

Mortality, seasonal variation, and susceptibility to acute exacerbation of COPD in the pandemic year: a nationwide population study

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Abstract

Background: Previous studies have suggested that the coronavirus disease 2019 (COVID-19) pandemic was associated with a decreased rate of acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Data on how the COVID-19 pandemic has influenced mortality, seasonality of, and susceptibility to AECOPD in the chronic obstructive pulmonary disease (COPD) population is scarce.

Methods: We conducted a national population-based retrospective study using data from the Health Insurance Institute of Slovenia from 2015 to February 2021, with 2015–2019 as the reference. We extracted patient and healthcare data for AECOPD, dividing AECOPD into severe, resulting in hospitalisation, and moderate, requiring outpatient care. The national COPD population was generated based on dispensed prescriptions of inhalation therapies, and moderate AECOPD events were analysed based on dispensed AECOPD medications. We extracted data on all-cause and non-COVID mortality.

Results: The numbers of severe and moderate AECOPD were reduced by 48% and 34%, respectively, in 2020. In the pandemic year, the seasonality of AECOPD was reversed, with a 1.5-fold higher number of severe AECOPD in summer compared to winter. The proportion of frequent exacerbators (≥ 2 AECOPD hospitalisations per year) was reduced by 9% in 2020, with a 30% reduction in repeated severe AECOPD in frequent exacerbators and a 34% reduction in persistent frequent exacerbators (≥ 2 AECOPD hospitalisations per year for 2 consecutive years) from 2019. The risk of two or more moderate AECOPD decreased by 43% in 2020. In the multivariate model, pandemic year follow-up was the only independent factor associated with a decreased risk for severe AECOPD (hazard ratio [HR]: 0.71; 95% confidence interval [CI]: 0.61–0.84; $p < 0.0001$). In 2020, non-COVID mortality decreased (–15%) and no excessive mortality was observed in the COPD population.

Conclusion: In the pandemic year, we found decreased susceptibility to AECOPD across severity spectrum of COPD, reversed seasonal distribution of severe AECOPD and decreased non-COVID mortality in the COPD population.

Keywords: acute exacerbation, COPD, COVID-19 pandemic, seasonality

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Introduction

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a common feature of COPD and leads to increased morbidity and mortality.¹ Infections are the most common

trigger,² with half of all AECOPD events linked to respiratory virus infection (RVI).³ AECOPD show seasonality; exacerbations in winter are more frequent than in summer, and a similar trend has been observed for mortality.^{4,5} The

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seasonality of AECOPD is explained, at least partly, by the seasonal variation in RVIs.⁶

In 2020, the world was confronted with a new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), characterised by high transmissibility.⁷ Countries have attempted to contain the virus with varying degrees of stringent public health measures.⁸ These public health measures reduced the circulation of all respiratory viruses in the community,⁹ demonstrated most notably by the severely reduced influenza burden during the pandemic year.¹⁰

A meta-analysis published recently found that all included studies reported a reduction in hospitalizations due to AECOPD in the first COVID-19 wave compared to the pre-pandemic period, and the pooled data showed overall reductions of 50% in hospital admission for COPD.¹¹ A subset of included studies also found a reduction in RVI, suggesting a potential mechanism underlying decreased AECOPD, although overall analysis failed to confirm a link between public healthcare restrictions and reductions in AECOPD. Concerning moderate AECOPD, the meta-analysis revealed no conclusive results regarding the impact of the pandemic. However, a population-based study from Scotland and Wales found a reduction of primary care consultation for AECOPD¹²

In addition to reduced RVI rates, other factors may have contributed to the observed decrease in AECOPD.¹¹ Among these, improved medication adherence,^{13,14} limited access to healthcare,¹⁵ modified behaviours, and reluctance to seek medical care have previously been reported.^{13,16}

All studies published to date examined the first months of the pandemic, and the long-term effects of the pandemic on AECOPD rates and on the seasonality of AECOPD are unknown. A pandemic effect on seasonality of AECOPD in relation to restrictions could indicate that reduction of RVI is the main cause of observed reductions in AECOPD.¹⁷ In addition, data on mortality in COPD patients can further elucidate the overall impact of the pandemic.

Therefore, our national population-based study aimed to analyse the pandemic's impact on the seasonal distribution of severe AECOPD and overall susceptibility to AECOPD. Furthermore,

we assessed the effect of the pandemic on moderate AECOPD and all-cause and non-COVID mortality rates in the COPD population.

Methods

Study design and data extraction

We conducted a nationwide retrospective observational study using routinely collected data on hospitalisations, medication use, and general insurance information from the Health Insurance Institute of Slovenia (HIIS) from 2015 onwards (a detailed description in the Supplement). The Slovenian health insurance system is compulsory for all citizens (population 2.1 million) and is managed by the HIIS.

All comparisons were made between annual periods from March to February, as the COVID-19 epidemic was officially declared on March 12, 2020; at this time, Slovenia started implementing public health measures, as evidenced by The Oxford COVID-19 Government Response Tracker (OxCGRT) stringency index.¹⁸

The results are reported according to the Reporting of Studies Conducted using Observational Routinely collected Health Data (RECORD) guidelines.¹⁹ The study was approved by the National Medical Ethics Committee (approval no. 0120-52/2021/4).

Analysis of severe AECOPD

We defined severe AECOPD as those requiring hospitalisation. We included all admissions of patients with a primary discharge diagnosis of COPD (J44.0-9) or acute respiratory failure (J96.0) combined with a secondary diagnosis of COPD with acute exacerbation. We excluded patients without long-acting inhalation therapy during the study period.

We extracted data on length of hospital stay (LOS), level of ventilatory support (no support, noninvasive, invasive – the highest level of support was recorded), sex, age, discharge diagnoses, and date of death (if applicable). The first hospitalisation was defined as hospitalisation for AECOPD after no AECOPD-related hospitalisation occurred in the previous 2 years. Patients were categorised according to exacerbation status as follows: (1) frequent exacerbators (≥ 2 AECOPD-related hospitalisations per year)

and (2) persistent frequent exacerbators (≥ 2 AECOPD-related hospitalisations per year for 2 consecutive years).

To compare changes in AECOPD hospitalisation numbers in 2020 to hospitalisation numbers for other diseases in order to control for the disease non-specific effects of the pandemic (especially reluctance to seek medical care and decreased access to the healthcare system), we analysed hospitalisations for heart failure, asthma, and influenza as the primary diagnoses and all hospitalisations for COPD as the secondary diagnosis (International Classification of Diseases, 10th revision, (ICD-10) codes in the Supplement).

To examine the effect of the pandemic year on patients after hospitalisation for AECOPD, we analysed rehospitalisation for AECOPD and mortality during follow-up for admitted patients from November 1 to February 28 of the study period.

Analysis of moderate AECOPD

Definition of COPD population. A national population of COPD patients was generated based on dispensed COPD medications from the medication database of the HIIS. We considered patients to have COPD if they were older than 45 years and redeemed two prescriptions for a long-acting muscarinic antagonist (LAMA), long-acting β -agonist (LABA), or both within the past year. Furthermore, a patient was considered to have COPD if they received triple inhalation therapy (a LAMA, LABA, and inhaled corticosteroid (ICS)). We excluded patients who received montelukast or ICS monotherapy (full criteria in the Supplement). In addition, we included patients in the COPD population if they were hospitalised in the analysis year when COPD was coded in the discharge diagnosis. We recorded sex, age, and time of death for all patients in the COPD population.

Definition and analysis of moderate AECOPD. We considered patients to have moderate AECOPD if they received antibiotics, oral corticosteroids, or both in an outpatient setting. We extracted data on medication prescriptions from HIIS. Only antibiotics typically used for AECOPD were included (details in the Supplement). To control for reduced access to healthcare, we also extracted data on dispensed antibiotics for urinary tract infection (UTI) in the same population of patients.

The COPD populations were defined separately each year; moderate AECOPD events were analysed for the following year.

To test the validity of our results, we analysed a subset of patients for whom COPD was coded as the primary or secondary diagnosis during hospitalisation. Furthermore, we performed sensitivity analyses with varying criteria to define COPD to ensure that the results were robust (Supplement). Last, to check for increased AECOPD rates with greater COPD severity (based on inhalation therapy), we performed subgroup analyses including surviving COPD patients with specific therapies: dual bronchodilatation and triple inhalation therapy (for 2018–2020).

Analysis of mortality in the COPD population

For survival analysis, we compared all-cause and non-COVID monthly/yearly mortality rates in the COPD population. We extracted the data of patients with COPD who died from COVID-19 in the hospital or within 30 days of discharge. Excessive mortality in the COPD population was calculated and compared with that in the general population. Data on mortality in the general population were acquired from the Statistical Office of the Republic of Slovenia SiStat Database.²⁰

Study endpoints

The primary endpoints of the study were changes in severe AECOPD (hospitalisations and rehospitalisations), seasonality pattern, and changes in the proportion of frequent exacerbators in 2020 compared to those in the pre-pandemic years. We further analysed moderate AECOPD event rates and all-cause mortality in the COPD population including and excluding those who died from COVID-19.

Secondary endpoints were changes in in-hospital mortality, and the rate of ventilatory support in 2020 compared to that in the pre-pandemic period. We also compared changes in hospitalisations for AECOPD and hospitalisations for heart failure, asthma, influenza, and for health failure and pneumonia in which COPD was the secondary diagnosis.

Statistical analysis

Data are expressed as absolute numbers and proportions (percentages), mean values with

standard deviations (SDs) or median values with interquartile ranges (IQRs), as appropriate. The annual incidence of exacerbations was calculated as a per-person per-year (PY) rate for moderate AECOPD and as an age-standardised number per 100,000 population for AECOPD hospitalisations. Age and sex were standardised using a direct standardisation method with 5-year age groups and the Slovenian population as the reference. Changes in all relevant indicators in the pandemic year were observed relative to 2015–2019 averages. If, however, exponential trend analysis revealed a strong ($R^2 > 0.5$) upwards or downwards trend in the 2015–2019 period and at the same time the observed values for 2019 were aligned with the trend values, changes in the pandemic year were observed relative to 2019. To assess the seasonality of AECOPD, 31-day moving averages were calculated based on daily hospitalisation data. Furthermore, to analyse the effect of follow-up in the pandemic year on the cumulative incidence of COPD rehospitalisations, we used a competing risk approach; we considered death before hospitalisation a competing risk. We constructed multivariable Fine-Gray regression models to adjust for the following important covariates: age, sex, LOS, ventilatory support at index hospitalization, and year of follow-up. We calculated the relative risk of moderate AECOPD in the pandemic year relative to exacerbations in the pre-pandemic period.

Mortality in the overall COPD population was calculated as the number of persons who died per 1000 person-years (PY) or person-months (PM), and mortality was compared between annual periods. Excessive mortality was calculated as the percentage change in the observed monthly/yearly death rate compared to that estimated based on the preceding year's average. For mortality rate and excessive mortality analysis, we separated all-cause and non-COVID all-cause mortality.

All analyses were performed with STATA V15.1 (Stata Corp, College Station, Texas, USA, 77845) or R version 4.0.2 and its affiliated packages. *P* values of $< .05$ were considered statistically significant.

Results

Severe AECOPD

During the study period (2015–2020), a total of 12,210 hospitalisations for AECOPD occurred

(0.60% of hospitalisations in Slovenia) among 5859 patients. We excluded 343 patients due to the lack of inhalation therapy. In the same period, 15,638 patients were hospitalised with either a primary or secondary diagnosis of COPD.

The baseline characteristics of the patients and AECOPD hospitalisations are summarised in Table 1. In 2020, a decline in the number of AECOPD hospitalisations (–48%) and patients (–44%) occurred (Table 1) compared to the average of preceding years. Patients in 2020, on average, were slightly older, and the mean LOS decreased by over 1 day (–11%).

Changes in the numbers of comparator diagnoses hospitalisations in 2020 are shown in Figure 1. The reduction in heart failure-related hospitalisations was only half of that of COPD- and asthma-related hospitalisations. In the subgroup of hospitalisations for which COPD was the secondary diagnosis, hospitalisations for pneumonia (–57%) decreased more than those for heart failure (–28%). We found the greatest reduction in influenza hospitalisation numbers. All 157 hospitalisations in 2020 were during the 2019/2020 influenza season. Of the 17,489 patients in the 2020 COPD cohort, 401 (2.3%) were hospitalised for COVID-19 in the 12 pandemic months, accounting for 2.6% of all COVID-19 hospitalisations.

In the pre-pandemic years, the proportion of AECOPD hospitalisations in winter was higher than that in summer (29% *vs* 21%). In 2020, the proportions were reversed, with 20% *vs* 30%, respectively. Figure 2 depicts the daily variations in admissions for AECOPD in 2020 compared to the average rates in 2015–2019; alongside, the OxCGRT stringency index is shown. The pattern of seasonality was reversed in 2020. Pre-pandemic AECOPD-related hospitalisation numbers peaked in midwinter and were lowest in late summer, while in 2020, AECOPD hospitalisation numbers were sustainably elevated from late May to early September. Daily rates of AECOPD admissions were; however, lower throughout 2020 compared to 2015–2019.

The number and proportion of hospitalisations of frequent exacerbators were stable over the pre-pandemic period (Table 1); however, in 2020, significant declines in both the number and proportion were observed. We found a 9% relative reduction in the proportion of frequent

Table 1. Baseline characteristics of patients hospitalised for AECOPD during the study period.

	2015	2016	2017	2018	2019	Average, 2015– 2019	2020
No. of patients	1529	1586	1473	1597	1495	1538	867
Age, years	71.3 ± 9.7	71.1 ± 9.4	70.9 ± 9.3	70.8 ± 9.7	71.0 ± 9.1	71.0 ± 9.4	71.8 ± 9.1
Sex, female	513 (33.6)	544 (34.3)	518 (35.2)	611 (38.3)	575 (38.5)	552 (36.0)	324 (37.4)
No. of surviving patients in current year	1253	1281	1228	1308	1240	1264	674
No. of hospitalizations	2153	2334	2122	2314	2129	2210	1158
Age-standardised hospitalisation rate	110.4	116.4	103.9	110.3	99.3		52.9
Length of stay, mean, days	9.6 ± 9.0	10.2 ± 10.7	9.6 ± 10.2	9.8 ± 10.6	9.8 ± 10.4	9.8 ± 10.2	8.7 ± 9.5
Length of stay, median, days	7.1 (7.7)	7.1 (7.6)	6.9 (7.2)	6.9 (6.9)	7.0 (6.9)	7.0 (7.4)	6.7 (6.2)
Proportion of hospitalizations with no ventilatory support	92.1	88.2	89.1	87.2	85.3	88.3	84.5
Proportion of noninvasive ventilation	5.1	7.4	7.4	8.4	11.8	8.0	12.3
Proportion of invasive ventilation	2.8	4.5	3.5	4.4	3.0	3.7	3.2
Specific subgroups of patients							
Frequent exacerbators ^a		557 (35.1)	567 (38.5)	560 (35.1)	548 (36.7)	558 ^b (36.3)	286 (33.0)
Frequent exacerbators ^a surviving in current year		424 (33.1)	453 (36.9)	427 (32.6)	433 (34.9)	434 ^b (34.4)	211 (31.3)
Frequent exacerbators ^a in previous year, hospitalised at least once in current year			212 (38.1)	226 (39.9)	207 (37.0)	215 ^c (38.3)	147 (26.8)
Frequent exacerbators ^a in previous year, hospitalised at least once in current year, and surviving in current year			153 (36.1)	167 (36.9)	151 (35.4)	157 ^c (36.1)	116 (26.8)
Persistent frequent exacerbators ^d			127 (22.8)	118 (20.8)	112 (20)	119 ^c (21.2)	76 (13.9)
Persistent frequent exacerbators ^d surviving in current year			93 (21.9)	81 (17.9)	80 (18.7)	85 ^c (19.5)	55 (12.7)
Data are presented as the no. (%), mean ± SD, or median (interquartile range), unless otherwise indicated;							
^a Patients with ≥ 2 AECOPD events.							
^b 2016–2019.							
^c 2017–2019.							
^d Patients with ≥ 2 AECOPD events in two consecutive years.							

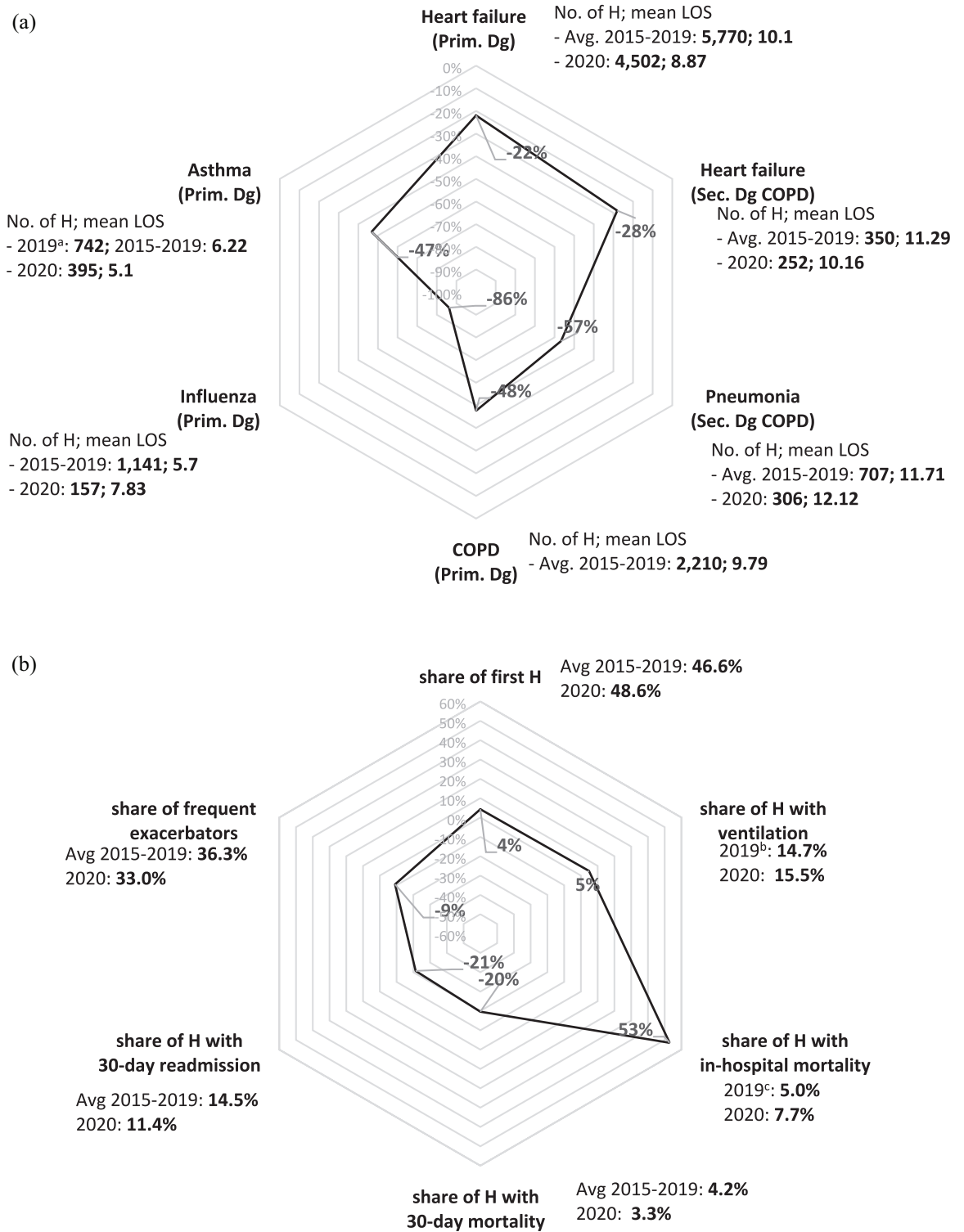


Figure 1. Relative changes in the pandemic year relative to the 2015–2019 average. (a) hospitalizations across diseases and (b) selected indicators for COPD hospitalizations.

H, hospitalizations; LOS, length of stay.

^a Negative exponential trend, average annual growth rate: -10.3%, R2 = 0.978.

^b Positive exponential trend, average annual growth rate: 14.1%, R2 = 0.8321.

^c Negative exponential trend; average annual growth rate: -5.3%; R2 = 0.5648.

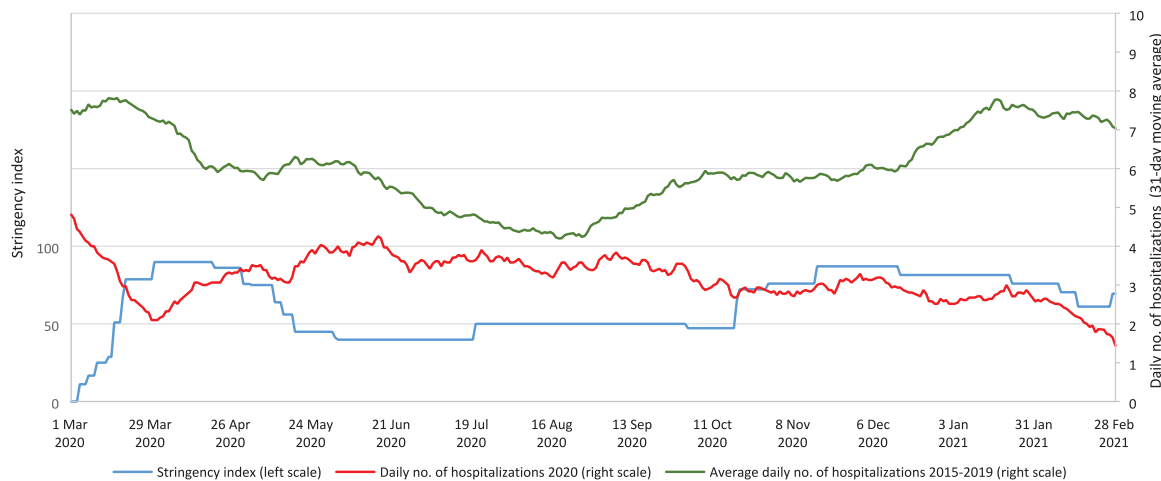


Figure 2. Comparison of the seasonality of AECOPD hospitalizations in the pandemic year vs previous years.

exacerbators in 2020, with a 30% reduction in the proportion of repeated severe AECOPD in 2020 (in the group of frequent exacerbators in 2019). The most striking decrease in the proportion, at 34%, occurred in the group of persistent frequent exacerbators.

There was a positive trend for the use of noninvasive ventilation (NIV) across years, with only a slight additional increase in 2020. The proportion of invasive ventilation (IV) remained stable throughout the years. In 2020, the proportion of hospitalisations requiring ventilatory support remained relatively stable throughout the year (summer 16.9% *vs* winter 15.6%). In-hospital mortality increased in 2020 (+53%), with the largest increase in those with NIV, at 133%, while mortality in those receiving IV increased by 38%. The absolute number of patients who died during AECOPD-related hospitalisation was lower in 2020 than the average in 2015 to 2019 (89 *vs* 116, respectively).

Figure 3 shows the Kaplan–Meier (KM) curves for COPD rehospitalisation (primary outcome) and all-cause mortality. When comparing the pre-pandemic years (2015–2019) to 2020, the rehospitalisation risk after the index hospitalisation was significantly lower in 2020. In the adjusted multivariable Fine-Grey model, the only significant predictor of rehospitalisation was follow-up in the pandemic year (hazard ratio [HR]: 0.71; 95% confidence interval [CI], 0.61–0.84; $p < 0.0001$) (Table in Supplement). However, all-cause mortality in those who were not rehospitalised for

AECOPD remained constant across years. The significant predictors of all-cause mortality according to the adjusted multivariable Fine-Grey model were sex (male), age, and LOS.

Moderate AECOPD

We estimated the COPD patient population in Slovenia from 2016 to 2020 as described; the COPD population increased from 14,128 in 2016 to 17,489 in 2020 (Table 2). The average age of patients remained stable across years; the majority of patients were men, although the proportion of women increased steadily.

Predictably, the baseline risk of moderate AECOPD increased with the severity of COPD; the risk was lower in the dual bronchodilatation subgroup and higher in the post-hospitalisation/triple-therapy subgroup (Table 2). The rate of moderate AECOPD events in the whole COPD population declined slightly during 2016–2019 and significantly in 2020, which was 66.2% of that in 2019. This decrease was mainly due to fewer antibiotic prescriptions, while the number of oral corticosteroid prescriptions remained unchanged. For comparison, the rate of UTI events was relatively stable during 2016–2020.

The risk of having at least one moderate AECOPD event decreased by 30.8% in 2020 relative to the 2016–2019 weighted average. In specific COPD patient subgroups, we observed similar decreases in risks, by 27.2% in previously hospitalised COPD patients, 28.7% in patients on triple therapy and

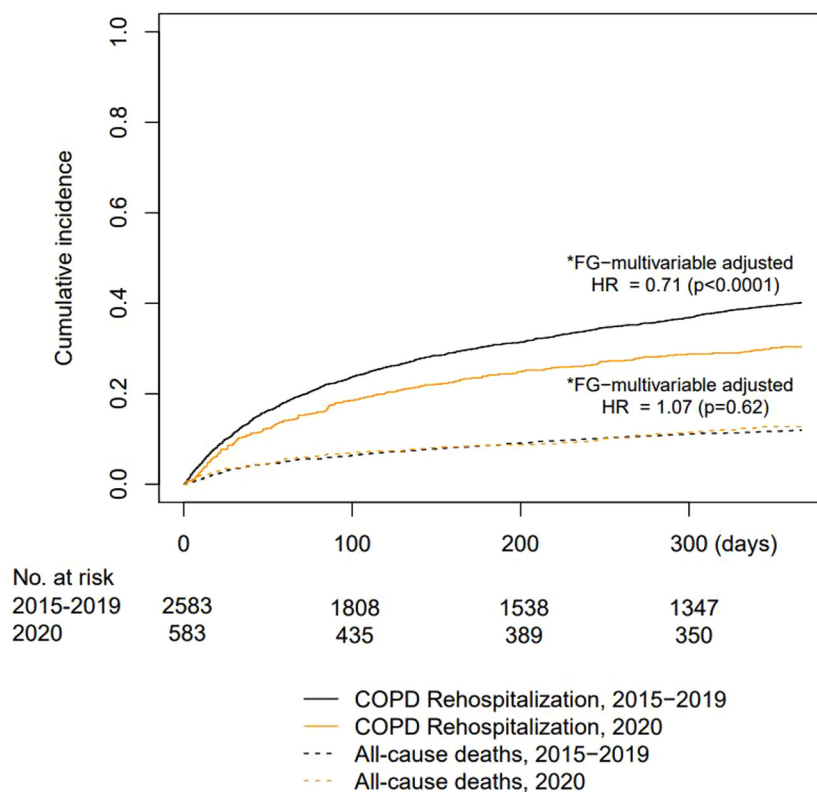


Figure 3. Cumulative incidence of COPD rehospitalizations and all-cause mortality (competing risk) according to the follow-up period.

32.6% in patients on dual bronchodilatation. The risk of two or more moderate AECOPD decreased in 2020 overall by 42.5% (Table 2).

Mortality in COPD population

The average yearly mortality rates in the COPD population in the pre-pandemic years were 78.9/1000 (± 5.0) PY; in 2020, it was 75.8/1000 PY and non-COVID mortality 66.8/1000 PY. The monthly mortality rate during the study period is represented in Figure 4. All-cause mortality in the pre-pandemic period showed a seasonal peak, with the highest mortality in winter (January and February). In 2020, it peaked in parallel with the second COVID-19 wave (October to December). During the first COVID-19 wave, all-cause mortality in the COPD population was decreased compared to previous years. Yearly excessive mortality in the 2020 annual period was +21.7% in the general population, -4.0% in the overall COPD population and -15.3% for non-COVID mortality in the COPD population.

Discussion

In our nationwide population study, we found that the seasonality of severe AECOPD was reversed and that the susceptibility of COPD patients to exacerbate and reexacerbate substantially decreased in the pandemic year. Furthermore, non-COVID mortality decreased in the COPD population.

Severe AECOPD

Analysing the full pandemic year allowed us to examine the seasonality of severe AECOPD. In the pre-pandemic years, we observed characteristic Northern Hemisphere seasonality. However, the pattern was reversed in 2020, with increased numbers of AECOPD in the summer. Nevertheless, reductions in exacerbations occurred throughout all seasons of the pandemic year, culminating in a 48% decrease in AECOPD hospitalisation numbers, thus confirming and expanding the results of previous, shorter studies.¹¹ AECOPD hospitalisation variation followed the reverse pattern of public health restrictions, suggesting a causal relationship

Table 2. Moderate AECOPD during the study period.

Population analysis for moderate exacerbations	2016	2017	2018	2019	2020	2020/2019 (%) or RR ^a
COPD population ^b	14,128	15,462	16,376	17,050	17,489	
Female sex (%)	35.5	36.6	37.5	38.3	39.2	
Age, years (mean ± SD)	69.4 ± 10.0	69.4 ± 9.9	69.5 ± 9.8	69.5 ± 9.7	69.6 ± 9.6	
All events ^c (No./COPD population)	0.85	0.78	0.80	0.77	0.51	-33.8
Antibiotics	0.62	0.56	0.58	0.55	0.34	-38.9
Systemic corticosteroids	0.13	0.13	0.13	0.12	0.12	-6.1
Antibiotics and corticosteroids	0.10	0.09	0.09	0.09	0.05	-41.1
No. events/exacerbator ^d	1.81	1.80	1.77	1.76	1.65	-6.1
Risk of experiencing at least 1 event	0.469	0.431	0.450	0.438	0.309	0.692 ^a
Risk of experiencing at least 2 events	0.215	0.195	0.202	0.193	0.115	0.575 ^a
Specific subgroups of patients						
COPD coded in hospitalisation						
Population	5218	6271	7080	7594	7528	
Events/population	1.18	1.06	1.05	1.02	0.71	-29.8
Risk of experiencing at least 1 event	0.599	0.534	0.539	0.529	0.398	0.728 ^a
Risk of experiencing at least 2 events	0.312	0.280	0.280	0.263	0.174	0.620 ^a
Patients receiving triple therapy 2018–2020						
Population			4510	4510	4510	
Events/population ^e			1.05	0.98	0.68	-32.9 ^f
Risk of experiencing at least 1 event			0.550	0.516	0.380	0.713 ^a
Risk of experiencing at least 2 events			0.276	0.254	0.173	0.651 ^a
Patients receiving dual bronchodilatation 2018–2020						
Population			2665	2665	2665	
Events/population ^e			0.51	0.50	0.33	-34.4 ^f
Risk of experiencing at least 1 event			0.345	0.341	0.232	0.674 ^a
Risk of experiencing at least 2 events			0.119	0.103	0.650	0.585 ^a
Population analysis for comparator event (UTI)						
UTI events/COPD population	0.076	0.077	0.079	0.085	0.078	-8.0

COPD, chronic obstructive pulmonary disease; SD, standard deviation; UTI, urinary tract infection.
^aRelative risk (risk in 2020 relative to the 2016–2019 or 2018–2019 weighted average risk).
^bEstimated separately for each year and based on COPD medication claims and hospitalisation events (e-Appendix 1).
^cBased on medication claims (antibiotics, oral corticosteroids, or both – e-Appendix 3).
^dRates for patients with exacerbations.
^eRates from 2018 on analysis of stable surviving subpopulation of dual/triple maintenance therapy (e-Appendix 2).
^fCompared to the 2018–2019 average.

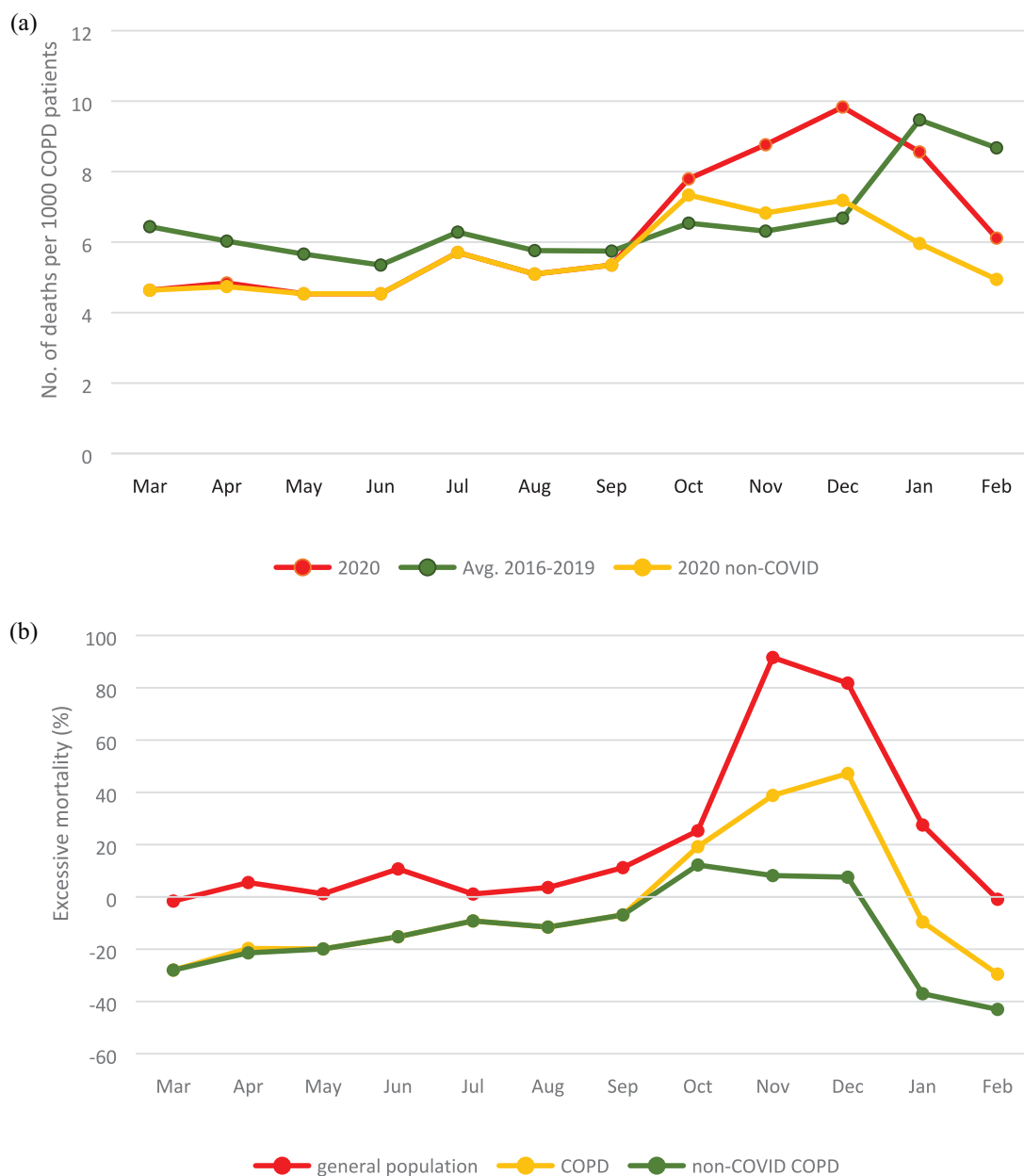


Figure 4. Mortality rate in the COPD population in pandemic vs pre-pandemic years: (a) monthly mortality rate over 12 months and (b) excessive mortality in the COPD population compared to excessive mortality in the general population.

between viral transmission prevention (restrictions) and AECOPD reduction.

Several studies and public health agency reports found that the emergence of SARS-CoV-2 and the resulting shutdowns were associated with significant reductions in the circulation of seasonal respiratory viruses.^{9,21–26} In fact, also in Slovenia, no patient tested positive for influenza in the

2020/21 season and respiratory syncytial virus infections were starkly reduced.^{22,23} These reductions in seasonal RVI caused by enforcement of public health measures likely substantially contributed to reductions in severe AECOPD. However, factors other than RVI have been linked to the seasonality of AECOPD.²⁷ Although we were not able to adjust for environmental factors, our finding of reversed seasonality in 2020

suggest that the major driving force of seasonal variation in AECOPD is the variation in RVI and that factors linked to winter (i.e. cold temperatures and increased pollution) are probably of lesser importance.²⁸

Further supporting the significant role of RVI in the pathogenesis of AECOPD (and in the pathogenesis of exacerbations of other respiratory diseases) is the fact that we found a disproportionately lower decrease in hospitalisations for heart failure (−20%) compared to diagnoses with a known infectious trigger that is, COPD (−48%) and asthma (−47%). Similar results were also observed in other studies.^{29–31} A lesser reduction in heart failure hospitalisations further indicates that fear and reduced access to healthcare played a minor role in the observed reduction in AECOPD. A misclassification of AECOPD as COVID-19 hospitalizations could also have contributed to the reduction in AECOPD hospitalisations. However, most patients with COPD hospitalised for COVID-19 have been found to have pneumonia and not AECOPD.³²

When analysing patients with the highest risk for COPD hospitalisation, especially frequent exacerbators, we found a decreased risk of AECOPD hospitalisation in 2020 by approximately 30%. In recently hospitalised patients, follow-up in 2020 was the only independent predictor of this reduction. In addition, we found a substantially decreased proportion of patients with two or more moderate AECOPDs. Our results suggest that the pandemic year influenced the susceptibility of patients to exacerbate and reexacerbate. The most plausible explanation for our findings is that lockdown measures with social distancing and shielding significantly impeded viral transmission and the likelihood of COPD patients acquiring an RVI, which reduced the risk of AECOPD. Our results further suggest that intrinsic susceptibility to exacerbation, which is likely of lesser importance in the pathogenesis of AECOPD,³³ requires, at least in some patients, an additional extrinsic factor to manifest as AECOPD.

In-hospital mortality due to AECOPD was increased (+53%) in 2020 compared to the previous years. Other studies have shown mixed results regarding the effect of the pandemic on in-hospital deaths.^{12,34} Increased in-hospital mortality is likely due to a combination of more severe patients being admitted (potentially due to fear of

using health care services) and the health system being overwhelmed with COVID-19 patients.

Interestingly, in patients with COPD hospitalisations for pneumonia decreased disproportionately more than those for heart failure. This finding potentially reflects the importance of RVI as a trigger for secondary bacterial infection in COPD thus corroborating the results of other studies.^{35–37}

Moderate AECOPD

We found an overall reduction of 33.8% in the exacerbation medication prescription, indicating a significantly lower incidence of moderate AECOPD. As the difference in the UTI antibiotic prescription rate in 2020 compared to previous years, was small, we believe that the reduced access to healthcare during the pandemic year probably played only a minor role in the reduction of AECOPD medication prescriptions. Furthermore, unmet moderate AECOPD treatment needs would likely lead to increased hospitalisation rates. Our results are consistent with the results of other populational studies that also observed reductions in moderate AECOPD exacerbations following the introduction of restrictions.¹²

Mortality in COPD population

We found a substantially decreased non-COVID all-cause mortality in COPD patients in 2020. Despite the fact that Slovenia was heavily impacted by the second COVID-19 wave, with one of the highest COVID-19 mortality rates worldwide at the time,³⁸ no excessive mortality occurred in the COPD population during the pandemic annual period, whereas substantial excessive mortality was detected (+21%) in the general population. Several studies have found that COPD patients have an increased risk for adverse COVID-19 outcomes, including death.³⁹ Better compliance with lockdown measures in the COPD population could account for this difference.

Several studies have reported increased mortality due to heart disease in the first pandemic wave, indicating increased out-of-hospital mortality due to poor access to health services.^{40,41} When comparing heart disease and COPD outcomes during the pandemic, a difference emerges. The reductions in AECOPD at all levels in our study likely translated into a decrease in non-COVID mortality, suggesting an actual protective effect of

pandemic measures on COPD and causality. The reverse is true for heart disease, where proportionally smaller reductions in health care utilisation, compared to that for COPD, were associated with increased overall mortality.

Strengths and limitations

Our population-based study has several strengths. This is one of only a few studies to examine the seasonality of severe AECOPD and long-term outcomes with complete national data, contributing to the Generalisability of the results. Patient-level information allowed us an in-depth analysis of patients with the highest risk. In addition, large data sets enabled us to simultaneously study the effect on AECOPD across the severity spectrum as well as overall and non-COVID mortality in the same population, providing unique insights into the pandemic's effect on the COPD population.

Our study is subject to the limitations of large administrative data research. In the hospitalisation database, some degree of inaccuracy in reporting and COPD overdiagnosis could have occurred. However, we previously found, that overdiagnosis of COPD was low (less than 8%).⁴² In addition, we improved the accuracy by excluding patients without inhalation therapy. Moreover, we believe inaccurate reporting was constant across years and thus did not affect our main results. The analysis of moderate AECOPD was limited by medication refills being used as a proxy for both defining the COPD population and moderate AECOPD events. However, both methods have been used previously.^{13,43} Moreover, the sensitivity analyses of different criteria for defining COPD showed no effect on our results.

Our detected COPD population increased over the years, similar to other studies,⁴⁴ potentially influencing the validity of comparisons across years. However, the overall rate of moderate AECOPD events and the average patient age did not differ substantially across the yearly COPD populations, suggesting similar severity among patients, validating the comparison.

Last, due to our population-based design, we could not address the underlying mechanism of the AECOPD reduction directly. Although alternative explanations to observed reductions of AECOPD that were outlined elsewhere (improved adherence to medication, decreased pollution,

and fear of using healthcare services)¹¹ are possible and likely contributed to observed reductions, we believe our data, taken together strongly indicate that the reduction in AECOPD was mainly due to reduction in RVI, achieved with pandemic measures. Further research is necessary to confirm this notion.

Conclusion

Using complete national data, we report a sustained significant reduction in the number of AECOPD events and reversed seasonality of severe AECOPD during the first pandemic year. The pandemic year was associated with decreased tendencies in exacerbations and reexacerbations and with a decreased number of frequent exacerbators. Non-COVID all-cause mortality in the COPD population decreased compared to the preceding years. Our findings have important implications for our understanding of susceptibility to exacerbation as well as future strategies for AECOPD prevention. The pandemic, in our view, demonstrated the potential of RVI prevention and control. New approaches involving targeted behaviour modifications and the prospect of new vaccination technologies could promote the benefits of pandemic measures without the harm of lockdown.

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Supplemental material

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