Comparison of combination skin substitutes and skin grafts versus skin grafts only for treating wounds measured by Vancouver Scar Scale: A comprehensive meta-analysis

Indri Lakhsmi Putri[1,2] (iD), Florencia Christina Sindhu[2],
Imaniar Fitri Aisyah[3] (iD), Rachmaniar Pramanasari[2]
and Citrawati Dyah Kencono Wungu[4]

Abstract

Background: Skin is the largest organ in the body and has multiple significant functions. A malformation or injury that compromises its integrity can lead to major issues or even mortality. Wound healing is a vital physiological process of the human skin which facilitates the repair of any damage and the preservation of homeostasis. Possible complications or infections that are fatal may ensue if the patient does not recover within the specified time. Therefore, it is essential to develop biomaterials which facilitate tissue regeneration and exhibit robust biological properties. We conducted a meta-analysis of randomized controlled trials to compare combinations of skin replacements and skin grafts to skin grafts alone for wound treatment, as measured by the Vancouver Scar Scale.

Methods: This meta-analysis utilized various databases, including as PubMed, ProQuest, Web of Science, Science Direct, Scopus, EBSCOhost, and ClinicalTrials.gov, to conduct a comprehensive search for randomized controlled trials that compared the effectiveness of combined skin substitutes and skin grafts to skin grafts alone in the treatment of wounds. The results primarily consisted of scar features assessed using the Vancouver Scar Scale.

Results: Meta-analysis was conducted on a sample of 216 participants from 7 randomized controlled trials. The trials were conducted from 2002 to 2015. The study demonstrated that the use of skin substitutes resulted in a statistically significant improvement in Vancouver Scar Scales ratings compared to skin grafts alone. The mean change was 1.38 (95% CI: 0.13–2.63; $p = 0.03$).

Conclusion: This meta-analysis indicates that the use of skin replacements provides substantial advantages and effectively aids in the closure of wounds. There is no inherent superiority among different skin substitutes. Instead, their suitability for specific patient wound circumstances is the determining factor. A comprehensive and advantageous skin substitute of significant magnitude is needed, rather than relying solely on grafts.

Keywords

Surgery, skin substitute, wound, Vancouver Scar Scale, dermatology

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[1]Faculty of Medicine, Department of Plastic Reconstructive and Aesthetic Surgery, Airlangga University, Surabaya, Indonesia
[2]Plastic Reconstructive and Aesthetic Surgery Unit, Airlangga University Hospital, Surabaya, East Java, Indonesia
[3]Department of Mechanical Engineering, Institut Teknologi Sepuluh Nopember, Surabaya, Indonesia
[4]Faculty of Medicine, Department of Physiology and Medical Biochemistry, Airlangga University, Surabaya, Jawa Timur, Indonesia

Corresponding author:
Indri Lakhsmi Putri, Faculty of Medicine, Department of Plastic Reconstructive and Aesthetic Surgery, Airlangga University, Jl. Mayjend Moestopo 6-8, Surabaya, East Java 60131, Indonesia. Plastic Reconstructive and Aesthetic Surgery Unit, Airlangga University Hospital, Surabaya, East Java, Indonesia.
Emails: indrilakhsmiputri@fk.unair.ac.id; indrilakhsmiputri@gmail.com

Key points

1. Skin grafts remain the gold standard for the closure of large wound.
2. A meta-analysis was performed to examine the efficacy of combined skin substitutes with skin grafts compared to skin grafts alone in the treatment of wounds.
3. Additional comprehensive research investigations are required to examine the utilization of skin replacements in the treatment of wounds.
4. The utilization of skin replacements offers notable advantages and effectively facilitates the closure of wounds.

Introduction

Skin is the largest organ in the body and has numerous important roles to play, such as protecting the internal organs and tissues from environmental, chemical, and biologic threats; absorbing and excreting excess water; forming keratin, vitamin D, and pigment; receiving signals from the nervous system; and regulating body temperature.[1,2] Malformation or injury resulting in a compromise of its integrity that may induce severe complications or mortality. Therefore, wound healing is an essential physiological function of the human skin which enables the restoration of any damage and the maintenance of homeostasis.[3] Although the skin has an impressive capacity for self-healing, surgeons nevertheless face substantial challenges when dealing with large and deep wounds resulting from severe burns or tissue damage. Failure to recover within the designated time frame may result in the development of potentially fatal complications or infection.[4] Hence, it is crucial to create biomaterials which promote tissue regeneration and possess strong biological capabilities.

Skin substitutes are a diverse range of materials used to cover wounds and may work as temporary or permanent replacements, depending on their specific features.[5] In situations where conventional wound care methods are undesirable, these substances serve as substitutes. Skin substitutes are typically divided into three types: classes 1, 2, and 3. These categories include single-layer durable skin substitutes, composite skin substitutes, and temporary impermeable dressing materials.[6] For the best results, the replacement should be biocompatible, antibacterial, hydrophilic, and biodegradable.[7]

The use of tissue-engineered skin substitutes has become an appropriate replacement for auto- and allografts. However, in one-stage grafting operations, it may have an impact on the overlaying epidermal replacement's longevity.[8] It was hypothesized that this occurred because nutrients and oxygen had a longer way to diffuse to the autograft following the substitute's interposition.[9] Notwithstanding this obstacle, experts in the fields of biology, chemistry, and engineering continue to strive toward the creation of detailed skin substitutes that are suitable to large-scale replacement.[10]

The process of replacing skin defects has experienced several advancements throughout history, beginning with the pioneering technique of grafting introduced by Reverdin in 1871. Since then, a variety of techniques for skin grafting have been effectively applied.[11] However, there are several limits to skin grafts, including the availability of the donor site, particularly in cases of substantial skin loss, immunological rejection in allogenic grafts, pain, scarring, sluggish healing, and infection. Therefore, scientists have devoted their efforts to finding substitutes to repair defects in the skin without depending on "natural" skin grafts.[12] Many studies have been conducted over the last 15 years on artificial epithelium and dermal replacements with the goal of enhancing functional and cosmetic results.[13] Published studies sometimes neglect to include essential patient outcomes, such as restoration of function, cosmetic results, and reduction in pain.[14] Despite the achievements made, a suitable skin substitute has not yet been developed.[15]

Prior to skin grafts, which are regarded as the gold standard for wound care, this study provides a concise overview of the advantages of skin substitutes. It has the potential to enhance our understanding of skin substitutes and provide recommendations for future research methodologies. The following skin substitutes will be discussed: Integra, Glyaderm, Matriderm, Polylactide-based Copolymer (SupraThel), cellulose sponge (Cellonex), and Cultured Epithelial Autografts (Epicell, JACE). Number ID Prospero CRD42023439579 was registered on 7 July 2023.

Materials and methods

Study selection

Three researchers, I.L.P, F.C.S, and R.P, looked for studies comparing different ways to treat wounds. They focused on randomized controlled trials (RCTs) and observational studies that compared skin grafts to skin substitutes. They only looked at studies involving humans, written in English, and with full access to the details. I.F.A and F.C.S were in charge of the original draft writing, editing, and reviewing process. If they disagreed on whether a study fit their criteria, they either discussed it until they reached an agreement or brought in a fourth researcher, C.D.K.W, to help them decide.

The most important factor they were interested in was the quality of the scar tissue that formed after treatment. They used a scoring system called the Vancouver Scar Scale to measure these studies with incomplete data, duplicate studies, case reports, case series, reviews, editorials, systematically reviews, meta-analysis, and studies without comparators, were excluded.

Literature search

This research followed strict guidelines for gathering and analyzing evidence, similar to how many scientific studies are conducted today. These guidelines are outlined in a

document called PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis).

Keywords used in this meta-analysis included wound, deep dermal wound, chronic wound, skin loss, skin avulsion, skin defect, burn, skin artificial, degloving injuries, skin substitute, amnion, tilapia, acellular dermal matrix, as well as their synonyms and controlled vocabulary (MeSH or Emtree terms) where applicable. The search term includes "wound" OR "deep dermal wound" OR "full thickness wound" OR "chronic wound" OR "skin loss" OR "skin defect" OR "burn" AND "skin substitute" OR "amnion" OR "tilapia" OR "dermal substitute" OR "acellular dermal matri*."

Relevant studies were identified from PubMed, ProQuest, Web of Science, Science Direct, Scopus, EBSCOhost, and the registry trial (www.clinicaltrials.gov) up until 22 September 2022. Subsequently, they were exported to Mendeley for further sorting.

Data extraction

The researchers carefully reviewed each of the studies they found. They looked for specific details like the authors' names, when the study was published, where it was done, what type of study it was, who participated, their average age, how long they were followed after treatment, and how many people participated overall. They also looked at how many people dropped out of the study and why. Importantly, two researchers did this review independently to make sure everything was accurate. They then compared their findings to ensure there weren't any mistakes or missing information.

Risk of bias and quality assessment

The quality of the observational case–control and cohort studies was evaluated using the Newcastle-Ottawa scale (NOS),[16] as shown in Table 1, while the Jadad scale[17] was used to evaluate RCT studies, as presented in Table 2. In general, a score of 7 or higher on the NOS and 3 or higher on the Jadad scale indicates a high-quality study.[18,19]

Statistical analysis

The researchers used specialized RevMan 5.4 software (Cochrane Training) to crunch the numbers from the studies, with pooled risk ratio (RR) of 95% confidence intervals (Cis) applied to analyze the random- or fixed-effect models. The significant outcome of the two-sided statistical tests was determined with a p-value < 0.05. Heterogeneity was assessed using inconsistency index statistic (I^2) to assess heterogeneity, and its level was reflected by the value of the I^2 statistic. The trials were deemed heterogeneous when $I^2 > 50\%$ and $p < 0.05$, and random-effects models were used. If the studies seemed low heterogeneity, the fixed-effects model was used. Publication bias analysis was performed minimally when the study contained more than 10 trials.

Table 1. Quality of included observational studies (cohort) evaluated using Newcastle-Ottawa scale (NOS).

Study (Cohort)	Selection				Comparability	Outcome			Total score
	Representativeness (1)	Selection of the non-exposed cohort (1)	Ascertainment of exposure (1)	Demonstration outcome of interest (1)	Comparability based on design or analysis (2)	Assessment of outcome (1)	Followed up long enough (1)	Adequacy of follow-up (1)	
Bloemen et al.[5]	1	1	1	1	2	1	1	1	9
Hayashi et al.[35]	1	1	1	1	2	1	1	1	9

Table 2. Quality of included RCT studies evaluated using Jadad scale.

Study	Randomization	Double blinding	Withdrawals	Total score
Boyce et al.[4]	2	0	1	3
Ryssel et al.[9]	2	0	0	2
Ryssel et al.[13]	0	0	1	1
Cervelli et al.[33]	1	0	0	1
Lagus et al.[46]	2	0	1	3
Selig et al.[37]	0	0	1	1
Pirayesh et al.[3]	2	1	1	4

Results

Study selection and characteristics

Numerous databases yielded a total of 17,879 reports. The studies were obtained from various databases, namely PubMed, ProQuest, Web of Science, Science Direct, Scopus, EBSCOhost, and ClinicalTrials.gov. The specific numbers of studies retrieved from each database are as follows: 4300 from PubMed, 6161 from ProQuest, 456 from Web of Science, 4896 from Science Direct, 1818 from Scopus, 152 from EBSCOhost, and 96 from ClinicalTrials.gov. The final selection of 12,875 studies was made in Mendeley following a process that involved sifting by full text availability, English language, human study, study articles, scholarly journal, completed and available study results. A total of 5607 studies were considered irrelevant, with the following reasons given: animal studies ($n = 4605$), duplicate studies ($n = 129$), and studies other than observational or RCT trials ($n = 873$). After applying appropriate screening criteria to the titles and abstracts, a total of 7237 studies were excluded from further analysis. Following comprehensive text evaluations, an additional 22 papers were excluded. Overall, a quantitative analysis was performed on a total of 9 suitable papers, consisting of 2 observational studies and 7 RCTs. Figure 1 displays the flow chart illustrating the process of selecting the study.

Observational studies

The two observational investigations were conducted as cohort studies and included a total of 85 patients from 2010 to 2014, comprising 59 males and 26 females. The study consisted of 31 participants in the control group, 8 participants in the intervention group, and 46 participants who were included in both the control and intervention groups. The International Statistical Institute stated in 2020 that all of the listed studies were carried out in developed countries. The patients' mean age, TBSA burnt, duration of stay, and follow-up ranged from (41.3 ± 18.7) to (56.38 ± 7.04), (24.3 ± 14.7) to (58.94 ± 3.89), (90.45 ± 12.04) to (106.57 ± 9.26), and 4 weeks to (11.82 ± 2.1) years, respectively. To conclude, Matriderm and JACE were utilized as skin substitutes in the investigations. Table 3 provides a comprehensive explanation.

RCTs

The study consisted of seven RCTs with a total of 216 individuals. The trials were conducted between 2002 and 2015. The skin substitutes utilized in the trials included integra, Glyaderm, Matriderm, and viscose cellulose sponge Cellonex. According to International Statistical Institute, every study that was included was carried out in a developed country. The average age and duration of follow-up varied from 10.6 to 70 years and from 1 week to 12 months after the surgery, respectively. The Vancouver Scar Scale[20] was utilized to evaluate the injuries, which were traumatic and burn related. Further information is shown in Table 4.

Studies' quality assessment and bias risk

The mean NOS score of 9 out of 9 indicates that the observational studies that were included of the study were of excellent quality. A mean Jadad scale score of 2.14/5 indicated that the RCTs were of inferior quality. The NOS evaluations of the two cohort studies that were part of the analysis are shown in Table 1. Meanwhile, Table 2 displays the Jadad scale assessment of the RCT studies. It should be emphasized that the majority of the studies were deemed representative and were consistent with those included in which the outcome of wound covering with a temporary skin substitute was superior to skin graft alone.

The primary outcomes

Vancouver scar scale. For wounds treated with skin replacements or skin grafts alone, three RCTs reported scar characteristics using the Vancouver scar scale.[20] In comparison to skin grafts alone, the use of skin substitutes was linked to a statistically significant improvement in the Vancouver scar scale scores, with a mean difference of 1.38 (95% CI: 0.13–2.63; $p = 0.03$). According to Figure 2, there was no intrinsic statistical heterogeneity in the studies that were assessed ($I^2 = 89\%$; $p < 0.0001$). The publication bias, however, could not be evaluated as a result of the restricted number of studies.

Table 3. Included observational studies characteristic.

Author, year, country, design	Number of patients	Sex		Mean age (years)	% TBSA	Group		Length of stay (days)	Follow up
		M	F			C	I		
Bloemen, 2010, Netherlands, Cohort[5]	46 burn patients (A: 26 and R: 20)	31	15	A: 41.3 ± 18.7. R: 42.3 ± 18.2	A: 24.3 ± 14.7. R: 30.5 ± 17.6	Split-thickness skin graft	Split-skin graft + Matriderm	NA	A: 11.8 ± 0.4 years. R: 11.8 ± 2.1
Hayashi, 2014, Japan, Cohort[35]	39 burn patients	C: 23. I: 5	C: 8. I: 3	C: 59.61 ± 3.85. I: 56.38 ± 7.04	C: 58.94 ± 3.89. I: 51.63 ± 4.17	Split-thickness skin graft	Split skin graft + JACE	C: 90.45 ± 12.04. I: 106.57 ± 9.26	4 weeks

M: male; F: female; TBSA total body surface area; A: acute; R: reconstructive; NA: not available; C: control; I: intervention; JACE: Japan autografts cultured epithelial.

Secondary outcome

Observational studies. Three months following surgery, reconstructive scars were the focus of the first of two investigations that were undertaken. The study determined that the elasticity parameters measured by the Cutometer Skin Elasticity Meter 575 (Courage and Khazaka GmbH, Cologne, Germany) are a trustworthy and valid tool for assessing skin elasticity. The study also discovered that the elasticity parameters were significantly greater in substituted scars ($p = 0.041$). Furthermore, a statistically significant disparity was noted in the melanin concentrations between replaced and reference scars.

The melanin content of substituted scars differed significantly from the patient's normal skin, with a 5% difference. The Derma Spectrometer, developed by Cortex Technology in Hadsund, Denmark, is a validated assessment tool that uses diodes to emit light at two specific wavelengths: green light (568 nm) and red light (655 nm). In the study, it was found that melanin levels in substituted scars varied more from the patient's normal skin compared to reference scars. The substitute-to-normal skin ratio was 1.05, while the reference-to-normal skin ratio was 1.00 ($p < 0.010$).

The assessments given by the observers for pliability, alleviation, and the overall score likewise demonstrated significantly superior outcomes for replacement scars ($p < 0.04$). Among patients with acute burns, the subjective assessment of scars showed a statistically significant advantage for the alternative treatment in all parameters, except for vascularization ($p < 0.02$). The second study assessed the duration of operations in the study group in comparison to the control group. The results showed a notable disparity in the duration of operations between the two groups ($p < 0.05$).

Both investigations discovered that elasticity and subjective scar assessment favored their replacement counterpart differently. As an alternative scar treatment demands expertise and time, the procedure has a prolonged duration. Furthermore, it has been discovered that replaced scars contain a higher concentration of melanin. Additional information is available in Table 5.

RCTs studies. It was found that regrafting of Autograft (AG) was not necessary in one of the seven RCTs ($p < 0.05$). However, autologous Cultured Skin Substitutes (CSS) reduces the requirement for skin grafting. CSS can increase by approximately 67 times the area of donor skin, while meshed AG has a value of 4 ($p < 0.01$). The color was pinker than AG at both POD 7 and 14, and the process of keratinization had slower and lower values compared to AG. Graft loss was observed in the CSS coverage of grafted sites between POD 7 and 14, whereas AG considerably increased coverage ($p < 0.05$). The qualitative results of the CSS and AG graft revealed a steady rise in pigmentation over the course of the initial year. After 1 year, AG exhibited a comparable appearance to normal skin, although with a statistically significant
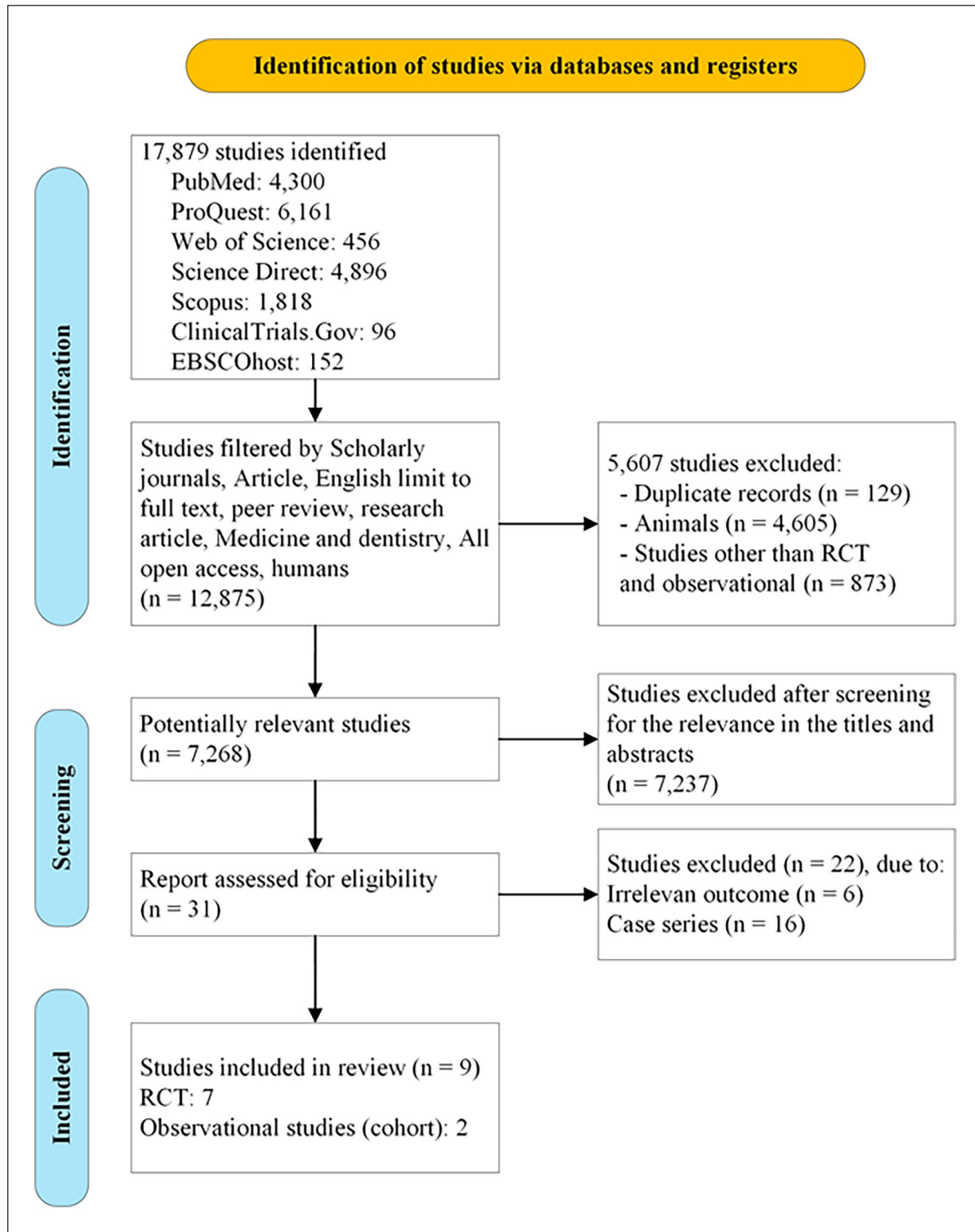
**Figure 1.** PRISMA flow chart.

distinction ($p < 0.05$). The incidence of raised scar was considerably lower for CSS compared to AG up to 1 year following grafting ($p < 0.05$).

The following research demonstrated a notable enhancement in flexibility ($p < 0.04$) in wounds that were treated with CSS in conjunction with sheet autografts. In contrast,

Table 4. Included RCT studies' characteristics.

Author, year, country, design	Number of patients	Sex M	Sex F	Mean age (years)	% TBSA	Group C	Group I	Follow up
Boyce, 2002, Ohio, RCT[4]	45 burn patients	34	11	10.6 ± 1.6	64.6 ± 2.0	STSG mesh	CSS	14 days, 28 days, one year postoperative
Ryssel, 2008, Germany, RCT[9]	10 burn patients	7	3	49.5 ± 16.2	45.6 ± 14.5	C1: STSG sheet without Matriderm. C2: STSG mesh without Matriderm	I1: STSG sheet with Matriderm. I2: STSG mesh with Matriderm	3 months postoperative
Ryssel, 2010, Germany, RCT[13]	18 burn patients	13	5	45.1 ± 17.4	43.8 ± 11.8	STSG sheet	STSG sheet with Matriderm	1 week and sixth months postoperative
Cervelli, 2011, Italy, RCT[33]	60 traumatic wound patients	38	22	30–70 years	NA	STSG only	STSG + Matriderm	2 weeks, 1, 3 months, sixth months postoperative
Lagus, 2013, Finland, RCT[45]	10 burn patients	9	1	36.8 ± 12.03	35.8 ± 7.16	STSG only	I1: STSG + Integra. I2: STSG + Viscose Cellulose Sponge Cellonex	Three and 12 months postoperative
Selig, 2013, Germany, RCT[37]	18 burn patients	NA	NA	NA	>60	STSG only	STSG + polylactide-based copolymer	1 year postoperative
Pirayesh, 2015, Netherlands, RCT[3]	55 burn patients	NA	NA	32.3 ± 21.02	NA	STSG only	STSG + Glyaderm	1, 3, 6, 12 months postoperative

M, male; F, female; TBSA, total body surface area; STSG, skin-thickness skin grafts; C, control; I, intervention; NA, not available.
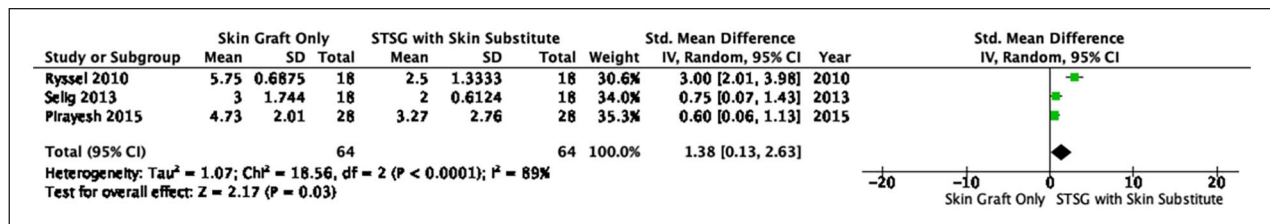
Figure 2. Total VSS.

the Manchester Scar Scale (MSS) was utilized to evaluate scar characteristics in the remaining trials. The scores of the items in the MSS were significantly different between the two groups, particularly in terms of color ($p < 0.001$), appearance ($p < 0.001$), and contour ($p = 0.005$). After 3 months of treatment, the rate of re-epithelialization was considerably higher in the skin graft with CSS compared to the skin graft alone ($p < 0.001$).

Additional research revealed that the group receiving dermal replacement demonstrated significantly improved range of motion as determined by the Finger-Tip-Palmar-Crease-Distance and Finger-Nail-Table-Distance ($p < 0.04$). The Observer Scar Scale showed significantly better results in terms of "relief" ($p < 0.036$) and "pliability" ($p < 0.019$),

while the Patient Scar Scale showed superior results in terms of "elasticity" ($p < 0.024$) for STSG with temporary replacement. STSG with dermal substitute exhibited considerably higher elasticity at 1 month ($p < 0.001$) and 12 months ($p < 0.03$) postwound closure. However, 1 year after the incision was closed, the average young modulus of normal skin was substantially more elastic than both STSG with dermal replacements ($p < 0.0001$) and STSG alone ($p < 0.0001$). The supplemental section includes further information.

Discussion

The term "skin substitute" refers to an accumulation of materials (biological, synthetic, or a combination of the two)

Table 5. Secondary outcome of included observational and RCTs studies.

Observational	Bloemen et al.[5]	Elasticity	$p < 0.05$ better in substituted scars
		Melanin	$p < 0.010$ better in control group scars
		Subjective evaluation	$p < 0.05$ better in substituted scars
	Hayashi et al.[36]	Operation times	$p < 0.05$ better in control group
RCT	Boyce et al.[4]	Percentage of engraftment	$p < 0.05$ better in control group
		Ratios of closed wound: donor skin areas	$p < 0.01$ better in study group
		Site assessment at POD 7 and 14	$p < 0.05$ better in control group
		Qualitative outcome after surgery	$p < 0.05$ better in control group
	Ryssel et al.[9]	VBSS 3–4 months after surgery	$p < 0.04$ better in study group
	Ryssel et al.[13]	The range of motion	$p < 0.04$ better in study group
	Cervelli et al.[34]	The percentage of re-epithelialization 3 months after the treatment	$p < 0.001$ better in study group
		MSS assessment	$p < 0.05$ better in study group
	Selig et al.[38]	Relief	$p < 0.036$ better in study group
		Pliability	$p < 0.019$ better in study group
		Elasticity	$p < 0.024$ better in study group
	Lagus et al.[46]	Inflammation	$p < 0.05$ highest in Cellonex
		Proliferation	$p < 0.05$ highest in Cellonex
	Pirayesh et al.[3]	Elasticity	$p < 0.05$ better in study group

POD: post operative day; VBSS: Vancouver burn scar scale; MSS: Manchester scar scale.

$p < 0.05$, significant.

applied to conceal wounds caused by deeper than epidermal-level skin injury.[21] A comprehensive classification of skin substitutes is proposed based on their categorization according to the fifth criteria: (1) the skin layer to be replaced, which is subdivided into epidermal (E), dermal (D), and dermal-epidermal composites (C); (2) the durability in the wound bed, which is divided into temporary (T) and permanent (P); (3) cellularity, which is divided into acellular (ac) and cellular (ce); and (4) the origin of grafting material, which is divided into biological (b), biosynthetic (bs), and synthetic (s), and (5) layering which is divided into single layer or bilayer.[21–24] This categorization designates temporary (T) products as those which are replaced by autogenous grafts after being in the wound for the length of time required to modify and enhance the lesion's features. Materials classified as permanent (P) are those that preserve the skin's structure in part or in its entirety and stay on the wound bed even after autogenous skin may be grafted to cover the entire lesion.[25] Laboratory-produced synthetic (s) materials are intended to replicate the structure of the skin, while biologic substitutes (b) are those manufactured using organic materials such as animal or human tissue. Assemblies of synthetic components including elements derived from living organisms give rise to biosynthetic materials (bs).[25]

The terms "dermal," "epidermal," and "dermal–epidermal" composite indicate that the skin substitute replaces both the dermal and epidermal components of the skin. Cellularity refers to the existence or nonexistence of cellular constituents in the skin. Skin substitutes can exist as either single or bilayer structures. Skin substitutes composed of a bilayer often serve as replacements for both the epidermal and dermal layers of the skin, while those consisting of a single layer only replace either one of them.[12,21]

The classification of certain skin substitutes now available includes Alloderm, Apligraf, Biobrane, Bioseed, Cadaveric skin Dermagraft, Epicel, E-Z Derm, Hyalomatrix, Integra, Laserskin, Matriderm, Myskin, OASIS Wound Matrix, OrCel, Permacol, PolyActive, Smart Matrix, SupraThel, and Transcyte.[24] As shown in Figure 3, the skin substitutes consist of the following: cellulose sponge (Cellonex), cultured epithelial autografts (Epicell, JACE), Integra, Glyaderm, Matriderm, Polylactide-based Copolymer (SupraThel), and Epicell.[26]

This study examined three RCTs that evaluated the effectiveness of skin grafts with skin replacements in the treatment of wounds. The Vancouver Scar Scale was employed to assess the extent of scar healing. The investigations demonstrated that the utilization of skin replacements resulted in markedly improved scar ratings (mean difference of 1.38, 95% CI: 0.13–2.63; $p = 0.03$) in comparison to solely employing skin grafts. The study also identified three unique examples that had the greatest enhancement with skin substitutes: In Pirayesh's study conducted in 2015, the product Glyaderm was utilized to treat full thickness burns or lower arm deformities. Glyaderm is a permanent, biological product that replaces both the dermis and epidermis.[3] The study reported an average scar score of 3.27 as a result of this treatment. Ryssel et al.[9] utilized Matriderm, a permanent biological substitute for the dermis, to treat full thickness burns on both hands. The treatment resulted in an average score of 2.5. In Selig's study conducted in 2013, either Polylactide Based Copolymer or SupraThel, a permanent synthetic
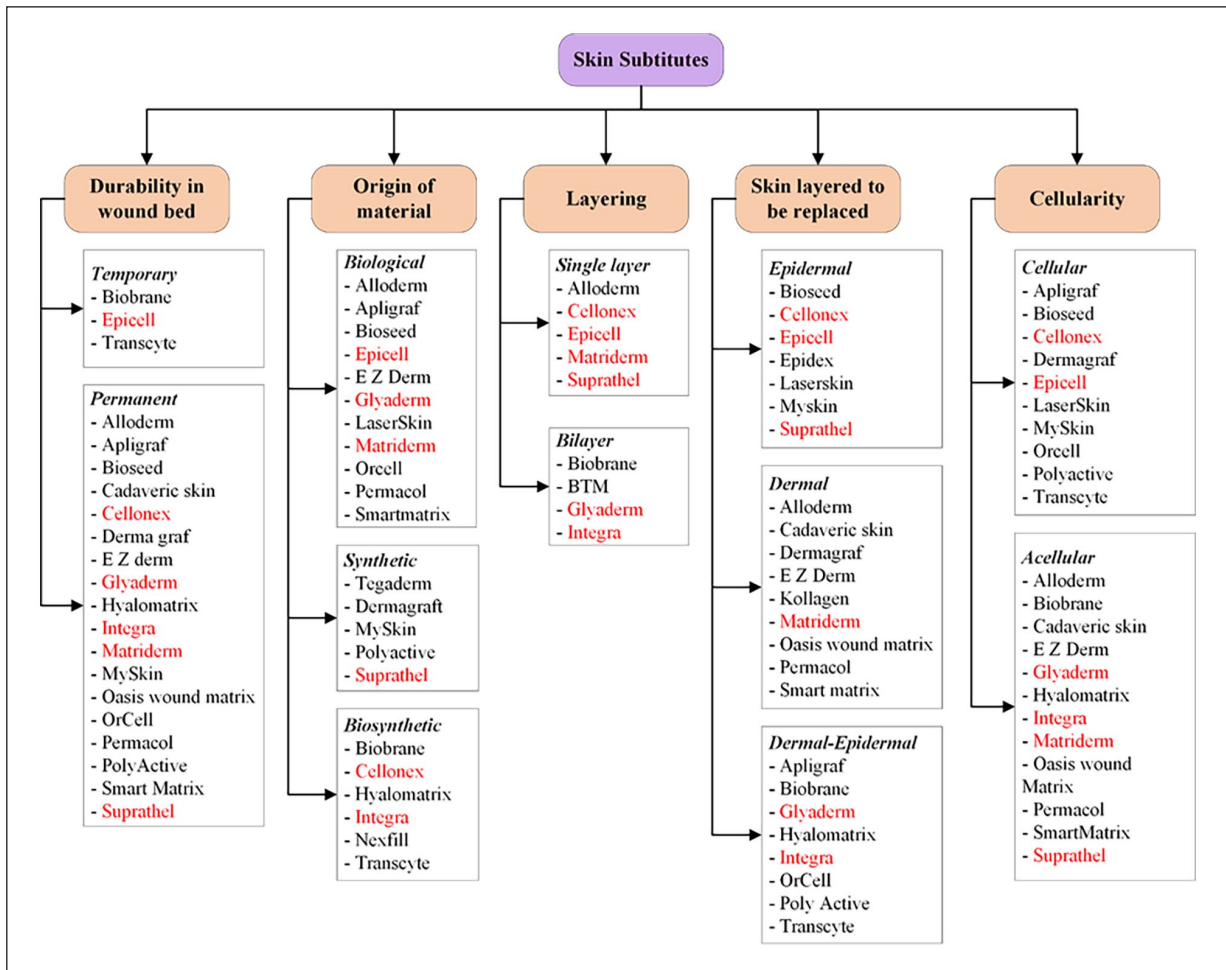
Figure 3. Classification of skin substitutes examined in this study.

material that replaces the epidermis, were used to treat deep dermal burns.[27]

The classification of skin substitutes is determined by several factors, including durability in the wound bed, cellularity, origin of material, layering, and the type of skin to be replaced. Among the skin substitutes mentioned, Glyaderm, Matriderm, and Suprathel are both permanent and acellular. However, when considering the origin of material, Glyaderm and Matriderm are biological, while Suprathel is synthetic. In terms of layering, Glyaderm is classified as Dermal-Epidermal, Matriderm as Dermal, and Suprathel as Epidermal. Lastly, Glyaderm is specifically used for replacing the layered skin.

Matriderm

Originating from bovine ligamentum nuchae, Matriderm is a dermal matrix composed of native bovine collagen (types I, III, and V) fibers covered with 3% (w/w) a-elastin.[28] Matriderm is used in a single-stage approach, which may be favored over Integra's multi-level reconstruction procedure.

The application of Matriderm in conjunction with split-thickness mesh grafts resulted in enhanced skin pliability and elasticity in scar repair wounds, as opposed to using split-thickness mesh grafts alone. Matriderm is the first endeavor to incorporate soluble elastin derivatives into dermal replacement scaffolds. However, it comprises a collagen scaffold that is wrapped by elastin. The advantages of the scaffold do not arise from the existence of an elastin fiber network or the elasticity of the scaffold.[29] The scaffold's animal-derived proteins may cause immunological rejection, pathogen transmission, and batch-to-batch variability. Lamy et al. (2013) reported that the mean price of Matriderm is 5.30 euros per cm.[30]

Bloemen et al.'s[5] observational studies have shown promising outcomes regarding the beneficial effects of Matriderm. Studies suggest that the use of Matriderm in combination with skin grafts can lead to improved scar flexibility compared to using grafts alone. The enhancement in elasticity is seen at 3 and 12 months after the treatment, with the elasticity reaching a level similar to that of healthy skin. The statistical analysis reveals a notable disparity with a p-value of

0.041. Min et al.[31] conducted a study showing that the elasticity of the skin treated with Matriderm did not show a statistically significant difference when compared to the nearby normal skin ($p = 0.518$). This demonstrated that transplanted skin combined with Matriderm had elasticity comparable to normal skin.[32]

A study conducted by Cervelli et al.[33] evaluated scar characteristics using the MSS, which was created by Beausang et al.[34] and is frequently used to evaluate different types of scars. Despite its usefulness for analyzing linear scars, MSS has been chastised for failing to identify symptoms. The study found that skin grafts coupled with Matriderm resulted in significantly higher scores on numerous MSS categories than skin grafts alone.[4] Color ($p < 0.001$), appearance ($p < 0.001$), and contour ($p = 0.005$) showed substantial improvement. Ryssel et al.[9] found that Matriderm significantly improved wound pliability ($p < 0.04$). However, after analyzing the degree of skin darkening using melanin and erythema levels, it was observed that the melanin value in the Matriderm region differed considerably from the surrounding normal skin. Furthermore, erythema increased, indicating that the therapy had a limited effect in reducing redness.[31] Bloemen et al.[5] discovered a statistically significant difference in melanin levels between replacement and reference scars. Melanin levels in substituted scars varied from normal skin by 5% (substitute-to-normal skin ratio, 1.05; reference-to-normal skin ratio, 1.00; $p < 0.010$).

Hayashi's et al.[35] observational research revealed a substantial disparity in the duration of the operation between the intervention and control groups ($p < 0.05$). Using grown epithelial cell sheets is expensive and needs expertise. As a consequence, JACE was Japan's first tissue-engineered skin replacement based on human cells and their organization. The CEAs known as "JACE" were recognized as a health insurance adaptation on 1 January 2009. Their operating time is extended since these sheets are sensitive, usually resulting in friable, unstable epithelium that can spontaneously blister, break down, and compress long after application.[36] However, the JACE used for grafting has a growth potential of 10,000 times the initial surface area.[24]

Scar characteristics were collected from three RCTs in this VSS meta-analysis. Skin replacements improved VSS scores more than skin grafts alone (mean difference = 1.38; 95% CI: 0.13–2.63; $p = 0.03$).[3,13,37] These skin replacements include the Polylactide-based Copolymer, a synthetic material for temporary wound covering. In surgery, pharmacology, and tissue engineering, degradable copolymers such sutures, hydrogels, and porous matrices are utilized or studied.[38] Biodegradable and fully absorbed derivatives have been employed in juvenile craniofacial or maxillofacial surgery for screw/plate fixation. For burn surgery, PolyMedics Innovations GmbH (Denkedorf, Germany) developed Suprathel, a cellular, biodegradable synthetic copolymer.[39] While its exact mechanism is uncertain, it has been shown to enhance wound healing and re-epithelialization in partial thickness burns and skin transplant donor sites.[37]

Glyaderm (Glycerol preserved in Acelullar Dermis), a novel approach to creating skin substitute created in 2008 by Richters et al.[40] is provided by The Euro Tissue Bank (ETB-BISLIFE, Skin Department, Beverwijk, The Netherlands). All antigenetic elements and cells are eliminated during glycerol preservation and Na-OH incubation.[41] The only two-stage Glyaderm treatment for full thickness problems has been documented until now. Initial treatment is given to a granulating wound bed under sterile cloths. After 5–7 days, split thickness autografting is conducted. Clinically, this method yields superior scar quality and aesthetics than STSG alone. Pirayesh et al.[3] found that Glyaderm and STSG improved elasticity 1 year after wound closure ($p = 0.003$). This technique's two-step process is its main drawback. However, Radboudumc (Nijmegen, the Netherlands) developed Glyaderm in 2017 to help close full-thickness wounds across joints or with a large surface. A novel procedure allows Glyaderm to be administered in one step.[41]

Various skin substitutes that are commercially available were incorporated into this systematic review, including Integra and Cellonex.[42] According to Selig et al.,[37] after a year (3–12 months), every option demonstrated an improvement in scar ratings. STSG, Integra, and Cellonex have ranges of 2.5–0.8, 2.5–1.3, and 2.9–0.8, respectively. Integra seemed to have the least improvement compared to Cellonex. They employed the VSS, a grading system established exclusively for burn scars in 1990.[43] The VSS evaluates four factors: vascularity, pigmentation, pliability, and elevated scar tissue. The scores range from 0, indicating a flawless scar, to 13, indicating the worst scar.[37]

In order to establish a standard for systematic scar assessment, the VSS employed a semiquantitative approach to collect subjective assessments. However, there are several challenges including the patient's subjective awareness, difficulties applying pigmentation markers to big and nonuniform scars, failure to identify evaluator-dependent mistakes, discomfort, and edema.[44] Scar quality improved the greatest and least in Cellonex and Integra-treated regions, respectively. Integra is the only dermal replacement with a long and broad clinical history across numerous applications. Numerous RCTs have found that Integra had better functional and cosmetic outcomes at long follow-up, not just using subjective scar metrics but also instrumentally. According to Lagus et al.,[45] patients reported favorable cosmetic outcomes using the Vancouver scar scale. Dantzer and Braye[23] assessed the Integra Dermal Regeneration Template's safety and efficacy in healing severe hand burns and repairing scars.

Integra

Integra was the first synthetic skin substitute and the most widely approved. It was initially used therapeutically in

1996. The Integra treatment is divided into two stages: scar excision and dermis restoration.[45,46] Integration is followed by delamination and split skin grafts. The time of the two processes depends on how they are combined. Because burn resurfacing is an elective operation, Integra's infection risk is lower than when used in acute burn wound care. Integra's functional and aesthetic effects have been shown to be consistent.

Integra is a bilaminar skin replacement comprised of cross-linked bovine collagen-glycosaminoglycan matrix with silicone elastomer on one side. It is applied in two steps as a split- or full-thickness skin graft.[4] The silicone "epidermis" cracks and sloughs off after 3–4 weeks as host tissue develops into the incision, leaving a thin STSG covering the integrated matrix. Integra is commonly used in burn and full-thickness wound closure and has strong long-term clinical dependability.[45] Its benefits include off-the-shelf availability, improved elasticity and cosmesis, and no cross infection. However, its two-stage approach may need a learning curve for future applications, and it is pricey. Despite these drawbacks, Integra is a popular synthetic skin substitute for burn patients.[47]

Lagus et al.[45] discovered that wound bed pretreatment before skin grafting had substantial early histological effects on STSGs pretreatment with a cellulose sponge increased STSG vessel size, M2-type macrophages, and keratinocyte proliferation. These data showed that skin grafts were more nutritious early on than other materials. This study used Cellonex, a high-grade viscose cellulose sponge.[45]

Cellonex covers wounds temporarily and promotes granulation tissue growth. With its "optimized" pore-size composition, open cell-to-cell structure, homogeneity, and purity, it may be used on many wounds.[48] A viscose cellulose matrix bound together by cotton fibers makes up the sponge. Elasticity allows repetitive compression and expansion without damaging the interior structure.[46] The sponge permits cells to readily access its internal chambers. Lack of hydrolases limits microbial and fungal enzymes from destroying cellulose in animal and human tissues. Degradation of the cellulose sponge in vivo involves chemical, biological, and mechanical factors. When cellulose is left in situ, it slowly dissolves.[49] When used as a temporary wound cover, viscose cellulose sponge is a relatively stable material for a short period of time. However, when used as a permanent implant, it should be considered biodegradable.[45]

Although extensive research has been conducted, autologous skin grafting is still the most commonly used surgical procedure for treating burn injuries because no skin substitute has been able to completely replace the function of the patient's own skin.[50,51] Skin substitutes have been shown to improve wound treatment outcomes when compared to normal therapy. Based on the findings, it can be concluded that the combination of STGS and skin replacements produces better scar treatment results. However, there is currently no comprehensive literature review determining the superiority of one skin substitute over another. As a result, more research is required to identify superior substitutes capable of completely replacing all skin functions, as well as to develop evidence-based guidelines for their application.

Limitation

In this study, the limitation was determined as the excessive number of diverse skin substitute products. Furthermore, there is variability in the scar scale assessment parameters used in various studies. There is also a limited amount of research on skin substitutes that has been published. Previous studies were missing several important parameters, including the duration till recovery, healing time, monitoring of healing rate, success of applying a combination or just skin graft, and length of hospital stay for large wounds. The cost-efficiency of skin substitute materials used to measure the effectiveness of wound healing is also rarely examined. Given the high cost of skin substitute materials, it is important to carefully analyze both the material itself and its ability to promote healing. It is anticipated that this research will account for and consider the parameters specified in this limitation in the future.

Conclusion

In conclusion, the meta-analysis shows that the application of skin substitutes has significant benefits and helps efficiently close wounds. In addition, the Vancouver Scar Scale (VSS) shows better results in the healing process compared to depending exclusively on skin grafts. Skin substitutes do not possess any inherent superiority over one another; rather, their suitability for individual patient wound conditions determines the critical factor in this regard. A large-scale beneficial skin substitute is required, as opposed to grafts alone.

Ethics approval

Not applicable.

Informed consent

Not applicable.

ORCID iDs

Indri Lakhsmi Putri ![iD](https://orcid.org/0000-0001-6668-6496)

Imaniar Fitri Aisyah ![iD](https://orcid.org/0009-0000-7209-6206)

Supplemental material

Supplemental material for this article is available online.

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