

**SYSTEMATIC REVIEW**

# Amputation versus Reconstruction in Severe Lower Extremity Injury: A Systematic Review and Meta-Analysis

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**Abstract**

**Objectives:** Cases of severe lower limb injuries that previously were amenable only to amputation can now, in certain circumstances, be managed with reconstruction. The present systematic review and meta-analysis was designed to compare the results of amputation and reconstruction in severe lower extremity injuries.

**Methods:** PubMed, EMBASE and Cochrane Central Register of Controlled Trails (CENTRAL) were comprehensively searched for studies comparing amputation and reconstruction for severe lower extremity injuries. The search terms used were the following: “amputation”, “reconstruction”, “salvage”, “lower limb”, “lower extremity”, and “mangled limb”, “mangled extremity”, “mangled foot”. Two investigators screened eligible studies, assessed the risk of bias and extracted the data from each study. Meta-analysis was conducted using the Review Manager Software (RevMan, Version 5.4). The  $I^2$  index was used to assess heterogeneity.

**Results:** Fifteen studies with 2,732 patients were included. Amputation is associated with lower rehospitalization rates, lower length of stay in the hospital, lower number of operations and additional surgery and fewer cases of infection and osteomyelitis. Limb reconstruction leads to faster return to work and lower rates of depression. The outcomes with respect to function and pain are variable among the studies. Statistical significance was achieved only with regards to rehospitalization and infection rates.

**Conclusion:** This meta-analysis suggests that amputation yields better outcomes in variables during the early postoperative period, while reconstruction is associated with improved outcomes in certain long-term parameters. Severe lower limb injuries should be managed on their individual merit. The results of this study may be a useful tool to aid in the decision-making for the treating surgeon. High-quality Randomized Controlled Studies are still required to further our conclusions.

**Level of evidence:** III**Keywords:** Amputation, Lower limb injury, Mangled, Meta-analysis, Reconstruction, Salvage**Introduction**

Severe injuries to the lower limb can result in significant morbidity and mortality. The mangled extremity has been historically associated with high amputation rates. More recent advances in both orthopedic and plastic surgery have led to limb salvage procedures to be potentially undertaken in cases that in the past were considered amenable only to amputation. However, although reconstruction may be technically

feasible, it may not be always in the best interest of the patient. The decision between undertaking an amputation and a reconstruction remains challenging with multiple clinical and additional quality of life factors that are unique to every patient, having to be taken into consideration. A number of studies have previously been published reporting the results of amputation and reconstruction after severe lower extremity injury but the results have

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been conflicting.

The purpose of the present systematic review and meta-analysis is to compare the results of amputation versus reconstruction in severe lower limb injuries in terms of recovery, functional outcome, pain, mental health and complications. These results may provide an additional tool to help in the guidance on the management of these injuries.

## Materials and Methods

### Search strategy

This systematic review and meta-analysis was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.<sup>1</sup> We undertook a comprehensive search in PubMed, EMBASE and Cochrane Central Register of Controlled Trails (CENTRAL) from their inception up to July 2022 for Randomized Controlled Trials (RCTs) and two-armed prospective or retrospective studies comparing amputation and reconstruction for severe lower extremity injuries. The search terms used were the following: "amputation", "reconstruction", "salvage", "lower limb", "lower extremity", and "mangled limb", "mangled extremity", "mangled foot" and "crush injury" with "AND" and "OR" as Boolean terms. Reference lists of the related articles were hand-searched for any additional eligible studies in a further effort not to miss out on any relevant publications. Two independent investigators screened eligible studies. When consensus could not be reached, a third reviewer was consulted to resolve the disagreement.

### Eligibility criteria

Articles were included in the meta-analysis based on the following criteria: (1) RCTs and two-armed prospective or retrospective studies comparing amputation and reconstruction for severe lower extremity injuries, (2) studies were designed to compare early amputation vs non-amputation. Exclusion criteria were as follows: (1) other article types (case reports, letters, comments, editorials, reviews, conference abstracts), (2) articles not in English, (3) studies comparing the results of salvage to delayed amputation following limb salvage injury, (4) studies comparing the results of salvage and amputation for lower limb deformity, (5) studies analyzing a subgroup of patients of a study already included in the meta-analysis.

### Extraction of the relevant data

Two investigators extracted the data from the eligible studies. To ensure consistency in the extraction of the data from each study, a structured form was used. Information retrieved from each study included author names, year of publication, study design, sample size, patient characteristics (age, gender, civilian/military), injury type, and outcomes.

### Quality assessment

Two investigators evaluated the risk of bias of each of the included studies using the ROBINS-I tool for observational studies.<sup>2</sup> Each of these factors was recorded as low, moderate, serious or critical risk of bias.

### Statistical analysis

The meta-analysis was conducted using the Review

Manager Software (RevMan, Version 5.4). The results were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). A P-value of less than 0.05 was considered statistically significant. The  $I^2$  index was used to assess heterogeneity. A value of  $I^2$  of less than 25% was interpreted as homogeneity, and values of 25% to 75% and 75% and more were interpreted as moderate and high heterogeneity respectively. The fixed-effect model was used for homogenous studies and the random-effect model was used when there was heterogeneity. Sensitivity analyses were performed to assess the changes in the overall results by omitting studies.

## Results

### Search results and study characteristics

A total of 208 studies were identified from PubMed (n=82), EMBASE (n=93) and CENTRAL (n=33) using the above methodology. After exclusion of the articles that did not meet the eligibility criteria by title or abstract, 24 studies were retrieved for full-article assessment. Three additional studies were identified by citation tracking and hand searching. Nine of the fully-retrieved studies (n=24) were excluded because they did not meet the eligibility criteria. This led to a total of 15 studies from 1993 to 2018 being included in the meta-analysis.<sup>3-17</sup> The total number of patients in the included studies was 2,732 (1,326 amputations and 1,406 reconstructions). The literature search and the selection process are summarized in a flow chart in [Figure 1]. The characteristics of the included studies are presented in [Table 1].

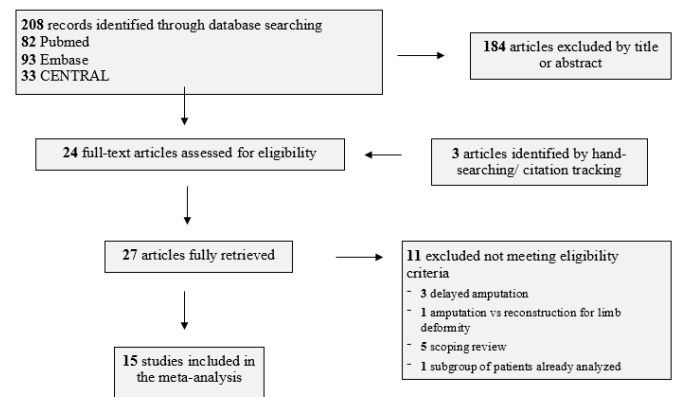


Figure 1. Flow chart summarizing the selection process

### Risk of bias in the included studies

Six of the included studies were found to have a low overall risk for bias based on the ROBINS-I tool. The remaining nine were found to have a moderate risk of bias. In all the included studies the risk of bias in classification of interventions, bias due to deviations from the intended interventions, bias due to missing data, bias in the measurements of outcomes and bias in selection of the reported results was found to be low [Table 2].

Table 1. Characteristics of the included studies

Author, year	Study design	Injury type*	Sample size		Gender, males (%)		Mean age (years)		Patient Characteristics	Follow-up (months) (mean/median)		Outcomes
			A	R	A	R	A	R		A	R	
Georgiadis, 1993	Retrospective	IIIB,C tibial fractures	18	27	NA	NA	32	33	Civilian	44	35	Pain Walking ability Function Employment Gait Range of motion Nottingham Health Profile General Well-Being Schedule Costs
Dahl, 1995	Retrospective	IIIB fractures	30	67	80	71.7	31	28	Civilian	91	108	Function (Questionnaire)
Hertel, 1996	Retrospective	IIIB,C tibial fractures	18	21	NA	NA	22	23	Civilian	83	86	Function (interview) Hospitalization Costs Employee compensation allowances
Dagum, 1999	Retrospective	IIIB,C lower limb fractures	9	46	33.3	71.7	33	37	Civilian	60		Short-Form 36 (SF-36) Western Ontario and McMaster Universities Arthritis Index (WOMAC)
Hoogendoorn, 2001	Retrospective	III tibial fractures	21	43	76.2	76.7	44.6	39.9	Civilian	60		Guides to the evaluation of permanent impairment Nottingham health profile (NHP) Short-form 36 (SF-36)
Bosse, 2002	Prospective	IIIB,C fractures below distal femur Selected IIIA Dyvascular limbs Major soft tissue injuries, IIIB ankle fractures III pilon fractures severe hindfoot/midfoot injuries	161	384	63.4	75	35.2	35.8	Civilian	24		Sickness Impact Profile (SIP), Limb Status Complications leading to Rehospitalization Return to work
Higgins, 2010	Prospective	IIIB,C fractures Selected IIIA Dyvascular limbs Major soft tissue injuries IIIB ankle fractures III pilon fractures Severe hindfoot/midfoot injuries	149	371	NA	NA	NA	NA	Civilian	24		Sickness impact profile (SIP) Return to work Infection, osteomyelitis
Doukas, 2013	Retrospective	IIIB,C fractures Selected IIIA Dyvascular limbs Major soft tissue injuries Severe foot injuries	126	113	96.8	98.2	NA	NA	Military	38.6		Short Musculoskeletal Function Assessment (SMFA) Paffenbarger Physical Activity Questionnaire Participation in a major role activity Revised Center for Epidemiologic Studies Depression Scale (CESD-R) Military version of the PTSD Checklist Chronic Pain Grade (CPG) scale
Ellington, 2013	Prospective	Major soft tissue injuries Severe foot injuries	58	116	NA	NA	NA	NA	Civilian	24		Sickness Impact profile (SIP) Walking speed Time to full weight-bearing Number of rehospitalizations Visual analogue pain scale (VAS) Return to work

Table 1. Continued												
Melcer, 2013	Retrospective	IIIB,C fractures Selected IIIA Vascular injuries Major soft tissue injuries Severe foot injuries	587	117	NA	NA	NA	NA	Military	Minimum 24		Physical complications Psychological diagnoses Health care use
Demiralp, 2014	Retrospective	Complex hind foot injuries (landmine explosions)	21	21	NA	NA	38.4	38.2	Civilian	15.7	14.57	Short-Form 36 (SF-36) Foot and Ankle Disability Index (FADI) Body Image Quality of Life Inventory (BIQLI) Physical complications Psychiatric treatments
Edelstein, 2016	Prospective	Crush injuries to the foot (some extending to the ankle) III fractures	5	16	20		NA	NA	Civilian	Up to 36		Sickness Impact Profile (SIP) Visual Analogue Scale (VAS) Number of rehospitalizations for secondary surgical procedures
Ladlow, 2016	Retrospective	Fractures Nerve damage Extensive soft tissue trauma/ Vascular trauma from blast fragments	79	21	98.7	95.3	38.4	38.2	Military	30/35*	22	6-minute walk test (6MWT) Defense Medical Rehabilitation Centre mobility and activities of daily living scores Depression (Patient Health Questionnaire [PHQ-9]) and general anxiety disorder (General Anxiety Disorder 7-item scale [GAD-7]) Mental health support Pain scores
Barla, 2017	Retrospective	III femoral, tibial and pilon fractures Closed fractures leading to amputation	20	16	75	68.6	47.6	37.4	Civilian	Minimum 12		Mangled Extremity Severity Score (MESS) Complications Bony union Function
Fioravanti, 2018	Retrospective	IIIB,C tibial fractures	24	27	95.8	92.6	43.74	42.37	Civilian	Minimum 24		Short-Form 36 (SF-36) Primary hospital stay Number of procedures Number of infections Function

A: Amputation, R: Reconstruction

\*Gustilo-Anderson Classification for open fractures

\*\* Unilateral/bilateral amputations

NA: Not available

Table 2. Risk of bias of the included studies									
Author, year	Bias due to confounding	Bias in selection of participants into study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result	Overall	
Georgiadis, 1993	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	
Dahl, 1995	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk	
Hertel, 1996	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Dagum, 1999	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk	
Hoogendoorn, 2001	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Bosse, 2002	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low Risk	Low risk	Moderate risk	

Table 2. Continued

Higgins, 2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Doukas, 2013	Moderate risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Ellington, 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Melcer, 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Demiralp, 2014	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Edelstein, 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ladlow, 2016	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Barla, 2017	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Fioravanti, 2018	Low risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk

### Results of the meta-analysis

#### Rehospitalization

The rehospitalization rate was reported in six of the studies<sup>3,8,9,11,12,14</sup> and four of them were included in the quantitative synthesis.<sup>3,8,9,11</sup> The meta-analysis revealed statistically significant lower rehospitalizations in the amputees relative to the patients having undergone a reconstruction (odds ratio [OR] 0.56, 95% confidence interval [CI] 0.42-10.75,  $P < 0.0001$ , and there was no heterogeneity among the included studies ( $I^2 = 0\%$ ) [Figure 2]. In the remaining two studies, Edelstein et al.,<sup>14</sup> in line with the results of the meta-analysis, reported a statistically higher number of rehospitalizations in the reconstructed patients, while Melcer et al.<sup>12</sup> reported higher rates of use of orthopedic wards and pain clinics in the amputees, but the differences between the groups were not significant.

#### Number of operations

The number of operations during the initial admission was reported in five of the included studies.<sup>3, 5, 7, 13, 16</sup> a meta-analysis could not be conducted due to missing mean or standard deviation values. However, in all of the included studies a lower number of operations was reported in the patients having undergone an amputation relative to the patients having undergone a reconstructive procedure. In two of the studies,<sup>5, 13</sup> the differences were reported to be statistically significant.

#### Length of stay

The length of stay was reported in five of the included studies.<sup>3, 5-7, 17</sup> A meta-analysis could not be conducted due to missing standard deviation values. In all of the included studies the length of stay was longer in patients in the reconstruction group, however, only Fioravanti et al.<sup>17</sup> reported statistically significant differences between the

groups.

#### Additional surgery

The number of patients that needed subsequent surgical intervention was reported in four of the included studies.<sup>3, 8,9,14</sup> The meta-analysis showed that amputees required less additional surgery compared to the patients in the reconstruction group, but the differences were not statistically significant (odds ratio [OR] 0.29, 95% confidence interval [CI] 0.08-1.06,  $P = 0.06$ , [Figure 3]) and the heterogeneity was high among the included studies ( $I^2 = 79\%$ ).

#### Return to work

The number of patients that returned to work after severe lower limb injury was reported in nine of the included studies.<sup>3, 4, 6, 8-11, 16, 17</sup> The results of the meta-analysis showed that a higher number of patients returned to work after a reconstructive procedure relative to an amputation, but the differences were not statistically significant (odds ratio [OR] 1.10, 95% confidence interval [CI] 0.89-1.35,  $P = 0.4$ , [Figure 4]). There was no heterogeneity among the included studies ( $I^2 = 17\%$ ).

#### Functional outcome

The functional outcome was reported with different methodological tools in the included studies and therefore a meta-analysis was not performed. Fourteen of the included studies reported functional outcomes. Three of those<sup>4, 8, 9</sup> reported similar outcomes in terms of function between patients with an amputation and patients with a reconstruction. Seven of the included studies<sup>3, 10, 11, 14-17</sup> showed better functional outcomes in patients having undergone an amputation and four of the included studies<sup>5-7, 14</sup> showed better functional outcomes in patients having



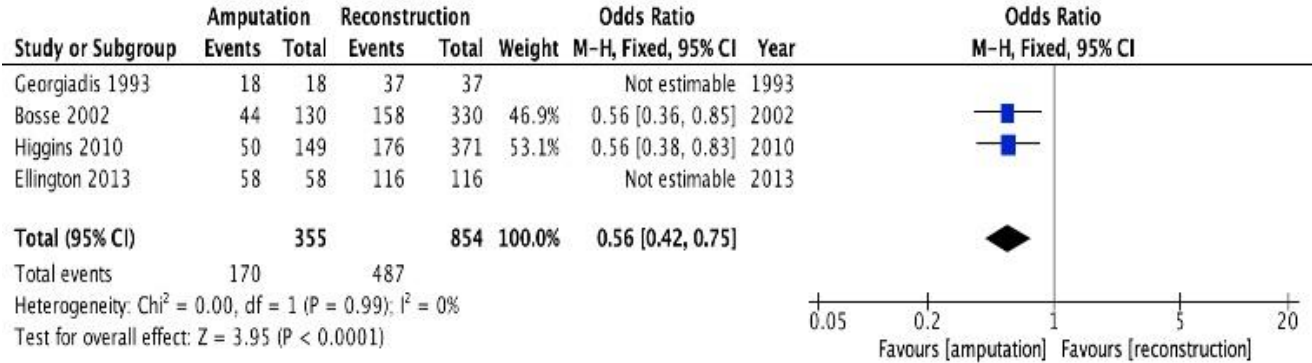


Figure 2. Forest plot of rehospitalization rate in amputation versus reconstruction in severe lower limb injury

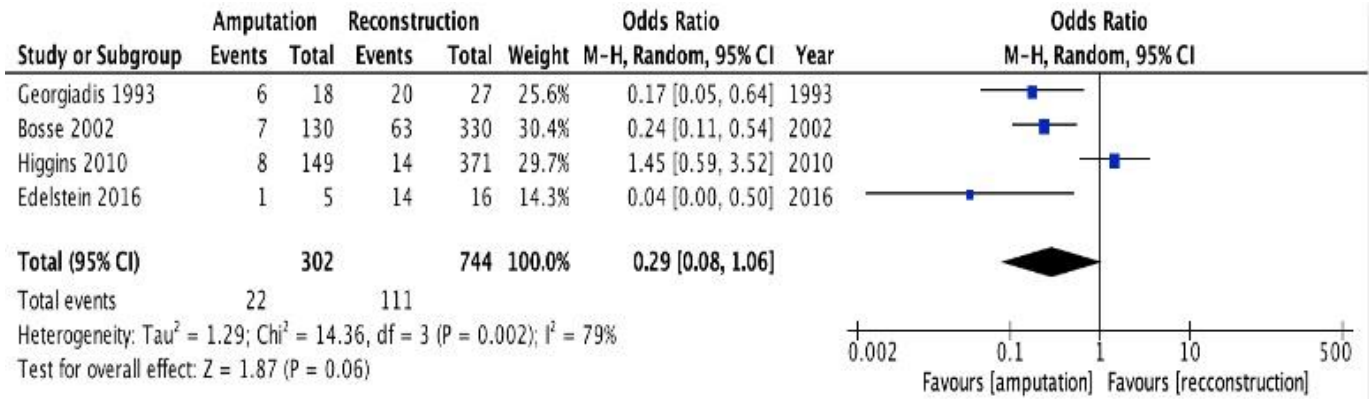


Figure 3. Forest plot of additional surgery in amputation versus reconstruction in severe lower limb injury

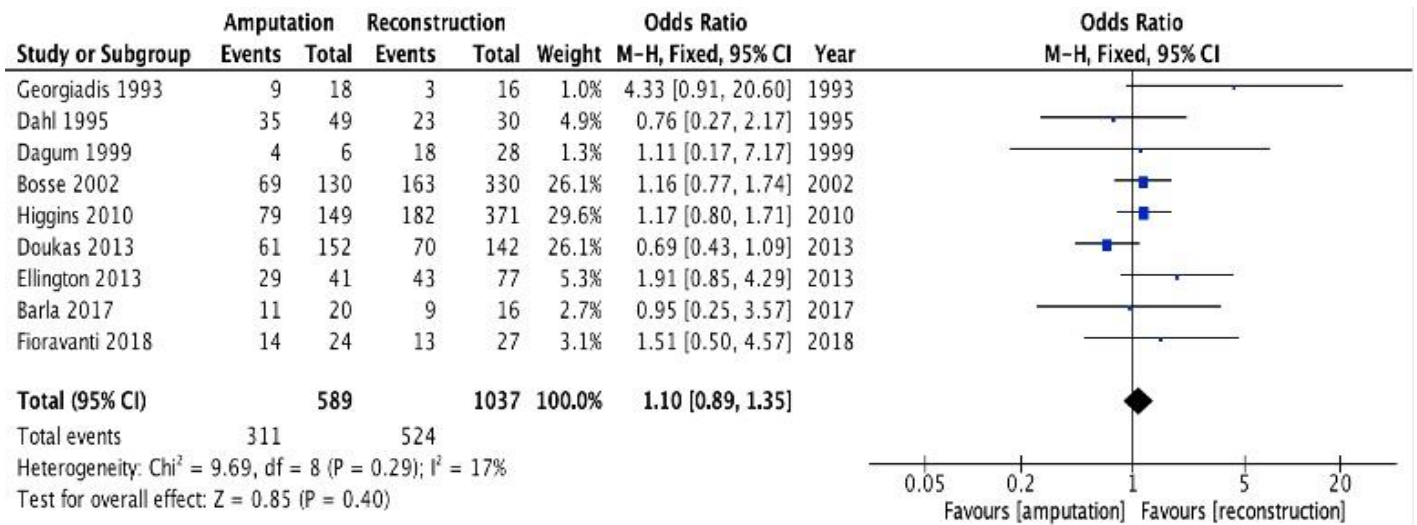


Figure 4. Forest plot of return to work in amputation versus reconstruction in severe lower limb injury

undergone a reconstruction. Interestingly, all the studies that compared results in the military population showed better functional outcomes with an amputation. The functional outcomes in the included studies are summarized in [Table 3].

### **Pain**

The severity of pain was reported in five of the included studies.<sup>3, 10,11,14,15</sup> A meta-analysis was not performed due to differences among the studies in the methodological tools

when reporting this outcome. In the study by Georgiadis et al.<sup>3</sup> patients with an amputation and patients with a reconstruction had the same pain scores. Similarly, Ellington et al. and Edelstein et al.<sup>11,14</sup> used the Visual Analogue Scale (VAS) and showed no differences between the groups in terms of pain. On the other hand, Doukas et al.<sup>10</sup> reported a lower percentage of patients with pain interfering with their daily activities in the amputation group and Ladlow et al.<sup>15</sup> reported that a greater proportion of patients with limb reconstruction reported uncontrolled pain.

**Table 3. Functional outcomes**

Author, year	Functional outcome	Favours
Georgiadis, 1993	Significantly longer time to full-weight bear in the reconstruction group More patients in the reconstruction group considered themselves disabled and had problems with performance in recreational and occupational activities	Amputation
Dahl, 1995	No differences between the groups apart from the complaints for leg swelling which were more in the reconstruction group	Similar results
Hertel, 1996	Compared walking and standing ability, quadriceps muscle wasting, and range of motion between the two groups and found a statistically significant better walking ability in the reconstruction group	Reconstruction
Dagum, 1999	Better results in the reconstruction group in SF-36 and WOMAC scores, but the differences were not statistically significant	Reconstruction
Hoogendoorn, 2001	Lower mean lower extremity impairment in patients having undergone a reconstruction No differences in NHP and SF-36 scores	Reconstruction
Bosse, 2002	No differences in SIP scores	Similar results
Higgins, 2010	No differences in SIP scores	Similar results
Doukas, 2013	Better results in the amputation group based on the SMFA scores	Amputation
Ellington, 2013	Better results in the amputation group based on the SIP scores Significantly longer time to weight-bear in the reconstruction group	Amputation
Demiralp, 2014	Significantly better results in the reconstruction group based on the BIQLI scores Better results in the reconstruction group based on the SF-36 scores (not significant)	Reconstruction
Edelstein, 2016	Better results in the amputation group based on the SIP scores	Amputation
Ladlow, 2016	Patients with a unilateral amputation could walk significantly farther than patients with a reconstruction Patients with a reconstruction could walk significantly farther than patients with bilateral amputation	Amputation
Barla, 2017	Patients with an amputation had a significantly superior walking distance and fewer walking aids	Amputation
Fioravanti, 2018	Walking distance, use of crutches, prolonged standing, climbing easily up and down stairs, running, jumping and return to adapted sports activity significantly better in the amputation group	Amputation

SF-36: Short-Form 36 (SF-36)

WOMAC: Western Ontario and McMaster Universities Arthritis Index

NHP: Nottingham health profile

SIP: Sickness Impact Profile

SMFA: Short Musculoskeletal Function Assessment

**Mental health**

Four of the included studies reported the number of patients with depression after severe lower limb injury and an amputation or reconstructive procedure.<sup>10, 12, 13, 15</sup> the results of the meta-analysis revealed that more patients suffered from depression following an amputation, but the differences were not significant. (Odds ratio [OR] 1.22, 95% confidence interval [CI] 0.65-2.29,  $P < 0.54$ , [Figure 5]). Moderate heterogeneity was found between the studies ( $I^2 = 61\%$ ).

**Infection**

The rate of infection was reported in three of the included studies<sup>3,9,12</sup> and the rate of osteomyelitis in four of the includes studies.<sup>3,6,9,12</sup> The meta-analysis showed a statistically significant lower number of infections (odds ratio [OR] 0.43, 95% confidence interval [CI] 0.19-0.95,  $P = 0.04$ , [Figure 6A]) and a statistically significant lower number of cases of osteomyelitis (odds ratio [OR] 0.14, 95% confidence interval [CI] 0.05-0.41,  $P = 0.0004$ , [Figure 6B]) in the amputation group and moderate heterogeneity among the studies ( $I^2 = 72\%$  and  $I^2 = 41\%$  respectively).

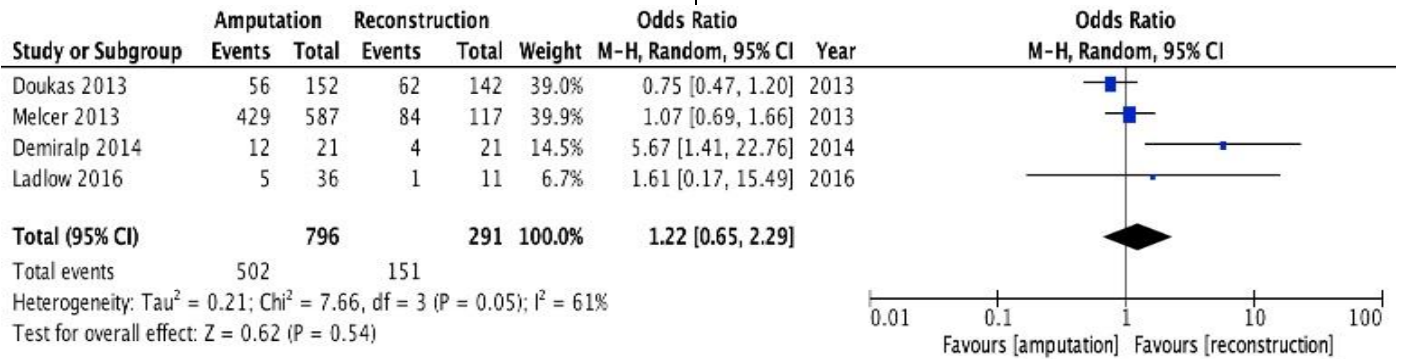
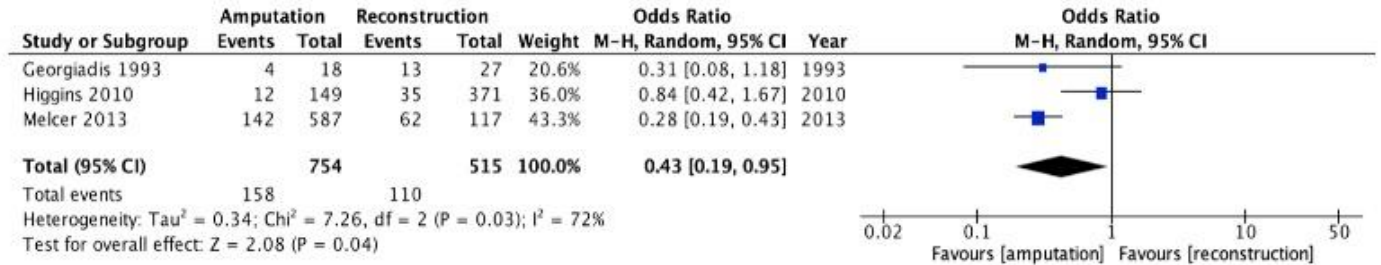
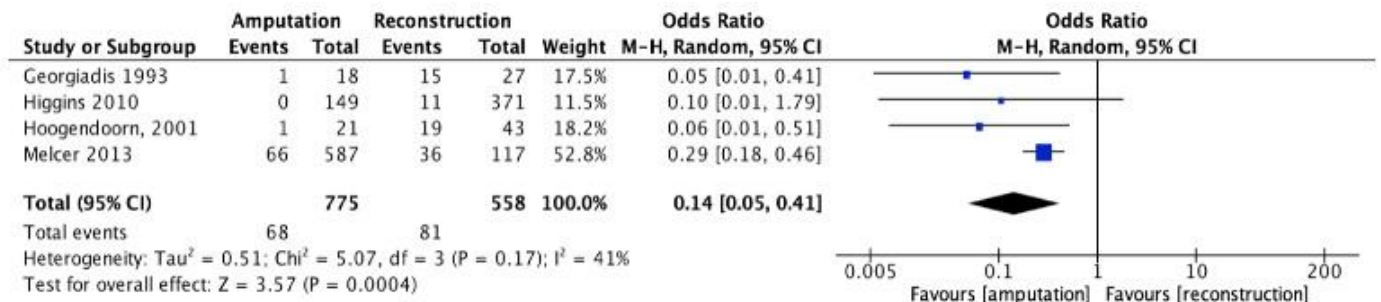


Figure 5. Forest plot of depression rate in amputation versus reconstruction in severe lower limb injury



**A**



**B**

Figure 6. Forest plot of A. infection rate and B. Cases of osteomyelitis in amputation versus reconstruction in severe lower limb injury



**Sensitivity analysis**

We conducted a sensitivity analysis by removing each study individually to assess the heterogeneity and robustness of the pooled results. The sensitivity analysis indicated that the results of the meta-analysis for all the outcomes were stable.

**Discussion**

The main results of this study demonstrate that following a severe lower extremity injury amputation is associated with procedure. Reconstruction of a mangled extremity is a complex process that often requires multiple operations, multiple rehospitalizations and additional surgeries and, as a result, a longer overall length of hospital stay. Interestingly, despite the faster recovery of amputees, this study demonstrated a tendency towards faster return to work and lower risk of adverse mental health outcomes in the long-term in the patients that undergo a reconstruction.

The outcomes in terms of function varied between the included studies. However, the studies in the military population consistently showed improved function following an amputation. It is well established that prosthetic ambulation requires more energy expenditure. Aerobic capacity decreases with age or associated comorbidities and this may be the reason why soldiers, who are in general young and fit, had improved functional outcomes with an amputation. However, the military population is not a representative sample of the entire population, therefore generalizability of these outcomes is not justifiable.

The decision as to whether to attempt to salvage or amputate a severely injured lower limb is always very challenging. This in part is due to the multiple factors that need to be taken into consideration for a life changing injury. Thirty years ago, Johansen and his colleagues developed the Mangled Extremity Severity Score (MESS) as a tool to predict the need for an amputation.<sup>18</sup> The MESS tool takes into consideration the skeletal and soft-tissue damage, the limb ischemia, the presence of shock, and the age of the patient. Nevertheless, several studies have subsequently questioned the diagnostic accuracy and the clinical utility of the MESS tool.<sup>19-21</sup> Most authors since then have advocated a more individualized approach for each patient. This study was designed to compare all the elements that the treating surgeon has to take into account when deciding between a reconstruction and an amputation.

A meta-analysis, by definition, is the quantitative synthesis of separate studies that uses statistical methods to combine the results and draw conclusions. Akula et al. performed a study to compare amputation and reconstruction in severe lower extremity injury.<sup>22</sup> However, they only compared functional outcomes from a patient's perspective and they were also not able to make a quantitative synthesis of the results. Busse et al. systematically reviewed the outcomes between an amputation and a salvage procedure.<sup>23</sup> They did not, however, combine their results by using statistical

lower rehospitalization rates, lower length of hospital stay, lower number of operations and additional surgery and fewer cases of infection and osteomyelitis. On the other hand, limb reconstruction leads to a faster return to work and lower rates of depression. The outcomes with respect to function and pain varied between the studies. It should be noted, though, that the results were statistically significant only with regards to rehospitalization and infection rate.

The meta-analysis clearly demonstrates that amputation leads to a faster recovery compared to a reconstructive methods. In addition, these studies were performed over a decade ago and since then reconstructive procedures have evolved significantly. To the best of our knowledge, this is the first quantitative synthesis of studies comparing amputation and reconstruction in severe lower limb injury.

The present study has to be seen in light of some limitations. Our results are based on the pooling of observational studies, which introduces selection bias due to the lack of randomization and bias related to measurement of the outcome, since there is no blinding of the participants or the assessors. Unfortunately, there are no Randomized Controlled Trials (RCTs) in the literature comparing reconstruction and amputation for lower extremity injuries and future studies should focus on that. The present meta-analysis includes data from heterogeneous study populations, civilian and military, and with heterogeneous injuries, either tibia or foot injuries or both. Different populations and different injuries may be associated with variable outcomes; therefore, these results should be interpreted with caution.

**Conclusion**

In conclusion, amputation is associated with a faster recovery in patients with severe lower limb injuries. On the other hand, reconstruction may lead to a faster return to work and may yield improved psychological outcomes. It is inconclusive as to which option leads to better function and less pain. High-quality RCTs are necessary for a more comprehensive evaluation of these treatments and to further our conclusions.

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