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Review

World J Oncol. 2024;15(3):355-371

Intercontinental Comparison of Immunohistochemical Subtypes Among Individuals With Breast Cancer in South-East Asia and South America: A Scoping Systematic Review and Meta-Analysis of Observational Studies

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Abstract

Background: Breast cancer (BC) remains a significant global concern, particularly among developing countries in South-East Asia (SEA) and South America (SA). The socioeconomic burdens of oncologic care in those countries were often originated from limited accessibility on attainable therapeutic options and reliability on identifying essential information of cancer cells, i.e., immunohistochemical (IHC) subtyping to determine suitable approaches. The triple-negative breast cancer (TNBC) is among the most aggressive category in breast malignancy, therefore, requiring more specific molecular pathway blocking to exhaust the cells. However, large-scale epidemiological investigation on its rate among BC remains unavailable to date. This study aimed to describe the prevalence of TNBC in the SEA and SA continents since it may guide the future direction of oncologic research and trials.

Methods: This review focuses on observational studies from the SEA and SA continents from the last decade. Each study represents its country or cities, period of observation, population size, and the TNBC-BC rate as the main outcomes. Therefore, we may also limit the reporting bias originated from same-patient data on the specific occasions. The analysis will be derived to SEA-SA comparison, plus SEA/SA-specific session as processed in Comprehensive Meta-Analysis (CMA) version 3.0. The statistical analysis will be performed in random effects model (REM) within 95% confidence interval (CI).

Results: From 46 studies included in the final analysis with a total enlisted population of 34,346 unique individuals with BC, the TNBC rate was higher in the SEA compared to the SA region (19.3% vs. 15.7%; $P < 0.05$ in 95% CI), with the highest prevalence observed in Vietnam (22.4%) and Peru (17.8%), if it was restricted on countries with two or more studies. Interestingly, both Laos and Argentina possessed significant differences compared to other countries within their respective continents, with the highest and lowest TNBC rates ($P < 0.05$).

Conclusions: The IHC characteristics in SEA differ from those in the SA continent as mainly represented by TNBC prevalence, possibly shaping the course of future trials in the respective region based on IHC expressivity status.

Keywords: Breast cancer; Epidemiology; Immunohistochemical subtype; South America; South-East Asia

Manuscript submitted January 29, 2024, accepted April 11, 2024
Published online May 7, 2024

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doi: https://doi.org/10.14740/wjon1788

Introduction

The importance of planning a grand design for better cancer care is progressively escalating every year, whether by identifying a potential molecular target, or by developing an excellent inter-professional collaboration, involving early cancer detection initiative to prevent costly treatment sessions. The tentative nature of oncology science is considered as the premier aspect in evidence-based medicine, as more progress reported, more study presented, and more individual involved in the community. Yet, we believe that capturing the culprit of a global-level issue may be a humble and simple idea, as straightforward as describing the epidemiological data based on descriptive investigations from parts of the globe. For instance, breast cancer (BC) possessed the highest incidence rate according to the GLOBOCAN 2020 report, with 11.7% of total malignancies worldwide and accountable for > 600,000

deaths annually. It even almost reaches a quarter percentage among females, leading to the higher demand of BC-related research, hence considerate framework arrangement for global effort on cancer groundwork should be based on the specified-demand from each region [1].

The triple-negative breast cancer (TNBC) can be viewed as the exemplary situation of the necessity to develop more population-based studies on aggressive subtypes, since it is predicted that the expression rate might differ among continents [2]. Generally, it was estimated to be 15-25% of all BC, and some race or ethnicity is observed to be at higher risk for not expressing both progesterone/estrogen receptor (PR/ER) and human epidermal growth factor-2 (HER-2) on its molecular profiling [3, 4]. Those missing links predetermined the initial treatment guideline, because the classical blockable targets are absent, and it will dictate the research direction to much more complex research involving more targeted treatment or personalized medicine.

To represent the urgency, the US National Library of Medicine on the clinicaltrials.gov stated that from 812 active trials on TNBC globally, only 4.1% and 4.6% of the studies originated from the South-East Asia (SEA) and South America (SA; or Latin America); respectively, per December 1, 2023. Interestingly, the USA holds at least 60% of the total trials, followed by the Europe (28.6%) and China (23.9%) [5]. Supporting the premise, a total of 339,833,728 and 250,584,187 females in both SEA and SA according to The World Bank data in 2022 are a plethora of potential cases, compared to "roughly" 168,266,219 from USA with significantly higher trial rates [6]. Therefore, there was a relative imbalance of trials-population rate on those continents, and it will be intriguing to deliver the immunohistochemistry (IHC) status from such populated regions of SEA and SA, since it may prove the necessity to include the continents in future investigations. Both continents also share many similarities, e.g., socioeconomic status which is dominated by developing nations, overall landscape, cultural aspects, etc., which creates a suitable soil to be compared from the quantitative-epidemiological perspectives. Geographically, both continents were separated by vast Pacific Ocean or the Africa continent, located on the different side of the globe quite literally [7, 8]. Some evidence also suggested a series of genetic linkages of the populations tracked back to early human migration, though thousand years of different influence in the regions may alter the varieties profoundly [9].

For that reason, this study aimed to provide a comparison of the TNBC rate in both SEA and SA regions as a representative and triggering statistical evidence of the IHC distribution across the globe in such similar demographic natures. Therefore, it is expected to reach the responsible stakeholders on why it is also required to provide additional considerations in incorporating those populations into the upcoming TNBC trials.

Materials and Methods

Study design and protocol registration

To fulfill the main objective of this review, we designed the analysis to focus on the TNBC distribution as reported by each study based on the IHC evaluations toward histopathologically confirmed BC. We prepared the study in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) protocol and performed double literature identification phases in the SEA and SA regions to improve the searching scope. Two authors (NNF and RHNS) introduced the screening strategy to the several scientific databases, including MEDLINE, ScienceDirect, and ProQuest by Boolean term method. They included vital keywords on MeSH such as "breast cancer", "immunohistochemical", "South-East Asia" or "South America", and country-specific words (utilizing its name such as Indonesia, Brazil, Thailand, etc., in the search box based on the respective region). We anticipated to gather descriptive or cross-sectional studies at most (plus cohorts), since the base reasoning to conduct our study is rather simple yet important.

The intended publication date was limited to last decade report, which included the percentage of TNBC per total population (pooled BC population), and it is mandatory to confirm the BC subtypes based on IHC screening by credible anatomical pathology (or laboratory) facility. Registry- or laboratory-based studies will be excluded from the final analysis, considering its "data"-oriented evaluation rather than direct investigator-participant interaction. Moreover, we also exclude studies that had objectives differing from our statistical questions, e.g., restricting age-specified population, analyzing the socioeconomic impact of BC, etc. To prevent overlapping between investigations, we selected the study based on geographical identity (country, city, and centers), the observation period, and population size. From that point, studies with "smaller" population sizes during the similar time period, fewer centers included in a city/region, or even with shorter observation period, were also be excluded. The protocol of this review has been registered in PROSPERO: International Prospective Register of Systematic Reviews under issued identification (ID) of CRD42023466295 [10].

Risk-of-bias assessment and data extraction

The risk of bias will be performed in "adapted Newcastle-Ottawa Scale (NOS)" by three reviewers (NNF, RHNS, and NND) independently. This method was recently applied by Ribeiro et al in their systematic review with focus on cross-sectional studies, and we agreed to conduct the quality assessment by using the previously used tool for this issue [11]. Disagreement of each author's judgement on the quality assessment will be resolved in separate internal discussion with the first author (DH). We interpreted the NOS assessment results based on the Agency for Healthcare Research and Quality (AHRQ) standards [12].

We identify key characteristics from each study such as first author's last name, observation period, and included centers (either single- or multi-center investigations), city, country, and geographical location based on the continent (SEA or SA). The total sample size along with participants' age description will also be included as supporting demo-

graphic identifiers. However, the main data extracted from the following studies will be oriented on TNBC distribution across specific period. To limit the tentative nature of patients reporting system between regions which represented by centers, we purposely restrict the reports by center-period identification, such as ABC General Hospital, Jakarta, Indonesia (July 2013 to December 2020). Therefore, the bias originated from the inclusion of the identical patient's group should be subsequently reduced; though, it remains impractical to eliminate those questionable possibilities completely, considering the base design of our review, i.e., systematic review of observational studies.

Statistical analysis

The statistical presentation of our findings was processed in Comprehensive Meta-Analysis (CMA) version 3.0, by accessing the event rate data calculation through events-and-sample size ratio (ranging from 0.000 to 1.000) [13, 14]. We perform the analysis in three different phases by using random effects model (REM) to minimize the heterogeneity aspects, according to the respective SEA and SA region plus pooled investigation of both continents. In each continent or sub-analysis, the studies will be arranged according to its country (as the subgroup) from the highest to lowest event rate cumulatively. The mean event rate produced by each sub-group analysis will be dotted in red as presented in the forest plots. For the continent-representative TNBC rate, we will rely on the collective data provided on the pooled SEA and SA analysis rather than each continent-specific overall event rate estimation, hence the cumulative TNBC rates of either SEA or SA are presented on the pooled analysis.

The logit event rate will be provided as an additional consideration to predict the significance of difference between countries or continents, by observing the possible overlapping of lower- and upper-limit outcomes. In the event of no overlapping of the logit event rate, one may consider the difference might be statistically significant. However, we also presented the meta-regression model to demonstrate the two-sided P value estimation between the covariates (continent or countries), with the P value of < 0.05 should be considered as statistically significant. The meta-regression's models will be constructed by linking the sub-covariates; hence we can estimate each inter-country P value based on the difference to the intercept covariate. This statistical presentation is aimed to furtherly enrich the perspective in assessing our review as a whole, albeit its main objective of issuing a descriptive meta-analysis of TNBC rate across SEA and SA continents.

Results

A total of 46 observational studies from both continents were included in the final analysis, with 28 investigations originating from the SEA region. Those studies encompassed 13,907 and 20,439 BC patients from SEA and SA regions, respectively; the total population of 34,346 individuals had been diagnostically validated through careful workup strategy plus mandatory IHC evaluations based on each center's standard. The literatures selection process is depicted on Figure 1 in PRISMA flow diagram, adapted to our review's specific *modus operandi*. The risk of bias and quality assessment of the included literatures were outlined here (Supplementary Material 1, www.wjon.org).

Based on the demographic characteristics (Table 1) [15-60], most of the studies from SEA and SA were based on Indonesia (2,788 patients) and Brazil (9,473 patients), respectively; though, Thailand holds the highest population number in SEA (6,685 patients). The SEA's report included 20 cities (24 centers plus three smaller regions comprised of unmentioned number of hospitals); whereas the SA consisted of five nation scale reports covering unmentioned number of centers, and 13 province/cities with at least 13 different centers plus several private referral center for cancer care in a region (Table 1). The mean or median age of the populations are comparable in the fifth to sixth decade of life, albeit earlier diagnosis age is observable in SEA, with higher number of studies with the mean or median age < 50 years old.

Our collective analysis on both continents demonstrated that the overall TNBC rate is higher in SEA (19.3% (17.3-21.4%)), compared to the SA (15.7% (14.1-17.5%), with the cumulative assessment on the continents having 17.4% (16.1-18.8%) as the even rate, though it seems that the difference between those regions is not statistically significant (Fig. 2). Interestingly, several studies in the SEA region even recorded $> 25.0\%$ TNBC rate, conversely on the SA with all of the event rate estimations falling $< 25.0\%$ mark. The meta-regression model estimated the two-sided P value between the continents of 0.0085 (< 0.05), hence the difference between the regions is statistically significant.

SEA analysis

The SEA-specific analysis is generally portrayed on the Figure 3a, revealing that Laos might possess the highest rate of TNBC (38.2% (28.0-49.5%)), yet it was reported by only one single study by Luangxay et al [30], in 2019, with only 76 individuals. It was followed by Vietnam and Myanmar with the reported TNBC rate of 22.4% (19.5-25.5%; 738 individuals), and 20.9% (13.7-30.4%; 91 individuals), respectively. Thailand placed next with 19.6% (16.2-23.4%), followed by Indonesia with 17.8% (14.4-21.9%), both supported by high number of patients (2,788 and 6,685 individuals, respectively). Malaysia holds the lowest number of TNBC rate, with 16.3% (11.4-22.8%) estimation followed by a considerable sample size (3,539 individuals). However, the authors failed to identify eligible reports from five countries, i.e., Brunei, Cambodia, East Timor, Philippines, and Singapore, which might be originated from limited investigations from the countries, or it does not meet our applied criterion.

The meta-regression of logit event rate from the SEA-based data is also presented in Figure 3b. As no overlapping of the event rates was present as proven by its lower- and upper-limit estimation, the difference of the countries' TNBC rate

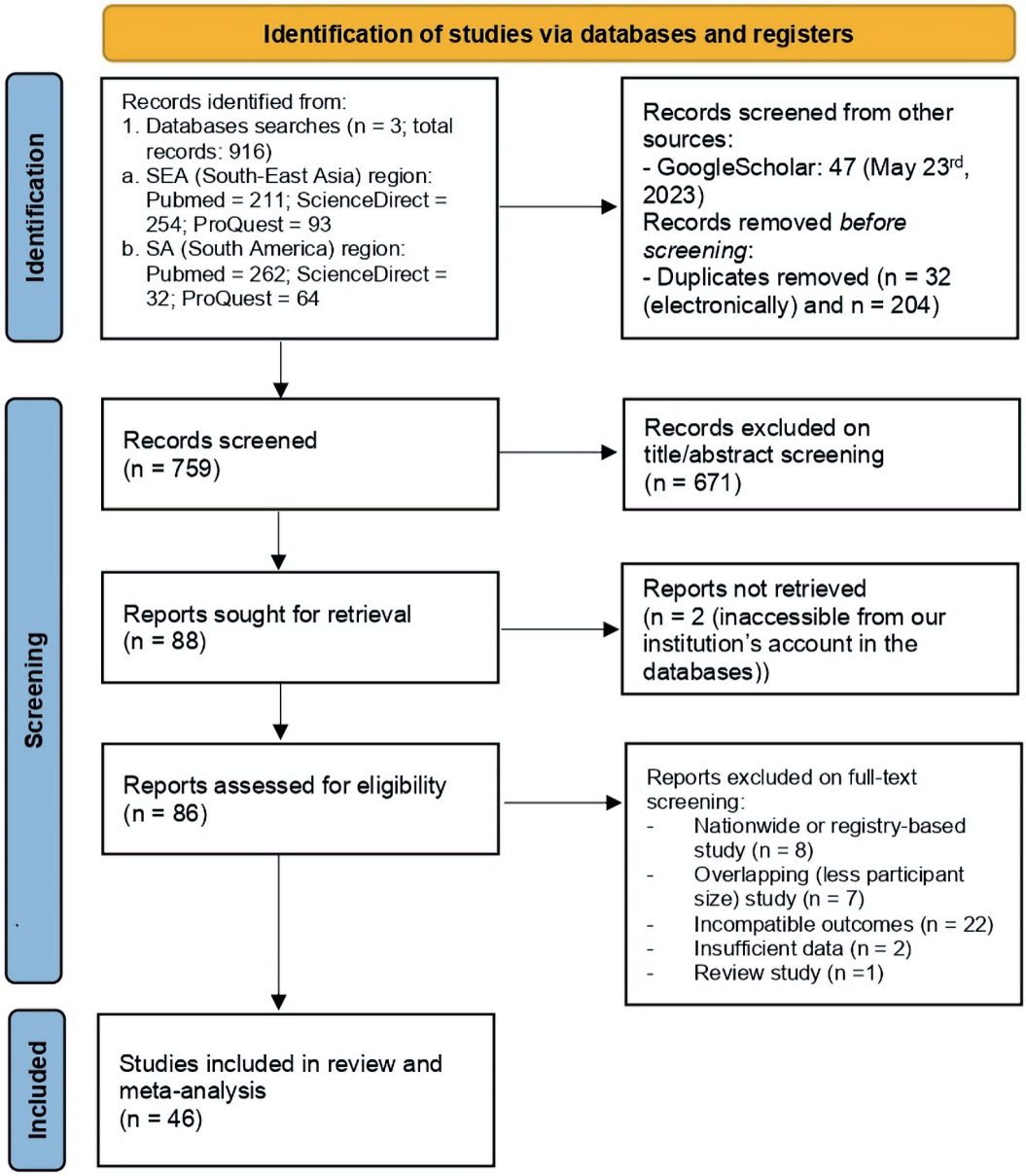

Figure 1. Study identification phases of this review in PRISMA flow diagram. PRISMA: the Preferred Reporting Items for Systematic Review and Meta-Analysis; SEA: South-East Asia; SA: South America.

was initially considered insignificant (predicted $P > 0.05$ for inter-country difference). However, we observed that there are several significant differences between countries such as Indonesia and Laos ($P = 0.015$), Malaysia and Laos ($P = 0.015$), and Thailand and Laos ($P = 0.032$). Other comparisons were not described further in this section as we estimated the P value to be > 0.05. It should be cautiously noted that Laos only possesses 76 BC samples in this study, remarkably lower than the other SEA countries, hence it might introduce some degree of biases. We suggest interpreting the outcomes carefully, considering that the observed significance within Laos may originated from its lack of samples; whilst sub-analysis to other SEA countries with larger sample size remains statistically acceptable.

SA analysis

Our analysis on the SA-specific analysis (Fig. 4a) demonstrated that Ecuador holds the highest TNBC rate of 20.1% (17.8-24.4%), though it only had one single study comprising 268 individuals. It was followed by Peru with 17.8% (15.1-20.9%) from 3,089 BC patients, Colombia with 16.7% (9.0-28.9%) from 607 BC patients, and Chile with 15.9% (9.1-26.3%)

Table 1. Geographical and Baseline Characteristics of the Included Studies

Study	Country	City	Observation period	Center	Sample size	Age (years)	NOS score	Continent
Arnetha et al, 2020 [15]	Indonesia	Bandung	January 2011 - September 2011	Hasan Sadikin GH	63	48.79 (mean)	8	SEA
Azhar et al, 2020 [16]			2014 - 2018		913	42.4 ± 18.6	7	
Juristiasa et al, 2022 [17]		Denpasar	January 2015 - June 2020	Sanglah GH	100	52.36 ± 1.21	7	
Felicia et al, 2022 [18]		Jakarta	January 2015 - December 2020	Dr. Cipto Mangunkusumo NH				
Gondhowiardjo et al, 2020 [19]			2001 - 2010		933	33.7% 41 - 50	8	
Gultom et al, 2021 [20]			September 2019	Siloam Semanggi H	208	34.1% 50 - 59	6	
Madyaningtias, 2021 [21]		Makassar	July 2014 - June 2017	Tertiary hospitals	365	38.1% 41 - 50	5	
Wijayanto et al, 2022 [22]			2016 - 2019	Dr. W. Sudirohusodo GH	172	31.4% 50 - 59	7	
Furqan et al, 2020 [23]		Medan	2016 - 2018	Haji Adam Malik GH	131	46.41 ± 9.90	5	
Arza et al, 2022 [24]		Padang	2020 - 2022	Dr. M. Djamil GH	68	91.2% > 40	5	
Dasman et al, 2021 [25]			2017 - 2018	Dr. M. Djamil GH, YARSI H, and Ropanasuri SH	418	54.1% > 50	6	
Paramita et al, 2019 [26]		Samarinda	January 2016 - December 2016	A.W. Sjahranie GH	92	48.3 ± 10.7	5	
Anwar et al, 2019 [27]		Yogyakarta	2012 - 2017	Dr. Sardjito GH	144	37 (median)	7	
Fathoni et al, 2022 [28]			July 2018 June 2019		162	52.57 ± 9.35	8	
Widodo et al, 2014 [29]			2008 - 2009		84	53.15 ± 10.89	6	
Luangxay et al, 2019 [30]	Laos	Vientiane	2013 - 2016	University of Health Science	76	49.1 ± 10.9	6	
Sung et al, 2020 [31]	Malaysia	Sarawak	2003 - 2015	Sarawak GH	2,994	51.6 ± 11.1	7	
Abdullah et al, 2016 [32]		Subang Jaya	2008 - 2012	Subang Jaya MC	675	53.0 ± 11.0	8	
San et al, 2017 [33]	Myanmar	Myeik and Yangon	January 2015 - December 2015	Myeik and Sakura	91	51.3 (mean)	6	
Chuangsuwanich et al, 2014 [34]	Thailand	Bangkok	2002 - 2004	Siriraj H	100	51 (mean)	8	
Laohanvinij et al, 2017 [35]			January 2015 - December 2013	Rajavithi H	232	51.5 (28 - 88)	7	
Ditsatham et al, 2022 [36]		Chiang Mai	January 2006 - December 2015	Chiang Mai UTH	3,153	64.5% 40 - 60	8	
Sripan et al, 2019 [37]			2004 - 2013	Maharaj Nakorn Chiang Mai H	3,228	45 (52 - 60)	8	
Kongsiang et al, 2014 [38]		Khon Kaen	January 1999 - May 2009	Srinagarind H	272	44.9 ± 55.1	7	
Sukpan et al, 2023 [39]		Narathiwat	June 2016 - May 2021	Naradhiwas Rajanagarindra H	234	52.6 ± 12.0	8	
Tubtimhin et al, 2018 [40]		Ubon Ratchthani	January 2022 - December 2016	Ubon Ratchathani CH	523	49.6 ± 9.8	8	
Nguyen et al, 2019 [41]	Vietnam	Hanoi	2011 - 2013	National CH	501	50 (median)	8	

Table 1. Geographical and Baseline Characteristics of the Included Studies - (*continued*)

Study	Country	City	Observation period	Center	Sample size	Age (years)	NOS score	Continent
Cong et al, 2020 [42]		Hue	June 2016 - August 2018	Hue UTH	237	54.7 ± 12.66	9	
Path et al, 2016 [43]	Argentina	Whole Argentina	January 2012 - December 2013	Multicenter	1,732	59 (23 - 92)	9	SA
Goncalves, 2018 [44]	Brazil	Juiz de Fora	2003 - 2005	Private Referral Center for Cancer Care	447	57.0 ± 13.0	9	
Fayer et al, 2016 [45]			January 2000 - December 2018	UNACON	195	57.8 (mean)	8	
Reis et al, 2020 [46]		Maranhao	January 2015 - December 2018		137	52.1 ± 11.8	9	
Freitas et al, 2022 [47]		Minas Gerais	2014 - 2016	Oncology Referral Center	430	42 (low-risk) and 63 (high-risk)	8	
Macedo Andrade et al, 2014 [48]		Paraiba	March 2013 - November 2013	Fundação de Assistência da Paraíba PH	269	55.4 ± 0.8	7	
Jeronimo et al, 2017 [49]		Paraiba and Joao	2013 - 2016	Fundação de Assistência	236	55.1 ± 12.3	9	
				da Paraíba PH and Hospital Napoleao Laureano				
Simon et al, 2019 [50]		Whole Brazil	2001 - 2006	28 Brazilian Institutions	2,296	54.0 (mean)	6	
Carvalho et al, 2014 [51]			July 2009 - March 2011	Consultoria em Patologia	5,687	55.5 ± 13.5	7	
Acevedo et al, 2020 [52]	Chile	Santiago	January 2009 - December 2019	Servicio de Salud Metropolitano Suroriente	439	51.7 (23 - 79)	7	
Merino et al, 2018 [53]			1997 - 2006	Pontificia Universidad Catolica de Chile and Red de Salud UC Christus	2,198	55 (19 - 101)	6	
Gomez et al, 2015 [54]	Colombia	Bogota	January 2009 - December 2011	Instituto de Cancerologia-Clinicas Las Americas	328	52.9 ± 11.3	7	
Serrano-Gomez et al, 2016 [55]		Bogota and Bolicar	2008 - 2012	Colombian National Cancer Institute and Hospital Universitario del Caribe	301	56.6 (mean)	8	
Aldaz-Roldan et al, 2023 [56]	Ecuador	Loja	2009 - 2019	SOLCA Nucleo de Loja	268	54.6 (mean)	6	
Bueno et al, 2017 [57]	Peru	Arequipa	January 2009 - December 2012	Hospital Nacional Carlos Alberto Seguín Escobedo	280	56 (27 - 91)		
Galvez et al, 2018 [58]		Surquillo	2003 - 2014	Instituto Nacional de Enfermedades Neoplasicas	435	49 (24 - 84)	6	
Zavala et al, 2023 [59]		Whole Peru	2010 - 2022	PEGEN-BC	1943	49.8 ± 11.0	9	
Yabar et al, 2017 [60]	Peru and Uruguay	Lima and Montevidio	2012 - 2013	Hospital Nacional Edgardo Rebagliatti Martins, Hospital Nacional Guillermo Almenara Irigoyen, Hospital Nacional Alberto Sabogal, Instituto Nacional de Cancer	580	58 (27 - 90)	7	

H: hospital; GH: general hospital; MC: medical center; NH: national hospital; PEGEN-BC: The Peruvian Genetics and Genomics of Breast Cancer Study; PH: public hospital; SH: state hospital; UNACON: Unidades de Alta Complexidade em Oncologia (High Complexity Care Units in Oncology); UTH: university hospital; NOS: Newcastle-Ottawa Scale; SEA: South-East Asia; SA: South America.

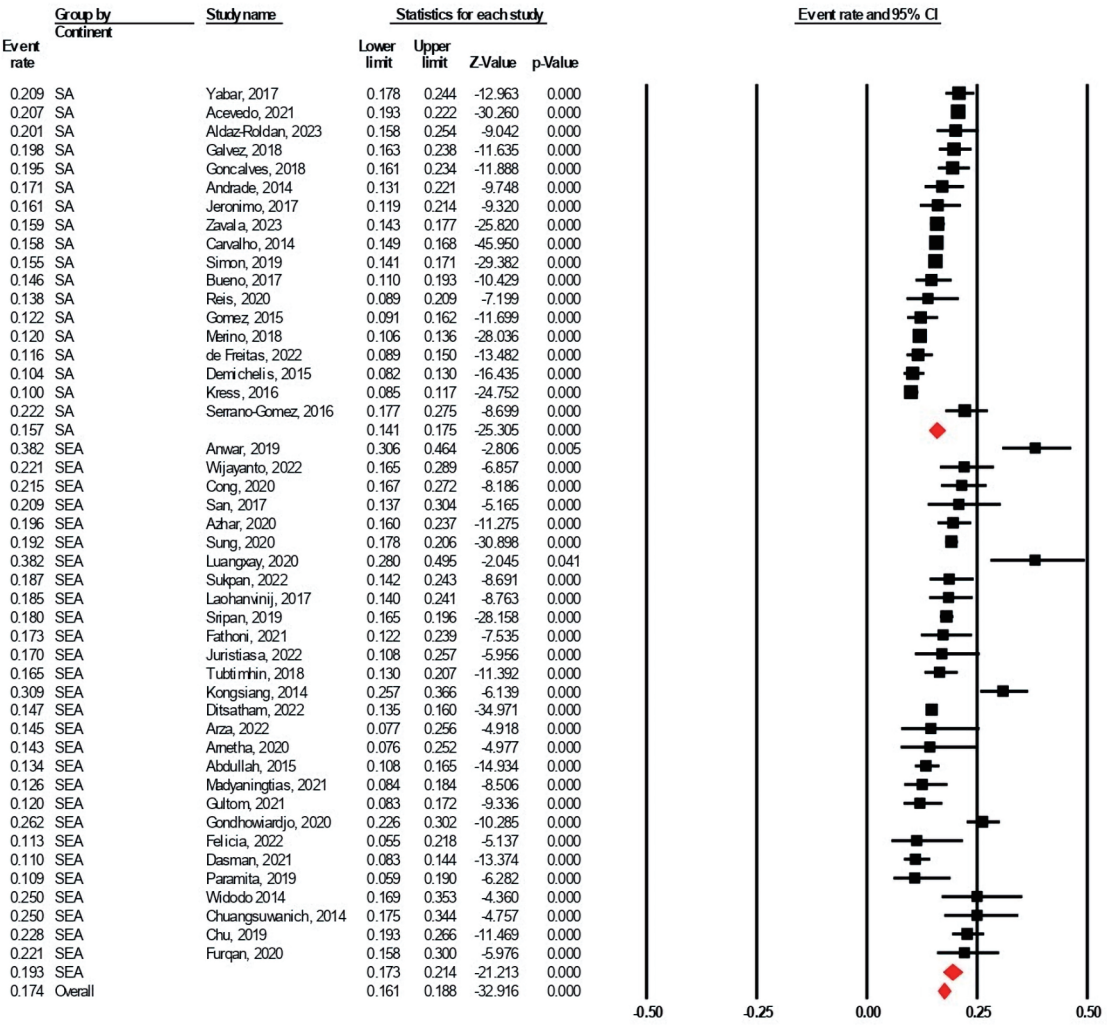

Figure 2. The TNBC subtype rate comparison in the SEA and the SA. The black squares and red diamond represent individual studies (countries) and continents, respectively, whereas the X-axis represented the TNBC rate per total BC population (0.00 to 1.00 for 0% to 100%). SEA: South-East Asia; SA: South America; CI: confidence interval; TNBC: triple-negative breast cancer; BC: breast cancer.

from 4,967 BC patients. Brazil with the highest patients count (9,473 individuals) reported TNBC rate of 15.8% (14.5-17.2%), which was estimated from seven different studies in several cities or regions in the country. Interestingly, there is a significant jump in Argentina's TNBC rate, as it was estimated to be the lowest in SA with only 10.1% (8.9-11.5%).

The forest plot of the SA-specific analysis disclosed that initially, the overlapping of the event rates was observed only in Argentina's TNBC rate lower- and upper-limit when it was compared to other SA countries (predicted $P < 0.05$ for analysis related to Argentina). This prediction was proven by analyzing the meta-regression model's construction (Fig. 4b), which demonstrated several significant findings related to Argentina, i.e., to Brazil ($P = 0.022$), to Chile ($P = 0.043$), to Colombia ($P = 0.035$), to Ecuador ($P = 0.019$), and to Peru ($P = 0.005$). Only Argentina possessed significant differences compared to other SA countries, as no other inter-SA country comparison demonstrated the P value of < 0.05, representing its observably lower TNBC rate among others.

Discussion

The basic principle of this review is to provide a generalized and wide-scoping meta-analysis on the TNBC distribution in both SEA and SA continents, hence we may capture the true epidemiological scale of the subtypes, and why it is necessary to extend the trials to the regions. We focused on the TNBC rate per total BC diagnosis, hence it is possible to estimate "how common a center may encounter those aggressive types in practice" statistically. Our work may also be able to be transcribed toward other issues in oncologic science, either by simply describing the histopathology-epidemiology characteristics of breast malignancy in the regions, or by any chance in-

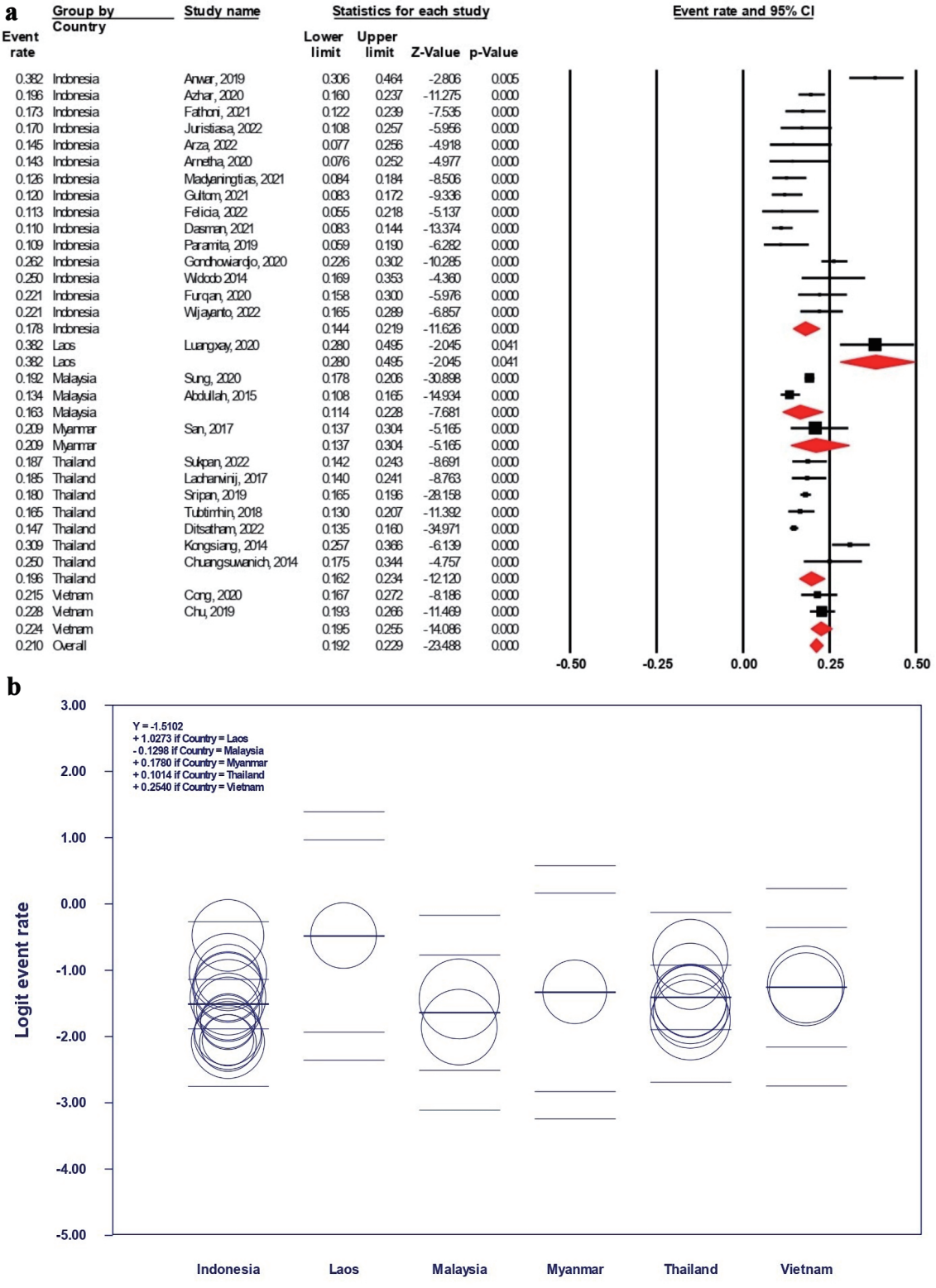

Figure 3. (a) The TNBC subtype rate estimation in SEA countries. (b) Scatterplot representation of logit event rate regression model among SEA countries. (a) The black squares and red diamonds represent individual studies (countries) and continents, respectively, whereas the X-axis represented the TNBC rate per total BC population (0.00 to 1.00 for 0% to 100%). (b) Each circle represents an individual study, whereas the thick line on the middle of each country section represents the estimated logit event rate. SEA: South-East Asia; CI: confidence interval; TNBC: triple-negative breast cancer; BC: breast cancer.

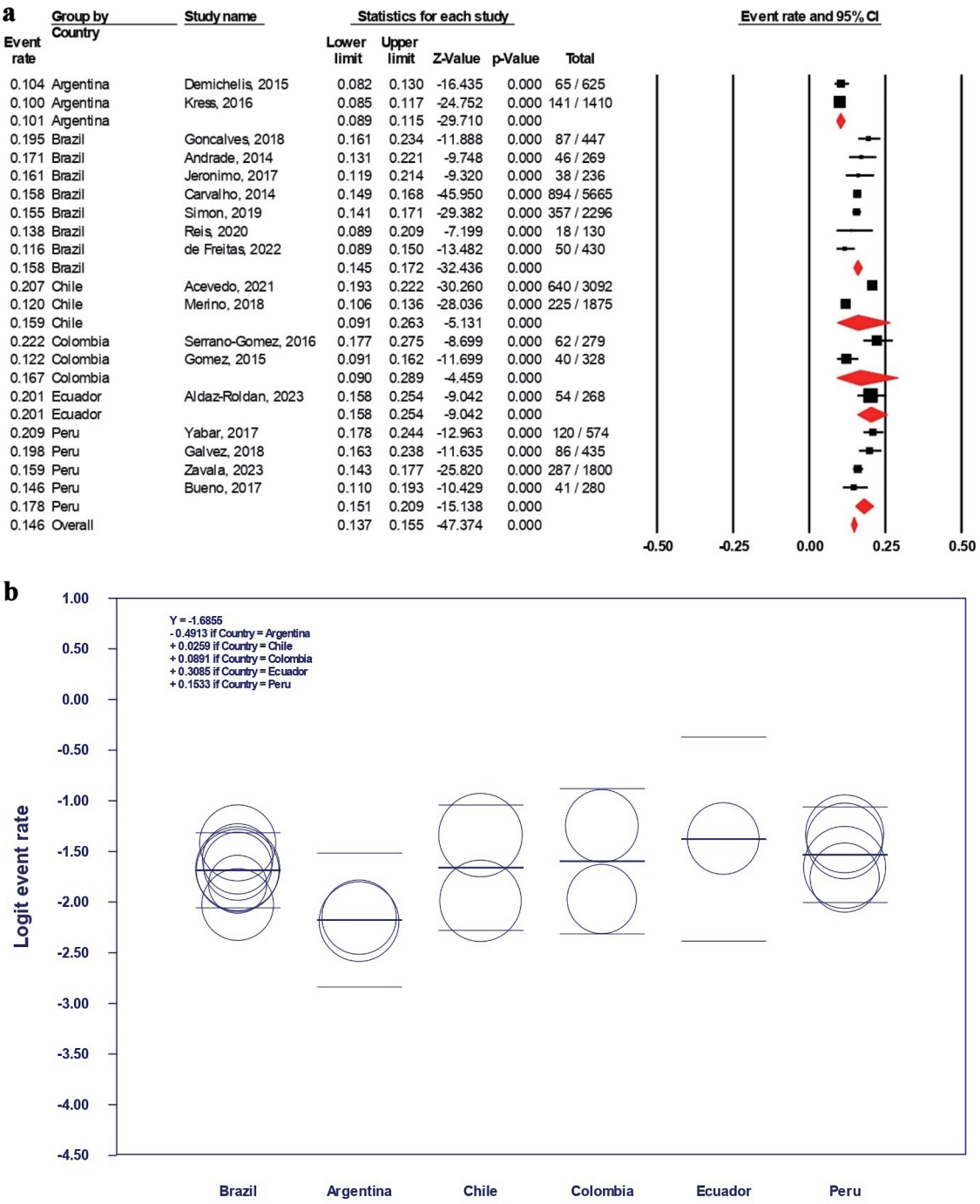

Figure 4. (a) The TNBC subtype rate estimation in SA countries. (b) Scatterplot representation of logit event rate regression model among SA countries. (a) The black squares and red diamonds represent individual studies (countries) and continents, respectively, whereas the X-axis represents the TNBC rate per total BC population (0.00 to 1.00 for 0% to 100%). (b) Each circle represents an individual study, whereas the thick line on the middle of each country section represents the estimated logit event rate. SA: South America; TNBC: triple-negative breast cancer; CI: confidence interval; BC: breast cancer.

fluencing the maneuver of healthcare provider in each country plus large pharmaceutical companies. To exemplify the benefit of this study in issuing the imbalance of trial-patient rate, the US National Library of Medicine only recorded a single-active trial of TNBC in Indonesia; though Indonesia is placing the fourth in total population (2023 report by the Worldometer, 49.7% is female; approximately ± 135 million individuals) [6, 61]. We also estimated that 17.8% of the BC diagnosis in Indonesia is triple-negative on IHC [12-26]. Supported by the GLOBOCAN 2020 country-specific report, at least there was

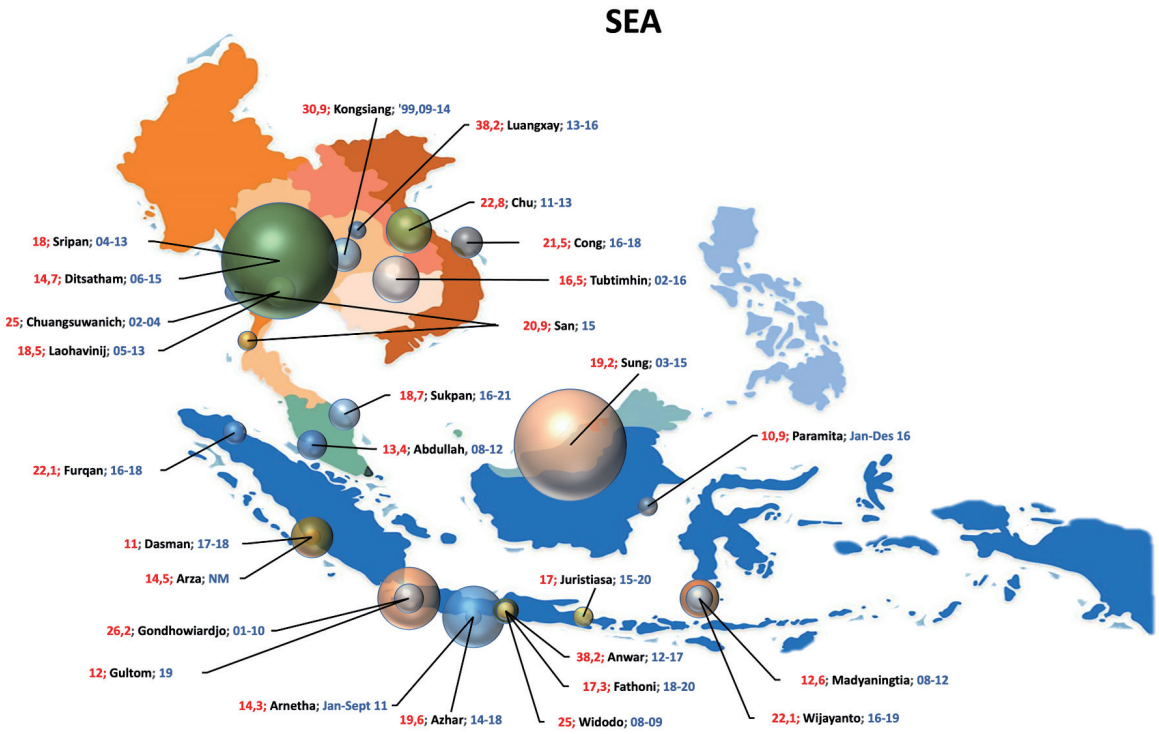

Figure 5. Schematic representation of the TNBC percentage and population size in SEA region. The numbers in red and blue represent TNBC percentage and year of observation (for example, "19.6; Azhar; 14-18" may stands for a study by Azhar et al, with TNBC rate of 19.6% and observation year of 2014 - 2018); respectively. TNBC: triple-negative breast cancer; SEA: South-East Asia.

65,858 total BC cases (in which 11,000 - 12,000 of the patients are estimated to be TNBC on testing) [1]. We attempted to depict our findings in schematics (Figs. 5, 6), representing SEA and SA, respectively, therefore it will be much easier to identify the TNBC rate based on each report (denoted by the first author's last name, sample size by each circle, and investigations' period and location by city as pointed on the maps).

Our estimation in both continents basically remains in line with the general prediction on the TNBC rate, which falls within the range of 15-25% [3, 4]. However, compared to other high-frequent trials countries (e.g., USA with 12% rate) which may be varied among reports (Dietze et al also estimated that the values among European-American vs. African American were 16% and 30%, respectively), the TNBC rate in our analyzed continents is proportional to global estimate [62, 63]. Though the European-based estimation of TNBC rate is not available at the moment, the close linkage between Europe and USA in term of the majority population should be considered, since ± 60% of the population was identified as European ancestry (or Caucasian) [64]. However, population with African ancestry was considered to possess higher risk of developing TNBC, which eventually worsened its prognostic. It is also believed that the TNBC rate may even reach > 40.0% limit in parts of Africa, underlining its common ground in genetics and raising the awareness to conduct region-based investigations [65, 66]. The genetic susceptibility of the Black population also shares the same idea to determine whether the collective ethnic groups in SEA (which mainly consisted of Austro-Asiatic, Austronesian, Negrito, etc.), or SA (which is often considered to be a mixture of individuals from multi-ethnic roots) may offer similar phenomenon occurred among the African descents [67, 68].

Nevertheless, considering the current global community demonstrating high societal diversity, the ethnic status was often overlooked as group-based studies, which eventually produce less satisfactions due to plurality of the subjects' ethnic roots. In other hand, populations in either SEA or SA are plural by nature, hence attempt to homogenizing the individuals should be exempted. Consequently, confirming the genetic vulnerability should never be performed solely through ethnic identification, as it is recommended to conduct a genome-wide association analysis on specific loci (although we never fully contradict the role of ethnic roots on its association) [69, 70]. The modern medicine might need to reconsider the functionality of race and ethnicity in representing genetics due to their basic nature as a social construct, which is conceptually different with gene as a basic unit of heredity. The gene transfers the trait of an individual, often recognized as ethic characteristics in a population-scale judgment (or phenotype), whilst gene truthfully manifested the genotype aspect as well [71]. Interpreting our studies based on the modern point-of-view of population under a flag should be preferred, though the limitation in utilizing the data from this review is basically absent. It might as well represent the non-modifiable risk factors from each country, as it is also widely accepted that the interacting environmental factors play immense role in cancers' pathogen-

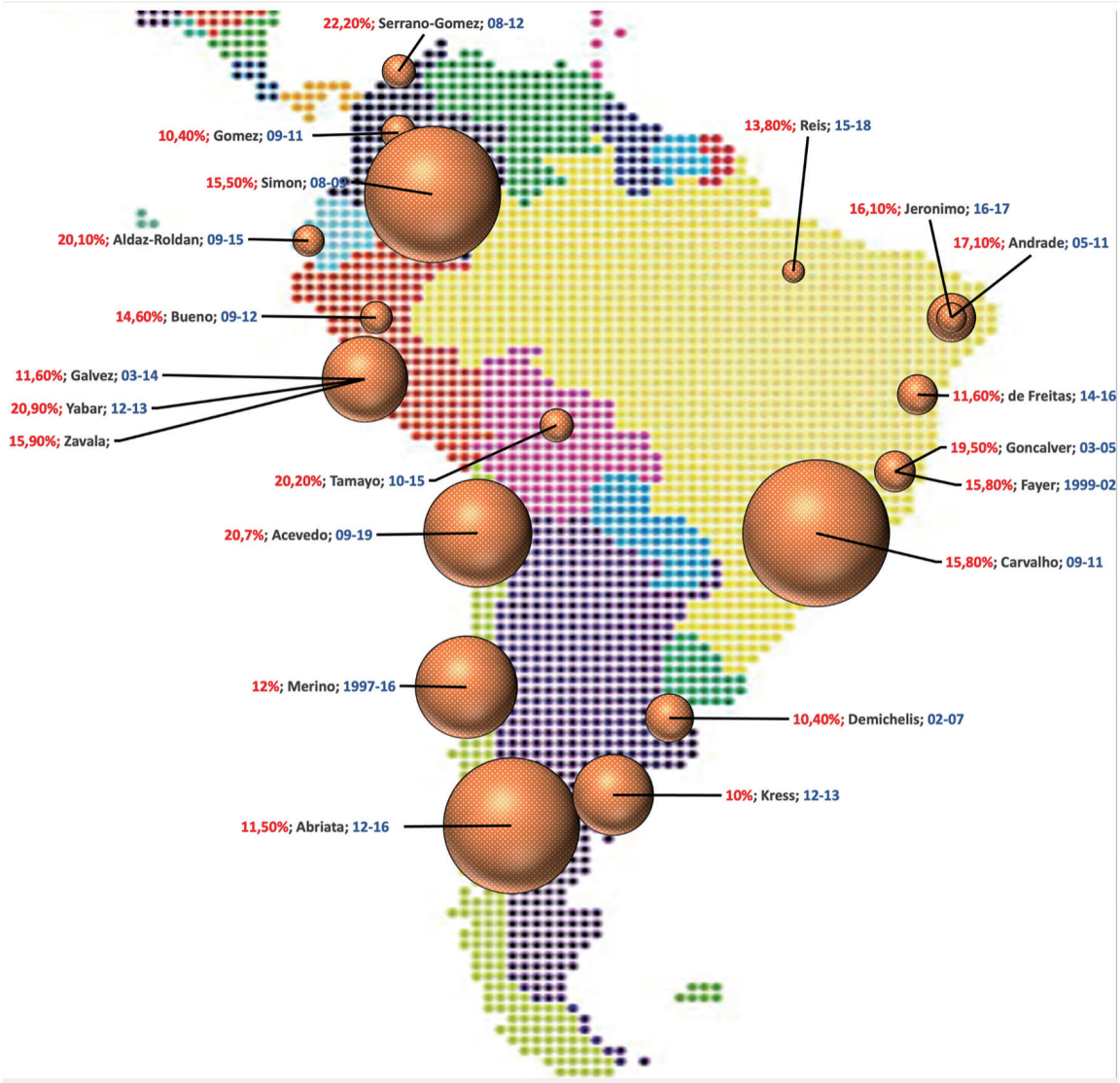

Figure 6. Schematic representation of the TNBC percentage and population size in SA region. The numbers in red and blue represent TNBC percentage and year of observation (for example "16.1; Jeronimo; 16-17" may stands for a study by Jeronimo et al, with TNBC rate of 16.1% and observation year of 2016 - 2017), respectively. TNBC: triple-negative breast cancer; SA: South America.

esis [72, 73].

However, the lateral comparison of our findings should be made to the other continent or its equal (in term of population size) level review. Upon in-depth analysis on the findings, it was revealed that Laos and Argentina stand out to be different among their counterparts, with the Laos possessed the highest TNBC rate in SEA, but Argentina was the lowest of all in SA [30, 43, 74]. However, it is important to emphasize that we are only able to identify a single study from Laos that consisted of 76 patients. Vietnam follows in the second place with 20.9% rate from 738 individuals, though no significant difference was observed compared to the other SEA countries [41, 42]. Argentina in other hand, was estimated to have a 10.1% rate from 2,035 individuals across two studies, yet this study also demonstrated significant TNBC rate compared to the other SA countries (does not closely followed by Brazil on the second place with 15.8% rate) [43, 44, 46-51, 74]. This observation produces valuable insights on how both Argentina and Laos (or Vietnam) emerged from the pool. Is it originated from the genetic ancestry of its major population (which may be unable to be proven in our review), or perhaps it highly favors the nature of environmental risk factors in influencing carcinogenesis? One possible point of understanding is Argentina might possess lower rate of native American and consequently comprised of higher European descent population, unlike the other SA countries, i.e., Ecuador, Peru, etc. [75]. In other hand, capturing the relation between ancestry and cancer risk in SA region remains a significant challenge, considering the genetic admixture of the population is proven to be diverse as a collective origin pool of European, African, and Native American roots [76]. Nevertheless, we are able to recognize remarkable points in both Argentina and Laos, whilst possibly introduc-

ing the necessity to intensify the TNBC-trial numbers in those countries.

We also aspire to shape the future of the oncologic research in the reviewed regions, as most of the times, the stakeholders spent larger attentiveness on the Western population as represented by the trials' number conducted. Regulating the TNBC markets should also consider both continents to be represented, as well in the populations, as many novel agents or even classes are being evaluated to date, yet very few trials have reached these regions. And yet, the most reasonable approaches to response our findings are to encourage higher TNBC trial recruitments, specifically among the evaluated region with higher disease rate per total BC population. Boosting the participant recruitments on TNBC trials from those nations will be the first step to keep up with significantly higher data availability from the Western population. Apart from the more favorable situation among the Western world for conducting trials, we believe that our study should be sufficient as a groundwork review to plan a priority list of upcoming trials based on the estimated TNBC rate.

The combination of pembrolizumab plus anthracycline, platinum agents, and taxane as a neoadjuvant regiment is the current standard approach for TNBC, followed by the individualized response or the *BRCA* gene testing results. It will eventually lead to much complex choices involving olaparib (and its derivatives from poly adenosine diphosphate (ADP) ribose polymerase (PARP) inhibitors), or other immune checkpoint inhibitors (ICIs), e.g., nivolumab, atezolizumab, etc., serving the role of personalized treatment in modern oncology [77, 78]. Despite the advancement of those classes as a whole, further exploration revealed that their administration was only effective on specific individuals, as determined by the BRCA status and the programmed death-ligand 1 (PD-L1) expressivity. Therefore, the landscape was even more limited among populations with metastatic lesion, without mutations of germline *BRCA*, or negatively expressing PD-L1 (< 1%), as sacituzumab govitecan being the only key agent to improve outcomes according to the phase III ASCENT trials [79, 80]. Interestingly, other trials involving trastuzumab deruxtecan (a HER-2 blocker), e.g., DAISY and Destiny-Breast06 (Destiny-06), also included HER2 non-expressing participants. Whilst it may indirectly extend the research on TNBC groups, the most recent reports continue to include the hormone receptor-positive BC as the evaluated subsets [81, 82]. The upcoming exploration within the Enhertu study involving trastuzumab has also revealed a likelihood of including TNBC patients for its trial, possibly expanding the pathology treatment choice in the future [83].

It is recorded that currently, there are 131 active trials of pembrolizumab on TNBC. All records involve both USA and Europe, but only 5.3% and 7.6% of the trials were conducted in SEA and SA, respectively [84]. Regardless the fact that pembrolizumab is one of the most prominent ICI agents in TNBC guidelines, less than 10% of the trials conducted involved representatives from at least 600 million women in the SEA and the SA [6]. Out of the total recorded trials, the trial numbers conducted on the PD-L1-related evaluation were slightly higher, with 11.2% and 13.4% from SEA and SA, respectively [85]. Similar phenomena were also observed in 333 identified trials involving anthracycline, taxane, and platinum agents, with 5.7% and 8.4% of the reports incorporating the population from the evaluated continents, regardless the fact that those agents had been around for longer than most of the ICI agents [86]. On total estimation of the trials utilizing the ICI agents, we were only able to identify 145 active studies from the US National Library of Medicine, which mentioned that at least 5.5% and 7.6% of the trials were regulated in both SEA and SA, with USA dominating the field with 73.8% of total reports [87]. For the record, the estimation was made based on the data provided on its website, aiming to at least represent the lower trial numbers conducted in both continents. However, we agreed that either the genetic susceptibility or the populations' lifestyles are greatly distinct from the Western countries.

The growing concern in obtaining better and attainable cancer treatment for better oncologic care is the main intention in conducting this review. We have proven that the TNBC rate in countries from the reviewed continents is similar to or even relatively higher than the one of USA or Europe (though the authors have yet to provide its comparison with other Asian countries or the data from the Africa continent). The potential end-users of the standard TNBC medication and the novel ICIs agents, e.g., cancer-referral hospital, oncology clinic or centers, and even retail clinics, are available as well on those countries. Moreover, ongoing approach on the personalized medicine as the future of disease-eliminating effort should prioritize the genetic or at least regionalized investigations as the mutual understanding between pharma companies and each countries' governmental stakeholders. Our review will accommodate the national or global attempt to capture the estimated TNBC rate and explore its implication for the populations' requirement. Utilizing our review to seize the *status quo* of the TNBC rate may positively influence the decision making or improve the accessibility of cancer care in those countries, encouraging each party that the urgencies to conduct further trials are prevailed.

This meta-analysis holds a number of limitations that should be considered before interpreting the outcomes. First of all, we establish a "one period, one center or city" policy to decrease the risk of reporting biases; hence often studies of smaller population that overlapped with the policy were excluded from the final analysis. We also recognized the abstraction of our review since a plethora of discussions may occur from every finding in this study, which might as well can be considered as this review's main strength. Next, the authors transcribed the significance of each country's differences based on the regression of logit event rate (presented by two-sided P value in 95% CI). Therefore, interpretation of the outcomes was structured from the estimated P value plus qualitative assessment on the scatterplot models; and it will be very much appreciated to receive feedback from our *modus operandi* in delivering the objectives. For that reason, we are highly open for discussion to improve the level of this meta-analysis by approaching the corresponding author (DH), considering the analysis might be limited by the authors' statistical performance in interpreting the outcomes, and we aimed to propose another review with similar model on the specific estrogen or progesterone receptors' expression rate.

Conclusions

This study highlights the epidemiological estimation of TNBC's prevalence on both SEA and SA regions, with specific consideration that SEA has higher TNBC rate compared to the SA populations in this review. We estimated percentage estimations, with some countries, i.e., Argentina or even Laos possess significant difference compared to the respective countries' neighbors. Nevertheless, better understanding on the current TNBC epidemiological status in the majority-improving countries from our review might theoretically improve cancer care, either by encouraging the government as the primary healthcare stakeholders or the trials-leading pharma companies. As we are able to slightly portray the imbalances of trials-patients ratio in both SEA and SA compared to the Western countries, this study might as well serve as a large-scale guide of epidemiological investigation in those continents. Consequently, our finding may also encourage TNBC trials' recruitment on the reviewed regions, considering the TNBC epidemiological status had been partially captured in this study.

Supplementary Material

Suppl 1. Risk of bias assessment of the studies in Newcastle-Ottawa scale.

Acknowledgments

The authors express gratitude to the Korean Society of Medical Oncology (KSMO) for accepting the abstract version of this study in their 2023 annual congress, allowing the authors to improve the reachability of our work to the global oncologic societies.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Author Contributions

The CRediT taxonomy captured each author's contribution in the preparation of this work: Conceptualization: DH, NNF. Data curation: DH, NNF, RHNS. Formal analysis: DH, NNF, RHNS. Funding acquisition: Not applicable. Investigation: DH, NNF, RHBS. Methodology: DH, NNF, RHNS, NND. Project administration: NNF, RHNS. Resources: DH, NNF. Software: DH, NNF, RHNS, NND. Supervision: DH. Validation: DH. Visualization: NNF, RHNS, NND. Writing - original draft: DH, NNF. Writing - review and editing: DH, NNF, RHNS.

Data Availability

All data and material are available on request by contacting the corresponding or first author. The inquiries will be considered after thorough evaluation.

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