

Impact of risk factor combinations on severe COVID-19 outcomes among outpatients

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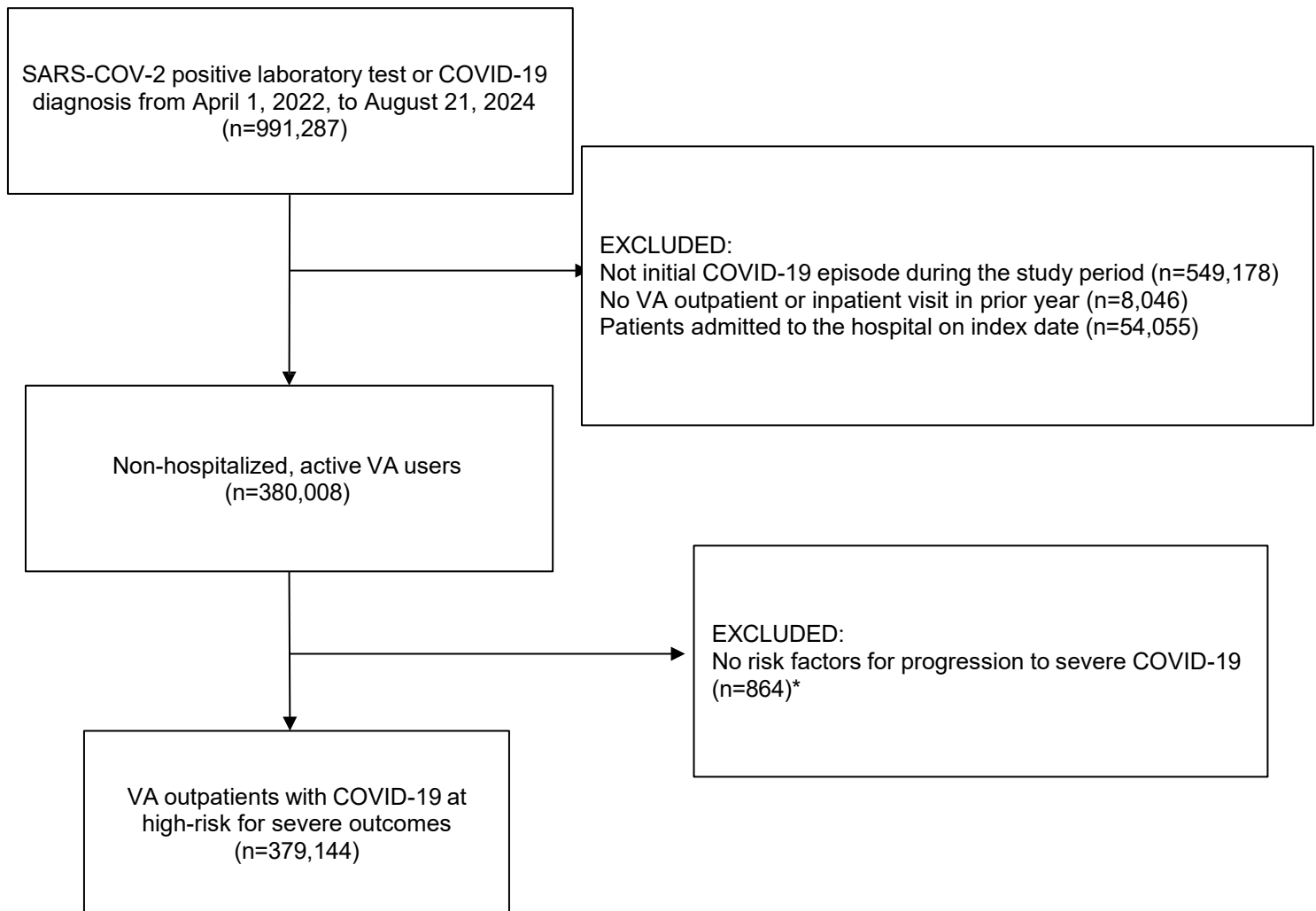
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SUPPLEMENTAL MATERIAL

eFigure 1. Study selection criteria

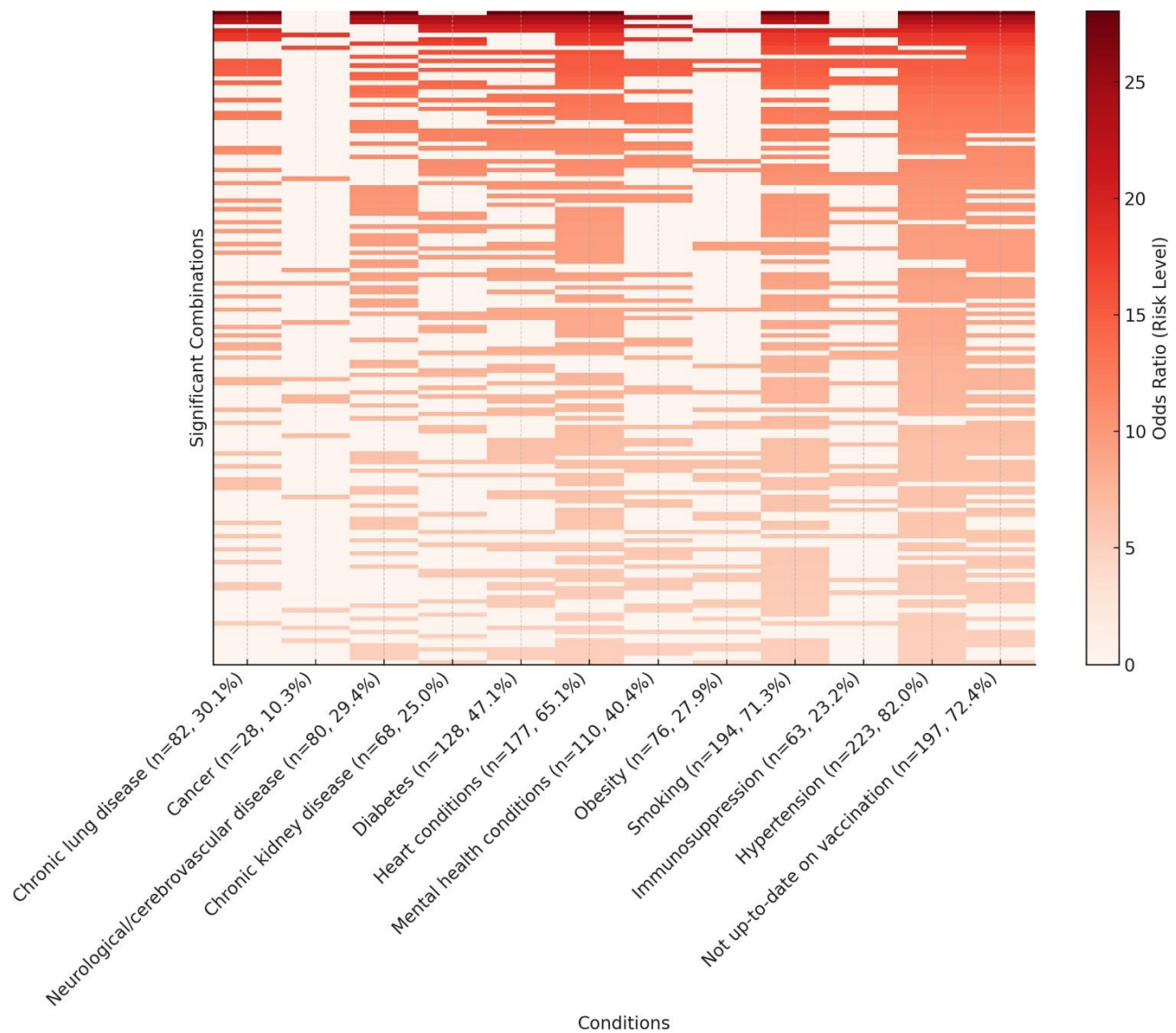


VA= Veterans Affairs

*Selected risk factors were those that commonly occur among the Veteran population and are associated with severe COVID-19, or were categorized as higher risk medical conditions with conclusive evidence for progression to severe COVID-19 as categorized by the CDC. The risk factors included in our study were 1) age ≥ 50 years, 2) chronic lung disease (asthma and chronic lung diseases), 3) cancer, 4) neurological conditions/ cerebrovascular disease, 5) chronic kidney disease, 6) chronic liver disease, 7) diabetes mellitus (type 1 and type 2), 8) heart conditions, 9) mental health conditions (mood disorders, Schizophrenia, and post-

traumatic stress disorder), 10) obesity, 11) smoking (current and former), 12) immunosuppression (immunosuppressive conditions, immunosuppressive medications, and HIV), 13) hypertension, and 14) not being up-to-date on COVID-19 vaccination. Underling conditions were identified using ICD-10 codes in the year prior to the index date, as defined by the CDC “Underlying Conditions ICD-10 Code List Methodology”.

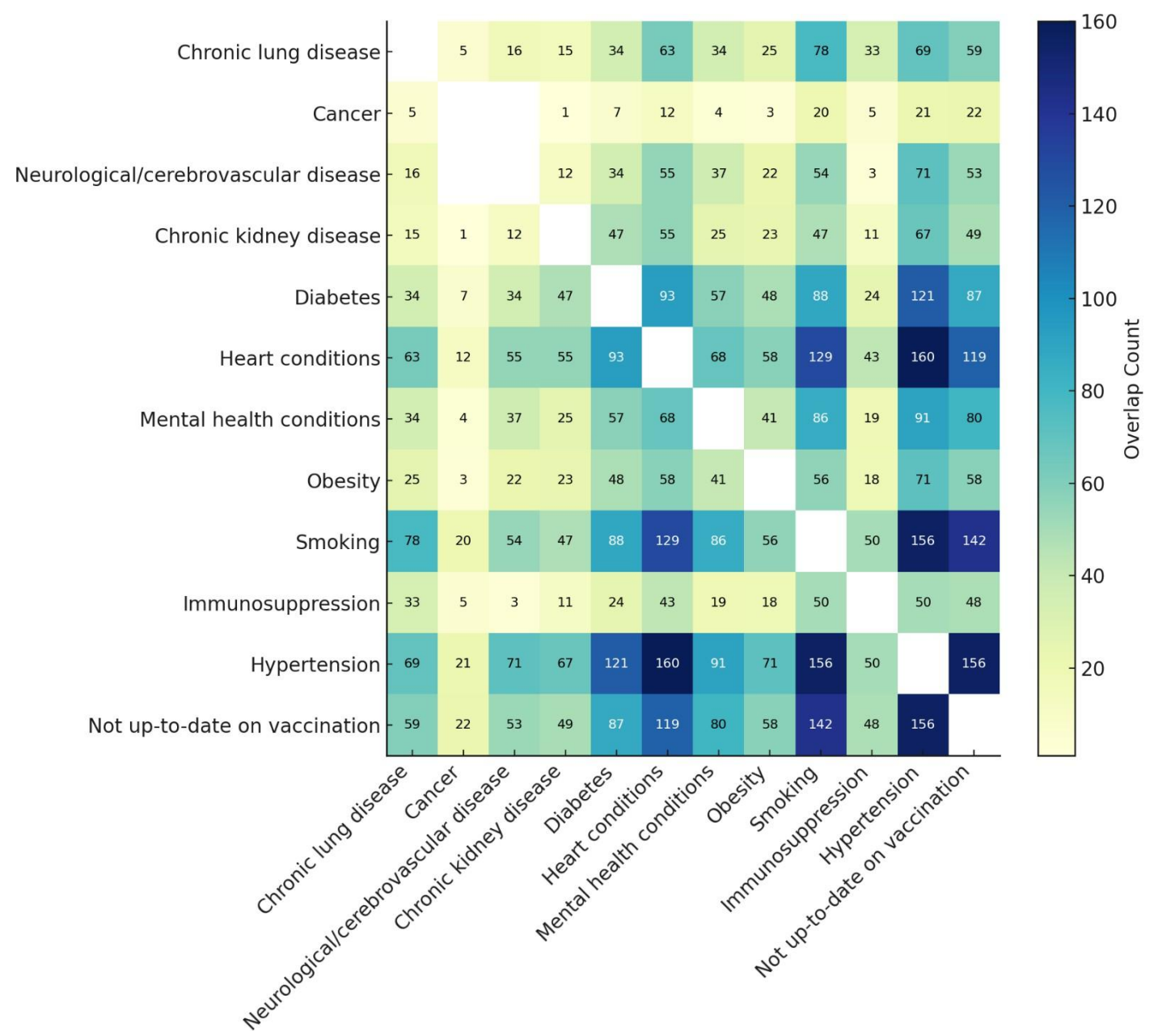
eFigure 2. Sensitivity analysis: Heatmap of all statistically significant risk combinations (excluding age ≥ 50)



In sensitivity analyses severe COVID-19 was defined as any hospitalization with COVID-19 listed as a primary or secondary diagnosis or all-cause mortality within 30 days of the index date.

Heatmap of the 272 significant risk factor combinations, cell color intensity represents the odds ratio (darkest red = highest odds ratio; lightest red = lowest [0]) and cell frequency indicates how often each condition appeared.

eFigure 3. Sensitivity analysis: Pairwise overlap of significant combinations



In sensitivity analyses severe COVID-19 was defined as any hospitalization with COVID-19 listed as a primary or secondary diagnosis or all-cause mortality within 30 days of the index date.

Pairwise overlap of conditions across the 272 significant combinations. Numbers within each cell represent the count of overlapping condition pairs, with color intensity reflecting the overlap count (light yellow = lowest [0], dark blue = highest [160]).

eTable 1. Full adjusted model

See separate attachment.

Each specific risk factor combination was compared to the same single reference group (aged ≥ 50 years with no other risk factors), while controlling for other variables.

Risk factor combination of interest represented by 14 string risk factor code, with 1s and 0s representing presence or absence of the condition respectively. The order of conditions in the string is as follows: 1) Age ≥ 50 years; 2) Obesity; 3) Diabetes; 4) Hypertension; 5) Heart conditions; 6) Chronic liver disease; 7) Chronic lung disease; 8) Chronic kidney disease; 9 Neurological conditions/ CVD; 10) Immunosuppression; 11) Cancer; 12) Smoking; 13) Mental health conditions; and 14) Not up-to-date on vaccination.

Aged ≥ 50 years with no other risk factors represented by code "1_0_0_0_0_0_0_0_0_0_0_0_0_0_0"

eTable 2. Effects of number of risk factors on 30-day severe COVID-19 in adults with COVID-19 in the outpatient setting

Risk factor combination	N (%)	Adjusted Odds Ratio (95% CI)
One factor	10,322 (2.7)	(reference)
Two risk factors	31,116 (8.2)	2.10 (1.37-3.23)
Three risk factors	54,833 (14.5)	2.31 (1.52-3.50)
Four risk factors	67,510 (17.8)	3.15 (2.09-4.75)
Five risk factors	67,608 (17.8)	4.62 (3.07-6.95)
Six risk factors	58,087 (15.3)	6.65 (4.42-9.99)
Seven risk factors	42,294 (11.2)	10.08 (6.70-15.16)
Eight risk factors	25,611 (6.8)	13.54 (8.98-20.41)
Nine risk factors	13,425 (3.5)	18.83 (12.44-28.50)
Ten risk factors	5,708 (1.5)	25.14 (16.44-38.46)
Eleven risk factors	2,029 (0.5)	24.55 (15.61-38.64)
Twelve risk factors	509 (0.1)	31.55 (18.19-54.72)
Thirteen risk factors	84 (0.0)	42.07 (18.05-98.05)
Fourteen risk factors	8 (0.0)	43.49 (4.94-382.66)

The adjusted odds ratios are estimated from multivariable analysis of the data. The multivariable unconditional logistic regression models compared individuals with one risk factor (reference group) to those with two, three, four, and so forth, risk factors and controlled for sex (male or female), race (white or other/unknown), ethnicity (Hispanic/Latino or non-Hispanic/Latino or unknown), region (Northeast, Midwest, South or West), and deprived (yes or no, based on area deprivation index). Analysis conducted in entire cohort (n=379,144).

eTable 3. Frequency of risk factors by vaccination status among significant combinations (n=239)

Risk Factor	Up-to-date on vaccination (n=173)	Not up-to-date on vaccination (n=66)
Age ≥50 years	171 (98.8%)	66 (100.0%)
Chronic lung disease	53 (30.6%)	18 (27.3%)
Cancer	19 (11.0%)	2 (3.0%)
Neurological disease/ cerebrovascular	49 (28.3%)	26 (39.4%)
Chronic kidney disease	49 (28.3%)	16 (24.2%)
Chronic liver disease	0 (0.0%)	0 (0.0%)
Diabetes	76 (43.9%)	36 (54.5%)
Heart conditions	106 (61.3%)	48 (72.7%)
Mental health conditions	63 (36.4%)	32 (48.5%)
Obesity	47 (27.2%)	20 (30.3%)
Smoking	121 (69.9%)	47 (71.2%)
Immunosuppression	40 (23.1%)	13 (19.7%)
Hypertension	137 (79.2%)	59 (89.4%)

eTable 4. Sensitivity analysis: Patient characteristics of adults with COVID-19 in the outpatient setting, by 30-day severe COVID-19 (broader hospitalization-based definition)

	Total (n=379,144)	30-day severe COVID-19 (broader hospitalization- based definition) (n=9,338)	No severe COVID-19 (n=369,806)	P value
Age group				<0.001
18-49 years	78,348 (20.7)	671 (7.2)	77,677 (21.0)	
≥50 years	300,796 (79.3)	8,667 (92.8)	292,129 (79.0)	
Sex				<0.001
Male	326,120 (86.0)	8,812 (94.4)	317,308 (85.8)	
Female	53,024 (14.0)	526 (5.6)	52,498 (14.2)	
Region				<0.001
Midwest	74,744 (19.7)	1,603 (17.2)	73,141 (19.8)	
Northeast	56,636 (14.9)	1,146 (12.3)	55,490 (15.0)	
West	86,879 (22.9)	2,166 (23.2)	84,713 (22.9)	
South	160,885 (42.4)	4,423 (47.4)	156,462 (42.3)	
Race				<0.001
Black or African American	81,174 (21.4)	2,143 (22.9)	79,031 (21.4)	
White	253,470 (66.9)	6,270 (67.1)	247,200 (66.8)	
Other race	44,500 (11.7)	925 (9.9)	43,575 (11.8)	
Ethnicity				0.228
Hispanic or Latino	38,151 (10.1)	905 (9.7)	37,246 (10.1)	
Not Hispanic or Latino	340,993 (89.9)	8,433 (90.3)	332,560 (89.9)	
Smoking				<0.001
Current and former	215,254 (56.8)	6,153 (65.9)	209,101 (56.5)	

No/unknown	163,890 (43.2)	3,185 (34.1)	160,705 (43.5)	
Deprivation based on area deprivation index				<0.001
Yes	55,696 (14.7)	1,707 (18.3)	53,989 (14.6)	
No	323,448 (85.3)	7,631 (81.7)	315,817 (85.4)	
Underlying medical condition*				
Chronic lung disease	75,044 (19.8)	3,137 (33.6)	71,907 (19.4)	<0.001
Cancer	42,108 (11.1)	2,127 (22.8)	39,981 (10.8)	<0.001
Neurological conditions/ cerebrovascular disease	49,087 (12.9)	3,033 (32.5)	46,054 (12.5)	<0.001
Chronic kidney disease	49,721 (13.1)	3,059 (32.8)	46,662 (12.6)	<0.001
Chronic liver disease	25,035 (6.6)	985 (10.5)	24,050 (6.5)	<0.001
Diabetes mellitus	118,077 (31.1)	4,218 (45.2)	113,859 (30.8)	<0.001
Heart conditions	129,972 (34.3)	5,561 (59.6)	124,411 (33.6)	<0.001
Mental health conditions	161,042 (42.5)	4,049 (43.4)	156,993 (42.5)	0.080
Obesity**	190,316 (50.2)	3,157 (33.8)	187,159 (50.6)	<0.001
Smoking	215,254 (56.8)	6,153 (65.9)	209,101 (56.5)	<0.001
Immunosuppression***	76,214 (20.1)	2,978 (31.9)	73,236 (19.8)	<0.001
Hypertension	218,048 (57.5)	7,105 (76.1)	210,943 (57.0)	<0.001
COVID vaccination status****				<0.001
Up-to-date	127,721 (33.7)	2,676 (28.7)	125,045 (33.8)	
Not up-to-date	251,423 (66.3)	6,662 (71.3)	244,761 (66.2)	

In sensitivity analyses severe COVID-19 was defined as any hospitalization with COVID-19 listed as a primary or secondary diagnosis or all-cause mortality within 30 days of the index date.

Data are n (%). Chi-squared or Fisher's Exact tests were used to compare differences in proportions between the groups. For continuous variables, comparisons were performed using the Wilcoxon Rank Sum test or a Student's t-test, depending on the distribution of the data for the given variable.

*Underling conditions were identified using ICD-10 codes in the year prior to the index date, as defined by the CDC “Underlying Conditions ICD-10 Code List Methodology”. Chronic lung disease included asthma and chronic lung diseases, mental health conditions included mood disorders, Schizophrenia, and post-traumatic stress disorder, and immunosuppression included immunosuppressive conditions, immunosuppressive medications, and HIV.

**Obesity was defined based on a BMI ≥ 30 kg/m² or otherwise ICD-10 codes for obesity if BMI was missing.

***Immunosuppressive medication exposures (alkylating agents, antibiotics, antimetabolites, antimitotics, monoclonal antibodies, other, immune-modulating agents, TNF Alpha antagonist, and steroids) were based on pharmacy data.

****Up-to-date COVID-19 vaccination status: at least one dose of XBB vaccine if the index date occurred between September 25, 2023 and August 21, 2024, at least one dose of a BA.4/5 bivalent vaccine if the index date occurred between September 1, 2022 and September 24, 2023, or at least three doses of wild-type COVID-19 vaccine if the index date occurred between April 1, 2022 and August 31, 2022.

eTable 5. Sensitivity analysis: Effects of number of risk factors on 30-day severe COVID-19 (broader hospitalization-based definition) in adults with COVID-19 in the outpatient setting

Risk factor combination	N (%)	Adjusted Odds Ratio (95% CI)
One factor	10,322 (2.7)	(reference)
Two risk factors	31,116 (8.2)	1.55 (1.15–2.10)
Three risk factors	54,833 (14.5)	1.95 (1.46–2.60)
Four risk factors	67,510 (17.8)	2.56 (1.93–3.40)
Five risk factors	67,608 (17.8)	3.48 (2.62–4.61)
Six risk factors	58,087 (15.3)	5.23 (3.95–6.93)
Seven risk factors	42,294 (11.2)	7.66 (5.78–10.16)
Eight risk factors	25,611 (6.8)	10.02 (7.54–13.31)
Nine risk factors	13,425 (3.5)	13.93 (10.44–18.59)
Ten risk factors	5,708 (1.5)	19.53 (14.48–26.35)
Eleven risk factors	2,029 (0.5)	20.07 (14.52–27.74)
Twelve risk factors	509 (0.1)	25.43 (17.04–37.95)
Thirteen risk factors	84 (0.0)	45.91 (24.84–84.83)
Fourteen risk factors	8 (0.0)	44.68 (8.49–235.11)

In sensitivity analyses severe COVID-19 was defined as any hospitalization with COVID-19 listed as a primary or secondary diagnosis or all-cause mortality within 30 days of the index date.

The adjusted odds ratios are estimated from multivariable analysis of the data. The multivariable unconditional logistic regression models compared individuals with one risk factor (reference group) to those with two, three, four, and so forth, risk factors and controlled for sex (male or female), race (white or other/unknown), ethnicity (Hispanic/Latino or non-Hispanic/Latino or unknown), region (Northeast, Midwest, South or West), and deprived (yes or no, based on area deprivation index). Analysis conducted in entire cohort (n=379,144).

eTable 6. Sensitivity Analysis: Combinations with the highest risk of 30-day severe COVID-19 (broader hospitalization-based definition) in adults with COVID-19 in the outpatient setting

Combination Rank	Age ≥50 years	Chronic lung disease	Cancer	Neurological disease/	Chronic kidney	Chronic liver disease	Diabetes	Heart conditions	Mental health	Obesity	Smoking	Immunosuppression	Hypertension	Not up-to-date on vaccination	Number of risk factors	N (%)	Adjusted Odds Ratio (95% CI)
1*	X	X		X			X	X			X		X	X	8	148 (0.05)	28.05 (14.46–54.40)
2**	X	X		X	X		X	X	X		X		X	X	10	108 (0.04)	24.52 (12.04–49.96)
3*	X	X		X	X		X	X			X		X	X	9	118 (0.04)	22.84 (11.21–46.54)
4*	X				X		X	X	X				X	X	7	143 (0.05)	20.49 (10.22–41.08)
5**	X	X			X		X	X		X	X	X	X	X	10	104 (0.04)	19.55 (9.19–41.56)
6**	X	X	X					X			X	X	X	X	8	121 (0.04)	17.88 (8.37–38.19)
7	X	X			X			X	X		X		X	X	8	107 (0.04)	17.81 (8.35–37.95)

8*	X			X	X			X			X		X	X	7	191 (0.07)	17.11 (8.88– 32.97)
9**	X		X								X	X		X	5	109 (0.04)	16.16 (7.15– 36.52)
10*	X				X		X	X			X	X	X	X	8	116 (0.04)	15.83 (6.91– 36.26)
11*	X			X				X						X	4	143 (0.05)	15.20 (7.25– 31.89)
12*	X	X			X		X	X	X	X	X	X	X	X	11	106 (0.04)	15.09 (6.56– 34.70)
13*	X	X		X				X	X		X	X	X	X	9	121 (0.04)	15.03 (6.83– 33.10)
14**	X	X			X		X	X	X	X	X		X	X	10	148 (0.05)	14.95 (7.09– 31.51)
15	X	X		X				X	X		X		X	X	8	175 (0.06)	14.71 (7.31– 29.62)
16*	X			X				X			X	X	X	X	7	128 (0.05)	14.19 (6.47– 31.12)

17																	14.18
*	X	X			X			X			X	X	X	X	8	103 (0.04)	(6.04– 33.27)
18																	13.76
*	X			X	X		X	X			X		X	X	8	261 (0.09)	(7.24– 26.16)
19																	13.70
*	X			X					X				X	X	5	168 (0.06)	(6.63– 28.30)
20																	13.11
*	X			X			X	X					X	X	6	230 (0.08)	(6.78– 25.34)

In sensitivity analyses severe COVID-19 was defined as any hospitalization with COVID-19 listed as a primary or secondary diagnosis or all-cause mortality within 30 days of the index date.

Shaded rows represent unique risk factor combinations not present in our original analysis (Table 2).

The adjusted odds ratios are estimated from multivariable analysis of the data (reference group age ≥50 years with no other risk factors). The multivariable unconditional logistic regression models included sex (male or female), race (white or other/unknown), ethnicity (Hispanic/Latino or non-Hispanic/Latino or unknown), region (Northeast, Midwest, South or West), and deprived (yes or no, based on area deprivation index) unless otherwise noted.

* Not adjusted for sex (male or female) due to small numbers.

** Not adjusted for sex (male or female) or ethnicity (Hispanic/Latino or non-Hispanic/Latino or unknown) due to small numbers

*** Not adjusted for ethnicity (Hispanic/Latino or non-Hispanic/Latino or unknown) due to small numbers.