



The prognosis outcomes of autologous fat transfer for breast reconstruction after breast cancer surgery: a systematic review and meta-analysis of cohort studies

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Background: Autologous fat transfer (AFT) is a minimally invasive technique that employs a patient's own fat to correct disfiguring sequelae for breast reconstruction in postoperative breast cancer patients. However, the results of studies on this topic were controversial. In order to explore the effect of AFT on breast reconstruction after breast cancer surgery, we included cohort studies and conducted a meta-analysis.

Methods: A literature search was conducted using PubMed, Embase, Cochrane Library, and Web of Science databases for relevant studies published up to September 14, 2020. We identified the eligible studies based on the PICOS principles, populations (patients diagnosed with breast cancer), interventions (patients undergoing AFT after breast cancer surgery), controls (patients who did not receive AFT after breast cancer surgery), outcomes [local recurrence (LR) rate, regional recurrence (RRR) rate, locoregional recurrence (LRR) rate, distant metastasis rate, systemic recurrence (SR) rate, and total death rate], study design (cohort studies). The I^2 statistic was conducted to estimate heterogeneity. Relative risks (RRs) with 95% confidence intervals (CIs) were presented to evaluate whether AFT compromises oncological safety in breast reconstruction. Funnel plots and Egger's test were adopted to assess publication bias. Quality assessment for the included studies using the Newcastle-Ottawa Scale (NOS).

Results: Twenty-two cohort studies involving 9,971 postoperative patients with breast cancer were identified, with 3,622 receiving AFT being the experimental group, and 6,349 not receiving AFT in the control group. The overall quality of the included studies was rated as high. No significant differences in the rate of LR (RR: 0.916, 95% CI: 0.704–1.192), RRR (RR: 1.175, 95% CI: 0.773–1.787), LRR (RR: 0.788, 95% CI: 0.617–1.006), distant metastasis (RR: 1.133, 95% CI: 0.906–1.417), and total deaths (RR: 0.753, 95% CI: 0.539–1.051) were observed between the experimental group and control group ($P > 0.05$). However, the AFT group had a lower rate of SR (RR: 0.671, 95% CI: 0.491–0.915, $P = 0.012$).

Conclusions: The AFT group did not increase the rate of LR, RRR, LRR, distant metastasis, and total deaths in postoperative patients, which may indicate that AFT can be performed safely in breast reconstruction after excision of breast tumor.

Keywords: Autologous fat transfer (AFT); breast reconstruction; after breast cancer operation; meta-analysis

Submitted Apr 20, 2022. Accepted for publication Jun 29, 2022.

doi: 10.21037/gs-22-297

View this article at: <https://dx.doi.org/10.21037/gs-22-297>

Introduction

Autologous fat transfer (AFT) is a minimally invasive technique that removes suctioned fat tissue from a patient's body and transplants it into their breasts (1). According to the American Society of Plastic Surgeons, 62% of plastic surgeons applied AFT in breast reconstruction in 2018, predominately for restoring volume defects in the upper quadrant of the breast to improve the aesthetic results (2). Considering the enhancement of breast contour and improvement of aesthetic outcomes, most female breast cancer patients are willing to receive AFT surgery (3,4). Although thousands of patients undergo AFT every year, there is still some concern over the oncological safety of AFT for breast reconstruction following breast cancer surgery.

The use of AFT to correct contour deformities in reconstructed breasts has obtained favorable results in recent years (5). Tayeh *et al.* found that cancer relapse and complications did not occur in breast cancer patients who underwent AFT (6). Several studies have reported AFT in combination with breast reconstruction after breast cancer treatment is safe oncologically, particularly in terms of not increasing the risk of locoregional recurrence (LRR) (7-9). Meanwhile, a case-control study (10) by Berti *et al.* showed an increased risk of local recurrence (LR) after AFT in women who were treated for invasive breast cancer. Chung *et al.* also found a significantly higher risk of cancer recurrence in a population of breast cancer patients who underwent immediate reconstruction (11). However, a monocentric cohort study (12) found a low incidence rate of tumor recurrence and metastasis following the use of AFT, and no evidence of increased risk in any of the survival outcomes was identified from another study evaluating the oncologic safety of AFT after breast cancer surgical treatment (13). The safety of AFT in the context of breast reconstruction is still a matter of controversy. A meta-analysis, as a statistical analysis method of evidence-based medicine, aims to increase the sample size by comprehensively analyzing the research results of multiple small samples on the same subject, thus improving the research efficiency of the original results and making the conclusions more representative (14). It is crucial to offer breast cancer patients information on the benefits and risks of AFT to further improve their quality of life.

Herein, we performed a meta-analysis based on eligible cohort studies to systematically explore the oncological safety of AFT treatment in breast cancer patients, which

may help clinicians, policymakers, and steering committees in decision-making and application. We present the following article in accordance with the MOOSE reporting checklist (available at <https://gs.amegroups.com/article/view/10.21037/ggs-22-297/rc>).

Methods

Search strategy

PubMed, Embase, Cochrane Library, and Web of Science databases were used to search for articles published up to September 14, 2020. The search terms from PubMed included "Breast Neoplasms" OR "Breast Neoplasm" OR "Neoplasm, Breast" OR "Breast Tumors" OR "Breast Tumor" OR "Tumor, Breast" OR "Tumors, Breast" OR "Neoplasms, Breast" OR "Breast Cancer" OR "Cancer, Breast" OR "Mammary Cancer" OR "Cancer, Mammary" OR "Cancers, Mammary" OR "Mammary Cancers" OR "Malignant Neoplasm of Breast" OR "Breast Malignant Neoplasm" OR "Breast Malignant Neoplasms" OR "Malignant Tumor of Breast" OR "Breast Malignant Tumor" OR "Breast Malignant Tumors" OR "Cancer of Breast" OR "Cancer of the Breast" OR "Mammary Carcinoma, Human" OR "Carcinoma, Human Mammary" OR "Carcinomas, Human Mammary" OR "Human Mammary Carcinomas" OR "Mammary Carcinomas, Human" OR "Human Mammary Carcinoma" OR "Mammary Neoplasms, Human" OR "Human Mammary Neoplasm" OR "Human Mammary Neoplasms" OR "Neoplasm, Human Mammary" OR "Neoplasms, Human Mammary" OR "Mammary Neoplasm, Human" OR "Breast Carcinoma" OR "Breast Carcinomas" OR "Carcinoma, Breast" OR "Carcinomas, Breast" AND "Fat Autografting" OR "Fat Grafting" OR "Fat Autograft" OR "Fat Graft" OR "Fat Transplantation" OR "Fat Injection" OR "Autologous Fat" OR "Lipostructuring" OR "Lipotransfer" OR "Lipomodelling" OR "Lipomodeling" OR "Autologous Fat Transplantation" OR "Autologous fat transfer" OR "AFT" OR "Fat Transfer".

Inclusion and exclusion criteria

Inclusion criteria were: (I) populations: patients diagnosed with breast cancer; (II) interventions: patients undergoing AFT after breast cancer surgery as the experimental group; (III) comparators: patients who did not receive AFT after breast cancer surgery as the control group; (IV) outcomes:

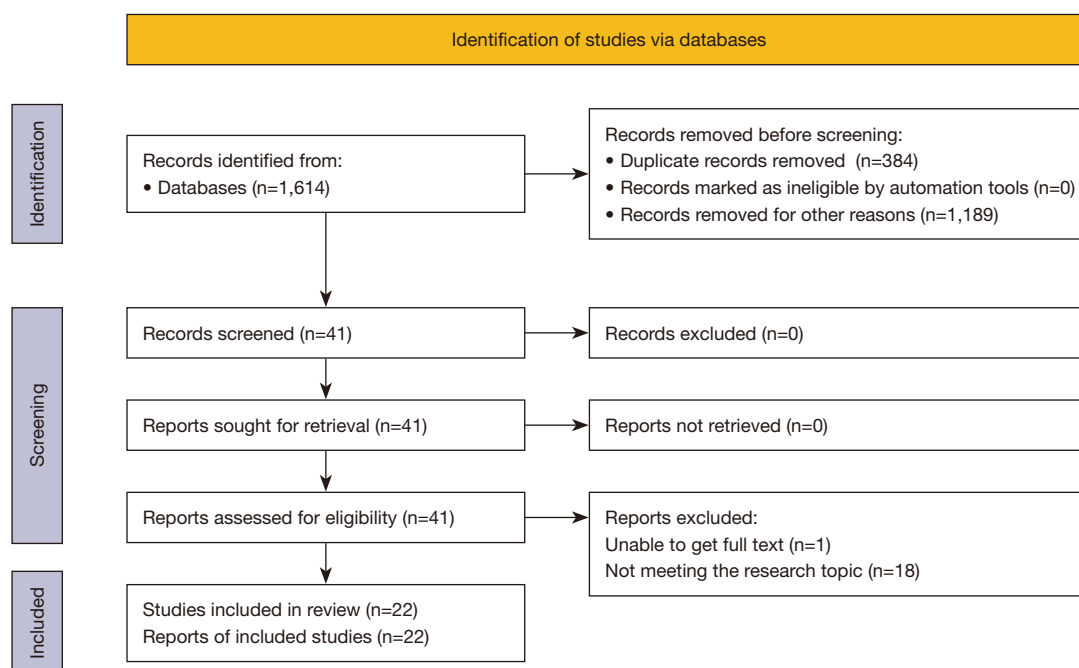


Figure 1 Flow diagram of literature search.

LR rate, regional recurrence (RRR) rate, LRR rate, distant metastasis rate, systemic recurrence (SR) rate, and total death rate; (V) study design: cohort studies; (VI) studies published in English; (VII) the most recent study of an author.

Exclusion criteria were: (I) animal experiments and pharmacological or pharmacokinetic studies; (II) women with a history of breast cancer and surgical management; (III) reviews, meta-analyses, case reports, conference abstracts, or letters; (IV) interventions other than AFT during treatment; (V) outcomes not relevant to AFT; (VI) literature published repeatedly or without complete data.

Data extraction and quality appraisal

Two researchers screened the articles independently, and a third researcher participated in the extraction of data if there was disagreement between them. Information extracted in the present study included the first author, year, country, total number of patients, age, type of surgery, outcomes, and quality assessment scores.

The modified Newcastle-Ottawa Scale (NOS) was employed for evaluating article quality (15). Three major separate items contributed to the overall NOS quality assessment tool: patient selection, comparability of the treatment and observation groups, and outcome assessment.

The scale has 10 points, with 1–4 considered to be low-quality articles and 5–10 high-quality articles.

Statistical analysis

STATA 15 software (Stata Corporation, USA) was used for data analysis. Relative risk (RR) was used as the efficacy statistic indicator, and effect size was described as 95% confidence intervals (CIs). The heterogeneity among the articles was explored using the I^2 test. When $I^2 \geq 50\%$, the random effects model was employed; otherwise, the fixed effect model was used. Sensitivity analysis was performed for all outcomes. The potential bias in studies was evaluated using a comparison-adjusted funnel plot, which serves as an intuitive visual instrument for detecting the presence of any dominant types of potential bias, such as publication bias, selective reporting, or other biases. Egger's test was performed to determine whether P values were less than 0.05. $P < 0.05$ was considered statistically significant.

Results

Literature search and study characteristics

The literature selection process is shown in *Figure 1*. Initially, 1,614 studies were identified in the electronic

search. After duplications were removed, 1,230 articles remained, among which 1,189 were excluded based on the inclusion and exclusion criteria. The titles and abstracts were then screened for 41 studies. Ultimately, 22 cohort studies (16-37) were included in the study based on the full text (*Figure 1*).

In total, 9,971 patients treated for breast cancer were included in this meta-analysis. Of those patients, 3,622 patients underwent AFT (experimental group), and 6,349 patients did not undergo AFT (control group). The results of the upgraded NOS indicated that the 22 articles were all regarded as high quality (*Table 1*).

Table 1 Details of included studies

Author	Year	Country	Group	Total patients	Age [range or \pm SD]	Type of surgery			Histology		Outcomes	NOS scores
						Mastectomy	BCS	Quadrantectomy	Invasive	<i>In situ</i>		
Petit	2012	Italy	AFT	321	45 [22–71]	196		125	284	37	ABCDF	6
			NFT	642	46 [26–69]	392		250	568	74		
Seth	2012	USA	AFT	90	49.4 \pm 8.8	90			50		B	6
			NFT	1,112	48.0 \pm 10.6	1,112			587			
Petit	2013	Italy	AFT	59	49 [33–65]	47		12			B	7
			NFT	118	50 [29–72]	94		24				
Kim	2014	Korea	AFT	102	46.3 [22–63]	102				42	A	5
			NFT	449		449						
Gale	2015	USA	AFT	211	52.2 [30–76]	176	35		184	27	ABCDF	7
			NFT	422	52.7 [30–72]	358	64		368	54		
Laporta	2015	Italy	AFT	20	44.8 [35–57]	20					B	6
			NFT	20	44.95 [35–59]	20						
Masia	2015	Italy	AFT	107	49.19 [31–65]	107	0		75	16	B	6
			NFT	107	48.98 [31–71]	107	0		72	14		
Pinell-White	2015	USA	AFT	51	49.6 [32–68]	51	0				A	5
			NFT	51	48.9 [32–66]	51	0					
Mestak	2016	Czech	AFT	32	53 [39–67]	0	32		24	4	AD	6
			NFT	45	64 [37–84]	0	45		41	3		
Kronowitz	2016	USA	AFT	719	47.7 \pm 9.6	639	79		552	108	AE	7
			NFT	670	46.5 \pm 10.5	591	73		548	61		
Cohen	2017	USA	AFT	414	52.6 \pm 11.1	414			319	83	BD	7
			NFT	162	47.8 \pm 8.7	162			111	51		
Fertsch	2017	Germany	AFT	100	49.6	100	0		73	9	A	7
			NFT	100	50.7	100	0		73	9		
Khan	2017	UK	AFT	35	49 [35–70]	0	35				B	5

Table 1 (continued)

Table 1 (continued)

Author	Year	Country	Group	Total patients	Age [range or \pm SD]	Type of surgery			Histology		Outcomes	NOS scores
						Mastectomy	BCS	Quadrantectomy	Invasive	In situ		
			NFT	64	54 [36–73]	0	64					
Petit	2017	Italy	AFT	322		0	322		322		BCDF	6
			NFT	322		0	322		322			
Silva-Vergara	2017	Spain	AFT	205	49.1 [23–72]	147	58		161	44	BCDF	7
			NFT	410	49.7 [24–72]	286	124		335	75		
Stumpf	2017	Brazil	AFT	27	53.6 \pm 10.9	0	27		27	0	BE	6
			NFT	167	56.4 \pm 12.0	0	167		167	0		
Calabrese	2018	Italy	AFT	64	50.3 [33–69]	64	0		23		AE	7
			NFT	64	47.7 [33–60]	64	0		25			
Krastev	2019	Netherlands	AFT	300	48.1 [9.0]	161	139		261	39	ADF	6
			NFG	300	49.4 [8.4]	150	150		260	40		
Sorrentino	2019	Italy	AFT	233	49.4 [\pm 9.0]	179	54		207	26	ADF	6
			NFT	597	50.7 [\pm 8.9]	53	444		535	62		
Hanson	2020	USA	AFT	72	53 [46.0–61.0]						A	7
			NFT	72	54 [46.5–64.0]							
Stumpf	2020	Brazil	AFT	65	53 [46.0–61.0]	0	65		65		BCD	6
			NFT	255	54 [46.5–64.0]	0	255		255			
Vyas	2020	USA		73	48.6 \pm 8.8						A	6
				200	50.2 \pm 9.2							

AFT, autologous fat transfer; NFT, non-autologous fat transfer; BCS, breast-conserving surgery; A, locoregional recurrence rate; B, local recurrence rate; C, regional recurrence rate; D, distant metastasis rate; E, systemic recurrence rate; F, total death rate; NOS, Newcastle-Ottawa Scale.

Overall results of the meta-analysis

LR rate

The LR rate (%) of breast cancer patients was analyzed in 12 studies. No significant heterogeneity was detected after merging studies ($I^2=0.0\%$). The fixed effect model demonstrated that the rate of LR in the AFT group was lower than that in the non-AFT group (RR: 0.92, 95% CI: 0.70–1.19). However, the difference was not statistically significant ($P=0.514$; Table 2, Figure 2).

RRR rate

The rates of RRR (%) were identified in 5 cohort studies. Analysis of the fixed effect model showed no difference between the RRR rate of the patients who underwent AFT

and those who did not receive AFT (RR: 1.17, 95% CI: 0.77–1.79, $P=0.451$; Table 2, Figure 3).

LRR rate

Twelve cohort studies reported the LRR rate. The fixed effect model showed that the AFT group had a relatively lower LRR rate compared with the control group (RR: 0.79, 95% CI: 0.62–1.01, $P=0.056$; Table 2, Figure 4).

SR rate

The SR rate was included in 3 studies. The results indicated that the SR rate in patients undergoing AFT was lower than in those who did not receive AFT (RR: 0.67, 95% CI: 0.49–0.92, $P=0.012$; $I^2=0.0\%$; Table 2,

Table 2 Results of overall meta-analysis

Characteristics	RR (95% CI)	P value	I ²
LR rate			
Overall	0.92 (0.70–1.19)	0.514	0.0
Sensitivity analysis	0.92 (0.70–1.19)		
Publication bias	t=1.04	0.310	
RRR rate			
Overall	1.17 (0.77–1.79)	0.451	0.4
Sensitivity analysis	1.17 (0.77–1.79)		
LRR rate			
Overall	0.79 (0.62–1.01)	0.056	0.0
Sensitivity analysis	0.79 (0.62–1.01)		
Publication bias	t=1.08	0.315	
Distant metastasis rate			
Overall	1.13 (0.91–1.42)	0.248	0.0
Sensitivity analysis	1.13 (0.91–1.42)		
Publication bias	t=1.27	0.225	
SR rate			
Overall	0.67 (0.49–0.92)	0.012	0.0
Sensitivity analysis	0.67 (0.49–0.92)		
Total death rate			
Overall	0.75 (0.54–1.05)	0.096	0.0
Sensitivity analysis	0.75 (0.54–1.05)		

LR, local recurrence; RRR, regional recurrence; LRR, locoregional recurrence; SR, systemic recurrence; RR, relative ratio.

Figure 5).

Distant metastasis rate

In total, 9 cohort studies investigated distant metastasis rate. The pooled RR showed no difference in the rate of distant metastasis between breast cancer patients who received AFT and those who did not (RR: 1.13, 95% CI: 0.91–1.42, P=0.248; I²=0.0%; Table 2, Figure 6).

Total death rate

Six studies reported the total death rate. Our analysis found that there was no significant difference in total death rate between patients who underwent breast cancer surgery with AFT and those without AFT (RR: 0.75, 95% CI: 0.54–1.05, P=0.096; I²=0.0%; Table 2, Figure 7).

Sensitivity analysis and publication bias assessment

In the current meta-analysis, sensitivity analysis was used to evaluate the robustness and reliability of pooled results. The outcome of sensitivity analysis showed that the removal of each study did not markedly affect the overall RRs, and the results of this meta-analysis were reliable and steady.

The publication bias of our study was evaluated using Egger's test, which showed that there was no publication bias in LR rate (t=1.04, P=0.310), LRR (t=1.08, P=0.295), and distant metastasis (t=1.27, P=0.225; Table 2).

Discussion

In the present study, we performed a comprehensive assessment of the oncological safety of AFT in terms of the rate of recurrence, metastasis, and total deaths in 9,971 postoperative breast cancer patients. Compared with the controls who did not receive AFT, our study found that there was no increased risk of LR, RRR, LRR, distant metastasis, and total deaths in breast cancer patients after AFT. However, a decreased risk of SR rate was observed in breast cancer patients receiving AFT. The results of this study confirmed that AFT could be conducted safely in breast reconstruction following breast cancer surgery.

The primary concern with the application of AFT in breast reconstruction is that it might directly or indirectly affect the rate of tumor recurrences. Our meta-analysis evaluating the oncological safety of AFT with a large sample size revealed that no significant differences were observed between the 2 groups regarding the rate of LR, RR, and LRR, and the AFT group displayed a lower SR. A retrospective review demonstrated that AFT did not increase the rate of LRR following breast reconstruction operations combined with improved radiographic imaging (18). Our results were also consistent with the LR rate in studies by Rigotti *et al.* (0.43%) (38) and Masia *et al.* (4%) (21) of patients undergoing AFT. These studies involved lengthy follow-up after AFT, but they did not include a control group of patients (21,38,39). A study conducted by the Nottingham Breast Institute found no evidence that AFT increased the risk of carcinoma in women who had formerly been treated for breast cancer. In contrast to controls, the LRR was slightly higher in the AFT group but not significantly (2.1% versus 1.1%, P>0.05). No significant additional tumor events were found in patients with AFT compared with controls in terms of LRR and RRR (16). These results supported our findings. In addition, we discovered a relatively low risk of SR in women diagnosed

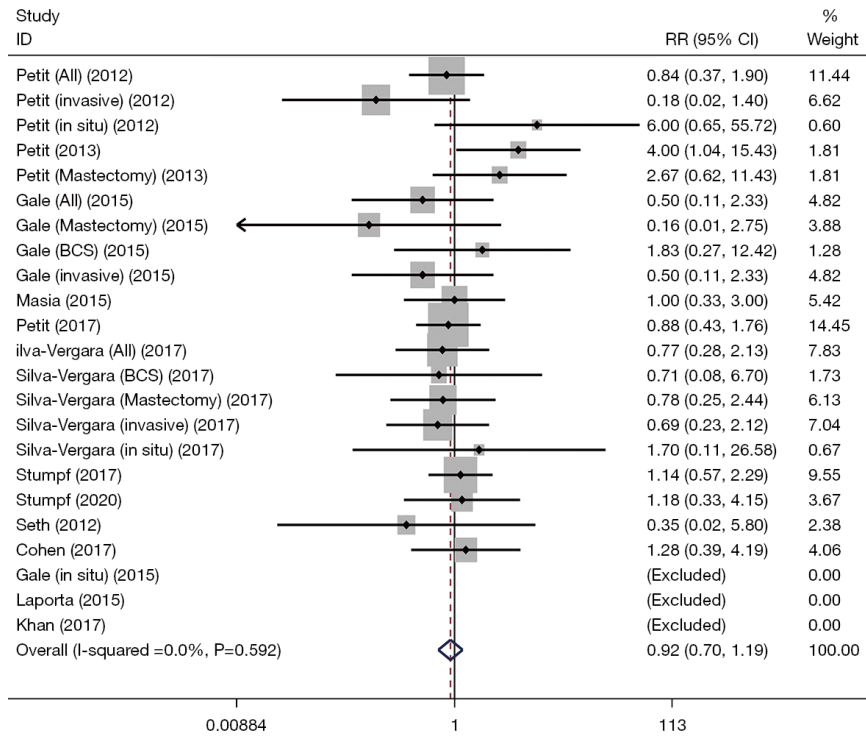


Figure 2 Forest plot of local recurrence rate. P value represents the P value of I^2 . RR, relative risk; CI, confidence intervals.

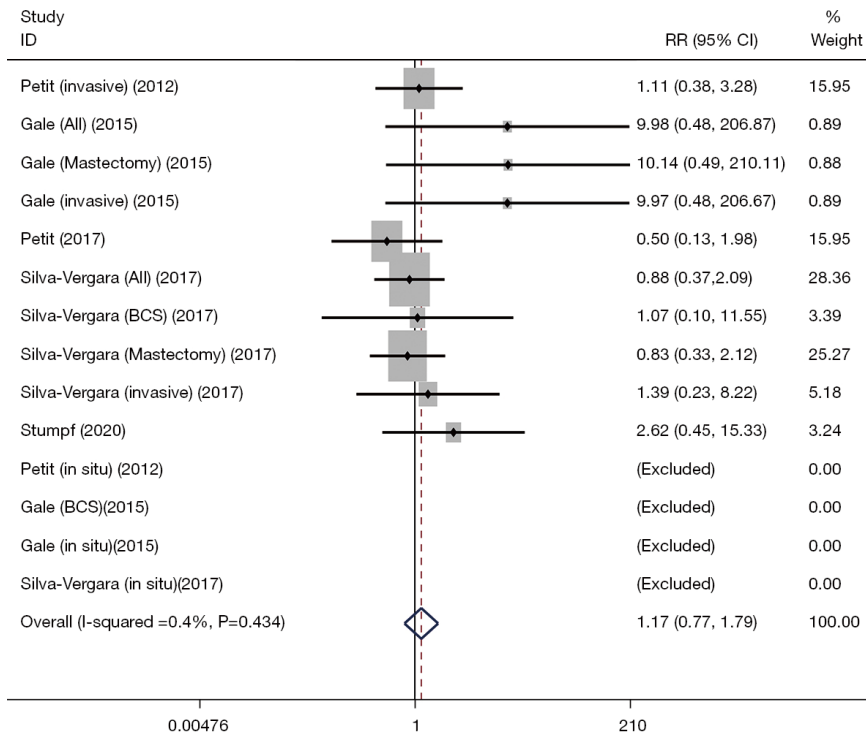


Figure 3 Forest plot of regional recurrence rate. P value represents the P value of I^2 . RR, relative risk; CI, confidence intervals.

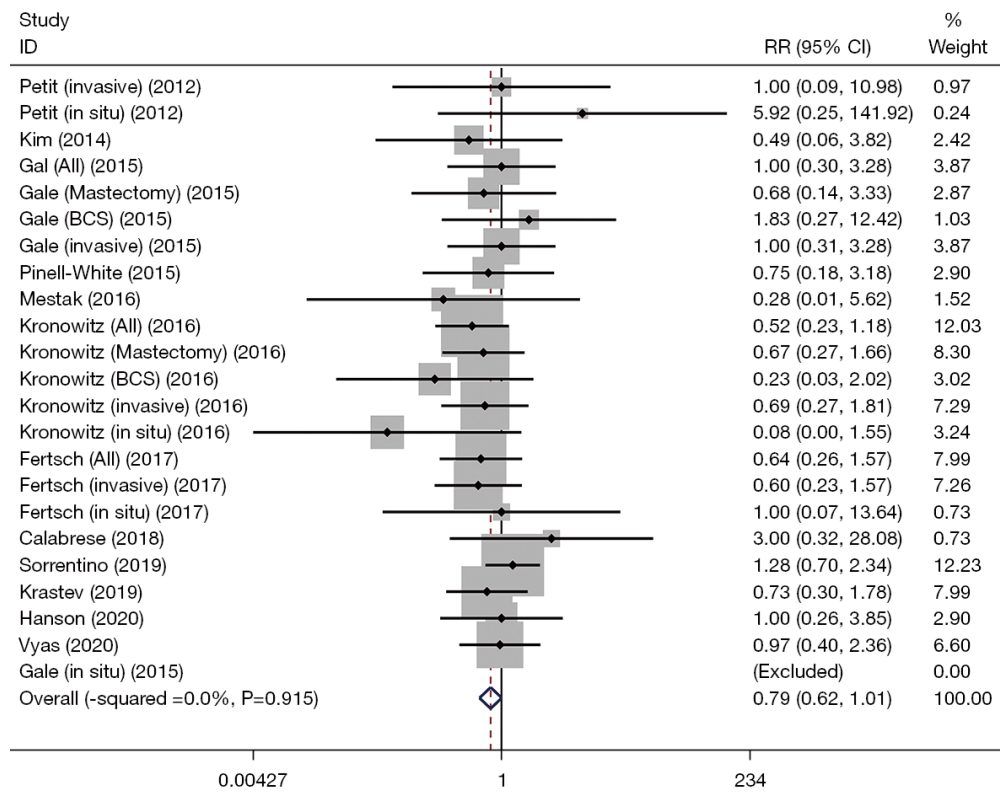


Figure 4 Forest plot of locoregional recurrence rate. P value represents the P value of I^2 . RR, relative risk; CI, confidence intervals.

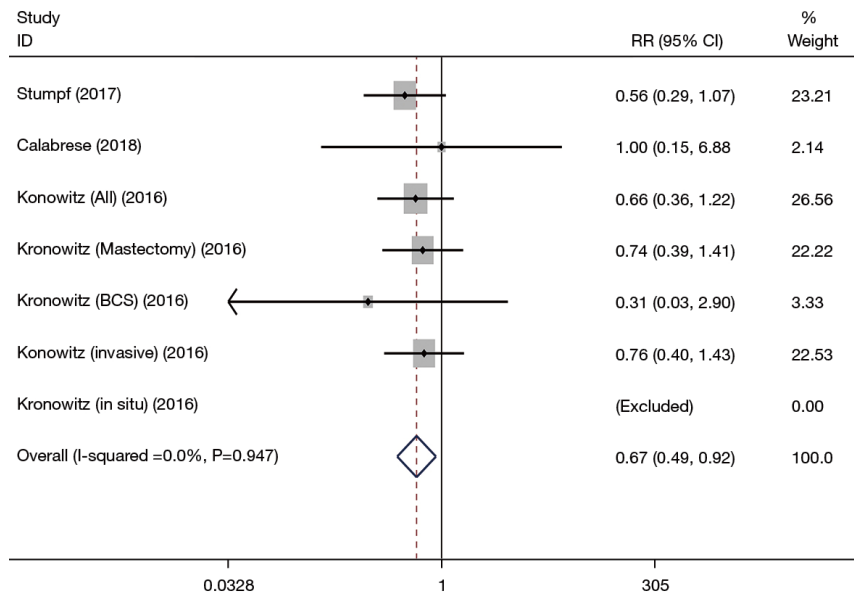


Figure 5 Forest plot of systemic recurrence rate. P value represents the P value of I^2 . RR, relative risk; CI, confidence intervals.

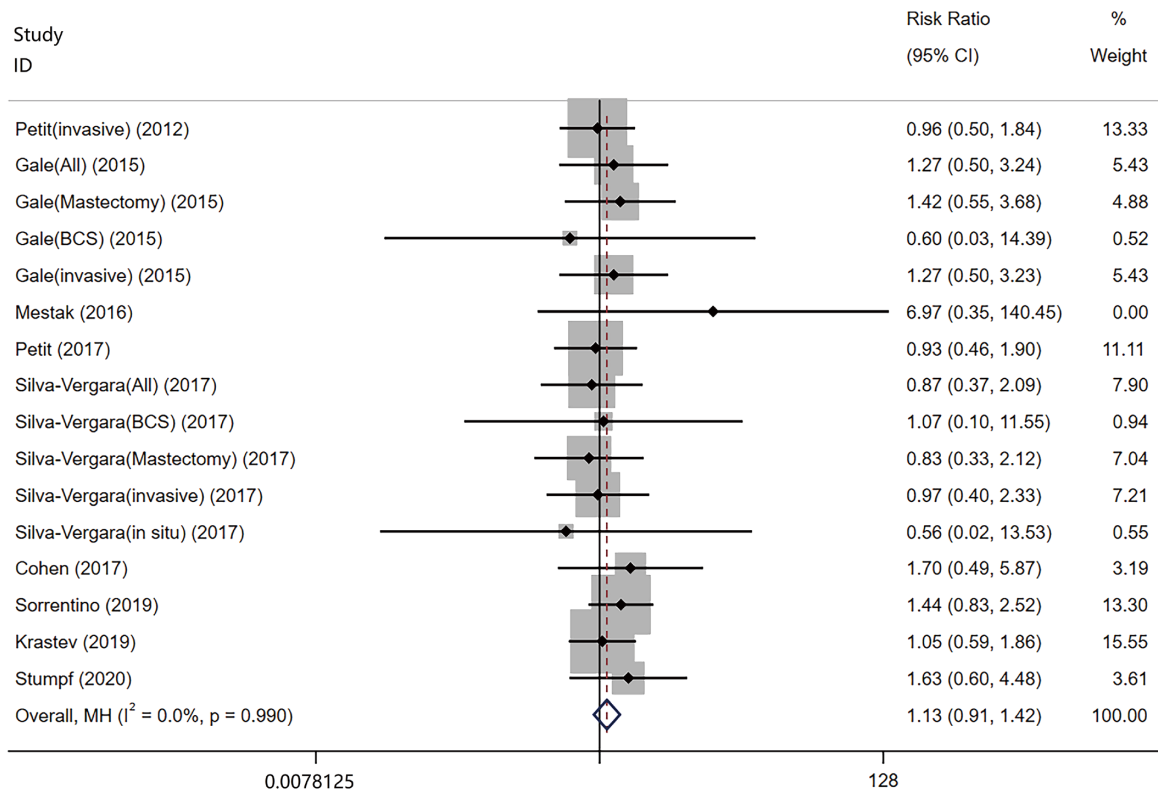


Figure 6 Forest plot of distant metastasis rate. P value represents the P value of I^2 . RR, relative risk; CI, confidence intervals.

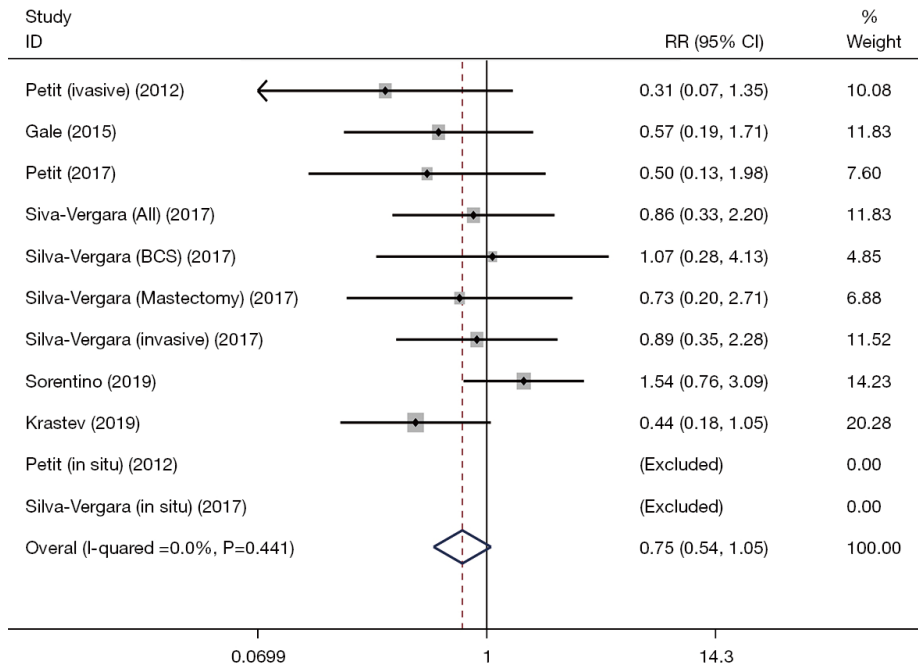


Figure 7 Forest plot of total death rate. P value represents the P value of I^2 . RR, relative risk; CI, confidence intervals.

with breast cancer who underwent AFT surgery. The possible reason is that aesthetic breast augmentation brings less trauma for women in pursuit of beauty.

Another major concern regarding the safety of AFT is the rate of distant metastasis after breast cancer surgery. In the present meta-analysis, there was no significant difference in distant metastasis between the AFT group and non-AFT group. Similarly, another study showed no remote metastasis was documented during the follow-up period (40). Only 6 studies included total deaths, and no prominent findings were found concerning the rate of distant metastasis because there was no significant difference between the 2 groups. A large prospective, randomized, multicenter clinical research is still needed to clearly evaluate the safety of AFT in a cancer setting.

AFT techniques are promoted, to a certain extent, to women seeking aesthetic breast augmentation in an oncologically safe way. Compared with other breast cancer surgeries, the benefits of AFT include low incidence of complications, easy access to donor sites, low morbidity, and the fact that it can be performed in an outpatient setting. Fat grafts are obtained by sucking accumulated fat from the abdomen, thighs, and other parts of the body, and thus breast cancer patients have less trauma, no obvious immune rejection response, natural feel, and postoperative morphological improvement. Low donor-site morbidity and improved cosmetic results are the main advantages of AFT, and these reasons make it easier for women who have received breast cancer surgery, and even doctors, to opt for the AFT procedure (41,42).

Our study had several strengths. Firstly, we searched multiple databases and collected as much literature as possible for inclusion in this meta-analysis. Secondly, we selected high-quality literature for analysis to enhance the persuasiveness of our findings. Finally, publication bias of the included studies was synthetically evaluated via Egger's test and funnel plots. However, there were several limitations that should be noted. First, corresponding factors influencing RR, LR, LRR, and SR were not reported in the included studies, such as tumor size and stage, surgical modalities (breast conservative operation or mastectomy), cancer histology types (*in situ* or infiltrating cancers), and postoperative radiotherapy. Second, further imaging in patients should be added in future studies. Last, our meta-analysis comprised only publications in English, which may cause language bias. Considering the above limitations, the findings of our study should be interpreted with caution.

Conclusions

This analysis found that there was no increased risk of LR, RR, LRR, distant metastasis, and total deaths in patients receiving AFT, providing valuable evidence-based support for the oncological safety of AFT. Overall, for breast cancer patients, AFT appeared to be a safe procedure. Further research with follow-up and oncological series are needed to validate the findings of this meta-analysis.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the MOOSE reporting checklist. Available at <https://gs.amegroups.com/article/view/10.21037/gS-22-297/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://gs.amegroups.com/article/view/10.21037/gS-22-297/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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(English Language Editor: A. Muijls)

Cite this article as: Tian D, Chu Y, Zhang G, Huang D, Huang J, Zeng J. The prognosis outcomes of autologous fat transfer for breast reconstruction after breast cancer surgery: a systematic review and meta-analysis of cohort studies. *Gland Surg* 2022;11(7):1180-1191. doi: 10.21037/gs-22-297