

Review

Proportion of Breast Cancer Patients with SARS-CoV-2 Infection during the COVID-19 Pandemic: A Systematic Review and Meta-Analysis

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Abstract

The coronavirus disease 2019 (COVID-19) is currently representing a global health threat especially for fragile peoples, such as cancer patients. A few studies have described that people with a breast cancer more likely to be infected with COVID-19. Here, we performed a meta-analysis to assess the proportion of breast cancer patients with SARS-CoV-2 infection during the COVID-19 pandemic. A comprehensive literature search of the PubMed, Web of Sciences, Scopus, MedRxiv, SID, and CNKI database was performed. A total of 26 studies with a total of 6,537 infected cancer patients and 1,093 breast cancer patients with COVID-19 met our inclusion criteria. Pooled data showed that the proportion of breast cancer patients with SARS-CoV-2 infection was 17.1% (95% CI 0.144-0.201) in total infected cancer patients. Stratified analysis showed that the proportion in Caucasian and Asian infected breast cancer patients was 17.6% and 14.5%, respectively. Moreover, the proportion was the highest in France (19.3%) followed by US (19.2%), China (14.8%) and UK (13.8%). Our combined data indicated that the proportion of breast cancer patients with SARS-CoV-2 infection during the COVID-19 pandemic was 17.1%. However, we need to more high-quality and multicenter studies from different ethnicities to draw more accurate findings.

Keywords: Breast cancer, COVID-19, infection, proportion, SARS-CoV-2.

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The outbreak of coronavirus disease 2019 (COVID-19) has created a global health crisis with a deep impact on people lives.^[1-3] The pandemic is caused by the severe acute respiratory syndrome associated coronavirus-2 (SARS-CoV-2).^[4-6] Its most common symptoms of the SARS-CoV-2 infection are fever, coughing and shortness of breath.^[7,8] According to the World Health Organization (WHO), the number of confirmed cases increased to more than 81 million cases with 1.8 million deaths until December 30, 2020.^[9] It is estimated that the mortality rate of COVID-19 was between 0.1% and 5%.^[10-12] However, the mortality rates of COVID-19 vary by locations and this may reflect differences in population age structure and case-mix of infected and deceased patients and other factors.^[13,14] For example, it has been found that the age distributions of COVID-19 mortality had a only small variation in Italy, Spain, and Japan, although the number of deaths per country has a large variation.^[15] Thus, differences in mortality rate of this disease across countries and by ethnicity might be main indicators of relative risk of death to policy decisions regarding burden of medical resource allocation during the pandemic.^[16-18]

It is well-known that certain group of people with cardiovascular disease, diabetes mellitus (DM), chronic respiratory disease, hypertension are at higher risk of SARS-CoV-2 infection.^[19-22] Moreover, some studies have described the characteristics of SARS-CoV-2 infections in patients with a malignancy.^[23,24] These groups of patients are likely to be more susceptible to COVID-19 than healthy people since their immune system state might be suppressed by anti-neoplastic therapy, supportive medications such as steroids, and the immunosuppressive properties of cancer itself.^[25,26] Moreover, people with a malignancy are often older with one or more major comorbidities, putting them at increased risk for COVID-19-related morbidity and mortality.^[20,27] Moreover, those patients often have high levels of contact with the health-care system for anticancer therapy, monitoring, and preventive and supportive care.^[27-29]

Cancer patients have been reported to be at higher risk of COVID-19 complications and deaths.^[27,30] As in many other types of cancer, there are challenges in the prevalence, management and consequence of COVID-19 among people with breast cancer due to the limited data and the investigations by the healthcare professionals according to the pandemic conditions.^[29,31,32] The COVID-19 pandemic has resulted in a major shift in how breast services are being utilized and managed.^[29] Whilst breast surgeons and associated treatment team staffs may not be directly managing the breast cancer patients with confirmed COVID-19, the proportion of COVID-19 in breast cancer patients are likely to impact services.^[33,34] To date, several studies have

revealed that people with breast cancer more likely to be infected with the COVID-19.^[35] But, data on those patients are lacking or inconclusive. In this review, we tried to explain the proportion of breast cancer patients with SARS-CoV-2 infection during the COVID-19 pandemic.

Methods

Literature Search

The ethical approval was not necessary since the current meta-analysis was not a clinical trial study and was based on previously published studies. A comprehensive literature search was performed on major electronic literature databases, including the PubMed, Web of Knowledge, MedRxiv, Web of Science, Embase, SciELO, Scientific Information Database (SID), WanFang, VIP, Chinese Biomedical Database (CBD), Egyptian Knowledge Bank (EKB) Journal, Scientific Electronic Library Online (SciELO) and China National Knowledge Infrastructure (CNKI) to find all studies reported breast cancer patients with SARS-CoV-2 Infection in up to 5 February, 2021. The following keywords and terms were used: ("COVID-19 virus disease" OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "SARS-CoV-2" OR "2019 novel coronavirus infection" OR "2019-nCoV infection" OR "coronavirus disease" OR "coronavirus disease-19" OR "2019-nCoV disease" OR "COVID-19 virus infection") AND ("breast cancer" OR "breast tumor" OR "breast neoplasm" OR "breast malignant tumor" OR "breast carcinoma") AND ("Cancer" OR "Malignancy" OR "Lung Cancer" OR "Colorectal Cancer" OR "Esophagus Cancer" OR "Bladder Cancer" OR "Pancreatic Cancer" OR "Cervical Cancer" OR "Hematological Cancer"). No restrictions were placed on the year of publication, ethnicity, and sample size. Moreover, we have also manually reviewed the reference lists of all retrieved articles, reviews and meta-analyses to find other potentially sources.

Inclusion and Exclusion Criteria

To select eligible studies in the current meta-analysis, the following criteria for inclusion were defined: a) Full-text publications with case-control, consecutive case series or cohort design; b) studies reported studies on cancer patients with SARS-CoV-2 infection; c) provide sufficient data to estimate the odds ratio (OR) with 95% confidence intervals (95% CI). The exclusion criteria were as follows: a) non-consecutive case series; b) case reports, abstracts, meeting reports, lectures, editorials, correspondence letters, reviews, previous meta-analyses; and c) overlapped data or duplicated publications. If there were multiple published articles from the same authors, the most recent study or study with larger sample size was included in this meta-analysis. More-

over, different case-control groups or cohorts in one publication were considered as independent studies.

Data Extraction

Two investigators independently reviewed all titles and abstracts of the selected studies in the primary search and extracted the necessary data carefully according to the inclusion and exclusion criteria. When the authors were not in agreement, a third author was involved to reach a consensus for all items. The following characteristics were collected from each eligible study: first author's name, year of publication, country or region, ethnic group of the study population, mean age (range), gender, total number of cancer patients with SARS-CoV-2 infection, total number of breast cancer patients with SARS-CoV-2 infection, and type of treatment.

Statistical Analysis

The proportion of breast cancer patients with SARS-CoV-2 infection was measured by odds ratio (OR) with its 95% confidence interval (CI). The significance of pooled ORs was tested by Z-test, in which $p < 0.05$ was considered significant. The between-heterogeneity was examined using chi-square. Moreover, I^2 test to quantify the heterogeneity, which ranges from 0 to 100% and represents the proportion of between-study variability attributable to heterogeneity rather than chance ($I^2 < 25\%$, no heterogeneity; I^2 25-50%, moderate heterogeneity; $I^2 > 50\%$, large or extreme heterogeneity). If the P value for heterogeneity tests was > 0.01 or $I^2 < 50\%$, a fixed effect model (Mantel-Haenszel method) was used to calculate the pooled OR. Otherwise, a random effect model (DerSimonian-Laird method) was employed to analyze data.^[36] The publication bias among the selected studies was tested by Begg's test, in which an asymmetric plot suggests a possible publication bias. Moreover, Egger's linear regression test was performed to determine the significance of the asymmetry, in which $p < 0.05$ indicated that publication bias was significant.^[37,38] Additionally, if publication bias was seen, the "trim and fill" method which conservatively imputes hypothetical negative unpublished studies to mirror the positive studies that cause funnel plot asymmetry was used to further analyses the possible effect of publication bias. All statistical analyses were performed using Comprehensive Meta-Analysis (CMA) Software version 2.0 (Biostat, Englewood, USA). All tests were two-sided, and the $P < 0.05$ was considered statistically significant.

Quality Assessment

The quality assessment for included studies was performed according to the Newcastle-Ottawa Scale case control study (NOS). This standard assessed 3 sections (selection, comparability, exposure) and 8 items. In the selection and exposure

categories, a quality research item received 1 star, and a comparable category could receive at most 2 stars. The quality assessment values ranged from 0 stars (worst) to 9 stars (best), and studies with a score ≥ 7 were defined as high quality. Generally, the study which scored at least 5 points was considered to be included in meta-analysis and any discrepant opinions were resolved by discussion and consensus.

Results

Characteristics of Eligible Studies

The study screening process was shown in Figure 1. Initially, a total number of 702 publications were identified from the online databases and manually. In accordance with the eligibility criteria, 291 articles were left after removing repeated studies and 193 studies were subsequently excluded for title and abstract review. In the end, the whole of the rest of the articles were checked based on the inclusion and exclusion criteria and 192 publications were excluded because were Reviews, case reports, letters to editors, evaluated only breast cancer, not reporting useful data, and non-consecutive case series. Finally, a total of 26 studies^[28,39,40,41-47, 48-57,58-63] with 6,537 infected cancer patients (lung cancer, colorectal cancer, breast cancer, esophagus cancer, bladder cancer, pancreatic cancer and cervical cancer, and hematological cancer) and 1,093 breast cancer patients with SARS-CoV-2 infection were included in the meta-analysis. The characteristics of the main studies are shown in Table 1. The studies were published in English and Chinese. The publication year of the all selected studies was in 2020 and published in English and Chinese. The sample size in total infected cancer patients was ranged 5 to 1289 and for breast cancer cases with SARS-CoV-2 infection varied from 0 to 191. The selected studies were published among Asian (n=12, with 1214 infected cancer patients and 196 cancer patients), Caucasian (n=13, with 5142 infected cancer patients and 857 cancer patients) and mixed population (n=1, with 181 infected cancer patients and 40 cancer patients). The majority of study patients came from the China (n=10) followed by the United States (n=5), France (n=4), United Kingdom (n=2), Pakistan (n=1), Iran (n=1), Spain (n=1), Italy (n=1), Brazil (n=1). The NOS score of eligible articles ranged from 6 to 8, which indicated that all included studies were of high quality (Table 1).

Data Synthesis

The summary results for the proportion of breast cancer patients with SARS-CoV-2 infection during COVID-19 pandemic are shown in Table 2. Combined data revealed that the proportion of breast cancer patients with SARS-CoV-2 infection was 17.1% (95% CI 0.144-0.201, $p \leq 0.001$, Fig. 2)

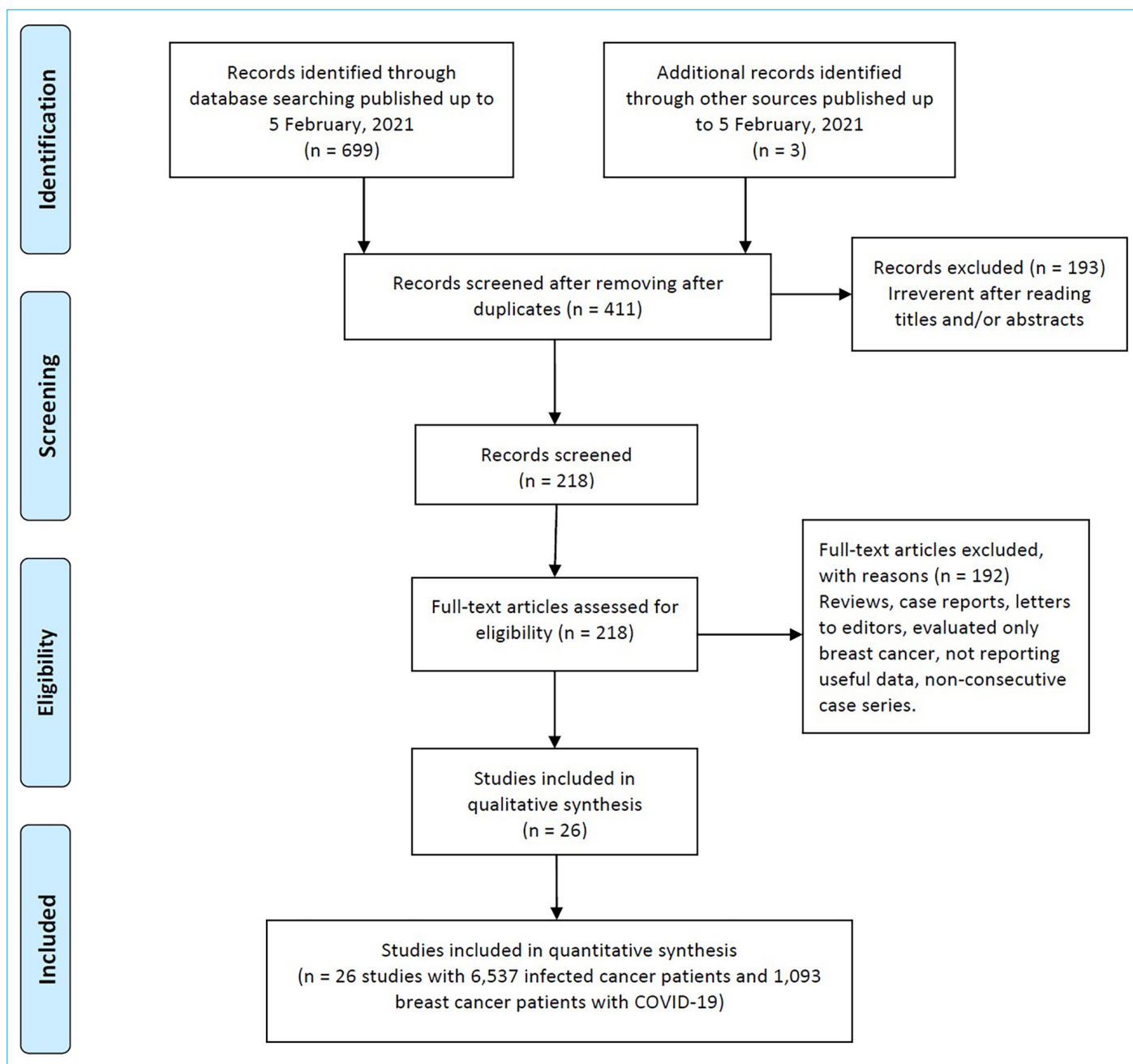


Figure 1. Flowchart of literature search and selection process in the meta-analysis.

in total infected cancer patients. Stratified analysis by ethnicity showed that the proportion in Caucasian and Asian infected breast cancer patients was 17.6% (95% CI 0.145-0.211, $p \leq 0.001$, Fig. 3a) and 14.5% (95% CI 0.095-0.214, $p \leq 0.001$, Fig. 3b), respectively. Moreover, subgroup analysis by country of origin showed that the proportion was the highest in France (19.3%, 95% CI 0.110-0.316, $p \leq 0.001$, Fig. 4a) followed by US (19.2%, 95% CI 0.163-0.226, $p \leq 0.001$, Fig. 4b), China (14.8%, 95% CI 0.125-0.174, $p \leq 0.001$, Fig. 4c) and UK (13.8%, 95% CI 0.120-0.159, $p \leq 0.001$, Fig. 4d) breast cancer patients with SARS-CoV-2 infection, respectively.

Sensitivity Analysis

We used a leave-one-out sensitivity analysis to identify the effects of individual publication on the overall pooled ORs. The significance of the pooled ORs was not influenced by excluding those studies, indicating that this study pooled ORs were statistically robust and our findings were not dependent on a single study.

Heterogeneity Test

In the current study there was statistically a significant between-study heterogeneity ($I^2 = 84.80$; $P_H \leq 0.001$) in overall

Table 1. Main characteristics of the included studies in the current meta-analysis

Author/year	Country/ Ethnicity	Sample size*	Age (range)	F/M	BC	Cancer treatment in total cases				NOS	
						Surgery	Radiotherapy	Chemotherapy	Targeted therapy		Immunotherapy
Yu et al., 2020	China (Asian)	12	66 (48-78)	2/10	1	0 (0.0)	3 (25.0)	3 (25.0)	1 (8.3)	2 (16.7)	7
Liang et al., 2020	China (Asian)	18	62 (56-68)	6/12	3	1 (5.6)	0 (0.0)	2 (11.1)	2 (11.1)	1 (5.6)	8
Ma et al., 2020	China (Asian)	37	62 (59-70)	17/20	7	NA	NA	NA	NA	NA	8
Zhang et al., 2020	China (Asian)	28	65 (56-70)	11/17	3	5 (17.9)	4 (14.3)	10 (35.7)	3 (10.7)	1 (3.6)	7
Zhang et al., 2020	China (Asian)	5	NA	NA	0	NA	NA	NA	NA	NA	6
Zhang et al., 2020	China (Asian)	107	66 (36-98)	47/60	10	5 (4.7)	NA	15 (14.0)	NA	6 (5.6)	6
Dai et al., 2020	China (Asian)	105	64 (55-69)	48/57	11	8 (7.6)	13 (12.4)	17 (16.2)	4 (3.8)	6 (5.7)	8
Yang et al., 2020	China (Asian)	205	63 (56-70)	109/96	40	4 (2.0)	9 (4.4)	31 (15.1)	12 (5.9)	4 (2.0)	8
Yang et al., 2020	China (Asian)	52	63 (56-70)	24/28	9	2 (3.8)	0 (0.0)	6 (11.5)	0 (0.0)	0 (0.0)	7
Wang et al., 2020	China (Asian)	283	63 (55-70)	142/141	38	23 (8)	NA	46 (16)	12 (4)	NA	6
Aznab et al., 2020	Iran (Asian)	161	NA	NA	0	NA	NA	NA	NA	NA	8
Ali et al., 2020	Pakistan (Asian)	201	45 (18-78)	115/86	74	22 (10.9)	13 (6.5)	146 (72.6)	2 (1)	0 (0.0)	8
Basse et al., 2020	France (Caucasian)	141	62 (52-72)	102/39	56	11 (7.8)	13 (9.2)	69 (48.9)	22 (15.6)	8 (5.7)	7
Barlesi et al., 2020	France (Caucasian)	137	61 (21-90)	79/58	23	0 (0.0)	0 (0.0)	48 (35.0)	18 (13.1)	12 (8.8)	7
Assaad et al., 2020	France (Caucasian)	302	58.2	158/144	42	NA	NA	NA	NA	NA	6
Lievre et al., 2020	France (Caucasian)	1289	67 (19-100)	494/795	173	56 (4.0)	95 (7.0)	385 (30.0)	114 (9.0)	27 (2.0)	8
Mehta et al., 2020	USA (Caucasian)	218	69 (10-92)	91/127	28	0 (0.0)	49 (22.5)	42 (19.3)	0 (0.0)	5 (2.3)	8
Jee et al., 2020	USA (Caucasian)	309	NA	150/159	54	NA	NA	102 (33.0)	49 (15.9)	18 (5.8)	6
Robilotti et al., 2020	USA (Caucasian)	423	0-64	211/212	86	NA	NA	191	NA	31	6
Kuderer et al., 2020	USA (Caucasian)	928	66 (57-76)	459/468	191	32 (3.4)	12 (1.3)	160 (17.2)	75 (8.1)	38 (4.1)	8
Kabaritti et al., 2020	USA (Caucasian)	107	70 (30-95)	54/53	28	NA	NA	NA	NA	NA	6
Lee et al., 2020	UK (Caucasian)	1044	70 (60-77)	445/595	143	29 (3.6)	76 (9.5)	281 (35.1)	72 (9.0)	44 (5.5)	8
Russels et al., 2020	UK (Caucasian)	156	65	66/90	23	NA	NA	NA	NA	NA	6
Yarza et al., 2020	Spain (Caucasian)	63	66 (63-68)	29/34	8	NA	NA	26 (41.2)	3 (4.7)	7 (11.2)	6
Stroppa et al., 2020	Italy (Caucasian)	25	71 (50-84)	5/20	2	NA	NA	8 (66.67)	NA	4 (33.33)	6
de Melo et al., 2020	Brazil (mixed)	181	55 (2-88)	110/71	40	12 (6.6)	10 (5.5)	63 (34.8)	9 (5.0)	NA	6

*: Multi-national (European countries); **: All cancer cases with SARS-CoV-2 Infection. F/M: Female/male; BC: Breast cancer; NOS: Newcastle-Ottawa Scale; NA: Not Available.

Table 2. Summary for the proportion of breast cancer patients with SARS-CoV-2 infection

Subgroup	Type of model	Heterogeneity			Odds ratio			Publication bias	
		I ² (%)	P _H	OR	95% CI	Z _{test}	P _{OR}	P _{Begg}	P _{Egger}
Overall	Random	84.80	≤0.001	0.171	0.144-0.201	-15.561	≤0.001	0.354	0.530
Ethnicity									
Caucasian	Random	86.82	≤0.001	0.176	0.145-0.211	-13.351	≤0.001	0.951	0.779
Asian	Random	83.49	≤0.001	0.145	0.095-0.214	-7.263	≤0.001	0.631	0.056
Country of origin									
France	Random	94.93	≤0.001	0.193	0.110-0.316	-4.261	≤0.001	0.308	0.467
United states	Random	62.49	0.031	0.192	0.163-0.226	-13.816	≤0.001	0.806	0.624
China	Fixed	7.68	0.371	0.148	0.125-0.174	-17.831	≤0.001	1.000	0.326
United kingdom	Fixed	0.00	0.724	0.138	0.120-0.159	-21.872	≤0.001	NA	NA

OR: Odds ratio; CI: Confidence interval; NA: Not Applicable.

breast cancer patients with SARS-CoV-2 infection. We performed stratified analyses by ethnicity and country of origin to explain the potential source of the heterogeneity. Results showed that the heterogeneity did not reduce in Asian (I²=86.82; P_H≤0.001) and Caucasian (I²=83.49; P_H≤0.001). How-

ever, subgroup analysis by country of origin it was reduced or disappeared in Chinese (I²=7.68; P_H=0.371) and British (I²=0.00; P_H=0.724) breast cancer patients with SARS-CoV-2 infection, indicating that ethnicity might be a source of heterogeneity in this meta-analysis (Table 2).

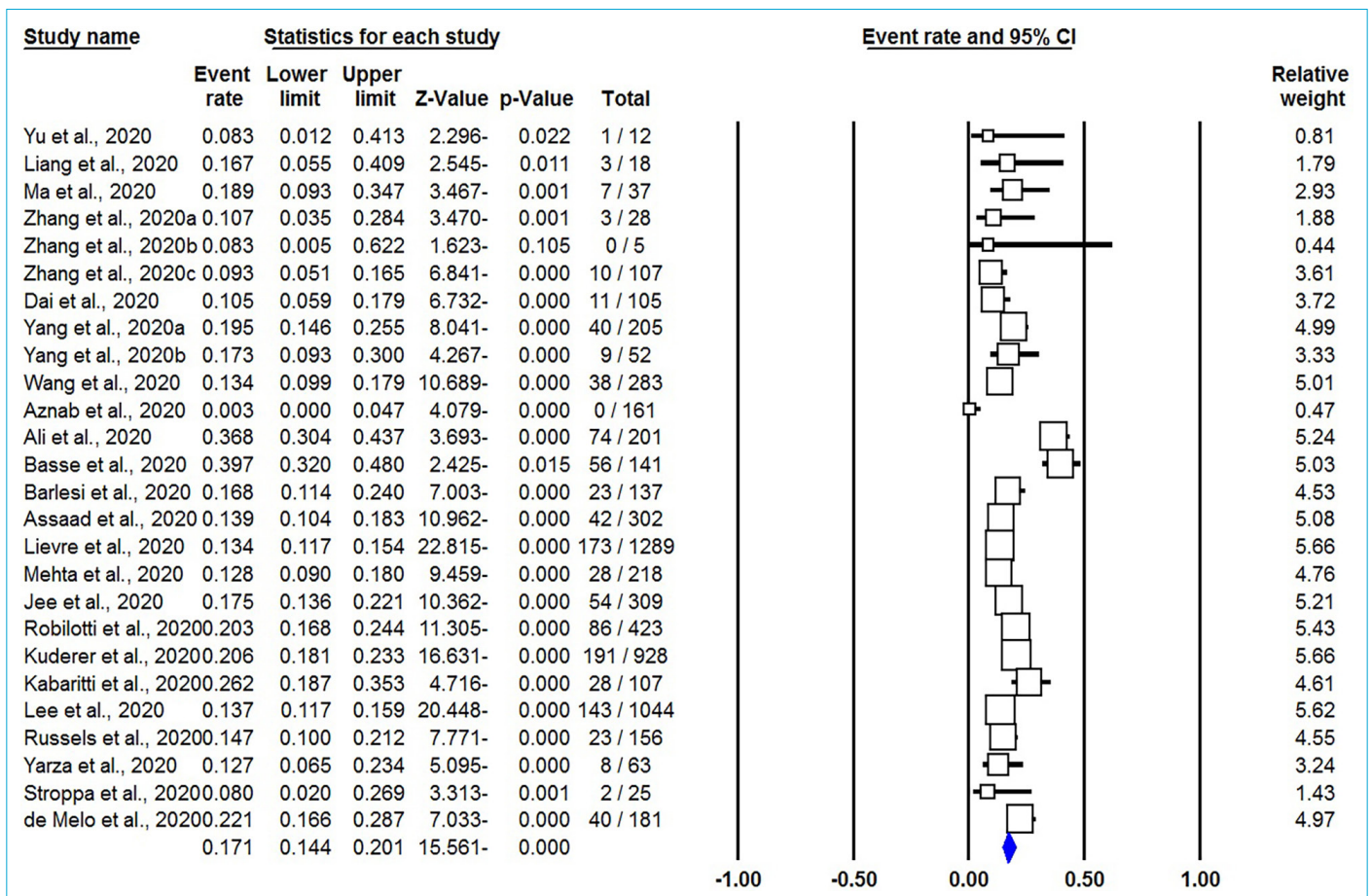


Figure 2. Forest plot for proportion of breast cancer patients with SARS-CoV-2 infection during the COVID-19 pandemic in overall cancer patients.

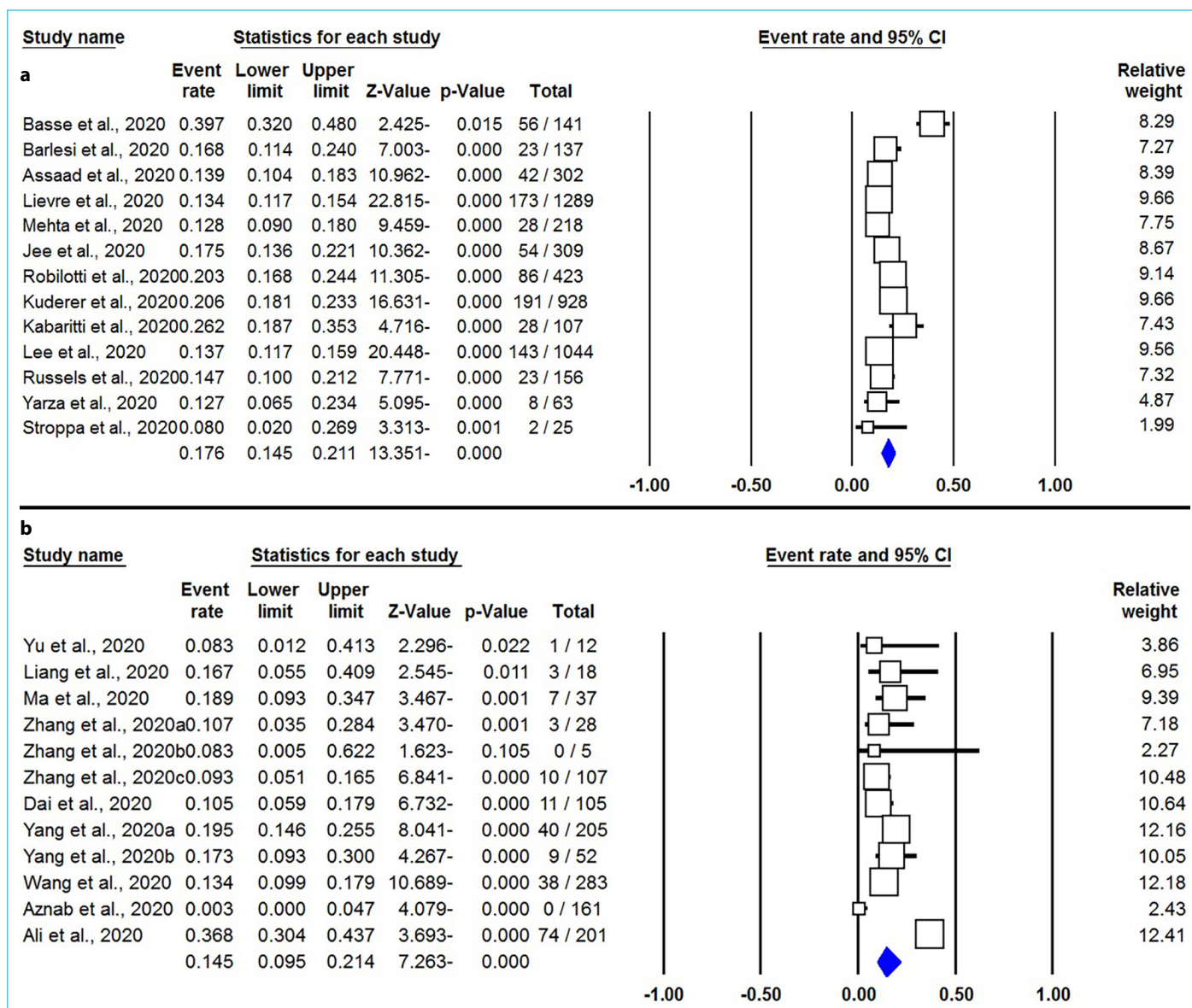


Figure 3. Forest plot for proportion of breast cancer patients with SARS-CoV-2 infection during the COVID-19 pandemic in by ethnicity. (a) Caucasian; and (b) Asian.

Publication Bias

The Begg’s and Egger’s linear regression tests were applied to test the potential publication bias in the literatures. As shown in Figure 5, the shapes of the Begg’s funnel plot did not show any evidence of publication bias in the current meta-analysis. Moreover, the Egger’s tests did not show an evidence of publication bias statistically ($P_{Begg's}=0.354$; $P_{Egger's}=0.530$), indicating that our pooled data were statistically robust and reliable.

Discussion

To date, several guidelines recommended continue to balance treatment of breast cancer against risk of COVID-19 exposure and infection until approval of a vaccine.^[64,65]

Moreover, it is recommended that at the end of COVID-19 pandemic, many benign and reconstructive cases must be return to the attention and their surgical treatment will be required as soon as possible.^[66] Studies indicated that various areas in health care were affected during COVID-19, but the impact seemed largest for breast cancer screening.^[67] It is obvious that knowledge about proportion of breast cancer patients with SARS-CoV-2 infection helpful to define those COVID-19 patients at higher risk. Moreover, special attention must be paid to underlying comorbidities when estimating the risk of SARS-CoV-2 infection in people with breast cancer. But, there was no exact estimation about proportion of SARS-CoV-2 infection in breast cancer patients during COVID-19 pandemic.

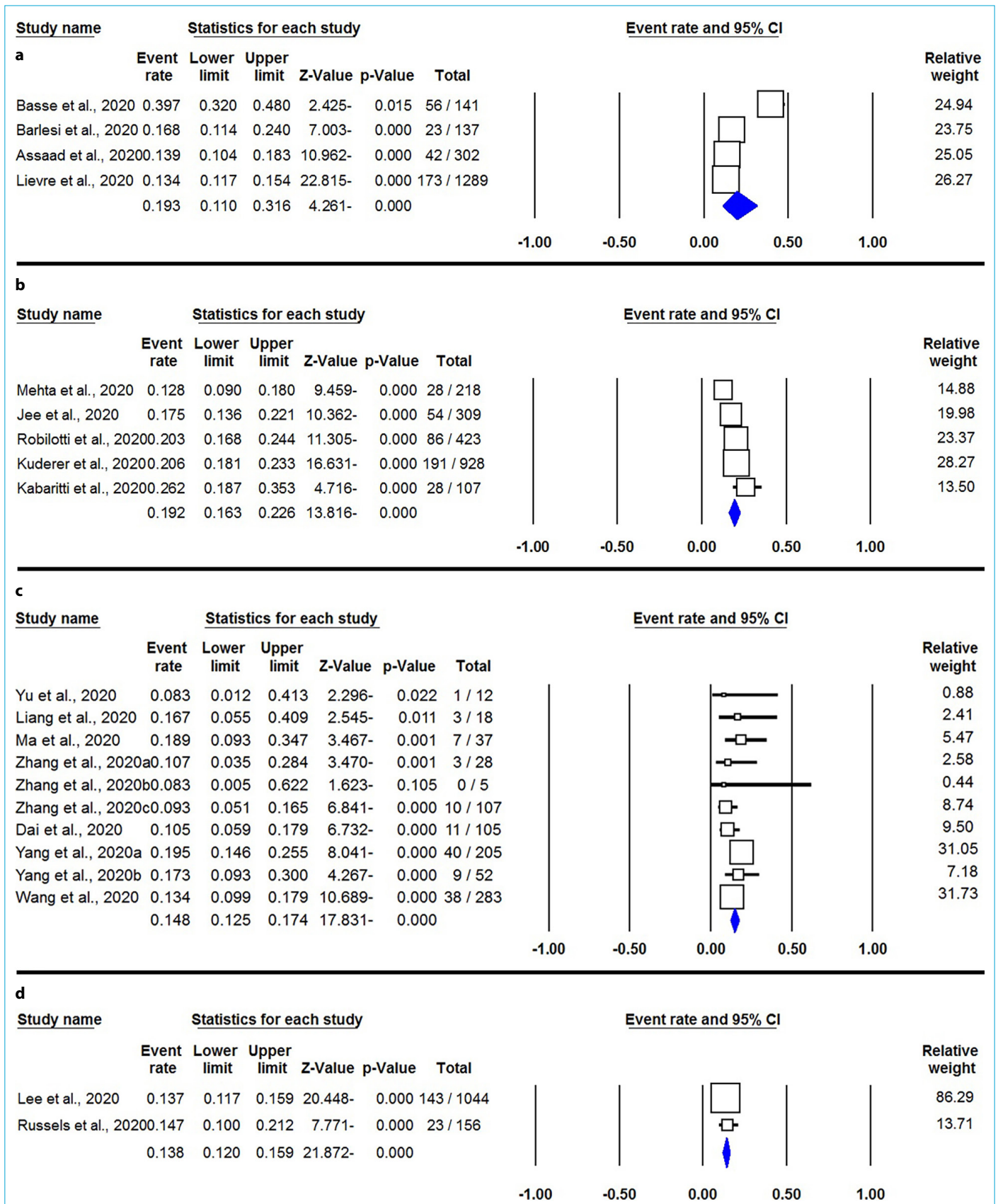


Figure 4. Forest plot for proportion of breast cancer patients with SARS-CoV-2 infection during the COVID-19 pandemic in by country of origin. (a) France; (b) China; (c) United States; and (d) United Kingdom.

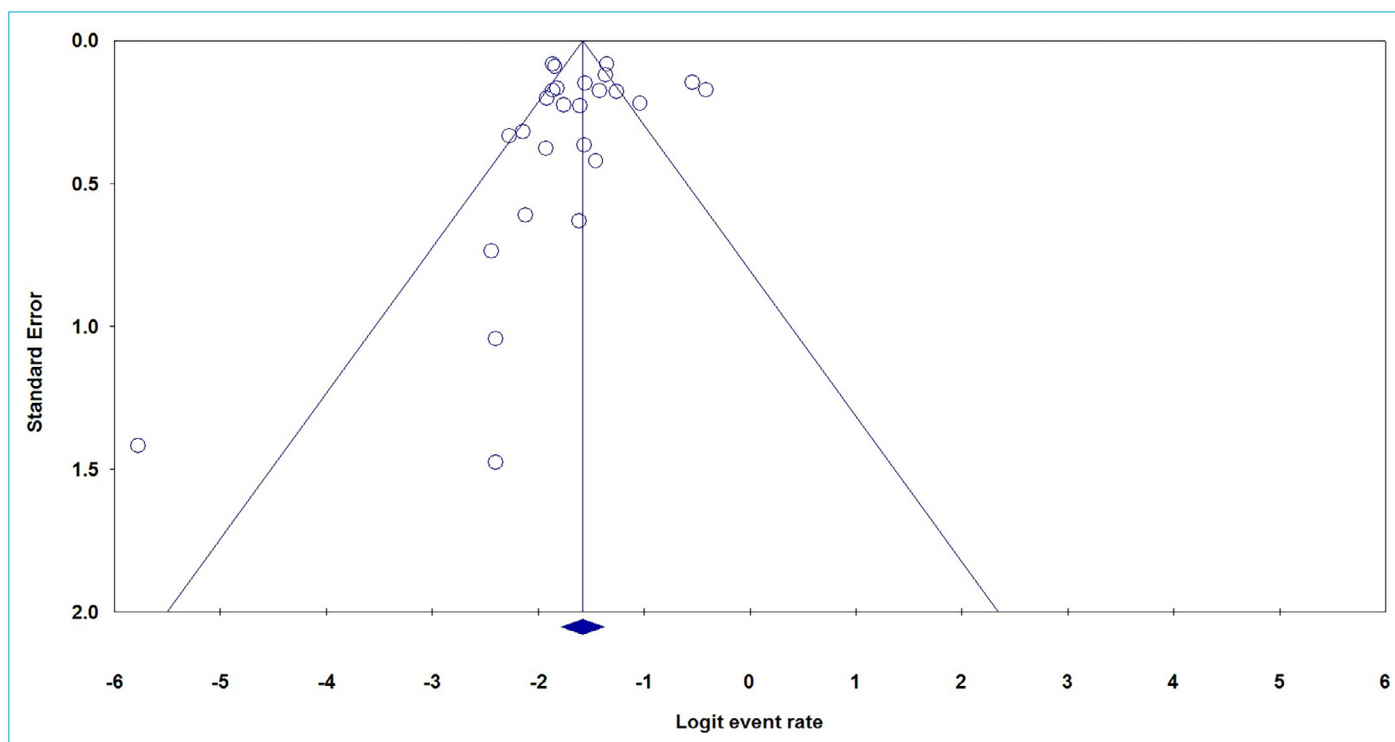


Figure 5. The funnel plots of publication bias for proportion of breast cancer patients with SARS-CoV-2 infection during the COVID-19 pandemic in overall cancer patients.

In this study a total of 6,537 infected cancer patients and 1,093 breast cancer patients with SARS-CoV-2 infection from 26 publications were selected. Our results revealed that the proportion of breast cancer patients with SARS-CoV-2 infection was 17.1% in total infected cancer patients. Our subgroup analysis by ethnicity showed that the proportion in Caucasian and Asian infected breast cancer patients was 17.6% and 14.5%, respectively. Moreover, subgroup analysis by country of origin showed that the proportion was the highest in France (19.3%) followed by US (19.2%), China (14.8%) and UK (13.8%) breast cancer patients with SARS-CoV-2 infection, respectively. Venkatesulu et al.,^[68] in a meta-analysis reported that the breast cancer (29.2%) was the most common type of cancer reported among COVID-19 patients after hematological malignancies. However, their results indicated that hematological cancer and lung cancer patients are at increased risk of mortality compared to other subtypes of cancer. Wang et al.,^[35] in meta-analysis analyzed the susceptibility to COVID-19 in seven different malignancies, including lung cancer, colorectal cancer, breast cancer, esophagus cancer, bladder cancer, pancreatic cancer, and cervical cancer. Their results revealed that compared with other types of cancer, lung cancer and colorectal cancer are more susceptible to SARS-CoV-2 infection. Liang et al.,^[40] published the first report on proportion of breast cancer patients with SARS-CoV-2 infection and its outcomes in a series of

18 Chinese patients with a history of cancer and a diagnosis of COVID-19, 7 (39%) had to be treated in the intensive care unit (ICU) and/or died. Dai et al.,^[43] in a multi-center study including 105 cancer patients and 536 age-matched non-cancer patients confirmed with COVID-19 reported that cancer patients appear more vulnerable to COVID-19 pandemic. Their results revealed that people with hematological cancer, lung cancer, or with metastatic cancer had the highest proportion of severe events. Recently, Vuagnat et al.,^[69] in a study among 15,600 patients who treated for early or metastatic breast cancer in Paris area reported that 76 patients were suspected SARS-CoV-2 infection. Among them, 59 cases were diagnosed with COVID-19 based on viral RNA testing or typical radiologic signs. Their data revealed that the COVID-19 mortality rate in breast cancer patients depends more on comorbidities than prior radiation therapy or current anti-cancer regimen. Zarifkar et al.,^[70] in a meta-analysis according to the available data revealed an unfavorable outcome of hospitalized patients with COVID-19 and cancer. Their pooled data showed that the prevalence of a cancer as a co-morbidity in hospitalized patients with COVID-19 was 2.6% (95% CI 1.8%-3.5%). In another meta-analysis, Zhang et al.,^[71] showed that the COVID-19 patients with cancer have a higher fatality rate compared with that of COVID-19 patients without cancer.

This systematic review and meta-analysis based 26 studies was the largest meta-analysis to the best of our knowl-

edge to evaluate the proportion of breast cancer patients with SARS-CoV-2 infection. However, there were several limitations in the current study. First, most of the included studies in were conducted in Asian and Caucasians, which may introduce ethnicity bias. In view of the limited study number in other ethnicities, the power used to estimate the proportion of breast cancer patients with SARS-CoV-2 infection may not be strong enough. Second, there were only studies published in English or Chinese language, which might introduce potential selection bias. Finally, this meta-analysis exclusively concentrated on the proportion of breast cancer patients with SARS-CoV-2 infection without stratified by other covariates such as age, treatment modality and mortality. Therefore, the findings in our meta-analysis should be interpreted with caution.

In summary, this study results revealed that the proportion of breast cancer patients with SARS-CoV-2 infection was 17.1%. Stratified analysis showed that the proportion in Caucasian and Asian infected breast cancer patients was 17.6% and 14.5%, respectively. Moreover, the proportion was the highest in France (19.3%) followed by US (19.2%), China (14.8%) and UK (13.8%). However, we need to more high-quality studies from different ethnicities to draw more accurate results in future studies.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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