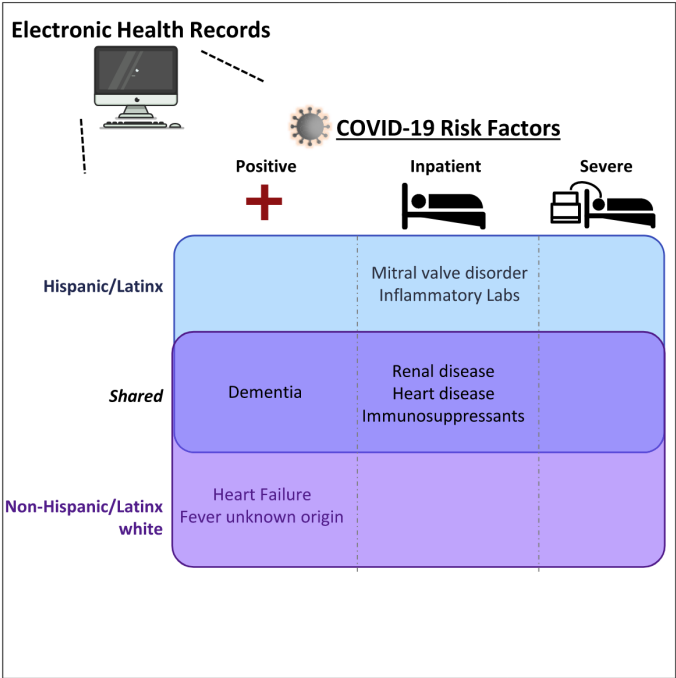


Article

Pre-existing conditions in Hispanics/Latinxs that are COVID-19 risk factors



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HIGHLIGHTS
Hispanics/Latinxs (HL) had worse COVID-19 outcomes than Non-HL whites (NHL-W)

The worse HL outcomes remained after correcting for common comorbid risk factors

Most risk factors were shared, but mitral valve disorder was only a risk in HL

Hospitalized HL presented with a greater inflammatory response

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Article

Pre-existing conditions
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that are COVID-19 risk factors

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SUMMARY

Coronavirus disease 2019 (COVID-19) has exposed health care disparities in minority groups including Hispanics/Latinxs (HL). Studies of COVID-19 risk factors for HL have relied on county-level data. We investigated COVID-19 risk factors in HL using individual-level, electronic health records in a Los Angeles health system between March 9, 2020, and August 31, 2020. Of 9,287 HL tested for SARS-CoV-2, 562 were positive. HL constituted an increasing percentage of all COVID-19 positive individuals as disease severity escalated. Multiple risk factors identified in Non-Hispanic/Latinx whites (NHL-W), like renal disease, also conveyed risk in HL. Pre-existing nonrheumatic mitral valve disorder was a risk factor for HL hospitalization but not for NHL-W COVID-19 or HL influenza hospitalization, suggesting it may be a specific HL COVID-19 risk. Admission laboratory values also suggested that HL presented with a greater inflammatory response. COVID-19 risk factors for HL can help guide equitable government policies and identify at-risk populations.

INTRODUCTION

While still in the midst of the coronavirus disease 2019 (COVID-19) pandemic (Center for Systems Science and Engineering at Johns Hopkins University, 2020; Centers for Disease Control and Prevention, 2020; The Lancet, 2020), knowledge of risk factors associated with COVID-19 susceptibility and severity can shape government policies, identify at-risk populations, guide clinical decision-making, and prioritize future COVID-19 research. COVID-19 has further exposed health care disparities exacting a greater toll on minority groups including Hispanic or Latinx communities. COVID-19 diagnosis rates are greater in US counties with a high Latinx proportion compared with those with a low Latinx proportion (91 vs 82 per 100,000) (Rodríguez-Díaz et al., 2020). The Los Angeles County of Public Health data showed the age-adjusted rate of COVID-19 cases is 113 per 100,000 individuals self-reporting as Hispanics/Latinxs (HL) but only 78 for individuals self-reporting as Non-Hispanic/Latinx whites (NHL-W) (Los Angeles County Department of Public Health, Chief Science Office, 2020). Similar findings have been reported by the New York City Health Department and Chicago Department of Public health where the rates of COVID-19 cases and severe outcomes are roughly twice as high in HL when compared with whites (Chicago Department of Public Health, 2020; New York City Health, 2020).

Linking county or zip code level data with aggregate patient data has shed light on conditions that may explain the higher risk of HL COVID-19 cases and disease severity. Many HL individuals work in the service industry (US Bureau of Labor Statistics, 2019), live in densely populated neighborhoods, and have limited access to both open spaces and nearby supermarkets (Ong et al., 2020; Rodríguez-Díaz et al., 2020). Counties with more monolingual Spanish speakers, higher unemployment rates, and air pollution were associated with higher COVID-19 cases (Rodríguez-Díaz et al., 2020). Less medical coverage and higher rates of comorbidities such as diabetes, cardiovascular disease, and renal disease in HL may contribute as well (Cheng et al., 2019; Rodríguez-Díaz et al., 2020; US Department of Health and Human Services, 2018).

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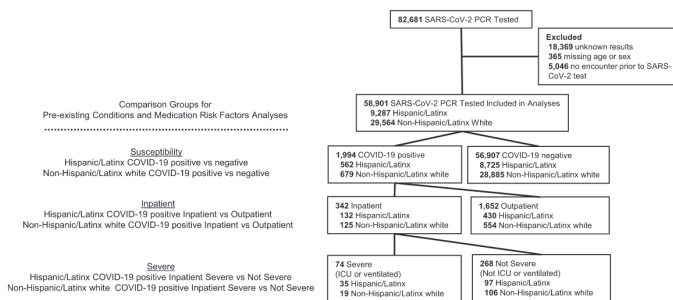


Figure 1. Flow diagram of subjects included in COVID-19 susceptibility, inpatient, and severe analyses for pre-existing conditions and medications

There are limited studies investigating HL characteristics for COVID-19 diagnosis and severe outcomes using individual-level data. In a Providence, Rhode Island, study of HL with COVID-19, 75% were younger than 50 years (Weng et al., 2020). In Baltimore, Maryland, hospitalized HL individuals were younger and had lower rates of comorbidities (hypertension, congestive heart failure, chronic obstructive pulmonary disease) compared with hospitalized non-HL white individuals (Martinez et al., 2020). No previous study using individual level data has investigated the risk factors for COVID-19 diagnosis, inpatient admission, or severe outcome in HL individuals.

In this retrospective study, we aimed to first validate the extendibility of known risk factors for COVID-19 and to determine whether there were pre-existing risk factors observed in HL, but not NHL-W for COVID-19 diagnosis susceptibility, inpatient admission, and severe outcome. We leveraged individual, patient-level, de-identified electronic health record data from the University of California Los Angeles (UCLA) Health System, a single homogeneous medical system. Although many previously identified risk factors were observed in both HL and NHL-W, we identified COVID-19 risk factors that were observed in HL, but not NHL-W. Individuals with numerous pre-existing conditions may be in a general state of poor health, conferring a high risk of hospitalization for any infection, not just COVID-19. To test the hypothesis that certain pre-existing conditions offer a specific risk for COVID-19, we determined if inpatient risk factors for COVID-19 were also inpatient risk factors for influenza.

RESULTS

Study subjects

The UCLA Health System includes two hospitals (520 and 281 inpatient beds) and 210 primary and specialty outpatient locations predominantly within Los Angeles County. We leveraged an extract of the de-identified electronic health records from the UCLA Health System known as the Data Discovery Repository, which contains longitudinal records for more than 1.5 million patients since 2013.

This retrospective analysis included individuals who were tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) via reverse-transcriptase polymerase chain reaction (RT-PCR) within the UCLA Health System between March 9, 2020, and August 31, 2020. Of the 58,901 individuals PCR-tested for SARS-CoV-2 (Tested) meeting inclusion/exclusion criteria (Methods), 1,994 were COVID-19 positive (3.3% of Tested), 342 were admitted in the hospital (Inpatient) (17% of COVID-19 positive), and 74 were treated in the intensive care unit or required intubation (Severe) (3.7% of COVID-19 positive) (Figure 1).

To determine pre-existing conditions and medications associated with COVID-19 outcome in HL, we included HL individuals self-identifying as HL ethnicity and any race. We included all race groups, not only white, as many HL individuals self-identify as "other race" (52% of HL COVID-19 Tested). We analyzed diagnoses entered in the electronic health record (EHR) before an individual's SARS-CoV-2 test. International Statistical Classification of Diseases codes were mapped to ~1,800 phecodes, which have been

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Table 1. Demographics of COVID-19 patient groups

	Demographic	Severe (N = 74)	Inpatient (N = 342)	COVID-19 positive (N = 1,994)	Tested (N = 58,901)
Age group	<18 years	4 (5%)	10 (2%) ↓	112 (5%) ↓	4,119 (6%)
	19–35 years	7 (9%)	34 (9%) ↓	601 (30%) ↑	12,281 (20%)
	36–50 years	11 (14%)	46 (13%) ↓	485 (24%) ↑	13,046 (22%)
	51–65 years	23 (31%)	78 (22%)	436 (21%) ↓	15,236 (25%)
	>65 years	29 (39%) ↓	174 (50%) ↑	360 (18%) ↓	14,219 (24%)
Sex	Female	35 (47%)	159 (46%)	1,021 (51%) ↓	32,193 (54%)
	Male	39 (52%)	183 (53%)	973 (48%) ↑	26,708 (45%)
Race	White or Caucasian	32 (43%)	171 (50%)	908 (45%) ↓	33,997 (57%)
	Black or African American	10 (13%)	33 (9%)	166 (8%) ↑	3,611 (6%)
	Asian	4 (5%)	24 (7%)	118 (5%) ↓	5,137 (8%)
	American Indian or Alaska Native	0 (0%)	0 (0%)	8 (0%)	218 (0%)
	Native Hawaiian or other Pacific Islander	0 (0%)	0 (0%)	2 (0%)	132 (0%)
	Other race	28 (37%)	108 (31%) ↑	490 (24%) ↑	9,695 (16%)
	Unknown race	0 (0%)	6 (1%) ↓	302 (15%) ↑	6,111 (10%)
Ethnicity	Hispanic or Latinx	35 (47%)	132 (38%) ↑	562 (28%) ↑	9,287 (15%)
	Not Hispanic or Latinx	38 (51%)	203 (59%) ↓	1,134 (56%) ↓	43,227 (73%)
	Unknown ethnicity	1 (1%)	7 (2%) ↓	298 (14%) ↑	6,387 (10%)

(↓/↑) indicates a statistically significant negative/positive association ($p < 0.05$) of the demographic and two patient groups. For age group and sex, percentage of Severe was compared with Inpatient, Inpatient was compared with COVID-19 positive, and COVID-19 positive was compared with Tested. Significant association of race and ethnicity for Severe compared Inpatient Severe versus Inpatient Not Severe; for Inpatient compared COVID-19 positive Inpatient versus COVID-19 positive Outpatient; and for COVID-19 positive compared COVID-19 positive versus COVID-19 negative while controlling for age group and sex.

shown to represent meaningful and interpretable phenotypes (Wei et al., 2017). We compared risk factors in HL with COVID-19 outcome risk factors in NHL-W, which has been the study population for many previous analyses (Argenziano et al., 2020; Goyal et al., 2020; Grasselli et al., 2020a; Hirsch et al., 2020; Lighter et al., 2020; Williamson et al., 2020). Of the 1,994 COVID-19 positive individuals, 562 were HL and 679 were NHL-W. Of the 342 COVID-19 positive inpatients, 132 were HL and 125 were NHL-W. Of the 74 COVID-19 positive inpatient severe group, 35 were HL and 19 were NHL-W (Figure 1).

We sought COVID-19 susceptibility risk factors by comparing the COVID-19 positive group with the COVID-19 negative group, inpatient risk factors by comparing the COVID-19 positive inpatient group with the COVID-19 positive outpatient group, and severe risk factors by comparing the COVID-19 positive inpatient severe group with the COVID-19 positive inpatient not severe group.

HL have worse COVID-19 outcomes

Compared with all tested individuals, COVID-19 positive individuals were significantly more likely to be male (48% male COVID-19 positive vs 45% male Tested; odds ratio OR = 1.2 [1.1, 1.3]; $p = 0.002$). Compared with COVID-19 positive individuals, inpatients were more likely to be older than 65 years (50% > 65 years old Inpatient versus 18% > 65 years old COVID-19 positive; OR = 8.1 [6.3, 11]; $p < 0.001$) (Table 1). These findings confirm in this population that males and older individuals face higher risks of severe disease (Chicago Department of Public Health, 2020; Los Angeles County Department of Public Health, Chief Science Office, 2020; New York City Health, 2020).

Self-identified HL individuals constituted an increasing percentage of COVID-19 individuals as disease severity escalated. HL comprised 15% of the Tested population, whereas they comprised 28% of COVID-19 positive individuals (28% COVID-19 positive versus 15% Tested; OR = 2.1 [1.9, 2.3]; $p < 0.001$), 38% of Inpatient individuals (38% Inpatient versus 28% COVID-19 positive; OR = 2.8 [2.1, 3.8]; $p < 0.001$), and 47% of Severe individuals (47% Severe versus 38% COVID-19 positive; OR = 1.4 [0.8, 2.5]; $p = 0.18$)

Table 2. Risk of COVID-19 disease outcome in individuals self-identifying as Hispanic/Latinx versus Non-Hispanic/Latinx white with and without correction of known risk factors, related to Table S2

Outcome (N _{Hispanic/Latinx} / N _{Non-Hispanic/Latinx white})	Model covariates	Odds ratio [95% CI]	p value
COVID-19 positive (562; 679) versus COVID-19 negative (8,725; 28,885)	Age, sex	2.6 [2.3, 3.0]	$<2.2 \times 10^{-22}$
	Age, sex, known risk factors	2.5 [2.2, 2.8]	$<2.2 \times 10^{-22}$
COVID-19 positive inpatient (132; 125) versus outpatient (430; 554)	Age, sex	2.8 [2.0, 4.0]	5.8×10^{-10}
	Age, sex, known risk factors	2.5 [1.8, 3.6]	1.4×10^{-7}

CI, confidence interval.

(Table 1). These findings show that HL had a higher risk of testing positive, and that when positive, suffered from more severe COVID-19 disease.

To evaluate if comorbidities contributed to disproportionate COVID-19 disease outcomes in HL compared with NHL-W, we next corrected for patient histories of known COVID-19 risk factors such as type 2 diabetes, hyperlipidemia, hypertension, and chronic renal disease (Methods and Table S1), many of which are known to disproportionately affect HL individuals (Dominguez et al., 2015; Velasco-Mondragon et al., 2016). After correction for these known risk factors, the odds ratio for having a positive test remained >2.5 in HL, and for being hospitalized remained >2.5 in HL (Tables 2 and S2). These findings support the hypothesis of HL-specific risk factors (medical and/or socioeconomic) that increase the risk of having COVID-19 disease and being hospitalized (Ong et al., 2020).

Pre-existing conditions in HL that are risk factors for testing COVID-19 positive

COVID-19 risk factors (coronary heart disease, congestive heart failure, chronic obstructive pulmonary disease, type 2 diabetes, hyperlipidemia, hypertension, obesity, and chronic renal disease [Goyal et al., 2020; Grasselli et al., 2020a; 2020b; Guan et al., 2020; Gupta et al., 2020; Li et al., 2020; Yang et al., 2020a; Zhou et al., 2020a; Zhu et al., 2020]) have been previously identified primarily from COVID-19 inpatient cohorts and white or Asian populations. By grouping phecodes into these known risk factor categories (Table S1), we determined if these were also risk factors in HL while controlling for age and sex. For COVID-19 diagnosis susceptibility, none of these known risk factors were significant in HL. In NHL-W, congestive heart failure (OR 1.7 [1.2–2.3], $p = 0.001$) and diabetes (OR 1.4 [1.1–1.7], $p = 0.02$) were COVID-19 susceptibility risk factors, whereas hyperlipidemia was protective (OR 0.69 [0.57–0.84], $p = 1.6 \times 10^{-4}$) (Figure 2).

To identify additional pre-existing conditions aside from known risk factors that may be COVID-19 susceptibility risk factors in HL, we evaluated all phecodes while controlling for age and sex. In HL, we did not identify any additional phecodes associated with COVID-19 diagnosis susceptibility after multiple testing correction (Methods). In contrast for NHL-W, dementia (OR 4.1 [2.7–6.1], $p = 3.4 \times 10^{-6}$), diastolic heart failure (OR 3.0 [1.9–4.4], $p = 5.2 \times 10^{-6}$), and fever of unknown origin (OR 2.0 [1.6–2.4], $p = 1.3 \times 10^{-10}$) were pre-existing susceptibility risk factors (Figure S1 and Table S3). Of these NHL-W risk factors, dementia was nominally significant and had a similar effect size in HL (OR 3.7 [1.8–7.0], $p = 8.3 \times 10^{-4}$). This suggests dementia was a shared risk factor in NHL-W and HL for testing COVID-19 positive. We did not identify an age- or sex-specific interaction for these significant phecodes in NHL-W.

We also evaluated if any of the NHL-W risk factor effects were significantly different than the HL risk factor effects by modeling the interaction term of ethnicity (HL versus NHL-W) and the phecode (Methods). The COVID-19 susceptibility odds ratio increased by 1.5 [95% CI 1.1–2.0] ($p = 0.004$) if individuals were NHL-W and exhibited pre-existing fever of unknown origin compared with individuals who were HL and had pre-existing fever of unknown origin.

To determine if the risk factors were not correlated with and not already explained by previously identified COVID-19 risk factors as above (coronary heart disease, congestive heart failure, chronic obstructive pulmonary disease, type 2 diabetes, hyperlipidemia, hypertension, obesity, and chronic renal disease [Goyal et al., 2020; Grasselli et al., 2020a; Guan et al., 2020; Li et al., 2020; Yang et al., 2020a; Zhou et al., 2020a; Zhu et al., 2020]) (Table S1 and Methods), we controlled for these in our model in addition to age and sex. For NHL-W, all pre-existing susceptibility risk factors including fever of unknown origin (OR 2.0 [1.6–2.4], $p =$

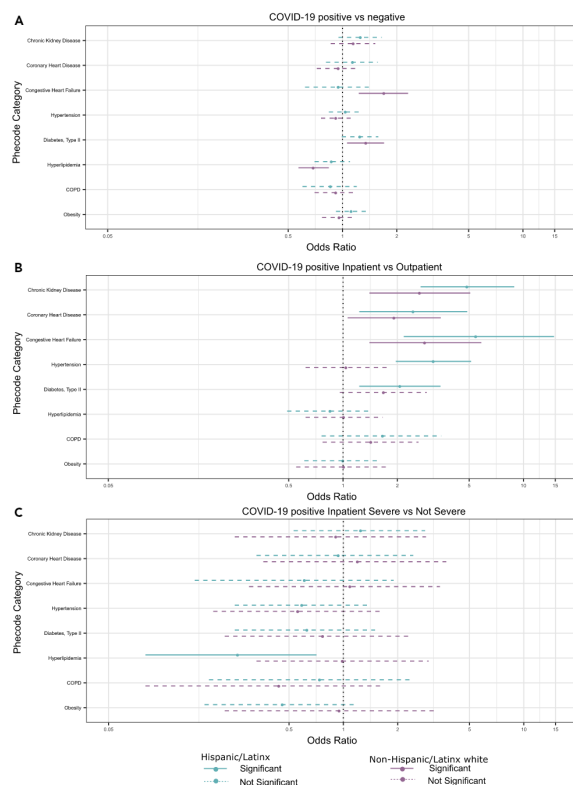


Figure 2. Association of known risk factors with COVID-19 outcomes

Odds ratios for known risk factor phcode categories correcting for age and sex in (A) COVID-19 positive versus negative, (B) COVID-19 positive Inpatient versus Outpatient, and (C) COVID-19 positive Inpatient Severe versus Not Severe. Hispanics/Latinxs (blue) and Non-Hispanic/Latinx whites (purple). 95% confidence intervals for odds ratios are shown. Solid lines indicate risk factors that are nominally significant. Dotted lines are not nominally significant. COPD, chronic obstructive pulmonary disease. Related to [Table S1](#).

1.7×10^{-10}) remained significant after controlling for these known risk factors ([Table S4](#)). This result showed that fever of unknown origin, which could occur in cancer, occult infections, and inflammatory conditions ([Roth and Basello, 2003](#)), was a risk factor for COVID-19 positive testing in NHL-W independent of previously identified risk factors, and not observed as a risk factor in HL.

Pre-existing conditions in HL that are risk factors for COVID-19 hospitalization

Of the known COVID-19 risk factors, chronic kidney disease (OR 4.9 [2.7, 8.9], $p = 2.1 \times 10^{-7}$), hypertension (OR 3.2 [2.0, 5.1], $p = 3.0 \times 10^{-6}$), congestive heart failure (OR 5.5 [2.2, 15], $p = 2.5 \times 10^{-4}$), diabetes (2.1 [1.2, 3.5], $p = 0.007$), and coronary heart disease (OR 2.5 [1.2, 4.9], $p = 0.01$) were significant risk factors for hospitalization in HL. Chronic kidney disease (OR 2.7 [1.4, 5.1], $p = 0.003$), congestive heart failure (OR 2.8 [1.4,

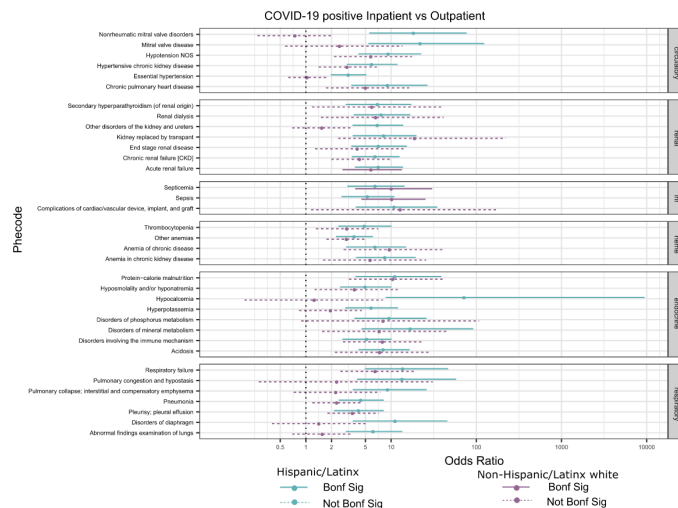


Figure 3. Significant pre-existing condition risk factors for COVID-19 inpatient admission correcting for age and sex grouped by pcode category, related to Tables S3, S4, S5, S6, and S7

Hispanics/Latinxs (blue) and Non-Hispanic/Latinx whites (purple). 95% confidence intervals for odds ratios are shown. Solid lines indicate risk factors that are Bonferroni significant. Dotted lines are not Bonferroni significant. inf, infectious; heme, hematopoietic; Bonf, Bonferroni

5.8], $p = 0.004$), and coronary heart disease (OR 1.9 [1.1, 3.5], $p = 0.03$) were also significant risk factors for hospitalization in NHL-W.

When evaluating additional pcodes that may be pre-existing risk factors for hospitalization in HL, we found nonrheumatic mitral valve disorder (OR 18 [5.5–77], $p = 1.1 \times 10^{-6}$), hypertension (OR 3.2 [2.0–5.1], $p = 3.0 \times 10^{-6}$), sepsis (OR 5.3 [2.6–11], $p = 4.5 \times 10^{-6}$), respiratory failure (OR 14 [4.9–47], $p = 1.3 \times 10^{-7}$), and pcodes consistent with severe renal disorders including chronic renal failure (OR 6.5 [3.5–13], $p = 7.5 \times 10^{-6}$), acute renal failure (OR 7.1 [3.8–14], $p = 1.4 \times 10^{-6}$), end-stage renal disease (OR 7.1 [3.4–15], $p = 2.0 \times 10^{-6}$), renal dialysis (OR 7.7 [3.6–17], $p = 2.0 \times 10^{-6}$), and kidney transplant (OR 8.3 [3.5–20], $p = 1.5 \times 10^{-6}$) to be significant inpatient risk factors after multiple testing correction (Figure 3 and Table S5). Sepsis and acute renal failure were also significant NHL-W inpatient risk factors (sepsis OR 10 [4.5–25], $p = 1.2 \times 10^{-6}$; acute renal failure OR 5.8 [2.7–13], $p = 6.4 \times 10^{-6}$) (Figure 3 and Table S5). Respiratory failure and the other renal disorders were nominally significant NHL-W inpatient risk factors and similar in effect size to HL (Figure 3 and Table S5).

For these significant inpatient admission risk pcodes in HL and NHL-W, we found that only kidney transplant had a significant age >65 years interaction in HL for inpatient admission. Although age >65 years (OR 11 [6.5–19], $p = 2.2 \times 10^{-23}$) and kidney transplant (OR 9.4 [4.1–23], $p < 2.4 \times 10^{-7}$) individually increased the inpatient admission risk, being both >65 years old and a kidney transplant recipient decreased this risk (OR 0.02 [1.4 $\times 10^{-4}$ –0.50], $p = 0.02$). We did not identify a sex-specific interaction for these significant pcodes in HL and NHL-W.

Nonrheumatic mitral valve disorder is a specific HL COVID-19 inpatient risk factor

The risk factor effects of nonrheumatic mitral valve disorder and hypertension for HL was significantly increased compared with their risk factor effects in NHL-W. The inpatient odds ratio increased by 25 [95% CI 5–140] ($p = 3.5 \times 10^{-5}$) if individuals were HL and had nonrheumatic mitral valve disorder compared

with individuals who were NHL-W and had nonrheumatic mitral valve disorder. The inpatient odds ratio increased by 2.3 [1.2–4.3] ($p = 0.01$) if individuals were HL and had hypertension compared with individuals who were NHL-W and had hypertension (Methods). Controlling for known risk factors in the HL group, non-rheumatic mitral valve disorders (OR 8.9 [2.3–42], $p = 0.001$) and respiratory failure (OR 6.5 [2.1–23], $p = 0.001$) remained significantly associated with inpatient admission suggesting they were not correlated with or already explained by previously identified COVID-19 risk factors (Table S6).

We determined if these COVID-19 inpatient risk factors observed in HL, but not in NHL-W, were also observed in another viral infection, influenza. Similar to COVID-19, HL ethnicity increased the risk of inpatient admission for individuals with influenza (OR 2.8 [2.1–4.0], $p = 2.2 \times 10^{-10}$) and remained significantly elevated when correcting for known risk factors (OR 2.4 [1.7–3.4], $p = 3.9 \times 10^{-7}$). In contrast to the observations in COVID-19 positive inpatients, nonrheumatic mitral valve disorder was not a pre-existing risk factor for hospitalization due to influenza for either HL or NHL-W individuals (Figure S2 and Table S7).

As with COVID-19, hypertension was a significant pre-existing risk factor for hospitalization due to influenza in HL individuals (OR 4.3 [2.4–7.8], $p = 1.4 \times 10^{-6}$), but not in NHL-W individuals (Figure S2 and Table S7). Pre-existing renal disorders also conferred a similar risk of hospitalization for COVID-19 as they did for influenza in HL and NHL-W. Severe renal disorders including end-stage renal disease (OR 19 [8.2–47], $p = 1.4 \times 10^{-11}$) and renal dialysis (OR 24 [9.1, 72], $p = 1.3 \times 10^{-10}$) remained risk factors for hospitalization due to influenza only for HL individuals. Acute renal failure was a risk factor for hospitalization due to influenza for HL (OR 15 [7.8–28], $p = 7.8 \times 10^{-16}$) and NHL-W (OR 8.5 [4.6–15], $p = 5.8 \times 10^{-11}$) (Figure S2 and Table S7).

Pre-existing conditions in HL that are risk factors for COVID-19 inpatient severe outcomes

Of the known COVID-19 risk factors, hyperlipidemia was protective in HL for the COVID-19 positive inpatient severe outcome (OR 0.26 [0.08–0.71], $p = 0.008$) (Figure 2). This finding was not observed in NHL-W. We did not identify any additional phecodes significantly associated with the COVID-19 Severe group, although our power was low ($N = 35$ HL, $N = 19$ NHL-W COVID-19 positive with severe outcome) compared to the COVID-19 Inpatient group ($N = 132$ HL, $N = 125$ NHL-W).

Admission vitals and labs among COVID-19 positive inpatients

One potential explanation for worse COVID-19 outcomes in HL could be that HL individuals presented to the health system with more severe disease. We therefore sought to determine if HL COVID-19 positive inpatient disease severity was reflected in more abnormal vital signs or laboratory values compared with NHL-W individuals. Controlling for age, sex, and known risk factors (Table S1), we analyzed vitals and labs ± 1 day of inpatient admission date. White blood cell count (mean $7.93 \pm$ standard deviation $4.2 \times 10^3/\mu\text{L}$ HL versus $6.85 \pm 4.0 \times 10^3/\mu\text{L}$ NHL-W, $p = 0.046$), platelet count ($216 \pm 91 \times 10^3/\mu\text{L}$ HL versus $187 \pm 93 \times 10^3/\mu\text{L}$ NHL-W, $p = 0.023$), creatinine (1.8 ± 2.7 mg/dL HL versus 1.3 ± 0.9 mg/dL NHL-W, $p = 0.045$), and C-reactive protein (9.0 ± 6.4 mg/dL HL versus 7.6 ± 6.5 mg/dL NHL-W, $p = 0.011$) were higher in HL COVID-19 positive inpatients compared with NHL-W COVID-19 positive inpatients (Table 3). This suggests hospitalized HL presented with a greater inflammatory response consistent with more advanced disease compared with hospitalized NHL-W.

Extremes of COVID-19 outcome susceptibility or resistance

Next, we identified HL individuals who were outliers based on what would be an expected COVID-19 clinical course predicated on their major predictive factors, namely, age and pre-existing conditions. These outlier groups included (1) individuals who were young with no major comorbidities (18–35 years old), but who were hospitalized, and (2) older individuals with high risk for a serious COVID-19 clinical course (>70 years old with at least three of the known risk factors), but who were not hospitalized. These individuals may represent extremes of COVID-19 susceptibility and resistance and therefore may carry genetic immunological susceptibilities or resistances to infection (Blanco-Melo et al., 2020; COVID-19 Host Genetics Initiative, 2020; Ellinghaus et al., 2020; Nguyen et al., 2020). Of the 105 young individuals with no major comorbidities, 8 (8%) were admitted to the hospital. These admitted individuals had either few pre-existing conditions (e.g., viral infection) or developmental delay. Of the 30 COVID-19 positive older individuals with a high risk for hospitalization, 9 (30%) were not hospitalized. These proportions were similar in NHL-W (5 inpatients of 138 young individuals with no major comorbidities [4%]; 40 not hospitalized of 88 COVID-19 positive older individuals with a high risk for hospitalization [45%]).

Table 3. Vitals and laboratory test results for Hispanic/Latinx COVID-19 positive inpatients and Non-Hispanic/Latinx white COVID-19 positive inpatients

Vital or Lab	Hispanic/Latinx		Non-Hispanic/Latinx white		p value
	Mean \pm SD	N (N total = 132)	Mean \pm SD	N (N total = 125)	
Temperature ($^{\circ}$ F)	97.9 \pm 2.6	114	97.8 \pm 1.4	125	0.492
Pulse (bpm)	81 \pm 25	115	78 \pm 21	125	0.761
Systolic blood pressure (mmHg)	121 \pm 19	115	124 \pm 22	125	0.375
White blood cell count ($\times 10^3/\mu$ L)	7.93 \pm 4.2	131	6.85 \pm 4.0	124	0.046
Absolute lymphocyte count ($\times 10^3/\mu$ L)	1.11 \pm 0.6	125	1.10 \pm 0.7	115	0.918
Platelet count ($\times 10^3/\mu$ L)	216 \pm 91	131	187 \pm 93	124	0.023
Hemoglobin (g/dL)	12.1 \pm 2.4	131	12.0 \pm 2.2	124	0.789
Hematocrit (%)	37 \pm 6.8	131	37 \pm 6.3	124	0.593
Sodium (mmol/L)	137 \pm 5.0	128	138 \pm 5.5	125	0.266
Potassium (mmol/L)	4.2 \pm 0.5	128	4.2 \pm 0.6	125	0.828
Urea nitrogen (mg/dL)	22.5 \pm 18	128	26.1 \pm 20	125	0.751
Creatinine (mg/dL)	1.79 \pm 2.7	130	1.31 \pm 0.9	125	0.045
C-reactive protein (mg/dL)	9.0 \pm 6.4	110	7.6 \pm 6.5	94	0.011
Sedimentation rate, erythrocyte (mm/h)	57 \pm 30	34	51 \pm 30	36	0.190

Pre-existing medications associated with COVID-19 outcomes

Controversy remains over the protective or detrimental effects of medication classes including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) (Mancia et al., 2020; Reynolds et al., 2020; Zhang et al., 2020c), immunosuppressants (D'Antiga, 2020; Mehta et al., 2020; Monti et al., 2020; Novi et al., 2020; Ritchie and Singanayagam, 2020), steroids (Shang et al., 2020; Zha et al., 2020), anticoagulants (Tang et al., 2020; Thachil, 2020; Thachil et al., 2020), and non-steroidal anti-inflammatory drugs (Little, 2020). We investigated whether the prescription of these medications 90 days before SARS-CoV-2 testing (see Table S8 for drugs assigned to each medication class) was associated with COVID-19 susceptibility, inpatient admission, or severe outcome while controlling for age, sex, and known risk factors (Methods). Comparing COVID-19 positive inpatients to outpatients, both HL and NHL-W individuals prescribed oral steroids (HL OR 3.5 [1.6, 7.8], $p = 0.002$; NHL-W OR 3.9 [1.9, 8.0], $p < 0.001$) or other immunosuppressants (HL OR 5.4 [2.3, 13], $p < 0.001$; NHL-W OR 4.6 [1.5, 13], $p = 0.006$) had increased risk of inpatient admission. We did not observe that being prescribed ACEI or ARBs increased the risk of testing positive for SARS-CoV-2, being admitted to the hospital, or having a severe course, as previously reported (Reynolds et al., 2020) (Tables 4 and S9).

Previous studies have not investigated the association of medication duration with COVID-19 outcomes as has been performed in influenza, where longer ACEI and ARB usage was protective for influenza incidence (Chung et al., 2020). In our study, comparing medication prescription of <1 year with no prescription and medication prescription of ≥ 1 year with no prescription did not show an association of ACEIs or ARBs with COVID-19 inpatient admission risk in HL or NHL-W (Figure S3). For HL, immunosuppressant prescription <1 year and ≥ 1 year compared with no prescription remained a risk factor for inpatient admission (<1 year OR 6.7 [1.6–31], $p = 0.008$; ≥ 1 year OR 4.2 [1.6–11], $p = 0.004$). Steroid prescription was only associated with increased inpatient admission risk for HL if prescribed less than 1 year compared with no prescription (<1 year OR 5.8 [1.7–20], $p = 0.005$) (Figure S3).

DISCUSSION

Identifying COVID-19 risk factors can inform patient care, public policies, and future research aimed at improving outcomes and reducing health care disparities. We leveraged our ability to query de-identified electronic health records to determine COVID-19 risk factors for HL in the UCLA Health System. Our analysis at the individual patient-level successfully captured the results of previously reported risk factors for more severe COVID-19 disease, such as chronic renal disease, diabetes, and hypertension across ethnicities (Goyal et al., 2020; Grasselli et al., 2020a, 2020b; Guan et al., 2020; Gupta et al., 2020; Li et al., 2020; Yang et al., 2020a; Zhou et al., 2020a; Zhu et al., 2020), validating our EHR-based approach. Our analysis

Table 4. Pre-existing medications associated with COVID-19 disease outcomes, related to Figure S3, Tables S8, and S9

Hispanic/Latinx									
Medication	COVID-19 Positive (N = 562) versus negative (N = 8,725)			Inpatient (N = 132) versus Outpatient (N = 430)			Severe (N = 35) versus Not Severe (N = 97)		
	OR [95% CI]	N _{pos}	N _{neg}	OR [95% CI]	N _{Inp}	N _{Out}	OR [95% CI]	N _{Sev}	N _{not Sev}
ACE Inh	1.4 [0.9, 2.1]	24	302	0.8 [0.3, 2.3]	9	15	1.8 [0.3, 8.5]	2	7
ARBs	0.9 [0.5, 1.5]	17	317	0.8 [0.3, 2.6]	9	8	1.5 [0.3, 7.6]	2	7
Immuno suppressants	1.1 [0.8, 1.6]	38	493	5.4 [2.3, 13]*	23	15	1.0 [0.3, 3.4]	6	17
Steroids	0.9 [0.7, 1.3]	44	712	3.5 [1.6, 7.8]*	23	21	0.4 [0.1, 1.3]	3	20
Anticoagulant	1.0 [0.5, 2.0]	8	134	0.7 [0.1, 3.6]	5	3	5.2 [0.7, 37]	2	3
NSAID	0.9 [0.6, 1.2]	42	749	0.6 [0.2, 1.3]	10	32	0.5 [0.1, 2.5]	1	9
Non-Hispanic/Latinx white									
Medication	COVID-19 positive (N=679) versus negative (N=28,885)			Inpatient (N=125) versus Outpatient (N=554)			Severe (N=19) versus Not Severe (N=106)		
	OR [95% CI]	N _{pos}	N _{neg}	OR [95% CI]	N _{Inp}	N _{Out}	OR [95% CI]	N _{Sev}	N _{not Sev}
ACE Inh	1.1 [0.7, 1.6]	22	934	1.1 [0.4, 3.0]	8	14	1.3 [0.12, 7.7]	1	7
ARBs	1.2 [0.8, 1.7]	30	1,237	1.1 [0.4, 3.1]	10	20	0.22 [0, 2.0]	0	10
Immunosuppressants	1.0 [0.6, 1.6]	19	788	4.6 [1.5, 13]*	10	9	0.2 [0, 1.5]	0	10
Steroids	1.1 [0.8, 1.5]	49	1,940	3.9 [1.9, 8.0]*	23	26	0.4 [0.1, 1.5]	2	21
Anticoagulant	1.0 [0.5, 1.6]	14	595	5.8 [1.3, 36]*	12	2	1.6 [0.3, 7.2]	2	10
NSAID	1.0 [0.8, 1.4]	52	2,259	2.6 [1.3, 5.4]*	18	34	0.6 [0.1, 2.2]	2	16

CI, confidence interval; pos, positive; neg, negative; Inp, Inpatient; Out, outpatient; Sev, Severe; not Sev, Not Severe, ACE inh, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; NSAID = non-steroidal anti-inflammatory drug.

*p < 0.05.

at the individual, patient level also successfully captured the results of previously reported health disparities in HL individuals who were identified at the aggregate level (Chicago Department of Public Health, 2020; Los Angeles County Department of Public Health, Chief Science Office, 2020; New York City Health, 2020; Rodríguez-Díaz et al., 2020). Moreover, we identified risk factors for COVID-19 inpatient admission, some of which were specific to HL and not observed as risk factors in NHL-W.

Having pre-existing nonrheumatic mitral valve disorder was an HL risk factor for hospitalization, but this condition was not observed as a risk factor in NHL-W. Nonrheumatic mitral valve disorder has not been previously reported to be a COVID-19 risk factor, possibly because it has not been evaluated in the HL population. Nonrheumatic mitral valve disorder was not correlated with known risk factors such as coronary heart disease and was specific to COVID-19, as it was not an influenza inpatient risk factor in HL individuals. Previous studies investigating influenza inpatient admission risk factors did not identify mitral valve disorders either (Ono et al., 2016; Puig-Barberà et al., 2016). It is possible that symptoms of mitral valve disorders such as underlying dyspnea may exacerbate COVID-19 symptoms leading to an increased risk of inpatient admission. Further studies are necessary to validate this risk factor and determine the mechanism of association.

Significant risk factors for becoming critically ill (intensive care unit admission or death) among hospitalized COVID-19 patients include hypertension, renal disease (chronic renal disease, acute kidney injury), cardiac disease (cardiac injury, coronary artery disease), pulmonary disease (chronic obstructive pulmonary disease, acute respiratory distress syndrome), diabetes, hyperlipidemia, and obesity (Argenziano et al., 2020; Hirsch et al., 2020; Huang et al., 2020; Li et al., 2020; Lighter et al., 2020; Wang et al., 2020b; Williamson et al., 2020; Zhou et al., 2020a). These analyses were performed in China, Italy, United Kingdom and United States, and not sub-grouped by ethnicity if applicable. Many of these risk factors including chronic kidney disease, hypertension, congestive heart failure, diabetes, and coronary heart disease were HL risk factors for inpatient admission. Additional renal disorders such as acute renal failure, end-stage renal

disease, and renal dialysis were risk factors for hospitalization in HL individuals and were also risk factors in NHL-W individuals. Hypertension, on the other hand, was a much stronger risk factor for hospitalization in HL than in NHL-W. For COVID-19 severe outcomes in our study, hyperlipidemia decreased risk in HL. Previous studies have been mixed on cholesterol risk in COVID-19 as hyperlipidemia increased the risk for mortality among patients in the intensive care unit (Grasselli et al., 2020b), but lower cholesterol levels were associated with COVID-19 inpatient severity (Wei et al., 2020). Last, reduced vitamin D has been variably associated with worse COVID-19 outcomes, and a pilot clinical trial of vitamin D treatment showed improved outcomes (Entrenas Castillo et al., 2020; Ilie et al., 2020; Jain et al., 2020; Rhodes et al., 2020). However, we did not find an association of pre-existing vitamin D insufficiency with any COVID-19 outcomes.

The risk of inpatient admission for HL compared with NHL-W remained elevated even when controlling for multiple comorbidities. One contributing explanation could be that HL patients present initially with more advanced disease. To address this objectively, we compared whether presenting vital signs or laboratory values were more severe for HL inpatients than NHL-W inpatients. Although vital signs were similar in both groups, we found that HL had higher white blood cell counts, platelets, creatinine, and C-reactive protein, all potential inflammatory and acute phase reactants consistent with more advanced disease (Ayalew, 2020; Kushner, 2020). Previous studies have shown leukocytosis, elevated creatinine, and elevated C-reactive protein were associated with a severe COVID-19 outcome among hospitalized patients (Ali et al., 2020; Cheng et al., 2020; Li et al., 2020; Zhang et al., 2020a, 2020b; Zhou et al., 2020a). Thrombocytopenia, rather than thrombocytosis, during hospitalization was a risk factor for severe COVID-19 outcome (Goyal et al., 2020; Guan et al., 2020; Huang et al., 2020; Lippi et al., 2020; Yang et al., 2020b).

There has been concern that some individuals with COVID-19 have an exaggerated immune response resulting in cytokine storm or secondary hemophagocytic lymphohistiocytosis, and studies have suggested that short-term immunosuppression is warranted (Mehta et al., 2020; Ritchie and Singanayagam, 2020; Zhou et al., 2020b). Previous studies investigated small numbers of COVID-19 positive individuals (<4) on immunosuppression before COVID-19 diagnosis, finding that these individuals in general did well and did not have a severe outcome (D'Antiga, 2020; Monti et al., 2020; Novi et al., 2020). Here we analyzed 150 individuals on either oral steroids or other immunosuppressants. Both HL and NHL-W individuals on oral steroids or immunosuppressants had an increased risk of inpatient admission. These medications did not increase the risk of an inpatient severe outcome, although the Severe analysis group had less power. The explanation for increased risk of inpatient admission may be biological or due to clinician bias. Immunosuppressed COVID-19 individuals may have more severe symptoms requiring inpatient admission. Clinicians may also have a lower threshold of inpatient admission for patients on immunosuppressive medication. We did not assess whether immunosuppressive medication was stopped, continued, or changed on admission, and therefore, we are unable to draw conclusions on whether to adjust immunosuppression in COVID-19 hospitalized patients.

Recognizing COVID-19 risk factors can encourage individuals with these risk factors to take appropriate precautions, understand how pre-morbid conditions may affect COVID-19 disease, anticipate necessary medical treatment, and possibly reduce risk by managing these conditions (CDC, 2020). Public health measures to promote accurate COVID-19 information for the general population may not be as effective in minority populations. In Pennsylvania, the Center for Disease Control and Prevention's (CDC) Racial and Ethnic Approaches to Community Health (REACH) program engaged HL community leaders and learned that the community had difficulty accessing reliable information in Spanish (Calo et al., 2020). As such REACH disseminated Spanish written resources for COVID-19 and hosted multiple Spanish-language community-facing COVID-19 information sessions. The Los Angeles County of Public Health recommended engaging communities to provide culturally and linguistically appropriate outreach, education, and engagement (Los Angeles County Department of Public Health, Chief Science Office, 2020). They established a COVID-19 website with information and educational materials in multiple languages including Spanish (Los Angeles County of Public Health, 2020). The Latino Coalition for a Healthy California also provided COVID-19 information and hosted webinars in Spanish (Latino Coalition for a Health California, 2020).

This study identifies risk factors for COVID-19 inpatient admission that are specific to HL and others that were shared with NHL-W. These risk factors should spur future work in understanding the mechanistic underpinnings of these observations and implementing equitable strategies to mitigate these risk factors.

Limitations of the study

Additional explanations for the increased HL inpatient admission risk compared with NHL-W may be environmental such as air pollution (Brandt et al., 2020), socioeconomic such as access to health care (Chowk-wanyun and Reed, 2020; Ong et al., 2020), delay from symptom onset to health care presentation (Chowell et al., 2012), and genetic susceptibility (COVID-19 Host Genetics Initiative, 2020; Kuo et al., 2020). These additional covariates were not available in our de-identified EHR dataset. Geographical location like zip codes was not available to link environmental exposures such as air pollution (Wang et al., 2020a; Zoran et al., 2020) or temperatures (Poirier et al., 2020). We also did not have data regarding socioeconomic factors such as income or health insurance, which has been used as a proxy for socioeconomic status in other studies (Casey et al., 2018). We did not analyze data from the fall and winter seasons of 2020 as the study period was from March 9, 2020, to August 31, 2020. We did not investigate all self-identified minority race groups such as African Americans. The sample size of African Americans with COVID-19 was 70% less than Hispanics/Latinx with only 10 African Americans with a severe outcome. Focusing on other minority groups, longer study periods, environmental factors, and socioeconomic factors are areas of future work to be pursued.

Resource availability

Lead contact

Requests for additional information can be directed to the Lead Contacts: Timothy S Chang (timothychang@mednet.ucla.edu); Manish J Butte (mbutte@mednet.ucla.edu); Bogdan Pasaniuc (bpasaniuc@mednet.ucla.edu).

Material availability

This study did not generate unique reagents.

Data and code availability

Individual electronic health record data are not publicly available due to patient confidentiality and security concerns. Collaboration with the study authors who have been approved by UCLA Health for Institutional Review Board-qualified studies are possible and encouraged. Code is available on GitHub: <https://github.com/TSCang-Lab/preexisting-conditions-HL-COVID19>.

METHODS

All methods can be found in the accompanying [Transparent methods supplemental file](#).

CONSORTIA

UCLA Precision Health Data Discovery Repository Working Group

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SUPPLEMENTAL INFORMATION

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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Supplemental information

Pre-existing conditions

in Hispanics/Latinxs

that are COVID-19 risk factors

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Supplemental Figures

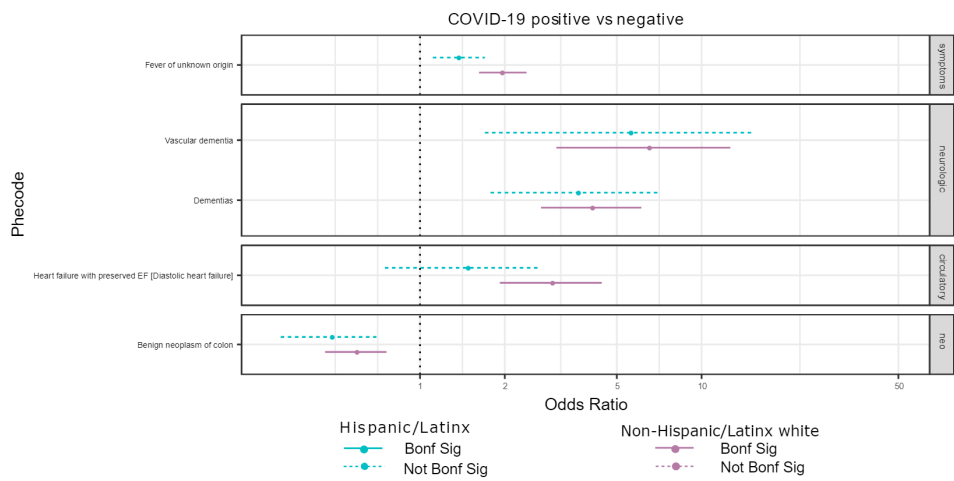


Figure S1. Related to Figure 3. Significant pre-existing condition risk factors for COVID-19 susceptibility correcting for age and sex (Model 1) grouped by phecode category for Hispanics/Latinxs (blue) and Non-Hispanic/Latinx whites (purple). 95% confidence intervals for odds ratios are shown. Solid lines indicate risk factors that are Bonferroni significant. Dotted lines are not Bonferroni significant. neo = neoplasm, Bonf = Bonferroni.

Influenza Inpatient vs Outpatient

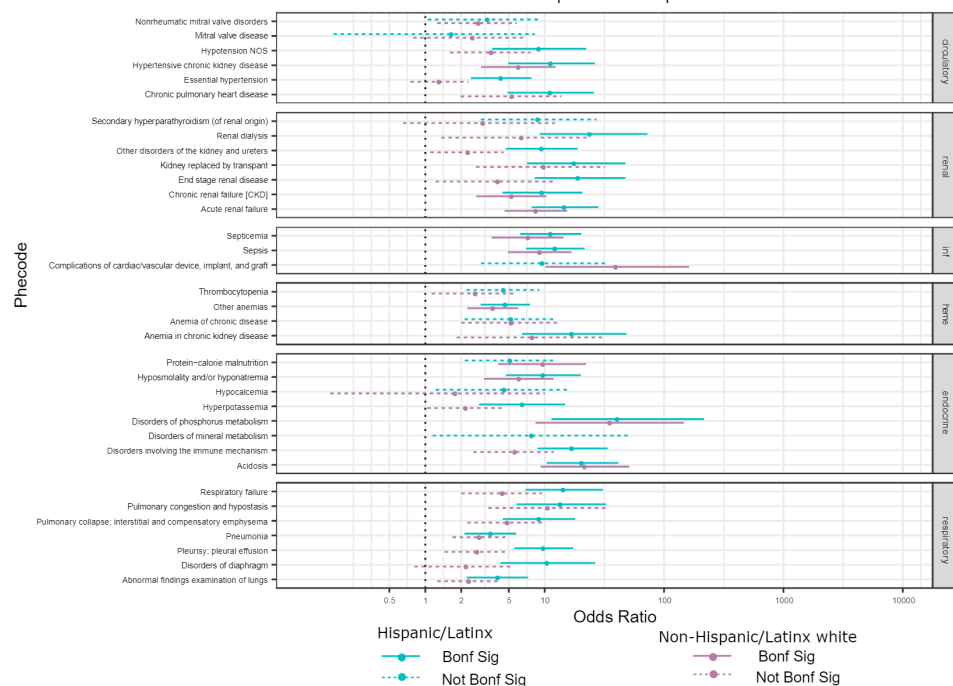


Figure S2. Related to Figure 3. For phecodes that were significant COVID-19 risk factors for hospitalization in Hispanics/Latinxs or Non-Hispanics/Latinx whites, the phecode odds ratios and 95% confidence intervals of influenza inpatient admission correcting for age and sex (Model 1) are shown for Hispanics/Latinxs (blue) and Non-Hispanics/Latinx whites (purple). Solid lines indicate risk factors that are Bonferroni significant. Dotted lines are not Bonferroni significant. inf = infectious, heme = hematopoietic, Bonf = Bonferroni

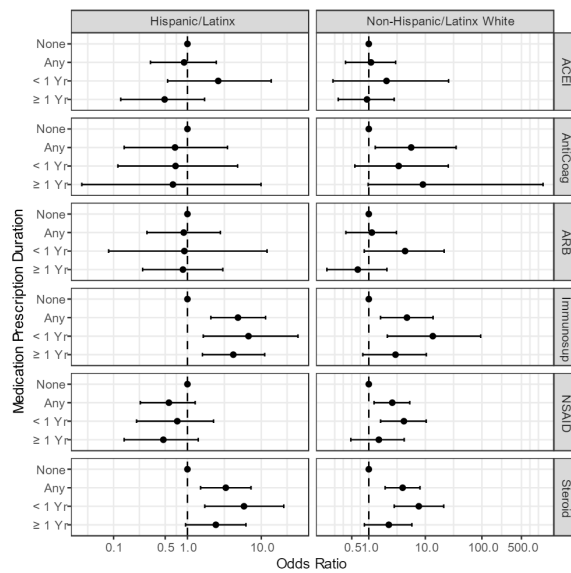


Figure S3. Related to Table 4. COVID-19 inpatient admission odds ratio for medication prescription 90 days prior to SARS-CoV-2 testing (Any), medication prescription duration for less than one year (< 1 Yr), and medication prescription duration greater than one year (≥ 1 Yr) for Hispanics/Latinxs and Non-Hispanic/Latinx whites. ACEI = angiotensin converting enzyme inhibitors, AntiCoag = anticoagulant, ARB = angiotensin receptor blockers, Immunosup = immunosuppressant, NSAID = non-steroidal anti-inflammatory drugs.

Supplemental Tables

Table S2. Related to Table 2. Risk of COVID-19 disease outcome in individuals self-identifying as Hispanic/Latinx versus Non-Hispanic/Latinx white with and without correction of known risk factors. Includes age and sex covariate effects. CI = confidence interval, HL = Hispanics/Latinxs, OR = odds ratio

Outcome (N _{Hispanic/Latinx} ; N _{Non-Hispanic/Latinx white})	Model Covariates	HL OR [95% CI]	HL p-value	Age OR [95% CI], p-val	Age ² OR (per 1000 years ²) [95% CI], p-val	Sex OR (Female) [95% CI], p-val
COVID-19 positive (562; 679) vs COVID-19 negative (8,725; 28,885)	age, sex	2.6 [2.3, 3.0]	<2.2 x 10 ⁻²²	1.0 [0.99-1.01], 0.89	0.94 [0.83-1.06], 0.30	0.85 [0.76-0.95], 5.4x10 ⁻³
	age, sex, known risk factors	2.5 [2.2, 2.8]		1.0 [0.99-1.01], 0.71	0.94 [0.83-1.07], 0.35	0.84 [0.75-0.95], 3.7x10 ⁻³
COVID-19 positive Inpatient (132; 125) vs Outpatient (430; 554)	age, sex	2.8 [2.0, 4.0]	5.8 x 10 ⁻¹⁰	0.96 [0.93-0.99], 0.03	2.4 [1.7-3.4], 2.1x10 ⁻⁷	0.65 [0.48-0.89], 6.4x10 ⁻³
	age, sex, known risk factors	2.5 [1.8, 3.6]		0.97 [0.94-1.01], 0.14	2.0 [1.4-2.7], 1.7x10 ⁻⁴	0.71 [0.52-0.98], 0.04

Transparent Methods

Study design

This was an observational case-control study within a cohort of patients registered at the UCLA Health System after January 1, 2013. The UCLA Health System includes two hospitals (520 and 281 inpatient beds) and 210 primary and specialty outpatient locations predominantly within Los Angeles County. We leveraged an extract of the de-identified EHR from the UCLA Health System known as the UCLA Data Discovery Repository (DDR), developed under the auspices of the UCLA Health Office of Health Informatics Analytics and the UCLA Institute of Precision Health. The DDR contains longitudinal electronic records for more than 1.5 million patients since 2013, including patient demographics, problems, medications, vital signs, past medical history, and laboratory data. UCLA Health serves roughly five percent of Los Angeles county, which is the main catchment area. Individuals in Los Angeles county are seen by other public and private hospitals, some of which service a higher percentage of Hispanic/Latinx (HL) individuals and some of which service a higher percentage of Non-Hispanic/Latinx white (NHL-W) individuals (UC Health, 2019; UCLA Health, 2020; U.S. Census Bureau, 2018). This study was considered human subjects research exempt by the UCLA Institutional Review Board because all electronic health records were de-identified (UCLA IRB# 20-001180).

Inclusion/Exclusion Criteria for Case/Control Selection

From March 9, 2020 to August 31, 2020, 82,681 individuals were tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) via reverse transcriptase polymerase chain reaction (RT-PCR) within the UCLA Health System. The first positive SARS-CoV-2 PCR test was reported on March 12, 2020. Three different levels of COVID-19 outcome were defined (Figure 1).

COVID-19 positive cases were those with a positive SARS-CoV-2 PCR test result (COVID-19 positive). To determine individuals with SARS-CoV-2 testing, lab tests in the DDR were searched for "SARS-CoV-2" or "COVID-19". The list of tests was manually reviewed to determine which tests were PCR based. SARS-CoV-2 PCR tests in our hospital system reported positive tests as "positive" or "detected" and negative tests as "negative" or "not detected". Other values such as "unknown" or "NULL" were considered unknown. Some individuals had more than one SARS-CoV-2 PCR test; in these cases, individuals were considered COVID-19 positive if they had at least one positive test. The controls for COVID-19 positive cases were COVID-19 negative individuals who were tested for SARS-CoV-2 but had negative results.

Inpatient cases were those who had a hospital admission within 14 days of their first positive SARS-CoV-2 PCR test (Inpatients). This time window was selected to identify individuals whose symptoms may not have been severe at initial testing, but may have progressed in severity warranting inpatient admission. The controls for inpatient cases were those who tested positive for COVID-19, but were not admitted as an inpatient within 14 days of their first positive SARS-CoV-2 PCR test (Outpatients).

Severe cases were those who were admitted to an intensive care unit or were intubated within 14 days of their first positive SARS-CoV-2 PCR test (Severe). Intubation was determined from a custom field based on the vitals flow sheet, "AirwayMinutes", which is the time in minutes a patient was intubated. The controls for Severe cases were those who had a hospital admission within 14 days of their first positive SARS-CoV-2 PCR test, but were not admitted to an intensive care unit and not intubated during the 14-day window (Inpatient Not Severe).

To determine pre-existing conditions and medications associated with COVID-19 outcome in HL and NHL-W, we performed separate analyses for the HL group and the NHL-W group. The HL group included individuals self-identifying as HL and any race. The NHL-W group included subjects self-identifying as Non-HL for ethnicity and white for race. We did not include all Non-HL races as this group included minorities such individuals who self-identified as Non-HL, Black or African American.

Individuals were excluded if all SARS-CoV-2 test results were unknown, their records were missing age, their records were missing sex, or there was no encounter in the UCLA Health System prior to the SARS-CoV-2 PCR test.

Confounding variables

We treated sex, age, and age² as potential confounders. Pre-existing known COVID-19 risk factors (coronary heart disease, congestive heart failure, chronic obstructive pulmonary disease, type 2 diabetes, hyperlipidemia, hypertension, obesity, and chronic renal disease (Goyal et al., 2020; Grasselli et al., 2020a, 2020b; Guan et al., 2020; Gupta et al., 2020; Li et al., 2020; Yang et al., 2020; Zhou et al., 2020; Zhu et al., 2020)) were also considered potential confounders for specific analyses as described below (see Table S1 for phecodes assigned to risk factors).

Statistical Analysis

Demographics

Age, sex, race and ethnicity were stratified by the Tested, COVID-19 positive, Inpatient and Severe groups. For age groups and sex, percentages of Severe was compared to Inpatient, Inpatient was compared to COVID-19 positive, and COVID-19 positive was compared to Tested using a Fisher's exact test (Fisher, 1922). Age groups were: <18 years, 19-35 years, 36-50 years, 51-65 years, and >65 years. Significant association of race and ethnicity in a COVID-19 outcome was analyzed in the following Firth logistic regression models (McCullagh and Nelder, 1989).

```
logit(outcome)= $\beta_0$  +  $\beta_1$ race +  $\beta_2$ age_group +  $\beta_3$ sex  
and  
logit(outcome)= $\beta_0$  +  $\beta_1$ ethnicity +  $\beta_2$ age_group +  $\beta_3$ sex
```

Outcome for Severe was considered Inpatient Severe vs. Inpatient Not Severe; for Inpatient was considered COVID-19 positive Inpatient vs COVID-19 positive Outpatient; and for COVID-19 positive was considered COVID-19 positive vs. COVID-19 negative.

We also compared HL to NHL-W controlling for age and sex using the Firth logistic regression model:

```
logit(outcome)= $\beta_0$  +  $\beta_1$ Hispanic/Latinx +  $\beta_2$ age +  $\beta_3$ age2 +  $\beta_4$ sex
```

We corrected for pre-existing known risk factors (coronary heart disease, congestive heart failure, chronic obstructive pulmonary disease, type 2 diabetes, hyperlipidemia, hypertension, obesity, and chronic renal disease (Goyal et al., 2020; Grasselli et al., 2020a, 2020b; Guan et al., 2020; Gupta et al., 2020; Li et al., 2020; Yang et al., 2020; Zhou et al., 2020; Zhu et al., 2020)) using the Firth logistic regression model:

```
logit(outcome)= $\beta_0$  +  $\beta_1$ Hispanic/Latinx +  $\beta_2$ age +  $\beta_3$ age2 +  $\beta_4$ sex +  $\beta_5$ coronary_artery_disease +  
 $\beta_6$ congestive_heart_failure +  $\beta_7$ chronic_obstructive_pulmonary_disease +  $\beta_8$ type_2_diabetes +  
 $\beta_9$ hyperlipidemia +  $\beta_{10}$ hypertension +  $\beta_{11}$ obesity +  $\beta_{12}$ chronic_renal_disease
```

See Table S1 for phecodes assigned to these known risk factors. Age and age squared were included in the model to correct for residual confounding effects of age due to possible non-linear effect. We used the likelihood ratio test to test for significance of HL ethnicity.

Pre-existing Conditions that are risk factors for COVID-19 outcomes

International Statistical Classification of Diseases (ICD)-9-CM and ICD-10-CM codes were mapped to 1866 phecodes, which represent meaningful and interpretable phenotypes (Wei et al., 2017; Wu et al., 2019). For HL and NHL-W, we evaluated the known risk factor phecode categories (coronary heart disease, congestive heart failure, chronic obstructive pulmonary disease, type 2 diabetes, hyperlipidemia, hypertension, obesity, and chronic renal disease) controlling for age and sex using the Firth logistic regression model (Firth, 1993; Heinze, 2006):

```
logit(outcome)= $\beta_0$  +  $\beta_1$ age +  $\beta_2$ age2 +  $\beta_3$ sex +  $\beta_4$ known_risk_factor_phecode_category
```

Outcome for Severe was considered Inpatient Severe vs. Inpatient Not Severe; for Inpatient was considered COVID-19 positive Inpatient vs COVID-19 positive Outpatient; and for COVID-19 positive was considered COVID-19 positive vs COVID-19 negative. We used the likelihood ratio test to test for phecode significance (McCullagh and Nelder, 1989) where p<0.05 was considered significant.

To identify additional phecodes that may be COVID-19 risk factors, we calculated the odds ratio of all phecodes correcting for age and sex (Model 1) using the Firth logistic regression model (Firth, 1993; Heinze, 2006), which accounts for phecodes with no counts within an outcome group:

$$(\text{Model 1}) \quad \text{logit}(\text{outcome}) = \beta_0 + \beta_1 \text{age} + \beta_2 \text{age}^2 + \beta_3 \text{sex} + \beta_4 \text{pcode}$$

We used the likelihood ratio test to test for pcode significance (McCullagh and Nelder, 1989). Multiple hypothesis testing correction was performed conservatively using a Bonferroni correction for the number of phecodes tested (Bonferroni et al., 1936). Nominal p-values are reported.

To account for known risk factors (coronary heart disease, congestive heart failure, chronic obstructive pulmonary disease, type 2 diabetes, hyperlipidemia, hypertension, obesity, and chronic renal disease), we tested Bonferroni significant phecodes from Model 1 in Model 2 using the Firth logistic regression model as follows:

$$(\text{Model 2}) \quad \text{logit}(\text{outcome}) = \beta_0 + \beta_1 \text{age} + \beta_2 \text{age}^2 + \beta_3 \text{sex} + \beta_4 \text{coronary_artery_disease} + \beta_5 \text{congestive_heart_failure} + \beta_6 \text{chronic_obstructive_pulmonary_disease} + \beta_7 \text{type_2_diabetes} + \beta_8 \text{hyperlipidemia} + \beta_9 \text{hypertension} + \beta_{10} \text{obesity} + \beta_{11} \text{chronic_renal_disease} + \beta_{12} \text{pcode}$$

For Model 1 Bonferroni significant phecodes, we determined if the pcode outcome risk effect was significantly different between HL and NHL-W by evaluating the pcode and HL interaction term in the following Firth logistic regression model (McCullagh and Nelder, 1989):

$$\text{logit}(\text{outcome}) = \beta_0 + \beta_1 \text{age} + \beta_2 \text{age}^2 + \beta_3 \text{sex} + \beta_4 \text{pcode} + \beta_5 \text{Hispanic/Latinx} + \beta_6 \text{pcode} \times \text{Hispanic/Latinx}$$

For Model 1 Bonferroni significant phecodes, we evaluate if there was an age or sex interaction with these pcode risk factors. We discretized age to greater or less than 65 years old. We considered there to be a significant sex by pcode or age by pcode interaction if there was a significant interaction term in the following Firth logistic regression model (McCullagh and Nelder, 1989):

$$\text{logit}(\text{outcome}) = \beta_0 + \beta_1 \text{age} + \beta_2 \text{age}^2 + \beta_3 \text{sex} + \beta_4 \text{pcode} + \beta_5 \text{sex} \times \text{pcode}$$

$$\text{logit}(\text{outcome}) = \beta_0 + \beta_1 \text{age}_{65} + \beta_2 \text{sex} + \beta_3 \text{pcode} + \beta_4 \text{age}_{65} \times \text{pcode}$$

We removed the age^2 term when testing the age > 65 years old and pcode interaction because multiple age terms would be present.

Pre-existing Conditions that are risk factors for Influenza Hospitalization

We identified patients in the UCLA DDR from July 1, 2018 to June 30, 2019 with an influenza pcode (Pcode 481). We chose this time period as it was before the COVID-19 pandemic so COVID-19 would not confound results. Influenza inpatient cases were those who had a hospital admission within 14 days of an influenza pcode diagnosis. The controls were those who had an influenza pcode, but were not admitted as inpatients within 14 days. After excluding individuals with missing age, missing sex, or no encounter prior to influenza diagnosis, there were 92 HL influenza inpatients, 859 HL influenza outpatients, 92 NHL-W influenza inpatients, and 1785 NHL-W influenza outpatients.

We determined if there was an association of HL ethnicity and inpatient admission using the following Firth logistic regression model (McCullagh and Nelder, 1989).

$$\text{logit}(\text{outcome}) = \beta_0 + \beta_1 \text{Hispanic/Latinx} + \beta_2 \text{age} + \beta_3 \text{age}^2 + \beta_4 \text{sex}$$

Outcome was influenza positive Inpatient vs influenza positive Outpatient. Hispanic/Latinx was HL compared to NHL-W. We also corrected for known risk factors using the following Firth logistic regression model (McCullagh and Nelder, 1989).

$$\text{logit}(\text{outcome}) = \beta_0 + \beta_1 \text{Hispanic/Latinx} + \beta_2 \text{age} + \beta_3 \text{age}^2 + \beta_4 \text{sex} + \beta_5 \text{coronary_artery_disease} + \beta_6 \text{congestive_heart_failure} + \beta_7 \text{chronic_obstructive_pulmonary_disease} + \beta_8 \text{type_2_diabetes} + \beta_9 \text{hyperlipidemia} + \beta_{10} \text{hypertension} + \beta_{11} \text{obesity} + \beta_{12} \text{chronic_renal_disease}$$

To determine pre-existing conditions associated with influenza inpatient admission for HL and NHL-W, we performed separate analyses for the HL group and the NHL-W group.

We calculated the odds ratio of all phecodes correcting for age and sex (Model 1) using the Firth logistic regression model (McCullagh and Nelder, 1989):

$$(\text{Model 1}) \quad \text{logit}(\text{outcome}) = \beta_0 + \beta_1 \text{age} + \beta_2 \text{age}^2 + \beta_3 \text{sex} + \beta_4 \text{pcode}$$

Outcome was influenza positive Inpatient vs influenza positive Outpatient. We used the likelihood ratio test to test for phecode significance (McCullagh and Nelder, 1989). Multiple hypothesis testing correction was performed conservatively using a Bonferroni correction for the number of phecodes tested (Bonferroni et al., 1936). Nominal p-values are reported.

Admission Vitals and Labs among COVID-19 positive inpatients

To determine if COVID-19 positive HL inpatients presented with more abnormal vitals or laboratory values compared to NHL-W inpatients, we compared vitals and labs within +/- one day of admission date between these two groups controlling for age, sex, and known risk factors in the following linear regression model:

$$\text{Vital or Lab} = \beta_0 + \beta_1 \text{Hispanic/Latinx} + \beta_2 \text{age} + \beta_3 \text{age}^2 + \beta_4 \text{sex} + \beta_5 \text{coronary_artery_disease} + \beta_6 \text{congestive_heart_failure} + \beta_7 \text{chronic_obstructive_pulmonary_disease} + \beta_8 \text{type_2_diabetes} + \beta_9 \text{hyperlipidemia} + \beta_{10} \text{hypertension} + \beta_{11} \text{obesity} + \beta_{12} \text{chronic_renal_disease}$$

P-values are reported for β_1 , the HL coefficient

Extremes of COVID-19 outcome susceptibility or resistance

We identified HL and NHL-W COVID-19 young individuals with no major comorbidities admitted as an inpatient and COVID-19 older individuals with comorbidities not admitted as an inpatient. We defined COVID-19 young individuals with no major comorbidities admitted as an inpatient as:

- COVID-19 positive
- 18-35 years old
- None of the known risk factor phecode categories: coronary heart disease, congestive heart failure, chronic obstructive pulmonary disease, type 2 diabetes, hyperlipidemia, hypertension, obesity, chronic renal disease (Table S1)
- Inpatient admission within 14 days of a SARS-CoV-2 positive test.

We defined COVID-19 older individuals with major comorbidities not admitted as an inpatient as:

- COVID-19 positive
- Greater than 70 years old
- At least three of the known risk factors phecodes (Table S1)
- No inpatient admission within 14 days of a SARS-CoV-2 positive test

Pre-existing Medications Associated with COVID-19

We investigated prescription of angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), immunosuppressants, oral steroids, oral anticoagulants, and non-steroidal anti-inflammatory drugs (see Table S7 for drugs assigned to medication classes) 90 days prior to SARS-CoV-2 testing. We controlled for age, sex, and known risk factors in the following Firth logistic regression model and used the likelihood ratio test:

$$\text{logit}(\text{outcome}) = \beta_0 + \beta_1 \text{age} + \beta_2 \text{age}^2 + \beta_3 \text{sex} + \beta_4 \text{coronary_artery_disease} + \beta_5 \text{congestive_heart_failure} + \beta_6 \text{chronic_obstructive_pulmonary_disease} + \beta_7 \text{type_2_diabetes} + \beta_8 \text{hyperlipidemia} + \beta_9 \text{hypertension} + \beta_{10} \text{obesity} + \beta_{11} \text{chronic_renal_disease} + \beta_{12} \text{medication}$$

Outcome for Severe was considered Inpatient Severe vs. Inpatient Not Severe; for Inpatient was considered COVID-19 positive Inpatient vs COVID-19 positive Outpatient; and for COVID-19 positive was considered COVID-19 positive vs. COVID-19 negative. We performed separate analyses for the HL group and the NHL-W group.

We investigated if medication prescription durations < 1 year or ≥ 1 year compared to no prescription were associated with COVID-19 inpatient admission risk. Medication duration was defined for a medication class from the first prescription to the most recent prescription within 90 days of SARS-CoV-2 testing. We controlled for age, sex, and known risk factors in the following Firth logistic regression model and used the likelihood ratio test:

$$\text{logit}(\text{inpatient admission}) = \beta_0 + \beta_1 \text{age} + \beta_2 \text{age}^2 + \beta_3 \text{sex} + \beta_4 \text{coronary_artery_disease} + \beta_5 \text{congestive_heart_failure} + \beta_6 \text{chronic_obstructive_pulmonary_disease} + \beta_7 \text{type_2_diabetes} + \beta_8 \text{hyperlipidemia} + \beta_9 \text{hypertension} + \beta_{10} \text{obesity} + \beta_{11} \text{chronic_renal_disease} + \beta_{12} \text{medication}_{<1\text{yr}} + \beta_{13} \text{medication}_{\geq 1\text{yr}}$$

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