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Clinical Trial Participation and COVID-19: a Descriptive Analysis from the American Heart Association's Get With The Guidelines Registry

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Abstract
As COVID-19 cases begin to decrease in the USA, learning from the pandemic experience will provide insights regarding disparities of care delivery. We sought to determine if specific populations hospitalized with COVID-19 are equally likely to be enrolled in clinical trials. We examined patients hospitalized with COVID-19 at centers participating in the American Heart Association's COVID-19 CVD Registry. The primary outcome was odds of enrollment in a clinical trial, according to sex, race, and ethnicity. Among 14,397 adults hospitalized with COVID-19, 9.5% ($n=1,377$) were enrolled in a clinical trial. The proportion of enrolled patients was the lowest for Black patients (8%); in multivariable analysis, female and Black patients were less likely to be enrolled in a clinical trial related to COVID-19 compared to men and other racial groups, respectively. Determination of specific reasons for the disparities in trial participation related to COVID-19 in these populations should be further investigated.

Keywords Disparities · COVID-19 · Race · Ethnicity

Introduction

COVID-19 continues to have a significant global impact over 1.5 years after its declaration as a global pandemic [1]. Given over 5,000,000 deaths globally attributed to SARS-CoV-2 and new variants leading to rising case counts in many countries, clinical trials studying strategies to reduce the impact from COVID-19 remain critical. From a research perspective, over 7,000 COVID-19 specific clinical trials have been registered on ClinicalTrials.gov to date. These trials range from focus on testing/diagnostics, interventions including drugs and devices, and post-infection recovery. Given the evolving evidence-based standards of care in the medical management of COVID-19, widespread enrollment in these trials is imperative to improving patient outcomes on a global scale.

Females and those of racial and ethnic minority backgrounds are consistently underrepresented in clinical trials

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[2–5]. There are multiple reasons for these findings specifically within racial and ethnic minority populations, including possible mistrust or consequent fear of participation [6]. Wendler et al. demonstrated that small differences in the willingness of minority populations to participate in health research compared to White individuals, suggesting opportunities and access to clinical studies may play a large role in these pre-existing disparities [7]. There are multiple studied conditions in which women are specifically underrepresented in clinical trials compared to men [8, 9]. Clinical trial participation among females within specific fields including oncology, neurology, and nephrology remains low [10]. Reasons for these findings are multi-factorial, including issues such as bias, sexism, and unequal opportunities to participate [11].

The COVID-19 pandemic has revealed and amplified long-standing health inequities in the USA, with a higher reported incidence of hospitalization and death due to COVID-19 among Black and Hispanic patients, accounting for over 50% of the hospitalizations [12, 13]. The American Heart Association's (AHA) COVID-19 Cardiovascular Disease (CVD) Registry collects clinically important information for patients hospitalized with COVID-19 across over 100 hospitals in the USA [14]. Using this registry, we sought to evaluate the characteristics of patients enrolled in clinical trials related to COVID-19, specifically focusing on racial and ethnic minority as well as female representation in trial enrollment.

Methods

Data were obtained from the American Heart Association (AHA) COVID-19 Cardiovascular Disease Registry, a part of the Get With The Guidelines (GWTG) initiative, which collects data from over 100 participating centers within the USA on treatment patterns and outcomes in adult patients hospitalized with COVID-19 [14]. GWTG is a hospital-based quality improvement initiative created by the AHA and the American Stroke Association to improve the care of patients with cardiac diseases and stroke. Hospitals retrospectively abstracted all consecutive patients who were 18 years of age or older and hospitalized with COVID-19 as an active diagnosis. An active diagnosis of COVID-19 included patients diagnosed prior to hospitalization and still symptomatic during the hospitalization, those with a positive test or diagnosis during hospitalization, those who are symptomatic during hospitalization and have a confirmed test available only after hospital discharge, and those with a diagnosis, with or without COVID-related symptoms. Data abstraction was considered incomplete until the patient was discharged from the hospital. Patients were followed for outcomes with a focus on cardiovascular events. For all hospitals, participation within the AHA Registry was approved or waived by an Institutional Review Board (IRB) or was classified as quality improvement and not under the purview of the IRB. All data on patient demographics, signs and symptoms, medications, clinical characteristics, and discharge information were entered for consecutive patients from the start of the pandemic. Statistical analyses were performed in R version 3.6 in the AHA Precision Medicine Platform (https://precision.heart.org). Definitions for each characteristic are available in the data dictionary on the registry's website.

We included all patients from hospitals with admission dates from January 10, 2020, through September 25, 2020, which captured information early in the COVID-19 pandemic and available data within the AHA COVID-19 Registry. Only one entry per patient was allowed, preferentially including observations that indicated clinical trial enrollment if multiple entries for hospitalization were present. The primary outcome of this study was clinical trial enrollment, defined as "enrolled in a clinical trial in which patients with a diagnosis of COVID-19 were being studied" within the registry. This data was collected from a direct question via case report form for participating centers.

The primary goal was to evaluate the association between sex, race, and ethnicity and clinical trial enrollment. Based on the registry's hierarchical schema, each patient was classified into one of 8 mutually exclusive racial/ethnic groups: Hispanic, Non-Hispanic Black, Native American, Asian, Pacific Islander, Non-Hispanic White, unable to determine (UTD), or missing. The secondary goals were to evaluate the associations between age group and clinical trial enrollment. Age was defined as age at the time of hospital admission. We grouped age into three categories, 18 to 49 years old, 50 to 64 years old, and older than 64 years. Age older than 64 years was used as the reference group in the age analyses.

We compared baseline characteristics between enrolled and non-enrolled patients using *t* tests and chi-squared tests. The association between clinical trial enrollment and sex, race, and ethnicity was estimated using mixed effects logistic regression, to allow for clustering by hospital for both univariate and multivariable analyses. Hospitals with fewer than 10 entries in the registry were excluded from regression analyses as recommended by AHA COVID-19 CVD Registry guidelines. The reference group for sex was male sex; for race/ethnicity, it was Non-Hispanic White; and for age group, those older than 64. In multivariable analysis, we adjusted for age, sex, body mass index (BMI), patient region, medical history, in-hospital confusion/mental status, primary insurance, date of admission, intensive care unit admission, region (derived from home zip code), and in-hospital death.

Analyses included 14,397 observations due to feature missingness and exclusion of sites with < 10 entries. The

rate of missingness was < 2% for all variables included in the multivariable model, except for: body mass index (BMI) (10.6%), ventilator support, lipid-lowering therapy, antihyperglycemic, antihypertensive, and anticoagulant (all < 2.5%). We grouped BMI into 4 categories: obese, overweight, normal, and underweight. We imputed BMI missing values using group mean imputation, with the means of the 4 BMI categories. We also accounted for time by including a continuous variable for admission month. Patients who were admitted before March were labelled "0," and the value increased by one unit for each month thereafter.

Results

Among 14,397 adults hospitalized with COVID-19 at 85 sites, 9.6% ($n = 1,377$) were enrolled in a clinical trial. The proportion of enrolled patients was the lowest for Black patients, at 8.0%. Patients enrolled in clinical trials were younger, more often male, and there were fewer Black patients (Table 1). While patients identified as Native Americans had the greatest percentage enrollment (20%) in clinical trials, they represented a small portion ($n = 65$) of the population studied (Fig. 1). Patients enrolled in trials less frequently had Medicare or Medicaid as their primary insurance and were also more often managed in the intensive care unit (ICU) and required mechanical ventilatory support. From a geographic perspective, patients localized in the western region of the country had greater representation in clinical trial participation. A clinical presentation with confusion or altered mental status during hospitalization was less common among patients enrolled in clinical trials. The proportion of patients enrolled in clinical trials changed over time (chi-squared = 260.5, $p = < 0.001$) with the largest percentage (37.3%) of trial enrollment occurring during April of 2020. In the multivariable analysis (Table 2), the odds of clinical trial enrollment were lower for female individuals (OR 0.77, 95% CI 0.68–0.89) and those identified as of Black race (OR 0.81, 95% CI 0.67–0.98).

Discussion

In this analysis, we found that fewer than 1 in 10 patients hospitalized with COVID-19 were enrolled in a clinical trial. Patients enrolled in clinical trials related to COVID-19 were younger and there were fewer female and Black patients. Additionally, patients who were hospitalized requiring ICU or mechanical ventilatory support were more often enrolled in a clinical trial. Most importantly, female sex and Black race were independently associated with less frequent participation in a clinical trial pertaining to COVID-19.

Clinical trials are an essential tool to progress medical research and the COVID-19 pandemic has revealed challenges in trial enrollment as well as disparities within trial participation [15]. Clinical trial value for society is even greater during a pandemic as the potential benefits of interventions can help both individual participants while rapid dissemination across a suffering global population can possibly slow the spread of SARS-CoV-2 [16].

The underrepresentation of Black patients within clinical trials remains a major healthcare issue in the USA [17]. Structural racism and discrimination undoubtedly exist in the US healthcare and may play a major role in the disparities in health, access to health care and enrollment in clinical trials for Black patients in the USA. Previous studies have demonstrated factors such as distrust of the medical/scientific community, poor access to primary medical care, lack of knowledge about clinical trials, language, and cultural barriers all as possible reasons for lower enrollment among Black Americans [18]. Also, in our analysis, it was found that patients with Medicare or Medicaid as primary insurance had lower representation in COVID-19 clinical trials. These findings help underscore the complex relationships between health insurance status, income, and racial and ethnic minority populations having lower participation in clinical trials in the USA [19]. Within this analysis, we do not have specific data as to why participation was lower among this group. Given the disproportionate impact of morbidity and mortality of the COVID-19 pandemic within these communities [20], it would seem imperative to actively pursue increasing enrollment of Black Americans in these clinical trials.

Representation of women in clinical trials has a complicated history in the USA including previous policies which excluded women of childbearing age regardless of their pregnancy status or preference to avoid pregnancy, either through lifestyle or birth control [11]. More recently, major organizations including the Food and Drug Administration (FDA) have taken positions in attempt to increase women's representation in studies [21]. Our analysis demonstrated that within the AHA COVID-19 CVD Registry, female sex was strongly associated with not participating in a clinical trial. While studies have shown that male sex is associated with worse outcomes (higher rate of intubation, longer length of hospital stay, higher death rate) in those hospitalized with COVID-19 [22], the disparity of enrollment in COVID-19 trials remains concerning. Given the sheer brunt of the social and economic consequences of the COVID-19 pandemic specifically on women, it is imperative to develop strategies to improve participation and outcomes of women with COVID-19 [23]. While there has been significant progress in terms of improving female representation in clinical trial cohorts [11], the reasons for

Table 1 Characteristics of patients hospitalized with COVID-19 in the USA, according to clinical trial enrollment status

Characteristic no. (%)	Enrolled ($n=1,377$)	Not enrolled ($n=13,020$)	p value
Age, mean years (SD)	58.4(16.1)	61.6 (17.9)	< 0.001
Age group			< 0.001
> 64	514 (37.3)	5,998 (46.1)	
50–64	470 (34.1)	3,695 (28.4)	
< 50	393 (28.5)	3,327 (25.6)	
Female sex	570 (41.4)	5,978 (45.9)	0.002
Race/ethnicity			< 0.001
Non-Hispanic White	492 (35.7)	4,495 (34.5)	
Hispanic	442 (32.1)	3,537 (27.2)	
Black	300 (21.8)	3,430 (26.3)	
Native American	13 (0.9)	52 (0.4)	
Asian and Pacific Islander	69 (5.0)	613 (4.7)	
Unknown	61 (4.4)	893 (6.9)	
Primary insurance			< 0.001
Medicaid	388 (28.2)	4,384 (33.7)	
Medicare	202 (14.7)	2,934 (22.5)	
Other	576 (41.8)	4,200 (32.3)	
Self-Pay	156 (11.3)	1,092 (8.4)	
Unknown	55 (4.0)	410 (3.1)	
Patient region			< 0.001
Northeast	339 (24.6)	5,950 (45.7)	
Midwest	254 (18.4)	1,570 (12.1)	
South	433 (31.4)	4,519 (34.7)	
West	351 (25.5)	981 (7.5)	
Body mass index			< 0.001
Obese	705 (53.6)	5,100 (44.2)	
Overweight	375 (28.5)	3,462 (30.0)	
Normal	220 (16.7)	2,691 (23.3)	
Underweight	15 (1.1)	298 (2.6)	
Past medical history			
Atrial fibrillation or atrial flutter	110 (8.0)	1,257 (9.7)	0.050
Heart failure	137 (9.9)	1,475 (11.3)	0.13
Hypertension	800 (58.1)	7,714 (59.2)	0.4
Cancer	181 (13.1)	1,502 (11.5)	0.085
Currently on dialysis	35 (2.5)	486 (3.7)	0.030
Diabetes mellitus	509 (37.0)	4,680 (35.9)	0.5
Dyslipidemia	516 (37.5)	4,532 (34.8)	0.052
Prior CABG	27 (2.0)	389 (3.0)	0.038
Prior myocardial infarction	71 (5.2)	646 (5.0)	0.8
Prior PCI	61 (4.4)	593 (4.6)	0.9
Chronic kidney disease	160 (11.6)	1,716 (13.2)	0.11
Pulmonary disease	277 (20.1)	2,367 (18.2)	0.084
COPD	103 (7.5)	1,087 (8.3)	0.3
Asthma	157 (11.4)	1,196 (9.2)	0.009
Other pulmonary disease	38 (2.8)	303 (2.3)	0.4
Pulmonary arterial hypertension	11 (0.8)	45 (0.3)	0.019
Cerebrovascular disease	84 (6.1)	1,435 (11.0)	< 0.001
DVT or pulmonary embolism	45 (3.3)	627 (4.8)	0.012
Smoking or vaping	86 (6.2)	847 (6.5)	0.8

Table 1 (continued)

Characteristic no. (%)	Enrolled ($n=1,377$)	Not enrolled ($n=13,020$)	p value
Medications			
Anti-hypertensive	602 (50.4)	6,783 (52.8)	0.11
Lipid-lowering therapy	437 (36.6)	4,927 (38.4)	0.2
Antiplatelet	339 (24.6)	3,410 (26.2)	0.3
Anticoagulant	97 (8.1)	1,616 (12.6)	<0.001
Anti-hyperglycemic	337 (28.2)	3,592 (28.0)	0.9
In-hospital events			
Managed in ICU	733 (53.2)	3,660 (28.1)	<0.001
Death	222 (16.1)	2,141 (16.4)	0.8
Mechanical ventilation	492 (35.7)	2,480 (19.0)	<0.001
Confusion or altered mental status	108 (7.8)	1,429 (11.0)	<0.001

CABG, coronary artery bypass grafting; *COPD*, chronic obstructive pulmonary disease, *DVT*, deep vein thrombosis; *ICU*, intensive care unit; *IQR*, interquartile range; *PCI*, percutaneous coronary intervention; *TIA*, transient ischemic attack

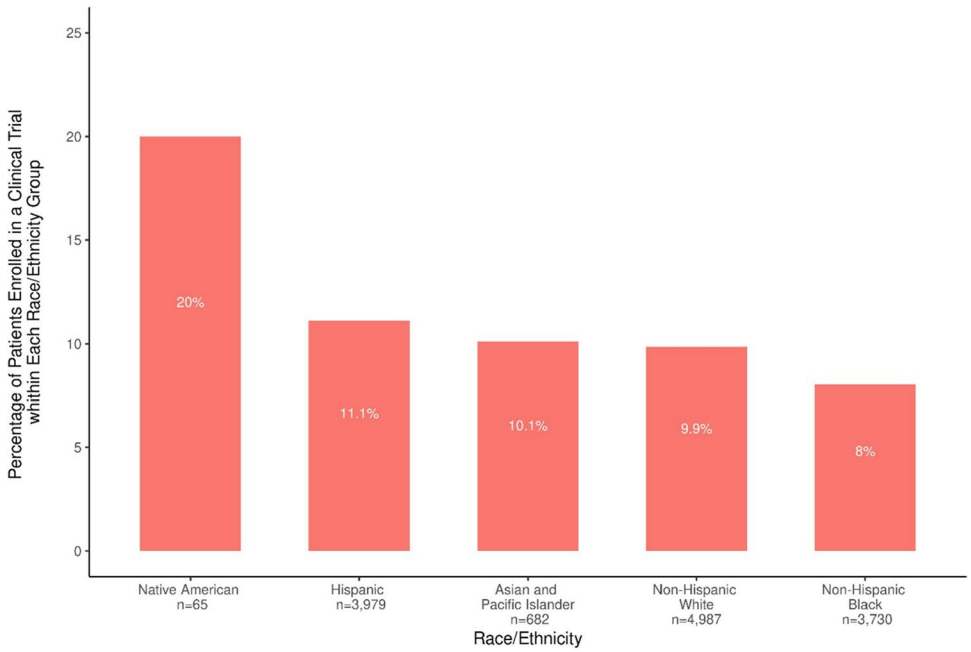

Fig. 1 Enrollment in clinical trials by race and ethnicity. Proportion of hospitalized COVID-19 patients enrolled in clinical trials, stratified by race/ethnicity subgroup. Among 14,397 patients, $n=954$ had unknown race/ethnicity. Group denominators as $n=$ below each bar

reduced representation in clinical trials related to COVID-19 should be further explored.

As the USA continues to make progress in COVID-19 pandemic and the impact of current variants, there are many lessons to be learned from the perspective of clinical trial enrollment. The findings from this analysis highlight the importance of potentially targeting populations including both female and Black participants in clinical trial enrollment. Moreover, a concerted effort to reduce barriers to trial participation should be pursued. Given the known racial/ethnic disparities during the COVID-19 pandemic, plus the overall COVID-19 disease burden, efforts are needed to understand and dismantle enrollment barriers.

Limitations

The Get With The Guidelines COVID-19 Registry is observational in nature and participation is voluntary; these results may not be generalizable to all hospitals. Race and ethnicity classifications were based on predefined categories; we could not evaluate race and ethnicity separately, as patients could not fall into multiple categories. Sample size limited further disaggregation of racial and ethnic subgroups. We do not know if race and ethnicity was patient-reported, and ascertainment could vary by hospital. The registry does not capture how many patients were approached for enrollment in a trial,

Table 2 Multivariable model with adjusted odds of clinical trial enrollment, among patients hospitalized with COVID-19 in the USA

	Adjusted odds ratio	95% CI	*p*value
Female sex	0.77	0.68–0.89	< 0.001
Race/ethnicity			
Non-Hispanic White	-	-	-
Hispanic	1.19	0.99–1.44	0.07
Black	0.81	0.67–0.98	0.027
Other	1.96	0.95–4.05	0.068
Asian and Pacific Islander	1.02	0.74–1.42	0.9
Unknown	0.89	0.63–1.25	0.5
Age group			
> 64	-	-	-
50–64	1.13	0.95–1.36	0.2
< 50	0.86	0.70–1.06	0.2

only if the patient was enrolled. We did not have access to information regarding trial participation not related to COVID-19, thus limiting our ability to examine differences specifically related to COVID-19 studies. Finally, the registry is limited to hospitalized patients and does not capture outpatient clinical trial enrollment for studies like vaccination trials.

Conclusion

As the USA continues to advance past the COVID-19, an important learning opportunity has emerged in terms of shedding light on participation in clinical trial development, enrollment, and execution. The pandemic has disproportionately affected some populations, and our analysis demonstrates disparities extend to clinical trial enrollment for female and Black patients. Further investigation of the reasons for these disparities, as well as efforts to help reduce them over time, will be critical in our ability to learn from the pandemic and future clinical trial enrollment.

Author Contribution Dr. K. Shah, Adriana Reyes-Miranda, and Dr. R. Shah authored the original versions of the manuscript and all co-authors revised and reviewed final versions of the manuscript.

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Data Availability Data was made available from the Get With the Guideline program for all co-authors. The data for this project is hosted with the Get With the Guidelines team.

Code Availability The authors will preserve data and code and can provide reasonable assistance to requests for clarification and replication.

Declarations

Ethics Approval The study was approved by all local Institutional Review Boards.

Consent to Participate and Consent for Publication Participants' consent to participate was obtained from all participants including for publication.

Conflict of Interest The authors declare no competing interests.

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