**Distribution Agreement**

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

# COVID-19 DIAGNOSES AND HOSPITALIZATIONS AMONG INSURED TRANSGENDER AND GENDER DIVERSE PEOPLE IN CALIFORNIA, USA

By

Chloe Donegan
MD, MPH

Epidemiology

_____

Michael Goodman MD, MPH
Committee Chair

# COVID-19 DIAGNOSES AND HOSPITALIZATIONS AMONG INSURED TRANSGENDER AND GENDER DIVERSE PEOPLE IN CALIFORNIA, USA

By

Chloe Donegan

B.S., Emory University, 2016

Thesis Committee Chair:
Michael Goodman MD, MPH

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2024

# Abstract

## COVID-19 DIAGNOSES AND HOSPITALIZATIONS AMONG INSURED TRANSGENDER AND GENDER DIVERSE PEOPLE IN CALIFORNIA, USA

By Chloe Donegan

**Background:** Transgender and gender diverse (TGD) people may be disproportionately affected by the COVID-19 pandemic due to barriers to timely care. Further, the potential role of gender-affirming hormone therapy on COVID-19 severity has not been well-studied.

**Specific Aims:** In this analysis of data from the Study of Transition, Outcomes & Gender nested in Kaiser Permanente health systems in Northern and Southern California, we sought to compare rates of COVID-19 diagnoses in transfeminine (TF) and transmasculine (TM) participants relative to cisgender referents. In addition, data on COVID-19 cases among TGD and cisgender study participants were analyzed to compare the likelihood of hospitalization in these groups.

**Methods:** Electronic health records (EHRs) were used to identify and validate a cohort of 6774 TM and 4607 TF Kaiser Permanente members who were enrolled in the 2 participating plans from January 1, 2020, through July 31, 2021. About 10 cisgender male (CM) and 10 cisgender female (CF) enrollees were matched to each TGD cohort member on year of birth, race or ethnicity, and study site. Rates of incident COVID-19 diagnoses and hospitalizations within 30 days of diagnosis among TGD cohort members were ascertained from the EHR and compared with those in the reference cohorts via Cox regression models, with results expressed as hazard ratios (HRs) and 95% CIs before and after adjusting for potential cofounding factors. Sensitivity analyses among TGD members on hormone therapy were also explored.

**Results:** COVID-19 incidence rates were lower in TF cohort members compared with CF and CM referents with HR (95% CI) estimates of 0.64 (0.56-0.73) and 0.71 (0.62-0.81), respectively. Similarly, TM participants were approximately 30% to 40% less likely to receive a COVID-19 diagnosis than cisgender referents, with all 95% CI estimates excluding unity. Although the unadjusted analyses suggested that hospitalization rates were higher among TF patients with COVID-19 than among cisgender referents, the association was attenuated after the results were controlled for covariates. More importantly, the association was no longer evident once the analyses were restricted to TF patients with evidence of gender-affirming hormone therapy receipt.

**Conclusions:** In this analysis of data from two large integrated health systems, there was no evidence that TGD people were disproportionately diagnosed or hospitalized with COVID-19. Although reassuring, the results of this study must be interpreted with caution because the data are limited to participants with COVID-19 diagnoses (not confirmed with tests), adequate access to care, and included only a few cases of diagnosed COVID-19 that necessitated intensive care.

# COVID-19 DIAGNOSES AND HOSPITALIZATIONS AMONG INSURED TRANSGENDER AND GENDER DIVERSE PEOPLE IN CALIFORNIA, USA

By

Chloe Donegan
B.S., Emory University, 2016

Thesis Committee Chair: Michael Goodman MD, MPH

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2024

# INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has disproportionately affected marginalized populations across the United States and exposed long-standing underlying health disparities (Khanijahani et al., 2021; Ruprecht et al., 2021; Tai et al., 2021). The literature shows increased rates of COVID-19 incidence, severity, and mortality in African Americans, Hispanics, Native Americans, persons with lower income and education, those living in poor housing conditions, and populations that speak minority languages. (Khanijahani et al., 2021; Tai et al., 2021). By contrast, the data on the impact of COVID-19 pandemic on gender minority populations are lacking.

The term "transgender and gender diverse (TGD)" refers to a diverse group of people whose gender identity and expression do not align with their sex assigned at birth (Coleman et al., 2022; Lombardi, 2001; Sequeira & Dayton, 2021). TGD people often experience neglect, harassment, discrimination, and other adverse political, social, and economic risk factors that may contribute to poor health outcomes and underutilization of medical care (Centers for Disease & Prevention, 2022; Flores et al., 2021; Herman et al., 2022; Reisner et al., 2016; Safer et al., 2016). These observations indicate that TGD people may need to be included among other population groups disproportionally affected by the COVID-19 pandemic both in terms of disease incidence and its severity.

A recognized pathophysiological hallmark of severe COVID-19, especially in the pre-vaccination era, is coagulopathy, usually presenting as thrombotic vascular events such as pulmonary embolism, deep vein thrombosis, or stroke (Driggin et al., 2020; Klok et al., 2020; Kollias et al., 2021; Nannoni et al., 2021). The International Society of Thrombosis and Hemostasis and the American Society of Hematology emphasize extra vigilance when patients

have additional risk factors such as older age, male sex, and obesity (Cuker et al., 2021; Thachil et al., 2020). While none of the guidelines mention TGD patients as a high-risk group, there is mounting evidence that feminizing gender affirming hormone therapy (GAHT) results in higher incidence of thrombotic events such as venous thromboembolism and ischemic stroke among transfeminine (TF) people (Chan Swe et al., 2022; Getahun et al., 2018; Hamidi & Davidge-Pitts, 2019; Nota et al., 2019). Although the evidence on venous thromboembolism and stroke in relation to masculinizing GAHT is more limited, recent studies demonstrated a strong association between testosterone and risk of erythrocytosis in transmasculine (TM) people (Antun et al., 2020), which may in turn lead to thrombotic complications (Velho et al., 2017).

It is also important to keep in mind that studies have consistently demonstrated lower COVID-19 incidence, mortality, and disease severity among cisgender women relative to cisgender men (Abate et al., 2020; Channappanavar et al., 2017). Recent data indicate that this difference is likely attributable to the effect estrogen, which has been shown to inhibit inflammation and reduce immune response in COVID-19 patients (Li et al., 2022).

Taken together, the available evidence is consistent with two competing hypotheses. On the one hand, there is good reason to expect that TGD people may experience higher rates of COVID-19 and COVID-19 hospitalizations due to inadequate access and utilization of medical care, and the potential thrombogenic effect of GAHT. On the other hand, it is also possible that TF individuals receiving feminizing GAHT may have less severe COVID-19 infections due to the anti-inflammatory effect of exogenous estradiol.

Based on the above considerations, the goal of this study was to compare the characteristics of the COVID-19 pandemic among TGD and cisgender people identified within the same population. We accomplished this by analyzing the data from the longitudinal Study of

Transition, Outcomes and Gender (STRONG) that included approximately 11,000 TGD participants and 224,500 cisgender referents enrolled in two Kaiser Permanent integrated health systems. The overall study goal was achieved by addressing two objectives. We first used the data from the STRONG cohort to compare rates of COVID-19 in TM and TF participants, relative to those observed among cisgender male (CM) and cisgender female (CF) cohort members. We then used data on COVID-19 cases among the TGD and cisgender groups to compare likelihood of hospitalization and to investigate whether receipt of GAHT played a role in COVID-19 severity, especially in the pre-vaccine period. We used both male and female cisgender reference groups because care utilization has been shown to differ substantially between male and female members of the Kaiser Permanente health plans (Ames et al., 2021; Schatz & Camargo, 2003), and because hormone serum concentrations among TGD people range from normal physiologic male to normal physiologic female levels, depending on receipt and dosage of hormone therapy and individual characteristics (Hembree et al., 2017).

# METHODS

## Cohort Ascertainment

The methods of STRONG cohort ascertainment and electronic health record (EHR) data collection were described in detail elsewhere (Getahun et al., 2018; Quinn et al., 2017). The validation studies of the algorithms used for cohort ascertainment and characterization were also published previously (Gerth et al., 2018; Xie et al., 2021).

The expanded cohort is nested within the 2 original STRONG Kaiser Permanente sites in northern and southern California, and all work was coordinated by Emory University with data

programming support from Kaiser Permanente Georgia. All activities were reviewed and approved by the institutional review boards of the institutions that participated in data collection and analyses. In keeping with the STRONG research protocol, cohort selection involved a 3-step algorithm that included initial EHR search to identify cohort candidates (step 1), validation of transgender status (step 2), and determination of TM or TF status (step 3).

The candidates for inclusion in step 1 were people of any age who had both a diagnostic code and a keyword consistent with transgender status and were enrolled in either of the participating sites between January 1, 2020, and July 31, 2021. In step 2, eligibility status of cohort candidates was independently verified by 2 trained investigators who reviewed transgender keyword-containing short strings of text extracted from the EHR. When assessing eligibility, the reviewers were also instructed to categorize each participant as TF, TM, or unknown. The disagreement between reviewers was adjudicated by a committee that included the project manager and the study principal investigator. Transgender people whose TM or TF status remained not clear after the initial review underwent additional evaluation (step 3). This was accomplished by reviewing another set of text excerpts that contained keywords reflecting natal sex anatomy (e.g., “testes” or “ovaries”), history of specific procedures (e.g., orchiectomy or hysterectomy), and evidence of feminizing or masculinizing hormone therapy (e.g, estrogen or testosterone). Text strings containing TM- and TF-specific keywords were reviewed and adjudicated as discussed above.

Once the analytic cohort of TGD people was finalized, up to 10 male and 10 female cisgender Kaiser Permanente enrollees were matched to each member on race or ethnicity (non-Hispanic White, non-Hispanic Black, Asian/Pacific Islander, Hispanic, and other), year of birth (within a 5-year interval), and study site. In addition, TGD and cisgender cohort members were

matched on enrollment dates to allow the same start of follow-up. The up to 10:1 ratio was used to allow future stratified analyses while ensuring a sufficient number of cisgender referents for each cohort member. Each transgender cohort member was linked to matched referents via a unique cluster ID. The matching was carried out without replacement (i.e., each matched referent was used in the analysis only once).

## Data Linkages and Variable Characterization

EHR data linkages for each study participant were used to ascertain events of interest. The follow-up was based on the enrollment data. Because administrative data often lag behind, the disenrollment periods of 90 days or less are typically considered as uninterrupted enrollment.

COVID-19 diagnoses were ascertained based on International Classification of Diseases and Current Procedure Terminology and internal Kaiser Permanent codes. These codes apply to Kaiser Permanente members who were tested and diagnosed both within and outside their respective health plans (personal communication, Darios Getahun, Kaiser Permanente Southern California, July 2021). The lists of codes for each event of interest are included in **the Appendix**. In addition, each new COVID-19 diagnosis was linked to all-cause hospitalization data based on utilization records. Following methods used in previous EHR-based research (Schmajuk et al., 2021), a hospitalization was considered COVID-19 related if it occurred within 30 days of diagnosis. Only events with a COVID-19 diagnosis date during the follow-up were used in the analyses.

Gender-affirming hormone therapy receipt was determined from national drug codes for filled prescriptions and drug names for medication orders as described previously (Getahun et al., 2018). Based on dates of filled prescriptions and the number of days of medication supply,

including refills, each TGD patient with COVID-19 was characterized as receiving or not receiving GAHT at the time of diagnosis. The patient was categorized as receiving GAHT if the dates of prescription supply (including refills) contained the date of -COVID-19- diagnosis.

In addition to the main exposure and outcome variables, all TGD and cisgender study participants were characterized with respect to their socioeconomic status (SES). The SES variables included insurance (Medicaid vs commercial) and residence in a federally designated poverty area, defined as a census tract with at least 20% of households living below the poverty level, based on the 2019 American Community Survey data. We selected an area-based measure of poverty because it has been found to be correlated with, but more robust than, the corresponding measures of education and wealth (Krieger et al., 2002).

In the analyses of disease severity, all newly diagnosed COVID-19- cases were characterized with respect to their Charlson comorbidity index, a composite measure of morbidity commonly used to quantify the overall burden of disease (Quan et al., 2011). The Charlson comorbidity index was expressed as a 3-level variable: 0 to 1 (reference), 2 to 3, and 4+. In addition, each case was characterized as having received at least 1 dose of a COVID-19 vaccine before diagnosis. Because the follow-up extended only through July 2021, the information on vaccination completion status was incomplete, and the data on booster receipt were not yet available. Because it can be argued that vaccination status may act as a mediator rather than a confounder in the analysis comparing rates of hospitalization after -COVID-19 diagnosis among TGD and cisgender people, we also conducted a sensitivity analysis that limited follow-up to the prevaccine- period (through December 31, 2020).

## Statistical Analyses

The data analyses were performed in SAS Software version 9.4 (SAS Institute Inc). For the analyses of COVID-19 testing and -COVID-19 diagnoses (aims 1 and 2), the follow-up continued from January 1, 2020, or initial enrollment at any time during the study period (both designated- as time 0) until the event of interest, disenrollment from Kaiser Permanente or the end of the study period (July 31, 2021), whichever occurred first. The previously confirmed cohort members remained enrolled on January 1, 2020, and all newly identified participants had to either be enrolled on January 1, 2020, or join a participating Kaiser Permanente plan during the study period. Not all previously confirmed cohort members were added to the current study for 2 reasons: (1) The original STRONG cohort included approximately 30% of participants with EHR text evidence but no diagnostic codes, whereas the present study was limited to participants who had diagnostic codes of interest in addition to keywords; (2) some of the original cohort members disenrolled from the participating health plans before January 1, 2020. The gaps in enrollment for 90 days or less were treated as continuous uninterrupted follow-up, as reported previously (Getahun et al., 2018). Subjects with gaps of more than 90 days were considered disenrolled, and the person-time under observation was counted only during active enrollment.

Matched referents were assigned the same date of start of follow-up as TGD participants if they were enrolled in the health plan on that day. The gaps in enrollment for the reference cohorts were handled via the same approach as for the TGD participants.

Rates of COVID-19 diagnoses among TM and TF participants and their matched cisgender referents were compared by constructing Kaplan-Meier curves for each event type. Separate Kaplan-Meier curves were used to compare rates of hospitalization among TGD and

cisgender patients with COVID-19. All Kaplan-Meier curves were accompanied by a log rank test for statistical significance. As an alternative, we also calculated *P* values for matched data by using unadjusted Cox proportional hazard models. We then used multivariable Cox proportional hazards models to compare COVID-19 incidence rates in the TF and TM cohorts and the respective reference groups after controlling for covariates. Each model was stratified on cluster ID to account for matching and adjusted for SES variables.

In the analyses of hospitalization rates among TGD and cisgender patients with COVID-19 (aim 3), the observation began on the day of COVID-19 diagnosis (time 0) and extended until hospitalization or the end of the 30-day follow-up. In the analyses of hospitalization rates after COVID-19 diagnosis, the TGD and cisgender patients with COVID-19 were no longer matched. For this reason, all Cox proportional hazards models were adjusted for age, study site, race or ethnicity, SES variables, Charlson comorbidity index, and receipt of at least 1 dose of a COVID-19 vaccine. Because covariate values were missing for less than 2% of study participants, imputation of missing values was not necessary. We tested proportional hazard assumptions by inspecting log minus log plots for each variable, and all models were examined for 2-way multiplicative interaction between the main independent variable of interest (TGD status) and each covariate. The results of Cox models were expressed as adjusted hazard ratios (HRs) with corresponding 95% CIs.

# RESULTS

Of the 11,209 new TGD cohort candidates, identified based on the presence of relevant diagnostic codes and keywords, 90% (*n*=10,034) were confirmed as eligible (**Figure 1**). After

inclusion of additional 2,932 TGD persons identified in earlier STRONG studies, the total cohort included 12,966 participants. Following exclusion of persons with unknown sex assigned at birth (*n*=1,386) and additional 199 individuals with inconsistent dates (e.g., COVID-19 diagnosis before 2020) or missing covariate information the final analysis dataset included 4607 TF and 6774 TM individuals.

TM persons comprised more than half (59.5%) of the transgender cohort. The majority of participants came from Kaiser Permanente's Northern California site for both TF (73.1%) and TM (65.2%) groups (**Table 1**). Around half of participants in both groups were non-Hispanic whites. Hispanics represented 20.2% of TF and 24.5% of TM participants. Non-Hispanic Blacks comprised 5.6% of TF and 7.0% of TM participants and Asians represented 12.0% of TF and 8.6% of TM. The remaining 6% of each group had race/ethnicity marked as other/unknown. The majority of both TF (69.9%) and TM (58.2%) cohorts were receiving GAHT. Similar percentages of TF and TM, 15.5% and 16.5% respectively, had Medicaid coverage, with 8.4% of TF and 9.0% of TM participants living in a federally designated poverty area (**Table 1**).

Among the TF cohort members, 5% were diagnosed with COVID-19, compared to 7.7% of CF and 6.9% of CM referents (**Table 2**). Of the TM cohort, 5.1% were diagnosed with COVID-19, compared to 8.4% of CF and 7.3% of CM referents (**Table 3**). Less than 1% of study participants in all groups were hospitalized for COVID-19 (**Tables 2** and **3**).

Kaplan-Meier survival curves (**Figure 2**) showed lower probability of receiving a COVID-19 diagnosis for both TF and TM cohorts versus matched referents (log rank test $p < 0.0001$). As shown in Table 4 the HR for COVID-19 diagnosis in TF was 0.64 (95% CI, 0.56 to 0.73) compared to CF referents and 0.71 (95% CI, 0.62 to 0.81) compared to CM referents

**(Table 4**). Increased rates of COVID-19 were associated with Medicaid coverage in the model comparing TF versus CF group and with living in a federally designated poverty area for both comparisons. The corresponding HRs among TM were 0.59 (0.53 to 0.66) and 0.67 (0.60 to 0.75) compared to CF and CM referents respectively. Living in a federally designated poverty area was also associated with increased rates of disease in both models (**Table 5**).

As shown in **Figure 3,** the probability of hospitalization following COVID-19 diagnosis was significantly higher for TF compared to cisgender referents (log rank test p = 0.007) but not appreciably different for TM (log rank test p = 0.364). In the multivariable analyses, the HRs for TF compared to CF were 1.41 (95% CI, 0.98 to 2.02) and 1.24 (95% CI, 0.86 to 1.79) compared to CM (**Table 6**). Across both comparisons, significantly increased rates of COVID-19 hospitalizations were associated with Non-Hispanic Black race, Medicaid coverage, and a Charlson comorbidity index of 2 or more, whereas associations with Hispanic ethnicity and living in a federally designated poverty area were only evident in the model comparing TF versus CM groups (**Table 6**). After restricting the data to TF patients on GAHT, (**Table 7**) the hospitalization rates in this group appeared closer to those of both CM (HR: 0.93; 95% CI: 0.57 to 1.52) and CF (HR: 1.24; 95% CI: 0.77 to 1.99) reference cohorts. As in the previous analysis, significantly increased rates were seen in persons with Medicaid coverage and those with a Charlson comorbidity index of at least 2. In addition, the GAHT-restricted TF versus CM model demonstrated a significant association with Hispanic ethnicity, while the corresponding model comparing TF to matched CF referents demonstrated a significant association with Non-Hispanic Black race (**Table 7**).

In the multivariable model comparing TM cohort members receiving GAHT to their matched referents, the HR (95% CI) estimates for COVID-19 hospitalizations were also close to the null value: 1.14 (0,79 to 1.65) relative to CM and 1.19 (0.83 to 1.71) relative to CF (**Table 8**). Statistically significant positive associations were also observed with Non-Hispanic Black race and Medicaid coverage in both models, with Hispanic ethnicity in the TM versus CF model, and with Charlson comorbidity index of 4+ in the TM versus CM model (**Table 8**). Restricting the analyses to TM participants on GAHT (**Table 9**) did not appreciably affect the results with adjusted HRs of 0.94 (95% CI, 0.60 to 1.51) and 1.06 (95% CI, 0.66 to 1.70) relative to CF and CM referents, respectively. The associations with Medicaid, Charlson comorbidity indices and race/ethnicity were generally in the same direction although the 95% CI were wider than in the overall analysis.

# DISCUSSION

Using data from the STRONG cohort, we sought to characterize the impact of the COVID-19 pandemic among TGD people by comparing rates of COVID-19 diagnoses and hospitalizations in TF and TM participants relative to cisgender referents. Additionally, we investigated whether receipt of GAHT played a role in COVID-19 severity, especially in the pre-vaccine period. The data analysis demonstrated that COVID-19 incidence rates were lower in TF cohort members compared to CM and CF referents with a relative risk reduction of about 30% to 35%. Similarly, TM participants were approximately 30% to 40% less likely to receive a COVID-19 diagnosis than cisgender referents. The models revealed increased rates of COVID-

19 diagnosis among cohort members living in a federally designated poverty area. Although unadjusted analyses suggested that hospitalization rates were higher among TF patients with COVID-19 than among cisgender referents, the association was attenuated after controlling for covariates. More importantly, the association was no longer evident after restricting the analysis to TF participants on GAHT. Additional risk factors associated with higher rates of hospitalization in several analyses included non-Hispanic Black race, Medicaid receipt, and a Charlson comorbidity index of at least 2. This is consistent with prior literature showing increased risk of COVID-19 infection and severity in racial/ethnic minority and lower SES groups, and in the presence of comorbidities (Khanijahani et al., 2021; Kim et al., 2021; Quan et al., 2011; Tai et al., 2021).

To-date, most studies investigating effects of the COVID-19 pandemic on TGD people focused on the psychosocial effects (e.g., social isolation, access to care), rather than actual rates and severity of the disease. The Center for Disease Control's (CDC) National Center for Health Statistics (NCHS) does not include demographic information related to TGD status. A 2022 systematic review investigating the potential role of sex hormones in COVID-19 diagnosis and severity identified 14 potentially relevant studies, but only 2 of those studies focused on TGD people and none was designed to evaluate COVID-19 incidence or severity in this population. (Ferraro et al., 2022).

It has been proposed that androgens may facilitate COVID-19 infection through upregulation of the ACE-2 receptor, through which SARS-CoV-2 enters host cells but may be protective of severe illness (Masterson et al., 2021). Multiple studies have shown that men with lower baseline levels of testosterone have worse COVID-19 outcomes. A retrospective cohort

study of 40 men hospitalized with COVID-19 found that low testosterone and elevated estradiol to testosterone (E2/T) ratios (a marker of aromatase activity) were both associated with a hyperinflammatory state and low testosterone level at time of admission was an independent marker of in-hospital mortality (Infante et al., 2021). Similarly, a prospective cohort study of 152 patients with COVID-19, 143 of whom were hospitalized, showed that lower testosterone concentrations and elevated E2/T ratios were associated with increased COVID-19 severity, hyperinflammatory states, and mortality (Dhindsa et al., 2021). Men with severe COVID-19 had testosterone levels 65-85% lower than men with more mild disease (Dhindsa et al., 2021). These studies suggest that masculinizing GAHT may exert a protective effect against severe COVID-19. Although we found no evidence in support of this hypothesis, it is important to note that testosterone levels and E2/T ratios were not included in our data. In a single center cross sectional study of 179 TM and 59 TF individuals, Durcan and coauthors observed that the proportion of participants with a COVID-19 diagnosis was higher in TM receiving testosterone therapy, compared with TF patients receiving estrogen and anti-androgen therapies. Among TM participants, longer duration of testosterone therapy was associated with increased likelihood of having contracted COVID-19. Estrogen has been hypothesized to protect against severe COVID-19, through modulating the immune responses and preventing hyperinflammatory states (Ding et al., 2020; Li et al., 2022; Vaninov, 2020). Studies have shown less severe COVID-19 in pre-menopausal compared to post-menopausal women and in post-menopausal women undergoing hormone replacement compared to those not receiving therapy (Ding et al., 2020; Seeland et al., 2020). A prospective case study of transgender women examined potential protective effects of estrogen and progesterone therapy from COVID-19 infection through downregulation of ACE-2 receptor by examining testicular tissue from orchiectomies (Masterson et al., 2021). Comparing

transgender women on estrogen and progesterone to cisgender males, the study showed reduced expression of ACE-2 receptor in testicular tissue. The authors concluded that there is a potential benefit of administering both estrogen and progesterone therapy in cisgender men and transgender women to protect against COVID-19 infection (Masterson et al., 2021).

In the present study, rates of COVID-19 diagnosis were lower among TM and TF participants than among their respective cisgender referents, although in our analysis these groups were not compared side-by-side. The results for COVID-19 incidence were not stratified by hormone use; however, most participants in both groups (TF: 60.9%, TM: 58.2%) were on GAHT. We were also unable to confirm previous reports that testosterone and feminizing GAHT may protect against severe disease. A handful of studies examined attitudes around COVID-19 vaccine and testing hesitancy among LGBTQIA+ (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex and Asexual) populations, but few have distinguished TGD populations from the larger group. Of the few studies examining rates of COVID-19 testing and diagnosis in TGD populations, one online study conducted between October 2020 and November 2020 found higher rates of testing among those with higher SES (Restar et al., 2021). The prevalence of COVID-19 testing in the study was 35.5% and in addition to higher SES, increased odds of testing among TGD participants were also seen in those with active alcohol use disorder, limited access to gender- affirming surgery, more than 20% reduction in income, and in individuals who had experienced mistreatment in a health facility due to gender identity (Restar et al., 2021). These characteristics are not generally associated with higher rates of healthcare utilization, suggesting a possible difference in the trends of COVID-19 specific healthcare utilization, which could be relevant to interpreting our results examining rates of COVID-19

diagnosis and hospitalization. This study did not compare TGD testing rates to the general population.

Examining potential differences in COVID-19 immunization, a 2023 scoping review on COVID-19 vaccine hesitancy among LGBTQIA+ populations, which reviewed 17 studies published after 2021, found that potential barriers for vaccine uptake in this community included concerns about the safety, side effects and efficacy of vaccines, mistrust of healthcare providers, discrimination due to gender identity, as well as a lack of LGBTQIA+ targeted information about vaccines and inequitable distribution (Balaji et al., 2023). There was not a significant difference in rates of vaccine acceptance between the LGBTQIA+ community and the general population, but there was a disparity in availability and access (Balaji et al., 2023). A lower rate of vaccine acceptance was seen among those of lower SES background (Balaji et al., 2023). A 2022 study examining data from the National Immunization Survey Adult COVID Module (NIS-ACM) that assessed COVID-19 vaccine coverage and confidence of LGBT individuals ≥18 years found similar vaccination rates among those who identified as transgender or nonbinary and those who did not (McNaghten et al., 2022). Additionally, it showed that 85% of the gay and lesbian population had received at least a single dose of the COVID-19 vaccine against 76% of heterosexual individuals in the fall of 2021 (McNaghten et al., 2022). A study using data from an online survey of 1350 sexual and gender minority participants, 58 of whom identified as a gender minority, found that sexual and gender minority participants who identified as Black reported lower COVID-19 vaccine acceptance than those who identified as White and Asian, which the authors attributed to psychosocial, economic, and structural factors (Teixeira da Silva et al., 2021). The identified LGBTQIA+ specific barriers to vaccination include systemic discrimination, social isolation, stigma, medical mistrust leading to inequitable vaccine access

and underutilization of health care, as well as the HIV crisis (Balaji et al., 2023). Because these barriers affect TGD populations at higher rates than other identities under the LGBTQ+ umbrella, it is reasonable to posit that TGD populations would have higher levels of vaccine hesitancy than the overall LGBTQ+ population. Our study period primarily captured individuals prior to initial vaccination or completion of the full vaccination series, so it is unlikely immunity from vaccination played a significant role in participants risk of diagnosis or hospitalization. Based on the 2022 study by McNaghten et al., if there were any effect of vaccination on the measured outcomes in this study, it likely equally affected the transgender and cisgender cohorts. Future studies examining COVID-19 diagnosis and severity in the era of vaccination should consider these factors.

## STRENGTHS AND LIMITATIONS

This study has several methodological strengths. The longitudinal design of our cohort study allows for evaluation of risk over time. The de-identified EHR-based cohort decreases the risk of ascertainment bias that a survey or opt-in or opt-out study would face. Additionally, multivariable analyses conducted with and without GAHT allowed for examination of the potential effects of testosterone, estrogen, and progesterone.

An important limitation of this study is the insufficient number of severe cases, such as those requiring intensive care unit (ICU) admission or resulting in death, which precludes a detailed analysis of these critical outcomes. Additionally, the study faces the challenge of distinguishing between hospitalizations directly attributed to COVID-19 and those occurring for

other reasons during the same period. There was a lack of data concerning the dose and duration of GAHT, which could play a significant role in the risk of COVID-19 disease and severity. Future research could benefit from incorporating measured serum hormone levels to address this issue. Our study's limited capacity to fully account for the influence of vaccination status could be mitigated in subsequent studies by extending the follow-up period. Finally, the absence of data on other medications is a noteworthy limitation, suggesting the need for future research to extend the follow-up to the present time to capture such information to provide a more comprehensive understanding of the factors influencing COVID-19 outcomes in this population. Another future study area should involve examining specific measures of coagulopathy, such as lab values and thrombotic outcomes, and serum hormone levels, in analysis of TGD patients on GAHT with diagnosed COVID-19.

# CONCLUSIONS

In this analysis of the data from an EHR-based cohort nested within 2 large integrated health systems, there was no evidence that TGD people were disproportionately diagnosed or hospitalized with COVID-19. Although reassuring, the results of this study must be interpreted with caution because the data are limited to participants with adequate access to care, recorded COVID-19 diagnoses rather than diagnostic tests, and only included a few cases of COVID-19 that necessitated intensive care.

# REFERENCES


Abate, B. B., Kassie, A. M., Kassaw, M. W., Aragie, T. G., & Masresha, S. A. (2020). Sex difference in coronavirus disease (COVID-19): a systematic review and meta-analysis. *BMJ Open, 10*(10), e040129. doi:10.1136/bmjopen-2020-040129

Ames, J. L., Massolo, M. L., Davignon, M. N., Qian, Y., & Croen, L. A. (2021). Healthcare service utilization and cost among transition-age youth with autism spectrum disorder and other special healthcare needs. *Autism, 25*(3), 705-718. doi:10.1177/1362361320931268

Antun, A., Zhang, Q., Bhasin, S., Bradlyn, A., Flanders, W. D., Getahun, D., . . . Goodman, M. (2020). Longitudinal Changes in Hematologic Parameters Among Transgender People Receiving Hormone Therapy. *J Endocr Soc, 4*(11), bvaa119. doi:10.1210/jendso/bvaa119

Balaji, J. N., Prakash, S., Joshi, A., & Surapaneni, K. M. (2023). A Scoping Review on COVID-19 Vaccine Hesitancy among the Lesbian, Gay, Bisexual, Transgender, Queer, Intersex and Asexual (LGBTQIA+) Community and Factors Fostering Its Refusal. *Healthcare (Basel), 11*(2). doi:10.3390/healthcare11020245

Centers for Disease, C., & Prevention. (2022). *Behavioral Risk Factor Surveillance System Survey Data*.

Chan Swe, N., Ahmed, S., Eid, M., Poretsky, L., Gianos, E., & Cusano, N. E. (2022). The effects of gender-affirming hormone therapy on cardiovascular and skeletal health: A literature review. *Metabol Open, 13*, 100173. doi:10.1016/j.metop.2022.100173

Channappanavar, R., Fett, C., Mack, M., Ten Eyck, P. P., Meyerholz, D. K., & Perlman, S. (2017). Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection. *The Journal of Immunology, 198*(10), 4046-4053. doi:10.4049/jimmunol.1601896

Coleman, E., Radix, A. E., Bouman, W. P., Brown, G. R., de Vries, A. L. C., Deutsch, M. B., . . . Arcelus, J. (2022). Standards of Care for the Health of Transgender and Gender Diverse People, Version 8. *Int J Transgend Health, 23*(Suppl 1), S1-s259. doi:10.1080/26895269.2022.2100644

Cuker, A., Tseng, E. K., Nieuwlaat, R., Angchaisuksiri, P., Blair, C., Dane, K., . . . Schünemann, H. J. (2021). American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. *Blood Adv, 5*(3), 872-888. doi:10.1182/bloodadvances.2020003763

Dhindsa, S., Zhang, N., McPhaul, M. J., Wu, Z., Ghoshal, A. K., Erlich, E. C., . . . Diwan, A. (2021). Association of Circulating Sex Hormones With Inflammation and Disease Severity in Patients With COVID-19. *JAMA Network Open, 4*(5), e2111398-e2111398. doi:10.1001/jamanetworkopen.2021.11398

Ding, T., Zhang, J., Wang, T., Cui, P., Chen, Z., Jiang, J., . . . Wang, S. (2020). Potential Influence of Menstrual Status and Sex Hormones on Female Severe Acute Respiratory Syndrome Coronavirus 2 Infection: A Cross-sectional Multicenter Study in Wuhan, China. *Clinical Infectious Diseases, 72*(9), e240-e248. doi:10.1093/cid/ciaa1022

Driggin, E., Madhavan, M. V., Bikdeli, B., Chuich, T., Laracy, J., Biondi-Zoccai, G., . . . Parikh, S. A. (2020). Cardiovascular Considerations for Patients, Health Care Workers, and

Health Systems During the COVID-19 Pandemic. *J Am Coll Cardiol, 75*(18), 2352-2371. doi:10.1016/j.jacc.2020.03.031

Flores, A. R., Meyer, I. H., Langton, L., & Herman, J. L. (2021). Gender Identity Disparities in Criminal Victimization: National Crime Victimization Survey, 2017-2018. *Am J Public Health, 111*(4), 726-729. doi:10.2105/ajph.2020.306099

Gerth, J., Becerra-Culqui, T., Bradlyn, A., Getahun, D., Hunkeler, E. M., Lash, T. L., . . . Goodman, M. (2018). Agreement between medical records and self-reports: Implications for transgender health research. *Reviews in Endocrine & Metabolic Disorders, 19*(3), 263-269. doi:10.1007/s11154-018-9461-4

Getahun, D., Nash, R., Flanders, W. D., Baird, T. C., Becerra-Culqui, T. A., Cromwell, L., . . . Goodman, M. (2018). Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons: A Cohort Study. *Ann Intern Med, 169*(4), 205-213. doi:10.7326/m17-2785

Hamidi, O., & Davidge-Pitts, C. J. (2019). Transfeminine Hormone Therapy. *Endocrinology and Metabolism Clinics of North America, 48*(2), 341-355. doi:https://doi.org/10.1016/j.ecl.2019.02.001

Hembree, W. C., Cohen-Kettenis, P. T., Gooren, L., Hannema, S. E., Meyer, W. J., Murad, M. H., . . . T'Sjoen, G. G. (2017). Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism, 102*(11), 3869-3903. doi:10.1210/jc.2017-01658

Herman, J. L., Flores, A. R., & O'Neill, K. K. (2022). *How Many Adults and Youth Identify as Transgender in the United States?* Retrieved from https://williamsinstitute.law.ucla.edu/wp-content/uploads/Trans-Pop-Update-Jun-2022.pdf

Infante, M., Pieri, M., Lupisella, S., D'Amore, L., Bernardini, S., Fabbri, A., . . . Morello, M. (2021). Low testosterone levels and high estradiol to testosterone ratio are associated with hyperinflammatory state and mortality in hospitalized men with COVID-19. *Eur Rev Med Pharmacol Sci, 25*(19), 5889-5903. doi:10.26355/eurrev_202110_26865

Khanijahani, A., Iezadi, S., Gholipour, K., Azami-Aghdash, S., & Naghibi, D. (2021). A systematic review of racial/ethnic and socioeconomic disparities in COVID-19. *International Journal for Equity in Health, 20*(1), 248. doi:10.1186/s12939-021-01582-4

Kim, D. H., Park, H. C., Cho, A., Kim, J., Yun, K.-s., Kim, J., & Lee, Y.-K. (2021). Age-adjusted Charlson comorbidity index score is the best predictor for severe clinical outcome in the hospitalized patients with COVID-19 infection. *Medicine, 100*(18), e25900. doi:10.1097/md.0000000000025900

Klok, F. A., Kruip, M., van der Meer, N. J. M., Arbous, M. S., Gommers, D., Kant, K. M., . . . Endeman, H. (2020). Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res, 191*, 145-147. doi:10.1016/j.thromres.2020.04.013

Kollias, A., Kyriakoulis, K. G., Lagou, S., Kontopantelis, E., Stergiou, G. S., & Syrigos, K. (2021). Venous thromboembolism in COVID-19: A systematic review and meta-analysis. *Vascular Medicine, 26*(4), 415-425. doi:10.1177/1358863X21995566

Krieger, N., Chen, J. T., Waterman, P. D., Soobader, M. J., Subramanian, S. V., & Carson, R. (2002). Geocoding and monitoring of US socioeconomic inequalities in mortality and cancer incidence: does the choice of area-based measure and geographic level matter?: the Public Health Disparities Geocoding Project. *Am J Epidemiol, 156*(5), 471-482. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12196317

Li, F., Boon, A. C. M., Michelson, A. P., Foraker, R. E., Zhan, M., & Payne, P. R. O. (2022). Estrogen hormone is an essential sex factor inhibiting inflammation and immune response in COVID-19. *Scientific Reports, 12*(1), 9462. doi:10.1038/s41598-022-13585-4

Lombardi, E. (2001). Enhancing transgender health care. *Am J Public Health, 91*(6), 869-872. doi:10.2105/ajph.91.6.869

Masterson, J. M., Bui, C., Zhang, Y., Yuan, X., Huynh, C., Jawanda, H., . . . Garcia, M. M. (2021). Feminising hormone therapy reduces testicular ACE-2 receptor expression: Implications for treatment or prevention of COVID-19 infection in men. *Andrologia, 53*(11), e14186. doi:10.1111/and.14186

McNaghten, A. D., Brewer, N. T., Hung, M. C., Lu, P. J., Daskalakis, D., Abad, N., . . . Singleton, J. (2022). COVID-19 Vaccination Coverage and Vaccine Confidence by Sexual Orientation and Gender Identity - United States, August 29-October 30, 2021. *MMWR Morb Mortal Wkly Rep, 71*(5), 171-176. doi:10.15585/mmwr.mm7105a3

Nannoni, S., de Groot, R., Bell, S., & Markus, H. S. (2021). Stroke in COVID-19: A systematic review and meta-analysis. *Int J Stroke, 16*(2), 137-149. doi:10.1177/1747493020972922

Nota, N. M., Wiepjes, C. M., Blok, C. J. M. d., Gooren, L. J. G., Kreukels, B. P. C., & Heijer, M. d. (2019). Occurrence of Acute Cardiovascular Events in Transgender Individuals Receiving Hormone Therapy. *Circulation, 139*(11), 1461-1462. doi:doi:10.1161/CIRCULATIONAHA.118.038584

Quan, H., Li, B., Couris, C. M., Fushimi, K., Graham, P., Hider, P., . . . Sundararajan, V. (2011). Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol, 173*(6), 676-682. doi:10.1093/aje/kwq433

Quinn, V. P., Nash, R., Hunkeler, E., Contreras, R., Cromwell, L., Becerra-Culqui, T. A., . . . Goodman, M. (2017). Cohort profile: Study of Transition, Outcomes and Gender (STRONG) to assess health status of transgender people. *BMJ Open, 7*(12), e018121. doi:10.1136/bmjopen-2017-018121

Reisner, S. L., Poteat, T., Keatley, J., Cabral, M., Mothopeng, T., Dunham, E., . . . Baral, S. D. (2016). Global health burden and needs of transgender populations: a review. *The Lancet, 388*(10042), 412-436. doi:10.1016/S0140-6736(16)00684-X

Restar, A., Garrison-Desany, H. M., Baker, K. E., Adamson, T., Howell, S., Baral, S. D., . . . Beckham, S. W. (2021). Prevalence and associations of COVID-19 testing in an online sample of transgender and non-binary individuals. *BMJ Glob Health, 6*(9). doi:10.1136/bmjgh-2021-006808

Ruprecht, M. M., Wang, X., Johnson, A. K., Xu, J., Felt, D., Ihenacho, S., . . . Phillips Ii, G. (2021). Evidence of Social and Structural COVID-19 Disparities by Sexual Orientation, Gender Identity, and Race/Ethnicity in an Urban Environment. *Journal of Urban Health, 98*(1), 27-40. doi:10.1007/s11524-020-00497-9

Safer, J. D., Coleman, E., Feldman, J., Garofalo, R., Hembree, W., Radix, A., & Sevelius, J. (2016). Barriers to healthcare for transgender individuals. *Curr Opin Endocrinol Diabetes Obes, 23*(2), 168-171. doi:10.1097/med.0000000000000227

Schatz, M., & Camargo, C. A., Jr. (2003). The relationship of sex to asthma prevalence, health care utilization, and medications in a large managed care organization. *Ann Allergy Asthma Immunol, 91*(6), 553-558. doi:10.1016/s1081-1206(10)61533-5

Schmajuk, G., Montgomery, A. D., Leonard, S., Li, J., Gianfrancesco, M., Seet, A., . . . Keyhani, S. (2021). Factors Associated With Hospitalization and Death After COVID-19 Diagnosis

Among Patients With Rheumatic Disease: An Analysis of Veterans Affairs Data. *ACR Open Rheumatol, 3*(11), 796-803. doi:10.1002/acr2.11328

Seeland, U., Coluzzi, F., Simmaco, M., Mura, C., Bourne, P. E., Heiland, M., . . . Preissner, S. (2020). Evidence for treatment with estradiol for women with SARS-CoV-2 infection. *BMC Med, 18*(1), 369. doi:10.1186/s12916-020-01851-z

Sequeira, G. M., & Dayton, K. (2021). Transgender and Gender-Diverse Youth. *JAMA Pediatrics, 175*(7), 756-756. doi:10.1001/jamapediatrics.2021.1014

Tai, D. B. G., Shah, A., Doubeni, C. A., Sia, I. G., & Wieland, M. L. (2021). The Disproportionate Impact of COVID-19 on Racial and Ethnic Minorities in the United States. *Clin Infect Dis, 72*(4), 703-706. doi:10.1093/cid/ciaa815

Teixeira da Silva, D., Biello, K., Lin, W. Y., Valente, P. K., Mayer, K. H., Hightow-Weidman, L., & Bauermeister, J. A. (2021). COVID-19 Vaccine Acceptance among an Online Sample of Sexual and Gender Minority Men and Transgender Women. *Vaccines (Basel), 9*(3). doi:10.3390/vaccines9030204

Thachil, J., Tang, N., Gando, S., Falanga, A., Cattaneo, M., Levi, M., . . . Iba, T. (2020). ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost, 18*(5), 1023-1026. doi:10.1111/jth.14810

Vaninov, N. (2020). In the eye of the COVID-19 cytokine storm. *Nature Reviews Immunology, 20*(5), 277-277. doi:10.1038/s41577-020-0305-6

Velho, I., Fighera, T. M., Ziegelmann, P. K., & Spritzer, P. M. (2017). Effects of testosterone therapy on BMI, blood pressure, and laboratory profile of transgender men: a systematic review. *Andrology, 5*(5), 881-888. doi:10.1111/andr.12382

Xie, F., Getahun, D., Quinn, V. P., Im, T. M., Contreras, R., Silverberg, M. J., . . . Goodman, M. (2021). An automated algorithm using free-text clinical notes to improve identification of transgender people. *Inform Health Soc Care, 46*(1), 18-28. doi:10.1080/17538157.2020.1828890

**Figure 1. Flow Diagram of Cohort Ascertainment**

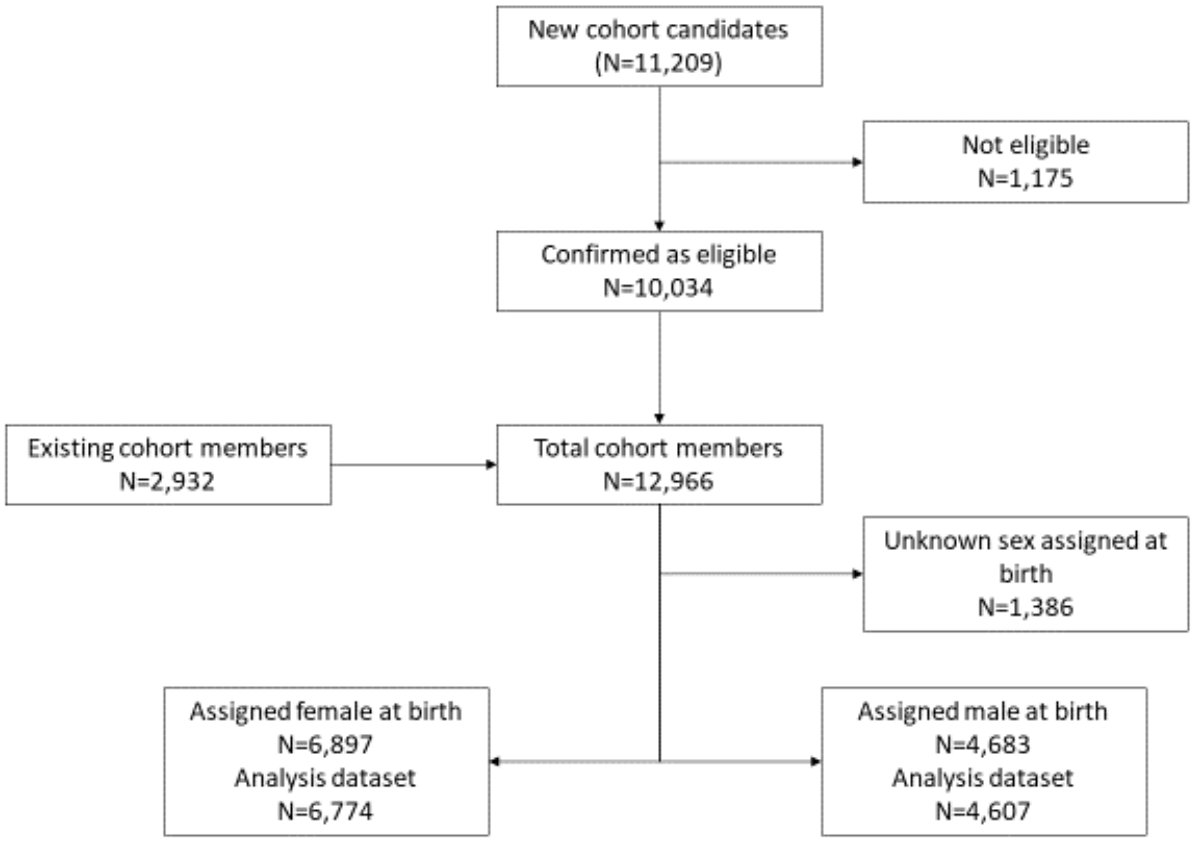


**Table 1. Characteristics of the Transgender and Gender-Diverse Cohort Members (N = 11 381)**

| Participant characteristics | TF cohort n (%) | TM cohort n (%) |
|---|---|---|
| Membership site | | |
| Kaiser Permanente Northern California | 3367 (73.1) | 4418 (65.2) |
| Kaiser Permanente Southern California | 1240 (26.9) | 2356 (34.8) |
| Age at baseline (January 1, 2020) | | |
| <18 y | 521 (11.3) | 1469 (21.7) |
| 18-25 y | 1259 (27.3) | 2461 (36.3) |
| 26-35 y | 1226 (26.6) | 1592 (23.5) |
| 36-45 y | 593 (12.8) | 702 (10.4) |
| 46-55 y | 413 (9.0) | 320 (4.7) |
| >55 y | 595 (12.9) | 230 (3.4) |
| Race | | |
| White | 2562 (55.6) | 3635 (53.7) |
| Black | 258 (5.6) | 476 (7.0) |
| Asian | 553 (12.0) | 585 (8.6) |
| Hispanic | 929 (20.2) | 1658 (24.5) |
| Other/unknown | 305 (6.6) | 420 (6.2) |
| Hormone therapy receipt | | |
| Yes | 3218 (69.9) | 3948 (58.2) |
| No | 1389 (30.2) | 2826 (41.7) |
| Medicaid insurance indicator | | |
| Yes | 714 (15.5) | 1117 (16.5) |
| No | 3893 (84.5) | 5657 (83.5) |
| Percentage of census tract households living in poverty | | |
| <20% | 4221 (91.6) | 6167 (91.0) |
| ≥20% | 386 (8.4) | 607 (9.0) |
| **Total** | 4607 | 6774 |

Abbreviations: TF, transfeminine; TM, transmasculine.

**Table 2. Characteristics of the COVID-19 Epidemic Among TF Cohort Members and Matched Referents**

| COVID-19 status variables | TF cohort n (%) | CF referents n (%) | CM referents n (%) |
|---|---|---|---|
| Diagnosed with COVID-19 | | | |
| Yes | 232 (5.0) | 3520 (7.7) | 3134 (6.9) |
| No | 4375 (95.0) | 41962 (92.3) | 42257 (93.1) |
| Hospitalized with COVID-19 | | | |
| Yes | 36 (0.8) | 333 (0.7) | 328 (0.7) |
| No | 4571 (99.2) | 45149 (99.3) | 45063 (99.3) |
| **Total** | 4607 | 45482 | 45391 |

Abbreviations: CF, cisgender females; CM, cisgender males; TF, transfeminine.

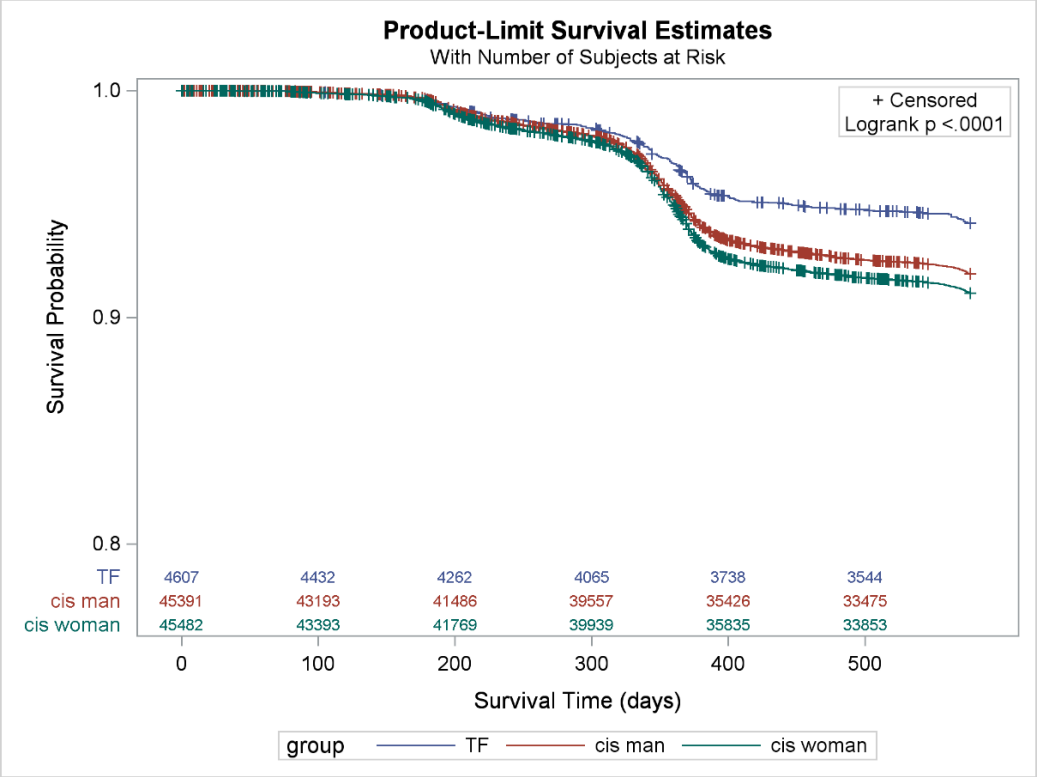
**Table 3. Characteristics of COVID-19 Epidemic Among TM Cohort Members and Matched Referents**

| COVID-19 status variables | TM cohort n (%) | CF referents n (%) | CM referents n (%) |
|---|---|---|---|
| Diagnosed with COVID-19 | | | |
| Yes | 345 (5.1) | 5619 (8.4) | 4847 (7.3) |
| No | 6429 (94.9) | 61263 (91.6) | 61958 (92.7) |
| Hospitalized with COVID-19 | | | |
| Yes | 34 (0.5) | 437 (0.7) | 388 (0.6) |
| No | 6740 (99.5) | 66445 (99.4) | 66417 (99.4) |
| **Total** | 6774 | 66882 | 66805 |

Abbreviations: CF, cisgender females; CM, cisgender males; TM, transmasculine.

**Figure 2. Probability of Remaining COVID-19-Free During Follow-up**

**A. Transfeminine (TF) cohort members vs matched referents**




**B. Transmasculine (TM) cohort members vs matched referents**

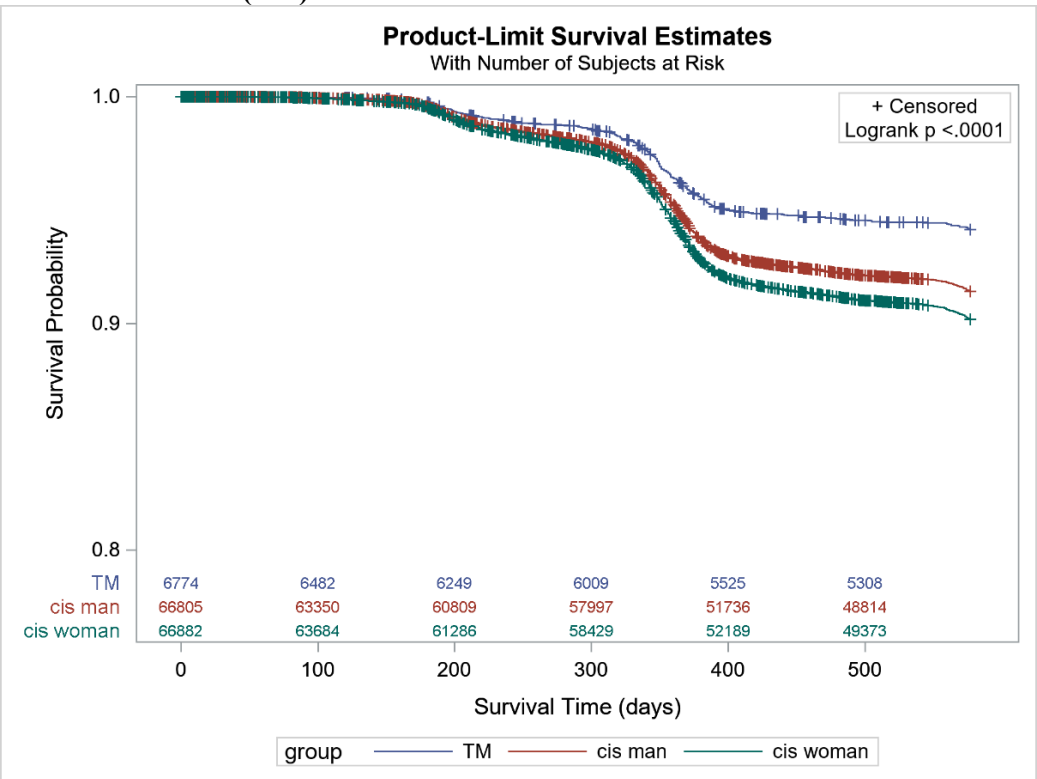


**Table 4. Multivariable Cox Model[a] Comparing Rates of COVID-19 Diagnosis in TF Cohort Members vs Matched Referents**

| Participant characteristics | TF vs CF | | TF vs CM | |
|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI |
| Gender identity | | | | |
| Cisgender | 1 | [Reference] | 1 | [Reference] |
| TF | 0.64 | (0.56-0.73) | 0.71 | (0.62-0.81) |
| Medicaid insurance indicator | | | | |
| No | 1 | [Reference] | 1 | [Reference] |
| Yes | 1.17 | (1.05-1.30) | 0.95 | (0.83-1.08) |
| Living in poverty area[b] | | | | |
| No | 1 | [Reference] | 1 | [Reference] |
| Yes | 1.27 | (1.13-1.42) | 1.21 | (1.07-1.37) |

Abbreviations: CF, cisgender females; CM, cisgender males; HR, hazard ratio; TF, transfeminine.
[a]Stratified by cluster ID to account for matching variables (age, race and ethnicity, site, and enrollment at start of follow-up); other participant characteristics listed in the table are included in the model as covariates.
[b]Defined as a census tract with ≥20% of households living in poverty.

**Table 5. Multivariable Cox Model[a] Comparing Rates of COVID-19 Diagnosis in TM Cohort Members vs Matched Referents**

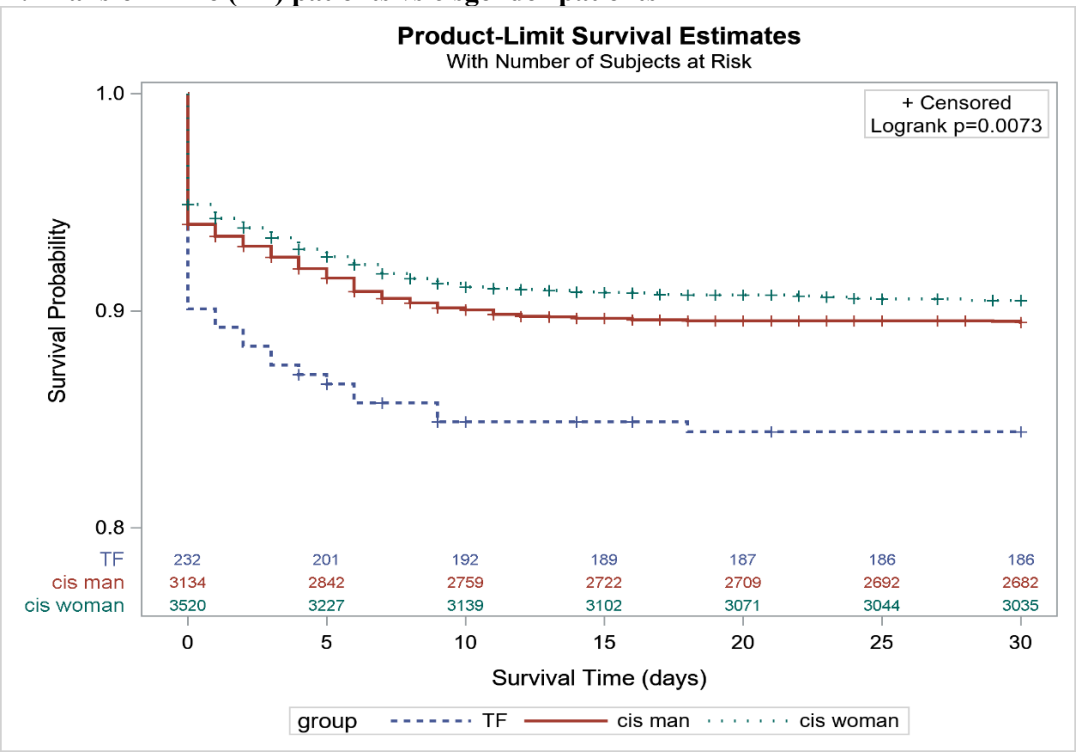
| Participant characteristics | TM vs CF | | TM vs CM | |
|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI |
| Gender identity | | | | |

| Participant characteristics | TM vs CF | | TM vs CM | |
|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI |
| Cisgender | 1 | [Reference] | 1 | [Reference] |
| TM | 0.59 | (0.53-0.66) | 0.67 | (0.60-0.75) |
| Medicaid insurance indicator | | | | |
| No | 1 | [Reference] | 1 | [Reference] |
| Yes | 1.06 | (0.98-1.14) | 0.93 | (0.85-1.03) |
| Living in poverty area[b] | | | | |
| No | 1 | [Reference] | 1 | [Reference] |
| Yes | 1.15 | (1.05-1.26) | 1.20 | (1.08-1.32) |

Abbreviations: CF, cisgender females; CM, cisgender males; HR, hazard ratio; TM, transmasculine.
[a]Stratified by cluster ID to account for matching variables (age, race and ethnicity, site, and enrollment at start of follow-up); other participant characteristics listed in the table are included in the model as covariates.
[b]Defined as a census tract with ≥20% of households living in poverty.

**Figure 3. Hospitalization-Free Survival Within 1 Month of Receiving COVID-19 Diagnosis**

**A. Transfeminine (TF) patients vs cisgender patients**



**B. Transmasculine (TM) patients vs cisgender patients**

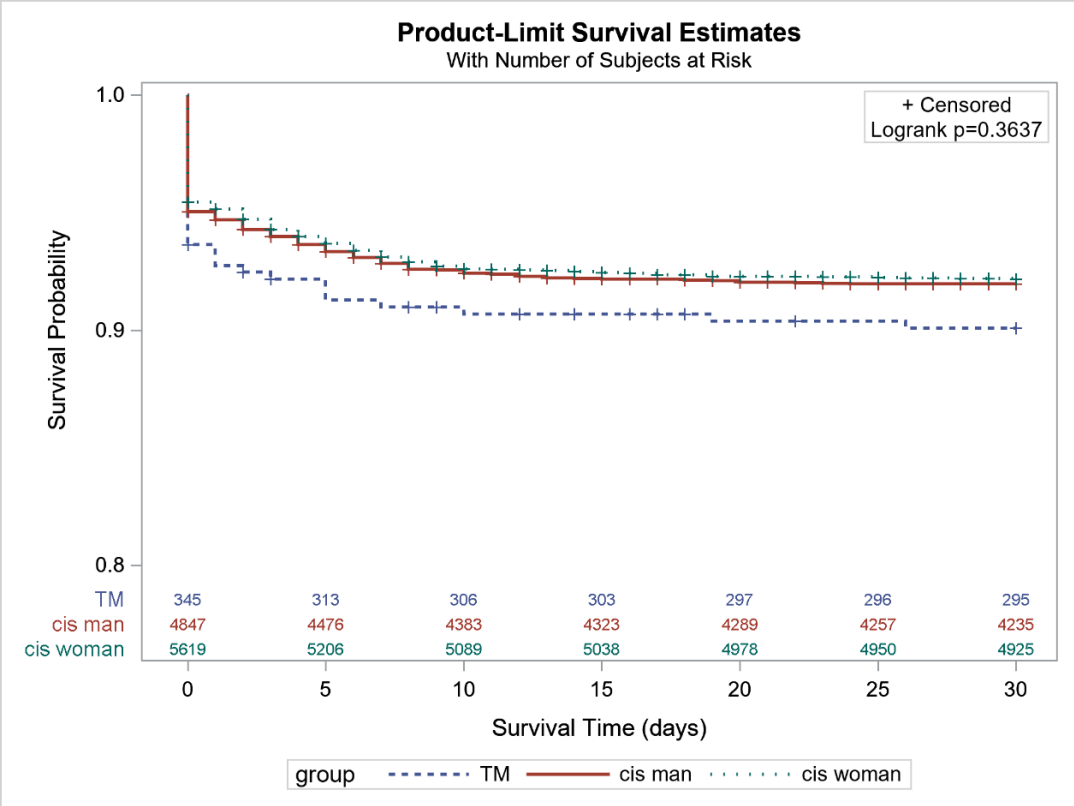



**Table 6. Multivariable Cox Model[a] Comparing Rates of Hospitalizations in TF and Cisgender Patients With COVID-19-**

| Participant characteristics | TF vs CF | | TF vs CM | |
|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI |
| Gender identity | | | | |
| Cisgender | 1 | [Reference] | 1 | [Reference] |
| TF | 1.41 | (0.98-2.02) | 1.24 | (0.86-1.79) |
| Membership site | | | | |
| Kaiser Permanente Northern California | 1 | [Reference] | 1 | [Reference] |
| Kaiser Permanente Southern California | 1.09 | (0.87-1.36) | 0.77 | (0.60-0.99) |
| Race | | | | |
| Non-Hispanic White | 1 | [Reference] | 1 | [Reference] |
| Non-Hispanic Black | 1.67 | (1.14-2.45) | 1.57 | (1.03-2.39) |
| Asian | 1.10 | (0.73-1.65) | 1.14 | (0.75-1.74) |
| Hispanic | 1.09 | (0.85-1.40) | 1.51 | (1.17-1.95) |
| Other/unknown | 1.34 | (0.81-2.22) | 1.13 | (0.67-1.89) |
| Medicaid insurance indicator | | | | |
| No | 1 | [Reference] | 1 | [Reference] |

| Participant characteristics | TF vs CF | | TF vs CM | |
|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI |
| Yes | 1.90 | (1.46-2.48) | 2.26 | (1.64-3.11) |
| Living in poverty area[b] | | | | |
| No | 1 | [Reference] | 1 | [Reference] |
| Yes | 1.27 | (0.93-1.73) | 1.44 | (1.05-2.00) |
| Charlson comorbidity index | | | | |
| 0-1 | 1 | [Reference] | 1 | [Reference] |
| 2-3 | 2.18 | (1.52-3.13) | 2.07 | (1.45-2.95) |
| 4+ | 3.52 | (2.17-5.72) | 3.22 | (2.13-4.86) |
| Received [3]1 dose of vaccine | | | | |
| No | 1 | [Reference] | 1 | [Reference] |
| Yes | 0.74 | (0.60-0.92) | 0.84 | (0.68-1.05) |

Abbreviations: CF, cisgender females; CM, cisgender males; HR, hazard ratio; TF, transfeminine.
[a]Stratified on age due to violation of proportional hazards assumptions; other participant characteristics listed in the table are included in the model as covariates.
[b]Defined as a census tract with ≥20% of households living in poverty.

**Table 7. Multivariable Cox Model[a] Comparing Rates of Hospitalizations in TF Patients With COVID-19 on GAHT and Cisgender Patients**

| Participant characteristics | TF on GAHT vs CF | | TF on GAHT vs CM | |
|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI |
| Gender identity | | | | |
| Cisgender | 1 | [Reference] | 1 | [Reference] |
| TF | 1.24 | (0.77-1.99) | 0.93 | (0.57-1.52) |
| Membership site | | | | |
| Kaiser Permanente Northern California | 1 | [Reference] | 1 | [Reference] |
| Kaiser Permanente Southern California | 1.03 | (0.77-1.36) | 0.80 | (0.58-1.09) |
| Race | | | | |
| Non-Hispanic White | 1 | [Reference] | 1 | [Reference] |
| Non-Hispanic Black | 1.74 | (1.08-2.81) | 1.40 | (0.81-2.43) |
| Asian | 0.98 | (0.60-1.61) | 1.04 | (0.64-1.69) |
| Hispanic | 1.13 | (0.83-1.52) | 1.43 | (1.05-1.94) |
| Other/unknown | 1.27 | (0.71-2.26) | 1.12 | (0.61-2.05) |
| Medicaid insurance indicator | | | | |
| No | 1 | [Reference] | 1 | [Reference] |
| Yes | 1.67 | (1.18-2.35) | 2.32 | (1.54-3.51) |
| Living in poverty area[b] | | | | |
| No | 1 | [Reference] | 1 | [Reference] |

| Participant characteristics | TF on GAHT vs CF | | TF on GAHT vs CM | |
|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI |
| Yes | 1.15 | (0.77-1.71) | 1.32 | (0.87-2.00) |
| Charlson comorbidity index | | | | |
| 0-1 | 1 | [Reference] | 1 | [Reference] |
| 2-3 | 2.38 | (1.52-3.72) | 2.06 | (1.29-3.30) |
| 4+ | 5.18 | (2.89-9.29) | 3.62 | (2.15-6.08) |
| Received at least ³1 dose of vaccine | | | | |
| No | 1 | [Reference] | 1 | [Reference] |
| Yes | 0.75 | (0.58-0.98) | 0.80 | (0.61-1.05) |

Abbreviations: CF, cisgender females; CM, cisgender males; GAHT, gender-affirming hormone therapy; HR, hazard ratio; TF, transfeminine.

[a]Stratified on age due to violation of proportional hazards assumptions; other participant characteristics listed in the table are included in the model as covariates.

[b]Defined as a census tract with ≥20% of households living in poverty.

**Table 8. Multivariable Cox Model[a] Comparing Rates of Hospitalization in TM and Cisgender Patients With COVID-19-**

| Participant characteristics | TM vs CF | | TM vs CM | |
|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI |
| Gender identity | | | | |
| Cisgender | 1 | [Reference] | 1 | [Reference] |
| TM | 1.19 | (0.83-1.71) | 1.14 | (0.79-1.65) |
| Membership site | | | | |
| Kaiser Permanente Northern California | 1 | [Reference] | 1 | [Reference] |
| Kaiser Permanente Southern California | 0.85 | (0.70-1.04) | 0.93 | (0.76-1.15) |
| Race | | | | |
| Non-Hispanic White | 1 | [Reference] | 1 | [Reference] |
| Non-Hispanic Black | 1.57 | (1.16-2.12) | 1.75 | (1.26-2.43) |
| Asian | 0.81 | (0.50-1.32) | 1.23 | (0.81-1.87) |
| Hispanic | 1.28 | (1.03-1.60) | 1.27 | (1.00-1.61) |
| Other/unknown | 0.79 | (0.44-1.39) | 1.25 | (0.74-2.11) |
| Medicaid insurance indicator | | | | |
| No | 1 | [Reference] | 1 | [Reference] |
| Yes | 1.65 | (1.31-2.08) | 2.02 | (1.53-2.67) |
| Living in poverty area[b] | | | | |
| No | 1 | [Reference] | 1 | [Reference] |
| Yes | 1.03 | (0.77-1.38) | 0.83 | (0.60-1.17) |
| Charlson comorbidity index | | | | |
| 0-1 | 1 | [Reference] | 1 | [Reference] |
| 2-3 | 1.38 | (0.88-2.18) | 1.44 | (0.92-2.25) |
| 4+ | 1.18 | (0.53-2.63) | 4.22 | (2.55-7.00) |
| Received ³1 dose of vaccine | | | | |
| No | 1 | [Reference] | 1 | [Reference] |
| Yes | 0.74 | (0.61-0.89) | 0.70 | (0.57-0.85) |

Abbreviations: CF, cisgender females; CM, cisgender males; HR, hazard ratio; TM, transmasculine.
[a]Stratified on age due to violation of proportional hazards assumptions; other participant characteristics listed in the table are included in the model as covariates.
[b]Defined as a census tract with ≥20% of households living in poverty.

**Table 9. Multivariable Cox Model[a] Comparing Rates of Hospitalizations in TM Patients With COVID-19 on GAHT and Cisgender Patients**

| Participant characteristics | TM on GAHT vs CF | | TM on GAHT vs CM | |
|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI |
| Gender identity | | | | |
| Cisgender | 1 | [Reference] | 1 | [Reference] |
| TM on GAHT | 0.95 | (0.60-1.51) | 1.06 | (0.66-1.70) |
| Membership site | | | | |
| Kaiser Permanente Northern California | 1 | [Reference] | 1 | [Reference] |
| Kaiser Permanente Southern California | 0.94 | (0.74-1.20) | 0.96 | (0.73-1.25) |
| Race | | | | |
| Non-Hispanic White | 1 | [Reference] | 1 | [Reference] |
| Non-Hispanic Black | 1.38 | (0.94-2.03) | 1.50 | (0.96-2.34) |
| Asian | 1.07 | (0.63-1.82) | 1.45 | (0.87-2.41) |
| Hispanic | 1.27 | (0.97-1.66) | 1.31 | (0.97-1.77) |
| Other/unknown | 0.26 | (0.08-0.81) | 0.87 | (0.39-1.90) |
| Medicaid insurance indicator | | | | |
| No | 1 | [Reference] | 1 | [Reference] |
| Yes | 1.77 | (1.33-2.36) | 2.05 | (1.44-2.91) |
| Living in poverty area[b] | | | | |
| No | 1 | [Reference] | 1 | [Reference] |
| Yes | 0.87 | (0.60-1.27) | 1.07 | (0.72-1.61) |
| Charlson comorbidity index | | | | |
| 0-1 | 1 | [Reference] | 1 | [Reference] |
| 2-3 | 1.49 | (0.88-2.53) | 1.77 | (1.03-3.02) |
| 4+ | 1.40 | (0.53-3.70) | 5.47 | (2.91-10.26) |
| Received ³1 dose of vaccine | | | | |
| No | 1 | [Reference] | 1 | [Reference] |
| Yes | 0.76 | (0.60-0.95) | 0.65 | (0.50-0.84) |

Abbreviations: CF, cisgender females; CM, cisgender males; GAHT, gender affirming hormone therapy; HR, hazard ratio; TM, transmasculine.

[a]Stratified on age due to violation of proportional hazards assumptions; other participant characteristics listed in the table are included in the model as covariates.

[b]Defined as a census tract with ≥20% of households living in poverty.