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PŮVODNÍ PRÁCE

A Systematic Review and Meta-Analysis of the Outcomes of Reconstruction with Vascularised vs Non-Vascularised Bone Graft after Surgical Resection of Primary Malignant and Non-Malignant Bone Tumors

Systematický přehled a metaanalýza výsledků rekonstrukce vaskularizovaným a prostým kostním štěpem po chirurgické resekci primárních maligních a nezhoubných kostních nádorů

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ABSTRACT

PURPOSE OF THE STUDY

Vascularised bone grafting (VBG) and non-vascularised bone grafting (NVBG) are crucial biological reconstructive procedures extensively employed in the management of bone tumours. The principal aim of this study is to conduct a comparative analysis of the post-resection outcomes associated with the utilisation of vascularised and non-vascularised bone grafts.

MATERIAL AND METHODS

A comprehensive and systematic literature review spanning the years 2013 to 2023 was meticulously executed, utilising prominent online databases including PubMed/Medline, Google Scholar, and Cochrane Library. Inclusion criteria were restricted to comparative articles that specifically addressed outcomes pertaining to defect restoration following bone tumour resection via vascularised and non-vascularised bone grafting techniques. The quality of research methodologies was assessed using the Oxford Quality Scoring System for randomised trials and the Newcastle Ottawa Scale for non-randomised comparative studies. Data analysis was conducted using SPSS version 24. Key outcome measures encompassed the Musculoskeletal Tumour Society Score (MSTS), bone union duration, and the incidence of post-operative complications.

RESULTS

This analysis incorporated four clinical publications, enrolling a total of 178 participants (comprising 92 males and 86 females), with 90 patients subjected to VBG and 88 to NVBG procedures. The primary endpoints of interest encompassed MSTS scores and bone union durations. Although no statistically significant distinction was observed in the complication rates between the two cohorts, it is noteworthy that VBG exhibited a markedly superior bone union rate ($P<0.001$).

CONCLUSIONS

Our systematic evaluation revealed that VBG facilitates expedited bone union, thereby contributing to accelerated patient recovery. Notably, complication rates and functional outcomes were comparable between the VBG and NVBG groups. Moreover, the correlation between bone union duration and functional scores following VBG and NVBG merits further investigation.

Key words: reconstruction techniques, vascularised bone grafting, non-vascularised bone grafting, bone tumor, resection.

INTRODUCTION

Primary bone tumours arise from primitive mesenchymal cells and are relatively infrequent compared to metastatic bone malignancies, with an estimated annual incidence rate of 0.8 cases per 100,000 individuals (30). The most prevalent malignant bone tumours include osteosarcoma, Ewing's sarcoma, and chondrosarcoma, whereas common benign bone tumours comprise osteochondromas and giant cell tumours (3, 10, 28). In the therapeutic management of various bone tumours, surgical excision followed by reconstruction holds a pivotal role (27). Reconstructive procedures encompass a spectrum of approaches, such as prosthetic implants, vascularised bone grafts (VBG), and non-vascularised bone grafts (NVBG) (12). Bone grafting entails the restoration of bone defects through the application of autografts or allografts and is widely employed for the correction of bone deformities and the restoration of bone loss (1).

Vascularised bone grafting involves the reconstruction of bone coupled with its vascular supply, ensuring

adequate blood circulation through the anastomosis of vascular pedicles (15, 26). Conversely, NVBG lacks an inherent blood supply and relies on nourishment from neighbouring bone cells and the medullary cavity.

Although recent systematic reviews have delved into aspects of bone grafting, they have not comprehensively addressed functional outcomes or the duration of bone union when comparing VBG and NVBG for the reconstruction of defects following the surgical excision of bone tumours. Allsopp et al. (2) sought to elucidate the origin of the "6cm rule" and to assess the robustness of evidence supporting the use of VBG versus NVBG for grafts of varying lengths. Landau et al. (18) demonstrated the utility of VBG but refrained from a direct comparison between VBG and NVBG. On the other hand, Othman et al. (24) and Houben et al. (13) conducted comparisons between VBG and NVBG but concentrated solely on the lower extremities. Consequently, a comprehensive review comparing VBGs and NVBGs in the context of tumour excision and reconstructive surgery, with the aim of establishing clinical guidelines, has been conspicuously absent.

The principal objective of this review is to assess the functional outcomes of vascularised and non-vascularised bone grafts following the resection of bone tumours. Specifically, our aim is to investigate disparities in functional outcomes, bone union duration, and the incidence of complications between VBGs and NVBGs.

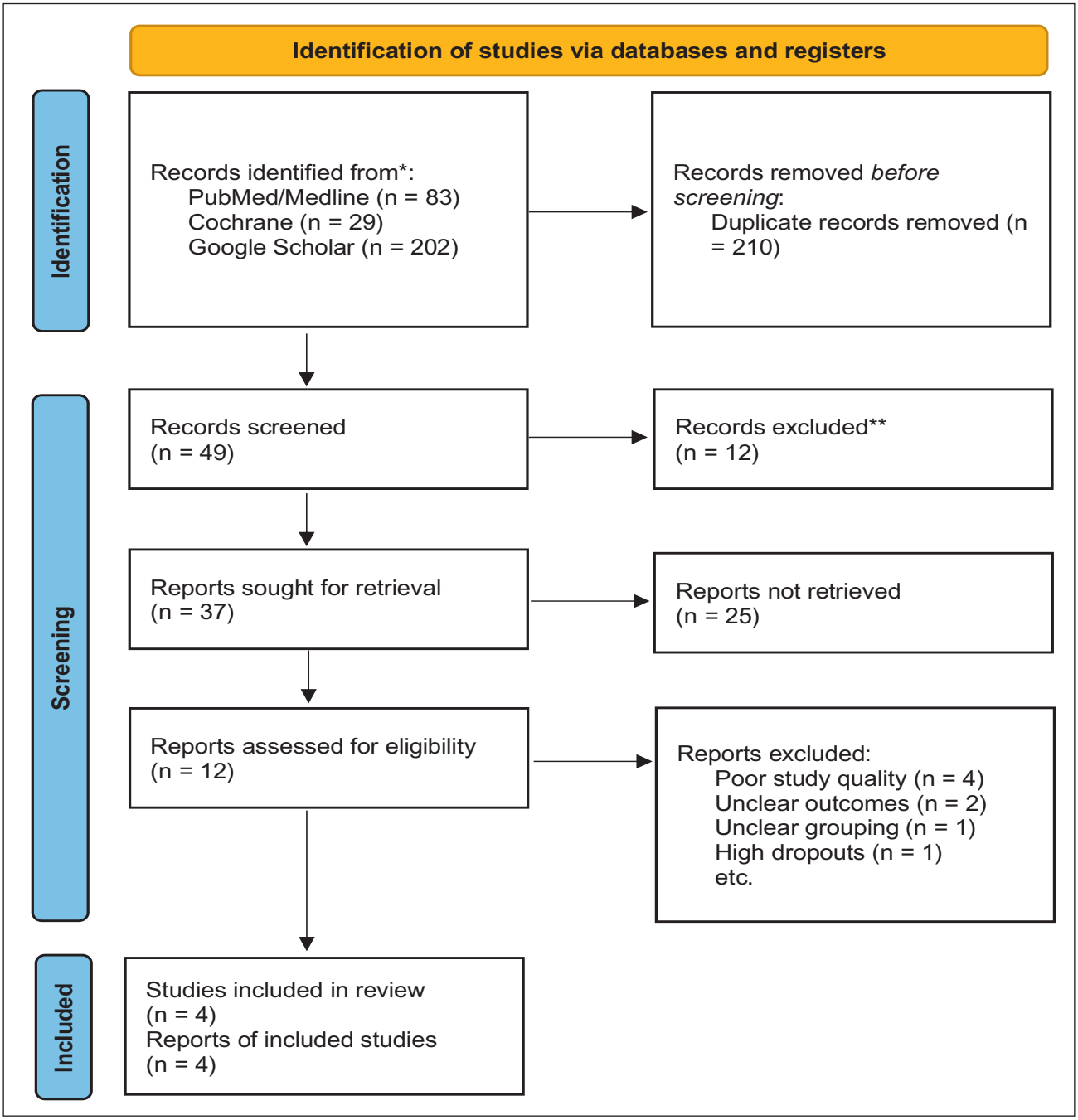

Fig. 1: PRISMA chart showing the inclusion and exclusion of studies.

MATERIAL AND METHODS

Strategy

The "Preferred reporting items for systematic reviews and meta-analysis (PRISMA)" tool was used to collect data on the results after reconstruction of Vascularised and Non-Vascularised bone graft after resection of bone tumors. To guarantee quality assessment ratings, the available literature was examined using the PRISMA tool. The PRISMA chart is shown in Fig. 1.

Database

PubMed/Medline, Google Scholar and Cochrane library were searched from 2012 to 2023 with the MESH terms "vascularized bone graft", "non-vascularized bone graft", "bone tumors" and "reconstruction" using various combinations for comparative trials in English on the human specimen. The references from these trials that were included were also examined for further relevant studies.

Inclusion and exclusion criteria

The formulation of inclusion and exclusion criteria was the result of meticulous deliberation among the research team. The inclusion criteria were exclusively restricted to comparative research studies, notably randomised trials and cohort studies, focusing on the evaluation of specific outcomes pertaining to defect restoration subsequent to the resection of bone tumors. Specifically, these studies examined and compared the use of vascularized and non-vascularized bone grafts. Our analysis encompassed studies involving primary treatment modalities, specifically complete surgical resection, or curettage, either as standalone approaches or in conjunction with pharmacological interventions such as denosumab, bisphosphonates, or steroids. Studies that included participants subjected to adjuvant or neoadjuvant radiotherapy were also incorporated into the review.

Conversely, individuals who had previously undergone any form of reconstructive surgery were categorically excluded from consideration in our study. Likewise, participants who had undergone bone graft procedures for the management of fractures were also excluded from our analysis. Furthermore, our study excluded literature typologies including letters, brief communications, commentaries, editorials, case reports, cohort studies, cross-sectional studies, conference papers, proceedings, and personal communications.

To ensure a comprehensive scope of data collection, our corresponding author proactively engaged with the authors of the included trials. The objective was to solicit any potentially pertinent outcomes that might have been inadvertently overlooked during the exclusion process, particularly in cases where no response or an inadequate response was received.

Risk of bias and quality assessment

Each of the authors independently assessed the methodological quality of the research employing the "Oxford Quality Scoring System (OQSS)" for randomized trials. As per the OQSS criteria, a trial was categorised as high-quality if it received a score of 5 or 4, while a score of 3 or 2 indicated an average-quality trial, and a score of 1 or 0 denoted a low-quality study (14). Non-randomized comparative research, on the other hand, was evaluated using the Modified Newcastle-Ottawa Scale. In this context, trials were considered excellent if they garnered a score exceeding 7 stars, designated as fair if they received 4 to 7 stars, and categorised as poor if they obtained less than 4 stars (23).

In instances where disparities in assessments emerged among the authors, internal deliberations were employed as a means of resolution. In cases where consensus could not be achieved through discussions, the senior author (RP) assumed the responsibility of making the ultimate determination. The summary of bias risk for each of the studies is presented in Table 1.

Data extraction

The following data was taken from each study by all authors i.e.: year of publication, country of the study, study design, population size, participants in each group, surgical intervention, gender, age, follow-ups, MSTS, duration time-to-union, and complications. The extracted data is displayed in Tables 1 and 2.

Table 1. Study characteristics of the studies included in review

Study name	Year	Country	Study design	Surgery performed	Total patient	VBG vs NVBG	Age	Gender M:F	Follow-up	Study quality
Estrella et al. (8)	2017	USA	Comparative study	Fibular grafting	52	25:27	23.8±9.8	25:27	37.5±30.95	Good
Schuhet al. (29)	2014	Austria	Comparative study	Diaphyseal resection and reconstruction	53	26:27	20.5±9.52	26:27	53.7±9.17	Good
Clarkson et al. (6)	2013	Canada	Comparative study	Wrist arthrodesis with fibular and iliac graft	27	14:13	32.5±10	11:16	NA	Fair
Errani et al. (7)	2021	USA	Comparative study	Femoral intercalary reconstruction	46	25:21	11.5±2.5	30:16	123.5±12.34	Fair

Table 2. Outcomes of included studies

Study name	MSTS in VBG	MSTS in NVBG	Complications in VBG	Complications in NVBG	Bone union time in VBG	Bone union time in NVBG
Estrella et al. (8)	83.5±10.6	81.8±15.3	3	7	12.8±5.8	10.6±4.2
Schuh et al. (29)	77.9±8.25	75.8±15	19	9	6.1±1.05	10±4.88
Clarkson et al. (6)	90±12.5	90±15	1	2	6.9±3.3	5.5±2
Errani et al. (7)	86.33±11.67	89±7.67	11	6	NA	NA

Outcomes

The primary outcomes of this systematic review are the functional outcome measured by the musculoskeletal tumour society score (MSTS) and the time-to-union. The secondary outcomes include the frequency of complications including infections, fractures, non-union, and reoperations (Table 3).

Statistical analysis

The data analysis process was initiated by the authors, who utilised SPSS version 24 for data analysis (IBM Corp, Armonk, New York). Categorical variables were presented as numerical values, while continuous variables were expressed as Mean +/- standard deviation. Within the forest plots, estimates were grouped based on the risk ratio (RR), along with its associated 95% confidence interval (95% CI). Categorical data was visually represented using a 2 x 2 table format.

To present the findings, the DerSimonian and Laird random-effects model was applied in conjunction with the generic inverse variance approach, facilitated by the OpenMetaAnalyst Software. The Risk Ratio (RR) pertaining to complications and re-operations following VBG and NVBG was synthesized using a random-effects model, accompanied by a 95% confidence interval (95% CI). Meanwhile, the estimates concerning the Musculoskeletal Tumor Society Score (MSTS) and the duration of union subsequent to VBG and NVBG were synthesized using the standardized mean difference (SMD).

The assessment of heterogeneity was performed through I2 statistics, where heterogeneity was considered negligible with an I2 below 25%, low with an I2 ranging from 26 to 50%, moderate with an I2 from 51 to 75%, and high when I2 exceeded 75%.

In order to discern the factors influencing the success or failure of VBG and NVBG, a random-effects meta-regression analysis was employed. This analysis was utilized specifically to investigate significant between-study heterogeneity that was moderate or high ($I2 > 50\%$, p-value < 0.05) with respect to primary outcomes.

RESULTS

Study characteristics

During the search for literature from databases, we identified 83 studies from PubMed/Medline, 29 studies from Cochrane and 202 studies from Google Scholar. The studies were screened by titles and 210 duplicate studies were removed. During the abstract screening of 49 articles after duplicate removal, 37 articles were excluded, while full texts of 12 studies were reviewed for eligibility according to the inclusion and exclusion criteria. Eight studies were excluded after reading the full text due to ineligibility, poor methodology, unclear outcomes, high rate of dropouts and ambiguous grouping.

Four studies, comprising 90 patients with VBG and 88 NVBG, totaling 178 subjects with 92 males and 86 females, were included in this review, as shown in Table I. The studies were based in Austria (n = 1), USA (n = 2), Canada (n = 1). Two studies were of good quality and two studies were of fair quality. The means of age and follow-up in months of the candidates in included studies were 22.08 ± 7.95 years and 71.57±17.47 months, respectively.

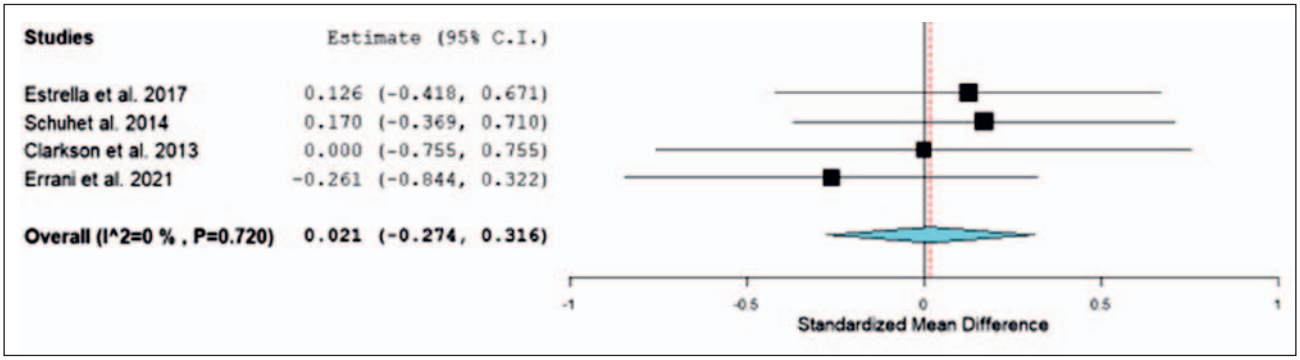

Fig. 2. Forest plot showing the SMD estimates for the MSTS after VBG vs. NVBG, in which the boxes show the effect size, with the length of the corresponding line explaining the 95% confidence interval and the diamond-shaped symbol representing the overall effect size.

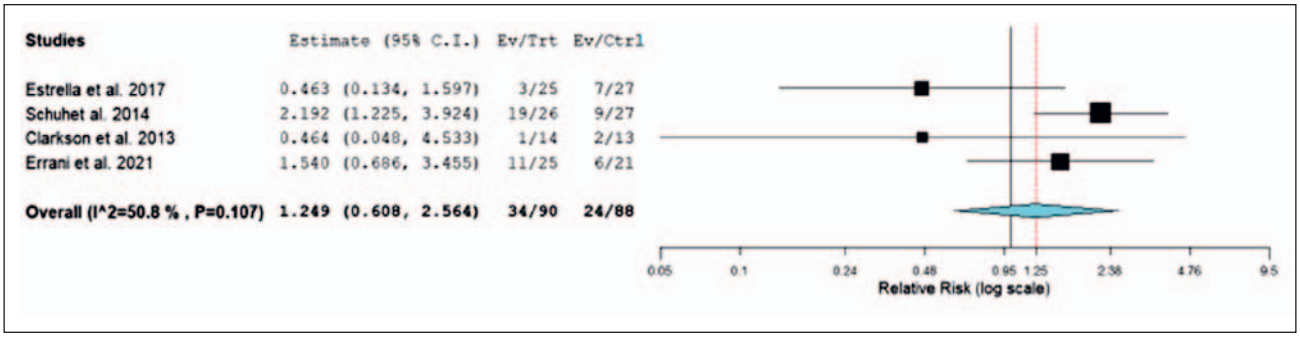

Fig. 3. Forest plot showing the risk ratio (RR) estimates for the incidence of complications after VBG vs. NVBG, in which the boxes show the effect size, with the length of the corresponding line explaining the 95% confidence interval and the diamond-shaped symbol representing the overall effect size.

MSTS

The primary outcomes of our systematic review focused on the MSTS score among VBG and NVBG groups. The difference in standardized mean difference (SMD) between VBG and NVBG was insignificant with 0.021 [95% CI= -0.274, 0.316; P> 0.05] with statistically insignificant heterogeneity (I^2=0%; P=0.72). Therefore, the functional outcomes were the same between both groups as shown in Fig. 2.

Complications

Complications among VBG and NVBG groups showed the risk ratio (RR) between VBG and NVBG was not significant with a value of RR=1.249 [95% CI= -0.608, 2.564; P> 0.05], with statistically insignificant heterogeneity (I^2=50.8%; P=0.107). Hence, the rate of complications is similar to those shown in Fig. 3.

Bone union time

One of the primary outcomes of our systematic review focused on the bone union time among VBG and NVBG groups. The difference in SMD between VBG and NVBG was not significant with a value of -0.064 [95% CI= -1.112, 0.984; P> 0.05] with statistically significant heterogeneity (I^2=88.19%; P< 0.001) as shown in Fig. 4. Therefore, odd one out was attempted to decrease heterogeneity by removing studies one by one.

After exclusion of Schuh et al.(17), the SMD between VBG and NVBG showed that the difference among the group was statistically significant with 0.452 (95% CI= 0.005, 0.899; P< 0.05) as shown in Fig. 5. The heterogeneity value dropped to 0% (I^2=0%; P= 0.897).

DISCUSSION

Surgical resection emerges as a necessary therapeutic recourse for bone tumours, primarily due to their inherent radioresistance and the limited chemotherapeutic efficacy within the osseous milieu. Subsequent to resection, the process of reconstruction assumes paramount significance, invariably pursued through either prosthetic or biological means. While prosthetic reconstruction offers the advantage of expeditious convalescence, it is not without the propensity for long-term complications. In light of these considerations, bone grafting has come to occupy a prominent role in mitigating post-resection bone defects stemming from either pathological or traumatic etiologies. Noteworthy among the donor sites for bone grafts are the iliac crest, proximal and distal tibia, proximal fibula, fibular strut, distal radius, and greater trochanter (22). Within this domain, an ongoing discourse pertains to the selection between vascularised and non-vascularised grafts. The present study seeks to undertake a comprehensive in-

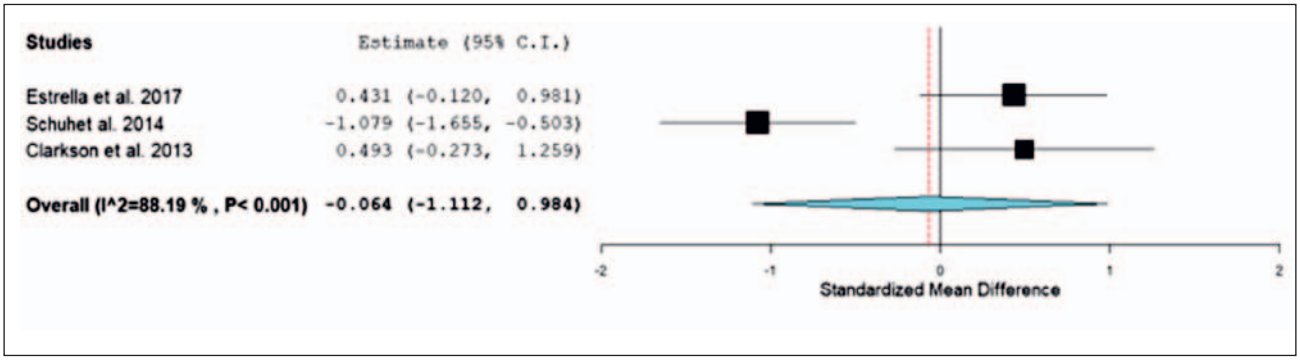

Fig. 4. Forest plot showing the standardized mean difference (SMD) estimates for the bone union time after VBG vs. NVBG, in which the boxes show the effect size, with the length of the corresponding line explaining the 95% confidence interval and the diamond-shaped symbol representing the overall effect size.

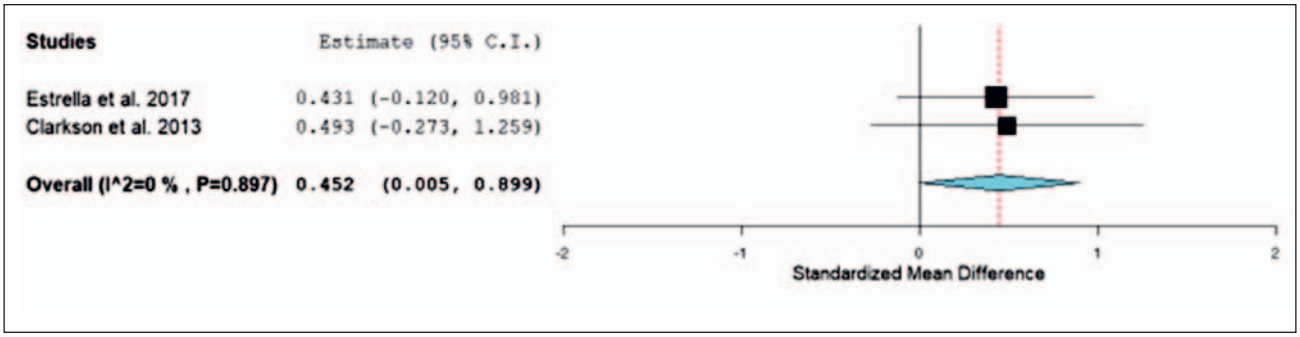

Fig. 5. Forest plot showing the standardized mean difference (SMD) estimates for the bone union time after VBG vs. NVBG, in which the boxes show the effect size, with the length of the corresponding line explaining the 95% confidence interval and the diamond-shaped symbol representing the overall effect size.

vestigation into the functional outcomes ensuing from vascularised bone grafts (VBG) as compared to non-vascularised bone grafts (NVBG) in the aftermath of bone tumour resection. Recent systematic reviews by Landau et al. (18), Othman et al. (24), and Houben et al. (13) have accentuated the potential utility of VBG; however, these assessments predominantly encompassed unipolar investigations and did not explicitly engage in the comparative evaluation of VBG vis-à-vis NVBG.

The synthesised findings from our meta-analysis lead us to proffer the conclusion that, from a statistical standpoint, discernible distinctions in functional outcomes between the two cohorts do not manifest. Consequently, the therapeutic utility of VBG and NVBG appears to maintain equipoise, as appraised across domains encompassing pain perception, range of motion, load-bearing capacity, and social reintegration. This observed contrast with antecedent systematic reviews (18, 13) should be contextualised within the confines of our approach, which rigorously adhered to the inclusion of studies featuring a binary design. Othman et al. (24), while delineating superior functional outcomes within both graft modalities, limited their purview exclusively to the lower extremities. The methodological robustness of our investigation is further buttressed by the conspicuous absence of substantive heterogeneity amongst the enlisted studies, following meticulous quality appraisal. Nonetheless, it is plausible that one of the graft categories may exhibit a proclivity for superior and expeditious functional recuperation during the postoperative trajectory. Drawing upon the insights gleaned from our comprehensive literature survey, a lacuna is discernible in the landscape, warranting further research endeavours to elucidate the temporal dynamics of functional amelioration in VBG and NVBG cohorts. Moreover, the paucity of studies that delve into the biochemical and physiological intricacies distinguishing VBG from NVBG remains noteworthy.

Within the purview of our review, a conspicuous salience is accorded to the expedited bone union achieved within the VBG cohort, a phenomenon corroborated by the findings posited by Othman et al. (24). It is imperative to underscore that the temporal dynamics of bone union are intricately intertwined with the vascular supply (16). The substantive involvement of macrophages in orchestrating bone remodelling processes, culminating in accelerated growth and debris clearance (5), constitutes a plausible explanatory avenue for this phenomenon. Nonetheless, it is incumbent to recognize the dearth of scholarly endeavours explicitly addressing the interrelationship between the temporal aspects of bone union and ensuing functional outcomes. Thus, VBG holds promise in facilitating expeditious convalescence and potentially curtailing the imperative for subsequent surgical interventions, an attribute of particular salience in the context of younger patients necessitating prompt rehabilitation (4). Notwithstanding these merits, the attendant longer intraoperative durations entailed by VBG procedures mandate judicious patient selection criteria (25).

Our review also furnishes an elucidation of complications observed within the purview of both VBG and NVBG groups. Notably, the incidence of complications demonstrates statistical equipoise across these two modalities. This departure from the findings reported by Allsopp et al. (2), Gorski et al. (11), and Eward et al. (9), which posited elevated complication rates in conjunction with VBG, is noteworthy. Within our purview, postoperative infections, bone resorption, and graft failures constitute the purview of complications. From a histological vantage point, the enhanced vascularity characterising vascularised bone grafts ostensibly augments circulatory dynamics, thereby fostering an accelerated healing milieu (31). Nevertheless, discerning scholarship posited by Zhang et al. (32) and Moran et al. (21) introduces a salient caveat, suggesting that heightened vascularisation may confer an enhanced vulnerability to tissue reperfusion injuries entailing free oxygen radicals. Additionally, the scholarship of Marenzana et al. (20) imparts an illuminative perspective, elucidating the capacity of bones to tolerate mild ischemic insults while manifesting a greater propensity for survival with a gradual reperfusion paradigm. In light of these considerations, judicious patient selection

for VBG may mitigate the incidence of complications, as antecedent research underscores the superior antioxidative potential in younger patients, attenuating the risks posed by reperfusion injuries (17).

Recent literature, exemplified by Lesensky et al.'s (2023) study, compared outcomes between two surgical methods for femoral diaphysis reconstructions following bone tumor resection: combined vascularised fibula-allograft constructs and plain allograft reconstructions (19). Their findings highlighted that successful fibular transfer significantly reduced the time to union at junction sites compared to unsuccessful transfers and allografts. Noteworthy incremental changes in bone density at 18 months post-surgery were observed in the combined graft group, suggesting enhanced bone incorporation. Lenskey et al. also found that patients with successful fibular transfers experienced higher bone density increases and better functional scores compared to those with unsuccessful transfers. However, the study underscored a 70% success rate for fibular transfer, with taller, skeletally mature patients at increased risk of failure, emphasizing the need for rigorous patient selection criteria, as corroborated by recent literature (19).

Limitations

Our systematic review is not without certain limitations that merit consideration. Firstly, it is important to note that our analysis was based on a limited data set comprising only four studies. Unfortunately, this restricted sample size precluded us from conducting regression analysis and publication bias tests due to inherent statistical limitations associated with such a diminutive dataset. Secondly, a notable limitation is the absence of randomised trial methodology in any of the studies identified within the existing literature. Thirdly, it should be underscored that our study's scope was explicitly delimited to the comparative assessment of vascularised bone grafts (VBG) versus non-vascularised bone grafts (NVBG), with a limited exploration of prosthetic interventions.

CONCLUSIONS

In conclusion, our systematic review showed that VBG produces earlier recovery due to accelerated bone union. The rate of complications and functional outcomes remained the same in both groups. Therefore, further studies are required to conclude VBG or NVBG as the sole successful method of treatment for bone defects in tumor and reconstruction surgery.

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