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Outcome Disparities Among Men and Women With COVID-19: An Analysis of the New York City Population Cohort

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ABSTRACT

Background: Growing evidence suggests a possible sex disparity in COVID-19 disease related outcomes.
Objective: To explore the sex disparity in COVID-19 cases and outcomes using New York City (NYC) population level data.
Setting: NYC surveillance data from February 29 to June 12, 2020.
Participants: Individuals tested for COVID-19 in metropolitan NYC.
Outcome Measurements and Statistical Analysis: Outcomes of interest included rates of COVID-19 case positivity, hospitalization and death. Relative risks and case fatality rates were computed for all outcomes based on sex and were stratified by age groups.
Results and Limitations: 911,310 individuals were included, of whom 434,273 (47.65%) were male and 477,037 (52.35%) were female. Men represented the majority of positive cases (n=106,275, 51.36%), a majority of hospitalizations (n=29,847, 56.44%), and a majority of deaths (n=13,054, 59.23%). Following population level adjustments for age and sex, testing rates of men and women were equivalent. The majority of positive cases and hospitalizations occurred in men for all age groups except age >75 years, and death was more likely in men of all age groups. Men were at a statistically significant greater relative risk of case positivity, hospitalization, and death across all age groups except those <18 years of age. The most significant difference for case positivity was observed in the 65–74 age group (RR 1.22, 95% CI 1.19–1.24), for hospitalization in the 45–65 age group (RR 1.85, 95% 1.80–1.90), and for death in the 18–44 age group (RR 3.30, 95% CI 2.82–3.87). Case fatality rates were greater for men in all age-matched comparisons to women. Limitations include the use of an evolving surveillance data set and absence of further demographic characteristics such as ethnographic data.
Conclusion: Men have higher rates of COVID-19 positivity, hospitalization, and death despite greater testing of women; this trend remains after stratification by age.

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INTRODUCTION

COVID-19 is caused by a coronavirus first identified after an outbreak of atypical pneumonia in Wuhan, China in December 2019. On January 7, 2020 the World Health Organization (WHO) officially recognized this novel virus as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2).[1] The spread of COVID-19 has been rapid; by March 11, 2020 the WHO declared COVID-19 a pandemic.[1] By July 2020, worldwide cases surpassed 12 million, with more than 550,000 deaths. In the United States, total cases exceed 3 million with more than 130,000 deaths.[2]

Early in the pandemic, researchers searched for predictors of viral infection and disease severity. This work suggested that increased age, ethnicity, and certain comorbidities were likely related to adverse outcomes.[3] Evidence of a sex disparity also became apparent.[4] Worldwide, differential outcomes for men were observed to varying degrees.[5] To date, no consensus on this observation exists, nor are there any definitive explanations for a possible sex discrepancy.

Currently, New York State leads the United States in both COVID-19 cases and deaths; NYC was specifically deemed a COVID-19 epicenter. We analyzed the NYC citywide dataset to further explore the sex disparity related to COVID-19. We report sex and age stratified data on testing rates together with COVID-19 related outcomes including positive cases, hospitalizations and deaths in almost one million individuals.

MATERIALS AND METHODS

Study Population

Data on COVID-19 test results were collected by NYC using syndromic and reportable disease surveillance strategies from February 29 (first confirmed case March 1, 2020) to June 12, 2020. After IRB approval, the NYC Department of Health and Mental Hygiene (NYCDOHMH) provided COVID-19 sex-specific age-matched data that included total number of tests, cases, hospitalizations, and deaths. Separately, data on the presence of unspecified comorbid conditions were collected through May 16, 2020 but were only available by gender and were not age-matched.[6] Only individuals with first-time viral tests were included, and those with unknown sex or age data were excluded.

Exposure and Covariates

Exposure of interest was self-reported sex (male or female only; transgender and gender-nonconforming were excluded). Data were stratified into age categories (0–17, 18–44, 45–64, 65–74, and 75+ years) per the NYCDOHMH based on trend similarity within each subgroup.

Outcomes

Outcomes of interest were COVID-19 case positivity, hospitalization rate and death rate. Cases included any New York City resident tested and/or treated in NYC and were defined based on positive nasopharyngeal swabs for SARS-CoV-2. Hospitalizations included reports from hospitals, hospital system and Regional Health Information Organizations, and additional sources were used when data were incomplete. Deaths were a combination of confirmed (NYC resident with positive COVID-19 test) and probable (NYC resident, or pending residency, with no known positive COVID-19 test but death certificate lists COVID-19 or an equivalent as cause of death) and were obtained from the Health Department's surveillance database.

Statistical Analysis

Case positivity, hospitalization and death rates were tabulated utilizing total tests as the denominator and were sex- and age-stratified. Rates per 100,000 individuals in NYC were further computed using 2018 United States Census Bureau data [7]. Relative risks (RR) of positive cases, hospitalization and death were calculated and stratified by age and sex. Relative risks for comorbidities were only calculated by gender. Sensitivity analyses were completed for hospitalization and death utilizing positive cases as the denominator. Case fatality rates (CFR) were calculated as percentages using deaths (probable and confirmed) as a proportion of the total number of positive cases. Missing data were not included, and therefore only complete case analysis was performed. Statistical significance was evaluated at an alpha of 0.05 and model estimates are presented with 95% confidence intervals. All analyses were performed using Stata v14.

RESULTS

A total of 914,541 first-time tests were provided, and after excluding those with unknown age, sex or outcome data, 911,310 (99.6%) individuals were analyzed. Sex and/or age were not reported in <0.5% of tests, cases, hospitalizations or death. Of the 911,310 tested individuals, 434,273 (47.65%) were male and 477,037 (52.35%) were female (Table 1). Overall negative testing rates were greater in women (53.44%) compared to men (46.56%). Test positive rates were 24.47% in men versus 21.10% in women (22.71% overall). The majority of cases, hospitalizations and deaths occurred in men; 51.36% (n=106,275), 56.44% (n=29,847), and 59.23% (n=13,054), respectively.

When stratified by age (Figures 1 and 2, Table 1), in all categories except those aged 0-17, the majority of tests were completed in women. With respect to cases, the majority occurred in men (except those >75 years), with the most significant sex difference observed in the 65–74 age group. Hospitalizations demonstrated a similar pattern with the greatest difference observed in the 45–64 age cohort (62.63%, n=11,189). The likelihood of COVID-19 death, in every age category, was higher in men, with the greatest differences in 18–44 and 45–64 age groups (74.35%, n=600 and 69.01%, n=3365, respectively).

Using gender-stratified population level data (per 100,000), overall rates of testing were almost identical in men and women, and all three outcomes of interest were greater in men (Table 1). Further stratification by age revealed that every age category displayed greater rates of case positivity, hospitalization and death for men compared to women.

The relative risk of case positivity, hospitalization and death was significantly higher in men when compared to women (RR 1.59, 95%CI 1.55–1.64 for death, Table 1). This difference persisted after age-stratification (Table 1). The greatest difference in case positivity was observed in men aged 65–74 years (RR 1.22, 95%CI 1.19–1.24). The greatest difference in hospitalization was observed in men aged 45–64 years (RR 1.85, 95% 1.80–1.90), while the greatest differences in death were in men aged 18–44 years and 45–64 (RR 3.30, 95% CI 2.82–3.87, and RR 2.46, 95%CI 2.31–2.61, respectively). For all remaining age-stratified categories, except for those aged 0-17, and for each outcome, men demonstrated a statistically significant increased risk compared to the age-matched group of women.

Hospitalizations and deaths due to COVID-19 in men and women were also compared to the total number of positive tests as opposed to the total number of tests (Table 2). Similarly, almost all age-matched comparisons demonstrated greater risks for men compared to women.

Analysis of comorbidity data (Table 3) revealed 78.5% of men who endorsed a comorbidity in comparison to 80.1% of women.

TABLE 1.

Total Number of Individuals With COVID-19 Tests, Rates per 100,000 Individuals, and Relative Risk of Outcomes of Male vs Female Sex Stratified by Age in NYC Until June 12, 2020

	Male		Female			
	(n, %)	Per 100,000	(n, %)	Per 100,000	Relative Risk	95% CI
Total Testing (n=911,310)						
0–17	24,154 (5.56%)	2713	20,508 (4.30%)	2394	–	–
18–44	177,978 (40.98%)	10923	202,790 (42.51%)	11721	–	–
45–64	149,224 (34.36%)	15317	164,617 (34.51%)	15194	–	–
65–74	49,063 (11.30%)	15788	49,413 (10.36%)	12518	–	–
75+	33,854 (7.80%)	16795	39,709 (8.32%)	11820	–	–
Overall	**434,273**	**10840**	**477,037**	**10860**	**–**	**–**
Tests Negative (n=704,394)						
0–17	21,033 (6.41%)	2363	17,895 (4.75%)	2089	–	–
18–44	139,015 (42.38%)	8532	165,748 (44.04%)	9580	–	–
45–64	110,540 (33.70%)	11346	128,053 (34.02%)	11819	–	–
65–74	35,066 (10.69%)	11284	37,817 (10.05%)	9580	–	–
75+	22,344 (6.81%)	11085	26,883 (7.14%)	8002	–	–
Overall	**327,998**	**8187**	**376,396**	**8569**	**–**	**–**
Cases (n=206,916)						
0–17	3,121 (2.94%)	351	2,613 (2.60%)	305	1.01	0.97–1.06
18–44	38,963 (36.66%)	2391	37,042 (36.81%)	2141	1.20	1.18–2.14
45–64	38,684 (36.40%)	3971	36,564 (36.33%)	3375	1.17	1.15–1.18
65–74	13,997 (13.17%)	4504	11,596 (11.52%)	2938	1.22	1.19–1.24
75+	11,510 (10.83%)	5710	12,826 (12.74%)	3818	1.05	1.03–1.07
Overall	**106,275**	**2653**	**100,641**	**2291**	**1.16**	**1.15–1.17**
Hospitalizations (n=52,883)						
0–17	282 (0.94%)	32	230 (1.00%)	27	1.04	0.88–1.23
18–44	4,334 (14.52%)	266	4,051 (17.59%)	234	1.22	1.17–1.27
45–64	11,189 (37.49%)	1148	6,675 (28.98%)	616	1.85	1.80–1.90
65–74	6,914 (23.16%)	2225	4,779 (20.75%)	1211	1.46	1.41–1.51
75+	7,128 (23.88%)	3536	7,301 (31.69%)	2173	1.15	1.11–1.18
Overall	**29,847**	**745**	**23,036**	**524**	**1.42**	**1.40–1.44**
Deaths (Confirmed and Probable) (n=22,038)						
0–17	9 (0.07%)	1	5 (0.06%)	1	1.53	0.51–4.56
18–44	600 (4.60%)	37	207 (2.30%)	12	3.30	2.82–3.87
45–64	3,365 (25.78%)	345	1,511 (16.82%)	139	2.46	2.31–2.61
65–74	3,469 (26.57%)	1116	1,874 (20.86%)	475	1.86	1.76–1.97
75+	5,611 (42.98%)	2784	5,387 (59.96%)	1604	1.22	1.18–1.26
Overall	**13,054**	**326**	**8,984**	**205**	**1.59**	**1.55–1.64**

FIGURE 1A. Total testing of COVID-19 in NYC by age and sex.

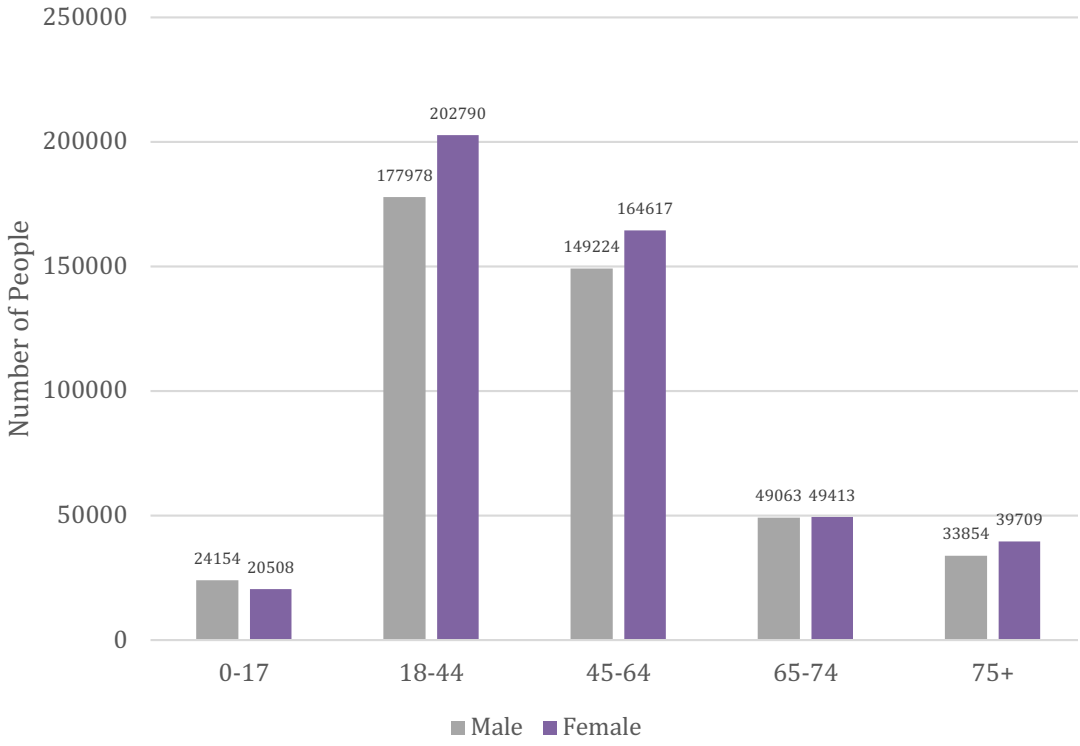

FIGURE 1B. Total cases of COVID-19 in NYC by age and sex.

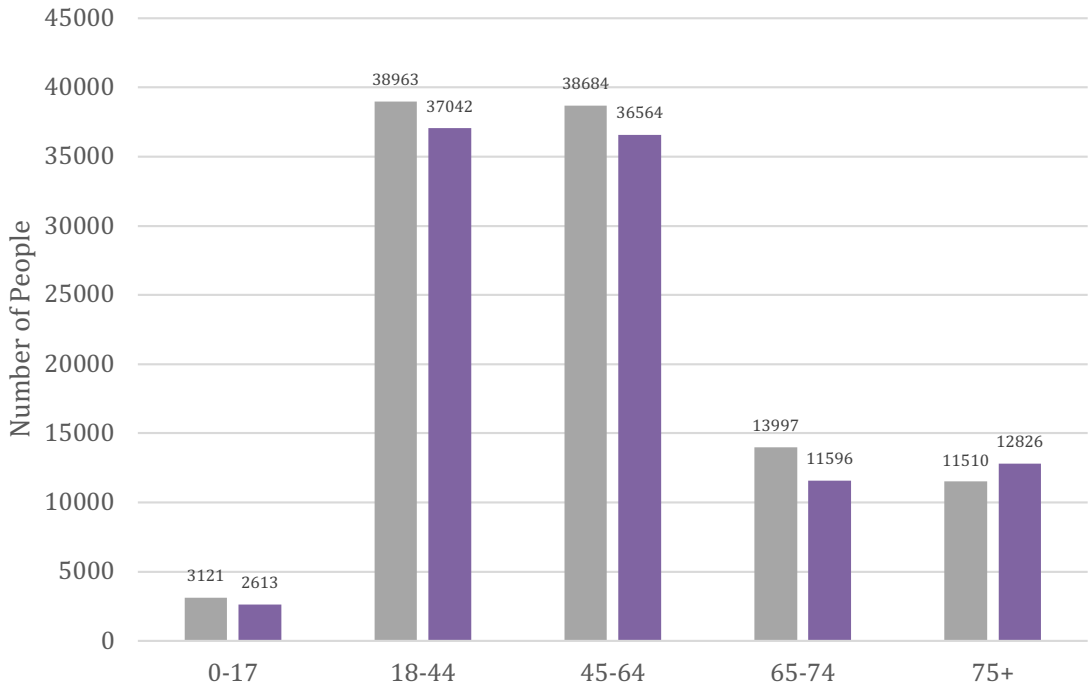

FIGURE 2A. Total hospitalizations of COVID-19 in NYC by age and sex.

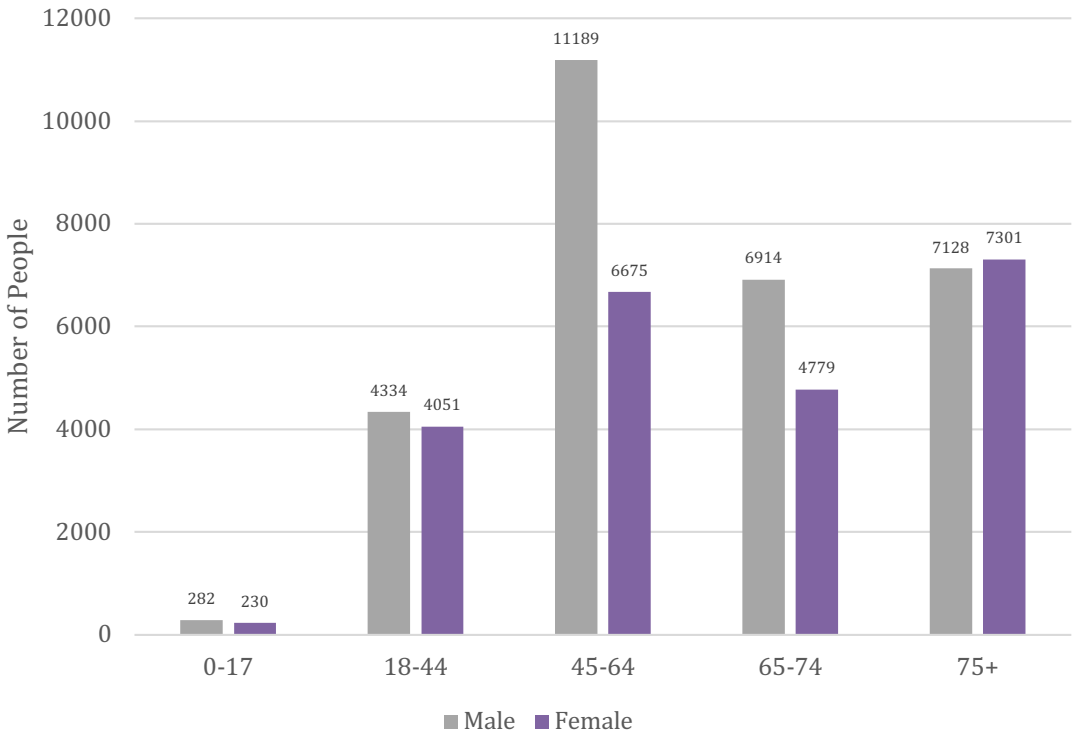

FIGURE 2B. Total deaths of COVID-19 in NYC by age and sex.

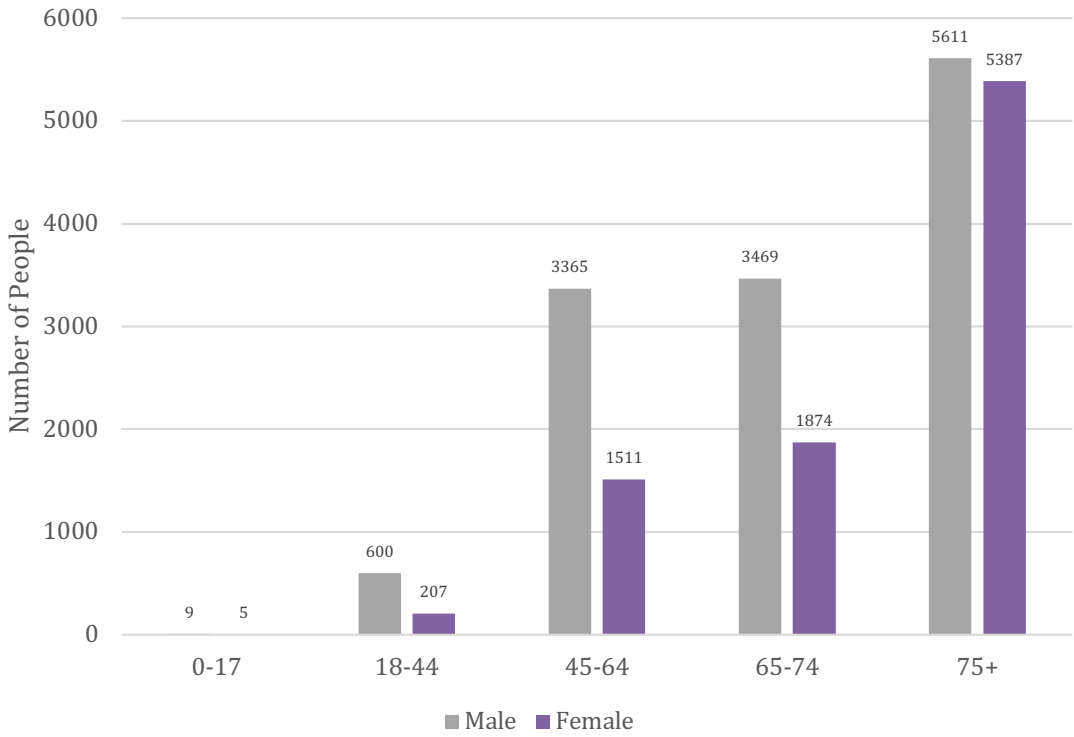

TABLE 2.

Relative Risks of COVID Outcomes of Male vs Female Sex Stratified by Age Groups Assessing Positive Cases Only in NYC Until June 12, 2020

	Hospitalizations		Death	
Age	Relative Risk	95% CI	Relative Risk	Per 100,000
0–17	1.03	0.87–1.21	1.51	0.51–4.49
18–44	1.02	0.97–1.06	2.76	2.35–3.23
45–64	1.58	1.54–1.63	2.10	1.98–2.32
65–74	1.20	1.17–1.23	1.53	1.46–1.61
75+	1.09	1.07–1.11	1.16	1.13–1.19
Overall	**1.23**	**1.21–1.24**	**1.37**	**1.34–1.41**

TABLE 3.

Rates and Relative Risk of Comorbidities in COVID-19 Related Deaths of Male vs Female

	Male (n, %) (n=9,634)	Female (n, %) (n=6,223)	Relative Risk	95% CI
Deaths as of May 16, 2020 (15,857)*	--	--	--	--
Underlying Conditions**	7,563 (78.50%)	4,985 (80.11%)	0.99	(0.99–0.99)
No Underlying Conditions	85 (0.88%)	11 (0.18%)	–	–
Unknown	1,986 (20.62%)	1,227 (19.71%)	–	–
Overall	**9,634**	**8,223**	**--**	**--**

*Sex data missing for n=3
**At least one of: diabetes, lung disease, cancer, immunodeficiency, heart disease, hypertension, asthma, kidney disease, gastrointestinal/liver disease, and obesity.

Data were missing for almost 20% of each gender group. The relative risk of having a comorbidity was 0.99 (95%CI 0.99–0.99) when comparing men and women dying from COVID-19.

The case fatality rate for the entire cohort was 10.6% (Table 4). Men had a greater CFR overall compared to women (12.28% vs 8.93%). In every age category, men had higher CFRs compared to age-matched female counterparts with the most significant difference in the 65–74 age category (24.78% in men versus 16.16% in women).

DISCUSSION

The COVID-19 pandemic has had an immeasurable impact, affecting healthcare systems, the global economy, and society as a whole. Exploration of trends within the existing COVID-19 data may guide directions for further study and novel treatment development. Our analysis demonstrates that despite higher absolute rates of testing in women in NYC, men in almost every age group had higher rates of test positivity, hospitalization and death. These findings persist after stratification for age. Our findings represent the largest current COVID-19 series of age matched data from a metropolitan region and elaborate upon trends observed in other countries across the globe.[5]

TABLE 4.

Case-Fatality Rates of COVID-19 in Males and Females in NYC Until June 12, 2020 Stratified by Age

0–17	0.24	0.29	0.19	–
18–44	**1.06**	**1.54**	**0.56**	--
45–64	**6.48**	**8.70**	**4.13**	
65–74	**20.88**	**24.78**	**16.16**	
75+	**45.19**	**48.75**	**42.00**	
Overall	**10.65**	**12.28**	**8.93**	

While our data represent a single metropolitan region (NYC), they mirror data from over 50 countries across six continents. In all but one country (Portugal), rates of death were equivalent or greater in men versus women, with an estimated 60% increased risk of severe illness or death.[5] Interestingly, many European countries report increased rates of female case positivity.[5,8] Larger datasets from other COVID-19 epicenters, Italy and China, demonstrate increased case numbers and poorer outcomes in men, but this may be confounded by comorbidities and lifestyle behaviors.[8]

Men aged 18–44, 45–64, and 65–74 were more likely than age matched women to be hospitalized or die as a result of COVID. This may be attributable to a sex-based physiologic difference in the course of the disease; this may be hormonal and/or non-hormonal, but also may be due to the underlying mechanism of disease. Pathophysiologically, SARS-CoV-2 viral spike proteins bind to the angiotensin converting enzyme-2 (ACE2) receptor, and are primed by acellular serine protease (TMPRSS2), ultimately facilitating entry into cells.[9] Studies demonstrate ACE2 and TMPRSS2 expression throughout the body, including the prostate and testis.[10] ACE2 expression is controlled by the X-chromosome, and therefore X-linked gene inactivation in women may be relevant.[11] ACE2 expression within the testis occurs in both Sertoli and Leydig cells as well as in spermatogonia and spermatids.[10] TMPRSS2 gene fusions (TMPRSS2-ERG) are involved in the development and progression of some prostate cancers.[12] Expression levels of both ACE2 and TMPRSS2 were detected at low levels in the testis, but co-expression was less than <0.1% suggesting that direct entry into testis was unlikely to occur.[13] In contrast, testicular or scrotal discomfort concerning for viral orchitis is reported with COVID-19. This condition was also reported with the original SARS coronavirus.[13,14] There is limited data regarding viral positivity in the testis, and no studies have assessed viral shedding in extra-prostatic secretions.[15,16] Overall, this suggests that ACE2 and TMPRSS2 expression in male specific organs may not provide an adequate explanation for this observed sex disparity.

Younger men in our series displayed a greater magnitude relative risk of death (age 18–44) and hospitalization (age 45–64) suggesting a possible differential disease course secondary to circulating androgen levels. The androgen receptor is a gene promoter of both gene transcription and expression of TMPRSS2.[17] Men with hyper-androgenic states, including male pattern baldness, comprised 71% of a series of COVID-19 hospitalized men.[18] The androgen receptor is composed of various lengths of CAG repeats which confer differential expression levels; this finding in men has been speculated as an explanation of ethnic differences in COVID-19 deaths.[19] Androgen depravation therapy (ADT) may confer a differential response to SARS-CoV-2 infection as evidenced by a large study demonstrating an approximate four-fold decrease in odds of case positivity and disease severity in men on ADT compared to controls.[20] Ongoing randomized trials are exploring the impact of ADT on COVID-19 outcomes including a non-steroidal anti-androgen, bicalutamide and a gonadotropin releasing hormone antagonist, degarelix (ClinicalTrials.gov NCT04374279 and NCT04397718). One study implied that 5-alpha reductase inhibitors, which prevent the conversion of testosterone to dihydrotesterone, might reduce ACE2 levels and thereby blunt viral infectivity, suggesting a potential differential impact of testosterone and dihydrotesterone levels.[21] Similarly, research suggests that spironolactone may have a protective effect with regard to COVID-19 given a weakly anti-androgenic activity as well as some cardio- and reno-protective effects.[22]

Our data suggest that the differences in risk of adverse outcomes diminish as men and women age; men older than 75 had the least magnitude difference in relative risk of hospitalization and death compared to age matched women. With increasing age, levels of testosterone are known to decrease, implying a role for testosterone levels in the outcomes of those infected by COVID-19.[23] Hypogonadism, the clinical state of testosterone deficiency, is associated with numerous comorbidities known to worsen COVID-19 outcomes; these include obesity, type 2 diabetes mellitus, and obstructive sleep apnea.[24] Low testosterone states are associated with elevated levels of pro-inflammatory cytokines such as IL-6, IL-1, and TNF-alpha; this may potentiate the COVID-19 related cytokine storm observed in severe disease states.[24] Other data implicated pro-inflammatory cytokines including IL-8, IL-10, IL-17a, and IL-23 in more severe disease course.[25] It remains to be seen whether these cytokines may be clinically useful in terms of predicting disease outcomes, or may manifest differently in men as opposed to women. Importantly, the largest absolute number of deaths occurs in both men and women of age > 75, arguing against any protective effect of an isolated age-related hormone decline.

It is possible that some of the observed age and sex based differential effect is not due to increased risk in men alone, but instead derives from a protective effect in women <75 as reflected by CFRs in this subgroup. If this effect is hormonally driven, it may become diminished when a women experiences menopause. The rheumatologic and immunologic literature suggests that women may have enhanced immune responses to a wide variety of pathogens, potentially due to the impact of progesterone and estrogens on the immune system (estrogen receptor expression occurs throughout immune system cell types), but also due to altered gene dosage of sex chromosomes.[26] Upon entrance into menopause, women may experience an "immune-senescence" resulting from an immune decline due to reduced hormone levels.[27] Additionally, estrogen is a known driver of ACE2 expression.[28] Nevertheless, an increase in estrogen levels may not alone offset the risk of worsened disease in men; males with obesity have increased circulating estrogen levels due to peripheral aromatization of testosterone to estrogen, yet continue to have worsened outcomes with COVID-19.[29] Prospective trials are underway assessing the impact of administration of female sex hormones including progesterone and estrogen to men hospitalized with COVID-19 (ClinicalTrials.gov NCT04365127 and NCT04359329).

Finally, the observed sex disparity in COVID-19 outcomes may relate to comorbidity differences. The Center for Disease Control lists potential risk factors for worsened outcomes with COVID-19.[30] Many of these comorbidities occur in greater rates amongst men.[31] Men have more severe disease profiles, reduced rates of healthcare utilization, and riskier lifestyle habits.[31] However, when analyzing these data, rates of comorbidities among those dying in NYC were comparable between sexes. Differences in comorbidities between men and women may not provide an adequate explanation for the observed sex disparity in COVID-19 outcomes.

Limitations of our study include the surveillance-based nature of this evolving dataset. Ethnographic data were missing in a large percentage of citywide data, prohibiting inclusion of ethnicity in our analysis. However, given our study size, including population-level adjustments, we can assume our findings are sufficiently powered, generalizable and externally valid. Data on antibody testing may permit more meaningful analysis, but at this time antibody testing remains suboptimal. While specific data on comorbidities in men and women would be ideal, these data were similarly not available given our cohort size and the rapid course of disease in our region. Furthermore, we were unable to temporally stratify our data, introducing possible bias from under sampling of earlier cases as testing was initially limited. This may overemphasize the absolute number of hospitalizations and deaths compared to cases, but is unlikely to be different between sexes. Case fatality rates in our series were calculated utilizing a broad definition of death (probable and confirmed), therefore the true magnitude of this effect is likely overestimated. Data were obtained in aggregate for age grouping and sex, thereby preventing further

in-depth modelling with narrower age categories. Sex was self-reported and no effort was made to query patients regarding transsexualism. Given rates of transsexualism nationwide ranging from 0.39–0.56%, discordance between reported sex and biologic sex is unlikely to impact our results.[32]

CONCLUSION

In the NYC population, men have higher rates of COVID-19 and higher rates of hospitalization and death due to COVID-19. Numerous theories have been postulated to explain these underlying differences, and while studies considering the role of androgens and other sex hormones offer the most robust evidence to date, this relationship is complex and warrants further study.

DISCLOSURES

Authors have no relevant conflicts to report.

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