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Original Article

Age and race distribution in patients in phase III oncology clinical trials

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Abstract: *Background:* Geriatric patients and minority patients are often under-represented in cancer clinical trials. The presence of multiple comorbidities makes geriatric patients ineligible for most clinical trials. Racial diversity may vary by geographical location and socio-economically backward areas may have a very different racial mix. The increase in cancer incidence in geriatric patients' raises the question of applicability of the results is such clinical trials. This study also explores the representation of different races in phase 3 clinical trials conducted in the past 10 years. *Methods:* Data about Phase III trials was extracted from the clinical trials.gov for 3 common solid organs and 3 hematological malignancies [breast, colon, lung, diffuse large B-cell lymphoma (DLBCL), acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)]. The time period studied was for the past 10 years and included only adult patients (≥18 years). The age and race distribution of the patient population in these trials were extracted and analyzed. *Results:* Geriatric patients and minorities are under-represented in all phase III cancer clinical trials. The range of the proportion of geriatric patients varied from 10% to 40%. African American and Asian patients are under-represented in all phase III cancer clinical trials. *Conclusions:* The results of phase III clinical trials that are currently conducted on non-geriatric and Caucasian patient population may not meaningfully be applicable to geriatric patients and minorities. This study highlights the disparity of age and race for patients enrolled in clinical trials as against the patients seen in the real world.

Keywords: Geriatric population, racial distribution, cancer clinical trial, minorities

Introduction

US Census Bureau predicts a rapid rise in the older population aged greater than 65 years. The number of individuals over the age of 65 years and 85 years is projected to double to nearly 62 million and 10 million, respectively, by the year 2030, and centenarians are anticipated to be the fastest-growing group within this demographic. As the population ages, it is unfortunate that they are underrepresented in the clinical trials. Patients especially with age >75 years and with multiple comorbidities are underrepresented in the clinical trials despite an increasing frequency of cancer diagnosis in this age group [1]. Geriatric patients are under-represented in cancer clinical trials due to the presence of multiple comorbidities which makes them ineligible for most of the clinical trials [2-5]. Consequently, physicians are uninformed of a given treatment's efficacy, and safety in the older population. A total of 1,806,590 new cancer cases and 606,520 deaths from cancer are projected to occur in the United States in 2020 [6].

In the late 1980s and early 1990s, Food and Drug Administration (FDA) had concerns about the generalizability of clinical trial results in the elderly population and established requirements that the clinical trials should adequately represent the general population [7]. The clinical applicability of the trial improves when the sample of patients in the clinical trial mimics the patient population with cancer that is being studied. The National Institutes of Health Revitalization Act of 1993 mandated that the appropriate inclusion of minorities in all NIH-funded research and after more than two decades, the participation of minorities remains persistently low [8, 9]. The proportion of minorities in the US population is 36.3% and

minorities remain burdened with cancer and under-representation in cancer clinical trial enrollments [10, 11]. Improved participation in the clinical trials offers benefits to overcome the barriers to screening and more advanced cancer stage distribution and can result in more effective intervention and improved survival [12, 13]. Physician's characteristics and attitudes along with the Community Clinical Oncology Program (CCOP) organizational factors influenced patient enrollment in cancer clinical trials among CCOP physicians. It was thought that there was a need to develop physician-directed strategies aimed at increasing the involvement of minorities in clinical research [14]. This study aims to investigate the age and racial distribution of the participants in the published trials in most common solid organ tumors and hematological malignancies.

Methods

The literature search was mainly focused on articles published from January 1st, 1999 to January 1st, 2019 which had drugs as intervention and results were published. For the studies that did not publish the detailed age categories and racial distribution, full-text articles were reviewed and obtained the detailed age categories and racial distribution. The following heading terms and keywords were used: Breast cancer, breast neoplasm, breast carcinoma, lung cancer, lung neoplasm, lung carcinoma, colon cancer, colon malignancy, colon carcinoma, AML, ALL, DLBCL. All Phase III clinical trials with drug intervention in the adult population, any funding source and, studies that were completed and had available results were included. The inclusion and exclusion criteria are mentioned below.

We analyzed data on age distribution and racial distribution in patients from the data available on NIH clinical trials in 6 most common cancer types from 1999 to 2019. Reviewed the published data in the cancer clinical trials and summarized the findings.

Inclusion criteria

I. Studies that were completed and with the available results. II. Participants age >18 years. III. Studies in which participants were treated with drug intervention only. IV. Studies that were completed in the last 10 years.

Exclusion criteria

I. Studies focusing on elderly age for medical reasons such as menopause. II. Studies that primarily focus on childhood cancer. III. Studies that included treatments other than drug intervention.

Figures S1, S2, S3, S4, S5 and S6 show the number of studies reviewed at various stages of data collection.

Data extraction

A total of 1436 studies were identified through the database search. The title and abstract were reviewed initially for the appropriate inclusion criteria. The screening was done using the predefined selection criteria for the 6 most common types of cancers. It included 3 solid organ cancers: breast, colon, lung cancer, and 3 hematological cancers: acute myeloid leukemia (AML), acute lymphoid leukemia (ALL), and diffuse large B-cell lymphoma (DLBCL).

Statistical analysis

A Chi-square test using excel software by Microsoft was used to determine statistically significant differences between various subgroups. It is a non-parametric test used to understand the independence of observed and expected variables. Degrees of freedom and alpha level was predetermined by the software. Comparison between different groups were made and values with $P<0.05$ were deemed to be statistically significant and independent.

Results

In breast cancer, altogether 512 Phase III studies were identified through the NIH clinical trials database from the last 10 years. In that, 415 studies were with the drug intervention. The results were available for only 74 studies and the full-text articles were reviewed for 69 studies, but the race categories were not published in 30 studies, and age was not published for 48 studies. Finally, 39 studies were included for racial analysis, and 21 studies were included for categorical age. In colon

cancer, altogether 245 Phase III studies were identified through the NIH clinical trials database from the last 10 years. In that, 205 studies were with the drug intervention. The results were available for only 20 studies and the full-text articles were reviewed for 17 studies, but the race categories were not published in 8 studies, and age was not published for 12 studies. Finally, 9 studies were included for racial analysis, and 5 studies were included for categorical age.

In Lung cancer, altogether 426 Phase III studies were identified through the NIH clinical trials database from the last 10 years. In that, 379 studies were with the drug intervention. The results were available for only 86 studies and the full text articles were reviewed for 69 studies, but the race categories were not published in 30 studies and age was not published for 35 studies. Finally, 39 studies were included for racial analysis, and 34 studies were included for categorical age.

In DLBCL, altogether 63 Phase III studies were identified through the NIH clinical trials database from the last 10 years. In that, 60 studies were with the drug intervention. The results were available for only 11 studies and the full-text articles were reviewed for 10 studies, but the race categories were not published in 7 studies, and age was not published for 8 studies. Finally, 3 studies were included for racial analysis, and 2 studies were included for categorical age. In AML, altogether 124 Phase III studies were identified through the NIH clinical trials database from the last 10 years. In that, 116 studies were with the drug intervention. The results were available for only 18 studies and the full-text articles were reviewed for 16 studies, but the race categories were not published in 9 studies, and age was not published for 12 studies. Finally, 7 studies were included for racial analysis, and 4 studies were included for categorical age. In ALL, altogether 66 Phase III studies were identified through the NIH clinical trials database from the last 10 years. In that, 61 studies were with the drug intervention. The results were available for only 9 studies and the full text articles were reviewed for 8 studies, but the race categories were not published in 2 studies, and age was not published for 5 studies. Finally, 6 studies were included for racial analysis, and 3 studies were included for categorical age.

From the current US cancer statistics (USCS) data, the cancer incidence rates (per 100,000) is increasing with the increase in the age group. Our study revealed that a higher age population is not adequately included in the clinical trials. For a total of 2551 patients included in the study of colon cancer about 1817 (71.2%) are age group less than 65 and 734 patients included in the study are age group greater than or equal to 65. Similarly for breast cancer, out of total 14526 included in the study, 12392 (85.3%) are age group less than 65 and 2134 (14.7%) patients included in the study are age group greater than or equal to 65. Numbers for lung cancer are: total 16694, 10219 (61.21%) less than 65 and 6475 (38.79%) are greater than or equal to 65. Numbers for DLBCL are: total 176, 107 (60.08%) less than 65 and 69 (39.2%) are greater than or equal to 65. Numbers for AML are: total 3114, 2212 (71.03%) less than 65 and 902 (28.97%) are greater than or equal to 65. Numbers for ALL are: total 1203, 1087 (90.36%) less than 65 and 116 (9.64%) are greater than or equal to 65. The age distribution is shown in **Figure 1**. The proportion of geriatric and non-geriatric patients in these malignancies are shown in **Table 1**.

The cancer incidence rates (per 100,000) from current USCS data indicate that whites (436.6) and blacks (433.2) have similar proportion followed by Hispanics (334.7), Asians (276.8), and American Indians/Alaska native (274.5) [15]. In our studies, blacks were underrepresented for all the cancer types except lung cancer. In breast cancer total of 24,170 pts were included in the study among which 4,209 are Asians (17.41%), 859 are Blacks (3.55%), 17,829 are Whites (73.76%), and the remaining 1,273 (5.27%) are in other categories which included Native Americans, Hawaiians and unknown or as reported as other in the original study. In colon cancer a total of 5,537 patients were included and in which 1,171 (21.15%) are Asians, 144 (2.6%) are Blacks, 4,111 (74.25%) are Whites and 111

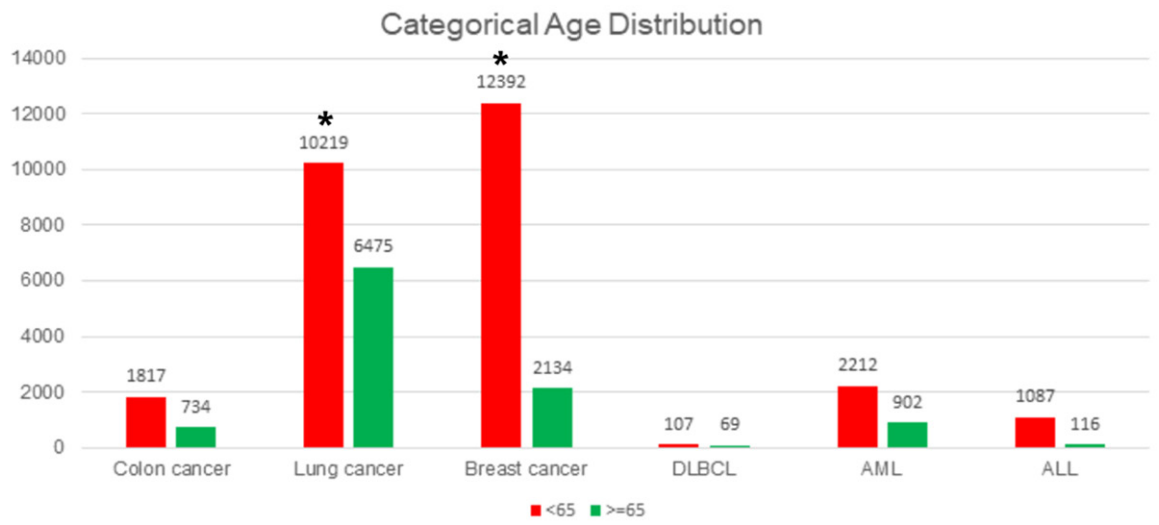

Figure 1. Age distribution in Phase III trials comparing between ages <65 and ≥65 for 6 most common malignancies are shown. Geriatric patients are disproportionately under-represented in all types of cancers.

Table 1. Proportion of geriatric versus non-geriatric patients in phase III clinical trials in 6 most common malignancies

S. No	Malignancy	No of Phase 3 trials	Provided Categorical Age	<65	<65 (%)	≥65	≥65 (%)	Total No. Pts
1	Colon cancer	20	5	1817	71.23	734	28.77	2551
2	Lung cancer	73	34	10219	61.21	6475	38.79	16694
3	Breast cancer	74	21	12392	85.31	2134	14.69	14526
4	DLBCL	10	2	107	60.8	69	39.2	176
5	AML	16	4	2212	71.03	902	28.97	3114
6	ALL	8	3	1087	90.36	116	9.64	1203

The below table shows the number and percentage of the population which included age <65 and ≥65.

(2%) are in others category. In lung cancer a total of 23,594 patients 6,148 (26.06%) are Asians, 7,227 (30.63%) are Blacks, 9,358 (39.66%) are Whites and 861 (3.65%) are in others category.

In the three most common hematological cancers that were considered in the study, DLBCL has a total of 687 patients were included in the study and among which 114 (16.59%) are Asians, 10 (1.46%) are Blacks, 534 (77.73%) are Whites and 29 (4.22%) are in others category. In AML, a total of 4,479 pts were included and 102 (2.28%) are Asians, 105 (2.34%) are Blacks, 4,159 (92.86%) are Whites and 113 (2.52%) are in others category. Whereas in ALL, a total of 1,940 pts were included and 114 (5.88%) are Asians, 130 (6.7%) are Blacks, 1,504 (77.53%) are Whites and 192 (9.9%) are in others category. The race distribution is shown in **Figure 2**. The proportion of different races in these malignancies are shown in **Table 2**.

Discussion

This study found that participants included in the clinical trials with drug intervention were significantly white population than other race categories ($P<0.05$). There were considerable differences in the proportion of people included in the study when compared to the nationwide reference population which was obtained from the US 2018 census. According to the United States Census Bureau, there are 76.6% Whites, 13.4% Blacks, 5.8%, Asians and, 4.2% of others. As per FDA guidelines, the study population should represent the general population to determine the appropriate application of the study trial to the general population.

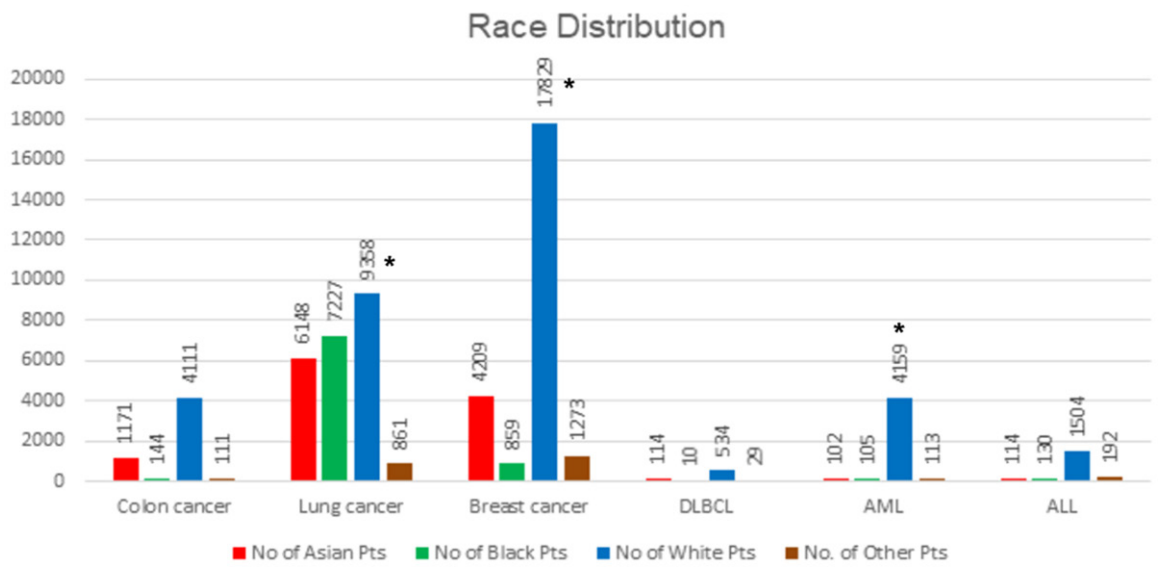

Figure 2. Racial distribution in Phase III trials for 6 different most common malignancies were studied and the above graph represents racial disparities. Minority racial population are significantly under-represented unlike the general population distribution.

Table 2. Proportion of racial distribution of patients in Phase III clinical trials among 6 most common malignancies

S. No	Malignancy	Number of Phase 3 trials	Studies included Race	% of Asian Pts	% of African American Pts	% of White Pts	% of Other pts	Total No pts
1	Colon cancer	20	9	21.15	2.6	74.25	2	5537
2	Lung cancer	73	51	26.06	30.63	39.66	3.65	23594
3	Breast cancer	74	39	17.41	3.55	73.76	5.27	24170
4	DLBCL	10	3	16.59	1.46	77.73	4.22	687
5	AML	16	7	2.28	2.34	92.86	2.52	4479
6	ALL	8	6	5.88	6.7	77.53	9.9	1940

The below table shows the percentage distribution of each racial group in 6 different malignancies.

Incidence of colon cancer, lung cancer and breast cancer are higher in African Americans. Survival rate of every cancer is low in African Americans than in Whites.

The relative risk of cancer death is 33% higher in African Americans when compared to whites and is even higher disparity is noted in American Indians [7].

In our study, 74.2% were whites in colon cancer, 39.6% Whites in lung cancer, 73.7% in Breast cancer. In hematological cancers there were 77.7% Whites in DLBCL, 92.8% AML and 77.5% in ALL. African Americans were 2.6% in colon cancer, 30.6% in Lung cancer, 3.5% in Breast cancer, 1.4% in DLBCL, 2.3% in AML and 6% in ALL. Asians were 21% in colon cancer, 28% in lung cancer, 17.4% in breast cancer, 16.5% in DLBCL, 2.2% in AML and 5.8% in ALL. Others are 2% in colon cancer, 3.6% in lung cancer, 5.2% in breast cancer, 4.2% in DLBCL, 2.5% in AML and 9.9% in ALL. These numbers show that there are significant racial disparities ($P<0.05$). Similarly, the representation of the geriatric population was also noted to be disproportionately lower (colon cancer: 71.2 vs. 28.7%; lung cancer: 61 vs. 38.7%; breast cancer: 85.3 vs. 14.7%; DLBCL: 60.8 vs. 39.2%; AML: 71 vs. 29% and ALL: 90.3 vs. 9.6%; $P<0.05$).

Minority racial/ethnic groups and the elderly were less likely to enroll in cooperative group cancer trials than were whites and younger patients. The proportion of trial participants

who are blacks has declined in recent years [16]. The awareness of the clinical trials appears to be lower in the minority population [17]. The awareness is more in the non-Hispanic Whites when compared to Asians, Blacks, and Hispanics [18, 19]. The increased participation in the clinical trials may lower the mortality based on a study performed in California [13]. In 2012, Food and Drug Administration Safety and Innovation Act (FDSIA) required the FDA to create an action plan to improve data quality and completeness for demographic subgroups (sex, age, race, and ethnicity) in applications for medical products [7]. NIH policy was released in Dec 2017, mentioned that NIH grantees to have a plan for including children and older adults in their research [20]. The results of this new impetus to broaden the participation of elderly patients and minorities may help make the results of future clinical trials more in line with the general population.

Conclusion

Most Phase III clinical trials except for lung cancer, predominantly consisted of Caucasian patients. Applying the results of these trials to patients of other races should be done with caution. This study highlights the disparity of race in patients enrolled in clinical trials when compared to diverse and different populations that are encountered in practice. Similarly, the results of Phase III clinical trials that are currently conducted on the non-geriatric patient population may not meaningfully apply to geriatric patients. This study highlights the disparity of age for patients enrolled in clinical trials against the patients seen in the real world. Efforts need to be made to recruit geriatric patients and minority races into clinical trials so that trial results can be applied meaningfully to these subpopulations.

Disclosure of conflict of interest

None.

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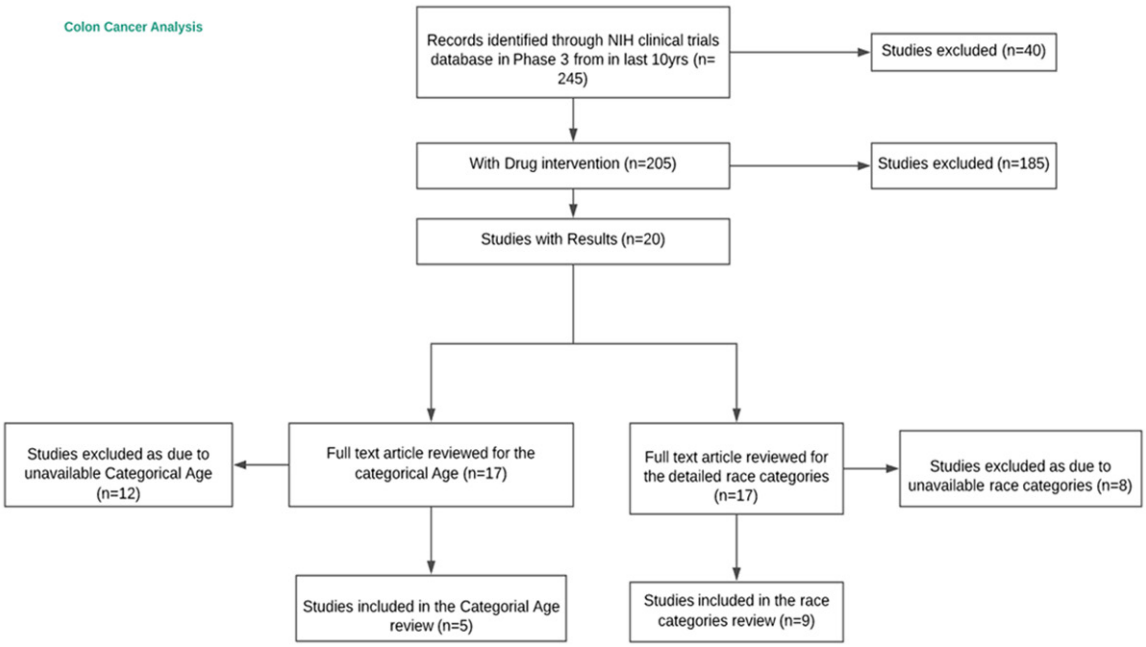

Figure S1. Consort diagram for age and race distribution for Colon Cancer.

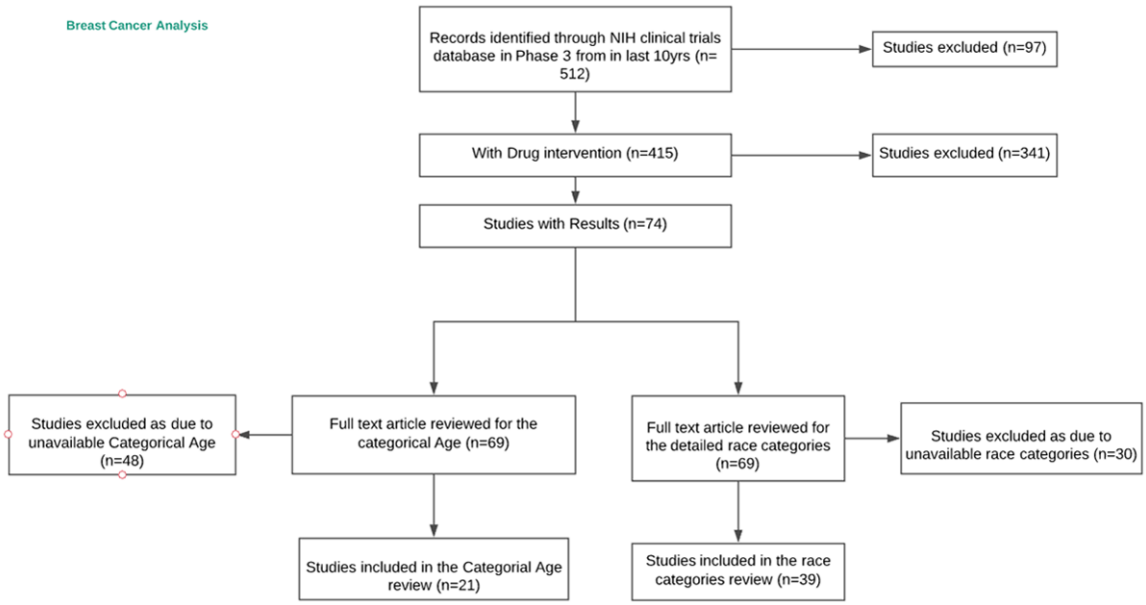

Figure S2. Consort diagram for age and race distribution for Breast Cancer.

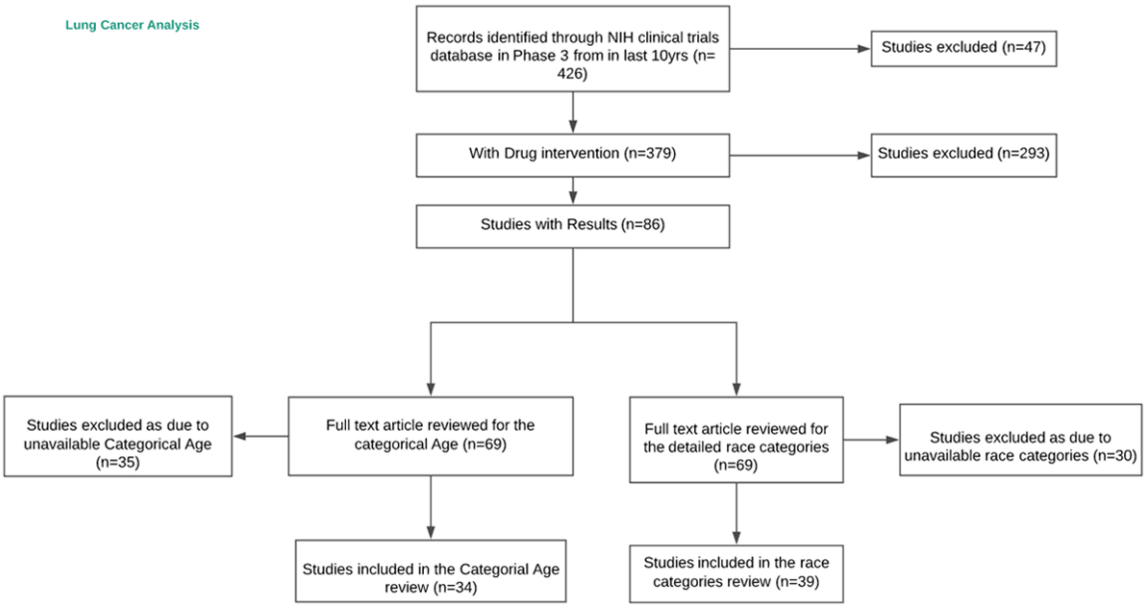

Figure S3. Consort diagram for age and race distribution for Lung Cancer.

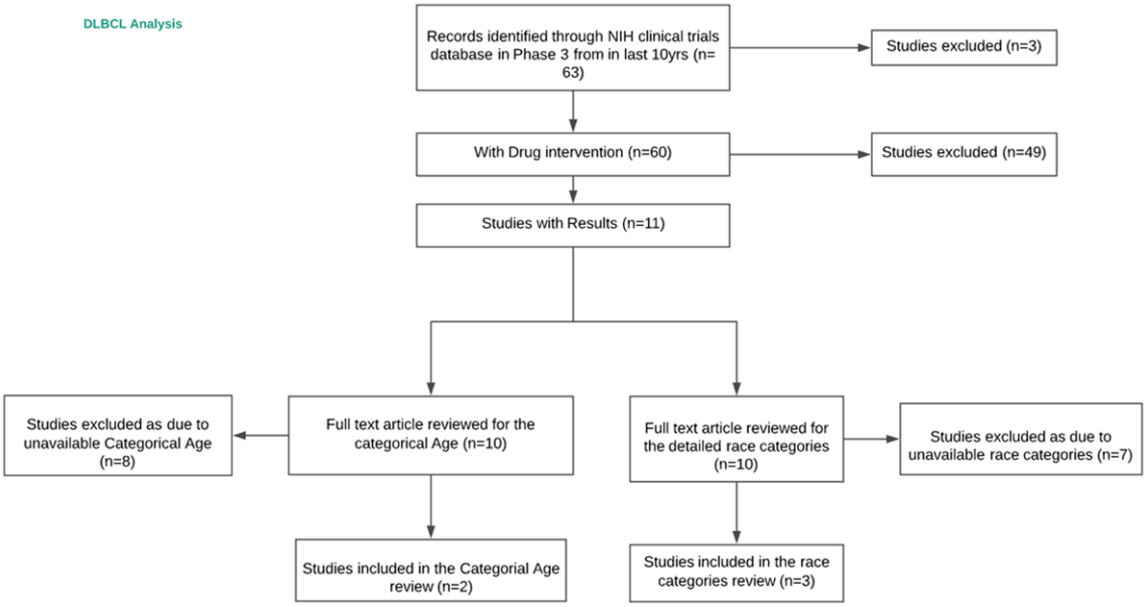

Figure S4. Consort diagram for age and race distribution for DLBCL.

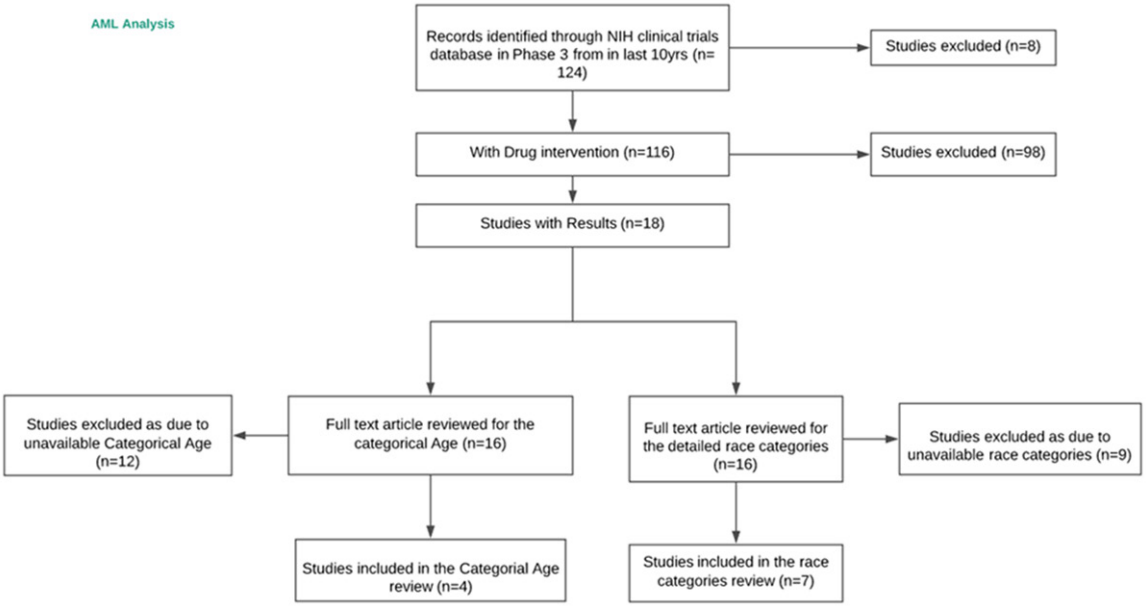

Figure S5. Consort diagram for age and race distribution for AML.

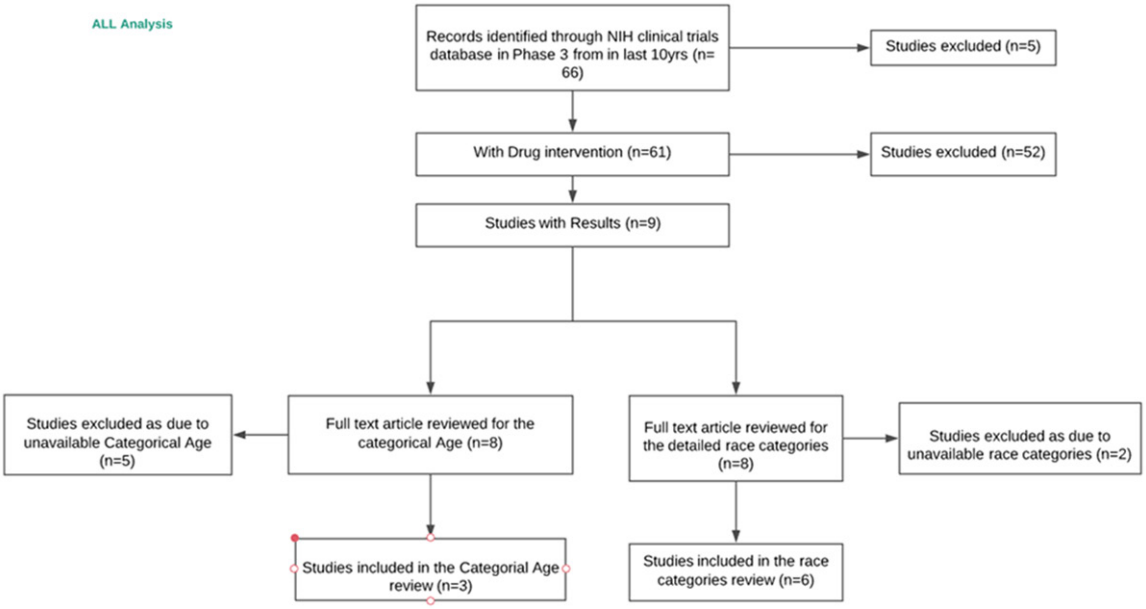

Figure S6. Consort diagram for age and race distribution for ALL.