Dear Bansal,

I hope this message finds you well. Thank you for your thoughtful feedback on our manuscript "The predictive value of ferroptosis biomarkers and the relationship between TMB and prognosis in HER2-positive breast cancer". We appreciate the time and effort you dedicated to reviewing our work. In response to your valuable comments, we have carefully revised the manuscript to address each of the concerns raised during the review process.

1 KINDLY COMMENT ON THE APPLICABILITY OF THE RESULTS FOUND IN THIS STUDY IN CONTEXT TO DIFFERENT GLOBAL POPULATIONS.

The training set included in this study was derived from the TCGA database of breast cancer data, and the validation set was derived from the METABRIC database. The TCGA database contains samples from hospitals in the United States and around the world, primarily from the Biospecimen Core Resource (BCR) of the International Genomics Consortium (IGC) in Phoenix, Arizona, and Nationwide Children's Hospital (NCH) in Columbus, Ohio. The TCGA database provides ethnicity as not reported, white, black or African American, Asian, unknown, other, American Indian or alaska native, native Hawaiian or other pacific islander, not allowed to collect[1](Figure 1). The METABRIC database (Molecular Taxonomy of Breast Cancer International Consortium) is a Canadian-UK collaborative project incorporating over 2,000 clinically annotated primary fresh breast cancers from UK and Canadian tumor banks of primary new frozen breast cancer specimens from data sources[2].

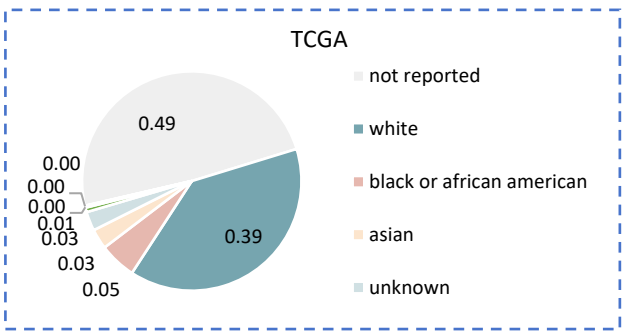

FIGURE 1 TCGA Database Ethnicity Information

From the data sources not reported and whites comprise a more significant percentage, black or African American, Asian, and other races are underrepresented. The current study suggests that the incidence of breast cancer is not the same in women from different national regions[3] (Figure 2). The highest incidence of breast cancer in white women, followed closely by black women, and the lowest incidence in Hispanic and Asian/Pacific Islander (API) women have the lowest incidence rates. Multiple studies have found differences in breast cancer among races. Possible risk factors include Socioeconomic status, Advanced stage of breast cancer at diagnosis, Differences in tumor biology and genetics, Differences in access to health care, and Differences in disease-related molecular mechanisms[4].

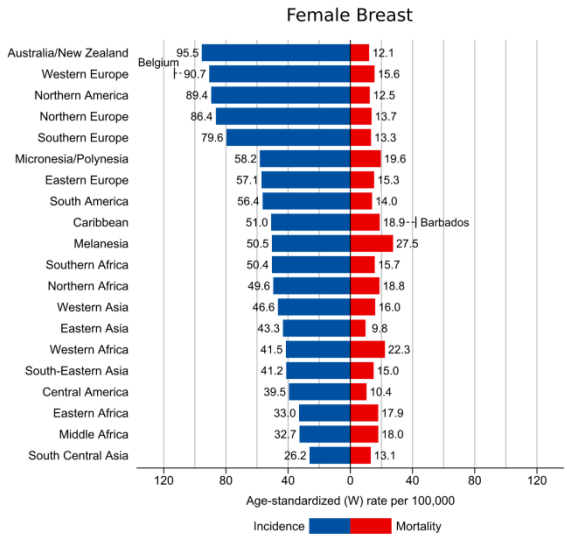

FIGURE 2[3]. Region-Specific Incidence and Mortality Age-Standardized Rates for Female Breast Cancer in 2020. Rates are shown in descending order of the world (W) age-standardized incidence rate, and the highest national age-standardized rates for incidence and mortality are superimposed.

Source: GLOBOCAN 2020.

From the above, we can know factors such as poverty, culture, and social injustice contribute directly or indirectly to differences in female breast cancer, **but racial and ethnic differences in incidence by breast cancer subtype and age show (Figure 3) that the proportion of HER2-positive breast cancers is similar across races and ethnicities, ranging from 4% to 6% for HR-negative disease, and 9% to 12% for HR-positive disease**[5]. Because we studied breast cancer patients with HER2+, the results are representative of different ethnic groups.

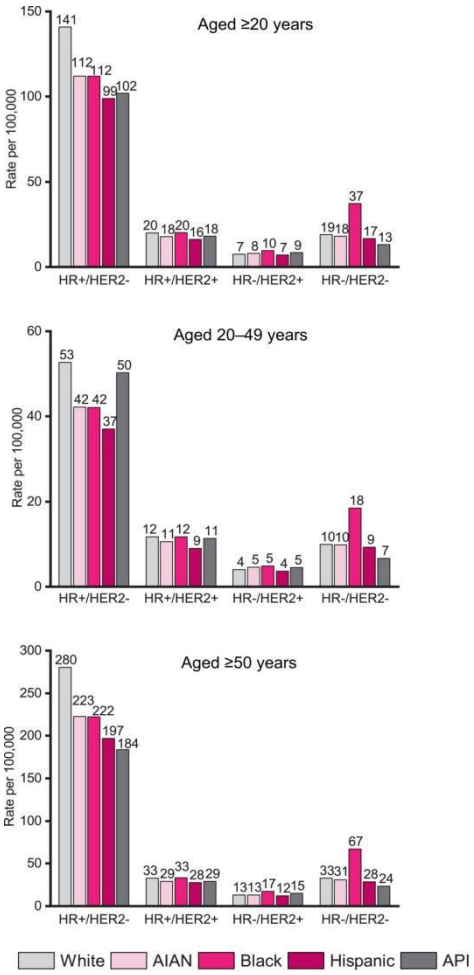

FIGURE 3[4]. Female breast cancer incidence rates by subtype and race/ethnicity and age, 2015–2019, United States. Note: Rates are age-adjusted to the 2000 US standard population. Ethnicity is exclusive of Hispanic origin. Hormone receptor (HR) status and human epidermal growth factor 2 (HER2) status were imputed for cases with missing information. −, negative; +, positive; AIAN, American Indian/Alaska Native; API, Asian/Pacific Islander.

2 TO WHAT EXTENT THE AUTHORS CONFIRM THEIR FINDINDS CAN BE USED AS A GENERALISED BASE GLOBALLY FOR BREAST CANCER PATIENTS?

From the data source, most of the data analyzed in the current study on the transcriptome level of breast cancer come from the TCGA and METABRIC databases. Methodologically, the data source of this study is scientific. **In terms of the different subtypes of breast cancer, the differences in HER2+ breast cancer in other races are minor.** Hence, the results of this study have some applicability to different races.

Reference

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2. Curtis, Christina, et al. "The genomic and transcriptomic architecture of 2,000 breast tumors reveals novel subgroups." Nature vol. 486,7403 346-52. 18 Apr. 2012, doi:10.1038/nature10983.
3. Sung, Hyuna, et al. "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries." CA: a cancer journal for clinicians vol. 71,3 (2021): 209-249. doi:10.3322/caac.21660
4. Yedjou, Clement G et al. "Health and Racial Disparity in Breast Cancer." Advances in experimental medicine and biology vol. 1152 (2019): 31-49. doi:10.1007/978-3-030-20301-6_3.
5. Giaquinto, Angela N et al. "Breast Cancer Statistics, 2022." CA: a cancer journal for clinicians vol. 72,6 (2022): 524-541. doi:10.3322/caac.21754.

Thank you for your valuable feedback on our manuscript. We have carefully addressed your suggestions, and the revisions have improved the overall quality of the paper. Your insights were instrumental in this process.

Please feel free to reach out if you have any further questions or require clarification. We appreciate your time and expertise.

Best regards,

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