SUPPLEMENTAL FILE
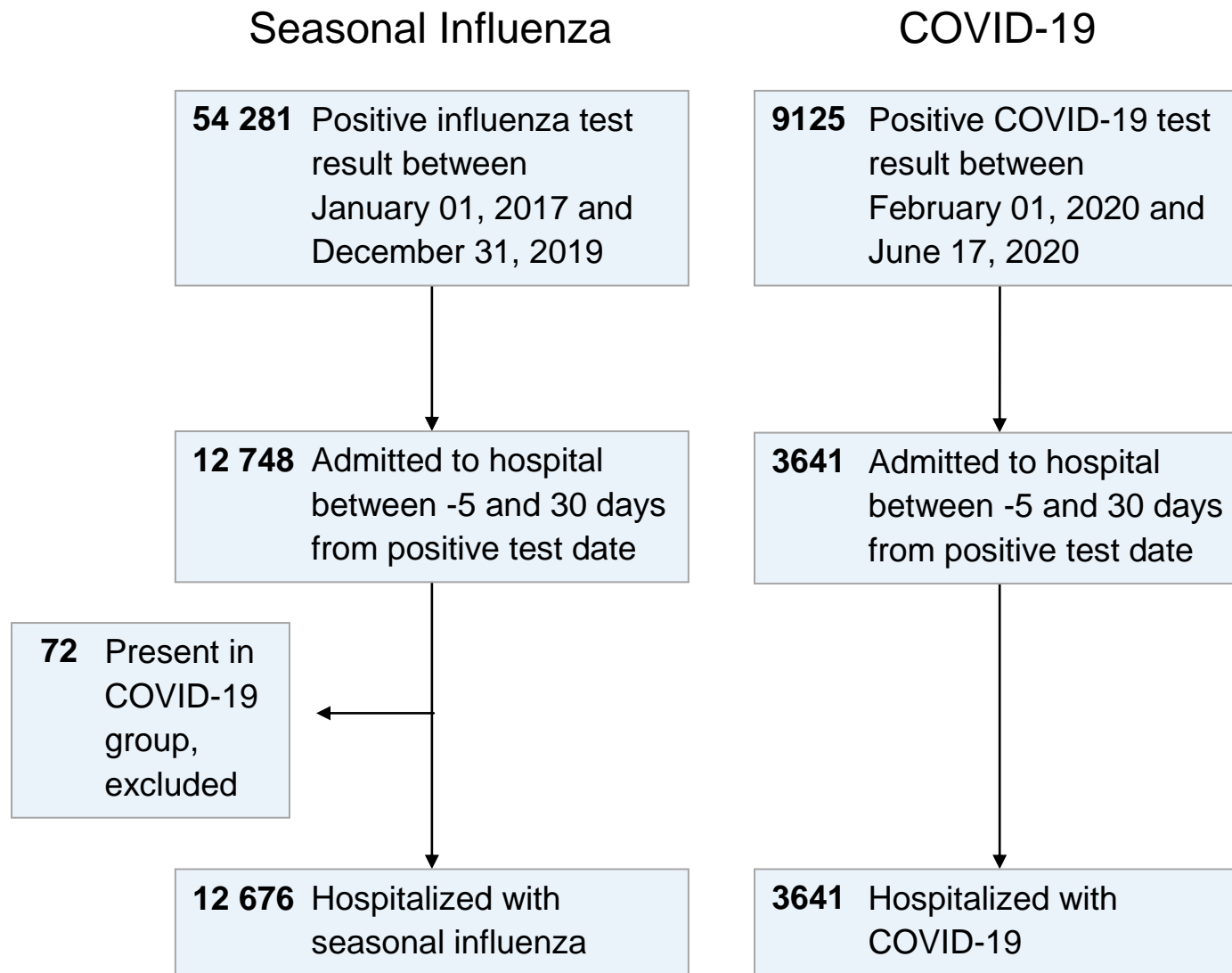
Comparative Evaluation of Clinical Manifestations and Risk of Death in Hospitalized Patients with COVID-19 and Seasonal Influenza

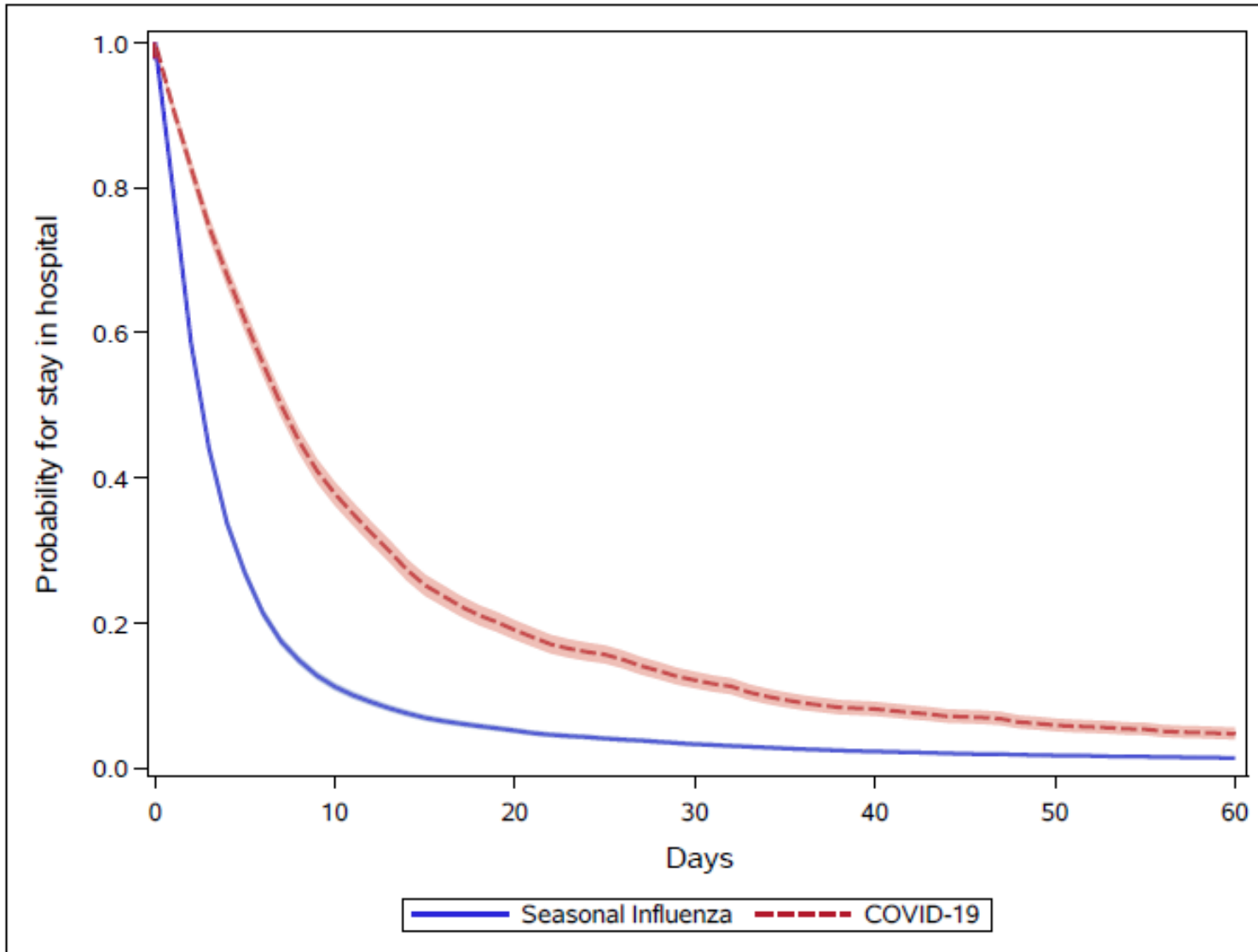Yan Xie; Benjamin Bowe; Geetha Maddukuri and Ziyad Al-Aly

Supplementary Figure S1. Cohort Flow

COVID-19=coronavirus disease 2019.

Supplementary Figure S2. Probability of remaining in the hospital in the influenza and the COVID-19 group

COVID-19=coronavirus disease 2019.

Supplementary Figure S3a. Propensity score distribution of the influenza and the COVID-19 group before adjustment
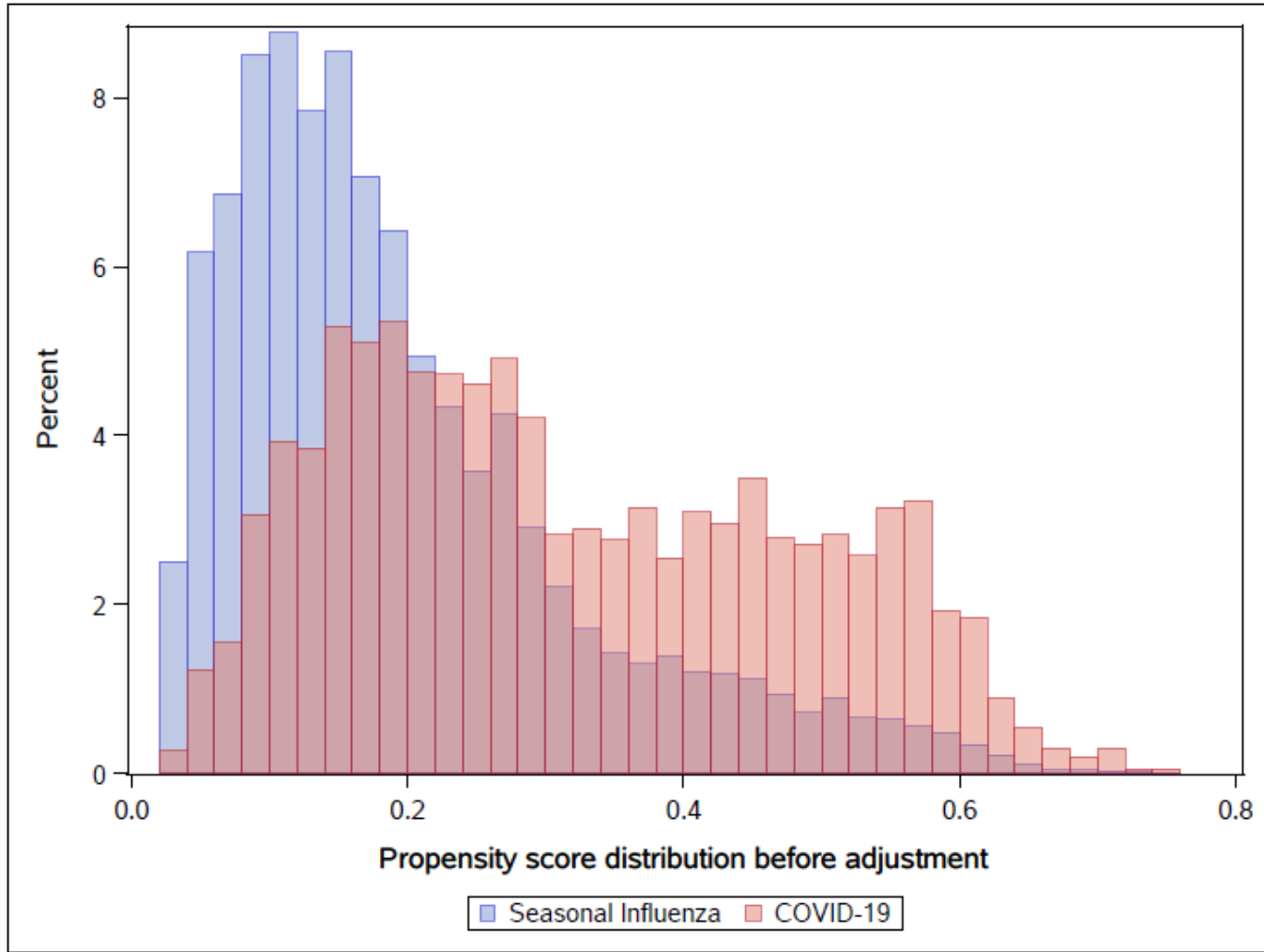
COVID-19=coronavirus disease 2019.

Supplementary Figure S3b. Propensity score distribution of the influenza and the COVID-19 group after inverse probability weighting
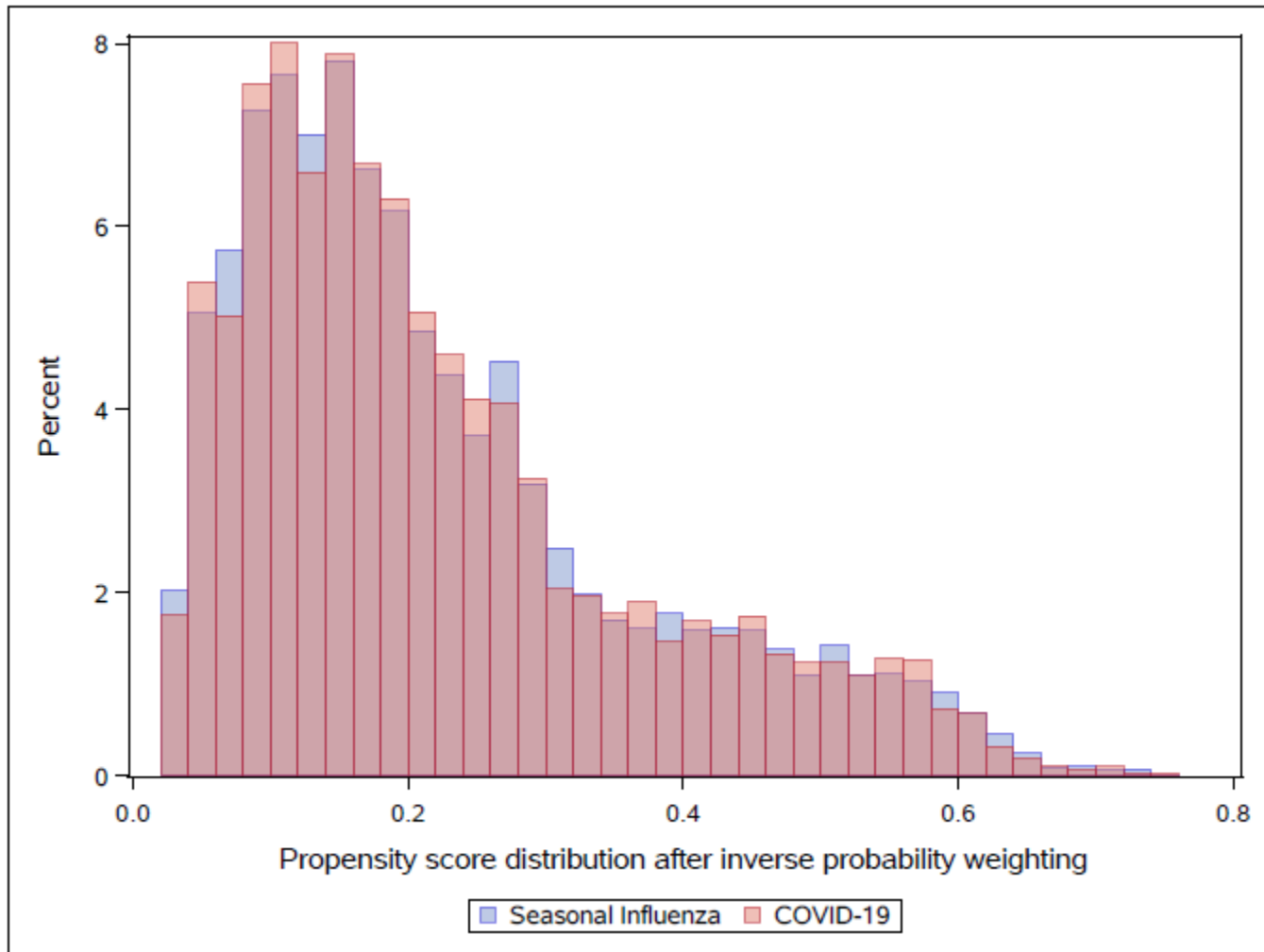
COVID-19=coronavirus disease 2019.

Supplementary Figure S3c. Propensity score distribution of the influenza and the COVID-19 group after overlap weighting
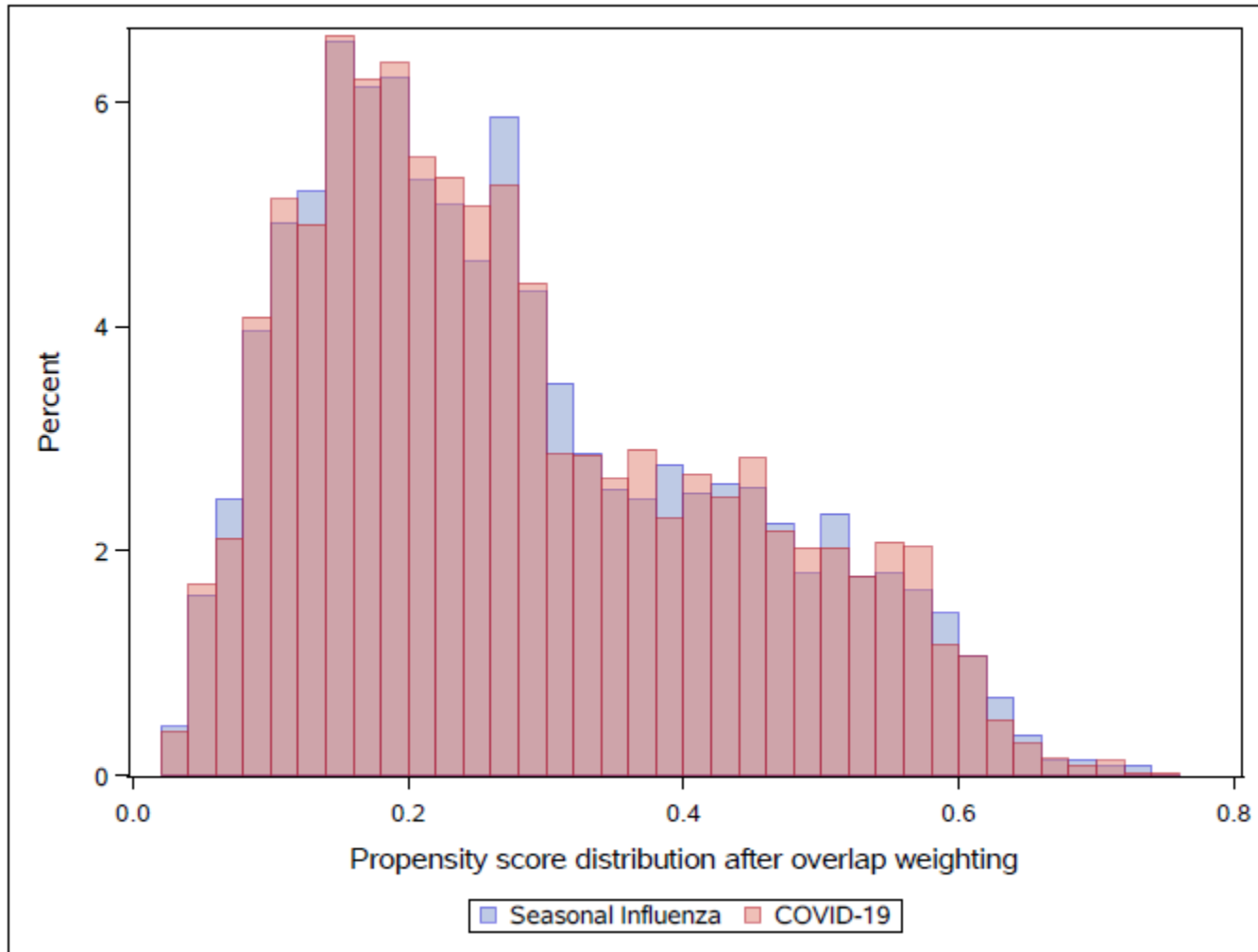
COVID-19=coronavirus disease 2019.

Supplementary Figure S4a. Standardized difference before and after application of the propensity score
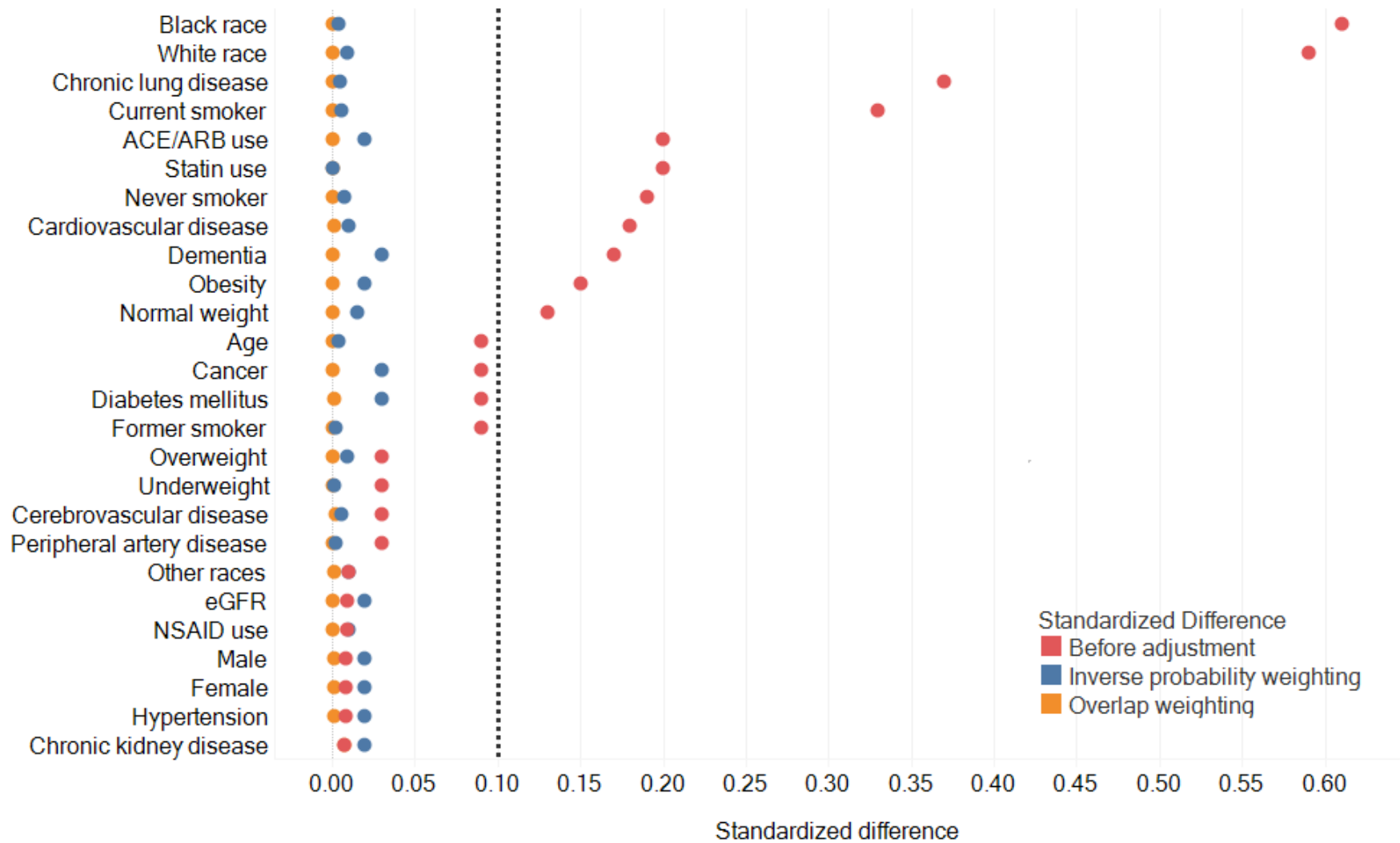
ACE/ARB=angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers. eGFR=estimated glomerular filtration rate. NSAID=nonsteroidal anti-inflammatory drugs.

Supplementary Figure S4b. P-value before and after application of the propensity score
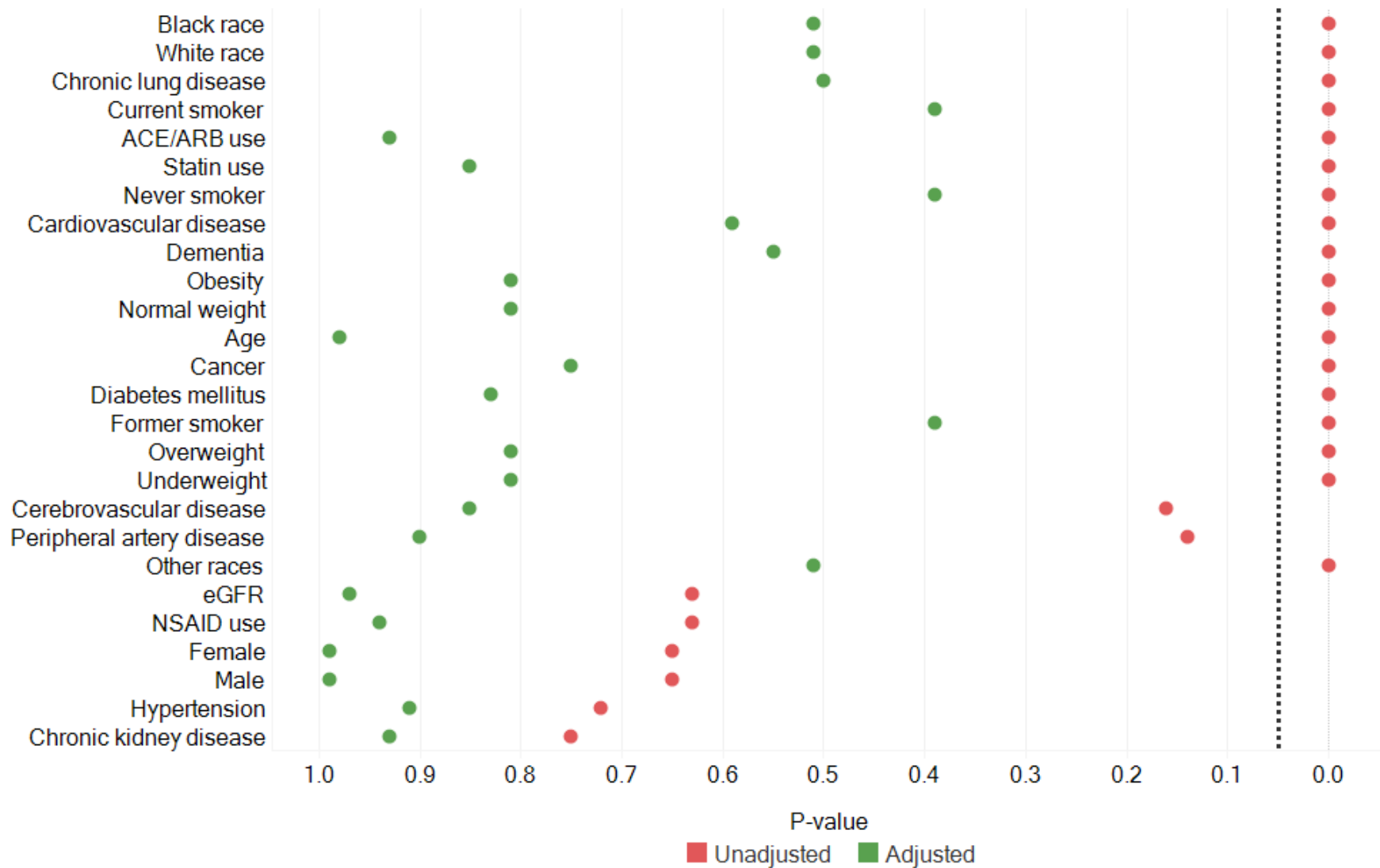
ACE/ARB=angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers. eGFR=estimated glomerular filtration rate. NSAID=nonsteroidal anti-inflammatory drugs.
P-value based on regression model where each characteristic was regressed by exposure group, conditional on other characteristics and the propensity score. A type III F test for continuous variable or Chi-square test for categorical variable P-value >0.05 indicated exposure group was not significantly associated with the baseline characteristics after the doubly robust adjustment.

Supplementary Figure S5a. Log negative log survival curve for death
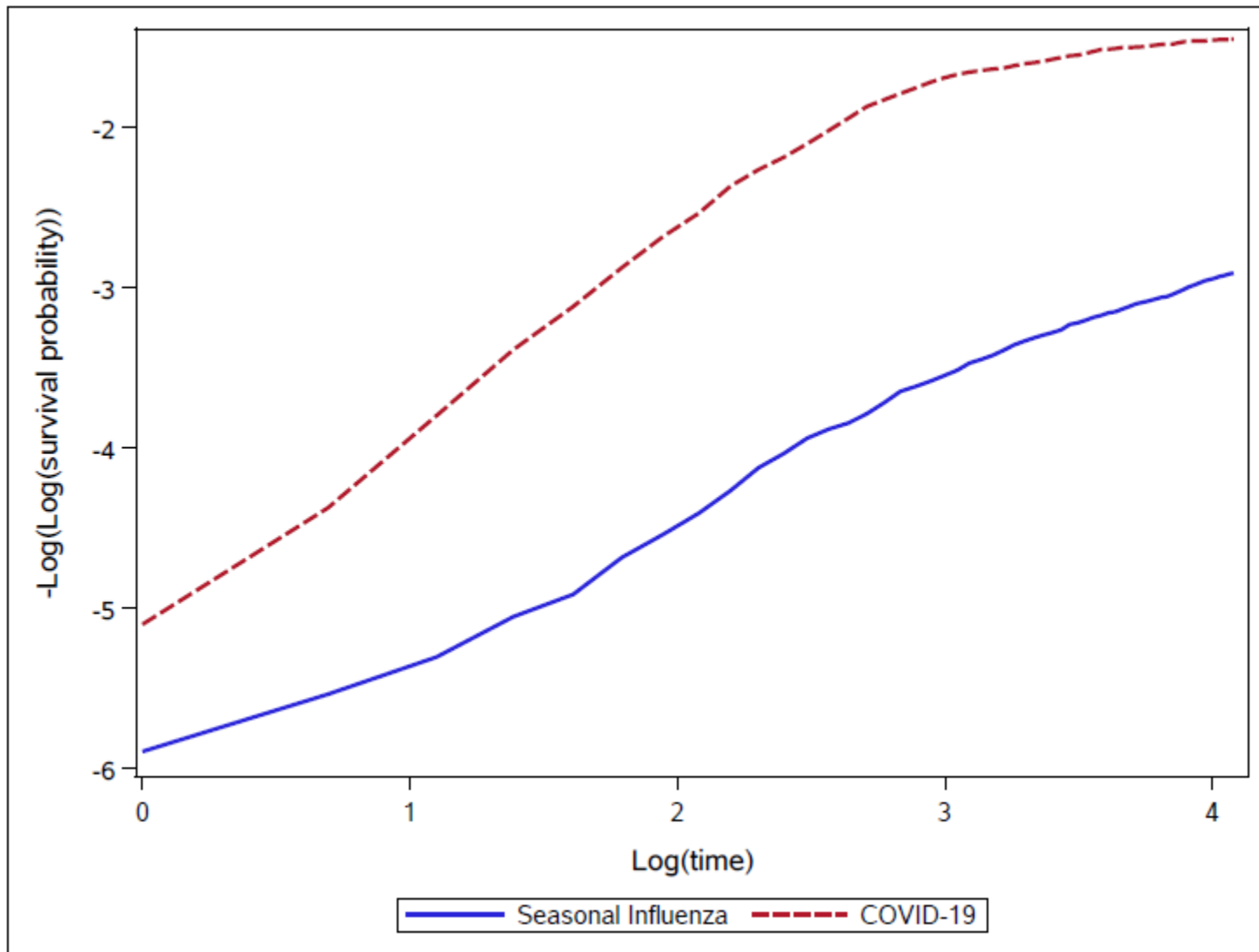
COVID-19=coronavirus disease 2019.

Supplementary Figure S5b. Log negative log survival curve for mechanical ventilation use
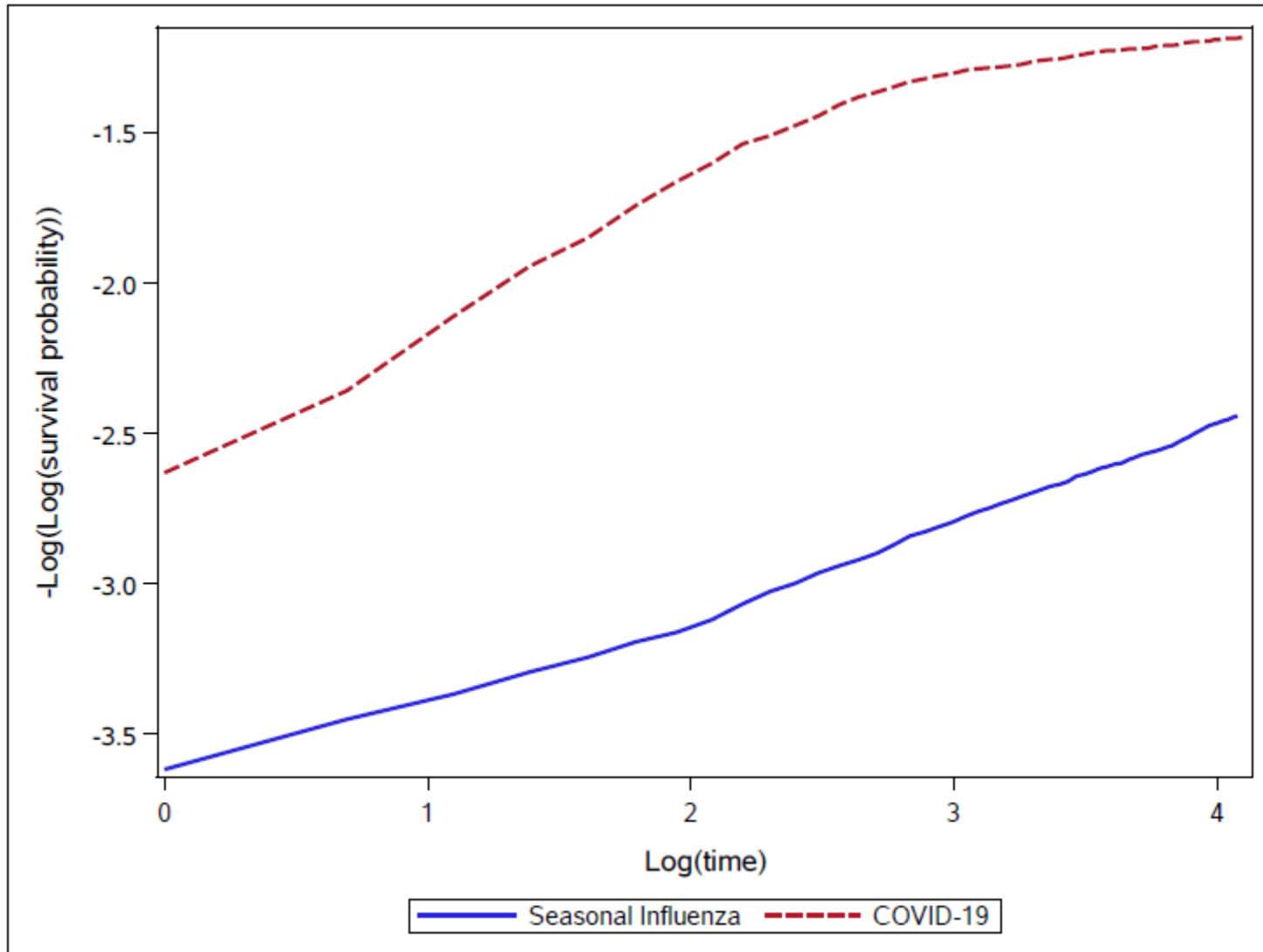
COVID-19=coronavirus disease 2019.

Supplementary Figure S5c. Log negative log survival curve for ICU admission
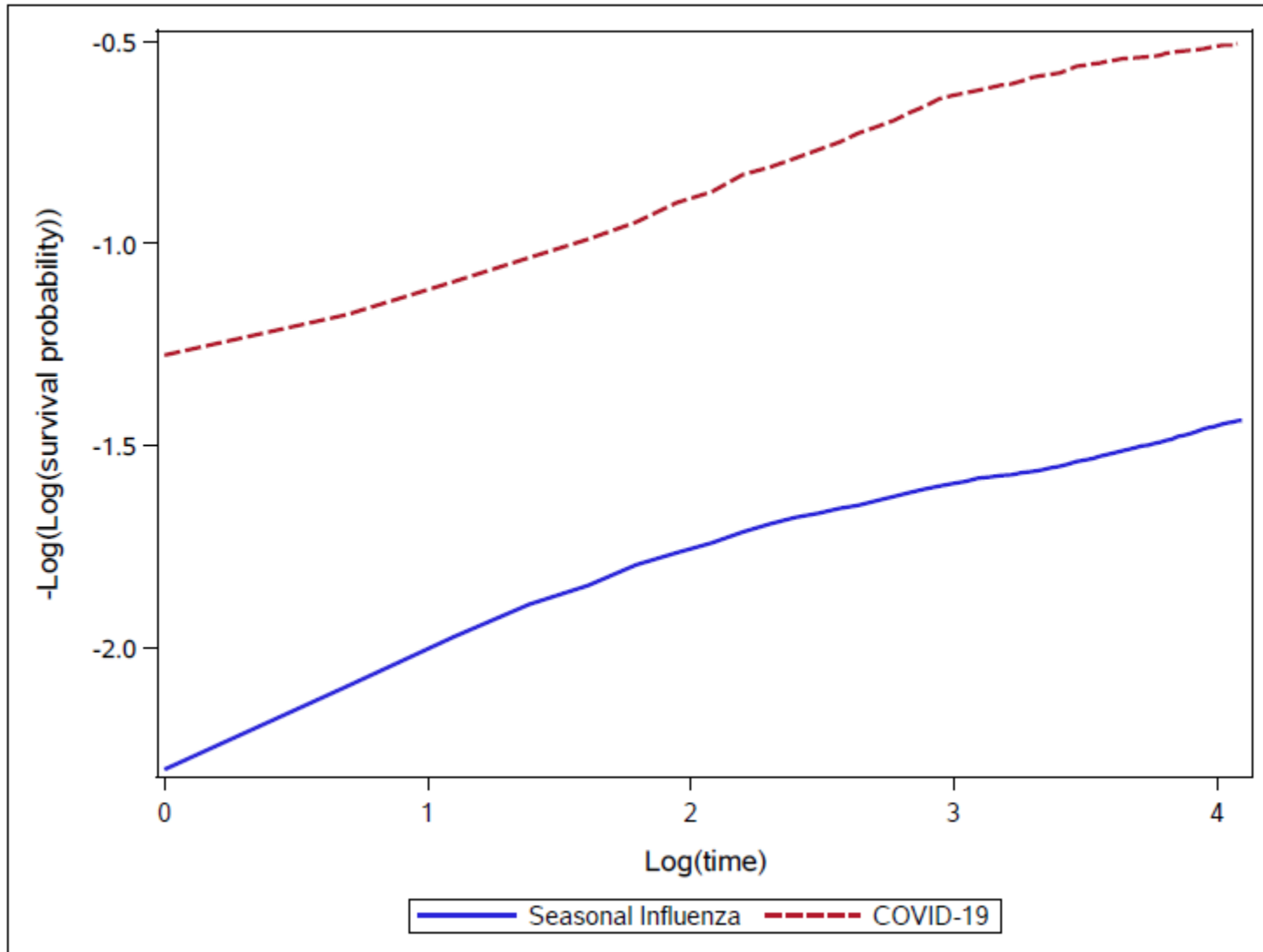
COVID-19=coronavirus disease 2019.

Supplementary Figure S6a. Overall distribution of occupancy of hospital beds

Mean (SD): 38.08 (10.46)

Median (IQR): 38.20 (30.76, 44.79)

Minimum: 2.90   Maximum: 77.82
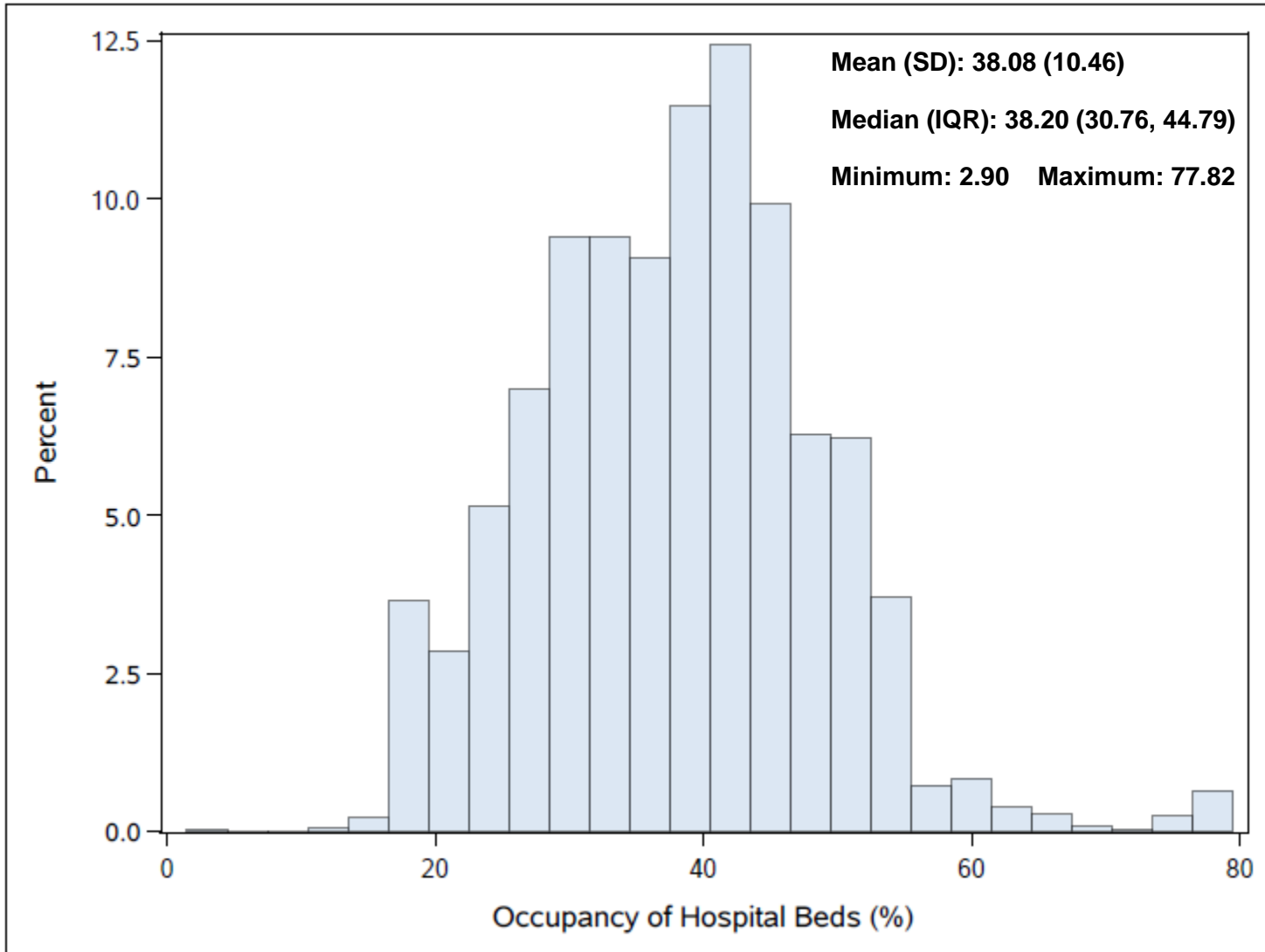
Supplementary Figure S6b. Distribution of occupancy of hospital beds by week of study period
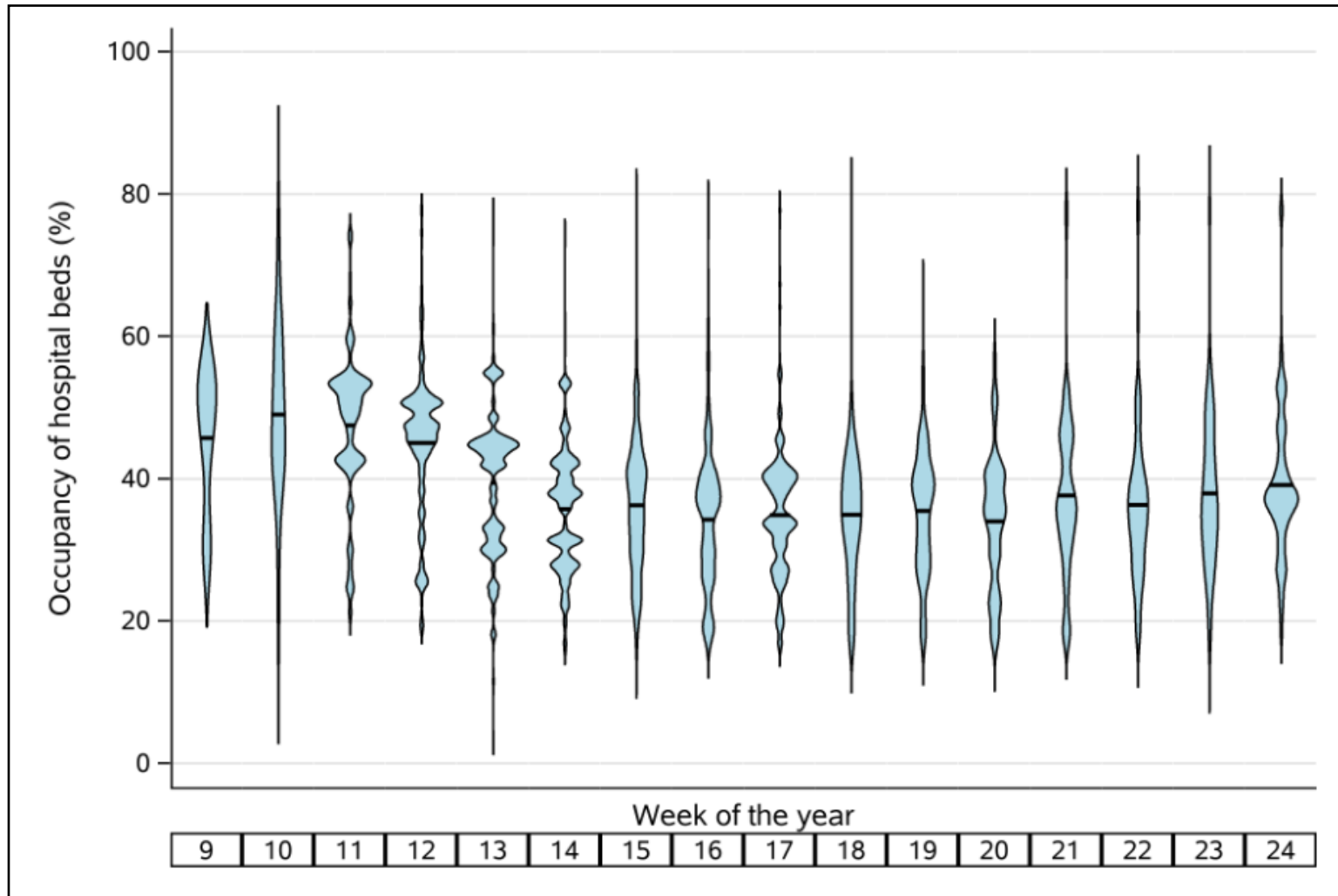
Supplementary Figure S6c. Overall distribution of occupancy of ICU beds

Mean (SD): 40.33 (20.67)

Median (IQR): 36.25 (25.89, 51.61)

Minimum: 0   Maximum: 102.38
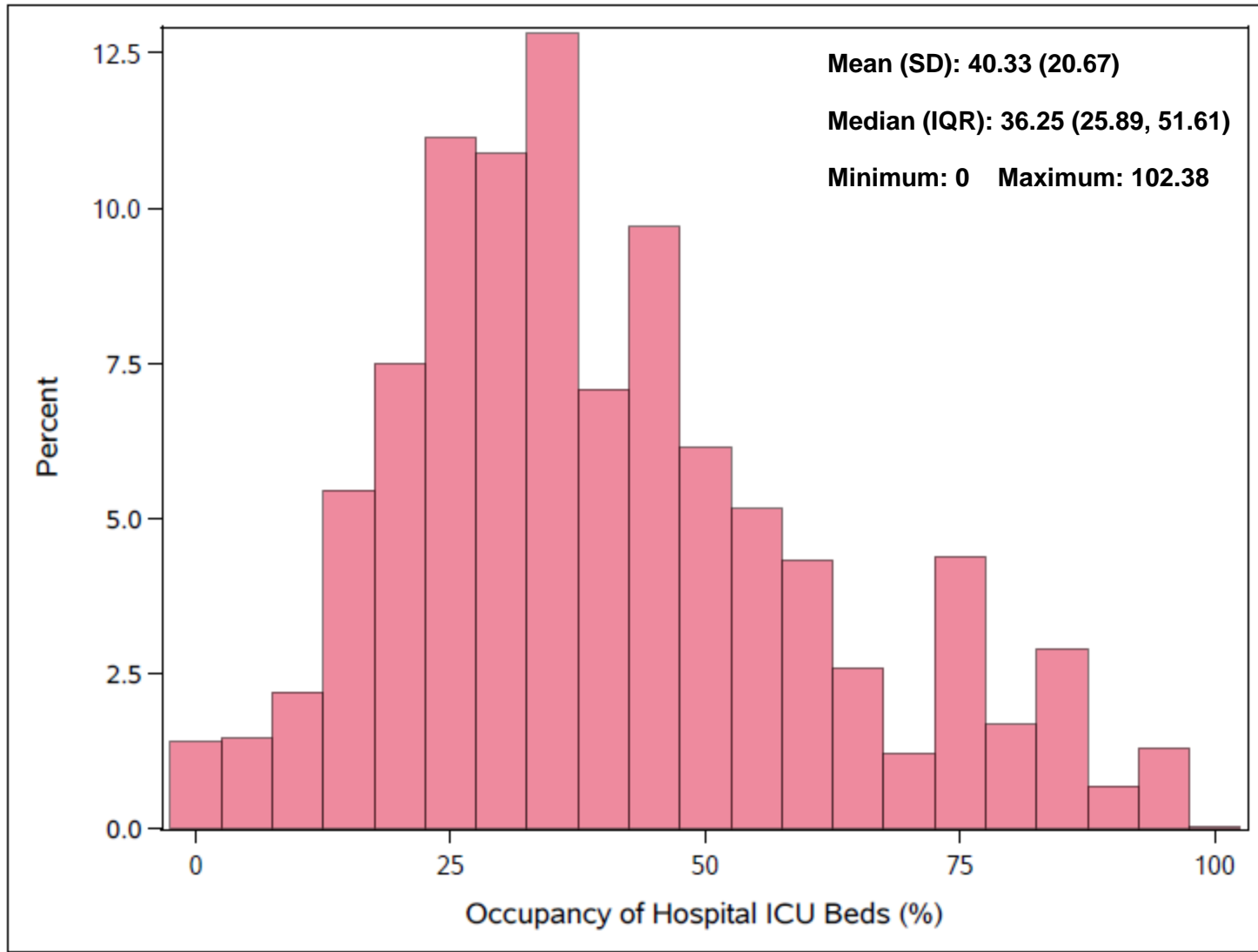
ICU=intensive care unit.

Supplementary Figure S6d. Distribution of occupancy of ICU beds by week of study period
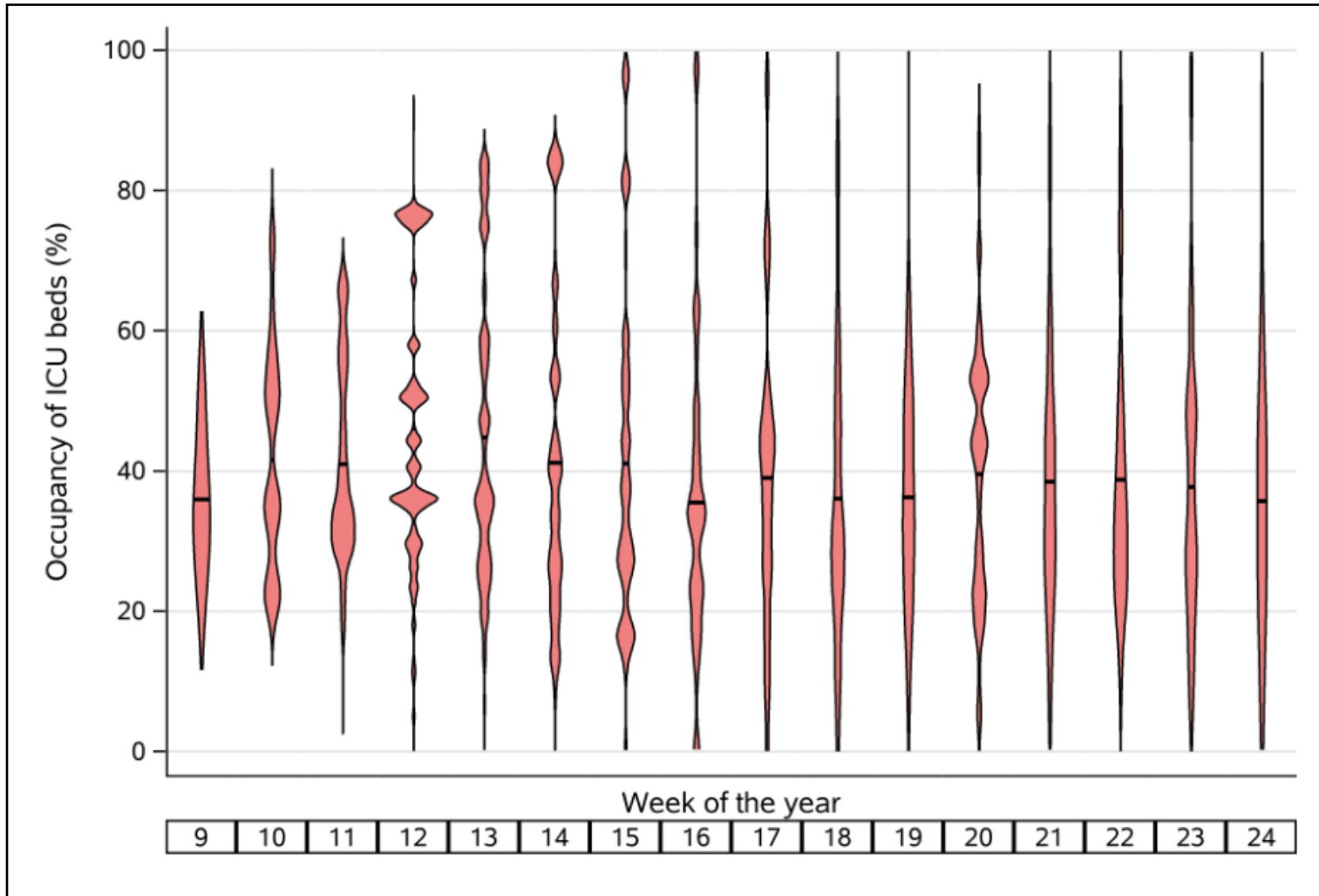
ICU=intensive care unit.

Supplementary Table S1. Covariate balance after application of the propensity score

	Standardized difference before adjustment	Standardized difference based on inverse probability weighting	Standardized difference based on overlap weighting	P-value after doubly robust adjustment*
Age	0.09	0.004	<0.001	0.98
Sex:				
Male	0.008	0.02	0.001	0.99
Female	0.008	0.02	0.001	0.99
Race:				
White	0.59	0.009	<0.001	0.51
Black	0.61	0.004	<0.001	0.51
Other	0.01	0.01	0.001	0.51
Smoke:				
Never	0.19	0.007	<0.001	0.39
Former	0.09	0.002	<0.001	0.39
Current	0.33	0.006	<0.001	0.39
BMI:				
Underweight (< 18.5 kg/m^2)	0.03	0.001	<0.001	0.81
Normal (18.5 to < 25 kg/m^2)	0.13	0.015	<0.001	0.81
Overweight (25 to < 30 kg/m^2)	0.03	0.009	<0.001	0.81
Obesity (≥ 30 kg/m^2)	0.15	0.02	<0.001	0.81
eGFR	0.009	0.02	<0.001	0.97
Chronic kidney disease	0.007	0.02	0.007	0.93
Cancer	0.09	0.03	<0.001	0.75
Cerebrovascular disease	0.03	0.006	0.002	0.85
Cardiovascular disease	0.18	0.01	0.001	0.59
Dementia	0.17	0.03	<0.001	0.55
Diabetes mellitus	0.09	0.03	0.001	0.83
Hypertension	0.008	0.02	0.001	0.91
Chronic lung disease	0.37	0.005	<0.001	0.50
Peripheral artery disease	0.03	0.002	<0.001	0.90
Statins	0.20	<0.001	<0.001	0.85
ACE/ARB	0.20	0.02	<0.001	0.93
NSAID	0.009	0.01	<0.001	0.94

Standardized difference <0.1 or P value >0.05 indicates covariate balance archived.

*P-value based on regression model where each characteristic was regressed by exposure group, conditional on other characteristics and the propensity score. A type III F test for continuous variable or Chi-square test for categorical variable P-value >0.05 indicated exposure group was not significantly associated with the baseline characteristics after the doubly robust adjustment.

Supplementary Table S2a. Rates of death in COVID-19 hospitalized patients overall, by age, by race, and by comorbid condition

	Overall, no. (95% CI)	Age, no. (95% CI)			Race, no. (95% CI)	
		≤65	65-75	>75	White	Black
Overall	20.05 (13.46 to 25.85)	9.27 (5.46 to 12.89)	19.36 (12.57 to 25.51)	27.79 (18.46 to 35.85)	17.71 (10.40 to 24.07)	28.12 (9.19 to 40.32)
Cancer	18.23 (11.27 to 24.34)	12.27 (4.08 to 19.63)	19.31 (10.83 to 26.83)	21.57 (12.02 to 29.91)	15.51 (7.58 to 22.42)	26.05 (9.64 to 37.43)
Chronic lung disease	18.67 (11.15 to 25.19)	10.88 (4.46 to 16.78)	17.39 (9.64 to 24.35)	24.38 (13.83 to 33.42)	16.87 (8.12 to 24.62)	25.88 (10.93 to 36.75)
Cardiovascular disease	19.24 (12.52 to 25.15)	12.30 (5.83 to 18.24)	20.03 (12.37 to 26.89)	24.28 (15.16 to 32.25)	16.79 (9.23 to 23.38)	26.88 (9.86 to 38.33)
Hypertension	19.43 (13.06 to 25.06)	10.64 (6.20 to 14.83)	18.93 (12.25 to 25.00)	25.91 (17.10 to 33.60)	17.11 (9.99 to 23.33)	27.19 (8.71 to 39.25)
Diabetes mellitus	20.05 (13.46 to 25.85)	13.27 (7.54 to 18.58)	22.30 (14.20 to 29.50)	28.51 (18.49 to 37.10)	22.77 (12.30 to 27.96)	30.90 (8.28 to 44.33)
Obesity	21.24 (14.52 to 27.10)	10.18 (6.01 to 14.11)	20.71 (13.58 to 27.10)	28.16 (18.91 to 36.13)	17.50 (10.75 to 23.42)	35.14 (8.91 to 48.92)
Cerebrovascular disease	21.96 (14.20 to 28.64)	9.08 (2.03 to 15.51)	20.41 (11.80 to 28.03)	31.26 (19.43 to 41.07)	19.64 (10.75 to 27.17)	28.51 (6.74 to 41.99)
Peripheral artery disease	22.22 (12.62 to 30.21)	7.33 (0.00 to 16.75)	25.75 (11.93 to 37.04)	27.27 (12.16 to 39.36)	21.58 (9.68 to 31.12)	26.07 (2.96 to 40.68)
Chronic kidney disease	24.92 (16.79 to 31.95)	15.51 (8.52 to 21.92)	25.94 (16.77 to 34.02)	35.54 (23.75 to 45.39)	21.62 (12.54 to 29.40)	35.25 (12.44 to 49.03)
Dementia	26.17 (15.86 to 34.61)	9.24 (0.00 to 18.06)	27.73 (14.73 to 38.38)	38.52 (23.86 to 49.88)	23.80 (13.52 to 32.26)	28.30 (3.32 to 44.96)

COVID-19=coronavirus disease 2019. CI=confidence interval.

Estimated number of deaths per 100 COVID-19 hospitalized patients for those with same demographic and comorbid condition pair. All estimations adjusted for age, sex, race, smoking status, body mass index, estimated glomerular filtration rate, chronic lung disease, cancer, cardiovascular disease, cerebrovascular disease, dementia, diabetes mellitus, hypertension, peripheral artery disease, use of statins, angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers, and nonsteroidal anti-inflammatory drugs as appropriated.

Supplementary Table S2b. Excess death in COVID-19 hospitalized patients compared to seasonal influenza hospitalized patients overall, by age, race, and comorbid condition

	Overall, no. (95% CI)	Age, no. (95% CI)			Race, no. (95% CI)	
		≤65	65-75	>75	White	Black
Overall	16.85 (14.85 to 18.99)	5.92 (3.48 to 8.21)	14.91 (9.74 to 19.49)	20.93 (14.01 to 26.69)	11.57 (6.89 to 15.50)	24.70 (7.73 to 35.02)
Cancer	10.99 (6.64 to 14.64)	4.19 (0.06 to 7.77)	13.38 (7.38 to 18.54)	12.80 (6.65 to 17.94)	7.25 (3.20 to 10.68)	20.27 (7.19 to 28.57)
Chronic lung disease	11.99 (6.96 to 16.18)	6.11 (1.99 to 9.81)	11.47 (6.08 to 16.17)	16.13 (8.79 to 22.14)	9.36 (4.27 to 13.76)	21.62 (9.08 to 30.21)
Cardiovascular disease	13.30 (8.68 to 17.22)	7.12 (3.11 to 10.71)	15.21 (9.45 to 20.24)	16.38 (10.14 to 21.63)	9.85 (5.45 to 13.57)	23.03 (8.23 to 32.39)
Hypertension	14.29 (9.67 to 18.23)	6.79 (3.97 to 9.40)	14.45 (9.41 to 18.92)	19.37 (12.85 to 24.86)	11.02 (6.50 to 14.84)	24.03 (7.38 to 34.34)
Diabetes mellitus	14.82 (10.03 to 18.89)	8.96 (5.25 to 12.32)	17.57 (11.30 to 22.98)	21.47 (14.05 to 27.58)	14.15 (8.53 to 18.71)	27.01 (6.84 to 38.12)
Obesity	17.32 (11.92 to 21.87)	8.04 (4.82 to 11.03)	17.35 (11.45 to 22.52)	22.81 (15.45 to 28.93)	13.11 (8.20 to 17.26)	32.09 (7.85 to 43.95)
Cerebrovascular disease	16.52 (10.79 to 21.25)	4.71 (0.75 to 8.24)	15.78 (9.27 to 21.37)	24.29 (15.25 to 31.46)	13.73 (7.54 to 18.75)	25.00 (5.71 to 36.13)
Peripheral artery disease	17.26 (9.90 to 23.12)	3.55 (0.00 to 8.80)	22.43 (10.81 to 31.61)	19.94 (8.53 to 28.57)	16.48 (7.42 to 23.38)	21.51 (2.19 to 32.63)
Chronic kidney disease	18.71 (12.72 to 26.70)	10.95 (6.15 to 15.27)	20.10 (13.13 to 26.06)	27.06 (18.23 to 34.08)	14.62 (8.54 to 19.62)	30.77 (10.60 to 42.05)
Dementia	19.87 (12.04 to 25.97)	6.04 (-0.14 to 11.94)	21.97 (11.81 to 29.91)	29.78 (18.58 to 37.89)	16.28 (9.36 to 21.66)	24.90 (2.67 to 38.94)

COVID-19=coronavirus disease 2019. CI=confidence interval.
Estimated excess death per 100 COVID-19 hospitalized patients compared to seasonal influenza patients for those with same demographic and comorbid condition pair. All estimations adjusted for age, sex, race, smoking status, body mass index, estimated glomerular filtration rate, chronic lung disease, cancer, cardiovascular disease, cerebrovascular disease, dementia, diabetes mellitus, hypertension, peripheral artery disease, use of statins, angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers, and nonsteroidal anti-inflammatory drugs as appropriated.

Supplementary Table S3. Sensitivity analyses

	Death, HR (95% CI)	Mechanical ventilator use, HR (95% CI)	ICU admission, HR (95% CI)
Compared to 2016-2017 seasonal influenza * (influenza n=2527)	4.27 (3.58 to 5.11)	3.29 (2.68 to 4.03)	2.29 (2.06 to 2.54)
Compared to 2017-2018 seasonal influenza † (influenza n=6219)	5.08 (4.43 to 5.83)	3.83 (3.28 to 4.46)	2.39 (2.20 to 2.59)
Compared to 2018-2019 seasonal influenza ‡ (influenza n=3360)	4.50 (3.77 to 5.37)	4.29 (3.50 to 5.25)	2.37 (2.15 to 2.61)
Compared to 2019-2020 seasonal influenza § (influenza n=570)	5.13 (3.36 to 7.83)	4.17 (2.66 to 6.52)	2.91 (2.33 to 3.64)
Compared to influenza type A (influenza n=9947)	5.03 (4.45 to 5.68)	3.89 (3.40 to 4.56)	2.38 (2.21 to 2.56)
Compared to influenza type B (influenza n=2484)	3.98 (3.33 to 4.76)	3.79 (3.07 to 4.68)	2.43 (2.18 to 2.71)
Compared to influenza type A in 2016-2017 influenza season* (influenza n=1898)	4.26 (3.50 to 5.19)	3.28 (2.61 to 4.13)	2.27 (2.02 to 2.56)
Compared to influenza type A in 2017-2018 influenza season† (influenza n=4493)	5.31 (4.55 to 6.19)	3.69 (3.11 to 4.38)	2.35 (2.15 to 2.57)
Compared to influenza type A in 2018-2019 influenza season‡ (influenza n=3165)	4.53 (3.78 to 5.44)	4.47 (3.62 to 5.53)	2.35 (2.13 to 2.60)
Compared to influenza type A in 2019-2020 influenza season§ (influenza n=390)	4.65 (2.79 to 7.72)	3.10 (1.92 to 5.00)	2.68 (2.07 to 3.47)
Compared to those who received influenza vaccine (influenza n=7021)	4.82 (4.22 to 5.51)	4.08 (3.50 to 4.74)	2.45 (2.25 to 2.65)
Compared to those who did not receive influenza vaccine (influenza n=5655)	4.82 (4.18 to 5.56)	3.72 (3.17 to 4.35)	2.36 (2.17 to 2.56)
Estimated risk within 30 days of hospitalization	5.96 (5.24 to 6.78)	4.16 (3.66 to 4.72)	2.42 (2.25 to 2.59)
Estimated risk when positive test date set as time zero	4.97 (4.44 to 5.58)	4.18 (3.67 to 4.76)	2.52 (2.34 to 2.71)
Hospital occupancy 0% to <20% (COVID-19 n=154)	4.99 (3.25 to 7.66)	2.92 (1.76 to 4.86)	1.78 (1.35 to 2.41)
Hospital occupancy 20% to <40% (COVID-19 n=1917)	4.36 (3.76 to 5.05)	3.76 (3.21 to 4.39)	2.39 (2.19 to 2.61)
Hospital occupancy 40% to <60% (COVID-19 n=1498)	6.15 (5.33 to 7.11)	4.68 (4.01 to 5.45)	2.57 (2.34 to 2.82)
Hospital occupancy 60 to 77.82% (COVID-19 n=75)	6.69 (3.62 to 12.35)	3.73 (1.94 to 7.18)	2.84 (1.99 to 4.06)
ICU occupancy 0% to <20% (COVID-19 n=484)	4.16 (3.21 to 5.38)	3.01 (2.26 to 4.01)	2.42 (2.08 to 2.82)
ICU occupancy 20% to <40% COVID-19 n=1509)	5.35 (4.59 to 6.23)	4.51 (3.85 to 5.28)	2.78 (2.54 to 3.04)
ICU occupancy 40% to <60% (COVID-19 n=971)	4.58 (3.77 to 5.55)	3.15 (2.56 to 3.89)	2.19 (1.94 to 2.47)
ICU occupancy 60 to <80% (COVID-19 n=384)	7.58 (5.79 to 9.93)	6.89 (5.43 to 8.75)	2.52 (2.13 to 2.98)
ICU occupancy 80% to 102.38% (COVID-19 n=201)	8.44 (6.13 to 11.63)	7.14 (5.30 to 9.62)	2.39 (1.88 to 3.02)
Time dependent analyses	4.83 (4.13 to 5.67)	4.22 (3.73 to 4.76)	2.45 (2.31 to 2.60)
Overlap weighting analyses	5.06 (4.49 to 5.70)	4.24 (3.70 to 4.85)	2.41 (2.24 to 2.58)
Inverse probability weighting analyses	4.63 (4.10 to 5.24)	3.74 (3.26 to 4.30)	2.35 (2.18 to 2.54)
Positive COVID-19/influenza test prior to and including the first day of hospitalization (n=14 253)	5.43 (4.79 to 6.15)	4.33 (3.78 to 4.97)	2.51 (2.33 to 2.70)
Positive COVID-19/influenza test before hospitalization (n=3396)	4.66 (3.62 to 6.02)	4.48 (3.39 to 5.90)	2.44 (2.10 to 2.84)
Male (n=15 432)	4.96 (4.42 to 5.57)	4.06 (3.57 to 4.61)	2.42 (2.26 to 2.60)
Female (n=885)	5.32 (2.36 to 11.99)	2.83 (1.48 to 5.42)	2.34 (1.73 to 3.18)
Never smoke (n=7673)	5.10 (4.33 to 6.00)	4.44 (3.70 to 5.33)	2.45 (2.22 to 2.71)
Former smoker (n=4420)	5.40 (4.44 to 6.58)	4.67 (3.71 to 5.89)	2.58 (2.27 to 2.92)
Current smoker (n=4224)	3.89 (2.84 to 5.32)	2.47 (1.82 to 3.37)	2.01 (1.70 to 2.37)
BMI 18.5 to < 25 kg/m^2 (n=4093)	3.52 (2.87 to 4.32)	2.55 (1.92 to 3.39)	1.85 (1.58 to 2.15)
BMI 25 to < 30 kg/m^2 (n=4872)	6.30 (5.08 to 7.81)	5.10 (3.96 to 6.56)	2.60 (2.28 to 2.97)
BMI $\geqslant$ 30 kg/m^2 (n=6802)	6.98 (5.64 to 8.63)	4.63 (3.87 to 5.55)	2.77 (2.50 to 3.07)

ICU=intensive care unit. HR=hazard ratio. CI=confidence interval. COVID-19=coronavirus disease 2019.
The seasonal influenza group served as the reference. All analyses adjusted for age, sex, race, smoking status, body mass index, estimated glomerular filtration rate, chronic lung disease, cancer, cardiovascular disease, cerebrovascular disease, dementia, diabetes mellitus, hypertension, peripheral artery disease, use of statins, angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers, and nonsteroidal anti-inflammatory drugs.
* Included seasonal influenza patients between January 01, 2017 and August 31, 2017 in the cohort
† Included seasonal influenza patients between September 01, 2017 and August 31, 2018 in the cohort
‡ Included seasonal influenza patients between September 01, 2018 and August 31, 2019 in the cohort
§ Included seasonal influenza patients between September 01, 2019 and December 31, 2019 in the cohort

Supplementary Table S4. Distribution of influenza subtypes during the study period

Influenza Subtype	H1N1	H3N2	Influenza Type A	Influenza Type B
Overall	265 (2.09%)	590 (4.65%)	9947 (78.47%)	2484 (19.60%)
2016-2017 influenza season * (n=2527)	12 (0.48%)	165 (6.53%)	1898 (75.17%)	555 (21.98%)
2017-2018 influenza season † (n=6219)	48 (0.77%)	307 (4.94%)	4493 (72.25%)	1610 (25.89%)
2018-2019 influenza season ‡ (n=3360)	175 (5.21%)	110 (3.28%)	3165 (94.25%)	146 (2.35%)
2019-2020 influenza season § (n=570)	30 (5.24%)	8 (1.40%)	390 (68.18%)	173 (30.24%)
* Included seasonal influenza patients between January 01, 2017 and August 31, 2017 in the cohort				
† Included seasonal influenza patients between September 01, 2017 and August 31, 2018 in the cohort				
‡ Included seasonal influenza patients between September 01, 2018 and August 31, 2019 in the cohort				
§ Included seasonal influenza patients between September 01, 2019 and December 31, 2019 in the cohort				