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ORIGINAL ARTICLE

Burns

Impact of Microsurgical Reconstruction Timing on the Risk of Free Flap Loss in Acute Burns: Systematic Review and Meta-Analysis

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Background: Free tissue transfer is usually considered as a last resort in severe burn cases, when skin substitutes and local flaps are not viable options. Prior studies have demonstrated a free flap loss rate ranging from 0% to 44%. The aim of this study is to identify the ideal timing to perform free flap reconstruction in acute burn-related injuries to minimize free flap loss.

Methods: A systematic review and meta-analysis was performed and reported according to PRISMA guidelines. PubMed, Embase, Web of Science, and Cochrane Library databases were queried. The review protocol was registered on PROSPERO database (CRD42023404478). Three time intervals from day of injury were identified: (1) 0–4 days, (2) 5–21 days, and (3) 22 days–6 weeks. The primary outcome was total free flap loss.

Results: A total of 17 articles met inclusion criteria. The analysis included 275 free flaps performed in 260 patients (88% men, 12% women) affected by acute burn injuries. The pooled prevalence of free flap failure in the three time intervals (0–4 days, 5–21 days, and 22 days–6 weeks) were 7.32% [95% confidence interval (CI): 2.38%–20.37%], 16.55% (95% CI: 11.35%–23.51%), and 6.74% (95% CI: 3.06%–14.20%), respectively.

Conclusions: Free flap reconstruction carries a high risk of failure in patients with acute burn. However, timing of the reconstruction appears to influence surgical outcomes. Free flap reconstruction performed between 5 and 21 days from burn injury had a trend toward higher flap loss rates and should be discouraged. *(Plast Reconstr Surg Glob Open 2024; 12:e6025; doi: 10.1097/GOX.0000000000006025; Published online 9 August 2024.)*

INTRODUCTION

Burn injuries can have an important impact on morbidity, social well-being and quality of life.[1] Skin grafting is the primary surgical treatment for partial- and full-thickness burns requiring skin coverage, and it is generally sufficient for most cases. However, severe burns may result in significant soft tissue loss. Consequently, exposure of critical structures such as bone, joints, and neurovascular structures may occur. In this scenario, the transfer of vascularized soft tissue is often necessary to achieve durable coverage and favorable outcomes.[2,3] When skin substitutes and local flaps cannot be considered as an option due to involvement of the tissue surrounding the injury or deemed unsuitable, free flaps may be the only appropriate alternative. Free flaps allow wound coverage in a single-stage procedure, potentially accelerating the healing process and reducing the risks related to prolonged hospitalization, such as infection and wound healing issues.[4–6]

Despite the advantageous properties of free flaps, they are performed with hesitancy in the acute phase of burn injury because of the patients' unstable clinical status making them not suitable candidates for long operations,[6] and the hypercoagulable state induced by the inflammatory cascade associated with burn injuries.[7] Despite these considerations, surgeons are sometimes faced with no other alternatives than to perform free

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tissue transfer to reconstruct these burn defects acutely. Prior studies have demonstrated a free flap loss rate as high as 44%.[8,9] However, debate still exists regarding the influence of timing on free flap reconstruction outcomes in acute burns.

The aim of this study is to investigate whether timing of the reconstruction impacts the free flap loss rate in acute burn-related injuries, to minimize free flap loss.

Takeaways

Question: What are the findings of this first meta-analysis investigating the impact of timing on free flap outcomes in acute burn reconstruction?

Findings: This study shows that free flaps performed between days 5 and 21 after injury are associated with the highest rate of free flap failure in acute burns.

Meaning: Results shown in this study might be explained by the prothrombotic state that peaks between 1 and 3 weeks after the acute injury in burn patients.

MATERIALS AND METHODS

A systematic review and meta-analysis was performed and reported according to the PRISMA guidelines.[10] Institutional review board approval and informed consents were not required for this study because all the reported data were obtained from the available published literature. The review protocol was registered on PROSPERO database (CRD42023404478).

Inclusion and Exclusion Criteria

The PICOS framework[11] was used in developing the literature search strategy:

- Population (P): acute burn patients;
- Intervention (I): microsurgical reconstruction;
- Comparator (C): none;
- Outcome (O): rate and timing of total free flap loss;
- Study type (S): randomized controlled trials, prospective and retrospective cohort studies, and case series.

Studies were excluded if (1) they were not in English; (2) they were not available in full-text form; (3) data on free flap timing were not extractable; (4) the study reported fewer than five patients; (5) the article type was a conference abstract, review, case report, book chapter, or letter to the editor; and (6) data presented were not specific to acute burn injuries. All articles had to be published in a peer-reviewed journal, and no restriction on publication date was applied.

Outcome Measures

The aim of this systematic review was to measure the impact of reconstruction timing on the risk of free flap loss. Three time intervals from day of injury were identified: (1) between days 0 and 4, (2) between days 5 and 21, and (3) between day 22 and week 6. The primary outcome was complete free flap loss. Free flap loss was defined as complete flap necrosis. Acute burn was considered any burn presenting within 6 weeks from the day of injury and not previously healed.

Data Source and Study Search

An electronic search was performed on PubMed, Embase, Web of Science and Cochrane Library using relevant keywords, phrases, and medical subject headings (MeSH) terms. The search strategy applied for PubMed was: (“Burns”[MeSH Terms] OR “burn”[All Fields]) AND (“Free Tissue Flaps”[MeSH Terms] OR “free tissue”[All Fields] OR “free flaps”[All Fields]) AND (“fail*”[All Fields] OR “issue*”[All Fields] OR “complic*”[All Fields]). The reference list of each selected article was checked to screen for potentially relevant studies (ie, snowballing method). The search was carried out on February 8, 2023.

Selection of Studies and Data Extraction

Two reviewers independently conducted the electronic literature search (J.A.K. and H.Y.L.). The reference lists from four databases (ie, PubMed, Embase, Web of Science, and Cochrane Library) were merged, and the duplicates were removed using the reference management software EndNote X9 (version X9.3.3). Titles and abstracts of unresolved papers were screened. Whenever appropriate, full texts of relevant articles underwent subsequent evaluation for eligibility. Discrepancies were resolved by the senior author (F.M.E.). Data extracted from selected articles were archived in a customized Excel (Microsoft Corp., Seattle, WA) spreadsheet. Variables collected include number of free flaps and free flap failures, timing of the reconstruction, and patients’ demographics [gender, age, percentage total body surface area (%TBSA), follow-up].

Risk of Bias and Study Quality Assessment

Methodological quality of included studies was assessed independently by two separate authors (J.A.K. and H.Y.L.). Because no randomized controlled trials were included, Methodological Index for Nonrandomized Studies (MINORS) criteria,[12] a validated instrument designed to assess the methodological quality of nonrandomized studies, were used to measure bias. MINORS maximum score for noncomparative studies is 16.[12]

Data Synthesis and Statistical Analysis

Data from the included studies were summarized using descriptive statistics. Dichotomous variables were reported as frequencies and percentages, whereas continuous variables were reported as median and 95% confidence interval (CI), calculated using the method described by McGrath et al.[13]

A single-arm meta-analysis of proportions was performed for all outcomes on the entire cohort using a logistic regression model. Maximum-likelihood estimator was used to estimate the between-study variance (τ^2). Results are presented as pooled estimates with 95% CIs. A forest plot graph was created for each outcome. Cochran’s Q method was used to assess between-study heterogeneity.[14] I^2 was calculated as a measure of heterogeneity.[15] An I^2 value represents the percentage of total variation across studies caused by heterogeneity rather than by chance. If

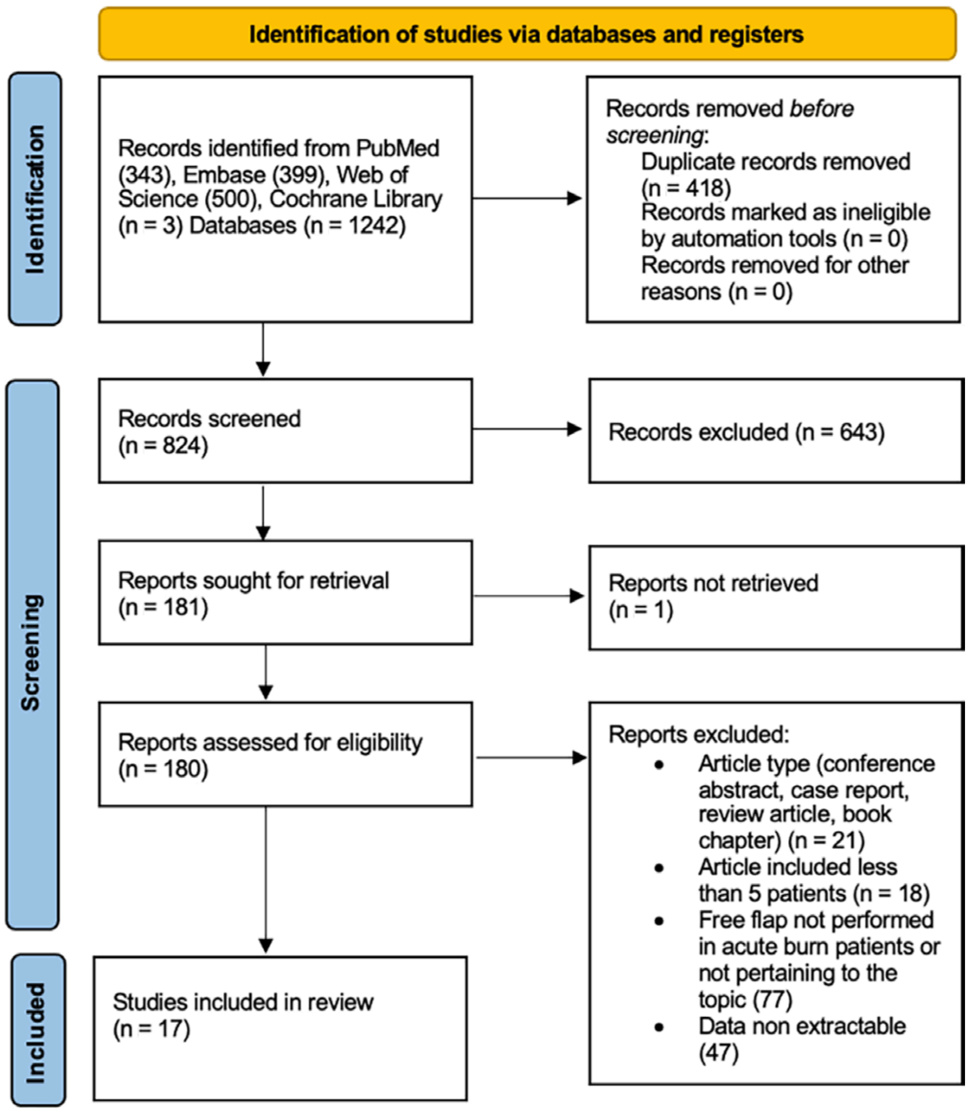

Fig. 1. PRISMA flow diagram.

the heterogeneity test produced a low probability value (Q-statistic, $P < 0.05$), a more conservative random effects model was used. If not, a fixed effects model was used.

Analysis of publication bias was performed by inspection of the funnel plot[16] and calculating the Peters' linear regression test, which statistically examines the asymmetry of the funnel plot.

All the analyses were performed using the R software for statistical computing (R version 4.0.1; "meta" package).

RESULTS

Electronic Database Search Results and General Features of the Studies Included

A total of 1245 eligible articles were retrieved from the preliminary search. After duplicate removal and screening of both titles and abstracts, 184 full-text articles were assessed for eligibility. After applying inclusion and exclusion criteria, 17 articles were included in the qualitative and quantitative synthesis.[5,7–9,17–29] A flow chart of the study inclusion process and the reasons justifying the exclusion of the 167 studies are shown in Figure 1. The lack of comparative studies did not allow direct comparison of different interval times.

The included studies comprised a total of 275 free flaps performed for reconstruction of complex acute burn wounds in 260 patients (88% males, 12% females). The patients' mean age was 37.9 (95% CI: 32.6–43.3). The mean follow-up was 15.5 months (95% CI: 13.0–18.0). The median %TBSA was 19%. The total number of free flaps performed between days 0 and 4 was 41, between days 5 and 21 was 146, and between day 22 and week 6 was 88. The general characteristics of the included studies are shown in Table 1.

Risk of Bias and Study Quality Assessment

In the 17 included studies, scores ranged from 10 to 13, with a median of 11. The major deficiencies were lack of

Table 1. General Characteristics of the Included Studies

Authors	Year of Publication	No. of Patients	Mean Age (y)	No. Male	No. Female	Mean % TBSA	No. Free Flaps	No. Free Flap Failures	Mean Follow-up (mo)
Baumeister et al[7]	2005	43	35	NS	NS	27	43	10	NS
Castro et al[17]	2018	5	26	5	0	NS	5	0	13
Chick et al[18]	1992	5	40	5	0	NS	7	0	18
Handschin et al[8]	2009	8	NS	NS	NS	NS	9	4	NS
Hsiao et al[19]	2013	5	42	5	0	11	5	1	48
Jabir et al[20]	2015	20	37	19	1	16	20	0	NS
Koul et al[5]	2008	13	33	11	2	22	16	1	20
Monga et al[21]	2021	20	25	NS	NS	NS	20	3	NS
Pan et al[9]	2007	38	38	30	8	24	38	0	NS
Pedrazzi et al[22]	2022	10	32	9	1	24	12	2	NS
Pessoa Vaz et al[23]	2018	14	62	9	4	10	15	2	NS
Saint-Cyr et al[24]	2008	14	34	14	0	NS	15	3	34
Sauerbier et al[25]	2007	21	35	NS	NS	28	21	4	NS
Stefanacci et al[26]	2003	8	33	NS	NS	15	12	1	3
Uslu[27]	2019	11	35	11	0	NS	11	0	18
Zhao et al[28]	2018	12	39	12	0	NS	12	0	16
Ziegler et al[29]	2020	13	47	10	3	12	14	1	9

%TBSA, percentage total body surface area; NS, not specified.

calculation of study size and lack of prospective collection of data. All studies showed a clearly stated aim, appropriate endpoints and no loss to follow-up. Most of the studies included consecutive patients. (**See figure, Supplemental Digital Content 1**, which displays MINORS scores for the included studies. **http://links.lww.com/PRSGO/D401**.)

Free Flap Loss in Acute Burns

The meta-analysis of proportions including all free flap reconstructions in all time intervals showed a pooled prevalence of 11.64% (95% CI: 8.35%–15.99%) of complete free flap loss in acute burns, as shown in the forest plot in Figure 2. Small between-study heterogeneity ($Q = 7.88$, $P = 0.95$) was measured $I^2 = 0\%$ (95% CI: 0%–51.1%) and $\tau^2 = 0.77$; hence, a fixed-effect model was used.

The Peters linear regression test showed no obvious publication bias ($t = 0.21$, $P = 0.84$). (**See figure, Supplemental Digital Content 2**, which displays the visual inspection of the funnel plot and shows a symmetric distribution of the points. **http://links.lww.com/PRSGO/D402**.)

Time Interval between Days 0 and 4

The meta-analysis of proportions including free flap reconstructions performed immediately between days 0 and 4 showed a pooled prevalence of 7.32% (95% CI: 2.38%–20.37%) of complete flap loss in acute burns as shown in the forest plot in Figure 3. No between-study heterogeneity ($Q = 1.57$, $P = 0.99$) was measured [$I^2 = 0\%$ (95% CI: 0%–58.3%) and $\tau^2 = 0$]; hence, a fixed-effect model was used. The Peters linear regression test showed potential publication bias ($t = 8.0$, $P = < 0.0001$), the visual inspection of the funnel plot shows an asymmetric distribution of the points, as shown in Supplemental Digital Content 2 (**http://links.lww.com/PRSGO/D402**).

Time Interval between Days 5 and 21

The meta-analysis of proportions including free flap reconstructions performed between days 5 and 21 from day of injury showed a pooled prevalence of 16.55% (95% CI: 11.35%–23.51%) of complete flap loss in acute burns as shown in the forest plot in Figure 4. No between-study heterogeneity ($Q = 5.57$, $P = 0.99$) was measured [$I^2 = 0\%$ (95% CI: 0%–51.1%) and $\tau^2 = 1.31$]; hence, a fixed-effect model was used. The Peters linear regression test showed no obvious publication bias ($t = -0.66$, $P = 0.52$), and the visual inspection of the funnel plot shows a symmetric distribution of the points, as shown in Supplemental Digital Content 2 (**http://links.lww.com/PRSGO/D402**).

Time Interval between Day 22 and 6 Weeks

The meta-analysis of proportions including free flap reconstructions performed between day 22 and 6 weeks from day of injury showed a pooled prevalence of 6.74% (95% CI: 3.06%–14.20%) of complete flap loss in acute burns, as shown in the forest plot in Figure 5.

No between-study heterogeneity ($Q = 0.57$, $P = 1$) was measured [$I^2 = 0\%$ (95% CI: 0%–56.6%) and $\tau^2 = 0$]; hence, a fixed-effect model was used. The Peters linear regression test showed potential publication bias ($t = 9.22$, $P \leq 0.0001$), the visual inspection of the funnel plot shows an asymmetric distribution of the points, as shown in Supplemental Digital Content 2 (**http://links.lww.com/PRSGO/D402**).

DISCUSSION

Strategies on acute burn management have been rapidly evolving in the recent years.[30] Limited and low-level evidence exists on free flap reconstruction of acute burn injuries. Most studies are retrospective in nature, with a small sample size, and are often limited to a single local institution's treatment algorithms and surgeon's preference. For these reasons, clear reconstructive guidelines are not available. When considering the complexity of burn wound management, free tissue transfer is often used as a last resort for very severe cases that do not have suitable local reconstructive options in which and skin

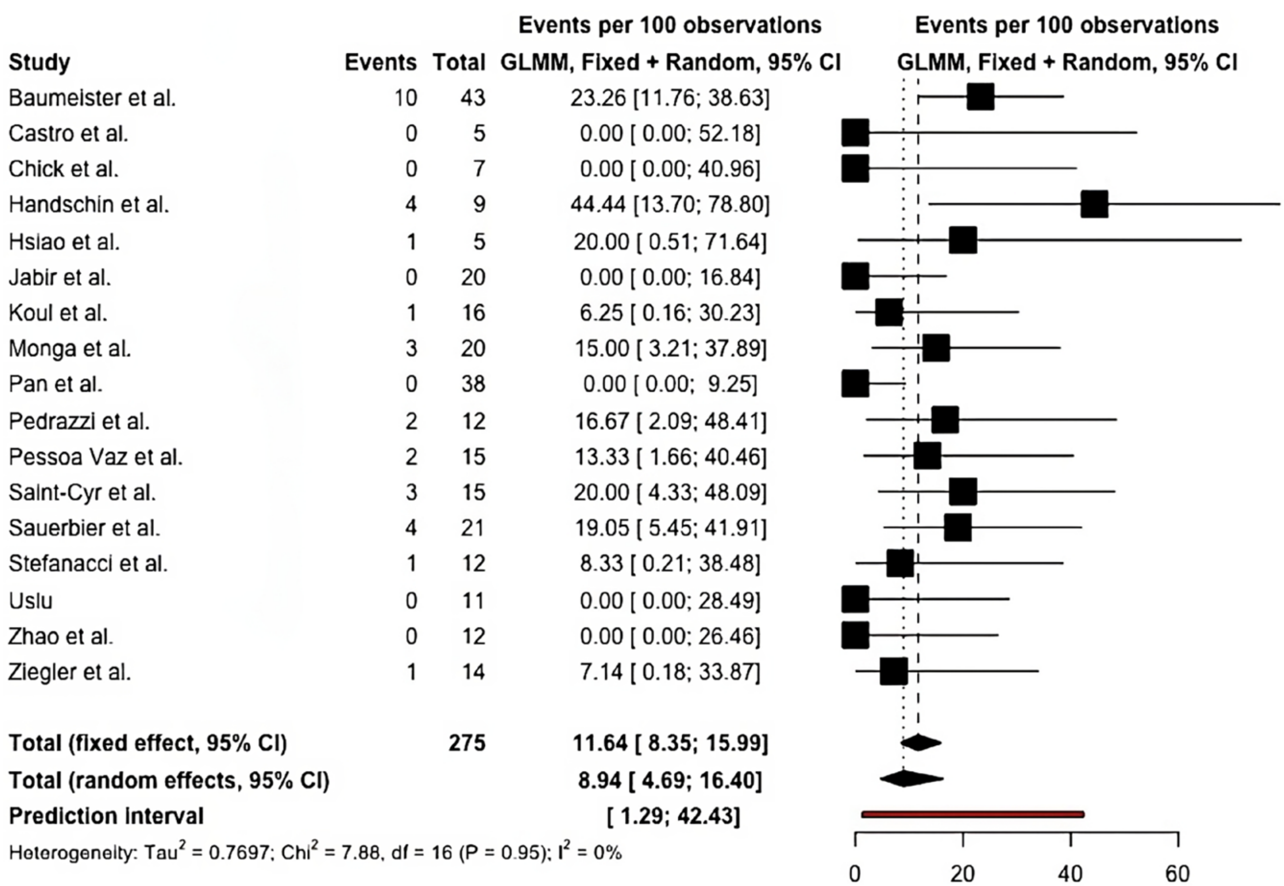

Fig. 2. Forest plot for overall complete free flap loss. GLMM, generalized linear mixed model.

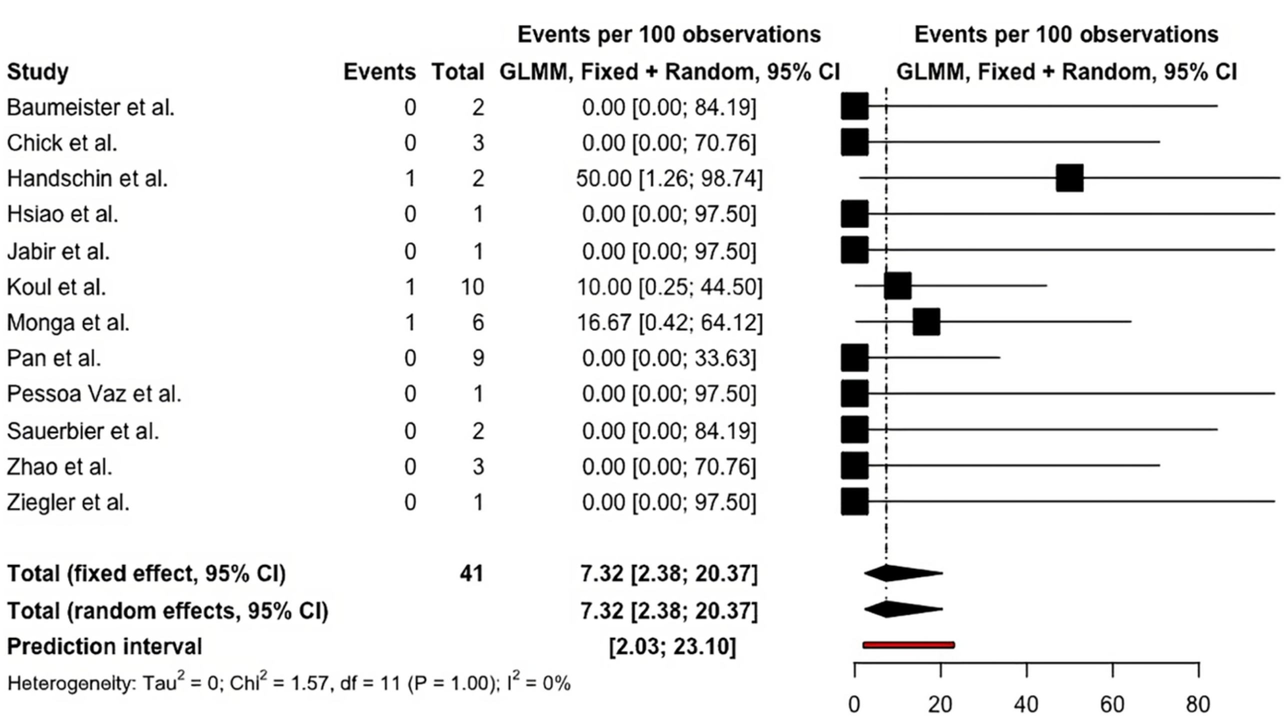

Fig. 3. Forest plot for complete free flap loss in reconstructive time interval between day of injury and day 4 from injury. GLMM, generalized linear mixed model.

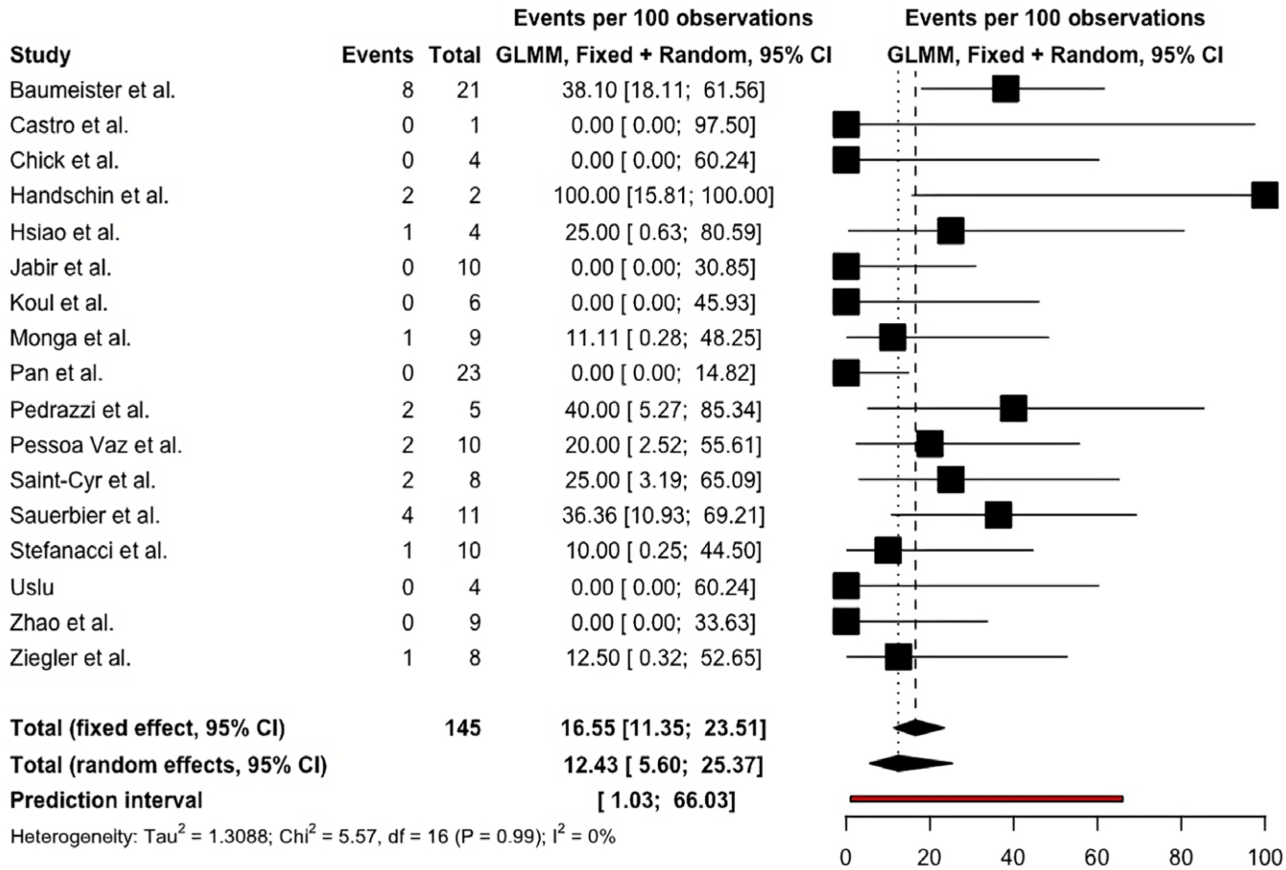

Fig. 4. Forest plot for complete free flap loss in reconstructive time interval between days 5 and 21 from injury. GLMM, generalized linear mixed model.

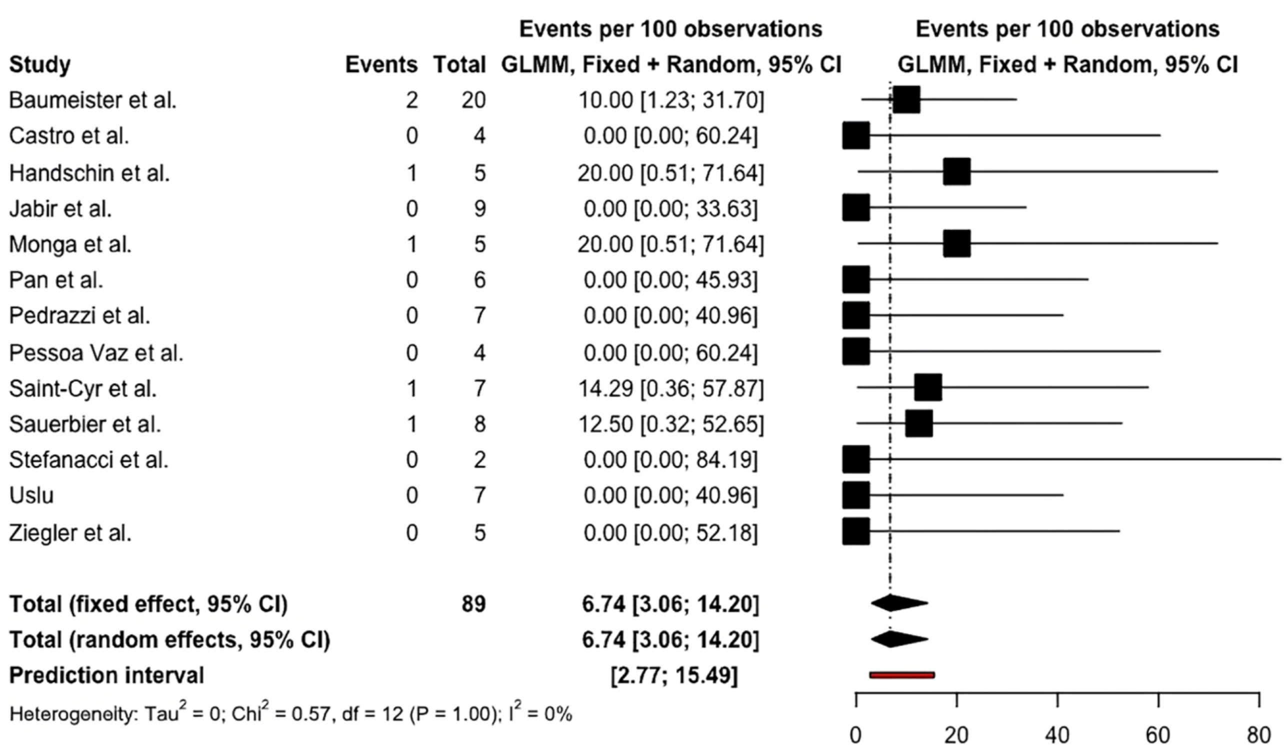

Fig. 5. Forest plot for complete free flap loss in reconstructive time interval between day 22 and 6 weeks from day of injury. GLMM, generalized linear mixed model.

substitutes are not indicated. Free flaps are rarely used in acute burn patients because of the critical clinical status of the patient and the high flap loss rate. Studies have shown a variable free flap loss rate ranging between 0% and 44%.[8,9] Although the body of literature reporting outcomes of free flaps in acute burn reconstructions is limited, a high risk of free flap loss is observed. Therefore, it is essential that as a community we explore factors that can potentially impact the outcomes of free flap reconstruction in this subgroup of patients, so that we can minimize morbidity and mortality.

Most studies divide timing of free flap reconstruction based on the three postinjury time intervals: between days 0 and 4, between days 5 and 21, between day 22 and 6 weeks.[7,9,21–23,25] For this reason, this study adopted the same definition. The largest study investigating the role of flap (pedicled and free) reconstruction timing in acute burn patients' surgical outcomes was published by Perrault et al.[6] The authors queried the Nationwide Inpatient Sample database and, differently from most of the available literature, divided timing of the reconstruction into three intervals: 1–4 days, 5–10 days, and greater than 10 days from hospitalization. The study found no impact of timing on risk of flap failure. However, their results are influenced by the fact that all types of flap reconstruction (pedicled and free flaps) were included, rather than focusing on free flap reconstruction alone. Pedicled and free flap survival differs significantly in these groups. Flap failure risk is higher in free tissue transfer because of anastomosis-related issues (blood flow turbulence, intimal injury, transient hypercoagulopathy), pedicle-related issues (kinking, twisting, and iatrogenic injury), perforator-related issues (spasm and iatrogenic injury), or other operative-related issues (flap ischemia time and operative time).[31] Our meta-analysis focused on free tissue transfer and demonstrated that free flap reconstruction performed between days 5 and 21 from injury had a higher flap loss rate (16.55%), whereas flap loss rate was remarkably lower between days 0 and 4 (7.32%) and between day 22 and week 6 (6.74%). The majority of the flaps were performed between days 5 and 21 (n = 146). This disproportion may have impacted the incidence of flap loss rate compared with other groups (between days 0 and 4, n = 41; between day 22 and week 6, n = 88). The overlapping 95% CIs and lack of statistical significance is presumably explained by the overall need of a larger sample size. As demonstrated by Perrault et al,[6] only a minority of acute burn patients are in need of flap reconstruction (526 of 306,923 patients) and even fewer require free tissue transfer. Thus, this meta-analysis attempted to answer a challenging question to a challenging problem that has limited available data.

The complex and specific pathophysiologic changes that occur after a burn injury may explain the high risk of free flap loss in acute burns. Indeed, the local and systemic hyperinflammatory state, which follows burn injuries, leads to increased vascular permeability and loss of vascular integrity leading to increased interstitial pressure and edema.[32–36] This, in turn, may impact the venous outflow due to the compressive forces caused by the interstitial edema. Furthermore, the increased perivascular scarring caused by the trauma and inflammation compromises the pliability of the vessels, may compromise both arterial inflow and venous outflow, and promote thrombi formation.[37] Additionally, burn injuries can cause endothelial damage and altered perivascular smooth muscle contractility function.[38] DeSpain et al[39] observed increased extracellular matrix protein expression, indicating changes in vascular wall following burn injury with an implied reduction in vasodilation capacity. These processes, in concert with the inflammatory response, are responsible for coagulation disorders in burn patients.[40,41] Studies have demonstrated that a transient hypercoagulability starts 24–48 hours after initial burn injury and peaks at the 2- to 3-week point.[42,43] Recently, Zhang et al[44] confirmed that the coagulation dysfunction of severely burn patients manifests as a significant hypercoagulability from 1 week postinjury. Therefore, the hypercoagulable state and the endothelial damage may increase the risk of arterial and venous thrombosis of the microvascular anastomosis, which may reflect the high incidence of free flap failure during this reconstructive period.[7,45,46] This would coincide with and explain the trend of increased free flap loss rate confirmed in our study between days 5 and 21 from burn injury.

Recent studies have attempted to investigate the imbalance of coagulation, anticoagulation and fibrolysis systems in burn patients through analysis of thrombelastography.[47] Thrombelastography data showed that coagulation dysfunction after severe burn was mainly characterized by procoagulant disorders and hyperfibrinolysis starting 24 hours after injury.[47] Although current evidence is mainly limited to burns characterized by a high %TBSA (greater than 60%), its application in confirming the best reconstructive timing could be a valuable future field of research.

Given the evidence of this study, the recommendation would be to delay free flap reconstruction at least 21 days after burn injury. Further strategies could also be used to minimize the impact of hypercoagulabilty on flap perfusion. The senior author's preference is to routinely anticoagulate patients at the time of anastomosis and after surgery. At the time of anastomosis a 5000 units bolus of intravenous heparin is given. Postoperatively, the following protocol is used: intravenous heparin at a rate of 500 units per hour, aspirin 325 mg per rectum at the end of surgery followed by daily 81 mg, use of sequential compressive devices while in bed, Bair hugger and warm room temperature, and early mobilization based on the location of the flap.

Our study has several limitations. The available sample size is small, and most of the included studies are retrospective case series. No single-group data on etiology and location of the burns or demographic information could be extracted from the included studies. No data on the severity of the injury were available, and it was not possible to identify whether it was the severity of the injury to influence the reconstructive timing. However, in our experience, in these patients, it is the patient's general clinical condition that guides the reconstructive timing rather than local characteristics. Moreover, reasons for free flap failure could not be extracted from the included studies. Also, given the overlap of 95% CIs and the potential publication bias measured for flap loss rate between days 0 and 4 and between day 22 and 6 weeks, no definitive assumption can be made.

However, the clinical experience from these studies, along with laboratory findings of transient hypercoagulable state starting after 24–48 hours and peaking at 2–3 weeks from injury, strengthen the reliability of the results obtained in this meta-analysis. The trend among timing groups (despite the lack of direct comparison) should urge the plastic surgery community to conduct further research. Future studies should focus on prospectively comparing different reconstructive time windows with a larger sample size and should assess the potential benefit of antiplatelet and anticoagulant agents in lowering the risk of flap failure.

CONCLUSIONS

Free flap reconstruction carries a high risk of failure in patients with acute burn. However, timing of the reconstruction appears to influence surgical outcomes. Free flap reconstruction performed between days 5 and 21 from burn injury had a trend toward higher flap loss rates. Further studies are needed to confirm these findings. The authors hope this study helps in providing new insights into the challenging reconstructive management of acute burns and helps plastic surgeons plan for complex acute burn reconstruction.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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