is conceivable that they could negatively affect these potentially protective effects of a type 2 inflammatory environment [36,37].

Only one patient not on biologic therapy contracted COVID-19 in the study period, making it difficult to draw definitive conclusions about the role of biologic therapy on COVID-19 severity.

A strength of this study is that we used objective measures of severe disease (hospitalization, intubation and death) to estimate the incidence of severe COVID-19 among our asthma patients on biologic therapy, and that we were able to compare these incidences with that of the general Dutch population as well as unselected COVID-19 patients in one of the RAPSODI hospitals. A limitation of this study is the possibly underestimated incidence of COVID-19 in the RAPSODI population, because, as in other real-life studies, asymptomatic patients or those with only mild symptoms were not tested during the first COVID-19 wave. In

addition, strict shielding as recommended by the Dutch Institute for Public Health and Environment and the World Health Organization, in particular for patients with chronic lung diseases, may have influenced infection rate. Still, COVID-19 incidence in the RAPSODI population was more than 4 times higher than in the general Dutch population, while the incidence of severe COVID-19 requiring hospitalization or intubation was increased even more. Another limitation of our study is that it was not possible to assess for predictors of severe outcome and adjust for confounding factors such as co-morbidities due to the small number of COVID-19 positive cases. However, since the known risk factors for severe COVID-19 (obesity, diabetes, hypertension) are relatively common in patients with severe asthma due to high oral corticosteroid exposure it may be difficult to disentangle which risk factor is the most important for developing severe COVID: the severity of the asthma, the use of biologics or the steroid-induced co-morbidities.

Our study has clinical implications. Because patients with severe asthma on biologic therapy may have a higher risk of hospitalization and intubation, which is often associated with long-term dysfunction of vital organs and loss of quality of life, it is important to coach these patients during their self-isolation, to secure access to care and medication, including biologics, and to ensure that they will be a priority in a future vaccination program.

5. Conclusion

This multicenter study in 634 well-characterized patients with severe asthma on biologic therapy shows that these patients may not only be more likely to contract COVID-19 but also to develop more severe COVID-19, with higher rates of hospitalisations, intubations and death as compared to the general Dutch population. The reasons why these patients with severe asthma on biologic therapy progressed to more severe COVID-19, and why the findings of this study differ from other reports are still uncertain. Only by analysing pooled data from multiple cohorts it will become clear to what extent patients on asthma biologics are at increased risk for severe COVID-19 and whether this would be due to the severity of asthmatic inflammation, the presence of comorbidities, the use of biologic therapies or a combination of these.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRedit authorship contribution statement

Katrien Eger: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. **Simone Hashimoto:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft. **Gert Jan Braunstahl:** Investigation, Writing - review & editing. **Anneke ten Brinke:** Investigation, Writing - review & editing. **Kornelis W. Patberg:** Investigation, Writing - review & editing. **Annelies Beukert:** Investigation, Writing - review & editing. **Frank Smeenk:** Investigation, Writing - review & editing. **Simone van der Sar-van der Brugge:** Investigation, Writing - review & editing. **Els J.M. Weersink:** Conceptualization, Investigation, Writing - review & editing. **Elisabeth H. Bel:** Conceptualization, Methodology, Writing - original draft, Supervision.

Declaration of competing interest

Katrien Eger: has nothing to declare.

Simone Hashimoto: has nothing to declare.

Gert Jan Braunstahl: reports grants and personal fees from AstraZeneca, GSK, Chiesi, Novartis, Boehringer Ingelheim, Sanofi/Regeneron, Teva, ALK Abello outside the submitted work.

Anneke ten Brinke: reports institutional grants from GSK, TEVA and

Astra Zeneca outside the submitted work and participated in advisory boards for AstraZeneca, TEVA and Sanofi Regeneron.

Kornelis W. Patberg: reports personal fees from Novartis, personal fees from TEVA, personal fees from GSK, personal fees from Boehringer, outside the submitted work.

Annelies Beukert: reports personal fees from Sanofi, personal fees from Astra Zeneca, personal fees and non-financial support from Novartis, personal fees from TEVA, personal fees from Esculaap media, outside the submitted work.

Frank Smeenk: has nothing to disclose.

Simone van der Sar: reports personal fees from Astra Zeneca, Chiesi, ALK, Novartis and GSK, outside the submitted work.

Els Weersink: reports other from Astra Zeneca, other from GSK, other from Novartis, from Sanofi/Regeneron, outside the submitted work.

Elisabeth H. Bel: reports grants and personal fees from AstraZeneca, grants and personal fees from GSK, grants and personal fees from Novartis, personal fees from Sanofi/Regeneron, grants and personal fees from Teva, personal fees from Sterna, personal fees from Chiesi, outside the submitted work.

Acknowledgements

We thank Mrs. P.F.M. Mau-Asam for her support, and all pulmonologists involved in the Dutch Severe Asthma Registry (The Registry of Adult Patients with Severe asthma for Optimal Disease management, RAPSODI) for providing information on COVID-19 cases in their severe asthma population.

References

- [1] World Health Organization, Weekly Epidemiological Update on Coronavirus Disease, 2019. <https://www.who.int/docs/default-source/coronaviruse/situatio-n-reports/20200907-weekly-epi-update-4.pdf>. (Accessed 15 October 2020).
- [2] Z. Wu, J.M. McGoogan, Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention, *JAMA, J. Am. Med. Assoc.* 323 (13) (2020) 1239–1242, <https://doi.org/10.1001/jama.2020.2648>.
- [3] S. Richardson, J.S. Hirsch, M. Narasimhan, et al., Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area, *JAMA, J. Am. Med. Assoc.* 323 (20) (2020) 2052–2059, <https://doi.org/10.1001/jama.2020.6775>.
- [4] X. Li, S. Xu, M. Yu, K. Wang, Y. Tao, Y. Zhou, Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan, *J. Allergy Clin. Immunol.* 146 (1) (2020) 110–118, <https://doi.org/10.1016/j.jaci.2020.04.006>.
- [5] M.S. Mughal, I.P. Kaur, A.R. Jaffery, et al., COVID-19 patients in a tertiary US hospital: assessment of clinical course and predictors of the disease severity, *Respir. Med.* 172 (June) (2020) 106130, <https://doi.org/10.1016/j.rmed.2020.106130>.
- [6] K.D. Chhiba, G.B. Patel, T.H.T. Vu, M.M. Chen, A. Guo, E. Kudlaty, Q. Mai, C. Yeh, L.N. Muhammad, K.E. Harris, B.S. Bochner, L.C.G.P. Grammer, Prevalence and characterization of asthma in hospitalized and non-hospitalized patients with COVID-19, *J. Allergy Clin. Immunol.* (2020), <https://doi.org/10.1016/j.jaci.2020.06.010>.
- [7] A. Beurnier, E.-M. Jutant, M. Jevnikar, et al., Characteristics and outcomes of asthmatic patients with COVID-19 pneumonia who require hospitalisation, *Eur. Respir. J.* (2020) 2001875, <https://doi.org/10.1183/13993003.01875-2020>.
- [8] M. Morais-Almeida, H. Pit e, R. Aguiar, I. Ansotegui, J. Bousquet, Asthma and the coronavirus disease 2019 pandemic: a literature review, *Int. Arch. Allergy Immunol.* 181 (9) (2020) 680–688, <https://doi.org/10.1159/000509057>.
- [9] Y.J. Choi, J.-Y. Park, H.S. Lee, et al., Effect of asthma and asthma medication on the prognosis of patients with COVID-19, *Eur. Respir. J.* (2020), <https://doi.org/10.1183/13993003.02226-2020>.
- [10] R. Broadhurst, R. Peterson, J.P. Wisnivesky, et al., Asthma in COVID-19 hospitalizations: an overestimated risk factor? *Ann Am Thorac Soc* (2020) 1–13, <https://doi.org/10.1513/annalsats.202006-613r1>, 0.
- [11] H.-G. Choi, J.H. Wee, S.Y. Kim, et al., Association between asthma and clinical mortality/morbidity in COVID-19 patients using clinical epidemiologic data from Korean Disease Control & Prevention, *Allergy* (2020), <https://doi.org/10.1111/all.14675>, 0–3.
- [12] S. Lovinsky-desir, D.R. Deshpande, A. De, L. Murray, Asthma among hospitalized patients with COVID-19 and related outcomes, *J. Allergy Clin. Immunol.* (2020), <https://doi.org/10.1016/j.jaci.2020.07.026>.
- [13] Y. Wang, G. Ao, X. Qi, B. Xie, The association between COVID-19 and asthma: a systematic review and meta-analysis, *Clin. Exp. Allergy* (August) (2020) 1–4, <https://doi.org/10.1111/cea.13733>.

- [14] Y. Wang, J. Chen, W. Chen, et al., Does asthma increase the mortality of patients with COVID-19?: a systematic review and meta-analysis, *Int. Arch. Allergy Immunol.* 230031 (117) (2020) 1–7, <https://doi.org/10.1159/000510953>.
- [15] J.L. Izquierdo, C. Almonacid, Y. González, et al., The impact of COVID-19 on patients with asthma, *Eur. Respir. J.* (2020) 2003142, <https://doi.org/10.1183/13993003.03142-2020>.
- [16] W. Lieberman-Cribbin, J. Rapp, N. Alpert, S. Tuminello, E. Taioli, The impact of asthma on mortality in patients with COVID-19, *Chest* 194 (2020) 2019–2020, <https://doi.org/10.1016/j.chest.2020.05.575>.
- [17] G. Carli, L. Cecchi, J. Stebbing, P.F.A. Parronchi, Carli Allergy 2020 Is Asthma Protective against COVID-19.Pdf, 2020, <https://doi.org/10.1111/all.14426>.
- [18] J. Dominguez-Ortega, V. Lopez-Carrasco, P. Barranco, M. Ifim, J.A. Luna, D.Q. S. Romero, Early experiences of SARS-CoV-2 infection in severe asthmatics receiving biologic therapy, *J Allergy Clin Immunol Pract* 8 (January) (2020) 2784–2786, <https://doi.org/10.1016/j.jaip.2020.06.027>.
- [19] L. Antonicelli, C. Tontini, G. Manzotti, et al., Severe asthma in adults does not significantly affect the outcome of COVID-19 disease: results from the Italian Severe Asthma Registry, *Allergy Eur J Allergy Clin Immunol* (4) (2020), <https://doi.org/10.1111/all.14558>, 0–2.
- [20] A. Maturci, M. Caminati, E. Vivarelli, et al., COVID-19 in severe asthmatic patients during ongoing treatment with biologics targeting type 2 inflammation: results from a multicenter Italian survey, *Allergy Eur J Allergy Clin Immunol* (June) (2020) 1–4, <https://doi.org/10.1111/all.14516>.
- [21] S. Hanon, G. Brusselle, M. Deschamphelire, et al., Early View COVID-19 and Biologics in Severe Asthma : Data from the Belgian Severe Asthma Registry, 2020.
- [22] M.J. Rial, M. Valverde, V. del Pozo, et al., Clinical characteristics in 545 patients with severe asthma on biological treatment during the COVID-19 outbreak, *J Allergy Clin Immunol Pract* (2020), <https://doi.org/10.1016/j.jaip.2020.09.050>.
- [23] K.A. Eger, E.H. Bel, The emergence of new biologics for severe asthma, *Curr. Opin. Pharmacol.* 46 (2019) 108–115, <https://doi.org/10.1016/j.coph.2019.05.005>.
- [24] National Institute for Public Health and the Environment, Online Report on the Epidemiology of COVID-19 in the Netherlands:1-5, 2020. <https://www.rivm.nl/documenten/epidemiologische-situatie-covid-19-in-nederland-3-mei-2020>. (Accessed 10 May 2020). Published online May 3, 2020.
- [25] Statistics Netherlands, StatLine – Dutch population; gender, age and marital status. <https://opendata.cbs.nl/statline/#/CBS/nl/>. (Accessed 19 July 2020).
- [26] National Intensive Care Evaluation Foundation, Online Report on ICU Care for COVID-19 Patients in the Netherlands, 2020. <https://www.stichting-nice.nl/covid-19-op-de-ic.jsp>. (Accessed 1 December 2020).
- [27] J.J.M.H. van Bragt, I.M. Adcock, E.H.D. Bel, et al., Characteristics and treatment regimens across ERS SHARP severe asthma registries, *Eur. Respir. J.* 55 (1) (2020), <https://doi.org/10.1183/13993003.01163-2019>.
- [28] S. Middeldorp, M. Coppens, T.F. van Haaps, et al., Incidence of venous thromboembolism in hospitalized patients with COVID-19, *J. Thromb. Haemostasis* 18 (8) (2020) 1995–2002, <https://doi.org/10.1111/jth.14888>.
- [29] Dutch National Institute for Public Health and the Environment, Prevalence of overweight and obesity in The Netherlands. <https://www.volksgezondheidenzorg.info/onderwerp/overgewicht/cijfers-context/samenvatting>, 2019. (Accessed 3 December 2020).
- [30] T. Volmer, T. Effenberger, C. Trautner, R. Buhl, Consequences of long-term oral corticosteroid therapy and its side-effects in severe asthma in adults: a focused review of the impact data in the literature, *Eur. Respir. J.* 52 (4) (2018), <https://doi.org/10.1183/13993003.00703-2018>.
- [31] A.W. Lindsley, J.T. Schwartz, M.E. Rothenberg, Eosinophil responses during COVID-19 infections and coronavirus vaccination, *J. Allergy Clin. Immunol.* (2020), <https://doi.org/10.1016/j.jaci.2020.04.021>.
- [32] M. Chaiubiński, A. Gajewski, M.L. Kowalski, The relationship between human coronaviruses, asthma and allergy—an unresolved dilemma, *Clin. Exp. Allergy* (2020), <https://doi.org/10.1111/cea.13718>, 0–1.
- [33] D.J. Jackson, W.W. Busse, L.B. Bacharier, et al., Association of respiratory allergy, asthma and expression of the SARS-CoV-2 receptor, ACE2. *J Allergy Clin Immunol.* (2020), <https://doi.org/10.1016/j.jaci.2020.04.009>.
- [34] P. Bradding, M. Richardson, T.S.C. Hinks, P. Howarth, D. Choy, J.R. Arron, S.E.S. S. Wenzel, ACE2, TMPRSS2, and furin gene expression in the airways of people with asthma—implications for COVID-19. <https://doi.org/10.1016/j.jaci.2020.05.013>, 2020, 146, 1, 208–210.
- [35] S. Liu, Y. Zhi, S. Ying, COVID-19 and asthma: reflection during the pandemic, *Clin. Rev. Allergy Immunol.* 59 (1) (2020) 78–88, <https://doi.org/10.1007/s12016-020-08797-3>.
- [36] J.M. Yang, H.Y. Koh, S.Y. Moon, et al., Allergic disorders and susceptibility to and severity of COVID-19: a nationwide cohort study, *J. Allergy Clin. Immunol.* 146 (4) (2020) 790–798, <https://doi.org/10.1016/j.jaci.2020.08.008>.
- [37] A. Vultaggio, I. Agache, C.A. Akdis, et al., Considerations on Biologicals for Patients with allergic disease in times of the COVID-19 pandemic: an EAACI Statement, *Allergy* (2020), <https://doi.org/10.1111/all.14407>, 0–3.
- [38] E Heffler, A Giovanni, COVID-19 in Severe Asthma Network in Italy (SANI) patients: clinical features, impact of comorbidities and treatments, *Allergy* (2020), <https://doi.org/10.1111/all.14532>. In press.