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Lower Extremity Limb Salvage and Amputation: A Systematic Review and Meta-Analysis of Reported Outcomes and the Role of Microsurgery

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Abstract

Background: Previously published literature has provided a large number of clinical data from hundreds of medical centers across the country among patients that have undergone limb salvage and lower extremity amputation. These studies commonly suffer from retrospective and prospective design flaws, low statistical power, non uniform inclusion criteria and inconsistent endpoints that are hard to assess.

Methods: A literature search was conducted, including terms related to outcomes in free flap reconstruction or amputation of the lower extremity. Inclusion criteria for this systematic review centered around the number or proportion of patients experiencing a specific outcome.

Results: The only outcomes unique to both cohorts were hospital length of stay and time- to-operate. In this meta-analysis, operative time was significantly longer in free flap reconstruction cases (p=0.041) than in those patients undergoing amputation.

Interestingly, the mean number of hospital days was reported to be only 23.36 days in free flap limb salvage patients and significantly higher in amputation patients (32.19 days, p=0.046).

Conclusion: Free flap reconstruction of the lower extremity was associated with lower post-operative risks associated with length of stay results of this comprehensive review of the literature demonstrate a diversity in reporting practices. Transitioning to a universally accepted reporting standard will strengthen the literature and help future clinicians in situations that require surgical intervention with no clear medical indication between either limb salvage or amputation.

Keywords: Lower extremity trauma; Microsurgical reconstruction; Amputation; Limb salvage

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Introduction

Management of post traumatic distal lower limb injury poses a significant challenge to the surgeon and patient and often requires free tissue transfer for coverage of exposed hardware, bone, cartilage, nerves, and major vessels [1]. Outcomes of lower extremity trauma depend on access to care including microsurgical interventions as well as the nature of the other injuries to a patient. In patients that are unstable or critically ill amputation may be the only option to stabilize their condition. However, in patients where all things are equal except access to microsurgical care, amputation may be required due to a lack of access to these resources. This is primarily as a result of peripheral arterial occlusive disease [2,3]. Even with the advent of vascular interventions and microsurgical reconstruction of lower extremity wounds, the rate of amputations has not declined [4-7]. This may also be due to an ageing population and a growing prevalence of atherosclerotic disease and diabetes mellitus [8].

Recently, optimization in microsurgical techniques, equipment, and training have allowed for more widespread reconstruction of soft tissue defects of the lower extremity, allowing for more consistent outcomes in limb salvage. The use of microsurgical free flaps has become a standard procedure in soft-tissue repair and has reduced the amputation rate among previously non-operable defects [9,10].

Even so, amputation secondary to trauma remains a significant cause of permanent impairment and functional limitation among patients with lower extremity wounds [7]. In most cases, limb loss leads to a significant decline in function, with the resulting impairments detrimentally affecting the patients' social, work, and home life. In addition to amputations due to trauma, amputation is also

Table 1: Systematic review inclusion and exclusion criteria.

	Inclusion Criteria	Exclusion Criteria
Title and Abstract Assessment	Free flap reconstruction and/or amputation as research theme.	Case report. Abstract only.
	Unilateral lower extremity operation. Patient outcomes reported.	Review article, letter, comments. Study prior to 2000 (1 exception).
		Full text not available.
Full Text Assessment	Patient outcomes as research theme.	Bilateral lower extremity operation.
	Individual adverse outcomes reported.	Includes redone free-flap reconstruction or amputation.
	Free-flap donor site defined.	Does not report number or proportion of patients experiencing outcomes.
	Data reported by free flap donor site.	Data not clearly labeled.
	Primary free-flap reconstruction or amputation assessed.	
	Etiology of free-flap reconstruction or amputation reported by number of proportion of patients.	

commonly secondary to comorbid conditions that have resulted in vascular insufficiency or infection of the affected limb [2]. Therefore, many patients that undergo major lower extremity amputation have comorbidities like diabetes mellitus, cardiovascular disease, or end stage renal disease [3]. As such, postoperative morbidity and mortality rates can be extremely significant, with some studies reporting 30-day postoperative mortality as high as 22% [11,12].

In contrast, reconstruction of soft tissue defects in lower extremity wounds using microsurgical free flaps is often reported to have a 30-day postoperative mortality rate of less than 10% [9]. Though this is in part due to the differences in medical morbidity between the groups of patients offered amputation *vs.* those offered reconstruction. MB salvage has grown in most trauma centers in the United States [13]. Studies that compare patients treated with microsurgical free flaps over those primarily amputated often do not consider post-operative complications and non-ambulatory outcomes such as hospitalization time, time to operate, patient quality of life before and after surgery, and patient satisfaction with treatment outcomes [6,10,12-15]. Furthermore, complications that are reported in the literature have not been uniformly summarized and assessed in the case of either amputation or free flap coverage.

The goal of this study is to estimate the rate of complications unique to each treatment option, as well as the relative risk of those complications shared by both. This study also sought to identify significant differences in the patient experience when undergoing microsurgical free flap reconstruction or amputation-namely differences in hospital length of stay, time to operate, and patient quality of life outcomes.

Previously published literature has provided a large number of clinical data from hundreds of medical centers. However, these commonly suffer from retrospective and prospective design flaws, low statistical power, non uniform inclusion criteria and a plethora of endpoints that are hard to assess. Therefore, it is necessary to summarize all existing studies to better understand complications, outcomes, and patient satisfaction associated with free flap coverage and amputation of lower extremity wounds. Secondary analysis is also necessary to characterize the diversity of reported outcomes in the literature to better compare both prospective and retrospective future studies.

Methods

The goal of this investigation was to determine the likelihood of reported outcomes from free flap reconstruction and amputation of the lower extremity. In addition, a comparison of microsurgical intervention and amputation was made with respect to Time to Operate (TTO) and hospital Length of Stay (LOS) in order to better differentiate between these two largely debated options in the treatment of patients with lower extremity trauma.

Literature search

A literature search was conducted using the citation database PubMed, which was searched for publications detailing outcomes from free flap reconstruction of the lower extremity using the following terms: ("Lower Extremity/surgery"[Mesh]) AND ("Free Tissue Flaps/adverse effects"[Mesh] OR "Free Tissue Flaps/statistics and numerical data"[Mesh] OR "Free Tissue Flaps/surgery"[Mesh] OR "Free Tissue Flaps/utilization"[Mesh]). A second search for citations of the same nature was subsequently conducted in PubMed using the following criteria: (("Free Tissue Flaps/adverse effects"[Mesh] OR "Free Tissue Flaps/standards"[Mesh] OR "Free Tissue Flaps/statistics and numerical data"[Mesh] OR "Free Tissue Flaps/surgery"[Mesh] OR "Free Tissue Flaps/therapeutic use"[Mesh] OR "Free Tissue Flaps/therapy"[Mesh] OR "Free Tissue Flaps/utilization"[Mesh])) AND "Lower Extremity"[Mesh]. Publications detailing outcomes from lower extremity amputation were searched in PubMed using the following terms: ("Lower Extremity/surgery"[Mesh]) AND "Amputation"[Mesh] outcomes; and lower limb amputation outcomes morbidity mortality. No limits were implemented in any of the search queries.

Study selection

On November 11, 2018, the authors conducted a search of published articles in PubMed, Medline, and Embase databases. The search was conducted with no restrictions. All studies published after 2000 (with one exception) were evaluated. After performing three subsequent searches, all authors collaboratively assessed the selected studies in two rounds based on specific search criteria summarized in Table 1.

If in the first round, inclusion or exclusion criteria could not be assessed from the title or abstract, the full text was surveyed for the inclusion or exclusion criteria. All authors were consulted if the inclusion criteria were not explicitly met, but the study did not meet any of the exclusion criteria. The reference list of each study was manually assessed for additional articles that could be included in the systematic review. Studies selected for review were agreed upon by all authors.

To be included in this systematic review, a study of patients with unilateral lower extremity free flap reconstruction or amputation had to include the number or proportion of patients experiencing

Table 2: Free flap study characteristics.

Source (Author, Year)	Mean Age (SD)	Study Size	Male/Female	Avg. Follow Up (Months)	Defect Size (cm²)	Flap Survival (%)
Fischer et al. [10]	46.3 (18.1)	114	94/25	9.2	NR	94.10%
Franco et al. [1]	37.0 (20)	24	17/7	29	81	91.70%
Hanasono et al. [23]	60.0 (15)	220	163/57	16.6	150	98.60%
Hashmi et al. [25]	30.5 (NR)	13	NR	NR	NR	92.30%
Hong et al. [26]	51.4 (NR)	71	50/21	11	92.1	98.60%
Hong et al. [27]	42.8 (NR)	28	21/7	18.2	120.2	100%
Hong et al. [28]	47.0 (NR)	79	45/34	12	75.5	96.20%
Kim et al. [31]	62.8 (NR)	16	12/4	12	NR	86.70%
Kim et al. [32]	42.0 (NR)	12	11/1	18	NR	100%
Kim et al. [33]	57.0 (NR)	16	13/3	11.8	74.1	93.80%
Kim et al. [34]	52.3 (NR)	12	05/7	12.7	NR	100%
Knobloch et al. [35]	53.0 (17)	75	NR	NR	NR	94.70%
Liu et al. [37]	38.0 (NR)	24	17/7	22	NR	100%
Maruccia et al. [39]	48.0 (NR)	4	NR	NR	233.5	100%
Olivan et al. [44]	56.0 (13.55)	25	14/11	NR	NR	92%
Osiogo et al. [45]	60.2 (NR)	45	25/20	27	NR	88.90%
Ozkan et al. [46]	39.4 (NR)	31	24/7	NR	194.9	96.80%
Ulucay et al. [51]	30.5 (NR)	13	08/5	23	203.3	92.30%
Philandrianos et al. [47]	36.1 (10.9)	27	NR	29.6	78.7	92.60%
Philandrianos et al. [47]	40.1 (19.4)	20	NR	38	94.4	95%
Spector et al. [49]	42.0 (NR)	26	21/5	NR	NR	96.40%
Van Landuyt et al. [52]	41.4 (NR)	24	15/9	NR	NR	95.80%
Yildirim et al. [56]	35.0 (NR)	21	19/2	NR	NR	95.20%
Kaminsky et al. [30]	45.0 (NR)	19	17/2	NR	131.9	89.50%
Xu et al. [54]	34.0 (NR)	82	58/24	30	NR	98.80%
Venkatramani et al. [53]	33.2 (NR)	19	18/1	NR	256.4	94.70%
Venkatramani et al. [53]	34.2 (NR)	13	12/1	NR	373.5	100%
Totals	**-**	**1073**	**679/260**	**-**	**-**	**-**

*NR: Not Reported

a specific outcome. Studies including redo operations, and studies detailing free flap reconstruction that did not report outcomes by free flap donor site, but grouped them together, were excluded.

The methodological quality of studies included in this systematic review was assessed using the Cochrane Collaboration's tool for assessing the risk of bias. The quality of this systematic review was assessed using the PRISMA checklist.

Data collection

Data from each free flap study were extracted into a form with the following parameters: Primary author, publication year, study design, number of patients, mean age, mean BMI, flap type assessed by each study, time to operate, pain values, ambulatory outcomes, quality of life assessment scores, time to follow up, flap survival, average defect size, all listed complications and rates, hospital days, and duration of surgery. Data from each amputation study were extracted into a form with the following parameters: Primary author, publication year, study design, number of patients, mean age, mean BMI, AKA or BKA, time to operate, pain values, ambulatory outcomes, time to formalization, indications for amputation, comorbid conditions, quality of life assessment scores, time to follow up, all listed complications and rates, hospital days, and duration of surgery.

Statistical analysis

Statistical analysis was performed using Microsoft Excel 2016 (Microsoft, Redmond, WA). Outcomes were evaluated using student's t-test, chi square test, and relative risk analysis with a p-value <0.05 considered significant in this study.

Results

The initial broad search of the databases (PubMed, Embase, and Medline) yielded 3999 citations. Results of secondary search less primary exclusion criteria then returned 726 unique manuscripts, of which 65 were selected as candidates for full-text review based on assessments of titles, abstracts, and keywords. Following full-text review, 46 studies were selected for inclusion in the meta-analysis based on secondary inclusion and exclusion criteria (Figure 1). Characteristics of the selected studies included study design, number of patients, mean age, mean BMI, average follow-up, defect size (free flap studies), flap survival (free flap studies), Below-the-Knee (BKA) or Above-the-Knee (AKA) amputation (amputation studies), and 30-day mortality (amputation studies) (Table 2 and 3). Reported outcomes for free flap studies include flap characteristics, time to operate, ambulation, Quality of Life (QoL), time to follow-up, flap survival, defect size, complications, surgery duration and any

Table 3: Amputation study characteristics.

Source (Author, Year)	Mean Age (SD)	Study Size	Male / Female	Avg. Follow Up (Months)	30 Day Mortality (%)
Morse et al. [41]	63 (NR)	50	25/25	33	6.00%
Gifford et al. [22]	54.5 (NR)	55	41/14	3.3	0.00%
Snyder et al. [48]	67 (NR)	81	NR	NR	3.70%
Monaro et al. [40]	78.3 (NR)	25	15/10	NR	12.00%
Ploeg et al. [2]	73 (NR)	97	49/48	25.7	11.40%
Nelson et al. [43]AKA	70.5 (13.3)	4032	2946/1086	NR	12.80%
Nelson et al. [43] BKA	65 (13.7)	5336	3527/1809	NR	6.50%
Yamada et al. [55]	73.2 (11.9)	8565	5435/3130	NR	6.40%
Nayak et al. [42]	71 (11.8)	81	47/34	3	21.00%
Toursarkissian et al. [50]	70 (11)	99	99/0	10	8.00%
Basu et al. [16]	68.9 (NR)	75	47/28	12	10%
Chu et al. [17]	69.3 (9.4)	245	145/100	60	NR
Cruz et al. [4]	68.6 (0.6)	229	221/8	NR	18.90%
Finch et al. [20]	72.2 (NR)	133	NR	30	15%
Fortington et al. [21]	74.1 (11.2)	199	178/121	NR	22%
Hasanadka et al. [24]	NR	4250	2521/1729	1	9.60%
Jordan et al. [29]	73 (NR)	122	72/50	42	15.30%
Lim et al. [36]	70.1 (14.3)	87	67/20	40.2	10.10%
Mckenzie et al. [38]	35.2 (13.3)	161	135/26	24	NR
Bosse et al. [13]	35.2 (NR)	161	130/31	24	NR
Corey et al. [18]	67.1 (11)	190	NR	NR	7.40%
Feinglass et al. [19]	67.9 (NR)	4061	4061/0	32	10.00%
Totals	**-**	**28334**	**19761/8269**	**-**	**-**

*NR: Not Reported

secondary operations (Table 4). Reported outcomes for amputation studies included length of hospital stay, QoL assessment, time to amputation, indication to amputation, post-operative mobility, time to follow-up, and any associated complications (Table 5) [1,2,4,10,13,16-56].

Outcome reporting diversity: Microsurgical studies

Of those studies included in this review, 27 reported outcomes of free flap reconstruction of the lower extremity. The only characteristic universally reported was the flap type used in the reconstruction of patients included in the study. Furthermore, post-surgical complications and flap-survival were also reported by the clear majority of studies (93% and 96% respectively). Time to follow-up was reported by 74% of the included studies.

In contrast, 22% of studies reported the time it took to operate, 19% reported post-operative ambulation, and only 19% reported patient QoL. Of the 6 studies that reported QoL, surveys and scoring systems were unique to each. Furthermore, no attempt was made to justify the use of specific QoL indices used by these studies. Although 93% reported post-surgical complications, many of which included reoperation, only 63% characterized the nature of secondary operations.

Outcome reporting diversity: Amputation studies

Diversity of outcomes reported by the 22 amputation studies was also investigated. No single study characteristic or outcome was universally reported by those studies included in this review. Specificity of AKA/BKA and post-operative complications were reported by 95% of these studies.

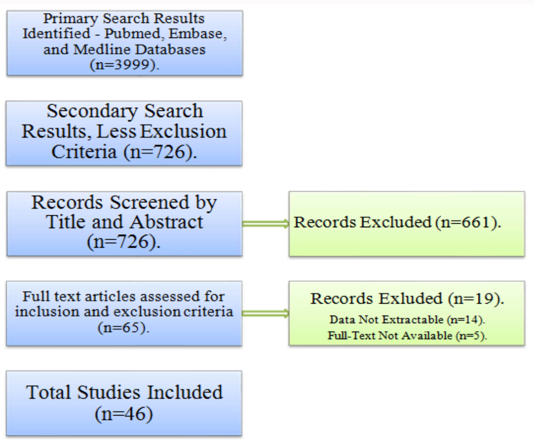

Figure 1: Flowchart depicting the stepwise approach for the identification of studies with a research theme of patients with unilateral lower extremity free flap reconstruction or amputation included in this review.

Similar to microsurgical intervention reporting practices, 14% reported QoL outcomes, 9% reported time to amputate, 27% reported post-operative mobility, and 36% reported time to follow-up with their patients.

Meta-analysis

Two key study characteristics were reported by both free flap and amputation prospective and retrospective cohort studies: Length of

Table 4: Diversity of reported outcomes among free flap reconstruction studies included in this review.

Source (Author, Year)	Flap Type	Time to Operate	Ambulation	QoL	Time to Follow-Up	Flap Survival	Defect Size	Complications	Surgery Duration	Secondary Operations
Fischer et al. [10]	X				X	X		X		X
Franco et al. [1]	X	X			X	X	X	X		X
Hanasono et al. [23]	X				X	X	X	X		X
Hashmi et al. [25]	X					X		X		
Hong et al. [26]	X				X	X	X	X		
Hong et al. [27]	X				X	X	X			
Hong et al. [28]	X				X	X	X	X		
Kim et al. [31]	X	X	X	X		X	X	X		
Kim et al. [32]	X		X	X	X	X		X		
Kim et al. [33]	X		X	X	X	X	X	X	X	
Kim et al. [34]	X		X	X	X	X				
Knobloch et al. [35]	X					X		X		X
Liu et al. [37]	X		X		X	X	X	X		X
Maruccia et al. [39]	X				X	X	X	X		X
Olivan et al. [44]	X			X	X	X	X	X		X
Osiogo et al. [45]	X				X	X		X		X
Ozkan et al. [46]	X					X	X	X		X
Ulucay et al. [51]	X	X			X	X	X	X		X
Philandrianos et al. [47]	X	X			X	X	X	X	X	X
Philandrianos et al. [47]	X	X			X	X	X	X	X	X
Spector et al. [49]	X				X	X	X	X		X
Van Landuyt et al. [52]	X							X		X
Yildirim et al. [56]	X					X		X		X
Kaminsky et al. [30]	X	X				X	X	X		X
Xu et al. [54]	X				X	X		X		X
Venkatramani et al. [53]	X				X	X	X	X		
Venkatramani et al. [53]	X				X	X	X	X		
Totals (%)	**27/27 (100%)**	**6/27 (22%)**	**5/27 (19%)**	**5/27 (19%)**	**20/27 (74%)**	**26/27 (96%)**	**18/27 (67%)**	**25/27 (93%)**	**3/27 (11%)**	**17/27 (63%)**

*NR: Not Reported

hospital stay and time to operate.

Hospital length of stay (LOS)

Seven studies were analyzed reporting the average number of hospital days in those patients that underwent free flap reconstruction of the lower extremity. This represented data on a total of 183 patients. A high level of heterogeneity was observed in the seven studies with respect to length of hospital stay with the assumption that a fixed-effect model fits the data (I2=88%, Q=33.64). However, with the assumption of a random-effect model, a milder level of heterogeneity was observed (I2v=54%, Qv=8.68). The mean number of hospital days across these seven studies was reported to be 23.36 (95% CI, 13.32 to 33.41) in patients with free flap reconstruction (Figure 2a).

In addition, nine studies were analyzed reporting the average number of hospital days in those patients that underwent amputation of their lower extremity (BKA or AKA). This represented data on a total of 555 patients prospectively followed and 8565 patients retrospectively analyzed by Yamada et al. [55]. A high level of heterogeneity was observed in the nine studies with respect to length of hospital stay with an assumed fixed-effect model (I2=88%, Q=33.64). In addition, assuming a random-effects model demonstrated a similar level of heterogeneity across these studies (I2v=54%, Qv=8.68). The mean number of hospital days was reported to be 32.19 (95% CI, 17.35 to 47.04) in patients with an amputated limb (Figure 2b). Intra-study ranges of hospital days were not reported by four studies; therefore, a standard deviation was used to assess confidence intervals.

Time to operate (TTO)

A total of 5 studies were investigated reporting TTO outcomes of free flap reconstruction. This represented data on 81 patients across all five studies. Heterogeneity was observed using both a fixed and random effects model (I2=88%, Q=33.64; I2v=54%, Qv=8.68). The mean time to operate was reported at 19.76 days (95% CI, 12.35 to 27.18) in patients undergoing a free flap reconstruction of the lower extremity (Figure 2c). An additional two studies reported the time to operate on patients undergoing amputation.

Both Lim et al. [36] and Monaro et al. [40] reported a mean time to operate of 11 days (SD=15). A confidence interval of reported outcomes could not be calculated for the Monaro et al. [40] study, as standard deviations and individual outcomes were not reported. Even

Table 5: Diversity of reported outcomes among amputation studies included in this review.

Source (Author, Year)	AKA/BKA Specified	Hospital Stay	QoL	Time to Amputate	Indication to Amputate	Mobility	Time to Follow-Up	Complications
Morse et al. [41]	X				X			X
Gifford et al. [22]	X				X			X
Snyder et al. [48]	X				X			X
Monaro et al. [40]		X		X	X			X
Ploeg et al. [2]	X				X		X	X
Nelson et al. [43]AKA	X							X
Nelson et al. [43] BKA	X							X
Yamada et al. [55]	X	X			X			X
Nayak et al. [42]	X				X		X	
Toursarkissian et al. [50]	X	X			X			X
Basu et al. [16]	X				X	X		X
Chu et al. [17]	X		X		X			X
Cruz et al. [4]	X				X			X
Finch et al. [20]	X	X				X	X	X
Fortington et al. [21]	X						X	X
Hasanadka et al. [24]	X						X	X
Jordan et al. [29]	X	X			X	X		X
Lim et al. [36]	X	X		X	X		X	X
Mckenzie et al. [38]	X	X	X		X	X	X	X
Bosse et al. [13]	X		X		X	X	X	X
Corey et al. [18]	X				X	X		X
Feinglass et al. [19]	X				X			X
Totals (%)	**21/22 (95%)**	**7/22 (32%)**	**3/22 (14%)**	**2/22 (9%)**	**17/22 (77%)**	**6/22 (27%)**	**8/22 (36%)**	**21/22 (95%)**

*NR: Not Reported

Table 6: Relative risk of experiencing an adverse event peri- or post-operatively among those patients that underwent either free flap reconstructive surgery or lower extremity amputation.

Adverse Events	No./Total Patients - Free Flap	No./Total No. Participants- Amputation	Relative Risk
Infection	29/1073	1614/28334	0.47
Osteomyelitis	52/1073	4/28334	343.28
Hematoma/Bleeding	15/1073	103/28334	3.85
Ulceration	17/1073	143/28334	3.14
Venous Thrombosis	6/1073	81/28334	1.96
Reoperation/Second Amputation	66/1073	1929/28334	0.9
Total Flap Loss	27/1073	NR	-
Partial Flap Loss	45/1073	NR	-
Partial Skin Site/Flap Loss	18/1073	NR	-
Vascular Compromise	26/1073	NR	-
Seroma	14/1073	NR	-
Postoperative Amputation	14/1073	NR	-
Flap Remodeling	34/1073	NR	-
Vascular Remolding	33/1073	NR	-
Pneumonia	NR	492/29334	-
Sepsis	NR	1657/28334	-
Stroke	NR	259/28334	-
Pulmonary Embolism	NR	93/28334	-
Cardiac Events (CHF, MI, Cardiac Arrest)	NR	822/28334	-

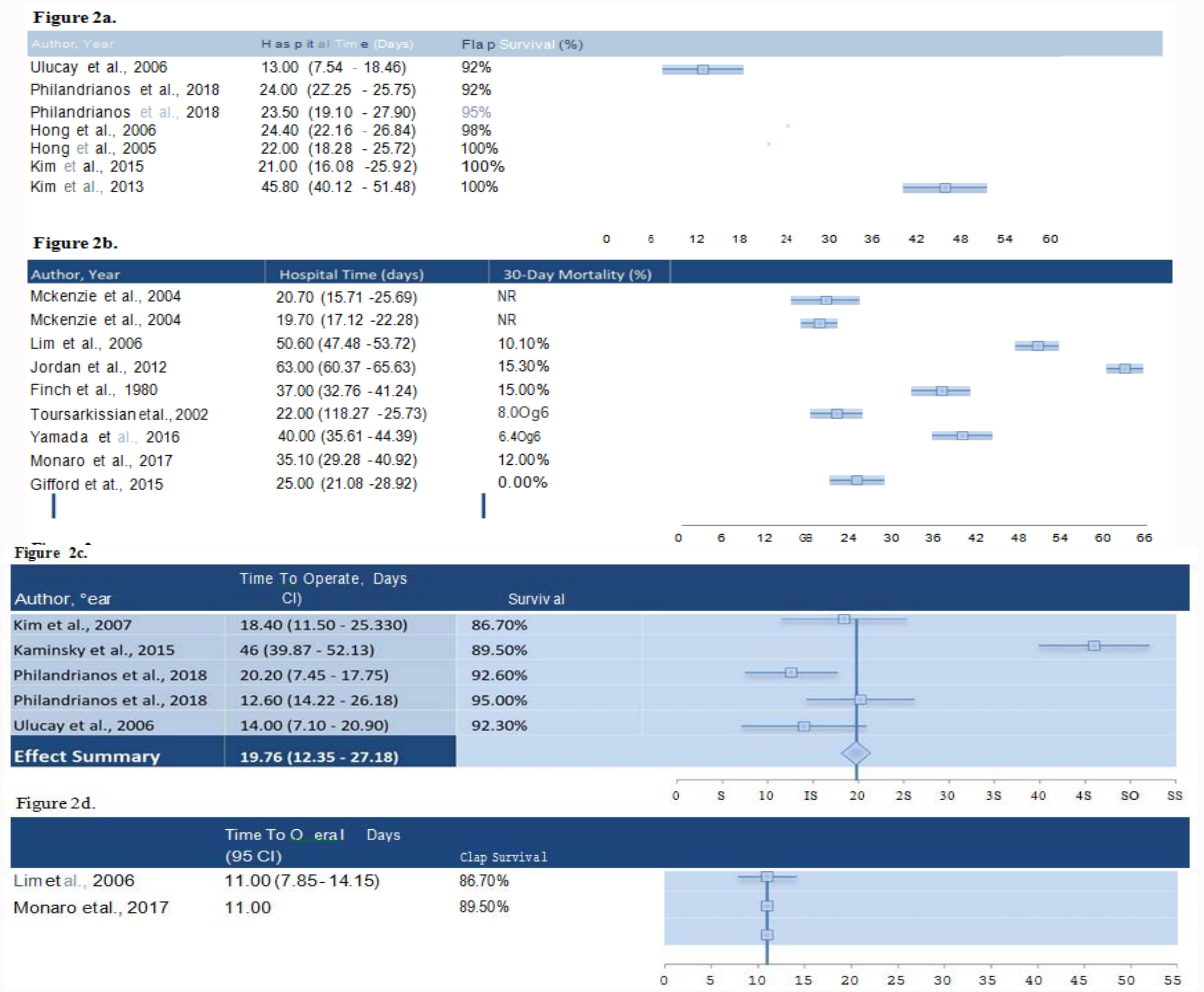

Figure 2: (a) Dot plot depicting the results of the meta-analysis of hospital length of stay (LOS) among patients treated with microsurgical free flap reconstruction of the lower extremity (b) Dot plot depicting the results of the meta-analysis of hospital LOS among patients treated by amputation of the lower extremity (c) Dot plot depicting the results of the meta-analysis of time to operate (TTO) among patients treated with microsurgical free flap reconstruction of the lower extremity (d) Dot plot depicting the results of the meta-analysis of TTO among patients treated by amputation of the lower extremity, with a distribution of absolute values around the central tendency.

so, with the currently available data, a mean time to operate of 11 days was reported for those patients requiring amputation (Figure 2d). Heterogeneity was observed using both a fixed and random effects model across the two studies that reported time to operate (I2=88%, Q=33.64; I2v=54%, Qv=8.68).

Adverse events

In this study, data was collected to demonstrate the relative risk of experiencing adverse events common to both amputation and reconstructive free flap operations. These results are summarized in Table 6.

Discussion

It is evident from the results of this review that there is a large dichotomy in reporting standards for those studies that investigates outcomes of free flap reconstruction or amputation of lower extremity injuries. It was found that very important characteristics and outcomes such as time it took to operate, post-operative ambulation, and patient quality of life indices were not reported by the vast majority of both amputation and free flap studies. Even so, several studies have shown that within 24 months of reconstruction or amputation, ambulatory outcomes are largely the same across these broad cohorts [57,58]. In light of this evidence it has still not been established whether or not there are significant differences in quality of life among these patients. Currently, it is very difficult to find a clinical need to reconstruct the limb rather than to amputate other than patient or physician preferences and any immediate medical indications [58-60]. It is therefore important that future studies investigating the outcomes of their primarily reconstructed or amputated patients, should collect quality of life indices. This may provide future guidelines for choosing between these two seemingly equivalent treatment options.

Furthermore, several studies have guided insights into those data that should be reported in the assessment of patients with a reconstructed limb or lower extremity amputation [13,58,59,61,62]. These include quality of life, long term ambulatory outcomes, operating time, time to operate, and hospital length of stay. It is well established that quality of life and ambulation should be a standard assessment in these patients. In situations where there is no clear medical indication to reconstruct or amputate the limb, data on post-operative QoL and ambulatory outcomes are necessary in order to improve overall patient outcomes and satisfaction following traumatic lower extremity injuries. It has also been hypothesized that length of operation, hospital stay, and time to operate may all significantly affect post-operative ambulatory outcomes and quality of life in these patients [7,38,57-59]. For example, a longer hospital stay may increase the risk of infection and decrease quality of life in the patient [63]. Additionally, a longer time to operate may introduce the patient to similar risk factors that may lead to increased morbidity [64]. Length of operation has both clinical implications and cost implications for all stakeholders- patients, physicians, and hospitals [57].

In this meta-analysis, time to operate was significantly longer in free flap reconstruction cases (p=0.041) than in those patients undergoing amputation using a one-tailed t-test. This may poorly affect outcomes in these patients, exposing them to pre-operative risk factors such as infection, bleeding, venous thromboembolism, vascular compromise, sepsis, stroke, cardiac events, and postoperative pulmonary embolism [58,60,65]. Unfortunately the nature of these injuries often requires a period for stabilization from a critical care or trauma standpoint and several trips to the OR for debridement while the crush and vascular injuries declare themselves allowing for adequate debridement of necrotic or diseased tissues.

Interestingly, the mean number of hospital days was reported to be only 23.36 days in free flap patients and it was significantly higher in amputation patients (32.19 days, p=0.046). This may be due to the differences in medical morbidity in these patients.

Amputees may require more medical stabilization if for instance the amputation was due to severe sepsis or diabetic complications compared to a young healthy trauma patient. Regardless, longer hospital stays expose amputation patients to significant post-operative risk factors. As demonstrated by several studies, these risk factors may be more detrimental to overall patient ambulatory outcomes and quality of life, than the pre-operative risks associated with a longer time to operate.

The results of this meta-analysis are fairly complicated. If all patient cohorts were identical, then this would be clear data in favor of free flap reconstruction in all eligible patients, under the assumption of time to operate and hospital Length of Stay (LOS) as the only significant attenuating factors. These findings are contrary to popular belief that amputation results in an overall shorter hospital stay and may have broad implications in trauma surgery.

When looking closely at the values of heterogeneity (I2, Q, I2v, Qv) across all four meta- analyses performed, a random-effect model demonstrated to be more viable. This supports the fact that TTO and hospital LOS are certainly not the only factors that influence post-operative outcomes in these patients. It has been well-documented in the literature that a plethora of different factors may all contribute to postoperative morbidity in patients with a reconstructed lower limb or amputation of the limb; many of which are unique to the surgical route chosen [7,13,38,58,59,62,65]. Therefore, although it is important to recognize the role of TTO and LOS in overall patient outcomes, there are many other factors at play that could not be differentiated by the study.

Despite a very thorough and comprehensive review of the literature, this meta-analysis presents with some significant limitations. Meta-analyses are limited by the quality of the studies used for the statistical comparisons. Since randomized control trials could not be found that directly compared the clinical characteristics and outcomes of amputation and lower extremity reconstruction, there was no appropriate level one evidence to include in the analysis. Other limitations presented in association with the variability of the studies included in this analysis, and the unreliability of I2 values calculated when conducting a small meta-analysis of level two studies [60]. To increase the statistical power, retrospective studies were included in addition to the prospective cohort studies that were investigated. All of the studies had a non-randomized design and therefore could have contributed to the heterogeneity observed in the meta-analyses conducted.

In addition, outcomes are always reported differently, especially in retrospective studies, and as demonstrated by the results of the review of the literature herein. As such, it was extremely difficult to homogenize the outcomes, and outcomes of time to operate and mean hospital days were the only possible variables to analyze. Understandably, as many pre- and post-operative characteristics should be examined, however the literature was limited due to the diversity of reporting standards across all included studies.

Notwithstanding these limitations, this study may serve as a guide to plastic surgeons for both clinical decision making and the development of further studies to better identify patients that would most benefit from free flap reconstruction or amputation of the lower limb.

Conclusion

Based on the results of this meta-analysis, free flap reconstruction was favorable for reducing the post-operative risks associated with length of stay in the hospital. These results are contrary to popular belief and thus must be incorporated into clinical decision-making models when trying to elect limb salvage or amputation in the setting of lower extremity trauma.

Furthermore, results of a comprehensive review of the literature demonstrate a significant diversity in reporting practices among studies that investigate clinical outcomes of both free flap reconstruction of the lower limbs and lower extremity amputation. It is critical that future studies include data on quality of life indices, ambulatory outcomes, and hospital length of stay, time to operate, and time to amputate. A universally accepted reporting standard may strengthen the literature and help future clinicians in situations that require surgical intervention with no clear medical indication between either free flap reconstruction or major amputation.

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