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ORIGINAL ARTICLE

Association of testosterone therapy with disease progression in older males with COVID-19

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Abstract

Importance: Low testosterone levels in males have been linked with increase in proinflammatory cytokines—a primary culprit in COVID-19 disease progression—and with adverse COVID-19 outcomes. To date, however, no published studies have assessed the effect of testosterone therapy on COVID-19 outcomes in older men.

Objective: To examine whether testosterone therapy reduced disease progression in older men diagnosed with COVID-19.

Design, setting, and participants: Nested within a national cohort of older (aged ≥50 years) male patients diagnosed with COVID-19 between January 1, 2020 and July 1, 2021 from the Optum electronic health record COVID-19 database, two matched case–control studies of COVID-19 outcomes were conducted. Cases—defined, respectively, as persons who (a) were hospitalized ≤30 days after COVID-19 diagnosis (n = 33,380), and (b) were admitted to the intensive care unit or received mechanical ventilation during their COVID-19 hospitalization (n = 10,273)—were matched 1:1 with controls based on demographic and clinical factors.

Exposures: Testosterone therapy was defined based on receipt of prescription at ≤60, ≤90, or ≤120 days before COVID-19 diagnosis.

Main outcomes and measures: Adjusted odds ratios (ORs) for the risk of hospitalization within 30 days of COVID-19 diagnosis and intensive care unit admission/mechanical ventilation during COVID-19 hospitalization.

Results: The use of testosterone therapy was not associated with decreased odds of hospitalization (≤60 days: OR = 0.92, 95% confidence interval [CI] = 0.70–1.20; ≤90 days: OR = 0.87, 95% CI = 0.68–1.13; ≤120 days: OR = 0.97, 95% CI = 0.72–1.32) or intensive care unit admission/mechanical ventilation (≤60 days: OR = 0.67, 95% CI = 0.37–1.23; ≤90 days: OR = 0.63, 95% CI = 0.36–0.11; ≤120 days: OR = 0.58, 95% CI = 0.29–1.19).

Conclusions and relevance: This study showed that testosterone therapy was not associated with decreased risks of COVID-19 adverse outcomes. These findings may provide clinically relevant information regarding testosterone treatment in older men with COVID-19 and other respiratory viral infections with similar pathogenesis.

KEYWORDS
COVID-19, testosterone therapy

1 | INTRODUCTION

Recent studies of men hospitalized for COVID-19 have shown that low serum testosterone concentrations are predictive of adverse hospital outcomes, including intensive care unit (ICU) admission, use of mechanical ventilators, and mortality.[1–5] These findings are thought to be mediated, at least in part, by increased inflammation associated with hypogonadism. Serum testosterone is reported to have anti-inflammatory functions via suppression of both the cellular and humoral immune systems[6]; and testosterone deficiency has been linked with an increase in inflammatory markers, such as C-reactive protein, tumor necrosis factor-α, and interleukin-6[7–10] and with autoimmune disease, including rheumatoid arthritis and lupus.[11–15] Low testosterone levels may also contribute to poor health outcomes via increased adiposity, reduced muscle mass, metabolic syndrome, and chronic illnesses, such as diabetes and renal insufficiency.[16–18]

Testosterone may play an important role in respiratory health. It is biologically plausible that testosterone deficiency exacerbates respiratory symptoms, either directly—via an anti-catabolic effect on respiratory muscle—or indirectly—by decreasing overall strength and exercise capacity.[19–21] Several studies have shown that low levels of circulating testosterone are associated with adverse respiratory outcomes, including reduced forced expiratory volume in 1 s and forced vitality capacity.[22–26] Likewise, a recent study showed that hypogonadism was common in mechanically ventilated patients with acute respiratory failure and was strongly associated with longer ICU stays.[27] Testosterone therapy in men with COPD has been linked with improved outcomes including skeletal muscle strength and exercise capacity[28–31] and reduced COPD exacerbations and hospitalization.[32] In view of these findings, understanding the potential therapeutic role of testosterone therapy in older men with COVID-19 holds broad clinical importance.

To our knowledge, there have been no published studies that have examined the impact of testosterone therapy on COVID-19 outcomes. We therefore conducted a matched case–control study using a nationally representative electronic health record (EHR) database to assess whether testosterone therapy reduced disease progression in older male patients diagnosed with COVID-19.

2 | METHODS

2.1 | Data source

This nested case–control study—based on Optum's de-identified longitudinal COVID-19 EHR database—included 6,421,125 patients from 38 hospital networks and 18 non-network hospitals in the US. The database incorporates clinical and medical administrative data from both inpatient and ambulatory EHRs, including diagnostic information specific to COVID-19. This study was approved by the Institutional Review Board at the University of Texas Medical Branch at Galveston.

2.2 | COVID-19 study cohort

The study cohort was restricted to male patients aged ≥50 years or above who were diagnosed with COVID-19 (by positive laboratory test [Table A4] or diagnosis [ICD-CM-10 = U07.1] between January 1, 2020 and July 1, 2021; and who received care in the above-described healthcare delivery network in the 12 months prior to COVID-19 diagnosis.

2.3 | Outcomes

Two nested case–control studies of COVID-19 outcomes were conducted. Cases—defined, respectively, as persons who (a) were hospitalized within 30 days of COVID-19 diagnosis (n = 33,380), and (b) were admitted to the ICU or received mechanical ventilation during their COVID-19 hospitalization (n = 10,273)—were matched 1:1 with controls (from the underlying COVID-19 cohort) based on sex, age (50–59, 60–69, 70–79, ≥80 years), race (white, non-white), hypogonadism, COPD, obesity, atherosclerotic cardiovascular disease, angina, diabetes, hypertension, and hyperlipidemia.

2.4 | Exposure to testosterone therapy

Patients who received at least one prescription for testosterone therapy ≤60, ≤90, and ≤120 days prior to their COVID-19 diagnosis date were defined as exposed.

2.5 | Covariates

For each case–control study, multivariable analyses were used to adjust for the following unmatched variables: Elixhauser comorbidity index score (with the seven matched conditions removed)[33] (0, 1, 2, ≥3), ethnicity (non-Hispanic, Hispanic), and region (midwest, northeast, south, west). For case–control study 2, remdesivir and dexamethasone were added to the models.

2.6 | Statistical analysis

Patient demographic and clinical characteristics for the overall COVID-19 cohort and each matched case–control study were summarized using percentages. To compare the baseline covariates

between groups, standardized differences were calculated. Next, for each nested matched case–control study, multivariable conditional logistic regression analysis—adjusting for each of the aforementioned unbalanced covariates—was used to calculate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the three outcomes.

3 | RESULTS

Table 1 presents the characteristics of cases versus controls in sample 1 (hospitalized) and sample 2 (mechanical ventilation/ICU). The standardized differences were minimal on each of the aforementioned matched categories but were substantial for the unmatched variables with especially large differences for region and Elixhauser comorbidity category. The demographic and clinical characteristics of the overall COVID-19 study cohort versus each of the case study samples are presented in Table A1.

Table 2 presents the results for each of the two case–control studies based on multivariable conditional logistic regression models. In study 1, the use of testosterone therapy at ≤60 days: OR = 0.92, 95% CI = 0.70, 1.20; ≤90 days: OR = 0.87, 95% CI = 0.68, 1.13; and ≤120 days: OR = 0.97, 95% CI = 0.72, 1.32 were not associated with a decreased risk of hospitalization. In study 2, the use of testosterone therapy at ≤60 days: OR = 0.67, 95% CI = 0.37, 1.23; ≤90 days: OR = 0.63, 95% CI = 0.36, 1.11; and ≤120 days: OR = 0.58, 95% CI = 0.29, 1.19 were not associated with a decreased risk in ICU admission/mechanical ventilation.

To assess the robustness of our findings, we conducted sensitivity analyses. Logistic regression models in which patients who were in hospital networks with <100 and <50 COVID-19 patients (along with their matched pairs) removed (Tables A1–A4) were conducted. In these analyses, hospital system was included as a fixed effect covariate. We also adjusted for receipt of statins. In each of the above sensitivity analyses, the direction and magnitude of the ORs for testosterone therapy were consistent with the overall study findings.

4 | DISCUSSION

In this national matched nested case–control study of older male patients diagnosed with COVID-19, we found that the use of testosterone therapy was not protective against adverse COVID-19 outcomes. Our methodologic approach accounted for multiple potentially confounding factors—including sex, age, race, ethnicity, region, and hypogonadism—as well as underlying medical conditions and medications. Our primary findings persisted across sensitivity analyses, adjusting for the use of statins and restricting to a cohort of patients treated in health systems with a high volume of COVID-19 patients.

To our knowledge, this is the first study to examine the effect of testosterone therapy on COVID-19 outcomes in older men. Previous investigations have reported possible mechanistic pathways whereby testosterone may improve outcomes in older men diagnosed with COVID-19 or other viral respiratory infections. Among men infected with SARS-CoV-2, younger age is strongly protective against adverse outcomes.[34,35] Research indicates that circulating testosterone, which declines with age, has a protective anti-inflammatory effect, decreasing proinflammatory cytokines and the cytokine storm.[7,8,10,36] Likewise, hypogonadism is associated with increased overall morbidity and mortality—particularly diabetes, metabolic syndrome, and cardiovascular disease—via increased adiposity and reduced muscle mass.[16–18] Testosterone deficiency has been hypothesized to have an adverse effect on respiratory symptoms via an anti-catabolic effect on respiratory muscle or by decreasing overall strength and exercise capacity.[19–21]

Although no published studies have reported the effect of testosterone therapy on COVID-19 outcomes, several recent studies of men hospitalized with COVID-19 have shown that low serum testosterone concentrations were predictive of inflammatory markers and adverse disease outcomes.[1–5] In a study of 86 men hospitalized with COVID-19, Dhindsa et al.[3] reported that low serum testosterone levels were associated with increased proinflammatory cytokines, disease severity markers—including hypoxia requiring supplemental oxygen, ICU admission, need for mechanical ventilation—and COVID-19 mortality. Likewise, in a study of 31 male patients with COVID-19, Rastrelli et al.[1] reported that low baseline serum testosterone was associated with inflammation, ICU admission, and mortality. In a study of 221 male patients with COVID-19, Çayan et al.[2] reported that testosterone levels were associated with increased risk of ICU admission and mortality. In a subcohort of 24 patients who had pre-COVID-19 gonadal tests, the investigators observed that low mean serum total testosterone decreased from 458 to 315 ng/dl ($p = 0.003$) following COVID-19 diagnosis. In a study of 221 men hospitalized with COVID-19, Vena et al.[4] reported that low serum testosterone at baseline was associated with acute respiratory insufficiency, need for oxygen support, and in-hospital mortality. Finally, in a study of 286 men hospitalized with COVID-19, Salonia et al.[5] reported that baseline serum testosterone levels were associated with ICU admission and death. For the majority of the above analyses, however,[1–5] serum testosterone levels were not measured before COVID-19 diagnoses, thereby limiting the ability to determine whether low testosterone was a marker versus a mediator of COVID-19 disease progression and mortality. It will be important for future studies to examine, in sufficiently large patient cohorts, whether testosterone levels measured prior to contracting COVID-19 are associated with COVID-19 disease outcomes.

The results of our study may have been influenced by several limitations. First, because medication use was defined by written prescriptions identified in the patient's EHR prior to COVID-19 diagnosis, we have no information on over-the-counter medications with potential effects on the study outcomes. Moreover, our data provide information on the date the medication was prescribed but not on the date it was filled, purchased, or picked up by the patient. It is possible, therefore, that some of the drug exposure periods used in this study underestimated the true medication exposure period.

TABLE 1 Characteristics of cases versus controls in sample 1 (all hospitalized) and sample 2 (mechanical ventilation/intensive care unit [ICU])

		Hospitalization status			Ventilation or ICU status		
Parameter	Level	Cases, *N* (%)	Controls, *N* (%)	Standardized difference	Cases, *N* (%)	Controls, *N* (%)	Standardized difference
Ethnicity	Non-Hispanic	27,873 (83.5)	27,978 (83.8)	0.1001	8381 (81.6)	8617 (83.9)	0.0788
	Hispanic	3160 (9.5)	2424 (7.3)		1067 (10.4)	980 (9.5)	
	Unknown	2347 (7.0)	2978 (8.9)		825 (8.0)	676 (6.6)	
Region	Midwest	14,847 (44.5)	16,062 (48.1)	0.165	4842 (47.1)	4432 (43.1)	0.1605
	Northeast	8408 (25.2)	9471 (28.4)		2213 (21.5)	2841 (27.7)	
	Other/unknown	890 (2.7)	935 (2.8)		251 (2.4)	270 (2.6)	
	South	7152 (21.4)	5271 (15.8)		2315 (22.5)	2110 (20.5)	
	West	2083 (6.2)	1641 (4.9)		652 (6.3)	620 (6.0)	
Elixhauser category	0	6410 (19.2)	11,718 (35.1)	0.4264	1514 (14.7)	2004 (19.5)	0.2475
	1	5830 (17.5)	6635 (19.9)		1431 (13.9)	1965 (19.1)	
	2	5075 (15.2)	4455 (13.3)		1464 (14.3)	1653 (16.1)	
	3+	16,065 (48.1)	10,572 (31.7)		5864 (57.1)	4651 (45.3)	
Age		68.8 (10.9)	68.5 (10.9)	0.0281	68.6 (10.4)	68.6 (10.6)	−0.0019
Race	African American	4755 (14.2)	4711 (14.1)	0.0693	1430 (13.9)	1582 (15.4)	0.0386
	Asian	856 (2.6)	639 (1.9)		290 (2.8)	257 (2.5)	
	Caucasian	23,850 (71.4)	23,850 (71.4)		7213 (70.2)	7213 (70.2)	
	Other/unknown	3919 (11.7)	4180 (12.5)		1340 (13.0)	1221 (11.9)	
Angina		8501 (25.5)	8501 (25.5)	0	2812 (27.4)	2812 (27.4)	0
Diabetes		9473 (28.4)	9473 (28.4)	0	3196 (31.1)	3196 (31.1)	0
Obesity		9387 (28.1)	9387 (28.1)	0	2948 (28.7)	2948 (28.7)	0
aCVD		1066 (3.2)	1066 (3.2)	0	285 (2.8%)	285 (2.8)	0
Hypertension		13,481 (40.4)	13,481 (40.4)	0	4562 (44.4%)	4562 (44.4)	0
Hyperlipidemia		18,513 (55.5)	18,513 (55.5)	0	5816 (56.6%)	5816 (56.6)	0
COPD		23,655 (70.9)	23,655 (70.9)	0	7556 (73.6%)	7556 (73.6)	0

Note: Each case–control study was matched on sex, race, age group, and each of the following medical conditions: COPD (ICD-10-CM = I27.8x, I27.9, J41.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3), obesity (ICD-10-CM = E66.x), atherosclerotic cardiovascular disease (aCVD) (ICD-10-CM = I25.10), angina (ICD-10-CM = I20.x), diabetes (ICD-10-CM = E11.x-E13.x), hypertension (ICD-10-CM = I10.x-I15.x), and hyperlipidemia (ICD-10-CM = E78.x, E88.1). Comparison was made between each sample versus the overall cohort.

TABLE 2 Unadjusted and adjusted odds ratios (ORs) for hospitalization and intensive care unit (ICU) admission/mechanical ventilation

Characteristic	Case, *N* (%)	Control,[a] *N* (%)	Unadjusted OR (95% CI)	Adjusted[b] OR (95% CI)
Case–control study predicting hospitalization				
Testosterone ≤60 days	146 (0.4%)	152 (0.5%)	0.95 (0.74, 1.22)	0.92 (0.70, 1.20)
Testosterone ≤90 days	168 (0.5%)	186 (0.6%)	0.88 (0.69, 1.11)	0.87 (0.68, 1.13)
Testosterone ≤120 days	114 (0.3%)	115 (0.3%)	0.99 (0.74, 1.32)	0.97 (0.72, 1.32)
Case–control study predicting ICU admission/mechanical ventilation				
Testosterone ≤60 days	29 (0.3%)	36 (0.4%)	0.74 (0.42, 1.32)	0.67 (0.37, 1.23)
Testosterone ≤90 days	32 (0.3%)	41 (0.4%)	0.72 (0.42, 1.23)	0.63 (0.36, 1.11)
Testosterone ≤120 days	19 (0.2%)	28 (0.3%)	0.59 (0.30, 1.17)	0.58 (0.29, 1.19)

Note: Cases were defined as patients who were admitted to the ICU (had one encounter during the hospitalization that was coded as "critical care unit [CCU]/ICU") or received mechanical ventilation (ICD-10-PCS: 5A09357, 5A09358, 5A09359, 5A0935A, 5A0935B, 5A0935Z, 5A09457, 5A09458, 5A09459, 5A0945A, 5A0945B, 5A0945Z, 5A09557, 5A09558, 5A09559, 5A0955A, 5A0955B, 5A0955Z, 5A19054, 5A1935Z, 5A1945Z, 5A1955Z; CPT: 94002, 94003, 94004).

Abbreviation: CI, confidence interval.

[a]Each case–control study was matched on sex, race, age group, and each of the following medical conditions: COPD (ICD-10-CM = I27.8x, I27.9, J41.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3), obesity (ICD-10-CM = E66.x), atherosclerotic cardiovascular disease (ICD-10-CM = I25.10), angina (ICD-10-CM = I20.x), diabetes (ICD-10-CM = E11.x-E13.x), hypertension (ICD-10-CM = I10.x-I15.x), and hyperlipidemia (ICD-10-CM = E78.x, E88.1).

[b]Multivariable analyses were adjusted for all unmatched variables including: ethnicity, region, and Elixhauser score. Second case–control studies were also adjusted for dexamethasone and remdesivir.

Second, we did not have consistent access to serum testosterone levels either before or during the COVID-19 diagnosis. Such information would have allowed us to better assess the extent to which underlying hypogonadism was effectively treated or normalized via testosterone therapy. Moreover, in view of recent reports[1–5] that low testosterone is a predictor or marker of disease progression and death in men diagnosed with COVID-19, it is possible that undertreated hypogonadism among testosterone users masked or attenuated a protective effect of testosterone therapy. Third, because our data source did not have consistent and reliable data on dose and duration of testosterone therapy, we were not able to examine a possible dose–response association between testosterone therapy and COVID-19 outcomes. Fourth, because the primary reason for hospitalization was not reliably or consistently captured in the Optum EHR data source, we were unable to exclude persons who were hospitalized for reasons other than COVID-19. Our restriction to hospitalizations that occurred ≤30 days following COVID-19 diagnosis, however, should have minimized misclassification. Fifth, our reliance on EHR data precluded assessment of a number of potential confounding factors, such as diet, alcohol, and other health behaviors. Sixth, because our EHR data source did not completely capture deaths that occurred following hospital discharge, we did not have sufficient statistical power to examine mortality as an outcome in this study. Finally, it is possible that testosterone exerted a modest protective effect but that our sample size was not sufficient to identify statistically significant findings. Despite these limitations, this study has a number of strengths including a national sample, matching based on sociodemographic and clinical factors, simultaneous adjustment for potentially confounding medical conditions and medications, and assessment of multiple exposure windows.

5 | CONCLUSION

Our study suggests that testosterone therapy was not associated with decreased risks of severe COVID-19 outcomes. These findings may provide clinically relevant information regarding testosterone treatment for older men with COVID-19 and other respiratory viral infections with similar pathogenesis.

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CONFLICT OF INTEREST

There are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Jacques Baillargeon had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: Jacques Baillargeon, Yong-Fang Kuo, Jordan Westra, David S. Lopez, and Mukaila A. Raji. *Analysis and interpretation of data*: Jacques Baillargeon, Yong-Fang Kuo, Jordan Westra, and Mukaila A. Raji. *Drafting of the manuscript and critical revision of the manuscript for important intellectual content*: Jacques Baillargeon, Yong-Fang Kuo, Jordan Westra, David S. Lopez, Randall J. Urban, Stephen B.

Williams, and Mukaila A. Raji. *Statistical analysis*: Jacques Baillargeon, Yong-Fang Kuo, and Jordan Westra. *Obtaining funding*: Jacques Baillargeon, Yong-Fang Kuo, and Mukaila A. Raji. *Administrative, technical, or material support and study supervision*: Jacques Baillargeon and Yong-Fang Kuo.

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APPENDIX A

TABLE A1 Characteristics of overall COVID-19 cohort—sample 1 (all hospitalized) and sample 2 (mechanical ventilation/intensive care unit [ICU])

Characteristic	Overall COVID-19 cohort ($n = 189,188$)	Sample 1[a]: all hospitalized ($n = 33,380$)		Sample 2[a]: mechanical ventilation/ICU ($n = 10,273$)	
	N (%)	*N* (%)	Standardized difference[b]	*N* (%)	Standardized difference[b]
Age (mean, SD)	64.7 (10.5)	69.2 (11.2)	0.4766	68.9 (10.5)	0.3960
Race			0.1444		0.1245
Black	20,698 (10.9%)	4755 (14.3%)		1430 (13.9%)	
White	141,637 (74.9%)	23,850 (71.5%)		7213 (70.2%)	
Asian	3579 (1.9%)	856 (2.6%)		290 (2.8%)	
Other	23,274 (12.3%)	3919 (11.7%)		1340 (13.0%)	
Ethnicity			0.1530		0.1420
Hispanic	13,579 (7.2%)	3160 (9.5%)		1067 (10.4%)	
Non-Hispanic	155,807 (82.4%)	27,873 (83.5%)		8381 (81.6%)	
Unknown	19,802 (10.5%)	2347 (7.0%)		825 (8.0%)	
Region			0.1378		0.1888
Midwest	91,716 (48.5%)	14,847 (44.5%)		4842 (47.1%)	
Northeast	47,717 (25.2%)	8408 (25.2%)		2213 (21.5%)	
South	31,738 (16.8%)	7152 (21.4%)		2315 (22.5%)	
West	12,550 (6.6%)	2083 (6.2%)		652 (6.4%)	
Unknown	5467 (2.9%)	890 (2.7%)		251 (2.4%)	
Comorbidities					
Angina	4825 (2.6%)	1066 (3.2%)	0.0473	285 (2.8%)	0.0147
CVD	33,089 (17.5%)	9387 (28.1%)	0.3173	2948 (28.7%)	0.2854
COPD	31,455 (16.6%)	8501 (25.5%)	0.2703	2812 (27.4%)	0.2784
Diabetes	50,445 (26.7%)	13,481 (40.4%)	0.3629	4562 (44.4%)	0.4011
Hyperlipidemia	87,791 (46.4%)	18,513 (55.5%)	0.2213	5816 (56.6%)	0.2173
Hypertension	100,422 (53.1%)	23,655 (70.9%)	0.4521	7556 (73.6%)	0.4593
Obesity	37,270 (19.7%)	9473 (28.4%)	0.2520	3196 (31.1%)	0.2811
Elixhauser index			0.8553		0.9037
0	86,959 (46.0%)	6410 (19.2%)		1514 (14.7%)	
1	36,311 (19.2%)	5830 (17.5%)		1431 (13.9%)	
2	21,391 (11.3%)	5075 (15.2%)		1464 (14.3%)	
≥3	44,527 (23.5%)	16,065 (48.1%)		5864 (57.1%)	

[a]Each case–control study was matched on sex, race, age group, and each of the following medical conditions: COPD (ICD-10-CM = I27.8x, I27.9, J41.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3), obesity (ICD-10-CM = E66.x), atherosclerotic cardiovascular disease (CVD) (ICD-10-CM = I25.10), angina (ICD-10-CM = I20.x), diabetes (ICD-10-CM = E11.x-E13.x), hypertension (ICD-10-CM = I10.x-I15.x), and hyperlipidemia (ICD-10-CM = E78.x, E88.1).
[b]Comparison was made between each sample versus the overall cohort.

TABLE A2 Sensitivity analyses: adjusted odds ratios (ORs) for hospitalization and intensive care unit (ICU) admission/mechanical ventilation

Characteristic	Hospitalization, OR (95% CI)	ICU admission/mechanical ventilation, OR (95% CI)
Adjusted for statins		
Testosterone ≤90 days	0.98 (0.75, 1.28)	0.69 (0.38, 1.27)
Testosterone ≤120 days	0.94 (0.73, 1.21)	0.64 (0.37, 1.12)
Restricted to large hospital networks		
Testosterone ≤90 days	0.92 (0.70, 1.20)	0.67 (0.37, 1.23)
Testosterone ≤120 days	0.87 (0.68, 1.13)	0.88 (0.40, 1.94)

Note: Each case–control study was matched on sex, race, age group, and each of the following medical conditions: COPD (ICD-10-CM = I27.8x, I27.9, J41.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3), obesity (ICD-10-CM = E66.x), atherosclerotic cardiovascular disease (ICD-10-CM = I25.10), angina (ICD-10-CM = I20.x), diabetes (ICD-10-CM = E11.x-E13.x), hypertension (ICD-10-CM = I10.x-I15.x), and hyperlipidemia (ICD-10-CM = E78.x, E88.1). Multivariable analyses were adjusted for all unmatched variables including: ethnicity, region, and Elixhauser score. Second case–control studies were also adjusted for dexamethasone and remdesivir. Cases were defined as patients who were admitted to the ICU (had one encounter during the hospitalization that was coded as "critical care unit [CCU]/ICU") or received mechanical ventilation (ICD-10-PCS: 5A09357, 5A09358, 5A09359, 5A0935A, 5A0935B, 5A0935Z, 5A09457, 5A09458, 5A09459, 5A0945A, 5A0945B, 5A0945Z, 5A09557, 5A09558, 5A09559, 5A0955A, 5A0955B, 5A0955Z, 5A19054, 5A1935Z, 5A1945Z, 5A1955Z; CPT: 94002, 94003, 94004).
Abbreviation: CI, confidence interval.

TABLE A3 Cohort flow chart

	Hospitalization		ICU admission/mechanical ventilation	
Step	Description	*N*	Description	*N*
1	All patients in data	6,421,125	All patients in data	6,421,125
2	Patients in an integrated delivery network	5,704,773	Patients in an Integrated Delivery Network	5,704,773
3	Patients with complete demographic data	5,694,848	Patients with complete demographic data	5,694,848
4	Male patients	2,481,999	Male patients	2,481,999
5	Patients with a COVID-19 positive lab test or diagnosis	358,000	Patients hospitalized within 30 days of diagnosis	42,561
6	Patients aged ≥50 years at COVID-19 diagnosis date	171,683	Patients aged ≥50 years at COVID-19 diagnosis date	33,380
6a	Patients hospitalized within 30 days of diagnosis	33,805	Patients with ventilation use or ICU stay in hospital	10,549
6b	Patients not hospitalized	137,878	Patients with no ventilation/ICU	22,831
7	Patients matched	66,760	Patients matched	20,546
7a	Cases	33,380	Cases	10,273
7b	Controls	33,380	Controls	10,273

Abbreviation: ICU, intensive care unit.

TABLE A4 LOINC codes for positive COVID-19 laboratory test

94306-8	SARS CoV-2 RNA panel, unspecified specimen
94307-6	SARS-CoV-2 N gene, unspecified specimen
94308-4	SARS-CoV-2 N gene, unspecified specimen
94309-2	SARS-CoV-2 RNA, unspecified specimen
94311-8	SARS-CoV-2 N gene, unspecified specimen
94312-6	SARS-CoV-2 N gene, unspecified specimen
94314-2	SARS-CoV-2 RdRp gene, unspecified specimen
94316-7	SARS-CoV-2 N gene, unspecified specimen
94500-6	SARS-CoV-2 RNA, respiratory specimen
94510-5	SARS-CoV-2 N gene, unspecified specimen
94511-3	SARS-CoV-2 ORF1ab region, unspecified specimen
94531-1	SARS CoV-2 RNA panel, respiratory specimen
94533-7	SARS-CoV-2 N gene, respiratory specimen
94534-5	SARS-CoV-2 RdRp gene, respiratory specimen
94558-4	SARS-CoV-2 Ag, respiratory specimen
94559-2	SARS-CoV-2 ORF1ab region, respiratory specimen
94565-9	SARS-CoV-2 RNA, nasopharyngeal specimen
94639-2	SARS-CoV-2 ORF1ab region, unspecified specimen
94640-0	SARS-CoV-2 S gene, respiratory specimen
94641-8	SARS-CoV-2 S gene, unspecified specimen
94642-6	SARS-CoV-2 S gene, respiratory specimen
94643-4	SARS-CoV-2 S gene, unspecified specimen
94644-2	SARS-CoV-2 ORF1ab region, respiratory specimen
94645-9	SARS-CoV-2 RdRp gene, unspecified specimen
94646-7	SARS-CoV-2 RdRp gene, respiratory specimen
94660-8	SARS-CoV-2 RNA, serum/plasma
94745-7	SARS-CoV-2 RNA, respiratory specimen
94746-5	SARS-CoV-2 RNA, unspecified specimen
94756-4	SARS-CoV-2 N gene, respiratory specimen
94757-2	SARS-CoV-2 N gene, respiratory specimen
94759-8	SARS-CoV-2 N overall result, nasopharyngeal specimen
94760-6	SARS-CoV-2 N gene result, nasopharyngeal specimen
94763-0	SARS-CoV-2, unspecified specimen
94764-8	SARS-CoV-2 whole genome
94766-3	SARS-CoV-2 N gene, serum, or plasma
94767-1	SARS-CoV-2 S gene, serum, or plasma
94819-0	SARS-CoV-2 N gene, unspecified specimen
94822-4	SARS-CoV-2 RNA, saliva
94845-5	SARS-CoV-2 RNA, saliva
95125-1	SARS-CoV-2 RNA, serum, or plasma
95406-5	SARS-CoV-2 RNA, nose
95409-9	SARS-CoV-2 N gene, nose
95410-7	SARS-CoV-2 neutralizing antibody, serum
95411-5	SARS-CoV-2 neutralizing antibody, serum
95424-8	SARS-CoV-2 RNA, respiratory specimen
95425-5	SARS-CoV-2 N gene, saliva
95521-1	SARS-CoV-2 N gene, respiratory specimen
95522-9	SARS-CoV-2 N gene, respiratory specimen

(Continues)