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MAJOR ARTICLE

Factors Associated With Enrollment into Inpatient Coronavirus Disease 2019 Randomized Controlled Trials: A Cross-sectional Analysis

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Background. Clinical trials for coronavirus disease 2019 (COVID-19) have struggled to achieve diverse patient enrollment, despite underrepresented groups bearing the largest burden of the disease and, presumably, being most in need of the treatments under investigation.

Methods. To assess the willingness of patients to enroll into inpatient COVID-19 clinical trials when invited, we conducted a cross-sectional analysis of adults hospitalized with COVID-19 who were approached regarding enrollment. Associations between patient and temporal factors and enrollment were assessed by multivariable logistic regression analysis.

Results. A total of 926 patients were included in this analysis. Overall, Hispanic/Latinx ethnicity was associated with a nearly half-fold decrease in the likelihood to enroll (adjusted odds ratio [aOR], 0.60 [95% confidence interval {CI}, .41–.88]). Greater baseline disease severity (aOR, 1.09 [95% CI, 1.02–1.17]), age 40–64 years (aOR, 1.83 [95% CI, 1.03–3.25]), and age ≥65 years (aOR, 1.92 [95% CI, 1.08–3.42]) were each independently associated with higher likelihood to enroll. Over the course of the pandemic, patients were less likely to enroll during the summer 2021 wave in COVID-19–related hospitalizations (aOR, 0.14 [95% CI, .10–.19]) compared with patients from the first wave in winter 2020.

Conclusions. The decision to enroll into clinical trials is multifactorial. Amid a pandemic disproportionately affecting vulnerable groups, Hispanic/Latinx patients were less likely to participate when invited, whereas older adults were more likely. Future recruitment strategies must consider the nuanced perceptions and needs of diverse patient populations to ensure equitable trial participation that advances the quality of healthcare for all.

Keywords. clinical trials; COVID-19; diversity; enrollment; participation.

Clinical trials serve as the preeminent method to evaluate the benefit of novel pharmaceutical interventions; however, the underrepresentation of vulnerable groups in sample populations is a longstanding and pervasive issue [1–4]. Differences in drug pharmacokinetics and pharmacodynamics based on genetic, metabolic, and lifestyle distinctions between both age and racial/ethnic groups underscore the need for diverse enrollment in trials assessing drug tolerability and effectiveness [5–7]. The coronavirus disease 2019 (COVID-19) pandemic has necessitated the robust and urgent implementation of clinical trials evaluating novel vaccines and therapies that are safe and effective for all populations [8].

Amid the pandemic, the underrepresentation of vulnerable groups persists, with many United States (US)–based COVID-19 vaccine trials failing to proportionately enroll communities of color and older adults [9–13]. Additionally, several large-scale, multicenter, randomized controlled trials (RCTs) evaluating COVID-19 therapies have also struggled to enroll diverse patient populations [14–16]. With roughly 75% of reported COVID-19–related deaths in the US occurring in patients aged ≥65 years [17] and heightened morbidity in communities of color [18], the greater burden of COVID-19 borne by underrepresented groups demands prompt remediation of trial protocols and recruitment strategies to allow equitable benefitting from the early access to treatments conferred by trials, and to ensure drug safety and efficacy in the populations most in need of interventions.

In this study, we sought to assess the willingness to enroll into inpatient COVID-19 clinical trials within various patient

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populations and over the course of the pandemic. We examined associations between patient and temporal factors and enrollment into 2 consecutively enrolling clinical trials evaluating novel investigational therapies for hospitalized patients with COVID-19 [19, 20].

METHODS

Patient Population

Data were obtained from 2 quaternary acute care hospitals, Rhode Island Hospital and The Miriam Hospital, both located in Providence, Rhode Island. The 2 clinical sites are a single academic medical center affiliated with the Warren Alpert Medical School of Brown University and provide care to the majority of Rhode Island inpatients with COVID-19. The 2 clinical sites are also covered by the same research team and are close in geographical proximity, and thus, were analyzed together. All hospitalized patients testing positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by polymerase chain reaction test were consecutively screened, and if eligible, approached between 14 September 2020 and 30 December 2021 for enrollment into 2 sequential, nonoverlapping clinical trials: Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for Hospitalized Adult Patients With COVID-19 (NCT04426695, hereafter "CAS + IMD") [19] or ACTIV-3: Therapeutics for Inpatients with COVID-19 (NCT04501978, hereafter "ACTIV-3") [20]. Among all clinical sites for the 2 multinational studies, The Miriam Hospital and Rhode Island Hospital, respectively, were the first- and second-highest enrolling sites for CAS + IMD, and the third- and fourth-highest enrolling sites for the ACTIV-3 protocols.

Consenting Process

After a patient was deemed eligible through review of their electronic medical record and consultation with their clinical care team, patients were contacted either via phone or in person by research coordinators. For non-English-speaking patients, research coordinators were able to utilize video interpreter services and translated versions of informed consent forms in the patients' respective language. When feasible, research coordinators who were fluent in Spanish and/or of Hispanic/Latinx descent approached Spanish-speaking patients. No additional resources, such as flyers, handouts, or videos were used to assist with the consenting process. Legally authorized representatives (LARs) were contacted on behalf of eligible patients who could not provide informed consent on their own. Key inclusion and exclusion criteria for both studies can be found in the Supplementary Methods.

Study Variables

Patient Characteristics

Throughout study recruitment, a prospective record was maintained documenting the date of screening, enrollment status, and LAR involvement in decision-making. For all patients invited to enroll, we extracted the following information through their electronic medical record: age, sex, race/ethnicity, preexisting medical conditions, baseline oxygen support, and baseline vital signs on the date of screening. Weighted van Walraven Elixhauser Index scores [21] and National Early Warning Score (NEWS) [22] were calculated to quantify comorbidity burden and acute illness severity on the date of screening, respectively.

Temporal Factors

We aimed to assess how enrollment likelihoods evolved over different time periods by utilizing patient-level data on when patients were approached for enrollment. Specifically, periods were defined with respect to Rhode Island COVID-19–related hospitalizations [23]. Wave 1, a period defined by high levels of hospitalizations, spanned 14 September 2020 to 12 May 2021; a period of low hospitalizations spanned from 13 May 2021 to 8 August 2021; and Wave 2, another period of high hospitalizations, spanned from 9 August 2021 to 30 December 2021.

Statistical Analysis

We used Pearson χ^2 test for independence to compare the differences in the study population characteristics by enrollment status. Continuous variables were represented as median with interquartile range (IQR). We then performed multivariable logistic regression analyses to examine the association between patient characteristics and temporal factors.

In one model, we categorized patients based on predefined age groups (18–39 years, 40–64 years, ≥65 years). In other models, we aimed to assess if likelihood to enroll differed by 1-year increments in age and across generational groups defined by birth year (Silent Generation, 1928–1945; Baby Boomers, 1946–1964; Generation X, 1965–1980; Millennials, 1981–1996; and Generation Z, 1997–2012).

Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated by logistic regression models. Following the primary analysis, we performed exploratory analyses in which we assessed if significant associations of interest were modified by LAR status. For the exploratory analyses, we utilized multivariable logistic regression models with an interaction term between the covariate of interest and LAR. Analyses were performed using Stata/SE version 1.70 (StataCorp LLC, College Station, Texas). Significance was set at $\alpha = .05$.

Ethical Considerations

This study was approved by the Lifespan Institutional Review Board. Patient informed consent was waived due to the study being a retrospective medical records review.

RESULTS

Baseline Characteristics

In Table 1, we present the baseline characteristics of the 926 patients included in the analysis. In total, 459 (49.6%) patients

enrolled, whereas 467 (50.4%) patients declined. The median age was 68 (IQR, 54–80) years, and 439 (47.4%) patients were women. Overall, 591 (63.8%) patients identified as non-Hispanic White, 171 (18.5%) as Hispanic/Latinx, 100 (10.8%) as non-Hispanic Black, and 64 (6.9%) as other/unreported. An LAR was involved in decision-making for 232 of the 926 (25.1%) patients. For CAS + IMD, 554 patients were invited to enroll, while ACTIV-3 invited 372 patients. Data on patients approached by clinical site are reported in Supplementary Table 1.

Outcomes of Interest

Race, Ethnicity, and Sex

Associations between patient characteristics and enrollment among the total study population are presented in Table 2. Overall, Hispanic/Latinx patients, compared with non-Hispanic White patients, were less likely to enroll (aOR, 0.60 [95% CI, .41–.88]; $P = .009$). Of note, in our exploratory analysis, we found that the odds of consenting for Hispanic/Latinx patients compared with non-Hispanic White patients were similar across LAR strata ($P = .96$; Table 3).

Compared with non-Hispanic White patients, the likelihood to enroll among non-Hispanic Black patients was not statistically significant (aOR, 0.63 [95% CI, .40–1.01]; $P = .06$; Table 2). Moreover, no difference in the likelihood to enroll was observed among men compared with women (aOR, 1.02 [95% CI, .77–1.35]; $P = .91$; Table 2).

Disease Severity and Comorbidity Burden

Overall, higher NEWS at the time of patient screening was associated with a greater likelihood to enroll (aOR, 1.09 [95% CI, 1.02–1.17]; $P = .008$; Table 2). Furthermore, a greater Elixhauser index score was not associated with the likelihood to enroll among all patients (aOR, 1.01 [95% CI, .99–1.03]; $P = .61$).

Age and Generation

Among the study population, patients aged between 40 and 64 years (aOR, 1.83 [95% CI, 1.03–3.25]; $P = .04$; Table 2) and patients aged ≥65 years (aOR, 1.92 [95% CI, 1.08–3.42]; $P = .03$) were both more likely to enroll compared with patients aged between 18 and 39 years. Of note, in our exploratory analysis, we found that the odds of consenting did not differ across LAR strata in patients aged 40–64 years or ≥65 years ($P = .62$ and $P = .77$, respectively; Table 3).

In a separate analysis, 1-year increments in age were not associated with the likelihood to enroll (aOR, 1.01 [95% CI, 1.00–1.02]; $P = .05$). When categorized by generation instead of age, compared with Millennials, Baby Boomers (aOR, 1.82 [95% CI, 1.00–3.33]; $P = .05$; Table 4) and members of the Silent Generation (aOR, 1.77 [95% CI, .96–3.29]; $P = .07$) and

Table 1. Baseline Characteristics of Patients Invited for Trial Enrollment

Characteristic	Total (N = 926)	Enrolled (n = 459)	Declined (n = 467)
Age, y, median (IQR)	68 (54–80)	69 (57–81)	66 (50–79)
Female sex	439 (47.4)	221 (48.1)	218 (46.7)
Race/ethnicity			
Non-Hispanic White	591 (63.8)	310 (67.5)	281 (60.2)
Non-Hispanic Black	100 (10.8)	44 (9.6)	56 (12.0)
Hispanic/Latinx	171 (18.5)	71 (15.5)	100 (21.4)
Other	64 (6.9)	34 (7.4)	30 (6.4)
Involved LAR	232 (25.1)	151 (32.9)	81 (17.3)
Weighted Elixhauser score			
<0	135 (14.6)	61 (13.3)	74 (15.8)
0	336 (36.3)	155 (33.8)	181 (38.8)
1–4	127 (13.7)	62 (13.5)	65 (13.9)
≥5	328 (35.4)	181 (39.4)	147 (31.5)
NEWS score			
0	78 (8.4)	43 (9.4)	35 (7.5)
Low	566 (61.1)	271 (59.0)	295 (63.2)
Medium	181 (19.5)	91 (19.8)	90 (19.3)
High	101 (10.9)	54 (11.8)	47 (10.1)
Clinical trial			
ACTIV-3[a]	372 (40.2)	94 (20.5)	278 (59.5)
CAS + IMD[b]	554 (59.8)	365 (79.5)	189 (40.5)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: IQR, interquartile range; LAR, legally authorized representative; NEWS, National Early Warning Score.

[a]ACTIV-3 refers to ACTIV-3: Therapeutics for Inpatients With COVID-19 (TICO). Our sites participated in 3 specific protocols within the controlled platform trial's master protocol.

[b]CAS + IMD refers to Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for Hospitalized Adult Patients With COVID-19.

Table 2. Adjusted Associations of Patient Characteristics and Study Enrollment, Total Patient Population

Characteristic	aOR (95% CI)	*P* Value
Age, y		
18–39	Reference	Reference
40–64	1.83 (1.03–3.25)	.04
≥65	1.92 (1.08–3.42)	.03
Patient sex		
Female	Reference	Reference
Male	1.02 (.77–1.35)	.91
Race/ethnicity		
Non-Hispanic White	Reference	Reference
Hispanic/Latinx	0.60 (.41–.88)	.009
Non-Hispanic Black	0.63 (.40–1.01)	.06
Other/unknown	0.97 (.55–1.72)	.41
Elixhauser score	1.01 (.99–1.03)	.61
NEWS score	1.09 (1.02–1.17)	.008
Hospitalization waves		
Wave 1[a]	Reference	Reference
Trough[b]	0.44 (.22–.86)	.02
Wave 2[c]	0.14 (.10–.19)	<.001

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; NEWS, National Early Warning Score.

[a]Wave 1 refers to 14 September 2020 to 12 May 2021.

[b]Trough refers to 13 May 2021 to 8 August 2021.

[c]Wave 2 refers to 9 August 2021 to 30 December 2021.

Table 3. Exploratory Analysis of Interaction Between Significant Associations and Legally Authorized Representative

Characteristic	LAR (n = 232) aOR (95% CI)	No LAR (n = 694) aOR (95% CI)	*P* Value
Age, y			
18–39	Reference	Reference	
40–64	1.08 (.12–9.76)	1.91 (1.05–3.50)	.62
≥65	1.08 (.14–8.20)	1.49 (.80–2.78)	.77
Race/ethnicity			
Non-Hispanic White	Reference	Reference	
Hispanic/Latinx	0.58 (.24–1.41)	0.60 (.39–.92)	.96

The aORs and 95% CIs were derived from multivariable logistic regression models with an interaction term between age and LAR, and then race/ethnicity and LAR, respectively. Individual models were adjusted for sex, acute disease severity, comorbidity burden, hospitalization wave, and either race/ethnicity or age.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; LAR, legally authorized representative.

Table 4. Adjusted Associations of Patient Characteristics and Study Enrollment by Different Age Definitions, Total Study Population

Characteristic	aOR (95% CI)	*P* Value
Generational group (birth year)[a]		
Millennials (1981–1996)	Reference	Reference
Silent Generation (1928–1945)	1.77 (.96–3.29)	.07
Baby Boomers (1946–1964)	1.82 (1.00–3.33)	.05
Generation X (1965–1980)	1.52 (.81–2.86)	.19
Generation Z (1997–2012)	0.51 (.09–2.74)	.43
Patient age[b]	1.01 (1.00–1.02)	.05

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

[a]Age was categorized into generational groups.

[b]Age was designated as a continuous variable of 1-year increments. Both models were adjusted for race/ethnicity, sex, acute disease severity, comorbidity burden, and hospitalization wave.

Generation X (aOR, 1.52 [95% CI, .81–2.86]; $P = .19$) were numerically more likely to enroll, though the findings were not statistically significant.

Hospitalization Waves

Compared with Wave 1, patients were less likely to enroll during the period of low hospitalizations (aOR, 0.44 [95% CI, .22–.86]; $P = .02$; Table 2) and during Wave 2 (aOR, 0.14 [95% CI, .10–.19]; $P < .001$). Figure 1 depicts trends in study recruitment over the course of the hospitalization waves. These trends across the 2 trial enrollment periods are depicted in Supplementary Figure 1.

DISCUSSION

Findings from this cross-sectional study demonstrate the intricacy of the decision to enroll into clinical trials and show how preexisting disparities in representation manifest in the context of COVID-19. Overall, patients who identified as Hispanic/Latinx were less likely to enroll, whereas patients with greater baseline acute illness severity, patients aged 40–64 years, and patients aged ≥65 years were more likely to enroll. Over the 15-month span, willingness to enroll decreased from the first wave in COVID-19 hospitalizations to the period of low hospitalizations and the subsequent second wave.

The underrepresentation of communities of color in clinical trials is widely recognized [1–3]. Nevertheless, Alegria et al uncovered a lack of significant improvement in RCT participant diversity between 2015 and 2019 [24]. The underrepresentation has even persisted in large-scale US-based COVID-19 trials, including the phase 3 Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies trial (NCT04427501) for the monoclonal antibody combination bamlanivimab plus etesevimab, in which only 12.6% of patients self-identified as non-White [15], and the Pfizer-BioNTech and Moderna vaccine trials in which patients self-identifying as non-White represented 18.1% and 20.6% of the trial cohorts, respectively [12]. Furthermore, in a systematic review and meta-analysis of 122 US-based COVID-19 trials, Xiao et al described aggregate differences in trial representation relative to COVID-19 incidence between racial/ethnic groups in both vaccine and treatment studies [13]. Amid a global pandemic that disproportionately affects communities of color [18], opportunities for early access to potentially effective treatments through trials, coupled with the need for findings that are generalizable to those bearing the greatest burden of COVID-19, necessitate diverse trial enrollment and the addressing of factors that discourage participation by underrepresented groups.

In our analysis, Hispanic/Latinx patients were associated with a nearly half-fold decrease in the likelihood to enroll compared with non-Hispanic White patients, consistent with trends of Hispanic/Latinx underrepresentation reported in other US-based COVID-19 trials. A review of 5 COVID-19 outpatient trials with results published in high-impact journals revealed Hispanic/Latinx representation ranging from 3.4% to 42.5%, despite this group's unequal suffering from the disease [16]. Notably, prior research suggests that all racial/ethnic groups participate equally in clinical trials when invited, citing system-level barriers such as lack of access to trials and implicitly discriminatory eligibility criteria as primary drivers of underrepresentation [25, 26]. However, in our study, the practice of approaching all eligible patients in the hospital setting suggests barriers beyond access alone.

At the individual level, Massett et al described a lack of trust in medical research along with limited cultural and linguistic diversity of research staff as challenges to enrollment for prospective Hispanic/Latinx participants [27]. In our trials, despite our ability to circumnavigate linguistic barriers with translated consent forms and video translators or research coordinators fluent in Spanish, a nearly half-fold decrease in the willingness to participate among this group compared with the non-Hispanic White group remained. While recruiting for 3 COVID-19 vaccine trials, Castellon-Lopez et al found success in enrolling a

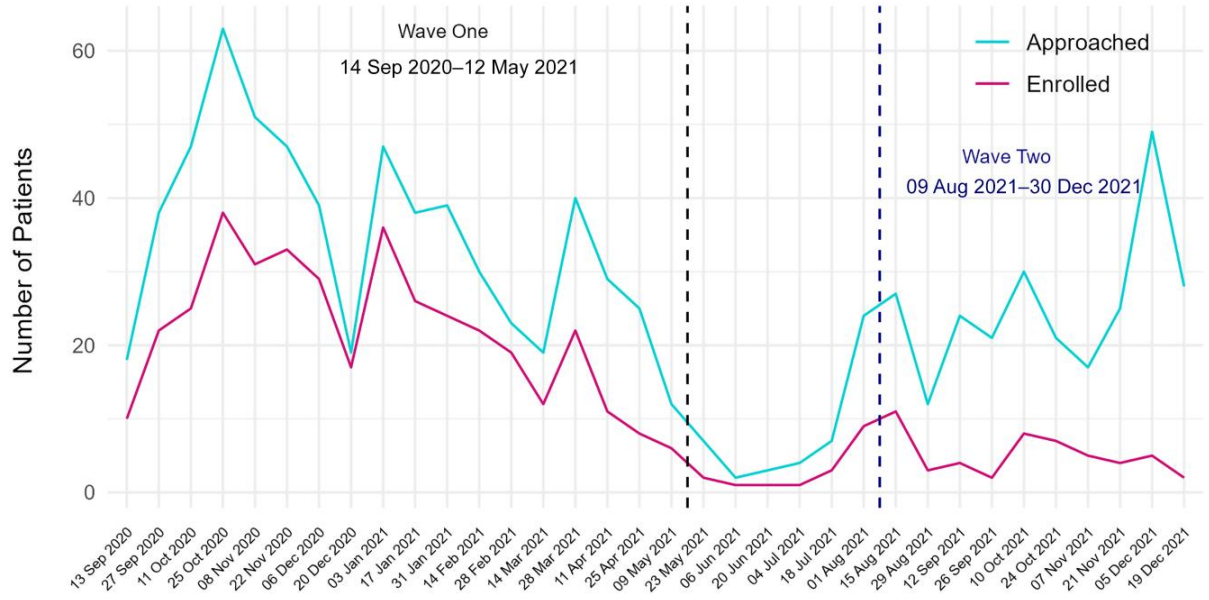

Figure 1. Study recruitment and enrollment throughout Rhode Island hospitalization waves. The x-axis depicts 2-week intervals, and the y-axis represents the number of patients either approached for enrollment (top line, blue) or enrolled (bottom line, pink). Vertical dotted lines partition periods of Rhode Island hospitalization waves (beginning of x-axis to first dotted line represents Wave 1 [14 September 2020 to 12 May 2021]; from the first dotted line to the second is a period of lower hospitalizations between waves [13 May 2021 to 8 August 2021]; from the second line to the end of the x-axis represents Wave 2 [9 August 2021 to 30 December 2021]).

range of 32%–47% Hispanic/Latinx participants after the implementation of a Community Consultant Panel—a diverse group of stakeholders from the local community charged with advising local trial teams on strategies to tailor recruitment toward underrepresented groups and to improve the cultural appropriateness of outreach efforts [28]. Recommendations brought forward by panel members included modified outreach material such as flyers displaying diverse populations, more inclusive wording on trial forms, and the identification of trusted venues and leaders in the local community to share trial opportunities and COVID-19 information with prospective participants through. Though the study by Castellon-Lopez et al was conducted in outpatients and recruited in a very racially/ethnically diverse region of the country (Los Angeles County, California) with the advantage of longstanding ties between the trial team and community, similar practices could be explored in other settings and can be leveraged as an opportunity to remediate the underrepresentation and mend the underlying fissures in trust among Hispanic/Latinx groups.

Prior studies have suggested that the involvement of family in medical decision-making can have a facilitative role in study enrollment [27, 29], particularly among Hispanic/Latinx communities wherein the role of family in medical decision-making is emphasized [30–32]. With these prior reports in mind, we speculated that shared decision-making may have alleviated certain apprehensions held by individual patients regarding enrollment such as mistrust, difficulty understanding trial information, or the sheer complexity of making an important personal decision while hospitalized and severely ill. Thus, to further investigate our finding of lower willingness among Hispanic/Latinx patients compared with non-Hispanic White patients, we assessed this association with and without an LAR involved in the recruiting process. Though our exploratory investigation found no interaction based on LAR status, our analysis was limited by a lack of information about the LAR involved in the decision-making process, such as their race/ethnicity, age, and relationship to the patient. With this information available, associations between LAR status and enrollment may be uncovered within specific subgroups of LARs as they were in our primary analysis for patients of certain age groups and racial/ethnic backgrounds. Despite our finding, the role of shared decision-making should not be overlooked as a possible method to ameliorate participation, especially among prospective participants of Hispanic/Latinx ethnicity.

Our analysis identified a series of other factors, such as higher baseline acute disease severity, that also may have influenced enrollment. Limited published literature is available evaluating the impact of acute disease severity on the decision to enroll in drug trials. A narrative review from Ireland examined patients' perspectives on participating in clinical trials and found that personal gain and the desire to improve personal health positively influenced enrollment [33]. Moreover, a survey evaluating factors associated with parental enrollment of neonates into an RCT found that parental perception of their neonate's

disease severity was significantly associated with the decision to enroll the neonate [34]. Altogether, the influence of disease severity on the decision to enroll into clinical trials requires further exploration and consideration in future studies.

Historically, older adults are underrepresented in clinical trials, with studies reporting both positive and negative attitudes toward trial participation within older populations [35, 36]. This trend persists in the context of COVID-19, with patients aged ≥65 years constituting less than 10% of the patient population in early COVID-19 vaccine trials despite being the most in need of vaccination [11]. Helfand et al found that half of the COVID-19 clinical trials and all of the COVID-19 vaccine trials analyzed were at risk for exclusion of older adults based on eligibility criteria [37]. In our studies, patients aged 40–64 years and those aged ≥65 years were more likely to enroll than younger patients. These findings suggest that older adults may be willing to participate when eligible and call attention to the need for eligibility criteria and tailored recruitment strategies that are inclusive to the patients who have suffered the greatest mortality from COVID-19 [17].

Assessing enrollment across a 15-month period provides insights into how the willingness to participate transformed alongside an evolving pandemic environment. Wave 1 (14 September 2020 to 12 May 2021) was marked by a limited repertoire of proven agents against COVID-19, with high Rhode Island COVID-19–related hospitalizations and a greater willingness for patients to enroll compared with Wave 2 (9 August 2021 to 30 December 2021). The overall decrease in willingness to enroll after Wave 1 parallels reports of an international decrease in COVID-19 trial participation following widespread vaccination, with a shrinking pool of eligible participants and an increasing reluctance to participate in trials given the rising availability of approved interventions cited as possible causes [38, 39]. These factors and a sense of security and protection might have contributed to the stark difference in enrollment observed when comparing Waves 1 and 2 in Rhode Island hospitalizations, despite both periods featuring similarly high numbers of COVID-19–related hospitalizations. With the relentless emergence of mutated variants capable of evading both natural and pharmaceutical defenses [40], and still-limited effective treatment options for hospitalized patients, the need for trials evaluating novel agents against COVID-19 remains crucial. Future research must adapt to the attitudes and environments of evolving times to recruit diverse trial cohorts and fully solve the persisting global health crisis.

An important consideration for our study of factors associated with enrollment into inpatient COVID-19 trials is the unprecedented pandemic environment in which our trials took place. Features such as our high consenting rate of 49.6% may differ from inpatient studies evaluating non–COVID-19 interventions with lower eligible patient populations and for which proven standard-of-care treatments are already available. For instance, a meta-analysis and systematic review of non–COVID-19 acute respiratory distress and sepsis trials published between 2009 and 2019 found a mean enrollment rate of <1 participant per trial site per month [41]. Nonetheless, our findings of differences in the willingness to enroll between racial/ethnic and age groups represent a continuation and possible exacerbation of preexisting disparities in trial enrollment given the high volume of hospitalized patients and the disproportionate impact of COVID-19 on vulnerable communities. Similar analyses assessing the willingness of various patient populations to enroll into non–COVID-19 clinical trials could be considered to quantify the pervasiveness of these inequities and to identify groups in need of tailored recruitment in other trial types.

Regarding study limitations, non-Hispanic Black patients were underrepresented in the analysis, as the percentage of the Rhode Island population that identifies as Black is below the national average [42]. Second, races/ethnicities such as Asian, American Indian/Alaska Native, and multiracial were grouped together due to a low number of approached patients. Third, for patients involving an LAR, demographic information of the LAR was not obtained, preventing assessment of the association between their characteristics and the decision to enroll their representee. Fourth, due to the eligibility criteria of the trials, our analysis does not include pediatric patients, an additional underrepresented population. Finally, the 2 trials differed in certain aspects such as their sponsor, the randomized odds for patients to receive treatment versus placebo, and the compensation provided to patients for attending follow-up visits. These differences may have uniquely influenced the willingness to enroll in each study.

CONCLUSIONS

Findings from this cross-sectional analysis of hospitalized COVID-19 patients reflect the multifactorial nature of clinical trial enrollment and the nuances of decision-making. While cultural aspects such as race/ethnicity are significant, characteristics including acute disease severity and age also warrant deliberation when strategizing recruitment. Moreover, environmental factors such as disease prevalence and the availability of true or perceived alternative interventions may also influence one's decision to enroll. Trial design should consider these multifaceted factors to develop tailored strategies capable of achieving clinical trial sample populations representative of our society.

Supplementary Data

Supplementary materials are available at *Open Forum 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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Author contributions. M. K., G. B., F. S., and E. M. conceptualized and designed the study and participated in data interpretation. M. K., G. B., Q.-L. T., E. A., M. T.-V., and S. K. participated in data collection and extraction. M. K., G. B., E. K. M., and F. S. prepared tables and figures and performed the statistical analysis. M. K. drafted the initial manuscript. All authors reviewed and revised the manuscript. All authors read and approved the final manuscript as submitted and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Potential conflicts of interest. All authors: No reported conflicts.

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