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ORIGINAL ARTICLE

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Biodegradable Temporising matrix in the reconstruction of complex wounds: A systematic review and meta-analysis

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Abstract

Objective: To assess the efficacy of biodegradable temporising matrix (BTM) in complex wound reconstruction.

Methods: The authors conducted a systematic review and meta-analysis as per the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines following a literature search assessing BTM in complex wound reconstruction. The primary outcome measures included the proportion of BTM integration as well as integration time. Secondary outcomes included graft take over BTM, infection rate and other complications as well as scar outcome.

Results: Twenty six studies met the inclusion criteria with a total of 1153 complex wounds. The mean proportional integration was 92.7% at (95% confidence intervals [CI] 88.57, 96.87, $p < 0.001$) with a mean integration time of 34.05 days (95% CI 33.33, 34.79, $p < 0.001$). The infection rate was low at 12.6% with an untransformed proportion metric assessment (0.126, 0.08–0.168, $p < 0.001$) at the site of BTM application. Favourable scar outcomes were reported using the matching assessment using photographs with scars (MAPS) and patient and observer scar assessment scales (POSAS).

Conclusion: BTM offers a robust dermal template in reconstruction of complex wounds. The authors recommend for randomised controlled trials to enhance the current evidence base.

George Lane and Niall Fitzpatrick contributed equally to this study and are equal first authors. They both take responsibility for this manuscript.

KEYWORDS
biodegradable temporising matrix, complex wound, dermal substitute

Key Messages

- BTM is a robust dermal template in complex wound reconstruction.
- The goal was to perform a systematic review and meta-analysis assessing the efficacy BTM in complex wounds.
- BTM has a high proportion of take in hostile wound beds with a low infection rate. BTM offers favourable scar outcome.

1 | INTRODUCTION

Biodegradable temporising matrix (BTM) is a synthetic dermal substitute constituted by a polyurethane foam utilised to reconstruct complex wounds. It possesses a fenestrated polyurethane seal acting as a pseudo-epidermis which allows egress of fluid[1] but concomitantly minimises fluid losses and scar contraction.[2] It has been used in complex wounds in many different settings for reconstruction including burns,[3] necrotising fasciitis,[4] bone denuded of periosteum,[5] tendon without paratenon[6] and pressure ulcers.[7]

BTM is used as a two staged reconstructive technique after initiating angiogenesis with subsequent application of a skin graft once the dermal component has biodegraded.[2] This is primarily by hydrolysis[2] with no toxic substance generation.[1] The initial phase involves a thorough debridement of the wound bed and a template cut to fit the defect that can be affixed with either suture material or staples. The sealing membrane is faced externally and removed at the second stage of delamination at which point the neodermis can be refreshed and a skin graft applied.[8,9]

BTM's increasing role as part of the surgeon's armamentarium has led to numerous reports within the literature depicting its outcomes.[1,2,5,7,10–12]

The authors' aim to perform a comprehensive systematic review and meta-analysis of the literature with an outcomes synthesis to enhance the current evidence base for this dermal substitute.

2 | METHODS

This systematic review and meta-analysis was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement standards.[13]

2.1 | Eligibility criteria

All studies including randomised, non-randomised trials, observational studies and case series with at least five patients were included assessing the efficacy of using BTM in complex wound reconstruction. A complex wound was defined as one that had exposed critical structures like bone or tendon, those caused by necrotising infections or deep burns and wound beds where split thickness grafts were not usually considered. More specifically Ferreira,[14] depicted a complex wound as one that came under the following categories, which, the authors adopted:

1. Extensive loss of the integument in acute or chronic wounds
2. Infection, as a complication in chronic wounds
3. Necrosis and compromised viability of surrounding tissue or signs of circulation impairment
4. Systematic pathologies that impair normal wound healing (e.g., diabetes, vasculitis or immune suppression).

In accordance with the aforementioned criteria, wounds included as part of the review consisted of deep burns, full-thickness wounds in the lower extremity, diabetic ulcers, pressure ulcers, chronic venous ulcers, as well as wounds following extensive necrotic processes caused by infection and those of ischaemic aetiology. Studies with no adult patients, those not reported in English, animal studies as well as those with fewer than five patients were all excluded. There was no restriction on patient comorbidities, wound aetiology or type of exposed structure on which BTM templates were applied over. A summation of the inclusion and exclusion criteria is given below.

2.2 | Inclusion criteria

1. BTM application in any complex wound reconstruction: full thickness or deep burns, complex lower/upper limb wounds with exposed muscle/bone/tendon, chronic wounds, pressure ulcers as well as diabetic wounds and those post debridement of infective and ischaemic aetiologies
2. Randomised or non-randomised trials or any observational/cohort study/case series
3. Minimum patient number of five

2.3 | Exclusion criteria

1. Studies with no adult patients
2. Studies with less than five patients
3. Animal/in-vitro/in-vivo studies
4. Individual case reports
5. Letters to the editor
6. Abstracts
7. Unpublished data
8. Review articles
9. Book chapters

2.4 | Outcome measures

The primary outcome measures included proportion of BTM integration as well as BTM integration time. BTM integration was reported as a percentage proportion of the wound surface area overall to which it was implanted to as well as the proportion of devices integrated relative to the total patient population within the different studies. Integration is routinely assessed clinically by checking for blanching on digital pressure as well as observing a uniform pink colouration.[10] The secondary outcomes included the percentage graft take over BTM, infection rate as well as other miscellaneous device related complications and scar appearance using matching assessment using photographs with scars (MAPS) and patient and observer scar assessment scale (POSAS) scores.

2.5 | Literature search strategy

Two authors (GL and SR) independently searched the electronic databases including Google Scholar, Pubmed, MEDLINE, Embase, CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL). The last search was performed on 9th of July 2024. The search terminologies included "biodegradable temporising matrix" or "BTM," "Novosorb," "complex wounds," "burns," "tendon," "bone," "diabetic foot ulcers," "pressure ulcers," "chronic wounds," and "necrotising infection." These search terms were chosen to comprehensively cover all relevant conditions and applications for BTM in wound care and reconstruction. The bibliographic lists of relevant articles were also screened to maximise search retrieval.

2.6 | Selection of studies

The titles and abstracts of the studies retrieved from the literature were independently assessed by two authors GL and SR. All articles that met the eligibility criteria were selected and the full texts of the articles were reviewed. Any discrepancy in selection was discussed with third author NF.

2.7 | Data extraction and management

An electronic data extraction spreadsheet in line with the Cochrane's data collection form for intervention was created. A pilot test was performed with the spreadsheet extracting data from articles selected and adjusted accordingly.

2.8 | Data synthesis

The authors conducted a meta-analysis for outcomes reported by at least three studies. The mean was used for measurement of continuous data and the untransformed proportion (PR) metric for all dichotomous data in a single group. The odds ratio (OR) was used as a summary measure for dichotomous variables in two groups. OpenMetaAnalyst software was instigated for data synthesis. The outcomes were reported in forests plot with 95% confidence interval (CIs).

The heterogeneity was assessed using the Cochran Q test (χ^2), which measures the degree of variation in the effect estimates from the different studies. The inconsistency was further quantified by calculating I^2, and this was interpreted as follows: 0%–25% (low heterogeneity), 25%–75% (moderate heterogeneity) and 75%–100% (considerable heterogeneity), indicating the proportion of variation across studies. For outcomes where the heterogeneity was high this was circumvented by adaptation of a random effects model or an inverse variance function. These statistical functions are conducted to account for scenarios when it is elevated and equates for any discrepancies in outcomes in the overall effect estimate.

2.9 | Sensitivity analyses

A sensitivity analysis was performed to assess the robustness of using BTM in wounds inherently more predisposed to infection despite thorough debridement. This included diabetic foot wounds, those produced from necrotising fasciitis as well as chronic wounds, pressure ulcers and any other previous infections or those with ischaemia. Diabetic patients in particular often suffer from neuropathy and can develop more profound infections before they are identified.[15] Endothelial dysfunction compromising vascularity as well as hyperglycaemia inhibiting a chemotaxic response all enhance the risk of

infection in diabetic cohorts.[15] In wounds with pre-existing necrotising fasciitis that have been debrided, there has still been a reluctance with the application of dermal substitutes for reconstruction due to the risk of infection.[4,16] The authors therefore conducted a sensitivity analysis to evaluate the infection rate when using BTM in diabetic wounds post debridement, those with a background of necrotising fasciitis as well as any chronic wounds or pressure ulcers and those with any previous infections or ischaemia. This would enable an assessment of the robustness of BTM in withstanding wound beds where the risk of infection is higher. The authors determined wounds pre-disposed to infection as those which were at increased risk and defined them in accordance with the below criteria:

1. Diabetic wounds
2. Chronic wounds
3. Previous infection
4. Pressure ulcers
5. Post debridement of necrotising fasciitis
6. Ischaemic injury

2.10 | Methodological quality and risk of bias

The methodological quality and risk of bias was evaluated using the Newcastle Ottawa scale for all observational studies.[17] This uses a star scoring system with a maximum total score of nine for each study. The score is calculated by awarding stars based on specific criteria within the three domains, with up to four stars for selection, two for comparability, and three for exposure. In each domain there are clear criteria for each star. A study with more stars is considered to have met more of the criteria for good methodological quality.

3 | RESULTS

3.1 | Literature search results

One hundred and eighty nine articles were identified with 26 meeting the inclusion criteria (Figure 1).

3.2 | Primary outcomes

3.2.1 | Proportion of BTM integration

Nine studies in total homogenously reported on the percentage of BTM integration during complex wound reconstruction with a mean rate of 92.7% take. This was the proportion of BTM integration as a percentage of the wound surface area overall to which BTM was implanted to and incorporated 502 wounds in total as shown in Figure 2. This was the point at which the BTM template had fully healed and successfully integrated into the wound bed and is normally assessed clinically for blanching on digital pressure as well as observing for a uniform pink colouration.[10] Heterogeneity was considerable but this was circumvented with adaptation of a random effects model. All studies reported good percentage integration rates on average. Wagstaff[16] had a 100% BTM integration rate over flap donor sites and although Lo; 88.6%,[2] as well as Greenwood; 88.4%[1] reported slightly lower percentage integration rates, wound aetiology was different. Both these studies reported on burn wounds with Lo[2] reporting a sizeable average area of 2137.8 cm^2 to which BTM was applied. Wagstaff[4] had a comparable average integration percentage of 99.8% to their previous 2015 study[16] as included within this analysis. All wounds again were flap donor sites. The overall average integration percentage for the nine studies incorporating the different wound types was very high at 92.7% during the analysis which also accounted for devices that had failed. Failures of BTM integration as part of the data synthesis are summarised below in table format (Table 1).

Eight other studies also reported on BTM integration but did so as the proportion of devices integrated in relation to the total population of patients within the study. Schlottman[7] recorded a high rate of BTM take amongst their patient cohort at 75% as did Austin[18] with a 97.8% success rate whilst Kuang[19] had complete wound healing in all 14 cases of BTM application with all devices successfully integrated. Wu[20] identified an integration success rate of 60.8% in patients. Chen[21] reported good BTM take in 33 out of 37 patients to which it was applied (89.2%) and Devine[22] identified 10 in 12 cases where BTM had integrated. Guerriero[23] had success with BTM in 15 out of 23 cases (65.3%) where it was implanted, these were all diabetic patients however. Kidd[24] reported successful integration in 70.3% of cases.

3.3 | BTM integration time

A cumulative synthesis of BTM integration time prior to skin graft application was calculated from 16 studies with a total of 709 wounds reporting this homogenously (Figure 3). The mean length of time was 34.05 days at a 95% confidence interval (33.326, 34.785), with an inverse variance function to account for considerable

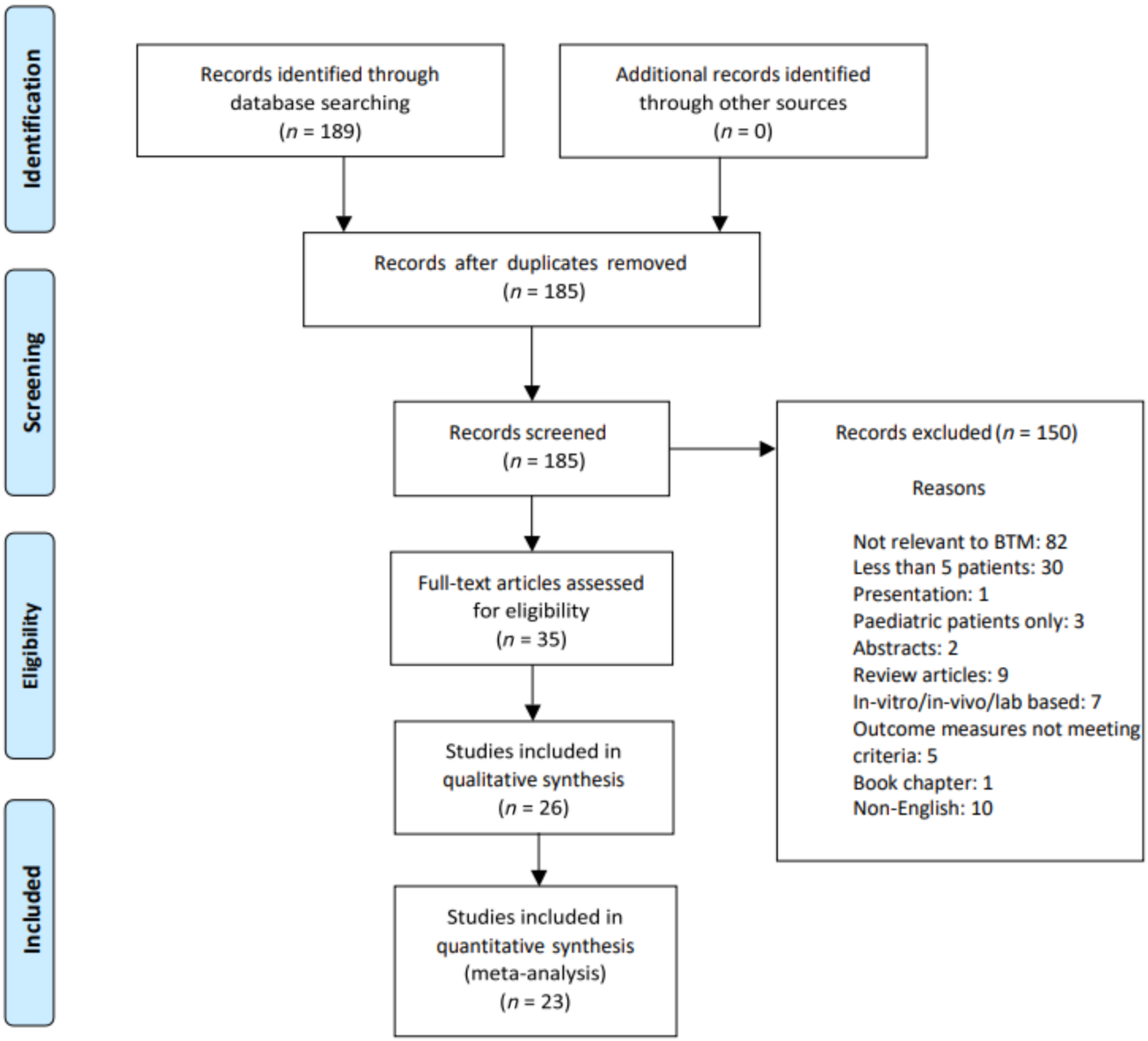

FIGURE 1 Preferred reporting items for systematic review and meta-analysis (PRISMA) flow chart illustrating article screening and selection.

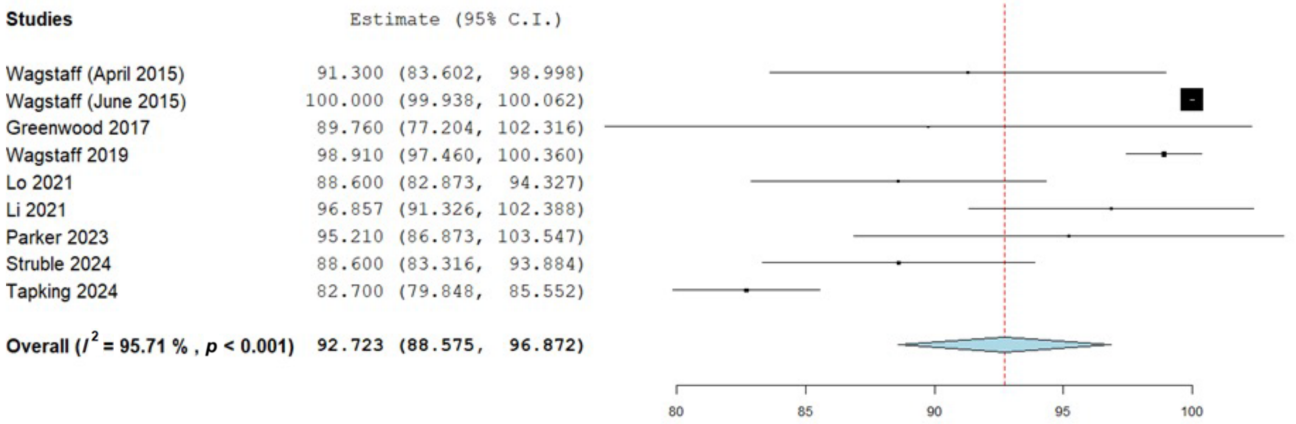

FIGURE 2 Percentage proportion of biodegradable temporising matrix (BTM) integration overall with a mean analysis; 92.7 (88.57, 96.87) standard error 2.117, $p < 0.001$.

heterogeneity. This was the time taken for the BTM template to fully integrate into the host wound bed prior to second stage skin graft application. The mean integration times ranged from 27.7[25] to 83 days.[26] A further analysis was conducted to compare integration times dependant on the wound bed type to evaluate any differences. Six studies homogenously reported the integration time of BTM applied to exposed bone comparing it against other wound bed types (Figure 4) which included tendon as well as neurovascular structures, fascia, fat, muscle, perichondrium, granulation tissue, submandibular gland, testicle and cartilage.

A significant difference was seen on mean difference analysis with a slower rate of integration for BTM on bone compared to other wound bed types. Heterogeneity was neglible on the Cochrane *Q*-test giving further consistency to the outcome and suggesting BTM should be applied for longer in cases where its applied directly on to bone. A mean metric analysis for BTM integration time applied to bone overall found it to be an average of 40.7 days (Figure 5).

BTM integration time on bone was also compared to tendons in 4 studies and homogenously reported. Results were found to be comparable with no significant difference seen in terms of integration times in both wound bed types (Figure 6).

A further sensitivity analysis was conducted to evaluate integration time for BTM on tendon compared to other tissues types as demonstrated in Figure 7 below with no significant differences seen. An overall analysis for time to integration on tendons was deduced at 37.4 from 4 studies (Figure 8).

TABLE 1 Summary of BTM failures as average percentage in relation to wound area and whether replaced.

Study	Number (*n*)	Average BTM failure/% (percentage of BTM in relation to wound area)	Replaced/not replaced
Wagstaff April 2015[16]	10	8.7%	Not replaced
Wagstaff June 2015[27]	10	Nil	N/A
Greenwood 2016[3]	5	13.9%	Replaced in 2 cases
Wagstaff 2019[27]	7	0.14%	Not replaced
Lo 2022[2]	26	11.4%	Replaced in 2 patients
Li 2021[5]	35	3.1%	Not replaced
Parker 2023[43]	24	2.4%	Not replaced
Struble 2024[25]	86	11.4%	Replaced in 4 cases
Tapking 2024[44]	300	6.6%	Not reported

Abbreviations: BTM, biodegradable temporising matrix; N/A, non-applicable.

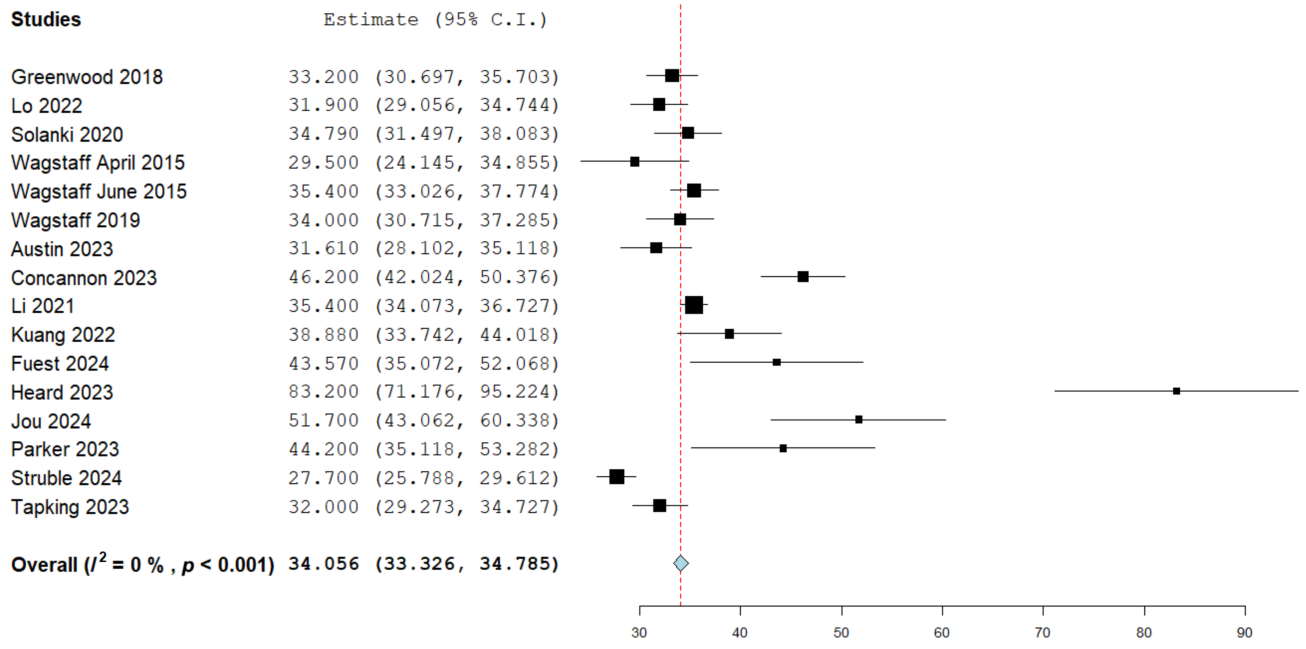

FIGURE 3 Biodegradable temporising matrix (BTM) integration (days) as analysed in 16 studies at 95% confidence intervals, mean time: 34.05 days (33.326, 34.785), standard error 0.372, $p < 0.001$.

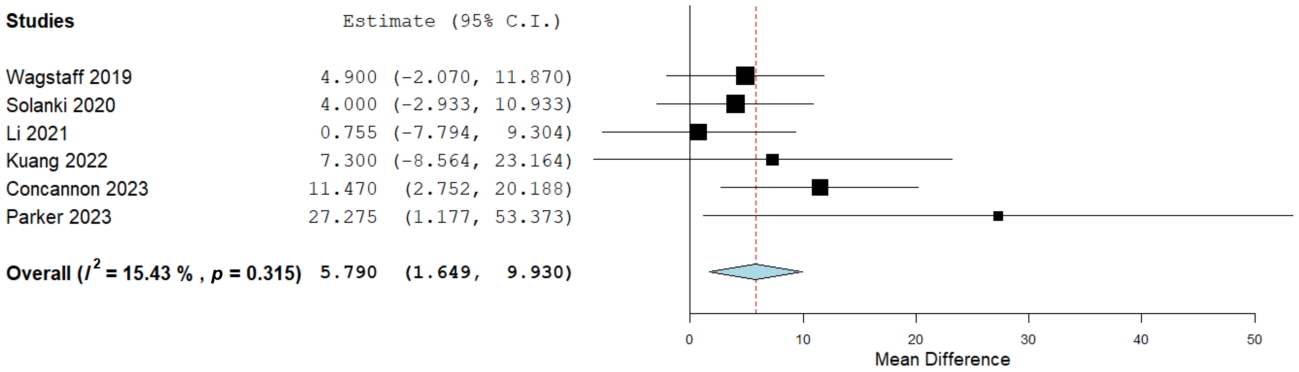

FIGURE 4 Mean difference analysis comparing biodegradable temporising matrix (BTM) integration time (days) on bone versus other wound bed types (neurovascular structures, fascia, fat, muscle, perichondrium, granulation, submandibular gland, testicle and cartilage). Mean difference: 5.790 (1.649, 9.930) $p = 0.006$.

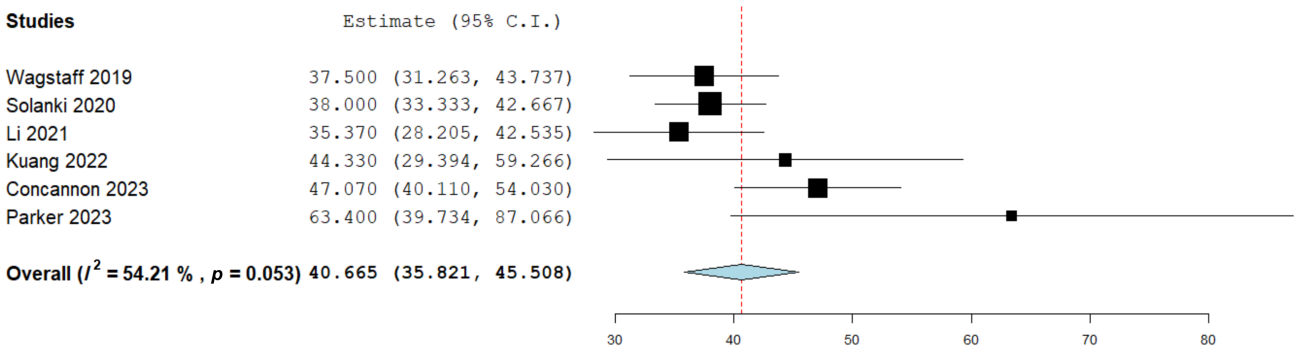

FIGURE 5 Mean analysis for biodegradable temporising matrix (BTM) integration time on bone (days): 40.665 (35.821, 45.508), standard error 2.47, $p < 0.001$.

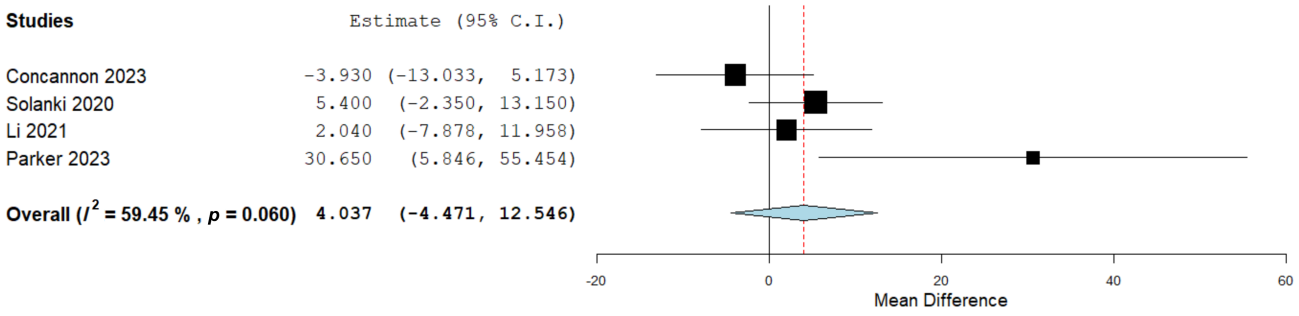

FIGURE 6 Mean difference analysis comparing biodegradable temporising matrix (BTM) integration time (days) on bone to tendon. No significant difference seen: 4.037 (−4.471, 12.546), $p = 0.352$.

3.4 | Secondary outcomes

3.4.1 | Graft take

A high percentage graft take over BTM of 98.9% was reported by nine studies with a total of 511 wounds (Figure 9). This was the proportion of take in relation to the wound surface area overall which was covered by BTM and the point at which the skin graft had successfully healed. All these wounds which were grafted had assumed successful BTM integration in the first stage and explains the high success rate. Where the BTM was not believed to have integrated, it was not grafted in those instances. All included studies within the analysis reported it homogenously with take rates seen ranging from averages of 70%[22] to 100%[4,27] across a variety of different wounds reconstructed. The analysis was conducted taking into account instances of graft failure too and the

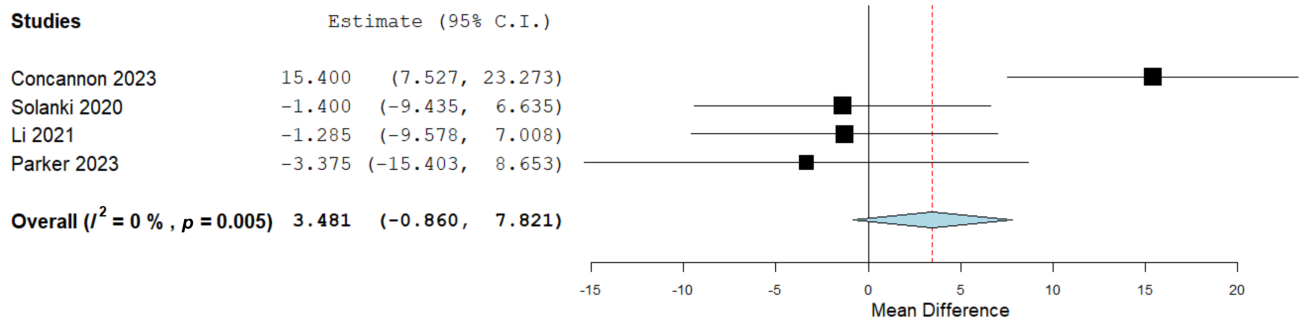

FIGURE 7 Mean difference assessment of biodegradable temporising matrix (BTM) integration time on tendon versus other soft tissues (neurovascular structures, fascia, fat, muscle, perichondrium, granulation, submandibular gland, testicle and cartilage). Mean difference 3.481 (−0.860, 7.821), $p = 0.116$.

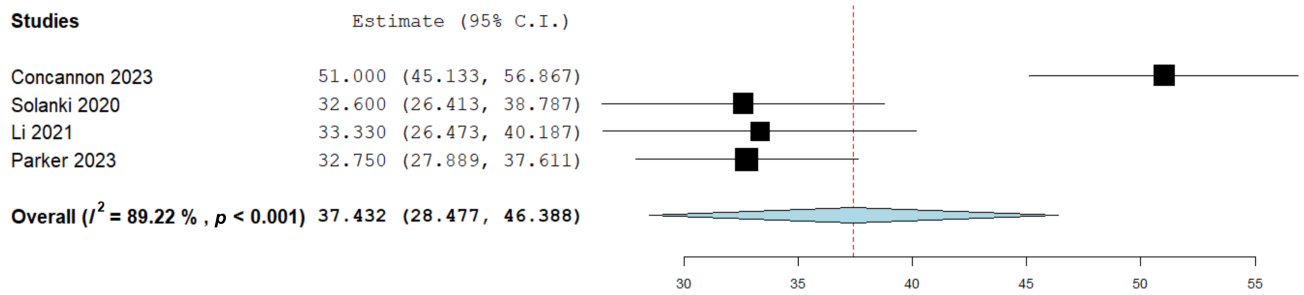

FIGURE 8 Mean assessment of average integration time for biodegradable temporising matrix (BTM) over tendons(days); 37.432 (28.477, 46.388), Standard error 4.569, $p < 0.001$.

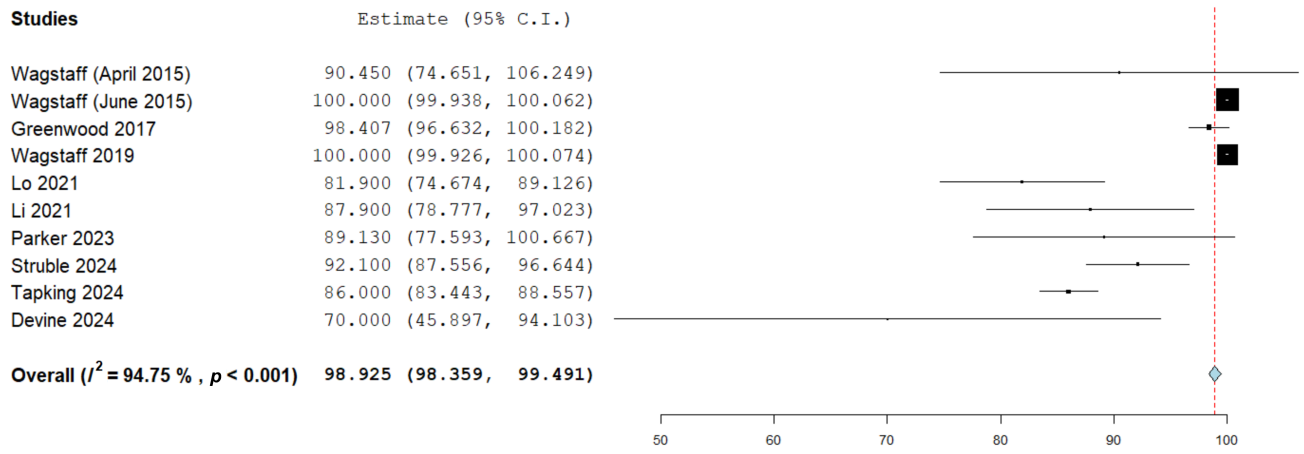

FIGURE 9 Split thickness skin graft (SSG) take over biodegradable temporising matrix (BTM) template as analysed in nine studies, mean percentage: 98.925% (95% confidence intervals: 98.359, 99.491), standard error 0.289, $p = 0.001$.

outcomes are summarised below in Table 2 in relation to these.

3.5 | Infection rate and other complications

Twenty one studies with a total of 577 wounds reported on the infection rate when applying BTM for complex wound reconstruction and an amalgamated incidence of 12.6% was reported in the outcome synthesis shown in Figure 10. Infection was defined as the presence of one or more; erythema, pain, purulence, swelling or confirmation with positive microbial swabs.

A further sensitivity analysis was conducted to assess wounds in the general population to high risk wounds predisposed to infection (necrotising fasciitis aetiology post debridement, diabetic foot wounds, pressure ulcers,

TABLE 2 Summary of average graft failure rates as percentage of area reconstructed with BTM.

Study	Number (*n*)	Average graft failure/% (percentage of graft failure in relation to wound area covered by BTM)	Regrafted Yes/No
Wagstaff April 2015[16]	10	9.6%	Yes: 1 case
Wagstaff June 2015[27]	10	Nil	N/A
Greenwood 2016[9]	5	0.4%	Yes: 2 cases
Wagstaff 2019[4]	7	0%	N/A
Lo 2022[2]	26	0.44%	N/R
Li 2021[5]	32	8.9%	Yes: 1 case
Parker 2023[43]	23	10.9%	Yes: 1 case
Struble 2024[25]	55	0.14%	N/R
Tapking 2024[44]	300	0.05%	N/R
Devine 2024[22]	9	6.6%	No

Abbreviations: BTM, biodegradable temporising matrix; N/A, non-applicable; NR; not reported.

any chronic wound, previous infections or wounds of ischemic aetiology). Overall, five studies reported on these two groups of patients and a comparable infection rate was identified on odds ratio assessment with no significant difference observed (Figure 11). This emphasised the robustness of BTM in hostile wound beds.

The overall infection rate for BTM in complex wound reconstruction has shown to be fairly low (12.6%, Figure 10) and in comparison to other complications that could be related to the BTM implant, such as haematomas, non-adherence as well as adhesions necessitating tenolysis, the infection rate occurred at a significantly lower incidence to these (Figure 12). This was observed on odds ratio assessment (Figure 12) where the infection rate was compared to the incidence of these other complications.

Haematomas were reported by numerous studies although of a low incidence. Austin[18] identified two in 79 wounds which were adequately drained allowing the BTM to successfully integrate. Li[5] only identified one in 35 wounds in their case series due to the patient having a fall and Concannon[10] shared a similar incidence with one report in 70 wounds. In Greenwood's[1] case series of five patients, five different sites of haematoma developed in one patient who was heparinised for dialysis following a burn injury whereas on the other hand in the study by Wu,[28] there were no reports and two in 51 within their other study in April 2022.[20] Li[5] demonstrated two cases

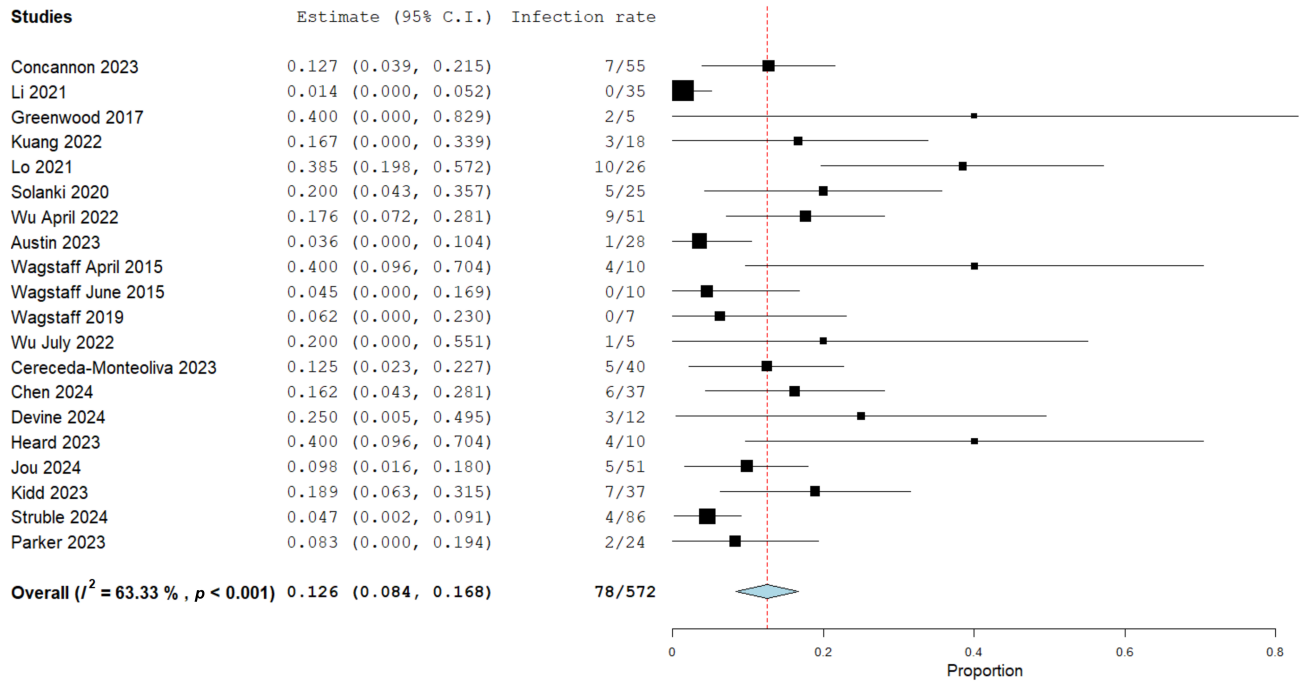

FIGURE 10 Infection rate for biodegradable temporising matrix (BTM) in complex wound reconstruction, 12.6% with an untransformed proportion metric (0.126, 0.084, 0.168), Heterogeneity, $I^2 = 63.33\%$, $p < 0.001$. Standard error 0.021, $p = 0.001$.

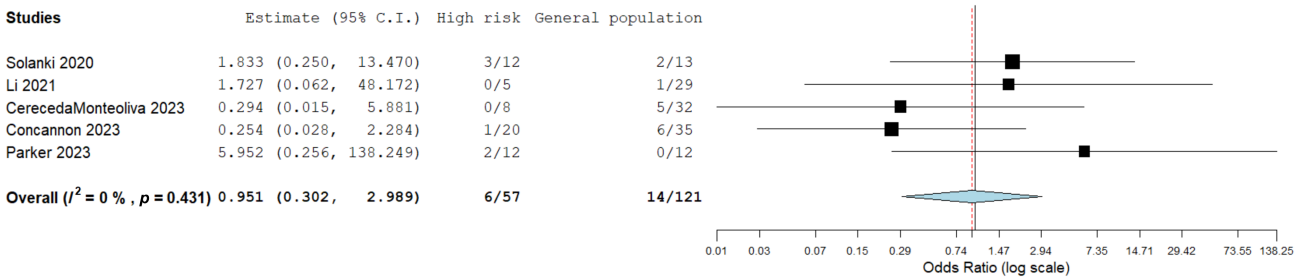

FIGURE 11 Sensitivity analysis of infection rate comparing high risk wounds (necrotising fasciitis post debridement, diabetic wounds, pressure ulcers, previous infection and any chronic or ischaemic wounds) versus those in the general population. No significant difference seen; odds ratio estimate 0.951 (0.302, 2.989), $p = 0.931$.

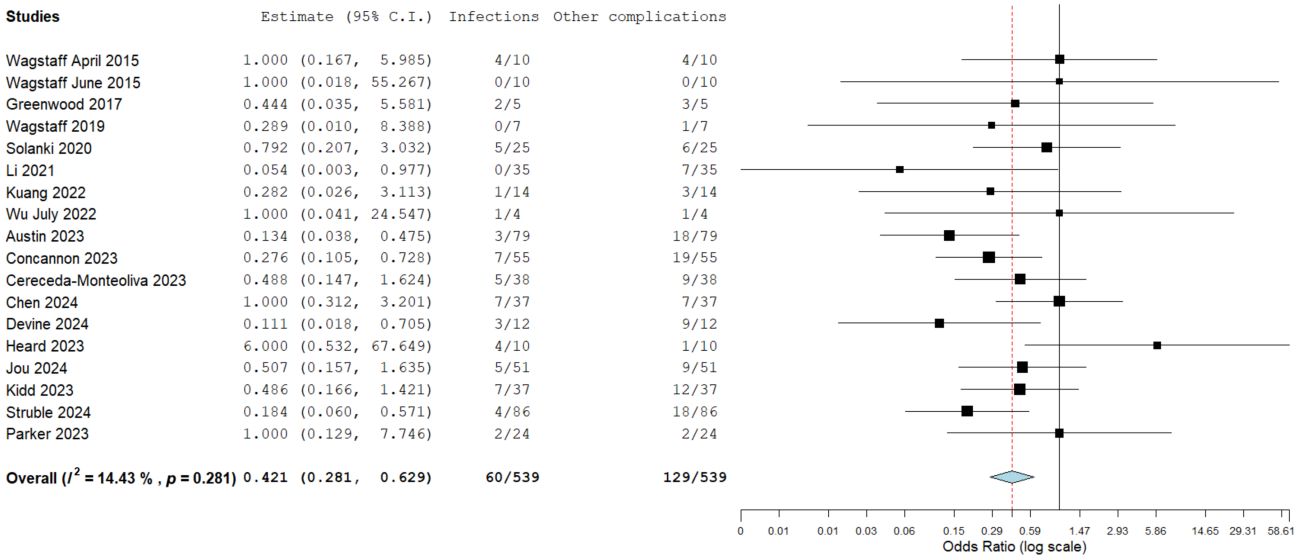

FIGURE 12 Odds ratio analysis of infection rate compared to other device related complications in biodegradable temporising matrix (BTM) application. The infection rate was significantly lower on assessment: 0.421 (0.281, 0.629, $p = 0.281$).

of failed BTM integration in 35 wounds with Concannon[10] reporting 4 in 50 cases. Concannon[10] also had two cases needing tenolysis in 21 wound beds where the templates were used to reconstruct defects with exposed tendon. Lo[2] reported 254 adverse events overall in a 30 patient cohort. These were categorised into 5.2% severe, 53.5% moderate, and 41.3% mild, with the predominant complication being infection related. This involved re-application, removal of BTM as well as antibiotic therapy. The authors excluded it from a quantitative comparison with the infection rate as it was not clear what percentage were device related. Four patients died of causes unrelated to BTM, and one patient required surgical release for a contracture. Solanki[11] reported non-adherence and lack of vascularisation in 5 cases and Wu[20] identified two cases of dehiscence. Concannon[10] reported 11 (39%) complications for BTM applied directly over 28 wounds with bone only and 6 in 9 (67%) over wounds with tendon only. These all included a range of infection, BTM and graft loss as well as haematoma. Solanki[11] reported 2 incidences in 7 wounds (29%) with bone only with non-adherence as well as lack of vascularisation. Five of the 9 wounds (56%) where BTM was applied to tendons developed complications all of which were infection related and other wound bed types reported a rate of 4 in 7 (57%).[5,11] This included non-adherence as well as lack of vascularisation. Li[5] reported 2 complications in 8 wounds (25%) with bone only. One was an infection and one suffered a breakdown.[5] One wound in 6 (17%) with tendon only sustained a graft loss.[5] The incidence was also fairly low in other wound bed types with 3 in 13 cases (23%) as reported by Li.[5] Kuang[19] had two cases of wound break down (14%) with both cases having BTM applied over granulation tissue. There were four cases of infection reported, 3 of these were over granulation tissue and only one over bone.[19] The current paucity of evidence in relation to lack of detailed descriptions of wound bed types in the review

studies and their reported complications limits a thorough assessment of how wound bed type can influence complications with BTM. A summary of all the studies and different complications is given in Tables 3 and 4 below.

3.6 | Scar appearance

Scar appearance was reported by numerous studies using both POSAS and MAPS assessment scales with Greenwood[1] reporting good objective outcomes. The average MAPS score was 3 with a mean observer score of 18. Lo[2] reported a significant improvement in the Vancouver scar scale with a decrease in the score from 5.6 at 3 months (95% CI 4.7, 6.6) to 3.0 at 12 months (95% CI 2.6, 3.5). A significant proportion (54.1%) of patients had normal pigmentation at the 12 month point with 36.7% also having normal vascularity and 82.8% demonstrating normal or supple pliability as well. Li[5] also reported good outcomes with POSAS observer scale showing consistently low scores with a mean overall patient score of 5.67 ± 2.82 out of 10 being observed. On this scale one represents normal skin and 10 being very different to normal skin. A mean overall observer score also from an independent plastic surgeon was 3.63 ± 2.04. In addition Li[5] reported average sensory restoration of 5.86 ± 2.72 out of 10 in their series. Wagstaff[16] reported low MAPS and POSAS scores both indicating good scar characteristics. Chen[21] used the Manchester scar scale for assessment which consisted of evaluating for colour, shine, contour, distortion, texture and overall rating with the Visual Analogue scale. Patients who underwent BTM application without grafting achieved better scar outcomes compared to those who had skin graft only. Lo[29] used the POSAS assessment scale to evaluate scar outcomes. Low to indeterminate scores were achieved for many domains including vascularity, pigmentation, thickness, relief pliability and surface area on both observer as well as patient assessments. Struble[25] briefly discussed long term scar outcomes although they didn't use any formal assessment tools but reported scars to be more softer and supple after BTM than directly going for a skin graft during reconstruction.

3.7 | Methodological quality assessment

Methodological quality was assessed using the Newcastle-Ottawa scale in which studies were scored across three domains using an advocated star system (Table 5). The star system uses predefined guidelines to score the selection of study groups, comparability of the groups, and the assessment of outcome.[17] All studies included in the meta-analysis were awarded three or four stars for selection, indicating that the studies appropriately represented their respective populations. However, comparability was limited due to the inherent nature of most of studies and the absence of a control arm in the majority of articles. All studies received scores of two or three stars for the assessment of outcomes, demonstrating that the outcomes were measured with appropriate rigour.

4 | DISCUSSION

The authors report a systematic review and meta-analysis of the literature on the application of BTM for complex wound reconstruction with an outcome synthesis. Previously, Ferreira,[14] depicted a complex wound as one which fell into the following catergories; extensive loss of the integument in acute or chronic wounds, infection as a complication in chronic wounds, necrosis and compromised viability of surrounding tissue or signs of circulation impairment as well as systematic pathologies that impair normal wound healing (e.g., diabetes, vasculitis or immune suppression). The authors abided to these criteria upon selection of wounds as part of this review for applying BTM with defects involving exposed bone, deep to full thickness burns post excision, wounds with exposed muscle, tendon, chronic wounds such as ulcers and wounds post debridement from infective as well as ischaemic aetiologies.

BTM offer an alternative to other complex therapies in soft tissue reconstruction such as free tissue transfer or locoregional flaps. These techniques are routinely instigated for large defects with non graftable wound beds or those where skin grafts would produce sub-optimal outcomes due to large volumes of tissue loss. The use of BTM for any complex wound routinely involves a two stage process for usage with the initial phase normally necessitating a thorough debridement with all burn wounds undergoing excision and a template cut to fit the defect that can be affixed with either suture material or staples. The sealing membrane is faced externally and removed at the second stage of delamination at which point the neodermis can be refreshed and a skin graft applied.[8,9]

Twenty one studies met the inclusion criteria for quantitative assessment overall and a high percentage of BTM take (92.7%) was evidenced across all wound types with an average of 34 days to integrate prior to the second stage of skin graft application. Secondary outcomes including the percentage graft take over integrated BTM was promising at 98.9%. The infection rate was low (12.6%) with a further sensitivity analysis comparing high

TABLE 3 Summary of complications recorded in each study.

Study and year	Wounds (*n*)	Number of complications	Complications
Wagstaff et al., April 2015,[16]	10	7	Infection under BTM–2 Serous collection under BTM–2 BTM failure–1 Necrotic wound bed–1 Infected donor site
Wagstaff et al., June 2015,[27]	10	4	Unrelated death–3 Lost to follow up–1
Greenwood et al., 2017[1]	5	12	Infection under BTM–2 Contracture–3 Haematoma under BTM–1 BTM failure on shoulder–1 Olecranon pressure ulcer–1 Faecal contamination–1 Necrotic wound bed–1 Graft failure over malleoli–1
Wagstaff et al., 2019,[4]	7	Not reported	Not reported
Solanki et al., 2020[11]	25	11	Infection–5 Non-adherence–3 Incomplete vascularization–3
Li et al., 2021,[5]	35	6	Infection under BTM–1 Graft failure–2 Haematoma–1 Abdominal sinus–1 Wound breakdown under graft–1
Lo et al., 2021,[2]	100	254	Not detailed
Kuang et al., 2022,[19]	18	Not reported	Infection–22%[4]
Schlottmann et al., 2022,[7]	27	Not reported	Not reported
Wu et al., April 2022,[20]	51	15	Infection or cellulitis–9 Dehiscence–2 Haematoma or seroma–2 Other–2
Wu et al., July 2022,[28]	5	1	Infection–1
Austin et al., 2023,[18]	79	Not reported	Infection–3 Haematoma–2
Cereceda-monteoliva et al., 2023,[12]	40	7	Infection–5 Non adherence–5 Haematoma–1 Delayed healing–1 Osteomyelitis–1 Seroma–1
Concannon et al., 2023,[10]	70	26	Wound infection–7 BTM loss–9 Skin graft loss–7

TABLE 3 (Continued)

Study and year	Wounds (*n*)	Number of complications	Complications
			Amputation–2 Tendon adhesions–2 Haematoma–1
Tapking et al (REF) Feb 2024	300	Not reported	Not reported
Struble et al., (REF), 2024	86	15	Cellulitis or infection–4 Haematoma or collection–7 Early delamination–4
Parker et al., (REF), July 2023	24	9	Wound break down–2 Overgranulation–1 Graft loss–4 Columella misalignment–1 Necrotic wound base–1
Meagher et al., (REF), March 2024	22	Not reported	Not reported
Lo et al., (REF) May 2023	16	Not reported	Not reported
Kidd et al., (REF), August 2023	37	19	Total BTM loss–9 Partial BTM loss–2 Cellulitis–5 Deep infection–2 Haematoma–1
Jou et al., (REF) May 2024	51	14	Infection–5 Harmatoma or sermoma–5 Total BTM loss–3 Partial BTM loss–1
Heard et al., (REF), 2023	10	5	Infection–4 Haematoma–1
Guerriero et al., Feb 2023	23	7	Infection–3 Minor amputation–3 Major amputation–1
Fuest et al., (REF), May 2023	27	Not reported	Not reported
Devine et al., (REF), Feb 2024	12	9	Infection–3 Haematoma–3 Failure of integration–2 Delayed wound break down–1
Chen et al., (REF), May 2024	37	10	Infection–6 BTM poor take–4

Abbreviation: BTM, biodegradable temporising matrix.

risk wounds to those in the general population demonstrating the rate to be comparable on odds ratio assessment evidencing the dermal template's resistance to infection (Figure 11). This included defects post debridement for necrotising fasciitis, diabetic foot wounds, any chronic wound, pressure ulcers as well as those with previous or current infections and ones of an ischaemic aetiology. The rate of infection was also found to be significantly lower compared to miscellaneous device related adverse effects (Figure 12) some of which included, haematomas, non-adherence as well as adhesions necessitating tenolysis. Scar appearance was

TABLE 4 Summary of demographic characteristics as well as wound aetiology, wound acuity, structures in wound base, anatomical location, area of wound, follow up periods for all included studies and outcomes analysed.

Study and year	Mean/ median Age/Range (yrs)	Patients (*n*)	Male/ Female (*n*)	Wounds (*n*)	Wound aetiology (*n*)	Acute/ Chronic	Wound base (*n*)	Wound location (*n*)	Average Surface area of BTM cm^2/ %TBSA	Follow up period (months)	Outcomes
Wagstaff et al., April 2015,[16]	62.2 (mean) (46–76)	10	Not reported	10	Alt flap–3 Fibular osseous flap–3 radial/ulnar forearm flap–4	10:0	Not reported	Upper limb–4 Lower limb–6	Not reported	12 months	Integration (91.0%) Integration time (29.5 days) SSG take (90.5%) Infection rate (40.0%)
Wagstaff et al., June 2015,[27]	58.5 (mean) (48–68)	10	Not reported	10	Fibular osseous flap–2 Radial forearm flap–7	10:0	Not reported	Upper limb–7 Lower limb–2	Not reported	2.9–14.1 months	Integration (100%) Integration time (35.4 days) SSG take (100%) Infection rate (4.5%)
Greenwood et al., 2017[1]	42.2 (mean) (18–70)	5	5 males	5	Burns–5	5:0	Extensive wound with burn eschar excision	Axilla–1 Upper limb–5 Trunk–3 Lower limb–3	23%	12 months	Integration (89.8%) Integration time (33.2 days) SSG take (98.4%) Infection rate (40.0%)
Wagstaff et al., 2019,[4]	51.6 (mean)	7	4 males 3 females	7	Post-debridement of necrotising fasciitis–7	7:0	Gland–1 Muscle–1 Blood vessels–2 Exposed bone denuded of periosteum–2 Exposed joints–1	Neck–2 Chest–2 Lower limb–3	8.57%	1–20 months (range)	Integration (98.1%) Integration time (34.0 days) SSG take (100%) Infection rate (6.2%)
Solanki et al., 2020[11]	50 (median) (15–86)	25	19 males 6 females	25	Acute full thickness burn–3 Burn scar/ contracture release–5 Necrotising soft tissue infection–7 Tumour excision–3 Traumatic loss–7	20:5	Exposed bone–8 exposed tendon–11 wound temporalisation with SSG–3 Desirable/aesthetic reconstruction–5	Head–2 Neck–2 Upper limb–9 Trunk–3 Lower limb–9	Not reported	3 months (median) 1–7 months (range)	Integration time (37.8 days) Infection rate (20.0%)

TABLE 4 (Continued)

Study and year	Mean/ median Age/Range (yrs)	Patients (*n*)	Male/ Female (*n*)	Wounds (*n*)	Wound aetiology (*n*)	Acute/ Chronic	Wound base (*n*)	Wound location (*n*)	Average Surface area of BTM cm^2/ %TBSA	Follow up period (months)	Outcomes
Li et al., 2021,[5]	73.7 (mean) (47–95)	27	19 males 8 females	35	Pressure ulcer–2 Failed SSG–5 Wound breakdown–4 Surgical wounds–12 Trauma–4	16:11	Muscle–10 Bone–7 Tendon–10 Fat–7 Paratenon–2 Perichondrium–3 Periosteum–2	Head and neck–12 Breast–1 Upper limb–7 Abdomen–1 Lower limb–14	Not reported	3–18 months (range)	Integration (96.9%) Integration time (35.4 days) SSG take (87.9%) Infection rate (1.4%)
Lo et al., 2021,[2]	45.2 (mean) (18–70)	26	22 males 4 females	100	Burn–26	26:0	Not reported	Chest–23 Abdomen–13 Back–2 Upper limb–34 Lower limb–28	2137.8 cm^2	12 months	Integration (88.6%) Integration time (31.9 days) SSG take (81.9%) Infection rate (38.5%)
Kuang et al., 2022,[19]	56 (median) (31–86)	18	16 males 2 females	18	Debridement–9 Amputation–8 Ulcer–1	17:1	Granulation tissue–12 Bone–3 Fascia/peroneal retinaculum/ plantar fascia–3	Foot–18	Not reported	3–18 months (range)	Intergration time (38.8 days) Infection rate (7.1%)
Schlottmann et al., 2022,[7]	50.8 (median) (15–82)	20	12 males 8 females	27	Pressure ulcer–2 Neurofibromatosis–1 Necrotising fasciitis–1 Burn–7 Chronic ulcer–2 Malignancy resection–2 Unstable scar–2 Full thickness soft tissue defect–3	14:6	Not reported	Head–3 Neck–2 Upper limb–6 Trunk–4 Lower limb–11 Genital–1	Not reported	Not reported	

(Continues)

TABLE 4 (Continued)

Study and year	Mean/ median Age/Range (yrs)	Patients (*n*)	Male/ Female (*n*)	Wounds (*n*)	Wound aetiology (*n*)	Acute/ Chronic	Wound base (*n*)	Wound location (*n*)	Average Surface area of BTM cm^2/ %TBSA	Follow up period (months)	Outcomes
Wu et al., April 2022,[20]	48.2 (mean) (18–93)	51	33 males 18 females	51	Burn–7 Trauma–24 Surgical wound/ pressure ulcer–10 Osteomyelitis–2 Compartment syndrome–2 Skin Malignancy–2 Others–4	Not categorised	Not reported	Head and neck–5 Upper limb–24 Trunk–1 Lower limb–21	110 cm^2	6.4 months (median)	Infection rate (17.6%)
Wu et al., July 2022,[28]	66 (mean)	5	3 males 2 females	5	Burn–2 Trauma–1 Surgical wound or pressure ulcer–1 Skin Malignancy–1	Not categorised	Not reported	Head and neck–5	213 cm^2	15.3 (median) Range: 3.8–26.8	Infection rate (20.0%)
Austin et al., 2023,[18]	46.6 (mean)	28	16 males 12 females	79	Burns–20 Complex wound–5 Trauma–3	23:5	Not reported	Not reported	1227 cm^2	Not reported	Integration time (31.6 days) Infection rate (3.8%)
Cereceda-monteoliva et al., 2023,[12]	60 (mean) (5–91)	38	26 males 12 females	40	Skin cancer–19 Burns–12 Scar revision–3 Infection–3 Trauma–3	35:3	Exposed tendon–14 Exposed bone–8 Exposed tendon and bone–10 exposed tendon and bone plus failed SSG–2 Failed skin graft–2 Pressure area–2 Delayed wound healing–1 Overlying umbilicus–1	Scalp–6 Face–2 Upper limb–8 Trunk–2 Lower limb–22 (including 1 perineal burn)	1.29%	3.4 months (mean)	Infection rate (13.2%)
Concannon et al., 2023,[10]	55 (mean) (17–94)	55	41 males 14 females	70	Burns–15 Trauma–19 Infection–10 Ischaemic–7 Oncological defect reconstruction–4	55:0	Exposed bone devoid of periosteum–42 Exposed tendon–21 Bone and tendon–7	Scalp–8 Neck–2 Upper limb–11 Trunk–5 Lower limb–31	Not reported	18 months (mean) 3–72 months (range)	Integration time (46.2 days) Infection rate (12.7%)
Tapking et al., Feb 2024,[44]	54.2 (mean)	300	199 males 101 females	300	Burns–179 Trauma–59 Chronic wound–39 Infection–14	39:261	Subcutis–144 Tendon–42 Joint capsule–46 Bone–29	Head and neck–8 Trunk–47 Upper limb–70	4.1	Not reported	Integration (82.7%) Integration time (32 days)

TABLE 4 (Continued)

Study and year	Mean/ median Age/Range (yrs)	Patients (*n*)	Male/ Female (*n*)	Wounds (*n*)	Wound aetiology (*n*)	Acute/ Chronic	Wound base (*n*)	Wound location (*n*)	Average Surface area of BTM cm^2/ %TBSA	Follow up period (months)	Outcomes
					Malignancy–6 Not mentioned–3		Not mentioned–49	Lower limb–141 Not mentioned–34			SSG take (86%)
Struble et al., 2024,[25]	16.9 (mean) (0.3–81.4)	54	28 males 23 females 3 transgender (FtM)	86	Trauma–31 Infection–16 Malignancy–10 Burns–9 Flap donor site–8 Chronic wound–6 Vasopressor necrosis–4 Flap loss–4 Fasciotomy site–1	80:6	Muscle–41 Tendon–33 Bone–19 Joints–11 Nerve–7 Blood vessel–6	Upper limb–45 Lower limb–41	60 cm2	Not reported	Integration (88.6%) Integration time (27.7 days) SSG take (92.1%) Infection rate (4.7%)
Parker et al., 2023,[43]	57 (mean) (19–89)	23	14 male 9 female	24	Infection–8 Malignancy–6 Burns–4 Chronic wound–3 Free flap failure–2 Surgical wound dehiscence–1	21:3	Muscle–8 Bone–5 Fascia–5 Tendon–4 Testicle–3 Fat and cartilage–1	Lower limb–10 Head and neck–6 Torso–3 Groin/ genitals–3 Upper limb–1	<1%	Not reported	Integration (95.2%) Integration time (44.2 days) SSG take (86.1%) Infection rate (8.3%)
Meagher et al., 2024,[6]	(30–95)	22	16 male 6 female	22	Peripheral vascular disease–5 Necrotising fasciitis–4 Pressure ulcers–4 Haematoma–3 Crush–2 Malignancy–1 Vasculitis–1	18:4	Not reported	Lower limb–21 Chest–1=	Not reported	Not reported	None
Lo et al., 2023,[29]	49.1 (mean)	15	13 male 2 female	16	Burns–13 Necrotising fasciitis–2	15:1	Subcutaneous fat–25 Fascia–11 Bone–2	Upper limb–11 Lower limb–17	25.2%	56	None

(Continues)

TABLE 4 (Continued)

Study and year	Mean/ median Age/Range (yrs)	Patients (*n*)	Male/ Female (*n*)	Wounds (*n*)	Wound aetiology (*n*)	Acute/ Chronic	Wound base (*n*)	Wound location (*n*)	Average Surface area of BTM cm^2/ %TBSA	Follow up period (months)	Outcomes
					Secondary burn reconstruction–1		Mixed wound bed–1	Trunk–4 Head and neck–1 Multiple area–6			
Kidd et al., 2023,[24]	52 (mean) (14–93)	37	24 male 13 female	37	Trauma–19 Chrnoic wounds–9 Infection–6 Malignancy–3	28:9	Muscle–17 Tendon–12 Bone–6	Lower limb–21 Upper limb–7 Torso–6 Head and neck–3	1% (0.5%–15%)	Not reported	Integration time (53 days) Infection rate (18.9%)
Jou et al., 2024,[45]	44.3 (mean) (13–97)	51	39 male 12 female	51	Trauma–30 Burns–12 Infection–8 Iatrogenic–1	51:0	Tendon–27 Bone–24	Upper limb–51	162.5 cm^2	2–40	Integration time (51.7 days) Infection rate (9.8%)
Heard et al., 2023,[26]	24.1 (mean) (10–41)	10	7 male 3 female	10	Burns–10	10:0	Not reported	Massive burns (mean 80.8% TBSA)	Not reported	Not reported	Integration time (83.2 days) Infection rate (40.0%)
Guerriero et al., 2023,[23]	67.3 (mean)	22	19 male 3 female	23	Diabetic foot wounds–22	22:0	Not reported	Foot–22	Not reported	5 months	Infection rate (13.0%)
Fuest et al., 2023,[46]	51 (mean) (12–77)	27	16 male 11 female	27	Trauma–20 Infection–4 Malignancy–1 Dupuyten's–1 Dermatomyositis–1	27:0	Not reported	Hand–27	Not reported	Not reported	Integration time (43.6 days) SSG take (96%)
Devine et al., 2024,[22]	70 (mean)	12	8 male 4 female	12	Malignancy–12	12:0	Not reported	Head and neck–8 Lower limb–3 Genirourinary–1	Not reported	Not reported	Integration time (49 days) SSG take (70.0%) Infection rate (25%)

TABLE 4 (Continued)

Study and year	Mean/ median Age/Range (yrs)	Patients (*n*)	Male/ Female (*n*)	Wounds (*n*)	Wound aetiology (*n*)	Acute/ Chronic	Wound base (*n*)	Wound location (*n*)	Average Surface area of BTM cm^2/ %TBSA	Follow up period (months)	Outcomes
Chen et al., 2024,[21]	51.8 (mean) (18–86)	37	22 male 15 female	37	Trauma–25 Necrotising fasciitis–6 Burn–4 Other–2	37:0	Not reported	Lower limb–19 Foot–10 Hand–4 Upper limb–3 Trunk–1	50.6 cm^2	7.0 months	Integration time (36.9 days) Infection rate (2.7%)

Abbreviation: BTM, biodegradable temporising matrix; SSG, split thickness skin graft: TBSA, total body surface area.

encouraging with improvements in both MAPS and POSAS assessment scales as reported by Greenwood, Li and Wagstaff.[1,5,27] Lo[2] identified an improvement in the Vancouver scar scale with a decrease in score at a 12-month period. A direct comparison of BTM application over bone compared to tendon showed no significant difference in terms of the integration time needed however the integration period was significantly longer for bone compared to other tissue wound beds. This would suggest that clinicians need to leave the device on for longer when using it to reconstruct bony defects. The authors found a comparable integration time for BTM in tendon reconstruction compared to general soft tissues on mean difference assessment with no significant difference seen. In the context of all quantified outcomes within the review heterogeneity was moderate to high for the majority of variables including integration time. This was circumvented by adaptation of a random effects model or an inverse variance function. These are statistical functions conducted to account for scenarios when heterogeneity is elevated and equates for any discrepancies in outcomes in the overall effect estimate.

In a recent systematic review by Grande,[30] they also identified a high integration rate of BTM with over 84% of wounds experiencing greater than 95% integration with a mean take of 95%. Similarly, the mean rate of skin graft survival over implanted BTM was 95%. These findings are comparable to the results of the current meta-analysis. Grande[30] also identified the time for BTM integration as 36.7 days which parallels to the author's finding of 34 days. The results of the current review identified a comparable infection rate between high risk wounds and those in the general population and while time to implantation can be prolonged with infection,[30] results for skin graft survival have shown to be equivocal by Grande.[30]

BTM's versatility in complex wound reconstruction has seen it to successfully integrate despite patients with multiple co-morbidities.[5] This offers a simplistic option in patients who are not suitable for more complex reconstructive techniques such as free tissue transfer. In addition, numerous cases have shown successful re-epithelialisation without second stage skin graft application as well.[5,19] BTM has drawn comparable outcomes to other dermal substitutes in the literature including integra, matriderm as well as glyaderm in burn injuries.[2] Near equivocal device integration and split thickness skin graft take rates have been reported as well as the duration to graft.[2,31–34] Although in some animal studies on direct comparison, BTM has demonstrated greater neovascularisation at similar time periods on histological assessment[35] and an increased wound regeneration capacity.[36] This would explain BTMs ability to form

TABLE 5 Newcastle-Ottawa assessment for methodological quality with good scores for selection and outcome domains but poor for comparability.

Study	Selection	Comparability	Outcome
Wagstaff et al., 2015[16]	****		**
Wagstaff et al., 2015[27]	****		**
Greenwood et al., 2016[3]	***		**
Wagstaff et al., 2019[4]	****		**
Solanki et al., 2020[11]	****		**
Lo et al., 2021[2]	****		***
Li et al., 2021[5]	****		**
Wu et al., 2022 (April)[20]	****	*	***
Wu et al., 2022 (July)[28]	****	*	***
Kuang et al., 2022[19]	****		**
Schlottman et al., 2022[7]	****		**
Austin et al., 2023[18]	****		***
Concannon et al., 2023[10]	****		***
Cereceda-Monteoliva et al., 2023[12]	****		**
Chen et al., 2024[21]	***		***
Devine et al., 2024[22]	***		***
Fuest et al., 2024[46]	**		**
Guerriero 2023[23]	**		*
Heard et al., 2023[26]	***		**
Jou et al., 2024[45]	**		***
Kidd et al., 2023[24]	**		**
Lo et al., 2023[29]	**		***
Meagher et al., 2024[6]	*		*
Parker et al., 2023[43]	****		***
Struble et al., 2024[25]	****		***
Tapking 2024[44]	****		***

Note: The Newcastle-Ottawa Scale awards stars for study quality across three domains: Selection, Comparability, and Outcome/Exposure. More stars indicate higher quality.

vascularised neo-dermal layers in complex avascular wound beds. The original work of Yannas and Burke[37] on requirements of dermal matrices already indicated that there is an optimal porosity. BTM's porosity is optimised to enhance cell migration and survival, as demonstrated in their research. It's more porous than collagen based dermal templates enabling increased cell migration and survival.[2] The additional potential for sensory restoration using BTM can enhance the quality of life in patients with lower limb defects. In the case series by Li,[5] partial sensory restoration was reported in most of the reconstructed wounds which is encouraging.

Integra which consists of bovine collagen and cross linked glycosaminoglycans has reported graft take rates between 90% and 93%[38] which although comparable appears inferior to that of BTM as evidenced from the authors' analysis (98.9%). This in addition to other studies having reported even lower graft take rates over Integra.[31,39] The comparison is similar for MatriDerm, another bovine derived dermal substitute with graft take rates of 83.4%[32] as well as 73.4%.[34] Cheshire[35] directly compared BTM and Integra in mice models with BTM demonstrating a more extensive vascular network which could explain its superior wound healing. MatriDerm and Integra have inherent limitations as well given their animal origin precluding their usage in certain religious groups.[40] BTM is purely synthetic and therefore mitigates this problem. Reported infection rates for Integra have been referenced as high as 19.3%[41] in contrast to BTM (12.6%) from the authors' quantification. Matriderm demonstrates a more comparable rate of 11.8%.[42] Both Integra and BTM are two stage devices and are seen to have comparable matrix integration rates with reports for Integra ranging at 95%–100%[31,33] and BTM identified as 92.7% from the current meta-analysis.

The authors report a systematic review and meta-analysis on the use of BTM in complex wound reconstruction. It collates 26 studies that have met the inclusion criteria for analysis. The limitations of this review include all studies being of an observational design with low comparability scores on methodological quality assessment, however there was a large number of wounds. Overall, 1153 wounds in 26 studies assessed the effectiveness of BTM in a variety of wound aetiologies with good scores for the selection and exposure domains on Newcastle-Ottawa assessment although comparability was very poor (Table 5). Many variables were not consistently reported by a lot of the articles which limited the number of studies that were amenable to meta-analysis. For instance, the proportion of BTM integration was reported heterogeneously with some reports recording it as the proportion of integration relative to the area implanted whereas others reported it as a success rate relative to the number of patients within which it was used. The meta-analysis did not include any randomsied control trials either which inherently limits it. Heterogeneity also varied from moderate to considerable but the authors adapted random effects models and inverse variance functions to circumvent this. To further enhance the evidence base, the authors recommend for randomised controlled trials directly comparing BTM with other dermal substitutes in complex wound reconstruction. In addition, sub cohort analyses assessing the effectiveness of BTM in different wound types is recommended to evaluate the differences in time to integration as well as complication rates. This current paucity in evidence would be helpful in guiding clinicians when using the device in different wound environments and with varying aetiologies.

5 | CONCLUSIONS

This systematic review and meta-analysis has comprehensively examined the existing literature on the efficacy and versatility of BTM in complex wound reconstruction. It has shown a high rate of take across a variety of wounds and shown promising results including secondary skin graft integration and low infection rates. These outcomes have been strengthened by positive scar outcome and the potential sensory restoration advantages of BTM. The authors recommend further randomised control trials directly comparing BTM with other dermal substitutes.

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CONFLICT OF INTEREST STATEMENT

The author(s) have no conflicts of interest with respect to the research, authorship, and/or publication of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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