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Heal rate of metatarsal fractures: A propensity-matching study of patients treated with low-intensity pulsed ultrasound (LIPUS) vs. surgical and other treatments

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ABSTRACT

Introduction: Whether to treat metatarsal fractures conservatively or surgically is controversial. We test a hypothesis that metatarsal fractures treated conservatively with non-invasive low-intensity pulsed ultrasound (LIPUS) obtain heal rates comparable to current surgical techniques.
Patients and methods: This is a retrospective observational cohort study, using patient outcomes from a prospectively-collected LIPUS registry required by the U.S. Food & Drug Administration. Registry data were collected over a 5-year period and were reviewed and validated by a registered nurse. Data required for analysis were days-to-treatment (DTT) with LIPUS and a dichotomous outcome of healed versus failed, as assessed by clinical and radiographic criteria. Registry patients (DTT < 365 days) were propensity-matched to metatarsal fracture patients from a health claims database that includes medical and drug expenses for ~90.1 million patients. The propensity match was based on patient demographic data (age, gender, body weight, fracture severity, and smoking status).
Results: A total of 594 metatarsal fractures were treated with LIPUS, including 161 Jones fractures. Compared to patients in the claims database, LIPUS-treated patients were more likely to: be overweight or obese; be male; have open fracture; and smoke (all, $P < 0.0001$), suggesting that these variables were perceived as nonunion risk factors by prescribing physicians. After propensity-matching, none of these differences between the registry and the health claims database remained significant. The heal rate with LIPUS treatment was 97.3%, comparable to the heal rate of 95.3% among claims patients in 2011 who did not receive LIPUS ($P = 0.0654$). When fresh fractures (0–90 days) and delayed unions (91–365 days) were analyzed separately, the LIPUS fresh fracture heal rate was superior to claims patients ($P = 0.0381$), and the delayed union heal rate was comparable. After exclusion of registry patients who received surgery, heal rate with LIPUS alone (97.4%) was significantly better ($P < 0.0097$) than the heal rate for matched patients in 2011 (94.2%).
Conclusions: LIPUS significantly improved the heal rate of metatarsal fractures <1 year old without surgery ($P = 0.0097$). Metatarsal fractures treated with LIPUS alone have a heal rate comparable to fractures treated by surgical intervention.

Introduction

Whether to treat metatarsal fractures conservatively or surgically is controversial; surgical intervention may reduce the incidence of nonunion, but the complication rate of surgery can be high, especially for the Jones (proximal diaphyseal fifth) metatarsal fracture [1]. An optimal metatarsal fracture treatment would

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reflect the surgical heal rate while avoiding the surgical complication rate.

We evaluate the heal rate of metatarsal fractures treated with low-intensity pulsed ultrasound (LIPUS). High-frequency LIPUS was patient self-administered to the fracture site with a home-use device that stimulates the bone-healing process when used once a day for 20 min. LIPUS-treated fractures are compared to fractures treated with a mix of other methods in 2011, using a propensity-matching approach [2]. Propensity can be defined as the probability that an individual patient will be treated with a particular intervention, given what is known about that patient [2]. A propensity score is thus a way of combining all relevant information about a patient into a single metric, so that a treated patient can be matched to a non-treated patient [2]. In this case, the treatment of interest is LIPUS, the source of data on LIPUS was a device registry required by the U.S. Food & Drug Administration (FDA), and registry patients were matched to similar patients from a 2011 health claims database (Truven Health Analytics, Durham, NC). We hypothesize that LIPUS yields heal rates comparable to current surgical techniques.

Patients and methods

This study was designed as a retrospective, observational cohort study of a convenience sample of consecutive consenting patients with metatarsal fracture, all of whom enrolled prospectively in a LIPUS registry. Metatarsal fractures in the registry were identified as such by X-ray and clinical findings. The protocol for the registry is publicly available [3]; inclusion criteria were that patients be males or non-pregnant females 18 years or older at enrollment and that patients sign an informed consent. Patients were instructed to use the device for 20 min daily until healed. Analysis of these patients was formally exempted from ethical approval by the Institutional Review Board of the Duke University School of Medicine, because data were derived from a post-market registry designed to satisfy FDA reporting requirements [3].

Registry data for the period from 14 Oct 1994 until 15 Oct 1998 were validated by a registered nurse who manually compared every patient's paper record to the digital record [3]. Each patient was required to have four data points [3]:

- **Date of fracture**: Calendar date when the fracture occurred
- **Date LIPUS treatment started**: Calendar date when LIPUS treatment began
- **Date LIPUS treatment ended**: Calendar date when LIPUS treatment ended
- **Outcome**: A dichotomous variable of healed/failed at treatment end, as determined by the prescribing physician. For a fracture to be healed, the registry protocol specified that a fracture had to meet both clinical and radiological criteria:
  - ◯ No motion or tenderness with palpation
  - ◯ At least three of four cortices bridged on X-ray views

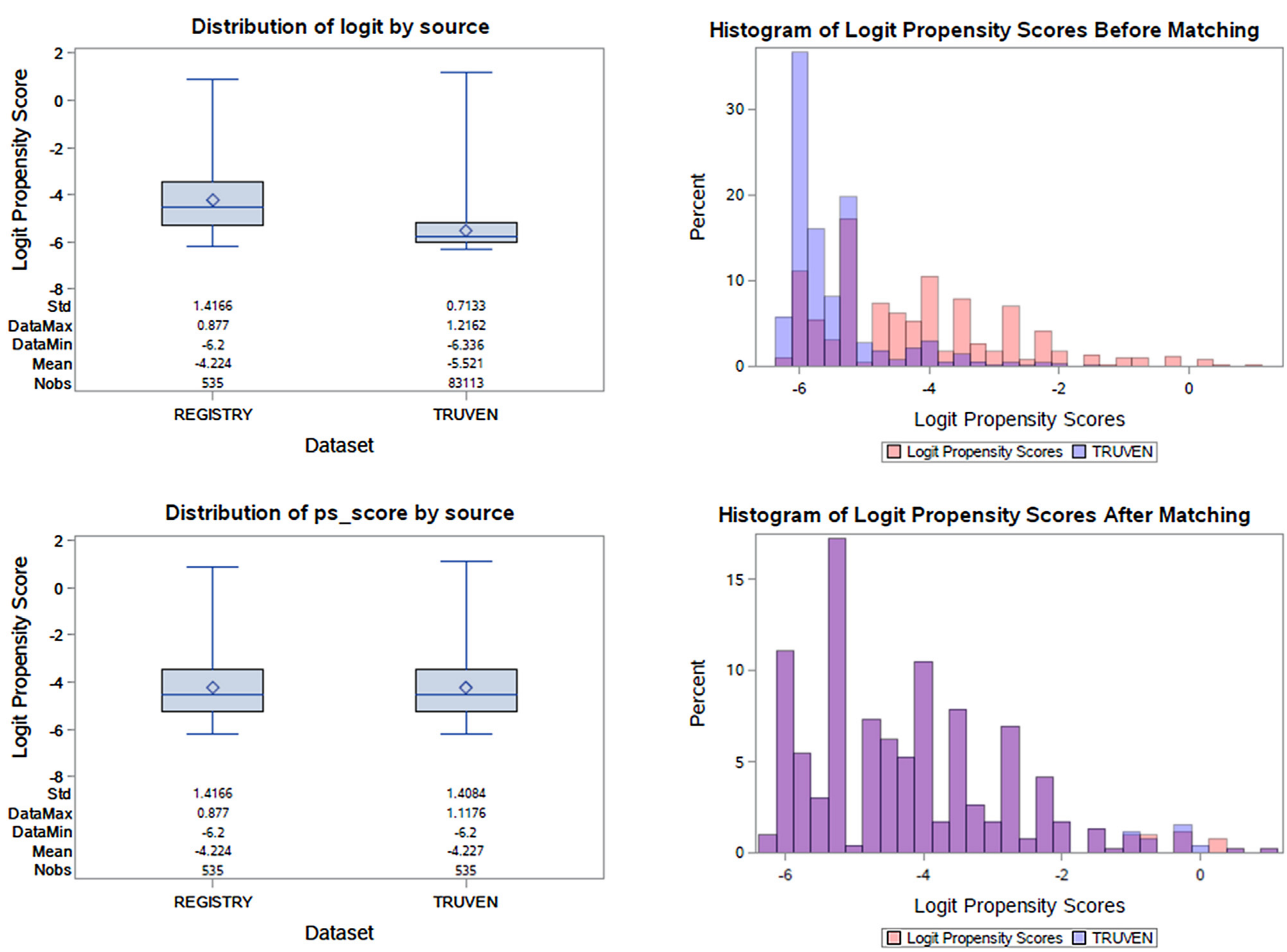

Fig. 1. Propensity score-matching of registry data to Truven data, for days 0–365, excluding surgery patients in the registry database. Panel A (top left) shows the distribution of logit scores by source prior to the match, and Panel B (top right) shows that the distribution of logit scores overlaps poorly prior to the match. After the propensity match, Panel C (bottom left) shows the distribution of logit scores, and Panel D (bottom right) shows that these scores overlap almost completely.

These data were used to calculate 2 derived variables of interest:

- **Days-to-treatment (DTT)**: Number of days until LIPUS treatment was initiated, calculated as “Date LIPUS treatment started” minus “Date of fracture”.
- **Days-on-treatment (DOT)**: Time the patient used LIPUS before attaining an outcome.

Registry patients with DTT and a dichotomous outcome of healed *versus* failed were propensity-matched to patients in a health claims database of medical and drug expenses obtained from Truven Health Analytics (Durham, NC). The Truven database includes ~90.1 million patients, with information compiled from patient-level health claims for medical and drug expenses, together with laboratory test results, hospital discharge, and death data. These data were submitted by hospitals, managed care organizations, Medicare and Medicaid programs, and roughly 300 large corporations, in exchange for benchmark reports. We obtained a download of data from Truven in February 2015.

We compared registry patients with metatarsal fracture to those Truven patients with both a coded metatarsal fracture in 2011 and continuous enrollment for 12 months after fracture. Registry patients were propensity-matched to Truven patients using demographic data (age, gender, body-mass index (BMI), fracture severity, and smoking status). The rationale for using demographic data only was that patient descriptors would likely not change much, even if surgical techniques and other treatments changed substantially. The propensity match was done with the logit method, using log-transformed data (Fig. 1). Analysis was conducted first for registry patients with DTT < 365 days, including both fresh fracture and delayed/nonunion fractures. Then, analysis was done separately for patients with fresh fracture (DTT < 90 days) and delayed/nonunion fracture (90 days < DTT < 365 days). We make no effort to discern between delayed union and nonunion because the boundary between the two conditions is controversial [4].

A *t*-statistic was used to test for significance when comparing continuous variables (*e.g.*, mean age) and a Cochran-Mantel-Haenszel test was used for categorical variables (*e.g.*, gender, BMI category, open/closed fracture, and smoking status). Since this is an exploratory study, no adjustment for multiplicity is needed and the significance level is 0.05. All data were analyzed using SAS software, v9.3 (Cary, NC).

Table 1
Fracture location and fracture type for all patients in the Registry (0–365 days). Heal rate is calculated as the number of patients healed divided by the number of patients treated.

	Category	Healed	Treated	Heal rate
Fracture location	Missing/Unknown	227	239	95.0
	Neck	8	8	100.0
	Proximal	62	64	96.9
	Middle	63	64	98.4
	Distal	31	31	100.0
	Jones fracture	159	161	98.8
	Mid-foot	5	5	100.0
	Distal shaft	7	7	100.0
	Proximal shaft	11	11	100.0
Fracture type	Simple closed fractures	371	377	98.4
	All other fractures	206	217	94.9
	Open	6	6	100.0
	Open Grade II	1	1	100.0
	Osteotomy	57	65	87.7
	Stress	47	48	97.9
	Open comminuted	2	2	100.0
	Closed comminuted	18	19	94.7
	Closed spiral	8	8	100.0
	Closed oblique	29	29	100.0
	Closed transverse	38	39	97.4

Results

A total of 594 metatarsal fracture patients were available for propensity-score matching in the Registry with fresh fracture or delayed/nonunion (DTT ≤ 365 days). In this cohort, 368 patients had fresh fracture (DTT ≤ 90 days) and 226 patients had delayed/nonunion fracture (90 days < DTT ≤ 365 days). Fracture location was unknown for 40.2% (239/594) of registry patients (Table 1), but 27.1% of these patients (161/594) had Jones fracture. Roughly 63.5% (377/594) of metatarsal fractures in the registry were simple closed fractures (Table 1).

Prior to the propensity match, metatarsal fracture patients in the registry differed from Truven patients in important ways (Table 2; Fig. 1). Registry patients were more likely to be overweight, obese, or morbidly obese; more likely to be male; more likely to have open fracture; and more likely to smoke (all, P < 0.0001). These differences suggest that BMI, gender, fracture severity, and smoking habit were all regarded as risk factors for nonunion when patients were enrolled in the registry. Despite these demographic differences, LIPUS-treated patients had a heal rate comparable to patients with metatarsal fracture in the 2011 Truven database.

Following the propensity match, all significant differences between registry and Truven patients were non-significant (Table 2; Fig. 1). Heal rate of LIPUS-treated patients was comparable (P = 0.0654) to the heal rate of patients treated in 2011.

Similar results were obtained when comparing fresh metatarsal fractures in the registry to propensity-matched fractures in Truven (Table 3). Prior to the match, registry patients were more likely to be heavy; more likely to be male; more likely to have an open fracture; and more likely to smoke (all, P < 0.0001). However, the heal rate in registry patients with these risk factors was comparable to the heal rate of Truven patients. After propensity-matching for potential risk factors, all demographic differences between the registry and Truven disappeared, but LIPUS-treated patients had a significantly and substantially better heal rate (P = 0.0381) at 98.1%. These findings confirm that the demographic variables seen as risk factors for nonunion in the registry did reduce the heal rate among patients in 2011 (Table 3). Similar results were seen in metatarsal fractures classified as delayed/nonunion fractures (90 days < DTT < 365 days), except the heal rate of delayed/nonunion fractures with LIPUS was comparable to the 2011 database (Table 4). This result may reflect the fact that the sample size at $N = 226$ (Table 4) was rather small.

When LIPUS-treated patients who received concurrent surgery are excluded from analysis (Table 5), the heal rate with LIPUS is 97.4%, significantly better than the heal rate of matched patients in the Truven database (P = 0.0097). Patients in the Truven database received standard treatment in 2011, which could have included operative intervention. This suggests that the heal rate with LIPUS may be superior to the heal rate with surgery (Table 5).

A literature review (Table 6) of clinical studies of metatarsal fracture [5–32] shows that operatively-treated metatarsal fractures have an overall heal rate of 96.8% (724 healed/748 treated). This heal rate is comparable to the heal rate in the Truven database (Table 2), as expected. The operative heal rate (96.8%) is significantly better (χ^2 test; P = 0.0002) than the heal rate of 92.3% (603 healed/653 treated) for conservatively-treated metatarsal fracture (Table 6). Overall, the metatarsal heal rate with LIPUS (98.5% or 331 healed/336 treated; Table 5) is comparable to the operative heal rate (χ^2 test; P = 0.8503) and significantly better than the conservative heal rate (χ^2 test; P < 0.0001).

Table 2
Comparison of all metatarsal fracture patients (0–365 days) treated with LIPUS (Registry) *versus* non-LIPUS treatment (Truven). P values shown are from *t*-tests for continuous variables (age) or Cochran-Mantel-Haenszel for dichotomous variables (gender, severity, smoking, outcome). The relative risk of nonunion in the Truven database compared to the registry is 1.75 (0.96; 3.20).

All fractures		Prior to propensity-match			Following propensity-match		
Variable	Category	Registry	Truven	P-value	Registry	Truven	P-value
Number of patients (no.)		594	83,113	–	594	594	–
Age, years (mean ± SD)		39.1 (±15.7)	40.4 (±21.3)	0.0524	39.1 (±15.7)	39.3 (±16.0)	0.8937
BMI (no., %)	Normal/Unknown	315 (53.0%)	77,409 (93.1%)	<0.0001	315 (53.0%)	345 (58.1%)	0.2955
	Overweight	155 (26.1%)	475 (0.6%)		155 (26.1%)	72 (12.1%)	
	Obese	101 (17.0%)	3197 (3.8%)		101 (17.0%)	143 (24.1%)	
	Morbidly obese	23 (3.9%)	2032 (2.4%)		23 (3.9%)	34 (5.7%)	
Gender (no., %)	Male	284 (47.8%)	27,992 (33.7%)	<0.0001	284 (47.8%)	269 (45.3%)	0.0501
	Female	310 (52.2%)	55,121 (66.3%)		310 (52.2%)	325 (54.7%)	
Severity (no., %)	Open	74 (12.5%)	413 (0.5%)	<0.0001	74 (12.5%)	71 (12.0%)	0.7904
	Closed	520 (87.5%)	82,701 (99.5%)		520 (87.5%)	523 (88.0%)	
Smoking (no., %)	Never	407 (68.5%)	78,760 (94.8%)	<0.0001	407 (68.5%)	410 (69.0%)	0.8511
	Ever	187 (31.5%)	4353 (5.2%)		187 (31.5%)	184 (31.0%)	
Outcome (no., %)	Failed	16 (2.7%)	3216 (3.9%)	0.1383	16 (2.7%)	28 (4.7%)	0.0654
	Healed	578 (97.3%)	79,897 (96.1%)		578 (97.3%)	566 (95.3%)	

Table 3
Comparison of fresh metatarsal fracture patients (0–90 days) treated with LIPUS (Registry) *versus* non-LIPUS treatment (Truven). P values shown are from *t*-tests for continuous variables (age) or Cochran-Mantel-Haenszel for dichotomous variables (gender, severity, smoking, outcome). The relative risk of nonunion in the Truven database compared to the registry is 2.43 (1.02; 5.79).

Fresh fractures		Prior to propensity-match			Following propensity-match		
Variable	Category	Registry	Truven	P-value	Registry	Truven	P-value
Number of patients (no.)		368	83,113	–	368	368	–
Age, years (mean ± SD)		36.9 (±15.6)	40.4 (±21.3)	<0.0001	36.9 (±15.6)	38.7 (±17.9)	0.1327
BMI (no., %)	Normal/Unknown	202 (54.9%)	77,409 (93.1%)	<0.0001	202 (54.9%)	209 (56.8%)	0.0303
	Overweight	102 (27.7%)	475 (0.6%)		102 (27.7%)	52 (14.1%)	
	Obese	54 (14.7%)	3197 (3.8%)		54 (14.7%)	78 (21.2%)	
	Morbidly obese	10 (2.7%)	2032 (2.4%)		10 (2.7%)	29 (7.9%)	
Gender (no., %)	Male	202 (54.9%)	27,992 (33.7%)	<0.0001	202 (54.9%)	186 (50.5%)	0.2378
	Female	166 (45.1%)	55,121 (66.3%)		166 (45.1%)	182 (49.5%)	
Severity (no., %)	Open	31 (8.4%)	412 (0.5%)	<0.0001	31 (8.4%)	27 (7.3%)	0.5845
	Closed	337 (91.6%)	82,701 (99.5%)		337 (91.6%)	341 (92.7%)	
Smoking (no., %)	Never	265 (72.0%)	78,760 (94.8%)	<0.0001	265 (72.0%)	267 (72.6%)	0.8693
	Ever	103 (28.0%)	4353 (5.2%)		103 (28.0%)	101 (27.4%)	
Outcome (no., %)	Failed	7 (1.9%)	3216 (3.9%)	0.0506	7 (1.9%)	17 (4.6%)	0.0381
	Healed	361 (98.1%)	79,897 (96.1%)		361 (98.1%)	351 (95.4%)	

Discussion

Low-intensity pulsed ultrasound (LIPUS) is well-documented to enhance heal rate of fractures under a range of conditions [33]. However, closed non-displaced metatarsal fractures are expected to heal well in any case. Consistent with this, we report that 98.4% of LIPUS-treated simple closed fractures healed (Table 1), as did 94.9% of all other metatarsal fractures (Table 1). The heal rate for metatarsal fractures treated with LIPUS is therefore comparable to the heal rate of metatarsal fractures treated with surgical or other

Table 4
Comparison of delayed/nonunion metatarsal fracture patients (91–365 days) treated with LIPUS (Registry) *versus* non-LIPUS treatment (Truven). P values shown are from *t*-tests for continuous variables (age) or Cochran-Mantel-Haenszel for dichotomous variables (gender, severity, smoking, outcome). The relative risk of nonunion in the Truven database compared to the registry is 1.56 (0.69; 3.52).

Delayed unions		Prior to propensity-match			Following propensity-match		
Variable	Category	Registry	Truven	P-value	Registry	Truven	P-value
Number of patients (no.)		226	83,113	–	226	226	–
Age, years (mean ± SD)		42.8 (±15.2)	40.4 (±21.3)	0.0166	42.8 (±15.2)	43.3 (±15.5)	0.7385
BMI (no., %)	Normal/Unknown	113 (50.0%)	77,409 (93.1%)	<0.0001	113 (50.0%)	116 (51.3%)	0.4016
	Overweight	53 (23.5%)	475 (0.6%)		53 (23.5%)	39 (17.3%)	
	Obese	47 (20.8%)	3197 (3.8%)		47 (20.8%)	48 (21.2%)	
	Morbidly obese	13 (5.8%)	2032 (2.4%)		13 (5.8%)	23 (10.2%)	
Gender (no., %)	Male	82 (36.3%)	27,992 (33.7%)	0.4092	82 (36.3%)	90 (39.8%)	0.4388
	Female	144 (63.7%)	55,121 (66.3%)		144 (63.7%)	136 (60.2%)	
Severity (no., %)	Open	43 (19.0%)	412 (0.5%)	<0.0001	43 (19.0%)	35 (15.5%)	0.3199
	Closed	183 (81.0%)	82,701 (99.5%)		183 (81.0%)	191 (84.5%)	
Smoking (no., %)	Never	142 (62.8%)	78,760 (94.8%)	<0.0001	142 (62.8%)	136 (60.2%)	0.5624
	Ever	84 (37.2%)	4353 (5.2%)		84 (37.2%)	90 (39.8%)	
Outcome (no., %)	Failed	9 (4.0%)	3216 (3.9%)	0.93	9 (4.0%)	14 (6.2%)	0.2851
	Healed	217 (96.0%)	79,897 (96.1%)		217 (96.0%)	212 (93.8%)	

Table 5
Comparison of metatarsal fracture patients (0–365 days) treated with LIPUS alone (Registry), without concurrent surgery, *versus* non-LIPUS treatment (Truven). P values shown are from *t*-tests for continuous variables (age) or Cochran-Mantel-Haenszel for dichotomous variables (gender, severity, smoking, outcome). The relative risk of nonunion in the Truven database compared to the registry is 2.21 (1.19; 4.11).

No surgery patients		Prior to propensity-match			Following propensity-match		
Variable	Category	Registry	Truven	P-value	Registry	Truven	P-value
Number of patients (no.)		535	83,113	–	535	535	–
Age, years (mean ± SD)		39.0 (±15.6)	40.4 (±21.3)	0.0424	39.0 (±15.6)	39.3 (±15.8)	0.7617
BMI (no., %)	Normal/Unknown	282 (52.7%)	77,409 (93.1%)	<0.0001	282 (52.7%)	293 (54.8%)	0.0099
	Overweight	144 (26.9%)	475 (0.6%)		144 (26.9%)	66 (12.3%)	
	Obese	89 (16.6%)	3197 (3.8%)		89 (16.6%)	130 (24.3%)	
	Morbidly obese	20 (3.7%)	2032 (2.4%)		20 (3.7%)	46 (8.6%)	
Gender (no., %)	Male	259 (48.4%)	27,992 (33.7%)	<0.0001	259 (48.4%)	238 (44.5%)	0.1982
	Female	276 (51.6%)	55,121 (66.3%)		276 (51.6%)	297 (55.5%)	
Severity (no., %)	Open	60 (11.2%)	412 (0.5%)	<0.0001	60 (11.2%)	47 (8.8%)	0.1855
	Closed	475 (88.8%)	82,701 (99.5%)		475 (88.8%)	488 (91.2%)	
Smoking (no., %)	Never	366 (68.4%)	78,760 (94.8%)	<0.0001	366 (68.4%)	366 (68.4%)	>0.99
	Ever	169 (31.6%)	4353 (5.2%)		169 (31.6%)	169 (31.6%)	
Outcome (no., %)	Failed	14 (2.6%)	3216 (3.9%)	0.1339	14 (2.6%)	31 (5.8%)	0.0097
	Healed	521 (97.4%)	79,897 (96.1%)		521 (97.4%)	504 (94.2%)	

Table 6
Literature heal rates for metatarsal fractures.

Pts treated	Healed	Failed	Heal rate (%)	Summary	Year	First author
Conservatively-treated Jones fractures						
40	33	7	82.5	Jones fracture treated with bandage or cast	1994	Josefsson
60	60	0	100.0	Prospective Jones fracture treatment with cast or dressing	1997	Wiener
18	12	6	66.7	Casting for treatment of Jones fracture	2005	Mologne
23	23	0	100.0	Conservative treatment of avulsion and Jones fractures	2007	Van Aaken
Conservatively-treated non-Jones fractures						
20	15	5	75.0	Fracture of proximal part of the fifth metatarsal shaft	1975	Dameron
25	19	6	76.0	Acute fracture of fifth metatarsal treated with a cast	1984	Torg
100	93	7	93.0	Fractures of the fifth metatarsal: Analysis of a registry	1995	Clapper
35	33	2	94.3	Distal fifth metatarsal shaft fracture in elite dancers	1996	O'Malley
50	47	3	94.0	RCT of acute metatarsal fracture treated with cast or bandage	2005	Zenios
37	35	2	94.6	Conservative treatment of tuberosity fractures	2008	Gray
24	20	4	83.3	Conservative treatment of fifth metatarsal fracture	2008	Chuckpaiwong
142	137	5	96.5	Nonoperative management of fifth metatarsal fracture	2013	Aynardi
79	76	3	96.2	Fifth metatarsal fractures managed conservatively	2014	Nagar
653	603	50	92.3	Overall heal rate with conservative treatment		
Operatively-treated Jones fractures						
22	22	0	100.0	Intramedullary screw fixation of Jones fracture	2003	Portland
17	16	1	94.1	Jones fractures in NFL players treated with IM screw	2004	Low
19	18	1	94.7	Early screw fixation for treatment of Jones fracture	2005	Mologne
23	23	0	100.0	Jones fracture fixation with a cannulated screw	2005	Porter
21	21	0	100.0	Cannulated screw for repair of Jones fracture	2008	Raikin
20	20	0	100.0	Jones fractures fixation with 4.5 and 5.5 mm cannulated screws	2009	Porter
53	50	3	94.3	Cannulated screw fixation of Jones fracture	2011	DeVries
23	23	0	100.0	Operative treatment of proximal fifth metatarsal fracture	2011	Mahajan
60	59	1	98.3	Headless compression screw for Jones fracture	2012	Nagao
55	51	4	92.7	Failed surgical management of Jones fracture	2015	Granata
25	25	0	100.0	Return to play in the NFL after operative Jones fracture	2015	Lareau
Operatively-treated non-Jones fractures						
37	37	0	100.0	Operative treatment of fifth metatarsal fracture	2008	Chuckpaiwong
124	124	0	100.0	Proximal fifth fracture treated with XS-nail or tension wire	2010	Renner
35	34	1	97.1	Displaced fifth metatarsal fractures using K-wires	2010	Koslowsky
20	19	1	95.0	Diaphyseal stress fracture in athletes treated with IM nails	2011	Pecina
26	25	1	96.2	Internal fixation of fifth metatarsal in athletes	2011	Murawski
168	157	11	93.5	Fifth metatarsal stress fracture treated with tension band	2013	Lee
748	724	24	96.8	Overall heal rate with surgical treatment		

techniques in 2011 even without propensity matching, although LIPUS-treated patients had more risk factors for fracture nonunion, including obesity, open fracture, and smoking (Table 2). When propensity-matching was used to match registry patients to Truven patients with similar risk factors, the heal rate of LIPUS-treated patients was superior to that of metatarsal fracture patients treated in 2011 (Table 2). Fresh metatarsal fractures treated with LIPUS also healed better than patients in 2011 (Table 3), and delayed/nonunion metatarsal fractures treated with LIPUS had a comparable healing rate (Table 4). Patients treated with LIPUS who did not receive surgery healed significantly better than patients with similar risk factors in 2011 (Table 5), some of whom likely received surgery. This argues strongly that LIPUS is effective, consistent with the surgical literature (Table 6).

LIPUS-treated patients at risk for nonunion healed at a rate comparable to patients in 2011 even without a propensity-match (Table 2). This suggests either that LIPUS was able to overcome the risk factors or that these risk factors were not actually important in determining nonunion. We believe that LIPUS was able to overcome risk factors that were important in determining the success of healing. This is because the heal rate of Truven patients was 96.1% overall; these patients represent a random selection of all metatarsal fracture patients (Table 2). Yet Truven patients who were propensity-matched to registry patients with risk factors healed at a rate of only 95.3% (Table 2), which is significantly less than unselected Truven patients. This suggests that BMI, gender, fracture severity, and smoking habit are all important risk factors for nonunion of metatarsal fracture.

There has been controversy as to whether metatarsal fractures should be treated conservatively or surgically. Some authors have claimed that, “All undisplaced metatarsal fractures . . . can be treated nonoperatively” [34], while other authors stated that “surgical treatment by open reduction and internal fixation . . . or closed reduction with percutaneous K-wiring is recommended” [35]. A recent systematic review specific to Jones fracture concluded that intramedullary screw fixation is more likely to lead to successful union than is any non-operative treatment [36]. Yet even in discussing Jones fracture there is controversy; some authors claim that “surgical intervention for the acute Jones fracture should be reserved for the athletic individual” [1], although it is not clear how to define an athletic individual. The pooled heal rate for Jones fractures treated with a screw was 96% [36], whereas we report a 98.8% heal rate for 161 Jones fractures treated with LIPUS (Table 1). Pooled literature-reported results (Table 6) strongly suggest that conservative treatment is not enough. However, conservative treatment with adjunctive LIPUS results in a heal rate superior to the metatarsal heal rate attained in 2011 (Table 5). Therefore, if a decision is made to treat a metatarsal fracture conservatively, then LIPUS should be considered as adjunctive therapy.

Several limitations of this study are worth noting. Most importantly, patients were not entered into the registry randomly; physicians were free to enter any patient whom they thought could benefit. Evidence is consistent with the idea that patients at risk of nonunion were preferentially enrolled in the registry (Table 2), but we cannot prove this. A second limitation is that patients in the registry from 1994 to 1998 were compared to patients who may have received surgery up to 17 years later. Surgical methods evolved between 1998 and 2011 and the conceptualization as to which metatarsal fracture patients require surgery may also have evolved [37]. Many patients may now receive surgery who would have been conservatively treated 20 years ago. If surgery truly is effective in facilitating healing, one would expect healing to be better in 2011, thereby creating a bias against patients in the registry. That non-surgical patients treated with LIPUS healed better than patients treated in 2011 (Table 5) argues strongly that LIPUS is effective. A third limitation is that there may be pitfalls inherent to the propensity-matching method itself. Propensity-matching is meant to compensate for “confounding by indication”; patients chosen to receive an intervention almost certainly differ from similar patients not chosen to receive that intervention [2]. However, propensity-matching can only balance patient characteristics that are considered in the matching effort; unknown risk factors that differ between treated and untreated patients may not be balanced [38].

Strengths of the present work are several-fold. Most importantly, the registry includes prospectively-assessed real-world patients that are likely to reflect the reality of the clinic. Secondly, the large sample size, especially of Jones fractures, means that this work is less prone to the random variation that can impact small studies, which may be vulnerable to reporting bias [39].

Conclusions

LIPUS treatment of metatarsal fractures yields heal rates that are at least comparable to surgical treatment and are superior to conservative treatment. That healing can happen in a less invasive way argues strongly that LIPUS should be considered for every metatarsal fracture patient.

Conflict of interest statement

Authors have disclosed all financial and personal relationships that could bias their work on the manuscript submission site, so we will simply restate that information here.

- Dr. Peter Nolte has been paid a speaker's honorarium by Bioventus LLC in the past.
- Dr. Robert Anderson has been a paid consultant for Bioventus LLC and for Wright Medical.
- Dr. Elton Strauss, Ms. Zhe Wang, Ms. Liuyi Hu, and Mr. Zekun Xu report no conflicts.
- Dr. R Grant Steen in an employee of Bioventus LLC

Bioventus LLC is the funding source and that has been acknowledged at the end of the text. Dr. Steen is also an employee of Bioventus LLC and he has consulted with Dr Peter Heeckt, *MD, PhD*, of Bioventus, who read the ms. critically. In addition, Mr. John Jones, *MS*, also of Bioventus, helped coordinate the statistical analysis. Both Dr. Heeckt and Mr. Jones are acknowledged in the text. Study sponsors were not otherwise involved in the study design; collection, analysis and interpretation of data; writing of the manuscript; or the decision to submit the manuscript for publication.

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