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Representativeness of Racial and Ethnic Groups in COVID-19 Outpatient Trials in the United States

To the Editor: In the context of racial and ethnic disproportionalities throughout the coronavirus disease 2019 (COVID-19) pandemic, one would expect that clinical trials testing therapeutic agents against severe acute respiratory syndrome coronavirus 1 (SARS-CoV-2) would have fair or overrepresentation of minorities. However, that appears not to be the case.¹

We performed a brief scoping review to evaluate the representativeness of racial and ethnic groups in COVID-19 outpatient randomized trials enrolling patients in the United



States. We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR).² Three large reference databases were searched by a medical librarian, and 467 citations were reviewed in duplicate. Searches were run in March 2021, in Ovid Cochrane Central Register of Controlled Trials (1991+), Ovid Embase (1974+), and Ovid Medline (1946+ including epub ahead of print, in-process and other nonindexed citations). Search strategies are provided in the [Supplemental Appendix S1](#) (available online at <http://www.mayoclinicproceedings.org>). We included studies of outpatients (nonhospitalized patients) infected with SARS-CoV-2 in which a therapeutic agent was tested using a randomized controlled trial (RCT)

design. Nonpublished studies and preprints were not considered. We restricted our eligibility to outpatient trials published in English and in which enrollment occurred in the US territory. For studies that met the eligibility criteria, we extracted data on the type of trial (single-center vs multicenter), total number of participants who reported race and ethnicity, and number of participants from each race and ethnicity as it appears in the US Census Bureau (White, Black or African American, American Indian and Alaska Native, Asian, Native Hawaiian or other Pacific Islander, and Hispanic or Latino). We calculated the proportion of each group by dividing the total number of participants with each race and ethnicity by the total number of participants who were enrolled in the trial and self-reported their

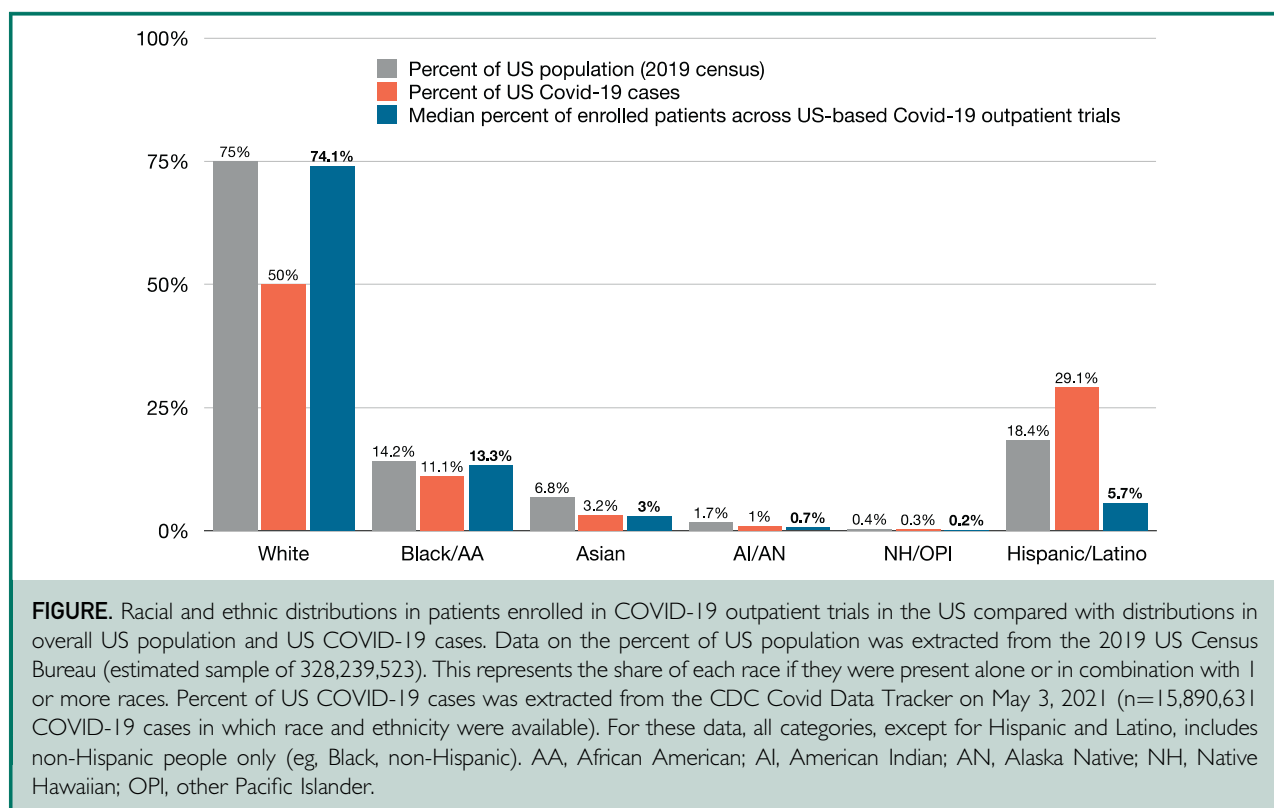


TABLE. Racial and Ethnic Distributions of Patients in COVID-19 Outpatient Trials in the United States

Study author, year of publication	Single or multicenter	White, n/N (%)	Black or African American, n/N (%)	Asian, n/N (%)	American Indian or Alaska Native, n/N (%)	Native Hawaiian or other Pacific Islander, n/N (%)	Hispanic or Latino, n/N (%)
Gottlieb, ³ 2021	Multi	507/567 (89.4%)	33/567 (5.8%)	19/567 (3.4%)	3/567 (0.5%)	1/567 (0.2%)	245/577 (42.5%)
Lenze, ⁴ 2020	Single ^a	106/151 (70.2%)	38/151 (25.2%)	4/151 (2.6%)	1/151 (0.7%)	0/151 (0.0%)	5/146 (3.4%)
Skipper, ⁵ 2020	Multi	235/491 (47.9%)	15/491 (3.1%)	196/491 (39.9%)	3/491 (0.6%)	5/491 (1.0%)	28/491 (5.7%)
Thomas, ⁶ 2021	Multi	152/205 (74.1%)	51/205 (24.9%)	NR	NR	NR	NR
Weinreich, ⁷ 2021	Multi	224/264 (84.8%)	35/264 (13.3%)	3/264 (1.1%)	2/264 (0.8%)	NR	NR
Median (range)	-	74.1% (47.9%-89.4%)	13.3% (3.1%-25.2%)	3.0% (1.1%-39.9%)	0.7% (0.5%-0.8%)	0.2% (0.0%-1.0%)	5.7% (3.4%-42.5%)

^aThis trial enrolled patients from St. Louis, Missouri, only. NR, not reported.

race and ethnicity. Median proportion across studies was also calculated.

We found 5 studies³⁻⁷ published in high-impact journals including a total of 1678 participants who met our eligibility criteria. PRISMA study flowchart is available in [Supplemental Appendix S2](#) (available online at <http://www.mayoclinicproceedings.org>). Among these 5 trials, the proportion of White participants ranged from 47.9%⁵ to 89.4%³ (median 74.1%). Although proportionately less affected by COVID-19 in the United States, White people were overrepresented ([Figure](#)). The proportion of Black or African American participants ranged from 3.1%⁵ to 25.2%⁴ (median 13.3%). The proportion of Hispanic or Latino participants ranged from 3.4%⁴ to 42.5%³ (median 5.7%). Despite being significantly affected by COVID-19, Hispanic or Latino people were greatly underrepresented in these trials and are likely the minority group most affected by enrollment disparities. Other groups (Asian, American Indian, and Native Hawaiian) were also underrepresented. ([Table](#) and [Figure](#))

By systematically reviewing the published literature, we noted potential disproportionalities in racial and ethnic distributions among participants enrolled in COVID-19 outpatient randomized trials. When the trial enrollments are combined, White people are overrepresented in these trials, whereas Hispanic and Latinos and other minorities are underrepresented. Although the median percent of Black people across these trials was close to the percent of Blacks in the US population ([Figure](#)), 2 trials had less than 6% of enrolled participants in this race category, highlighting its likely underrepresentation. In aggregate, these results raise concern about the

applicability of outpatient COVID-19 trial findings in minorities.

Several limitations need to be acknowledged in our scoping review. First, we included trials enrolling participants in the United States only, so the results are not applicable to research in other countries. Second, only trials involving nonhospitalized patients (ie, outpatient trials) were considered, and if we were to consider a larger body of trials without restriction to the outpatient setting, results might have been different. Third, we used published trial data, and reports of race and ethnicity were missing in some studies. Finally, although 4 of 5 trials were multicenter, different trial geographies may have skewed the distribution of certain races, and we did not take that into account in our analysis.

It is evident that a concerted effort to actively engage minority communities is necessary when designing COVID-19 clinical trials and beyond. Potential solutions are the development of guidelines driving organizations to place further and more robust emphasis on integration of racial and ethnic minorities in clinical research of all kinds. Second, better access to interpreter services and research personnel from minority groups that can approach the communities. Third, increase funding for investigators from underrepresented groups, as representation matters. Fourth, mandatory reporting of race and ethnicity in clinical trials, including reach for enrollment to underserved and minority communities while planning the study. Fifth, efforts to address bias among health care workers and increase community trust in health care. Racial and ethnic disproportionalities in enrollment affect the generalizability of clinical trial results

and may limit the appropriate application of interventions.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mayoclinicproceedings.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.



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Vax-Plasma in Patients With Refractory COVID-19



To the Editor: Convalescent plasma (CP) therapy uses neutralizing antibodies harvested from recovered patients to treat viral infections, including severe acute respiratory syndrome coronavirus (SARS-CoV) and influenza A.¹ The emerging data from randomized controlled trials and observational studies suggest—consistent with historical precedent—that CP therapy has limited efficacy in severely ill patients with coronavirus disease 2019 (COVID-19) treated late in the disease course. However, early treatment with high-titer CP exhibits signs of efficacy.² Additionally, CP use in immunocompromised hosts unable to generate endogenous antibodies suggests a mortality benefit and rapid clinical improvement.^{3,4} One group of patients who benefit from CP therapy are those with primary or secondary B-cell deficiencies with a high risk of severe COVID-19 due to their reduced ability to produce neutralizing antibodies.^{5,6} These patients can also have prolonged refractory COVID-19 that

can last many months and include the generation of novel viral variants. In this context, Vax-plasma is CP from patients who have recovered from natural infection and have been subsequently vaccinated. It can have 10 to 100 times higher antibody titers than does standard high-titer CP with a broad coverage of known COVID-19 variants.⁷ Herein, we present our first experience using Vax-plasma in an immunocompromised patient with refractory COVID-19.

In the fall of 2020, a 68-year-old patient with a history of mantle cell lymphoma and recently diagnosed with COVID-19 presented in the emergency department with shortness of breath, cough, and fever. His medical history was remarkable for metastatic mantle cell lymphoma treated with 6 cycles of rituximab and bendamustine, followed by an autologous stem cell transplant 2 years before this admission. He received maintenance therapy with rituximab every 2 months with the last infusion 2 months before this presentation. His examination was remarkable for nonlabored breathing and coarse crackles in both bases. His white blood cell count was 3800 cells/ μ L; lymphocyte count, 140 cells/ μ L; C-reactive protein level, 141 mg/L; ferritin level, 849 μ g/L; and D-dimer level, 19,418 ng/mL. Chest radiography revealed airspace opacities bilaterally, and computed tomography of the lungs revealed numerous ground-glass opacities consistent with COVID-19 pneumonia (Figure 1 A and B). The patient received remdesivir for 5 days but developed hypoxia, with repeated lung imaging revealing worsening patchy infiltrates. The patient next received broad-spectrum antibiotics along with dexamethasone and