Comorbidities and Risk of Hospitalization and Death with COVID-19

Kieran Gallagher, MPH; Alejandro Munoz del Rio, PhD; Doug Winesett, MD; Jackie Gerhart, MD

Purpose: Investigate risk of hospitalization and death over time as a function of comorbidities.

Data: Data were examined for 190,194 COVID-19 positive patients. Data are pooled from 45 health systems that represent 470 hospitals, spanning 20 states and covering 50 million active patients, collected on May 13, 2020.

Observations: Diabetes, heart failure, COPD, immunocompromise, and BMI greater than or equal to 40 were most strongly associated with increased risk of death and hospitalization among COVID-19 positive patients.

Background

People with serious chronic conditions potentially have higher risk of severe illness with COVID-19.[1] Here we examine the relationship between COVID-19 hospitalization and death and the following comorbidities: hypertension, diabetes, immunocompromise, cancer, heart failure, cerebrovascular disease/stroke, valve disorder, vascular disease, congenital heart disease, chronic obstructive pulmonary disease (COPD), obesity, and moderate/severe asthma. Our analysis complements a recent study in the UK that examined the relationship between a similar set of comorbidities and risk of death among COVID-19 patients.[2]

Hypertension
In the Wuhan COVID-19 population, hypertension was the most common comorbidity in patients that developed acute respiratory distress syndrome.[3] Patients with hypertension are frequently treated with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), which increase expression of ACE2 and are thus theorized to increase risk of infection.[5] However, due to the vascular and organ protective effect of these drugs, discontinuation of therapy may result in worse outcomes in the context of COVID-19.[6]

Obesity
A study on 124 patients in a French health center found that the proportion of COVID-19 patients who required invasive mechanical ventilation increased with BMI categories.[7] Similarly, a study on a New York population found that patients with a BMI greater than 35 were more likely to be admitted to acute and critical care.[8]

Diabetes
The Chinese Center for Disease Control and Prevention found a case-fatality rate of 7.3% among COVID-19 positive patients with diabetes, compared to an overall case-fatality rate of 2.3%.[9] Another study found evidence that diabetic patients are more susceptible to an inflammatory storm with COVID-19,[10] which suggests a mechanism behind why these patients may deteriorate more rapidly.

Immunocompromise
Previous research has suggested no association between immunocompromise and outcomes with COVID-19.[11] An article in the Lancet acknowledges that immunosuppressant medications present a tradeoff between beneficial anti-inflammatory effects and the potentially harmful effects of anti-viral immunity.[12] Timing of immunosuppression may be relevant, as the most severe stages of COVID-19 are characterized by systemic hyperinflammation. Treatment with immunomodulatory agents has been recommended during this most severe stage.[13]

Cancer
A nationwide analysis of COVID-19 positive patients in China found that cancer patients showed a higher risk of severe events, including admission to the ICU, invasive ventilation, and death.[14] This has been validated by another study on COVID-19 in China.[15] A letter to the Lancet suggests that this association could be subject to confounding by age and asserts that the greater risk to cancer patients comes from reduced ability to access medical care due to the outbreak.[16]

Cardiovascular Diseases
Cardiovascular conditions have been associated with increased fatality among COVID-19 patients.[17]
A meta-analysis examining cardiovascular diseases and COVID-19 in China found that, for COVID-19 patients, the prevalence of cardiovascular disease among patients in the ICU with COVID-19 was three times the prevalence in non-ICU patients.[18] The same study found a higher incidence of cardiovascular injury among patients with more severe cases as well.[18] Other research has validated that COVID-19 can lead to cardiac injury, so cardiovascular events may be both a risk factor and downstream effect of more severe COVID-19 cases.[19] Patients with underlying cardiovascular conditions may be more susceptible to severe cardiovascular manifestations of COVID-19, and may therefore experience worse outcomes. In this sample, we examined the following cardiovascular conditions: heart failure, cerebrovascular disease/stroke, valve disorder, vascular disease, and congenital heart disease.

COPD
A meta-analysis on the effect of COPD on COVID-19 severity found that COPD is associated with a fivefold increased risk of severe COVID-19 infection.[20] COPD has also been associated with increased ACE2 expression in lower airways; as SARS-CoV-2 uses ACE2 as a receptor to enter cells, increased expression has been suggested as a mechanism for the relationship between COPD and excess adverse outcomes.[21]

Moderate/Severe Asthma
Previous analyses have found that asthma is overrepresented among patients hospitalized for COVID-19;[22,23] the US CDC lists moderate or severe asthma as a risk factor for severe COVID-19 illness.[1] However, a recent letter to the Journal of Allergy and Clinical Immunology suggested that allergic asthma may be associated with reduced ACE2 expression, which could confer a protective effect against COVID-19.[24]

Methods

Our sample included 190,194 SARS-CoV-2 positive patients from 41 health systems, spanning 23 states. We evaluated diagnoses corresponding to each comorbidity at the first time that patients received a positive SARS- patients in the sample had not been seen before at the health system where they were being treated for COVID-19, so comorbidities were frequently documented after the COVID-19 diagnosis. For example, a previous version of this analysis found that 6,318 patients out of 28,262 had a diagnosis of diabetes documented during their COVID-19 infection. To account for this, we also included diagnoses that were documented during the course of COVID-19 treatment.

More explicitly, a patient was said to have a certain comorbidity if one of the codes indicated in Table 1 met one of the following conditions:

(1) Diagnosis was on their problem list at the time that they were confirmed to be COVID-19 positive or before the earliest of the following dates: discharge date of first COVID-19 admission, COVID-19 death date, or 42 days after COVID-19 diagnosis date.

(2) Diagnosis was listed as an encounter or billing diagnosis for an encounter in the two years prior to the time that they were confirmed to be COVID-19 positive.

Table 1 includes additional considerations for certain comorbidities. We report the percentage of COVID-19 patients with each comorbidity as well as the age group and sex distribution within each comorbidity. We

compared the age and sex distribution between patients with and without each comorbidity using a chi-squared goodness-of-fit test.

We used Cox proportional hazards analysis to model death and hospitalization, determining the hazard ratios for each comorbidity in both a model adjusting for age group and sex and a model that controlled for age group, sex, and all other comorbidities. Hypothesized relationships between age, sex, COVID-19 outcomes, and all comorbidities were represented as a causal diagram in a directed acyclic graph (not shown) to understand the potential for over-adjustment in a multivariate model; based on the causal pathways, we consider the likelihood of over-adjustment low. Time to event was computed as number of calendar days between when the patient received a positive test or diagnosis for COVID-19 and when a death or admission was documented in the EHR. Patients were followed up for up to 42 days. We assessed multicollinearity by calculating the variance inflation factor (VIF) and assessed goodness-of-fit by calculating the measure of explained variation (R^2). The proportional hazards assumption was assessed via the score test.

Age group was given as one of eight categories: 0-3, 4-18, 19-44, 45-54, 55-64, 65-74, 75-84, and 85+ years of age. The model includes dummy variables for each age group. Patients with a sex of "other" (n=98) were excluded because the sample size was too small to assess any meaningful effects.

Results

Table 2 shows the prevalence of each comorbidity in this population of COVID-19 positive patients and Table 3 shows the distribution of age and sex for each comorbidity. The age distribution of patients with each comorbidity was different from the COVID-19 population as a whole ($p < 0.001$); those with a comorbidity appeared to be older. Comorbidities other than moderate/severe asthma showed a more similar sex distribution compared to the overall COVID-19 patient population. The asthmatic population included a higher than expected number of females.

Table 4 and Figure 1 show hazard ratios for each comorbidity with respect to death in a model that controlled for age and sex alone and a model that controlled for age, sex, and all other comorbidities. Patients were at the highest risk of death if they had heart failure (HR=1.59 [1.52, 1.67]), immunocompromise (HR=1.53 [1.43, 1.63]), diabetes (HR=1.58 [1.52, 1.65]), COPD (HR=1.40 [1.34, 1.47]), or a BMI above 40 (HR=1.31 [1.23, 1.40]) after adjustment. Patients with moderate/severe asthma and vascular disease appeared to be at reduced risk (HR=0.79 [0.69, 0.90] and HR=0.87 [0.83, 0.91]). All other comorbidities showed weaker associations or were insignificant.

Table 5 and Figure 1 show hazard ratios for each comorbidity with respect to hospitalization in a model that controlled for age and sex alone and a model that controlled for age, sex, and other conditions. Similar conditions showed the strongest association: Patients were at the highest risk of hospitalization if they had diabetes (HR=1.57 [1.54, 1.60]), heart failure (HR=1.51 [1.47, 1.54]), immunocompromise (HR=1.39 [1.35, 1.44]), COPD (HR=1.33 [1.29, 1.36]), a BMI above 40 (HR=1.29 [1.27, 1.32]), hypertension (HR=1.29 [1.27, 1.32]), or asthma (HR=1.20 [1.14, 1.27]) after adjustment. Patients with vascular disease appeared to be at reduced risk (HR=0.81 [0.79, 0.84]). All other comorbidities showed weaker associations or were insignificant.

The measure of explained variation (R^2) was 0.75 for the multivariate model for death and 0.43 for the multivariate model for admissions, indicating that the models explained 75% and 43% of variation in outcomes respectively. In both models, VIF was less than 1.5 for all variables other than age, which indicated that there was no evidence for multicollinearity. Individual variables had a correlation less than 0.3 except for the following: heart failure and valve disorder (0.35), heart failure and vascular disease (0.32), and diabetes and hypertension (0.40).

For both hospitalization and death the proportional hazards assumption was violated by virtually all terms in the multivariable model ($p < 0.01$). This may be due to our large sample size, as small deviations may appear

to be statistically significant. The hazard ratios we present should be interpreted as the weighted average of the true hazard ratios over the follow-up period.[25]

Discussion

We identified conditions that increase risk of hospitalization and death in a large sample of patients with COVID-19 collected from 45 health systems across the US. We were able to replicate findings recently reported in this newly emerging field. Our large sample size may help inform decision-making and generate hypotheses for future research.

Hypertension
In our models, patients with hypertension showed a statistically insignificant association with death and an increased risk of hospitalization. This is consistent with a similar study in the UK, which found that hypertension was associated with hazard ratio of 1.07 [1.00, 1.15] for death.[2] Similar to this analysis, the UK study evaluated patients with a diagnosis of hypertension rather than a recent measure of blood pressure. However, they also performed a sensitivity analysis that evaluates a recent measure of blood pressure and saw that this predicted lower risk (HR=0.61 [0.56, 0.67]). Seeing reduced risk when measuring blood pressure directly suggests that blood pressure itself may impact outcomes with COVID-19. Future research is needed to understand this mechanism.

Obesity
Increasing BMI among obese patients was associated with increased risk of death and hospitalization, which is consistent with previous studies. Our analysis had 26% patients with unknown BMI and grouped known BMI into four categories based on obesity class. Future studies may examine a numeric value for BMI to determine whether overweight or underweight patients are at increased risk of hospitalization or death.

Diabetes
Patients with diabetes were at significantly increased risk for death and hospitalization. Future research should continue to examine whether the type of diabetes and quality of diabetes management impacts this relationship.

Immunocompromise
Immunocompromised patients in our models showed higher risk of death or hospitalization. Our sample only included patients using immunosuppressant medications 14 to 30 days prior to testing positive. This timing is important, as previous work has suggested that patients show systemic hyperinflammation in late stages of the disease.[18] Although our results indicate an increased risk of severe outcome, immunosuppressants may still be indicated for patients with hyperinflammation in the late stages of the disease. Further analysis is needed to determine whether immunomodulation after COVID-19 onset impacts outcomes.

Cancer
Cancer patients in this sample did not show increased risk for death or hospitalization. It is possible that immunodeficiency is the proximate cause for increased morbidity among cancer patients, so controlling for immunocompromise may be responsible for this finding. Future studies should further examine relationships between specific types of cancer and treatments to better understand the mechanism for the relationship between cancer and COVID-19 outcomes.

Cardiovascular Diseases
Heart failure showed a strong positive association with both hospitalization and death. It is not clear within this analysis whether heart failure is occurring as a result of severe COVID-19 or contributing to the risk of more severe cases. Cerebrovascular disease/stroke was weakly associated with increased risk of hospitalization and death, although stroke may also occur as a downstream manifestation of COVID-19, as coagulopathy has been

observed in COVID-19 patients.[26] Valve disorder was not significantly associated with hospitalization or death.

Vascular disease and congenital heart disease appeared to weakly predict reduced risk of death or hospitalization, but these conditions both showed strong correlation with heart failure. Vascular disease and congenital heart disease may influence risk among patients with COVID-19 by increasing the risk of heart failure or stroke, so controlling for stroke and heart failure in the fully adjusted model would attenuate the hazard ratios associated with these underlying cardiovascular risk factors.

COPD
Patients with COPD showed slightly increased risk for death and hospitalization. Compared with a meta-analysis of previous studies on COPD and COVID-19,[20] our effect size was smaller with a narrower confidence interval (HR=1.40 [1.34, 1.47]). The sample size in this analysis is larger than studies combined in the meta-analysis, which accounts for the narrower confidence interval. The effect observed here may be more precise due to the larger sample size, although it may also be attenuated by incomplete documentation.

Moderate/Severe Asthma
Patients with moderate to severe asthma seemed to show reduced risk of death and increased risk of hospitalization. This is possibly because patients with asthma were more likely to be younger compared to patients with other comorbidities; due to the categorization of age, we may not have completely controlled for its impact and the resulting protective effect may be due to residual confounding. A study with similar methods found that asthma increased risk controlling for use of medications,[2] so the protective effect seen here may come from the relationship between asthma medications and COVID-19. Given previous findings that certain types of asthma may provide a protective effect, future research should further investigate whether different types of asthma differently affect risk of adverse outcomes with COVID-19.

Limitations
One important limitation of this analysis is the inclusion of diagnoses that were added to the chart during a patient's infection. Cardiovascular damage is a known consequence of COVID-19, so the hazard ratios for heart failure and stroke are potentially inflated in this analysis. In addition, including potential downstream effects of COVID-19 in the model may have attenuated the association for other predictors by controlling for mediating factors. For example, underlying vascular disease could increase risk of death with COVID-19 by increasing risk of heart failure. By controlling for heart failure in our model, we may be obscuring an effect of these cardiovascular conditions.

Including documentation added after testing was necessary to avoid incomplete charts for patients new to the health system. As mentioned in our methods, we noticed that some conditions showed close to 30% of patients had chronic conditions documented after receiving a diagnosis for COVID-19. In addition to late documentation, it is possible that some comorbidities were not documented at all, which could change estimated effect sizes in our model.

Another key limitation is our definition of age as one of eight categories, which prevented us from adequately controlling for age. Most comorbidities are likely subject to some residual confounding, as patients with these conditions tend to be older. As a result, our estimates may be overstated.

While our model for death shows relatively robust fit (R^2 = 0.75), the fit of our model for hospitalization is weaker (R^2 = 0.43). This is likely because hospitalization is not purely a function of disease severity; it also varies based on the demographic, social, and economic factors that influence health care utilization more broadly. Reduced ability to access care means certain patients may be likely to seek care later in the course of their disease. Certain comorbidities included may be positively associated with COVID-19 severity, but negatively associated with ability to access care, which would complicate the interpretation of the effects seen here. Our analysis would benefit from the inclusion of additional variables, such as social determinants of health, vitals, lab results, and medications.

Finally, there are limitations associated with the time-to-event calculations in our survival analysis. The patient observation window and time-to-event calculation began at the first positive test or COVID-19 diagnosis. This is biased by testing capacity and access to care, as certain patients are more likely to be diagnosed sooner in the disease progression. Time to event is then calculated as the number of calendar days between when a patient tested positive for COVID-19 and their death or hospitalization, so patients that were already admitted in a critical state when they had a diagnosis or test result documented had skewed time-to-event estimates. If some of these chronic conditions are associated with access to testing, this may bias the effects observed here.

Conclusion

Heart failure, diabetes, immunocompromise, COPD and having a BMI above 40 appear to be positively associated with death and hospitalization among COVID-19 positive patients. Clinicians may seek to provide extra monitoring for patients with these comorbidities during the COVID-19 pandemic. Future research should more thoroughly explore nuance and mitigating factors for these and the other comorbidities included in this analysis.

Table 1. Data definitions for each comorbidity.

Hypertension	SNOMED: 38341003 Patients with this SNOMED code were excluded if they also had an ICD-10-CM code that starts with "O," as these are pregnancy-related conditions and were excluded from this analysis.
Diabetes	SNOMED: 46635009, 44054006
Immunocompromised	SNOMED: 86553008, 234532001, 420721002, 313039003, 707147002, 127040003 Patients were also included if they had an outpatient prescription for an immunosuppressant between 14 and 30 days prior to their COVID-19 diagnosis that had at least two refills and started before 3/1/2020. In addition, patients were included if they had an inpatient administration of an immunosuppressant within six weeks of being diagnosed with COVID-19.
Cancer*	SNOMED: 363346000 Patients were also included if they had an inpatient administration or outpatient prescription for a systemic antineoplastic medication within 6 weeks prior to being diagnosed with COVID-19.
Heart Failure	SNOMED: 84114007
Valve Disorder	SNOMED: 368009
Vascular Disease	SNOMED: 53741008
Congenital Heart Disease	SNOMED: 128599005 AND 66091009
COPD	SNOMED: 68917000 AND 13645005
Moderate/Severe Asthma	ICD-10 codes: J45.4, J45.40, J45.41, J45.42, J45.5, J45.50, J45.51, J45.52
*Patients included based on encounter/billing diagnosis within the last 1 year rather than 2 years	

Table 2. Number of patients with each comorbidity and prevalence within this sample of COVID-19 patients.

	Number of Patients with Comorbidity	Percentage of Sample with Comorbidity
Hypertension	75,376	39.6%
Diabetes	40,906	21.5%
Immunocompromised	7,508	3.9%
Cancer	14,085	7.4%
Heart Failure	16,615	8.7%
Valve Disorder	12,060	6.3%
Vascular Disease	12,413	6.5%
Cerebrovascular Disease or Stroke	12,563	6.6%
Congenital Heart Disease	1,397	0.7%
COPD	13,797	7.3%
Moderate/Severe Asthma	3,726	2.1%
Obesity: BMI 30-34.9	31,487	16.6%
Obesity: BMI 35-39.9	16,649	8.8%
Obesity: BMI >= 40	18,412	9.7%

Table 3. Age and Sex distribution within each comorbidity.

	Age Group								Sex	
	0-3	4-18	19-44	45-54	55-64	65-74	75-84	85+	Female	Male
Total	0%	2%	32%	18%	19%	13%	9%	6%	54%	46%
Hypertension	0%	0%	10%	16%	25%	22%	16%	11%*	52%	48%*
Diabetes	0%	0%	10%	16%	25%	24%	17%	9%*	49%	51%*
Immunocompromised	0%	1%	18%	16%	23%	21%	13%	6%*	56%	44%
Cancer	0%	0%	7%	11%	21%	26%	22%	13%*	52%	48%*
Heart Failure	0%	0%	4%	7%	17%	24%	25%	23%*	49%	51%*
Valve Disorder	0%	0%	7%	9%	18%	23%	23%	19%*	53%	47%
Vascular Disease	0%	0%	2%	7%	20%	27%	27%	18%*	40%	60%*
Cerebrovascular Disease or Stroke	0%	0%	5%	7%	18%	25%	25%	19%*	52%	48%*
Congenital Heart Disease	3%	3%	20%	13%	21%	18%	14%	9%*	51%	49%
COPD	0%	0%	3%	7%	22%	28%	25%	15%*	51%	49%*
Moderate/Severe Asthma	0%	2%	29%	20%	23%	14%	8%	4%*	72%	28%*
Obesity: BMI 30-34.9	0%	0%	30%	20%	23%	15%	8%	4%	53%	47%*
Obesity: BMI 35-39.9	0%	0%	32%	22%	23%	14%	6%	2%	60%	40%*
Obesity: BMI >= 40	0%	0%	37%	22%	21%	12%	5%	2%*	64%	36%*
*$\chi 2$ test shows that distribution differs significantly ($p<0.001$) among people with comorbidity										

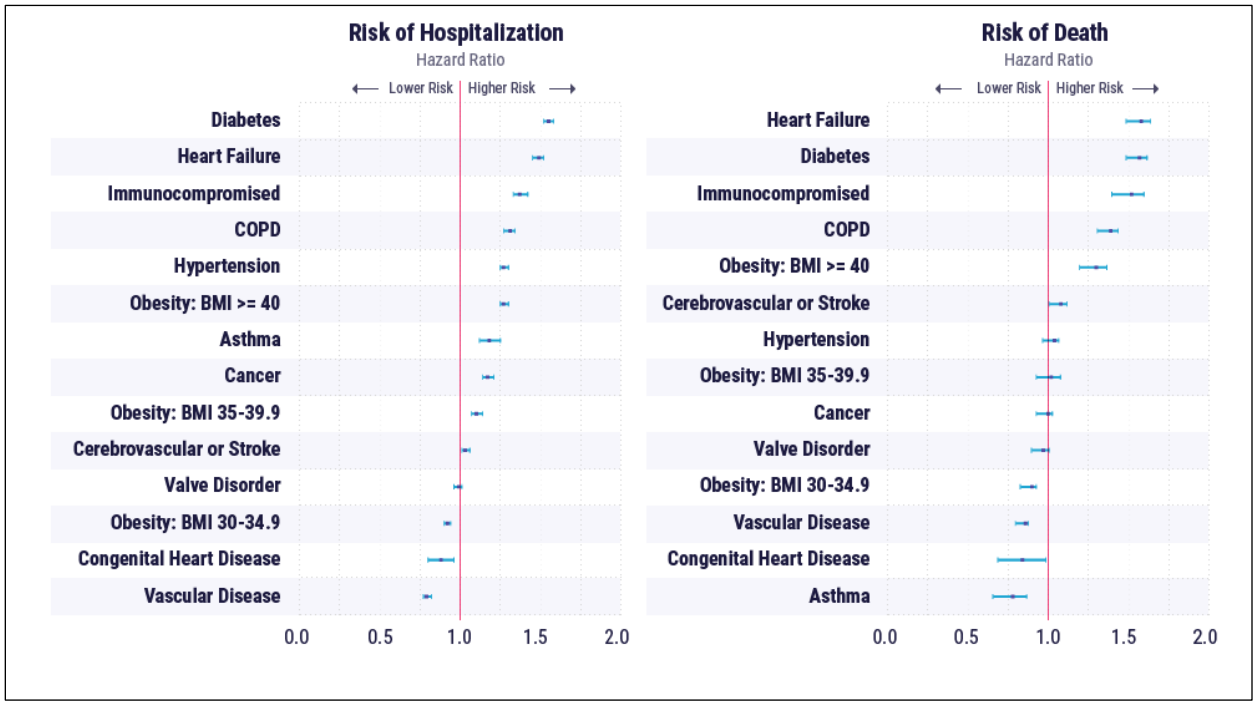
Table 4. Hazard Ratios and 95% confidence intervals for death with each comorbidity examined independently and in a fully adjusted model.

	Model Adjusting for Age/Sex	Fully Adjusted Model
Hypertension	1.49 [1.43, 1.56]	1.05 [1.00, 1.10]
Diabetes	1.87 [1.80, 1.94]	1.58 [1.52, 1.65]
Immunocompromised	1.92 [1.80, 2.04]	1.53 [1.43, 1.63]
Cancer	1.17 [1.12, 1.23]	1.01 [0.96, 1.06]
Heart Failure	2.02 [1.94, 2.10]	1.59 [1.52, 1.67]
Valve Disorder	1.36 [1.30, 1.43]	0.98 [0.93, 1.04]
Vascular Disease	1.23 [1.18, 1.29]	0.87 [0.83, 0.91]
Cerebrovascular Disease or Stroke	1.34 [1.28, 1.41]	1.09 [1.04, 1.15]
Congenital Heart Disease	1.10 [0.92, 1.31]	0.85 [0.72, 1.02]
COPD	1.78 [1.71, 1.86]	1.40 [1.34, 1.47]
Asthma	1.08 [0.95, 1.23]	0.79 [0.69, 0.90]
Obesity: BMI 30-34.9	0.98 [0.93, 1.03]	0.91 [0.86, 0.96]
Obesity: BMI 35-39.9	1.19 [1.11, 1.28]	1.03 [0.96, 1.11]
Obesity: BMI >= 40	1.53 [1.44, 1.62]	1.31 [1.23, 1.40]

Table 5. Hazard Ratios and 95% confidence intervals for each comorbidity examined together.

	Model Adjusting for Age/Sex	Fully Adjusted Model
Hypertension	1.95 [1.92, 1.99]	1.29 [1.27, 1.32]
Diabetes	2.02 [1.98, 2.06]	1.57 [1.54, 1.60]
Immunocompromised	1.83 [1.77, 1.89]	1.39 [1.35, 1.44]
Cancer	1.19 [1.16, 1.23]	1.19 [1.16, 1.23]
Heart Failure	2.02 [1.98, 2.07]	1.51 [1.47, 1.54]
Valve Disorder	1.43 [1.39, 1.47]	1.01 [0.98, 1.03]
Vascular Disease	1.25 [1.21, 1.28]	0.81 [0.79, 0.84]
Cerebrovascular Disease or Stroke	1.40 [1.36, 1.43]	1.05 [1.03, 1.08]
Congenital Heart Disease	1.17 [1.08, 1.27]	0.90 [0.82, 0.98]
COPD	1.76 [1.72, 1.80]	1.33 [1.29, 1.36]
Asthma	1.20 [1.14, 1.27]	1.20 [1.14, 1.27]
Obesity: BMI 30-34.9	1.02 [0.99, 1.04]	0.94 [0.92, 0.96]
Obesity: BMI 35-39.9	1.12 [1.09, 1.16]	1.12 [1.09, 1.16]
Obesity: BMI >= 40	1.29 [1.26, 1.33]	1.29 [1.09, 1.16]

Figure 1. Effect of COVID-19 on Hospitalization and Death by Comorbidity (n=190,194). ***Hazard ratios and 95% confidence intervals for each comorbidity, controlling for age group, sex, and other comorbidities.***



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