TECHNOLOGY REVIEW (MINI-HTA)

HUMAN SKIN ALLOGRAFT FOR BURNS

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
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EXECUTIVE SUMMARY

Background
Burns are devastating injuries, often resulting in significant morbidity, impairment of emotional well-being, and quality of life. Burns are a global public health problem, with an estimated 180,000 deaths annually. The majority of these deaths occur in low- and middle-income countries and almost two-thirds occur in the WHO African and South-East Asia regions.

Major burns are often associated with early and long-term complications and usually require a prolonged hospital stay. Treatment for major burns can be challenging but the results may be unsatisfactory with the patients usually suffering lifelong disabilities and having to undergo long-term treatment with multiple outpatient visits as well as multiple reconstructive surgical procedures. Early burn excision and immediate grafting are described as the optimal management for acute burn injury and was shown to be a major cause mortality reduction in major burn patients.

Autografting remains the golden standard of wound covering after debridement but it is limited by feasibility and availability of autograft skin. Various skin substitutes are currently available for temporary wound coverage, and allograft skin is one of the most used materials. Human skin allograft is derived from human cadaver donors and its use and demand have increased rapidly since previous decades. However, the use of human skin allografts is severely hindered by a number of difficulties including inadequate availability, graft rejection, the possibility of disease transmission, and reliance on the tissue banks.

Hence, this technology review was requested by the Head of the Department of Plastic and Reconstructive Surgery, Hospital Sungai Buloh to assess the evidence and feasibility of using human skin allograft in the management of burns

Objective/ aim
The objective of this technology review was to evaluate the effectiveness, safety, organisational and economic implications of the use of human skin allograft in burns.

Methods
A comprehensive search was conducted on the following databases without any restriction on publication language and publication status. The Ovid interface: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to Jan 9, 2023. Searches were also run in PubMed and INAHTA databases. Google was used to search for additional web-based materials and information. Additional articles were identified by reviewing the references of retrieved articles. The last search was conducted on 9th January 2023.

Results and conclusions:

Search results

A total of 245 records were identified through the Ovid interface and PubMed while nine were identified from references of retrieved articles. No duplicate references were found; 254 potentially relevant titles were screened using the inclusion and exclusion criteria. Of these, 23 relevant abstracts were retrieved in full text. After reading, appraising, and applying the inclusion and exclusion criteria to the 23 full-text articles, 15 were included while the other eight were excluded since the studies were already included in one systematic review (SR), irrelevant population (cases with ulcers), and irrelevant outcome. All full-text articles finally selected for this review were one systematic review and meta-analysis, three case-control studies, nine cross-sectional studies, one cost-utility analysis, and one cost-analysis.

Effectiveness

There was very limited retrievable evidence showing that the use of human skin allograft was associated with significantly higher patient survival and lower likelihood of death in patients with major burns of >50% TBSA. Very limited evidence showed that its use in burn patients of >30% TBSA was associated with significantly lower 90-day inpatient mortality. There was very limited evidence showing that the use of human skin allograft had better wound healing and graft take percentage in burn patients however the difference did not reach statistical significance. Some evidence showed its use was associated with a significantly shorter hospital stay in patients with less severe burns but significantly longer hospitalisation in patients with more severe burns.

Safety

Based on limited available evidence, the use of human skin allograft for burns appeared to be safe. The use of human skin allograft was approved and regulated through tissue banks in the USA by United States Food and Drug Administration (USFDA). Although very limited evidence showed increased inpatient complications with the use of human skin allograft for burn patients, the complications reported were related to diagnosis in five domains including hospital-acquired pneumonia, sepsis, venous thromboembolic disease, peri-procedural bleeding, and postoperative wound complications, which were not directly related to the use of human skin allograft.

Organisational

Limited number of skin banks were established in several developing countries. A sustainable skin banking model by National Burns Centre in India along with Rotary International and Euro Skin Bank outlined four aspects in establishing a skin bank; the finance of setting-up and running a skin bank, the technical assistance in terms of preservation techniques of skin allograft, the procurement, processing, preservation and distribution of skin allograft, and the continuous large-scale skin donation awareness campaign programme for the public. In addition, all skin banks are regulated, and many are accredited according to country or region. In Asia Pacific region, Asia Pacific Burn Association Guidelines for Skin Banking in Therapeutic Applications 2020, offer a comprehensive manual that addresses governance and contracts, staff responsibilities, quality management; facilities, equipment and supplies management,

donor consent and testing, and recommendations of good practices related to skin recovery, processing, storage, and distribution of human skin allograft.

Economic implication

Very limited evidence showed that the use of human skin allograft for partial thickness burn of 20% TBSA had an incremental cost-utility ratio of [redacted] compared to [redacted] compared to SSD, which was considered cost-effective with willingness-to-pay thresholds of $100,000/QALY. Limited evidence also showed that the use of human skin allograft in burns was associated with higher cost compared to other skin substitute [redacted]

Conclusion

Based on the review, highly limited evidence found that the use of human skin allograft may be effective in terms of patient survival and inpatient mortality for patients with major burns. Its use was considered safe through the pathway of the skin bank. Very limited evidence showed its use for burn patients was associated with higher cost compared to other skin substitutes but can be cost-effective depending on the willingness-to-pay thresholds.

TABLE OF CONTENTS

ABBREVIATION

AATB	American Association of Tissue Banks
AEs	Adverse events or adverse effects
AHRQ	Healthcare Research and Quality
APBA	Asia Pacific Burn Association
ATE	Average Treatment Effect
CAD	Canadian Dollars
CASP	Critical Appraisal Skills Programme
CI	Confidence interval
CMV	Cytomegalovirus
HCUP	Healthcare Cost and Utilization Project
HUSM	Hospital Universiti Sains Malaysia
HIV	Human Immunodeficiency Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HTLV	Human T-cell lymphotropic Virus
INAHTA	International Network of Agencies for Health Technology Assessment
MaHTAS	Malaysian Health Technology Assessment Section
MOH	Ministry of Health
NIS	Nationwide Inpatient Sample
PSI	Patient Safety Indicator
QALY	Quality adjusted life year
RCT	Randomised controlled trial
ROBIS	Risk of Bias in Systematic reviews
TBSA	Total Body Surface Area
USA	United States of America
USFDA	United States Food and Drug Administration
WHO	World Health Organization

1.0 BACKGROUND

Burns are devastating injuries, often resulting in significant morbidity, impairment of emotional well-being, and quality of life. Burns are a global public health problem, with an estimated 180,000 deaths annually.[1] Majority of these deaths occur in low- and middle-income countries and almost two-thirds occur in the WHO African and South-East Asia regions.[1] The worldwide trends for burn incidence and mortality rate are of downward trends, particularly in very highly developed countries.[2] Conversely, the child mortality rate from burns is currently over seven-fold higher in low- and middle-income countries than in high-income countries.[1] In Malaysia, data on the epidemiology of burn is extremely scarce. An increasing trend for hospitalisation due to burns in a hospital in Malaysia was reported in one study[3] while another study in 2003 reported that burns represent 5.6% of all domestic injuries in Malaysia.[4]

Major burns are often associated with early and long-term complications and usually require a prolonged hospital stay.[1] Treatment for major burns can be challenging but the results may be unsatisfactory with the patients usually suffering lifelong disabilities and having to undergo long-term treatment with multiple outpatient visits as well as multiple reconstructive surgical procedures.[2] These health-related consequences of burns are often accompanied by additional socioeconomic burdens for burn victims and their families.[2] Burns injuries lead to serious adverse effects due to loss of the skin barrier including pain, exposure to infection, increased fluid loss, and dehydration as well as shock, particularly for major burns.[5] Treatment of burn wound depends on the total body surface area (TBSA) and the depth of burns, where superficial partial thickness burns could heal by wound dressing alone while deep partial- and full-thickness burns need early burn excision and wound coverage.[5] Early burn excision and immediate grafting are described as the optimal management for acute burn injury and were shown to be a major cause of mortality reduction in major burn patients.[6]

Autografting remains the golden standard of wound covering after debridement but it is limited by the availability of autograft skin or not feasible due to wound bed factors thus requiring alternative methods.[5-7] Various type of skin substitutes are currently available for temporary wound coverage, and allograft skin is one of the most used materials.[5] Skin allograft is derived from human cadaver donors and its use and demand has increased rapidly since previous decades.[8] However, the use of human skin allograft is severely hindered by a number of difficulties including inadequate availability, graft rejection, the possibility of disease transmission, and reliance on the tissue banks.[5-8]

Hence, this technology review was requested by the Head of the Department of Plastic and Reconstructive Surgery, Hospital Sungai Buloh to assess the evidence and feasibility of using human skin allograft in the management of burns.

2.0 OBJECTIVE / AIM

The objective of this technology review was to evaluate the effectiveness, safety, organisational and economic implications of the use of human skin allograft in patients with burns.

3.0 TECHNICAL FEATURE

Burn injuries are common injuries that can result in significant morbidity and mortality. One of the primary objectives in burn care is to provide a form of definitive skin coverage that enhances wound healing with minimal scarring and impact on quality of life.[9] For decades, the standard approach to treatment has involved early excision and grafting.[10] When burn injuries are more extensive, patients may need temporary coverage using alternative materials like allografts, xenografts, skin substitutes, or other biological or semi–biological dressings.[10] This is necessary due to the insufficiency of healthy donor sites available or suitable for grafting purposes.[10]

Human skin allograft has been used for burns for over 100 years and it has gained popularity in previous decades for the management of major burns.[7-8] Allograft is defined as the transplantation of cells, tissues, or organs, sourced from a genetically non-identical member of the same species as the recipient.[9] Human skin allograft is described as the use of human skin from other individuals mostly cadaveric skin.[7] Skin allograft can be classified into:

a) Viable: This contains viable cells including keratinocytes, fibroblasts, endothelial cells and Langerhans cells (dermal macrophages). It may be fresh or cryopreserved.
b) Non-Viable: This may be glycerolised or gamma-irradiated, freeze dried or ethylene oxide treated.[7]

A viable skin allograft, similar to an autologous split-thickness skin graft, can establish revascularisation through the process of inosculation. Additionally, skin allografts can provide growth factors and essential cytokines that promote chemotaxis and cell proliferation at the wound site. By increasing vascularity and encouraging angiogenesis, the skin allograft has been utilized in the preparation of burn wound beds. When applied to freshly excised burn wounds, the skin allograft optimizes and conditions the wound for subsequent autografting. In the sandwich grafting technique, where the skin allograft is layered over the autograft, it prevents drying out of the wound bed between widely expanded autografts and reduces bacterial colonization. It also provides protection to the autograft against shearing forces. Furthermore, the application of a skin allograft speeds up the epithelialization process of the wound bed.[11]

Human skin allograft has been used for various purposes in the management of acute burns of different thicknesses.[5,8] Clinical indications of human skin allograft use in burns are the following:

- Coverage of extensive full-thickness wounds
- Coverage of widely meshed skin autografts

- Healing of partial-thickness wounds
- Wound bed preparation and testing before autografting [5,8,9,11,12]

In superficial partial thickness burns, human skin allograft is used as a biological dressing over freshly debrided wounds as it has been shown to promote epithelialisation. In full-thickness burns, human skin allografts can be used as a temporary biological dressing, ideally suited to preparing the wound bed for future grafting with autograft.[5,8] The utilization of human skin allografts to temporarily close extensive wounds is claimed to offer several advantages. As these allografts encompass both the epidermis and dermis layers, they are claimed to serve as natural barriers. Consequently, the human skin allografts minimize the loss of water, proteins, electrolytes, and heat, thereby preventing wound dehydration, improving thermoregulation, and positively impacting the patient's overall condition and nutritional status. Additionally, the use of human skin allografts is claimed to alleviate pain, decrease the risk of wound infection, and inhibit bacterial growth in contaminated wounds. Moreover, through the transfer of the allograft's dermal components to the wound bed, they facilitate the healing process and enhance the functionality of the eventual graft while improving the quality of the resulting scar. Temporary coverage of wounds with allografts also is claimed to reduce the need for subsequent autografts and improve the success of autograft integration by promoting epithelialization and preparing the wound bed.[9]

Human skin allograft is made available for use in the management of burns in many countries through established skin banks.[13,14] The skin allograft undergoes a series of processes including procurement, processing, preservation, storage, and distribution of tissue, from the donor skin to the recipients.[5] After potential tissue donor screening is complete and authorization has been obtained, procurement of skin from cadavers is then carried out.[5,9] The skin is processed and preserved often using two common preservation techniques which are cryopreservation or glycerol preservation, at the skin bank and transported to hospitals in secure containers and rewarmed before use.[5,9] In low- and middle-income countries (LMIC), including Malaysia, human skin allograft remains a limited resource.[14] In Malaysia, human skin allograft is procured from established vendors and currently, there is no national skin bank available yet in the country.

4.0 METHODS

A systematic review was conducted. Search strategy was developed by the main author and an *Information Specialist*.

4.1 SEARCHING

The following electronic databases were searched through the Ovid interface: **MEDLINE (R) ALL 1946 to Jan 9, 2023.**

Other databases:

- PubMed

- Other websites: INAHTA.

General database such as Google Scholar was used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles. The search was limited to articles on human. There was no language limitation in the search. **Appendix 1** showed the detailed search strategies. The last search was conducted on 9th January 2023.

4.2 SELECTION

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria. Relevant articles were then critically appraised using *Critical Appraisal Skills Programme (CASP) checklist*. Studies were graded according to *US/ Canadian Preventive Services Task Force* (**Appendix 2**). All data were extracted and summarised in the evidence table as in **Appendix 3**.

The inclusion and exclusion criteria were:

Inclusion criteria:

a.	**Population**	Patients with burn injuries
b.	**Intervention**	Human skin allograft, cadaveric skin allograft, deceased donor skin allograft
c.	**Comparator**	Other skin substitutes
d.	**Outcomes**	**Effectiveness:** Healing time, mortality, survival, length of stay **Safety:** Mortality, adverse events (AEs), complications **Organisational issues:** Hospital utilisation (readmission, length of stay), procedural time points and training or learning curve **Economic implications:** Cost, cost-effectiveness, cost-utility analysis

e.	**Study design**	HTA reports, systematic review (SR) with/out meta-analysis, randomised controlled trial (RCT), cohort, case-control, economic evaluation studies, case series
f.	Full text articles published in English	

Exclusion criteria:

a.	**Study design**	Case report, animal study, laboratory study, narrative review
b.	Non-English full text articles	

5.0 RESULTS

Search results

An overview of the search is illustrated in **Figure 3**. A total of **245** records were identified through the Ovid interface and PubMed while **nine** were identified from references of retrieved articles. No duplicate references were found; **254** potentially relevant titles were screened using the inclusion and exclusion criteria. Of these, **23** relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the **23** full-text articles, **15** were included while the other **eight** were excluded since the studies were already included in one SR, irrelevant population (cases with ulcers) and irrelevant outcome. All full-text articles finally selected for this review were one systematic review and meta-analysis, three case-control studies, nine cross-sectional studies, one cost-utility analysis and one cost-analysis.

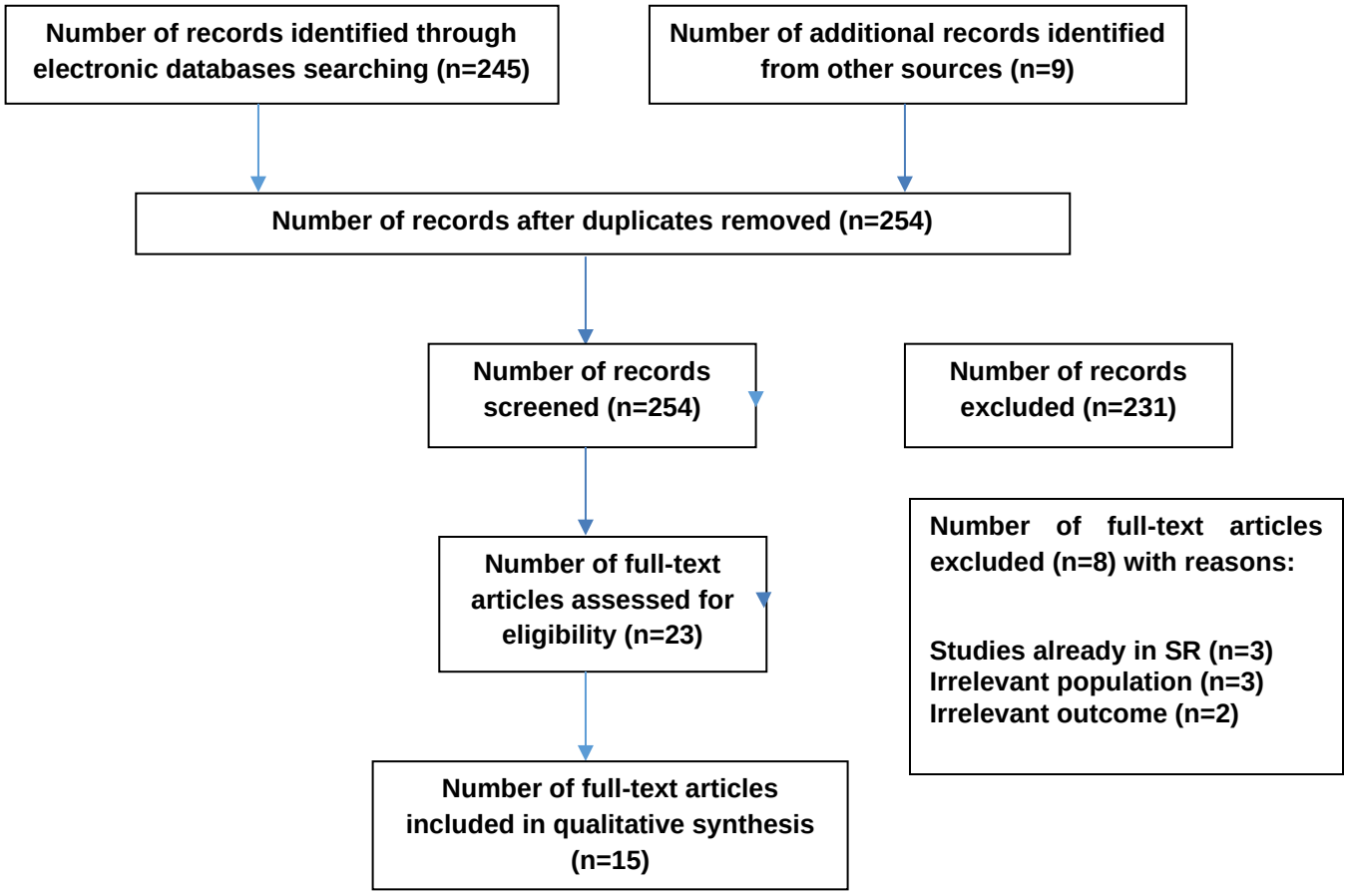

Figure 3: Flow chart of retrieval of articles used in the results

Assessment of risk of bias in included studies

Risk of bias was assessed using Risk of Bias in Systematic reviews (ROBIS) for systematic review and meta-analysis, and Critical Appraisal Skills Programme (CASP) for case-control studies. These assessments involved answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias.

Risk of bias assessment for included systematic review and meta-analysis

Paggiaro A O et al. (2019) was rated to have an overall low risk of bias. The review had pre-specified its clinical question and inclusion criteria for study eligibility. No language restriction was applied. There was some concern regarding the method used for data collection and study appraisal. While the study selection was mentioned in the article conducted by the selection committee consisting of two reviewers, the information with regards to the extraction of data from the included studies was quite unclear. The use of a structured data extraction form and if second reviewer was involved in checking the extracted data for accuracy was not mentioned. Information on study characteristics for all included studies was also not mentioned in detail in the article.

Table 3: Summary of risk of bias assessment for systematic review and meta-analysis using ROBIS

REVIEW	D1	D2	D3	D4	OVERALL
Paggiaro A O et al. (2019)[15]	+	+	-	+	+

Domains
D1: Study eligibility
D2: Identification and selection of studies
D3: Data collection and study appraisal
D4: Synthesis and findings

Judgement
High risk
Unclear
Low risk

Risk of bias assessment for included case-control studies

All case-control studies that were included in this review were judged to have low risk of bias.

Criteria assessed	Selection (cases and control recruited in an acceptable way?	Exposure accurately measured to minimise bias?	Confounding factors identified and taken account?
Sheckter CC et al. (2018)[16]	+	+	+
Choi Y H et al. (2018)[17]	+	+	+
Azizian M et al. (2022)[18]	+	+	+

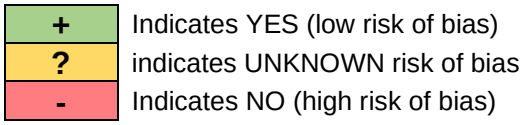

Figure : Assessment of risk of bias of case control using CASP

Characteristics of included studies

There were one SR and meta-analysis, three case-control studies, and six cross-sectional studies, which reported on the effectiveness of human skin allograft for the management of burn patients. The same SR and meta-analysis, two case-control studies, two cross-sectional studies with the addition of another three cross-sectional studies, reported on the safety aspects including hypertrophic scar formation, complications as well as bacterial contamination and reasons for the discards of human skin allograft. For cost-effectiveness, one cost-utility analysis, one cost-analysis and a case-control study reported on incremental cost-utility ratio, overall cost, and total charges of using human skin allograft for burns, respectively. The included studies were conducted mainly in Asia, United States of America (USA) and Europe. Most studies were observational studies involving cadaveric skin allograft, and few of studies had small sample size. The studies were published between the year of 2007 to 2022. Table 2 displays the characteristics of included studies in this review.

Table 2. Characteristics of included studies

Study	Study design	Number of patients	Intervention	Comparison	Outcomes
1.Paggiaro A O et al. (2019)[15]	SR and Meta-Analysis	18 trials: 12 RCT 6 NRCT Burn patients -TBSA varied greatly 0.5% to 95%	Human skin allograft -13 trials used it for wound bed preparation or cover autografts (sandwich technique) -5 trials used it for wound healing on partial thickness burns -1 trial evaluate both	Other skin substitutes	Effectiveness -Healing -Graft take percentage -Scar appearance Safety -Hyperthropic scar formation

Study	Study design	Number of patients	Intervention	Comparison	Outcomes
2. Azizian M et al. (2022)[18]	Case-control study	112 cases 224 controls Burn patients Mean burn %: Cases: 51.29±15.11 Control: 52.74±13.29	Human skin allograft	No skin allograft	Effectiveness -Duration of hospitalization -Status of patients at discharge (alive, deceased)
3. Megahed MA et al. (2021)[19] -Egypt	Cross-sectional study	36 burn patients >25% TBSA	Human Skin Allograft	No comparison	Effectiveness - Patient survival - Healing
4. Sheckter CC et al. (2018)[16] -USA	Case-Control Study	3557 burn patients: 771 received allograft while 2786 patients did not. -20 to 50% TBSA	Human skin allograft	Operative burn treatment without allograft placement.	Effectiveness -Mortality -Length of stay -Operations Safety -Complications Cost -Total charges
5. Choi Y H et al. (2018)[17] -Korea	Case-Control Study	1,282 burn patients >30% TBSA: 698 cadaver group 584 non-cadaver group	Human skin allograft -cadaveric	Conventional burn treatment without allograft	Effectiveness -In-hospital mortality
6. Kitala D et al. (2016)[20]	Cross-sectional study	46 burn patients -average 37% TBSA	Human skin allograft	Group 1: Allogeneic skin dressings after wound resection (33 patients) Group 2: Free autologous split-thickness skin grafts (STSG) (13 patients)	Effectiveness -Hospitalisation time Safety -Complications
7. Chua A et al. (2007)[21] -Singapore	Cross-sectional Study	102 burn patients ≥40% TBSA	Human skin allograft -cadaveric	Comparison: pre–skin-banking (1993 to 1997) and	Effectiveness -Mortality -Length of stay

Study	Study design	Number of patients	Intervention	Comparison	Outcomes
				post–skin-banking periods (1998 to 2003)	
8. Khoo TL et al. (2010)[22] -HUSM, Malaysia	Cross-sectional study	43 burn patients Mean TBSA 28.7% ± 18.5%,	Human skin allograft -glycerol preserved	No comparison	Effectiveness -Complete healing time -Length of stay -Mortality Safety -Bacterial growth
9. See P et al. (2001)[23]	Cross-sectional study	17 severe burn patients -average 58% TBSA	Human skin allograft	No comparison	Effectiveness -Patient oucome
10. Eldad A et al. (1997)[24]	Cross-sectional study	12 flame burn patients -average 40.5% TBSA	Human skin allograft -cryopreserved	No comparison	Effectiveness -Healing
11. Pianigiani E et al. (2006)[25] -Italy	Cross-sectional study	461 cadaveric donors	Human skin allograft	No comparison	Safety -Eligibility after screening
12. Meneghetti K L et al. (2018)[26] -Brazil	Cross-sectional study	32 batches of cadaveric donors	Human skin allograft	No comparison	Safety -Bacterial contamination
13. Gaucher S et al. (2015)[27] -France	Cross-sectional study	336 donors	Human skin allograft	No comparison	Safety -reason for discard
14. Sheckter CC et al. (2020)[28]	Cost-utility study	Base case: a 20% TBSA partial thickness burn	Human skin allograft	Silver sulfadiazine (SSD) and Mepilex Ag	Incremental cost-utility ratio
15. Austin R E et al. (2015)[29] -Canada	Cost-analysis study	45 patients with upper extremity burns	Human skin allograft	Biosynthetic temporary skin substitute	Cost

5.1 EFFECTIVENESS

Paggiaro A O et al. (2019) have conducted a systematic review and meta-analysis to compare allograft skin with other skin substitutes in the treatment of burns. Trials comparing human skin allograft to any other skin substitute for burns treatment were identified from medical databases and critically appraised. Outcomes of interest were healing, self-grafting, scar appearance, and mortality. The review included 18 trials with 12 were RCTs and six were NRCTs. The trials were conducted between the years of 1980 to 2009. Most of the trials included were found to have methodologies that presented a high risk of bias. Thirteen studies used human skin allograft for wound bed preparation or cover autografts while five studies used it to stimulate wound healing (re-epithelisation) on partial-thickness burns. Only one study evaluated both aspects in partial- and full-thickness burn patients. Most studies used small sample sizes and included both adults and children. There was variation in the percentage of total body surface area (TBSA) of the burn patients from 0.5% to 95%. Substantial variation was also noted with regards to the types of treatments compared to human skin allograft and the follow-up time ranged from acute stage to up till two years particularly those assessing scar quality and pliability. The meta-analysis evaluated only two outcomes; healing and graft take percentage. The results from the analysis showed that wound healing and graft take percentage in the allograft skin group and other skin substitutes was quite comparable. However, when considering the confidence interval, there was a slightly higher tendency towards allograft skin.[15, Level I]

A case-control study was conducted by Azizian M et al. (2022) which was aimed to evaluate and report the outcomes of skin allograft on burn patient survival in Iran. Patients who were admitted to the burn centre of Imam Khomeini Hospital in Tehran between July 15, 2017 and April 27, 2021 were included in the study. Patients who received skin allograft were allocated to cases group (n = 112) while patients who did not were allocated to control group (n = 224). The control group was matched with the case group in terms of sex, age, and percentage of burns. With the exception of using human skin allografts, the two groups underwent similar procedures for initial resuscitation, nutrition, wound care, and indications for the use of the burn intensive care unit. Outcomes compared between the two groups were the duration of hospitalization, and status of patients at discharge. Overall, 39% of the case group (44 patients) and 39% of the control group (88 patients) had burns over 50% of TBSA. The study reported that 34% (38 cases) of the case group and 37% (82 cases) of the control group had died before discharge ($p = 0.633$). The length of hospital stays in the case group (43.3±11.5) was higher than the control group, (22.4±11.2) ($P<0.001$). While most of the patients who died in the control group (61%) had more than 50% burns, only 31% of the patients who died in the case group had more than 50% burns ($P<0.001$). Survival analysis showed that the average survival time in the case group (53 days, 95% CI=45-56) was higher than in the control group (49 days, 95% CI=39-58) ($P=0.012$). The analysis also showed that the likelihood of death was found to slightly increases with age (odds ratio [OR] = 1.03, 95% confidence interval [CI] = 1.005-1.070).

Conversely, the utilisation of skin allografts acts as an effective preventive measure against death (OR = 0.038, 95% CI = 0.142-0.945).[18 Level II-2]

A cross-sectional study was conducted by Megahed MA et al. (2021) involving 36 patients who were admitted to the burn unit in Egypt from August 2016 to November 2019, to evaluate the application of human skin allograft as a skin substitute used for coverage of major deep burn wounds, and its effect on the clinical outcome of the patients. Patients with major deep burn more than 25% TBSA with limited donor sites for autograft coverage were included in the study. Patients were divided into three groups according to the availability of different types of skin allograft, as follows: Group I included nine patients with mean age of 4.75 years and mean burn percentage of 37.42% TBSA, in whom burn debridement was done without allograft coverage as it was not available, Group II included 15 patients with mean age of 7.50 years and mean burn percentage of 28.68% TBSA, in whom allograft source was discarded skin of body contouring operations (abdominoplasty, reduction mammoplasty or body lifting) from unrelated patients, and Group III included 12 patients with mean age of 6.44 years and mean burn percentage of 33.55% TBSA, in whom allograft was harvested from a first-degree relative (mother, father, brother or sister). The results showed that the number and percentage of patients that needed auto-grafting after surgical intervention was lower in the two groups receiving human skin allografts, with nine (100%) in Group I, 13 (86.66%) in Group II, and eight (66.7%) in Group III. Patient survival was higher in the two groups receiving human skin allografts with 55.6% in Group I, 86.7% in Group II and 91.7% in Group III. There was significant difference between the groups regarding time to complete healing, with 30.54 ± 2.54 days in Group I, 26.35 ± 6.46 days in Group II, and 18.65 ± 8.67 days for Group III ($P<0.05$). The two groups receiving human skin allografts (Group II and Group III) had significantly reduced time to complete healing compared to Group I.[19, Level III]

Sheckter CC et al. (2018) conducted a case-control study in United States of America (USA), to assess utilisation of allograft in 20–50% TBSA burns and to evaluate the inpatient outcomes. Discharge data from the Nationwide Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality was used to identify patient who underwent operative treatment for a major burn (>second degree depth and 20–50% TBSA). The treatment group consisted of all patients who received allograft placement, and the control group consisted of all patients who received operative burn treatment without allograft placement. The primary outcome of interest was inpatient mortality. Secondary clinical outcome included total burn-related operations, length of stay, and total charges. The treatment effect of allograft in major burns was evaluated using propensity score matching in order to minimize the effects of confounding by indication. A total of 3557 patients were included in the cohort with 771 patients received allograft during their admission while 2786 patients did not. The results showed that allograft treatment increased inpatient mortality by an average of 2.8% (p=0.041). When stratified by Abbreviated Burn Severity Index (ABSI), the overall mortality increase associated with allograft was only present in the higher ABSI group (>10 or severe), with a 9.2% increase (95% CI 1.0–17.3%, p=0.028). The use of allograft was associated with

a significantly longer length of stay by 8.4days (95% CI 6.1– 10.7, p<0.001), and more total burn operations by 1.6 operations (95% CI 1.4–1.9, p<0.001).[16, Level II-2]

Another case control study was conducted by Choi Y H et al. (2018) in Korea, to analyse the effect of cadaveric skin allograft on mortality rates in patients with burns involving >30% of TBSA. Electronic medical records of patients admitted with burns affecting over 30% of TBSA to four hospitals in Korea between June 1, 2008 and December 31, 2016 were reviewed and 1,282 patients who were admitted to four hospitals in the period were included in the study. Patients were categorised according to whether they received cadaver skin allograft (cadaver group, n=698) or not (non-cadaver group, n=584). Propensity score matching was performed and generated 474 propensity score- matched pairs. All surgeons working in the four hospitals included in this study performed cadaveric skin allografts (cryopreserved) using similar surgical techniques. The primary outcome of interest was in-hospital mortality. The results showed that overall 90-day in-hospital mortality rate among all patients was 35.3% (453/1282). There was a significant difference in 90-day in-hospital mortality between the two groups for propensity-matched groups [cadaver group (37.8%) vs. non-cadaver group (47.3%); difference, 9.5; (95% CI: 3.2% to 15.8%)]. Logistic regression analyses showed a significant association between receiving a cadaver skin allograft and lower 90-day in-hospital mortality in the propensity-matched groups (odds ratio, 0.42; 95% CI:0.29 to 0.62). Cox regression analysis showed a significant difference in 90-day in hospital mortality between cadaver and non-cadaver groups in the propensity-matched groups (hazard ratio, 0.39; 95% CI: 0.33 to 0.49).[17, Level II-2]

In Poland, a cross-sectional study was conducted by Kitala D et al. (2016) which involved 46 patients who were patients hospitalized in the Centre for Burns Treatment between 2012 and 2013 due to severe thermal burns of on average 37% TBSA, and underwent allogeneic skin grafts. The study was aimed to determine how the use of skin allografts improves the conditions for the intake of autografts in the treatment in burns, and how it accelerates wound healing in comparison to the autografts-only option. In addition, the study was also conducted to determine if multiple autologous spit thickness skin grafting is a more effective way of treatment and whether it shortens hospitalization time and reduces pain in comparison to only allogeneic skin treatment. Before applying allogeneic skin grafts, the wounds underwent preparation in the form of wound debridement and necrosis demarcation. This involved removing necrotic tissues either through tangential excisions or deep resection. Allogeneic skin grafts were utilized as the primary treatment following the removal of necrotic tissues, or alternatively, as a secondary therapy after the dissolution of free autologous split-thickness skin grafts, which served as the intended final treatment approach. Out of the total of 46 patients, allogeneic skin was applied as the initial dressing after wound debridement in 36 patients, while in the remaining 10 patients, a STSG from the autogeneic system was used as the first dressing. Results for the two groups of patients have been compared with a third group of patients who had both the autologous and allogeneic skin graft to highlight the difference. The progress of healing and final healing of burns under the dressing were assessed. The results showed that there was a statistically significant difference between the duration of hospitalization in the

group of patients who underwent STSG preceded by allogeneic skin graft transplantation in comparison to the group of patients who had allogeneic skin application ($p < 0.05$) and the group of patients who were grafted with autologous skin ($p < 0.05$). The length of the hospital stay was significantly longer in the group of patients who had STSG in comparison to the patients who had allogeneic skin grafts ($p < 0.05$). No statistically significant difference was noted in pain perception between the group of patients who received allogeneic skin application and the group of patients who underwent autologous skin grafting.[20, Level III]

A cross-sectional study was carried out by Chua A et al. (2007) to assess the efficacy of early wound debridement and wound coverage with skin allografts introduced in 1998 with the establishment of a skin banking facility in Singapore. Data of burn patients with deep dermal to full-thickness burns and TBSA of at least 40% were obtained from admission records of the Singapore General Hospital (SGH) Burns Centre from 1993 to 2003. Mortality rate and length of stay were compared for burn patients admitted between the pre–skin-banking (1993 to 1997) and post–skin-banking periods (1998 to 2003). The results showed that there was no significant reduction was observed for mortality rate between 1993 to 1997 and 1998 to 2003. However, length of stay was significantly reduced in post skin-banking periods (pre-skin-banking period 61.3 ±27.8 versus post skin-banking period 45.6 ± 25.1, P = 0.028).[21, Level III]

Khoo TL et al. (2010) conducted a cross-sectional study to analyse the use of glycerol-preserved skin allograft for burn treatment from October 2001 to May 2008 at the Burns Unit, Hospital Universiti Sains Malaysia (HUSM), Kelantan, Malaysia. The study involved a total of 43 consecutive cases of burns which were managed with the application of glycerol-preserved skin allograft. The overall mean age was 23.3 years. Most patients (83.7%) sustained deep partial- or full-thickness burns. The mean TBSA of burn was 28.7% ± 18.5%, ranging from 3% to 70%. Twenty-nine patients (67.4%) were indicated for skin allograft as skin substitute for wound-bed preparation, nine patients (20.9%) were treated with skin allograft according to the sandwich technique to protect the meshed split-skin graft or the Meek micrograft, and the remaining five patients received skin allograft as definitive dressing. For patients treated with skin allograft as skin substitute for wound-bed preparation prior to autografting, the duration of skin allograft treatment and adherence was 7.9 ± 2.0 days, ranging from 5 to 13 days. The percentage of autograft take was 88.4 ± 13.6%. Complete wound healing was achieved in about 38.7 ± 18.0 days, ranging from19 to 78 days. Mean length of hospital stay was 42.9 days for these patients. The mortality rate in this group of patients was 41.1% as these patients suffered severe burns with mean TBSA of 49.6%. The most common causes of death were sepsis and acute respiratory distress syndrome. For patients who were treated with skin allograft using sandwich grafting technique, the mean autograft take was 74.4%. About four patients (44.4%) had complete wound healing after the sandwich technique; another four patients required one repeat autografting. The average duration of healing was 48.9 days, and the mean length of hospital stay was 65.5 days. All nine patients recovered from burns except one patient who died due to sepsis, in this group of patients. In the last group of patients who received skin allograft as definitive dressing, four patients (80%) had complete healing at an

average of 19 days without further intervention. The length of stay was averaged at 16.6 days and no mortality was observed in this group of patients.[22, Level III]

See P et al. (2001) conducted a cross-sectional study in Singapore, to report the early clinical experience with cryopreserved cadaveric allograft in treating extensive burn wounds in 17 severely burned patients with TBSA averaging 58% (range 33–90). All the burn injuries were caused by flames. Eight patients with concomitant inhalation injury were intubated and started on fluid resuscitation upon admission. Patients with stable physiologic parameters had early excision of their burn wounds within 72 hours and had their burn wounds covered with cadaveric allograft. The study reported that the skin allografts achieved good adherence rate of 70% at one-week post-operation, indicated by intact, stable graft with no signs of infection or graft breakdown. Seven patients had recovered from their burn injury and ten died of overwhelming sepsis. Post-mortem autopsy performed on all the deceased patients listed septicaemia and bronchopneumonia as one of the major contributing cause.[23,Level III]

An earlier cross-sectional study was done by Eldad A et al. (1997) in Jerusalem, involving 12 patients who had flame partial thickness burns, which was aimed to compare the use of cryopreserved skin allograft as a biological dressing, with conservative treatment of silver sulfadiazine (SSD). Twelve patients with flame partial thickness burns areas were allografted after mechanical debridement without excision of the burn wounds. The allografts consisted of cadaveric skin that had been cryopreserved using a programmed freezing method and stored at a temperature of -180 degrees Celsius for a period of 30 to 48 months. Burns of similar size and depth were treated using SSD once or twice per day until either healing occurred or debridement and grafting became necessary. The study found that 80% of the cryopreserved allografts adhered well and 76 per cent of the treated areas healed within 21 days, whereas only 40% of the SSD-treated burns healed within 21 days.[24 Level III]

5.2 SAFETY

A systematic review and meta-analysis which was conducted by Paggiaro A O et al. (2019) to compare allograft skin with other skin substitutes in the treatment of burns as described earlier, reported that from the review, most studies included found no statistical difference between allograft skin with other skin substitutes in terms of hypertrophic scar formation.[15, Level I]

Sheckter CC et al. (2018) described in their case-control study, complications for patients were evaluated using a Patient Safety Indicator (PSI) composite score, as recommended by the Agency for Healthcare Research and Quality (AHRQ). The PSI variable consisted of post-admission diagnoses with a high-positive predictive value for complications in surgical populations. The composite score (ranging from 1 to 5) included diagnoses related to five domains: hospital-acquired pneumonia, sepsis, venous thromboembolic disease, peri-

procedural bleeding, and postoperative wound complications. The results showed that the use of allograft was associated with greater composite complication index at 0.13 (95% CI 0.07–0.20, p<0.001) which were not directly caused by human skin allograft.[16, Level II-2]

Kitala D et al. (2016) reported in their cross-sectional study, among the patients initially treated with allogeneic grafts, 10 cases resulted in mortality. These cases had an average burn surface area of 50.5%, which included 25% of severe third or fourth-degree burns. Regarding the patients who received autologous skin treatment from the beginning, there were 4 mortal cases with an average burn surface area of 40%, including 26% of severe third or fourth-degree burns. All deaths were attributed to multiple organ dysfunction syndrome. There was no statistically significant relationship (p ≥ 0.05) between the use of allogeneic skin free split-thickness grafts (STSG) and patient mortality.[17,Level III]

In the cross-sectional study which was conducted by See P et al. (2001) reported 10 patients died due to overwhelming sepsis and post-mortem autopsy revealed septicaemia and bronchopneumonia as one of the major contributing cause, which were not directly related to human skin allograft.[23, Level III]

In the cross-sectional study which was conducted by Khoo TL et al. (2010) at the Burns Unit of Hospital Universiti Sains Malaysia (HUSM), Kelantan, Malaysia, it was reported that the wound swab cultures from the burn wounds were positive for bacterial growth in 32 patients (74.4%) when the skin allograft rejected. The positive culture results were not significantly different between those admitted within 24 hours of injury and those admitted after 24 hours of injury (71.4% vs. 80.0%, p = 0.719). The swab cultures were positive in 79.3% cases which used skin allograft for wound-bed preparation and 88.9% cases that used skin allograft for sandwich grafting. For the use of skin allograft in definitive dressing, only one patient was positive for culture. The most common organisms isolated from the culture were Pseudomonas sp., followed by mixed growth, Acinetobacter sp., Enterobacter and methicillin-resistant Staphylococcus aureus. The duration of skin allograft adherence to the wound bed was found significantly shorter when the wound cultures were positive as compared to negative culture (7.9 days versus 11.1 days, p = 0.009).[22, Level III]

The use of human skin allograft presupposes rigorous qualitative and safety standards defined by international and national regulations. The possibility of transmission of infections is nevertheless impossible to be completely excluded as in other organ transplants. In addition, skin transplant recipients as in the case of extensive burn patients, are often more susceptible to infections due to immune depression.[17] In a cross-sectional study which was conducted by Pianigiani E et al. (2006) reported that among 461 cadaveric donors who underwent serological and microbiological PCR screening for transmissible agents including human immunodeficiency virus (HIV), hepatitis B (HBV), hepatitis C (HCV) human T-cell lymphotropic virus (HTLV), cytomegalovirus (CMV) and Treponema pallidum, at Siena Skin Bank, Italy between the year of 2000 and 2004, 16.1% donors were found ineligible under the current

regulations.[25,Level III] This highlights the importance of screening at the skin bank in providing human skin allograft for the management of burn patients.[25, Level III] In another cross-sectional study which was conducted by Meneghetti K L et al. (2018), a total of 32 batches of human skin allografts procured from cadaveric donors between July 2012 to November 2014, were available from a skin bank in Brazil, were analysed for bacterial contamination. These samples were already discarded due to microbial contamination.[26, Level III] The identification of the bacteria isolated from skin allografts was performed by matrix assisted laser desorption ionization–time of flight. The study reported that 21 (65.6%) skin samples were contaminated with Gram-positive bacteria: one (4.7%) with Paenibacillus sp., 12 (61.9%) with Bacillus sp., six (28.5%) with Staphylococcus sp., and two (9.5%) with Bacillus sp. and Staphylococcus sp. Several resistance profiles, including multiresistance, were found among the isolates.[20] Most of the isolates were susceptible to at least one of the antimicrobials used in the skin bank. All isolates were susceptible to amikacin, gentamicin, and tetracycline.[26, Level III] In another cross-sectional study which was done earlier by Gaucher S et al. (2015), reasons for skin discard for 11 years at The Saint Louis hospital tissue bank that provides skin allografts to pediatric and adult burn units in the Paris area were reviewed.[27, Level III] The study included all skin donors harvested between June 2002 and June 2013, representing a total of 336 donors and 2770 zones.[27, Level III] The results showed that microbial contamination continues to be the main reason for discarding potential skin allografts (29 %).[27, Level III] Most contaminants were of low pathogenicity.[27, Level III] Other reasons for discard included positive serologic tests for two donors [17 zones (0.61 %)], unsuitable physical skin characteristics for 3 zones (0.11 %), the donor's medical history for 53 zones (1.91 %), and technical issues with processing or distribution for 61 zones (2.2 %).[27, Level III] The microbial contaminants were mostly bacteria. All the isolated gram-positive cocci were sensitive to vancomycin and resistant to clindamycin, while all the isolated gram-positive bacilli were sensitive to vancomycin. Among the gram-negative bacilli, the A. baumannii, P. aeruginosa and K. pneumoniae isolates were resistant to gentamicin, whereas the E. cloacae, P. mirabilis, E. coli, E. aerogenes and M. morganii isolates were sensitive to gentamicin.[27, Level III]

In the USA, the use of human skin allograft for burn was approved and regulated through the pathway of tissue banks by the United States Food and Drugs Administration (USFDA).[30]

5.3 ORGANISATIONAL ISSUES

In relation to human skin allograft, skin banking methods have also evolved through the years. Different preservation techniques including the use of glycerol preservation, deep freezing and cryopreservation for human skin allograft are often seen in skin bank according to the suitability and needs of specific region covered.[31] Since use of human skin allograft is the gold standard for the treatment of burn wound, in-house skin banking for a burn unit hospital is prerequisite to make the treatment procedure affordable. There are very few skin banks in developing countries albeit the burden of extensive burn patients is concentrated at these regions. In India,

National Burns Centre (a tertiary burn care centre) along with Rotary International and Euro Skin Bank joined hands to plan and develop a sustainable skin banking model in Mumbai, Maharashtra, India which could be easily replicated in other parts of the country and abroad. The model consisted of mainly four aspects which are the finance of setting-up and running a skin bank, the technical assistance in terms of preservation techniques of skin allograft, the procurement, processing, preservation and distribution of skin allograft, and lastly, the continuous large-scale skin donation awareness campaign programme for the public.[31] In addition, skin bank infrastructure along with the necessary equipment as well as training for skin bank team are also emphasized. The skin bank team includes skin donation awareness team, skin harvesting and skin processing team.[31] Serological and microbiological screening are also important routine in skin bank to ensure safety of human skin allograft before distribution from donor to the recipients.[32] In Malaysia, Ministry of Health has yet to establish skin bank facility to cater the needs for human skin allograft for the management of burns.

In developed countries for example in the USA, all tissue banks are regulated by the USFDA. Numerous tissue banks also seek voluntary accreditation from American Association of Tissue Banks (AATB). The USFDA provides broad legislative oversight while AATB provides a framework which covers technical specifications, organizational management and quality management that guides tissue banks on the steps required to achieve regulatory compliance.[33] In Asia Pacific region, recently in 2020, a new skin banking guidelines was developed through a comprehensive review and collation of best international practices for the Asia Pacific Burn Association (APBA) members, covering from donor screening and testing, to skin recovery, processing, storage and distribution, and quality assurance.[33] The review includes national regulatory requirements from the European directives, Australia's Therapeutic Goods Administration and Singapore's tissue banking standards. Further technical and quality management recommendations are referenced from the AATB, the USFDA standards and guidance documents, various relevant European guides, Japanese Society of Tissue Transplantation guidelines and the Asia Pacific Association of Surgical Tissue Banking.[33] The new Asia Pacific Burn Association Guidelines for Skin Banking in Therapeutic Applications offer a comprehensive manual that addressees governance and contracts, staff responsibilities, quality management; facilities, equipment and supplies management, donor consent and testing, and recommendations of good practices related to skin recovery, processing, storage and distribution.[33] It is noted that increasing regulation and accreditation of skin banks by governmental and intergovernmental agencies have further strengthened skin processing and banking standards, thus ensuring high levels of safety and efficacy in the use of human skin allograft in various parts of the world.[31-33]

5.4 ECONOMIC IMPLICATION

There were one cost-utility analysis, one case-control, and one cost-analysis retrieved, related to the economic implication of the use of human skin allograft for burns.

Sheckter CC et al. (2020) conducted a cost-utility analysis which aimed to assess the incremental cost and effectiveness of human skin allograft compared to topical silver dressings in the acute treatment of partial thickness burns. A cost-utility analysis was performed comparing skin allograft to silver sulfadiazine (SSD) and [redacted] using decision-tree analysis. The base case modeled a superficial partial thickness 20% total body surface area burn. Utilities were determined based on expert opinions and personal experience. A payer perspective was adopted using 2019 Medicare reimbursements for the base case of a 20% TBSA partial thickness burn**.** Quality-adjusted life years were computed using the rollback method, assuming average life expectancies in the United States. To evaluate the model's reliability, a probabilistic sensitivity analysis was conducted. The analysis showed that the incremental costs of human skin allograft to [redacted] and SSD were [redacted] and [redacted] respectively. The incremental quality-adjusted life year (QALY) gains from allograft over [redacted] and SSD were 0.011 and 0.016. This yielded an incremental cost-utility ratio for allograft vs. [redacted] of [redacted]/QALY compared with an incremental cost-utility ratio of [redacted]/QALY for allograft vs. SSD. Assuming willingness-to-pay thresholds of [redacted]/QALY, probabilistic sensitivity analysis demonstrated that allograft was cost effective to [redacted] in 62.1% of scenarios and cost-effective to SSD in 64.9% of simulations.[28]

In the case-control study mentioned earlier, which was conducted by Sheckter CC et al. (2018), reported that the use of human skin allograft for burn patients was significantly associated with greater total charges [redacted], $p<0.001$) compared to the control group.[16]

One cost analysis retrieved which was conducted by Austin R E et al. (2015), assessing cost and outcome between cadaveric allograft and biosynthetic temporary skin substitute composed of a silicone membrane and nylon mesh impregnated with porcine dermal collagen namely [redacted], in 45 patients who had undergone treatment for isolated upper extremity burns in a regional burn unit at a single tertiary trauma centre in Canada.[23] Burn database was reviewed retrospectively and analysed. Of 45 patients who were included in this study: 15 treated with cadaveric allograft and 30 treated with [redacted] skin substitute. Costs for treatment procedures were determined based on unit costs provided by the operating room manager, and are calculated and expressed in Canadian Dollars (CAD). Total cost was based on skin substitute materials, as well as materials used to secure these dressings. Costs for operating room time, surgeon, anaesthesia and nursing staff were excluded from these calculations as these are fixed costs at our institution. Cadaveric allograft was made available through the hospital's tissue bank[redacted] dressing materials included the [redacted] glove (cost based on size) and the [redacted] 10"x15" sheet dressing. The primary outcome of interest

was the impact of choice of dressing had on operative time and operating room cost. The analysis found that there was no statistically significant difference in overall cost and procedure time between cadaveric allograft and [redacted]. The absolute difference in cost between the procedures was [redacted], with cadaveric allograft being the more expensive dressing. When standardised by %TBSA treated, cadaveric allograft was found to be statistically significantly associated with higher cost compared to [redacted]. The average cost per minute per %TBSA excised with cadaveric allograft was [redacted] compared to just [redacted] for [redacted] ($p = 0.002$).[29]

5.5 LIMITATIONS

It is acknowledged that there were limitations in this review and these should be considered when interpreting the results. The selection of the studies and appraisal was done by one reviewer. Although there was no restriction in language during the search, only the full-text articles in English published in peer-reviewed journals were included in the report, which may have excluded some relevant articles and further limited our study numbers. Above all, most studies included in this review were observational studies and few had small number of participants which could limit its validity.

6.0 CONCLUSION

Based on the review, highly limited evidence found that the use of human skin allograft may be effective in terms of patient survival and inpatient mortality for patients with major burns. Its use was considered safe through the pathway of the skin bank. Very limited evidence showed its use for burn patients was associated with higher cost compared to other skin substitutes but can be cost-effective depending on the willingness-to-pay thresholds.

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8.0 APPENDIX

APPENDIX 1: LITERATURE SEARCH STRATEGY

Database: Ovid MEDLINE(R) ALL <1946 to March 03, 2023>
Search Strategy:
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1 Burns/
2 burn*.tw.
3 Allografts/
4 (allogeneic adj1 graft*).tw.
5 (allogeneic adj1 transplant*).tw.
6 allograft*.tw.
7 homograft*.tw.
8 (homologous adj1 transplant*).tw.
9 dermoplast*.tw.
10 (skin adj1 grafting*).tw.
11 (skin adj1 transplantation*).tw.
12 human skin allograft.tw.
13 Cadaver/
14 cadaver*.tw.
15 corpse*.tw.
16 Skin/
17 Skin.tw.
18 Human cadaveric skin.tw.
19 Skin Transplantation/
20 1 or 2
21 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
22 20 and 21

APPENDIX 2: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS

DESIGNATION OF LEVELS OF EVIDENCE

I	Evidence obtained from at least one properly designed randomized controlled trial.
II-I	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 3: EVIDENCE TABLE

Evidence Table : Effectiveness / Safety
Question : Is Human Skin Allograft effective/safe for burns?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up	Outcome Measures/ Effect Size	General Comments
1.Paggiaro AO, Bastianelli R, Carvalho VF et al. Is allograft skin, the gold-standard for burn skin substitute? A systematic literature review and meta-analysis. J Plast Reconstr Aesthet Surg. 2019;72(8):1245-1253.	**Systematic Review and Meta-Analysis** Aim: To perform a systematic literature review and meta-analysis on studies that compared AS to other skin substitutes or therapies, in the treatment of burn patients. Methods: -Systematic search was performed in these databases; Web of Science, Scopus, EMBASE, and PubMed. -Articles published until May 2018 were included in the database search. -randomized clinical trial (RCT) or nonrandomized clinical trial (NRCT) when comparing AS to another skin substitute in the treatment of burns were included -Selected only studies in which skin allograft was used as a temporary coverage for partial- and full-thickness burns. -In partial-thickness burns, studies used skin allograft to simulate wound healing (reepithelization), and in deep burns, it was used as a mechanism of wound bed preparation to increase autograft integration or as a “sandwich”on	I	18 trials using human skin allograft for burn patients: 12 RCTs 6 NRCTs - 13 studies used it for for wound bed preparation or cover autografts (sandwich technique) to in-crease integration. - 5 studies had studied the effect of human skin allograft to stimulate wound healing (re-epithelization) on partial- thickness burns. - 1 study evaluated both aspects in dif-ferent kinds of patients (partial- and full-thickness burn pa-tients).	Human Skin Allograft	Other skin substitutes	Varied widely. Some followed up to 14 days, some up to 2 years.	**Outcome –healing:** Meta-analysis showed no statistically significant difference between skin allograft group and other skin substitutes group (RR 0.8, 95% CI: 0.61, 1.26) **Outcome –graft take percentage:** Meta-analysis showed no statistically significant difference between skin allograft group and other skin substitutes group (mean difference -1.27, 95% CI: -6.47, 3.93) **Outcome –scar appearance:** No meta-analysis can be done. No statistical difference in hypertrophic scar formation, between groups **Outcome –mortality:** No meta-analysis can be done. Two studies were self-controlled, with the intervention and control being performed on the same wound. Mortality cannot be related to any treatment, as the patient receives both. Only 1 study and reported 0% mortality (0/16), while in the group receiving sulfadiazine, there was 23% mortality (3/13)	Studies included were of high risk of bias, small sample studies

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	the autografts to stimulate autograft take were included.							

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Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up	Outcome Measures/ Effect Size	General Comments
2. Azizian M, Ghasemi Darestani N, Mohammadzadeh Boukani L, et al. The effectiveness of skin allografts in survival rate of patients with major burns. Int J Burns Trauma. 2022;12(2):45-51	Case-control Study Aim: To evaluate and report the outcomes of skin allograft on burn patient survival in Iran. Methods: -Data on burn patients who underwent skin allografts was extracted from the hospital information system between July 15, 2017 and April 27, 2021. -Cases: allograft surgery performed 219 times on 112 patients. Control: patients admitted to the burn ward who were not undergoing skin allografts. This group was matched with the case group in terms of sex, age, and percentage of burns. -outcome of the study: duration of hospitalization and status of patients at discharge (alive, deceased) -Except for the use of allografts, other therapeutic measures such as initial resuscitation, nutrition, wound care, and indications for the use of the burn intensive care unit were performed similarly in the two groups.	II-2	Cases: 112 patients Control: 224 patients Matching for sex, age (5-year interval), and burn percentage (10% interval) Baux score similar in both. 77 in cases, 78 in control.	Allograft	Control -wihout allograft		**Results:** -Length of hospital stay in the case group (41.13±11.7) was considerably longer than the control group (24.6±12.1) (P<0.001), -Mortality rate in the two groups was not statistically different (P=0.633). -Average survival time of case group (53 days, 95% CI=45-56) was higher than the control group (49 days, 95% CI=39-58) (P=0.012). -Number of allograft usage (OR=0.038, 95% CI=0.142-0.945) and also Age (OR=1.03, 95% CI=1.005-1.070) were predictors of death.	

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Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up	Outcome Measures/ Effect Size	General Comments
3. Megahed MA, Elkashity SA, Talaab AA et al. The Impact Of Human Skin Allograft As A Temporary Substitute For Early Coverage Of Major Burn Wounds On Clinical Outcomes And Mortality. Ann Burns Fire Disasters. 2021;34(1):67-74.	Clinical Trial **Aim:** To evaluate the application of skin allograft as a skin substitute used for coverage of major deep burn wounds, and its effect on the clinical outcome of the patients. **Methods:** - Involved 36 patients who were admitted to the burn unit from August 2016 to November 2019. - Inclusion criteria included: major deep burn more than 25% TBSA with limited donor site for autograft coverage	II-3	36 patients: Divided to 3 groups: -Group I (9 patients and mean burn percentage of 37.42% TBSA, in whom burn debridement was done without allograft coverage as it was not available. -Group II (15 patients with mean burn percentage of 28.68% TBSA, in whom allograft source was discarded skin of body contouring operations from unrelated patients. -Group III (12 patients with mean burn percentage of 33.55% TBSA, in whom allograft was harvested from a first-degree relative	Human Skin Allograft	No comparison	32days post surgery	Patients that needed auto-grafting after surgical intervention: 9 (100%) in Group I, 13 (86.66%) in Group II and 8 (66.7%) in Group III. Patient survival: 55.6% in Group I, 86.7% in Group II and 91.7% in Group III. Significant difference between the groups regarding time to complete healing, with: 30.54 ± 2.54 days in Group I, 26.35 ± 6.46 days in Group II, and 18.65 ± 8.67 days for Group III ($P<0.05$).	

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Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up	Outcome Measures/ Effect Size	General Comments
4.Sheckter CC, Goverman J. Reply: The impact of skin allograft on inpatient outcomes in the treatment of major burns 20-50% total body surface area - A propensity score matched analysis using the nationwide inpatient sample. Burns. 2019;45(6):1487-1488.	Case-Control Study **Aim:** To evaluate clinical outcomes associated with allograft, and determine whether allograft impacts inpatient length of stay and total cost of care. **Methods:** -Discharge data from the Nationwide Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality assessed 3557 major burn patients (>second degree depth and 20–50% TBSA) undergoing operative treatment. -Outcomes were evaluated with propensity score matching. -Primary outcome was mortality with secondary outcomes including complications, length of stay, total burn operations, and charges.	II-2	771 allografted patients were paired with 1774 controls -matching ratio was set at minimum 1:1 using greedy nearest-neighbor selection with replacement	Treatment group consisted of all patients who received allograft placement,	the control group consisted of all patients who received operative burn treatment without allograft placement.	-	Results: **Mortality**: Significant increase in mortality for patients receiving allograft, with an average treatment effect (ATE) of 2.8% (95% CI 0.2–5.3%, p=0.041) -Stratifying by Abbreviated Burn Severity Index (ABSI), overall mortality increase associated with allograft was only present in the higher ABSI group (i.e.>10), with a 9.2% increase (95% CI 1.0–17.3%, p=0.028) -The ABSI <5 cohort yielded an insignificant mortality decrease of -1.3% (95% CI:2.8–0.1%, p=0.078), and the ABSI 6–9 cohort showed an insignificant mortality increase of 0.7% (95% CI: 1.8– 3.3%, p=0.541). **Secondary outcomes:** Use of allograft was associated with a significantly longer **length of stay** by 8.4days (95% CI 6.1– 10.7, p<0.001), more **total burn operations** by 1.6 operations (95% CI 1.4–1.9, p<0.001), **higher charges** at $139,476 (95% CI $100,716–$178,236, p<0.001), and **greater composite PSI score** at 0.13 (95% CI 0.07–0.20, p<0.001). The secondary outcomes were all significantly higher in the allografted group regardless of ABSI stratification.	

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Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up	Outcome Measures/ Effect Size	General Comment
5.Choi YH, Cho YS, Lee JH et al. Cadaver skin allograft may improve mortality rate for burns involving over 30% of total body surface area: a propensity score analysis of data from four burn centers. Cell Tissue Bank. 2018;19(4):645-651.	Case-Control Study **Aim:** To analyze the effect of cadaveric skin allograft on mortality rates in patients with burns involving >30% of total body surface area (TBSA). **Methods:** **-**Retrospective review of 1282 patients with >30% of TBSA burned admitted to four hospitals in Korea between June 1, 2008 and December 31, 2016 were conducted. - 698 patients underwent cadaver skin allograft (cadaver group), and 584 were treated with conventional treatment (noncadaver group) - propensity score matching generated 474 propensity score-matched pairs -Primary outcome of interest was in-hospital mortality	ıI-2	1282 burn patients: 698 cadaver group 584 non-cadaver group 474 propensity score matched pairs	Human Skin Allograft	Conventional treatment without human skin allograft	90 days	**Results:** **In-hospital Mortality** -Significant difference in 90-day in-hospital mortality between groups for both unmatched [cadaver vs. conventional, 31.7 vs. 39.7%; difference, 8.0; 95% confidence interval (CI) 2.8–13.3] and propensity matched groups (37.8 vs. 47.3%; difference, 9.5; 95% CI 3.2–15.8). -Logistic regression showed significant association between cadaver skin allograft and lower 90-day in-hospital mortality in the propensity-matched groups (odds ratio, 0.42; 95% CI 0.29–0.62).	

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Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up	Outcome Measures/ Effect Size	General Comment
6.Kitala D, Kawecki M, Klama-Baryła A et al. Allogeneic vs. Autologous Skin Grafts in the Therapy of Patients with Burn Injuries: A Restrospective, Open-label Clinical Study with Pair Matching. Adv Clin Exp Med. 2016;25(5):923-929	Cross-sectional study **Aim:** To determine how the use of allografts improves the conditions for the intake of autografts in burns treatment, and how it accelerates wound healing in comparison to the autografts-only option. **Methods:** - 2012-2013, allogeneic skin was grafted on 46 patients - autologous split-thickness skin graft was applied to 32 patients -Outcomes: relationship between the duration of hospitalization and the number of skin transplantations, the relationship between the time of admission to debridement of the necrotic tissues and the total duration of hospitalization.	III	46 patients received allogeneic skin 32 patients received autologous split thickness skin graft	Allograft	Autologous split thickness skin graft		**Results:** -Statistically significant difference between duration of hospitalization in the group of patients who underwent STSG graft transplantation in comparison to the group of patients who had allogeneic skin application only between 8 to 14 days from admission to the allografts' application procedure. -Length of the hospital stay was significantly longer in the group of patients who had STSG in comparison to the patients who had allogeneic skin grafts ($p < 0.05$). -No statistically significant difference between pain perception in the group of patients who underwent allogeneic skin application in comparison to that of the group of patients who were grafted with autologous skin	

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Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up	Outcome Measures/ Effect Size	General Comments
7.Chua A, Song C, Chai A et al. Use of skin allograft and its donation rate in Singapore: an 11-year retrospective review for burns treatment. Transplant Proc. 2007;39(5):1314-1316.	Cross-Sectional Study **Aim:** To ascertain the current state of skin allograft transplantation in Singapore **Methods:** -Data of burn patients were obtained from admission records of the SGH Burns Centre from 1993 to 2003. -Clinical profiles of burn patients with deep dermal to full-thickness burns and TBSA of at least 40% were recorded in SPSS for Windows, Version 10.1 including age, sex, and TBSA. -Mortality rate (MR) and LOS were compared for burn patients admitted between the pre–skin-banking (1993 to 1997) and post–skin-banking periods (1998 to 2003).	III	102 burn patients 1993 to 1997: 44 patients 1998 to 2003: 58 patients	Skin allograft -cadaveric	Compare 1993 to 1997 vs 1998 to 2003	11 years review	Mortality: There was no significant reduction for MR but LOS was significantly reduced by 15.7 days (pre-skin-banking period 61.3 ±27.8 versus post skin-banking period 45.6 ± 25.1, P = 0.028).	

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Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up	Outcome Measures/ Effect Size	General Comment
8.Khoo TL, Halim AS, Saad AZ et al. The application of glycerol-preserved skin allograft in the treatment of burn injuries: an analysis based on indications. Burns. 2010;36(6):897-904.	Cross-Sectional Study **Aim:** To analyse the experience of skin allograft application and its efficacy in treating burned patients according to indications in the burn-care facility. **Methods:** - All burned patients admitted and treated in the burn centre of the Hospital Universiti Sains Malaysia and had been treated with skin allograft from Oct 2001 to May 2008**.** **-**Patients categorised based on indication -profile; TBSA and depth of burn; operation; and outcomes such as percentage of autograft take, duration of wound healing, length of hospital stay and mortality rate were analysed	III	477 burn victims: 43 managed with human skin allograft - overall mean age was 23.3 years. -Mean TBSA of burn was 28.7 ± 18.5%, ranging from 3% to 70%. -Burn most commonly secondary to flame burn (55.8%), followed by hot water scalds (27.9%), chemical burn (2.3%), electrical burn (2.3%) and others (11.6%). -29 patients: wound bed preparation -9 patients: sandwich technique -5 patients: definitive dressing	Human skin allograft	No comparison		**Results:** **<u>Human skin allograft as GPA as skin substitute in wound-bed preparation:</u>** Complete wound healing- 38.7 ± 18.0 days, ranging from 19 to 78 days. Length of hospital stay: averaged 42.9 days. Mortality rate: 41.1%. These patients sustained severe burns with mean TBSA of 49.6%. Most common causes of death were sepsis and acute respiratory distress syndrome. **<u>Sandwich grafting technique:</u>** Mean autograft take 74.4%. Complete wound healing- Four patients (44.4%) who had complete wound healing after the sandwich technique; another four patients required repeat autografting. Average duration of healing: 48.9 days, Mean length of hospital stay: 65.5 days. 8 patients recovered. 1 patient (11.1%) died due to sepsis **<u>Definitive dressing in partial-thickness burn:</u>** 5 patients with superficial partial-thickness burn (average 10% TBSA) Complete wound healing- 4 patients, average 19 days without further surgical intervention, 1 patient lost to follow-up. Mean length of hospital stay was 16.6 days. No mortality in this group of patients.	

Evidence Table : Effectiveness / Safety
Question : Is Human Skin Allograft effective/safe for burns?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up	Outcome Measures/ Effect Size	General Comment
8. Khoo TL, Halim AS, Saad AZ et al. The application of glycerol-preserved skin allograft in the treatment of burn injuries: an analysis based on indications. Burns. 2010;36(6):897-904.							**Safety:** -Wound swab cultures from burn wounds, when allograft rejected: positive for bacterial growth in 32 patients (74.4%) Positive culture results not significantly different between those admitted within 24 h of injury and those admitted after 24 h of injury (71.4% vs. 80.0%; p-value was 0.719). -When used for wound-bed preparation and sandwich grafting, the cultures were positive in 79.3% and 88.9% cases, respectively. -Only one patient was positive for culture when applied as definitive dressing. -Most common organisms isolated were Pseudomonas sp., followed by mixed growth, Acinetobacter sp., Enterobacter and methicillin-resistant Staphylococcus aureus -Adherence to the wound bed was significantly shorter (7.9 days) when the wound cultures were positive as compared to negative culture (11.1 days)(p = 0.009). -Percentage of autograft take was lower when wound cultures were positive (81.9% vs. 88.3%) but not statistically significant. -Complete wound healing was achieved later if the wound cultures were positive (39.5 days vs. 29.3 days) but not statistically significant.	

Evidence Table : Effectiveness / Safety
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Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up	Outcome Measures/ Effect Size	General Comment
9. See P, Phan TT, Chua JJ, Song C, Tan KC, Lee ST. Our Clinical Experience using Cryopreserved Cadaveric Allograft for the Management of Severe Burns. Cell Tissue Bank. 2001;2(2):113-7.	Cross-sectional study **Aim:** To describe early clinical experience with cryopreserved cadaveric allograft in treating extensive burn wounds **Methods;** - 17 patients with extensive thermal injury were admitted between January 1998 and July 2000 to Burns Centre at the Singapore General Hospital - Cryopreserved cadaveric allografts were used on patients who sustained burn injuries of more 30% of their BSA. -All patients were given fluid resuscitation, assessed for the past underlying medical problems and examined for concomitant injuries.	III	12 men and five women. -average age at the time of injury was 31 years (range 19–48 years) and the average BSA burned were 58% (range 33–90%). -average full thickness - burns was 48% (range 21–80%). -All the burn injuries were caused by flames.	allograft			**Results:** -The average amount of cryopreserved cadaveric allograft grafted on 17 severely burned patients was 13% BSA (range 3–30%). -Active intervention involving early excision and allografting were carried out within 72 h after admission. -The allografts achieved good adherence rate of 70% at one week post-operation. -Clinical indicators were manifested by intact, stable graft with no signs of infection and graft breakdown. -30% cadaveric allograft suffered from graft loss due to infection and excessive bleeding. -Seven patients had recovered from their burn injury and ten died. Those patients who died had overwhelming sepsis, which made mortality expected and unavoidable. Eight patients who died had complications of inhalation injuries.	

Evidence Table : Effectiveness / Safety
Question : Is Human Skin Allograft effective/safe for burns?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up	Outcome Measures/ Effect Size	General Comment
10. Eldad A, Din A, Weinberg A, et al. Cryopreserved cadaveric allografts for treatment of unexcised partial thickness flame burns: clinical experience with 12 patients. Burns. 1997;23(7-8):608-614.	Cross-sectional study **Aim:** To compare the use of 'old cryopreserved cadaveric skin on unexcised partial thickness burn (PTB) as a biological dressing with conservative treatment with SSD **Methods:** **-** Twelve patients with flame, patchy, PTB and SPTB areas were grafted with cryopreserved skin after mechanical debridement of the burn wound without surgical excision. **-** Allografts were cryopreserved at -180°C by programmed freezing (- i"C/min) and stored for 30-48 months (average 38 months) before use. -Matching burns for depth and area were covered with a thick layer (1 cm) SSD, one to two times daily, until healing, or until debridement and grafting were necessary -	III	Seven men and five women, with an average age of 28 years (range lo-61 years) with sustained patchy flame or Sash burns over 15-60 per cent of their body surface area (BSA) (average 40.5 per cent) and with FTB O-46 per cent (average 18 per cent) were included in this study	Cryopreserved cadaveric skin	SSD dressing		**Results:** A total of 80.4% of the cryopreserved homograft adhered (range 25-100%) and 76% of the treated areas healed with good/ very good cosmetic results within 21 days, whereas in the parallel SSD-treated burns only 40% healed within 21 days	

Evidence Table : Safety
Question : Is Human Skin Allograft safe for burns?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comment
11. Pianigiani E, Risulo M, Ierardi F et al. Prevalence of skin allograft discards as a result of serological and molecular microbiological screening in a regional skin bank in Italy. Burns. 2006;32(3):348-351	Cross-sectional study **Aim:** To report the results of serological screening and experience with exclusion criteria for donor skin in Tuscany between 2000 and 2004. **Methods:** -cadaveric donors underwent serological and molecular microbiological (polymerase chain reaction, PCR) screening at Siena Skin Bank between 2000 and 2004. - Skin specimens must be screened for transmissible agents including human immunodeficiency virus (HIV), hepatitis B (HBV) and C (HCV) virus, human T-cell lymphotropic virus (HTLV), cytomegalovirus (CMV) and Treponema pallidum.	III	461 cadaveric donors	Human skin allograft	-	-	**Results:** Of the 461 donors screened, 74 (16.1%) were rejected due to a positive finding in at least one of the microbiological assays. -Serological evidence of past or present HBV infection was detected in 68 (14.8%) 3 (0.7%), 2 (0.4%) and 1 (0.2%) cases with HCV, HTLV and HIV infection, respectively. 51 (76.5%) of the HBV-positive donors had an isolated HBcAb IgG positive reaction, though HBV DNA was only detected in one (2.0%) of them.	

Evidence Table : Safety
Question : Is Human Skin Allograft safe for burns?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comment
12.Meneghetti KL, do Canto Canabarro M, Otton LM et al. Bacterial contamination of human skin allografts and antimicrobial resistance: a skin bank problem. BMC Microbiol. 2018;18(1):121.	Cross-sectional study **Aim:** To perform a bacteriological analysis by identifying bacteria from human skin allografts and analyzing their antimicrobial susceptibility profile **Methods:** - A total of 32 batches of human skin samples procured from cadaveric donors between July 2012 to November 2014, - Microbiological analyzes are performed at all stages of the skin bank processing. If rthe considered nonacceptable microorganisms: aerobic or anaerobic Gram-negative bacilli, Gram-negative cocci, Clostridium sp., Bacillus anthracis, Streptococcus pyogenes (beta hemolytic); Staphylococcus aureus; Enterococcus sp. and filamentous fungi or yeasts, the tissue is discarded. -all 32 batches included were already discarded - The identification of the bacteria isolated from skin allografts was performed by matrix assisted laser desorption ionization–time of flight		32 batches of human skin allograft from cadaveric donors	Human skin allograft	-	-	**Results:** -21 (65.6%) skin samples were contaminated with Gram-positive bacteria: 1 (4.7%) with Paenibacillus sp., 12 (61.9%) with Bacillus sp., 6 (28.5%) with Staphylococcus sp., and 2 (9.5%) with Bacillus sp. and Staphylococcus sp. -Several resistance profiles, including multiresistance, were found among the isolates. -Most of the isolates were susceptible to at least one of the antimicrobials used in the skin bank. All isolates were susceptible to amikacin, gentamicin, and tetracycline.	

Evidence Table : Safety
Question : Is Human Skin Allograft safe for burns?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up	Outcome Measures/ Effect Size	General Comment
13.Gaucher S, Khaznadar Z, Gourevitch JC et al. Skin donors and human skin allografts: evaluation of an 11-year practice and discard in a referral tissue bank. Cell Tissue Bank. 2016;17(1):11-19.	Cross-sectional study **Aim:** To analyse reasons for skin discard. **Methods:** - all skin donors harvested between June 2002 and June 2013, representing a total of 336 donors and 2770 zones, were reviewed. -Viral contamination is assessed by serological testing of the donor - Microbiological sampling is done during skin processing:	III	336 donors -multi-organ heart beating	Human skin allograft	-	-	**Results:** All the donors were seronegative for HIV, HTLV and syphilis (TPHA and/or VDRL). One donor (0.3 %) was HCV-seropositive and therefore excluded. -HBV surface antigen (HBsAg) was not detected in any of the 336 donors, ruling out active infection. -Main reason for discarding harvested skin was microbial contamination, in 99 donors (29 %). - microbial contaminants were mostly bacteria, low pathogenicity - Other reasons for discard included positive serologic tests for 2 donors [17 zones (0.61 %)], unsuitable physical skin characteristics for 3 zones (0.11 %), the donor's medical history for 53 zones (1.91 %), and technical issues with processing or distribution for 61 zones (2.2 %).	

Evidence Table : Cost/Cost-effectiveness
Question : Is Human Skin Allograft cost-effective for burns?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comment
14. Sheckter CC, Meyerkord NL, Sinskey YL et al. The Optimal Treatment for Partial Thickness Burns: A Cost-Utility Analysis of Skin Allograft vs. Topical Silver Dressings. J Burn Care Res. 2020 May 2;41(3):450-456.	Cost-utility analysis **Aim:** To assess the incremental cost and effectiveness of skin allograft compared to topical silver dressings in the acute treatment of partial thickness burns **Methods:** - A cost-utility analysis was performed comparing skin allograft to SSD and Mepilex Ag using decision-tree analysis. -The base case modeled a superficial partial thickness 20% total body surface area burn. -Utilities were derived from expert opinion on the basis of personal experience. -Costs were derived from 2019 Medicare payments. Quality adjusted life years were calculated using rollback method assuming standard life expectancies in the US. -Probabilistic sensitivity analysis was performed to asses model robustness.		A payer perspective was adopted using 2019 Medicare reimbursements for the base case of a 20% TBSA partial thickness burn	Skin allograft	SSD and [redacted]		**Results:** -Incremental costs of skin allograft to [redacted] and SSD were [redacted] respectively. -The incremental QALY gains from allograft over [redacted] This yielded an incremental cost utility ratio (ICUR) for allograft vs. Mepilex Ag of [redacted] compared to an [redacted] for allograft vs. SSD. -Assuming willingness-to-pay thresholds of $100,000/QALY, probabilistic sensitivity analysis demonstrated that allograft was cost effective to [redacted] in 62.1% of scenarios, and cost-effective to SSD in 64.9% of simulations.	

Evidence Table : Cost/Cost effectiveness
Question : Is Human Skin Allograft cost-effective for burns?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up	Outcome Measures/ Effect Size	General Comment
15.Austin RE, Merchant N, Shahrokhi S et al. A comparison of Biobrane™ and cadaveric allograft for temporizing the acute burn wound: Cost and procedural time. Burns. 2015;41(4):749-753.	Cost analysis **Aim:** To determine cost and outcome between cadaveric allograft and biosynthetic temporary skin substitute composed of a silicone membrane and nylon mesh impregnated with porcine dermal collagen Biobrane™ **Methods:** **-** A review of the NTRACS Burn Database1 was performed for all patients admitted to the regional burn unit at a single tertiary trauma center between January 1, 2008 and December 31, 2012 was conducted. -Inclusion criteria: patients who had undergone primary excision of the burned upper extremity in the operating room, with application of either cadaveric allograft or [redacted] skin substitute. - %TBSA was documented from the Lund–Browder charts completed by the attending physician at the time of admission. -Procedure time was defined as the length of the operative procedure itself.		45 patients with upper extremity burn injuries with temporary wound coverage -The groups were comparable in regards to age, gender, length of hospital stay, and average upper extremity percentage total body surface area (%TBSA) involved.	Human skin allograft	Biobrane		**Results:** -No statistically significant difference between two groups in overall cost and procedure time -The absolute difference in cost between the procedures was [redacted], with cadaveric allograft the more expensive dressing. -Average cost per minute per %TBSA excised with cadaveric allograft was [redacted] compared to just [redacted] [redacted] (p = 0.002)	

Evidence Table : Cost/Cost effectiveness
Question : Is Human Skin Allograft cost-effective for burns?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comment
15.Austin RE, Merchant N, Shahrokhi S et al. A comparison of Biobrane™ and cadaveric allograft for temporizing the acute burn wound: Cost and procedural time. Burns. 2015;41(4):749-753.	-Costs for these procedures were determined based on unit costs provided by the operating room manager, and are calculated and expressed in Canadian Dollars (CAD). -Total cost was based on skin substitute materials, as well as materials used to secure these dressings -Cadaveric allograft was made available through hospital's tissue bank. - [redacted] dressing materials included the [redacted] glove (cost based on size) and the [redacted] 10 x 15" sheet dressing. -For patients treated with the [redacted] glove but who were missing sizing information, the unit cost of a medium sized glove was used for the purpose of data analysis.							