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ORIGINAL RESEARCH

Reduced risk of COVID-19 hospitalization in asthmatic and COPD patients: a benefit of inhaled corticosteroids?

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ABSTRACT

Background: The comorbidities and clinical signs of coronavirus disease 2019 (COVID-19) patients have been reported mainly as descriptive statistics, rather than quantitative analysis even in very large investigations. The aim of this study was to identify specific patients' characteristics that may modulate COVID-19 hospitalization risk.

Research design and methods: A pooled analysis was performed on high-quality epidemiological studies to quantify the prevalence (%) of comorbidities and clinical signs in hospitalized COVID-19 patients. Pooled data were used to calculate the relative risk (RR) of specific comorbidities by matching the frequency of comorbidities in hospitalized COVID-19 patients with those of general population.

Results: The most frequent comorbidities were hypertension, diabetes mellitus, and cardiovascular and/or cerebrovascular diseases. The RR of COVID-19 hospitalization was significantly ($P < 0.05$) reduced in patients with asthma (0.86, 0.77–0.97) or chronic obstructive pulmonary disease (COPD) (0.46, 0.40–0.52). The most frequent clinical signs were fever and cough.

Conclusion: The clinical signs of hospitalized COVID-19 patients are similar to those of other infective diseases. Patients with asthma or COPD were at lower hospitalization risk. This paradoxical evidence could be related with the protective effect of inhaled corticosteroids that are administered worldwide to most asthmatic and COPD patients.

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Asthma; copd; covid-19; hospitalization; pooled analysis; sars-CoV-2

1. Introduction

The outbreak of coronavirus disease 2019 (COVID-19) poses a very grave threat worldwide and it has been ranked as being the public enemy number one by the WHO Director-General [1]. Unexpectedly, in mid-February 2020 there was a sharp increase in cases and deaths due to COVID-19 in the Chinese province of Hubei, mainly related with the improvement of the diagnostic method due to the inclusion of clinically diagnosed cases via CT scan showing infected lung, rather than relying only on the genetic tests [2,3].

This scenario clearly suggests that the clinical profile of potentially infected subjects is crucial in the knowledge and prompt diagnosis of COVID-19. In this respect, comorbidities and clinical signs of COVID-19 patients have been included in epidemiological studies, although reported mainly as descriptive statistics [2,4–13] even in very large investigations [14].

Therefore, we performed a quantitative synthesis to assess whether there are specific patients' characteristics that may modulate the risk of COVID-19 hospitalization.

2. Patients and methods

2.1. Study question and search strategy

This study has been performed in agreement with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [15] in order to identify potential-specific characteristics of patients infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that may modulate the risk of hospitalization due to COVID-19. The PRISMA-P flow diagram of the study is reported in Figure 1. This research satisfied all the recommended items reported by the PRISMA-P checklist [16].

The MEDLINE search was performed on 25 May 2020 by using the following search string: (COVID-19 OR SARS-CoV-2 OR 2019-nCoV) AND epidemiology AND (comorbidity OR comorbidities OR comorbid). Two reviewers performed the comprehensive literature search without language restriction. As an example, Table 1 reports the literature search terms used for OVID MEDLINE.

2.2. Study selection

Epidemiological studies published in high ranked journals (Q1) and reporting data of ≥10 patients were selected to detect at

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Article highlights

- Comorbidities and clinical signs in COVID-19 have been reported mainly as descriptive statistics.
- This study identifies patients' characteristics that modulate the risk of COVID-19 hospitalization.
- The most frequent comorbidities in COVID-19 were hypertension, diabetes mellitus, and cardiovascular and/or cerebrovascular diseases.
- Patients with asthma or COPD were at lower risk of COVID-19 hospitalization.
- Inhaled corticosteroids may have a protective effect against COVID-19 hospitalization.

least very common comorbidities and clinical signs (frequency ≥10%) in agreement with European Medicines Agency (EMA) recommendation [17].

Table 1. Literature search terms used for OVID MEDLINE. The final search strategy applied to conduct this pooled analysis is reported at step #10.

#	Search strategy
1	COVID-19.mp. [mp = ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
2	SARS-CoV-2.mp. [mp = ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
3	2019-nCoV.mp. [mp = ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
4	epidemiology*.mp. [mp = ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
5	comorbidity*.mp. [mp = ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
6	comorbidities*.mp. [mp = ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
7	comorbid*.mp. [mp = ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
8	1 or 2 or 3
9	5 or 6 or 7
10	4 and 8 and 9

COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; 2019-nCoV: new coronavirus 2019.

2.3. Endpoints

The co-primary endpoints were the frequencies (%) of comorbidities and clinical signs and the risk of hospitalization accordingly with comorbidities.

2.4. Data extraction

Data from included studies were extracted in agreement with Data Extraction for Complex Meta-anALysis (DECiMAL) recommendations [18].

2.5. Data analysis

A pooled analysis was performed to quantify the frequency of comorbidities and clinical signs in COVID-19 patients. Pooled data were also used to calculate the relative risk (RR) of asthma, cardiovascular and/or cerebrovascular diseases, COPD, diabetes mellitus, and hypertension by matching the frequency of these comorbidities in COVID-19 hospitalized patients with those in the general population by using high-quality large epidemiological reports [19–29] as gold standard for each comorbidity, as previously described [30]. Data on the general population included official National reports [19–29] that were selected to specifically cover the same geographical area in which patients were hospitalized to COVID-19, so that in turn the subjects hospitalized to COVID-19 were themselves included in the above reported high-quality large epidemiological reports. Raw data were extracted from each study and report included in the pooled analysis.

The pooled analysis was performed in agreement with standardized procedures [31]. Heterogeneity (I^2) was not

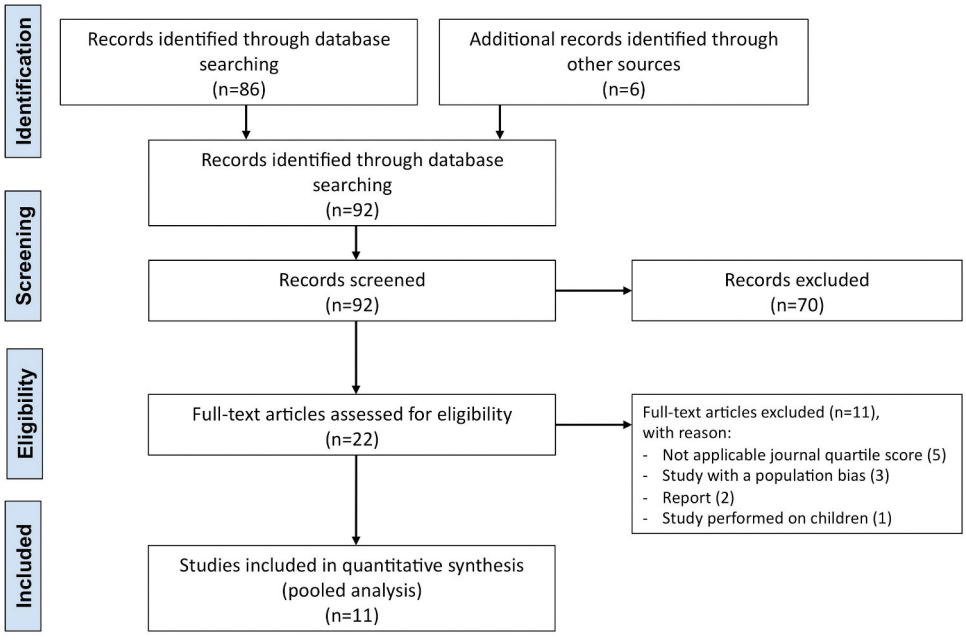

Figure 1. PRISMA-P flow diagram for the identification of epidemiological studies included in the pooled analysis concerning the risk of hospitalization due to COVID-19. COVID-19: coronavirus disease 2019; PRISMA: preferred reporting items for systematic review and meta-analysis.

calculated as this is a pooled analysis and not a meta-analysis. The effect estimate was expressed as the prevalence (%) or RR with 95% confidence interval (95%CI), with statistical significance for $P < 0.05$. Raw data concerning positive and negative outcomes of experimental and control groups (COVID-19 hospitalized patients and general population, respectively) were extracted from the original studies and reports, and then included in the 2×2 table to calculate the RR and 95%CI via the Mantel-Haenszel approach by using the OpenEpi software [31–33].

2.6. Study quality

A modified version of the Newcastle-Ottawa Scale (NOS) was used to assess the quality of the studies and it was adapted to fit the intrinsic characteristics of the included epidemiological studies [34]. According to NOS, a study can be awarded with a maximum of one star for each item within the 'Selection' and 'Outcome' categories, and a maximum of two stars can be given for 'Comparability' [34]. In the present pooled analysis, the NOS quality assessment score was established to be in the range between zero and a maximum of six stars. The detailed modifications to make the NOS suitable for the specific studies included in this pooled analysis are described in the legend of Tables 2 and 3. Two reviewers independently assessed the quality score of individual studies, and any difference in opinion was resolved by consensus.

3. Results

3.1. Study characteristics

Data of 8476 COVID-19 hospitalized patients (age 53.29, 95%CI 48.19–58.40) were extracted from 11 epidemiological studies [2,4–13] including cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection from 11 December 2019 to 4 April 2020. Table 2 reports the characteristics of the studies included in the pooled analysis, whereas Table 3 describes the characteristics of the large epidemiological reports on the general population, used as gold-standards for each comorbidity.

3.2. Comorbidities

The most frequent comorbidities were hypertension (23.24%), diabetes mellitus (13.89%), and cardiovascular and/or cerebrovascular diseases (11.84%). Chronic obstructive pulmonary disease (COPD) and asthma were reported in only 1.76% and 1.20% of COVID-19 hospitalized patients. Details on the prevalence of comorbidities are reported in Table 4.

A significant ($P < 0.05$) increased risk of hospitalization due to COVID-19 was detected in patients affected by diabetes mellitus (RR 2.02, 95%CI 1.89–2.16), cardiovascular and/or cerebrovascular diseases (RR 1.13, 95%CI 1.05–1.22), and hypertension (RR 1.10, 95%CI 1.07–1.15). The risk of hospitalization was significantly ($P < 0.05$) reduced in patients affected by asthma (RR 0.86, 95%CI 0.77–0.97) or COPD (RR 0.46, 95%CI 0.40–0.52) Figure 2 reports the risk of hospitalization for COVID-19 patients concerning different comorbidities.

3.3. Clinical signs

The most frequent clinical signs were fever (90.88%), cough (71.27%), fatigue (40.34%), dyspnea (34.98%), and myalgia (21.52%). Less frequent (≤20.00%) although statistically significant clinical signs were expectoration, diarrhea, headache, nausea, and/or vomiting, anorexia, chest pain, sore throat, chill, abdominal pain, dizziness, rhinorrea, hemoptysis, and conjunctival congestion. Details on the prevalence of clinical signs are reported in Table 5.

4. Expert opinion

The clinical profile of patients hospitalized due to COVID-19 is mainly characterized by subjects with fever and cough affected by hypertension in ≈23.00% of cases, diabetes mellitus in ≈14.00% of cases, and cardiovascular and/or cerebrovascular diseases in ≈12.00% of cases.

Such a clinical profile is not specific of COVID-19, leading to partially incorrect informing practice that SARS-CoV-2 infection is most likely to occur in older people with comorbid conditions, as is the case of influenza (available at https://www.jwatch.org/na50821/2020/01/31/clinical-characteristics-2019-novel-coronavirus-infection). Certainly, fever and cough are typical of several infective respiratory disorders; however, we have to highlight that first, an average age of ≈53 years does not include elderly patients [35]; second, clinical signs are related with the disease, not with the infection [36]; third, comorbidities do not necessarily have to be positively associated with an infectious disease.

The last point is of specific interest by considering the risk of hospitalization for COVID-19. While there was a significantly increased risk of hospitalization in COVID-19 patients affected by diabetes mellitus, cardiovascular and/or cerebrovascular diseases, and hypertension, paradoxically we have found that asthmatic and COPD patients were at reduced risk of hospitalization. This finding is consistent with recent observation that despite a high burden of asthma and COPD, these chronic respiratory disorders have not been consistently identified as a significant comorbidity for COVID-19 [37].

The evidence provided by this study, based on the risk analysis of more than 8000 COVID-19 patients matched with gold standard epidemiological reports in the general population, is in contrast with the potentially misleading information provided by Lippi and Henry [38] that COPD is associated with severe forms of COVID-19. Such a discrepancy could be related with the fact that there is no consensus on the rank of severity in COVID-19 patients, and that defining whether a patient has all the features of acute respiratory distress syndrome (ARDS) instead of acute lung injury (ALI) may be difficult or impossible in non-intubated subjects [39–41]. However, it is expectable that hospitalized COVID-19 patients with asthma or COPD may result in worse outcomes than those without respiratory comorbidities.

SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE-2) as the cellular entry receptor; considering that subjects with chronic obstructive respiratory disorders, especially COPD patients, may have increased expression of ACE-2 receptor [42], it was expected that these subjects would have been at higher risk of hospitalization. Indeed, the reduced risk of hospitalization

Table 2. Characteristics of the epidemiological studies conducted on hospitalized COVID-19 patients and included in the pooled analysis.

Author and year	References	Journal and quartile score	Type of epidemiological study	Area of study	Period of study	Number of patients	Age (mean)	Male (%)	Hospitalization	Data on comorbidities	Data on clinical signs	NOS Quality Assessment[§]	
												Selection[#]	Outcome
Chen et al., 2020	[5]	Lancet (Q1)	Retrospective, single-center, observational case series	Wuhan (Hubei province); China	01 Jan – 20 January 2020	99	55.5	68.0	yes	yes	yes	***	**
Chen et al., 2020	[8]	British Medical Journal (Q1)	Retrospective, single-center, observational case series	Wuhan (Hubei province); China	13 Jan – 12 February 2020	274	59.5	62.0	yes	yes	yes	***	***
Guan et al., 2020	[11]	European Respiratory Journal (Q1)	Retrospective, multi-center, observational case series	Mostly Wuhan (Hubei province); China	11 December 2019–31 January 2020	1590	48.9	57.3	yes	yes	yes	**	***
Huang et al., 2020	[6]	Lancet (Q1)	Retrospective, single-center, observational case series	Wuhan (Hubei province); China	16 December 2019–2 January 2020	41	49.3	73.0	yes	yes	yes	***	*
Meng et al., 2020	[12]	Plos Pathogens (Q1)	Retrospective, single-center, observational case series	Wuhan (Hubei province); China	16 Jan – 4 February 2020	168	56.7	51.2	yes	yes	yes	***	***
Richardson et al., 2020	[13]	Journal of American Medical Association (Q1)	Retrospective, multi-center, observational case series	Long Island, Westchester County, and New York City (State of New York); USA	1 Mar – 4 April 2020	5700	63.3	60.3	yes	yes	no	***	**
Wang et al., 2020	[4]	Journal of American Medical Association (Q1)	Retrospective, single-center, observational case series	Wuhan (Hubei province); China	01 Jan – 28 January 2020	138	55.5	54.3	yes	yes	yes	**	**
Xu et al., 2020	[2]	British Medical Journal (Q1)	Retrospective, multi-center, observational case series	Hangzhou, Wenzhou, Taizhou, Wenling, Zhoushan, Ningbo (Zhejiang province); China	10 Jan – 26 January 2020	62	41.5	58.0	yes	yes	yes	**	*
Zhang et al., 2020	[7]	Allergy (Q1)	Retrospective, single-center, observational case series	Wuhan (Hubei province); China	16 Jan – 3 February 2020	140	56.5	50.7	yes	yes	yes	***	*
Zheng et al., 2020	[9]	Pharmacological Research (Q1)	Retrospective, single-center, observational case series	Shiyan (Hubei province); China	16 Jan – 4 February 2020	73	43.0	54.8	yes	yes	yes	*	***
Zhou et al., 2020	[10]	Lancet (Q1)	Retrospective, multi-center, observational cohort study	Wuhan (Hubei province); China	29 December 2019–31 January 2020	191	56.3	62.0	yes	yes	yes	***	*

[§]The NOS category 'Comparability' was not included in the quality assessment due to the intrinsic nature of the included epidemiological studies, that do not have any 'non-exposed group' to compare with the 'exposed group' of COVID-19 patients.
[#]The NOS category 'Selection' was modified to fit the intrinsic characteristics of the included epidemiological studies, that do not have any 'non-exposed group'.
COVID-19: coronavirus disease 2019; NA: not available; NOS: Newcastle-Ottawa Scale.

Table 3. Characteristics of large epidemiological reports performed on the general population and used as gold-standard to estimate the risk of COVID-19 hospitalization for different comorbidities.

Author and year	References	Type of epidemiological study	Area of study	Number of patients	Age (mean)	Male (%)	Comorbidity	NOS quality assessment		
								Selection	Comparability[§]	Outcome[#]
U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2020	[21]	National, cross-sectional survey	U.S.	2000[$]	≥18	NA	Diabetes	***	/	*
Huang et al., 2019	[29]	National, cross-sectional, with multistage stratified cluster-sampling design survey	China	48,381°	≥20	56.5	Asthma	****	*	*
Liu et al., 2019	[27]	Analysis of the Global Burden of Disease epidemiological study	China	100,000	NA	NA	Cardiovascular disease	***	/	*
Croft et al., 2018	[20]	National survey	U.S.	426,838	≥18	NA	COPD	***	/	*
Dorans et al., 2018	[19]	Retrospective, observational, cross-sectional, with a multistage stratified probability sampling design survey	U.S.	38,276	≥20	NA	Hypertension	****	*	*
Fang et al., 2018	[25]	National, cross-sectional survey	China	66,753	≥40	NA	COPD	****	*	*
National Center for Health Statistics, 2018	[22]	National health interview, with multistage stratified cluster-sampling design survey	U.S.	2000[$]	≥18	NA	Asthma	***	/	*
National Center for Health Statistics, 2018	[23]	National health interview, with multistage stratified cluster-sampling design survey	U.S.	2000[$]	≥18	NA	Cardiovascular and cerebrovascular disease	***	/	*
Wang et al., 2018	[24]	National, cross-sectional, with multistage stratified sampling design survey	China	451,755	≥18	NA	Hypertension	***	*	*
Wang et al., 2017	[26]	National, cross-sectional, with multistage stratified sampling design survey	China	170,287	43.5	42.7	Diabetes	***	*	*
Wang et al., 2017	[28]	National, cross-sectional, with multistage stratified sampling design survey	China	100,000	≥20	NA	Cerebrovascular disease	****	*	*

[§]A maximum of 1 star (*) was allotted for the NOS category 'Comparability' due to the intrinsic nature of the epidemiological reports, since the 'exposed' and 'non-exposed' groups could not be perfectly matched and/or adjusted for confounders.
[#]The NOS category 'Outcome' was modified according to the intrinsic nature of the included epidemiological reports, as all were devoid of a 'follow-up' period.
°The total population was estimated from the reported number and percentage of people suffering from asthma.
[$]Data adjusted by using the projected 2000 U.S. population.
COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019; NA: not available; NOS: Newcastle-Ottawa Scale; U.S.: United States.

Table 4. Prevalence of comorbidities in hospitalized COVID-19 patients.

	Prevalence (%)	95%CI	P
Comorbidities:			
hypertension	23.24	7.18–39.30	**0.005**
endocrine system disease, mainly diabetes mellitus	13.89	5.42–22.36	**0.001**
cardiovascular and/or cerebrovascular diseases	11.84	7.21–16.47	**<0.001**
metabolic disease	6.48	0.00–13.25	0.061
chronic kidney disease	2.34	0.23–4.45	**0.030**
malignant tumor	2.02	0.46–3.58	**0.011**
COPD	1.76	0.35–3.18	**0.014**
chronic liver disease	1.44	0.67–2.21	**<0.001**
asthma	1.20	0.00–2.66	0.105
obstructive sleep apnea	0.64	0.00–1.38	0.092
HIV infection	0.42	0.17–0.66	**<0.001**
history of organ transplant	0.40	0.01–0.79	**0.044**
other respiratory system diseases	0.12	0.00–0.30	0.211
digestive system disease	0.10	0.00–0.27	0.232
autoimmune disease	0.01	0.00–0.04	0.312
nervous system disease	0.01	0.00–0.04	0.312

Bold values highlight statistically significant prevalence. COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019; HIV: human immunodeficiency virus; 95%CI: 95% confidence interval.

Table 5. Prevalence of clinical signs in hospitalized COVID-19 patients.

	Prevalence (%)	95%CI	P
Clinical signs:			
fever	90.88	87.27–94.48	**<0.001**
cough	71.27	57.17–85.38	**<0.001**
fatigue	40.34	21.74–58.94	**<0.001**
dyspnea	34.98	19.67–50.28	**<0.001**
myalgia	21.52	13.29–29.76	**<0.001**
expectoration	16.16	12.31–20.00	**<0.001**
diarrhea	9.20	5.16–13.24	**<0.001**
headache	8.48	4.56–12.40	**<0.001**
nausea and/or vomiting	7.45	4.25–10.66	**<0.001**
anorexia	6.20	3.99–8.42	**<0.001**
chest pain	5.24	3.14–7.34	**<0.001**
sore throat	5.23	2.10–8.37	**0.001**
chill	1.62	0.15–3.09	**0.030**
abdominal pain	1.47	0.54–2.40	**0.002**
dizziness	1.30	0.41–2.20	**0.004**
rhinorrea	1.17	0.19–2.15	**0.020**
hemoptysis	0.82	0.35–1.30	**<0.001**
conjunctival congestion	0.44	0.18–0.69	**<0.001**
confusion	0.22	0.00–0.52	0.139
belching	0.16	0.00–039	0.162
pharyngeal hyperemia	0.05	0.00–0.14	0.231

Bold values highlight statistically significant prevalence. 95%CI: 95% confidence interval.

in asthmatic and COPD patients with COVID-19 could be associated with the widespread therapeutic use in these subjects of inhaled corticosteroids (ICSs) that, recently, have been proved to be characterized by protective effect against virus infections, specifically those due to coronaviruses [43].

In this respect, recently Halpin et al. [44] published a short commentary questioning which factors could account for the fact that asthma and COPD seem under-represented across the comorbidities reported by COVID-19 patients. The proposed hypotheses included the unlikely possibility of underdiagnosis of chronic obstructive respiratory disorders and the theory that asthma and COPD may protect themselves against COVID-19 due to different immune response elicited by both chronic diseases. However, a third and most likely theory was that concerning the beneficial impact of ICSs as therapy for chronic obstructive respiratory diseases, which could reduce the infection risk and the development of symptoms related with COVID-19 [44]. This hypothesis seems to be supported by in vitro studies documenting the efficacy of ICSs alone or combined with bronchodilators in inhibiting coronavirus replication and cytokine production, but also by in vivo evidence [45–47]. Interestingly, it was demonstrated that asthmatic patients treated with ICSs present a reduced sputum cell expression of ACE-2 and transmembrane protease serine 2 (TMPRSS2), the latter considered a key player in the process of virus-cell membrane fusion [48,49].

In any case, the role of ICSs as preventive therapy in patients at risk of infection by Sars-CoV-2 remains unclear. Nevertheless, it is essential to systematically collect data on comorbidities and therapeutic history of patients, in order to

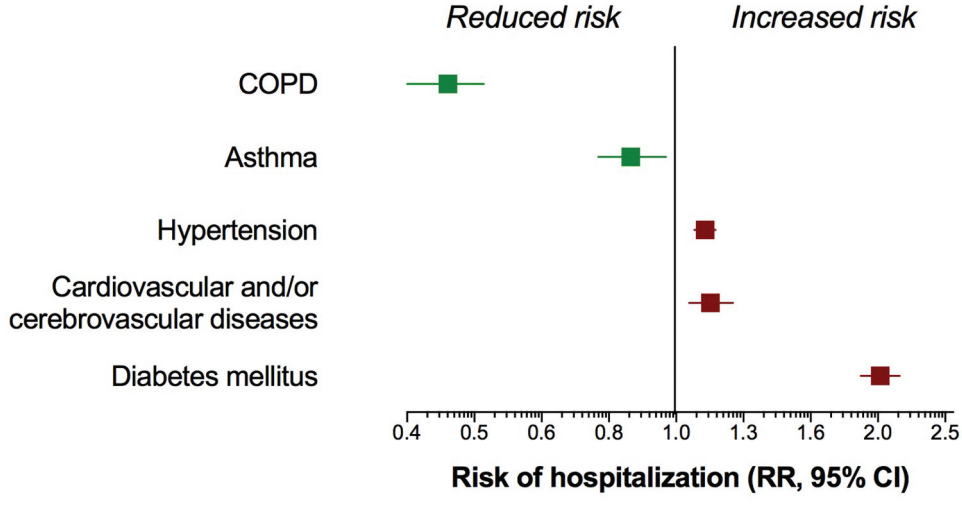

Figure 2. RR of hospitalization due to COVID-19 in patients with different comorbidities. COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019; RR: relative risk.

characterize the potential benefit-risk ratio of therapy for asthma and COPD against the spread of Sars-CoV-2.

The main limitation of this study is related with the intrinsic characteristics of simple pooling approach, that fails to weight individual studies or subgroups [33]. However, considering that the analysis was performed on a very large sample size, that the selected studies were comparable with respect to designs, data collection and reporting, and that generally the NOS reported a more than acceptably quality score for the investigated studies, it is improbable that the pooled results were affected by type 1 error or bias [31].

5. Conclusion

Since most asthmatic and COPD patients are currently treated worldwide with an ICS [50–53], this concise quantitative synthesis indirectly supports the evidence that ICSs may improve the clinical course of COVID-19, probably by modulating the mRNA expression not only of ACE-2 receptor, but also of TMPRSS2 that facilitates the viral entry into the host cells [48,53].

Author contributions

All authors were involved in the conceptualization, design, analysis, and interpretation of the data, along with the drafting and critical revising of the manuscript. The authors read and approved the final version of the manuscript.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Ghebreyesus TA Coronavirus should be seen as 'public enemy number one', says WHO. Tue 11 Feb 2020 15.36 GMT. Last modified on Wed 12 Feb 2020 01.05 GMT. 2020 [cited 2020 May 20]. https://www.theguardian.com/world/2020/feb/11/coronavirus-vaccine-could-be-ready-in-18-months-says-who
2. Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. Bmj. 2020;368:m606.
3. BBC. Coronavirus: sharp increase in deaths and cases in Hubei. 2020 [cited 2020 May 20]. https://www.bbc.com/news/world-asia-china-51482994
4. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061–1069.
5. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–513.
6. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.
7. Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected by SARS-CoV-2 in Wuhan, China. Allergy. 2020;75(75):1730–1741.
8. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1091.
9. Zheng Y, Xiong C, Liu Y, et al. Epidemiological and clinical characteristics analysis of COVID-19 in the surrounding areas of Wuhan, Hubei Province in 2020. Pharmacol Res. 2020;157:104821.
10. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–1062.
11. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020;55(5):2000547.
12. Meng Y, Wu P, Lu W, et al. Sex-specific clinical characteristics and prognosis of coronavirus disease-19 infection in Wuhan, China: a retrospective study of 168 severe patients. PLoS Pathog. 2020;16(4):e1008520.
13. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. Jama. 2020;323(20):2052–2059.
14. Wu Z, McGoogan JM. 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. 2020;323(13):1239–1242.
15. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. Bmj. 2015;349:g7647.
16. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.
17. European Commission. A guideline on summary of product characteristics (SmPC). 2009 [cited 2017 Jun 22]. http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf.
18. Pedder H, Sarri G, Keeney E, et al. Data extraction for complex meta-analysis (DECiMAL) guide. Syst Rev. 2016;5(1):212.
19. Dorans KS, Mills KT, Liu Y, et al. Trends in prevalence and control of hypertension according to the 2017 American college of cardiology/American heart association (ACC/AHA) guideline. J Am Heart Assoc. 2018;7(11). DOI:10.1161/JAHA.118.008888.
20. Croft JB, Wheaton AG, Liu Y, et al. Urban-rural county and state differences in chronic obstructive pulmonary disease - United States, 2015. MMWR Morb Mortal Wkly Rep. 2018;67(7):205–211.
21. Centers for Disease Control and Prevention. National diabetes statistics report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2020.

22. National Center for Health Statistics. Tables of summary health statistics for U.S. adults: 2018 national health interview survey. Table A-1c. Centers for Disease Control and Prevention website. 2018 [cited 2020 May 20]. https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2018_SHS_Table_A-1.pdf
23. National Center for Health Statistics. Tables of summary health statistics for U.S. adults: 2018 national health interview survey. Table A-2c. Centers for Disease Control and Prevention website. 2018 [cited 2020 May 20]. https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2018_SHS_Table_A-2.pdf
24. Wang Z, Chen Z, Zhang L, et al. Status of hypertension in China: results from the China hypertension survey, 2012-2015. Circulation. 2018;137(22):2344–2356.
25. Fang L, Gao P, Bao H, et al. Chronic obstructive pulmonary disease in China: a nationwide prevalence study. Lancet Respir Med. 2018;6(6):421–430.
26. Wang L, Gao P, Zhang M, et al. Prevalence and ethnic pattern of diabetes and prediabetes in China in 2013. JAMA. 2017;317(24):2515–2523.
27. Liu S, Li Y, Zeng X, et al. Burden of cardiovascular diseases in China, 1990-2016: findings from the 2016 global burden of disease study. JAMA Cardiol. 2019;4(4):342–352.
28. Wang W, Jiang B, Sun H, et al. Prevalence, incidence, and mortality of stroke in China: results from a nationwide population-based survey of 480 687 adults. Circulation. 2017;135(8):759–771.
29. Huang K, Yang T, Xu J, et al. Prevalence, risk factors, and management of asthma in China: a national cross-sectional study. Lancet. 2019;394(10196):407–418.
30. Jhee JH, Bang S, Lee DG, et al. Comorbidity scoring with causal disease networks. IEEE/ACM Trans Comput Biol Bioinform. 2019;16(5):1627–1634.
31. Blettner M, Sauerbrei W, Schlehofer B, et al. Traditional reviews, meta-analyses and pooled analyses in epidemiology. Int J Epidemiol. 1999;28(1):1–9.
32. Sullivan KM, Dean A, Soe MM. OpenEpi: a web-Based epidemiologic and statistical calculator for public health. Public Health Rep. 2009; 124(3):471–474
33. Bravata DM, Olkin I. Simple pooling versus combining in meta-analysis. Eval Health Prof. 2001;24(2):218–230.
34. Wells GA, D O'Connell BS, Peterson J, et al. The newcastle-ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2014 [cited 2020 Sept 16]. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
35. World Health Organization. Proposed working definition of an older person in Africa for the MDS project: Geneva: World Health Organization; 2018 [cited 2020 Jun 15]. https://www.who.int/healthinfo/survey/ageingdefnolder/en/
36. World Health Organization. Infections and infectious diseases: a manual for nurses and midwives in the WHO European Region. Copenhagen: WHO Regional Office for Europe; 2001 [cited 2020 Sep 1]. https://www.euro.who.int/__data/assets/pdf_file/0013/102316/e79822.pdf
37. To T, Viegi G, Cruz A, et al. A global respiratory perspective on the COVID-19 pandemic: commentary and action proposals. Eur Respir J. 2020;56(1):2001704

• **A commentary highlighting that chronic respiratory disorders such as asthma and COPD have not been consistently identified as significant comorbidities related to COVID-19, despite representing a high burden in the general population.**

38. Lippi G, Henry BM. Chronic obstructive pulmonary disease is associated with severe coronavirus disease 2019 (COVID-19). Respir Med. 2020;167:105941.
39. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50(2):1602426.
40. Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome. Jama. 2012;307(23):2526–2533.
41. Costa ELV, Amato MBP. The new definition for acute lung injury and acute respiratory distress syndrome: is there room for improvement? Curr Opin Crit Care. 2013;19(1):16–23.
42. Leung JM, Yang CX, Tam A, et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. Eur Respir J. 2020;55(5):2000688.
43. Halpin DMG, Singh D, Hadfield RM. Inhaled corticosteroids and COVID-19: a systematic review and clinical perspective. Eur Respir J. 2020;55(5):2001009.

• **An interesting systematic review suggesting that the use of ICSs in asthmatic and COPD patients could account for the reduced risk of COVID-19 hospitalization.**

44. Halpin DMG, Faner R, Sibila O, et al. Do chronic respiratory diseases or their treatment affect the risk of SARS-CoV-2 infection? Lancet Respir Med. 2020;8(5):436–438.

•• **An important short commentary describing the factors possibly accountable for the fact that asthma and COPD seem underrepresented across the comorbidities reported by COVID-19 patients.**

45. Yamaya M, Nishimura H, Deng X, et al. Inhibitory effects of glycopyrronium, formoterol, and budesonide on coronavirus HCoV-229E replication and cytokine production by primary cultures of human nasal and tracheal epithelial cells. Respiratory Invest. 2020;58(3):155–168.
46. Iwabuchi K, Yoshie K, Kurakami Y, et al. Therapeutic potential of ciclesonide inhalation for COVID-19 pneumonia: report of three cases. J Infect Chemother: Off J Jpn Soc Chemother. 2020;26(6):625–632.
47. Matsuyama S, Kawase M, Nao N, et al. The inhaled corticosteroid ciclesonide blocks coronavirus RNA replication by targeting viral NSP15. Published online March 12 (preprint). bioRxiv. 2020. doi:10.1101/2020.03.11.987016
48. Peters MC, Sajuthi S, Deford P, et al. COVID-19 related genes in sputum cells in Asthma: relationship to demographic features and corticosteroids. Am J Respir Crit Care Med. 2020;202(1):83–90

• **A study documenting that the use of ICSs in asthmatic patients gives a reduced susceptibility to SARS-CoV-2 infection and a lower COVID-19 morbidity.**

49. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271–280.e8.
50. Cazzola M, Segreti A, Bettoncelli G, et al. Change in asthma and COPD prescribing by Italian general practitioners between 2006 and 2008. Primary Care Respir J: J Gen Pract Airways Group. 2011;20(3):291–298.
51. Su VY-F, Yang K-Y, Yang Y-H, et al. Use of ICS/LABA combinations or LAMA is associated with a lower risk of acute exacerbation in patients with coexistent COPD and asthma. J Allergy Clin Immunol. 2018;6(6):1927–1935. e3.
52. Rottenkolber M, Fischer R, Ibanez L, et al. Prescribing of long-acting beta-2-agonists/inhaled corticosteroids after the SMART trial. BMC Pulm Med. 2015;15:55.
53. Maes T, Bracke K, Brusselle GG. COVID-19, Asthma, and inhaled corticosteroids (ICS): another beneficial effect of ICS? Am J Respir Crit Care Med. 2020;202(1):8–10.