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Effect modification by age of the association between obstructive lung diseases, smoking, and COVID-19 severity

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ABSTRACT

Introduction Obstructive lung diseases (asthma and chronic obstructive pulmonary disease (COPD)) and smoking are associated with greater risk of respiratory infections and hospitalisations, but conflicting data exist regarding their association with severity of COVID-19, and few studies have evaluated whether these associations differ by age.

Objectives To examine the associations between asthma, COPD and smoking on the severity of COVID-19 among a cohort of hospitalised patients, and to test for effect modification by age.

Methods We performed a retrospective analysis of electronic health record data of patients admitted to Massachusetts General Hospital, assigning the maximal WHO Clinical Progression Scale score for each patient during the first 28 days following hospital admission. Using ordered logistic regression, we measured the association between maximal severity score and asthma, COPD and smoking and their interaction with age.

Measurements and main results Among 1391 patients hospitalised with COVID-19, we found an increased risk of severe disease among patients with COPD and prior smoking, independent of age. We also found evidence of effect modification by age with asthma and current smoking; in particular, asthma was associated with decreased COVID-19 severity among older adults, and current smoking was associated with decreased severity among younger patients.

Conclusions This cohort study identifies age as a modifying factor for the association between asthma and smoking on severity of COVID-19. Our findings highlight the complexities of determining risk factors for COVID-19 severity, and suggest that the effect of risk factors may vary across the age spectrum.

Key messages

- How does age affect the severity of COVID-19 in patients with a history of obstructive lung disease and smoking?
- Asthma is associated with decreased COVID-19 severity among older adults, and current smoking is associated with decreased severity among younger patients.
- To our knowledge, this is the first study to specifically examine how age might affect the relationship between the most common lung diseases, smoking and COVID-19 severity. Our findings suggest that the effect of commonly identified risk factors may vary across the age spectrum.

INTRODUCTION

The majority of severe COVID-19 and COVID-19-related deaths occur among those with comorbidities, including those with chronic respiratory disease.[1 2] The United States Center for Disease Control and Prevention currently classifies chronic obstructive pulmonary disease (COPD, moderate-to-severe asthma and current and former smoking as associated with increased risk of severe COVID-19 complications.[3 4] Though the majority of deaths due to COVID-19 occur among older adults, chronic respiratory diseases may increase the risk of severe outcomes even among younger patients. In the spring 2020 surge, chronic respiratory diseases were present in 20.9% of people under age 65 who died of COVID-19 in the USA through 18 May 2020,[5] and a large study in the UK found that 20.9% of patients aged 16–49 and 44.4% of those aged 50–69 hospitalised with COVID-19 were diagnosed with asthma.[6] By contrast, in a large cohort of hospitalised patients with COVID-19 in China, only 2.8% of patients had chronic respiratory disease.[7]

Since viruses (including non-SARS coronaviruses) are associated with both asthma and COPD exacerbations,[8 9] patients with either obstructive lung disease would be expected to have a higher rate of severe outcomes due to COVID-19. Despite initial reports of

low prevalence of asthma among patients hospitalised with COVID-19 in China,[10] investigators have reported prolonged intubation course among asthmatics,[11] increased risk of death among asthmatics with recent oral corticosteroid use,[2] and worse clinical outcomes, especially among those with non-allergic asthma.[12] Multiple studies have also reported increased risk of death among patients with COPD, with an even greater risk among men.[13]

Smoking increases the risk of acquiring respiratory infections[14 15] by impairing macrophage and cytokine responses and upregulating pathogen receptors.[16–20] It is the primary risk factor for developing COPD, and contributes to development and exacerbations of asthma.[21–24] Smoking is also associated with upregulation of the ACE-2 receptor in airways, raising concerns early in the pandemic regarding increased entry of SARS-CoV-2 into host cells.[25–28] An initial report from patients in Wuhan in December/January 2019 noted that patients with a history of smoking had significantly increased odds of disease progression,[29] but subsequent meta-analyses have reported lower-than-expected prevalence of smoking among hospitalised patients with COVID-19.[30 31]

To better understand the relative contributions of obstructive lung disease and smoking on the severity of COVID-19 across the age spectrum, we analysed data from the first 1391 patients admitted to Massachusetts General Hospital (MGH) with COVID-19. We hypothesised that obstructive lung diseases and smoking would be associated with severe COVID-19 disease, and that these associations would be greater among older patients.

METHODS

Study design and data sources

We performed a retrospective analysis of electronic health record data of patients admitted to MGH between 11 March and 3 June 2020. Demographic, hospitalisation, laboratory and body mass index (BMI) data were extracted from the MGH Enterprise Data Warehouse using structured query language procedures. Clinical data, including medical history, treatments in the hospital and outcomes were manually abstracted by trained chart reviewers and entered into a Redcap (Research Electronic Data Capture) database hosted on a MassGeneral Brigham server.[32]

Population

We included all patients in the MGH COVID-19 Registry, a cohort of children and adults with positive SARS-CoV-2 PCR testing who were inpatients during the study period and had 28-day outcome data available at the time of the analysis.[33] The inclusion criteria for the cohort were (1) any positive SARS-CoV-2 PCR test, infection flag that indicates COVID-19 infection, or ICD-10 diagnosis of U07.1, and (2) at least one hospitalisation at MGH with an admission date within 45 days after criterion (1). Patients who did not satisfy these criteria were excluded.

Variable definitions

Demographic data and medical history (including prior diagnoses of asthma and COPD) were obtained from the health record. BMI was calculated from height and weight measured within ±14 days of hospitalisation. We used results of laboratory testing closest to the time of admission to the hospital.

The primary outcome used for this analysis is the WHO Clinical Progression Scale (WHO CPS), which was developed to measure the full range of disease severity and progression in COVID-19 disease.[34] While the scale as created ranges from 0 (uninfected) to 10 (dead), our analysis focuses on severity of illness among hospitalised patients and therefore only includes WHO CPS scores 4 and higher (moderate and severe disease, see table 1). We calculated the maximal WHO CPS for each patient during the first 28 days following hospital admission using the highest oxygen flow rate, fraction of inspired oxygen (FiO_2), or mode of ventilatory support; and the presence of haemodialysis, vasopressor or extracorporeal membrane oxygenation (ECMO) use reported in the registry. Because concurrent arterial partial pressure of oxygen (PaO_2), arterial oxyhaemoglobin saturation

Table 1 WHO CPS among hospitalised patients

Patient state	Descriptor	Score
Hospitalised: moderate disease	Hospitalised; no oxygen therapy	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe disease	Hospitalised; oxygen by non-invasive ventilation or high flow	6
	Intubation and mechanical ventilation with $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7
	Mechanical ventilation with $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors	8
	Mechanical ventilation, with $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) and vasopressors, dialysis or extracorporeal membrane oxygenation	9
Dead	Dead	10

Adapted from Marshall *et al*.[34]
FiO_2, fraction of inspired oxygen; pO_2, partial pressure of oxygen; SpO_2, arterial oxyhaemoglobin saturation; WHO CPS, WHO Clinical Progression Scale.

Table 2 Demographic and clinical characteristics by WHO Clinical Progression Score

	Total	4	5	6	7	8	9	10	
	N=1391	n=362	n=553	n=17	n=11	n=96	n=180	n=172	P value
Age (years)	59.0 (18.7)	52.8 (20.3)	59.0 (18.0)	62.3 (17.2)	50.2 (17.8)	57.7 (16.9)	56.9 (13.2)	75.5 (13.2)	<0.001
Sex									0.0015
Male	795 (100%)	196 (25%)	297 (37%)	11 (1%)	7 (1%)	53 (7%)	116 (15%)	115 (14%)	
Female	596 (100%)	166 (28%)	256 (43%)	6 (1%)	4 (1%)	43 (7%)	64 (11%)	57 (10%)	
Race/ethnicity									0.0458
White	550 (100%)	137 (25%)	220 (40%)	5 (1%)	3 (1%)	30 (5%)	49 (9%)	106 (19%)	
Black/African American	149 (100%)	52 (35%)	48 (32%)	3 (2%)	3 (2%)	9 (6%)	18 (12%)	16 (11%)	
Hispanic	492 (100%)	132 (27%)	205 (42%)	9 (2%)	5 (1%)	37 (8%)	79 (16%)	25 (5%)	
Other	84 (100%)	23 (27%)	30 (36%)	0 (0%)	0 (0%)	10 (12%)	13 (15%)	8 (10%)	
BMI (kg/m^2)	30.1 (7.0)	28.6 (6.2)	30.7 (6.9)	28.7 (5.3)	26.9 (7.0)	30.4 (6.8)	32.3 (7.2)	29.5 (8.0)	0.0003
BMI category (kg/m^2)									0.0594
<25	274 (100%)	90 (33%)	94 (34%)	4 (1%)	3 (1%)	17 (6%)	22 (8%)	44 (16%)	
25.0–29.9	411 (100%)	118 (29%)	171 (42%)	5 (1%)	4 (1%)	27 (7%)	40 (10%)	46 (11%)	
30.0–34.9	302 (100%)	67 (22%)	126 (42%)	3 (1%)	0 (0%)	24 (8%)	49 (16%)	33 (11%)	
35.0–39.9	147 (100%)	30 (20%)	71 (48%)	2 (1%)	0 (0%)	8 (5%)	24 (16%)	12 (8%)	
>40	114 (100%)	20 (18%)	51 (45%)	0 (0%)	1 (1%)	9 (8%)	20 (18%)	13 (11%)	
Smoking history									<0.001
Never	777 (100%)	226 (29%)	315 (41%)	9 (1%)	6 (1%)	54 (7%)	103 (13%)	64 (8%)	
Yes—past	404 (100%)	73 (18%)	166 (41%)	8 (2%)	2 (0%)	25 (6%)	48 (12%)	82 (20%)	
Yes—current	102 (100%)	44 (43%)	34 (33%)	0 (0%)	2 (2%)	6 (6%)	7 (7%)	9 (9%)	
Unknown	108 (100%)	19 (18%)	38 (35%)	0 (0%)	1 (1%)	11 (10%)	22 (20%)	17 (16%)	
Asthma									0.0329
No	1209 (100%)	314 (26%)	462 (38%)	15 (1%)	9 (1%)	89 (7%)	162 (13%)	158 (13%)	
Yes	182 (100%)	48 (26%)	91 (50%)	2 (1%)	2 (1%)	7 (4%)	18 (10%)	14 (8%)	
COPD									0.0006
No	1248 (100%)	346 (28%)	477 (38%)	17 (1%)	10 (1%)	90 (7%)	173 (14%)	135 (11%)	
Yes	143 (100%)	16 (11%)	76 (53%)	0 (0%)	1 (1%)	6 (4%)	7 (5%)	37 (26%)	
Bronchodilator use									0.2180
No	1169 (100%)	312 (27%)	459 (39%)	14 (1%)	6 (1%)	82 (7%)	165 (14%)	131 (11%)	
Yes	222 (100%)	50 (23%)	94 (42%)	3 (1%)	5 (2%)	14 (6%)	15 (7%)	41 (18%)	
Inhaled corticosteroid use									0.7889
No	1239 (100%)	327 (26%)	485 (39%)	17 (1%)	10 (1%)	84 (7%)	165 (13%)	151 (12%)	
Yes	152 (100%)	35 (23%)	68 (45%)	0 (0%)	1 (1%)	12 (8%)	15 (10%)	21 (14%)	

Continued

Table 2 Continued

	Total	4	5	6	7	8	9	10	
	N=1391	n=362	n=553	n=17	n=11	n=96	n=180	n=172	P value
Montelukast use									0.6712
No	1372 (100%)	356 (26%)	545 (40%)	17 (1%)	11 (1%)	96 (7%)	179 (13%)	168 (12%)	
Yes	19 (100%)	6 (32%)	8 (42%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	4 (21%)	
Any cardiac/metabolic disorder									<0.001
No	334 (100%)	132 (40%)	127 (38%)	0 (0%)	6 (2%)	20 (6%)	38 (11%)	11 (3%)	
Yes	1057 (100%)	230 (22%)	426 (40%)	17 (2%)	5 (0%)	76 (7%)	142 (13%)	161 (15%)	
Coronary artery disease/ myocardial infarction									0.0008
No	1180 (100%)	322 (27%)	463 (39%)	15 (1%)	9 (1%)	87 (7%)	166 (14%)	118 (10%)	
Yes	211 (100%)	40 (19%)	90 (43%)	2 (1%)	2 (1%)	9 (4%)	14 (7%)	54 (26%)	
Heart failure									<0.001
No	1227 (100%)	333 (27%)	491 (40%)	11 (1%)	11 (1%)	86 (7%)	170 (14%)	125 (10%)	
Yes	164 (100%)	29 (18%)	62 (38%)	6 (4%)	0 (0%)	10 (6%)	10 (6%)	47 (29%)	
Hypertension									<0.001
No	694 (100%)	231 (33%)	262 (38%)	6 (1%)	7 (1%)	48 (7%)	92 (13%)	48 (7%)	
Yes	697 (100%)	131 (19%)	291 (42%)	11 (2%)	4 (1%)	48 (7%)	88 (13%)	124 (18%)	
Diabetes									<0.001
No	941 (100%)	280 (30%)	377 (40%)	15 (2%)	7 (1%)	53 (6%)	113 (12%)	96 (10%)	
Yes	450 (100%)	82 (18%)	176 (39%)	2 (0%)	4 (1%)	43 (10%)	67 (15%)	76 (17%)	
Kidney disease									<0.001
No	1132 (100%)	313 (28%)	455 (40%)	15 (1%)	10 (1%)	79 (7%)	155 (14%)	105 (9%)	
Yes	233 (100%)	47 (20%)	89 (38%)	2 (1%)	0 (0%)	15 (6%)	23 (10%)	57 (24%)	

Values indicate count (proportion) and mean (SD) as appropriate.
P values calculated using the Wald χ^2 test in an ordered logistic regression model with a single predictor variable.
BMI, body mass index; COPD, chronic obstructive pulmonary disease.

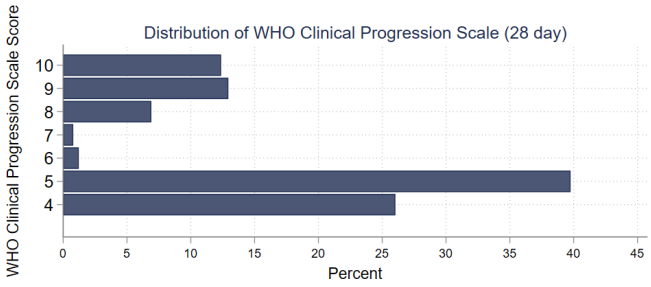

Figure 1 Distribution of WHO clinical progression scale.

(SpO_2) and FiO_2 data were not consistently available in the registry, we approximated the minimum SpO_2/FiO_2 ratio[35] by using the maximal reported FiO_2 and assuming an SpO_2 of 90% based on the target SpO_2 in the hospital's standard mechanical ventilation order set and usual target for oxygen supplementation.

Statistical/analytic methods

After calculating descriptive statistics for major variables of interest, we measured the unadjusted association between potential predictors of disease severity (including the CDC underlying conditions on which data were available) and the WHO CPS using ordered logistic regression. We then constructed a multivariable model that included the variables of interest as well as demographic variables and cardiometabolic comorbidities. We also tested for effect modification creating two-way interaction terms between age and asthma, age and COPD and age and smoking. We estimated predicted probabilities of each WHO CPS level across age, at the mean level of each covariate, using the Stata *margins* and *marginsplot* commands. Standard errors and 95% CI were calculated using the delta method.[36 37] Finally, we compared biomarkers of disease severity and host response between patients with and without asthma, between patients with and without COPD and among patients with varying exposures to smoking, using Wilcoxon rank-sum and Kruskal-Wallis tests as appropriate. All analyses were performed in Stata V.16.1 (StataCorp, College Station, Texas, USA).

Human subjects approval

The MGH COVID-19 registry was reviewed and approved by the MassGeneral Brigham Human Research Committee (#2020P000829). The present analysis was reviewed and determined to be exempt.

Patient and public involvement

Patients were not directly involved in the design of this data analysis, though the question of how obstructive lung diseases and smoking affect COVID-19 outcomes was raised by many of our patients and their families.

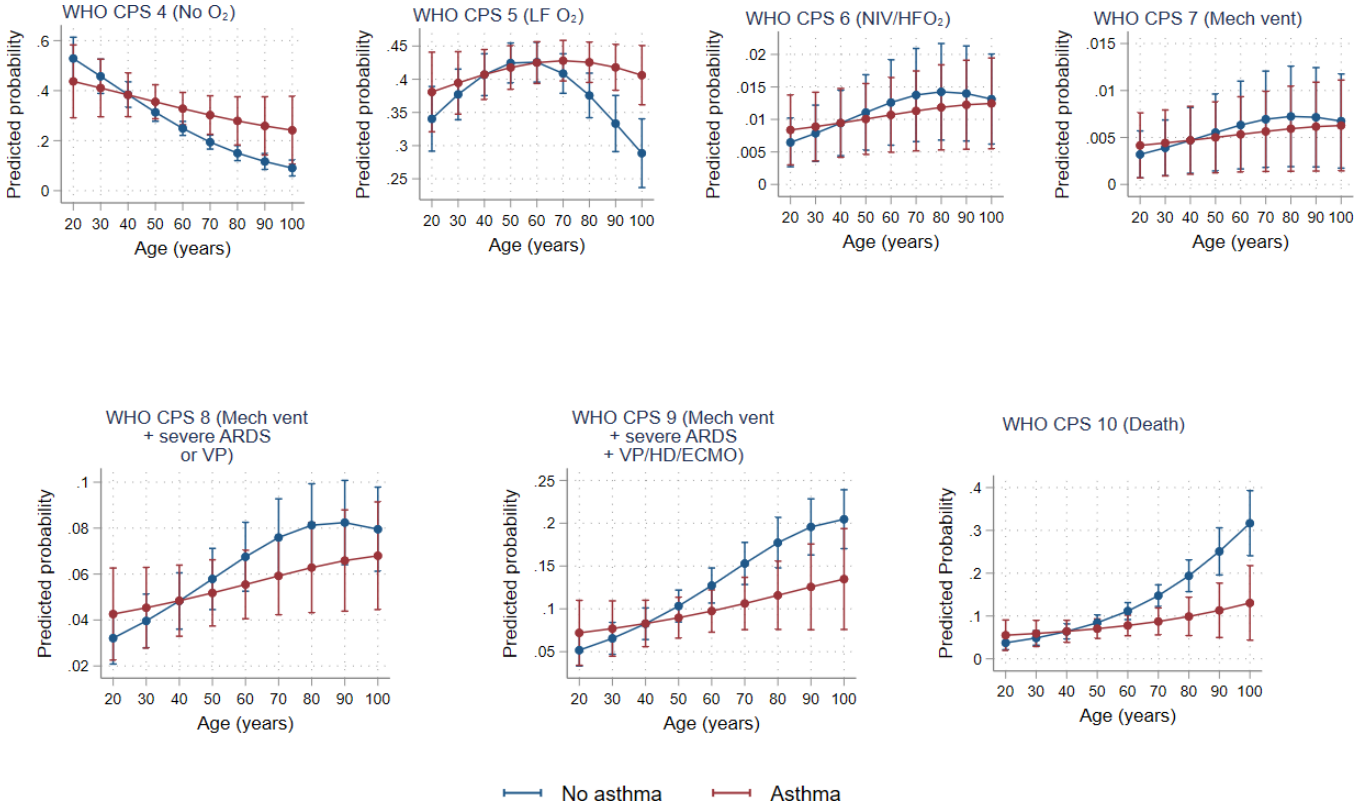

Figure 2 Predicted probability of WHO CPS score levels by age and asthma. ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; HD, hemodialysis; VP, vasopressors; WHO CPS, WHO Clinical Progression Scale.

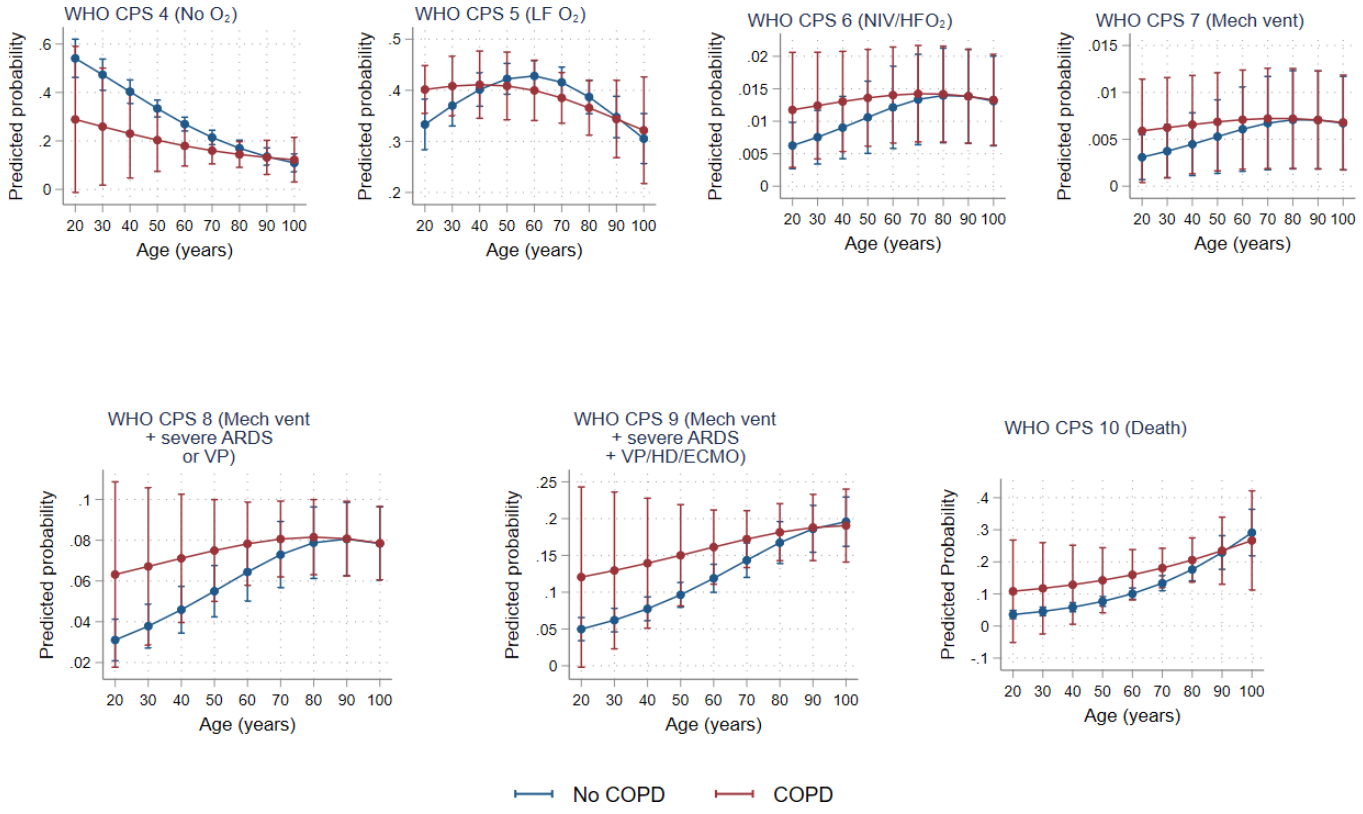

Figure 3 Predicted probability of WHO CPS score levels by age and COPD. COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; VP, vasopressors; HD, hemodialysis; ECMO, extracorporeal membrane oxygenation; WHO CPS, WHO Clinical Progression Scale.

RESULTS

We analysed data from 1391 patients who were hospitalised with COVID-19 and had complete 28-day outcome data. Baseline characteristics of the study population are summarised in the first column of table 2. Patients ranged in age from newborn to 99 years (mean age: 59 years), were predominantly men (57%), and were primarily white or Hispanic. The majority (78%) of patients were overweight or obese and 76% had a cardiac or metabolic disorder. Among all admitted patients, 22% (301/1391) had a prior diagnosis of obstructive lung disease: asthma (158/1391), COPD (119/1391) or both (24/1391). The majority of patients were either never (55.9%) or previous smokers (29.0%); 102 (7%)/1391 reported currently smoking. Six (0.4%) patients reported current use of electronic nicotine delivery systems. Inhaled corticosteroid use was common among both patients with asthma (40.1%) and COPD (43.4%).

Figure 1 demonstrates the distribution of the WHO CPS among the study population. Most patients (74%) required oxygen or other ventilator support during hospitalisation, and 12% died during the 28-day period of data review. The majority (69%) of patients were treated on hospital floors; 31% were admitted an intensive care unit (ICU) during their hospitalisation. On univariate analysis (table 2), we found a strong positive association between WHO CPS score and age, male sex, BMI, previous smoking, COPD, coronary artery disease (CAD), heart failure, hypertension, diabetes and chronic kidney disease. We found a negative unadjusted association between WHO CPS score and Hispanic ethnicity, asthma and current smoking. We did not find any significant association between WHO CPS score and prior use of inhaled bronchodilator medications, inhaled corticosteroids or montelukast.

We then estimated the association between asthma, COPD and smoking status with WHO CPS score in a multivariable model adjusting for relevant demographic and comorbidity covariates and interaction terms by age for the three risk factors of interest (online supplemental table 1). We found that a history of asthma was associated with an increased risk of requiring oxygen among younger patients and a reduced risk of severe disease among older patients (figure 2, $p_{\text{interaction}}$=0.006), that no significant effect modification was observed by age with COPD (figure 3, $p_{\text{interaction}}$=0.61), and that current smoking was associated with a reduced risk of severe disease among younger patients but not among older patients (figure 4, $p_{\text{interaction}}$=0.002). The effect of asthma on WHO CPS ranged from OR 1.51 (95% CI: 0.76 to 2.99) at age 20 to OR 0.44 (95% CI: 0.26 to 0.74) at age 80, and the effect of smoking ranged from OR 0.07 (95% CI: 0.02 to 0.26) at age 20 to OR 0.375 (95% CI: 0.66 to 3.59) at age 80 (see table 3). Other significant covariates in the multivariable model included age (OR: 1.02 (95% CI: 1.01 to 1.03)), female sex (OR: 0.71 (95% CI: 0.55 to

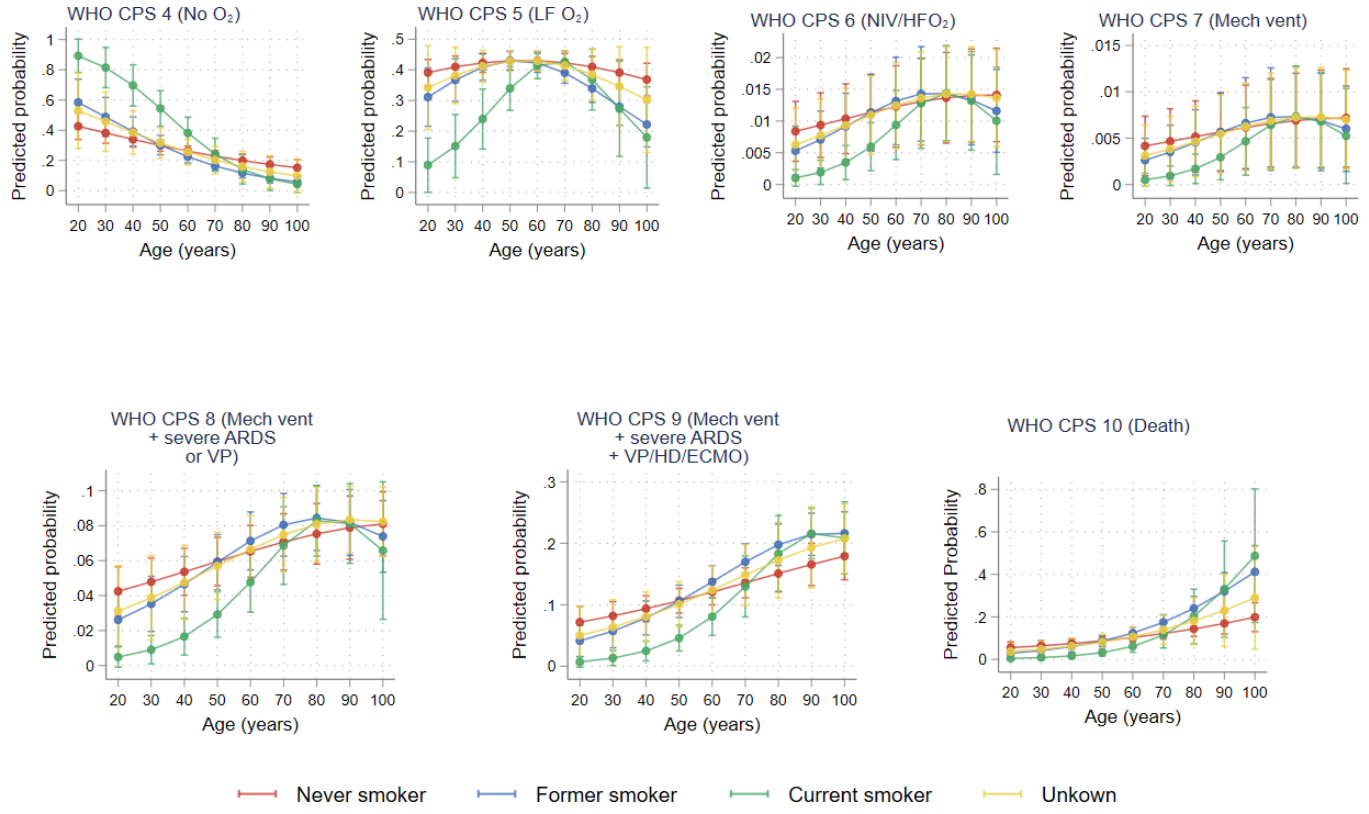

Figure 4 Predicted probability of WHO CPS score levels by age and smoking status. ARDS, acute respiratory distress syndrome; VP, vasopressors; HD, hemodialysis; ECMO, extracorporeal membrane oxygenation; WHO CPS, WHO Clinical Progression Scale.

0.90)), BMI (OR: 1.06 (95%: 1.04 to 1.08)) and diabetes (OR: 1.37 (95% CI: 1.05 to 1.79)).

To further characterise the effects of asthma, COPD and smoking on the host response to SARS-CoV-2 infection, we compared laboratory testing at the time of hospital admission between patients with and without asthma, between patients with and without COPD and among patients across categories of smoking history (table 4). We observed an increased absolute lymphocyte count and reduced levels of inflammatory markers (ferritin, CRP, ESR and procalcitonin) among patients with asthma and among patients who reported currently smoking. Patients with COPD also had reduced levels of inflammatory markers but increased markers of cardiovascular stress (troponin, D-dimer and NT-proBNP).

DISCUSSION

In this cohort of 1391 hospitalised patients with COVID-19, we found evidence of significant effect modification of the association between asthma, smoking and COVID-19 severity by age. In particular, we found that asthma was

Table 3 OR for WHO CPS score for asthma, COPD and smoking across levels of age

	Asthma		COPD		Smoking	
Age (years)	OR	P value	OR	P value	OR	P value
20	1.51 (0.76 to 2.99)	0.232	3.40 (0.59 to 19.66)	0.170	0.07 (0.02 to 0.26)	<0.001
30	1.23 (0.72 to 2.11)	0.444	2.87 (0.68 to 12.22)	0.153	0.12 (0.05 to 0.33)	<0.001
40	1.00 (0.66 to 1.51)	0.982	2.42 (0.77 to 7.65)	0.131	0.20 (0.10 to 0.42)	<0.001
50	0.81 (0.58 to 1.13)	0.231	2.04 (0.86 to 4.84)	0.104	0.34 (0.20 to 0.58)	<0.001
60	0.66 (0.48 to 0.92)	0.004	1.72 (0.94 to 3.15)	0.077	0.56 (0.34 to 0.93)	0.024
70	0.54 (0.37 to 0.80)	0.013	1.45 (0.95 to 2.23)	0.088	0.93 (0.50 to 1.74)	0.817
80	0.44 (0.26 to 0.74)	0.002	1.23 (0.78 to 1.92)	0.375	1.54 (0.66 to 3.59)	0.321

OR and 95% CIs calculated from ordered logistic regression model adjusting for age, sex, race, asthma, age × asthma, COPD, age × COPD, smoking, age × smoking, body mass index, coronary artery disease, heart failure, hypertension, diabetes and chronic kidney disease.
COPD, chronic obstructive pulmonary disease; WHO CPS, WHO Clinical Progression Scale.

Table 4 Laboratory test values at the time of admission

		Asthma			COPD			Smoking				
	Total	Yes	No		Yes	No		Yes—current (in past 30 days)	Yes—past	Never	Unknown	
	N=1391	n=182	n=1209	P value	n=143	n=1248	P value	n=102	n=404	n=777	n=108	P value
White blood cell count (×1000)	6.78 (5.11 to 9.23)	6.96 (4.95 to 9.04)	6.76 (5.13 to 9.23)	0.94	6.34 (4.84 to 8.38)	6.82 (5.15 to 9.24)	0.057	6.81 (5.21 to 9.05)	6.80 (5.11 to 9.14)	6.71 (5.07 to 9.25)	7.27 (5.31 to 9.32)	0.74
Absolute lymphocyte count (K/µL)	0.98 (0.67 to 1.41)	1.06 (0.74 to 1.54)	0.96 (0.66 to 1.39)	0.022	0.82 (0.53 to 1.32)	1.00 (0.69 to 1.42)	0.001	1.10 (0.75 to 1.87)	0.89 (0.60 to 1.28)	1.03 (0.72 to 1.42)	0.95 (0.66 to 1.29)	<0.001
Haemoglobin (g/dL)	13.3 (12.0 to 14.5)	13.3 (12.1 to 14.6)	13.3 (12.0 to 14.5)	0.92	12.6 (10.8 to 13.9)	13.4 (12.1 to 14.6)	<0.001	12.9 (11.5 to 14.3)	13.2 (11.5 to 14.7)	13.3 (12.1 to 14.4)	14.0 (12.6 to 15.1)	0.002
Platelets (K/µL)	203 (156 to 264)	201 (156 to 257)	203 (156 to 264)	0.81	189 (153 to 236)	207 (157 to 265)	0.034	208 (154 to 268)	193 (148 to 265)	207 (159 to 264)	199 (162 to 260)	0.18
Lactate (mmol/L)	1.5 (1.1 to 2.1)	1.4 (1.0 to 2.0)	1.5 (1.2 to 2.1)	0.080	1.4 (1.0 to 1.7)	1.5 (1.2 to 2.1)	0.007	1.6 (1.1 to 2.7)	1.5 (1.2 to 2.0)	1.5 (1.1 to 2.1)	1.7 (1.1 to 2.2)	0.37
Anion gap (mmol/L)	15 (14 to 17)	15 (14 to 16)	15 (14 to 17)	0.039	15 (13 to 17)	15 (14 to 17)	0.002	14 (13 to 17)	15 (14 to 17)	15 (14 to 17)	16 (14 to 18)	0.008
BUN (mg/dL)	14 (10 to 22)	12 (9 to 17)	15 (10 to 23)	<0.001	21 (16 to 33)	14 (9 to 21)	<0.001	15 (11 to 22)	19 (13 to 30)	12 (9 to 19)	13 (9 to 20)	<0.001
Creatinine (mg/dL)	0.95 (0.78 to 1.28)	0.86 (0.72 to 1.05)	0.97 (0.79 to 1.30)	<0.001	1.13 (0.90 to 1.65)	0.93 (0.77 to 1.22)	<0.001	0.98 (0.79 to 1.28)	1.07 (0.86 to 1.56)	0.90 (0.73 to 1.13)	0.91 (0.79 to 1.25)	<0.001
Glucose (mg/dL)	124 (106 to 161)	118 (103 to 165)	125 (106 to 161)	0.23	117 (103 to 149)	126 (106 to 162)	0.013	115 (99 to 145)	127 (107 to 163)	124 (106 to 159)	129 (109 to 191)	0.021
Haemoglobin A1C (%)	6.5 (6.0 to 8.4)	6.8 (5.8 to 8.4)	6.5 (6.0 to 8.4)	0.71	6.9 (6.2 to 9.0)	6.5 (6.0 to 8.4)	0.42	6.8 (6.0 to 8.4)	6.5 (6.0 to 8.4)	6.5 (6.0 to 8.3)	6.8 (5.9 to 9.9)	0.96
LDH (U/L)	314 (242 to 419)	305 (231 to 393)	315 (243 to 422)	0.24	288 (214 to 370)	318 (245 to 427)	<0.001	262 (212 to 361)	312 (240 to 399)	315 (244 to 423)	381 (284 to 520)	<0.001
Ferritin (µg/L)	512 (242 to 1027)	408 (189 to 719)	546 (256 to 1058)	<0.001	296 (150 to 793)	540 (260 to 1048)	<0.001	330 (110 to 1047)	552 (237 to 1075)	496 (257 to 967)	682 (395 to 1205)	0.002
CRP (mg/L)	72.6 (30.8 to 143.4)	63.0 (28.1 to 125.0)	73.8 (32.4 to 144.3)	0.025	56.4 (20.8 to 113.7)	74.1 (32.5 to 145.3)	0.003	42.5 (9.3 to 117.5)	71.8 (32.5 to 140.1)	74.5 (33.2 to 143.4)	105.9 (36.6 to 155.6)	<0.001
ESR (mm/hour)	39 (23 to 60)	36 (21 to 54)	39 (23 to 61)	0.086	37 (22 to 54)	39 (23 to 60)	0.67	31 (13 to 54)	38 (25 to 59)	39 (23 to 61)	44 (28 to 61)	0.010
Procalcitonin (ng/mL)	0.15 (0.09 to 0.30)	0.13 (0.07 to 0.20)	0.15 (0.09 to 0.34)	<0.001	0.17 (0.09 to 0.29)	0.14 (0.09 to 0.30)	0.46	0.11 (0.06 to 0.31)	0.17 (0.10 to 0.35)	0.13 (0.09 to 0.26)	0.18 (0.09 to 0.36)	0.001
IL-6 (pg/mL)	26.6 (12.9 to 57.6)	17.6 (6.9 to 42.2)	28.6 (14.3 to 63.6)	0.008	16.9 (14.5 to 44)	28.6 (12.6 to 60.6)	0.19	22.3 (11.6 to 77.2)	27.1 (12.2 to 63.2)	25.4 (13.3 to 54.8)	35.4 (17.3 to 139.25)	0.59

Continued

Table 4 Continued

	Total	Asthma			COPD			Smoking				
	N=1391	Yes n=182	No n=1209	P value	Yes n=143	No n=1248	P value	Yes—current (in past 30 days) n=102	Yes—past n=404	Never n=777	Unknown n=108	P value
Troponin (ng/L)	11 (0 to 31)	8 (0 to 17)	12 (0 to 33)	<0.001	27 (16 to 56)	10 (0 to 25)	<0.001	12 (0 to 36)	22 (10 to 44)	8 (0 to 20)	10 (0 to 24)	<0.001
D-dimer (ng/mL)	1020 (658 to 1854)	874 (592 to 1440)	1059 (678 to 1917)	0.005	1400 (812 to 2334)	987 (643 to 1770)	<0.001	868 (473 to 1514)	1172 (709 to 1925)	981 (627 to 1767)	1224 (773 to 2209)	0.008
NT-proBNP (pg/mL)	259 (68 to 1190)	191 (38 to 880)	267 (70 to 1233)	0.37	598 (230 to 2349)	203 (57 to 1005)	<0.001	350 (112 to 1745)	503 (142 to 2469)	143 (47 to 562)	207 (69 to 1766)	<0.001

Median and IQR are reported. P values reflect between-group or among-group comparisons using the Wilcoxon rank-sum test (for asthma and COPD) or the Kruskal-Wallis test (for smoking).
COPD, chronic obstructive pulmonary disease; IL-6, interleukin-6.

associated with decreased COVID-19 severity among older patients, and that current smoking was associated with decreased severity among younger patients. We found an increased risk of severe disease among patients with COPD and prior smoking, independent of age. We also noted differences in inflammatory biomarkers between patients with and without asthma and across smoking statuses. We did not find any evidence of association between use of bronchodilators, inhaled corticosteroids or montelukast prior to hospitalisation and COVID-19 severity.

Our findings extend prior studies that have evaluated the relationship between obstructive lung diseases, smoking and COVID-19 outcomes. While other studies have reported associations between both asthma and COPD and severe COVID-19,[6 7] to our knowledge this is the first analysis to specifically test for and identify effect modification by age. Our analysis may explain the variability of reports of the effects of asthma and smoking on COVID-19 severity. These findings raise the possibility of subgroup-specific effects of these risk factors and suggest that generalised statements regarding increased risk may be incomplete.

Several studies have suggested that asthma may be protective in some patients, including a Chicago study of 1003 patients with COVID-19 that reported lower rate of ARDS and death among those with asthma,[11] and an analysis of a smaller cohort of patients with COVID-19 at our hospital that found a lower risk of ICU admission among those with asthma but no significant difference in risk of death compared with control patients without asthma.[38] Two recent meta-analyses confirmed the lack of an association between presence of asthma and mortality,[39 40] but two large studies in Korea and the UK reported that while asthma in general was not a risk factor for disease severity, asthma exacerbation within the past year was associated with an increased risk for death.[2 41]

The mechanism of the observed protective effect of asthma is unclear, and may be in part related to increased care seeking or a lower threshold for hospitalisation among patients with asthma. For example, patients with asthma may be more likely to be hospitalised for milder symptoms and therefore have lower WHO CPS scores. The effect of asthma on the severity of COVID-19 disease may likely be also determined by the underlying asthma phenotype and immunology of the host.[42] Several investigators have postulated that the allergic phenotype may increase the risk of viral infection[43] but may decrease the risk of the hyperimmune response that characterises severe disease.[44 45] The severe asthma phenotype that is associated with worse COVID-19 outcomes may vary by atopy, age of onset, race/ethnicity and obesity.[46] Obesity is associated with more severe and non-allergic asthma, through mechanisms that include altered pulmonary mechanics, adipokine changes, Th-1 and ILinterleukin-17-related airway inflammation,[47–49] and our analysis confirmed the previously reported association between obesity and COVID-19 severity.[50–52]

The observed inverse correlation between current smoking status and COVID-19 severity adds to the existing literature regarding the association between current smoking and risk of SARS-CoV-2 infection, disease severity and mortality.[53–57] Our findings contrast with observations from other common respiratory pathogens, including Middle East Respiratory Syndrome, in which smoking has been associated with increased risk of both infection and mortality,[58 59] influenza, in which history of smoking is associated with increased risk of hospital admission,[60] and respiratory syncytial virus, in which maternal smoking is associated with increased risk of acute lower respiratory infection in children.[61] Compared with former smokers and never smokers, current smoking is associated with an increased risk of death from pneumococcal pneumonia.[62]

Postulated mechanisms for a protective effect of current smoking include an inhibitory effect of nicotine on the production of proinflammatory cytokines and increased tolerance of airway or lung injury among current smokers.[63–65] The clinical relevance of these hypotheses cannot be fully tested without accounting for potential confounders, including differences in behaviours leading to SARS-CoV-2 exposure, differences in thresholds for seeking testing, and access to healthcare. While we found evidence of age-specific effects of smoking, it is likely that the effects of smoking are also modified by other host factors that we did not examine, including amount of smoking, type of smoking, race/ethnicity and genetics.

Our study does not address several important questions relating to the effects of obstructive lung disease and smoking on COVID-19 outcomes. First, our cohort is limited to inpatients with COVID-19 and is therefore unable to assess the effect of these risk factors on becoming infected with SARS-CoV-2 or developing mild disease. The small number of children included in the sample (n=16), all of whom were non-smokers, also limits our ability to draw conclusions about children. Second, because the WHO CPS focuses on supportive measures provided during hospitalisation, decisions to forgo life-sustaining treatment including mechanical ventilation, vasopressor support or renal replacement therapy may bias the score downward for some severely ill patients.[34] Because of institutional infection control practice patterns, few patients were treated with high-flow oxygen or non-invasive ventilation (WHO CPS 6), and most patients with cute respiratory distress syndrome (ARDS) ultimately developed either severe ARDS or required vasopressors (WHO CPS 8 or higher), which limits our ability to draw conclusions regarding WHO CPS scores 6 and 7. Third, our analysis relies on accurate reporting and abstraction of data from the medical record; these data may inaccurate or incomplete, especially for patients who did not previously receive their care within the MassGeneral Brigham system. Finally, the presence or absence of obstructive lung disease was determined based on diagnoses present during chart review, which is subject to underdiagnosis, overdiagnosis and misdiagnosis.[66 67] In addition, we were unable to characterise or stratify by severity of obstructive lung disease or duration and amount of smoking, which may affect the severity of COVID-19. Further studies are required to evaluate these factors and to test for other potential effect modifiers, including asthma phenotype, the nature of inflammatory responses, and the effects of asthma/COPD treatment. In addition, future studies should examine the effects of these risk factors on the long-term sequelae of COVID-19.

Conclusion

In summary, this study identifies age as a modifying factor for the association between asthma and smoking on severity of COVID-19. Our findings highlight the complexities of determining risk factors for COVID-19 severity, and suggest that predicting disease severity based on single risk factors may not be appropriate.

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