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How timing and preexisting pain affect outcomes of TMR: a systematic review

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Abstract

Introduction: Targeted muscle reinnervation (TMR) is increasingly common in the care of major limb amputation to limit amputation-related pain. This review aims to elucidate how chronic pain states and length of delay prior to TMR affect its success and outcomes.

Methods: Manuscripts were collected from three databases. Articles were first screened and excluded based on exclusion criteria. The remaining manuscripts were independently reviewed to determine inclusion. Article and patient demographics, as well as pain outcomes, were extracted. Data were analyzed based on pain condition, amputation *vs.* neuroma, and time from amputation/injury to surgery.

Results: The literature search yielded 723 articles, with 41 meeting the inclusion criteria. Twenty-one articles included patients with residual limb pain (RLP) and phantom limb pain (PLP), including 14 on amputation and 6 on neuroma excision. Five articles included cancer-related amputation. Complex Regional Pain Syndrome (CRPS) was discussed in 3 articles, ischemia or infection in 2 articles, and neurofibromatosis 1 in 1 article. Twenty-two articles described TMR at the time of amputation.

Conclusions: TMR is effective at preventing neuroma formation and limiting pain when performed at the time of amputation. Delayed patients had a greater improvement in RLP but less of an improvement in PLP, when assessed against immediate TMR patients who were compared to non-TMR standard amputees. In the presence of chronic pain states, such as CRPS, there is also improved analgesia. However, current clinical data are limited, indicating a need for further research into the use of TMR for chronic pain management.

Keywords: Targeted muscle reinnervation, neuroma, phantom limb pain, residual limb pain

INTRODUCTION

Targeted muscle reinnervation (TMR) and regenerative peripheral nerve interfaces (RPNI) are rapidly becoming a standard technique in acute management of major limb amputation to prevent or limit amputation-related pain. TMR is effective in limiting both residual limb pain (RLP) and phantom limb pain (PLP)[1-4]. Growing evidence shows that a delay from amputation to TMR may result in less effective treatment or prevention of RLP and PLP[1,3,5,6]. Goodyear *et al.* found that immediate TMR (iTMR) led to decreased rates of neuroma formation compared to TMR after neuroma excision[5]. Likewise, animal studies demonstrate reduced analgesia associated with TMR if performed in a delayed fashion[7]. The underlying physiology of this phenomena is unknown; thus, our capacity to make informed clinical decisions is handicapped.

The role of timing in the effectiveness of TMR is challenging to delineate in clinical studies. TMR may be delayed due to patient-related obstacles, such as stability for elective procedures in polytrauma, or more commonly, health system obstacles such as lack of availability of TMR or amputation at a time before TMR was widely available. This is further complicated by the wide range of "delayed" time to TMR; delays of 1 month and up to 10 years after amputation may both be categorized as delayed within the same study[6,8]. A consequential delay and a non-consequential delay cannot be distinguished when all non-iTMR interventions are grouped together. For example, a 3-week delay in a rodent model of neuropathic pain made no difference in pain behaviors compared to iTMR, while a delay of 12 weeks resulted in a lack of analgesia[7]. Moreover, the degree of injury may also be critical: the delay preventing analgesia is likely very different for a single neuroma compared to limb amputation.

An additional complexity is preexisting pain states. Chronic pain, defined as "pain that persists or recurs for more than three months and has multiple potential etiologies," can be due to amputation itself or caused by comorbid conditions[9-15]. Painful conditions that may lead to amputation include diabetes mellitus, chronic limb ischemia, and Complex Regional Pain Syndrome (CRPS). Other multifactorial pain states such as fibromyalgia, cancer-related pain, radiation-induced neuropathy, or sickle-cell disease may also pre-date amputation. Valerio *et al.* remarked that the only patients who continued to have severe pain following amputation and TMR were those with a history of severe chronic pain for years preceding surgical intervention[2]. These data suggest that it may not only be the delay to TMR, but the presence and length of time the patient has chronic pain.

When a delay to TMR occurs, there is a chronic axotomy state in the peripheral nerve, an injury state in the dorsal root ganglia, and evolving central changes, most notably cortical reorganization associated with amputation[10-15]. Chronic pain states unrelated to amputation also affect the peripheral and central nervous systems[16-19]. Some of these changes may be sensitive to TMR and some may be irreversible. Differentiating these effects is critical to predicting when TMR will be successful for a patient. The goal of this review is to elucidate how chronic pain states and length of delay prior to TMR may affect the success and outcomes of TMR.

METHODS

Three databases (PubMed, Web of Science, and Scopus) were searched, and further bibliographic search of relevant articles was undertaken. The following keywords and operators were used: ("TMR") AND (treatment outcome OR pain OR analgesia OR "phantom limb" OR outcome) AND [(nerve transfer AND muscle) OR " TMR"]. This study was conducted in accordance with PRISMA guidelines.

Two independent reviewers screened articles for eligibility (ED and AB), first by title, then by reading abstracts, and finally by reading the entire manuscript. If a disagreement existed, a consensus was reached by discussion. All articles were required to satisfy the eligibility criteria to be included. For studies to meet inclusion criteria, they must (1) evaluate patient-reported pain scores post TMR; (2) focus on upper and/or lower extremities, or abdominal wall surgery; and (3) involve indication for TMR being prophylaxis at the time of amputation, or treatment of pain in amputees and non-amputees. Review articles, technique papers, animal and non-human studies, cadaveric studies, and non-English papers were excluded.

In the papers meeting the inclusion criteria, we selected the following data: number of patients, patient age, number and level of lower and upper extremity (UE) procedures (if extremity data), reason for TMR, preexisting pain condition, average and maximum follow-up time, and patient-reported pain outcomes assessing RLP, PLP, and other associated pain, if available. Pain outcomes collected included number of patients with no pain or improved pain postoperatively, numerical rating scale (NRS) scores, visual analog scale (VAS) scores, Patient-Reported Outcomes Measurement Information System (PROMIS) scores, and other pain scales when available. Randomized controlled trials were independently assessed using the revised Cochrane risk-of-bias tool[20]. Data were analyzed systematically based on pain condition, amputation *vs.* neuroma surgery, and time from amputation/injury to surgery. Analysis of average pain scores across groups was done using weighted means with Microsoft Excel software.

RESULTS

The literature search returned 723 unique articles after duplicate screening. Manuscripts were independently reviewed by three reviewers (ED, AB, JLZ), resulting in the inclusion of 41 articles, including one RCT with a low risk of bias [Figure 1]. Twenty-one articles included patients with RLP and PLP, 14 of which described amputation surgery, and 6 described neuroma excision/nerve repair surgery. Five articles included cancer-related amputation. CRPS was discussed in 3 articles, ischemia or infection in 2 articles, and neurofibromatosis 1 (NF1) in 1 article. Additionally, 22 articles described completion of TMR at the time of amputation/injury, 11 of which involved patients with preexisting pain conditions. The remaining articles discussed delayed TMR. Three articles compared iTMR to delayed TMR[5,6,21]. Ten preventative TMR articles were analyzed and included a total of 211 patients. Details are presented in Table 1.

Several articles compared outcomes of immediate to delayed TMR, and their numeric findings are available in Table 2. While Reid had decreased VAS scores in the immediate group, there were no changes in opioid consumption between groups[6]. Goodyear found that 1% of acute TMR patients experienced severe pain while 30% of delayed TMR patients experienced severe pain. Furthermore, 1.4% of acute TMR patients developed a subsequent neuroma compared to 18.8% of delayed TMR patients, demonstrating that delayed patients had 16.6 times greater odds of neuroma development[5].

Twenty-one articles included patients with preexisting neuroma pain or PLP. Of these, six articles with 41 patients described neuroma management with TMR. Several reported subjective pain measurements - Daugherty *et al.* reported a 75% improvement in pain symptoms at three months post-op; 16 of 19 patients in the study by Moradian *et al.* experienced complete resolution of pain during long-term follow-up[22,23]. Fourteen articles comprising 327 patients described amputation. Souza *et al.* did not use pain scales, but all patients had resolved or improved pain and 23 of 26 patients were successfully fit with a prosthesis[24]. Kang *et al.* compared outcomes in UE and lower extremity (LE) amputees[25]. Both groups had improved pain outcomes, but UE patients showed greater improvement than LE patients [Table 3]. Twelve LE patients experienced the unmasking of additional neuromas after their initial TMR. The remaining articles used objective pain scales and/or PROMIS scores [Table 3]. One article explored the use of TMR to treat

Table 1. Outcomes for TMR at the time of amputation without preexisting pain

Author(s) year	Article type	Number# of patients	Age average	Average follow-up (months)	RLP pain scale		PLP pain scale		RLP PROMIS Intensity Behavior Interference		PLP PROMIS Intensity Behavior Interference	
					Control	TMR	Control	TMR	Control	TMR	Control	TMR
Valerio *et al.*, 2019[2]	Cohort study	51	35-59	330 days	4	1	5	1	46.8 57.3 57.3	30.7 36.7 40.7	48.4 56.6 55.8	36.3 50.1 40.7
O'Brien *et al.*, 2021[28]	Retrospective review	16	59	23.1	4	0.5	4	0	46.8 53.1 48.2	33.5 36.7 40.7	46.8 53.1 50.0	33.5 50.1 40.7
Frantz *et al.*, 2020[53]	Prospective cohort	25	47.5	14.1	--	--	--	--	-- -- --	4 7 8	-- -- --	4 14 8
Chang *et al.*, 2024[3]	Retrospective review	41	67.4	9.5	--	4.9	--	--	-- -- --	-- -- --	-- -- --	-- -- --
Gomez-Eslava *et al.*, 2023[54]	Cohort study	30	50	3.9	--	2.1	--	--	-- -- --	46.3 -- 52.1	-- -- --	-- -- --
Galbraith *et al.*, 2023[55]	Case report	1	75	6	9	2.5	--	--	-- -- --	-- -- --	-- -- --	-- -- --
Cheeseborough *et al.*, 2014[56]	Case report	1	54	8	--	--	--	--	-- -- --	-- 37 39	-- -- --	-- -- --

TMR: Targeted muscle reinnervation; RLP: residual limb pain; PROMIS: Patient-Reported Outcomes Measurement Information System.

abdominal wall neuromas [Table 3]. They lacked preoperative pain data and the objective data from patients who received TMR and allograft reconstruction were combined. However, 85% of patients had significant improvement in pain at their first preoperative visit. Additionally, 15% of patients required further surgical treatment; among them, two underwent TMR after a failed allograft and experienced complete resolution of their pain.

Three articles comprising 18 patients described the use of TMR in CRPS patients [Table 4]. Stoehr *et al.* described the implementation of TMR at the time of amputation, while the other two reports delayed TMR associated with neuroma excision[26]. In all, 17 of 18 patients showed improvement in pain postoperatively. Interestingly, in the CPRS paper by Shin *et al.*, all patients met the definition of chronic pain (> 3 months); however, two patients were treated within one year and had better outcomes than those treated after one year[27].

Table 2. Immediate *vs.* delayed TMR for amputation

Author(s) year	Article type	Number# of patients	Age average Immediate/ delayed	Average follow-up (months) Immediate/ delayed	RLP pain scale		PLP pain scale		RLP PROMIS Intensity Behavior Interference		PLP PROMIS Intensity Behavior Interference	
					Acute	Delayed	Acute	Delayed	Acute	Delayed	Acute	Delayed
Reid *et al.*, 2024[6]	Prospective cohort	25/18	46.0/42.5	11.0/10.0	1.9	6.2	--	--	--	--	--	--
Goodyear *et al.*, 2024[5]	Retrospective review	73/32	52.2/51.7	18.0/22.9	0	3	0	2.5	36.3 48.0 40.7	46.5 53.0 45.3	36.3 50.1 40.7	40.2 52.6 48.9
Hoyt *et al.*, 2021[21]**	Retrospective Review	28/59	35	14	1.0	1.7	--	--	--	--	--	--

**Outcome data are combined with RPNI and combination procedures. TMR: Targeted muscle reinnervation; RLP: residual limb pain; PLP: phantom limb pain; PROMIS: Patient-Reported Outcomes Measurement Information System.

One article reported on two patients who received TMR at the time of amputation for painful neurofibromas associated with NF1 [Table 4]. Both patients had improved pain 18 months after amputation, with no new neuromas or fibromas noted, and were able to successfully use prosthetics.

A total of 151 cancer patients treated with TMR at the time of amputation were included in 5 articles. Two articles reported control group pain metrics [Table 4][28,29]. Of note, O'Brien *et al.* did not separate outcomes between oncologic patients and others[28]. Additionally, Valerio *et al.* showed that no patients developed neuromas, and 75% had resolution of their PLP by 3 to 6 months post-op[30]. Although chemotherapy induced neuropathy and pain directly associated with tumor burden may have been present prior to amputation, these data are not reported.

Ischemia and infection were combined for analysis in all articles. Two articles involving 112 patients described treatment with TMR [Table 4]. O'Brien *et al.* combined their data with that of oncologic patients, demonstrating improvements in pain over time[28]. Chang *et al.* reported 14% of patients living with RLP and 19% living with PLP, compared to 57% and 47%, respectively, in the non-TMR cohort[31]. Again, the role of pre-amputation pain was not distinguished.

Finally, we sought to determine the overall change in pain scores within comparison groups. When assessing the timing of TMR, delayed TMR patients were compared to iTMR patients. Delayed patients had a greater improvement in RLP but less of an improvement in PLP, when assessed against iTMR patients who were compared to non-TMR standard amputees [Table 5]. Summary of outcomes and changes in pain scores for comparison groups are presented in Tables 5 and 6.

Table 3. Delayed TMR for the treatment of preexisting neuroma or phantom limb pain

Author(s) year	Article type	Neuroma or amputation	Number# of patients	Age average	Average follow-up (months)	RLP pain scale		PLP pain scale		RLP PROMIS Intensity Behavior Interference		PLP PROMIS Intensity Behavior Interference	
						Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
Dumanian *et al.*, 2019[57]	Randomized control trial	Amputation	15	39.6	12	6.6	3.0	5.8	2.3	55.7 61.5 64.4	44.5 56.8 56.8	52.4 58.3 60.2	38 50.7 50.4
Felder *et al.*, 2022[58]	Case series	Amputation	2	55.2	7.5	9	1.5	--	--	-- -- --	-- -- --	-- -- --	-- -- --
Roubaud *et al.*, 2023[59]	Retrospective cohort study	Amputation	7	45.5	12	--	2.8	--	4	-- -- --	-- -- --	-- -- --	-- -- --
Vincitorio *et al.*, 2020[60]	Case report	Amputation	1	27	24	6.5	3.0	--	--	-- -- --	-- -- --	-- -- --	-- -- --
Kang *et al.*, 2022[25]	Retrospective review	Amputation	36	49	18	5.3 UE 7.65 LE	0.4 UE 3.6 LE	6.4 UE 7.55 LE	2.0 UE 4.95 LE	-- -- --	-- -- --	-- -- --	-- -- --
Mioton *et al.*, 2020[61]	Prospective cohort	Amputation	33	42.2	40.6	6.4	3.6	6	3.6	53.4 55.9 60.4	44.4 51.9 51.7	49.3 55.5 57.7	43.2 50.6 50.8
Daugherty *et al.*, 2019[22]	Case report	Neuroma	1	60	72	8	2	--	--	70 - 70	40 - 55	-- -- --	-- -- --
Takagi *et al.*, 2020[62]	Case report	Neuroma	1	49	6	3*	0*	--	--	-- -- --	-- -- --	-- -- --	-- -- --
van Opijnen *et al.*, 2022[63]	Case report	Neuroma	1	55	12	9	4	--	--	-- -- --	-- -- --	-- -- --	-- -- --
Chappell *et al.*, 2021[51]	Retrospective cohort study	Neuroma	10	46.5	18.9	--	avg: 2.8# max: 4.6#	--	--	-- -- --	-- -- --	-- -- --	-- -- --
Chang *et al.*, 2021[31]	Retrospective cohort study	Neuroma	14	53.1	8.1	7.9	4.3	--	--	-- -- --	-- -- --	-- -- --	-- -- --
Ferrin *et al.*, 2024[64]	Case series	Neuroma	3	28	14.3	7.6	1	--	--	-- --	-- --	-- --	-- --

											--	--	--	--	
Cavadas and Téllez Palacios, 2020[65]	Case report	Neuroma	1	49	12	8	3	--	--	--	--	--	--		
											--	--	--	--	
											--	--	--	--	

[#]Article reported outcomes for TMR and non-TMR allografts were combined; [*]VAS scores converted from 100-point scale to 10-point scale for comparison. TMR: Targeted muscle reinnervation; RLP: residual limb pain; PLP: phantom limb pain; PROMIS: Patient-Reported Outcomes Measurement Information System.

DISCUSSION

As TMR becomes the standard of care in treating and preventing amputation-related pain, it has become more evident that chronic or preexisting pain can affect the success of the procedure. Figure 2 demonstrates the TMR construct for a trans-humeral amputation. Studies included in our data show that patients without a preexisting pain condition who received iTMR did not develop neuromas. Several patients still developed PLP, but this pain was rated less severely than those who did not undergo TMR. In contrast, amputees with preexisting RLP and/or PLP and non-amputees with painful neuromas tended to have reduced pain following TMR but were less likely to have their pain entirely extinguished[5,6,21].

Considering the nature of amputation-related pain, it is possible to understand some of the reasons why TMR is successful as a preventative measure. RLP is a direct consequence of neuroma formation and TMR appears to prevent neuroma formation. In an animal model of TMR, excising the neuroma alone does not result in analgesia; the coaptation of the injured nerve to a small motor branch is still necessary. In this sense, TMR can "restart the clock" and prevent neuroma re-formation. However, the residual effects of the previous neuroma, such as increased inflammation and sympathetic innervation in the dorsal root ganglia, may remain and contribute to pain[32-35]. These changes increase neuronal sensitization and support spontaneous afferent activity which translates to pain[36,37]. Removing the neuroma may reverse some of these changes, but in the transition from acute to chronic pain, there may be a threshold after which the changes cannot be reversed.

PLP, although much less understood, is known to be associated with cortical reorganization in which the neighboring portions of the sensorimotor cortex move into the areas of cortex previously inhabited by the amputated part. However, the relationship between reorganization and pain remains controversial, with some data supporting that maladaptive reorganization contributes to pain, while others propose that chronic pain drives neural plasticity, resulting in reorganization[38-41]. TMR, in a human study and an animal study, partially reversed this type of reorganization. An important caveat is that the patients underwent TMR 0.5-1.5 years following amputation[15,42]. Even in the animal study where iTMR was performed, full normalization was not apparent[12]. Again, there may be a threshold after which these changes may not be fully, or sufficiently, reversible. Whether the change itself is maladaptive remains to be determined.

Table 4. Preexisting pain conditions

Author(s) year	Article type	Pain condition	Number# of patients	Age average	Average follow-up (months)	RLP pain scale		PLP pain scale		RLP PROMIS Intensity Behavior Interference		PLP PROMIS Intensity Behavior Interference	
						Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
Chang *et al.*, 2021[31]	Randomized control trial	Infection[+]/ chronic wound, ischemia	100	59.7	9.6	5.2	3.2	--	--	-- -- --	-- -- --	-- -- --	-- -- --
Roubaud *et al.*, 2023[59]	Case series	Cancer[*]	63	53.3	11.3	--	1.3	--	1.9	-- -- --	6.2 14.6 39	-- -- --	-- -- --
Huffman *et al.*, 2024[66]	Retrospective cohort study	Cancer[*] and infection[+]	8	61	--	--	2.2	--	--	-- -- --	-- -- --	-- -- --	-- -- --
O'Brien *et al.*, 2022[28]	Case report	Cancer[*], infection, ischemia[+]	81	52.1	2.4	4	1.04	5	0.96	-- 57.3 43.07	-- 57.3 44.1	-- 56.6 45.6	-- 55.8 42.4
Shin *et al.*, 2022[27]	Case report	CRPS II	13	42.1	9.8	6	2.45	--	--	-- -- --	-- -- --	-- -- --	-- -- --
Stoehr *et al.*, 2020[26]	Case report	CRPS	4	47.3	12.75	--	5	--	2	-- -- --	50.7 54.7 60.5	-- -- --	46.1 55.2 57.5
Adu *et al.*, 2024[67]	Case report	CRPS	1	28	8	6	2	--	--	-- -- --	-- -- --	-- -- --	-- -- --
Shin *et al.*, 2023[68]	Retrospective cohort study	NF1	2	33	14	8	1	--	--	-- -- --	1	-- -- --	-- -- --

[*]Cancer includes all patients who received amputation with TMR due to an oncologic diagnosis with or without defined preoperative pain; [+]Ischemia and infection were not separated in most articles, so they are combined here for simplicity. RLP: Residual limb pain; PLP: phantom limb pain; PROMIS: Patient-Reported Outcomes Measurement Information System; CRPS: complex regional pain syndrome; NF1: neurofibromatosis 1.

Table 5. Average changes in pain scores based on condition

Category	Subcategory	Number# of articles*	Total number# of patients	Delay timeline	Numeric pain score**	
					RLP	PLP
Neuroma pain	Limb neuroma	5	39	1-5 years	-4.03	--
	Abdominal wall neuroma	1	10	Not stated	--	--
Chronic pain state	CRPS	2	14	4 mo. to > 1 year	-3.58	--
	NF1	1	2	years	-7	+1
Timing of TMR	Immediate TMR	7	235	NA	-2.58	-4.26
	Delayed TMR	6	91	90 days to > 10 years	-3.7	-2.7

*Includes only articles with pre- and post-pain scores, except for immediate TMR where patients were compared to non-TMR standard amputees; **All pain scores were reported on a 0-10 scale. RLP: Residual limb pain; PLP: phantom limb pain; CRPS: complex regional pain syndrome; NF1: neurofibromatosis 1; TMR: targeted muscle reinnervation.

Table 6. Summary of results by category

Category	Subcategory	Articles	Total patients	Key findings
Preexisting pain	Limb neuroma	6	40	Observed pain score reductions; decreased PROMIS pain intensity and interference scores.
	Amputation-related RLP and PLP	22	556	Immediate TMR appears superior to delayed; reduced neuroma development and pain scores.
	Abdominal wall case	1	10	Improvement in pain at first post-op visit for 85%; 15% required further surgery.
Chronic pain state	CRPS	3	18	Improvement post-op; better outcomes within 1 year of diagnosis.
	NF1	1	2	Improved pain 18 months post-amputation, no new neuroma/fibroma development.
	Oncologic	5	151	Less RLP and PLP; observed resolution of PLP by 3-6 months post-op.
	Ischemia/ infection	2	112	Improved RLP and PLP scores post-TMR.
Timing of TMR for amputation	Immediate TMR	11	303	Lower neuroma development compared to delayed, high success with TMR prosthesis
	Delayed TMR	15	253	Higher pain scores, increased neuroma development.

RLP: Residual limb pain; PLP: phantom limb pain; CRPS: complex regional pain syndrome; NF1: neurofibromatosis 1; TMR: targeted muscle reinnervation; PROMIS: Patient-Reported Outcomes Measurement Information System.

The relative severity of injury, whether a single affected nerve versus multiple nerves injured in an amputation, likely also influences the degree of analgesia achieved with TMR. Sensory neuron loss is non-linear in relationship to the number of nerves injured[43-46]. In the case of a single nerve injury, sensory neurons will die, but are still surrounded by healthy tissue, leading to less overall nerve damage. In contrast, multiple nerves are severed in a major limb amputation and there are fewer healthy neurons to support the injured neurons, so there is greater neuronal loss[47]. Hu *et al.* showed that if the sural nerve is

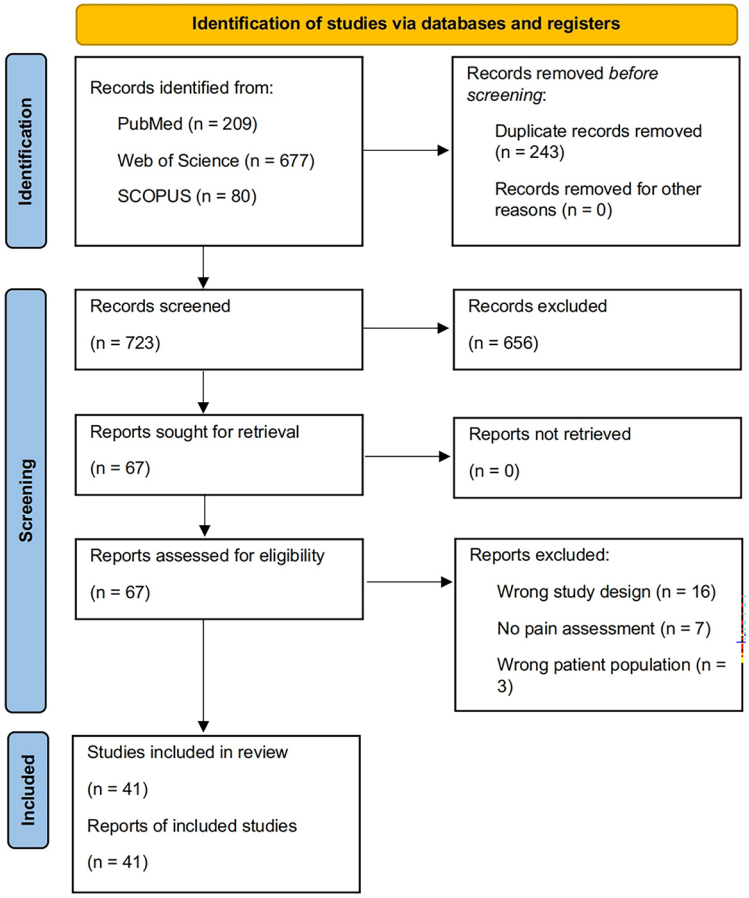

Figure 1. PRISMA diagram outlining screening of articles to be included in final analysis.

approximately 30% of the sural nerve neurons will die, and if the entire sciatic is cut, 58% of the sural nerve will die[45]. To account for this, we analyzed single-nerve neuroma TMR separately from major limb amputation. We found that patients with a single neuroma repaired by TMR experienced pain resolution, which enabled them to regain the function that had been lost due to the pain. Single neuromas are an interesting subset of TMR indications because they are often smaller sensory-only nerves and, by definition, present with preexisting pain. The lack of accompanying motor fibers may or may not play a role: the environment of TMR favors motor neuron regeneration, but a lack of competing motor axons may facilitate sensory neuron regeneration[48-50]. The preexisting pain environment of a neuroma would favor a poorer outcome, but the overall smaller size of the nerve may support a healthier neuron population. Although preventative management of neuromas is generally not possible, sooner intervention would be advantageous.

There were no strong trends in pain location affecting outcomes, although the data are sparse. One paper examined 10 patients who underwent TMR or nerve allograft for painful abdominal wall neuromas[51]. This is one of the very few studies reporting TMR outcomes for non-limbs. As more of these studies are done, we can better evaluate how to apply TMR to manage neuroma pain in broader patient populations, including those with breast, abdominal, and cosmetic issues. Additionally, Kang *et al.* found that 12 of the 29 lower extremity patients experienced the "unmasking" of additional neuromas after TMR[25]. This raises questions about which nerves should be treated in areas where multiple nerves are affected, as unmasking represents a

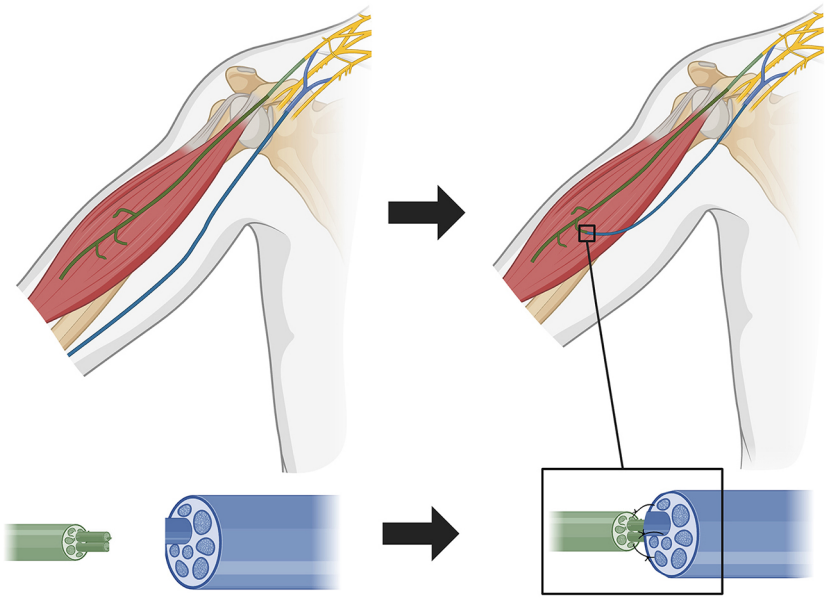

Figure 2. TMR involves the coaptation of amputated nerves (often large mixed motor and sensory nerves) to much smaller intramuscular motor branches. In a trans-humeral amputation, the median nerve is coapted to a musculocutaneous branch. This allows median nerve signals to create an electromyographic signal to facilitate prosthesis control. Clinically, TMR has been found to prevent and treat amputation-related pain. Created in BioRender. Dominguez, E. (2024) BioRender.com/n95n750. TMR: Targeted muscle reinnervation.

preventable delay in treatment.

CRPS is a tremendously debilitating condition, and although symptoms are generally focused on a limb, amputation is often ineffective or deleterious[52]. Although only 18 patients in our data received TMR for the treatment of CRPS, it appears to be a promising treatment option for patients with longstanding disease, refractory to other therapies. Patients in this group had both neuroma repair and amputation, and nearly all patients reported improvement in pain and functionality. Interestingly, all patients in Shin *et al.*'s study met the definition of chronic pain (> 3 months); however, the three patients who were treated within one year (4 to 11 months) had better pain-related outcomes than those treated after one year[27]. These findings suggest that TMR, as a peripheral intervention, remains impactful and may give insight into the mechanisms underlying CRPS.

Neurofibromatosis, cancer-related pain, and pain related to vascular insufficiency and chronic infection are also sources of pain that might affect TMR outcomes. Across these patient populations, there was a general improvement in pain with TMR, but future studies will need to parse out these variables so that we can better predict outcomes. For example, in the setting of cancer, there is generalized pain from the tumor itself and pain related to therapy: radiation neuritis and chemotherapy-induced neuropathy, three separate pain mechanisms. Without a better understanding of the mechanistic pathway by which TMR analgesia is effective, it is challenging to predict outcomes with TMR.

This review highlights the broadening use of TMR and describes its effectiveness in the presence of chronic pain and in relationship to delayed treatment, but there are significant limitations. Often only some pain and quality of life measures could be compared across studies. Character and duration of preexisting pain require detailed exploration as they very likely have a role in response to TMR. However, the focus of these studies has been limited to pain related to the affected anatomic area. The most significant limitation was

the timeline of delayed TMR: large variation existed both across and within studies. We aimed to characterize how an increase in the delay of TMR affected pain outcomes; however, since many studies combined data with variable timelines (months to greater than 10 years), this was limited. Studies have shown that delayed TMR is not as effective as immediate; however, further delineating the most effective window of opportunity is still a critical goal of future research.

CONCLUSIONS

TMR is highly effective at preventing neuroma formation and limiting RLP and PLP when performed at the time of amputation. Additionally, TMR is successful in treating single neuroma pain in the trunk and limbs. TMR also shows promise as a treatment option for certain chronic pain conditions, such as CRPS and NF1; however, current sample sizes are quite small. When TMR is delayed, it leads to milder pain improvements, and the exact mechanism for this difference is unclear. Further research into the basic science and pathophysiology of TMR is warranted to better understand and optimize its effectiveness in pain control and prevention.

DECLARATIONS

Authors' contributions

Study design, data collection and analysis, manuscript writing and revision, creation of figures and graphics: Dominguez E
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All authors declared that there are no conflicts of interest.

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Not applicable.

Consent for publication

Not applicable.

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