Free-Flap Lower Extremity Reconstruction: A Cohort Study and Meta-Analysis of Flap Anastomotic Outcomes between Perforator and Nonperforator Flaps

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Abstract

Introduction Free-flap outcomes in lower extremity reconstruction carry the lowest anastomotic success rates compared with other anatomical sites. Despite their advantages over traditional nonperforator flaps, free perforator flaps have only recently become established in this area due to the additional challenges faced. It is therefore crucial to assess the anastomotic outcomes of perforator and nonperforator free flaps.

Methods We performed a single-center retrospective cohort study and combined this with a meta-analysis of the relevant literature. We evaluated three flap anastomotic outcomes: reexploration, operative salvage, and flap failure rates.

Results Between January 2010 and June 2015, our center managed 161 patients who underwent lower extremity free-flap reconstruction, which included 76 perforator flaps and 85 nonperforator flaps. The perforator flaps had higher reexploration rates compared with the nonperforator flaps, but this was not statistically significant (18.4 and 10.6%; $p = 0.18$). Perforator flaps had a higher flap salvage rate but were not statistically significant (78.6 and 22.2%; $p = 0.374$). Lastly, although not statistically significant, perforator flaps had a lower rate of complete failure due to anastomotic complications (3.9 and 8.2%; $p = 0.336$). The meta-analysis included 12 studies (inclusive of the index study) and found no statistical difference in all three outcomes.

Conclusion Our meta-analysis is the first reported study and serves as an indication that free perforator flaps in lower extremity are as reliable as their traditional nonperforator counterparts. This does come with the prerequisite appreciation of the anatomical variations, the delicate handling of these flaps, and a low threshold for reexploration.

Keywords
- lower extremity
- perforator flap
- meta-analysis

Godina's landmark paper in 1986[1] paved the way for free-flap transfer in lower extremity reconstruction and salvage, especially with large defects involving the foot and ankle region. Not long after, Koshima's 1989 landmark paper[2] marked the beginning of the perforator flap renaissance. Despite this, the use of perforator flaps in lower extremity reconstruction has only become established recently due to the added level of challenges to complex reconstruction. A shift in reconstructive principle was characterized by Gottlieb and Krieger[3] in 1994. They described the "reconstructive elevator," where the simplest

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method is not always the best, and where reconstructive surgery should entail parallel, creative thought rather than sequential thought.

The challenges of free perforator flap reconstruction in the lower extremity warrant an evaluation of anastomotic safety of the smaller caliber vessels in comparison to the traditional nonperforator flaps. We therefore performed a single-center retrospective cohort study and combined this with a meta-analysis of the relevant literature.

Patients and Methods

Index Cohort Study

A retrospective cohort study was conducted to review all lower extremity free-flap reconstructions performed in Singapore General Hospital between January 2010 and June 2015. The cohort was divided into two groups: perforator flaps and nonperforator flaps. The data fields collected included demographic date (age, race, and sex), comorbidities, location and etiology of the defect, type of free flaps, and flap success. We defined vascular complications as flaps that appeared compromised during postoperative monitoring and were reexplored. These complications encompassed arterial and venous thrombosis. Flap salvage was defined as those that underwent reexploration and were successfully rescued. Complete failure was defined as flaps that were taken down after reexploration.

All information was gathered with institutional review board approval from the proprietary electronic medical record system and enterprise data warehouse. For the index cohort study, categorical variables were analyzed using χ2 and Fisher's exact tests. Statistical software used for data analysis was SPSS 23.0 (SPSS, Chicago, IL).

Meta-Analysis

To further evaluate the anastomotic outcomes comparing both groups in the available literature, a meta-analysis with the inclusion of the index cohort study was performed. The review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The literature search was performed by two independent reviewers (C. T. S. and T. G.) using MEDLINE and Cochrane databases. A free text search or a MeSH term search was used wherever appropriate, and Boolean operators were used to combine the terms. The MeSH search terms included "flap lower extremity" "lower extremity" AND "anterolateral" OR "ALT" OR "Superior Iliac Circumflex Artery Perforator" OR "SCIP" OR "Medial Sural Artery Perforator."

There were no restrictions on patient demographics, publication date, status, or language. The inclusion criteria consisted of any cohort studies or case series comparing the outcomes with lower extremity reconstruction for both perforator and muscle flaps. Articles or patients excluded were those that described pedicled flaps, osteocutaneous flaps, omental flaps, and insufficient information provided to account for the separate outcomes for each respective free-flap type. Citations found through the databases search were screened for eligibility by title and/or abstract. The full-text papers were then evaluated for final inclusion into the meta-analysis. We looked specifically for information similar to that extracted by the index cohort study.

Statistical meta-analysis was performed by random effects model using the RevMan review software package.[4] The analysis was performed by Mantel–Haenszel risk ratio (RR) analysis for dichotomous data. Statistical heterogeneity was estimated using I^2. I^2 values of 30 to 50% represented a moderate level of heterogeneity. Significance was set at a value of $p < 0.05$ in both models. We established forest plots to illustrate the effect of the size of the studies. Funnel plots with 95% confidence intervals (CIs) were used to assess for publication bias.

Results

Index Cohort Study

Between January 2010 to June 2015, 161 patients underwent free-flap transfer to lower extremity defects at Singapore General Hospital. Of these, 76 were perforator flaps, whereas 85 were nonperforator flaps. The patient demographics for each category with the respective p-values are described (►**Table 1**). There were no statistically significant differences in patient variables between both groups.

The three most common perforator flaps used were anterolateral thigh (ALT, 46), superficial circumflex iliac artery perforator (SCIP, 21), and thoracodorsal artery perforator (TAP, 4) (►**Table 2**). Nine (19.6%) of the 46 ALT flaps required anastomotic revision, and venous thrombosis was found in seven and arterial thrombosis in five. Three (6.5%) ALT flaps were taken down with venous thrombosis as the culprit in one and arterial thrombosis in the other two. For the SCIP flaps, five (23.8%) of the flaps required anastomotic revision for which thrombosis was found in three venous and three arterial anastomoses. There were no complete SCIP flap failures. For nonperforator flaps, the most common flaps were rectus abdominis (33), gracilis (30) and latissimus dorsi (LD, 17). There were no salvaged flaps and three flap failures (9.1%) for rectus abdominis flaps, where venous thrombosis was found in two and arterial thrombosis in three. For gracilis flaps, there were no salvaged flaps and three flap failures (10%). For gracilis flap failures, venous thrombosis was found in two and arterial thrombosis in three. For LD flaps, two flaps (11.8%) were reexplored and venous thrombosis was found in the salvaged flap (50%), whereas both venous and arterial thromboses were found in the takedown flap (50%). The other salvaged nonperforator flap was of the groin subtype.

In ►**Table 3**, the perforator flaps had higher vascular complications compared with the nonperforator flaps, but this was not statistically significant (14 [18.4%] and 9 [10.6%]; $p = 0.18$). Eleven (78.6%) out 14 of the perforator flap reexplorations and 7 (77.8%) out of 9 of the nonperforator flap reexplorations occurred within postoperative day 0. All vascular complications occurred within 48 hours of the initial surgery. Perforator flaps had a higher rate of salvage but were not statistically significant (11 [78.6%] and 2 [22.2%]; $p = 0.374$). Lastly, although not statistically significant, perforator flaps had a lower rate of complete failure due to anastomotic complications (three [3.9%] and seven [8.2%]; $p = 0.336$).

Table 1 A comparison demographics of patients who underwent lower extremity reconstruction with free perforator flaps versus free nonperforator flaps

	Total	Perforator	Nonperforator	*p*-Value
No. of patients, *n* (%)	161 (100)	76 (47.2)	85 (52.8)	
Age				
Mean	49.4	48.3	50.3	0.417
Range	15–88	20–88	15–80	
Sex, *n* (%)				
Male	117 (72.7)	53 (69.7)	64 (75.3)	0.43
Comorbidities, *n* (%)				
Diabetes	53 (32.9)	24 (31.6)	29 (34.1)	0.74
Tobacco	21 (13)	14 (18.4)	7 (8.2)	0.055
Peripheral vascular disease	16 (9.9)	7 (9.2)	9 (10.6)	0.799
Renal disease	14 (8.7)	7 (9.2)	7 (8.2)	0.826
Ischemic heart disease	9 (5.6)	5 (6.6)	4 (4.7)	0.736
Etiology, *n* (%)				
Infective	74 (46)	35(46)	39 (45.8)	0.36
Trauma	57 (35.4)	30 (39.5)	27 (31.8)	–
Tumor resection	27 (16.8)	9 (11.8)	18 (21.2)	–
Others	3 (1.9)	2 (2.6)	1 (1.2)	–
Region, *n* (%)				
Foot	79 (49.1)	43 (56.6)	36 (42.4)	0.871
Leg (distal one-third)	44 (27.3)	14 (18.4)	30 (35.3)	–
Knee	13 (8.1)	8 (10.5)	5 (5.9)	–
Leg (middle one-third)	12 (7.5)	8 (10.5)	4 (4.7)	–
Thigh	9 (5.6)	1 (1.3)	8 (9.4)	–
Leg (upper one-third)	4 (2.5)	2 (2.6)	2 (2.4)	–
Size, *n* (%)				
> 50 cm^2	106 (65.8)	48 (63.2)	58 (68.2)	0.498
< 50 cm^2	55 (34.2)	28 (36.8)	27 (31.8)	–

Table 2 Breakdown of the type and number of free perforator and nonperforator flaps used for lower extremity reconstruction of the index study

Free flaps	*n* (%)
Perforator	76 (100)
Anterolateral thigh	46 (60.5)
Superficial circumflex iliac artery	21 (27.6)
Thoracodorsal artery	4 (5.3)
Others	5 (6.5)
Nonperforator	85 (100)
Rectus Abdominis	33 (38.8)
Gracilis	30 (35.3)
Latissimus dorsi	17 (20)
Others	5 (5.9)

Table 3 Comparison of the index study anastomotic outcomes between perforator and nonperforator free flaps

	Perforator	Nonperforator	*p*-Value
Vascular complications, *n* (%)	14 (18.4)	9 (10.6)	0.18
Salvaged, *n* (%)	11 (78.6)	2 (22.2)	0.374
Complete failure, *n* (%)	3 (3.9)	7 (8.2)	0.336

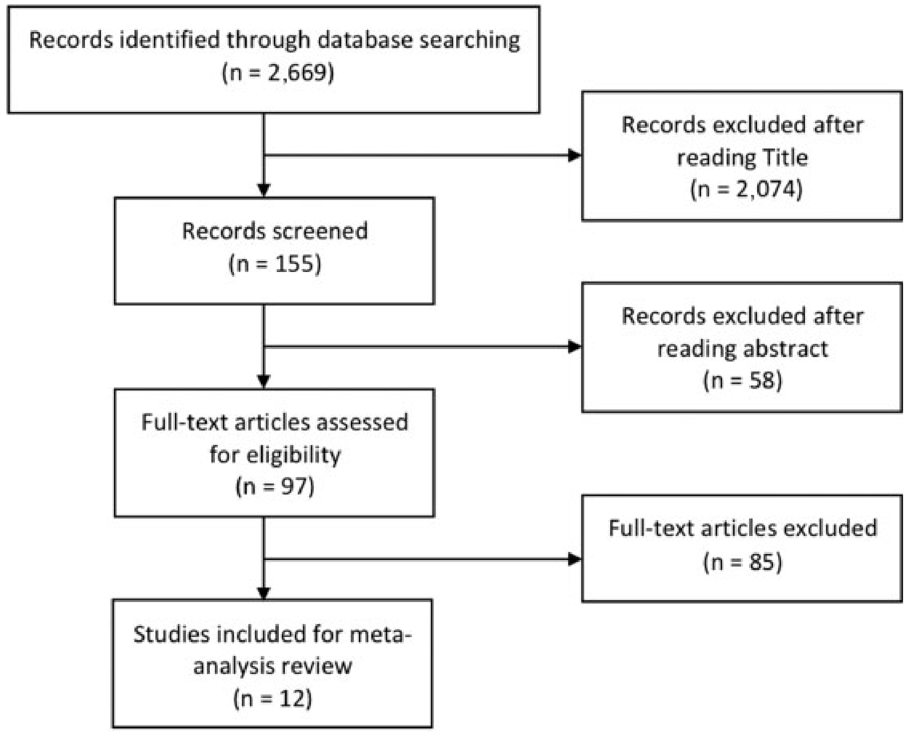

Fig. 1 Study attrition diagram, outline of search process, and excluded studies in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

Meta-Analysis

►**Fig. 1** outlines the literature search conducted through the PRISMA guidelines. In total, 2,669 articles were identified through the initial search, and 155 publications remained after title screening. This was further reduced to 97 articles after reading the abstracts. A further 85 articles were omitted as the full papers did not match the eligibility criteria. There were 12 literature articles in addition to our index study that were included for the purposes of the meta-analysis.[5–16] There were a total of 810 flaps for the 12 studies, of which 347 (42.8%) were perforator flaps and 463 (57.2%) were nonperforator flaps. Pooled patient comorbidities, defect etiology, and location in each group were described (►**Table 4**).

The three most common perforator flaps included in the meta-analysis were 277 (79.8%) ALT perforator flaps, 21 (6.1%) SCIP flaps, and 13 (3.7%) both medial sural artery perforator flaps and deep inferior epigastric perforator flaps each (►**Table 5**). For the nonperforator group, this included 153 (33%) LD flaps, 128 (27.6%) gracilis flaps, and 109 (23.5%) rectus abdominis flaps (►**Table 6**).

►**Table 7** illustrates the pooled outcomes for each flap group and the respective breakdown of the types of complications. Vascular complication rates for perforator flaps were higher at 9.5% (nonperforator flaps were at 8.6%). Perforator flaps showed a higher aggregated flap salvage rate (51.5 and 45%) and marginally lower complete flap loss rates (4.6 and 4.8%). ►**Fig. 2** depicts the meta-analyses comparing perforator flaps with nonperforator flap outcomes. The meta-analysis found no significant difference between both groups for all three outcomes, namely, vascular complications (►**Fig. 2** *top*) (RR: 1.25; CI: 0.79–1.98; $p = 0.33$), salvaged rate (►**Fig. 2** *center*) (RR: 1.31; CI: 0.76–2.27; $p = 0.33$), and complete failure (►**Fig. 2** *bottom*) (RR: 1.19; CI: 0.63–2.27; $p = 0.59$). Funnel plots showed that all studies were within the 95% CI (►**Fig. 3**).

Discussion

In the current age of limb salvage for lower extremity defects, amputations have become increasingly avoided.[17] It has been reported that the free-flap success for lower limb reconstruction are the lowest in comparison to other anatomical sites such as the head and neck, trunk, and upper limb.[18–21] It is consequently crucial to assess the outcomes of free perforator flaps in the lower extremity reconstruction for limb salvage, especially in the face of greater technical demand in comparison to their nonperforator counterparts.

The results of this study exhibit similarity of free perforator flaps to the robustness and reliability of their traditional nonperforator counterparts. The advantages of perforator flaps compared with nonperforator flaps are well described by Hallock.[22] In complex or composite defects, perforator-based chimeric flaps are raised on perforators rather than main arterial branches, allowing more selective tissue components, a single donor site morbidity, greater freedom of inset, and arguably better contouring and improved aesthetic result.[23]

A study of 47 patients who underwent large-to-medium lower extremity defect free-flap reconstruction concluded better flap aesthetic outcome and lower donor site morbidity in ALT flaps compared with the LD flap. They also found no statistical difference in flap survival between both groups.[24]

Table 4 Pooled patient demographics of all studies meeting the inclusion criteria of the meta-analysis of free-flap reconstruction in the lower extremity

	Total	Perforator	Nonperforator
Total	810 (100)	347 (42.7)	463 (57.2)
Age, mean	32.3	30	34.6
Comorbidities, *n* (%)			
Diabetes	92 (11.4)	49 (14.1)	43 (9.3)
Tobacco	88 (10.9)	43 (12.4)	45 (9.7)
PVD	52 (6.4)	28 (8.1)	24 (5.2)
Cardiovascular	21 (2.6)	13 (3.7)	8 (1.7)
Renal impairment	18 (2.2)	10 (2.9)	8 (1.7)
Radiotherapy	6 (0.7)	1 (0.3)	5 (1.1)
Etiology, *n* (%)			
Trauma	542 (66.9)	242 (69.7)	300 (64.8)
Infective	162 (20)	70 (20.2)	92 (19.9)
Tumor	103 (12.7)	33 (9.5)	70 (15.1)
Others	3 (0.4)	2 (0.6)	1 (0.2)
Location, *n* (%)			
Foot	366 (45.2)	162 (46.7)	204 (44.1)
Distal third	260 (32.1)	106 (30.5)	154 (33.3)
Thigh	26 (3.2)	6 (1.7)	20 (4.3)
Middle third	81 (10)	38 (11)	43 (9.3)
Knee	47 (5.8)	24 (6.9)	23 (5)
Proximal third	30 (3.7)	11 (3.2)	19 (4.1)

Abbreviation: PVD, peripheral vascular disease.

Table 5 Breakdown of types of free perforator flaps used across all studies included in the meta-analysis

No.	Study	Sample size	ALT	SCIP	MSA	TAP	DIEP	Others
	Total, *n* (%)	**347 (100)**	**277 (79.8)**	**21 (6.1)**	**13 (3.7)**	**6 (1.7)**	**13 (3.7)**	**17 (4.9)**
1	Ohjimi et al, 2000[5]	15	3	–	–	1	11	–
2	Langstein et al, 2002[6]	2	–	–	–	–	–	2
3	Akoz et al, 2004[7]	2	2	–	–	–	–	–
4	Yildirim et al, 2008[8]	1	1	–	–	–	–	–
5	Ulusal et al, 2008[9]	1	1	–	–	–	–	–
6	Demirtas et al, 2010[10]	23	23	–	–	–	–	–
7	Tamimy et al, 2010[11]	29	29	–	–	–	–	–
8	Lee et al, 2012[12]	12	12	–	–	–	–	–
9	Hallock, 2013[13]	92	67	–	11	1	2	11
10	Jang et al, 2014[14]	10	9	–	–	–	–	1
11	Bibbo et al, 2015[15]	49	49	–	–	–	–	–
12	Paro et al, 2016[16]	35	35	–	–	–	–	–
13	Index	76	46	21	2	4	–	3

Abbreviations: ALT, anterolateral thigh; DIEP, deep inferior epigastric perforator; MSA, medial sural artery; SCIP, superficial circumflex iliac artery perforator; TAP, thoracodorsal artery perforator.

Table 6 Breakdown of types of free nonperforator flaps used across all studies included in the meta-analysis

No.	Study	Sample size	Gr	LD	RA	RF	VL	SA	Sc	Gro	Others
	Total, *n* (%)	**463 (100)**	**128 (27.6)**	**153 (33)**	**111 (24)**	**9 (1.9)**	**41 (8.8)**	**6 (1.3)**	**7 (1.5)**	**3 (6.5)**	**5 (1.1)**
1	Ohjimi et al, 2000[5]	13	–	3	4	1	–	–	4	1	–
2	Langstein et al, 2002[6]	18	4	2	5	6	–	–	–	–	1
3	Akoz et al, 2004[7]	3	–	1	2	–	–	–	–	–	–
4	Yildirim et al, 2008[8]	3	–	3	–	–	–	–	–	–	–
5	Ulusal et al, 2008[9]	23	12	9	1	–	–	–	–	1	–
6	Demirtas et al, 2010[10]	30	–	13	17	–	–	–	–	–	–
7	Tamimy et al, 2010[11]	31	–	31	–	–	–	–	–	–	–
8	Lee et al, 2012[12]	12	–	–	–	–	12	–	–	–	–
9	Hallock 2013[13]	107	58	39	1	–	1	5	–	–	3
10	Jang et al, 2014[14]	1	–	–	–	–	1	–	–	–	–
11	Bibbo et al, 2015[15]	51	–	7	21	–	23	–	–	–	–
12	Paro et al, 2016[16]	86	24	28	27	–	3	1	3	–	–
13	Index	85	30	17	33	2	1	–	–	1	1

Abbreviations: Gr, gracilis; Gro, groin; LD, latissimus dorsi; RA, rectus abdominis; RF, radial forearm; SA, serratus anterior; Sc, scapular; VL, vastus lateralis.

Table 7 Comparison of anastomotic outcomes pooled from the meta-analysis between perforator and nonperforator free flaps

	Total	Perforator	Nonperforator
Total, *n* (%)	810 (100)	347 (42.8)	463 (57.2)
Vascular Complications, *n* (%)	73 (9)	33 (9.5)	40 (8.6)
Salvaged, *n* (%)	35 (47.9)	17 (51.5)	18 (45)
Complete failure, *n* (%)	38 (4.7)	16 (4.6)	22 (4.8)

For defects up to medium size, a single-center study[25] of 52 patients advocated the SCIP flap due to its on-table thinness (5 mm mean thickness). They accomplished this through suprasuperficial fascia dissection and this obviated the need for secondary debulking procedures. This is advantageous to muscle flaps in that there is no need to await muscle atrophy in time to achieve a desired contour, which may prove to be unpredictable. A single-center case series of 24 free gracilis flaps for medium-sized defect coverage in lower extremity reconstruction found that four (19%) needed secondary debulking procedures and that the average time to debulking was 14.5 months.[26] Although there remains a worry of a short pedicle for the SCIP flap, the SCIP study[25] reported a mean of 4.5 cm in length with no anastomotic and flap inset issues. Our index study included 21 SCIP flaps with a 100% flap survival, and we concur that the thinness and well-concealed donor scar make this flap a useful addition to the reconstructive armamentarium.

The rate of ulceration in weight-bearing areas between perforator and nonperforator flaps is likely to be similar. A systematic review and meta-analysis[27] of a pooled sample of 163 free-flap reconstructions of the heel found no statistically significant difference between rates of ulceration in muscles flaps (26%) and fasciocutaneous flaps (17%). This may be due to the fact that such patients with a weight-bearing area reconstruction, regardless of flap type, will require podiatry assessment and special footwear that, as the former study concluded, will likely improve ulceration rates.

Anastomotic Revision

From the index study, we have found a higher anastomotic revision rate of 18.4% in perforator flaps compared with a rate of 10.6% in nonperforator flaps. We also observed higher salvage rates found in perforator flaps in the index study, although no statistical difference was found in the index and meta-analysis studies. This may mean that although the smaller caliber vessels in perforator flaps were more prone to anastomotic complications, they displayed signs of compromise early and granted timely reexploration and successful salvage. This minimized flap ischemia time and was key to a favorable anastomotic outcome since the no-reflow phenomenon is also time-dependent.[28,29]

In the index study, all vascular compromises occurred within 48 hours of initial surgery. This finding is consistent with the results found by Bui et al's study of 117 nonperforator free flaps for lower extremity reconstruction.[30] Unfortunately, this information was not present in all studies of the meta-analysis. This 48-hour postoperative monitoring window is especially crucial for free perforator flaps for lower extremity reconstruction.

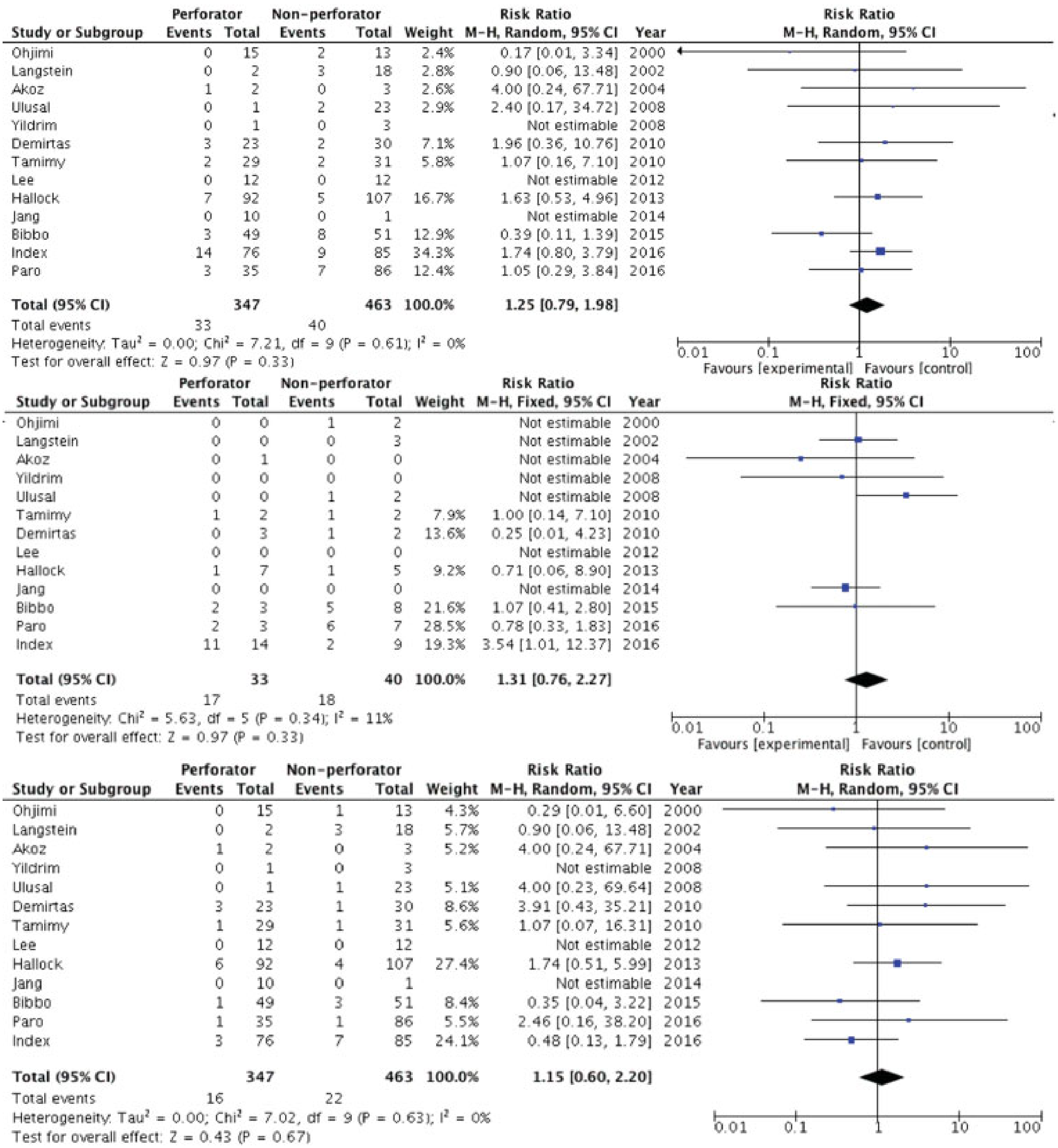

Fig. 2 Forest plots representing pooled effect of free perforator flaps versus free nonperforator flaps on anastomotic revision (top), flap salvage rate (center), and flap failure and takedown (bottom). Each square represents the effect size for a particular study, with the size of the square proportional to the study size. Horizontal lines represent 95% confidence intervals. A random effects model was used for all analyses. Diamonds represent pooled data for each subgroup and the overall effect size. M-H, Mantel–Haenszel.

Complete Anastomotic Failure

Our failure rate in perforator flaps was lower than that in nonperforator flaps (3.9% vs. 8.2%), although this was nonsignificant. The meta-analysis of the 13 studies that evaluated anastomotic outcomes for both groups also yielded no significant difference between complete anastomotic failure in perforator and nonperforator flaps. These results suggest that respect for the greater demands of free perforator flaps can produce equally reliable coverage as their nonperforator flap counterparts in lower extremity reconstruction.

The supplied cutaneous territory of a perforator remains to be unpredictable.[31,32] The course of the perforator artery and its venae comitantes are not always parallel beyond the deep fascia, and failing to adequately capture the venous outflow can result in worrisome congestion.[33] Despite this unpredictability, recent anatomical studies have enhanced harvest safety by better characterizing the vascular variability of perforator flaps. This includes a systematic review of the ALT perforator anatomy with a total of 1,251 flaps[34] and a single-center experience with 210 SCIP flaps.[35] In addition, according to

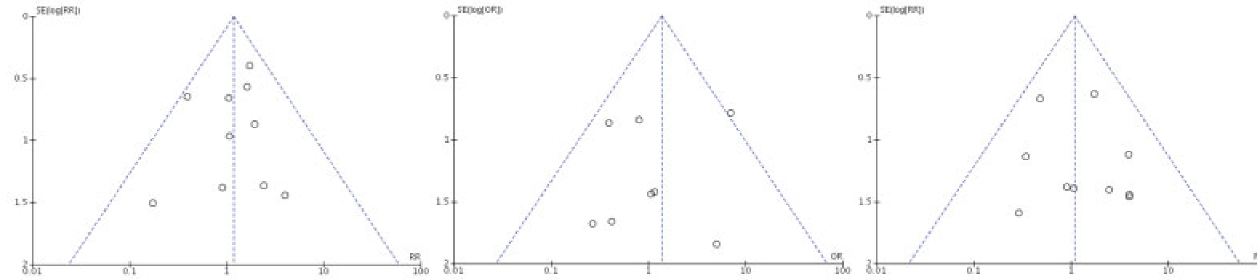

Fig. 3 Funnel plots graphically assessing for publication bias on anastomotic revision (left) successful flap salvage (center), and flap failure and takedown (right). The plot represents the standard error for each study plotted against the measured effect size. The vertical line represents the combined effect for all studies. The diagonal lines represent the 95% confidence interval. All studies were confined within the 95% confidence interval, suggesting a lack of significant publication bias. RR, risk ratio.

the angiosome concept, although vascular anatomy may vary among individuals, the basic perforator "blueprint," is constant and this is fundamental to the design of safe perforator flaps.[36] Last but not least, the advent use of computed tomographic angiography has effectively negated the unpredictability of perforator course.[37]

Limitations

Due to the limitation of data collection, certain information such as surgery length, vessel diameter, and the exact time frame to surgical reexploration was not included in the index study.

We performed a power analysis with R statistical software[38] for the index study. If the sample flap failure rate of 5% from the accepted flap failure rate for lower extremity flap reconstruction was to be clinically significant, assuming a power level of 80% and an α of 0.05, we calculated that the study would need a minimum of 326 patients undergoing free-flap procedures to detect a meaningful difference between two flap types in lower extremity reconstruction. Therefore, the meta-analysis with a pooled population of 810 was performed.

This meta-analysis was observational in nature, and a randomized controlled trial would be ideal although impractical on such a large scale. The results of this study are broad and general and may not account for individual factors that influence optimal flap choice. The meta-analysis was limited by the available published studies that summarize various surgical techniques (performed by different surgeons), which are highly variable and not standardized. The nature of such surgery also makes it difficult to standardize patient selection (comorbidities, localization, defect size, and etiology) and flap anatomy (defect size, number of perforators, length of pedicle, and quality of recipient vessels). Therefore, this is a potential limitation, and a larger sample will allow subanalysis with variability. Our index study and the published series do not represent homogenous consecutive series of patients with lower extremity wounds, but sometimes represent series of wounds where the pedicled flaps were chosen over a free flap. Last, we were unable to factor in the various surgeon thresholds for surgical intervention in the index study and the meta-analysis.

Conclusion

Our meta-analysis is the first reported and serves as an indication that free perforator flaps in lower extremity are as reliable as their traditional nonperforator counterparts. This does come with the prerequisite that the microsurgeon appreciates the anatomical variations and the delicacy of these flaps and anticipates the crucial commitment in the 48-hour postoperative monitoring with a low threshold for reexploration.

Conflict of Interest
None.

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