Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Advanced age, comorbidity and the risk of mortality in COVID-19 infection

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Abstract: Background: Advanced age and comorbidities have been described to increase the risk of mortality associated with COVID-19 infection. However, the degree to which comorbidities influence mortality among younger and older adults with and without comorbidity in COVID-19 infection has not been clearly elucidated.

Objective: To examine the impact of comorbidity on mortality among younger and older unvaccinated adults with COVID-19 infection admitted to a safety-net hospital.

Methods: This is a retrospective study in which 638 unvaccinated COVID-19 positive study participants admitted to a safety-net hospital between March 1, 2020, and August 31, 2020 were included. The risk of in-hospital mortality or referral to hospice (adverse outcome) was compared among younger and older participants with and without comorbidity.

Results: A total of 62 patients had adverse outcome while in the hospital (10%). Risk factors independently associated with adverse outcome included advanced age (OR(CI) 9.21 (2.29-37.06), p=.002), male sex (OR(CI) 2.6(1.34-5.16), p=.005), living in most disadvantaged area (OR(CI) 2.42(1.8-5.42), p=.03), history of diabetes (OR(CI) 2.35(1.12-4.95), p=.023), and history of heart failure (OR(CI) 4.00(2.09-7.63), p<.001). Further analysis after creating risk groups based on participants age and the presence of diabetes and / or heart failure was performed. The probability of adverse outcome was highest among older male participants with comorbidities (Pr =0.315 (CI: 0.176-0.454)). The probability of adverse outcome among older participants without diabetes and heart failure (Pr =0.081 (CI: .010 -0.152) was less than the probability for younger patients with diabetes and heart failure (Pr: 203 (CI: 0.103 – 0.303)

Conclusions: While older adults with comorbidities were the most vulnerable for adverse outcome, the risk of adverse outcome among older adults without comorbidities was less than that of younger adults with comorbidities.

Keywords: COVID-19■ Advanced age■ Comorbidity■ Mortality■ Safety-net hospital

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INTRODUCTION

Normal aging is associated with decline in physiological reserve in the different organ systems of the body,[1] and this decline predisposes older adults to adverse outcomes associated with acute illness. Coexisting chronic diseases (comorbidity) are also associated with decrease in physiological reserve and increased risk for adverse outcomes.[2] However, the separate and combined impact of advanced age and comorbidity in the association between acute illness and adverse outcome has not been clearly elucidated. For example, whether younger adults with comorbidity have higher mortality than older adults without comorbidity have not been clearly shown. Clarifying this matter would have important clinical as well as public health implications in the management of acute illnesses.

Previous studies have reported multiple risk factors for increased mortality among adult patients with COVID-19 infection, and these include advanced age, male sex, presence of comorbidity and low socio-economic status.[3-7] Reports on the relationship between race and mortality in covid-19 infection have indicated conflicting results, with previous studies showing both significant and non-significant associations.[8-12] In the current study, we explored the risk of mortality among patients with COVID-19 infection admitted to a safety net hospital. We examined whether advanced age and comorbidity independently predict mortality among patients admitted to Grady Memorial Hospital. We also compared the risk of mortality between older participants without comorbidity and younger participants with comorbidity. Grady Memorial Hospital is a safety net hospital that serves predominantly low-income, uninsured, and indigent residents of Fulton and Dekalb counties of the state of Georgia.

METHODS

Patients admitted to Grady Memorial Hospital between March 1, 2020, and August 31, 2020, who tested positive for COVID-19 infection were included in the study. Demographic and clinical data were obtained from Electronic Medical Record (EMR). Demographic data included age, sex, race, and marital status. Social and economic status was determined based on area deprivation index rankings obtained from Neighborhood Atlas website created by the Department of Medicine, University of Wisconsin (https://www.neighborhoodatlas.medicine.wisc.edu). Area deprivation index (ADI) is a composite index based

on the education, employment, housing quality and poverty status of people living in an area, and this index is used to create rankings of areas or zip codes by socioeconomic disadvantage status.[13] The Georgia state ADI rankings ranges between 1 and 10, with rank 1 indicating least disadvantaged zip codes and rank 10 indicating most disadvantaged zip codes. Nine-digit zip codes obtained from participants' medical records were used to determine ADI ranking of the areas in which the participants reside. These rankings were used to determine the social and economic status of study participants. Participants were grouped in to tercile groups based on the ADI rankings and this was used in the current analysis.

Information on chronic diseases were obtained from participants' EMR. Current use of medications was used to determine the diagnosis of hypertension, diabetes mellitus and hypercholesterolemia. Use of oral loop diuretics were considered to indicate the diagnosis of heart failure (HF). Glomerular filtration rate obtained from blood work results were used to determine stages of chronic kidney disease. Data on the diagnosis of chronic lung disease and cancer were incomplete, and for this reason these conditions were not included in the current analysis. The duration of these chronic diseases or duration of use of medications for chronic diseases were not clearly stated in the EMR.

The outcome of interest was in-hospital mortality defined as death in the hospital or transfer to hospice during the participant's hospital stay, and these will be referred to as adverse outcome from here on.

Statistical analysis

Demographic and clinical characteristics of participants with and without adverse outcome were compared using Chi square statistics for categorical variables and Wilcoxon Rank-Sum test and one way ANOVA test for continuous variables. Logistic regression analysis was used to determine the association between age group as the main exposure variable and adverse outcome as the outcome variable, with sex, race, ADI rankings, hypertension, diabetes mellitus, hyperlipidemia, congestive heart failure and chronic kidney disease as covariates.

To examine the separate and combined impact of advanced age and comorbidity on the risk of adverse outcome in more detail, participants were grouped into six risk groups based on their age (younger (< 65 years of age) or older (>= 65 years of age)), and the presence or absence of chronic diseases which showed significant association with adverse outcome in the logistic regression model, namely diabetes mellitus and heart failure. The groups created were: (1) younger with no diabetes mellitus and no HF; (2) younger with diabetes mellitus or HF; (3) younger with diabetes mellitus and HF; (4) older with no diabetes mellitus and no HF; (5) older with diabetes mellitus or HF; (6) older with diabetes mellitus and HF. Logistic regression analysis was performed with adverse outcome as the outcome variable and risk groups created above as the main exposure variable with sex, race, ADI rankings as covariates. Probability of adverse outcome for these risk groups, with other covariates held constant at their mean values, was calculated using the margins command. Analysis was conducted using STATA version 14 and p value of <=0.05 indicated statistical significance. The study was approved by Morehouse School of Medicine Institutional Review Board.

RESULTS

A total of 638 unvaccinated participants, 296 (46%) men and 342 (54%) women, were included in the analysis. The overall mean (sd) and median age were 54.3(18.3) and 56 years respectively, and 452 (71%) were younger than 65 years old. Seventy four percent of participants reported their race as African American, with 16% and 6% of participants reporting their race as Hispanic and White respectively.

A total of 179 participants (28%) were admitted to intensive care unit. Overall, 62 participants (10%) had adverse outcome, and of those admitted to the ICU, 47 participants (26%) had adverse outcome.

Table 1 shows the demographic and clinical characteristics of participants by adverse outcome. As shown, the proportion of study participants with adverse outcome were significantly higher among those with advanced age, males, participants who reported living in the most disadvantaged areas and those with chronic disease. Of note, we could find the nine-digit zip codes that is required to obtain state ADI rankings only for 580 study participants. Participants with no state ADI rankings were more likely to be male (p=.029) and white race (=.001); otherwise, there was no significant difference in the rate of adverse outcome, age, or comorbidity between the two groups. While participants older than 65 years of age accounted for 29% of the total study participants, they accounted for 60% of participants that had adverse outcome, indicating the higher occurrence of adverse outcome among this group of the population.

Two separate logistic regression (LR) models were created, with adverse outcome as the outcome variable. In the first model, covariates included age, sex, race, hypertension, diabetes mellitus, heart failure, hypercholesterolemia, chronic kidney disease (n=638) and in the second model, covariates included all variables mentioned

Table 1. Demographic and clinical characteristics of study participants by adverse outcome

	Total (n=638)	Discharged (n=576)	Died/Hospice (n=62)
Age in years***			
(mean ±Sd)	54.3(18.3)	52.9(18.1)	67.8(14.5)
Median(qi)	56 (40-67)	55(38-65)	70 (59-77)
Age Group in years***			
15 – 39	159 (25%)	156 (27%)	3 (5%)
40 – 64	293 (46%)	271 (47%)	22 (35%)
65-74	98 (15%)	80 (14%)	18 (29%)
>= 75	88 (14%)	(69 (12%)	19 (21%
Sex*** Female	296	276(48%)	20(32%)
Male	342	300(52%)	42 (68%)
Race			
African American	469 (74%)	421 (73%)	48 (77%)
Hispanic	101 (16%)	95 (16%)	6 (10%)
White	36 (6%)	32 (6%)	4 (6%)
Other	32 (5%)	28 (5%)	4 (7%)
Area Deprivation Index Tertile*	(n-580)		
Least disadvantaged area	218(37%)	203 (39%)	15 (27%)
Medium disadvantaged area	214(37%)	196 (37%)	18 (33%)
Most disadvantage area	148 (26%)	126 (24%)	22 (40%)
Married Yes	106(17%)	97 (17%)	9(15%)
No	532 (85%	479 (83%	53 (85%)
Diabetes mellitus***			
No	333(55%)	319(55%)	14(23%)
Yes	305(48%)	257(45%)	48(77%)
Congestive Heart Failure***			
No	468(73%)	445 (77%)	23 (37%)
Yes	170 (27%)	131 (23%)	39 (63%)
Hypertension**			
No	239 (37%	226(39 %)	13(21%)
Yes	399 (63)	350 (61%)	49 (79%)
Hyperlipidemia**			
No	383 (60%)	356 (62%)	27 (44%)
Yes	255 (40%)	220 (38%)	35 (56%)
Chronic Kidney Disease***			
Stages 1 and 2	396(67%)	370(70%)	26(45%)
Stage 3	107(18%)	93(17%)	14(24%)
Stage 4	34 (6%)	25(5%)	9(15%)
Stage 5	51 (9%)	42(8%)	9(15%)

*** *<.001;*

** *<.01;*

* *<.05; sd = standard deviation; iqr = interquartile range*

above and ADI ranking, which is an indicator of socioeconomic status (n=580). The results of LR analysis in both models showed similar pattern of associations between the covariates and adverse outcome. Given the similar pattern of associations, we have chosen to report results of the model which included ADI ranking as a covariate. This provides information on the potential impact of socioeconomic status on the outcome. Table 2 shows the results of this LR analysis with age group as the exposure variable, before and after adjustment for demographic and

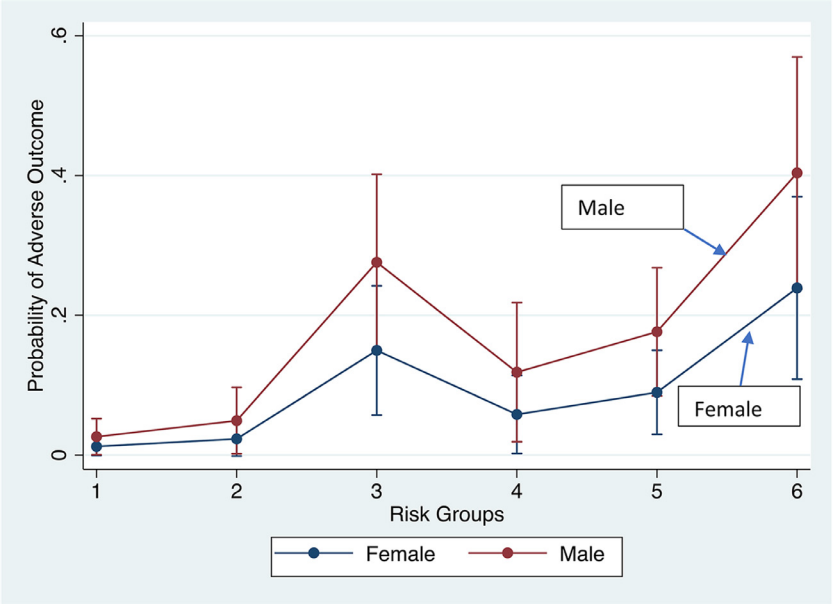
Table 2. Results of logistic regression analysis showing the association between age group and adverse outcome** before and after adjustment for demographic and clinical variables.

	OR(CI), p value(Unadjusted)	OR(CI), p value(Adjusted for demographic variables)	OR(CI), p value(Adjusted for demographic and clinical variables)
Age Group in years			
15 – 39	Referent	Referent	Referent
40 – 64	4.22(1.24-14.33), p=.021	3.26 (0.95-11.26)9), p=.061	2.48 (.66-9.28) p=.174
65-74	11.70 (3.34-40.90), p<.001	8.56 (2.36-30.99), p=.001	5.93 (1.45-24.12), p=.013
>= 75	14.32 (4.10-49.98), p<.001	13.64 (3.73-49.88), p<.001	9.21 (2.29-37.06), p=.002
Sex			
Female		Referent	Referent
Male		2.34 (1.23-4.43), p=.009	2.63 (1.34-5.16), p=.005
Race			
African American		Referent	Referent
Hispanic		1.17 (0.44 -3.08), p=0755	1.03 (.35-2.96), p=0.954
White		1.08 (0.29-4.01), p=0.900	1.27(.32-4.94), p=0.726
Other		1.82 (0.47=-7.05), p=0.387	1.90 (.40-8.91), p=0.411
ADI ranking groups			
Least disadvantaged area		Referent	Referent
Medium disadvantaged area		1.69(.78-3.65), p=.181	1.61 (.70-3.67), p=0.255
Most disadvantaged area		2.02(1.04-4.65), p=.038	2.42 (1.08-5.42), p-0.030
Diabetes mellitus			
No			Referent
Yes			2.35 (1.12-4.95), p=0.023
Probable Heart Failure			
No			Referent
Yes			4.00(2.09-7.63), p<.001
Hypertension			
No		-	Referent
Yes			0.72(.31-1.64), p=0.445
Hyperlipidemia			
No			Referent
Yes			0.74(0.37-1.48), p=0.399
Chronic Kidney Disease			
Stages 1 and 2			Referent
Stage 3			1.00(044-2.25), p=0.992
Stage 4			1.66 (0.57-4.82), p=0.344
Stage 5			1.44 (0.54-3.80), p=0.460

*Interaction terms: Age group*sex: p=.035.*

** *Adverse outcome = In-hospital mortality or transfer to hospice.*

Fig. 1. Probability of adverse outcome by risk groups among female and male study participants.



Risk Groups: 1= Younger with no diabetes and no heart failure; 2 = Younger with diabetes or heart failure; 3 = younger with diabetes and heart failure; 4 = Older with no diabetes and no heart failure; 5 = Older with diabetes or heart failure; 6 = Older with diabetes and heart failure.

clinical characteristics of study participants. As shown, the odds of adverse outcome were significantly higher among those with advanced age, male sex, participants living in most disadvantaged areas, those with diabetes mellitus and congestive heart failure. There was significant interaction between age group and sex ($p<.05$), suggesting that the magnitude of association between age and adverse outcome may be modified based on the sex of participants.

Fig. 1 shows the probability of adverse outcome by risk group stratified by sex of participants, adjusted for race and ADI ranking. Overall, the probability of adverse outcome was highest among older participants with comorbidity (0.325 (CI =0.175 – 0.454)), followed by younger adults with comorbidity (0.203 (CI = 0.103-0.303)). It is noteworthy that the probability of adverse outcome among older adults without comorbidity (0.081(CI=0.010 - 0.152) was less than that for younger adults with comorbidity. Overall, the risk of adverse outcome was significantly higher among male participants (p value = 0.015).

DISCUSSION

Results of the current study corroborate previous reports that indicated significantly increased risk of mortality associated with advanced age, comorbidity, and male sex in COVID-19 infection.[4,5,14] In addition, the current study advances knowledge in the field by describing the extent to which advanced age and comorbidity, in tandem and separately, impact the risk of adverse outcome. While the probability of adverse outcome was highest among older participants with comorbidity, probability of adverse outcome was lower among older participants without comorbidity in comparison to younger participants with comorbidity (Fig. 1). This indicates that comorbidity may pose a greater risk of adverse outcome than just advanced age alone.[15]

There was no significant association between race and adverse outcome in the current study that included predominantly African American participants. On the other hand, the risk of adverse outcome was significantly higher among participants living in most disadvantaged areas, indicating the impact of socioeconomic status on adverse outcome as previously reported.[11] The conflicting results on the association between race and adverse outcome in COVID-19 infection previously reported may indicate the intricate relationship between race and socio-economic status.[16]

As previously reported,[3] male participants had higher rate of adverse outcome in all risk groups in the current study (Fig. 1). Previous studies have reported both biological and environmental / health style factors to account for this difference in morality between men and women.[17]

The current study has several strengths. Data is derived from a safety net hospital which predominantly serves patients in low socio-economic strata. As shown, significant proportion of study participants were young (less than 40-year-old) and predominantly African American. Hence the results provide a unique picture of in-hospital adverse out-

come in this group of the population The study also has its limitations. Data for the current study was a convenience sample of participants admitted to one safety-net hospital, thus results may not be generalizable. However, given the similarities in social and economic status of individuals who get their medical care from safety net hospitals, we would expect these individuals to have similar demographic and clinical characteristics.[18] Data on comorbidity were limited to only five chronic diseases and leaves out diseases such as asthma and chronic obstructive pulmonary disease which have been shown to increase risk of adverse outcome in COVID-19 infection. Analysis in the current study is limited to adverse outcome that occurred during hospitalization, and it is possible that adverse outcome may have occurred after discharge from the hospital. This may have resulted in underestimation of the rate of adverse outcome.

In conclusion, advanced age and comorbidity in tandem and separately increase the risk of adverse of outcome in COVID-19 infection, making older adults with comorbidity the most vulnerable for adverse outcome, followed by younger adults with comorbidity and older adults without comorbidity.

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