Effect of Timing on Outcomes of Free Flap Reconstruction following Traumatic Injury to the Extremity: Systematic Review and Meta-Analysis

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INTRODUCTION: Microvascular free flap coverage is one of the most common methods of soft tissue reconstruction for complex traumatic extremity defects involving fractures or neurovascular injuries, yet optimal time from injury to reconstruction remains controversial. The aim of this systematic review and meta-analysis was: 1) to establish updated guidelines using comprehensive time frames for early, delayed, and late reconstruction; 2) to investigate if there is a period between early and late reconstruction associated with worse outcomes. We hypothesized that success of outcomes following free flap reconstruction would be bimodal, with early and late reconstructions leading to superior outcomes and intermediate delays resulting in inferior outcomes.

METHODS: The target population of this study was patients who underwent free flap reconstruction of an upper or lower extremity traumatic injury. The primary outcome of interest was rate of total flap failure based on time from injury to surgery. Secondary outcomes of interest included rate of partial flap failure, infection, bone nonunion, reoperation, and complications. A systematic literature search was conducted using the following databases from their inception to July 2021: PubMed, OVID Databases, Web of Science, and Scopus. Studies examining upper and/or lower extremity free flap reconstruction were included. Articles were required to report rate of flap failure as well as time from injury to surgical intervention related to free tissue transfer. Of the 1,297 identified articles, 75 full-length articles were assessed, and 21 articles (1,436 flaps) were included. Rates of flap failure, bone nonunion, reoperation, and complications were compared across time frames using two classification systems for time to surgery: 1) ≤72 hours or >72 hours; 2) 72 hours to ≤7 days, >7 days to ≤30 days, or >30 days.

RESULTS: For the first timing classification system, flap failure rate was 4.78% in the ≤72 hours group and 9.26% in the >72 hours group; partial flap failure rate was 4.46% in the ≤72 hours group and 2.96% in the >72 hours group. However, these differences were not statistically significant (*P*>.05). Of note, infection rate was lower at 3.18% vs. 7.16% (RR=.44; *P*=.015) and complication rate was lower at 10.83% vs. 18.91% (RR=.57; *P*=.001) for ≤72 hours than for >72 hours. For the second timing classification system, flap failure rate was 13.73% in the 72 hours to ≤7 days group, 5.56% in the >7 to ≤30 days group, and 9.43% in the >30 days group; partial flap failure rate was 0.00% in the 72 hours to ≤7 days group, 2.38% in the >7 to ≤30 days group, and 0.29% in the >30 days group. Differences in full or partial flap failure rates among each group were not statistically significant (*P*>.05). Of note, bone nonunion rate was higher at 19.61% vs. 0.79% (RR=.038; *P*<.001) and reoperation rate was higher at 27.45% vs. 6.35% (RR=0.220; *P*<.001) for 72 hours to ≤7 days than for >7 to ≤30 days. Likewise, bone nonunion rate was higher at 19.61% vs. 0.29% (RR=.038; *P*<.001) and reoperation rate was higher at 27.45% vs. 2.86% (RR=.099; *P*<.001) for 72 hours to ≤7 days than for >30 days; infection rate was also higher at 17.65% vs. 4.86% (RR=.253; *P*=.002) for 72 hours to ≤7 days than for >30 days. There were no statistically significant differences when comparing outcomes for >7 to ≤30 days and >30 days.

DISCUSSION AND CONCLUSION: Our findings, in conjunction with conclusions from the literature, demonstrate that immediate reconstruction within 72 hours continues to be most effective. However, outcomes of free flap reconstruction after the 72-hour window are more nuanced. One theory to investigate is whether or not there exists a period of a hyperinflammatory state where free flap reconstruction should be avoided. Given the heterogeneity with which time to surgery is categorized in the existing literature, additional studies reporting individual patient data or using more frequent time intervals are necessary to allow for more precise conclusions regarding optimal time to free flap reconstruction. Furthermore, there is a need for increased investigation of traumatic upper limb defects.

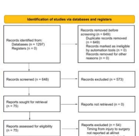
Identification of studies via databases and registers
Identification
Records identified from:
Databases (n = 1297)
Registers (n = 0)
Records removed before screening (n = 649):
Duplicate records removed (n = 649)
Records marked as ineligible by automation tools (n = 0)
Records removed for other reasons (n = 0)
Screening
Records screened (n = 648)
Records excluded (n = 573)
Reports sought for retrieval (n = 75)
Reports not retrieved (n = 0)
Reports assessed for eligibility (n = 75)
Reports excluded (n = 54):
Timing from injury to surgery not reported at all/not reported in enough detail (n = 18)
Article not available in English (n = 15)
Atraumatic coverage (n = 3)
Not extremity-based (n = 1)
Not original data (n = 1)
Paediatric population (n = 1)
Not free flap coverage (n = 4)
No flap failure rate (n = 1)
Other (n = 10)
Included
Studies included in review (n = 21)
Reports of included studies (n = 21)

Figure 1. Study selection process for systematic review of timing to free flap repair.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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Table 1. Characteristics of included studies.

First author and Year of publication	Country	Study design	Level of evidence	Individually reported data
Arslan 2019	Turkey	Retrospective cohort	4	Multiple cohorts
Bakhach 2017	Lebanon	Retrospective cohort	4	Single cohort
Choudry 2008	USA	Retrospective cohort	4	Multiple cohorts
Godina 1986	Yugoslavia	Retrospective cohort	4	Multiple cohorts
Gordon 1985	USA	Case report	6	Single cohort
Hamid 2020	Indonesia	Case report	6	Single cohort
Hertel 1999	UK	Prospective cohort	4	Multiple cohorts
Hill 2013	USA	Retrospective cohort	4	Multiple cohorts
Hong 1998	Singapore	Retrospective cohort	4	Multiple cohorts
Hwang 2015	Korea	Retrospective cohort	4	Multiple cohorts
Kalra 2013	India	Retrospective cohort	4	Multiple cohorts
Karanas 2008	USA	Retrospective cohort	4	Multiple cohorts
Kloeters 2017	Germany	Prospective cohort	4	Multiple cohorts
Kolbenschlag 2015	Germany	Retrospective cohort	4	Multiple cohorts
Kumar 2009	USA	Retrospective cohort	4	Multiple cohorts
Lee 2019	USA	Retrospective cohort	4	Multiple cohorts
Liu 2012	Australia	Retrospective cohort	4	Multiple cohorts
Raju 2014	Singapore	Retrospective cohort	4	Single cohort
Riccio 2003	Italy	Retrospective cohort	4	Single cohort
Singh 2020	India	Prospective cohort	4	Single cohort
Steiert 2009	Germany	Retrospective cohort	4	Multiple cohorts

Table 2. Postoperative outcomes based on reconstruction ≤72 hours or >72 hours from injury.

	≤72 hours	>72 hours	≤72 hours vs. >72 hours
Flap failure	15 (4.78%)	97 (9.26%)	RR = 0.52; OR = 0.49 P = 0.460
Partial flap failure	14 (4.46%)	31 (2.96%)	RR = 1.51; OR = 1.53 P = 0.262
Infection	10 (3.18%)	75 (7.16%)	RR = 0.44; OR = 0.43 P = 0.015*
Bone nonunion	4 (1.27%)	30 (2.87%)	RR = 0.44; OR = 0.44 P = 0.148
Reoperation	30 (9.55%)	61 (5.83%)	RR = 1.64; OR = 1.71 P = 0.028*
Complications	34 (10.83%)	198 (18.91%)	RR = 0.57; OR = 0.52 P = 0.001*

RR = relative risk; OR = odds ratio.
*p<0.05 is considered statistically significant.

Table 3. Postoperative outcomes based on early, delayed, or late reconstruction.

	Early	Delayed	Late
Flap failure	7 (13.73%)	7 (5.56%)	33 (9.43%)
Partial flap failure	0 (0.0%)	3 (2.38%)	1 (0.29%)
Infection	9 (17.65%)	11 (8.73%)	17 (4.86%)
Bone nonunion	10 (19.61%)	1 (0.79%)	1 (0.29%)
Reoperation	14 (27.45%)	8 (6.35%)	10 (2.86%)
Complications	5 (9.80%)	24 (19.05%)	52 (14.86%)

Early = 72 hours to ≤7 days; Delayed = >7 days to ≤30 days; Late = >30 days.
*p<0.05 is considered statistically significant.

Table 4. Comparison of postoperative outcomes based on early, delayed, or late reconstruction.

	Early vs. delayed	Early vs. late	Delayed vs. late
Flap failure	RR = 0.361; OR = 0.372 P = 0.119	RR = 0.613; OR = 0.655 P = 0.322	RR = 1.497; OR = 1.768 P = 0.196
Partial flap failure	RR = 1.238; OR = -- P = 0.558	RR = 0.149; OR = -- P = 1.000	RR = 0.091; OR = 0.118 P = 0.059
Infection	RR = 0.454; OR = 0.449 P = 0.115	RR = 0.253; OR = 0.240 P = 0.002*	RR = 0.514; OR = 0.534 P = 0.124
Bone nonunion	RR = 0.038; OR = 0.033 P < 0.001*	RR = 0.014; OR = 0.012 P < 0.001*	RR = 0.181; OR = 0.359 P = 0.460
Reoperation	RR = 0.220; OR = 0.181 P < 0.001*	RR = 0.099; OR = 0.079 P < 0.001*	RR = 0.403; OR = 0.432 P = 0.100
Complications	RR = 1.651; OR = 2.156 P = 0.179	RR = 1.288; OR = 1.604 P = 0.398	RR = 0.755; OR = 0.742 P = 0.320

RR = relative risk; OR = odds ratio.
Early = 72 hours to ≤7 days; Delayed = >7 days to ≤30 days; Late = >30 days.
*p<0.05 is considered statistically significant.