Survival rates among hospitalized COVID-19 patients in Washington State have improved

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What do we already know?

Mortality rates due to COVID-19 infection have been in decline, though it has not always been clear what the primary contributors to these declines have been; for example, if they are due to shifting demographics of the epidemic. Some studies have suggested that improvements in clinical management have reduced the mortality rates of those severely ill with COVID-19 over time. Emerging evidence on the effectiveness of various treatments and clinical practices are continuously being utilized to improve clinical management of COVID-19.

What does this report add?

We estimate age- , sex-, comorbidity-, and admit-month specific survival probabilities for hospitalized patients in Washington State from March to October 2020. The predicted survival curves generated from our model suggests **improving survival in admitted patients over time**. Controlling for age, sex, and comorbidities, we find that patients admitted in October had only roughly two-thirds the risk of death (0.64 (0.52 to 0.79 95%CI)) compared to someone admitted in March. Additionally, we confirm global evidence that **age is associated with exponentially increasing mortality risk**, and that age alone is more strongly associated with mortality risk than any other risk factor analyzed.

What are the implications for public health practice?

This decrease in mortality rates among hospitalized patients suggests that the **changes in clinical management of COVID-19 have been overall beneficial in reducing the mortality risk of a COVID-19 infection**. While this is welcome news, mortality risk due to COVID-19 remains very high, with an estimated infection-fatality-ratio in Washington State of 4.9 deaths per 1,000 infections. Infections are currently on the rise throughout Washington, and **continued vigilance to prevent transmission remains necessary, as overwhelmed hospitals will likely be unable to deliver the standard of care responsible for these improvements.**

Introduction

The COVID-19 epidemic in the US was first acutely understood as an outbreak in a Washington long-term care facility during the end of February. At this stage, relatively little was known regarding transmission and effective clinical care practices. The high ratio of cases to mortality spurred a strong public health response throughout March.

As the pandemic has worn on, a growing evidence base has informed both the public health response to curbing transmission, as well the clinical practices to treat those with severe illness. Specifically, clinical practices have been modified to incorporate proning of patients, use of steroids, and more judicious use of ventilators. Some evidence suggests that these improvements in clinical management have reduced the mortality rates of those severely ill with COVID-19, thus reducing the overall fatality rate of those infected with SARS-CoV-2, relative to the early phase of the pandemic. In this report, we use data on all hospitalized COVID-19 cases in Washington state to understand the change in fatality rates over the course of the epidemic thus far.

Fatality rates are not straightforward to study, as various comorbidities, age, and sex have been to known to play a role in symptom severity. Simple comparisons of cases and deaths are misleading because shifting disease dynamics and testing improvements change the meaning of a case and the baseline characteristics of the people hospitalized. To address these issues, we fit a Cox proportional hazards model to assess survival probabilities among hospitalized patients, controlling for age, sex, admit month, and comorbidities. We include only hospitalized patients in our analysis to control for changing case reporting rates; changing testing over time is less likely to affect the number of people with severe enough disease to be admitted as inpatients than overall case count.

Model

We use a Cox proportional hazards model to estimate comorbidity-, age-, sex-, and admit-month-specific survival probabilities for hospitalized patients during their hospital stays. Pre-existing health conditions (comorbidities) included are: heart disease, diabetes, kidney disease, liver disease, and lung disease. Age was treated as a categorical variable on decade intervals starting with those over 40 years old. Comorbidity categories, admit month, and sex were binary fields. Exposure time began upon admission.

The Cox proportional hazards model estimates how much mortality risk departs from a baseline. In this analysis, we defined the baseline as an under-40 female patient with no risk factors or comorbidities who was admitted in March 2020 or prior.

Key inputs and assumptions

- We used data from the Washington State Disease Reporting System (WDRS) compiled on November 15, 2020.

- We limited our analysis to patients who were marked as hospitalized in the WDRS prior to November 1, had complete age information, and, where appropriate, had complete date-of-death information (N=8709).
- Some level of data was missing for all provided comorbidities. Information on smoking and cardiac disease was missing in over 75% of cases, so we did not include these in the analysis. Of the remaining five comorbidities, 59% observations were missing at least one, with missingness increasing over time. To account for this we included missing as a level in the model for each comorbidity. See Supplementary Figure 1.
- The statistical model we use assumes that the risk of mortality at a given time (hazard) varies proportionally across covariates.
- As discharge dates were not provided in the dataset, we also assume that all deaths occurred during hospitalization and not after discharge.
- We assume that most inpatient hospitalizations with COVID are due to severe disease. While some may have been admitted as part of routine screening during admission for other purposes, this number is likely relatively small and unchanging such that the impact of admission month can in large part be interpreted as the result of improved clinical management of severe COVID-19. Nonetheless, this is a limitation with the analysis, and future work should aim to better classify hospitalized patients by their reason for admission.

Results

Statewide hospitalizations peaked in April, with a smaller peak in the summer, followed by a recent autumn increase. As would be expected, these trends were mirrored by trends in deaths (see Figure 1). Of the 8709 hospitalizations in our dataset, 16.8% (N=1464) were under 40 years old, 66.3% (N=5771) were between 40 and 79 years old, and 16.9% (N=1474) were 80 and older. 52.6% (N=4580) were male. Of those hospitalized, the most common comorbidity was diabetes (17.3% of admissions), followed by chronic heart, kidney, and lung diseases. Information on comorbidities was missing about half the time for most categories while information on admission time, sex, and age were complete (see Table 1).

Figure 2 visualizes the empirical survival curves (Kaplan-Meier curves) for patients in Washington admitted with COVID-19 by month of admission. Most deaths occur within the first two weeks after admission, and this property—along with the general shape of the survival curves—has stayed relatively stable over time. Meanwhile, the overall risk of death has reduced consistently month on month since the start of the epidemic in early spring. In particular the pre-April period has very low survival compared to the other months, with more than 25% of inpatients not surviving, while 12% of those admitted in October did not survive. However, the relationships shown in this plot can be confounded by the changing characteristics of patients admitted. For example, early cases were predominantly elderly patients, with elevated risks of mortality. To better understand the independent effect of admission month, we turn to the results of the statistical model.

	Variable	Total number of entries (% of total)	Entries missing information (% of total)	Percentage with observed mortality
	COVID-19 mortality	1604 (18.4%)		100%
Sex	Female	4129 (47.4%)		16.6%
	Male	4580 (52.6%)		20.0%
Comorbidity	Diabetes	1509 (17.3%)	4638 (53.3%)	29.1%
	Chronic heart disease	1099 (12.6%)	4800 (55.1%)	44.7%
	Chronic liver disease	121 (1.4%)	5152 (59.2%)	35.5%
	Chronic lung disease	507 (5.8%)	4849 (55.7%)	13.4%
	Chronic kidney disease	599 (6.9%)	5054 (58.0%)	49.9%
Age Bracket	Under 40	1464 (16.8%)		1.3%
	40 to 50	1082 (12.4%)		5.3%
	50 to 60	1447 (16.6%)		9.3%
	60 to 70	1711 (19.6%)		17.8%
	70 to 80	1531 (17.6%)		28.2%
	over 80	1474 (16.9%)		44.6%
Month of admission	Before April	1504 (17.3%)		27.2%
	April	1395 (16.0%)		22.1%
	May	730 (8.4%)		20.7%
	June	863 (9.9%)		17.4%
	July	1264 (14.5%)		17.2%
	August	1040 (11.9%)		13.9%
	September	774 (8.9%)		13.6%
	October	1139 (13.1%)		10.4%

Table 1: *Sample description for the data informing the statistical model.*

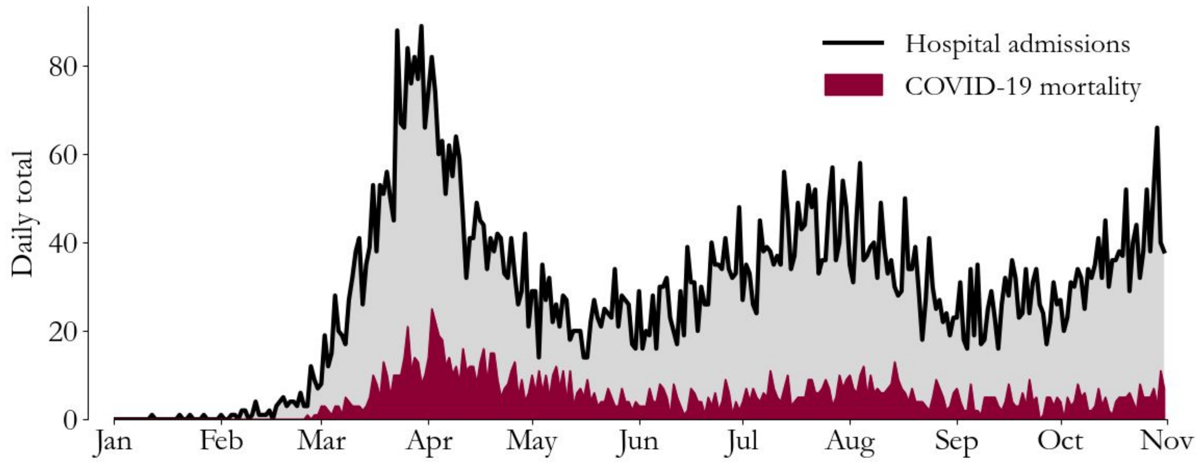


Figure 1: *Total hospital admissions (black) and deaths (red) due to COVID-19 in Washington.*

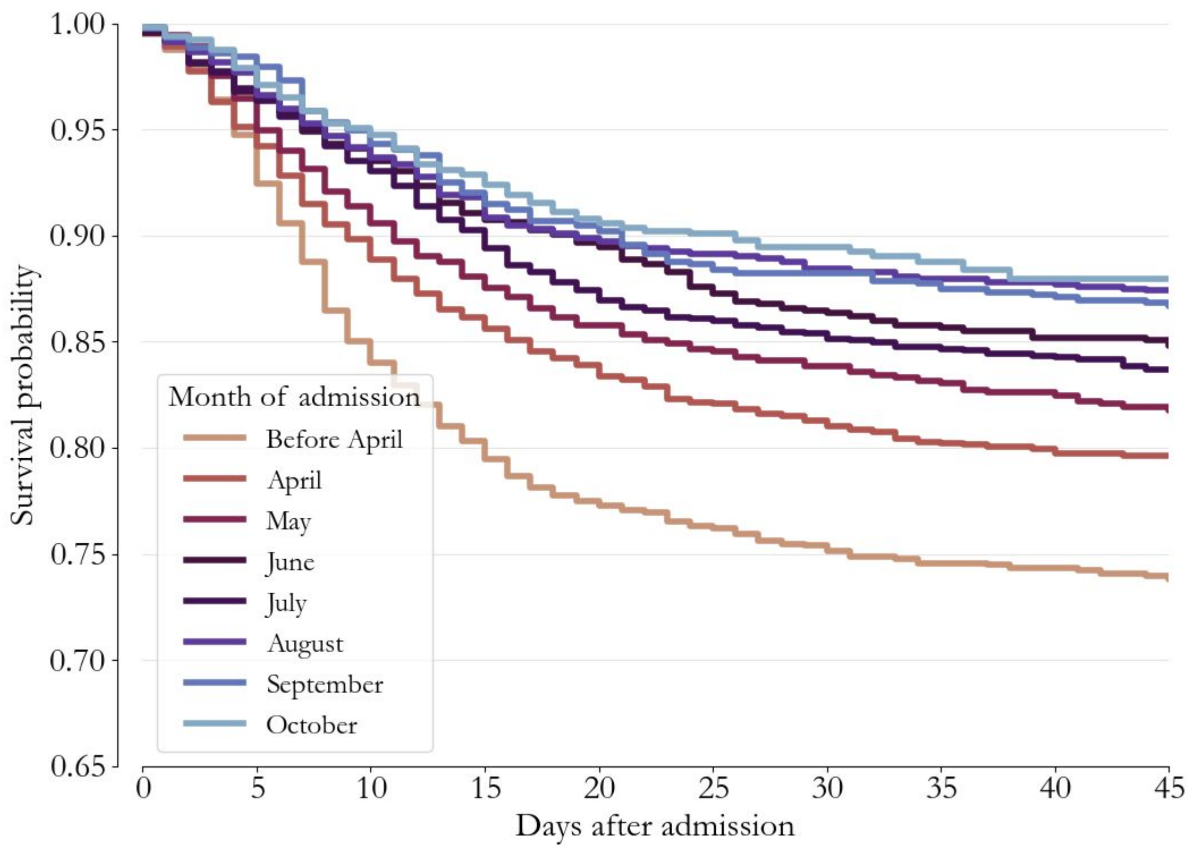


Figure 2: *Kaplan-Meier survival curves for Washington inpatients, stratified by month of admission. These curves represent the empirical survival probabilities for the population hospitalized. Prior to April, 75% of patients eventually survived, by September survival had increased to over 87%.*

We fit a survival regression in order to better understand the marginal changes in survival over time, controlling for patient characteristics. **Figure 3** shows the coefficient estimates from the survival regression. Coefficients are interpretable as hazard ratios, or the risk of death at a given moment in time, relative to the baseline category for each group. In this model, hazards are assumed to be proportional throughout the duration of hospital stay. We found that there was a significantly elevated risk of mortality for males relative to females (HR: 1.24, 95%CI 1.13-1.37). All comorbidities were associated with elevated risk, with kidney disease highest among them, with a hazard ratio of 1.69 (95%CI 1.45-1.97). Mortality risk among hospitalized Washingtonians grew exponentially with age, with those 80+ at 34.9 (95%CI 22.1-55.3) times higher hazard than those under 40. Age alone was associated with significantly higher mortality risk than any of the measured comorbidities. Finally, we observe large declines in mortality associated with the month of admission starting in August. Compared to admissions prior to April, someone admitted in October had a 0.64 (95%CI 0.52-0.79) times lower hazard. In other words, the survival benefits of being admitted in October relative to March are about the same in magnitude as the added mortality risk of most comorbidities. We saw similar trends for all age groups (see Supplementary Figure 2).

Conclusions

This report highlights the population-level impact of improved clinical management of severe COVID-19 in Washington State. Clinical management has evolved over the course of the pandemic, with marked improvements over time. Early confusion has solidified into safer, more effective care with more tools and knowledge with which to treat patients. At the beginning of the pandemic, many hospitals were quick to support infected patients with ventilators. However, doctors have since been more judicious in their use, realizing early ventilation is unnecessary and perhaps harmful. Other therapeutics considered promising early, such as remdesivir, have had mixed or negative evidence, with doctors increasingly avoiding reliance on experimental therapies. Better evidence now supports the effectiveness of widely-available tools such as proning and steroids such as dexamethasone.

We have found that—controlling for age, sex, and comorbidities—the probability of mortality following hospital admission in Washington State has decreased significantly over the course of the epidemic. While the case-fatality-ratio has also decreased during the same period, testing changes make this an unstable metric over time. Hospitalizations, meanwhile, have stayed relatively stable as an indicator of severe disease. While screening for COVID-19 infection is now standard procedure for any admission, COVID-19 admissions via routine care are quite rare relative to acute COVID-19 infections (see Supplementary Figure 3), particularly since infection prevalence has remained below 1% in most of the state. As such, we believe the mortality declines described here are in fact largely due to improved clinical management.

Those infected in Washington today have better chances of survival than those infected earlier in the epidemic. The hard-fought efforts to flatten the curve in March and April may have deferred some infections to this relatively safer time. Still, for every 1000 infections in Washington State today, we expect 4.9 [2.9 to 6.9] to eventually die. The gains have depended thus far on the ability of hospitals to provide attentive inpatient care and remain precarious if heightened community transmission stresses hospitals beyond their capacity to properly support all patients.

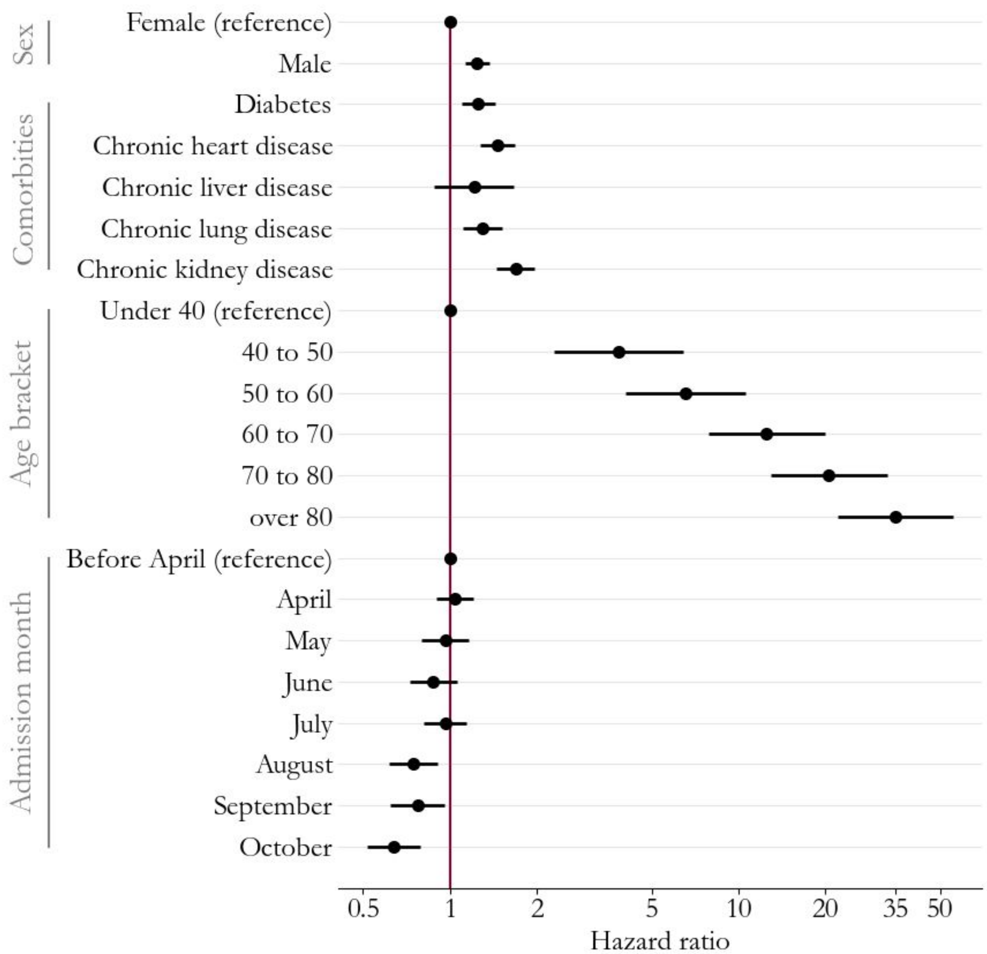
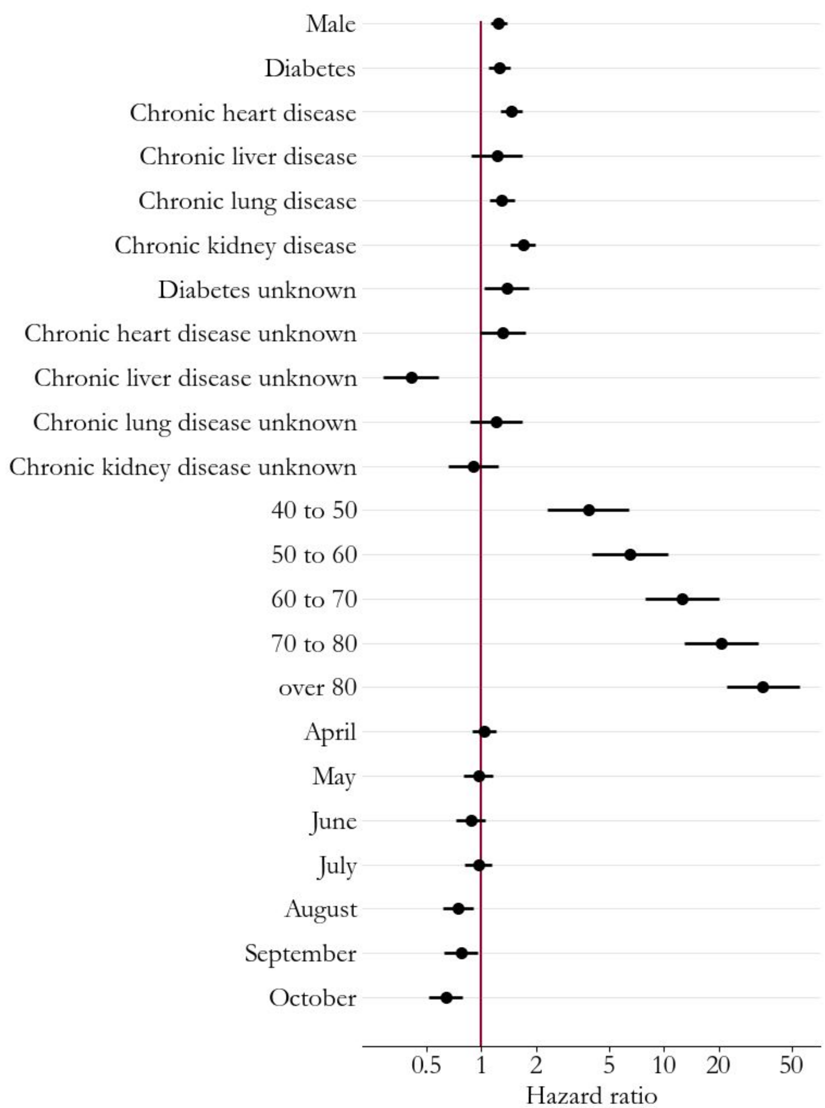
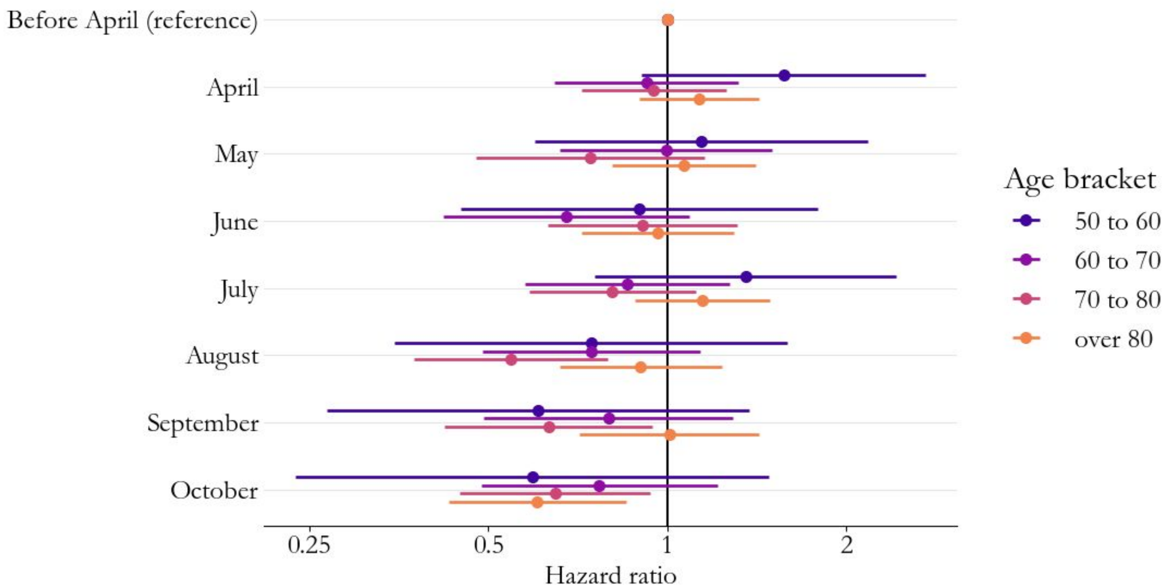


Figure 3: *Model coefficients of the fitted Cox proportional hazards model. Covariates of model included binned age, sex, comorbidities, and admit month. The red line corresponds to the baseline hazard of the model, specifically an under-40 female patient with no comorbidities who was admitted prior to April. Note that the x-axis is on a log scale.*

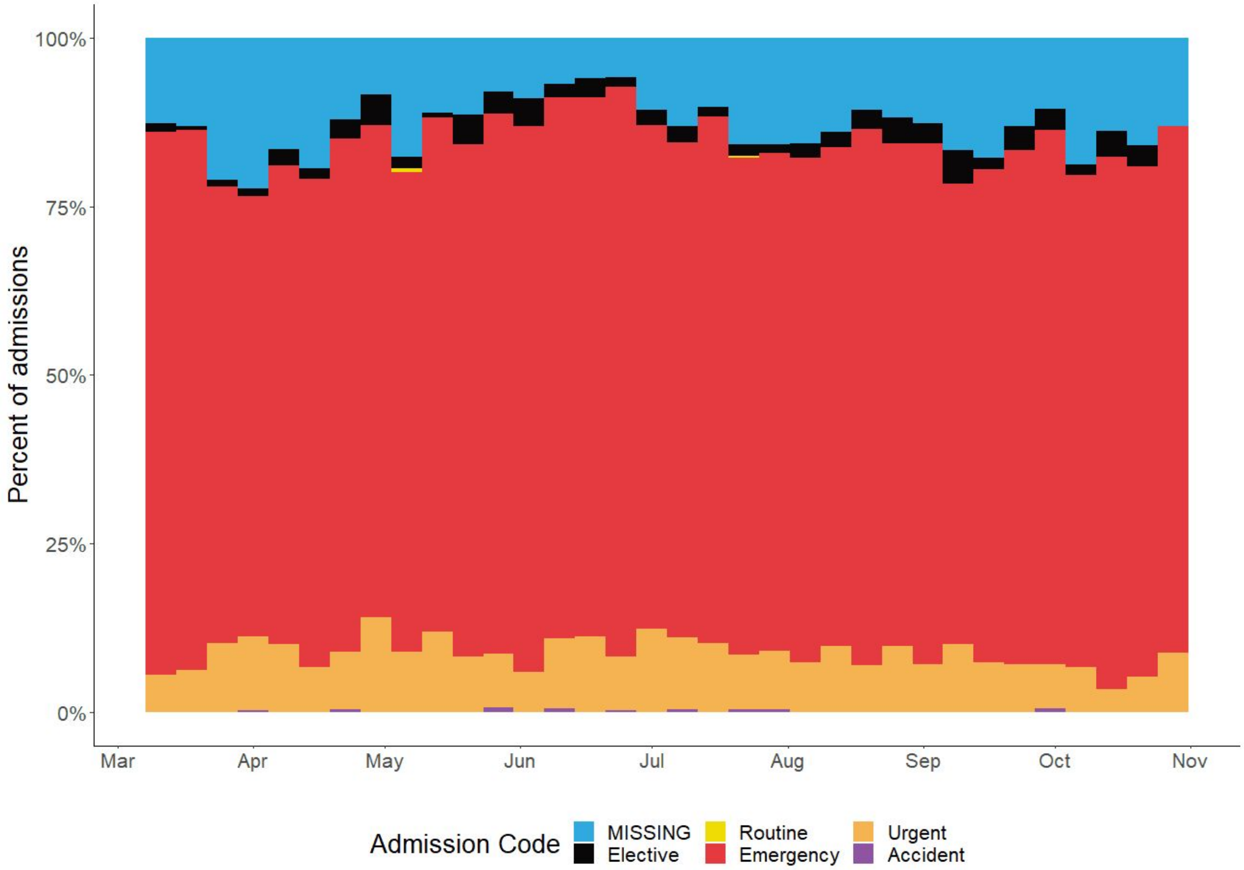
Supplementary figures



Supp. Figure 1: *Full model results, including coefficients for missing values of comorbidities, which were suppressed in Figure 2 (hazard ratios relative to each comorbidity marked as 'No' as reference). Data for comorbidities was missing in 53% to 59% of cases, with higher missingness in recent months. Since comorbidity status was unknown in these cases, we treated this as a separate level in the model. Of those with missing information on at least one comorbidity, 84% were missing data on all comorbidities, thus we do not believe the coefficients for these missing values are directly interpretable, as they are affected by multicollinearity (Variance Inflation Factors (VIF) for all missing comorbidity indicators were greater than 15).*



Supp. Figure 2: *Models were run independently for each of the oldest four age brackets in order to investigate the improvement in time for each age grouping. Younger age brackets were not included because there were too few deaths in those groups to make stable estimates. Broadly, we see consistent improvements over time, with perhaps the oldest group not improving until October, though estimates have large uncertainty intervals, often crossing 1 (no effect).*



Supp. Figure 3: *Weekly proportion of hospitalized COVID-19 cases by admission codes. Codes were obtained by merging WDRS cases to data from Washington's Rapid Health Information Network (RHINO) (N=8843 admissions from 6480 cases). 13% of admissions were missing codes. Over 95% of admissions with a known code were admitted via emergency departments or urgent care rather than via elective care, with proportions consistent since mid-April. This indicates that most cases admitted were likely due to severe disease rather than cases caught through routine inpatient screening, though may not preclude admissions of emergency room patients for reasons such as injuries who may also have been infected with COVID-19.*