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ORIGINAL ARTICLE

The Impact of Age, Sex, and Race on the Association of Risk Factors and Mortality in COVID-19 Patients

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Abstract

Background: Several comorbidities and demographic factors are associated with mortality in Covid-19 patients. However, limited analysis exists of interactions between comorbidities and demographics for Covid-19 outcomes.

Methods: Retrospective analysis of adult patients with laboratory-confirmed Covid-19 from March 3rd - May 31st 2020 at NYU Langone Health. Patients selected had visited emergency departments, outpatient testing clinics, or were discharged from an inpatient location as of May 31st 2020. We assessed the moderating effects of patient demographics on the relationship between comorbidities and mortality.

Results: The research cohort included 8,324 patients, 918 (11.0%) of whom died. After adjustment, females with depression (OR 1.2, 95% CI 0.8-1.6, p = 0.44) had increased mortality risk compared to males with depression. Younger patients with cardiac arrhythmia (OR 15.3, 95% CI 9.0-25.9, p < 0.001), neurological disorders (OR 4.6, 95% CI 2.9-7.3, p < 0.001), paralysis (OR 2.5, 95% CI 1.0-6.1, p = 0.04), and pulmonary disorders (OR 4.5, 95% CI 2.7-7.4, p < 0.001) had increased mortality risk compared to older patients with these comorbidities, respectively. White patients with anemia (OR 1.2, 95% CI 0.8-1.7, p = 0.32) and Black patients with solid tumor without metastasis (OR 2.0, 95% CI 1.0-3.9, p = 0.03) had an increased risk of mortality compared to patients of other racial groups with the same comorbidity.

Conclusions: While generally at lower risk, patients with Covid-19 who were female, younger, white or black were at higher risk of mortality with certain comorbidities, compared to their appropriate control counterpart. This information can be used to inform the public, influence triage, care decisions, and vaccination plans.

Keywords

Covid-19 mortality, Modification effect, Social determinants, Covid-19 risk factors

Introduction

The emergence of coronavirus disease 2019 (Covid-19), caused by the SARS-CoV-2 virus, has triggered an ongoing global pandemic [1]. As of March 25th 2021 there have been over 124 million reported cases worldwide and over 2.7 million reported deaths. In the United States, there over 30 million confirmed cases with over 540,000 deaths [2]. In the spring of 2020 New York City was hit particularly hard, as infection occurred on a population-wide scale prior to when testing became readily available.

Covid-19 manifests with a variety of symptoms and degrees of severity; while the majority of people experience no or mild symptoms, many require hospitalization for acute or intensive care and experience high mortality [3,4]. Previous studies have established risk factors among hospitalized patients,

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those who require critical care, and patients with Covid-19-associated mortality. Studies show patients who are older, male, and have comorbidities such as diabetes and hypertension (HTN) are at increased risk for adverse outcomes [5-7]. These demographic and comorbidity trends associated with Covid-19 hospitalization and mortality are similar to disparities found in overall adverse health outcomes [8]. Establishing these initial trends is important for clinicians to target limited therapeutics and prioritize vaccine strategies for vulnerable populations who are at risk of hospitalization or even death. Prior observations have been reported for large groups but these may not be applied to certain patient subsets. It is essential, in light of the sustained high number of Covid-19 cases and deaths throughout the United States [9], that we identify subsets of the population at high risk for Covid-19 mortality.

To date, many studies have focused on descriptive analyses of comorbidities and demographic differences among patients with Covid-19, and relied on comprehensive data collection at different institutions to establish a research cohort [7,8], or focused on a small cohort in one hospital system [1,10,11]. Studies have also focused on patient outcomes and their association with comorbidities and demographic factors [12-14]. Several papers have described the comorbidities, demographics, and clinical outcomes of US patients [15,16], as well as created models to predict Covid-19 mortality risk [17,18]; however analyses that identify disparities in mortality risk within demographic groups, especially potential interaction effects, are limited in the US literature [19,20].

The aim of the study was to assess the impact of demographic factors of sex, age, and race on the association between comorbidities and mortality in Covid-19 patients. Statistically significant modification effects indicate the relationship between comorbidities and mortality varies as a function of the patient demographic. We identify patient groups with Covid-19 previously thought to be at low risk for severe disease in whom specific comorbidities make them more vulnerable to death.

Methods

Study population

This retrospective study includes a cohort of 8,324 adult patients who presented to NYU Langone Health System and were diagnosed with Covid-19 between March 3rd and May 31st 2020. The academic medical system comprises 2,000 inpatient beds among four major hospitals in urban and suburban settings in Manhattan, Brooklyn, and Long Island NY, with diverse patient populations. Patients were diagnosed with Covid-19 when symptomatic for Covid-like symptoms and had a positive SARS-CoV-2 nasopharyngeal PCR.

Data collection

We identified patients with Covid-19 by extracting positive SARS-CoV-2 PCR results from the electronic medical record (EMR) system Epic (Epic Systems, Verona, WI). Comorbidity and demographic information, as well as information on in-hospital critical care and death, was extracted from the EMR for all patients with Covid-19. Comorbidity data was collected by extracting ICD-9/ICD-10 problem list and billing diagnosis codes.

Comorbidity/demographic selection

Comorbidities used to determine the Elixhauser comorbidity score were selected for analysis [21]. Some modifications were made to these established ICD-9 and ICD-10 codes due to potential data quality issues (Appendix 1). These modifications included: 1) Drug abuse and weight loss 2) Deficiency anemia and blood loss anemia were combined to create Anemia, and only diabetes with complications was included. Additional comorbidities from the Charlson comorbidity index [22] that were not identified in the Elixhauser comorbidity index were also assessed, including cerebrovascular disease, dementia, and myocardial infarction. Finally, hyperlipidemia, a risk factor not identified by Charlson or Elixhauser, was included due to its common prevalence in the US population [23].

The literature has suggested certain Charlson and Elixhauser comorbidities are not risk factors but rather caused by Covid-19 infection specifically Coagulopathy [24] and fluid and electrolyte disorders [25], therefore excluded them from the analysis. Previous studies for other medical conditions have shown that demographic factors can modify associations between risk factors and outcomes such as peritoneal dialysis and mortality [26,27]. Here we assess whether sex, age, and race affected the relationship between the aforementioned comorbidities and mortality. The researchers chose to focus on the demographic factors of sex, age, and race, due to the observed differences in Covid-19 disease outcomes within these groups [28-31].

Statistical analysis

To identify which comorbidity-mortality relationships are moderated by demographic factors, we developed three fully specified models for sex, age, and race. First, we performed a univariate analysis of the demographic characteristics and comorbidities with mortality in Covid-19 patients to identify significant relationships. Next, we assessed for potential demographic modification effects on the association between comorbidities and mortality to determine if the relationship differs among sub-demographic groups. We did this by assessing the significance of each interaction effect between the demographic, comorbidity and outcome.

The final model included all the identified

Table 1: Univariate analysis of demographic/comorbidities and mortality of adult patients with Covid-19 at NYU Langone Health from March 3 - May 31 2020 (N = 8324).

Risk Factor	Survivor (N = 7406)	Expired (N = 918)	OR (CI)	P Value
Demographics				
Female	3955 (53.4)	333 (36.3)		
Male	3451 (46.6)	585 (63.7)	2.0 (1.7-2.3)	< 0.001
Age (years)	52.0 ± 17.9	73.2 ± 14.0		< 0.001
Age > = 60 yo	2594 (35.0)	778 (84.7)	10.3 (8.6-12.4)	< 0.001
Age < 60 yo	4812 (65.0)	140 (15.3)		< 0.001
White	2972 (40.1)	449 (48.9)	1.4 (1.2-1.7)	< 0.001
Black	1350 (18.2)	105 (11.4)	0.6 (0.5-0.7)	< 0.001
Hispanic[a]	1060 (14.3)	221 (24.1)	1.9 (1.6-2.2)	< 0.001
Asian	536 (7.2)	80 (8.7)	1.2 (1.0-1.6)	0.11
Other Race/Unknown	2548 (34.4)	284 (30.9)	1.0 (0.8-1.1)	0.71
Comorbidities				
BMI (kg/m^2)	29.1 ± 6.8	29.2 ± 7.3		0.71
Morbid Obesity (BMI > = 35 kg/m^2)	956 (12.9)	138 (15.0)	1.2 (1-1.4)	0.08
HIV/AIDS	48 (0.6)	9 (1.0)	1.5 (0.7-3.1)	0.25
Alcohol Misuse	110 (1.5)	22 (2.4)	1.6 (1-2.6)	0.04
Asthma	701 (9.5)	97 (10.6)	1.1 (0.9-1.4)	0.29
Anemia	345 (4.7)	87 (9.5)	2.1 (1.7-2.7)	< 0.001
Cardiac Arrhythmia	2144 (28.9)	795 (86.6)	15.9 (13-19.3)	< 0.001
CHF	464 (6.3)	269 (29.3)	6.2 (5.2-7.4)	< 0.001
Cerebrovascular Disease	378 (5.1)	149 (16.2)	3.6 (2.9-4.4)	< 0.001
Coagulopathy	550 (7.4)	345 (37.6)	7.5 (6.4-8.8)	< 0.001
CPD	1067 (14.4)	239 (26.0)	2.1 (1.8-2.5)	< 0.001
Cancer[b]	395 (5.3)	124 (13.5)	2.8 (2.2-3.4)	< 0.001
Hematologic Malignancy	33 (0.4)	18 (2.0)	4.5 (2.5-8)	< 0.001
Solid Tumor (without Metastasis)	321 (4.3)	95 (10.3)	2.5 (2-3.2)	< 0.001
Lymphoma	50 (0.7)	16 (1.7)	2.6 (1.5-4.6)	0.001
Dementia	270 (3.6)	139 (15.1)	4.7 (3.8-5.9)	< 0.001
Depression	641 (8.7)	137 (14.9)	1.9 (1.5-2.3)	< 0.001
Diabetes with Complications	566 (7.6)	243 (26.5)	4.4 (3.7-5.2)	< 0.001
Fluid and Electrolyte Disorders	2026 (27.4)	819 (89.2)	22 (17.7-27.2)	< 0.001
HLD	2067 (27.9)	564 (61.4)	4.1 (3.6-4.7)	< 0.001
HTN	2715 (36.7)	744 (81.0)	7.4 (6.2-8.8)	< 0.001
Hypothyroidism	600 (8.1)	139 (15.1)	2 (1.7-2.5)	< 0.001
Liver Disease	312 (4.2)	121 (13.2)	3.5 (2.8-4.3)	< 0.001
Myocardial Infarction	316 (4.3)	222 (24.2)	7.2 (5.9-8.6)	< 0.001
Neurological Disorder	613 (8.3)	381 (41.5)	7.9 (6.7-9.2)	< 0.001
Paralysis	85 (1.1)	47 (5.1)	4.6 (3.2-6.7)	< 0.001
Psychoses	127 (1.7)	32 (3.5)	2.1 (1.4-3.1)	< 0.001
PUD	70 (0.9)	21 (2.3)	2.5 (1.5-4)	< 0.001
Pulmonary Disorders	334 (4.5)	203 (22.1)	6 (5-7.3)	< 0.001
PV Disorders	425 (5.7)	159 (17.3)	3.4 (2.8-4.2)	< 0.001
Renal Disease	794 (10.7)	397 (43.2)	6.3 (5.5-7.4)	< 0.001
Renal Failure	719 (9.7)	370 (40.3)	6.3 (5.4-7.3)	< 0.001
Rheumatic Disease	164 (2.2)	31 (3.4)	1.5 (1-2.3)	0.029
Smoking	246 (3.3)	23 (2.5)	0.7 (0.5-1.1)	0.16
Valvular Heart Disease	499 (6.7)	261 (28.4)	5.5 (4.6-6.5)	< 0.001

Abbreviations: HIV/AIDS: Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome; CHF: Congestive Heart Failure; CPD: Chronic Pulmonary Disease; HLD: Hyperlipidemia; HTN: Hypertension; PUD: Peptic Ulcer Disease; PV: Peripheral Vascular.

[a]In the EMR, Hispanic is defined as an ethnicity and can be selected along with any of the options for race. Therefore the number of Hispanic patients overlaps with the number of patients of different racial groups and cannot be used to compute the total number of patients; [b]Cancer does not correspond to the total of solid tumor (non-metastatic), non-solid tumor, and lymphoma as the cancer row only counts the total number of cancer patients, who may have multiple types of cancer.

significant modifiers/interactions (alpha at 0.10), significant comorbidity variables (alpha at 0.05), and all demographic variables to allow for adjustment. Backward stepwise regression was used to identify the final fully specified models. To illustrate the magnitude of the demographic modification effects, the association between comorbidities and mortality were stratified by demographic subgroup, adjusting for all other demographic factors, comorbidities, and interactions. Additionally, significant modification effects/interactions were visualized to further illustrate the difference in trend across demographic groups. Univariate and multivariate analyses were performed using SAS, version 9.4 (SAS Institute, Cary NC).

Results

Table 1 shows the univariate associations of demographics/comorbidities and mortality in Covid-19 patients. Of the 8,324 adult patients reviewed for this study, 918 (11%) died. Of patients who died, 64% were male (OR 2.0, 95% CI 1.7-2.3, $p < 0.001$), 85% were older than 60 years of age (OR 10.3, 95% CI 8.6-12.4, $p < 0.001$), 49% were white (OR 1.4, 95% CI 1.2-1.7, $p < 0.001$), 11% were Black (OR 0.6, 95% CI 0.5-0.7, $p < 0.001$), and 9% were Asian (OR 1.2, 95% CI 1.0-1.6, $p = 0.11$) (Table 1).

Thirty of the 34 comorbidities (88%) assessed were significantly associated with mortality ($p < 0.05$). Comorbidities with the highest mortality risk were: cardiac arrhythmia (OR 15.9, 95% CI 13-19.3, $p < 0.001$), coagulopathy (OR 7.5, 95% CI 6.4-8.8, $p < 0.001$), fluid and electrolyte disorders (OR 22, 95% CI 17.7-27.2, $p < 0.001$), hypertension (OR 7.4, 95% CI 6.2-8.8, $p < 0.001$), myocardial infarction (OR 7.2, 95% CI 5.9-8.6, $p < 0.001$), and neurological disorders (OR 7.9, 95% CI 6.7-9.2, $p < 0.001$) compared to not having the condition.

Table 2 shows the results from univariate analysis of comorbidities and demographic factors as well significant modification (interaction) effects. Significance was denoted using (*) to indicate unadjusted modification significant at $p < 0.10$, and (**) to indicate significance at $p < 0.05$. Forty-eight unadjusted modifications/interaction effects were found to be significant at $p < 0.10$; 43 of these interactions were significant at $p < 0.05$. Sex, age, and race significantly modified 18, 23, and 7 unadjusted associations, respectively.

Significant demographic modification (interaction) effects were introduced into final models to determine modifications (interactions) that continued to stay significant. The demographic modification (interaction) effects that remained significant included the following: sex and depression, age and cardiac arrhythmia, age and neurological disorders, age and paralysis, age and paralysis, age and pulmonary disorders, race and anemia, and race and solid tumor without metastasis.

Demographic characteristics found to significantly modify the association of comorbidity and mortality were stratified to provide more context of the effect. Figure 1, Figure 2 and Figure 3 show the differing mortality risk when comorbidities were stratified by sex, age, and race. The different pitches in regression line slopes depicted in Figure 1a illustrate the increased risk of mortality for females with depression compared to males with depression. Specifically, the regression line for females with depression is steeper, which shows a greater association with mortality, compared to males with depression. Figure 1b shows the adjusted odds of mortality in females with depression was 1.2 (95% CI 0.8-1.6, $p = 0.44$), compared to 0.5 for males with depression (95% CI 0.4-0.7, $p < 0.001$) Figure 2 illustrates the increased mortality risk for patients younger than 60 years of age with (a) Cardiac arrhythmia, (b) Neurological disorders, (c) Paralysis, (d) Pulmonary disorders, compared to patients 60 years and older with these comorbidities. The adjusted odds of mortality in patients younger than 60 years of age with cardiac arrhythmia (OR 15.3, 95% CI 9.0-25.9, $p < 0.001$), neurological disorders (OR 4.6, 95% CI 2.9-7.3, $p < 0.001$), paralysis (OR 2.5, 95% CI 1.0-6.1, $p = 0.04$), or pulmonary disorders (OR 4.5, 95% CI 2.7-7.4, $p < 0.001$), were higher compared to people older than 60 years with cardiac arrhythmia (OR 5.5, 95% CI 4.4-7.0, $p < 0.001$), neurological disorders (OR 2.6, 95% CI 2.1-31, $p < 0.001$), paralysis (OR 1.2, 95% CI 0.8-2.0, $p = 0.39$), or pulmonary disorders (OR 1.8, 95% CI 1.4-2.3, $p < 0.001$), respectively (Figure 2e). Figure 3 illustrates the increased mortality risk for White patients with anemia (a) and Black patients with solid tumors (without metastasis) (b), compared to other racial groups with these comorbidities. The adjusted odds of mortality for White patients with anemia was 1.2 (95% CI 0.8-1.7, $p = 0.32$), compared to 0.2 for Black patients (95% CI 0.1-0.7, $p = 0.009$), 0.4 for Asian patients (95% CI $p = 0.11$), and 1.0 for patients with other/unknown racial backgrounds (95% CI 0.5-1.7, $p = 0.9$) (Figure 3c). The adjusted odds of mortality for Black patients with solid tumors without metastasis was 2.0 (95% CI 1.0-3.9, $p = 0.03$) compared to 1.2 for White patients (95% CI 0.8-1.8, $p = 0.29$), 0.3 for Asian patients (95% CI 0.1-1.6, p

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Table 2: Univariate analysis of demographic and comorbidities in adult Covid-19 patients at NYU Langone Health from March 3 - May 31 2020 (N = 5473).

Risk Factor	Male (N = 4036)	Female (N = 4288)	Sex p-value	Old (N = 3372)	Young (N = 4952)	Age p-value	White (N = 3421)	Black (N = 1455)	Asian (N = 616)	Other/ Unknown (N = 2832)	Race p-value
Age < 60 yo	2221 (55.0)	2731 (63.7)	< 0.001	-	-	-	1681 (49.1)	922 (63.4)	372 (60.4)	1977 (69.8)	< 0.001
Female	-	-	-	1557 (46.2)	2731 (55.1)	< 0.001	1727 (50.5)	907 (62.3)	312 (50.6)	1342 (47.4)	< 0.001
HIV/AIDS	50 (1.2)	7 (0.2)	< 0.001	28 (0.8)	29 (0.6)	0.19**	15 (0.4)	9 (0.6)	1 (0.2)	32 (1.1)	0.003
Alcohol Misuse	115 (2.9)	17 (0.4)	< 0.001	43 (1.3)	89 (1.8)	0.063**	40 (1.2)	21 (1.4)	4 (0.7)	67 (2.4)	< 0.001
Asthma	318 (7.9)	480 (11.2)	< 0.001**	346 (10.3)	452 (9.1)	0.084	287 (8.4)	174 (12.0)	46 (7.5)	291 (10.3)	< 0.001**
Anemia	201 (5.0)	231 (5.4)	0.40	267 (7.9)	165 (3.3)	< 0.001**	206 (6.0)	83 (5.7)	33 (5.4)	110 (3.9)	0.002
Morbid Obesity (BMI > = 35)	520 (12.9)	740 (17.3)	0.001	440 (13.0)	820 (16.6)	< 0.001**	479 (14.0)	335 (23.0)	20 (3.2)	426 (15.0)	< 0.001
Cardiac Arrhythmia	1751 (43.4)	1188 (27.7)	< 0.001**	1899 (56.3)	1040 (21.0)	< 0.001**	1352 (39.5)	469 (32.2)	210 (34.1)	908 (32.1)	< 0.001
CHF	422 (10.5)	311 (7.3)	< 0.001**	612 (18.1)	121 (2.4)	< 0.001**	395 (11.5)	115 (7.9)	38 (6.2)	185 (6.5)	< 0.001
Cerebrovascular Disease	306 (7.6)	221 (5.2)	< 0.001	428 (12.7)	99 (2.0)	< 0.001**	260 (7.6)	93 (6.4)	33 (5.4)	141 (5.0)	< 0.001
Coagulopathy	577 (14.3)	318 (7.4)	< 0.001	607 (18.0)	288 (5.8)	< 0.001**	505 (14.8)	140 (9.6)	81 (13.1)	314 (11.1)	< 0.001*
CPD	594 (14.7)	712 (16.6)	0.018**	763 (22.6)	543 (11.0)	< 0.001	590 (17.2)	242 (16.6)	77 (12.5)	397 (14.0)	< 0.001
Cancer	276 (6.8)	243 (5.7)	0.027	405 (12.0)	114 (2.3)	< 0.001**	261 (7.6)	85 (5.8)	33 (5.4)	140 (4.9)	< 0.001**
Hematologic Malignancy	36 (0.9)	15 (0.3)	< 0.001	38 (1.1)	13 (0.3)	< 0.001	28 (0.8)	3 (0.2)	3 (0.5)	17 (0.6)	0.09
Solid Tumor (without Metastasis)	214 (5.3)	202 (4.7)	0.22	329 (9.8)	87 (1.8)	< 0.001	211 (6.2)	74 (5.1)	29 (4.7)	102 (3.6)	< 0.001**
Lymphoma	34 (0.8)	32 (0.7)	0.62*	50 (1.5)	16 (0.3)	< 0.001	32 (0.9)	10 (0.7)	2 (0.3)	22 (0.8)	0.42**
Dementia	184 (4.6)	225 (5.2)	0.15**	401 (11.9)	8 (0.2)	< 0.001	263 (7.7)	48 (3.3)	27 (4.4)	71 (2.5)	< 0.001*
Depression	350 (8.7)	428 (10.0)	0.041**	499 (14.8)	279 (5.6)	< 0.001	445 (13.0)	97 (6.7)	39 (6.3)	197 (7.0)	< 0.001
Diabetes with Complications	471 (11.7)	338 (7.9)	< 0.001	646 (19.2)	163 (3.3)	< 0.001**	333 (9.7)	173 (11.9)	53 (8.6)	250 (8.8)	0.010
Fluid and Electrolyte Disorders	1749 (43.3)	1096 (25.6)	< 0.001	1903 (56.4)	942 (19.0)	< 0.001**	1317 (38.5)	455 (31.3)	238 (38.6)	994 (35.1)	< 0.001**
HLD	1468 (36.4)	1163 (27.1)	< 0.001**	1916 (56.8)	715 (14.4)	< 0.001**	1298 (37.9)	451 (31.0)	186 (30.2)	696 (24.6)	< 0.001
HTN	1949 (48.3)	1510 (35.2)	< 0.001**	2464 (73.1)	995 (20.1)	< 0.001**	1559 (45.6)	700 (48.1)	247 (40.1)	953 (33.7)	< 0.001
Hypothyroidism	220 (5.5)	519 (12.1)	< 0.001	507 (15.0)	232 (4.7)	< 0.001	428 (12.5)	94 (6.5)	39 (6.3)	178 (6.3)	< 0.001
Liver Disease	278 (6.9)	155 (3.6)	< 0.001**	243 (7.2)	190 (3.8)	< 0.001**	190 (5.6)	56 (3.8)	38 (6.2)	149 (5.3)	0.059
Myocardial Infarction	350 (8.7)	188 (4.4)	< 0.001**	447 (13.3)	91 (1.8)	< 0.001**	536 (15.7)	189 (13.0)	78 (12.7)	304 (10.7)	< 0.001

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Neurological Disorder	597 (14.8)	397 (9.3)	< 0.001**	770 (22.8)	224 (4.5)	< 0.001**	516 (15.1)	136 (9.3)	83 (13.5)	259 (9.1)	< 0.001
Paralysis	82 (2.0)	50 (1.2)	< 0.001**	86 (2.6)	46 (0.9)	< 0.001**	63 (1.8)	26 (1.8)	7 (1.1)	36 (1.3)	0.22
Psychoses	87 (2.2)	72 (1.7)	0.11	99 (2.9)	60 (1.2)	< 0.001	88 (2.6)	31 (2.1)	8 (1.3)	32 (1.1)	< 0.001
PUD	56 (1.4)	35 (0.8)	0.013	54 (1.6)	37 (0.7)	< 0.001**	43 (1.3)	17 (1.2)	4 (0.6)	27 (1.0)	0.46
Pulmonary Disorders	326 (8.1)	211 (4.9)	< 0.001**	381 (11.3)	156 (3.2)	< 0.001**	241 (7.0)	95 (6.5)	52 (8.4)	149 (5.3)	0.005
PV Disorders	367 (9.1)	217 (5.1)	< 0.001**	481 (14.3)	103 (2.1)	< 0.001**	310 (9.1)	108 (7.4)	27 (4.4)	139 (4.9)	< 0.001
Renal Disease	733 (18.2)	458 (10.7)	0.18**	940 (27.9)	251 (5.1)	< 0.001**	535 (15.6)	264 (18.1)	75 (12.2)	317 (11.2)	< 0.001
Renal Failure	669 (16.6)	420 (9.8)	< 0.001**	870 (25.8)	219 (4.4)	< 0.001**	491 (14.4)	238 (16.4)	67 (10.9)	293 (10.3)	< 0.001
Rheumatic Disease	48 (1.2)	147 (3.4)	< 0.001*	119 (3.5)	76 (1.5)	< 0.001	77 (2.3)	52 (3.6)	11 (1.8)	55 (1.9)	0.006
Smoking	171 (4.2)	98 (2.3)	< 0.001	100 (3.0)	169 (3.4)	0.063	110 (3.8)	62 (5.4)	12 (2.8)	85 (4.2)	0.058
Valvular Heart Disease	423 (10.5)	337 (7.9)	< 0.001	614 (18.2)	146 (2.9)	< 0.001**	411 (12.0)	102 (7.0)	60 (9.7)	187 (6.6)	< 0.001

Abbreviations: HIV/AIDS: Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome; CHF: Congestive Heart Failure; CPD: Chronic Pulmonary Disease; CPD: Chronic Pulmonary Disease; HLD: Hyperlipidemia; HTN: Hypertension; PUD: Peptic Ulcer Disease; PV: Peripheral Vascular.

*indicates comorbidities with a demographic modification significant at p-value < 0.10 for mortality risk; **indicates comorbidities with a demographic modification significant at p-value < 0.05 for mortality risk.

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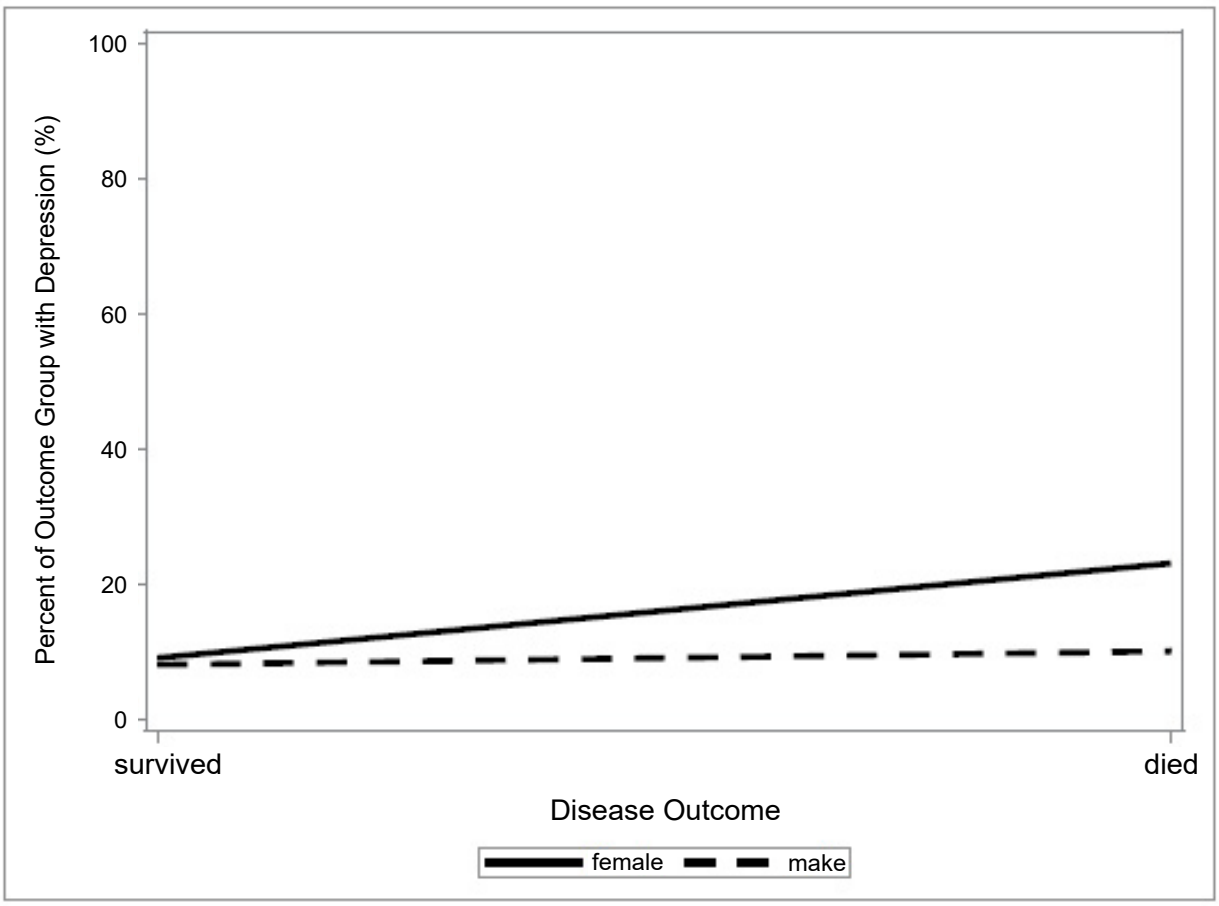
a.



b.

Risk Factor	Survived (Male) (N=3451)	Died (Male) (N=585)	OR* (CI) (Male)	P-value* (Male)	Survived (Female) (N=3955)	Died (Female) (N=333)	OR* (CI) (Female)	P-value* (Female)
Depression	289 (8.4)	61 (10.4)	0.5 (0.4-0.7)	<.001	352 (8.9)	76 (22.8)	1.2 (0.8-1.6)	0.44

*adjusted by age, race, significant comorbidities and interactions (depression, cardiac arrhythmia, neurological disorders, paralysis, pulmonary disorders, anemia, solid tumor without metastasis)

Figure 1: Illustration of the moderation/interaction effect of sex on the association of depression and mortality in adult NYU Langone Health Covid-19 patients from March 3 - May 31 2020 (N = 8324), by a) Visualization of the moderation/interaction effect, and b) Multivariate analysis of significant comorbidity and mortality interaction stratified by sex.

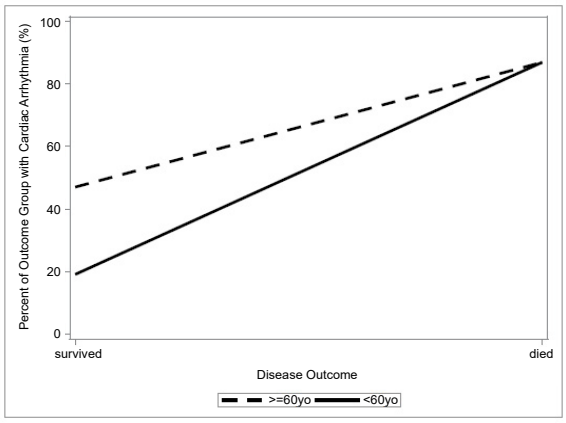
= 0.15), and 1.1 for patients with other/unknown racial backgrounds (95% CI 0.6-2.1, p = 0.64) (Figure 3c).

Discussion

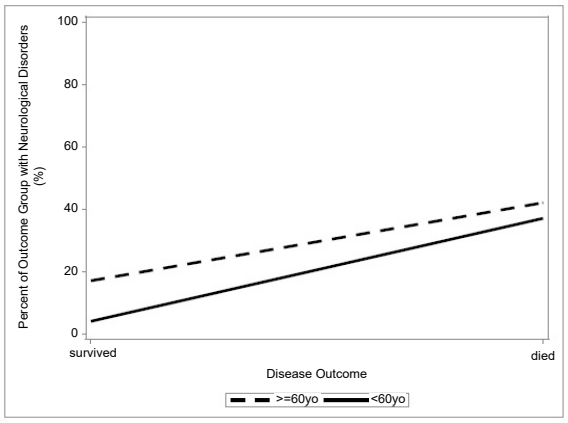
To our knowledge, this is one of the first studies to examine the modification (interaction) effects of demographics on the association of comorbidities and mortality in a large urban US cohort of adult Covid-19 patients. Publications thus far have described the demographic differences observed between patients who die from Covid-19 illness and those who survive, generally concluding that females and people younger than 60 years of age with Covid-19 have lower risk of severe disease and mortality [32]. Patients belonging to different racial groups have been shown to have disparate risk of mortality, with the mortality burden particularly affecting Black and Hispanic patients. Our analysis highlights the importance of certain comorbidities and their effect on the risk of mortality for certain demographic groups generally considered "low risk", such as females and young people.

Our findings regarding the association between comorbidities and mortality in patients with Covid-19 are consistent with other studies showing that patients with conditions such as diabetes, hypertension, and renal disease have increased risk of mortality [5,7]. Our study also expounds on the risk of mortality by assessing a more comprehensive list of comorbidities (Charlson and Elixhauser indices). In terms of demographics, our cohort demonstrated males and patients older than 60 years of age generally have increased risk of

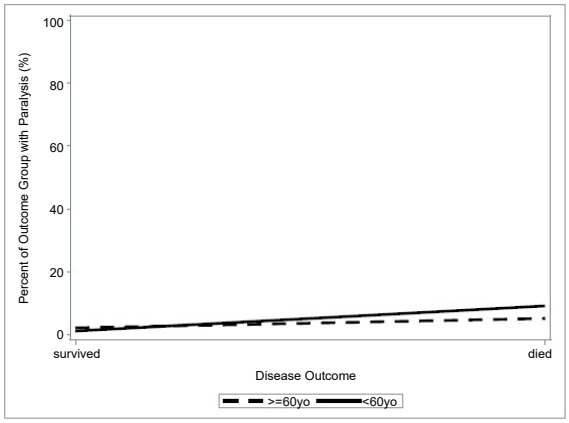
a.



b.



c.



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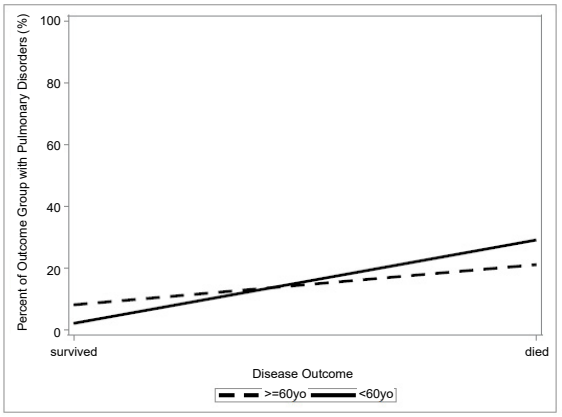


e.

Risk Factor	Survived (≥60yo) (N=2594)	Died (≥60yo) (N=778)	OR* (CI) (≥60yo)	P-value* (≥60yo)	Survived (<60yo) (N=4812)	Died (<60yo) (N=140)	OR* (CI) (<60yo)	P-value* (<60yo)
Cardiac Arrythmia	1226 (47.3)	673 (86.5)	5.5 (4.4-7.0)	<.001	918 (19.0)	122 (87.1)	15.3 (9.0-25.9)	<.001
Neurological Disorder	441 (17.0)	329 (42.3)	2.6 (2.1 (3.1)	<.001	172 (3.6)	52 (37.1)	4.6 (2.9-7.3)	<.001
Paralysis	51 (2.0)	35 (4.5)	1.2 (0.8-2.0)	0.39	34 (0.7)	12 (8.6)	2.5 (1.0-6.1)	0.04
Pulmonary Disorders	218 (8.4)	163 (21.0)	1.8 (1.4-2.3)	<.001	116 (2.4)	40 (28.6)	4.5 (2.7-7.4)	<.001

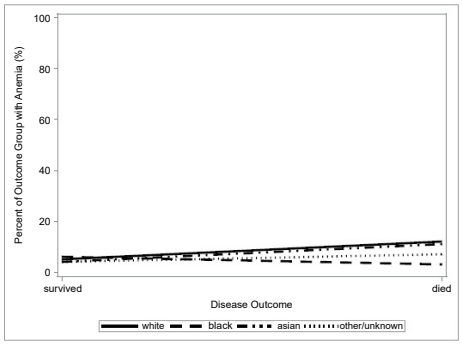
*adjusted by age, race, significant comorbidities and interactions (depression, cardiac arrhythmia, neurological disorders, paralysis, pulmonary disorders, anemia, solid tumor without metastasis)

Figure 2: Illustration of the moderation/interaction effect of age on the association of significant comorbidities and mortality in adult NYU Langone Health Covid-19 patients from March 3 - May 31 2020 (N = 8324), by visualization of the moderation/interaction effect on the association between a) Cardiac arrhythmia, b) Neurological disorders, c) Paralysis, d) Pulmonary disorders and mortality, and e) Multivariate analysis of significant comorbidity and mortality interaction stratified by age.

mortality [13]. Our results of the risk of mortality in racial populations also approximate the infection and mortality statistics for New York City overall [33,34].

In this study, we found generally considered low-risk demographic groups-females and people younger than 60 years of age-with certain comorbidities were actually at increased risk of mortality compared to their high-risk counterparts with the same comorbidity. Additionally, we found differences in risk among racial groups with certain comorbidities. Age significantly modified the greatest number of comorbidity associations with mortality, and in all age stratifications people younger than 60 years of age with the comorbidity had a greater mortality risk compared to people older than 60 years of age with the same comorbidity. Sex significantly modified the association between depression and mortality, and females with depression had greater

a.



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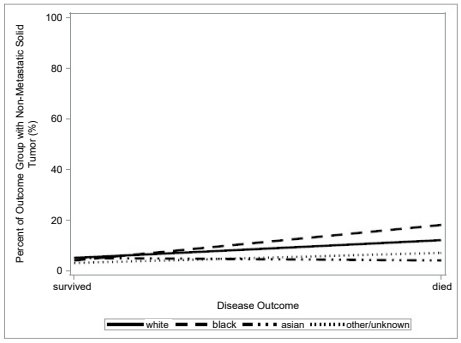

c.

Table 5: Multivariate analysis of significant comorbidities and mortality interaction stratified by race in adult NYU Langone Health patients from March 3 – May 31 2020 (N = 8324)

Risk Factor	Died (White) (N= 449)	OR* (CI) (White)	P-value* (White)	Died (Black) (N= 105)	OR* (CI) (Black)	P-value* (Black)	Died (Asian) (N= 80)	OR* (CI) (Asian)	P-value* (Asian)	Died (Other/ Unknown) (N= 284)	OR* (CI) (Other/ Unknown)	P-value* (Other/ Unknown)
Anemia	56 (12.5)	1.2 (0.8-1.7)	0.32	3 (2.9)	0.2 (0.1-0.7)	0.009	9 (11.3)	0.4 (0.1-1.2)	0.11	19 (6.7)	1.0 (0.5-1.7)	0.90
Solid Tumor (without Metastasis)	52 (11.6)	1.2 (0.8-1.8)	0.29	19 (18.1)	2.0 (1.0-3.9)	0.03	3 (3.8)	0.3 (0.1-1.6)	0.15	21 (7.4)	1.1 (0.6-2.1)	0.64

*adjusted by sex, age, significant comorbidities and interactions (depression, cardiac arrhythmia, neurological disorders, paralysis, pulmonary disorders, anemia, solid tumor without metastasis)

Figure 3: Illustration of the moderation/interaction effect of race on the association of significant comorbidities and mortality in adult NYU Langone Health Covid-19 patients from March 3 - May 31 2020 (N = 8324), by visualization of the moderation/interaction effect on the association between a) Anemia and b) Solid tumor (without metastasis) and mortality, and c) Multivariate analysis of significant comorbidity and mortality interaction stratified by race.

mortality risk than males. Race significantly modified the association between anemia, and solid tumor without metastasis, and mortality; White patients with anemia had the greatest mortality risk of all anemia patients, and Black patients with solid tumors had the greatest mortality risk of all solid tumor patients. These modification (interaction) effects require further research into the root causes of these effects, but these results show the presence of previously unidentified at-risk subgroups.

Further studies are needed to understand the relationship between demographics, comorbidities, and mortality in Covid-19 patients, including the impact of access and delivery of medical care. Studies have begun to investigate the effect of comorbidities such as obesity on certain subgroups' risk of severe Covid-19 disease [35,36], suggesting the need for more comprehensive analysis of demographic modification effects on the association of comorbidities and severe outcomes. Additionally, research has started to probe the underlying mechanisms responsible for the sex disparities in mortality in Covid-19 patients [37]. Research focusing on additional demographic factors-such as socioeconomic status-and their potential modification effects on the association of comorbidities and mortality is needed to fully understand disparities in the Covid-19 pandemic and their effect on communities.

Identifying groups with Covid-19 at greater risk for mortality can lead to increased awareness and targeted health interventions at the individual and community level to improve Covid-19 outcomes. Vulnerable groups who are aware of their increased risk may prioritize social distancing, vaccination and other preventive measures, and seek medical care sooner. Additionally, as states and countries around the world lift restrictions on travel and congregate settings, public health authorities may advise vulnerable groups of their increased risk in order to help them protect themselves. The modification effect of demographics found in our study may also have clinical implications for triage and care in the healthcare setting.

Limitations

A major limitation of our study was missing or incomplete data in the EMR. Moreover, comorbidities were extracted from patients' problem lists associated with the ED/hospital encounter, without associated dates to identify their onset. Other limitations include

the limited availability and sensitivity of SARS-CoV-2 PCR nasopharyngeal testing and the generalizability of our conclusions to other patient populations within the United States and in other countries. Additionally, differences in admission/discharge and triage decisions among groups could affect mortality. This study made the assumption patients did not die after discharge from the ED or inpatient service -there is potential for patients being discharged and subsequently readmitted/dying elsewhere. To investigate this potential impact we performed an ad hoc analysis of deaths post-discharge in our EMR in our patient cohort. Our EMR regularly reconciles deaths with local vital statistic registries which showed 2.7% of our original inpatient cohort had expired post-discharge, compared to 0.02% of the ED/outpatient cohort. These findings suggest that the majority of deaths were likely captured during the visit in the study and happened at similar rates from the ED and hospital encounter. Generally, it can be assumed outpatients did not have severe enough symptoms at time of encounter to require hospitalization, making them less likely to expire compared to patients who developed severe symptoms and presented to the hospital.

Funding

This work was not supported by any funding.

Conflict of Interest

We declare no competing interests.

Ethical Approval

This study was approved by the NYU Grossman School of Medicine Institutional Review Board (No. s20-00671). The IRB granted both a waiver of informed consent and a waiver of the Health Information Portability and Privacy Act.

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Statement of Contribution

All authors contributed equally to this work.

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Appendix 1: ICD9 and ICD10 codes for identifying comorbidities from the Charlson and Elixhauser comorbidity indices in the electronic medical record.

Comorbidity	ICD9/ICD10 Codes
HIV/AIDS	042,043,044,B20,B21,B22,B24
Alcohol Misuse	F10,E52,G62.1,I42.6,K29.2,K70.0,K70.3,K70.9,T51,Z50.2,Z71.4,Z72.1,265.2,291.1,291.2,291.3,291.5,291.8,291.9,303.0,303.9,305.0,357.5,425.5,535.3,571.0,571.1,571.2,571.3,980,V11.3
Asthma	J45.2,J45.3,J45.4,J45.5,J45.90,J45.990,J45.991,J45.998,493
Anemia	D50.0,280.0,D50.8,D50.9,D51,D52,D53,280.1,280.8,280.9,281
Cardiac Arrhythmia	I44.1,I44.2,I44.3,I45.6,I45.9,I47,I48,I49,R00.0,R00.1,R00.8,T82.1,Z45.0,Z95.0,426.0,426.13,426.7,426.9,426.10,426.12,427.0,427.1,427.2,427.3,427.4,427.6,427.8,427.9,785.0,996.01,996.04,V45.0,V53.3
Congestive Heart Failure	398.91,402.01,402.11,402.91,404.01,404.03,404.11,404.13,404.91,404.93,425.4,425.5,425.7,425.8,425.9,428,I09.9,I11.0,I13.0,I13.2,I25.5,I42.0,I42.5,I42.6,I42.7,I42.8,I42.9,I43,I50,P29.0
Cerebrovascular Disease	362.34,430,431,432,433,434,435,436,437,438,G45,G46,H34.0,I6
Coagulopathy	D65,D66,D67,D68,D69.1,D69.3,D69.4,D69.5,D69.6,286,287.1,287.3,287.4,287.5
Chronic Pulmonary Diseases	416.8,416.9,490,491,492,493,494,495,496,500,501,502,503,504,505,506.4,508.1,508.8,J40,J41,J42,J43,J44,J45,J46,J47,J60,J61,J62,J63,J64,J65,-J66,J67,I27.8,I27.9,J68.4,J70.1,J70.3
Cancer	140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,170,171,172,174,175,176,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,200,201,202,203,204,205,206,207,208,238.6,C00,C01,C02,C03,C04,C05,C06,C07,C08,C09,C10,C11,C12,C13,C14,C15,C16,C17,C18,C19,C20,C21,C22,C23,C24,C25,C26,C30,C31,C32,C33,C34,C37,C38,C39,C40,C41,C43,C45,C46,C47,C48,C49,C50,C51,C52,C53,C54,C55,C56,C57,C58,C60,C61,C62,C63,C64,C65,C66,C67,C68,C69,C70,C71,C72,C73,C74,C75,C76,C81,C82,C83,C84,C85,C88,C90,C91,C92,C93,C94,C95,C96,C97
Hematologic Malignancy	C92,C93,C90.1,C91,C95,C94.2,C94.8,C94.0,204,205,206,207,208
Solid Tumor (without Metastasis)	C00,C01,C02,C03,C04,C05,C06,C07,C08,C09,C10,C11,C12,C13,C14,C15,C16,C17,C18,C19,C20,C21,C22,C23,C24,C25,C26,C30,C31,C32,C33,C34,C37,C38,C39,C40,C41,C43,C45,C46,C47,C48,C49,C50,C51,C52,C53,C54,C55,C56,C57,C58,C60,C61,C62,C63,C64,C65,C66,C67,C68,C69,C70,C71,C72,C73,C74,C75,C76,C97,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195
Lymphoma	C81,C82,C83,C84,C85,C88,C96,C90.0,C90.2,200,201,202,203.0,238.6
Dementia	290,294.1,331.2,F00,F01,F02,F03,F05.1,G30,G31.1
Depression	F20.4,F31.3,F31.4,F31.5,F32,F33,F34.1,F41.2,F43.2,296.2,296.3,296.5,300.4,309,311
Diabetes with Complications	250.4,250.5,250.6,250.7,E10.2,E10.3,E10.4,E10.5,E10.7,E11.2,E11.3,E11.4,E11.5,E11.7,E12.2,E12.3,E12.4,E12.5,E12.7,E13.2,E13.3,E13.4,E13.5,E13.7,E14.2,E14.3,E14.4,E14.5,E14.7
Fluid and Electrolyte Disorders	E22.2,E86,E87,253.6,276
Hyperlipidemia	E78.4,E78.5,E78.2,E78.3,E78.1,272.2,272.4
Hypertension	401,402,403,404,405,I10,I11,I12,I13,I15
Hypothyroidism	E00,E01,E02,E03,E89.0,240.9,243,244,246.1,246.8

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Liver Disease	B18,I85,I86.4,I98.2,K70,K71.1,K71.3,K71.4,K71.5,K71.7,K72,K73,K74,K76.0,K76.2,K76.3,K76.4,K76.5,K76.6,K76.7,K76.8,K76.9,Z94.4,070.22,070.23,070.32,070.33,070.44,070.54,070.6,070.9',456.0,456.1,456.2,570,571,572.2,572.3,572.4,572.8,573.3,573.4,573.8,573.9,V42.7
Comorbidity	**ICD9/ICD10 Codes**
Myocardial Infarction	410,412,I21,I22,I25.2
Neurological Disorder	G10,G11,G12,G13,G20,G21,G22,G25.4,G25.5,G31.2,G31.8,G31.9,G32,G35,G36,G37,G40,G41,G93.1,G93.4,R47.0,R56,331.9,332.0,332.1,333.4,333.5,333.92,334,335,336.2,340,341,345,348.1,348.3,780.3,784.3
Paralysis	334.1,342,343,344.0,344.1,344.2,344.3,344.4,344.5,344.6,344.9,G81,G82,G04.1,G11.4,G80.1,G80.2,G83.0,G83.1,G83.2,G83.3,G83.4,G83.9
Psychoses	F20,F22,F23,F24,F25,F28,F29,F30.2,F31.2,F31.5,293.8,295,296.04,296.14,296.44,296.54,297,298
Peptic Ulcer Disease	531,532,533,534,K25,K26,K27,K28
Pulmonary Disorders	I26,I27,I28.0,I28.8,I28.9,415.0,415.1,416,417.0,417.8,417.9
Peripheral Vascular Disorders	093.0,437.3,440,441,443.1,443.2,443.8,443.9,447.1,557.1,557.9,V43.4,I70,I71,I73.1,I73.8,I73.9,I77.1,I79.0,I79.2,K55.1,K55.8,K55.9,Z95.8,Z95.9
Renal Disease	403.01,403.11,403.91,404.02,404.03,404.12,404.13,404.92,404.93,582,583.0,583.1,583.2,583.4,583.6,583.7,585,586,588.0,V42.0,V45.1,V56,N18,N19,N05.2,N05.3,N05.4,N05.5,N05.6,N05.7,N25.0,I12.0,I13.1,N03.2,N03.3,N03.4,N03.5,N03.6,N03.7,Z49.0,Z49.1,Z49.2,Z94.0,Z99.2
Renal Failure	N18.3,N18.4,N18.5,N18.6,N18.9,N19,Z49.01,Z49.02,Z49.31,Z49.32,Z91.15,Z94.0,Z99.2,403.01,403.11,403.91,404.02,404.03,404.12,404.13,404.92,404.93,585.3,585.4,585.5,585.6,585.9,586,V42.0,V45.1,V45.11,V45.12,V56
Rheumatic Disease	446.5,710.0,710.1,710.2,710.3,710.4,714.0,714.1,714.2,714.8,725,M05,M32,M33,M34,M06,M31.5,M35.1,M35.3,M36.0
Smoking	From triage checklist
Valvular Heart Disease	A52.0,I05,I06,I07,I08,I09.1,I09.8,I34,I35,I36,I37,I38,I39,Q23.0,Q23.1,Q23.2,Q23.3,Z95.2,Z95.3,Z95.4,093.2,394,395,396,397,424,746.3,746.4,746.5,7466,V42.2,V43.3

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