Accessed on: http://jkb.ub.ac.id/index.php/jkb/article/view/3757
Jurnal Kedokteran Brawijaya Vol. 33, No. 3, Februari 2025, pp. 226-235
Article History: Received 9 December 2024, Accepted 10 February 2025

Literature Review

Optimizing Burn Injury Care: A Comparative Network Meta-Analysis of Skin Grafts' Efficacy

Optimalisasi Perawatan Luka Bakar: Komparasi Efikasi Cangkok Kulit (*Skin Graft*) dalam Network Meta-Analisis

Imke Maria Del Rosario Puling, Nyoman Deva Pramana Giri, Teresa Almadita, Jane Limantara, Arviansyah Arviansyah

Department of Reconstructive Plastic Surgery General Hospital Saiful Anwar Malang

ABSTRACT

Burn injuries, causing approximately 180,000 deaths. Skin grafting serves as a cornerstone intervention in burn injury management. This study aimed to evaluate the efficacy of different types of skin grafts in promoting the healing process of burn injuries. The outcomes of the study were the reepithelialization time and repigmentation rate of skin graft. Quality appraisal was done using ROBINS-I and the Newcastle Ottawa Scale, while network and single arm meta-analysis were conducted using R-Studio. A literature search across 6 databases resulted in the selection of 7 articles. Quality assessment categorized 6 studies as low- and 1 as moderate-risk of bias studies. The device facilitated autologous skin cell increase in reepithelialization rate (OR=5.21; 95% CI=0.24-114.41), followed by autologous skin cell and synthetic graft (OR=0.47; 95% CI=0.04-5.98), topical agent (OR=0.30; 95% CI=0.06-1.47), and Xenograft (OR=0.09; 95% CI=0.00-4.89). Furthermore, the single-arm meta-analysis showed an overall repigmentation rate of 61.49%, with xenograft displaying the highest repigmentation rate (87.50%), followed by synthetic graft (70.32%), and autologous skin cell (37.54%). Xenografts have proven effective in promoting burn wound healing. Nevertheless, the outstanding efficacy and minimal repigmentation of device-facilitated autologous skin cell transplantation highlight its potential in clinical practice.

Keywords: *Burn injury, efficacy, reepithelialization, repigmentation, skin grafts*

ABSTRAK

Luka bakar merupakan salah satu penyebab utama morbiditas dan mortalitas, dengan sekitar 180.000 kematian per tahun di seluruh dunia. Cangkok kulit menjadi salah satu intervensi utama dalam pengelolaan luka bakar. Penelitian ini bertujuan untuk mengevaluasi efikasi berbagai jenis cangkok kulit dalam mempercepat proses penyembuhan luka bakar. Hasil yang dianalisis mencakup waktu reepitelisasi dan tingkat repigmentasi dari cangkok kulit. Penilaian kualitas studi dilakukan menggunakan ROBINS-I dan Newcastle Ottawa Scale, sedangkan *Network Meta-Analysis* dan *Single Arm Meta-Analysis* dilakukan menggunakan R-Studio. Pencarian literatur pada 6 database menghasilkan 7 artikel yang terpilih. Berdasarkan penilaian kualitas, 6 studi dikategorikan sebagai studi dengan risiko bias rendah, sedangkan 1 studi memiliki risiko bias sedang. Hasil *Meta-Analisis* menunjukkan bahwa device-facilitated autologous skin cell memberikan peningkatan tertinggi pada reepitelisasi (OR=5,21; 95% CI=0,24-114,41), diikuti oleh autologous skin cell dan synthetic graft (OR=0.47; 95% CI=0.04-5.98), topical agent (OR=0.30; 95% CI=0.06-1.47), dan Xenograft (OR=0.09; 95% CI=0.00-4.89). Selain itu, *Single Arm Meta-Analysis* menunjukkan tingkat repigmentasi keseluruhan sebesar 61,49%, dengan xenograft menunjukkan tingkat repigmentasi tertinggi (87,50%), diikuti oleh synthetic graft (70,32%), dan autologous skin cell (37,54%). Penelitian ini menyimpulkan bahwa xenograft efektif dalam mendorong penyembuhan luka bakar. Namun, efektivitas reepitelisasi yang sangat baik serta tingkat repigmentasi yang rendah dari transplantasi device-facilitated autologous skin cell menyoroti potensinya untuk aplikasi klinis di masa mendatang.

Kata Kunci: Cangkok kulit, efikasi, luka bakar, reepitalisasi, repigmentasi

Correspondence: Arviansyah Arviansyah. Department of Reconstructive Plastic Surgery General Hospital Saiful Anwar, Jl. Jaksa Agung Suprapto No. 2, Malang 65112 Tel. +6281332034500 Email: arvianbedahplas@ub.ac.id

DOI: http://dx.doi.org/10.21776/ub.jkb.2025.033.03.8

INTRODUCTION

Burn injuries are among the major global public health concerns, with an estimated 11 million cases reported annually worldwide, according to WHO (1). Both minor and severe burn injuries can lead to an increase in mortality rates. Burn shock is the major cause of burn-related mortality, accounting for 58% of deaths within the first 72 hours post-injury, highlighting the necessity of immediate treatment (2). Burn injuries significantly impact patients' health, with many experiencing disabling and detrimental effects (3). Effective treatments require comprehensive approach considering not only life-threatening conditions but also factors affecting physiological well-being and aesthetic outcomes. Therefore, burn injury treatment requires interventions that optimize efficacy while ensuring satisfactory aesthetic results.

The current standard treatments include dressing or surgical intervention, such as skin grafting (4). Silver-based dressings are the most commonly used, with 52.78% of burn patients treated using this method, followed by dry materials (18.06%), fatty gauze (15.97%), and miscellaneous dressing (13.19%) (5). Among these, silver sulfadiazine (SSD) remains the standard regimen for due to its anti-bacterial effect properties. However, concerns over delayed wound healing and undesirable side effects in topical treatments have increased the demand for better alternatives (6). Surgical interventions, particularly skin grafting, have been majorly developed in burn injury management by accelerating wound closure and reducing morbidity and mortality (7).

Various types of skin grafts, including allografts, xenografts, synthetic skin substitutes, and autografts, are employed for burn injuries. Effective skin grafts must exhibit characteristics such as water loss prevention, wide availability, biodegradability, support for cellular adhesion, and infection resistance (8). A study conducted Bognadov *et al.,* demonstrated that full-thickness skin grafts effectively treat facial burns, providing superior cosmetic results and reducing scar formation (9). Skin grafting has also been associated with shorter hospital stays for burn patients (10).

Gao *et al.,* compared different skin grafting techniques and found that 90% of patients undergoing Meek skin grafting showed better post-operative recovery compared to stamps and skin grafting methods (11). Despite its advantages, skin grafting poses challenges, particularly regarding post-operative pigmentation issues caused by melanin accumulation. Different skin grafting techniques influence pigmentation outcomes. Kubota *et al.,* found that thick split-thickness skin grafts following full-thickness debridement significantly reduced repigmentation risk compared to medium split-thickness grafts (12). Comparative investigations into diverse skin grafting techniques are crucial to identify the most effective method for mitigating complication like repigmentation.

Although widely used, the effectiveness of employing one type of skin graft over another remains a subject of ongoing debate. The objective of this study is to assess the comparative efficacy of different skin grafting methodologies to identify the optimal approach for superior outcomes in skin graft treatment.

METHOD

This meta-analysis was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (13). This study was under ongoing review for PROSPERO registration.

Search Strategy

The literature search was carried out on six databases, namely PubMed, ScienceDirect, EBSCO, Cochrane, ProQuest, and Scopus until March 2024. The literature search was done with keywords using boolean operators as detailed in Table 1.

Table 1. Literature search terms for included studies

Database	Keywords
PubMed	#1 “burn injury” [MeSH Terms] #2 ((“burn injury”[Title/Abstract]) OR (“burn accidents"[Title/Abstract])) #3 #1 OR #2 #4 ((“xenograft"[Title/Abstract]) OR ("autologous dermal-epidermal skin substitute" [Title/Abstract]) OR ("artificial dermis"[Title/Abstract]) OR ("graft"[Title/Abstract]) OR ("synthetic graft"[Title/Abstract])) #5 #3 OR #4 #6 #5 AND (“reepithelialization”[Title/Abstract] OR “repigmentation”[Title/Abstract]) #7 #6, Filter : Clinical Trial
ScienceDirect	(“injury” OR “trauma” OR “accident”) AND (“burn”) AND (“xenograft” OR “autologous dermal-epidermal skin substitute” OR “artificial dermis” OR graft OR “synthetic graft”) AND (“reepithelialization”) AND (“repigmentation”)
Scopus	(“injury” OR “trauma” OR “accident”) AND (“burn”) AND (“xenograft” OR “autologous dermal-epidermal skin substitute” OR “artificial dermis” OR graft OR “synthetic graft”) AND (“reepithelialization”) AND (“repigmentation”)
EBSCO	(“injury” OR “trauma” OR “accident”) AND (“burn”) AND (“xenograft” OR “autologous dermal-epidermal skin substitute” OR “artificial dermis” OR graft OR “synthetic graft”) AND (“reepithelialization”) AND (“repigmentation”)
Cochrane	#1 MeSH descriptor: [burn injury] explode all trees #2 (“burn injury” OR “burn accidents”):ti,ab,kw #3 #1 OR #2 #4 (“xenograft” OR “autologous dermal-epidermal skin substitute” OR “artificial dermis” OR graft OR “synthetic graft”):ti,ab,kw #5 (“reepithelialization”):ti,ab,kw #6 (“repigmentation”):ti,ab,kw #7 #3 AND #4 AND #5 AND #6 #8 #7 AND (“clinical trial”)
ProQuest	#1 mesh.Exact(“burn injury”) #2 noft(“burn injury” OR “burn accidents”) #3 noft(“xenograft” OR “autologous dermal-epidermal skin substitute” OR “artificial dermis” OR graft OR “synthetic graft”)

Table 1. Literature search terms for included studies

Database	Keywords
ProQuest	#4 noft("reepithelialization") #5 noft("repigmentation") #6 noft("clinical trial") #7 (#1 OR (#2 AND #3)) AND #4 AND #5 AND #6

Study Eligibility Criteria

Before conducting the literature search, the inclusion and exclusion criteria were established to ensure the homogeneity of the selected studies. The inclusion criteria were (1) availability of data in the English language, (2) studies involving burn injury patients as the sample, (3) studies comparing outcomes between various types of skin grafts, and (5) studies including at least one of the two parameters examined in this study, namely reepithelialization and repigmentation rates. The exclusion criteria were (1) non-human sampling, (2) irretrievable articles, (3) articles in incompatible languages, and (4) non-peer-reviewed articles. Each study was independently assessed by the researchers to determine whether it met the eligibility criteria. The exclusion criteria for this meta-analysis were designed to focus on studies that were most relevant and reliable. During the comprehensive screening process, numerous articles were excluded because they were not aligned with the research objectives or failed to meet the set criteria. Emphasis was placed on including studies involving clinical trials to ensure the findings were evidence-based and robust. Consequently, grey literature, such as unpublished reports, dissertations, and other non-peer-reviewed sources, was excluded to uphold methodological rigor and minimize the risk of bias. Any discrepancies were resolved through discussion until consensus was reached.

Data Extraction

Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart for study identification and selection. The original database search resulted in 633 studies from six databases searched, namely PubMed, ScienceDirect, EBSCO, Cochrane, ProQuest, and Scopus. Through title and abstract screening, 567 articles were removed, and 66 articles were screened for duplication. Duplicate screening resulted in 20 removed articles. Eighteen were further assessed for eligibility and eleven articles were removed due to unrelated or insufficient data. The final step resulted in seven clinical trials included in the qualitative synthesis. Following the elimination of duplicate studies and abstract screening, a total of 23 studies underwent a comprehensive evaluation. Ultimately, seven studies were chosen for inclusion in the meta-analysis, as depicted in Figure 1. One study was excluded due to irrelevant study design, and four others were excluded due to irrelevant outcomes to this study. The inclusion of only seven articles in this meta-analysis, despite the common guideline of using at least ten for robust conclusions, was a result of applying strict inclusion criteria. To ensure the analysis was both valid and relevant, only studies that demonstrated strong methodological rigor, directly addressed the research question, and provided the required statistical data were considered. Although this reduced the number of eligible articles, it improved the overall quality and accuracy of the analysis.

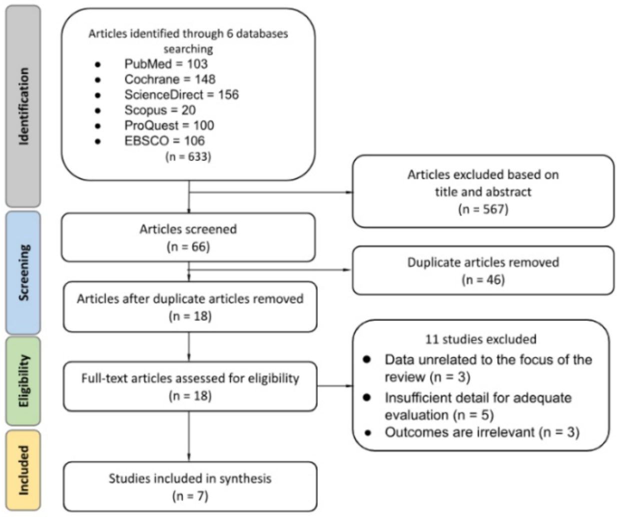

Figure 1. PRISMA flowchart of literature search

Outcome Measures

This study examined two outcome parameters to evaluate the efficacy of skin grafts in burn injury patients: reepithelialization and repigmentation rates. The researchers independently extracted data for these outcomes from the included studies. Differences in interpretation were resolved through discussion to ensure the accuracy of the results for subsequent quantitative analysis.

Quality Assessment

The quality of the included studies was assessed independently by three reviewers using critical appraisal tools. The ROBINS-I tool (Risk Of Bias In Non-randomized Studies of Interventions) tool and the NOS (Newcastle-Ottawa Scale) were employed to evaluate the risk of bias in non-randomized studies included in the meta-analyses and systematic reviews (14–16). ROBINS-I evaluates study quality across seven domains, while NOS assesses studies based on selection, comparability, and outcome domains. Disagreements among the reviewers were resolved by a fourth investigator through discussion. The ROBINS-I assessment results were recorded in a Microsoft Excel 2021 spreadsheet and visualized using the ROBVIS tool's traffic light system (17).

Statistical Analysis

RStudio was utilized to perform both network and single-arm meta-analysis to accommodate the varying strategies and outcomes reported across studies. Network meta-analysis was conducted to compare direct and indirect effects of the strategies against a control group using the "netmeta" package in RStudio 2020 (18). The "netgraph" function was used to create network graph, visually connecting and comparing all intervention strategies with the control group.

Statistical estimations were performed using a 95%

confidence interval (CI) for dichotomous data. Fixed or random effect models were chosen based on the heterogeneity observed for each outcome, with the inverse variance model employed for analysis. The heterogeneity was assessed using I2 statistics, with cutoff values of 0%, 25%, 50%, and 75% indicating insignificant, low, moderate, and high levels of heterogeneity, respectively. Closed loops were established and verified to ensure the consistency of the network. The publication bias was assessed using symmetric funnel plots, while forest plots were utilized to summarize the comparisons of pooled strategies, with the control group serving as the reference.

RESULTS

Seven experimental articles that met the inclusion criteria discussed the skin grafts in burn injury. The characteristics and summary of the seven valid studies are summarized in the Table 2 (Appendix).

Skin Graft Reepithelialization Rate

Network Meta-Analysis Graph Plot and Forest Plot

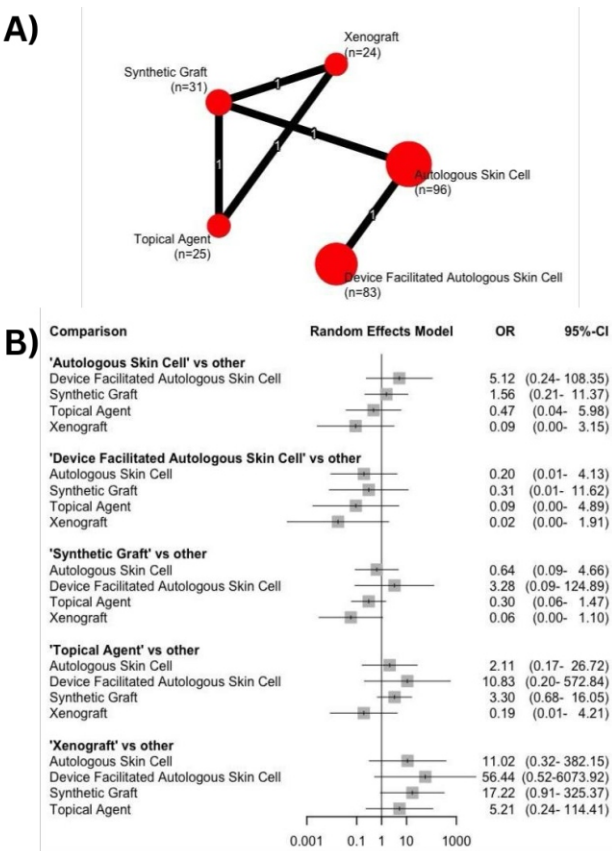

Figure 3. The result of Network Meta-analysis (A) Network Meta-analysis graph plot of seven included studied (B) Network Meta-analysis random effect model forest plot for skin graft reepithelialization rate of five different interventions.

Reepithelialization rates were reported in five studies and analyzed using network meta-analysis. The graph plot in Figure 3A illustrates the direct comparison between all skin graft methods. The node size represents the number of patients in each treatment arm, with autologous skin cells having the largest node (96 patients), followed by device-facilitated autologous skin cells (83 patients), synthetic grafts (31 patients), topical agents (25 patients), and xenografts (24). The numbers on the connecting lines indicate the number of studies comparing each skin graft procedure. The forest plot for the random effect model of reepithelialization rates, presented in Figure 3B, favored device-facilitated autologous skin cells, with an odds ratio (OR) of 10.83 [95% CI=0.20-572.84] compared to topical agents. Other results included synthetic grafts (OR=3.30 [95% CI=0.68-16.05]), autologous skin cells (OR=2.11 [95% CI=0.17-26.72]), and xenografts (OR=0.19 [95% CI=0.01-4.21]).

Table 3. Sucra table of skin graft reepithelialization rate

Reepithelialization	SUCRA Value (Random)
Device Facilitated Autologous Skin Cell	0.8398
Synthetic Graft	0.7112
Autologous Skin Cell	0.5418
Topical Agent	0.3215
Xenograft	0.0858
Device Facilitated Autologous Skin Cell	0.8398

The SUCRA (Surface Under the Cumulative Ranking) values for reepithelialization rates are presented in the table. The highest value was observed in device-facilitated autologous skin cells (0.8398), followed by synthetic grafts (0.7112), autologous skin cells (0.5418), topical agents (0.3215), and xenografts (0.0858) (Table 3). These findings align with the forest plot results shown in Figure 3B.

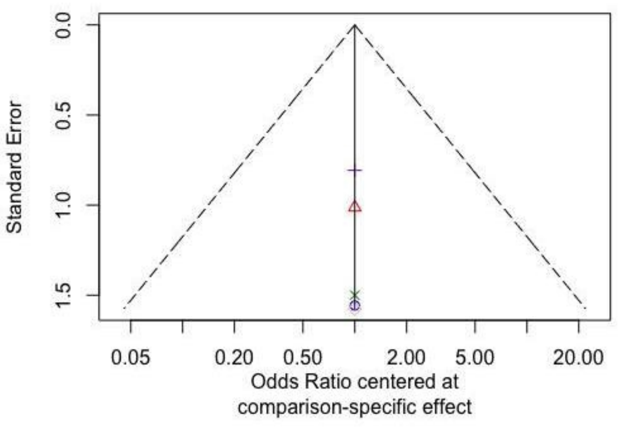

Figure 4. Funnel plot of skin graft reepithelialization rate

Funnel plot of the skin graft reepithelialization rate shows no evidence of heterogeneity due to publication bias (p>0.1) found in each intervention study, indicated by the symmetry of the funnel plot (Figure 4). The symbols of each intervention were listed Table 2.

Skin Graft Repigmentation

Forest Plot of Skin Graft Repigmentation using Single Group Analysis Method

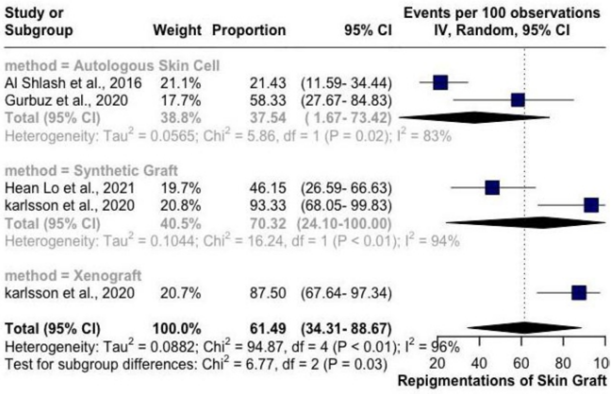

Figure 5. Single group meta analysis forest plot of skin graft repigmentation rate

The forest plot for the single-arm meta-analysis of each skin graft method indicated an overall repigmentation risk (calculated as an odds ratio) of 61.49 [95% CI=34.31-88.67]. The subgroup analysis revealed the following repigmentation risks for specific skin graft methods: xenograft (OR=87.50 [95% CI=67.64-97.34], synthetic grafts (OR=70.32 [95% CI=24.10-100.00]), and autologous skin cells (OR=37.54 [95% CI=1.67-73.42]). High heterogeneity was noted across all groups and in the overall analysis ($p<0.1$) (Figure 5).

DISCUSSION

Current Application of Various Skin Grafts in Burn Injury

Skin grafting has long been an essential procedure in plastic surgery for treating burn injuries, particularly second- and third-degree burns (25). While the skin has inherent regenerative potential, damage extending beyond the dermis impedes natural healing, necessitating the use of alternative methods to promote wound recovery. Autologous split-thickness skin grafts (STSG) remain the gold standard for covering burn wounds due to their numerous advantages and reduced risk of rejection, as they are sourced from the patient's uninjured skin. However, in cases of extensive burn injury where donor skin is insufficient, allografts and xenografts can be employed for temporary wound coverage (26). Despite their utility, STSG and allografts are not without drawbacks. The formation of scar often leads to complications such as hypertrophy, reduced skin elasticity, joint dysfunction, and suboptimal cosmetic outcomes. These factors contribute to poor functional and aesthetic results for patients (27).

Current research has been focusing on the development of artificial replacements to enhance the functional and cosmetic outcomes of skin grafting. Synthetic skin grafts are promising alternatives that can reduce scarring, alleviate pain, accelerate wound healing, and provide bioactive dermal-like qualities (26). Device-facilitated skin grafts, such as ReCell, have shown potentials in promoting healing, reducing discomfort, and minimizing scarring (28). Topical agents, when used in conjunction with skin grafts, can also provide enhanced pain relief (19). In a study by Karlsson *et al.,* higher POSAS (Patient and Observer Scar Assessment Scale) and VSS (Vancouver Scar Scale) scores were found to correlate positively with the duration of complete wound healing (24). These findings align with another study by Lo *et al.,* which reported that a wound closure of 35% resulted in a VSS score of 8, while a 41.4% wound closure within four weeks yielded a lower VSS score of 4,3. The use of cultured epithelial autograft (CEA) is advantageous because it necessitates fewer donor sites compared to STSG, leading to a shorter healing period. In order to create epithelial cells for CEA, a small portion of a patient's skin will be collected and cultured in a lab. However, since CEA lacks a dermal matrix, it results in reduced skin elasticity post-healing (21).

Skin grafting is not limited to treating burns; it can also be used to treat a range of clinical conditions, including traumatic wounds, structural reconstruction, scar contracture release, congenital skin deficiencies, vitiligo, hair restoration, and cancer (29). FTSG are widely used in nasal reconstruction to correct defects on the nasal sidewall and septum (30). In cancer treatment, wide local excision that prevents primary closure is often needed to treat the malignancies and leaving the wound open for more problems as these cases require postoperative radiotherapy. The use of skin grafting in cancer is needed to close the excision wound and improve quality of life of the patients (31).

Mechanism of Skin Grafts

Autologous split-thickness skin grafts (STSG), the gold standard for treating burn injuries, contain epidermis and a portion of the dermis and thus rely on the underlying wound bed for nutrients and blood supply (26). When harvesting a skin graft, the donor site's appearance must be considered to ensure the skin graft can be properly placed onto the burned wound area (25). The mechanism of this graft can be described in three phases; imbibition, inosculation, and revascularization. During the imbibition phase, when the skin graft is first placed in the wound bed and has yet to establish vascularization, it relies on diffusion for the delivery of nutrition and oxygen (32). Diffusion allows the graft to survive the ischemic condition before revascularization occurs. A graft can typically tolerate ischemia for three to five days, depending on the type of graft (33). In the inoculation phase, vessels from the skin graft begin to form a vascular connection with the capillaries in the wound bed (32). The skin graft adheres to its bed through the proliferation of fibroblasts and the deposition of collagen to replace the fibrin (33). By day 5, new blood vessels will emerge to nourish the skin graft (34). Vascular connections that have just formed will differentiate into afferent and efferent vessels. The presence of lymphatic drainage is noted on the fifth or sixth post-graft day (33).

emporary wound coverage can be obtained by using allografts or xenografts. These grafts are used when the skin autograft cannot be used due to limited uninjured skin on the patients. However, the use of an allograft carries an increased risk of infection and must be removed after two weeks. Human leukocyte antigens (HLA) must be considered, as they are related to the incidence of graft rejection (26).

Efficacy of Skin Graft in Increasing Reepithelialization Rate

Interpreting these findings requires considering the relationship between reepithelialization and the efficacy of grafts in burn injury patients. Burn injury care involves various stages, with reepithelialization playing a crucial role in the later phases of wound healing. The reepithelialization rate, primarily induced by keratinocyte

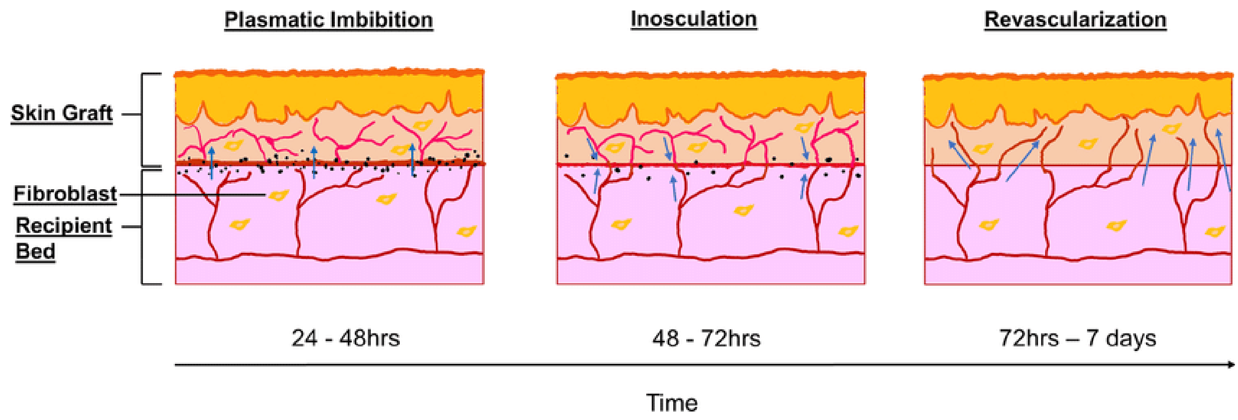

Figure 7. Translational stem cell therapy: vascularized skin grafts in skin repair and regeneration (34)

activity, serves as an indicator of graft efficacy. This rate is essential for wound healing after a thermal burns and is triggered by transforming growth factor (TGF). Reepithelialization creates optimal conditions for tissue regrowth, preventing complications and mitigating potential issues like scarring (35). Following a burn injury, reepithelialization begins promptly and can continue for several weeks. During this phase, epithelial at the wound's periphery proliferate and migrate, effectively covering the wound surface and enclosing the affected area. This cellular activity highlights the adaptability of epithelial cells during skin wound healing, enabling the rapid reestablishment of the skin's protective barrier and promoting overall healing (36).

In the study by Lo *et al.*, participants with burns covering more than 35% TBSA, were evaluated, with seven receiving synthetic graft and thirteen undergoing autologous skin cell graft. The findings showed that, after 7-10 days, epithelialization was highest (90.1%) with the application of cultured epithelial autograft (CEA), particularly when combined with autologous split-thickness skin graft (SSG). In contrast, autologous skin cell grafts using the Cuono method required further debridement and grafting at most sites, reaching a 50% debridement rate. Moreover, wounds treated using the Cuono method were associated with poorly vascularized or inadequately integrated cadaver allografts and necrotic debris, contributing to extended reepithelialization periods. The Cuono method also involves dermabrasion, which can result in bleeding and the aerosolization of abraded bloody particles, leading to challenges such as impaired visibility and health risks for operating room staff. Additionally, the presence of dermal elements has been shown to enhance the take rate of cultured epithelial autografts (CEA) (21).

In the study by Karlsson *et al.*, in 2014, both synthetic graft and xenograft (Mediskin Porcine Xenograft) healed significantly faster than Allevyn dressing as topical agent ($p < 0.01$). At, day 14 they did re-epithelialization showed significant difference, supporting xenograft with highest re-epithelialization rate (90.4%) followed by skin graft (82.8%). However, xenograft is reported to be the most painful without little infection reported (19). Another study by Holmes *et al.*, in 2024 shows the incidence of definitive closure, as defined as ≥95% re-epithelialization, was 97.6% (81/83) for the device facilitated autologous skin cell (ReCell-generated ASCS) treated site and 100% (83/83) for the control autologous skin cell–treated site (20). Hence, it can be inferred that utilizing autologous skin cell suspensions (ASCS) represents a secure and efficient substitute for traditional meshed autografting in managing deep partial-thickness burns. It leads to shallower donor site wounds compared to conventional grafting methods, which is likely to alleviate pain and enhance healing results (20,37,38).

In summary, the network meta-analysis of the included studies, investigating various skin grafts in burn injury patients in direct comparison with topical agents, revealed positive impacts on reepithelialization, with the device facilitated autologous skin graft group showing the most significant improvement followed by the synthetic graft, autologous skin cell, and xenograft. This is also reflected by the SUCRA Table that resulted in device facilitated autologous skin cell with the highest SUCRA value of reepithelialization rate, followed by synthetic graft, autologous skin cell, topical agent, and xenograft with the lowest value. This indicates the high recommendation of using device facilitated autologous skin cell as a treatment for patients with burn injury to increase the reepithelialization rate of the injured skin.

Efficacy of Skin Graft in Decreasing Repigmentation Rate

Repigmentation is a common adverse effect experienced by patients undergoing skin graft treatment in burn injury management. This can lead to patient's dissatisfaction with treatment outcomes. It is known that several factors contribute to repigmentation. For example, individuals of Asian descent tend to have a higher risk of repigmentation compared to Caucasians, due to differences in skin function, particularly in the regulation of melanocytes and melanosomes (12). Tsukada *et al.*, found that the number of active melanocytes 7 to 14 days after skin graft applications plays a role in increased in pigmentations (39). Additionally, the donor site of the skin graft can affect the repigmentation rate; grafts taken from lighter donor sites tend to result in lighter skin at the recipient site (40). Female patients typically show lighter graft pigmentations than males, likely due to reduced sun exposure in females. Different types of skin grafts also exhibit varying outcomes regarding repigmentation. A study conducted by Kubota *et al.*, showed that repigmentation outcomes differed between partial-thickness dermis (PTD) followed by medium split-thickness skin graft (STSG) and full-thickness dermis (FTD) followed by thick STSG, with the FTD followed by thick STSG group exhibiting better result (12).

Kim *et al.,* found that split-thickness skin grafts generally appeared lighter than full-thickness skin grafts. Their study emphasized that selecting a donor site with the lightest skin help reduce the risk of repigmentation (40).

Our study findings indicate that different skin graft types can influence the risk of repigmentation. Xenografts, in particular, have the highest risk of repigmentation. Karlsson et al. reported that abnormal repigmentation occurred in 35 participants treated with xenografts (24). The thickness of the skin graft can also play a role, as thinner grafts are associated with higher vessel density and poorer skin quality, leading to increased scarring and a greater chance of abnormal pigmentation (41). The autologous skin cell method was found to have the lowest risk of abnormal pigmentation. Gurbuz *et al.,* reported that autologous skin cell grafts yielded excellent aesthetic and functional results in 21 of 24 anatomic regions, with 42% showing normal pigmentations post-treatment (22).

Reducing the skin graft repigmentation rate is key to achieving patient satisfaction. The study conducted by Liu et al showed that patients given autologous skin cell skin grafts achieved 85.2% satisfaction 6 months after treatment and 94.7% satisfaction 12 months after treatment (42). Skin graft repigmentation can affect the cosmetic aspect of burn injury treatment therefore minimizing it is crucial in the management of burn injuries patients.

Skin grafting is a remarkable medical procedure that serves as a fundamental tool in reconstructive surgery and wound care. Some of the benefits included are as follows; skin grafts are invaluable in the medical realm, particularly in the treatment of extensive burns, wounds, venous ulcers, pressure ulcers, and diabetic ulcers. By facilitating the regeneration of new skin tissue, skin grafting serves as a critical tool in the restoration of damaged or lost skin (43). This process not only aids in closing wounds but also promotes faster healing, reducing the risk of complications such as infections and further tissue damage (44). Beyond promoting healing, skin grafts play a pivotal role in reconstructive surgery. This restoration is not only cosmetic but also functional, allowing patients to regain mobility and sensation in affected areas. Skin grafts also serve as a barrier against potential infections (45). By reestablishing the continuity of the skin, grafts create a protective layer that shields underlying tissues from pathogens. This not only reduces the risk of infections but also minimizes insensible fluid losses, contributing to the overall stability of the patients' condition. Also, the impact of skin grafting significantly influences patients' psychological and emotional well-being profoundly enhancing a patients' self-esteem and overall quality of life.

In developing countries, skin grafting is crucial for treating severe burn injuries and other skin defects. Although skin grafting is a standard therapy for severe burns, its use is limited in these regions due to high costs and extended hospital stays. However, recent studies have highlighted the advantages of early excision by skin grafting in reducing hospital stays, preventing infection, and lowering mortality rates (46). In summary, skin grafting plays a pivotal role in the management of severe burn injuries and skin defects, particularly in Indonesia (47). Continued research and the implementation of advanced techniques are essential for improving patient outcomes and optimizing the benefits of this critical medical procedure.

Systematic reviews have identified alternative approaches to burn care, including composite cultured skin (CCS) and bioengineered human skin. CCS, a biological dressing, stimulates skin regeneration using the patient's own tissue. Its effectiveness, however, is primarily limited to second-degree burns, where it aids in reducing infection risk and promoting complete healing (48). Bioengineered human skin, conversely, shows promise in treating deep partial thickness burns and is being explored as a potential substitute for autografts. While this intervention may decrease the necessity for donor site procedures and minimize adverse effects and patient discomfort, additional research and direct comparisons with autografts are still necessary to fully evaluate its efficacy (49).

The primary outcomes of our network meta-analysis provide a comprehensive insight into different skin grafting approaches for treating burn injuries. The findings highlight significant advancements in graft efficacy, particularly in enhancing reepithelialization rates and reducing repigmentation. Notably, the use of network meta-analysis has allowed us to identify the most effective grafting methods among a range of options. An important aspect that distinguishes our study is the limited existing literature on skin grafts in burn injury management, emphasizing the importance of our research in addressing this gap.

It is crucial to recognize the constraints of this investigation. A notable limitation is the lack of Asian samples, primarily attributed to insufficient studies from that geographical area. Furthermore, the variability in intervention durations and materials across different groups may introduce confounding factors, potentially impacting the overall efficacy and reliability of the results. The observed heterogeneity in each outcome could also affect the study's reliability. However, such heterogeneity is an inherent characteristic of network meta-analyses incorporating diverse interventions. To address this, the effectiveness of individual interventions was discussed separately in the analysis section. Further research and updated meta-analyses focusing on specific interventions are warranted. Additionally, this study did not evaluate the cost-effectiveness of various skin grafts, a factor that can influence treatment decisions for burn injuries. Consequently, future investigations should assess the economic efficiency of different skin graft modalities. The limited number of primary studies and relatively small sample size in this area of research also may impact the statistical significance of the analysis. This underscores the need for future studies to delve deeper into these complexities and provide more nuanced perspectives.

In conclusion, this study examining five skin graft variants for treating burn injuries demonstrates that the utilization of device-facilitated autologous skin cells has proven highly effective in promoting burn wound healing, despite the challenge of increased repigmentation. Reepithelialization and repigmentation with lower efficacy have also been shown with the synthetic graft, autologous skin cell, topical agent, and xenograft respectively. Further research should be conducted focusing on the device-facilitated autologous skin cell approach due to its demonstrated efficacy in enhancing reepithelialization and decreasing repigmentation as two major determinants of burn injury treatment. Additionally, extensive research is essential for novel skin grafts or topical agents to elucidate their potential advantages and safety profiles.

ACKNOWLEDGEMENT

None.

REFERENCES

1. Jeschke MG, van Baar ME, Choudhry MA, Chung KK, Gibran NS, Logsetty S. *Burn Injury*. Nature Reviews Disease Primers. 2020; 6(1): 1-26.
2. Rae L, Fidler P, and Gibran N. *The Physiologic Basis of Burn Shock and the Need for Aggressive Fluid Resuscitation*. Critical Care Clinics. 2016; 32(4): 491-505.
3. Won P, Celie KB, Rutter C, Gillenwater TJ, Yenikomshian HA. *Burn Patient Perspectives on Disability Weights and the Philosophy of Disability: A Gap in the Literature.* European Burn Journal. 2023; 4(4): 563-572.
4. Żwierełło W, Piorun K, Skórka-Majewicz M, Maruszewska A, Antoniewski J, and Gutowska I. *Burns: Classification, Pathophysiology, and Treatment: A Review.* International Journal of Molecular Sciences. 2023; 24(4): 3749.
5. Opriessnig E, Luze H, Smolle C, *et al. Epidemiology of Burn Injury and the Ideal Dressing in Global Burn Care–Regional Differences Explored*. Burns. 2023; 49(1): 1-4.
6. Levin NJ, Erben Y, Li Y, Brigham TJ, and Bruce AJ. *A Systematic Review and Meta-Analysis Comparing Burn Healing Outcomes Between Silver Sulfadiazine and Aloe Vera*. Cureus. 2022; 14(10): 1-8.
7. Ozhathil DK, Tay MW, Wolf SE, and Branski LK. *A Narrative Review of the History of Skin Grafting in Burn Care*. Medicina. 2021; 57(4): 1-28.
8. Paggiaro AO, Bastianelli R, Carvalho VF, Isaac C, and Gemperli R. *Is Allograft Skin, The Gold-Standard for Burn Skin Substitute? A Systematic Literature Review and Meta-Analysis*. Journal of Plastic, Reconstructive & Aesthetic Surgery. 2019; 72(8): 1245-1253.
9. Bogdanov SB, Gilevich IV, Melkonyan KI, Sotnichenko AS, Alekseenko SN, and Porhanov VA. *Total Full-Thickness Skin Grafting for Treating Patients with Extensive Facial Burn Injury: A 10-Year Experience*. Burns. 2021; 47(6): 1389-1398.
10. Wang Y, Beekman J, Hew J, *et al*. *Burn Injury: Challenges and Advances in Burn Wound Healing, Infection, Pain and Scarring.* Advanced Drug Delivery Reviews. 2018; 123: 3-17.
11. Gao G, Li W, Chen X, *et al*. *Comparing the Curative Efficacy of Different Skin Grafting Methods for Third-Degree Burn Wounds.* Medical Science Monitor. 2017; 23: 2668-2673.
12. Kubota Y, Mitsukawa N, Chuma K, *et al. Hyperpigmentation After Surgery for a Deep Dermal Burn of the Dorsum of the Hand: Partial-Thickness Debridement Followed by Medium Split-Thickness Skin Grafting VS Full-Thickness Debridement Followed by Thick Split-Thickness Skin Grafting*. Burns & Trauma. 2016; 4: 1-11.
13. Page MJ, McKenzie JE, Bossuyt PM, *et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews*. The BMJ. 2021; 372: 1-9.
14. Sterne JA, Hernán MA, Reeves BC, *et al*. *ROBINS-I: A Tool for Assessing Risk of Bias in Non-Randomised Studies of Interventions*. The BMJ. 2016; 355: 1-7.
15. Bae JM. *A Suggestion for Quality Assessment in Systematic Reviews of Observational Studies in Nutritional Epidemiology*. Epidemiology and Health. 2016; 38: 1-6.
16. Lo CK, Mertz D, and Loeb M. *Newcastle-Ottawa Scale: Comparing Reviewers' to Authors' Assessments.* BMC Medical Research Methodology. 2014; 14: 1-5.
17. McGuinness LA and Higgins JPT. *Risk-of-Bias Visualization (Robvis): An R Package and Shiny Web App for Visualizing Risk-of-Bias Assessments.* Research Synthesis Methods. 2021; 12(1): 55-61.
18. Allaire JJ. *RStudio: Integrated Development Environment for R*. (Online). https://www.r-project.org/conferences/useR-2011/abstracts/180111-allairejj.pdf
19. Karlsson M, Lindgren M, Jarnhed-Andersson I, and Tarpila E. *Dressing the Split-Thickness Skin Graft Donor Site: A Randomized Clinical Trial*. Advances in Skin & Wound Care. 2014; 27(1): 20-25.
20. Iv JHH, Molnar JA, Carter JE, *et al. A Comparative Study of the Recell® Device and Autologous Split-Thickness Meshed Skin Graft in the Treatment of Acute Burn Injuries*. Journal of Burn Care & Research. 2018; 39(5): 694-702.
21. Lo CH, Akbarzadeh S, McLean C, *et al. Wound Healing After Cultured Epithelial Autografting in Patients with Massive Burn Injury: A Cohort Study.* Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS. 2019; 72(3): 427-437.
22. Gurbuz K, Demir M, and Das K. *The Use of Dermal Substitute in Deep Burns of Functional/Mobile Anatomic Areas at Acute Phase after Early Excision and Subsequent Skin Autografting: Dermal Substitute Prevents Functional Limitations.* Journal of Burn Care & Research. 2020; 41(5): 1079-1083.
23. Lo CH, Brown JN, Dantzer EJG, *et al. Wound Healing and Dermal Regeneration in Severe Burn Patients Treated with Novosorb® Biodegradable Temporising Matrix: A Prospective Clinical Study*. Burns. 2022; 48(3): 529-538.
24. Karlsson M, Steinvall I, Sjöberg F, Olofsson P, and Elmasry M. *Burn Scar Outcome at Six and 12 Months After Injury in Children with Partial Thickness Scalds: Effects of Dressing Treatment*. Burns. 2020; 46(3): 546-551.
25. Al Shlash SO, Al Madani JO, El Deib JI, *et al. Demographic Characteristics and Outcome of Burn Patients Requiring Skin Grafts: A Tertiary Hospital Experience.* International Journal of Burns and

Trauma. 2016; 6(2): 30-36.

26. Radzikowska-Büchner E, Łopuszyńska I, Flieger W, Tobiasz M, Maciejewski R, and Flieger J. *An Overview of Recent Developments in the Management of Burn Injuries.* International Journal of Molecular Sciences. 2023; 24(22): 1-59.
27. Ryssel H, Gazyakan E, Germann G, and Öhlbauer M. The Use of Matriderm® in Early Excision and Simultaneous Autologous Skin Grafting in Burns—A Pilot Study. Burns. 2008; 34(1): 93-97.
28. Holmes IV JH, Molnar JA, Shupp JW, *et al. Demonstration of the Safety and Effectiveness of the RECELL® System Combined with Split-Thickness Meshed Autografts for the Reduction of Donor Skin to Treat Mixed-Depth Burn Injuries.* Burns. 2019; 45(4): 772-782.
29. Shimizu R and Kishi K. *Skin Graft.* Plastic Surgery International. 2012; 2012: 1-5.
30. Weathers WM, Bhadkamkar M, Wolfswinkel EM, and Thornton JF. *Full-Thickness Skin Grafting in Nasal Reconstruction*. Seminars in Plastic Surgery. 2013; 27(2): 90-95.
31. Lal ST, Banipal RP, and Bhatti DJ. *Tolerance of Skin Grafts to Postoperative Radiotherapy.* International Journal of Applied & Basic Medical Research. 2015; 5(3): 187-189.
32. Braza ME, Marietta M, and Fahrenkopf MP. *Split-Thickness Skin Grafts.* Treasure Island: StatPearls Publishing; 2023
33. Ray S and Rao K. *Full Thickness Skin Grafts.* In: Spear M (Ed). Skin Grafts - Indications, Applications and Current Research. London; IntechOpen; 2011.
34. Phua QH, Han HA, and Soh BS. *Translational Stem Cell Therapy: Vascularized Skin Grafts in Skin Repair and Regeneration.* Journal of Translational Medicine. 2021; 19: 1-11.
35. Weber CE, Li NY, Wai PY, and Kuo PC. *Epithelial-Mesenchymal Transition, TGF-B, and Osteopontin in Wound Healing and Tissue Remodeling after Injury.* Journal of Burn Care & Research. 2012; 33(3): 311-318.
36. Sun X, Joost S, and Kasper M. *Plasticity of Epithelial Cells During Skin Wound Healing.* Cold Spring Harbor Perspectives in Biology. 2023; 15(5): 1-14.
37. Cheng RY, Eylert G, Gariepy JM, *et al. Handheld Instrument for Wound-Conformal Delivery of Skin Precursor Sheets Improves Healing in Full-Thickness Burns.* Biofabrication. 2020; 12(2): 025002.
38. Lin H, Yang Y, Wang Y, *et al. Effect of Mixed Transplantation of Autologous and Allogeneic Microskin Grafts on Wound Healing in a Rat Model of Acute Skin Defect.* PLoS One. 2014; 9(1): 1-11.
39. Tsukada S. *Studies on the Pigmentation of Skin Grafts: The Ultrastructure of Epidermal Melanocytes*. Plastic and Reconstructive Surgery. 1977; 59(1): 98-106.
40. Kim JS, Park SW, Choi TH, *et al. The Evaluation of Relevant Factors Influencing Skin Graft Changes in Color Over Time.* Dermatologic Surgery. 2008; 34(1): 32-39.
41. Chan RK, Rose LF, Wu JC, *et al. Autologous Graft Thickness Affects Scar Contraction and Quality in a Porcine Excisional Wound Model.* Plastic and Reconstructive Surgery. Global Open. 2015; 3(7): 1-9.
42. Liu T, Chen J, Wei B, Nie F, and Zhu G. *Safety and Efficacy of Autologous Skin Tissue Cells Grafting for Facial Sunken or Flat Scars*. Heliyon. 2023; 9(6): 1-6.
43. Hicks K and Thomas JR. *Skin and Composite Grafts.* Plastic and Aesthetic Research. 2022; 9(2): 1-11.
44. Elseth A and Nunez Lopez O. *Wound Grafts.* Treasure Island: StatPearls Publishing; 2022.
45. Kohlhauser M, Luze H, Nischwitz SP, and Kamolz LP. *Historical Evolution of Skin Grafting-A Journey through Time.* Medicina (Kaunas). 2021; 57(4): 1-14.
46. Lumbuun RF and Wardhana A. *Peranan Eksisi Dini dan Skin Graft pada Luka Bakar Dalam.* Cermin Dunia Kedokteran. 2017; 44(4): 249-254.
47. Elfiah U, Perdanakusuma DS, Saputro ID, Riasa IN, Lumintang LM, and Naufal MF. *Skin Graft as a Modality Reconstruction of Post-Burn Contractures during Pandemic Area: Case Series.* Bali Medical Journal. 2023; 12(1): 244-248.
48. Lee H, Chun W, and Kim G. *Three-Dimensional Artificial Skin Construct Bioprinted with a Marine-Based Biocomposite.* Biomacromolecules. 2023; 24(6): 2864-2878.
49. Šuca H, Čoma M, Tomšů J, *et al. Current Approaches to Wound Repair in Burns: How far Have We Come from Cover to Close? A Narrative Review*. Journal of Surgical Research. 2024; 296: 383-403.

Table 2. Baseline characteristics of included studies

Author, Year	Country	Center	Study Design	Type of Disease	Type of Intervention	Control	Sample Size (M/F)		Age Mean ± SD/Media (IQR)		Duration (months)
							Intervention	Control	Intervention	Control	
Karlsson *et al.,* 2014 (19)	America and Sweden	Hand and plastic surgery, department with burn unit.	Prospective randomized 3-arm, clinical study	Donor sites of split-thickness skin grafts.	Synthetic Graft (Aquacel), Xenograft (Mediskin I)	Allevyn (Topical Agent)	Skingraft: 24, Xenograft: 24	Topical Agent: 25	Synthetic Graft: 63, Xenograft: 62	Topical Agent: 60	14
Holmes *et al.,* 2024 (20)	America	U.S. Food and Drug Administration (FDA) Investigational Device Exemption	Multicenter Prospective RCT Study	Burn Injury (1-20% TBSA)	ReCell (Device Facilitated Autologous Skin Cell)	STSG (Autologous Skin Cell)	83 Total (70 Male, 13 Female)			39.5 (13.1)	52
Lo *et al.,* 2018 (21)	Australia	Victorian Adult Burns Service at The Alfred	Observational Cohort Study	Deep dermal and full-thickness burns	Cultured Epithelial Autografting (Synthetic Graft)	Cuono Method (Autologous Skin Cell)	7	13		49 (22-67)	36
Gurbuz *et al.,* 2020 (22)	Turkey	Burn Center, Department of General Surgery, Adana City Training and Research Hospital, Adana, Turkey	Retrospective Study	Acute phase of major burn	Autologous split-thickness Skin Graft (Autologous Skin Cell)	NA	12 (9 Male, 3 Female)		22.62 ± 10.99		12
Hean Lo *et al.,* 2021 (23)	Australia and France	Victorian Adult Burns Service at The Alfred	Multicenter Prospective Clinical Study	Deep dermal and full-thickness thermal burn injuries	Biodegradable Temporising Matrix (BTM) (Synthetic Graft)	NA	26 (22 Male, 4 Female)			45.2 (16.5)	36
Karlsson *et al.,* 2020 (24)	Sweden	Department of Hand Surgery, Plastic Surgery and Burns, Linköping University, Linköping, Sweden	Randomized Control Trial	Acute partial thickness scalds,	Porcine Xenograft (Xenograft)	Silver Foam (Synthetic Graft)	24 (15 Male, 9 Female)	15 (9 Male, 6 Female)	24 (6-66) months	17 (6-40) months	36
Al Shlash *et al.,* 2016 (25)	Saudi Arabia	Department of Plastic and Burns Surgery, Prince Sultan Military Medical City, Riyadh, Saudi Arabia	Retrospective Study	Burn patients who had undergone skin grafting	STSG (Autologous Skin Cell)	FTSG (Autologous Skin Cell)	56	29			60