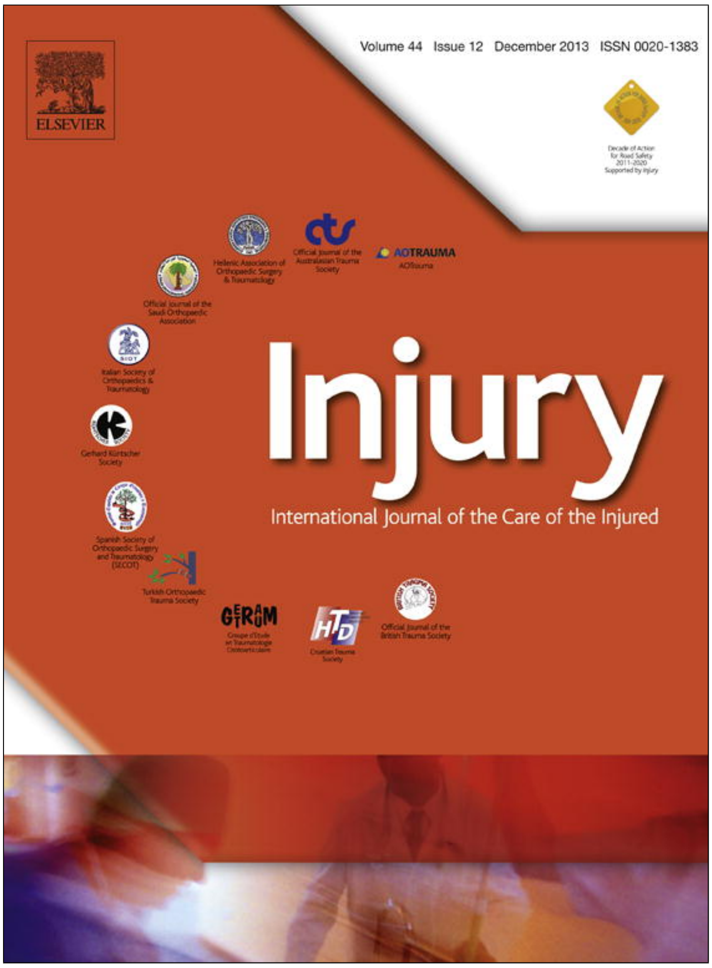
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Cost effectiveness of tibial nonunion treatment: A comparison between rhBMP-7 and autologous bone graft in two Italian centres

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ABSTRACT

Current evidences show that recombinant human bone morphogenetic protein 7 (rhBMP-7, eptotermin alfa) can be considered an effective alternative to autologous bone graft (ABG) in the treatment of tibial nonunions. Few studies, so far, have analysed the costs of treating tibial nonunions with either rhBMP-7 or ABG and none of them has specifically considered the Italian situation. The aim of the present study was to capture, through observational retrospective methods, the direct medical costs associated with the treatment of tibial nonunions with rhBMP-7 or ABG in Italy and to compare the cost effectiveness of the two interventions. The secondary objective was to perform a cost-reimbursement analysis for hospitalisations associated with the two treatments. Data of 54 patients with indication for tibial nonunion were collected from existing data sources. Of these patients, 26 were treated with ABG and 28 with rhBMP-7. The study captured the direct medical costs for treating each tibial nonunion, considering both inpatient and outpatient care. The hospital reimbursement was calculated from discharge registries, based on diagnosis-related group (DRG) values. A subgroup of patients ($n = 30$) was also interviewed to capture perceived health during the follow-up, and the quality-adjusted life years (QALYs) were subsequently computed.

The two groups were similar for what concerns baseline characteristics. While the medical costs incurred during the hospitalisation associated with treatment were on average €3091.21 higher ($P < 0.001$) in patients treated with rhBMP-7 (reflecting the product procurement costs), the costs incurred during the follow-up were on average €2344.45 higher ($P = 0.02$) in patients treated with ABG. Considering all costs incurred from the treatment, there was a borderline statistical evidence ($P = 0.04$) for a mean increase of €795.42, in the rhBMP-7 group. Furthermore, the study demonstrated that, without appropriate reimbursement, the hospital undergoes significant losses ($P = 0.003$) when using rhBMP-7 instead of ABG. In contrast to these losses, in Italy, the average cost to achieve a successful outcome was €488.96 lower in patients treated with rhBMP-7 and, additionally, the cost per QALY gained was below the cost-utility threshold of $50,000.

Introduction

Tibial nonunions may occur as a consequence of many factors and they represent a chronic disabling condition, which often requires long-lasting therapies and multiple hospitalisations. Nonunions result in worsening of muscle wasting and joint stiffness around the fracture. They are also associated with societal effects, such as loss of employment, relationship difficulties and psychological effects. In addition, they have negative effects on society, such as loss of tax revenue and dependency on state benefits as well as ongoing demands on the health service. The incidence of tibial nonunions is high despite recent advances in orthopaedics, with a nonunion rate ranging from 5% to 10% of tibial fractures,[1–3] which constitute the most commonly reported long bone fracture nonunion. Based on these premises, the societal and economic burden of tibial nonunions is expected to be high, but so far few studies have tried to estimate this cost.[4,5] The accepted current treatment for tibial nonunions often includes, besides debridement at the nonunion site and revision of the fixation, the application of osteopromotive and osteoinductive agents.

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Autologous bone grafting (ABG), for its osteopromotive and osteoinductive properties, is still considered the gold standard treatment, but its use has been associated with morbidities at the donor site and limitations in relation to the availability and quality of the grafting material.[6–9] Several studies[2,10–12] indicate that there is a sufficient body of knowledge to consider recombinant human bone morphogenetic protein 7 (rhBMP-7, eptotermin alfa), at least as effective as ABG in the treatment of tibial nonunions, due to its osteoinductive properties. Its effectiveness in the treatment of the same condition was reported to be greater than the effectiveness of other bone-stimulating agents such as platelet-rich plasma (PRP).[12] However, the debate is still open about the appropriateness of rhBMP-7 use in clinical practice, in relation to its costs and to cost-effectiveness considerations. Systematic reviews on the topic[10,11] have underlined the need for further economic assessments in order to allow health economic evaluations. In fact, few studies have so far analysed the costs of treating tibial nonunions,[13–15] showing disparities in relation to the health system considered, the nonunion site and clinical characteristics.

The aim of this study therefore was to capture, through an observational retrospective study, the direct medical costs associated with the treatment of tibial nonunions with rhBMP-7 or ABG in Italy and to compare the cost effectiveness of the two interventions. The secondary objective was to perform a cost-reimbursement analysis for hospitalisations associated with the two treatments. Medical costs constitute a relevant part of the cost associated with the treatment of the tibial nonunions and are mainly sustained by the Italian regional health system.

Materials and methods

The study was approved by the ethical committees of two Italian orthopaedic referral hospitals, acting as experimental centres. The study focuses on two interventions: rhBMP-7, the only BMP available in Italy with indication for tibial nonunions, and ABG, which is considered the gold standard treatment for this condition.

Between December 2010 and October 2011, the investigators screened the archives of the experimental centres to identify patients who underwent surgery for tibial nonunion, either with rhBMP-7 or ABG, in the period 1997–2009. The clinical medical records of these patients were reviewed to select eligible subjects.

The patients, to be included in the study, had to fulfil the following inclusion criteria: diagnosis of posttraumatic tibial nonunion, defined as the failure of the fracture to progress to a union after a period of at least 9 months and after at least one unsuccessful surgery, and the availability of clinical medical records and outpatient visit registries for a follow-up time sufficient to define the surgeries as successful or for at least 12 months. Patients were excluded from the study if they showed any of the following criteria: skeletal immaturity, pregnant/breast-feeding at the time of the surgery, active systemic infections, infected nonunions, pathological fractures or auto-immune/neoplastic disorders.

All patients meeting the inclusion and exclusion criteria were recruited for the study. Two groups of patients, the first including patients receiving ABG and the second rhBMP-7 for the treatment of tibial nonunion, in both cases as unique osteopromotive and osteoinductive factors, were formed. Patients were followed up after surgery at regular intervals until union had been achieved and then as required.

Clinical data collection

The collection of clinical data, covering the whole period from fracture until the end of the follow-up, was performed through electronic case report forms (eCRFs) and it was based on existing data sources (i.e., clinical medical records, outpatient visit records and radiological documentation).

Data related to hospitalisations in the experimental centres, as recorded in the clinical medical records, were cross-checked with the information from patient discharge registries for quality-assurance purposes. Furthermore, to best evaluate the clinical course of nonunions, the patients recruited in one of the experimental centres ($N = 30$) were interviewed at the time of data collection. During the interview, an EQ-5D[16] questionnaire, already applied in orthopaedics[17] was administered to patients recruited in one of the experimental centres, in order to capture their perceived health at 1, 6 and 12 months of follow-up (FU). The questionnaire was not administered to the patients recruited in the second experimental centre, due to organisational issues.

The parameters considered as indicators of tibial nonunion clinical severity are based on published evidences[18] and, besides demographic information, they include all parameters foreseen for nonunion severity score (NUSS) calculation with the exception of complete blood count (CBC) values, which were excluded from being available for a minority of patients. The NUSS was computed as described in a previous study[19].

The effectiveness was evaluated in relation to the main surgery (MS), defined as the last surgery performed for the treatment of a persistent tibial nonunion, in which either ABG or rhBMP-7 was applied as the only osteopromotive and osteoinductive factor, in a subject responding to inclusion and exclusion criteria.

The primary outcome considered was union rate, defined as a successful clinical course after MS, including cases, which underwent nail dynamisation and minor fixation revisions before full union. A successful clinical course was ascertained when the patient experienced both (1) clinical union, defined as pain-free full weight bearing and (2) radiological union, defined as evidence of bridging callus of three of the four cortices as viewed in two different planes.

Secondary outcomes were also considered: (1) time to radiological union; (2) time to clinical unionand and (3) perceived health – quality-adjusted life year (QALY)[20] based on patients' preferences, expressed in EQ-5D indexes.

During the follow-up, adverse events were recorded and they were classified as intra-operative (occurred during MS), perioperative (occurred during MS hospitalisation) or late-onset adverse events (reported at follow-up visits at least 1 month after MS).

Cost estimation

The study collected all inpatient and outpatient direct costs recorded from the initial tibial injury until the end of the follow-up. The costs were then divided into three time periods: from the initial injury up to MS, the MS hospitalisation and after MS. The study is based on individual data due to the lack of reliable and published national or regional cost estimates for tibial nonunion in Italy. Although the cost-of-illness methodology recommends the adoption of a societal perspective,[21] in our study it was possible to retrospectively collect information neither on patients' out-of-pocket expenses nor on indirect costs, and therefore it focussed on direct medical costs. Direct medical costs were estimated for outpatient visits (rooms costs, personnel and devices), hospitalisation (daily cost including personnel fees, patient units' depreciation and servicesand mean department occupancy), each type of surgery performed on the tibial fractures/nonunions in examination (operating room costs, personnel fees, depreciation costs for surgical tools, consumables, including implanted material, and medical devices) and physiotherapy sessions. For MS-related hospitalisations, information on drugs used and blood units administered was available. The costs were calculated separately

Table 1
List of unit costs estimates for the medical services (access to healthcare).

	Personnel	Diagnostic examination (if standard)	Consumables	Medical equipment	Other production costs (rooms including technologies depreciation)	Total
1st pre-surgical visit	€24.22				€0.14	€24.36
Additional pre-surgical visits	€18.79				€0.10	€18.89
Follow up visits	€31.27				€0.17	€31.43
Pre-hospitalisation	€24.41				€0.10	€24.51
Hospitalisation (orthopeadic ward)	€126.54				€49.28	€175.83
Hospitalisation * (rehab. wards)	€63.33				€75.08	€138.41
Surgeries						
Plating	€367.35	€22.75	€784.05 ± €4290 BMP7	€18.07	€215	€1407.29 ± €4290 BMP7
Plating with ABG	€513.77	€22.75	€784.05	€18.07	€256.67	€1595.52
Nailing	€454.18	€22.75	€522.74 ± €4290 BMP7	€18.04	€247.39	€1265.10 ± €4290 BMP7
Nailing with ABG	€585.73	€22.75	€522.74	€18.41	€297.24	€1446.86
External fixation	€324.55	€22.75	€2470.05 ± €4290 BMP7	€17.87	€255.57	€3027.61 ± €4290 BMP7
External fixation with ABG	€453.46	€22.75	€2470.05	€18.36	€321.83	€3209.91
Plate removal*	€275.28	€23.80	€85.70	€10.17	€255.57	€650.53
Nail removal	€278.99	€22.75	€97.05	€5.09	€196.42	€590.32
Nail dynamisation	€140.07	€22.75	€97.05	€5.09	€158.65	€413.62
Arthroscopy*	€272.69		€108.39		€174.95	€556.03
Local flap*	€359.87		€108.39		€132.06	€600.33
Free flap*	€1243.18		€108.39		€329.59	€1681.16
Cast with traction	€240.72		€108.39		€98.20	€469.02
Physiotherapy						
Active physiotherapy session	€16.04				€3.46	€19.50
Shock wave therapy session (in DH)*	€24.22				€114.99	€139.21
Magneto-therapy (equipment rental)					€100	€100/month

Average costs in the two Experimental Centres are presented, with the exception of few services (*) that were reported only in one Experimental Centre.

for the two experimental centres, based on medical resource utilisation that was estimated for each access to healthcare. All unit costs were computed based on the 2009 hospital costs (in euros), as obtained from the budget control departments of the two experimental centres. Information on drug costs was provided by pharmacies and blood unit costs were provided by the hospital's individual blood bank. The costs related to diagnostic examinations were taken from the regional administrative database.

Table 1 presents an overview of the unitary costs calculated per each tibial-fracture-related access to healthcare.

The experimental centres' reimbursements were calculated attributing the 2009 regional diagnosis-related group (DRG) value to the DRG codes recorded in the patient discharge registries.

Statistical analysis

Statistical analysis tested if a difference existed between the two treatment groups in terms of severity of the nonunions, treatment success, time to clinical and radiological union, number and lengths of the hospitalisations, and costs incurred during MS hospitalisation and before and after MS.

Since patients' baseline characteristics, clinical outcomes and costs did not follow a normal distribution, we used non-parametric tests. In particular, we performed the Mann–Whitney *U* two-sided test for all quantitative baseline characteristics, time to radiological and clinical healing, length of hospitalisations, number of hospital re-admissions after MS and for all cost data. For all costs considered, the study reports mean and standard deviations (SD) as summary measures, in accordance with existing recommendations.[22]

Chi-squared tests were used for qualitative data as patients' clinical characteristics, union rate and adverse event rate.

All analyses were performed using STATA 10, considering P values < 0.05 as statistically significant.

Economic evaluation

The economic evaluation adopted the viewpoint of the Italian regional health system. It was based on effectiveness and cost estimates produced from the present study. In the cost-reimbursement analysis, the study adopted a hospital perspective. Furthermore, to take into consideration inaccuracies in the estimates, a series of one-way sensitivity analyses were performed, assuming variations based on the parameter confidence intervals for all cost values and on literature estimates for what concerns union rates.

Cost-effectiveness analysis

The cost-effectiveness analysis was meant to estimate and compare the average cost-effectiveness rate (ACER), associated with rhBMP-7 or ABG treatment, representing the average direct medical cost to resolve a tibial nonunion. ACERs were calculated as: (total medical costs from $\text{MS})_{\text{each group}}$/(number of nonunions resolved after the $\text{MS})_{\text{each group}}$.

An incremental cost-effectiveness ratio (ICER) was calculated to estimate the cost for each extra successful case gained through the introduction of the most effective treatment. The cost to gain an extra union was calculated as: [(total medical costs from $\text{MS})_{\text{rhBMP-7 group}}$ − (total medical costs from $\text{MS})_{\text{ABG group}}$]/[(number of nonunions resolved after $\text{MS})_{\text{rhBMP-7 group}}$ − (number of nonunions resolved after $\text{MS})_{\text{ABG group}}$].

The cost-utility analysis was performed on the subsample of patients recruited in one of the two experimental centres. The study estimated the cost of a QALY gained, through the introduction of rhBMP-7. The cost per QALY gained was calculated as: [mean difference (total medical costs from $\text{MS})_{\text{rhBMP-7 group}}$ − (total medical costs from $\text{MS})_{\text{ABG group}}$]/[$(\text{QALY})_{\text{rhBMP-7 group}}$ − $(\text{QALY})_{\text{ABG group}}$]. Due to the limited sample size, in order to have a more reliable estimate, QALYs were computed using both mean and median health indexes. A cost of $50,000 per QALY gained was considered as the threshold to define if the intervention was costeffective.

Cost-reimbursement analysis

For each treatment group, the delta (Δ) between hospitalisation-associated costs and hospitalisation reimbursement (as obtained from the regional health system) was calculated. We performed the Mann–Whitney *U* test to assess if the difference in Δ, between the two treatment groups, was statistically significant.

Results

Sample characteristics

The sample was composed of 54 patients: 28 patients treated with rhBMP-7 and 26 with ABG.

Table 2 describes the baseline characteristics of the patients and the distribution of the items used for NUSS calculation, divided per treatment group. The two treatment groups were not significantly different with respect to any of the baseline characteristics considered: gender (χ^2 test; $P = 0.42$), age (*U* Mann–Whitney; $P = 0.86$), time from original fracture to MS (*U* Mann–Whitney; $P = 0.47$), type of fixation used during MS (χ^2 test; $P = 0.21$)and duration of the follow-up (*U* Mann–Whitney; $P = 0.15$).

The modified NUSS has a mean of 34.31 (SD 10.08) and 30.36 (SD 8.20) in the ABG and rhBMP-7 groups, respectively, and it was not significantly different in the two treatment groups (*U* Mann–Whitney; $P = 0.11$).

Table 3 summarises the effectiveness of the two treatments considered. Overall, 45 nonunions resolved successfully, 20 were treated with ABG and 25 with rhBMP-7. The treatment success was 89.3% for rhBMP-7 and 76.9% for ABG (χ^2 test; $P = 0.22$).

The odds ratio (OR) for obtaining a successful union was 2.5 higher in the rhBMP-7 group (OR 2.5; 95%CI 0.54–11.57; $P = 0.23$). Among successful cases, patients in the rhBMP-7 group showed a shorter mean time to clinical union (*U* Mann–Whitney; $P = 0.23$) and a shorter mean time to radiological union (*U* Mann–Whitney; $P = 0.25$).

The differences in treatment success and in times to clinical and radiological healing did not reach statistical significance.

Adverse events occurring from the MS until the end of the follow-up are summarised in Table 4. Intra-operative bleeding was significantly higher in the ABG group (χ^2 test; $P = 0.001$). Perioperative and late-onset adverse events are both significantly higher in the ABG group (χ^2 test; $P = 0.006$ and $P < 0.001$, respectively).

Hospital stay and re-hospitalisations

The postoperative hospital stay, during MS, was 4.64 days (SD 2.87) and 5.5 days (SD 3.94) for patients treated with rhBMP-7 and ABG, respectively, the difference not being statistically significant (*U* Mann–Whitney; $P = 0.65$). When looking at the overall length of hospitalisations before MS, the two groups showed comparable characteristics (*U* Mann–Whitney; $P = 0.19$; Table 6), while the mean length of hospitalisation from the MS until the end of the follow-up was significantly higher in patients treated with ABG (*U* Mann–Whitney; $P = 0.007$; Table 7). The mean number of re-hospitalisations was 0.54 (SD 0.64) and 1.11 (SD 1.14) for the rhBMP-7 and ABG groups, respectively (*U* Mann–Whitney; $P = 0.07$).

Cost analysis

Table 5 describes the type of osteosynthesis adopted during MS and MS costs, divided per cost class. It shows that the costs are significantly higher (*U* Mann–Whitney; $P < 0.001$) in patients treated with rhBMP-7, the mean difference being equal to €3091.21.

Table 6 presents the characteristics of hospitalisations (and related costs) that occurred before the MS. The mean costs incurred from the fracture to MS were €6553.65 (SD €4902.18) and €9131.89 (SD €5931.73), respectively, in the rhBMP-7 and ABG groups, the difference not being statistically significant (*U* Mann–Whitney; $P = 0.09$).

Table 7 presents the characteristics of hospitalisations that occurred after the MS, including re-hospitalisations, length of hospitalisations and costs. Costs incurred after MS hospitalisation were significantly lower in patients treated with rhBMP-7, with the mean saving per patient being equal to €2344.45 (*U* Mann–Whitney; $P = 0.016$).

Table 8 shows that direct medical costs sustained by the health system, from the MS to the end of the follow-up, were higher in the rhBMP-7 group, €8461.12, compared to those in the ABG group, €7665.70, with the mean increase per patient being equal to €795.42 (*U* Mann–Whitney; $P = 0.04$).

Cost-reimbursement analysis

The hospital sustained higher losses during MS hospitalisation using rhBMP-7 rather than ABG, with the mean difference in Δ between costs and reimbursements being equal to€-2744.63 (€-3336.05 for rhBMP-7 and €-591.42 for ABG)(*U* Mann–Whitney; $P < 0.001$). On the contrary, for surgeries performed after the MS, the hospital gained if patients were previously treated with rhBMP-7, with the mean difference in Δ between costs and reimbursements being equal to €536.08, though the difference was not statistically significant (+613.98 for rhBMP-7 and +77.90 for ABG) (*U* Mann–Whitney; $P = 0.68$). When considering hospital costs and reimbursements for all hospitalisations from MS until the end of the follow-up, the overall hospital losses remained higher in the rhBMP-7 group, with the mean difference in Δ between costs and reimbursements being equal to €-2256.86 (€-2749.40 for rhBMP-7 and €-492.53 for ABG) (*U* Mann–Whitney; $P = 0.003$).

Cost-effectiveness evaluation

The average cost to resolve a tibial nonunion (ACER) was €9476.45 and €9965.42 for the rhBMP-7 and ABG groups, respectively. Therefore, rhBMP-7 was the less expensive alternative, with a mean saving for the health system of €488.96 per successful case. The incremental cost to obtain extra successful cases (ICER) with rhBMP-7, on top of the costs for treating the less severe cases with the less expensive treatment (ABG), was equal to €7520,70.

Cost utility

The EQ-5D index median scores (μ) increased from 0.59 at 1 month after MS up to 1 at 12 months after MS (Table 8). The mean and median utility scores (health perceived) over time were higher for patients treated with rhBMP-7 than with ABG (Table 9). The mean and median differences for the first year after the MS were 0.022 and 0.08 QALY, respectively. Considering a mean difference of €795.42 in costs between the two treatments, the cost per QALY gained in the range from €9730 to €35,637, considering median and mean μ scores, respectively.

Table 2
Patients baseline characteristics.

	ABG Group (*n* = 26)	BMP-7 Group (*n* = 28)	Total cohort (*n* = 54)	Significance
Gender				*P* = 0.42
Male	19	23	42	
Female	7	5	12	
Age (years)	40.73 (13.18)	43.5 (17.73)	42.17 (15.62)	*P* = 0.86*
Time from fracture to MS (months)	17.65 (15.47)	17.57 (12.29)	17.61 (13.78)	*P* = 0.47*
Type of fixation used during MS				*P* = 0.21
Plating	14	8	22	
Nailing	5	11	16	
External fixation	2	4	6	
Other	5	5	10	
Follow up duration (months)	25.96 (19.86)	17.64 (15.20)	21.65 (17.93)	*P* = 0.15*
Bone quality				*P* = 0.09
Good	4	5	9	
Moderate (mildly osteoporotic)	14	19	33	
Poor (severe porosis or bone loss)	8	2	10	
Very poor (necrotic, appears avascular or septic)	0	2	2	
Primary injury				*P* = 0.304
Closed	14	15	29	
Open 1° grade	4	8	12	
Open 2°–3° A grade	8	4	12	
Open 3° B–C grade	0	1	1	
Number of previous interventions on this bone (standard deviation)	2.42 (1.53)	1.93 (0.90)	2.17 (1.26)	*P* = 0.32*
Invasiveness of previous interventions				*P* = 0.33
Minimally invasive	8	6	14	
Internal intra-medullary	5	9	14	
Internal extra-medullary	9	11	20	
Any osteosynthesis which includes bone grafting	4	1	5	
Adequacy of primary surgery				*P* = 0.22
Adequate stability	14	10	24	
Inadequate stability	12	17	29	
Weber and Cech group				*P* = 0.06
Hypertrophic	4	4	8	
Oligotrophic	3	11	14	
Atrophic	18	12	30	
Bone alignment				*P* = 0.1
Not anatomical alignment	16	11	27	
Anatomical alignment	10	17	27	
Bone defect				*P* = 0.05
No defect	11	21	32	
0.5–1 cm	10	5	15	
1–3 cm	5	2	7	
>3 cm	0	0	0	
Soft tissue status				*P* = 0.05
Intact	0	0	0	
Previous uneventful surgery	22	24	46	
Previous treatment of soft tissues defect	3	1	4	
Previous complex treatment of soft tissues defect	1	2	3	
Bad vascularity	0	0	0	
Presence of a lesion/cutaneous defect	0	1	1	
ASA grade				*P* = 51
1 or 2	24	27	51	
3 or 4	2	1	3	
Diabetes				*P* = 0.37
No	25	24	49	
Yes, well controlled	0	1	1	
Yes, poorly controlled	1	0	1	
Clinical Infectious Status				*P* = 0.94
Clean	24	26	50	
Previously infected or suspicion of infection	2	2	4	
Septic	0	0	0	
Steroids users	0	1	1	*P* = 0.35
NSAIDs users	7	8	15	*P* = 0.83
Smokers	10	9	19	*P* = 0.63
Modified NUSS	34.31 (10.08)	30.36 (8.20)	32.26 (9.28)	*P* = 0.11

The number of subjects for each category for qualitative variables and mean value and SD for quantitative variables are reported. *P*-values refer to χ^2 tests in case of qualitative variables and to *U* Mann–Whitney tests in case of quantitative variables (*).

Table 3
Treatment effectiveness.

	ABG group (n = 26)	rhBMP-7 group (n = 28)	Total cohort (n = 54)	Significance
Success	20	25	45	P = 0.22
Failure	6	3	9	
Time to clinical union (months)	6.95 (2.87)	6.08 (3.63)	6.47 (3.31)	P = 0.23*
Time to radiological union (months)	11.6 (6.73)	9.34 (6.29)	10.39 (6.52)	P = 0.25*

The number of subjects for each category for qualitative variables and mean value and SD for quantitative variables are reported. P-values refer to χ^2tests in case of qualitative variables and to U Mann–Whitney tests in case of quantitative variables (*).

Table 4
Adverse events.

	ABG group (n = 26)	rhBMP-7 group (n = 28)	Total cohort (n = 54)	Significance
Intraoperative bleeding				P = 0.001
Lower than 150 cc	4	17	21	
Between 150 and 300 cc	9	2	11	
Higher than 300 cc	13	9	22	
Perioperative adverse events	10**	2	12	P = 0.006
Severe pain at donor site	10**	0	10	P < 0.001
Other adverse events	1**	2	3	P = 0.64
Late onset adverse events	10	0	10	P < 0.001
Pain at donor site	8	0	8	P = 0.001
Other adverse events	2	0	2	P = 0.135

The number of patients experiencing adverse events after MS and the degree of intraoperative bleeding experienced during MS are described. P-values refer to χ^2 test.

** One patient experienced both severe pain at donor site and another adverse event.

The results of this economic evaluation were sensitive to variations in costs occurring after MS; in fact, when considering different scenarios (mean costs incurred after MS being equal to lower and higher values of the 95% CI), the ACER was in favour of ABG in the case of a less expensive follow-up and in favour of rhBMP-7 in the case of the more expensive follow-up. The results of this economic evaluation were also sensitive to variations in effectiveness parameters considered.

Discussion

Existing literature is sparse with regard to economic evaluations comparing the cost effectiveness of rhBMP-7 and ABG for the treatment of tibial nonunions.

The two treatment groups can be considered comparable in terms of clinical condition, surgical techniques used and co-morbidities associated with impaired bone healing, since none of these characteristics showed any statistically significant difference between the rhBMP-7 and ABG groups. In the present study, which represents the most relevant economic evaluation conducted so far in terms of sample size, the percentages of nonunion recovery after intervention with rhBMP-7 or ABG were 89.3% and 76.9%, respectively, in agreement with the published literature,[1,2,23] with the difference not being statistically significant.

Union times were comparable with those reported in previous studies,[14] and they did not show significant differences in relation to the treatment used.

Intra-operative bleeding and adverse events were significantly higher in patients treated with ABG, as previously observed.[2] Higher adverse event rates observed among patients treated with ABG were associated with pain at the donor site, which was reported as a late-onset event in 30.77% of cases, in agreement with the range reported in the literature.[11]

The mean cost for treating a tibial nonunion, from MS to the end of the follow-up, was €795.42 higher in patients treated with rhBMP-7 (P = 0.04), the cost difference between the two treatments being much less than the unit cost of rhBMP-7 (€4260). In fact, while the costs incurred during MS hospitalisation were significantly higher in patients treated with rhBMP-7, the follow-up costs were significantly higher in patients treated with ABG (P = 0.02), in relation to the higher re-hospitalisation rates observed in the ABG group.

These observations are comparable with the results of previous studies conducted in other European countries, which indicated a non-significant cost difference between the two treatments in the UK[14] and a difference of €808 in Germany.[15]

The mean cost per patient, from the MS to the end of the follow-up, is considerably lower than the mean costs reported in German and UK studies, even if the mean length of hospitalisation observed in the present study is comparable with that in the UK report.[14] Therefore, the observed difference in costs is likely to be associated with differences in unitary costs (i.e., cost per hospitalisation day and hourly cost for the surgical room), which, when reported (i.e., hospitalisation costs £900/day[14] and $445/day[24]), are higher than

Table 5
Main surgery hospitalisation characteristics.

	ABG group (n = 26)	rhBMP-7 group (n = 28)	Difference (BMP7-ABG)	Significance
Type of osteosynthesis				P = 0.214*
Plating	14	8		
Nailing	5	11		
External fixation	2	4		
Other	5	5		
Cost type				
Orthopaedic material and drugs during the surgery	€1014.29 (999.23)	€4910.31 (536.35)	€3896.01	P < 0.0001
Surgery room and personnel costs during the surgery	€946.98 (148.36)	€771.53 (118.09)	€−175.44	P = 0.0001
Drugs used during the hospitalisation	€57.37 (73.92)	€61.14 (85.92)	€3.77	P = 0.755
Blood transfusion	€44.54 (140.26)	0	€−44.54	P = 0.07
Diagnostic examinations as inpatient	€167.44 (92.08)	€142.23(49.47)	€−25.21	P = 0.48
Hospitalisation costs	€1930.26 (1346.99)	€1358.10(763.83)	€−572.15	P = 0.17
Follow up visits and examinations	€137.24 (65.08)	€139.91(106.78)	€2.67	P = 0.55
Total	€4300.01 (1969.90)	€7391.22 (1153.1)	€3091.21	P < 0.0001

The number of subjects for each type of osteosynthes is performed during the MS and the costs of the related hospitalisation are described. For every cost type it is reported mean and SD. P-values refer to χ^2 tests (*) in case of qualitative variables and to U Mann–Whitney tests in case of quantitative variables.

Table 6
Characteristics of hospitalisations occurred before main surgery.

	ABG Group (n = 26)	rhBMP-7 Group (n = 28)	Total cohort (n = 54)	Significance
First surgery				0.117*
Osteosynthesis type				
Plating	11	5	16	
Nailing	5	9	14	
External fixator	6	8	14	
Combined osteosynthesis	2	3	5	
Other	4	0	4	
Length of hospitalisation	17.34 (21.19)	12.39 (15.73)	14.78 (18.55)	0.21
Costs for surgery*	€2137.36 (1310.13)	€2042.76 (1167.53)	€2088.31 (1227.33)	0.51
Costs for hospitalisation	€2946.99 (3308.09)	€2095.66 (2412.79)	€2505.56 (2883.06)	0.10
Follow up visits and examinations	€212.35 (101.48)	€199.28 (98.40)	€205.57 (99.16)	0.61
Total *A*	€5327.57 (4152.26)	€4360.98 (3304.48)	€4826.376 (3732.72)	0.12
Following hospitalisations				
Costs for surgery	€1498.84 (2485.65)	€819.70 (1150.79)	€1146.69 (1925.19)	0.42
Costs for hospitalisations	€1561.88 (2241.34)	€716.86 (1051.55)	€1123.73 (1764.82)	0.34
Follow up visits and examinations	€270.58 (493.85)	€194.68 (273.65)	€231.23 (393.27)	0.76
Total *B*	€3804.32 (5674.43)	€2192.67 (3133.51)	€2968.65 (4566.29)	0.35
Total costs before MS (*A* + *B*)	€9131.89 (5931.73)	€6553.65 (4902.18)	€7795.03 (5246.76)	0.09
Total length of hospitalisations before MS	20.54 (22.02)	14.5 (15.73)	17.41 (19.08)	0.19

The type of osteosynthesis used in the first surgery, the costs incurred during the first hospitalisation after trauma and the following surgeries prior to MS are described. For every cost type it is reported mean and SD. *P*-values refer to χ^2 tests (*) in case of qualitative variables and to *U* Mann–Whitney tests in case of quantitative variables.

Table 7
Characteristics of hospitalisations occurred after the main surgery.

	ABG group (n = 26)	rhBMP-7 group (n = 28)	Difference (BMP7–ABG)	Significance
Number of surgeries after MS	0.54 (0.64)	1.11 (1.14)	−0.58	$P = 0.07$
Length of hospitalisation: hospitalisations after MS (days)	6.54 (9.52)	1.43 (2.63)	−5.11	$P = 0.06$
Length of hospitalisation from MS until end of FU (days)	17.69 (12.77)	9.43 (5.77)	−8.26	$P = 0.007$
Total costs incurred after MS (visits and examinations included)	€3526.92(4770.64)	€1182.47 (1694.95)	−€2344.45	$P = 0.02$

The number of surgeries and lengths of hospitalisation occurred after MS and overall costs incurred after MS are described. For each of them it is reported mean and SD. *P*-values refer to the *U* Mann–Whitney test.

the costs estimated in this Italian study (€175.83/day). It is also possible that such a difference is partially due to the retrospective nature of the present study, which might have underestimated the follow-up costs, and in particular the number of visits and examinations occurring after MS. In any case, it is unlikely that are porting bias has occurred, since follow-up times and patients' characteristics are comparable across the two treatment groups.

We believe that, to date, this study is the first to analyse the Italian situation in terms of cost effectiveness, indicating an ACER for treating successfully a tibial nonunion slightly in favour of rhBMP-7. Similar results are described in a previous study showing comparable ACERs between the two treatments in UK and Germany.[15] This observation is particularly interesting, considering the different methodologies adopted in the two studies, with the present study being based on individual data and the UK/German study using an economic model based on expert opinions.

Since, in the present study, the MS success rate varied across the two treatments, we estimated the incremental cost per successful case gained through the use of rhBMP-7. The cost to gain a successful case with rhBMP-7 (ICER) is lower than the cost of a new

Table 8
Overview of the costs of tibial non-unions.

	A (mean cost MS hospitalisation)	*P*	*B* (mean cost FU, other hospitalisations included)	*P*	*C* (mean cost from MS to end of FU (*A* + *B*))	*P*
rhBMP-7 group	7278.65		1182.47		8461.12	
ABG group	4138.78		3526.92		7665.70	
Total cohort	5766.86		2311.28		8078.14	
Δ	+3139.87	< 0.0001	−2344.45	0.02	+795.42	0.04

It shows: mean costs related to MS hospitalisation (*A*), meancosts related to the follow up after MS hospitalisation (*B*), mean costs incurred from the MS hospitalisation onward (*C* = *A* + *B*). For each period considered, it was tested if costs estimates were different between the treatment groups, using *U* Mann–Whitney test.

Table 9
EQ-5D indexes, estimated duration per each index and QALY estimates in the two treatment groups.

	ABG Group (n = 26)	rhBMP-7 Group (n = 28)	All cohort (n = 54)	Estimated duration (months)
EQ-5D index: 1 month from surgery	0.52 (0.26–0.69)	0.62 (0.52–0.69)	0.59 (0.32–0.69)	1.5
EQ-5D index: 6 month from surgery	0.796 (0.71–1)	0.796 (0.62–1)	0.796 (0.65–1)	5
EQ-5D index: 12 months from surgery	0.85 (0.71–1)	1 (0.86–1)	1 (0.71–1)	5.5
QALY median	0.868	0.786		
QALY mean	0.79	0.768		

For EQ-5D Indexes (μ) are described as median scores and 25th and 75th percentiles.

ABG surgery and its follow-up. To the best of our knowledge, no previous study has ever calculated the ICER for the use of rhBMP-7 in tibial nonunions.

The number of re-hospitalisations after the treatment with rhBMP-7 (0.54) is lower than that reported in the UK study (1.2).[13] This difference could be due to sample characteristics since the present study focuses on tibial nonunions, while the UK study considered long bone nonunions.

Considering the hospital perspective and analysing hospital costs and revenues (DRG-based reimbursements), the study shows that the hospital undergoes an economic loss when treating patients with rhBMP-7, even if the cost-effectiveness ratio is slightly in favour of rhBMP-7. The Δ between costs and reimbursements is significantly different between the two treatment groups when considering both MS hospitalisation and all hospitalisations from MS until the end of the follow-up.

The present study is the first to perform a cost-utility analysis on rhBMP-7, based on information collected from patients. The EQ-5D index median scores reported at 1 month after MS are higher in the rhBMP-7 group and, for both groups, are lower than the utility value of 0.7 associated with 'leaving the hospital on crutches, with limited activities', estimated through expert elicitation.[24] However, the scores are higher than those estimated for 'experiencing a postoperative complication' and 'nonunion that requires re-operation' both of 0.5.[24] EQ-5D index median scores at 1 year after MS were 0.85 and 1, in the ABG and rhBMP-7 groups, respectively, ranging across the utility value 0.9, attributed to 'returning to normal activities', by expert elicitation.[24] The results of cost-utility analysis indicate that costs to gain a whole year in perfect health (1 QALY) using rhBMP-7 are below the cost-effectiveness threshold ($50,000), considering both mean and median health index scores.

The economic evaluation is sensitive to variations in the number of re-hospitalisations after the main surgery and to variations in effectiveness parameters.

The possible limitations of the present study include: (1) clinical data inaccuracy, associated with the retrospective nature of the study. We have tried to overcome this limit using mainly data recorded during the hospitalisation and follow-up time. Some information related to habits (smoke, anti-inflammatory drugs assumption before main surgery) and to physiotherapy sessions has been collected at the time of the study and is more prone to inaccuracy. However, in the present study, we have used standard tools for data collection; therefore, reasonably, the information accuracy should be comparable between the two groups of treatment. (2) The comparability of economic data collected from the two experimental centres was assured by the use of this standard data collection tool. However, in some cases, it was impossible to obtain the requested information, due to limitations posed by the cost monitoring systems used in the two hospitals. The main differences among collected economic data are related to implanted material and drugs used during MS hospitalisation. (3) Although effectiveness estimates obtained from the present study are largely comparable with the ones reported in the literature, a further validation of treatment effectiveness and QALY would be desirable through a prospective study with a sample size allowing higher statistical power.

Conclusions

The study concludes that:

(1) the regional health system sustains comparable costs when treating a tibial nonunion with ABG and rhBMP-7, with a mean difference being equal to €795.42;
(2) the average cost to achieve a successful outcome was €488.96 lower in patients treated with rhBMP-7 than those treated with ABG;
(3) rhBMP-7 is more costeffective than ABG, but this estimate is sensitive to variations in the effectiveness parameters considered. Therefore, more evidence on the effectiveness of the two parameters is desirable to decrease the uncertainty around this estimate;
(4) when adopting a hospital perspective, the cost-reimbursement analysis shows that the hospital undergoes a significant loss when rhBMP-7 is used for the treatment of tibial nonunions;
(5) considering patients' perceived health, the costs of 1 QALY gained, using rhBMP-7, is below the $50,000 threshold (€40,751), and it can therefore be considered costeffective.

Finally, taking into consideration the above evidences together with the fact that intangible costs associated with the different invasiveness of the two surgeries are likely to be different (around 30% of patients treated with ABG reported chronic pain at the donor site), attention should be paid in order to avoid penalising hospitals economically using rhBMP-7, as it currently occurs in the Italian context.

Conflict of interest statement

The authors declare that their Institutions received funding for the study which generated the data described on this article from a Commercial Party. One of the authors is affiliated to a Biotech Company commercializing rhBMP-7.

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