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REVIEW

BREAST SURGERY

The Efficacy of Cell-Assisted Lipotransfer Versus Conventional Lipotransfer in Breast Augmentation: A Systematic Review and Meta-Analysis

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Abstract

Background Cell-assisted lipotransfer (CAL) is novel and controversial technique for breast augmentation.

Objective This review and meta-analysis aimed to assess the clinical efficacy of CAL as compared with conventional lipotransfer.

Methods PubMed databases were searched with no restrictions for randomized controlled trials (RCTs) and observational studies with control groups. Keywords included "fat graft," "lipotransfer," "lipofilling," "autologous fat," "fat transplantation," "stromal vascular fraction (SVF)," "stem cell," "adipose tissue-derived stromal cell (ADSC)," "adipose tissue-derived stromal cell (ASC)," "called adipose derived progenitor cells (ADRC)," "cell-assisted," "progenitor-enriched," "cell-enhanced" and "breast." Review Manager software (RevMan, version 5.3) was used to compute the pooled effect estimates for fat survival rate and complication rates. Outcomes were expressed as standard mean differences (SMDs) or odds ratios (ORs) and 95% confidence intervals (CIs). Subgroup analyses were performed based on different methods of cell-enhanced fat preparation.

Results Six studies were included (n_{total} = 353 adult patients). The fat survival rate was significantly higher in the CAL group than in the control group (SMD = 1.79, 95% CI = 0.28, 3.31; P = 0.02). There were no significant differences in complication rates between the CAL group and the control group (OR = 1.34, 95% CI = 0.65, 2.73; P = 0.43). Subgroup analyses found no significant differences between the SVF and control groups in fat survival rate (SMD = 1.52, 95% CI = −0.21, 3.24; P = 0.08) among both manual and automatic subgroups (P = 0.28 and P = 0.10, respectively). The data analysis showed a significant heterogeneity between manual and automatic subgroups (I^2 = 57.0%, P = 0.15).

Conclusion This study suggests that cell-assisted lipotransfer is superior to conventional lipotransfer for improved fat survival rate in breast augmentation. However, analyses comparing the SVF-enhanced fat graft with the conventional fat graft noted no differences in fat survival rate. It is necessary to determine which protocol is most beneficial for patients, establish standardized methods of SVF isolation or adipose tissue-derived stromal cells (ADSCs) culture, and a constant percentage of injected cells in the graft. The long-term efficacy and safety of CAL should also be evaluated in further studies, and additional RCTs with larger sample sizes and better comparability are needed.

Level of Evidence IV This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors www.springer.com/00266.

Keywords Autologous fat · Lipotransfer · Cell-assisted · Breast · Fat survival rate · Complication · Meta-analysis

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Introduction

Autologous fat is currently considered an ideal filler due to its histocompatibility, versatility, accessibility, nonimmunogenic properties, and low risk of complications [1]. The autologous fat graft was first described in 1919 and now is a common procedure for correction of volume and contour defects after trauma, cancer, radiotherapy, or purely aesthetic reasons [2]. Illouz first described autologous fat grafting of the breast using liposuctioned adipose tissue in 1983, and Bircoll published this approach in 1987 [3, 4]. Breast augmentation continues to be the most prevalent plastic surgical procedure worldwide [5, 6]. Currently, lipotransfer is an alternative strategy for breast augmentation, correction, and reconstruction without concerns about postoperative complications induced by artificial implants, such as rupture, capsular contracture, unnatural contour, hardness, neurologic symptoms, or immune response [7]. However, the main limitation of lipotransfer is an inconstant graft resorption rate ranging from 20 to 80%, leading to multiple procedures [8].

Various products such as insulin, vascular endothelial growth factor (VEGF), platelet-rich plasma (PRP), and stromal cells have been used to increase fat graft retention and make the procedure a more reliable and attractive alternative, especially in slim patients with limited fat resources [9–11]. A systematic review by Vyas and Vasconez et al. showed that the majority of enrichment strategies demonstrated positive benefit for fat graft survival, particularly with growth factors and ADSCs enrichment and ADSCs had the strongest evidence to support efficacy in human studies and may demonstrate a dose-dependent effect [12]. ADSCs can differentiate into various cell lineages, including adipogenic, osteogenic, chondrogenic, myogenic, cardiomyogenic, and neurogenic and also release paracrine factors to display angiogenic properties and help the surrounding tissue resist hypoxia and ischemia [13–15]. They are present in large amounts in the SVF, which can be obtained after enzymatic digestion of the lipoaspirate, and have the advantages of abundance and being easy to isolate [16].

CAL, defined as autologous fat transplantation enriched with stromal cells, is proposed to increase fat graft survival and reduce complications [17]. In 2008, Yoshimura et al. conducted a clinical trial that investigated the use of CAL in breast augmentation and facial lipoatrophy [11, 18]. Since then, a series of studies have examined CAL's efficacy in terms of fat graft retention rates and the postoperative complications induced by this technique in breast enhancement, with the inconsistent results. For example, a comparative translational study conducted by Gentile et al. found that the patients treated with SVF-enhanced autologous fat grafts showed a 63% maintenance of contour restoring and three-dimensional volume after 1 year as compared with control group patients treated with a centrifuged fat graft, who showed a 39% maintenance [10]. A randomized controlled clinical trial (RCT) by Kølle et al. showed that ex vivo-expanded autologous ADSCs ensured enhanced fat graft retention in breast augmentation [6]. In contrast, a prospective comparative study by Peltoniemi suggested that CAL did not warrant a higher graft survival in lipofilling of the breast [19]. Finally, a meta-analysis by Zhou et al. suggested that CAL slightly (but not significantly) increased the fat survival rate in breast fat grafting and was not superior to a conventional fat graft in reducing complications [20].

Therefore, the objective of this review and meta-analysis was to assess the efficacy of CAL compared with conventional lipotransfer in improving fat retention and reducing complications in breast augmentation.

Methods

This systematic review and meta-analysis were conducted in accordance with the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement [21] and the Cochrane Handbook for Systematic Reviews of Interventions [22].

Search Strategy and Study Selection

On August 15, 2020, we conducted an electronic literature search in PubMed. The following search terms were used: ("fat graft" OR "lipofilling" OR "fat transfer" OR "lipotransfer" OR "lipografts" OR "fat transplantation") AND ("SVF" or "stem cell" or "ADSC" OR "ASC" OR "ADRC" OR "cell assisted" OR "progenitor-enriched" OR "cell-enhanced") AND "breast." After excluding duplicates, both authors screened the titles and abstracts of all the retrieved articles. Studies found manually or through the reference lists of included studies were also eligible for inclusion. Studies were eligible for inclusion if (a) their participants were patients who had undergone breast reconstruction or filling with fat grafting as the only treatment, (b) they assessed the clinical efficacy of autologous CAL, (c) patients in the control group were treated with fat grafting alone, and (d) they assessed fat survival rate. Any discrepancies between the two authors were resolved by discussion, and the authors unanimously agreed on the final decisions.

Data Extraction

The following information would be extracted: bibliographical information (i.e., author, year), study design, sample size, mean age, mean body mass index (BMI), follow-up period, intervention strategies, and study outcomes.

Statistical Analysis

Pooled effect estimates were computed with Review Manager software (RevMan, version 5.3, Copenhagen, Denmark). Random effects models were used if heterogeneity ($I^2 > 25\%$) was present between individual studies, and outcomes were expressed as odds ratios (ORs) or standardized mean differences (SMDs) with their associated 95% confidence intervals (CIs). The complication rate was estimated using a random effects Mantel–Haenszel model, where an $I^2 > 50\%$ indicated significant heterogeneity. Statistical significance was set at $P < 0.05$.

Results

Figure 1 presents a flow diagram of the literature search and selection process. The initial search of PubMed and other sources identified 124 citations after the removal of duplicates. Based on the assessment of titles and abstracts, 35 studies were of the inclusion criteria and were included in the meta-analysis [6, 7, 10, 19, 23, 24]. Two of the included studies were carried out by Gentiled et al. [7, 10] However, based on the reported diagnoses of the included patients, we determined that there was no duplication between the two studies [7, 10]. Dates were extracted by reading the studies and contacting the studies' corresponding authors as necessary by email. One of the included studies provided the medians and ranges of survival rates and sample sizes. We used these data to calculate means and standard deviations using standard methods [6, 25]. The baseline characteristics of the included studies are summarized in Table 1. The methods used in cell-enhanced lipotransfer preparation and concentration of cells are summarized in Table 2.

Meta-Analysis

Fat Survival Rate

As shown in Fig. 2, six studies compared the fat survival rate between CAL and control groups. Significant heterogeneity was observed among the individual studies (I^2 = 95%, $P < 0.00001$), so a random effects model was used to pool estimates of fat survival rate. The fat survival rate was

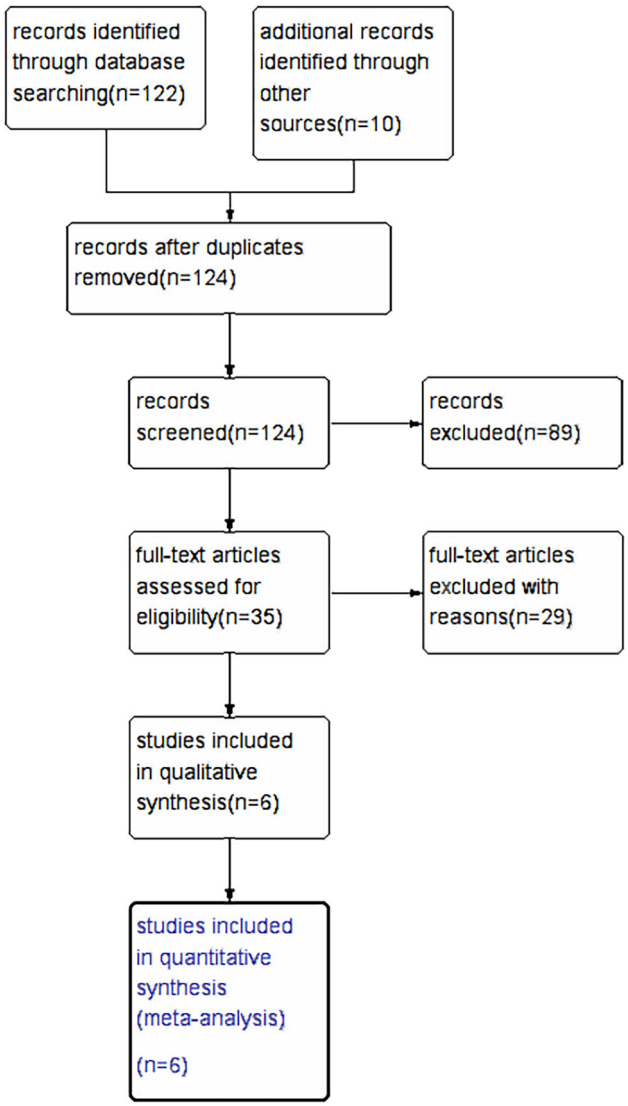

Fig. 1 Flow diagram of the literature search and selection process

significantly higher in the CAL group than in the control group (SMD = 1.79, 95% CI = 0.28, 3.31; P = 0.02).

Subgroup Analyses

We performed a subgroup analysis of fat survival rate between CAL and control groups. Subgroups were defined according to lipofilling was enhanced with SVF or cultured ADSCs (Fig. 3). Only one included study used cultured ADSCs and the other studies were categorized into the SVF subgroup. The results indicated that there was no significant difference in fat survival rate between SVF and control groups (SMD = 1.52, 95% CI = −0.21, 3.24; P=0.08) and that significant heterogeneity was present among the studies (I^2 = 96%, P<0.00001). Testing for the overall effect showed that the CAL group had a significantly increased fat retention relative to the control group

Table 1 Baseline characteristics of the included studies

Author/year	Study design	Groups	Size of sample (*n*)	BMI, kg/m^2 (±SD range)	Age/ years (±SD, range)	Donor sites	No. of operation	Mean volume of liposolution, ml (± SD, range)	Volume of stem cell isolation, ml (± SD, range)	Mean volume injected, ml (± SD, range)	Volumetric measurement method	Fat survival rate, % (±SD)	Follow-up (mon)	Patients satisfaction *n*(%)	Complication *n* (%)
Kolle S.T. 2020	Randomized clinical trial	ADSCs+Fat	6	19.2 (18–22.5)	29 (21–42)	Abdomen/ thigh/hips	1	NR	100	222.5 (270–182.5)	MRI	87.6% ± 17.32%	4	NR	0
		Fat	6	20.8 (19.7–23.8)	32.5 (24–39)		1	NR		260 (310.6–240)	MRI	44.35% ± 4.12%	4	NR	0
Gentile, P 2019	Retrospective observational case-series study	SVF + Fat	46	27 (21–33.6)	36.2 (22–53)	Abdomen/ flanks/ thigh/inner knees	1 (85%) and 2 (15%)	715.4 (250–1080)	234.46 (50%)	180 (80–280)	MRI	58% ± 8%	36	100%	11
		Fat	30	27 (21–33.6)	38.5 (21–56)		1 (70%) and 2 (30%)	NR		180 (80–280)	MRI	29% ± 8%	36	63%	9
Chiu, C. H. 2019	Retrospective observational case-series study	SVF + Fat	101	20.3 (±2.4)	37 (±7.4)	Abdomen/ flanks/hips/ thigh/calves	NR	1655 ± 507 (1200–3700)	100	334 (±44)	3D laser scan	68.7% ± 5.6%	12	NR	6
		Fat	105	18.8 (±1.6)	33 (±9.4)		NR	1456 ± 294 (1200–1960)		310 (±36)	3D laser scan	67.9% ± 8.3%	12	NR	4
Tissiani, L. A. 2016	Retrospective observational case-series study	SVF + Fat	11	NR	NR	NR	NR	NR	600 (67%)*	134.3	MRI	78.8% ± 74.9%	NR	NR	4
		Fat	10	NR	NR		NR	NR		111.5	MRI	51.4% ± 18.4%	NR	NR	0
Peltoneimi, H. H. 2013	Prospective controlled clinical trial	SVF + Fat	10	23.4 (20.3–32.5)	51 (29–58)	NR	NR	NR	(240–360) (50%)*	292 (180–438)	NR	50% ± 10%	NR	NR	2
		Fat	8	23.4 (20.3–25.9)	39 (33–63)		NR	NR		NR	NR	54% ± 7%	NR	NR	1
Gentile, P 2012	Retrospective observational case-series study	SVF + Fat	10	NR	(19–60)	Abdomen	NR	715.4 (250–1080)	234.46 (50%)*	197.7	MRI	63% ± 5%	12	NR	NR
		Fat	10	NR	(21–56)		NR	NR		197.7	MRI	39% ± 5%	12	NR	NR

NR Not reported

*The percentage of the lipoaspirate used to lipoaspirate used to isolated SVF in the total harvested lipoaspirate

Table 2 Method used in cell-enhanced lipotransfer preparation and concentration of cells

Author/year	CAL groups	SVF extraction method	Cell concentration	System	Volume of stem cell isolation, ml (± SD, range)
Kolle S.T. 2020	ADCSs + Fat	ADSCs+Fat	$\geq 20 \times 10^6$ADCSa/ml		100
Gentile, P 2019	SVF + Fat	Automatic	448403 ±35645 SVF cells/ml	Celution™ 800/CRS system	234.46
Chiu, C. H. 2019	SVF + Fat	Manual	6.78×10^5 SVF cells/ml		100
Tissiani, L. A. 2016	SVF + Fat	Manual	11088182 ± 18292904 SVF cells/ml		600
Peltoneimi, H. H. 2013	SVF + Fat	Automatic	NR	NR	(240–360)
Gentile, P 2012	SVF + Fat	Automatic	250000 ± 34782 nucleated cells/ml	Celution™ 800/CRS system	234.46

NR Not reported

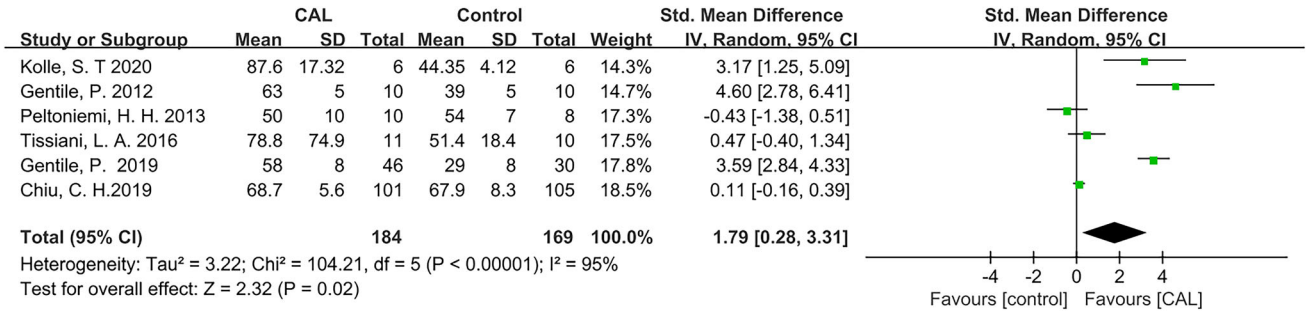

Fig. 2 Comparison between CAL and control group regarding fat survival rate

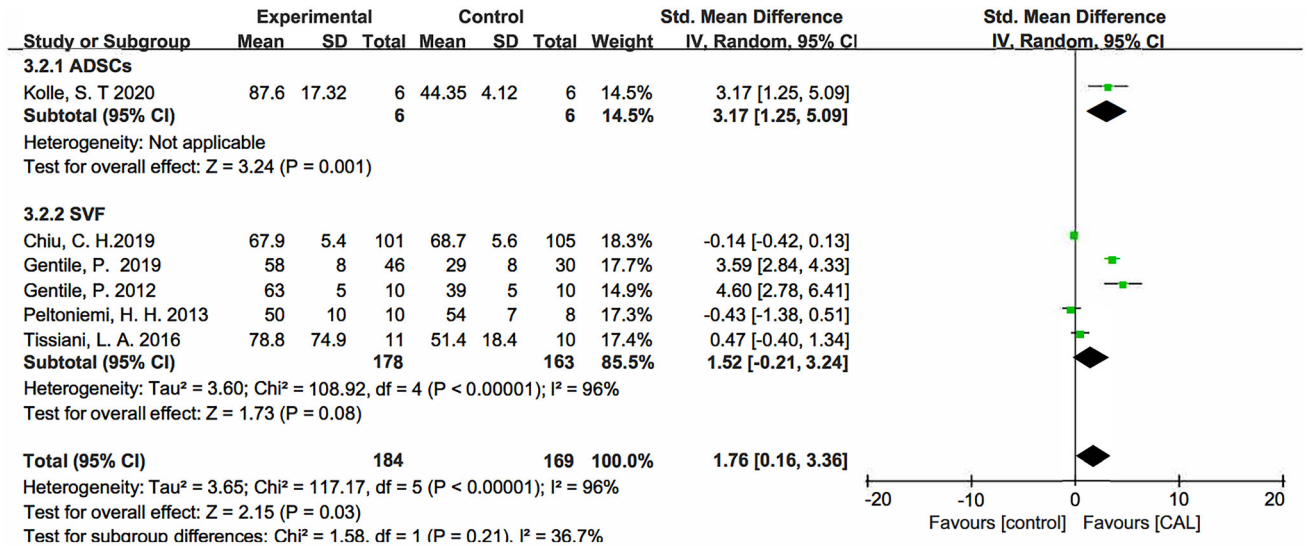

Fig. 3 Subgroup analysis of CAL compared with control group in fat survival rate. Subgroups were delimited based on lipofilling enhanced with SVF or cultured ADSCs

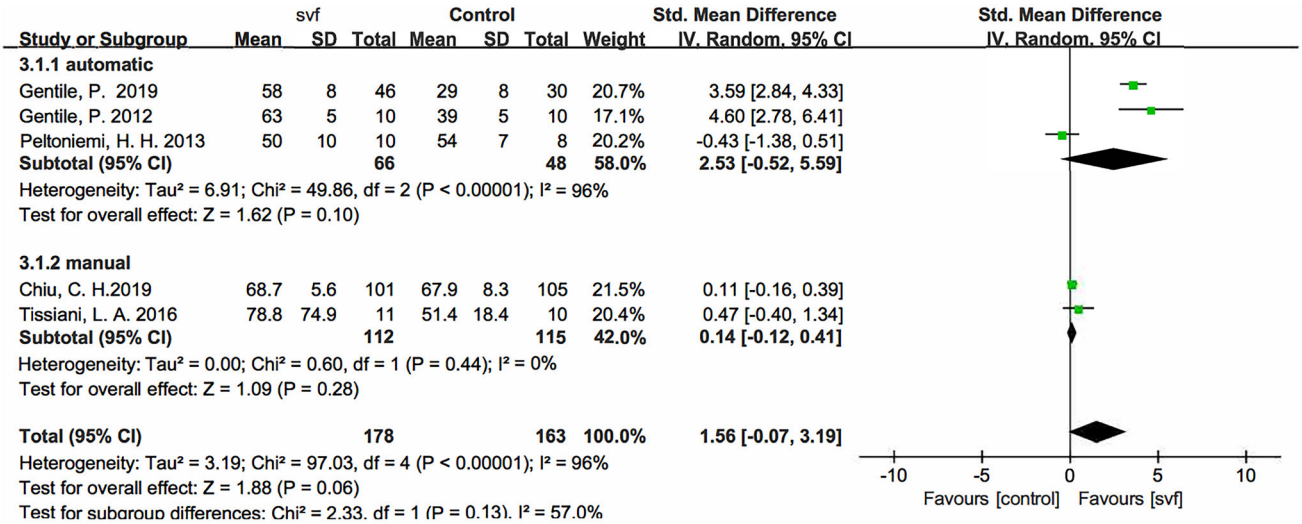

Fig. 4 Subgroup analysis of SVF group compared with control group in fat survival rate. Subgroups were delimited based on SVF isolation by automatic method or manual method

($P = 0.03$), with heterogeneity between the subgroups ($I^2 = 36.7\%$, $P = 0.21$).

In addition, we found that methods for SVF isolation were inconsistent between included studies and could be divided into automatic and manual method subgroups. A subgroup analysis of fat survival rate between the SVF and control groups was performed (Fig. 4). The analysis found a significant heterogeneity between manual and automatic subgroups ($I^2 = 57.0\%$, $P = 0.15$) and no significant difference between the SVF and control groups (both in manual and automatic subgroups) in fat survival rate ($P = 0.28$ and $P = 0.10$, respectively).

Complication Rate

As shown in Fig. 5, five studies assessed the postoperative complication rate of the CAL group compared with the control group. No significant heterogeneity was observed among individual studies ($I^2 = 13\%$, $P = 0.33$), and a fixed effects model was used to pool estimates of complication rates. There was no significant difference in complication rates between the CAL and control groups (OR = 1.34, 95% CI = 0.65, 2.73); $P = 0.43$).

Discussion

This study aimed to systematically evaluate the clinical efficacy of CAL compared with conventional fat graft in breast augmentation. Based on our meta-analysis, fat survival rate was significantly higher for patients using CAL and no significant difference was found in postoperative complication rates between the CAL and control groups.

Currently, the CAL technique is not widely used due to a lack of high-level evidence of efficacy, particularly in breast augmentation. Moreover, in the present literature, the opinions about CAL's clinical efficacy in breast procedures are inconsistent. Peltoniemi et al. and Chiu et al. failed to demonstrate the positive effect of SVF cell enrichment on fat graft survival using CAL, as compared with conventional lipotransfer in breast augmentation [19, 24]. Nevertheless, several studies have described the

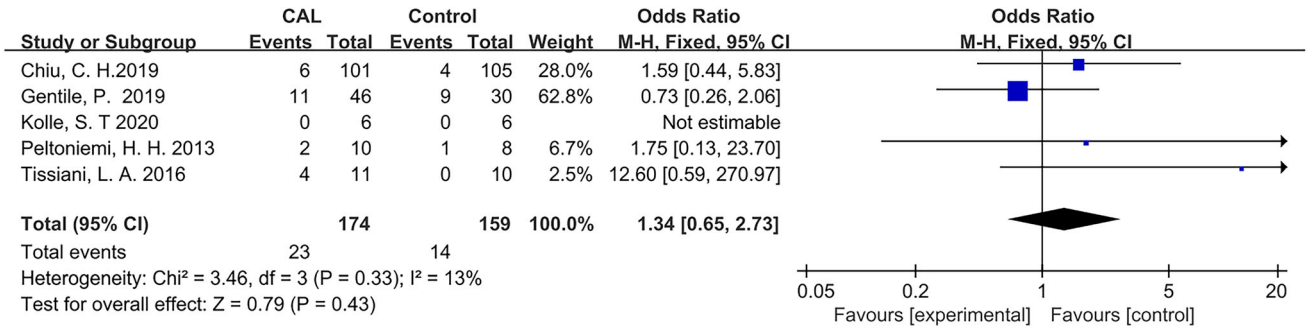

Fig. 5 Assessment of postoperative complication rate of the CAL group compared with control group

positive effects of CAL on fat graft tissue survival in breast procedure [6, 7, 10, 23, 26]. Zhou's meta-analysis demonstrated the efficacy of CAL for filling of the face region, but found that CAL did not reduce the rate of complications. They concluded that CAL seemed not to be beneficial for breast procedures [20].

Furthermore, the procedures used for lipofilling, including ADSCs culture and SVF extraction, were very heterogeneous among the studies. Only one of these included studies enriched the fat graft with cultivated ADSCs. It demonstrated that ADSCs-enriched lipotransfer had a better survival rate than conventional lipotransfer in breast augmentation [6]. An advantage of this approach is the use of only cultivated ADSCs, without red blood cells or hematopoietic cells. However, a good manufacturing practice (GMP)-laboratory is needed to isolate and cultivate ADSCs, which is costly and time-consuming. Further, prolonged exposures involving labor-intensive and manual procedures may increase the risk of transmission of viral or bacterial agents and potential immune rejection [6, 27]. The use of cultivated ADSCs also requires a second procedure. Finally, the debate about the possible oncological risks after CAL is still ongoing [28]. Adult ADSCs do not seem to have the same tumorigenic potential as embryonic stem cells [28]. No serious adverse events have been reported in thousands of patients and over 500 clinical trials using ex vivo-expanded mesenchymal stem cells (MSCs)/ADSCs [29]. However, the potential of oncological risks remains as perhaps the least positive aspect of their use in the clinic.

Since two procedures are required in lipotransfer enhanced with cultured ADSCs, the benefits of ADSC-assisted lipotransfer may should be weighed against two consecutive conventional lipotransfers. We found only three studies that investigated the efficacy of enriched lipofilling with cultivated ADSCs in the face, breast, and arm, respectively. They demonstrated that ADSC-enriched lipofilling had a better survival rate than conventional fat graft and SVF-enriched fat graft [6, 26, 30]. One of these studies demonstrated that adipose-derived stem cells enhanced the survival of fat grafted into the face (resorption = 20.59 vs. 46.81%). In this study, lipotransfers were performed twice in both the CAL and control groups, and test patients simultaneously received 1×10^7ADSCs in the secondary fat grafts [30]. Another of the included studies used vivo-expanded ADSCs in breast augmentation. Intervention patients underwent minor liposuction (100 ml) for the isolation and subsequent expansion of ADSCs, and two weeks later, participants in both the intervention and control groups were subjected to standard liposuction and breast augmentation by a fat graft with or without ADSCs enrichment [6]. To date, no study has compared the efficacy of a single ADSC-assisted lipotransfer with two consecutive conventional lipotransfers in breast or other regions. Liposuction to obtain ADSCs is a minor procedure compared with conventional lipotransfer for breast augmentation. From a scientific point of view, the current approach is acceptable. However, in a clinical setting the number of procedures is very relevant. Whether an ADSC-enriched fat graft is effective enough to be worth the trouble of a complicated procedure has yet to be determined. Overall, the efficacy and long-term safety of lipotransfer enhanced with cultured ADSCs require further study.

The obvious advantages of SVF include its accessibility and that it can be extracted within a single operation. However, the methods used to extract SVF varied among the five included studies and consisted of automatic and manual isolation methods with collagenase digestion [7, 10, 19, 23, 24]. Automatic methods using available systems reported heterogeneous and sometimes not univocal results. A study by Gentile et al. demonstrated that the Celution and FATstem Systems were the best automatic systems for obtaining SVF, improving the maintenance of fat volume, and preventing reabsorption (i.e., 63% and 52% maintenance of contour restoring, respectively, as compared with 39% for the manual method) [31]. Doi et al. reported no differences between automatic and manual methods in the number of extracted cells from adipose tissue and cell viability [32]. The Tissue Genesis Cell Isolation System was used in the study. Our meta-analysis did not find a significant difference between SVF and control groups in fat survival rate, both within the manual and automatic subgroups.

A critical factor in CAL is the concentration of stromal cells in the injected fat. As a supplement for autologous fat grafting, ADSCs may improve fat retention in the following ways: (a) they differentiate into adipocytes and regenerate the adipose tissue, (b) they differentiate into endothelial cells and promote angiogenesis, (c) they release growth factors and help the surrounding tissue to resist hypoxia and ischemia, and (d) they survive as original adipose-derived stem cells [33].

There is no consensus about the amount of ADSCs needed for the optimum survival of the lipotransfer and the volume of harvested fat that should be used to isolate SVF containing that amount of ADSCs. In a study by Dos Anjos et al., the amount of utilized cell enhancement was used to categorize procedures as low (<50,000 SVF cells/cm^3 graft) versus high (>200,000 SVF cells/cm^3 graft) cell enhancement [34]. The study demonstrated that high dose cell-enhanced fat grafts decreased early postsurgical breast edema and significantly improved long-term volume retention.

The volume of lipoaspirate needed to obtain SVF during an operation is a key clinical question, especially in

patients with limited donor sites. The volume of fat used to extract SVF in the included studies is listed in Tables 1 and 2 [7, 10, 19, 23, 24]. In three of the included studies, half of the harvested lipoaspirate used to obtain SVF to enrich another aliquot of lipoaspirate to produce a stem cell-enriched fat graft and the results are inconsistent [7, 10, 19]. Yoshimura et al. and Gentile et al. used "half of the aspirated fat" to isolate SVF and they all supported that CAL is superior to conventional lipotransfer in fat survival rate [7, 10, 11, 35, 36]. In Tissiani's study, 600ml lipoaspirate (two-thirds of the lipoaspirate) was used to isolate SVF, then mixed with 300ml fat and the results showed that intervention group did not present a better volumetric persistence rate [23]. Chiu's study demonstrated that SVF-enriched fat grafting is not superior to conventional lipotransfer for breast augmentation in terms of fat survival and postoperative complications, in which conventional group used 100ml of harvested fat to isolate SVF and the mean volume of grafted fat to the breasts was 310mL [24]. A study by Wang et al. reported that SVF-enriched fat graft showed no significant advantage over the conventional technique in resorption at six months postoperatively (51.84% ± 16.74%, 40–60% reported) [37]. This result suggests that SVF cells harvested from 250mL aspirated fat and 500mL liposuction fluid were insufficient to average 250mL grafted fat for each breast in this study, and more SVF cells are needed to achieve lower resorption. Although the preparation of SVF varies among studies, the methods used to calculate fat retention rate (i.e., the gained volume divided by the injected volume) are consistent between studies. Future research should consider comparing volume augmentation with lipotransfer for both the original lipotransfer volume and the volume that was needed for SVF.

Moreover, there were no differences between the SVF-enhanced fat graft and conventional fat graft in fat survival rates in our meta-analysis. Given the heterogeneity in the methods used for SVF extraction in the included studies, the efficacy of SVF-enhanced lipotransfer has yet to be demonstrated. Most importantly, it is necessary to determine which protocol is the most effective and beneficial for patients and establish standardized methods for SVF isolation and ADSC culturing, as well as a constant percentage of stromal cells in the graft.

The CAL technique is associated with the same complications as conventional lipofilling [7, 8]. These include oil cyst formation, microcalcifications, macrocalcifications, and cytosteatonecrotic areas. Most of the published studies did not find a significant difference between the CAL and conventional fat graft in postoperative complication rates, which is in line with our results [20, 24].

Our study has several limitations. First, our analyses only included six studies and 353 participants. Five of the included studies had relatively small sample sizes (n <100). Second, there was a lack of RCTs that investigated SVF-enhanced lipotransfer, and it is not possible to eliminate all biases in retrospective studies. Furthermore, the included studies applied different protocols for cell-enhanced fat graft preparation, which may have led to potential heterogeneity that we were unable to fully minimize through a random effects model and subgroup analyses. Therefore, more RCTs with larger sample sizes and complete descriptions of the methodology used are needed.

Conclusion

The results of our study suggest that CAL lipotransfer is superior to conventional lipotransfer for improved fat survival rate in breast augmentation. However, we did not find any differences between SVF-enhanced fat grafts and conventional fat grafts in fat survival rate. Given the limitations of our study, additional RCTs with larger sample sizes and better comparability are needed to demonstrate the safety and efficacy of different CAL lipotransfer protocols. It is also necessary to determine which protocols are most beneficial to patients, establish standardized methods for SVF isolation and ADSC culturing, and a constant percentage of injected cells in the graft. Lastly, the long-term efficacy of CAL should be evaluated in future studies.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Informed consent is not required for this type of study.

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