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ORIGINAL RESEARCH

Clinical Characteristics and Outcomes of Hospitalized AECOPDs Secondary to SARS-CoV-2 versus Other Respiratory Viruses

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Video abstract

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Objective: To compare clinical characteristics and outcomes of hospitalized acute exacerbations of COPD (AECOPD)s secondary to SARS-CoV-2 versus other respiratory viruses amongst a highly vaccinated population in the Omicron era.

Design: Retrospective cohort study; analysis of hospital medical records and linked pathology and radiology reports.

Setting: Tertiary health network in Victoria, Australia; January 2022–August 2022.

Main Outcome Measures: Key clinical information including comorbidities, vaccination status, treatments administered and outcomes such as hospital length of stay, ICU admission, non-invasive ventilation usage and inpatient mortality.

Results: One hundred ninety-nine viral AECOPDs - 125 SARS-CoV-2 and 74 other viruses were identified. Of the SARS-CoV-2 group. 13.6% were unvaccinated, 17.6% partially and 68.0% fully vaccinated. The SARS-CoV-2 group were older (77.2 vs 68.9, $p < 0.00001$) with more comorbidities (1[1–2] vs 1[0–2], $p = 0.008$) and lower candidacy for full resuscitation (25.6% vs 56.8%, $p < 0.0001$). Mortality tended to be higher among SARS-CoV2 admission (9.6% v 2.7%, $p = 0.066$) but rates of ICU admission (10.4% v 13.5%, $p = 0.507$), length of hospitalisation (5[3–8] vs 5[3–9], $p = 0.9$) and readmission within 30 days (25% vs 33.3%, $p = 0.184$) were similar.

Conclusion: In a highly vaccinated population in the Omicron era, COPD patients requiring hospitalisation with SARS-CoV-2 are older with more comorbidities than those admitted with other respiratory viruses. Length of hospitalisation and ICU utilisation was similar. Inpatient mortality may be higher.

Keywords: SARS-CoV2, coronavirus, COPD, viral exacerbations

Introduction

Patients with chronic obstructive pulmonary disease (COPD) are vulnerable to severe acute exacerbations (AECOPDs) when they contract respiratory viruses.[1] Exacerbations of COPD are cardinal events in the disease, associated with accelerated decline in lung function, reduced quality of life, hospitalization and mortality.[2–4] Viral infection appears to be responsible for up to 50% of AECOPDs.[5,6] The prognosis of virus-associated exacerbation appears different to other exacerbation etiotypes, with a slower recovery and prolonged hospitalization.[7,8] In general, studies examining hospitalized AECOPDs have considered all respiratory viruses as a generic grouping, with outcomes compared between "viral" and "non-viral" exacerbations or versus alternative broad etiologies such as bacterial or eosinophilic exacerbations.[9–11] Studies of individual viruses such as rhinovirus ("common cold"), influenza and Respiratory Syncytial Virus (RSV) have been performed, although there are very limited data to indicate whether specific respiratory viruses have different impacts as causes of severe AECOPDs. The relative impact of SARS-CoV-2 versus previously circulating respiratory viruses as a cause of severe AECOPD has been little studied. One prospective observational cohort study in the United Kingdom compared outcomes from AECOPDs secondary to SARS-CoV-2 versus groups with either alternative

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infections (bacterial or viral), or non-infective AECOPDs.[10] They reported higher 30-day mortality, longer hospital stays and more frequent requirement for positive pressure ventilatory support among the SARS-CoV-2 group. Much of this data was collected during the early phases of the pandemic with circulating wild-type, alpha and delta strains. Since the onset of the COVID pandemic, widespread vaccination and development of effective therapeutics have been achieved, limiting applicability of early pandemic data to the current era.

SARS-CoV-2 is now an endemic community respiratory virus, and it is therefore necessary to evaluate the clinical phenotype of AECOPD secondary to SARS-CoV-2 contextualized alongside other commonly circulating respiratory viruses. We hypothesized that sub-populations of COPD patients may be more vulnerable when hospitalized with AECOPD due to SARS-CoV-2 compared to other respiratory viruses, which may inform and guide clinical management, prevention strategies and prognosis. We therefore analyzed hospitalizations for AECOPD due to respiratory viruses in 2022, a period of time in which widespread SARS-CoV-2 vaccination had been achieved among the population studied, and when the dominant circulating SARS-CoV-2 strain was Omicron derived. In this context, we directly compared clinical characteristics and outcomes between AECOPDs hospitalized with SARS-CoV-2 infection versus other respiratory viral infections.

Materials and Methods

We conducted a multicenter retrospective observational cohort study. Medical records of adult patients (>18 years) admitted under either the general medicine or respiratory units between January 2022–August 2022 to three acute care hospitals (each equipped with an intensive care unit) in a tertiary health service network in Melbourne, Australia, were identified.

To ensure accurate identification of acute exacerbations of COPD, multiple broad diagnoses or symptoms were initially used to identify all possible patients. Thereafter, each identified case record was manually reviewed to assess whether cases met the inclusion criteria (see Figure 1). Duplicate cases were removed. The definition employed for AECOPD was a worsening of respiratory symptoms requiring an increase in therapy.[12]

Patients with a documented medical history of COPD and/or a physician diagnosis of exacerbation of COPD as well as a positive test for multiplex respiratory viral polymerase chain reaction (PCR) or COVID rapid antigen testing (RAT) were eligible for inclusion.

Patients with both COPD and other respiratory comorbidities including asthma, interstitial lung disease, lung cancer and bronchiectasis were not excluded if AECOPD was the primary clinical diagnosis. Patients with exacerbations who tested positive to both SARS-CoV-2 and another respiratory virus simultaneously were excluded from the study. Patients who were asymptomatic with an incidentally positive viral PCR were excluded.

Medical records data – demographic characteristics, comorbidities, vaccination status, resuscitation status, examination data, laboratory results, imaging findings, treatments administered and clinical outcomes including re-admission data were recorded. “Fully vaccinated” status was based on patients who had received the number of vaccinations consistent with local health recommendations at the time; two COVID vaccinations if hospitalized prior to 10 February 2022 and three vaccinations after 11 February 2022.

Data Analysis

Group characteristics were summarized using descriptive statistics for parametric or non-parametric data. Data are presented as number (percentage), mean ± standard deviation, or median [interquartile range].

Relationships between clinical outcomes and virus groups for continuous variables were analyzed by *t*-test (normally distributed data) or Mann–Whitney testing (non-parametric data). Chi-square analyses were used for categorical data.

Logistic regression models were applied in the cohort to estimate odds ratios with 95% confidence intervals of possible risk factors for inpatient mortality. For multivariate regression analysis, we first used a $p \leq 0.2$ to identify candidate predictors. We then explored collinearity and excluded variables based on correlation coefficients >0.5, visual inspection of scatter graph matrices and variance inflation factors <5. In addition to these factors, the multivariate model included fixed covariates of age, sex and SARS-CoV-2 status. Statistical significance was accepted if $p < 0.05$ (two-sided) . All analyses were conducted on Stata MP 14.1 (Statacorp, College Station, TX).

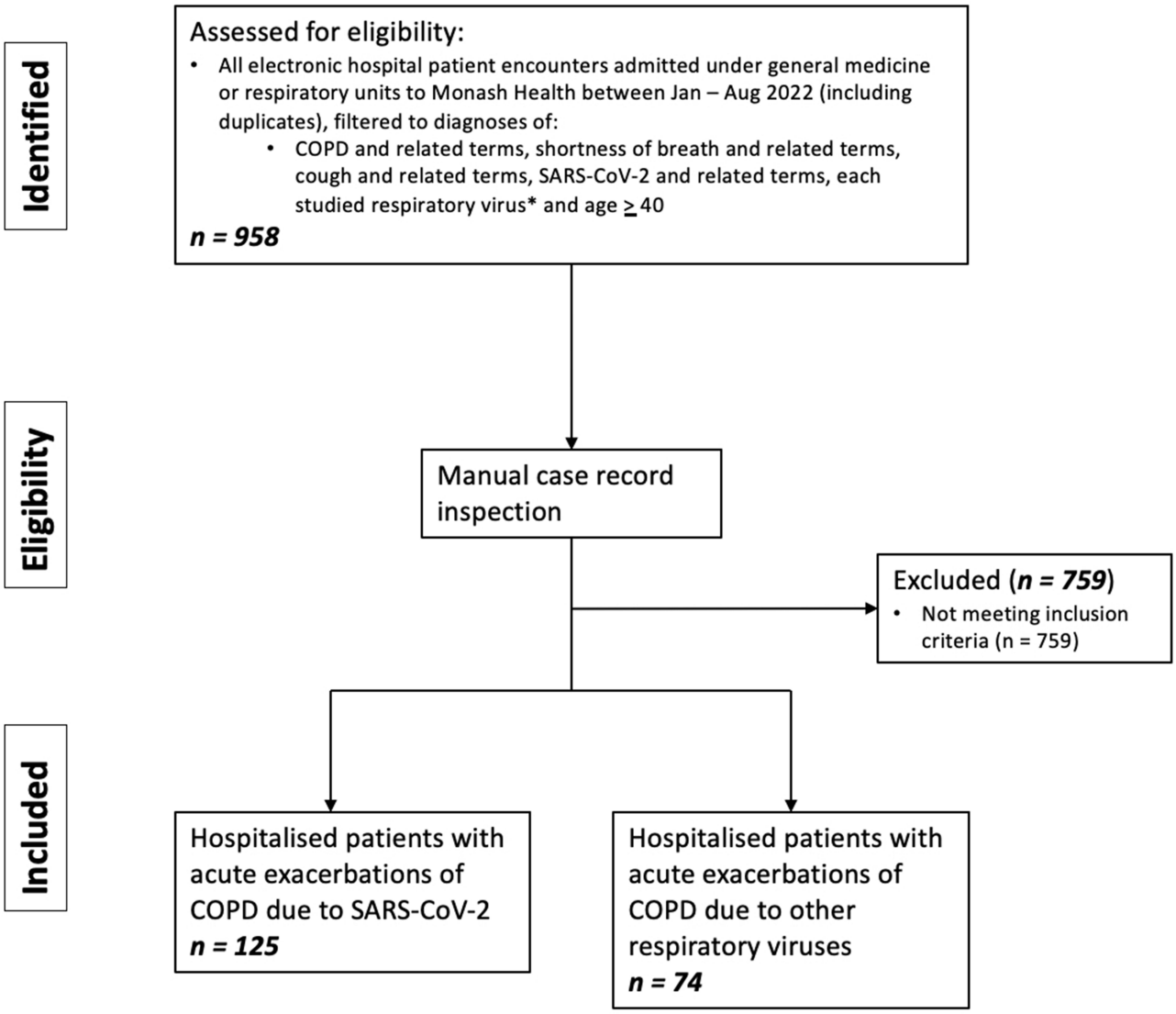

Figure 1 Flow-chart demonstrating methods for identification of hospitalized patients with AECOPD secondary to SARS-CoV-2 and the other respiratory viruses (parainfluenza, influenza, human metapneumovirus, rhinovirus, adenovirus and respiratory syncytial virus).

Ethical Approval

This study was approved as a clinical audit/quality assurance project by Monash Health research office (Quality Assurance No. 88630) and thus exempt from Human Research Ethics Committee review. All data collected complied with relevant data protections and privacy regulations.

Results

Between January 2022 and August 2022, 199 hospitalized AECOPD secondary to viruses were identified – 125 secondary to SARS-CoV-2 and 74 secondary to other respiratory viruses (see Figure 2).

Patient demographics and baseline comorbidities in each group are shown in Table 1. Those hospitalized with AECOPD secondary to SARS-CoV-2 were significantly older with more comorbidities and lower candidacy for full resuscitation when compared to other respiratory viruses. The proportion of patients in both groups from residential care facilities were similar; though there was a non-significant trend for more patients in the SARS-CoV-2 AECOPD group to require assistance with activities of daily living (ADLs) than other respiratory virus AECOPDs. The proportion of unvaccinated patients was significantly higher in the population admitted with SARS-CoV-2 associated AECOPD. Most

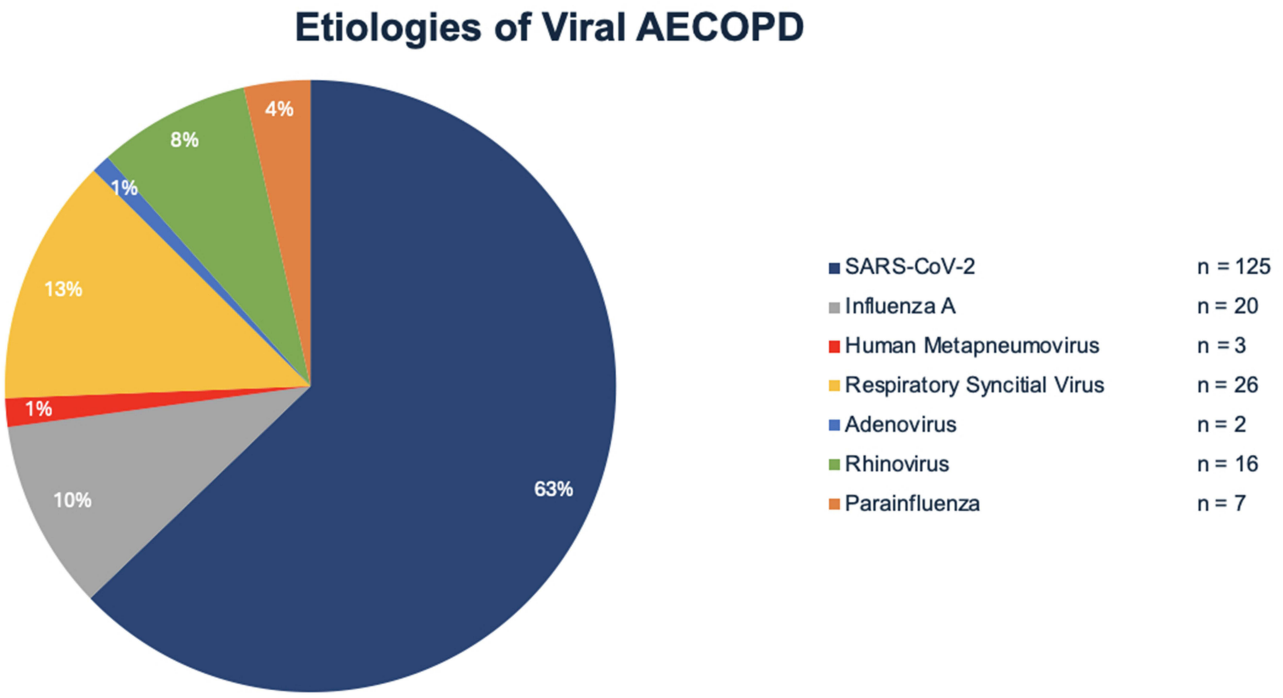

Figure 2 Pie chart demonstrating percentage of cases per respective viral AECOPD.

cases (183/199, 92.0%) had multiplex virus PCR testing with the remaining cases diagnosed via rapid antigen testing (RAT).

Patients with SARS-CoV-2 AECOPD more frequently had chest X-ray infiltrates than other respiratory viral AECOPD, but there was no significant difference in total white cell count or C-reactive protein.

Table 1 Patient Characteristics of Hospitalized Patients with Acute Exacerbations of COPD Secondary to SARS-CoV-2 Compared with the Other Respiratory Viruses Across Study Period Between January 2022 and August 2022. Data are Presented as Number (Percentage), Mean ± Standard Deviation, or Median [Interquartile Range]

Parameter	SARS-CoV-2 (n = 125)	Other viruses (n = 74)	P value
Average Age (years)	77.2 ± 9.2	68.9 ± 11.4	<0.00001
Male gender	71 (56.8)	38 (51.4)	0.455
From Home	117 (93.6)	71 (95.9)	0.49
Assistance with activities of daily living	34 (27.2)	12 (16.2)	0.076
Candidacy for full resuscitation	32 (25.6)	42 (56.8)	<0.0001
Comorbidities			
Number of comorbidities	1 [1–2]	1 [0–2]	0.008
Hypertension	62 (49.6)	28 (37.8)	0.107
Ischemic heart disease	39 (31.2)	19 (25.7)	0.407

(*Continued*)

Table 1 (Continued).

Parameter	SARS-CoV-2 (n = 125)	Other viruses (n = 74)	P value
Congestive cardiac failure	42 (33.6)	18 (24.3)	0.168
Chronic kidney disease	28 (22.4)	4 (5.4%)	0.002
Diabetes	29 (23.2)	19 (25.7)	0.693
Vaccination status			
Unvaccinated	17 (13.6)	2 (2.7)	0.02
Partially vaccinated	22 (17.6)	20 (27)	0.115
Fully vaccinated	85 (68.0)	42 (56.8)	0.584
Missing data	1 (0.8%)	9 (12.1%)	<0.001
Infection markers			
C-reactive protein (mg/L)	55.5 [14.5–150.5]	39 [12–100]	0.09
Infiltrates on chest x-ray	80[a] (65.0)	34[b] (45.9%)	0.009
Viral aetiology			
SARS-CoV-2	126 (100%)	N/A	
Parainfluenza	N/A	7 (9.5%)	-
Influenza A	N/A	20 (27.0%)	-
Respiratory Syncytial Virus	N/A	26 (35.1%)	-
Rhinovirus	N/A	16 (21.6%)	-
Adenovirus	N/A	2 (2.7%)	-
Human metapneumovirus	N/A	3 (4.1%)	-
Therapeutics			
LAMA	81 (64.8)	54 (72.9)	0.233
Inhaled corticosteroid use	80 (64.0)	55 (74.3)	0.132
Systemic corticosteroid use	112 (89.6)	66 (89.1)	0.927
Antiviral	77 (61.6)	19 (25.7)	<0.001
Antibiotics	93 (74.4)	66 (89.2)	0.012
Baricitinib	28 (22)	N/A	–

Notes: [a]Missing data for 2 patients, [b]Missing data for 1 patient.
Abbreviation: LAMA, long-acting muscarinic antagonist.

Rates of systemic corticosteroid and antibiotic prescription were similar in both groups. Some important differences in pharmacotherapy were observed, reflecting the rapid acquisition of effective therapies for COVID-19. In contrast to other respiratory viruses, antivirals (remdesivir, nirmatrelvir/ritonavir and molnupiravir) were used more often in SARS-CoV-2 AECOPDs. Among the other viral group, only anti-influenza antivirals were used in 19/20 influenza cases.

There was no significant difference between the two groups for rates of oxygen utilization, non-invasive ventilation (defined as either continuous positive airway pressure or bi-level positive airway pressure ventilation) or mechanical ventilation (Table 2).

Table 2 shows that rates of ICU admission, length of hospitalization in days and re-hospitalization within 30 days were not significantly different. Inpatient mortality tended to be higher among SARS-CoV2 admission. Of the 14 deaths, 10/14 were due to respiratory cause and 4 due to other causes (3 cardiac, 1 gastrointestinal bleed).

The proportion of the SARS-CoV-2 group who were unvaccinated was small (17/126, 13.6%). Inpatient mortality with SARS-CoV-2 AECOPD was not higher in the unvaccinated group (11.8 vs 8.3%, p = 0.64).

Univariate logistic regression analysis identified a number of factors predictive of inpatient mortality for the overall population (Table 3), although SARS-CoV-2 positivity was p = 0.085. There were no statistically significant predictors of inpatient mortality on multivariate logistic regression analysis.

Table 2 Clinical Outcomes of Hospitalized Patients with Acute Exacerbations of COPD Secondary to SARS-CoV-2 Compared with the Other Respiratory Viruses Across Study Period Between January 2022 and August 2022. Data are Presented as Number (Percentage)

Parameter	Sars-CoV-2 (n = 125)	Other Viruses (n = 74)	P value
High flow nasal cannula O_2	49 (38.9)	31 (41.8)	0.708
Low flow O_2	105 (84)	61 (82.4)	0.774
NIV usage	23 (18.4)	19 (25.7)	0.224
Intubation	2 (1.6)	4 (5.4)	0.129
Length of stay (median [IQR])	5 [3–8]	5 [3–9]	0.9
ICU admission	13 (10.4)	10 (13.5)	0.507
In-hospital mortality	12 (9.6)	2 (2.7)	0.066
Re-admission 30 days[a]	28 (24.3)	24 (33.3)	0.184

Note: [a]Denominators adjusted to account for in-hospital deaths.
Abbreviations: NIV, non-invasive ventilation (including bi-level and continuous positive airway pressure); ICU, intensive care unit.

Table 3 Multivariate Logistic Regression Analysis of Inpatient Mortality Predictors with Corresponding Univariate Odds Ratios for Candidate Variables

	Univariate				Multivariate			
	OR	CI 95%		p	OR	CI 95%		p
Age	1.06	0.99	1.12	0.083	1.01	0.92	1.11	0.79
Male	1.53	0.49	4.74	0.461	1.31	0.26	6.74	0.74
SARS-CoV-2	3.82	0.83	17.6	0.085	2.54	0.25	25.7	0.43
From home	0.1	0.03	0.4	0.001	0.78	0.05	13.1	0.86
Admission SpO_2 (%)	0.93	0.9	0.97	0.001	0.96	0.90	1.02	0.2
C-reactive protein (mg/L)	1.01	1	1.01	0.001	1.01	1.0	1.02	0.13

(*Continued*)

Table 3 (Continued).

	Univariate				Multivariate			
	OR	CI 95%		p	OR	CI 95%		p
Respiratory rate	1.11	1.04	1.19	0.002	1.06	0.96	1.18	0.26
Creatinine (μmol/L)	1.01	1	1.02	0.004	1.01	1.0	1.02	0.22
GCS < 15	3.57	1.15	11.1	0.028	0.83	0.15	4.5	0.83
NIV use	3.1	1.01	9.51	0.047	1.41	0.19	10.4	0.74
For full resuscitation	0.26	0.06	10.2	0.085	0.48	0.04	5.2	0.55

Abbrevition: NIV, non-invasive ventilation (including bi-level and continuous positive airway pressure).

Discussion

This study is the first to directly compare clinical outcomes among hospitalized AECOPD secondary to SARS-CoV-2 versus other respiratory viruses. We observed that the characteristics of the population requiring hospitalization for a viral AECOPD appeared notably different if the virus was SARS-CoV-2 versus another respiratory virus. In particular, patients with SARS-COV-2 were older and frailer, with more co-morbidities. The majority of SARS-CoV-2 AECOPDs were deemed not to be candidates for full resuscitation. Treatment of exacerbations between the two groups was largely similar, although the SARS-CoV-2 group had access to effective antiviral and anti-inflammatory therapies that were not available for most other viruses. Markers of clinical severity (including the need for oxygen, ventilatory support, length of stay and readmissions) were no higher among the SARS-CoV-2 group. On the other hand, inpatient mortality showed a trend towards being higher in the SARS-CoV-2 population. These data allow for intriguing speculations and are of value to clinicians treating and informing their COPD patients. Although overall clinical outcomes from SARS-CoV-2 AECOPDs appear similar to other respiratory viruses, interpretation of the data requires careful consideration.

The key differences between SARS-CoV-2 versus other viral AECOPDs are in the population demographics rather than the clinical outcomes. These study data were acquired from a population with high levels of "up to date" SARS-CoV-2 vaccination, during a period when the dominant circulating variant was mostly Omicron derived. The protective benefits of vaccination against severe disease and mortality at that time were very high.[13] Given the "other respiratory virus" group were acquiring viral infections during a period when SARS-Co-V-2 was prevalent in the community, it is reasonable to assume that this same population were being simultaneously exposed to SARS-CoV-2. High levels of vaccine-induced immunity may have provided sufficient protection against SARS-CoV-2 in this younger, less comorbid group, but may have been less effective in the older, frailer, more comorbid group.

Following hospitalization, the benefits of specific antiviral and anti-inflammatory therapies for the SARS-CoV-2 group may have improved clinical outcomes among that population. The lower candidacy for full resuscitation in the SARS-CoV-2 group likely reflects their older age and frailty. The decision making in this area was conducted on a case-by-case basis between clinicians and patients and was not standardized. Whilst the difference in resuscitation status is likely to reflect a frailer population with SARS-CoV-2, it is possible that a diagnosis of SARS-CoV-2 may have negatively influenced both patient and clinician expectations of survival given the poor outcomes with mechanical ventilation observed in early SARS-CoV-2 cohorts.[14]

Some notes of caution are advised. Whilst the difference in inpatient mortality observed fell short of statistical significance, this may represent an inadequate sample size. The extent to which higher mortality reflects the older age and frailty of the SARS-CoV-2 population versus the relative virulence of SARS-CoV-2 cannot be reliably assessed in this study. Of note, however, the inpatient mortality rate of 9.6% in our SARS-CoV-2 AECOPD group is relatively high in the modern COPD era in Australasia. Recent data (prior to the COVID pandemic) from our own healthcare networks have generally shown mortality amongst AECOPD cohorts of around 3%, albeit the SARS-CoV-2 subgroup studied here are

older than those cohorts.[11] Our data were acquired at a period of time when local population vaccination status was "up to date" in a very high proportion, particularly the elderly with serious comorbidities.[15] The degree of protection afforded by vaccination is known to wane over time and may decline further with the emergence of new viral variants.

Furthermore, similar outcomes for SARS-CoV-2 versus common respiratory viruses among hospitalized AECOPD should not be misinterpreted as an equivalence in virus severity for the general population. Infection with rhinovirus ("common cold") rarely causes severe illness in a general population but is among the most frequent causes of hospitalization and acute respiratory failure for those with COPD.[1]

At the onset of the global SARS-CoV-2/COVID-19 pandemic in late 2019 it was reasonable to anticipate that patients with COPD acquiring SARS-CoV-2 infection would be particularly vulnerable to hospitalization and death. Reports on early hospitalized cohorts did identify comorbid COPD as associated with a modest increase in mortality, hospital length of stay and oxygen utilization.[16,17] Nonetheless, the dominant predictors of adverse outcome in SARS-CoV-2 infection proved to be age, male sex, obesity and cardiometabolic comorbidities,[18,19] with COPD appearing less relevant than might have been anticipated.

In Victoria, Australia, stringent social isolation measures achieved control of SARS-CoV-2 outbreaks during the early phases of the pandemic. These measures were not relaxed until early 2022 by which time high vaccination levels had been achieved in the community. Over the same period of time, optimal respiratory support techniques, healthcare service preparedness and the efficacy of therapies including dexamethasone, remdesivir, nirmatrelvir/ritonavir and anti-inflammatory medications such as tocilizumab and baricitinib were well established.[20–24] Moreover, viral mutations had altered the natural history of SARS-CoV-2 resulting in increased transmissibility but reduced disease severity.[25] As a result, when the first very large-scale cohorts of COPD patients hospitalized with SARS-CoV-2 occurred in Victoria in early 2022 (when our study data were collected), circumstances had changed substantially relative to the earliest reports of SARS-CoV-2 outcomes from 2020.

Similar studies investigating SARS-CoV-2 AECOPD are limited. A large UK prospective study compared outcomes of SARS-CoV-2 associated AECOPD hospitalizations versus those with either alternate infection (bacterial or viral) or non-infective etiology. They observed a 30-day mortality of 16.9% (n = 138/816). Whilst not directly comparable, our crude in-hospital mortality rate appeared lower at 9.6% (n=12/125). Utilization of positive pressure support in SARS-CoV-2 AECOPD (n=151/816, 18.5%) was similar to our SARS-CoV-2 cohort. Whilst they observed higher rates of ventilatory support, longer hospital stays and increased mortality among AECOPDs due to SARS-CoV-2, these differences were no longer statistically significant when their analyses were restricted to the period of Omicron dominance.[10]

Limitations

The retrospective data collection limits conclusions regarding characterization of AECOPD due to SARS-CoV-2 and the other viruses. Our case definition of AECOPD was based on physician diagnosis and spirometry to confirm COPD was not available in all cases. COPD severity based on FEV1 as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification could not be accurately known. We were able to collect information about hospital readmissions within our healthcare network but may have missed readmission events presenting to alternative healthcare networks. Whilst most cases had multiple virus PCR testing featuring a panel of respiratory viruses including SARS-CoV -2, resource limitations during acute "surges" of COVID-19 occasionally led to rapid antigen test (RAT) or restricted panel virus testing being the accepted diagnostic test and some co-infections may have been missed.

Conclusion

SARS-CoV-2 has changed the epidemiology of respiratory viruses and will remain circulating in the community for the foreseeable future. As clinicians, it is important to understand its impact on vulnerable COPD patients. To our knowledge, this study is the first to document and describe the clinical characteristics and outcomes of SARS-CoV-2 AECOPD in the contemporary era by direct comparison with AECOPD due to other respiratory viruses. In a highly vaccinated population, those hospitalized with SARS-CoV-2 appear older and frailer, with more comorbidities than those admitted with other respiratory viruses. Length of hospitalization and ICU utilization was similar. Although not reaching statistical

significance in our cohort, inpatient mortality may be higher. Whilst inherent limitations exist due to the retrospective nature of the study, we suggest that a particular focus on efforts to prevent hospitalized AECOPD for the older, more physically frail and comorbid COPD patients via keeping up-to-date with COVID vaccinations, social distancing measures where appropriate and closer outpatient management of AECOPD due to SARS-CoV-2 such as enrolment in hospital in the home programs where available. Future prospective studies are essential to further characterize the phenotype of SARS-CoV-2 AECOPD.

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The abstract of this paper was also presented at the Thoracic Society of Australia and New Zealand Society of Respiratory Science (TSANZSRS) Annual Scientific Meeting 2024 as a poster presentation with interim findings. This was published in 'TSANZ Abstracts' in Respirology: https://doi.org/10.1111/resp.14673.

Disclosure

The authors report no conflicts of interest in this work.

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