



Prognostic factors in ankle sprains: a review

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- Ankle sprains are one of the most common musculoskeletal injuries, being the most frequent musculoskeletal trauma among athletes.
- Most of these injuries are successfully treated conservatively; however, up to 70% of patients can develop long-lasting symptoms. Therefore, understanding prognostic factors for an ankle sprain could help clinicians identify patients with poor prognosis and choose the right treatment.
- A suggested approach will be presented in order to positively identify the factors that should warrant a more aggressive attitude in the initial conservative treatment.
- There are some prognostic factors linked to a better recovery and outcome; nevertheless, prognostic factors for full recovery after initial ankle sprain are not consistent.

Keywords: ankle sprains; prognostic factors in ankle sprains

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Introduction

Ankle sprains are one of the most common musculoskeletal injuries, with an estimated incidence rate of 11.6 per 1000 exposures and a prevalence of 11.9%.^{1,2} They are the most frequent musculoskeletal trauma among athletes, representing 10–30% of all sports injuries.^{3–5}

Whenever we refer to ankle sprains, we are not describing the diagnosis but instead the injury mechanism. Inversion and adduction with a plantarflexed foot is the mechanism in 85% of ankle sprain injuries.⁶ The most commonly affected ligament is the anterior talofibular ligament (ATFL), which is the weakest of the three lateral ankle ligaments, followed by injury of the calcaneofibular ligament (CFL) and the posterior talofibular ligament (PTFL).^{3,6–11} However, injury may not be confined to the

lateral ligament complex and may extend to the subtalar, transverse, syndesmosis and/or medial side of the ankle.⁷ Thus, involvement of the interosseous, cervical, bifurcate, tibiofibular (syndesmotic) or deltoid ligaments is not rare and associated injuries to the tendons around the ankle, cartilage damage and bone bruises are frequently induced in cases of acute ankle sprains.^{6,7} These cases represent complex injuries of the ankle joint that have a different natural history from simple ankle sprains, this is, isolated lateral ligament injuries. When referring to ankle sprains, one must not forget that other mechanisms may have occurred, resulting in different patterns of injury.

Current treatment approach involves rest, ice, compression, and elevation followed by active range of motion, neuromuscular training and peroneal strengthening, since a large majority of these injuries are successfully treated conservatively.^{1,8,12,13} Ranging from 2 weeks to 36.2 months follow-up, 36% to 85% of all patients reported full recovery.¹ The great variation in recovery time and full recovery rate represents the great variability of such injuries, highlighting the importance of defining prognostic factors in these situations. There are no clear indications for cases demanding acute surgical treatment, hence final treatment may be delayed in some cases because conservative treatment is always attempted before surgery. The goal of this review was to identify prognostic factors that may guide our initial approach and can provide information for the expectations of these patients.

Defining unsuccessful outcomes

After an acute ankle sprain, up to 70% of patients can develop long-lasting symptoms: feeling of ankle instability ('giving way'), pain, swelling and recurrent sprains, ultimately resulting in functional limitations.³ The proportion of patients who reported that they still experienced

Table 1. Prognostic factors and their relationship to clinical outcome

Better outcome	Undetermined	Worst outcome
Young ¹⁴ Low grade ²⁰ Low activity level ^{1,14,17} Good functional status ^{14,18} Good neuromuscular function ¹⁹ No associated injury ^{6,9,14,20}	Sex ^{1,14,17,21} Body mass index (BMI) ²²⁻²⁴	Systemic laxity ^{12,25} Joint geometry ^{12,17,26} Limb/foot malalignment ^{17,26,27} Re-sprain ^{25,28} Multiligament ^{14,20,25,28}

pain at 1-year follow-up or longer ranged from 5% to 33%. After 3 years, 5% to 25% of patients still experienced pain. The occurrence of a re-sprain ranged from 3% to 34% of the patients, and a subjective instability ranged from 0% to 33%.^{1,3,14-16} These persistent symptoms are the main features of chronic ankle instability (CAI). Chronic ankle instability is defined as the perception of ‘giving way’ in combination with a history of recurrent ankle sprains, along with the sensation of ankle instability and persistent disability (pain, swelling etc.) that was not resolved in the time-frame from the initial sprain to the 12-month follow-up.¹⁶

Historically, a differentiation has been made between functional ankle instability and mechanical ankle instability or a combination of these. Mechanical ankle instability corresponds to an augmented laxity and has been linked to subsequent degenerative changes of the ankle.³ In functional instability, objective joint laxity is not increased, but functional insufficiencies such as impaired proprioceptive and neuromuscular control are present.

Chronic ankle instability has often been referred to as the insufficiency of the lateral ligament complex, but recently, attention to associated ligament injuries has brought authors to describe terms such as ‘global ankle instability’, ‘rotational ankle instability’, and ‘multidirectional ankle instability’, to define complex multiligament ankle injuries. Such definitions are relatively recent to the orthopaedic community, thus evidence using these concepts is lacking. Insufficient diagnosis may be the reason for such different outcomes and for the unclear indication of which injuries may benefit from early surgical repair.

Prognostic factors

Understanding prognostic factors for an ankle sprain could help clinicians identify patients with a poor prognosis and choose the right treatment. Conversely, identifying patients with a good prognosis could have benefits for healthcare, health cost and resource use. Many prognostic variables are proposed (see Table 1).

Despite insufficient evidence to recommend any factor as an independent predictor of outcome,¹⁴ there were some prognostic factors linked to a better recovery and outcome: young age, low activity level, low grade injury,

good functional status, good neuromuscular function and no other associated injury.^{14,17,18,20,25,28}

Thompson et al¹⁴ concluded that higher baseline age was associated with poor recovery in short, medium and long-term follow-up periods. Sports activities at a high exercising level (training three times a week or more) was a significant prognostic factor for residual symptoms in comparison to a low exercising level (training less than three times/week) and no sports activities.^{1,14,17} De Bie et al¹⁸ concluded that prediction for two-week recovery can be given based on initial functional score, where patients with better functional status experience faster recovery and no long-term sequelae. This conclusion was corroborated by Thompson et al’s study, which states that measures of functional ability explained the larger part of the variance of recovery,¹⁴ and Kobayashi et al¹⁹ observed that normal muscle activity patterns are important for a good outcome after injury.

Langner et al,²⁰ using 3 Tesla Magnetic Resonance Imaging (3T MRI) evaluation found three baseline prognostic factors associated with greater time to return to sports activities: greater number of injured ligaments determined by MR, more severe MR grading of injury, and presence of a bone bruise. However, other authors argue that injury grade does not seem to be a strong predictor for the course of lateral ankle sprains.¹ Relation between degree of injury and CAI has been matter of debate: only a minority of patients with CAI have an isolated injury to the ATFL while the majority have two or more injuries.^{9,14,20} Although bone bruises may represent a bad sign in terms of prognosis, their natural history is generally good, with normalization of the MR appearance within 6 to 12 months after trauma.⁶ Subchondral bone oedema may represent a cartilage injury, which may carry a different outcome.^{6,11} Prognostic factors associated with a bad outcome are systemic laxity,^{12,25} joint geometry,^{12,17,26} re-sprain,^{25,28} limb/foot malalignment^{17,26,27,29} and multiligament injuries.^{14,20,25,28}

Some anatomic factors may predispose to CAI – hind-foot varus, pathologic ligament laxity, and an osseous configuration of the ankle joint where the talus is less restrained in the ankle mortise.¹³ A larger talar radius (a flatter talus), and a tibiotalar sector $\leq 82^\circ$ (the angle of the lines drawn from the centre of the talus to both the anterior and posterior margins of the distal tibia, indicating the tibial coverage of the talus) (Fig. 1), reflects less restraint of the talus in the tibia, which are significantly correlated with CAI and could, therefore, be considered intrinsic risk factors for CAI after an ankle sprain.¹⁵ Other factors such as a frontal curvature ≥ 2 mm, and an anterior position of the talar centre of rotation to the anatomical axis of the tibia ≥ 4 mm (Fig. 2)²⁷ may also represent risk factors for CAI.

Hubbard-Turner and colleagues¹² concluded that a significant relationship between mechanical ankle laxity



Fig. 1 Measurements of the osseous ankle configuration on lateral radiographs - TibCOR = distance between the tibial axis and the talar center of rotation. Sector = tibiotalar sector (the angle of the lines drawn from the center of the talus to both the anterior and posterior margins of the distal tibia, indicating the tibial coverage of the talus).



Fig. 2 Measurements of the osseous ankle configuration on frontal radiographs FroCu = depth of the frontal curvature of the talus.

and a decrease subjective function of the ankle exists. Increased laxity, caused by improper ligament healing, may lead to neuromuscular impairment, altering ankle joint stability. In another study, Medina McKeon et al²⁸ have concluded that after the first sprain, tissue damage alone is not a good prognostic indicator; however, there is higher risk of a new and more severe ankle sprain.

At the time of the initial sprain, limb/foot malalignment, such as a posterior fibular position, a varus plafond, or a cavus foot may predispose patients to chronic ankle instability.²⁶ The evaluation of a plantarflexed first ray is also important to mention since it explains why the cavus is forefoot driven and the flexible cavovarus foot.²⁹

Lastly, there is not an homogeneous conclusion about gender and body mass index (BMI) effects on prognosis.^{1,14,17,21–24} Regarding gender, some studies demonstrate that men have an increased risk of residual symptoms compared with women.¹ On the other hand, others observed slower and incomplete recovery in the female gender.^{14,21} Although high BMI is linked to a higher risk of

ankle sprain,^{22–24} the effect on the injury’s prognosis is not as clear. Weight-bearing ability after injury is related to a better short-term prognosis.¹⁴

Poor outcomes may also be related to associated injuries (Table 2) in a stable ankle or an ankle that has healed properly, where pain is the only reported symptom – osteochondral lesions are present in up to 89% of ankle sprains with chronic instability.^{3,30} It is well known that subtalar disorders, for example, sinus tarsi syndrome or subtalar instability, are the major causes of chronic ankle pain after an inversion ankle sprain.⁷

Various forms of peroneal tendon pathology, including tenosynovitis, tendon or retinaculum rupture and dislocation can result in chronic symptoms following an ankle injury.^{5,33} In patients undergoing surgery for chronic lateral ankle instability, 77% had peroneal tenosynovitis, 54% had an attenuated peroneal retinaculum, and 25% had a peroneus brevis tear.³³ Chronic peroneal tenosynovitis is often misdiagnosed initially as an ankle sprain in patients with a history of inversion injuries.⁵

Ankle sprain is the leading cause of impingement syndromes.^{5,34} It is estimated that the incidence of anterolateral impingement syndrome is 3% following ankle sprains, and, in this condition, the synovial membrane hypertrophies and scars in response to repeated sprains, causing severe morbidity and pain, particularly amongst athletes and the younger population.⁵ Despite evidence of the limitations of its efficacy, nonsurgical treatment remains the initial approach to the management of impingement syndromes.³⁴ However, most patients will be subjected to surgical approaches to treat this syndrome, mainly when it affects normal activities of a daily living or athletic performance.³⁴

The exact incidence of peroneal nerve palsy following ankle sprain is unknown, but peroneal nerve injury associated with inversion ankle sprains has been reported.³⁵ Peroneal nerve injury results in a weakness of ankle musculature, which is evident during rehabilitation.³⁵ Conservative and surgical treatments have been described for peroneal nerve palsy. In all cases, complete recovery

Table 2. Ankle sprain associated injuries

Associated injuries	Incidence
Bone bruise	7.4–40% ^{6,31}
Osteochondral lesions	50–89% ^{1,30,31}
Subchondral lesion of talus	11–12% ^{11,31}
Sinus tarsi syndrome	3% ^{11,32}
Peroneal lesions	30% ^{11,31,33}
Peroneal tenosynovitis	77% ³³
Attenuated peroneal retinaculum	54% ³³
Peroneus brevis tear	25% ³³
Syndesmosis instability	9% ¹¹
Impingement	
Anterolateral	3% ^{5,34}
Posterior	Rare ^{5,34}
Nerve palsy	Unknown ³⁵

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Table 3. Approach to the patient with an acute ankle sprain

	History	Clinical exam	Imaging
Day 1–3	<ul style="list-style-type: none"> - Previous sprains - Age - Activity level - Gender - BMI 	<ul style="list-style-type: none"> - Weight bearing ability - Functional status (FADI, FAAM) - Injury grade - Tender points - Systemic laxity - Limb and foot alignment 	<ul style="list-style-type: none"> - Radiography - US
Day 4–14	<ul style="list-style-type: none"> - Evolution 	<ul style="list-style-type: none"> - Tender points - Special tests: <ul style="list-style-type: none"> • Lateral-anterior drawer, pivot, talar tilt; Syndesmosis: cotton, squeeze • AP-fibula translation • Medial-external rotation, anterior drawer with hindfoot in varus - Assess associated injuries: <ul style="list-style-type: none"> • Lateral talar fracture (snowboarder), anterior calcaneal fracture, bifurcate injury, sinus tarsi/subtalar injury, cartilage injury 	<ul style="list-style-type: none"> - MRI

Note. BMI, body mass index; AP, anteroposterior; FADI, Foot and Ankle Disability Index; FAAM, Foot and Ankle Ability Measure; US, ultrasonography; MRI, magnetic resonance imaging.

occurred within 3 weeks to 6 months after the ankle sprain, and there was no convincing evidence that the early surgical exploration of the nerve is indicated.³⁵

Approach to the acute ankle sprain

The authors suggest a systemized approach to the patient with an acute ankle sprain (Table 3). Early evaluation, despite limited clinical exam, can determine many prognostic factors. The positive identification of these factors should warrant a more aggressive attitude in the initial conservative treatment. An orthotic with functional brace, or even a rigid fixation in high-grade/low-functional cases, should be emphasized in these cases. Weight-bearing progression should also be delayed. The threshold for radiography should be low and performed with weight-bearing as tolerated. Ultrasound can be considered where there is a suspicion of associated injuries such as peroneal tendon dislocation.

The value of stress radiographs in the acute clinical setting is questionable because the findings are severely influenced by the radiographic technique, the amount of force applied to the joint and the patient’s cooperation.²⁰ However, the stability of the ankle joint could be influenced by its osseous configuration and this can be calculated with an X-ray.

Delayed evaluation (day 4 to day 14) is of the utmost importance. At this point it is possible to understand the character of the injury, depending on the recovery from day 1. It is also possible at this point to conduct a good physical exam, and full characterization of ligament injury, laxity and associated lesions must be made. Magnetic resonance imaging (MRI) can be considered in severe cases with bad evolution or when an associated lesion is suspected. According to several studies, the MRI seems to be a good initial instrument to demonstrate the anatomy and extent of injuries of the ligamentous complex.^{18,20} It has a correlation among surgical findings and it is a significant predictor of the clinical outcome.^{9,20} However, MRI fails to show the dynamic function of the ligaments.³⁶

It is true that conservative treatment provides excellent clinical outcomes in the majority of acute injuries, but comprehensive characterization of the injury can provide better guidance for the timing of weight-bearing progression, start and progression of the rehabilitation programme, and orthotic wear-off. Future studies should further refine the diagnosis of ankle sprains, defining which ligaments are injured and distinguishing ligament injury from pathologic ligament laxity. The authors believe that with such characterization it will be possible to define patients who would benefit from initial surgical treatment.

Conclusion

Prognostic factors for full recovery after initial ankle sprain are not consistent, thus it is still unknown who benefits from acute surgical treatment. Nevertheless, many factors have been identified that increase the probability of a poor outcome. Currently, early surgical treatment may be considered for: high-level/high-demand athletes, severe injuries (bone bruise, multiligament, persistent pain, re-sprains) and associated injuries (bony avulsion or cartilage injury).

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REFERENCES

1. van Rijn RM, van Os AG, Bernsen RMD, Luijsterburg PA, Koes BW, Bierma-Zeinstra SMA. What is the clinical course of acute ankle sprains? A systematic literature review. *Am J Med* 2008;121:324–331.e6.
2. Doherty C, Delahunt E, Caulfield B, Hertel J, Ryan J, Bleakley C. The incidence and prevalence of ankle sprain injury: a systematic review and meta-analysis of prospective epidemiological studies. *Sports Med* 2014;44:123–140.
3. van Dijk CN, Vuurberg G. There is no such thing as a simple ankle sprain: clinical commentary on the 2016 International Ankle Consortium position statement. *Br J Sports Med* 2017;51:485–486.
4. Fong DT-P, Hong Y, Chan L-K, Yung PS-H, Chan K-M. A systematic review on ankle injury and ankle sprain in sports. *Sports Med* 2007;37:73–94.
5. Mansour R, Jibri Z, Kamath S, Mukherjee K, Ostlere S. Persistent ankle pain following a sprain: a review of imaging. *Emerg Radiol* 2011;18:211–225.
6. Roemer FW, Jomaah N, Niu J, et al. Ligamentous injuries and the risk of associated tissue damage in acute ankle sprains in athletes: a cross-sectional MRI study. *Am J Sports Med* 2014;42:1549–1557.
7. Tochigi Y, Yoshinaga K, Wada Y, Moriya H. Acute inversion injury of the ankle: magnetic resonance imaging and clinical outcomes. *Foot Ankle Int* 1998;19:730–734.
8. Khor YP, Tan KJ. The anatomic pattern of injuries in acute inversion ankle sprains: a magnetic resonance imaging study. *Orthop J Sports Med* 2013;1:2325967113517078.
9. Crim JR, Beals TC, Nickisch F, Schannen A, Saltzman CL. Deltoid ligament abnormalities in chronic lateral ankle instability. *Foot Ankle Int* 2011;32:873–878.
10. Yasuda T, Shima H, Mori K, Tsujinaka S, Neo M. Simultaneous reconstruction of the medial and lateral collateral ligaments for chronic combined ligament injuries of the ankle. *Am J Sports Med* 2017;45:2052–2060.
11. Kim JS, Young KW, Cho HK, Lim SM, Park YU, Lee KT. Concomitant syndesmotism instability and medial ankle instability are risk factors for unsatisfactory outcomes in patients with chronic ankle instability. *Arthroscopy* 2015;31:1548–1556.
12. Hubbard-Turner T. Relationship between mechanical ankle joint laxity and subjective function. *Foot Ankle Int* 2012;33:852–856.
13. Knupp M, Lang TH, Zwicky L, Löttscher P, Hintermann B. Chronic ankle instability (medial and lateral). *Clin Sports Med* 2015;34:679–688.
14. Thompson JY, Byrne C, Williams MA, Keene DJ, Schlüssel MM, Lamb SE. Prognostic factors for recovery following acute lateral ankle ligament sprain: a systematic review. *BMC Musculoskelet Disord* 2017;18:421.
15. Frigg A, Magerkurth O, Valderrabano V, Ledermann H-P, Hintermann B. The effect of osseous ankle configuration on chronic ankle instability. *Br J Sports Med* 2007;41:420–424.
16. Vuurberg G, Wink LM, Blankevoort L, et al. A risk assessment model for chronic ankle instability: indications for early surgical treatment? An observational prospective cohort – study protocol. *BMC Musculoskelet Disord* 2018;19:225.
17. Guillo S, Bauer T, Lee JW, et al. Consensus in chronic ankle instability: aetiology, assessment, surgical indications and place for arthroscopy. *Orthop Traumatol Surg Res* 2013;99:S411–S419.
18. de Bie RA, de Vet HC, van den Wildenberg FA, Lenssen T, Knipschild PG. The prognosis of ankle sprains. *Int J Sports Med* 1997;18:285–289.
19. Kobayashi T, Gamada K. Lateral ankle sprain and chronic ankle instability: a critical review. *Foot Ankle Spec* 2014;7:298–326.
20. Langner I, Frank M, Kuehn JP. Acute inversion injury of the ankle without radiological abnormalities: assessment with high-field MR imaging and correlation of findings with clinical outcome. *Skelet Radiol* 2011;40:423–430.
21. Akacha M, Hutton JL, Lamb SE. Modelling treatment, age- and gender-specific recovery in acute injury studies. *Univ Warwick Cent Res Stat Methodol* 2010;10:11–12.
22. Tyler TF, McHugh MP, Mirabella MR, Mullaney MJ, Nicholas SJ. Risk factors for noncontact ankle sprains in high school football players: the role of previous ankle sprains and body mass index. *Am J Sports Med* 2006;34:471–475.
23. Waterman BR, Belmont PJ Jr, Cameron KL, Deberardino TM, Owens BD. Epidemiology of ankle sprain at the United States Military Academy. *Am J Sports Med* 2010;38:797–803.
24. Gribble PA, Terada M, Beard MQ, et al. Prediction of lateral ankle sprains in football players based on clinical tests and body mass index. *Am J Sports Med* 2016;44:460–467.
25. Hiller CE, Kilbreath SL, Refshauge KM. Chronic ankle instability: evolution of the model. *J Athl Train* 2011;46:133–141.
26. Scranton PE Jr, McDermott JE, Rogers JV. The relationship between chronic ankle instability and variations in mortise anatomy and impingement spurs. *Foot Ankle Int* 2000;21:657–664.
27. Magerkurth O, Frigg A, Hintermann B, Dick W, Valderrabano V. Frontal and lateral characteristics of the osseous configuration in chronic ankle instability. *Br J Sports Med* 2010;44:568–572.
28. Medina McKeon JM, Bush HM, Reed A, Whittington A, Uhl TL, McKeon PO. Return-to-play probabilities following new versus recurrent ankle sprains in high school athletes. *J Sci Med Sport* 2014;17:23–28.
29. Chilvers M, Manoli A II. The subtle cavus foot and association with ankle instability and lateral foot overload. *Foot Ankle Clin* 2008;13:315–324. vii.
30. Ichiro T, Konsei S. Articular cartilage lesions in ankles with lateral ligament injury: an arthroscopic study. *Am J Med* 1993;21(1).
31. Longo UG, Loppini M, Romeo G, van Dijk CN, Maffulli N, Denaro V. Bone bruises associated with acute ankle ligament injury: do they need treatment? *Knee Surg Sports Traumatol Arthrosc* 2013;21:1261–1268.
32. Barg A, Tochigi Y, Amendola A, Phisitkul P, Hintermann B, Saltzman CL. Subtalar instability: diagnosis and treatment. *Foot Ankle Int* 2012;33:151–160.
33. Roster B, Michelier P, Giza E. Peroneal tendon disorders. *Clin Sports Med* 2015;34:625–641.
34. Lavery KP, McHale KJ, Rossy WH, Theodore G. Ankle impingement. *J Orthop Surg Res* 2016;11:97.
35. Mitsiokapa E, Mavrogenis AF, Drakopoulos D, Mauffrey C, Scarlat M. Peroneal nerve palsy after ankle sprain: an update. *Eur J Orthop Surg Traumatol* 2017;27:53–60.
36. Jolman S, Robbins J, Lewis L, Wilkes M, Ryan P. Comparison of magnetic resonance imaging and stress radiographs in the evaluation of chronic lateral ankle instability. *Foot Ankle Int* 2017;38:397–404.

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