Clinical Infectious Diseases

MAJOR ARTICLE

Impact of Sex and Metabolic Comorbidities on Coronavirus Disease 2019 (COVID-19) Mortality Risk Across Age Groups: 66 646 Inpatients Across 613 U.S. Hospitals

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Background. The relationship between common patient characteristics, such as sex and metabolic comorbidities, and mortality from coronavirus disease 2019 (COVID-19) remains incompletely understood. Emerging evidence suggests that metabolic risk factors may also vary by age. This study aimed to determine the association between common patient characteristics and mortality across age-groups among COVID-19 inpatients.

Methods. We performed a retrospective cohort study of patients discharged from hospitals in the Premier Healthcare Database between April–June 2020. Inpatients were identified using COVID-19 ICD-10-CM diagnosis codes. A priori-defined exposures were sex and present-on-admission hypertension, diabetes, obesity, and interactions between age and these comorbidities. Controlling for additional confounders, we evaluated relationships between these variables and in-hospital mortality in a log-binomial model.

Results. Among 66 646 (6.5%) admissions with a COVID-19 diagnosis, across 613 U.S. hospitals, 12 388 (18.6%) died in-hospital. In multivariable analysis, male sex was independently associated with 30% higher mortality risk (aRR, 1.30, 95% CI: 1.26–1.34). Diabetes without chronic complications was not a risk factor at any age (aRR 1.01, 95% CI: 0.96–1.06), and hypertension without chronic complications was a risk factor only in 20–39 year-olds (aRR, 1.68, 95% CI: 1.17–2.40). Diabetes with chronic complications, hypertension with chronic complications, and obesity were risk factors in most age-groups, with highest relative risks among 20–39 year-olds (respective aRRs 1.79, 2.33, 1.92; *P*-values ≤ .002).

Conclusions. Hospitalized men with COVID-19 are at increased risk of death across all ages. Hypertension, diabetes with chronic complications, and obesity demonstrated age-dependent effects, with the highest relative risks among adults aged 20–39.

Keywords. COVID-19; metabolic comorbidities; hypertension; sex; claims data.

Despite increased clinical experience with severe acute respiratory syndrome coronavirus -2 (SARS-CoV-2) and its resulting disease, coronavirus disease-2019 (COVID-19), and a rapidly expanding body of literature, the relationship between common risk factors and mortality from COVID-19 remains incompletely understood. Prior studies have identified male sex, older age, and metabolic comorbidities such as hypertension, obesity, and diabetes as risk factors for poor outcomes and mortality in COVID-19 patients [1–7]. However, these comorbidities often co-occur and are more common among men and older age groups [8–10]. Emerging data also suggest that the effect of metabolic comorbidities on risk of severe COVID-19 outcomes may be age-dependent [11–14]. Without large sample sizes, isolating the independent effects of these clustered characteristics and examining effects by age is challenging. Many studies have also combined comorbidity severities in order to maintain adequate strata sizes, thereby obscuring potentially meaningful clinical granularity. Given that half of American adults are men and more than half have hypertension or diabetes [15, 16], evaluating the precise relationship between these common characteristics and mortality in U.S. patients is important. The availability of large claims databases makes studying these questions possible.

To address these knowledge gaps, the objective of the current study was to determine the effect of common patient characteristics on mortality risk across age groups in a large sample of more than 60 000 COVID-19 inpatients across more than 600 geographically diverse U.S. hospitals.

METHODS

Study Design and Data Source

We conducted a retrospective observational cohort study of patients who were discharged from hospitals in the Premier Healthcare Database ("Premier Database"), an all-payer repository of claims and clinical data from more than 120 million

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U.S. inpatient admissions [17]. Premier Database hospitals cover highly geographically diverse areas across the U.S. and capture approximately 1 of every 4 U.S. hospital discharges (see Supplementary Material for further database detail). Premier internally validates all data before its release into the Premier Database. This study did not include personally identifiable information and was exempt from institutional review board review.

Study Population and COVID-19 Case Definition

All inpatient admissions with discharge dates in the second quarter of 2020 (April, May, and June) and present in the Premier Database as of the data extract date of July 20, 2020 were included in the study. Inpatients were designated as COVID-19 positive if their admission included an ICD-10-CM diagnosis code of "COVID-19" (U07.1). The U07.1 diagnosis code became formally effective for use on April 1, 2020 and is assigned for diagnoses of COVID-19 based upon: (1) documented confirmed or presumptive-positive test results; or (2) a clinical provider's statement that a patient has COVID-19 (neither documentation of the type of test nor a copy of the test results in the record are required) [18–20]. In order to ensure national uniformity and accurate code usage, substantial governmental and professional organization guidance accompanied release of the U07.1 diagnosis code [18, 19]. We stratified admissions by (a) any COVID-19 diagnosis (principal, secondary, and/or admitting), and (b) admitting and/or principal COVID-19 diagnoses only.

Outcome

The primary study outcome was mortality during the current hospitalization. Because select hospitals may transfer severely ill patients for higher-acuity care, and our analysis includes patients who transferred into Premier Database hospitals, to avoid double-counting some patients we performed sensitivity analyses excluding patients who were discharged to another hospital for acute care.

Collected Data and Primary Patient Characteristics of Interest

For each admission, we extracted data on hospital characteristics, including teaching status, urban versus rural location, and U.S. census geographic region and division. To approximate resource utilization intensity, we calculated each hospital's monthly percentage of COVID-19 patients and of mechanically ventilated patients. We also extracted the following patient-level data for each admission: (a) admission and discharge characteristics (eg, pre-admission location, discharge location or death, month of admission and discharge); (b) sociodemographics (eg, age, sex, race, and ethnicity); (c) all ICD-10-PCS procedure codes; and (d) all ICD-10-CM diagnosis codes, including whether a diagnosis was present-on-admission. We mapped present-on-admission diagnosis codes to Elixhauser comorbidities using standardized Agency for Healthcare Research and Quality (AHRQ) methodology and software [21].

Our primary, a priori-defined patient characteristics of interest were sex and the following Elixhauser comorbidities present-on-admission: hypertension with no other hypertension end-organ complications (herein referred to as "uncomplicated hypertension," as defined by Elixhauser et al.), hypertension with other end-organ complications ("complicated hypertension,") uncomplicated and complicated diabetes using the same criteria for end-organ complications, and obesity. As defined in the Elixhauser Comorbidity Index, end-organ complications primarily include heart disease, renal disease, and/or vascular complications [22]. We hypothesized based upon emerging evidence from prior, smaller studies that the effect of the preceding comorbidities on mortality risk may also vary by age [11–14] and tested for age-based interaction effects during model-building (see Statistical Methods).

Statistical Methods

Descriptive statistics for patient and hospital characteristics were calculated using mean (standard deviation [SD]), median (range or interquartile range [IQR]), or frequency count (percentage). We included all patients with COVID-19 diagnoses in the primary study cohort. To calculate age-stratified rates of study outcomes, we categorized age by decade of life.

We analyzed the relationship between in-hospital mortality and patient, hospital, and temporal characteristics among adult patients using log-binomial models to estimate relative risk (RR) and corresponding 95% confidence intervals (CIs). Based on our a priori hypotheses that the relationship between metabolic comorbidities and mortality may vary by age, we evaluated age-specific interaction terms for complicated and uncomplicated diabetes, complicated and uncomplicated hypertension, and obesity. If these interactions were not statistically significant based upon a global Wald Chi-square test (ie, if the effect of a comorbidity did not differ significantly between age groups), we did not include the interaction between age and the comorbidity in our final model. Our final model therefore included (1) our primary characteristics of interest, which were parameterized separately for each age strata if there was significant interaction between the characteristic and age; and (2) confounding variables (hospital-level variables, temporal variables, and other patient-level variables such as chronic pulmonary disease or liver disease) that were selected a priori through literature review and expert clinical consensus (A. H., E. P., A. L., and J. B.). Because two selected confounders, cardiovascular failure and renal failure, may be complications of hypertension or diabetes, we evaluated these variables for collinearity before including them in the final model. We also performed a sensitivity analysis excluding them. All tests were 2-tailed, and P values $\leq .05$ were used for statistical significance testing. Analyses were performed using SAS version 9.4 (SAS Institute Inc.) and STATA 15.0 (Stata Corp.). Log-binomial models were fit using the

modified Poisson regression approach described by Zou (2004) [23–25].

RESULTS

During the study period, which included discharges in the second quarter of 2020, we identified 1 028 032 unique admissions across 763 hospitals. 66 646 (6.5%) admissions from 613 hospitals had a COVID-19 diagnosis. Of the COVID-19 admissions, 42 102 (63.1%) had a principal or admitting diagnosis of COVID-19. COVID-19 patients were identified from every U.S. census geographic division. However, the majority (33 148; 49.7% of COVID-19 admissions) were hospitalized in the Middle Atlantic (New York, New Jersey, and Pennsylvania) (see Supplementary Material for geographic distribution data).

The mean (SD) age of COVID-19 patients was 62.8 (17.9) years, and 35 246 (52.9%) were male (Table 1). A total of 14 758 (22.1%) COVID-19 patients received ICU-level care, and 10 908 (16.4%) received mechanical ventilation (Table 2). On average, COVID-19 patients had 3 Elixhauser comorbidities (SD, 2.1) present-on-admission. Compared to non-COVID-19 patients, COVID-19 patients were more likely to be Black (22.9% vs. 14.3%) and Hispanic (19.8% vs. 9.9%) (Table 1).

Mortality Rates and Risk Factors in COVID-19 Inpatients

Overall, 12 388 (18.6%) of COVID-19 patients died in the hospital (Table 2). Figure 1 reflects crude mortality rates by patient age. In-hospital mortality was lowest among pediatric patients. Among adults, mortality increased with each decade of life (1.6%, 20–29 years — 34.4%, 80+ years) (Fig. 1). Across every adult age-strata, men had a higher rate of death compared to women (Supplementary Fig. 1). In the sub-sample of patients with a principal or admitting diagnosis of COVID-19, 6288

Table 1. Patient and Hospital Characteristics of COVID-19 and Non-COVID-19 Inpatients Among Discharges in the Second Quarter of 2020

Characteristic	Non-COVID-19 Admissions n = 961 386 (n, %)	COVID-19 Admissions n = 66 646 (n, %)
Admission Characteristics		
Transfer from another acute care hospital	68 038 (7.1%)	4806 (7.2%)
Admitted from skilled nursing or intermediate care facility	9570 (1.0%)	3721 (5.6%)
Admission month		
Pre-March	2705 (0.3%)	57 (0.1%)
March	58 026 (6.0%)	10 033 (15.1%)
April	385 997 (40.2%)	37 493 (56.3%)
May	351 607 (36.6%)	14 754 (22.1%)
June	163 051 (17.0%)	4309 (6.5%)
Hospital length of stay, days (mean, SD)	4.46 (7.80)	8.46 (10.4)
Demographic Characteristics		
Age, mean (SD)	46.80 (27.96)	62.83 (17.89)
Age decade of life, y		
Less than 10	151 289 (15.7%)	222 (0.3%)
10–19	22 758 (2.4%)	398 (0.6%)
20–29	102 170 (10.6%)	2682 (4.0%)
30–39	114 495 (11.9%)	4689 (7.0%)
40–49	71 416 (7.4%)	6847 (10.3%)
50–59	106 308 (11.1%)	11 138 (16.7%)
60–69	140 497 (14.6%)	14 343 (21.5%)
70–79	134 510 (14.0%)	12 855 (19.3%)
80 and Older	117 943 (12.3%)	13 472 (20.2%)
Male sex	421 328 (43.8%)	35 246 (52.9%)
Race		
White	679 239 (70.7%)	29 085 (43.6%)
Black	137 275 (14.3%)	15 270 (22.9%)
Unknown	46 649 (4.9%)	5612 (8.4%)
Other	98 223 (10.2%)	16 679 (25.0%)
Hispanic ethnicity	94 865 (9.9%)	13 178 (19.8%)
Elixhauser Comorbidities, present-on-admission[a]		
Alcohol abuse	52 841 (5.5%)	1404 (2.1%)
Any hypertension	422 326 (43.9%)	42 813 (64.2%)
Blood loss anemia	21 256 (2.2%)	605 (0.9%)

Table 1. Continued

Characteristic	Non-COVID-19 Admissions n = 961 386 (n, %)	COVID-19 Admissions n = 66 646 (n, %)
Chronic peptic ulcer disease	8143 (0.9%)	358 (0.5%)
Chronic pulmonary disease	170 623 (17.8%)	13 606 (20.4%)
Coagulopathy	47 284 (4.9%)	5722 (8.6%)
Congestive heart failure	147 780 (15.4%)	9893 (14.8%)
Deficiency anemias	156 262 (16.3%)	13 583 (20.4%)
Depression	109 163 (11.4%)	6827 (10.2%)
Diabetes, complicated	147 724 (15.4%)	16 186 (24.3%)
Diabetes, uncomplicated	67 176 (7.0%)	9425 (14.1%)
Fluid and electrolyte disorders	232 638 (24.2%)	31 237 (46.9%)
HIV and AIDS	1993 (0.2%)	216 (0.3%)
Hypertension, complicated	194 661 (20.3%)	17 978 (27.0%)
Hypertension, uncomplicated	227 665 (23.7%)	24 835 (37.3%)
Hypothyroidism	103 638 (10.8%)	8248 (12.4%)
Liver disease	51 189 (5.3%)	2698 (4.1%)
Lymphoma	6607 (0.7%)	486 (0.7%)
Metastatic cancer	27 104 (2.8%)	740 (1.1%)
Obesity	150 659 (15.7%)	14 044 (21.1%)
Other neurological disorders	87 275 (9.1%)	8329 (12.5%)
Paralysis	23 526 (2.5%)	1836 (2.8%)
Peripheral vascular disease	40 991 (4.3%)	2159 (3.2%)
Psychoses	44 583 (4.6%)	3786 (5.7%)
Pulmonary circulation disease	8428 (0.9%)	1250 (1.9%)
Renal failure	144 732 (15.1%)	13 770 (20.7%)
Rheumatoid arthritis/ collagen vascular diseases	23 889 (2.5%)	1736 (2.6%)
Solid tumor w/out metastasis	22 172 (2.3%)	1057 (1.6%)
Substance use disorder	58 762 (6.1%)	1123 (1.7%)
Valvular disease	46 290 (4.8%)	2198 (3.3%)
Weight loss	49 784 (5.2%)	4664 (7.0%)
Total Elixhauser score, present-on-admission (mean, SD)	2.57 (2.40)	3.30 (2.10)
Hospital Characteristics		
Bed size		
000–099	61 851 (6.4%)	2032 (3.1%)
100–199	123 812 (12.9%)	6295 (9.5%)
200–299	163 154 (17.0%)	12 214 (18.3%)
300–399	163 593 (17.0%)	14 116 (21.2%)
400–499	117 386 (12.2%)	5947 (8.9%)
500+	331 590 (34.5%)	26 042 (39.1%)
Urban[b]	833 394 (86.7%)	61 708 (92.6%)
Teaching	474 327 (49.3%)	42 951 (64.5%)
US Census Division[c]		
East North Central	163 758 (17.0%)	7452 (11.2%)
East South Central	63 411 (6.6%)	1305 (2.0%)
Middle Atlantic	129 720 (13.5%)	33 148 (49.7%)
Mountain	39 160 (4.1%)	1583 (2.4%)
New England	20 005 (2.1%)	2015 (3.0%)
Pacific	87 274 (9.1%)	1799 (2.7%)
South Atlantic	260 328 (27.1%)	11 983 (17.9%)
West North Central	70 500 (7.3%)	2856 (4.3%)
West South Central	127 230 (13.2%)	4505 (6.8%)

Abbreviations: COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; SD, standard deviation.

[a] Elixhauser comorbidity categories were modified to include principal diagnoses, in addition to secondary diagnoses, that were present-on-admission. Elixhauser scores represent unweighted Elixhauser comorbidity sums (1 point per comorbidity present-on-admission).

[b] Designation provided by Premier, based upon American Hospital Association Annual Survey response.

[c] U.S. census divisions comprise four U.S. census regions: NORTHEAST (Middle Atlantic, New England), SOUTH (South Atlantic, East South Central, West South Central), MIDWEST (East North Central, West North Central), WEST (Mountain, Pacific). States in each U.S. census division are the following: (New England Division): Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont; (Middle Atlantic Division): New Jersey, New York, Pennsylvania; (East North Central Division): Illinois, Indiana, Michigan, Ohio, Wisconsin; (West North Central Division): Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, South Dakota; (South Atlantic Division): Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia; (East South Central Division): Alabama, Kentucky, Mississippi, Tennessee; (West South Central Division): Arkansas, Louisiana, Oklahoma, Texas; (Mountain Division): Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming; (Pacific Division): Alaska, California, Hawaii, Oregon, Washington.

Table 2. In-Hospital Mortality Status by Patient and Hospital Characteristics of COVID-19 Inpatients

Characteristics	All COVID-19 Patients	Died in-Hospital
Receipt of ICU-Level Care		
No	51 888	6698 (12.9%)
Yes	14 758	5690 (38.6%)
Time-to-ICU, days (mean, SD)[a]	2.8 (3.9)	3.4 (5.0)
Receipt of Mechanical Ventilation		
No	55 738	6152 (11.0%)
Yes	10 908	6236 (57.2%)
Time-to-ventilation, days (mean, SD)[a]	4.07(13.9)	4.70 (18.1)
Admission Characteristics (%)		
Admitted from skilled nursing facility		
No	62 925	11 106 (17.6%)
Yes	3721	1282 (34.5%)
Transferred from another acute care hospital		
No	61 840	11 220 (18.1%)
Yes	4806	1168 (24.3%)
Admission month		
Pre-March	57	15 (26.3%)
March	10 033	2452 (24.4%)
April	37 493	7684 (20.5%)
May	14 754	1935 (13.1%)
June	4309	302 (7.0%)
Length of stay (time-to-death for patients who died in-hospital), days (mean, SD)	8.5 (10.4)	10.0 (15.5)
Demographic Characteristics (%)		
Age, y (mean, SD)	62.8 (17.9)	73.3 (12.8)
Age, decade of life		
Less than 10	222	2 (0.9%)
10–19	398	2 (0.5%)
20–29	2682	42 (1.6%)
30–39	4689	142 (3.0%)
40–49	6847	398 (5.8%)
50–59	11 138	1183 (10.6%)
60–69	14 343	2575 (18.0%)
70–79	12 855	3412 (26.5%)
80 and Older	13 472	4632 (34.4%)
Male sex		
No	31 400	5169 (16.5%)
Yes	35 246	7219 (20.5%)
Race		
White	29 085	5935 (20.4%)
Black	15 270	2602 (17.0%)
Other	16 679	2872 (17.2%)
Unknown	5612	979 (17.4%)
Hispanic ethnicity		
No	53 468	10 680 (20.0%)
Yes	13 178	1708 (13.0%)
Elixhauser comorbidities, present-on-admission (%)[b]		
Alcohol abuse		
No	65 242	12 175 (18.7%)
Yes	1404	213 (15.2%)
Hypertension (any)		
No	23 833	2960 (12.4%)
Yes	42 813	9428 (22.0%)
Blood loss anemia		
No	66 041	12 330 (18.7%)
Yes	605	58 (9.6%)
Chronic peptic ulcer disease		
No	66 288	12 323 (18.6%)
Yes	358	65 (18.2%)
Chronic pulmonary disease		
No	53 040	9494 (17.9%)
Yes	13 606	2894 (21.3%)
Coagulopathy		
No	60 924	10 794 (17.7%)
Yes	5722	1594 (27.9%)
Congestive heart failure		
No	56 753	9356 (16.5%)
Yes	9893	3032 (30.6%)
Deficiency anemias		
No	53 063	9141 (17.2%)
Yes	13 583	3247 (23.9%)
Depression		
No	59 819	11 044 (18.5%)
Yes	6827	1344 (19.7%)
Diabetes, complicated		
No	50 460	8307 (16.5%)
Yes	16 186	4081 (25.2%)
Diabetes, uncomplicated		
No	57 221	10 806 (18.9%)
Yes	9425	1582 (16.8%)
Fluid and electrolyte disorders		
No	35 409	4795 (13.5%)
Yes	31 237	7593 (24.3%)
HIV and AIDS		
No	66 430	12 352 (18.6%)
Yes	216	36 (16.7%)
Hypertension, complicated		
No	48 668	7201 (14.8%)
Yes	17 978	5187 (28.9%)
Hypertension, uncomplicated		
No	41 811	8147 (19.5%)
Yes	24 835	4241 (17.1%)
Hypothyroidism		
No	58 398	10 440 (17.9%)
Yes	8248	1948 (23.6%)
Liver disease		
No	63 948	11 872 (18.6%)
Yes	2698	516 (19.1%)
Lymphoma		
No	66 160	12 224 (18.5%)
Yes	486	164 (33.7%)
Metastatic cancer		
No	65 906	12 141 (18.4%)
Yes	740	247 (33.4%)
Obesity		
No	52 602	10 077 (19.2%)
Yes	14 044	2311 (16.5%)
Other neurological disorders		
No	58 317	10 202 (17.5%)
Yes	8329	2186 (26.2%)

Table 2. Continued

Characteristics	All COVID-19 Patients	Died in-Hospital
Paralysis		
No	64 810	11 823 (18.2%)
Yes	1836	565 (30.8%)
Peripheral vascular disease		
No	64 487	11 798 (18.3%)
Yes	2159	590 (27.3%)
Psychoses		
No	62 860	11 592 (18.4%)
Yes	3786	796 (21.0%)
Pulmonary circulation disease		
No	65 396	12 148 (18.6%)
Yes	1250	240 (19.2%)
Renal failure		
No	52 876	8230 (15.6%)
Yes	13 770	4158 (30.2%)
Rheumatoid arthritis/collagen vascular diseases		
No	64 910	12 015 (18.5%)
Yes	1736	373 (21.5%)
Solid tumor without metastasis		
No	65 589	12 089 (18.4%)
Yes	1057	299 (28.3%)
Substance use disorder		
No	65 523	12 276 (18.7%)
Yes	1123	112 (10.0%)
Valvular disease		
No	64 448	11 760 (18.2%)
Yes	2198	628 (28.6%)
Weight loss		
No	61 982	11 042 (17.8%)
Yes	4664	1346 (28.9%)
Total Elixhauser score (mean, SD)	3.3 (2.1)	4.2 (2.1)
Hospital Characteristics (%)		
Bed size		
000–099	2032	228 (11.2%)
100–199	6295	911 (14.5%)
200–299	12 214	2551 (20.9%)
300–399	14 116	2786 (19.7%)
400–499	5947	1187 (20.0%)
500+	26 042	4725 (18.1%)
Urban hospital[c]		
No	4938	846 (17.1%)
Yes	61 708	11 542 (18.7%)
Academic hospital		
No	23 695	4041 (17.1%)
Yes	42 951	8347 (19.4%)

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; SD, standard deviation.

[a] Calculated only among patients who experienced the outcome (receipt of ICU-level care or mechanical ventilation).

[b] Elixhauser comorbidity categories were modified to include principal diagnoses, in addition to secondary diagnoses, that were present-on-admission. Elixhauser scores represent unweighted Elixhauser comorbidity sums (1 point per comorbidity present-on-admission).

[c] Designation provided by Premier, based upon American Hospital Association Annual Survey response.

(14.9%) died in-hospital (age-stratified rates in Supplementary Fig. 2). When excluding patients transferred on discharge to other acute care hospitals (n = 2171), the percentage of patients with in-hospital mortality in the total cohort rose to 19.2% (12 388/64 475).

In a multivariable model controlling for patient, hospital, and temporal characteristics based upon month of admission, male sex was independently associated with a 30% higher risk of death during the admission (adjusted RR, 1.30, 95% CI: 1.26–1.34) (Table 3). The adjusted risk of in-hospital death increased with every decade of life; relative to patients aged 50–59, patients aged 60–69, 70–79, and 80+ had 1.7, 2.7, and 4.3 times the risk of death, respectively (adjusted RRs and 95% CIs: 1.72, 1.53–1.94; 2.70, 2.40–3.03; 4.26, 3.82–4.75). Relative to White race, Black race was associated with lower risk of in-hospital death (adjusted RR 0.90, 95% CI: 0.87–0.94). Admission to an academic hospital was associated with a 7% lower risk of in-hospital death (adjusted RR 0.93, 95% CI: 0.90–0.97) (Table 3).

The association between uncomplicated diabetes (diabetes without chronic complications) and mortality did not significantly vary by age. Uncomplicated diabetes was not a risk factor for in-hospital death (adjusted RR 1.01, 95% CI: 0.96–1.06) (Table 3). The association between other metabolic comorbidities and mortality varied by age (P values ≤ .007), and we estimated the effect of these comorbidities separately for each age group. Uncomplicated hypertension was only a risk factor for in-hospital death among patients aged 20–39 years and was not a risk factor in any other age groups (adjusted RR in 20–39 year-olds, 1.68, 95% CI: 1.17–2.40; P value for interaction = .007). Complicated hypertension, complicated diabetes, and obesity were independent risk factors in most age groups and the relative risks differed significantly by age (P values ≤ .001). The relative risk for each comorbidity was highest among 20–39 year-olds and generally decreased with each decade of life (Table 3 and Supplementary Table 1; P value for trends ≤ .002). Apart from complicated diabetes, which did not maintain an inverse trend with age, all other multivariable model estimates were similar when restricting to patients with principal/admitting COVID-19 diagnoses (Supplementary Table 2).

Temporal Trends

For every adult age group, mortality was lower among patients admitted in May than among patients admitted in April, and equal or lower again among patients admitted in June (Fig. 2). After controlling for patient and hospital characteristics, patients admitted in May averaged a 19% lower risk of death (RR, 0.81, 95% CI: 0.77–0.85) compared to patients admitted in April (Table 3). This estimate accounted for a hospital's percentage of COVID-19 patients and mechanically ventilated patients during the same time period, which we calculated to approximate a hospital's resource utilization intensity. As each of these percentages increased, a patient's mortality risk also independently increased (Table 3).

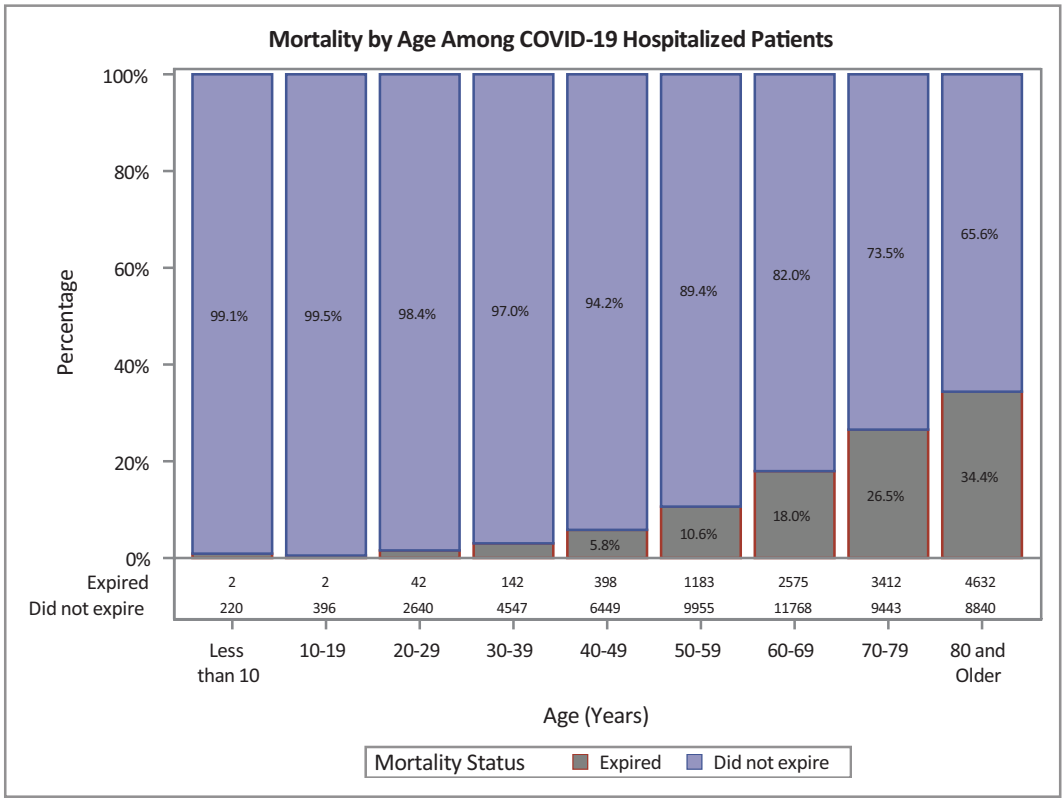

Figure 1. In-hospital mortality by decade of life among inpatients with coronavirus disease 2019 (COVID-19) diagnoses (n = 66 646).

DISCUSSION

To our knowledge, this study of 613 U.S. hospitals and more than 66 000 COVID-19 hospitalizations is the largest peer-reviewed and published U.S. study to-date analyzing risk factors and outcomes among patients hospitalized with COVID-19. As expected, mortality rates increased with each decade of life. Notably, mortality rates were higher among adult men compared to women in every decade of life, and male sex was independently associated with a 30% greater risk of mortality during hospitalization. The data also demonstrated that among adult hospitalized patients, patients with uncomplicated diabetes were not at increased risk of death, and patients with uncomplicated hypertension were not at increased risk of death unless they were in the youngest age demographic. Adjusting for many hospital and patient characteristics, patients admitted in May had improved survival compared to patients admitted in April.

Our finding that male sex is a risk factor for increased mortality is supported by prior studies [1, 5–7, 26, 27]. However, our study controlled for numerous other comorbid conditions that are more common among men and demonstrated that men have higher mortality than women in every decade of adult life. Thus, we are confident that male sex is a strong, independent risk factor for mortality among hospitalized COVID-19 patients. This finding also comports with hypotheses that immune function differences may explain higher COVID-19 mortality rates in men [28], including recent data demonstrating sex-based differences in COVID-19 immune responses [29].

Previous studies have examined whether hypertension and diabetes are risk factors for mortality in hospitalized COVID-19 patients but have reached conflicting results. These studies generally did not stratify by comorbidity severity or patient age [1–3, 30]. Our large sample permitted a more detailed evaluation of hypertension and diabetes as risk factors. Unexpectedly, uncomplicated diabetes was not associated with in-hospital mortality in any age group, and uncomplicated hypertension was only associated with in-hospital mortality among adults in their 20s and 30s after adjustment for other model variables. Understanding that most hypertensive or diabetic patients are not at increased risk of death compared to other comparable hospitalized patients, provided they do not have additional complications such as heart disease or renal failure, may guide resource allocation and intervention efforts among hospitalized patients.

In contrast, complicated diabetes, complicated hypertension, and obesity were strong, independent risk factors for death in most age groups. As with uncomplicated hypertension, these comorbidities demonstrated pronounced age-specific trends that persisted in full multivariable models. The relative risk for each of these comorbidities was highest among 20–39 year-olds, after which it generally decreased with each subsequent decade

Table 3. Association between Patient, Hospital, and Temporal Characteristics and Mortality During the Hospital Admission Among COVID-19 Inpatients in a Multivariable Model[a]

Characteristic	Relative Risk (aRR) and 95% CI for In-Hospital Death (n = 66 026[b])	*P* Value
Transferred from another acute care hospital	1.31 (1.24–1.37)	<.001
Male sex	1.30 (1.26–1.34)	<.001
Age, y[c]		
20–39	0.21 (0.17–0.27)	<.001
40–49	0.47 (0.39–0.57)	<.001
50–59	REF	REF
60–69	1.72 (1.53–1.94)	<.001
70–79	2.70 (2.40–3.03)	<.001
80+	4.26 (3.82–4.75)	<.001
Race		
White	REF	REF
Black	0.90 (0.87–0.94)	<.001
Unknown	1.16 (1.09–1.23)	<.001
Other	1.02 (0.98–1.06)	.37
Hispanic ethnicity	0.95 (0.90–0.99)	.02
Elixhauser Comorbidities, present-on-admission[d]		
Congestive heart failure	1.16 (1.11–1.21)	<.001
Pulmonary circulation disorders	1.04 (0.93–1.16)	.48
Chronic pulmonary disease	1.02 (0.99–1.06)	.21
Liver Disease	1.09 (1.01–1.18)	.03
Renal failure	1.12 (1.07–1.17)	<.001
Malignancy[e]	1.30 (1.22–1.38)	<.001
Uncomplicated diabetes	1.01 (0.96–1.06)	.63
Comorbidity score of all other Elixhauser comorbidities not included in the model as binary variables (above), Present-on-Admission[f]	1.12 (1.11–1.14)	<.001
Uncomplicated hypertension by age[g]		
20–39	1.68 (1.17–2.40)	.01
40–49	1.08 (0.86–1.35)	.52
50–59	0.91 (0.80–1.04)	.17
60–69	0.85 (0.78–0.93)	.001
70–79	0.87 (0.80–0.95)	.001
80+	0.81 (0.76–0.87)	<.001
Complicated hypertension by age[g]		
20–39	2.33 (1.50–3.60)	<.001
40–49	1.88 (1.46–2.42)	<.001
50–59	1.34 (1.15–1.56)	<.001
60–69	1.03 (0.93–1.14)	.62
70–79	0.98 (0.89–1.07)	.58
80+	0.79 (0.74–0.85)	<.001
Diabetes with chronic complications by age[g]		
20–39	1.79 (1.23–2.61)	.002
40–49	1.44 (1.15–1.80)	.001
50–59	1.23 (1.09–1.39)	.001
60–69	1.32 (1.22–1.43)	<.001
70–79	1.13 (1.06–1.20)	<.001
80+	1.05 (0.99–1.11)	.09
Obesity by age[g]		
20–39	1.92 (1.43–2.57)	<.001
40–49	1.57 (1.30–1.90)	<.001
50–59	1.33 (1.19–1.49)	<.001
60–69	1.26 (1.16–1.36)	<.001
70–79	1.16 (1.08–1.25)	<.001
80+	1.11 (1.02–1.22)	.02
Academic hospital	0.93 (0.90–0.97)	<.001
Urban hospital	1.06 (1.00–1.13)	.05
Admission month		
Pre-March	N/A[h]	–
March	N/A[h]	–
April	REF	REF
May	0.81 (0.77–0.85)	<.001
June	0.53 (0.48–0.59)	<.001
Hospital's percentage of COVID-19 patients (monthly)[i]	1.004 (1.003–1.004)	<.001
Hospital's percentage of mechanically ventilated patients (monthly)[i]	1.03 (1.02–1.03)	<.001

Abbreviations: aRR, adjusted relative risk; CI, confidence interval; COVID-19, coronavirus disease 2019; N/A, not applicable; REF, reference; RR, relative risk.

[a]Assocations were evaluated using a multivariable modified poisson regression model with robust variance estimation.

[b]Patients aged <20 years (n = 620) were excluded from adjusted analyses.

[c] aRR estimates for each age strata reflect the adjusted effect of age, relative to the reference category of 50–59 years, among those without complicated or uncomplicated hypertension, diabetes with chronic complications, or obesity. For all variables (eg, sex, race) not estimated separately by age group, effect estimates reflect the independent effect of that variable, holding age constant.

[d]Elixhauser comorbidity categories were modified to include principal diagnoses, in addition to secondary diagnoses, that were present-on-admission.

[e]A combined category of the following Elixhauser comorbidities: lymphoma, metastatic cancer, and solid tumor without metastasis.

[f]Elixhauser scores represent unweighted Elixhauser comorbidity sums (1 point per comorbidity present-on-admission) counting only among Elixhauser comorbidities that were not already included in the model as binary variables. The aRR of 1.12 reflects a 12% increase in mortality risk for each one-unit increase in the Elixhauser comorbidity score, ie, for each additional comorbidity that a patient had present-on-admission, such as fluid and electrolyte disorders or iron-deficiency anemia.

[g]Comorbidity effects were estimated separately for each age group in the final multivariable model if there was evidence of statistically significant effect modification by age based upon a global Wald Chi-square test. Each adjusted RR estimate reflects the adjusted effect of a given comorbidity in patients of this age, holding other factors constant. The reference categories for complicated hypertension and complicated diabetes are patients with no hypertension or no diabetes, respectively.

[h]Patients were not eligible for cohort inclusion unless they were discharged on or after April 1, 2020. Therefore, adjusted mortality estimates for admission dates prior to April are not validly interpretable, because only patients who survived long enough to be discharged in April are present in the cohort. These patients may not be representative of the broader patient population if mortality is associated with length of stay.

[i]Calculated to approximate resource-utilization intensity. Variables were calculated by admission month for each hospital as the number of COVID-19 admissions or the number of admissions with mechanical ventilation divided by the total number of the hospital's admissions during the same month.

of life (*P* value tests for trend all ≤ .002). After age 59, complicated hypertension was not associated with increased mortality risk, and once patients reached the oldest age group (80+ years), complicated diabetes was also no longer associated with increased mortality risk. Obesity was an independent risk factor

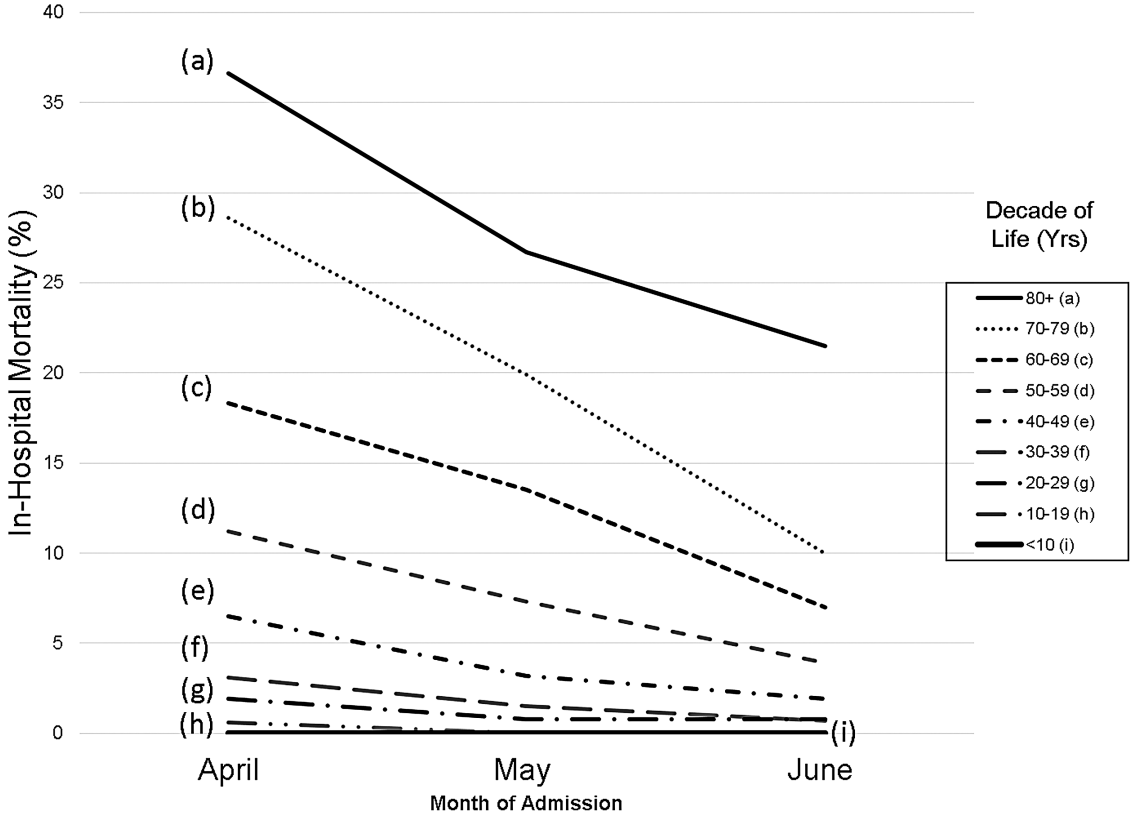

Figure 2. In-hospital mortality by decade of life and month of admission among inpatients with coronavirus disease 2019 (COVID-19) diagnoses (n = 66 646).

for all age groups, consistent with a recent meta-analysis [31]. However, the magnitude of its effect decreased with age. This finding extends observations from 3 previous, smaller studies in U.S. hospitalized patients which found that the effect of obesity on risk of severe COVID-19 outcomes was greater in younger patients [12–14].

Our findings suggest that among hospitalized patients, young adults are particularly vulnerable from metabolic comorbidities. Better understanding whether differences in metabolic phenotypes or biological pathways, such as inflammatory processes [32], in younger patients may underlie our observed associations would be an important area of future study. Moreover, the role of common antihypertensive and diabetes medications, including angiotensin-converting enzyme (ACE) inhibitors and metformin, on COVID-19 clinical outcomes has become an active research area, with emerging research suggesting possibly protective effects [33–37]. National cohorts have documented age-based differences in antihypertensive and diabetes medication prescribing patterns and disease control among U.S. adults [38–40]. Evaluating whether differences in metabolic disease control and medication usage between younger and older adults mediate COVID-19 mortality risk would be an important area for future research.

Yet even without a full understanding of why young hospitalized adults with these comorbidities face higher mortality risks, these findings may still inform current clinical decision-making, such as earlier or more aggressive therapeutic intervention in younger patients with these comorbidities. They may also suggest, although they cannot definitively establish, that lifestyle modifications to reduce body mass index and blood pressure might reduce COVID-19 mortality risk in younger adults [11, 12, 41, 42]. Ultimately, although the absolute mortality among young patients with comorbidities may still be less than older patients with no comorbidities, the years of potential life lost among young patients is greater, making these findings important.

Our study consists of hospitalized patients and should not be generalized to the wider population of all individuals who acquire COVID-19 infection. For example, Black race and/or Hispanic ethnicity were associated with lower mortality risk in adjusted models. This finding is consistent with some prior studies [43, 44]. However, these and other studies have also observed that Black and/or Hispanic patients are hospitalized for COVID-19 at higher rates than White patients [43–45], and we observed that Black and/or Hispanic patients were over-represented among COVID-19 admissions in our cohort. Our study was not designed to determine whether specific characteristics or comorbidities are risk factors among the broader population of infected patients.

This study is a retrospective analysis of administrative claims data and is therefore subject to several limitations.

First, claims data may misclassify some patient characteristics, and the U07.1 COVID-19 code has not been externally validated. However, many strong COVID-19 risk factors (eg, age, sex) are robustly captured in claims data; we identified COVID-19 patients and Elixhauser comorbidities using the same standardized ICD-10-CM diagnosis code sets that are used for national COVID-19 surveillance; and clinician statements that a patient has COVID-19 will support use of the U07.1 code even where testing may have been unavailable [18, 21, 46, 47]. Moreover, isolated elevated blood pressure or glucose readings are insufficient to trigger hypertension or diabetes codes [48]. Rather, there are separate codes for elevated readings without formal diagnoses, thus reducing the risk that features of patients' COVID-19 clinical course at admission would be miscategorized as pre-existing comorbidities [49, 50]. Second, although routine COVID-19 screening was not widespread during the cohort period, it is possible that some cohort patients were identified incidentally through hospital-based screening. We therefore performed sensitivity analyses restricted to only the subset of patients with principal or admitting COVID-19 diagnoses, and results were substantially similar to primary analyses. Third, although our database included a large and diverse number of U.S. hospitals, regions where COVID-19 was most prevalent in the second quarter of 2020 were over-represented, and state-level data were not available. We also did not have outpatient mortality or medication data. Investigating whether age-dependent differences in the effect of metabolic comorbidities on mortality risk persist after accounting for use of antihypertensive and diabetes medications would be an important area of future study. Finally, due to our data extract date, some longer June and possibly late May admissions may not be in our cohort. If longer admissions have different mortality rates, this could have introduced some bias, although our findings comport with large international studies and a study in one U.S. health system that have also identified improving survival in hospitalized patients [51–53]. More research is necessary to investigate reasons for declining mortality, such as clinical practice changes and new therapeutics.

This study of more than 66 000 COVID-19 hospitalizations across 613 U.S. hospitals found that even after controlling for many co-occurring characteristics, men face a 30% greater risk of in-hospital mortality compared to women. Given that half of U.S. adults are men, population-based interventions and COVID-19 prevention efforts that target men could have a significant public health impact. Moreover, we found that 20–39 year-olds are especially vulnerable from metabolic comorbidities, including uncomplicated hypertension and obesity, compared to older age groups. Although the absolute mortality risk remains lower among 20–39 year-olds, the years of life lost in these patients are significant. Our findings suggest this is a higher-risk subgroup whom prevention efforts should not neglect.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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