Lymphology 56 (2023) 41-60

UNDERREPORTING AND UNDERREPRESENTATION OF RACIAL AND ETHNIC MINORITY PATIENTS IN LYMPHEDEMA CLINICAL TRIALS: A SYSTEMATIC REVIEW

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ABSTRACT

The generalizability of findings from Clinical Trials (CTs) investigating lymphedema treatment modalities requires an accurate representation of the target population. This study aims to evaluate racial and ethnic reporting and representation in lymphedema CTs. A comprehensive systematic literature search was conducted during May 2023 using multiple databases, following the PRISMA guidelines. All CTs published from 2018 to 2023 were included. A total of 84 articles were included in this review, from which 6,546 participants were included in the analysis. Seventy-four (88.1%) articles addressed secondary lymphedema, of which 60 (81.1%) were related to breast cancer. Only 12 (13%) of CTs reported at some extend race or ethnicity. Of these, five (41.6%) reported race and two (16.6%) reported ethnicity according to FDA guidelines. White race had the highest pooled prevalence (80%; 95% CI 72-86%; I2=90%), followed by Black (7%; 95% CI 2- 15%; I2= 94.3%) and Asian (4%; 95% CI 1-8%; I2= 89.9%). In studies reporting ethnicity, participants were predominantly non-Hispanic (92.1%; 95% CI 90 - 94%). There is an underreporting and underrepresentation of racial and ethnic minorities among lymphedema CTs, limiting their generalizability. It is imperative to future development of strategies to enhance diversity in the study sample.

Keywords: Lymphedema, Ethnicity, Racial Groups, Minority Groups, Breast Cancer Lymphedema

Healthcare disparities are a shared public health crisis around the world. The impact of sociodemographic factors disproportionately affecting racial and ethnic minorities has been extensively described (1). For this reason, racial and ethnic representation in clinical trials (CTs) account for a criterion of equity in the medical practice and are a starting point for under-standing the social determinants of health (1). Despite multiple efforts from the National Institutes of Health (NIH) and Food and Drug Administration (FDA) to address this issue, underrepresentation and underreporting of minorities in CTs is an ongoing challenge in several medical fields (1-5). Most notably, of all CTs conducted in the United States (U.S.) from 2000 to 2020, only 43% reported race and ethnicity (2), Moreover, among U.S. dermatologic CTs, African Americans are the least represented racial group (6). Ignoring diversity in CTs threatens the generalizability of the studies' results. It implies not only increased health risks but also an obstacle to developing individualized treatments across

diverse populations (7).

Lymphedema is a debilitating and chronic disease (8,9). Over 250 million patients worldwide suffer from this condition, resulting in a profound health burden that greatly reduces patient's quality of life (10). To date, disparities in access to screening and treatment among racial and ethnic minorities living with lymphedema have been described, particularly regarding breast cancer-related lymphedema (BCRL) (11). Inequitable access to care is especially salient, considering Black race and Hispanic ethnicity have been identified as independent risk factors for BCRL (12). Racial and ethnic disparities in access to care are reflected in other plastic surgery specialties such as craniofacial surgery, evidenced by increased complications rate among Hispanic patients after orthognathic surgery, cleft palate repair, and craniosynostosis surgery (13-15).

To properly study the effects of lymphedema treatment amongst and between racial and ethnic groups, it is imperative to ensure adequate representativeness in CTs. In spite of this, no studies to date have assessed the representation of diversity in the study populations of lymphedema CTs worldwide. Thus, this systematic review aims to evaluate race and ethnicity representation in lymphedema CTs and to evaluate the breadth of diversity in the current literature.

METHOD

Search Strategy

A comprehensive systematic literature search was conducted on May 5, 2023, following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The electronic databases MEDLINE, Web of Science, and Cochrane were used. The search strategy included the MeSH term "Lymphedema" and was restricted by the type of publication, including "Clinical Trial" and "Randomized Controlled Trial", and by publication date, including all CTs published from 2018 to 2023. (*Fig. 1*).

Eligibility Criteria

CTs, randomized CTs, and quasi-experimental studies evaluating any treatment option for lymphedema were considered eligible for inclusion in this review. Any other trials evaluating diagnostic or preventive interventions were excluded, as well as other study designs (e.g., observational studies, protocols).

Study Selection

The search results were uploaded into the online systematic review program Covidence to conduct study selection (16). A two-stage screening process by two independent reviewers (M.J.E and J.E.F.) was conducted to identify articles that met the inclusion criteria. A third researcher (V.P.B.) helped resolved any disagreement encountered. All English-language randomized con-trolled trials and CTs were included. Articles were considered relevant to the research question if they evaluated any treatment option for lymphedema. The protocol for this systematic review was registered on PROSPERO under the identification number CRD42023424868.

Data Extraction and Outcome

Data extraction was guided by a predetermined checklist. First, we identified if the authors reported race or ethnicity. If reported, we reviewed concordance with the 2016 Food and Drug Administration (FDA) Guidance (5). In summary, the FDA recommends self-reporting of race and ethnicity using a two-question format (5). The suggested classifications of race include "American Indian or Alaska Native", "Asian", "Black or African American", "Native Hawaiian or Other Pacific Islander", and "White" (5). Similarly, "Hispanic or Latino", and "Not Hispanic or Latino" are the recommended options for ethnicity.

The following assumptions were made during the data extraction process. Regarding race, if authors did not classify all racial categories but reported the total sample size, it

was assumed that unreported racial groups were not represented in the trial. In cases where there was a discrepancy between the reported data and the total sample size, the number of non-reported participants was treated as missing data. Concerning ethnicity, if authors reported "Hispanic" or "Latino" patients, it was assumed that ethnicity was reported, even if mislabeled as race. Subsequently, if authors reported "Hispanic" or "Latino" patients without specifying a "non-Hispanic" category, it was assumed that the remaining patients, excluding Hispanic and unknown, were non-Hispanic. Finally, the reporting was categorized as mixed, mislabeled, or adequate. Mixed reporting referred to studies that reported race and ethnicity as a single category, such as "Race/Ethnicity". Mislabeled reporting included studies that labeled race as "Ethnicity" or ethnicity as "Race". Proper reporting encompassed articles that appropriately labeled the reported categories following FDA guidance (5).

We also recorded the specific type of lymphedema and interventions studied. The types of treatment were categorized as follows: surgery, medication, and other therapies. The 'other therapies' category encompassed a wide range of treatment options, including, massage, exercise, laser, kinesio taping, compression, and holistic therapies, among others. In addition, information regarding the country in which the study was conducted, journal cate-gory, journal impact factor, publication date, and the first author's name were collected.

Quality Assessment

Finally, to assess the risk of bias, we utilized Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB2). (17). This tool evaluates five domains covering all types of bias that arise from the randomization process, intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result (17).

Statistical Analysis

Categorical data regarding race were analyzed, while ethnic data were not included due to the limited number of reporting articles (less than ten). The pooled prevalence of each race category (White, African American, Asian, American Indian, Pacific Islander, Other, and Missing data) was estimated using proportion meta-analysis with Stata Software/BE (Version 18.0). The study-specific proportions with 95% exact confidence interval (CI) and effect size by Freeman-Tukey-transformed proportion were used (18-21). All CIs reported in this manuscript reflect 95% threshold. For each individual study, the effect size and weight were exposed. In addition, I2 statistics were used. Significant heterogeneity was considered if I2 >50% or P <0.05 (18-21).

RESULTS

Study Selection

A total of 1,406 articles were initially identified through database searching. After removal of duplicates, 518 articles were screened by the authors. After screening, 104 articles were sought for retrieval and 84 studies met the final inclusion criteria (*Fig. 1*).

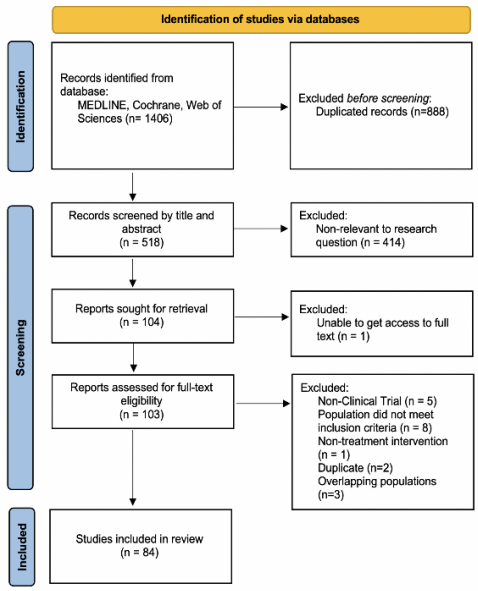

Fig. 1. PRISMA Flow diagram

TABLE 1
Studies Characteristics

	Total
N of Patients	6,546
Age (sd)	57.4 (4.9)
Patients reporting ***Race*** *n (%)*	1,807 (27,6)
White	1,353 (74.9)
Black/African American	235 (13)
Asian	110 (6.1)
American Indian/Alaska native	1 (0.1)
Pacific islander or Native Hawaiian	0 (0)
Other (nonwhite/multiple races)	92 (5.1)
Missing data	16 (5.1)
Patients reporting Ethnicity n (%)	1,218 (18,6)
Hispanic/Latino	52 (4.3)
Non-Hispanic/Latino	1122 (92.1)
Missing data	44 (3.6)
Gender n (%)	
Male	724 (11.5)
Female	5589 (88.5)
Type of intervention n (%)	
Medication	10 (11.9)
Surgery	3 (3.6)
Other therapies (massage, exercise, laser, kinesio taping, compression, and holistic therapies, among others)	71 (84.5)
Type of lymphedema n (%)	
Primary	3 (3.6)
Secondary	74 (88.1)
Both	7 (8.3)
Type of Secondary lymphedema n (%)	
Breast cancer	60 (81.1)
Other cancer	9 (12.2)
Obesity	2 (2.7)
Lymphatic filariasis	2 (2.7)
Trauma / Inflammation	1 (1.4)
Journal category n (%)	
Lymphology	18 (21.4)
Cancer	24 (28.6)
Physiotherapy	11 (13.1)
Surgery	7 (8.3)
Nutrition	3 (3.6)
Miscellaneous	21 (25)
Country n (%)	
United States	11 (13.1)
Oceania	5 (6.0)
Europe	20 (23.8)
Asia	32 (38.1)
Africa	8 (9.5)
Canada	2 (2.4)
South America	5 (6.0)
International	1 (1.2)

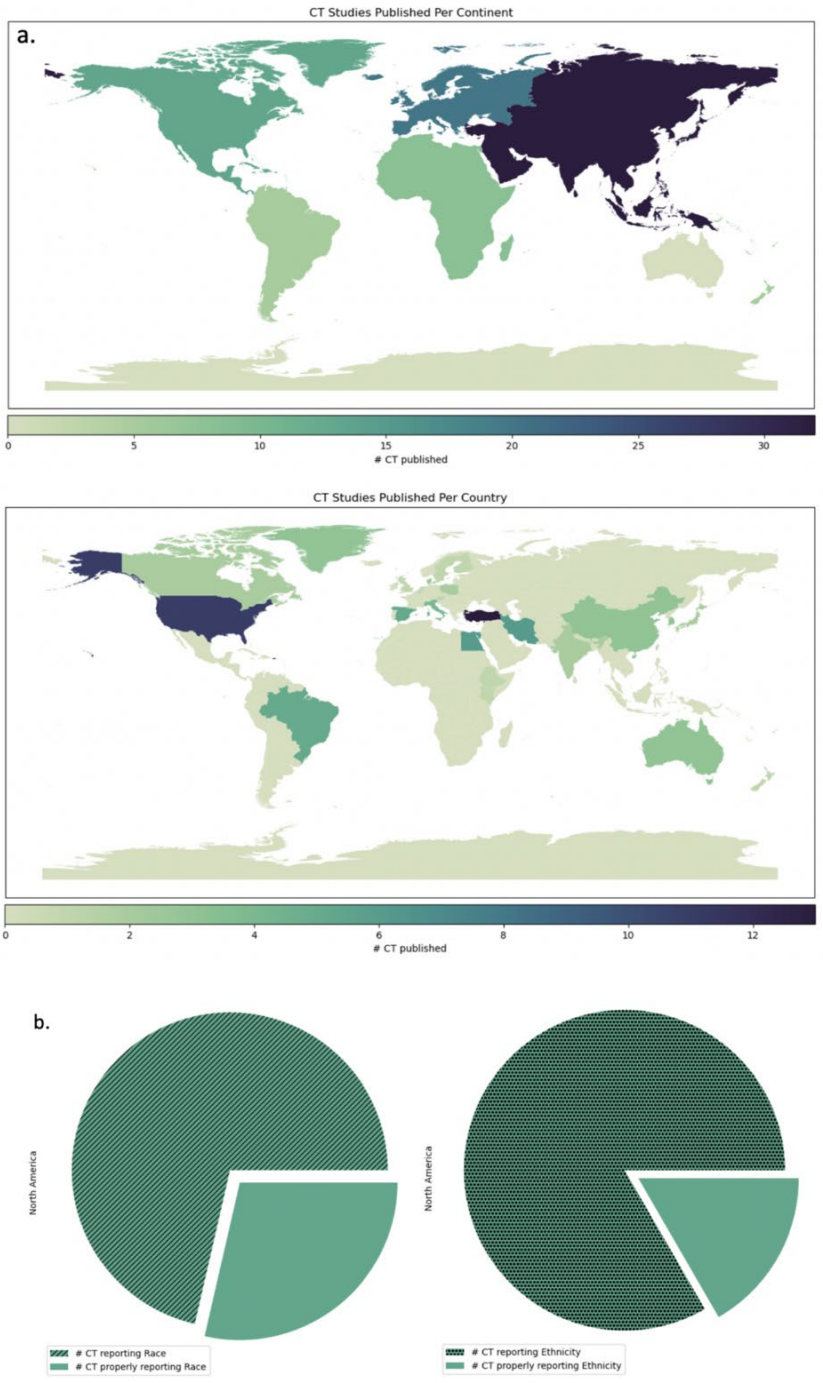

Fig. 2. (a) Heatmaps showing the number of lymphedema clinical trials published per continent and country. (b) Pie charts showing the distribution of proper race and ethnicity reporting in North America.

Study Characteristics

The characteristics and extracted data from the studies are reported in *Table 1* (8,9,22-103). A total of 6,546 participants were included in the analysis, of which 5,589 (88.5%) were females and 724 (11.5%) were males. The mean age of participants was 57.4 years old (SD 4.9 years). Geographically, 32 (38.1%) of the CTs were conducted in Asia, followed by 20 (23.8%) in Europe and 11 (13.1%) in the United States. Eight (9.5%) studies were performed in Africa, five (6%) in Oceania, five (6%) in South America, two (2.4%) in Canada, and one (1.2%) was a multi-center study taken place in multiple countries (*Fig. 2*).

Seventy-four (88.1%) articles addressed secondary lymphedema, of which 60 (81.1%) were related to breast cancer (*Table 1*). Other identified causes of lymphedema included: other types of cancer, obesity, lymphatic filariasis, and trauma. The following types of therapy were reported: other therapies (71, 84.5%), medication (10, 11.9%), and surgical procedures (3, 3.6%). Notably, the 'other therapies' category encompassed a wide range of treatment options including: massage, exercise, laser, kinesio taping, compression, and holistic therapies.

The distribution of journal categories included 24 (28.6%) articles published in cancer related journals (18; 21.4%) appeared in lymphatic journals, and 11 (13.1%) published in physiotherapy journals. Notably, surgical journals represented only 7 (8.3%) of the CTs, with 3 being nutrition focused publications. Twenty-one articles (25%) were published in journals related to miscellaneous categories. The proportion of published CTs related to the journal impact factor is reported in (*Fig. 3*).

Race Findings

Seventy-two (85.7%) analyzed studies did not report race or ethnicity. A minority of articles (12; 14.2%) provided information on race. Among these, five (41.6%) accurately reported race according to FDA guidance, four (33.3%) had mislabeled reporting, and three (25.0%) had mixed reporting (*Table 2*). (5). In terms of geographic distribution, nine (75%) CTs were completed in the U.S., while one study each was conducted in Canada (8.3%), New Zealand (8.3%), and internationally (Australia, U.S.) (8.3%). The pooled prevalence of races will be reported in the meta-analysis section.

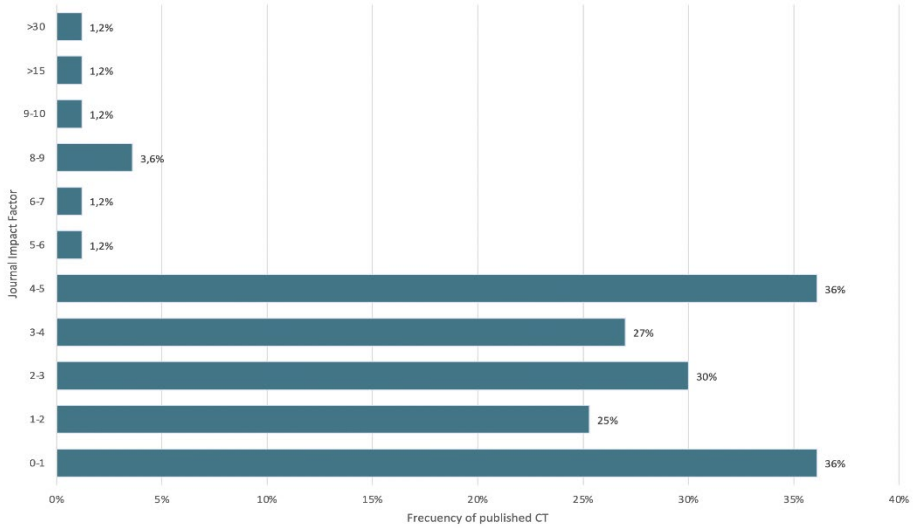

Fig. 3. Proportion of published clinical trials related to the journal impact factor.

TABLE 2
Clinical Trials Reporting Race or Ethnicity Details and Classification

Author, year	Title	Journal	Country / Region	Report Race	Report Ethnicity	Classification of Reporting[a]
Rockson SG, 2018	*Pilot studies demonstrate the potential benefits of antiinflammatory therapy in human lymphedema*	*JCI Insight*	*U.S. / West*	*Yes*	*No*	*Adequate*
Baxter GD, 2018	*Low level laser therapy for the management of breast cancer-related lymphedema: A randomized controlled feasibility study*	*Lasers Surg Med*	*New Zealand*	*Yes*	*No*	*Mislabeled*
Schmitz K, 2019	*Effect of Home-Based Exercise and Weight Loss Programs on Breast Cancer–Related Lymphedema Outcomes Among Overweight Breast Cancer Survivors: The WISER Survivor Randomized Clinical Trial*	*JAMA oncology*	*U.S. / Northeast*	*Yes*	*No*	*Mixed*
Ridner SH, 2020	*A Randomized Clinical Trial Comparing the Impact of a Web-Based Multimedia Intervention Versus an Educational Pamphlet on Patient Outcomes in Breast Cancer Survivors with Chronic Secondary Lymphedema*	*J Womens Health (Larchmt)*	*U.S. / South*	*Yes*	*Yes*	*Adequate*
Ridner SH, 2020	*Advanced pneumatic compression for treatment of lymphedema of the head and neck: a randomized wait-list controlled trial*	*Support Care Cancer*	*U.S. / South*	*Yes*	*No*	*Adequate*
Lampinen R, 2021	*Treatment of Breast Cancer-Related Lymphedema Using Negative Pressure Massage: A Pilot Randomized Controlled Trial*	*Arch Phys Med Rehabil*	*U.S. / West*	*Yes*	*Yes*	*Mixed*
Fu MR, 2021	*The Effects of Kinect-Enhanced Lymphatic Exercise Intervention on Lymphatic Pain, Swelling, and Lymph Fluid Level*	*Integr Cancer Ther*	*U.S. / Northeast*	*Yes*	*Yes*	*Mislabeled*
Deng J, 2021	*Photobiomodulation Therapy in Head and Neck Cancer-Related Lymphedema: A Pilot Feasibility Study*	*Integrative Cancer Therapies*	*U.S. / Northeast*	*Yes*	*No*	*Adequate*
McNeely ML, 2022	*Nighttime compression supports improved self-management of breast cancer-related lymphedema: A multicenter randomized controlled trial*	*Cancer*	*Canada*	*Yes*	*No*	*Mislabeled*
Ridner SH, 2022	*A Comparison of Bioimpedance Spectroscopy or Tape Measure Triggered Compression Intervention in Chronic Breast Cancer Lymphedema Prevention*	*Lymphat Res Biol*	*International (Australia, U.S.)*	*Yes*	*Yes*	*Adequate*
Rockson SG, 2022	*Safety and effectiveness of a novel nonpneumatic active compression device for treating breast cancer-related lymphedema: A multicenter randomized, crossover trial (NILE)*	*J Vasc Surg Venous Lymphat Disord*	*U.S. / West*	*Yes*	*Yes*	*Mixed*
Fu R, 2022	*A Web- and Mobile-Based Intervention for Women Treated for Breast Cancer to Manage Chronic Pain and Symptoms Related to Lymphedema: Results of a Randomized Clinical Trial*	*JMIR Cancer*	*U.S. / Northeast*	*Yes*	*Yes*	*Mislabeled*

[a]Mixed reporting refers to studies reporting race and ethnicity as a single category. Mislabeled reporting refers to studies labeling race as "Ethnicity" or ethnicity as "Race". Adequate reporting refers to articles properly labeling the reported categories following FDA guidance.

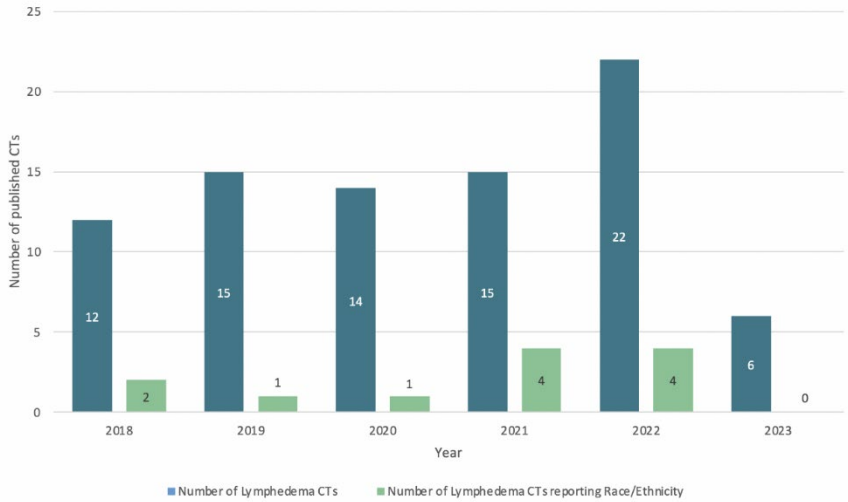

Fig. 4. Trends of lymphedema Clinical Trials publications per year and by report of race/ethnicity

Ethnicity Findings

Out of the 84 analyzed studies, six (7.1%) articles reported ethnicity. Among these, two (33.3%) were classified as mixed reporting, two (33.3%) as mislabeled reporting, and two (33.3%) as proper reporting (*Table 2*). It is worth noting that all articles reporting ethnicity also reported race. Of the six articles re-porting both race and ethnicity, five (83.3%) were conducted in the U.S., while the remaining article (16.7%) was conducted

internationally (Australia, U.S.). The pooled prevalence of ethnicity was not analyzed due to the limited number of reporting articles. However, the prevalence calculated from raw data indicated a predominantly non-Hispanic population (92.1%; CI 90 – 94%) compared to Hispanic (4.3%; CI <3.2-5.6%).

Trends of Publications per Year

Figure 4 illustrates the trends of lymphedema CTs publications per year and the frequency of racial and ethnicity reporting. Overall, there was a gradual increase in publications per year from 2018 to 2023. 2022 had the most published CTs (n=22). While minimal, there was also an observed increase in the number of reports publishing race and ethnicity, increasing from 1 in 2019 and 2020 to 4 in 2021 and 2022.

Quality Assessment

We assessed 59 CTs as being of some concern of bias, 14 CTs as being high risk of bias, and 11 CTs as being low risk of bias (See Document, Supplemental Digital Content 2). In the randomization process, some concerns of bias were encountered in 35% of CTs, while high risk was encountered in 6% of them. Fifty-five percent of the articles were evaluated to have low risk of bias in terms of deviations from intended interventions, while some concerns and high risk of bias represented 36% and 8%, respectively. Almost all CTs (92%) were evaluated as having a low risk of bias in missing outcome data, while 76% of those had low risk of bias in measurement of outcomes. Additionally, 68% of the reports were assessed to have some concerns in the selection of the reported result. See Document, Supplemental Digital Content 3 for percentage of risk of bias for each domain.

Meta-Analysis

The pooled prevalence of White race among the lymphedema CTs reporting race was 80% (95% Confidence interval [CI] 72%–86%; I2 = 90%) (*Fig. 5*). The prevalence for African Americans was 7% (CI 2%–15%; I2 = 94.3%) (*Fig. 6*), and for Asians was 4% (CI 1%–8%; I2= 89.9%) (*Fig. 7*). The prevalence of reported American Indians was 0% (CI 0%-0%; I2 = 0.0%) (*Fig. 8*) and Pacific Islanders was 0% (CI 0%–0%; I2 = 0.0%) (*Fig. 9*). Finally, the prevalence of other races (Non-White, prefer not to say, multiple races) was 4% (CI 2–7%; I2 = 71.4%) (*Fig. 10*). Missing data constituted 0% of the data (CI 0–1%; I2 = 51.8%) (*Fig. 11*).

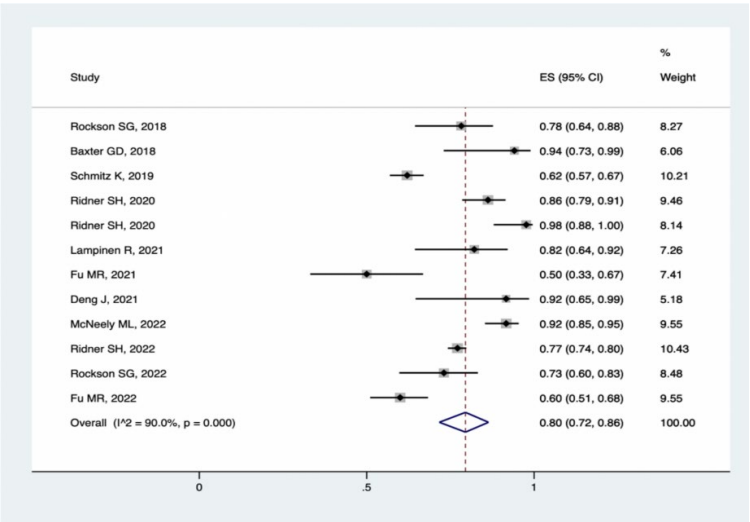

Fig. 5. Pooled prevalence of White race among the lymphedema CTs reporting race.

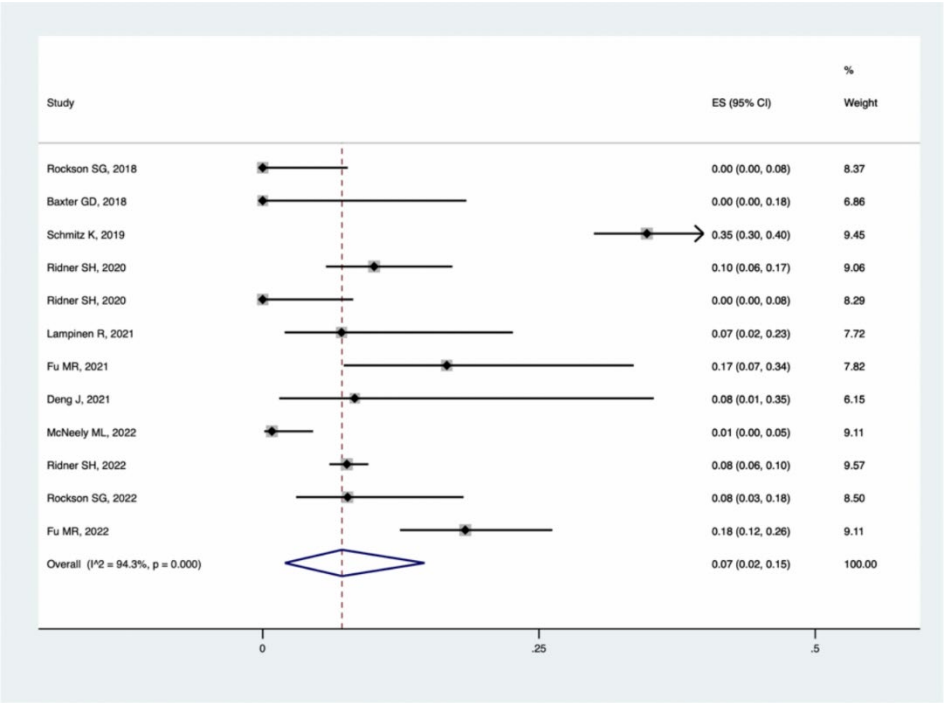

Fig. 6. Pooled prevalence of African American race among the lymphedema CTs reporting race.

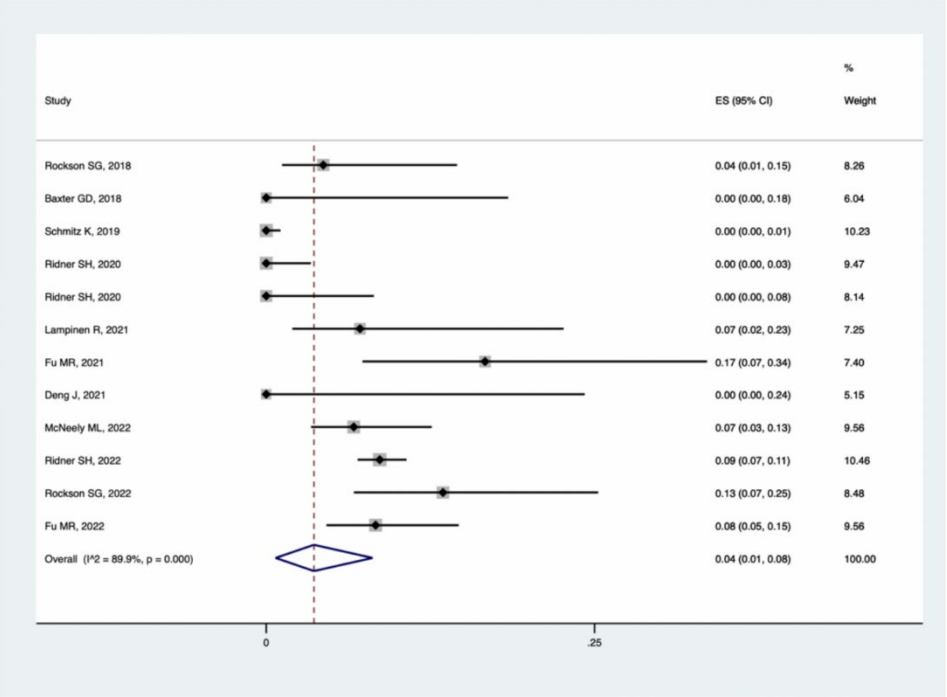

Fig. 7. Pooled prevalence of Asian race among the lymphedema CTs reporting race.

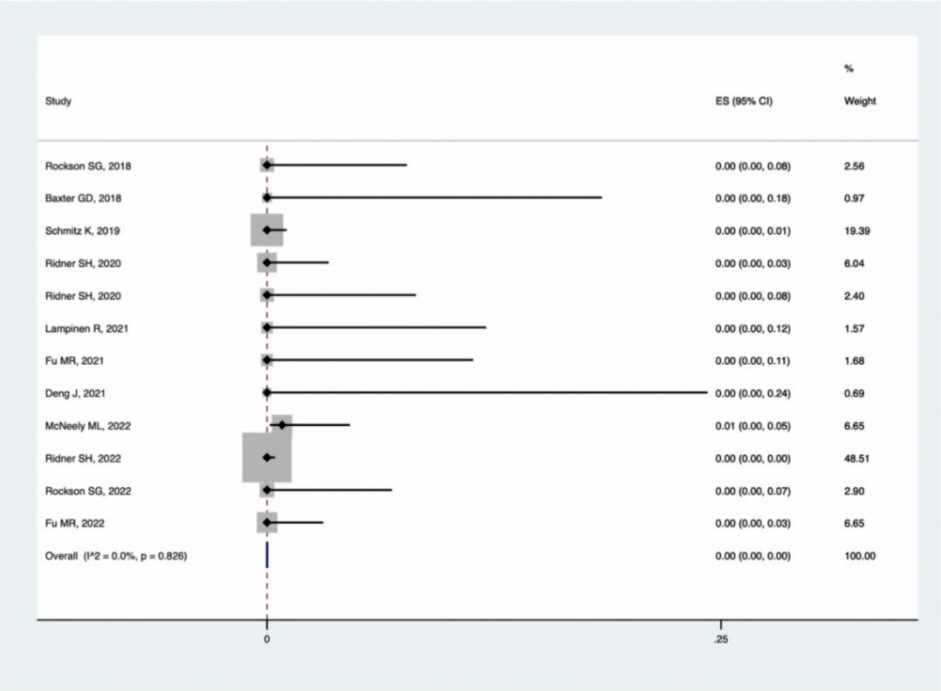

Fig. 8. Pooled prevalence of American Indian race among the lymphedema CTs reporting race.

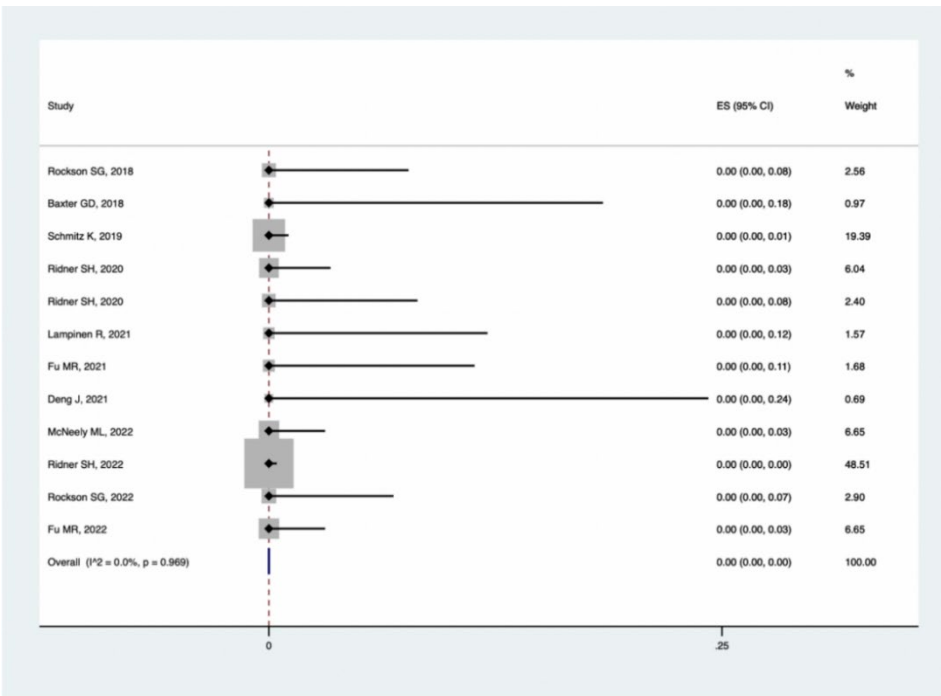

Fig. 9. Pooled prevalence of Pacific Islander race among the lymphedema CTs reporting race.

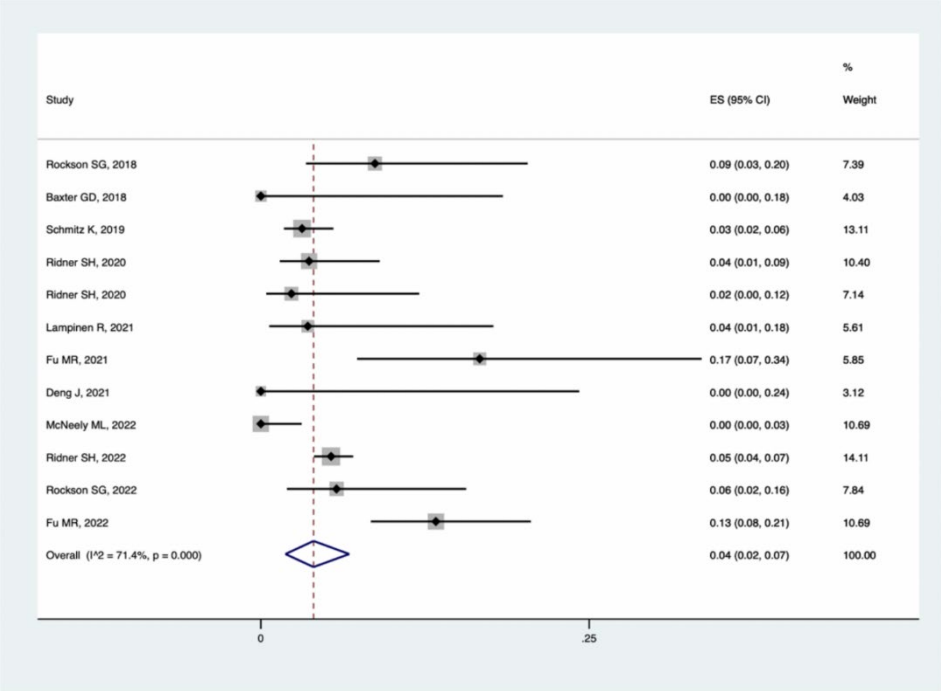

Fig. 10. Pooled prevalence of other races among the lymphedema CTs reporting race.

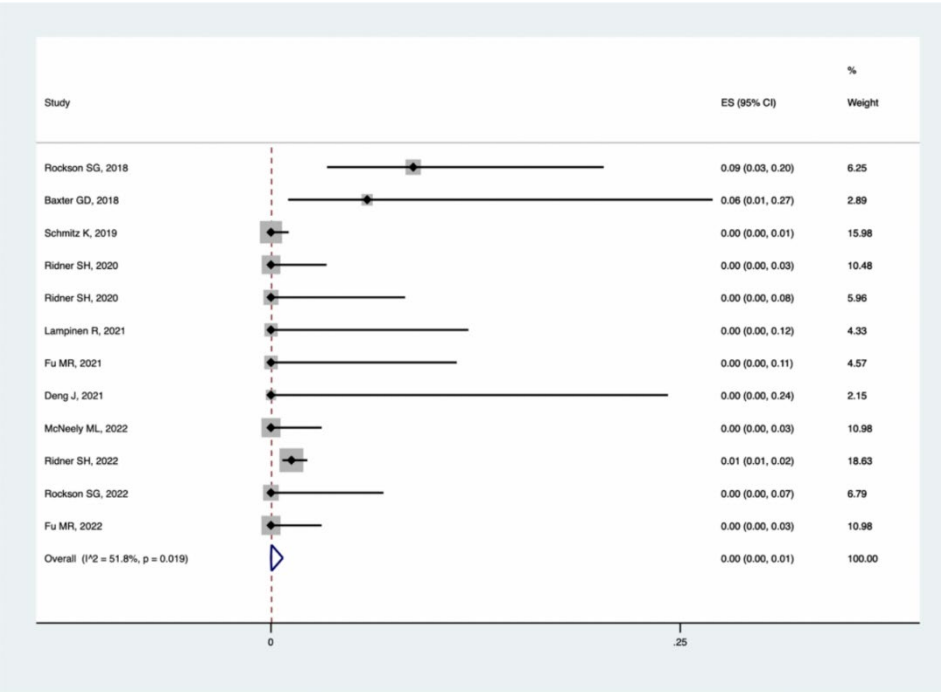

Fig. 11. Pooled prevalence of missing race data among the lymphedema CTs reporting race.

DISCUSSION

To our knowledge, our study is the first to describe race and ethnicity representation in lymphedema CTs worldwide. We found that among all CTs, only 14% of the trials reported any racial or ethnic demographic data. From these studies, only 42% properly reported race and 17% properly reported ethnicity in accordance with FDA guidance. Moreover, most of the trials were conducted in Asia and Europe. However, CTs conducted in the U.S. had the greatest rate of reporting race and ethnicity. Among the CTs, the primary focus was on secondary lymphedema and alternative therapies other than medication and surgery. CTs were most frequency published in cancer journals. Within the last five years, there has been a gradual increase in the number of CTs published, along with a slight rise in the number of CTs appropriately reporting race and ethnicity.

Among the studies that reported race/ethnicity, 75% were conducted in the U.S. When comparing the latest U.S. census data to the population reported in the U.S. CTs, there was a notable discrepancy in the representation of racial groups (104). African Americans, the second-largest racial group in the U.S., represent 13.6% of the total population, followed by Asians at 6.1% (104). However, our results showed that the pooled prevalence of Black patients was 9% and Asian patients was 3% when considering only U.S. published CTs. Similarly, a significant disparity was identified in the frequency of ethnicity reporting. While 18.9% of the U.S. population reports Hispanic/Latino ethnicity, only 4.3% of participants in the included studies belonged to this ethnicity (104). Overall, our findings suggest a significant underrepresentation of racial and ethnic minority populations in the U.S. among lymphedema CTs conducted in the U.S.

Adequate inclusion of racial and ethnic groups in CTs is considered an important metric of health equity in the medical field (1). Indeed, the goals of recruiting diverse participants to CTs can be grouped into three categories: building trust, promoting fairness, and developing knowledge (105). First, the historical legacy of Western medicine and unethical research practices has resulted in enduring negative perceptions and mistrust towards medical research among racial and ethnic minorities (105). Increasing diversity in CT participation is a necessary component of rectifying this legacy and facilitating opportunities to build trust by removing obstacles to access of medical care (105,106). Second, promoting fairness requires implementing recruitment strategies to provide equitable conditions, trial opportunities, and potential benefits regardless of the participant's background (105). Lastly, ensuring diversity in CTs serves as a tool for improving our understanding of the health-disease process and its influence, which directly contributes not only to generating new biomedical knowledge but also to generalizing the findings across populations (105).

To achieve these goals, it is necessary to understand the current state of health disparities in lymphedema. Kwan et al (2016) conducted a prospective cohort study that reported a more than two-fold risk of BCRL in Black women and non-obese Hispanic women com-pared to White women (106). While the authors also found associations of BCRL with genetic ancestry, it is plausible that this increased risk is reflective of socioeconomic inequality within the United States (107). Similarly, Ren et al (2022) studied BCRL and found a higher hazard ratio in Black women compared to women in other racial groups (108). Acebedo et al (2021) highlighted delays in medical care experienced by Hispanic women diagnosed with breast cancer (109). Reduced access to timely care may inform the increased risk of developing BCRL (109). Notably, the authors observed that the incidence of BCRL is increasing among Hispanic women (109). Recognizing the roles of race and ethnicity in these studies illuminates how different effects can be observed across racial and ethnic groups, particularly in terms of treatment access. For example, prior studies have identified a heightened cardiovascular disease risk among

the Black population, possibly linked to variations in vasodilation and vasoconstrictive responses (110). These discoveries within the cardiovascular system hint at the likelihood of similar associations in the lymphatic system. Thus, ensuring proper diversity representation in clinical trials, especially those investigating conditions with poorly understood mechanisms, is imperative (103).

Similarly, previous studies have evaluated strategies to promote fairness in the recruitment process of diverse populations (4). For instance, Sturgeon et al (2018) aimed to report challenges and strategies in the enrollment of minority patients with BCRL for the WISER Survivor trial involving lifestyle intervention (4). The challenges encountered by the authors included a lack of public awareness of the disease, underdiagnosis of BCRL, the requirement of multiple in-person attendances, and geographic and travel barriers. Through community-based strategies and hospital partnerships, the authors achieved successful recruitment of more than 35% of Black women (4). Nonetheless, the barriers to diversifying research are multifactorial, and include financial, social, cultural, linguistic obstacles (1). Of note, the WISER Survivor trial by Schmitz et al (2019) is one of the U.S. lymphedema CTs reporting race and included in our analysis. Their successful recruitment of African American participants may have influenced the crude similar proportions found when compared with the latest U.S. census (84,104). Likewise, Turner et al (2022) assessed the race and ethnicity reporting in all U.S. CTs registered in ClinicalTrials.gov (2). Their findings suggested fewer than 44% of CTs reported any racial or ethnic demographic data information and adequately represented U.S. minority groups (2). These findings further reinforce the importance of adequate representation and reporting in CTs to facilitate achieving fairness.

Multiple efforts have been made to increase racial and ethnic diversity in data collection and representation in CTs. For instance, the NIH Revitalization Act of 1993 established policies on the inclusion of women and minority groups in CTs, which were last updated in 2017 (111). The National Institute on Minority Health and Health Disparities (NIMHD), established by the NIH in 2000, focuses on reducing health disparities through ongoing strategies, funding, and educational initiatives (112,113). Similarly, in 2016, the FDA released guidelines to standardize the collection of race and ethnicity data in Cts (5). In 1998, the European Medicines Agency developed the International Conference on Harmonization Guidance (ICH-E5) (114). The ICH-E5 guideline provided a framework to address ethnic representation as a component of evaluating and extrapolating foreign clinical data (114). The presence of numerous national initiatives, which are continuously evolving, may explain why most of the studies reporting race/ethnicity were from the U.S. However, less than 50% of U.S. CTs reported racial and ethnic demographic data following the FDA Guidance. Despite growing adherence to these initiatives, underreporting and mislabeling persist within the U.S. and globally. More national and international efforts are needed to achieve greater consensus in reporting to reduce this disparity.

Greater attention and coordinated efforts are needed to standardize the recruitment, collection, and reporting of race and ethnicity. As well, sustained efforts to promote greater representation in trial participants is a necessary step toward improving health outcomes among patients, especially racial and ethnic groups disproportionately affected by social determinants of health and structural barriers to care.

Strengths and Limitations

Our study has several strengths. First, it evaluates the latest literature in lymphedema management without the restriction of country or subset of journals, which allows a larger sample size and an estimate of trends around the world. Second, the broad use of multiple databases allows for a broader inclusion of current literature worldwide. Third, it provides an extended overview of treatment modalities for primary, secondary,

and tertiary lymphedema. Most of the included CTs addressed secondary causes of the disease, particularly BCRL. This finding is consistent with literature, which identifies secondary etiology to be more prevalent than primary causes (8,9). Similarly, gender and age were accurately represented in the evaluated population, as young and middle-aged women are most commonly affected by the disease (8). Finally, a quality assessment was performed for all the included articles, which resulted in some concerns of bias for most of them.

Nonetheless, this study should be analyzed in the context of limitations. First, we only found a small number of reports with adequate race and ethnicity reporting, thus statistical analysis may be limited in power. Furthermore, a comparison between CTs across countries was intended, but was not feasible given the low number of eligible studies. Additionally, even among the studies that did report race and ethnicity, the high rates of inconsistency and mislabeling difficulted in a more accurate data analysis. Despite the authors' efforts of retrieving more information, missing data necessitated exclusion from analysis. However, the low proportion of missing information may have not significantly impacted the results, as demonstrated by our statistical analysis. Future studies are needed to pilot effective strategies not only to increase collection and reporting of race and ethnicity data in CTs, but also to recruit and maintain minority participants while conducting the study.

CONCLUSION

This study suggests a paucity of racial and ethnic reporting and representation among lymphedema CTs. As the number of CTs addressing lymphedema management continue to increase, our findings serve as a call for future studies to not only appropriately present the demographic profiles of participants, but also to develop strategies to enhance diversity in their sample. Failing to re-port pertinent sociodemo-graphic data affects the external validity of the trials and limits the generalizability of the results. Despite CTs having significant negative or positive results and impacting clinical practice, the extent to which they can be replicated in the target population remains unclear.

CONFLICT OF INTEREST AND DISCLOSURE

The authors declare no competing financial interests exist.

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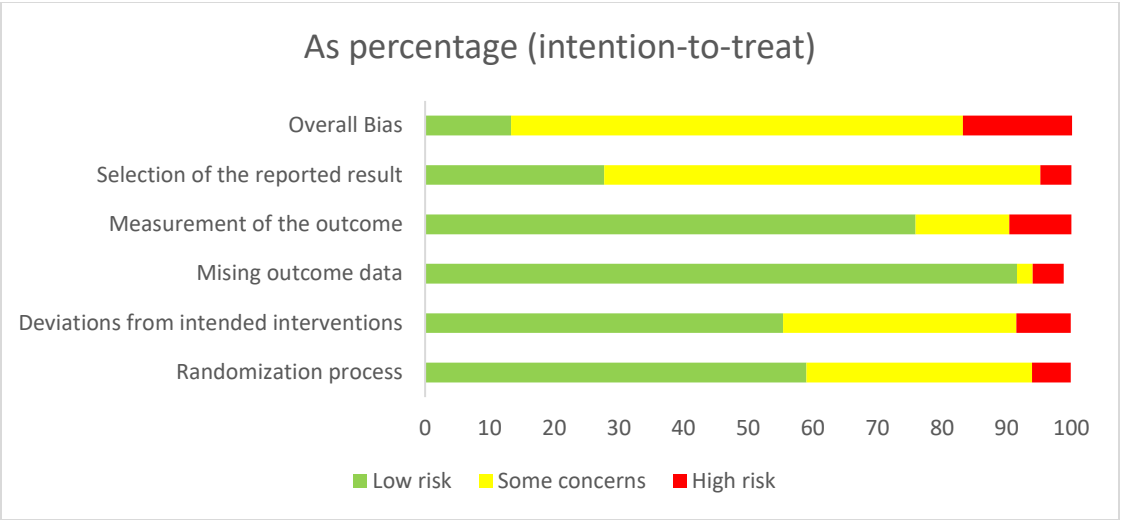

Fig: Supplemental Digital Content 2. Quality Assessment of Clinical Trials by type of bias

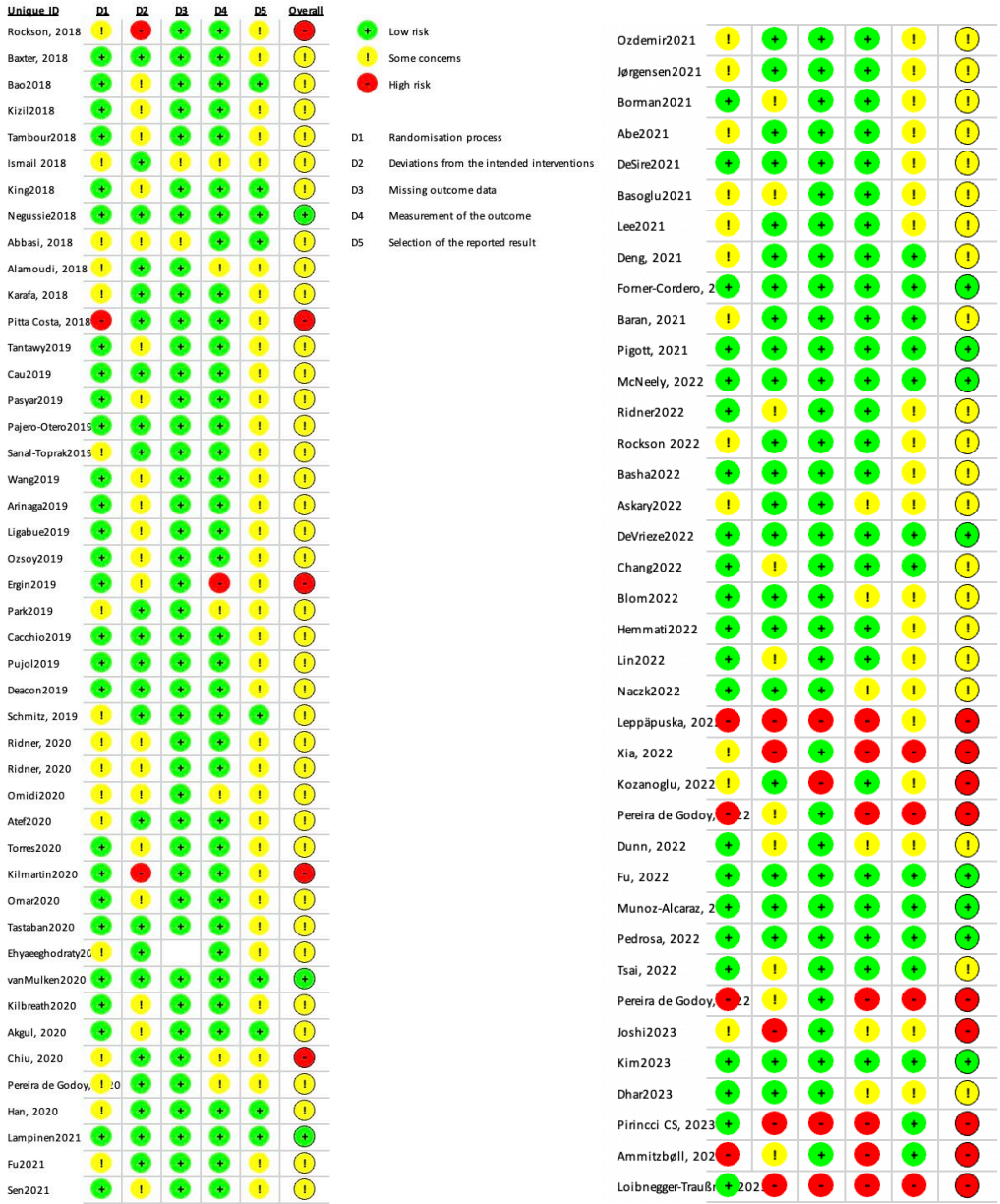

Fig: Supplemental Digital Content 3. Quality Assessment of Clinical Trials