

Drivers of Reduction of Inpatient Mortality in Hospitalized COVID-19 Patients

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Abstract

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Inpatient mortality is an important indicator of the COVID-19 pandemic, both to understand the pandemic's trajectory and to improve clinical outcomes. A reduction in inpatient mortality from COVID-19 has been described in the United States and the United Kingdom. We analyzed 21,037 patients admitted from March 1, 2020, to November 30, 2020, as part of the American Heart Association's COVID-19 registry, and performed logistic regression on person-level hospital records. The outcome variable was in-hospital death, and covariates included demographic, clinical, and constructed hospital-level factors. Constructed variables included hospital load and time between diagnosis and hospitalization. We tested the hypothesis that hospital-level burden was associated with inpatient mortality. Of 21,037 patient admitted between March and November, 3,246 (15.4%) died in-hospital. Mortality decreased from 18.7% in March-April to 10.7% in September-November. Adjusted odds ratios for each time period were 0.68 (95% CI 0.59-0.78, $P < .001$) for May and June, 0.59 (0.49-0.71, $P < .001$) for July and August, and 0.60 (0.48-0.75, $P < .001$) for September through November. Hospital load was not significantly associated with inpatient mortality, and so we fail to reject the null hypothesis of this thesis. Further explanations of time effect may include mortality displacement, non-invasive oxygenation techniques, or other unmeasured factors.

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Abbreviations

AHA = American Heart Association

CABG = Coronary artery bypass graft

CKD = Chronic kidney disease

COVID-19 = Coronavirus disease 2019

CVD = Cardiovascular disease

DX = Diagnosis

GBD = Global Burden of Disease

GWTG = Get With The Guidelines

SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2

OR = Odds ratio

PCI = Percutaneous coronary intervention

RE = Random effect

SD = Standard deviation

MICE = Multiple imputation by chained equations

Introduction

Inpatient mortality is an important indicator of the COVID-19 pandemic, both to understand the pandemic's trajectory and to improve clinical outcomes¹. Although surveillance in the US has been limited by testing availability and the lack of a central registry², hospital systems have been an important source of data since early in the pandemic. Tracking inpatient mortality over the course of the pandemic is important to understand and improve clinical outcomes.

A reduction in inpatient mortality over the course of the pandemic from COVID-19 has been described in the United States^{3,4} and the United Kingdom⁵. There are several hypotheses for this reduction. First, that medications and clinical interventions have improved survival⁶. Second, that the demographic profiles of patients has changed, or that mortality displacement explain the change⁷. Third, that mask wearing in the community has reduced the infective doses transmitted from infected persons⁸.

A fourth hypothesis is that hospital systems were overwhelmed early in the pandemic, and patient management has improved on a systems level⁹. An early COVID-19 wave in New York in the spring of 2020 and raised concerns about excess mortality in hospitals with insufficient beds, staff, or supplies for their patient load^{10,11}. At the time, public health efforts were focused on "flattening the curve" to avoid such hospital capacity problems¹². A more recent study in Israel examined inpatient mortality in hospital systems at various load levels, finding increased mortality rates in hospitals with higher patient loads (defined as number of severely ill patients)⁹. It is important to quantify hospital load and understand its relationship to inpatient mortality in the US.

Previous analyses have been limited in temporal scope or to hospital-level analysis. Asch et al. described evolving inpatient mortality rates in the US, but did not extend their analysis past June, 2020³. Roth et al., in a study I contributed to, did not consider group-level features like testing availability or hospital load⁴.

This thesis asks: How has inpatient COVID-19 mortality changed over the course of the pandemic? Which demographic, clinical, or hospital-level factors contributed to changes in mortality rates? The hypothesis of this thesis is: Hospital-level burden is associated with inpatient mortality rates and explains some of the change in mortality over the first nine months of the pandemic.

Methods

Overview

We assessed the association between 23 factors and in-hospital mortality using person-level hospital records from the AHA's COVID-19 CVD registry, described below. The outcome variable was in-hospital death, and covariates included demographic, clinical, and constructed hospital-level factors. Constructed variables included hospital load and time between diagnosis and hospitalization. We tested the hypothesis that hospital-level burden is associated with inpatient mortality and explains some of the change in mortality from March to November, 2020.

Data source

The AHA's COVID-19 CVD registry was established in April 2020 as a large, diverse, multi-site capture of hospitalized COVID-19 patients. The registry is powered by Get With the Guidelines (GWTG), an ongoing quality improvement initiative, and has been described in detail elsewhere¹³. In brief, participating sites retroactively and consecutively uploaded data for all

adults patients hospitalized with a confirmed SARS-COV-2 infection. Infection was confirmed by PCR test, IGG antibody test, or clinical diagnosis. Abstracted data points included (1) patient demographics, such as age, sex, race, and ethnicity; (2) medical comorbidities; vital signs; clinical features, including admission and serial laboratory values; (3) in-hospital interventions and medications; and (4) vital status or discharge destination. Race and ethnicity variables were abstracted from the chart, not self-reported. The full intake form is available at <https://www.heart.org/-/media/files/professional/quality-improvement/covid-19-cvd-registry/ahacovidcvdcrf428-fillable-pdf.pdf?la=en>. The list of participating sites is available at <https://www.heart.org/en/professional/quality-improvement/covid-19-cvd-registry>. Information on participating hospitals, such as total inpatient beds or teaching status, was provided by the American Hospital Association.

We accessed de-identified data through a secure platform hosted by the AHA Precision Medical Platform and Amazon Web Services. Access to the AHA COVID-19 CVD data was provided at no charge as part of the GBD study (IRB STUDY00009060).

Constructed variables

Hospital load was calculated as the average proportion of inpatient beds occupied by COVID-19 patients during an individual's hospital stay. We used admission and discharge dates for each patient to calculate the number of COVID-19 patients present in each hospital, by day. We used total inpatient beds in each hospital as a denominator to calculate load by hospital and day. For each patient, we calculated the average daily hospital load experienced during their stay.

Time from diagnosis to hospitalization was calculated as the number of days between SARS-CoV-2 diagnosis date and admission date. Values below zero represent patients diagnosed during their hospitalization, including those found to be COVID-19 positive during an unrelated

hospitalization. These values were binned into the reference category, fewer than 3 days from diagnosis to admission. Values above zero represent patients diagnosed with COVID-19 before hospitalization. Values of zero represent patients diagnosed with COVID-19 upon admission.

Analysis

We analyzed all patients in the AHA COVID-19 CVD registry admitted between March 1, 2020, and November 30, 2020. We limited our analysis to patients' first admission, if readmitted during the study period, as subsequent admissions may capture chronic or unrelated disease states. We examined four time periods: admission in March and April; May and June; July and August; and September, October, and November.

The outcome of interest was in-hospital death. Patients were assigned to the time period during which they were admitted. Covariates of interest were time period, age, sex, race/ethnicity, past medical history (smoking, pulmonary disease, hypertension, heart failure, diabetes, CKD, cerebrovascular disease, cancer, and CABG or PCI), admission vital signs (systolic blood pressure, use of supplemental oxygen upon admission, SP02, respiratory rate, presence of interstitial infiltrates on X-ray upon admission, heart rate, creatinine, and BMI), hospital load, and days between diagnosis and admission. Medical comorbidities were abstracted as binary variables following chart review. Pulmonary disease included COPD, interstitial lung disease, asthma, and pulmonary arterial hypertension. Cerebrovascular disease included stroke and transient ischemic attack. Vital signs were abstracted as measured values. We limited our analysis to features known at admission and did not include in-hospital interventions, such as medications or being placed on a ventilator.

We examined patterns of missingness in the data. We used multiple imputation to impute missing values five times using all covariates included in the final analysis (R package MICE¹⁴).

We binned continuous variables, such as heart rate upon admission, into clinically relevant bins and assigned reference values to binary variables (Table 3). For medical history variables, the reference value was “No history of disease”. For vital signs variables, reference values were normal clinical values such as a systolic blood pressure of 110-120 mmHg. Reference values for constructed variables were low hospital load (0-10% of beds occupied by COVID-19 patients) and COVID-19 diagnosis early in hospitalization (prior to 3 days after admission, including those diagnosed prior to admission). The reference bin for age was 50-55, chosen for sufficient sample size and clinical relevance. All reference values and bins were constructed with clinical consultation.

We performed three sequential mixed-effects logistic regression models to assess the relationship between covariates and log-odds of inpatient death. The first model included time period, age, sex, race/ethnicity, and past medical history. In the second model, we added admission vital signs. In the third model, we added hospital load and days between diagnosis and admission. Each model included a random effect on hospital ID to account for within- and between-hospital variability. Model performance was assessed using a Hosmer–Lemeshow goodness of fit test.

All analysis was done in R, version 3.6.0 (R Foundation), and conducted in the AHA Precision Medical Platform. Coefficients for each covariate were exponentiated to produce odds ratios. 95% confidence intervals were calculated from standard errors for each covariate. P-values below 0.05 were considered significant.

Results

Patient characteristics

21,037 patients admitted from March 1, 2020, to November 30, 2020, were included in our analysis (Figure 1). Total admissions and reporting hospitals, by month, are shown in Figure 2. The majority of admissions were recorded in March and April. 107 hospitals across 31 states were represented: 9 states in the Midwest census bureau region, 9 in the Northeast, 9 in the South, and 4 in the West. 3,246 patients (15.4%) died in-hospital: 2,241 of 11,987 (18.7%) admitted in March and April; 490 of 4,191 (11.7%) admitted in May and June; 298 of 2,783 (10.7%) admitted in July and August; and 217 of 2,076 (10.5%) admitted in September, October, and November (Table 1).

Patient characteristics in four time periods are shown in Table 1. The mean age of patients was 61.9 (SD=17.9). 9,969 (46%) were female. 8,001 (38%) were categorized as non-Hispanic white, 5,407 (25.7%) as non-Hispanic black, 5,360 (25.5%) as Hispanic, and 2,269 (10.8%) as other or unspecified race/ethnicity groups (including 1,322 patients [6.02%] marked as “unable to be determined”). 12,328 (58.6%) had a history of hypertension, 7,402 (35.2%) had a history of diabetes, and 3,871 (18.4%) had a history of pulmonary diseases, a category that includes chronic obstructive pulmonary disease. Upon admission, average oxygen saturation was 93.8 (6.7) and 5,693 (27.1%) presented with supplemental oxygenation initiated. 13,931 (66.2%) presented with interstitial infiltrates on imaging. Across the four time periods, the proportion of female patients increased (from 43.7% in March and April to 48.4% in September, October, and November), the proportion of non-Hispanic white patients increased (from 32.7% to 66.5%), the prevalence of pulmonary infiltrates decreased (from 71.0% to 60.3%), and the proportion of patients admitted on supplemental oxygen increased (from 23.0% to 35.7%).

Unadjusted mortality

Unadjusted mortality is shown in Table 2. Mortality was higher in males than females (17.3% compared to 13.1%), highest amongst non-Hispanic white and other/unspecified race/ethnicity groups (17.0% and 17.1%, respectively), and increased with age, from 2.3% in patients aged 18-30 to 33.8% in patients 90+. Unadjusted mortality by age and month of admission is shown in Figure 3. For all months of admission, mortality was higher in older patients than younger patients. Inpatient mortality fell most dramatically from March to June, 2020, and remained relatively constant in all age groups from July to September.

Constructed covariates

Figure 4 shows hospital load for each site, over time. Average load across the time series was 12.9%. Site-specific peaks can be observed in New York (15 sites that peak in March and April), Virginia (5 sites that peak in April and May), Indiana (2 sites that peak in March and April), Illinois (3 sites that peak in March), and Missouri (3 sites that peak in October). Figure 5 shows the number of days between SARS-CoV-2 diagnosis and hospital admission in each time period. In all time periods the mode was 0 days, showing that the vast majority of patients were diagnosed with COVID-19 upon admission. The average number days between diagnosis and admission increased from 0.17 in March and April to 3.23 in September, October, and November, showing that patients were increasingly diagnosed prior to admission.

Mixed-effects regression results

Figure 6 shows the results of three mixed-effects logistic regression models. In all models, time periods relative to March and April were significant and associated with increased survival. Adjusted odds ratios for each time period (from Model 3) were 0.68 (95% CI 0.59-0.78, $P < .001$) for May and June, 0.59 (0.49-0.71, $P < .001$) for July and August, and 0.60 (0.48-0.75, $P < .001$) for September through November.

Age and sex were associated with inpatient mortality in all models. Relative to patients 50-55, age 45 and below conferred a significant survival benefit, and age 60 and above a significant increased risk of mortality. Female sex was associated with survival, with adjusted odds ratio (from Model 3) 0.74 (0.68 - 0.81, $P < .001$).

Although unadjusted mortality varied by race/ethnicity groups, this was not significant in all models. In model 1, categorization as other or unspecified race/ethnicity was significantly associated with increased mortality, odds ratio 1.20 (1.03-1.38, $P < .05$); in model 3, that category lost significance and instead categorization as non-Hispanic Black was significantly associated with survival, odds ratio 0.83 (0.74-0.94, $P < .001$).

In model 1, past medical history of pulmonary disease, hypertension, heart failure, diabetes, CKD, cerebrovascular disease, and cancer were significantly associated with an increased risk of mortality. After adjusting for clinical vital signs at admission (models 2 and 3), only heart failure, diabetes, cerebrovascular disease, and cancer retained significance. Systolic BP below 110, use of supplemental oxygen, SP02 below 94, respiratory rate above 20, presence of interstitial infiltrates, heart rate above 100, elevated creatinine, and BMI above 45 were significantly associated with increased mortality.

Hospital load relative to 0-10% of beds occupied by COVID-19 patients was not predictive of inpatient mortality. Increased time between diagnosis and admission (reflecting patients diagnosed 3+ days before admission) was significantly associated with increased survival in the fully adjusted model. 3-10 days between diagnosis and admission had an OR of 0.75 (95% CI 0.65-0.87, $P < .001$), and 10+ days an OR of 0.76 (95% CI 0.60-0.97, $P < .05$).

Discussion

In this thesis, I report factors associated with inpatient mortality in 21,037 patients across 107 US sites from March to November, 2020. Age, oxygenation status at admission, and SP02 predicted mortality most strongly. However, a time effect persisted even after accounting for disease severity and patient features. Relative to March and April, each subsequent time period was associated with a 30-40% reduction in adjusted inpatient mortality. Surprisingly, hospital load was not predictive of inpatient mortality.

We found a strong relationship between age, sex, previous medical conditions, and mortality, consistent with other descriptive and predictive reports. Age was most strongly associated; patients aged 95+ had an adjusted odds ratio of 4.9 relative to patients 50-55. Female sex was protective compared to male sex. Oxygenation status upon admission and several comorbidities, including heart failure and diabetes, were additionally associated with inpatient mortality. There is ongoing research into the biological mechanisms of these relationships, especially the protective effect of female sex.

Race and ethnicity were not found to be predictive. Racial disparities in COVID-19 burden are well described; the CDC estimates that rates of infection, hospitalization, and death are 1-3x higher in American Indian or Alaska Native, Black, and Hispanic populations compared to White populations¹⁵. Racism and systemic bias contribute to health outcomes, both broadly and in the context of the COVID-19 pandemic^{16,17}, including disparities in access to primary care¹⁸, environmental exposures such as air pollution¹⁹, and risk of household or workplace exposure to COVID-19²⁰. In this study, the significance of race/ethnicity groups varied by model, with only a slight protective effect for non-Hispanic Black patients in the fully-adjusted

model. However, markers of systematic bias, such as education, income, occupation, and chronic stress are not present in this dataset.

Hospital load was hypothesized to be associated with higher mortality, but significance was not found. There are several explanations for this effect. First, the proportion of hospital beds used by COVID-19 patients may be a poor proxy for hospital load. Second, the variable may combine two contradictory factors, the load of the system but also how much experience they may have treating COVID-19 patients. Finally, this result may reflect a true lack of association between hospital load and mortality.

Features of the pandemic have changed over time, making it difficult to attribute changes in mortality to a single cause. Various patient populations and geographic regions were affected at different points in time, such as New York in March-April 2020 or nursing homes in Washington in the early spring. Care has been influenced by outbreaks in other parts of the globe, notably in China and Italy, as well as previous domestic waves. Medications such as hydroxychloroquine were adopted and discontinued quickly by hospital systems, with effectiveness proving mixed in randomized controlled trials. Our analysis adjusts for patient demographics and disease severity, but may not capture other factors that changed throughout the course of the pandemic and proved influential for inpatient mortality. More qualitative research, such as structured interviews of clinicians, may be helpful in elucidating these factors.

Inpatient mortality is an important indicator of the pandemic, both to understand the pandemic's trajectory and to improve clinical outcomes. Understanding factors associated with mortality is important for disease surveillance and improving clinical outcomes. This thesis

describes inpatient mortality across 107 sites in the US, and expands upon the impact of hospital load on mortality.

Limitations

This thesis has several limitations. First, it is a retrospective analysis of abstracted data. Some variables, including proning and other oxygenation techniques, were not abstracted and may represent unmeasured confounders. To address this, we performed a propensity-score matched regression as a sensitivity analysis, with similar results. Second, the data were uploaded retroactively, with sites inputting records in batches when they were able. There are more hospitals and admissions represented in March and April than subsequent months, despite a wave of COVID-19 cases in the US over the summer months, and a higher proportion of non-Hispanic white patients in the September-November time period. This may represent selection bias, as only some hospitals have been able to input more recent data. Third, although we include race/ethnicity as a covariate, this variable is not self-reported and includes 1,266 patients with an “unable to be determined” race/ethnicity. Therefore, there may be biases or errors in the classification of patients’ race/ethnicity. Fourth, data were only available through November, 2020, and we were not able to study the winter surge. Fifth, in an effort to avoid confounding, this thesis did not explore in-hospital interventions such as medications, ICU admission, and ventilation status, or time-varying clinical features like serial laboratory values. Future analyses could explore the impact of in-hospital events on inpatient mortality.

Conclusions

Unadjusted inpatient mortality decreased in 107 sites across the US from March to November, 2020 from a peak of 18.7% in March and April. Although several demographic, clinical, and hospital-level factors were associated, these variables did not fully explain the observed mortality reduction. Hospital load was not significantly associated with inpatient mortality, and so we fail to reject the null hypothesis of this thesis. Further explanations of the reduction in mortality observed from March-April 2020 onwards may include mortality displacement, non-invasive oxygenation techniques, or other unmeasured factors.

Tables and Figures

Table 1: Patient Characteristics in Four Time Periods

	Total (n=21,037)	March - April (n=11,987)	May - June (n=4,191)	July - August (n=2,783)	September - November (n=2,076)
Inpatient death, n (%)	3,246 (15.4%)	2,241 (18.7%)	490 (11.7%)	298 (10.7%)	217 (10.5%)
Demographics					
Age, mean (SD)	61.9 (17.9)	62.1 (17.3)	59.7 (18.9)	59.3 (18.4)	61.4 (18.3)
Female, n (%)	9969 (46%)	5237 (43.7%)	2067 (49.3%)	1361 (48.9%)	1004 (48.4%)
Race/ethnicity					
Non-hispanic white	8,001 (38.0%)	3,914 (32.7%)	1,502 (35.8%)	1,204 (43.3%)	1,381 (66.5%)
Non-hispanic black	5,407 (25.7%)	3,164 (26.4%)	1,098 (26.2%)	895 (32.2%)	250 (12.0%)
Hispanic	5,360 (25.5%)	3,392 (28.3%)	1,250 (29.8%)	497 (17.9%)	221 (10.6%)
Other	2,269 (10.8%)	1517 (12.7%)	341 (8.1%)	187 (6.7%)	224 (10.8%)
Admission features					
BMI, mean (SD)	30.8 (8.5)	30.4 (8.1)	30.9 (8.6)	31.7 (9.2)	31.5 (9.0)
SpO ₂ , mean (SD)	93.8 (6.7)	93.4 (6.7)	94.3 (6.5)	93.9 (6.9)	94.0 (6.1)
Heart rate, mean (SD)	93.8 (19.8)	95.0 (19.7)	93.5 (19.9)	91.7 (19.6)	90.9 (20.2)
Systolic BP, mean (SD)	131.1 (23.9)	130.9 (24.0)	131.1 (24.1)	131.2 (24.0)	131.6 (23.4)
Creatinine, mean (SD)	1.7 (5.4)	1.8 (5.5)	1.8 (6.6)	1.7 (4.4)	1.5 (3.6)
Pulmonary infiltrates, n (%)	13,931 (66.2%)	8,512 (71.0%)	2,574 (61.4%)	1,594 (57.3%)	1,251 (60.3%)
Supplemental O ₂ , n (%)	5,693 (27.1%)	2,762 (23.0%)	1,278 (30.5%)	912 (32.8%)	741 (35.7%)
Past medical history, n (%)					
Chronic kidney disease	2682 (12.7%)	1502 (12.5%)	570 (13.6%)	327 (11.7%)	283 (13.6%)
Diabetes	7402 (35.2%)	4088 (34.1%)	1562 (37.3%)	1031 (37%)	721 (34.7%)
Hypertension	12328 (58.6%)	6924 (57.8%)	2437 (58.1%)	1707 (61.3%)	1260 (60.7%)
Pulmonary disease	3871 (18.4%)	2147 (17.9%)	724 (17.3%)	466 (16.7%)	534 (25.7%)
Smoking	1360 (6.5%)	722 (6%)	290 (6.9%)	186 (6.7%)	162 (7.8%)
Hospital features and outcome					
Managed in ICU, n (%)	6470 (30.8%)	3673 (30.6%)	1155 (27.6%)	940 (33.8%)	702 (33.8%)
Placed on ventilator, n (%)	4093 (19.5%)	2785 (23.2%)	598 (14.3%)	430 (15.5%)	280 (13.5%)

Table 2: Unadjusted Inpatient Mortality

	Unadjusted Inpatient Mortality
Total	15.4% (3,246/21,037)
Age	
18-29	2.3% (25/1,095)
30-39	3.9% (70/1,792)
40-49	5.4% (137/2,574)
50-59	10.5% (394/3,747)
60-69	14.9% (667/4,466)
70-79	23.4% (905/3,861)
80-89	28.5% (731/2,563)
90+	33.8% (317/939)
Sex	
Female	13.1% (1,269/9,669)
Male	17.3% (1,977/11,368)
Race/ethnicity	
Non-hispanic white	17.0% (1,364/8,001)
Non-hispanic black	14.4% (777/5,407)
Hispanic	12.8% (718/5,360)
Other	17.1% (387/2,269)
Past medical history	
Chronic kidney disease	24.0% (643/2,682)
Diabetes	18.7% (1,382/7,402)
Hypertension	18.8% (2,313/12,328)
Pulmonary disease	18.3% (708/3,871)
Smoking	16.4% (223/1,360)

Table 3: Reference values and bins for binned covariates

Covariate	Reference value	Covariate values
Time period	March and April, 2020	May and June, 2020; July and August, 2020; September, October, and November, 2020
Age	50-55	5-year bins: 18-25, 25-30, ..., 95-100
Sex	Male	Female
Race/ethnicity	White Non-Hispanic	Hispanic, Non-Hispanic Black, Other
Systolic blood pressure	110-120 mmHg	<110, 120-150, 150+
SP02	>94%	<70, 70-85, 85-93
Respiratory rate	<20	20-25, 25-30, 30+
Heart rate	<100	100-130, 130+
Creatinine	<1.5	1.5-2, 2+
BMI	20-25	<20, 25-30, 30-35, 35-40, 40-45, 45+
Hospital load	<10%	10-20%, 20-30%, 30-45%, 45-60%, 60+%
Days between diagnosis and hospitalization	<3	3-10, 10+

Reference values and bins were identified with clinical consultation. Bins were created to be clinically relevant and reflective of data distribution. Reference values for all past medical history variables were “No history of disease”.

Figure 1: Flowchart of COVID-19 Patients

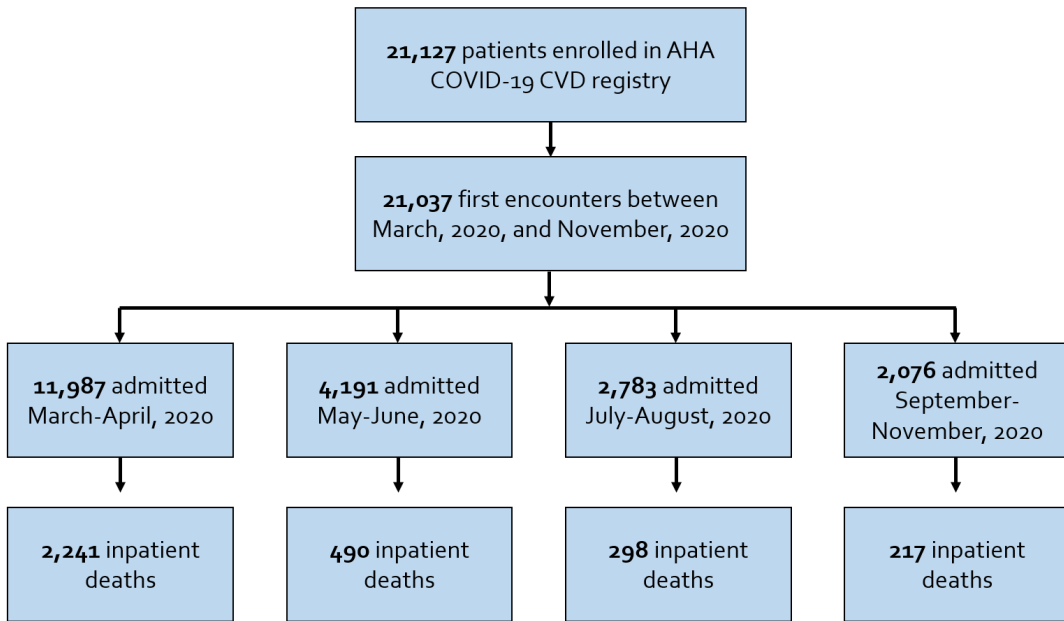


Figure 2: Number of Hospitals and Admissions Reported to the Registry, by Month

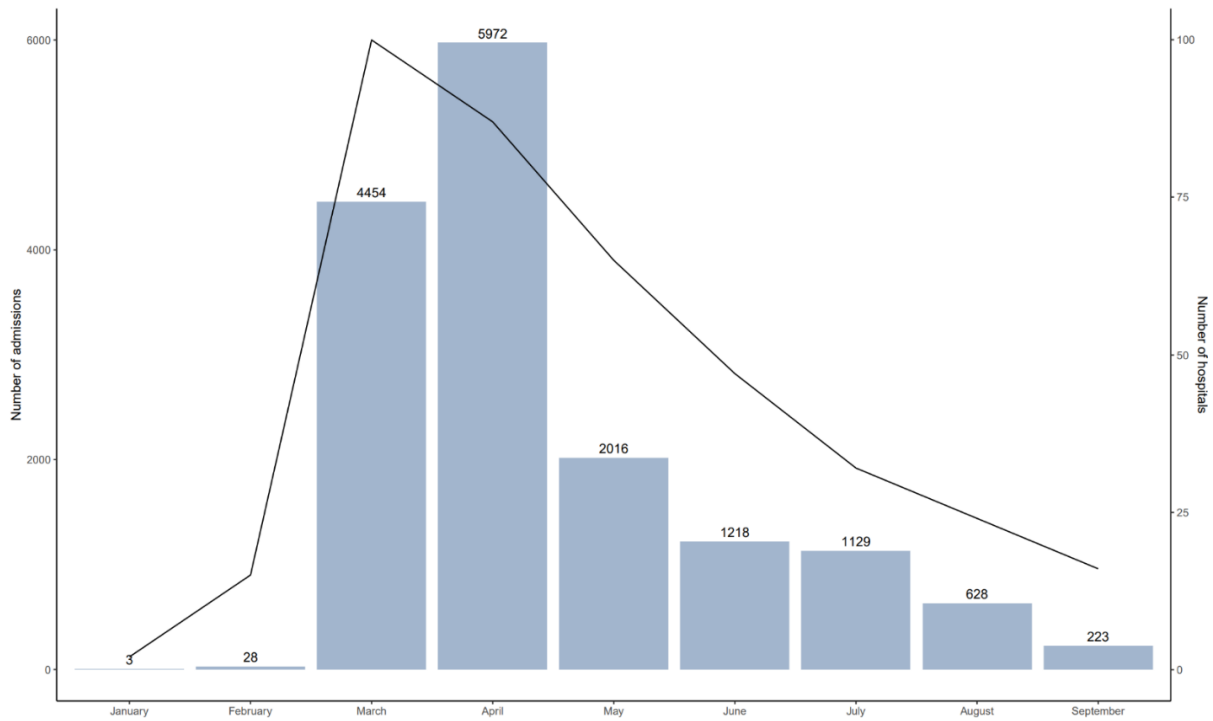


Figure 3: Unadjusted Inpatient Mortality by Age and Admission Month

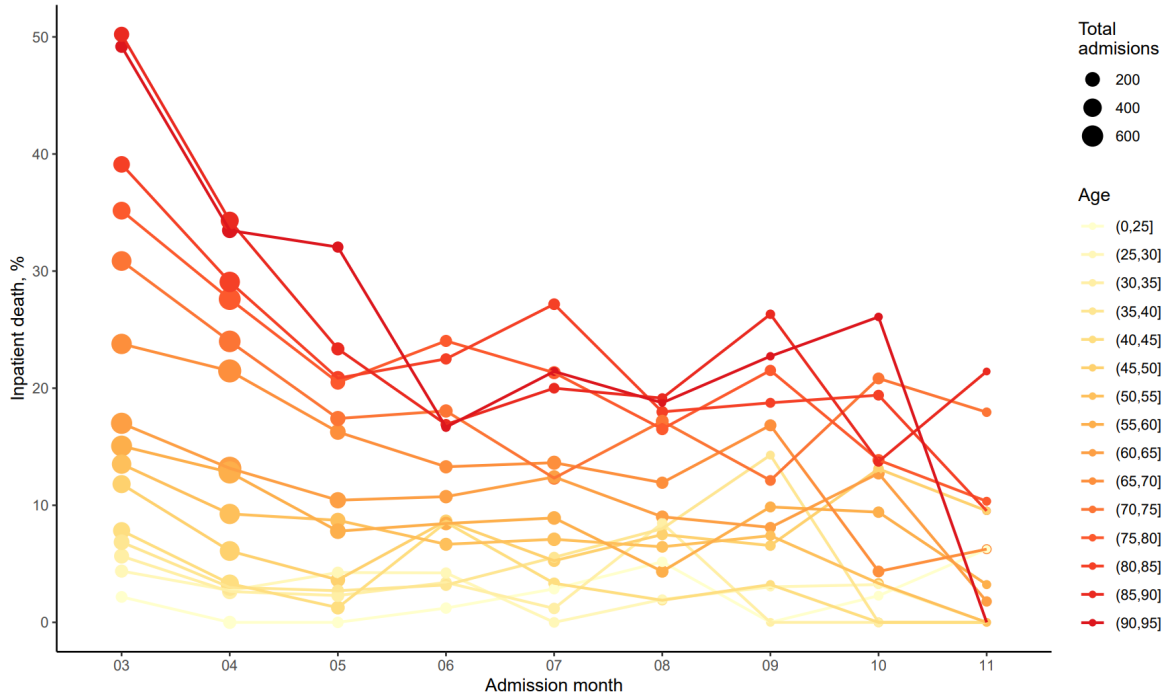


Figure 4: Hospital Load over Time, by Region

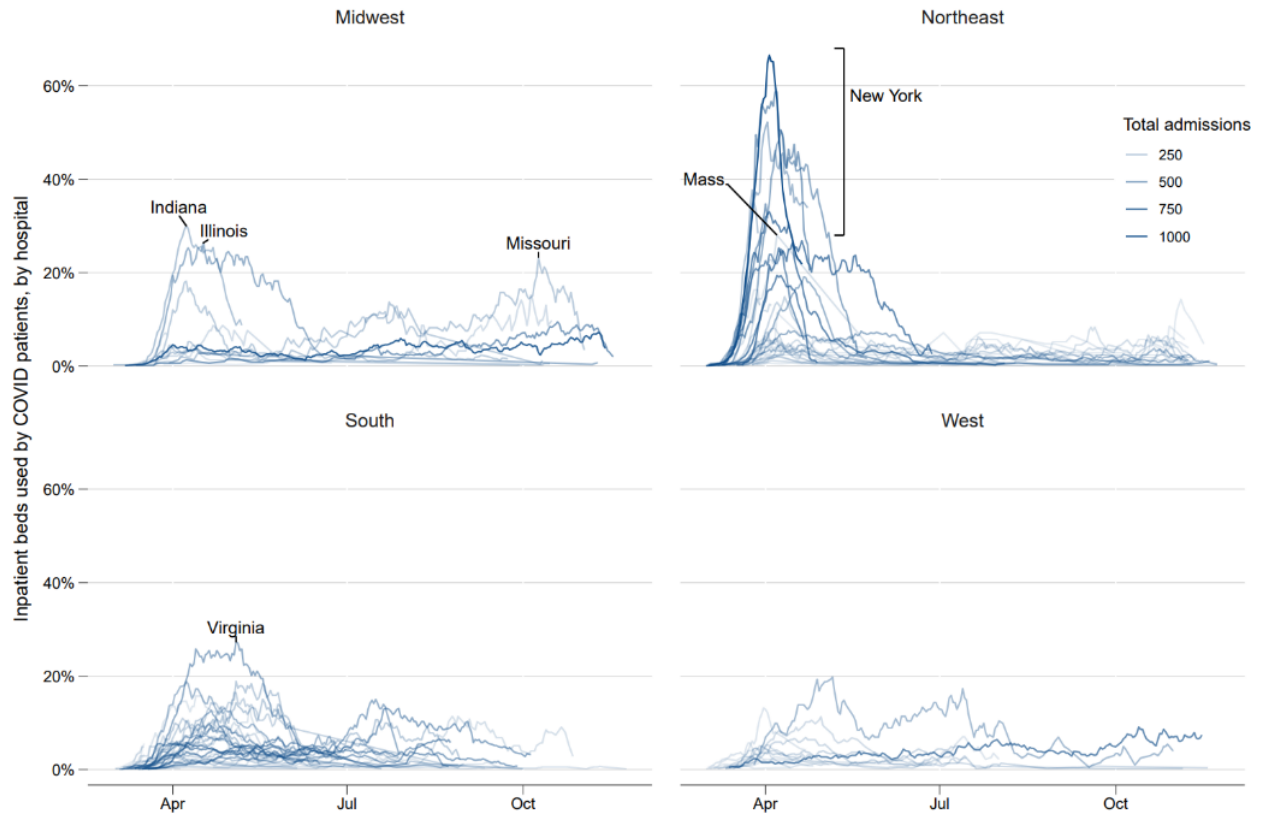


Figure 5: Time from Diagnosis to Admission, by Time Period

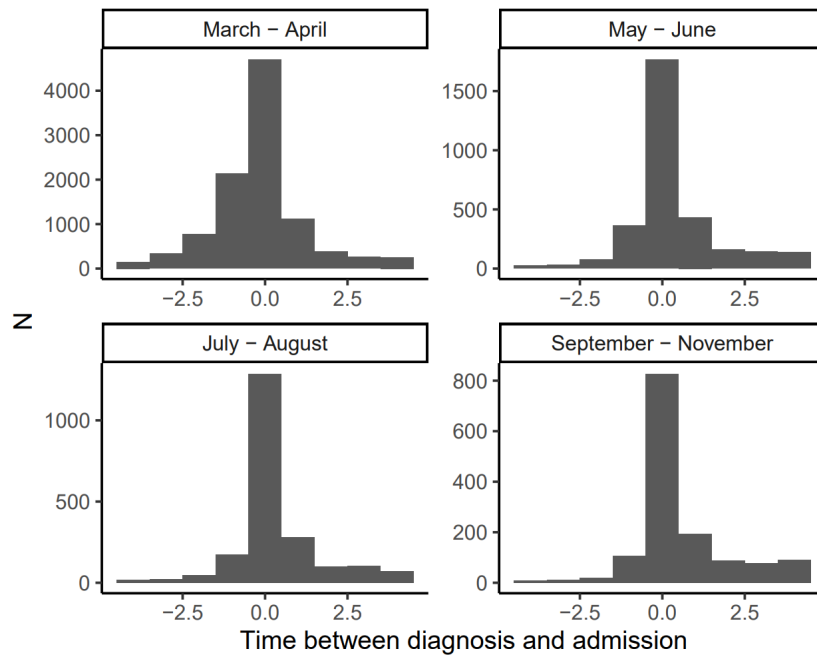
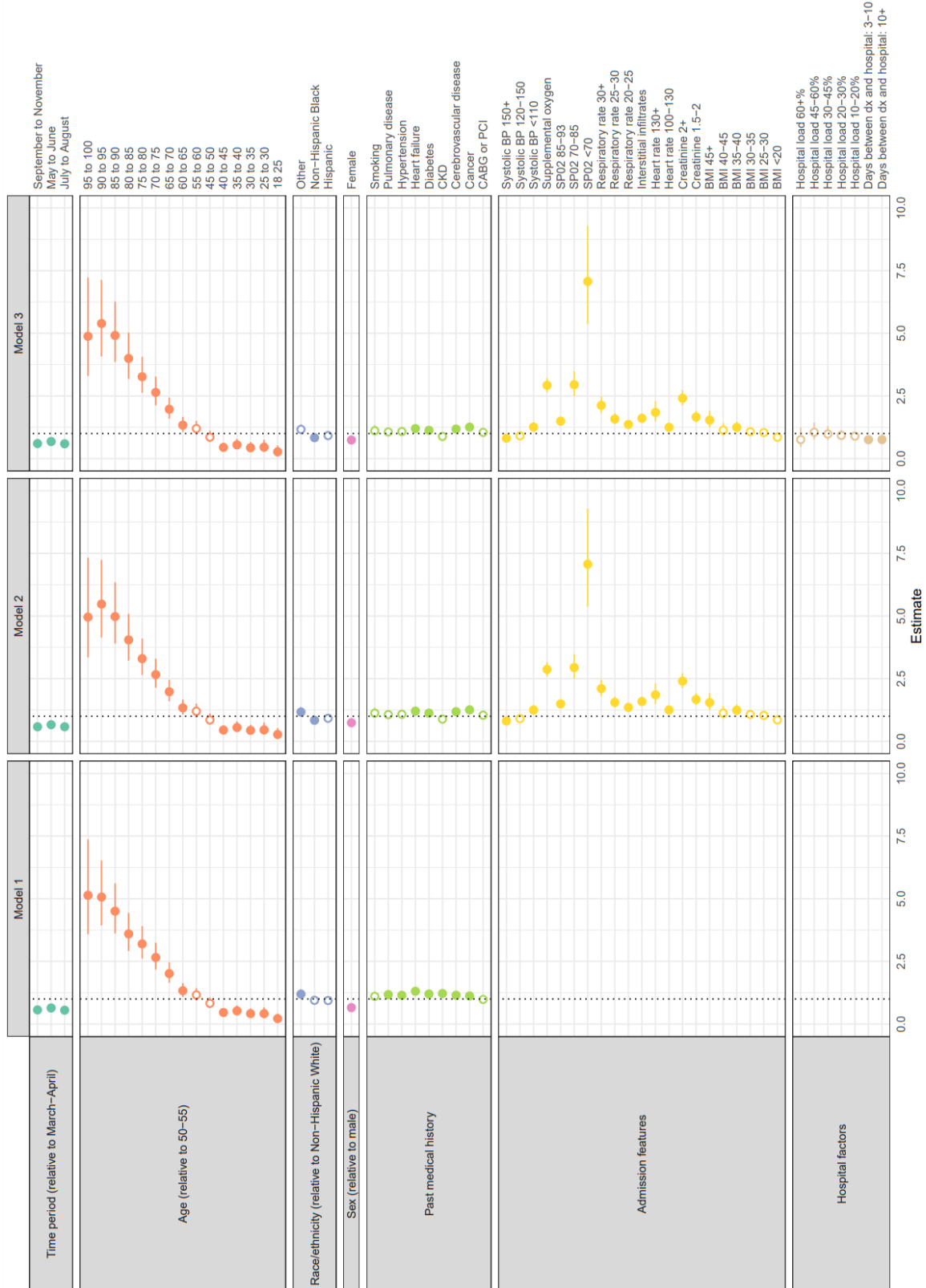


Figure 6: Logistic Regression Results for Three Models



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