SYNDESMOSIS INVOLVEMENT IN ACUTE LIGAMENTOUS ANKLE INJURIES

IMPLICATIONS FOR DIAGNOSIS AND PROGNOSIS

Thomas P.A. Baltes

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TABLE OF CONTENTS

Chapter 1	General introduction	7
Chapter 2	Acute clinical evaluation for the diagnosis of lateral ankle ligament injuries is useful: A comparison between the acute and delayed settings	23
Chapter 3	Acute clinical evaluation for syndesmosis injury has high diagnostic value	49
Chapter 4	Diagnostic value of ultrasonography in acute lateral and syndesmotic ligamentous ankle injuries	71
Chapter 5	Limited intrarater and interrater reliability of acute ligamentous ankle injuries on 3T MRI	91
Chapter 6	Does involvement of the anterior syndesmosis affect the functional outcome of acute ligamentous ankle injuries?	119
Chapter 7	The prevalence, size and anatomic location of cartilage and osteochondral lesions in athletes with an acute ligamentous ankle injury	143
Chapter 8	General discussion	163
Appendices	Summary	173
	Nederlandse samenvatting	179
	PhD portfolio	187
	List of publications	193
	Curriculum Vitae	199
	Acknowledgements	203

CHAPTER 1

General introduction

INTRODUCTION

Acute ankle sprains are one of the most common sport-related injuries.[1] Historically, the term 'acute ankle sprain' has been used to describe injuries of the lateral ankle ligaments. However, acute ankle sprains may also affect other structures.[2] Concomitant injuries may include (avulsion-) fractures, cartilage lesions, tendon injuries and other ligamentous injuries.[3] Depending on the mechanism of injury, an ankle sprain may affect the lateral ankle ligaments, syndesmosis and medial ankle ligaments. Ligamentous ankle injuries, and syndesmosis injuries in particular, can be challenging to diagnose in the acute clinical setting. The primary aim of this thesis was therefore to evaluate the use of clinical evaluation and ultrasound in the diagnosis of acute ligamentous ankle injuries. In elite athletes, MR imaging is commonly used to diagnose acute ligamentous ankle injuries. MR imaging frequently demonstrates edema or partial discontinuity of the anterior syndesmosis. However, it remains unclear whether involvement of the anterior syndesmosis affects the prognosis of acute ligamentous ankle injuries. Therefore, the secondary aims were to determine 1) the prognosis of clinically stable syndesmosis injuries and 2) determine the association of syndesmosis injury with cartilage and osteochondral lesions ((O)CLs).

ANATOMY AND INJURY-MECHANISM

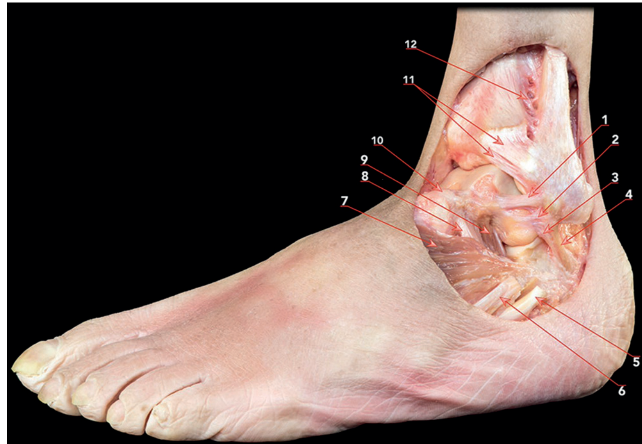
The bones comprising the ankle joint are bound by ligamentous structures. Based on their anatomical position, these ligamentous structures can be divided in three major complexes; 1) Lateral ligament complex, 2) Syndesmosis complex and 3) Medial ligament complex.[4]

The lateral ankle complex is injured most frequently (0.93/1000 athlete exposures).[5] The lateral ankle ligament complex consists of three individual ligaments originating from the fibula and attaching to the talus and calcaneus; anterior talofibular ligament (ATFL), the calcaneofibular ligament (CFL) and the posterior talofibular ligament (PTFL). (Figure 1&2) The classic mechanism of injury is a supination-inversion of the foot. The ATFL is the first and often only ligament to be injured, followed by the CFL and infrequently the PTFL.[3,6,7]

The syndesmosis complex is injured second most commonly (0.38/1000 athlete exposures).[5] The syndesmosis is comprised of five individual ligaments spanning the distal tibiofibular joint; anteroinferior tibiofibular ligament [AITFL], the interosseous ligament [IOL], interosseous membrane [IOM], posteroinferior tibiofibular ligament [PITFL] and transverse tibiofibular ligament [TTFL]. (Figure 1-3) The typical mechanism of injury is dorsiflexion and external rotation of the foot. However, other trauma-mechanisms have been described.[8] Of the five ligaments comprising the syndesmotic complex, the AITFL is the first to be injured, followed by the IOL/IOM and PITFL.[9]

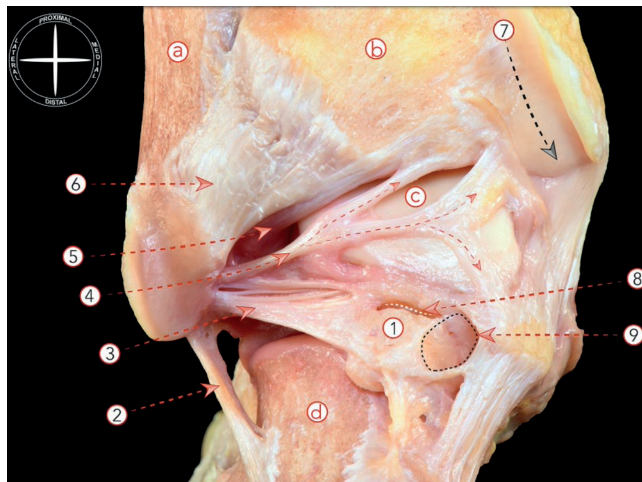
Isolated injuries of the medial ankle ligaments are rare (0.06/1000 athlete exposures).[5] The medial ankle complex is a multi-fascicular complex which can be divided into two layers 1) superficial deltoid ligaments and 2) deep deltoid ligament.[10] (Figure 4) The superficial deltoid ligament consists of four parts, originating from the tibia and fanning out to attach to the navicular bone, spring ligament, calcaneus and talus; tibionavicular [TN], tibiospring [TS], tibiocalcaneal [TC] and posterior tibiotalar [PT]. The deep layer consists of two parts originating from the tibia and attaching to the talus; anterior tibiotalar ligament [ATT] and posterior tibiotalar ligament [PTT]. Various mechanisms of injury have been proposed including pronation-eversion, external rotation, supination-external rotation and abduction.[11,12] In isolation, injury of the medial ligamentous complex is virtually always limited to the superficial ligaments. Complete rupture of the deep deltoid ligaments is almost always associated with a fracture or syndesmosis injury.[13]

Figure 1. Osteo-articular dissection showing the ligamentous structures of the anterolateral ankle joint.



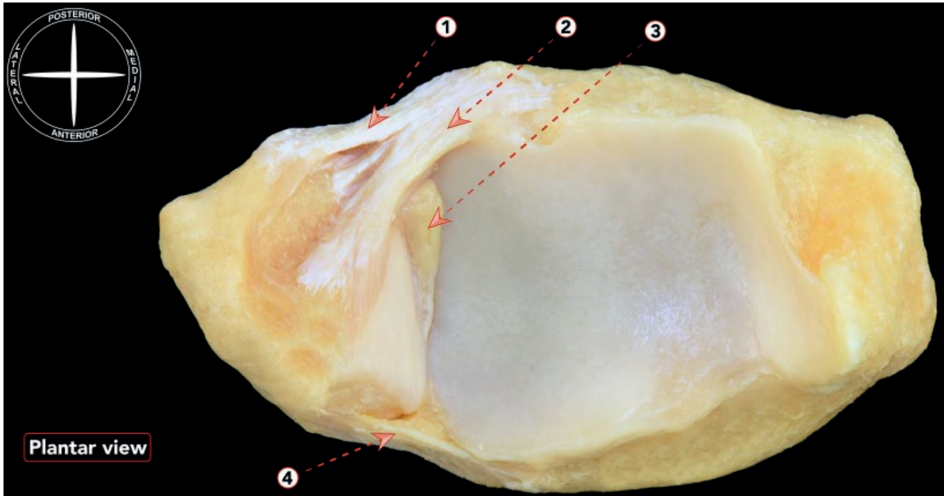
1) Anterior talofibular ligament [ATFL] superior fascicle, 2) ATFL inferior fascicle, 3) Arciform fibres of the lateral fibulotalocalcaneal ligament complex, 4) Calcaneofibular ligament [CFL], 5) Peroneus longus tendon, 6) Peroneus brevis tendon, 7) Extensor digitorum brevis muscle, 8) Cervical ligament, 9) Interosseous talocalcaneal ligament, 10) Dorsal talonavicular ligament, 11) Anteroinferior tibiofibular ligament [AITFL] 12) Interosseous ligament [IOL]. Reproduced with permission from: The lateral fibulotalocalcaneal ligament complex: an ankle stabilizing isometric structure. Knee Surg Sports Traumatol Arthrosc (2020) 28:8–17.[14]

Figure 2. Osteo-articular dissection showing the ligamentous structures of the posterior ankle joint.



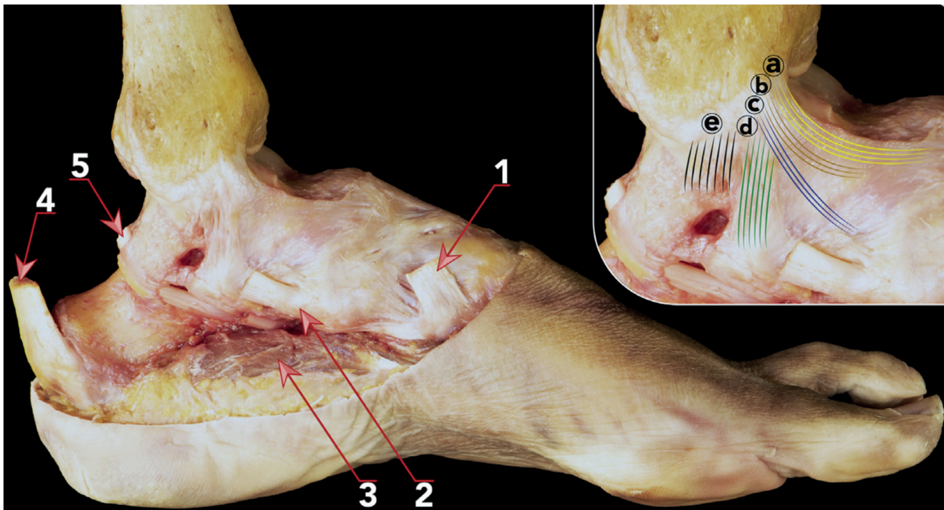
A) Fibula. B) Tibia. C) Talus. D) Calcaneus. 1) Os trigonum, 2) Calcaneofibular ligament [CFL] 3) Posterior talofibular ligament [PTFL], 4) Intermalleolar ligament, 5) Transverse tibiofibular ligament [TTFL], 6) Posteroinferior tibiofibular ligament [PITFL], 7) Tibial retromalleolar groove for the tibialis posterior tendon, 8) Broken synchondrosis between talus and os trigonum, 9) Tunnel for the flexor hallucis longus tendon. Reproduced with permission from: Letter Regarding: Cadaveric Analysis of the Distal Tibiofibular Syndesmosis. Foot Ankle Int (2017) 38: 343-345.[15]

Figure 3. Osteo-articular dissection showing a plantar view of the ankle syndesmosis.



1) Transverse tibiofibular ligament [TTFL], 2) Posterior tibiofibular ligament [PITFL], 3) Syndesmotic synovial fringe, 4) Anteroinferior tibiofibular ligament [AITFL]. Reproduced with permission from: Letter Regarding: Cadaveric Analysis of the Distal Tibiofibular Syndesmosis. Foot Ankle Int (2017) 38: 343-345.[15]

Figure 4. Osteo-articular dissection showing the ligamentous structures of the medial ankle joint.



1) Anterior tibial tendon, 2) Posterior tibial tendon, 3) Abductor hallucis muscle, 4) Calcaneal tendon, 5) Flexor hallucis longus tendon. Upper right corner: magnified view of the deltoid ligament and its fascicles. A) Tibionavicular fascicle [TN], B) Anterior tibiotalar fascicle [ATT], C) Tibiospring fascicle [TS]. D) Tibiocalcaneal fascicle [TC]. E) Posterior tibiotalar fascicle [PT/PTT]. Reproduced with permission from: Anatomy of the Deltoid-Spring Ligament Complex. Foot Ankle Clin (2021) 26:237-247.[16]

CLINICAL EVALUATION OF ACUTE LIGAMENTOUS ANKLE INJURIES

The presence of a fracture should be excluded in the acute setting (e.g. Emergency Department) using conventional radiographs. Various clinical decision rules (e.g. Ottawa ankle rules) have been introduced to avoid unnecessary use of radiographic imaging. Using the Ottawa ankle rules, fractures can be identified with a 86%–99% sensitivity and 25%-46% specificity which reduces the need for radiographic examination.[17]

Ligamentous injuries should be considered after the presence of fractures has been excluded. The lateral ankle ligaments are injured most frequently. Injuries of the lateral complex are primarily diagnosed through physical examination, with advanced imaging modalities (e.g. MRI) reserved for elite athletes. In the acute setting (within 48 hours post-injury) the combination of swelling, hematoma and a positive anterior drawer test demonstrated limited diagnostic value in a cohort of 160 patients.[18] When performed in the delayed setting (4-5 days post-injury) sensitivity improved from 71% to 96% and specificity from 31% to 84%. Current clinical guidelines therefore recommend delaying clinical evaluation for lateral ligament injuries until 4-5 days post-injury.[17] As this recommendation is based on one study only, additional studies are required to validate these findings.

The diagnosis of syndesmosis injury is considered notoriously difficult and in the acute setting primarily relies on clinical evaluation. Various syndesmosis stress tests have been described, including the squeeze test, cotton test, and dorsiflexion external-rotation stress test.[19] Currently only two high-quality studies have evaluated the diagnostic accuracy of clinical syndesmosis tests using MRI as reference standard.[20,21] One cohort study of 96 patients reported that syndesmosis test had insufficient accuracy to diagnose syndesmosis injury within 24 hours post-injury. In another cohort study of 87 athletes, tenderness over the anterior syndesmosis had 92% sensitivity and the squeeze test had 88% specificity when performed within seven days post injury. As both studies reported conflicting results, a large prospective study evaluating the diagnostic value of clinical evaluation for the diagnosis of syndesmosis injury is warranted.

IMAGING OF ACUTE LIGAMENTOUS ANKLE INJURIES

Imaging studies can be used to confirm ligamentous injuries when suspected based on injury history and clinical evaluation. MR imaging is considered the golden standard with 61-78% sensitivity and 80-95% specificity for lateral ankle ligament injuries and 100% sensitivity and 92% specificity for syndesmosis injuries.[22–24] However, MR imaging is expensive and not always readily available. Ultrasound might provide a valuable alternative that could be used for early diagnosis (e.g. field-side) of both lateral ligament and syndesmosis injuries.[25,26] Preliminary studies on the diagnostic value of ultrasound in the diagnosis of acute ligamentous ankle injuries have demonstrated promising results.[25,27–29] However, a large prospective cohort study evaluating the diagnostic value for injuries of all ankle ligaments is required to validate these conclusions.

GRADING OF ACUTE LIGAMENTOUS ANKLE INJURIES

Clinical grading of lateral ligament injuries is traditionally performed using a four-grade system; (grade 0) intact ligament, (grade 1) partial discontinuity of a ligament, (grade 2) incomplete discontinuity of a ligament with moderate functional impairment, (grade 3) complete discontinuity with loss of integrity.[30] This gradings system enables health care professionals to communicate injury severity with patients and allied health care professionals and helps to identify athletes that might require surgery.

Clinical grading of syndesmosis injuries is performed using the West Point Ankle Grading system. Developed in 1992 by Gerber et al this classification can be used to grade injury severity of the syndesmosis: (grade I) sprain or partial tear of the AITFL; (grade II) rupture of the AITFL and consequent injury of the IOL; (grade III) Complete disruption and diastasis of the syndesmosis.[31] In 2016 the classification was modified by Calder et al., differentiating stable injuries (Grade I and Grade IIa) from unstable injuries (grade IIb and grade III).[9] In the modified West Point grading system, grade IIa injury and grade IIb are differentiated by the presence of a positive squeeze test or combined deltoid injury. Using this grading system patients with stable injuries requiring conservative treatment can be differentiated from patients with unstable injuries requiring surgery.

MR grading of ligamentous ankle injuries is performed using the Schneck grading system.[32] Using the Schneck grading system the integrity of the three major ligamentous ankle complexes of the ankle: (1) lateral ankle ligaments, (2) syndesmosis and (3) medial ankle ligaments can be assessed. The Schneck grading system consists of four grades; (grade 0) no abnormality of ligament; (grade 1) peri-ligamentous high signal/edema on proton density-weighted sequence; (grade 2) partial discontinuity but preserved remnant fibers; (grade 3) complete discontinuity. The Schneck grading system provides a detailed description of MR findings and enables musculoskeletal healthcare professionals to communicate injury severity of the individual ligaments. As the inter- and intrarater reliability is unknown a cross-sectional study exploring the diagnostic reliability of this grading system is required.

Prognostic scoring for return to play after syndesmosis injury using MR findings has been performed in two studies. In a small series of 17 NFL players, except for syndesmosis width, no association between prognostic scoring and return to play was established.[33] Sikka et al introduced a four-grade grading system; (grade I) isolated injuries of the AITFL; (grade II) injury of the AITFL, IOL and IOM; (grade III) Injury of the AITFL, IOL/IOM and PITFL; (grade IV) injury of the AITFL, IOL/IOM, PITFL and deltoid ligament.[34] In a cohort of 36 NFL players increasing grade of injury was associated with increased time to return to play. The interrater reliability of this classification has not been evaluated.

MANAGEMENT OF ACUTE LIGAMENTOUS ANKLE INJURIES

In the acute setting treatment should be aimed at reducing pain and preventing swelling according to the Rest, Ice, Compression, Elevation (RICE) principles.[17] Although beneficial for pain reduction, immobilization with a boot or cast should be limited to the acute setting. Non-Steroidal Anti-Inflammatory Drugs (NSAID'S) can be taken within the first few days to reduce pain and swelling, however, use thereafter should be limited as evidence suggests it might delay healing.[17] Most acute ankle injuries are treated conservatively with a supervised rehabilitation programme consisting of strengthening and propriocepsis exercises. However, treatment should be tailored to the involved ligamentous structures and injury severity.[17,35]

Lateral ankle ligament injuries are typically treated conservatively. Treatment consists of progressive weightbearing with use of a functional support (e.g. brace or taping) followed by a (supervised) rehabilitation program.[17] Rehabilitation therapy is recommended to improve functional outcomes and reduce recurrence. The rehabilitation strategy should address strength, proprioception and functional deficits.[17] In the majority of patients satisfactory outcome can be obtained with functional rehabilitation only. Surgery is therefore reserved for patients with chronic ankle instability and professional athletes with complete discontinuity of the lateral ankle ligaments.[36]

Treatment of syndesmosis injuries has been a matter of debate for decades. Current evidence supports treatment of stable syndesmosis injuries (West Point grade I-IIa) with a prolonged period of boot/cast immobilization followed by a supervised rehabilitation program.[35] Unstable syndesmosis injuries (West Point IIb-III) require surgical stabilization in order to prevent long-term sequela such as anterolateral impingement, osteoarthritis and synostosis formation. In addition, it reduces the time required to return to play in professional athletes.[9,35] However, high quality prospective studies on the treatment and outcome of stable and unstable syndesmosis injuries are lacking.

Medial ligamentous complex injuries are rare and seldom occur in isolation.[35] Treatment of isolated injury of the superficial deltoid is conservative by immobilization and rest, followed by supervised rehabilitation. Complete tears of the deep deltoid ligaments are almost always accompanied by a concomitant fracture or syndesmosis injury. When surgical treatment is indicated for an associated injury (e.g. syndesmosis injury, osteochondral lesion or fracture) ligamentous repair of the deep deltoid ligaments may prevent infolding of the deltoid ligaments and malreduction.[35]

PROGNOSIS OF ACUTE LIGAMENTOUS ANKLE INJURIES

Functional outcome and return to play prognosis are crucial when treating athletes with an acute ligamentous ankle injury. Data on functional outcome can help counsel patients and their support staff on what to expect from the rehabilitation program or surgical procedure and is essential in the shared decision process. In elite athletes, there are important constraints on return to play and providing accurate return to play prognosis is therefore essential in managing athletes' expectations.

Return to sport and functional outcome after syndesmosis injury were evaluated in a recent systematic review.[37] In a sub-analysis, including a total of five studies (305 patients), a prolonged return to play was observed for conservatively treated syndesmosis injury compared to lateral ligament injury (40 days vs 4 days). Only one of the included studies described functional outcome and no patient reported outcome measures were used.[31] In addition, most studies use physical examination to differentiate syndesmosis injuries from lateral ligament injuries. Thus far, only one high-quality study has compared return to play after conservative treatment for lateral ligament injuries and syndesmosis injuries using MRI as reference standard.[38] In this study conservative treatment of syndesmosis injuries resulted in a return to play of 62 days compared to 15 days for lateral ligament injuries.[38] In this study injury severity was not taken into consideration. In elite athletes with acute ligamentous ankle injuries, MR imaging often demonstrates interstitial edema and partial discontinuity of the AITFL. Based on current literature it is unclear whether these injuries affect the prognosis of acute ankle injuries.

The return to play prognosis after surgical fixation of syndesmosis injuries has been investigated in two studies.[9,39] In a cohort of 24 athletes with unstable syndesmosis injuries (West Point IIb) an average return to play of 64 days (range, 27 to 104 days) was reported after surgical stabilization. Another cohort study of 110 male football players with unstable syndesmosis injuries (West Point >IIB-III) reported an average return to on field rehabilitation of 37 (±12) days; return to team training of 72 (±28) days and return to match play after 103 (±28) days.[39] In the latter study an association was found between age, presence of osteochondral lesions and a prolonged return to play.

Osteochondral defects are found in up to 8% of athletes with an acute ligamentous ankle injury when using 1.5T MRI.[3] The presence of cartilage and osteochondral lesions is hypothesized to negatively affect functional outcome of acute ligamentous ankle injuries. Currently it is unknown whether certain injury patterns (e.g. syndesmosis injuries) predispose for the presence of cartilage and osteochondral lesions. A study prospectively evaluating the size, prevalence and anatomical lesions of cartilage and osteochondral lesions after acute ligamentous ankle injuries using 3T MRI is warranted.

OUTLINE OF THIS THESIS

The research described in this thesis evaluated the diagnosis and prognosis of acute ligamentous ankle injuries and concomitant lesions. Current literature is primarily focused on the diagnosis and prognosis of lateral ankle ligament injuries. The aim of this thesis was therefore to investigate the implications of syndesmosis involvement on the diagnosis and prognosis of acute ligamentous ankle injuries.

Clinical evaluation is the cornerstone of diagnosing ligamentous ankle ligament injuries. Current clinical guidelines recommend delaying clinical evaluation of suspected lateral ligament injuries until 4-5 days post-injury as reduced pain and swelling improves diagnostic accuracy. However, evidence supporting this claim is based on one study only. In **chapter 2** we determined the diagnostic value of injury history, clinical findings, and overall clinical suspicion in the acute (0-2 days post-injury) and delayed setting (5-8 days post-injury). Secondarily, discussion pertaining the diagnostic value of acute clinical evaluation for syndesmosis injury persists. In **chapter 3** we determined the diagnostic value of injury history, physical examination, six syndesmosis tests and overall clinical suspicion for the diagnosis of syndesmosis injury in the acute setting (0-7 days post-injury).

Despite an increase in the use of advanced imaging techniques (e.g. MRI and ultrasound) in athletes with acute ligamentous ankle injuries, high-quality evidence pertaining its diagnostic value is lacking. In **chapter 4** we investigated the diagnostic value of (dynamic-) ultrasound for acute ligamentous ankle injuries (syndesmosis injury in particular). Subsequently, we investigated the diagnostic reliability of two commonly used grading systems in the diagnosis of ligamentous ankle injuries. In **chapter 5** we established the intra- and interrater reliability of the Schneck grading system for injuries of the individual ankle ligaments and the three major ligamentous complexes and the Sikka classification for syndesmosis injury.

In elite athletes, MR imaging often demonstrates edema or partial discontinuity of the anterior syndesmosis. However, prospective data on the functional outcome of acute ligamentous ankle injuries with stable involvement of the anterior syndemosis is lacking. In **chapter 6** we compared the functional outcome of acute ligamentous ankle injuries with and without involvement of the anterior syndesmosis (without signs of clinical instability). Cartilage and osteochondral lesions ((O)CLs) are frequently observed after an acute ligamentous ankle injury. However, the association between syndesmosis injury and (O)CLs has not been

elucidated. In **chapter 7** we therefore determined the prevalence, size and anatomical location of cartilage and osteochondral lesions ((O)CLs) in athletes with an acute ligamentous ankle injury and explored the association with syndesmosis injury.

Finally, in **chapter 8** a summary of the most important findings and their implications for clinical practice and future research is provided.

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CHAPTER 2

Acute clinical evaluation for the diagnosis of lateral ankle ligament injuries is useful: A comparison between the acute and delayed settings

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ABSTRACT

Purpose: To determine the diagnostic value of seven injury history variables, nine clinical tests (including the combination thereof) and overall clinical suspicion for complete discontinuity of the lateral ankle ligaments in the acute (0-2 days post-injury) and delayed setting (5-8 days post-injury).

Methods: All acute ankle injuries in adult athletes (≥18 years) presenting up to 2 days post-injury were assessed for eligibility. Athletes were excluded if imaging studies demonstrated a frank fracture or 3T MRI could not be acquired within 10 days post-injury. Using standardized history variables and clinical tests, acute clinical evaluation was performed within 2 days post-injury. Delayed clinical evaluation was performed 5-8 days post-injury. Overall clinical suspicion was recorded after clinical evaluation. MRI was used as the reference standard.

Results: Between February 2018 and February 2020, a total of 117 acute ankle injuries were screened for eligibility, of which 43 were included in this study. Complete discontinuity of lateral ankle ligaments was observed in 23 (53%) acute ankle injuries. In the acute setting, lateral swelling had 100% (95% confidence interval [CI] 82-100) sensitivity, hematoma had 85% (95% CI: 61-96) specificity and the anterior drawer test had 100% (95% CI: 77-100) specificity. In the delayed setting, sensitivity for the presence of hematoma improved from 43% (95% CI: 24-65) to 91% (95% CI: 70-98; $p<0.01$) and the sensitivity of the anterior drawer test improved from 21% (95% CI: 7-46) to 61% (95% CI: 39-80; $p=0.02$). Clinical suspicion had a positive likelihood ratio (LR) of 4.35 (95% CI: 0.55-34.17) in the acute setting and a positive LR of 6.09 (95% CI: 1.57-23.60) in the delayed setting.

Conclusions: In the acute setting, clinical evaluation can exclude complete discontinuity (e.g. absent lateral swelling) and identify athletes with a high probability of complete discontinuity (e.g. positive anterior drawer test) of the lateral ankle ligaments. In the delayed setting the sensitivity of common clinical findings increases resulting in an improved diagnostic accuracy. In clinical practice, this study underlines the importance of meticulous clinical evaluation in the acute setting.

INTRODUCTION

Acute injuries of the lateral ankle ligaments are the most common injury in sports.[1] Accurate diagnosis is essential for adequate therapy and prevention of chronic ankle instability and post-traumatic osteoarthritis.[2] For the diagnosis, clinical evaluation is considered the mainstay, with advanced imaging techniques (i.e. magnetic resonance imaging [MRI]) predominantly reserved for elite athletes. In the acute setting, of the first 0-2 days post-injury, pain and swelling might negatively affect the reliability of physical examination. Current clinical guidelines therefore recommend delayed physical examination 4-7 days post-injury.[3,4]

The recommendation for delayed physical examination is based on one study.[5–7] In a prospective cohort study of 160 patients presenting to an emergency department after an inversion trauma, physical examination was performed within 2 days and after 4-7 days. In the acute setting (0-2 days post-injury), the combination of lateral hematoma, tenderness over the anterior talofibular ligament (ATFL) and a positive anterior drawer test had 71% sensitivity and 33% specificity. When performed in the delayed setting (4-7 days post-injury) the diagnostic value for the combination of these three clinical tests improved to 96% sensitivity and 84% specificity. However, only the diagnostic value for these three clinical tests was evaluated and no injury history variables were included. In the athletic setting, where there are important time constraints for return to sport, an early accurate diagnosis and therefore appropriate management are important considerations.[8] Accordingly, understanding the veracity of clinical examination, injury history and the combination thereof is required.

The aim of this study is to determine the diagnostic value of seven injury history variables, nine clinical tests (including the combination thereof) and overall clinical suspicion for complete discontinuity of the lateral ankle ligaments in the acute (0-2 days post-injury) and delayed setting (5-8 days post-injury). The hypothesis of this study is that acute clinical evaluation can be used to diagnose complete discontinuity of the lateral ankle ligaments in athletes.

MATERIALS AND METHODS

Ethics approval was acquired from the Anti-Doping Lab Qatar Review Board (Institutional Review Board [IRB] No. F2016000153). Written informed consent was obtained from all athletes at the time of inclusion. This study was part of a prospective cohort study conducted at Aspetar Orthopaedic and Sports Medicine Hospital from February 2018 until February 2020. The inclusion criteria for this specific study are as follows: all acute ankle injuries in adult athletes (≥18 years), participating in sports at a professional or recreational level and presenting up to 2 days post-injury. Ankle injuries were excluded if imaging demonstrated a fracture, if the 3T MRI study could not be acquired within 10 days post-injury or if the patient did not undergo delayed physical examination 5-8 days post-injury.[9,10]

Acute clinical evaluation

Initial clinical evaluation was performed up to 2 days post-injury by an Orthopaedic Surgeon or Sports Medicine Physician. Using a standardized form, injury history was recorded and a standardized physical examination was performed.

Delayed clinical evaluation

Patients underwent a second (delayed) evaluation 5-8 days post-injury. The physician was blinded to the results of the initial acute clinical evaluation and MRI findings. To determine the interrater reliability a second physician repeated the clinical evaluation.

Injury history

A total of seven injury history variables were recorded during acute and delayed clinical evaluation using a previously described form[11]: (1) Injury [new/recurrent] (2) Occasion [game/training/non-sports injury], (3) Contact [contact/non-contact], (4) Mechanism of injury [inversion/eversion/external-rotation/internal-rotation], (5) Perceived presence of swelling [yes/no], (6) Perceived ankle instability [yes/no] and (7) Sensation of pain radiating up the leg [yes/no].

Physical examination

Nine standardized clinical tests were recorded during acute and delayed physical examination using a previously described standardized form[11]: (1) Presence of hematoma [yes/no] (2) Tenderness to palpation [lateral/medial/anterior/posterior], (3) Ability to walk normally [yes/no], (4) Ability to walk on toes [yes/no], Ability to walk on heels [yes/no], (5) Passive range of motion in dorsal flexion, plantar flexion, inversion and eversion [full/restricted/painful], (6) Presence of swelling [yes/no], (7) Swelling site [laterally/medially/anterior/posterior/syndesmosis], (8) anterior drawer

test [grade 0-2] and (9) talar tilt test [grade 0-2]. The anterior drawer test and the talar tilt test were graded as grade 0: normal; grade 1: mild laxity; and grade 2: moderate to gross laxity.[7] The laxity tests were considered to indicate complete discontinuity when scored grade 2.

Overall clinical suspicion of lateral ligament injury

Clinical suspicion of lateral ligament injury was recorded by the examining physician once the clinical evaluation had been completed. Clinical suspicion was scored on a four-grade scale; grade 0: intact ligament, grade 1: partial discontinuity of a ligament, grade 2: incomplete discontinuity of a ligament with moderate functional impairment, and grade 3: complete discontinuity with loss of integrity. The overall clinical suspicion was based on the physicians' overall interpretation of injury history, physical examination, and clinical tests. Clinical suspicion was considered positive when scored grade 3.

Reference standard

MRI was used as the reference standard. Surgical exploration is considered the gold standard for ligamentous ankle injuries. However, this would only be justified in patients with an injury requiring surgical treatment. MRI has a reported 78% sensitivity and 80% specificity for complete discontinuity of the ATFL.[12] For complete discontinuity of the calcaneofibular ligament (CFL), MRI has a sensitivity of 61% and a specificity of 95%. MRI was used as a reference standard as it is the best available alternative to surgical exploration. All patients underwent a 3.0-T MR scan (GE Discovery, GE Healthcare) with an 8-channel receive only Foot & Ankle array (Invivo, Philips Healthcare). The imaging protocol has been described before.[10] In the sagittal plane T1-weighted and Proton-Density Fat-Saturated [PD-FS] sequences were acquired, axial T2-weighted and PD-FS sequences were obtained and in the coronal plane a PD-FS sequence was acquired.

MRI grading of lateral ankle ligaments

Using a standardized scoring form the MR scans were scored by two radiologists (J.A. & M.A.) with *11* and *3* years of experience in musculoskeletal imaging. Although anatomically closely related, the ATFL and CFL were graded according to the Schneck grading system separately[13–15]: normal (Grade 0); low-grade sprain (Grade 1: peri-ligamentous high signal/edema on proton density-weighted sequences and no discontinuity of fibers); partial discontinuity (Grade 2: partial discontinuity but preserved remnant fibers) and complete discontinuity (Grade 3). Previous reports on this cohort demonstrated limited interrater reliability for the ATFL (K=0.55) and CFL (K=0.31) when using the Schneck grading system.[10] The radiologists resolved

disagreement about the grading of individual ligaments by case discussion during a consensus meeting. To calculate the diagnostic value for complete discontinuity of the lateral ankle ligaments the Schneck grading system was dichotomized.[10] Acute ankle injuries were considered disease-positive when there was complete discontinuity (Grade 3) of the ATFL and/or CFL.

Dichotomization of injury history and clinical test variables

Variables obtained during injury history and physical examination were dichotomized as previously described.[11] Injury occasion [game/training/non-sports injury] was dichotomized to [game/other]. Mechanism of injury [inversion/eversion/external-rotation/internal-rotation] was dichotomized per individual mechanism of injury, that is, [inversion/other]. Tenderness to palpation [lateral/medial/anterior/posterior] was dichotomized per location: i.e. lateral tenderness to palpation [yes/no] and passive range of motion per direction [full/restricted/painful] was dichotomized: that is, passive dorsal flexion painful [yes/no]. The laxity tests were dichotomized as (1) normal [grades 0-1] and (2) complete discontinuity [grade 2].

Statistical analysis

Statistical analysis was performed using Rstudio (Rstudio v3.6.3). Descriptive statistics was used to report demographic data (i.e. gender, age or sport) and injury distribution.

The diagnostic value for injury history (seven variables), physical examination (nine clinical tests) and overall clinical suspicion were calculated using MRI findings as the reference standard. Contingency tables were created to calculate sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-). Diagnostic values were calculated for complete discontinuity of the ATFL and/or CFL. For each variable, the area under the curve (AUC) was calculated. To compare the diagnostic value (sensitivity/specificity) of each variable between the acute and delayed settings, McNemar's test was used.[16]

The association between the independent variables and the presence of complete discontinuity of the lateral ankle ligaments in the acute and delayed settings were evaluated by univariate logistic regression analyses. Independent variables with a p-value <0.15 in the univariate logistic regression analysis were entered in a multivariate logistic regression analysis. Overall clinical suspicion was not included in the multivariate analyses, as the aim was to determine what combination of objective variables could predict injury. To address quasi-complete separation, Firth's penalized maximum likelihood estimation was used to perform logistic regression analyses using R package logistf.[17]

The data analyzed for this study was part of a prospective cohort study on the functional outcome and return to play of athletes with an acute ligamentous ankle injury. Therefore, no a priori sample size calculations were performed for the current study.

Interrater reliability for physical examination and overall clinical suspicion in the delayed setting was reported using unweighted kappa statistics and overall agreement. Reliability was interpreted using the Landis and Koch classification: poor if <0, slight 0.00–0.20, fair 0.21– 0.40, moderate 0.41–0.60, substantial 0.61–0.80 and almost perfect if 0.81–1.00.[18]

RESULTS

Participants

A total of 117 acute ankle injuries (116 athletes) were assessed for eligibility. Forty-three acute ankle injuries (43 athletes) were included. (Figure 1) Most included athletes were male (86%). Of the 43 included athletes, 58% played football, 12% handball, 9% volleyball, 7% basketball and 14% participated in other sports. The median age at time of injury was 24 years (interquartile range [IQR] 20-28). Clinical evaluation in the acute setting was performed after a median of 1 day (IQR 1-2). The MR scans were obtained at a median of 3 days (IQR 2-4) post-injury. The delayed clinical evaluation was performed after a median of 7 days (IQR 6-8). Using MR imaging as the reference standard, complete discontinuity of the ATFL was observed in 23 (53%) acute ankle injuries. Complete discontinuity of the CFL was observed in 8 (19%) acute ankle injuries. Complete discontinuity of the ATFL and/or CFL was observed in 23 (53%) acute ankle injuries.

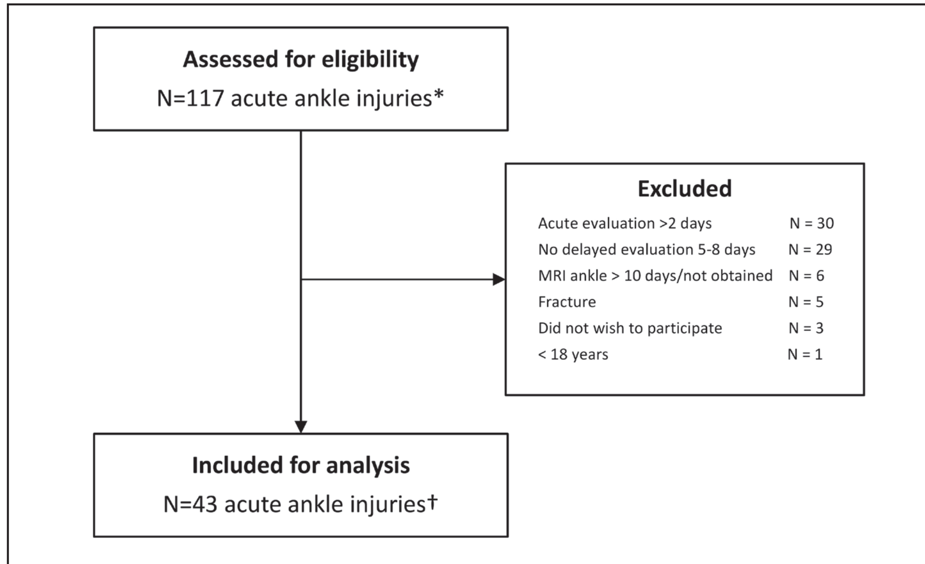
Diagnostic value of injury history

The diagnostic value of injury history in the acute and delayed settings is detailed in Table 1. In the acute setting, the patient's perceived swelling had 100% sensitivity and 100% negative predictive value. When the patient reported a recurrence of the injury, this had 90% specificity and a positive LR of 3.04 (95% CI: 0.71-13.01) for complete discontinuity of the lateral ankle ligaments.

Physical examination in the acute setting

The diagnostic value of physical examination in the acute setting is reported in Table 2. At the time of acute clinical evaluation, a median VAS score for pain of 5 (IQR 3-8) was recorded in 39 patients. Tenderness and swelling over the lateral aspect of the ankle had a 100% sensitivity. The presence of hematoma had 85% specificity with a positive LR of 2.90 (95% CI: 0.92-9.09). The anterior drawer and talar tilt test demonstrated 100% specificity with a positive predictive value of 100%. The results for the univariate logistic regression analyses are demonstrated in supplementary appendix 1. In the multivariate logistic regression analysis swelling on the lateral (OR: 36.74; 95% CI: 2.82-5529.44; $p \leq 0.01$) and medial (OR: 12.06; 95% CI: 2.67-76.74; $p \leq 0.01$) aspect of the ankle were associated with complete discontinuity of the lateral ankle ligaments. (Table 3)

Figure 1 Flowchart for in-/exclusion



*In 116 athletes; † in 43 athletes

Physical examination in the delayed setting

The diagnostic value of physical examination in the delayed setting is reported in Table 4. At the time of delayed clinical evaluation, a median VAS score for pain of 3 (IQR 1-5) was recorded. The diagnostic value of tenderness over the lateral aspect did not change significantly compared to the acute setting. The sensitivity for the presence of hematoma increased from 43% in the acute setting to 91% in the delayed setting ($p \leq 0.01$). The anterior drawer test demonstrated an improvement in sensitivity from 21% in the acute setting to 61% in the delayed setting ($p=0.02$). In the multivariate analysis, the presence of hematoma (OR: 10.72; 95% CI: 1.93-83.79; $p \leq 0.01$) and swelling over the posterior aspect of the ankle (OR: 12.77; 95% CI: 2.59-82.74; $p \leq 0.01$) were associated with complete discontinuity of the lateral ankle ligaments. (Table 3) Inter-rater reliability for physical examination in the delayed setting is demonstrated in supplementary appendix 2.

Table 1 Diagnostic accuracy of injury history for complete discontinuity of the lateral ankle ligaments in 43 athletes.

	Positive findings	Sensitivity %	Specificity %	LR+	LR-	PPV %	NPV %	AUC
Clinical history								
Injury [recurrent]	9/43 (21%)	30 (14-53)	90 (67-98)	3.04 (0.71-13.01)	0.77 (0.58-1.02)	78 (40-96)	53 (35-70)	0.60 (0.43-0.77)
Occasion [game]	25/43 (58%)	65 (43-83)	50 (28-72)	1.30 (0.77-2.22)	0.70 (0.36-1.34)	60 (39-78)	56 (31-78)	0.58 (0.40-0.75)
Contact [contact]	23/41 (56%)	57 (35-76)	44 (22-69)	1.02 (0.59-1.76)	0.98 (0.54-1.79)	57 (35-76)	44 (22-69)	0.51 (0.33-0.69)
Mechanism of injury								
• Inversion	33/43 (77%)	78 (56-92)	25 (10-49)	1.04 (0.75-1.45)	0.87 (0.30-2.53)	55 (37-71)	50 (20-80)	0.52 (0.34-0.69)
• Eversion	4/43 (9%)	9 (2-30)	90 (67-98)	0.87 (0.13-5.62)	1.01 (0.88-1.16)	50 (9-91)	46 (30-63)	0.49 (0.32-0.67)
• External Rotation	3/43 (7%)	0 (0-18)	85 (61-96)	-	1.18 (1.16-1.20)	0 (0-69)	43 (27-59)	0.43 (0.25-0.60)
• Internal Rotation	0/43 (0%)	0 (0-18)	100 (80-100)	-	1.00 (1.00-1.00)	-	47 (31-62)	0.50 (0.33-0.68)
Acute setting								
Perceived swelling	38/43 (88%)	100 (82-100)	25 (10-49)	1.33 (1.04-1.72)	-	61 (43-76)	100 (46-100)	0.63 (0.45-0.80)
Perceived instability	9/37 (24%)	35 (15-61)	85 (61-96)	2.35 (0.69-8.02)	0.76 (0.53-1.10)	67 (31-91)	61 (41-78)	0.60 (0.42-0.79)
Pain radiating up	22/42 (52%)	18 (6-41)	65 (41-84)	0.52 (0.18-1.51)	1.26 (0.98-1.62)	36 (12-68)	42 (25-61)	0.42 (0.24-0.59)
Delayed setting								
Perceived swelling	34/43 (79%)	91 (70-98)	35 (16-59)	1.40 (0.99-1.98)	0.25 (0.06-1.12)	62 (44-77)	78 (40-96)	0.63 (0.46-0.80)
Perceived instability	15/42 (36%)	41 (21-63)	70 (46-87)	1.36 (0.59-3.15)	0.84 (0.57-1.25)	60 (33-83)	52 (32-71)	0.55 (0.38-0.73)
Pain radiating up	16/43 (37%)	22 (8-44)	45 (24-68)	0.40 (0.17-0.94)	1.74 (1.24-2.43)	31 (12-59)	33 (17-54)	0.33 (0.17-0.50)

Note: MR imaging was used as reference standard. The prevalence of positive findings and diagnostic value of clinical history in the acute and delayed settings are presented. Diagnostic values are presented with 95% confidence interval (CI 95%); positive likelihood ratio (LR+); negative likelihood ratio (LR-); positive predictive value (PPV%); negative predictive value (NPV); area under the curve (AUC). Abbreviation: MR, magnetic resonance.

Table 2 Diagnostic accuracy of acute physical examination for complete discontinuity of the lateral ankle ligaments in 43 athletes.

	Positive findings	Sensitivity%	Specificity%	LR+	LR-	PPV%	NPV%	AUC
Clinical findings								
Presence of hematoma	13/43 (30%)	43 (24-65)	85 (61-96)	2.90 (0.92-9.09)	0.66 (0.46-0.97)	77 (46-94)	57 (38-74)	0.64 (0.48-0.81)
Tenderness to palpation								
• Lateral	39/43 (91%)	100 (82-100)	20 (7-44)	1.25 (1.00-1.56)	-	59 (42-74)	100 (40-100)	0.60 (0.43-0.77)
• Medial	30/43 (70%)	78 (56-92)	40 (20-64)	1.30 (0.86-1.98)	0.54 (0.22-1.37)	60 (41-77)	62 (32-85)	0.59 (0.42-0.76)
• Anterior	19/43 (44%)	57 (35-76)	70 (46-87)	1.88 (0.88-4.03)	0.62 (0.37-1.03)	68 (43-86)	58 (37-77)	0.63 (0.46-0.80)
• Posterior	8/43 (19%)	26 (11-49)	90 (67-98)	2.61 (0.59-11.50)	0.82 (0.64-1.06)	75 (36-96)	51 (34-68)	0.58 (0.41-0.75)
• Syndesmosis	24/43 (56%)	65 (43-83)	55 (32-76)	1.45 (0.82-2.56)	0.63 (0.33-1.20)	63 (41-80)	58 (34-79)	0.60 (0.43-0.77)
- Unable to walk normal	30/43 (70%)	87 (65-97)	50 (28-72)	1.74 (1.09-2.77)	0.26 (0.08-0.83)	67 (47-82)	77 (46-94)	0.69 (0.52-0.85)
- Unable to walk on toes	33/43 (77%)	87 (65-97)	35 (16-59)	1.34 (0.93-1.91)	0.37 (0.11-1.28)	61 (42-77)	70 (35-92)	0.61 (0.44-0.78)
- Unable to walk on heels	30/43 (70%)	87 (65-97)	50 (28-72)	1.74 (1.09-2.77)	0.26 (0.08-0.83)	66 (47-82)	77 (46-94)	0.69 (0.52-0.85)
- Range of motion								
• Pain on dorsal flexion	28/43 (65%)	78 (56-92)	50 (28-72)	1.57 (0.96-2.55)	0.43 (0.18-1.04)	64 (44-81)	67 (39-87)	0.64 (0.47-0.81)
• Pain on plantar flexion	29/43 (67%)	78 (56-92)	45 (24-68)	1.42 (0.91-2.23)	0.48 (0.20-1.18)	62 (42-79)	64 (36-86)	0.62 (0.45-0.79)
• Pain on inversion	31/43 (72%)	78 (56-92)	35 (16-59)	1.20 (0.82-1.77)	0.62 (0.24-1.62)	58 (39-75)	58 (29-84)	0.57 (0.39-0.74)
• Pain on eversion	28/43 (65%)	70 (47-86)	40 (20-64)	1.16 (0.74-1.82)	0.76 (0.35-1.63)	57 (37-75)	53 (27-78)	0.55 (0.37-0.72)
Presence of swelling								
• Lateral	36/43 (84%)	100 (82-100)	35 (16-59)	1.54 (1.12-2.12)	-	64 (46-79)	100 (56-100)	0.68 (0.51-0.84)
• Medial	21/43 (49%)	74 (51-89)	80 (56-93)	3.70 (1.49-9.18)	0.33 (0.16-0.66)	81 (57-94)	73 (50-88)	0.77 (0.62-0.92)
• Anterior	15/43 (35%)	57 (35-76)	90 (67-98)	5.65 (1.45-22.08)	0.48 (0.30-0.78)	87 (58-98)	64 (44-81)	0.73 (0.58-0.89)
• Posterior	4/43 (9%)	9 (2-30)	90 (67-98)	0.87 (0.13-5.62)	1.01 (0.88-1.16)	50 (9-91)	46 (30-63)	0.49 (0.32-0.67)

Table 2 Continued

	Positive findings	Sensitivity%	Specificity%	LR+	LR-	PPV%	NPV%	AUC
Laxity tests								
- Anterior Drawer test	4/36 (11%)	21 (7-46)	100 (77-100)	Infinity	0.79 (0.63-1.00)	100 (40-100)	53 (35-70)	0.61 (0.42-0.79)
- Talar Tilt	2/33 (6%)	12 (2-38)	100 (76-100)	Infinity	0.88 (0.74-1.05)	100 (20-100)	52 (33-69)	0.56 (0.36-0.76)
Clinical suspicion								
- Complete discontinuity	6/43 (14%)	22 (8-44)	95 (73-100)	4.35 (0.55-34.17)	0.82 (0.66-1.03)	83 (36-99)	51 (35-68)	0.58 (0.41-0.76)

Note: MR imaging was used as reference standard The prevalence of positive findings and diagnostic value of physical examination in the acute setting are presented. Diagnostic values are presented with 95% confidence interval (95% CI); positive likelihood ratio (LR+); negative likelihood ratio (LR-); positive predictive value (PPV%); negative predictive value (NPV); area under the curve (AUC). Abbreviation: MR, magnetic resonance.

Table 3 Multivariate logistic regression analysis for the association between injury history, physical examination and laxity tests for complete discontinuity of the lateral ankle ligaments**.**

	Multivariate			
	N	**OR (95%CI)**	**SE**	**P-value**
Acute setting				
- Lateral swelling	43	36.74 (2.82-5529.44)	1.80	<0.01
- Medial swelling	43	12.06 (2.67-76.74)	0.84	<0.01
Delayed setting				
- Presence of hematoma	43	10.72 (1.93-83.79)	0.96	<0.01
- Posterior swelling	43	12.77 (2.59-82.74)	0.89	<0.01

Note: The odds ratio of the predictors associated with complete discontinuity of the lateral ankle ligaments are presented. Values are presented as β-coefficients with corresponding 95% confidence interval (95% CI) and standard error (SE)

Table 4 Diagnostic accuracy of delayed physical examination for complete discontinuity of the lateral ankle ligaments in 43 athletes.

	Positive findings	Sensit-ivity%	p-value	Specifi-city%	p-value	LR+	LR-	PPV%	NPV%	AUC
Clinical findings										
Presence of hematoma	27/43 (63%)	91 (70-98)	<0.01	70 (46-87)	n.s.	3.04 (1.54-6.01)	0.12 (0.03-0.49)	78 (57-91)	88 (60-98)	0.81 (0.67-0.95)
Tenderness to palpation										
• Lateral	35/43 (81%)	100 (82-100)	n.s.	40 (20-64)	n.s.	1.67 (1.17-2.38)	-	66 (48-80)	100 (60-100)	0.70 (0.54-0.86)
• Medial	27/43 (63%)	78 (56-92)	n.s.	55 (32-76)	n.s.	1.74 (1.02-2.96)	0.40 (0.17-0.93)	67 (46-83)	69 (41-88)	0.67 (0.50-0.83)
• Anterior	19/43 (44%)	65 (43-83)	n.s.	80 (56-93)	n.s.	3.26 (1.29-8.23)	0.43 (0.24-0.78)	79 (54-93)	67 (45-84)	0.73 (0.57-0.88)
• Posterior	16/43 (37%)	61 (39-80)	0.04	90 (67-98)	n.s.	6.09 (1.57-23.60)	0.43 (0.26-0.73)	88 (60-98)	67 (46-83)	0.75 (0.61-0.90)
• Syndesmosis	28/43 (65%)	74 (51-89)	n.s.	45 (24-68)	n.s.	1.34 (0.84-2.14)	0.58 (0.26-1.30)	61 (41-78)	60 (33-83)	0.60 (0.42-0.77)
- Unable to walk normal	15/43 (35%)	52 (31-73)	0.02	85 (61-96)	0.04	3.48 (1.14-10.60)	0.56 (0.36-0.88)	80 (51-95)	61 (41-78)	0.69 (0.53-0.85)
- Unable to walk on toes	15/43 (35%)	39 (20-61)	<0.01	70 (46-87)	0.04	1.30 (0.56-3.03)	0.87 (0.60-1.26)	60 (33-83)	50 (31-69)	0.55 (0.37-0.72)
- Unable to walk on heels	15/43 (35%)	39 (20-61)	<0.01	70 (46-87)	n.s.	1.30 (0.56-3.03)	0.87 (0.60-1.26)	60 (33-83)	50 (31-69)	0.55 (0.37-0.72)

Table 4 Continued

	Positive findings	Sensitivity%	p-value	Specificity%	p-value	LR+	LR-	PPV%	NPV%	AUC
- Range of motion										
• Pain on dorsal flexion	29/43 (67%)	83 (60-94)	n.s.	50 (28-72)	n.s.	1.65 (1.03-2.66)	0.35 (0.13-0.93)	66 (46-81)	71 (42-90)	0.66 (0.50-0.83)
• Pain on plantar flexion	19/43 (44%)	57 (35-76)	n.s.	70 (46-87)	n.s.	1.88 (0.88-4.03)	0.62 (0.37-1.03)	68 (43-86)	58 (37-77)	0.63 (0.46-0.80)
• Pain on inversion	34/43 (79%)	83 (60-94)	n.s.	25 (10-49)	n.s.	1.10 (0.80-1.51)	0.70 (0.21-2.27)	56 (38-72)	56 (23-85)	0.54 (0.36-0.71)
• Pain on eversion	27/43 (63%)	70 (47-86)	n.s.	45 (24-68)	n.s.	1.26 (0.78-2.04)	0.68 (0.32-1.41)	59 (39-77)	56 (31-79)	0.57 (0.40-0.75)
Presence of swelling										
• Lateral	36/43 (84%)	100 (82-100)	n.s.	35 (16-59)	n.s.	1.54 (1.12-2.12)	-	64 (46-79)	100 (56-100)	0.68 (0.51-0.84)
• Medial	25/43 (58%)	78 (56-92)	n.s.	65 (41-84)	n.s.	2.24 (1.19-4.22)	0.33 (0.15-0.77)	72 (50-87)	72 (46-89)	0.72 (0.56-0.88)
• Anterior	26/43 (60%)	74 (51-89)	n.s.	55 (32-76)	0.02	1.64 (0.96-2.82)	0.47 (0.22-1.02)	65 (44-82)	65 (39-85)	0.65 (0.48-0.81)
• Posterior	22/43 (51%)	83 (60-94)	<0.01	85 (61-96)	n.s.	5.51 (1.91-15.90)	0.20 (0.08-0.51)	86 (64-96)	81 (57-94)	0.84 (0.71-0.97)
Laxity tests										
- Anterior drawer test	16/41 (39%)	61 (39-80)	0.02	89 (64-98)	n.s.	5.48 (1.42-21.07)	0.44 (0.26-0.74)	88 (60-98)	64 (43-81)	0.75 (0.60-0.90)
- Talar tilt	13/41 (32%)	52 (31-73)	0.03	94 (71-100)	n.s.	9.39 (1.34-65.65)	0.51 (0.33-0.78)	92 (62-100)	61 (41-78)	0.73 (0.60-0.89)

Table 4 Continued

	Positive findings	Sensitivity%	p-value	Specificity%	p-value	LR+	LR-	PPV%	NPV%	AUC
Clinical suspicion										
- Complete discontinuity	16/43 (37%)	61 (39-80)	0.02	90 (67-98)	n.s.	6.09 (1.57-23.60)	0.43 (0.26-0.73)	88 (60-98)	67 (46-83)	0.75 (0.61-0.90)

Note: MR imaging was used as reference standard The prevalence of positive findings and diagnostic value of physical examination in the delayed setting are presented. Diagnostic values are presented with a 95% confidence interval (CI 95%). Comparison of sensitivity and specificity between the acute and delayed settings is reported using p-values. positive likelihood ratio (LR+); negative likelihood ratio (LR-); positive predictive value (PPV%); negative predictive value (NPV); area under the curve (AUC). not statistically significant (n.s.). Abbreviation: MR, magnetic resonance.

DISCUSSION

The most important finding of the present study was that in the acute setting (0-2 days post-injury) physical examination is useful to exclude complete discontinuity of the lateral ankle ligaments. When swelling over the lateral malleolus is absent in the first 2 days, complete discontinuity is unlikely. In the acute setting clinical findings with high specificity (e.g. hematoma, anterior drawer test and talar tilt test) can identify athletes with an increased probability of complete discontinuity. Within 2 days post-injury the combination of lateral and medial swelling best identified acute ankle injuries at risk for complete discontinuity of the lateral ankle ligaments. In the delayed setting the diagnostic value of common clinical findings is improved as pain and swelling subsides. After 5-8 days post-injury the presence of hematoma and posterior swelling best identified ankle injuries at risk for complete discontinuity of the lateral ankle ligaments. When in the acute or delayed setting the physician's overall clinical suspicion is positive, and a high probability for complete discontinuity of the lateral ankle ligaments exists.

Diagnostic value of injury history

A history of injury recurrence had a positive predictive value of 78% for complete discontinuity of the lateral ankle ligaments. This is in contrast with previous studies which did not find a correlation between prior injury and complete discontinuity.[19,20] Patient's perceived swelling had a negative predictive value of 100% in the acute setting. In the study by van Dijk et al. no negative predictive value for perceived swelling was provided. However, patients reported immediate swelling in 78% of patients with ligament lesions compared to 55% of those without lesion.[5–7] No previous study has investigated the diagnostic value of perceived instability. In our study, perceived instability had a specificity of 85% (61-96) and a positive LR of 2.35 (0.69-8.02) within 2 days post-injury. The observations in our study underwrite the importance of clinical history in the diagnosis of complete discontinuity of the lateral ankle ligaments.

Physical examination in the acute setting

In the acute setting, the presence of swelling or tenderness over the lateral malleolus had 100% sensitivity. The anterior drawer test and the talar tilt test, both demonstrated 100% specificity. The specificity for the presence of hematoma and tenderness over the posterior aspect of the ankle was 85% and 90%, respectively. The diagnostic values observed in the current study are in stark contrast with the findings in the study by van Dijk et al.[5–7] In this study the combination of lateral hematoma, tenderness over the ATFL and a positive anterior drawer test within 48 hours post-injury only had 71%

sensitivity and 33% specificity. The findings of our study demonstrate that physical examination in the acute setting can be used to exclude complete discontinuity of the lateral ankle ligaments and identify athletes with a high probability of complete discontinuity.

Physical examination in the delayed setting

In the delayed setting sensitivity for the presence of hematoma improved significantly from 43% (0-2 days) to 91% (5-8 days). Sensitivity for swelling over the posterior aspect of the ankle improved significantly from 9% to 61%, making it the most discriminatory finding in the delayed setting. Similar observations were made in a previous study that noted that swelling and tenderness along the posterior border of the lateral malleolus were associated with complete rupture of the ATFL and CFL.[20] Finally, the sensitivity of both laxity tests improved in the delayed setting. The anterior drawer test demonstrated a positive LR of 5.48 and negative LR of 0.44. This corresponds with a recent meta-analysis of six studies (885 observations), which reported a pooled positive LR of 3.97 and a negative LR of 0.54.[21] In line with previous studies, the talar tilt test demonstrated a positive LR of 9.39 and a negative LR of 0.51.[21] The findings of the current study confirm that the sensitivity of physical examination is improved when performed 5-8 days post-injury.[5–7]

Overall clinical suspicion

This is the first study to investigate the physician's overall clinical suspicion for complete discontinuity of the lateral ankle ligaments. Clinical suspicion had a positive LR of 4.35 in the acute setting (post-test probability of 83%) and a positive LR of 6.09 in the delayed setting (post-test probability of 88%). The sensitivity of clinical suspicion improved significantly in the delayed setting.

Strengths and limitations

This study is the first to validate the notion that the diagnostic value of physical examination improves when performed 5-8 days post-injury. The strength of this study lies in its prospective design and use of 3T MR imaging as the reference standard. A limitation of this study is that only complete discontinuity of the lateral ankle ligaments was considered disease positive. This might have influenced the reported diagnostic accuracy as partial discontinuity might mimic the clinical signs and symptoms of complete discontinuity. In addition, all athletes were examined by a senior Sports Medicine Physician or Orthopaedic Surgeon which might decrease the external validity of this study. Finally, by only including patients who underwent acute clinical evaluation within 2 days post-injury and delayed clinical evaluation 5-8 days post-injury, a selection bias may have occurred.

Clinical implications

This study demonstrates that physical examination in the acute setting (0-2 days post-injury) is useful to exclude complete discontinuity of the lateral ankle ligaments. (Figure 2) Patients with a high probability of complete discontinuity of the lateral ankle ligaments can be identified using clinical findings with high specificity (hematoma, anterior drawer test and talar tilt test). This is especially relevant in elite athletes where there are important time constraints on return to play and early and accurate diagnosis is essential. In the delayed setting, sensitivity of common clinical findings increases significantly as pain and swelling subsides. Therefore, the ability of physical examination to rule out complete discontinuity is enhanced when performed in the delayed setting (5-8 days post-injury). In clinical practice, these findings may expedite the diagnosis of lateral ligament injuries in athletes and may reduce the need for delayed follow-up clinical evaluation. As demonstrated by this study, physical examination is an accurate diagnostic method and MR imaging should therefore be reserved for selected cases, including elite athletes. When a concomitant injury is suspected (e.g., syndesmosis injury), alternative diagnostic strategies might be considered.[9,11,22,23]

Figure 2 Proposed diagnostic work-up of acute lateral ligament injuries

Acute ankle injuries
36 athletes*

Acute clinical evaluation
0-2 days

Lateral swelling absent (100% sensitivity)

Anterior drawer test positive (100% specificity)

No complete discontinuity
7/7 athletes (100%)

Complete discontinuity
4/4 athletes (100%)

Accurate diagnosis
11/11 athletes (100%)

Uncertain diagnosis
25/36 athletes (69%)

Delayed clinical evaluation
5-8 days

Hematoma absent (91% sensitivity)

Hematoma present (70% specificity)

No complete discontinuity
8/9 athletes (89%)

Complete discontinuity
14/16 athletes (88%)

Accurate diagnosis
22/25 athletes (88%)

Accurate diagnosis
33/36 athletes (92%)

* Data on the the Anterior Drawer Test in the acute setting was missing in 6 patients

CONCLUSION

In the acute setting (0-2 days post-injury) clinical evaluation can exclude complete discontinuity of the lateral ankle ligaments and identify athletes with a high probability of complete discontinuity. Complete discontinuity is unlikely when swelling over the lateral malleolus is absent. Clinical findings with high specificity (e.g. positive anterior drawer test) can be used to identify patients with a high probability of complete discontinuity. In the delayed setting (5-8 days post-injury) the diagnostic accuracy of common clinical findings (e.g. hematoma or the anterior drawer test) is improved due to increased sensitivity. When the physician's overall clinical suspicion is positive, a high probability of complete discontinuity of the lateral ankle ligaments exists.

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Supplementary appendix 1 Univariate logistic regression analysis for the association between injury history, physical examination, syndesmosis tests and clinical suspicion for complete discontinuity of the lateral ankle ligaments in the acute and delayed settings**.**

	Acute setting				Delayed setting			
	N	OR (95% CI)	SE	P-value	N	OR (95% CI)	SE	P-value
Clinical history								
- Injury [recurrent]	43	3.36 (0.76-20.06)	0.84	n.s.	43	3.36 (0.76-20.06)	0.84	0.11
- Occasion [game]	43	1.82 (0.56-6.19)	0.63	n.s.	43	1.82 (0.56-6.19)	0.63	n.s.
- Contact [contact]	41	1.04 (0.31-3.52)	0.63	n.s.	43	1.04 (0.31-3.52)	0.63	n.s.
- Mechanism of injury								
• Inversion	43	1.19 (0.30-4.77)	0.72	n.s.	43	1.19 (0.30-4.77)	0.72	n.s.
• Eversion	43	0.86 (0.12-6.09)	1.05	n.s.	43	0.86 (0.12-6.09)	1.05	n.s.
• External Rotation	43	0.11 (0.00-1.20)	1.77	n.s.	43	0.11 (0.00-1.20)	1.77	n.s.
• Internal Rotation	43	1.00 (N/a)	N/a	N/a	43	1.00 (N/a)	N/a	N/a
- Perceived swelling	43	16.68 (1.69-2248.43)	1.65	0.01	43	4.78 (1.08-28.70)	0.85	0.04
- Perceived instability	37	2.83 (0.66-14.05)	0.80	n.s.	42	1.56 (0.46-5.63)	0.65	n.s.
- Pain radiating up	42	0.44 (0.10-1.67)	0.72	n.s.	43	0.25 (0.06-0.85)	0.67	0.03
Clinical findings								
- Presence of hematoma	43	3.89 (1.02-17.99)	0.74	0.05	43	19.18 (4.41-119.07)	0.84	<0.01
- Tenderness to palpation								
• Lateral	43	12.82 (1.24-1742.70)	1.70	0.03	43	31.96 (3.48-4260.69)	1.58	<0.01
• Medial	43	2.29 (0.64-8.75)	0.68	n.s.	43	4.07 (1.17-15.67)	0.67	0.03
• Anterior	43	2.86 (0.86-10.28)	0.64	n.s.	43	6.69 (1.87-28.01)	0.70	<0.01
• Posterior	43	2.75 (0.60-16.60)	0.86	n.s.	43	11.29 (2.71-66.91)	0.81	<0.01
• Syndesmosis	43	2.21 (0.67-7.56)	0.63	n.s.	43	2.22 (0.65-8.04)	0.65	n.s.
- Unable to walk normal	43	5.86 (1.52-27.61)	0.75	<0.01	43	5.43 (1.45-25.18)	0.73	0.01

Supplementary appendix 1 Continued

	Acute setting				Delayed setting			
	N	OR (95% CI)	SE	P-value	N	OR (95% CI)	SE	P-value
- Unable to walk on toes	43	3.25 (0.81-15.48)	0.77	n.s.	43	1.46 (0.43-5.20)	0.65	n.s.
- Unable to walk on heels	43	5.86 (1.52-27.61)	0.75	<0.01	43	1.46 (0.43-5.20)	0.65	n.s.
- Range of motion								
• Pain with passive DF	43	3.36 (0.97-12.86)	0.67	0.06	43	4.33 (1.20-17.95)	0.70	0.03
• Pain with passive PF	43	2.78 (0.79-10.60)	0.67	n.s.	43	2.87 (0.86-10.28)	0.64	n.s.
• Pain with inversion	43	1.87 (0.51-7.21)	0.69	n.s.	43	1.54 (0.37-6.66)	0.75	n.s.
• Pain with eversion	43	1.50 (0.44-5.22)	0.64	n.s.	43	1.82 (0.54-6.32)	0.64	n.s.
- Presence of swelling								
• Lateral	43	26.11 (2.80-3488.72)	1.60	<0.01	43	26.11 (2.80-3488.72)	1.60	<0.01
• Medial	43	9.87 (2.67-43.42)	0.72	<0.01	43	6.05 (1.72-24.08)	0.68	<0.01
• Anterior	43	9.51 (2.29-56.00)	0.81	<0.01	43	3.26 (0.96-11.90)	0.65	n.s.
• Posterior	43	0.86 (0.12-6.09)	1.05	n.s.	43	21.67 (5.19-117.92)	0.80	<0.01
Laxity tests								
- Anterior drawer test	36	10.16 (0.96- 1387.78)	1.70	0.05	41	10.07 (2.40-60.01)	0.82	<0.01
- Talar tilt	33	5.32 (0.39-757.24)	1.93	n.s.	41	12.68 (2.51-128.12)	0.98	<0.01
Clinical suspicion								
- Complete discontinuity	43	3.86 (0.68-40.36)	1.05	n.s.	43	11.29 (2.71-66.91)	0.81	<0.01

The odds ratio of the predictors associated with complete discontinuity of the lateral ankle ligaments are presented. Values are presented as β-coefficients with corresponding 95% confidence interval (95% CI); Standard Error (SE); Not applicable (N/a)

Supplementary appendix 2 Interrater reliability of delayed physical examination and delayed clinical suspicion for complete discontinuity of the lateral ankle ligaments.

	N	Kappa (95% CI)	Landis & Koch	Agreement (%)
Clinical findings				
- Presence of hematoma	39	0.54 (0.27-0.80)	Moderate	77%
- Tenderness to palpation				
• Lateral	39	0.27 (0.00-0.66)	Fair	82%
• Medial	39	0.79 (0.60-0.98)	Substantial	90%
• Anterior	39	0.48 (0.21-0.75)	Moderate	74%
• Posterior	39	0.41 (0.13-0.70)	Moderate	74%
• Syndesmosis	39	0.43 (0.16-0.71)	Moderate	72%
- Normal walk	39	0.47 (0.16-0.77)	Moderate	79%
- Walk on toes	39	0.83 (0.65-1.00)	Almost perfect	92%
- Walk on heels	39	0.69 (0.44-0.94)	Substantial	87%
- Range of motion				
• Pain with passive DF	39	0.38 (0.10-0.66)	Fair	69%
• Pain with passive PF	38	0.53 (0.28-0.79)	Moderate	76%
• Pain with inversion	38	0.37 (0.04-0.70)	Fair	76%
• Pain with eversion	38	0.40 (0.13-0.66)	Fair	68%
- Presence of swelling				
• Lateral	39	0.59 (0.26-0.91)	Moderate	87%
• Medial	39	0.54 (0.28-0.80)	Moderate	77%
• Anterior	39	0.51 (0.26-0.75)	Moderate	74%
• Posterior	39	0.41 (0.18-0.63)	Moderate	69%
Laxity tests				
- Anterior drawer test	38	0.19 (0.00-0.50)	Slight	61%
- Talar tilt	38	0.15 (0.00-0.48)	Slight	66%
Clinical suspicion				
- Complete discontinuity	39	0.34 (0.06-0.61)	Fair	67%

The interrater reliability of physical examination and clinical suspicion in the delayed setting are presented. The interrater reliability is reported as unweighted-kappa (K) with corresponding 95% confidence interval (95% CI) and overall agreement.

CHAPTER 3

Acute clinical evaluation for syndesmosis injury has high diagnostic value

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ABSTRACT

Purpose: To determine the diagnostic value of injury history, physical examination, six syndesmosis tests and overall clinical suspicion for syndesmosis injury.

Methods: All athletes (≥18 yrs) with an acute ankle injury presenting within 7 days post-injury were assessed for eligibility. Acute ankle injuries were excluded if imaging studies demonstrated a frank fracture or 3T MRI could not be acquired within 10 days post-injury. Standardized injury history was recorded, and physical examination was performed by an Orthopaedic Surgeon or Sports Medicine Physician. Overall clinical suspicion was documented prior to MRI. Multivariate logistic regression was used to determine the association between independent predictors and syndesmosis injury.

Results: Between September 2016 and July 2019, a total of 150 acute ankle injuries were included. The median time from injury to acute clinical evaluation was 2 days (IQR 2). Prior to clinical evaluation the median patient reported Visual Analogue Scale for pain was 8/10 (IQR 2). Syndesmosis injury was present in 26 acute ankle injuries. An eversion mechanism of injury had a positive LR 3.47 (95% CI 1.55-7.77). The squeeze tests had a positive LR of 2.20 (95% CI 1.29-3.77) and a negative LR of 0.68 (95% CI 0.48-0.98). Overall clinical suspicion had a sensitivity of 73% (95% CI 52-88) and negative predictive value of 89% (95% CI 78-95). Multivariate regression analyses demonstrated significant association for eversion mechanism of injury (OR 4.99; 95% CI 1.56-16.01) and a positive squeeze test (OR 3.25; 95% CI 1.24-8.51).

Conclusions: In an acute clinical setting with patients reporting high levels of ankle pain, a negative overall clinical suspicion reduces the probability of syndesmosis injury. Eversion mechanism of injury and a positive squeeze test are associated with higher odds of syndesmosis injury.

INTRODUCTION

Acute ankle sprains are among the most common sport-related injuries.[1] Sprains can affect the lateral ligaments, medial ligaments and the syndesmosis ankle ligaments. Complete rupture of the lateral ligaments is observed most commonly (40%).[2] Within 2 days after injury, physical examination for diagnosing lateral ligament injury has a sensitivity of 71% and a specificity of 33%.[3] Delayed physical examination 5 days post-injury increases the sensitivity (96%) and specificity (84%). Syndesmosis injury is observed less frequently (20%) and is notoriously difficult to diagnose.[2] In the acute setting the diagnosis of syndesmosis injury primarily relies on clinical evaluation.[4]

Conflicting reports on the diagnostic value of physical examination have been published.[5] Two recent high-quality studies investigated the diagnostic value of clinical tests for partial or complete discontinuity of the syndesmosis using MRI.[6,7] In a cohort of 96 patients presenting to an emergency department within 24 hours after an acute ankle sprain, sensitivity (14%-56%) and specificity (48%-83%) of syndesmosis tests were reported as insufficient.[7] In a cohort of 87 athletes examined within 7 days after a suspected syndesmosis injury, tenderness of the anterior syndesmosis was reported to have the highest sensitivity (92%) and the squeeze test was found to have the highest specificity (88%).[6] The heterogeneity in reported diagnostic values might be explained by the timing of physical examination and higher pre-test probability in the latter study. A study investigating the diagnostic value of injury history, physical examination, and overall clinical suspicion in athletes with an acute ankle injury is therefore warranted.

The aim of this study was to determine the diagnostic value of injury history, clinical findings, six syndesmosis tests (including the combination of these variables) and overall clinical suspicion for partial or complete discontinuity of the syndesmosis. The hypothesis is that in the acute setting, the diagnostic value of injury history, physical examination and overall clinical suspicion are sufficient to detect syndesmotic involvement in athletes with an acute ankle injury.

MATERIALS AND METHODS

Participants

Ethics approval was acquired from the Anti-Doping Lab Qatar Review Board (IRB No. F2016000153). Written informed consent was obtained from all athletes at time of inclusion. Between September 2016 and July 2019 athletes with acute ankle injuries were recruited for this prospective cohort study. All athletes presenting to the outpatient department of Aspetar Orthopaedic and Sports Medicine Hospital within 7 days after an acute ankle injury were assessed for eligibility. Inclusion criteria were: acute ankle injuries in adult athletes (≥18 yrs), participating in sports at a professional or recreational level. Ankle injuries were excluded if imaging demonstrated a frank fracture or if the 3T MRI study could not be acquired within 10 days post-injury.

Clinical setting

A daily clinic for athletes with acute sports injuries is organized by Aspetar Orthopaedic and Sports Medicine Hospital. Patients can be seen by an Orthopaedic Surgeon or Sports Medicine Physician without the requirement of a referral. This results in a high volume of patients of which the majority presents within 24 hours post-injury. The main language spoken by the medical staff at our institution is English; therefore during consultation a nurse is present to provide Arabic translation.

Injury history and physical examination

An Orthopaedic Surgeon or Sports Medicine Physician recorded injury history and performed physical examination. Findings were recorded on a standardized reporting form. Injury history included: (1) Injury [new/recurrent] (2) Occasion [game/training/non-sports injury], (3) Contact [contact/non-contact], (4) Mechanism of injury [inversion/eversion/external-rotation/internal-rotation], (5) Perceived presence of swelling [yes/no], (6) Perceived ankle instability [yes/no], (7) Sensation of pain radiating up the leg [yes/no]. Physical examination included; (1) Presence of hematoma [yes/no] (2) Tenderness to palpation [lateral/medial/anterior/posterior] (3) Tenderness length over the syndesmosis [in cm], (4) Ability to walk normally [yes/no], (5) Ability to walk on toes [yes/no], Ability to walk on heels [yes/no], (6) Passive range of motion in dorsal flexion, plantar flexion, inversion and eversion [full/restricted/painful], (7) Presence of swelling [yes/no], (8) Swelling site [laterally/medially/anterior/posterior/syndesmosis]

Syndesmosis tests

The physicians performing the syndesmosis tests were provided with a short description of the clinical tests. No calibration session was organized prior to initiation of this study, to reflect a true clinical setting. The standardized clinical examination

included a total of six syndesmosis tests: palpation of the AITFL [4], squeeze test [4,8], weight-bearing dorsiflexion external rotation (WB DF ER) test, non-weight-bearing dorsiflexion external rotation (NWB DF ER) test [4,9], fibular translation test [10] and the Cotton test [11] (Supplementary appendix). Tests were considered positive if they provoked pain over the distal tibiofibular joint or if the examiner noticed instability of the ankle syndesmosis (Cotton test).[8–11] If the patient was unable to weight-bear (WB DF ER) or if a clinical test was too painful to be completed fully (Squeeze test, NWB DF ER test, Fibular translation test) they were considered positive (Cotton test excluded).

Overall clinical suspicion of syndesmosis injury

Clinical suspicion was based on the physicians' overall interpretation of injury history, physical examination, and syndesmosis tests. Clinical suspicion was recorded using the modified West Point grading system[12]: partial rupture of the Anterior Inferior Tibiofibular Ligament (AITFL) with a stable syndesmosis (Grade I); complete rupture of the AITFL and injury to the Interosseous Ligament (IOL) with a stable syndesmosis (Grade Iia); complete rupture of the AITFL, IOL and the Posterior Inferior Tibiofibular Ligament (PITFL) or Deltoid ligaments with dynamic instability of the syndesmosis (Grade Iib) and complete disruption of the syndesmosis with frank diastasis (Grade III). Overall clinical suspicion for syndesmosis injury was considered positive when the modified West Point grading system was scored grade I or higher.

Reference standard

In this study, MRI was used as reference standard. With a sensitivity of 100% and specificity of 93% for injury of the AITFL, MRI has demonstrated to be a valuable alternative to arthroscopy.[13] Patients underwent MRI scans using a wide-bore 3.0-T MRI system (GE Discovery, GE Healthcare, Chicago, Illinois, United States) with an 8-channel receive only Foot & Ankle array (Invivo, Philips Healthcare, Best, The Netherlands). In the sagittal plane T1-weighted and Proton-Density Fat-Saturated [PD-FS] sequences were obtained, axial T2-weighted and PD-FS sequences were acquired and in the coronal plane PD-FS sequences were obtained.[14]

Grading of syndesmosis ligaments

The obtained MR scans were graded by two musculoskeletal radiologists (J.A. & M.A.) with *11* and *3* years of experience in MSK-imaging, respectively. Acute injuries of the AITFL, IOL and PITFL were graded according the four grade Schneck grading system[15]: normal (Grade 0); low-grade sprain (Grade 1: peri-ligamentous high signal/edema on proton density-weighted sequences and no discontinuity of fibers); partial discontinuity (Grade 2: partial discontinuity but preserved remnant fibers) and complete discontinuity (Grade 3).

Due to limited interrater and intrarater reliability for grading of the individual syndesmosis ligaments according the Schneck grading system (K 0.37-0.89), diagnostic disagreements between the radiologists were resolved in a consensus meeting.[14]

Evaluation of MRI-findings

In this study, we evaluated the diagnostic value of injury history, physical examination, syndesmosis tests and clinical suspicion for partial or complete discontinuity of the AITFL and/or IOL and/or PITFL. The individual syndesmosis ligament (AITFL/IOL/PITFL) with the highest grade of injury was used as reference standard. For this analysis, grading was dichotomized as: (1) No discontinuity (normal ligament or peri-ligamentous edema) (2) Discontinuity (partial or complete discontinuity).

Statistical analysis

The diagnostic value of injury history, clinical findings, syndesmosis tests and clinical suspicion were evaluated using the MRI findings. The results of injury history and physical examination were dichotomized if needed; Occasion was dichotomized to (1) game (2) other; Each mechanism of injury was dichotomized to i.e. (1) inversion (2) other mechanism of injury. Tenderness to palpation and presence of swelling were dichotomized per location to i.e. (1) tenderness to palpation laterally (2) no palpation to tenderness laterally and range of motion was dichotomized per direction to i.e. (1) dorsal flexion painful (2) dorsal flexion not painful.

For each variable, a contingency table was created. From the 2x2 tables prevalence of positive test results, sensitivity, specificity, positive and negative likelihood ratio's (LR+ and LR-), positive predictive value (PPV) and negative predictive value (NPV) were calculated, including confidence intervals (95% CI). For tenderness length an optimal cut-off (Youden's index = maximal value) was calculated using a ROC curve. For each variable the area under the curve (AUC) was calculated.

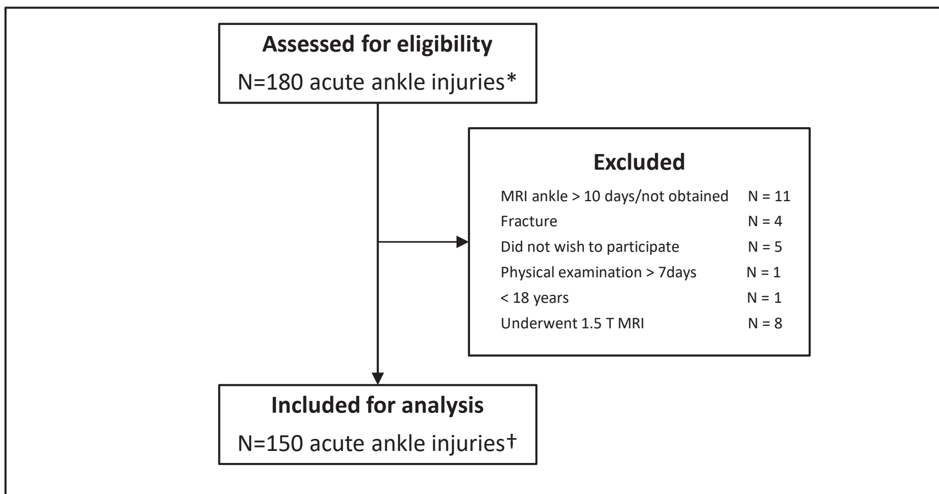
To test if a combination of variables could predict the presence of syndesmosis injury, we performed a logistic regression analysis. First, we analyzed the association between each variable and the presence of syndesmosis injury in a univariate logistic regression analysis. Variables with a p-value <0.15 were included in a multivariate logistic regression model. Regression analysis was performed using the forward method. Odds ratios for each variable were presented with their corresponding confidence intervals (95% CI) and statistical significance was set at p-value <0.05. Statistical analysis was performed using SPSS software (V.21; IBM Corp). No a priori power analysis was performed for the outcome of this study.

RESULTS

Baseline characteristics

Between September 2016 and July 2019, a total of 180 acute ankle injuries were assessed for eligibility. (Figure 1) One-hundred-fifty were included in this study. (Flowchart 1) Of the included ankle injuries, four were subsequent injuries of the contralateral ankle and one was a re-injury (>1 year). Most patients were male (91%). The median age at time of injury was 24 years (IQR 8). The median time from injury to physical examination was 2 days (IQR 2). At presentation, a median patient reported Visual Analogue Scale (VAS) for pain of 8/10 (IQR 2) was recorded (in 129 patients). The MR scans were obtained a median 3 days (IQR 3) post-injury. Partial or complete discontinuity of the syndesmosis ligaments was observed in 26 of 150 (17%) acute ankle injuries. Injury of the AITFL was present in 26 acute ankle injuries (17%; 7 partial, 19 complete). The IOL was injured in 20 acute ankle injuries (13%; 8 partial, 12 complete) and the PITFL in 11 acute ankle injuries (7%; 10 partial, 1 complete). Concomitant injuries of the IOL or PITFL were not observed without injury of the AITFL.

Figure 1 Flowchart of patient inclusion



*In 172 athletes; † In 145 athletes

Table 1 Diagnostic accuracy of injury history for injury of the syndesmosis ligaments in 150 athletes with an acute ankle injury.

Clinical history	Positive findings	Sensitivity %	Specificity %	LR+	LR-	PPV %	NPV %	AUC
- Injury [recurrent]	37/150 (0.25)	12 (3-31)	73 (64-80)	0.42 (0.14-1.27)	1.22 (1.05-1.41)	8 (2-23)	80 (71-86)	0.42 (0.31-0.53)
- Occasion [game]	78/150 (0.52)	58 (37-76)	49 (40-58)	1.14 (0.78-1.65)	0.86 (0.54-1.37)	19 (12-30)	85 (74-92)	0.53 (0.41-0.66)
- Contact [contact]	69/138 (0.50)	38 (19-61)	48 (39-57)	0.73 (0.41-1.29)	1.29 (0.91-1.84)	12 (5-22)	81 (70-95)	0.44 (0.34-0.54)
- Mechanism of injury								
• Inversion	126/150 (0.84)	65 (44-82)	12 (7-19)	0.74 (0.56-0.99)	2.86 (1.50-5.44)	13 (8-21)	63 (41-80)	0.39 (0.26-0.52)
• Eversion	19/150 (0.13)	31 (15-52)	91 (84-95)	3.47 (1.55-7.77)	0.76 (0.59-0.98)	42 (21-66)	86 (79-91)	0.61 (0.48-0.74)
• External Rotation	4/150 (0.03)	8 (1-27)	98 (94-99)	4.77 (0.70-32.33)	0.94 (0.84-1.05)	50 (9-91)	50 (9-91)	0.53 (0.40-0.66)
• Internal Rotation	6/150 (0.04)	8 (1-27)	97 (91-99)	2.38 (0.46-12.34)	0.95 (0.85-1.07)	33 (6-76)	83 (76-88)	0.52 (0.40-0.65)
- Perceived swelling	126/149 (0.85)	85 (64-95)	15 (10-23)	1.00 (0.84-1.20)	1.00 (0.37-2.68)	17 (11-25)	83 (60-94)	0.50 (0.38-0.62)
- Perceived instability	37/130 (0.28)	21 (8-43)	70 (60-78)	0.69 (0.30-1.59)	1.13 (0.92-1.40)	14 (5-30)	80 (70-87)	0.47 (0.36-0.57)
- Pain radiating up	37/146 (0.25)	26 (11-49)	75 (66-82)	1.04 (0.49-2.20)	0.99 (0.77-1.27)	16 (7-33)	84 (76-90)	0.50 (0.38-0.63)

Note: MR imaging was used as reference standard. The prevalence of acute syndesmosis injuries and the diagnostic values of clinical history are presented. All values are presented with 95% confidence interval (95% CI); positive likelihood ratio (LR+); negative likelihood ratio (LR-); positive predictive value (PPV); negative predictive value (NPV); area under the curve (AUC). Abbreviation: MR, magnetic resonance.

Table 2 Diagnostic accuracy of physical examination for injury of the syndesmosis ligaments in 150 athletes with an acute ankle injury.

Clinical findings	Positive findings	Sensitivity %	Specificity %	LR+	LR-	PPV %	NPV %	AUC
- Presence of hematoma	49/148 (0.33)	28 (13-50)	66 (57-74)	0.82 (0.42-1.61)	1.09 (0.85-1.41)	14 (6-28)	82 (73-89)	0.47 (0.35-0.59)
- Tenderness to palpation								
• Lateral	135/150 (0.90)	88 (69-97)	10 (5-17)	0.97 (0.84-1.13)	1.19 (0.35-4.00)	17 (11-25)	80 (51-95)	0.49 (0.37-0.61)
• Medial	82/150 (0.55)	38 (21-59)	42 (33-51)	0.66 (0.40-1.10)	1.47 (1.06-2.03)	12 (6-22)	76 (64-86)	0.40 (0.28-0.52)
• Anterior	47/150 (0.32)	23 (10-44)	67 (58-75)	0.70 (0.33-1.47)	1.15 (0.92-1.43)	13 (5-26)	81 (71-87)	0.45 (0.33-0.57)
• Posterior	19/150 (0.13)	12 (3-31)	87 (80-92)	0.89 (0.28-2.85)	1.02 (0.88-1.17)	16 (4-40)	82 (75-88)	0.49 (0.37-0.61)
- Tenderness length [≥2.5cm]	69/139 (0.50)	67 (45-84)	54 (44-63)	1.45 (1.02-2.04)	0.62 (0.35-1.10)	23 (14-35)	89 (78-95)	0.60 (0.48-0.73)
- Normal walk	77/150 (0.51)	62 (41-79)	51 (42-60)	1.25 (0.88-1.78)	0.76 (0.46-1.25)	21 (13-32)	86 (76-93)	0.56 (0.44-0.68)
- Walk on toes	89/147 (0.61)	69 (48-85)	41 (33-51)	1.18 (0.88-1.59)	0.74 (0.41-1.36)	20 (13-30)	86 (74-93)	0.55 (0.43-0.67)
- Walk on heels	79/144 (0.55)	56 (35-75)	45 (36-55)	1.03 (0.70-1.51)	0.97 (0.61-1.54)	18 (10-28)	83 (71-91)	0.51 (0.38-0.63)
- Range of motion								
• Pain on dorsal flexion	94/150 (0.63)	58 (37-76)	36 (28-45)	0.90 (0.63-1.29)	1.17 (0.72-1.88)	16 (9-25)	80 (67-89)	0.47 (0.35-0.59)
• Pain on plantar flexion	83/150 (0.55)	56 (35-75)	43 (35-53)	0.99 (0.68-1.45)	1.01 (0.64-1.61)	17 (10-27)	83 (71-91)	0.50 (0.37-0.62)
• Pain on inversion	99/150 (0.66)	69 (48-85)	34 (26-43)	1.05 (0.79-1.40)	0.90 (0.49-1.65)	18 (11-27)	84 (70-92)	0.52 (0.40-0.64)
• Pain on eversion	85/150 (0.56)	56 (35-75)	42 (33-50)	0.95 (0.65-1.39)	1.06 (0.67-1.70)	16 (10-26)	82 (70-90)	0.49 (0.36-61)
Presence of swelling								
• Lateral	102/131 (0.78)	88 (67-97)	24 (17-34)	1.16 (0.96-1.39)	0.51 (0.17-1.57)	21 (13-30)	90 (72-97)	0.56 (0.44-0.68)
• Medial	47/131 (0.36)	38 (20-59)	64 (55-73)	1.06 (0.59-1.88)	0.97 (0.70-1.33)	19 (10-34)	82 (72-89)	0.51 (0.38-0.64)
• Anterior	37/131 (0.28)	25 (11-47)	71 (61-79)	0.86 (0.41-1.83)	1.06 (0.83-1.34)	16 (7-33)	81 (71-88)	0.48 (0.35-0.61)
• Posterior	12/131 (0.09)	8 (1-28)	91 (83-95)	0.89 (0.21-3.81)	1.01 (0.89-1.14)	17 (3-49)	82 (73-88)	0.50 (0.37-0.62)

Note: MR imaging was used as reference standard. The prevalence of acute syndesmosis injuries and the diagnostic values of clinical findings are presented. All values are presented with 95% confidence interval (95% CI); positive likelihood ratio (LR+); negative likelihood ratio (LR-); positive predictive value (PPV); negative predictive value (NPV); area under the curve (AUC). Abbreviation: MR, magnetic resonance.

Table 3 Diagnostic accuracy of six syndesmosis tests and clinical suspicion for injury of the syndesmosis ligaments in 150 athletes with an acute ankle injury.

	Positive findings	Sensitivity %	Specificity %	LR+	LR-	PPV %	NPV %	AUC
Syndesmosis tests								
- Tenderness AITFL	78/150 (0.52)	58 (37-76)	49 (40-58)	1.14 (0.78-1.65)	0.86 (0.54-1.37)	19 (12-30)	85 (74-92)	0.52 (0.43-0.61)
- Squeeze test	38/150 (0.25)	46 (27-66)	79 (71-86)	2.20 (1.29-3.77)	0.68 (0.48-0.98)	32 (18-49)	88 (80-93)	0.60 (0.49-0.71)
- NWB DF ER test	74/148 (0.50)	58 (37-76)	52 (42-61)	1.19 (0.82-1.74)	0.82 (0.52-1.30)	20 (12-32)	85 (75-92)	0.53 (0.44-0.62)
- WB DF ER test	99/149 (0.66)	69 (48-85)	34 (26-43)	1.05 (0.79-1.40)	0.90 (0.49-1.65)	18 (11-27)	84 (70-92)	0.51 (0.42-0.61)
- Fibular translation test	26/147 (0.18)	15 (5-36)	82 (74-88)	0.85 (0.32-2.25)	1.03 (0.87-1.22)	15 (5-36)	82 (74-88)	0.49 (0.37-0.61)
- Cotton test	21/139 (0.15)	27 (12-48)	88 (80-93)	2.17 (0.98-4.84)	0.83 (0.66-1.06)	33 (15-57)	84 (76-90)	0.59 (0.45-0.73)
- All tests negative	35/147 (0.23)	23 (10-44)	76 (67-83)	0.96 (0.45-2.08)	1.01 (0.82-1.26)	17 (7-34)	82 (74-88)	0.50 (0.37-0.62)
Clinical suspicion								
- Syndesmosis injury	79/143 (0.55)	73 (52-88)	49 (39-58)	1.43 (1.06-1.91)	0.55 (0.29-1.06)	24 (15-35)	89 (78-95)	0.61 (0.49-0.73)

Note: MR imaging was used as reference standard. The prevalence of acute syndesmosis injuries and the diagnostic values of six syndesmosis tests (including the combination of these six tests) and clinical suspicion are presented. All values are presented with 95% confidence interval (95% CI); positive likelihood ratio (LR+); negative likelihood ratio (LR-); positive predictive value (PPV); negative predictive value (NPV); area under the curve (AUC). Abbreviation: MR, magnetic resonance.

Diagnostic value of injury history, physical examination and overall clinical suspicion

The diagnostic value of injury history and physical examination are detailed in Table 1 and 2. We found that an external rotation mechanism and eversion mechanism of injury had a positive LR of 4.77 (95% CI 0.70-32.33) and 3.47 (95% CI 1.55-7.77), respectively. Length of tenderness [≥2.5cm] had a positive LR of 1.45 (95% CI 1.02-2.04). Tenderness to palpation over the medial aspect of the ankle had a negative LR of 1.47 (95% CI 1.06-2.03). The diagnostic values for the syndesmosis tests and clinical suspicion are detailed in Table 3. The squeeze test had the most diagnostic value with a positive LR of 2.20 (95% CI 1.29-3.77) and a negative LR of 0.68 (95% CI 0.48-0.98). Clinical suspicion for syndesmosis injury had a sensitivity of 73% and a negative predictive value of 89%.

Univariate analysis

Various predictors were associated with injury of the syndesmosis ligaments in univariate logistic regression analysis. (Table 4). Eversion mechanism of injury (OR 4.57; 95% CI 1.62-12.89; p<0.00), a positive squeeze test (OR 3.23; 95% CI 1.34-7.82; p=0.01), tenderness length [≥2.5cm] (2.34; 95% CI0.93-5.90; p=0.07) and clinical suspicion (OR 2.58; 1.01-6.60; p=0.05) were associated with higher odds of syndesmosis injury. Inversion mechanism of injury (OR 0.26; 0.10-0.69; p=0.01) was associated with lower odds of syndesmosis injury.

Multivariate analysis

In the multivariate logistic regression analysis mechanism of injury [eversion] (OR 4.99; 95% CI 1.56-16.01; p=0.01) and a positive squeeze test (OR 3.25; 95% CI 1.24-8.51); p=0.02) were associated with higher odds of syndesmosis injury. (Table 5).

Table 4 Univariate logistic regression analysis for the association between injury history, physical examination, syndesmosis tests and clinical suspicion for the presence of syndesmosis injury**.**

	N	OR (95%CI)	SE	P-value
Clinical history				
- Injury [recurrent]	150	0.35 (0.10-1.23)	0.65	**0.10**
- Occasion [game]	150	1.32 (0.56-3.10)	0.44	n.s.
- Contact [contact]	138	0.57 (0.22-1.46)	0.49	n.s.
- Mechanism of injury				
• Inversion	150	0.26 (0.10-0.69)	0.50	**0.01**
• Eversion	150	4.57 (1.62-12.89)	0.53	**0.00**
• External Rotation	150	5.08 (0.68-37.87)	1.03	**0.11**
• Internal Rotation	150	2.50 (0.43-14.43)	0.89	n.s.
- Perceived swelling	149	1.01 (0.31-3.25)	0.60	n.s.
- Pain radiating up	146	1.05 (0.38-2.89)	0.52	n.s.
Clinical findings				
- Presence of hematoma	148	0.75 (0.29-1.94)	0.48	n.s.
- Tenderness to palpation				
• Lateral	150	0.82 (0.22-3.14)	0.69	n.s.
• Medial	150	0.45 (0.19-1.07)	0.44	**0.07**
• Anterior	150	0.61 (0.23-1.63)	0.50	n.s.
• Posterior	150	0.85 (0.24-3.27)	0.67	n.s.
- Tenderness length [≥2.5cm]	139	2.34 (0.93-5.90)	0.47	**0.07**
- Normal walk	150	1.65 (0.70-3.93)	0.44	n.s.
- Walk on toes	147	1.59 (0.64-3.93)	0.46	n.s.
- Walk on heels	144	1.06 (0.44-2.52)	0.44	n.s.
- Range of motion				
• Pain with passive dorsal flexion	150	0.77 (0.33-1.84)	0.44	n.s.
- Presence of swelling	142	1.26 (0.34-4.67)	0.67	n.s.
• Lateral	131	2.25 (0.62-8.15)	0.66	n.s.
• Medial	131	1.09 (0.44-2.72)	0.47	n.s.
• Anterior	131	0.82 (0.30-2.25)	0.52	n.s.
• Posterior	131	0.88 (0.18-4.31)	0.81	n.s.
Syndesmosis tests				
- Tenderness AITFL	150	1.32 (0.56-3.10)	0.44	n.s.
- Squeeze test	150	3.23 (1.34-7.82)	0.45	**0.01**
- NWB DF ER test	148	1.00 (0.98-1.01)	0.01	n.s.
- WB DF ER test	149	1.00 (0.97-1.02)	0.01	n.s.
- Fibular translation test	147	0.82 (0.26-2.61)	0.59	n.s.
- Cotton test	139	1.00 (0.99-1.00)	0.00	n.s.
- All clinical tests negative	147	0.92 (0.35-2.60)	0.51	n.s.

Table 4 Continued

	N	OR (95%CI)	SE	P-value
Clinical suspicion				
- Syndesmosis injury	143	2.58 (1.01-6.60)	0.48	**0.05**

The odds ratio of the independent variables associated with syndesmosis injury are presented. Values are presented as β-coefficients with corresponding 95% confidence interval (95% CI); Standard Error (SE); P-value >0.15 (n.s.)

Table 5 Multivariate logistic regression analysis for the association between injury history, physical examination and syndesmosis tests for the presence of syndesmosis injury**.**

		Multivariate		
	N	OR (95%CI)	SE	P-value
Clinical history				
- Mechanism of injury [eversion]	150	4.99 (1.56-16.01)	0.60	0.01
Physical examination				
- Tenderness to palpation [medial]	150	0.32 (0.12-0.83)	0.49	0.02
Syndesmosis tests				
- Squeeze test	150	3.25 (1.24-8.51)	0.49	0.02

The odds ratio of the independent variables associated with syndesmosis injury are presented. Values are presented as β-coefficients with corresponding 95% confidence interval (95% CI); Standard Error (SE)

DISCUSSION

The most important finding in this study is that despite high levels of pain in the acute clinical setting, a negative overall clinical suspicion reduces the probability of syndesmosis injury. An eversion mechanism of injury and a positive squeeze test are associated with higher odds of syndesmosis injury. None of the included variables had sufficient diagnostic value to completely rule out syndesmosis injury.

Diagnostic value of injury history

Injury history is of major importance for the diagnosis of syndesmosis injury as demonstrated in this study. With an external rotation mechanism of injury the probability of syndesmosis injury increased from a pre-test probability of 17% to a post-test probability of 49%. An eversion mechanism of injury changed the post-test probability to 42%. Despite high specificity, external rotation did not reach significance in the logistic regression analyses as only few patients reported this mechanism of injury. A previous study investigating the diagnostic value of the mechanism of injury reported a positive likelihood ratio of 1.07 (95% CI 0.87-1.32) with an external rotation and/or dorsiflexion mechanism.[6] As the study by Sman et al. only included patients with at least one positive syndesmosis test or a clinical suspicion of syndesmosis injury selection bias may have occurred. Based on our results we emphasize the importance of history taking and the mechanism of injury in particular.[16–18]

Diagnostic value of physical examination

The test characteristics of physical examination were insufficient to completely rule out syndesmosis injury in the acute setting. The presence of tenderness over the syndesmosis [≥2.5cm] resulted in a post-test probability of 23%. While peri-ligamentous edema of the syndesmosis was considered disease negative, it is an important source of tenderness and might therefore have had a negative effect on the diagnostic value.[3,19] Medial tenderness to palpation demonstrated an inverse association in the multivariate logistic regression analysis. Two previous studies reported similar findings.[6,7] This might be due to the low number of high-grade syndesmosis injuries with associated deltoid ligament injury included in these studies.[20] In contrast, compression injury of the deltoid ligaments is commonly observed in inversion injuries.[2,19] To put our findings into perspective, physical examination of the lateral ankle ligaments within 48 hours post-injury has a sensitivity of 71% and a specificity of 33%.[3] Delayed physical examination has a sensitivity of 96% and specificity of 84%. Future studies should therefore aim to investigate the diagnostic value of delayed physical examination for syndesmosis injury.

Diagnostic value of the individual syndesmosis tests

The squeeze test had the highest discriminative value for the presence of syndesmosis injury in the acute setting. A positive squeeze tests resulted in a post-test probability of 31% and a negative squeeze test resulted in a post-test probability of 12%. None of the six individual syndesmosis tests had sufficient diagnostic value to completely rule out syndesmosis injury. A previous study reported on the diagnostic value of five syndesmosis tests in a cohort of patients presenting to an Emergency department within 24 hours post-injury.[7] Of the included tests, the external rotation stress test was found to have the highest sensitvity (56%). It was therefore concluded that clinical tests could not be relied upon. In another study the diagnostic value was investigated in a cohort of athletes examined within 7 days after a suspected syndesmosis injury.[6] The squeeze test was found to have the highest positive likelihood ratio (positive LR 2.15 95% CI 0.86-5.39). Sensitivity was highest for tenderness over the syndesmosis ligaments (92%) and the non-weight-bearing dorsiflexion external rotation test (71%). Sman et al. therefore advised to combine sensitive tests (tenderness of the syndesmosis ligaments and the dorsiflexion-external rotation stress test) with specific tests (the squeeze tests). As high levels of pain are present in the acute setting, the discrepancy of reported diagnostic values might be attributed to the timing of physical examination. Based on our results, we recommend use of the squeeze test in the acute clinical setting.

Diagnostic value of clinical suspicion

This is the first study investigating the diagnostic value of clinical suspicion for syndesmosis in the acute clinical setting. Despite high levels of pain, overall clinical suspicion had a sensitivity of 73% and negative predictive value of 89%. When there was no clinical suspicion of syndesmosis injury the post-test probability of syndesmosis injury was reduced to 10%.

The strengths of this study include its prospective design, broad inclusion criteria and acquisition of 3T MR scans within 10 days post-injury.[21] Standardized clinical examination was performed by 19 physicians, trained in 10 different countries. This provides external validity to our findings. To date, this is the largest study evaluating the diagnostic value of injury history, physical examination, syndesmosis tests and overall clinical suspicion for syndesmosis injury. A limitation of this study is that most patients presented to our walk-in clinic within 48 hours post-injury. High levels of pain might therefore have affected the reported diagnostic values negatively. Despite our aim to recruit female athletes, only few presented to our walk-in clinic. Although physical examination was standardized and clear test instructions were provided, minor variations in the execution might have influenced the reported diagnostic accuracy. Finally, MRI was used as reference standard despite its inability to diagnose syndesmosis instability.[22,23]

In the acute setting, clinical evaluation may aid in the early recognition of syndesmosis injuries.[24] Clinical evaluation can be used to decide whether to refer for immediate further diagnostic tests or delayed physical examination. Athletes reporting an external rotation mechanism of injury and/or a positive squeeze test might be referred for MRI. Athletes with a negative overall clinical suspicion can be referred for delayed physical examination 5-10 days post-injury. In the acute setting none of the included variables was sufficient to completely rule out the presence of syndesmosis injury. When the aim is to completely rule out syndesmosis injury, diagnostic methods such as (dynamic-) ultrasound might provide a viable alternative.[25]

CONCLUSION

In an acute clinical setting with patients reporting high levels of ankle pain, a negative overall clinical suspicion reduces the probability of syndesmosis injury. An eversion mechanism of injury and a positive squeeze test are associated with higher odds of syndesmosis injury.

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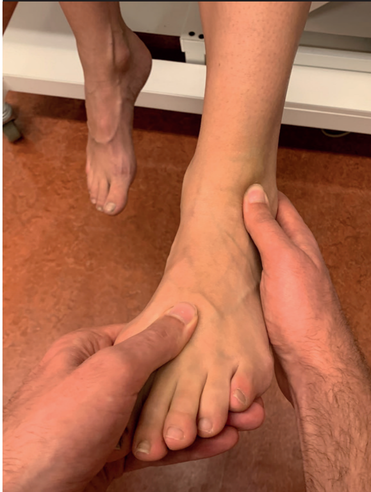
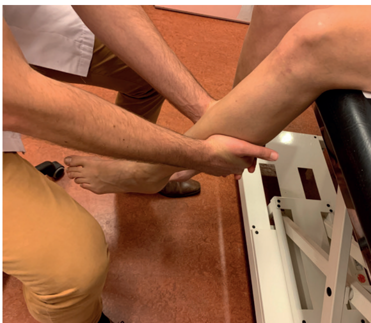
Supplementary appendix description of the six included syndesmosis tests



Palpation of the AITFL [4]

- *Palpation over the AITFL*
- *Positive if pain over the syndesmosis ligaments*



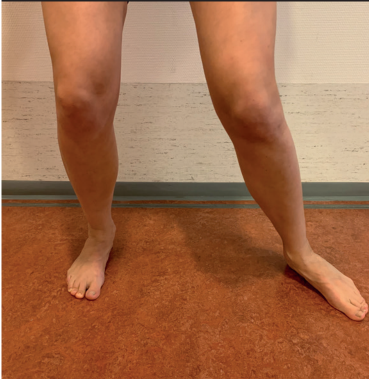
Squeeze test [4,8]

- *Patient sitting over the side of the bed. Compression of fibula to the tibia above the midpoint of the calf*
- *Positive if pain over the syndesmosis ligaments*

Non-weight-bearing dorsiflexion external rotation [4,9]

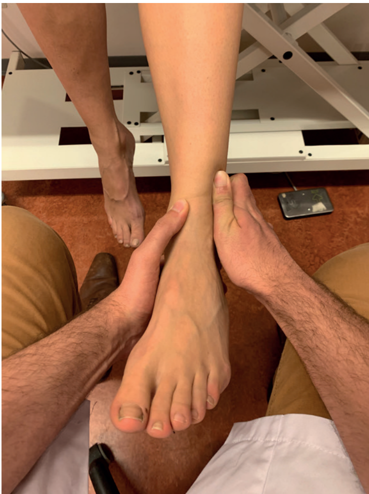
- *External rotation stress to affected foot and ankle with the knee in 90° and ankle passively in maximal dorsiflexion*
- *Positive if pain over the syndesmosis ligaments*

Supplementary appendix Continued



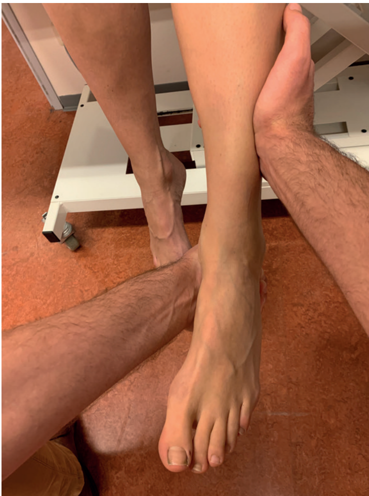
Weight-bearing dorsiflexion external rotation

- *Active external rotation of the affected foot and ankle in weight-bearing position, with the knee in approximately 30° flexion.*
- *Positive if pain over the syndesmosis ligaments*



Fibular translation test [10]

- *Apply anterior-posterior translation of the fibula*
- *Positive if anteroposterior displacement of the fibula is greater than contralateral side, or with pain over the syndesmosis ligaments*



Cotton test [11]

- *Distal tibia stabilised and lateral force applied to the foot*
- *Positive if increased lateral translation of the talus from medial to lateral compared with contralateral side*

CHAPTER 4

Diagnostic value of ultrasonography in acute lateral and syndesmotic ligamentous ankle injuries

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ABSTRACT

Objectives: To determine the diagnostic value of ultrasonography for complete discontinuity of the anterior talofibular ligament (ATFL), the calcaneofibular ligament (CFL) and the anterior inferior tibiofibular ligament (AITFL).

Methods: All acute ankle injuries in adult athletes (≥18 years old) presenting to the outpatient department of a specialised Orthopaedic and Sports Medicine Hospital within 7 days post-injury were assessed for eligibility. Using ultrasonography, one musculoskeletal radiologist assessed the ATFL, CFL and AITFL for complete discontinuity. Dynamic ultrasound measurements of the tibiofibular distance (mm) in both ankles (injured and contra-lateral) were acquired in the neutral position (N), during maximal external rotation (Max ER) and maximal internal rotation (Max IR). MR imaging was used as a reference standard.

Results: Between October 2017 and July 2019, 92 acute ankle injuries were included. Ultrasound diagnosed complete discontinuity of the ATFL with 87% (95% CI 74-95%) sensitivity and 69% (95% CI 53-82%) specificity. Discontinuity of the CFL was diagnosed with 29% (95% CI 10-56%) sensitivity and 92% (95% CI 83-97%) specificity. Ultrasound diagnosed discontinuity of the AITFL with 100% (95% CI 74-100%) sensitivity and 100% (95% CI 95-100%) specificity. Of the dynamic measurements, the side-to-side difference in external-rotation had the highest diagnostic value for complete discontinuity of the AITFL (sensitivity 82%, specificity 86%; cut-off 0.93 mm).

Conclusions: Ultrasound has a good to excellent diagnostic value for complete discontinuity of the ATFL and AITFL. Therefore, ultrasound can be used to screen for injury of the ATFL and AITFL. Compared with ultrasound, dynamic ultrasound has inferior diagnostic value for complete discontinuity of the AITFL.

INTRODUCTION

Acute ligamentous ankle injuries are one of the most common injuries in sports.[1] Depending on the trauma mechanism, acute ankle sprains may injure the lateral ankle ligaments and/or syndesmotic and/or the deltoid ligaments.[2] As physical examination in the acute phase (day 1-5) has proven to be of limited diagnostic accuracy, m agnetic Resonance Imaging (MRI) is increasingly used in athletes.[3–6] Ultrasound has the potential to provide an inexpensive and easily accessible alternative that could be used to screen for ligamentous ankle injuries.[7]

The diagnostic value of ultrasound for acute injury of the anterior talofibular ligament (ATFL) has been investigated in various studies.[8] However, the diagnostic value of a systematic approach (including the calcaneofibular ligament (CFL) and syndesmosis) to acute ligamentous ankle injuries has only been reported in two studies.[9,10] The main limitation in these studies is that the diagnostic values were reported for ligamentous injury, without the differentiation between partial and complete tears. As only complete tears are considered amenable to surgical repair, a study investigating the diagnostic value of ultrasound for complete ligamentous discontinuity is warranted.[11,12]

Dynamic ultrasound has been reported as an accurate method of diagnosing syndesmosis injury.[13] However, no prospective cohort study in an unselected cohort of athletes has been performed. Therefore, a study validating the diagnostic accuracy of dynamic ultrasound in a large prospective cohort of athletes with acute ankle injuries is necessary.

The aim of this study was to establish the diagnostic value of ultrasound for complete discontinuity of the lateral ankle ligaments and AITFL in athletes with an acute ankle injury. Our secondary aim was to establish the diagnostic value of dynamic ultrasound for complete discontinuity of the AITFL. Our hypothesis is that in athletes with an acute ankle injury, (dynamic-) ultrasound has excellent diagnostic accuracy for complete discontinuity of the ATFL, CFL and AITFL.

METHODS

Patient selection

Between October 2017 and July 2019, all patients presenting to the outpatient department of a specialised Orthopaedic and Sports Medicine Hospital within 7 days after an acute ankle injury were asked to participate in this study. Inclusion criteria were as follows: acute ankle injuries in adult athletes (≥18years old), participating in sports at a professional or recreational level and presenting within 7 days of injury. Ankle injuries were excluded if imaging studies demonstrated an ankle fracture or if the ultrasound and MRI studies could not be acquired within 10 days post-injury. Ethical approval was acquired from the Anti-Doping Lab Qatar review board (IRB No. F2016000153). Written informed consent was obtained from all patients at the time of inclusion.

Power calculation

This study was part of a large prospective cohort study on the functional outcome and return to play of acute ligamentous ankle injuries. The sample size estimations were therefore based on an expected difference in functional outcome. No a priori sample size calculation was performed for the present study.

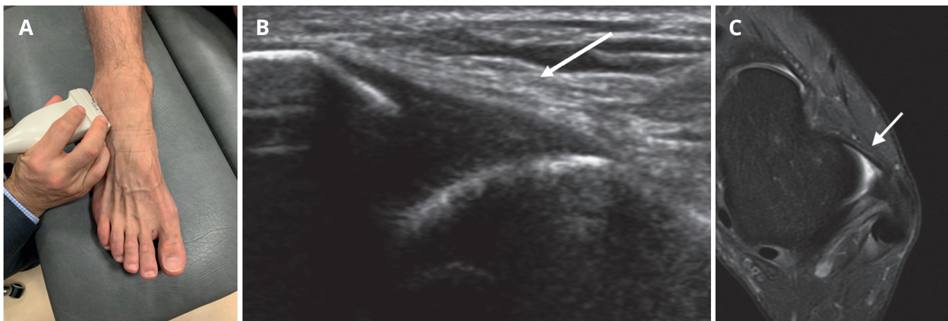
Ultrasound imaging

All examinations were performed by the same MSK-radiologist (J.A.), with 13 years of experience in MSK-ultrasound. An ultrasound device (iU22, Philips) with a high-frequency linear transducer (5-12 MHz) was used for standardized sonographic evaluation. Patients were examined in a supine position with their knees in 90° flexion. Ultrasound of the ATFL was performed by placing the transducer in the transverse plane (longitudinal to the ATFL) anterior to the tip of the lateral malleolus. (Figure 1a) The CFL was visualised with the probe in the frontal plane (longitudinal to the CFL). (Figure 2a) For visualisation of the anterior tibiofibular ligament, the transducer was placed over the AITFL in the axial plane, about 1 cm proximal to the joint line. (Figure 3a) During the examination of the AITFL, an assistant provided 5-10° passive dorsal flexion of the ankle.

After the initial sonographic examination, dynamic ultrasound measurements were obtained, as originally described by Mei-Dan et al.[13] With the knees kept together in 90° flexion, the foot of the injured ankle was passively brought into 5-10° dorsal flexion. (Figure 3a) The transducer was placed over the AITFL in the axial plane, about 1 cm proximal to the joint line. After the tibiofibular distance was measured (in mm) in the neutral position (N), maximal external rotation (Max ER) and maximal internal

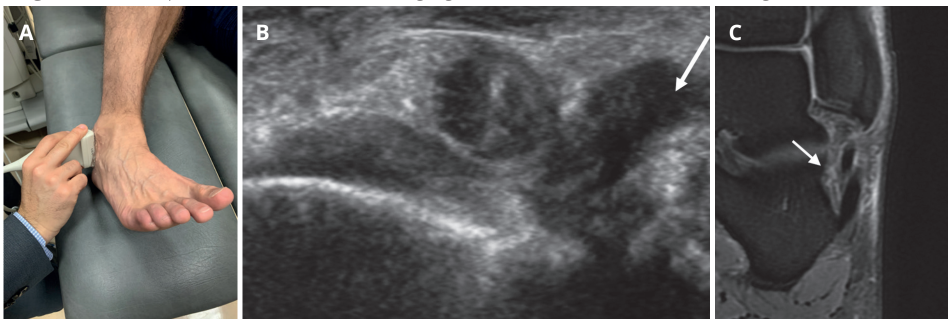
rotation (Max IR) manoeuvres were performed. (Figure 4a; 4b) The radiologist applied external rotation and internal rotation stress until a firm endpoint was reached.[13] During the stress manoeuvres, a digital video clip was recorded from which the tibiofibular distance was measured at the point of maximal external rotation and maximal internal rotation. The examination was repeated for the contralateral uninjured ankle.

Figure 1 Probe position and (US/MR) imaging results for the anterior talofibular ligament (ATFL)



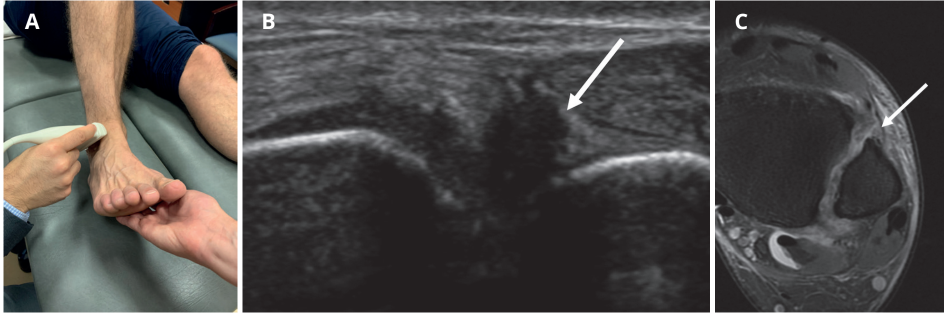
Ultrasound for the diagnosis of anterior talofibular ligament (ATFL) injury. (**A**) The ultrasound probe is placed in the transverse plane (longitudinal to the ATFL) anterior to the tip of the lateral malleolus. (**B**) Ultrasound findings consistent with an intact anterior talofibular ligament. (arrow) (**C**) Axial PD-FS image showing an intact anterior tibiofibular ligament. (arrow)

Figure 2 Probe position and (US/MRI) imaging results for the calcaneofibular ligament (CFL)



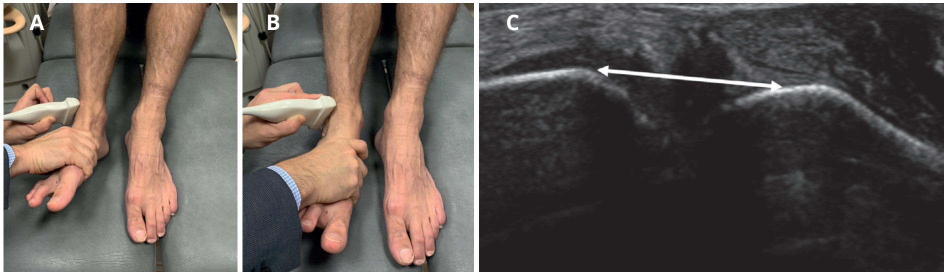
Ultrasound for the diagnosis of calcaneofibular ligament (CFL) injury. (**A**) The ultrasound probe is placed in the frontal plane (longitudinal to the calcaneofibular ligament). (**B**) Ultrasound findings consistent with a complete tear of the calcaneofibular ligament. (arrow) (**C**) Axial PD-FS image showing waviness of the calcaneofibular ligament consistent with a complete tear. (arrow)

Figure 3 Probe position and (US/MR) imaging findings for the Anterior Tibiofibular ligament (AITFL)



Ultrasound for the diagnosis of anterior tibiofibular ligament injury. (**A**) The ultrasound probe is placed over the AITFL in the axial plane (about 1 cm proximal to the joint line) (**B**) Ultrasound findings consistent with a complete tear of the anterior tibiofibular ligament. (arrow) (**C**) Axial PD-FS image showing disruption of the anterior tibiofibular ligament, consistent with a complete tear. (arrow)

Figure 4 Probe position and manoeuvres for dynamic measurement of the tibiofibular clear space



Dynamic manoeuvres of the ankle. (**A**) Passive dorsal flexion and maximal external rotation manoeuvre of the ankle. (**B**) Passive dorsal flexion and internal rotation manoeuvre of the ankle. (**C**) Measurements of the tibiofibular clear space in mm (double-headed arrow).

Magnetic resonance imaging

MRI was used as the reference standard, since MRI has demonstrated excellent diagnostic accuracy for injury of the lateral ankle ligaments and syndesmosis ligaments.[14–16] Patients underwent a wide-bore 3.0-T MRI (GE Discovery, GE Healthcare) using an 8-channel receive-only foot & ankle array (Invivo, Philips Healthcare). In the sagittal plane T1-weighted (repetition time [TR] 400-680ms; echo time [TE] 10-11ms; 3.0-mm slice thickness; 0.5-mm interslice gap; 416x288 pixel matrix; 2 excitations [NEX] 16 cm^2 field of view [FOV]; echo train length [ETL] 3) and proton density fat saturated [PD-FS] (TR 2500-3200ms, TE 32-35ms, 3.0-mm slice thickness, 0.5-mm interslice gap; 352x526 pixel matrix; 2 NEX; 20 cm^2 FOV; ETL 8) sequences were obtained, axial T2-weighted (TR 5500-6700ms; TE 72-80ms; 3.5-mm slice thickness, 0.5-mm interslice gap; 320x224 pixel matrix; 2 NEX; 13 cm^2 FOV;

ETL 16) and PD-FS sequences (TR 2900-4000; TE 35-39ms; 3,5-mm slice thickness, 0.5-mm interslice gap; 320x224 pixel matrix; 2 NEX; 13 cm^2 FOV; ETL 6) were acquired and in the coronal plane a PD-FS (TR 2700-3400; TE 35-38ms; 3.5-mm slice thickness; 0.5-mm interslice gap; 320x224 pixel matrix; 2 NEX; 16 cm^2 FOV; ETL 6) sequence was obtained.

Outcome measurements

Blinded to clinical information, the same MSK radiologist (J.A.) graded the ultrasound and MR scans. The ultrasound scans were graded during the sonographic examination. To assure blinding of the radiologist to the results of the ultrasound scan, MR scans were graded after a period of minimal 28 days. Injury of the individual ligaments (ATFL; CFL, AITFL) were graded according to the Schneck grading system[17] (Supplementary Appendix 1; grade 0: normal; grade 1: peri-ligamentous high signal/edema on proton density-weighted sequences and no discontinuity of fibres; grade 2: partial discontinuity but preserved remnant fibres; grade 3: complete discontinuity).

The following individual ankle ligaments were graded according to the four grade grading system: the lateral ankle ligaments (anterior talofibular ligament [ATFL]; calcaneofibular ligament [CFL]) and one of the syndesmosis ligaments (anterior inferior tibiofibular ligament [AITFL])

Dynamic measurements

The dynamic measurements included the tibiofibular distance (in mm) in the three positions: neutral (N); maximal internal rotation (Max IR); maximal external rotation (Max ER). From these measurements, two composite dynamic measurements were calculated. The first measurement (Δ ER-N) was calculated by subtracting the tibiofibular distance in the neutral position from the tibiofibular distance in maximal external rotation. The second composite measurement (Δ N-IR) was calculated by subtracting the tibiofibular distance in maximal internal rotation from the tibiofibular distance in the neutral position.

Statistical analysis

To evaluate the diagnostic value of ultrasound for complete ligamentous discontinuity, the Schneck grading of the individual ligaments, was dichotomised to (1) no complete discontinuity (grade 0: normal ligament, grade 1: peri-ligamentous edema and grade 2: partial discontinuity) or (2) complete discontinuity (grade 3: complete discontinuity). For an exploratory post-hoc analysis of the diagnostic values for injury of the individual ankle ligaments, the Schneck grading was dichotomised as (1) no injury (grade 0 and grade 1) and (2) injury (grade 2 and grade 3).

The diagnostic value of the dynamic measurements to distinguishing both groups (group A: no complete discontinuity AITFL vs. group B: complete discontinuity AITFL) was established in two comparisons. For the first comparison, the tibiofibular clear space was compared between group A (no complete discontinuity AITFL) and group B (complete discontinuity AITFL). For the second comparison, the side-to-side differences in tibiofibular distance between the injured and contralateral (uninjured) ankle were compared between group A (no complete discontinuity AITFL) and group B (complete discontinuity AITFL)

Descriptive statistics was used to present patient demographics and number of ligamentous lesions observed. Categorical data was presented as frequencies with percentages; continuous variables were presented as mean with standard deviation (SD) for data with a normal distribution and as median with interquartile range (IQR) in case of non-normal distribution. Data distribution was assessed using the Shapiro-Wilk test and visual inspection.

The diagnostic value of ultrasound for complete ligamentous discontinuity including; sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and positive and negative likelihood ratio's (LR+ and LR-) that were calculated using a 2x2 table.

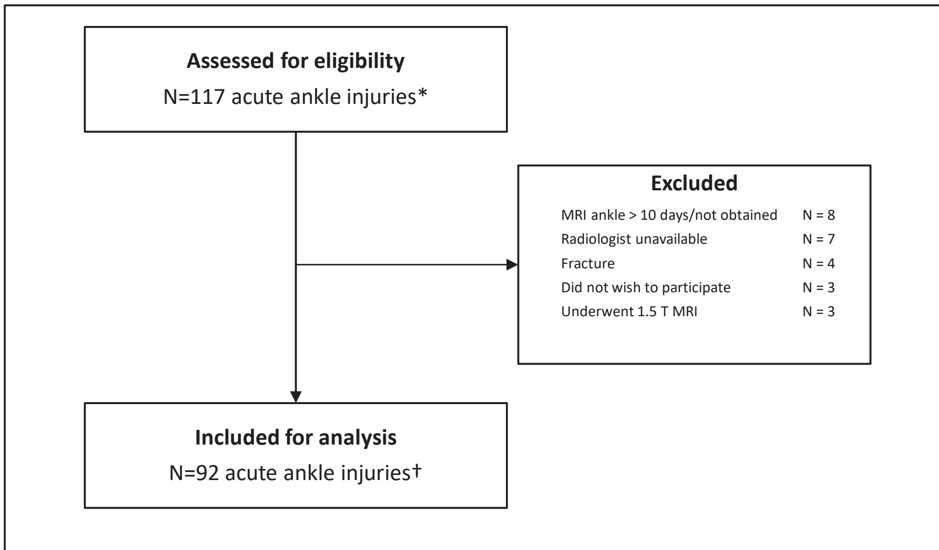
The diagnostic value and optimal cut-off (Youden's index = maximal value) for each dynamic measurement were calculated using a ROC-curve. If a dynamic measurement was missing, the patient was excluded from the analysis of the specific dynamic measurement. An independent t test was used to compare groups for each dynamic measurement. Significance was set at $p<0.05$. Statistical analysis was performed using Rstudio (Rstudio V 1.2.1335, Boston, Massachusetts, USA).

RESULTS

Baseline characteristics

Between October 2017 and July 2019, a total of 117 acute ankle injuries were assessed for eligibility. (Figure 5) Ninety-two acute ankle injuries were included in this study, of which one was a subsequent contra-lateral ankle injury. The median age at the time of injury was 25 years (IQR 8), with a range of 18 to 45 years. The majority of included patients were male (92%). The median time from injury to ultrasound was 2 days (IQR 3). The MR scans were acquired with a median of 3 days (IQR 3) post-injury. Of the 91 included patients, 50 (55%) played football/futsal, 18 (20%) volleyball, 8 (9%) handball, 6 (7%) basketball and 9 (10%) participated in other sports.

Figure 5 Flowchart



* In 116 athletes; † In 91 athletes

Grading of individual ligaments

The prevalence and diagnostic values [sensitivity/specificity, likelihood ratio's, negative/positive predictive value] per individual ligament are detailed in Table 1. Grading of the individual ligaments prior to dichotomisation is provided in Supplementary Appendix 2. On the reference standard (MRI) complete discontinuity of the ATFL was observed in 47 (51%) and for the CFL in 17 (18%) acute ankle injuries. For the lateral ankle ligaments, the diagnostic value of ultrasound for complete discontinuity of the ATFL was 87% (95% CI 74-95%) for sensitivity and 69% (95% CI 53-82%) for specificity.

Complete discontinuity of the CFL was diagnosed with 29% (95% CI 10-56%) sensitivity and 92% (95% CI 83-97%) specificity. For the syndesmosis, complete discontinuity of the AITFL was present in 12 (13%) out of 92 included acute ankle injuries. Ultrasound diagnosed complete discontinuity of the AITFL with 100% (95% CI 74-100%) sensitivity and 100% (95% CI 95-100%) specificity. The analysis for the diagnostic values for injury (defined as partial or complete discontinuity) of the individual ligaments is provided in Table 2.

Dynamic measurements (tibiofibular distance)
The mean tibiofibular distance per dynamic measurement (N, Max IR, Max ER, Δ ER-N and Δ N-IR) and the corresponding diagnostic values (AUC, cut-off point, sensitivity/ specificity) are detailed in Table 3. Due to discomfort, dynamic measurements were only acquired in 89 out of 92 acute ankle injuries (internal rotation in 88). The mean tibiofibular distance in the neutral position (10.08 mm vs. 11.32 mm, $p = 0.02$) and in the maximal external rotation position (10.13 mm vs. 11.75 mm, $p = 0.002$) was higher for the group with a discontinuous AITFL. The sensitivity and specificity of these dynamic measurements were 58% and 79-90%, respectively. The other dynamic measurements (IR, Δ ER-N, Δ N-IR) were not significantly different between groups.

Dynamic measurements (side-to-side difference)
The mean side-to-side difference per dynamic measurement (N, Max IR, Max ER, Δ ER-N and Δ N-IR) and the corresponding diagnostic values (AUC, cut-off point, sensitivity/specificity) are detailed in Table 3. Dynamic measurements in the contralateral ankle were performed in 83 ankles (internal rotation in 81). The mean side-to-side difference in tibiofibular distance in the neutral position (0.20 mm vs. 2.04 mm, $p<0.001$), during maximal internal r otation (0.04 mm vs. 1.71 mm, $p<0.001$) and during maximal external rotation (-0.03 mm vs 1.89 mm, $p<0.001$) were higher for the group with complete discontinuity of the AITFL. The highest AUC was observed for the side-to-side difference in maximal external rotation (AUC 0.88; sensitivity 82%, specificity 86% at cut-off 0.93 mm). The side-to-side difference for the other dynamic measurement (Δ ER-N, Δ N-IR), was not significantly different between groups and resulted in poor diagnostic values.

Table 1: The prevalence and diagnostic values of ultrasonography for complete discontinuity of the individual ankle ligaments in 92 athletes presenting with an acute ankle injury.

	Prevalence (MR)	Prevalence (US)	Sensitivity	Specificity	LR+	LR-	PPV	NPV
Lateral ankle ligaments								
- ATFL	47/92 (0.51)	55/92 (0.60)	0.87 (0.74-0.95)	0.69 (0.53-0.82)	2.80 (1.79-4.39)	0.19 (0.09-0.40)	0.75 (0.61-0.85)	0.84 (0.68-0.94)
- CFL	17/92 (0.18)	11/92 (0.12)	0.29 (0.10-0.56)	0.92 (0.83-0.97)	3.68 (1.27-10.65)	0.77 (0.56-1.05)	0.45 (0.17-0.77)	0.85 (0.76-0.92)
Syndesmosis ligaments								
- AITFL	12/92 (0.13)	12/92 (0.13)	1.00 (0.74-1.00)	1.00 (0.95-1.00)	Infinity (N/a-Inf.)	0.00 (0.00-N/a)	1.00 (0.74-1.00)	1.00 (0.95-1.00)

Note: MR imaging was used as reference standard. All diagnostic values are presented with 95% confidence interval (95%CI) anterior talofibular ligament (ATFL); calcaneofibular ligament (CFL); anterior inferior tibiofibular ligament (AITFL); magnetic resonance imaging (MR); ultrasonography (US); positive likelihood ratio (LR+); negative likelihood ratio (LR-); positive predictive value (PPV); negative predictive value (NPV); Not applicable (N/a); Infinity (Inf.).

Table 2: The prevalence and diagnostic values of ultrasonography for partial and complete discontinuity of the individual ankle ligaments in 92 athletes presenting with an acute ankle injury.

	Prevalence (MR)	Prevalence (US)	Sensitivity	Specificity	LR+	LR-	PPV	NPV
Lateral ankle ligaments								
- ATFL	61/92 (0.66)	58/92 (0.63)	0.89 (0.77-0.95)	0.87 (0.69-0.96)	6.86 (2.74-17.20)	0.13 (0.07-0.27)	0.93 (0.82-0.98)	0.79 (0.62-0.91)
- CFL	45/92 (0.49)	26/92 (0.28)	0.49 (0.34-0.64)	0.91 (0.79-0.97)	5.74 (2.15-15.36)	0.56 (0.42-0.75)	0.85 (0.64-0.95)	0.65 (0.52-0.76)
Syndesmosis ligaments								
- AITFL	14/92 (0.15)	12/92 (0.13)	0.86 (0.56-0.97)	1.00 (0.94-1.00)	Infinity (N/a-Inf.)	0.14 (0.04-0.52)	1.00 (0.70-1.00)	0.98 (0.90-1.00)

Note: MR imaging was used as reference standard. All diagnostic values are presented with 95% confidence interval (95%CI); anterior talofibular ligament (ATFL); calcaneofibular ligament (CFL); anterior inferior tibiofibular ligament (AITFL); magnetic resonance imaging (MR); ultrasonography (US); positive likelihood ratio (LR+); negative likelihood ratio (LR-); positive predictive value (PPV); negative predictive value (NPV); not applicable (N/a); infinity (Inf).

Table 3: Mean tibiofibular distance (in mm, ± SD) per dynamic manoeuvre in *N* acute ankle injuries; Comparison 1: mean tibiofibular distance in group A (no complete discontinuity of AITFL) versus group B (complete discontinuity of the AITFL); Comparison 2: the mean difference between tibiofibular distance in the injured ankle and the contra-lateral (uninjured) ankle, compared between group A and group B.

	N (group A vs. group B)	**TFD group A**	**TFD group B**	**P-value**	**AUC (95%CI)**	**Cut-off**	**Sensitivity**	**Specificity**
Comparison: tibiofibular distance								
N	89 (77 vs. 12)	10.1 (± 1.6)	11.3 (± 2.3)	p = 0.018	0.65 (0.47-0.84)	11.3	0.58	0.79
IR	88 (76 vs. 12)	10.1 (± 1.6)	11.1 (± 2.1)	p = 0.054	0.65 (0.44-0.85)	10.6	0.67	0.72
ER	89 (77 vs. 12)	10.1 (± 1.6)	11.8 (± 2.1)	p = 0.002	0.72 (0.54-0.90)	11.9	0.58	0.90
Δ ER-N	89 (77 vs. 12)	0.1 (± 0.7)	0.4 (± 1.2)	p = 0.132	0.60 (0.40-0.80)	0.3	0.58	0.66
Δ N-IR	88 (76 vs. 12)	0.0 (± 0.9)	0.3 (± 1.2)	p = 0.412	0.58 (0.34-0.81)	0.6	0.58	0.83
Comparison: side-to-side difference tibiofibular distance								
N	83 (72 vs. 11)	0.2 (± 1.3)	2.04 (± 1.8)	p <0.001	0.79 (0.65-0.94)	1.2	0.73	0.76
IR	81 (70 vs. 11)	0.0 (± 1.4)	1.71 (± 1.9)	p <0.001	0.77 (0.59-0.96)	1.4	0.73	0.83
ER	83 (72 vs. 11)	0.0 (± 1.2)	1.89 (± 1.4)	p <0.001	0.88 (0.79-0.98)	0.9	0.82	0.86
Δ ER-N	83 (72 vs. 11)	0.2 (± 1.1)	-0.15 (± 1.1)	p = 0.824	0.48 (0.29-0.68)	-0.4	0.58	0.64
Δ N-IR	81 (70 vs. 11)	0.2 (±1.3)	0.32 (± 1.6)	p = 0.71	0.50 (0.28-0.71)	-0.7	0.80	0.36

Group A: all acute ankle injuries with no complete discontinuity of the AITFL per MR scan; Group B: all acute ankle injuries with complete discontinuity of the AITFL per MR scan. AUC values are presented with corresponding 95% confidence interval (95%CI); neutral (N); maximal internal rotation (Max IR); maximal external rotation (Max ER); maximal external rotation-neutral (Δ ER-N); neutral-maximal internal rotation (ΔN-IR); number of included measurements (*N*); tibiofibular distance (TFD); area under the curve (AUC); cut-off at Youden's index = maximal-value (in mm)

DISCUSSION

The most important finding of this study is that ultrasonography resulted in good to excellent diagnostic values for complete discontinuity of the ATFL and AITFL compared with the reference standard of MR imaging. In contrast to our hypothesis, ultrasound had poor sensitivity for complete discontinuity of the CFL. Based on these findings, ultrasonography can only be used to screen for the presence of complete discontinuity of the ATFL and the AITFL. For dynamic ultrasound the side-to-side difference in the tibiofibular distance during maximal external rotation had the highest diagnostic accuracy. However, the included dynamic measurements had inferior diagnostic accuracy compared with plain ultrasonography of the AITFL.

Diagnostic value of US for the individual ligaments

The diagnostic value of ultrasound in the diagnosis of acute injury of the ATFL has been investigated in various studies, primarily by comparing ultrasound with surgical findings as a reference standard.[8] However, the methodological quality of these studies is limited as surgical exploration in most studies was restricted to those patients with positive imaging findings only. Therefore, establishing the diagnostic value of ultrasound with MRI as a reference is a valuable alternative. So far two studies have compared the diagnostic value of ultrasound for injury of the lateral ankle ligaments against MRI.[18,19] In the first study by Margetic et al. in 30 patients with an acute ankle sprain, ultrasound had a sensitivity of 60% and specificity of 100% for complete tears of the ATFL. Tears of the CFL were diagnosed with 0% sensitivity and 100% specificity.[18] Although the methodology is similar to our study, the reported specificity was higher and sensitivity lower for both lateral ankle ligaments. This can be contributed to the low number of disease-positive cases (complete tear) in their study, making the findings less robust. In a more recent study by Gun C et al. 65 patients underwent bedside ultrasound, followed by MRI. In this study, ultrasound had 93.8% sensitivity and 100% specificity for injury of the ATFL. However, no grading of injury severity was applied, hindering the comparison of outcomes.[19]

The systematic ultrasound approach to the diagnosis of ligamentous ankle injuries has been investigated in two studies.[7,8] In a prospective study by Milz et al, 64 patients with an acute ankle injury underwent ultrasound followed by a 0.2 T MR scan. In this study, ultrasound had a sensitivity of 98% and a specificity of 83% for injury (complete and partial tears) of the ATFL. Injury of the CFL was diagnosed with 87% sensitivity and 89% specificity.[8] In a more recent study by Lee et al, injury (complete and partial tears) of the ATFL was diagnosed with 99-100% sensitivity and 95% specificity. Injury of the CFL was diagnosed with 96-100% sensitivity and 97-100% specificity. Compared with

MR imaging, ultrasound established injury of the AITFL with a 100% sensitivity and 100% specificity.[7] The superior diagnostic values for the ATFL and CFL in the study by Lee et al. might be explained by the fact that in our study, differentiation of partial tears from complete tears was applied.

Diagnostic value of dynamic US measurements

Only one previous study has reported on the diagnostic value of dynamic ultrasound measurements in the diagnosis of syndesmosis injury.[13] In this study, Mei-Dan et al. compared dynamic tibiofibular clear space measurements in 9 patients with a recent syndesmotic injury to a control group of 20 patients clinically diagnosed with a lateral ankle sprain and 18 uninjured control subjects. They found the side-to-side difference in tibiofibular clear space between those with a syndesmosis injury and the control group, to be statistically significant in all positions (N, IR, ER). The diagnostic accuracy for the side-to-side difference in the N and ER positions was 100% at a cut-off of 0.7 mm and 0.9 mm, respectively. Our study confirmed the side-to-side difference in external rotation as the superior dynamic measurement. However, we obtained inferior diagnostic values compared with the study by Mei-Dan et al. This can potentially be explained by the fact that in our study, an unselected cohort of athletes was included.

In comparison with the study by Mei-Dan et al, the mean tibiofibular distance in both groups (injured and uninjured) of our study was higher. A possible explanation for this discrepancy is that we might have measured the tibiofibular distance more superficially, towards the posterior border of the AITFL. Alternatively, anatomical variations between patient populations, might have contributed to the difference in the findings.

Few other studies have looked at dynamic measurements of the tibiofibular distance, but none of these studies reported diagnostic values (sensitivity/specificity) for the individual dynamic tibiofibular clear space measurements.[20–22]

Strength and limitations

This is the first study to prospectively compare the diagnostic values of (dynamic-) ultrasound in an athletic cohort of acute ankle injuries. However, minor shortcomings are present in this study. In this study, we used a 5-12 MHz probe. In theory, a high-frequency probe (5-18 MHz) could have yielded more accurate results. However, as we strived to provide an outcome that could easily be translated into clinical practice we investigated the most commonly used 5-12 Mhz probe.[23] Secondarily, for the dynamic manoeuvres we used unstandardised dynamic measurements as

this was most applicable to the clinical situation.[13] Future research investigating standardised (instrumented) dynamic measurements may be able to improve the diagnostic accuracy and aid in the diagnosis of syndesmotic instability. However, clinical applicability should be an important element in such research. In addition, due to the low prevalence of deltoid lesions in acute ankle injuries, the diagnostic value of ultrasound for the diagnosis of deltoid injury was not evaluated. Furthermore, all ultrasounds were performed and graded by a single senior MSK radiologist with extensive experience in MSK sonography. As the inter-rater reliability of ultrasound for ligamentous ankle injuries was not established in this study, inferior results might be expected in less-experienced sonographers.

Implications for clinical practice

As injury of the ATFL can be diagnosed accurately by delayed physical examination, the need for ultrasound evaluation of lateral ankle sprains is limited.[5] However, when suspecting a syndesmosis injury, ultrasound may be used to detect complete discontinuity of the AITFL. In acute ankle sprains involving the syndesmosis, the AITFL is the first ligament to be injured.[3] Therefore, ultrasound can be used to differentiate acute ankle sprains affecting the lateral ankle ligaments from those with an increased risk of syndesmotic instability. When an injury of the AITFL is detected with ultrasound imaging, syndesmotic stability can be further evaluated by MRI or arthroscopy.[24] Although a useful addition to the ultrasonographic evaluation of ligamentous ankle injuries, dynamic ultrasound should not be used as the sole method of diagnosing syndesmosis injury.

Conclusion

Ultrasound has a good to excellent diagnostic value for the presence of complete discontinuity of the ATFL and AITFL. Therefore, ultrasound can be used to detect complete discontinuity of the ATFL and the anterior ligament of the ankle syndesmosis (AITFL). Compared with ultrasound, dynamic ultrasound has inferior diagnostic value for the diagnosis of complete discontinuity of the AITFL.

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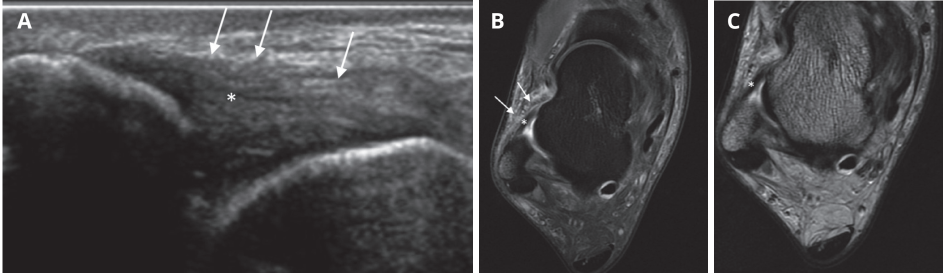
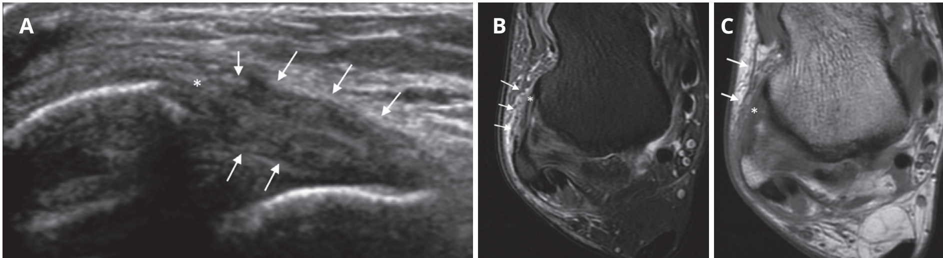
Supplementary appendix 1A Cross-reference of Schneck Grade I injury of the anterior talofibular ligament (ATFL)



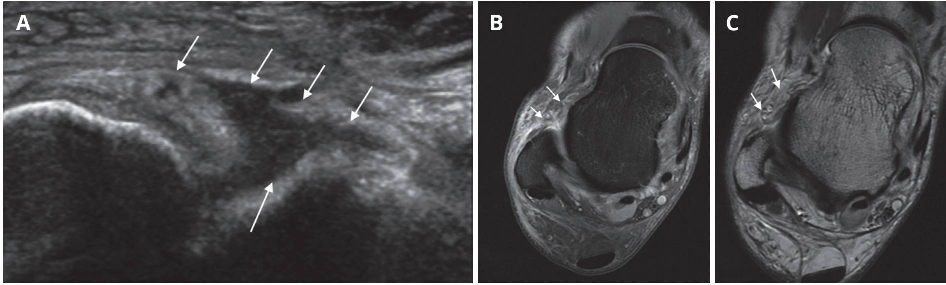
Cross-reference of Schneck grade I injury of the anterior talofibular ligament (ATFL) on Ultrasound and MRI; (**A**) Ultrasound image showing intact ATFL fibers (Asterisk) with peri-ligamentous hypoechoic halo consistent with soft tissue edema (Arrows) (**B**) Axial PD-FS image showing peri-ligamentous high signal/edema (Arrows) with intact fibers of the ATFL (Asterisk) (**C**) Axial T2-weighted image showing intact fibers of the ATFL (Asterisk).

Supplementary appendix 1B Cross-reference of Schneck Grade II injury of the anterior talofibular ligament (ATFL)



Cross-reference of Schneck grade II injury of the anterior talofibular ligament (ATFL) on Ultrasound and MRI; (**A**) Ultrasound image showing thickening and decreased echogenicity of the ATFL (Arrows) with partial discontinuity (Asterisk) (**B**) Axial PD-FS image showing a soft tissue edema surrounding the ATFL (Arrows) with some fibers of the ATFL remaining intact (Asterisk) (**C**) Axial T2-weighted image showing a partial tear of the ATFL (Arrows) with some fibers of the ATFL remaining intact (Asterisk)

Supplementary appendix 1C Cross-reference of Schneck Grade III injury of the anterior talofibular ligament (ATFL)



Cross-reference of Schneck grade III injury of the anterior talofibular ligament (ATFL) on Ultrasound and MRI (**A**) Ultrasound image showing a complete discontinuity of the ATFL (Arrows) (**B**) Axial PD-FS image showing soft tissue edema and complete ATFL discontinuity (**C**) Axial T2-weighted image showing no ATFL fibers remaining.

Supplementary appendix 2: Cross-tabulation for the grading of individual ankle ligaments according to Ultrasound and MR imaging.

Lateral ankle ligaments					
ATFL			**Grading per MRI**		
	Grading per US	Normal	Grade 1	Grade 2	Grade 3
	Normal	20	7	1	5
	Grade 1	0	0	1	0
	Grade 2	0	0	2	1
	Grade 3	3	1	10	41
CFL			**Grading per MRI**		
	Grading per US	Normal	Grade 1	Grade 2	Grade 3
	Normal	37	6	16	7
	Grade 1	0	0	0	0
	Grade 2	0	1	9	5
	Grade 3	2	1	3	5
Syndesmosis ligaments					
AITFL			**Grading per MRI**		
	Grading per US	Normal	Grade 1	Grade 2	Grade 3
	Normal	74	4	2	0
	Grade 1	0	0	0	0
	Grade 2	0	0	0	0
	Grade 3	0	0	0	12

Cross-tabulation of the Schneck grading by the MSK-radiologist according Ultrasound and MR imaging is provided for the individual ankle ligaments; 1) For the lateral ankle ligaments; anterior talofibular ligament (ATFL) and calcaneofibular ligament (CFL) and 2) the Syndesmosis ligaments; anterior inferior tibiofibular ligament (AITFL)

CHAPTER 5

Limited intrarater and interrater reliability of acute ligamentous ankle injuries on 3T MRI

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ABSTRACT

Objectives: To determine the diagnostic reliability of the Schneck grading system for acute ligamentous injuries of (1) the three major ligamentous ankle complexes (2) the individual ankle ligaments and (3) the Sikka classification for syndesmosis injury.

Methods: All acute ankle injuries in adult athletes (≥18 years), presenting to the outpatient department of a specialised Orthopaedic and Sports Medicine Hospital, within 7 days post-injury were screened for inclusion. Ankle injuries were excluded if imaging demonstrated a frank ankle fracture or if the 3T MRI study could not be acquired within 10 days post-injury. Two radiologists graded the three major ligamentous complexes (lateral ankle complex, deltoid complex and syndesmosis complex) and their comprising individual ligaments according the four-grade Schneck grading system. Syndesmotic injuries were classified according the four-grade Sikka classification for consequent injury of the individual syndesmosis ligaments and the deltoid complex. Agreement and kappa (K) statistics were calculated to determine intrarater and interrater reliability.

Results: Between September 2016 and September 2018, a total of 92 MR scans were obtained (87 patients). Interrater and intrarater reliability of the Schneck grading system was moderate to substantial for the lateral ankle complex (K=0.47-0.76), fair to almost perfect for the syndesmosis complex (K=0.37-0.89) and fair to moderate for the deltoid complex (K=0.14-0.51). For the individual ligaments, kappa values ranged from moderate to substantial for the anterior talofibular ligament (ATFL) (K=0.55-0.73), fair to substantial for the calcaneofibular ligament (CFL) (K=0.31-0.62) and fair to almost perfect for the anteroinferior tibiofibular ligament (AITFL) (K=0.36-0.89). Diagnostic reliability of the Sikka classification ranged from moderate to almost perfect. (K=0.51-0.95).

Conclusions: Grading of the three major ligamentous complexes and of the individual ankle ligaments according the Schneck grading system resulted in limited diagnostic reliability. When dichotomised for the presence of complete discontinuity, the interrater reliability of the Schneck grading system improved to substantial and almost perfect for the ATFL and AITFL, respectively. Classification of syndesmosis injury according the Sikka classification resulted in moderate interrater reliability.

INTRODUCTION

Acute ankle sprains are among the most common sport-related injuries.[1] The lateral ankle ligaments are most frequently injured (0.93/1000 athlete exposures), followed by the syndesmosis (0.38/1000 athlete exposures) and deltoid ligaments (0.06/1000 athlete exposures).[2] In athletes, Magnetic Resonance Imaging (MRI) is increasingly used for initial diagnosis and prognosis of ligamentous ankle injuries.[3–5] To categorise and translate these MR findings into clinical practice, standardized grading systems with high diagnostic reliability are warranted.

Diagnostic reliability of standardized grading systems for acute ligamentous ankle injuries have been described in various studies.[6–8] However, only the grading system used by Roemer et al. included grading of injury in multiple ligamentous complexes (lateral ankle complex, deltoid complex and syndesmosis complex).[9] In this study, two radiologists determined intrarater and interrater reliability of a five-grade system for acute and chronic ligamentous ankle injury, based on 30 MR scans (1.5T).[9] The main limitation in this study was that it reported diagnostic reliability per ligamentous complex (e.g. lateral ligaments) and not per individual ligament (e.g. anterior talofibular ligament (ATFL)), leaving diagnostic reliability of scoring acute injury of individual ankle ligaments on 3T MRI unknown.

Reliability of prognostic scoring for syndesmosis injury has been evaluated in two previous studies.[7,10] In a retrospective cohort study by Howard R et al. prognostic scoring of syndesmosis injury in 16 NFL players resulted in fair to almost perfect interobserver reliability. However, except for syndesmotic joint width, no association between prognostic scoring and time to return to play was established. Sikka et al. evaluated a prognostic syndesmosis injury classification in a retrospective cohort study on 36 NFL players with MRI-confirmed (1.5 T) syndesmosis injury. The main limitation in this study was that it lacked evaluation of the classifications' interrater reliability.

Given these two limitations, a diagnostic reliability study on grading of the individual ankle ligaments, the ligamentous complexes and classification of syndesmotic injury severity is warranted. Therefore, the aim of this study was to determine the diagnostic reliability of the Schneck grading system for acute ligamentous injuries of (1) the three major ligamentous ankle complexes (2) the individual ankle ligaments and (3) the Sikka classification for syndesmosis injury.[10,11]

METHODS

Patient selection

Patients presenting to the outpatient department of a specialised Orthopaedic and Sports Medicine Hospital within 7 days after an acute ankle injury were asked to participate in this study. Inclusion criteria were: acute ankle injuries in adult athletes (≥18 years), participating in sports at a professional or recreational level and presenting within 7 days of injury. Ankle injuries were excluded if imaging studies demonstrated a frank ankle fracture or if the 3T MRI study could not be acquired within 10 days post-injury. After clinical history and physical examination was performed by a Sports Medicine Physician or Orthopaedic Surgeon, MRI images were obtained. Ethical approval was acquired from the Anti-Doping Lab Qatar review board (IRB No. F2016000153). Written informed consent was obtained from all patients at time of inclusion.

Magnetic Resonance Imaging

All MR scans were obtained using a wide-bore 3.0-T MRI system (GE Discovery, GE Healthcare) with an 8-channel receive only Foot & Ankle array (Invivo, Philips Healthcare, Best, The Netherlands). In the sagittal plane T1-weighted (repetition time (TR) 400-680 ms; echo time (TE) 10-11 ms; 3.0 mm slice thickness; 0.5 mm interslice gap; 416x288 pixel matrix; two excitations (NEX) 16 cm^2 field of view (FOV); Echo train length (ETL) 3) and Proton Density Fat Saturated (PD-FS) (TR 2500-3200 ms, TE 32-35 ms, 3.0 mm slice thickness, 0.5 mm interslice gap; 352x526 pixel matrix; 2 NEX; 20 cm^2 FOV; ETL 8) sequences were obtained. In the axial plane T2-weighted (TR 5500-6700ms; TE 72-80ms; 3.5 mm slice thickness, 0.5 mm interslice gap; 320x224 pixel matrix; 2 NEX; 13 cm^2 FOV; ETL 16) and PD-FS (TR 2900-4000; TE 35-39 ms; 3,5 mm slice thickness, 0.5 mm interslice gap; 320x224 pixel matrix; 2 NEX; 13 cm^2 FOV; ETL 6) sequences were acquired. In the coronal plane a PD FS (TR 2700-3400; TE 35-38 ms; 3.5 mm slice thickness; 0.5 mm interslice gap; 320x224 pixel matrix; 2 NEX; 16 cm^2 FOV; ETL 6) sequence was obtained.

Standardized MRI grading

The MR scans were scored by two radiologists specialised in musculoskeletal radiology (J.A. and M.A.) with *11* and *3* years of experience in MSK-imaging, respectively. The two radiologists, hereafter referred to as R1 and R2, scored the lesions using a standardized scoring form. Prior to assessing the MR scans both radiologists participated in an individual familiarization session, followed by a joint calibration session. During a 2-hour familiarisation session, the use of the standardised score form was practised, assessing 10 ankle MR scans that were not included in this data-

set. To assure accurate interpretation of the scoring form during the calibration session consensus was reached on the scoring of another 10 ankle MR scans, not included in this data-set. To assure blinding of the radiologists to the clinical findings, the MR scans were scored in presence of a post-graduate medical researcher. In order to determine intrarater reliability, one radiologist (R1) repeated the scoring process. To minimise recall bias, the radiologist repeated scoring after a period of 28 days.

Grading system for ligamentous complexes and individual ligaments

The ligamentous complexes were graded as normal (grade 0) or in accordance with the highest graded acute lesion (grade 1-3) in one of its comprising individual ligaments. All individual ligaments were graded according to the four grade Schneck grading system.[11] (Table 1)

Table 1 Schneck grading system and Sikka classification for grading of the ligamentous complexes and individual ligaments

Schneck grading system	
- Grade 0	No abnormality of ligament
- Grade 1	Peri-ligamentous high signal/oedema on proton density-weighted sequences
- Grade 2	Partial discontinuity but preserved remnant fibres
- Grade 3	Complete discontinuity
Sikka classification*	
- Grade I	Isolated injuries to the AITFL
- Grade II	Injury to the AITFL, interosseous ligaments, and interosseous membrane
- Grade III	Injury to the AITFL, interosseous ligament, interosseous membrane and PITFL
- Grade IV	Injury to the AITFL, interosseous ligament, interosseous membrane, PITFL and deltoid ligament.

* Ligamentous injury was defined as partial or complete tear of the respective ligament. Anterior tibiofibular ligament (AITFL); Posterior tibiofibular ligament (PITFL).

Classification of syndesmotic injury

In patients with an observed syndesmotic injury, the severity of the syndesmotic injury was classified in accordance to the classification proposed by Sikka RS et al.[10] (Table 1)

Grading of ligamentous complexes

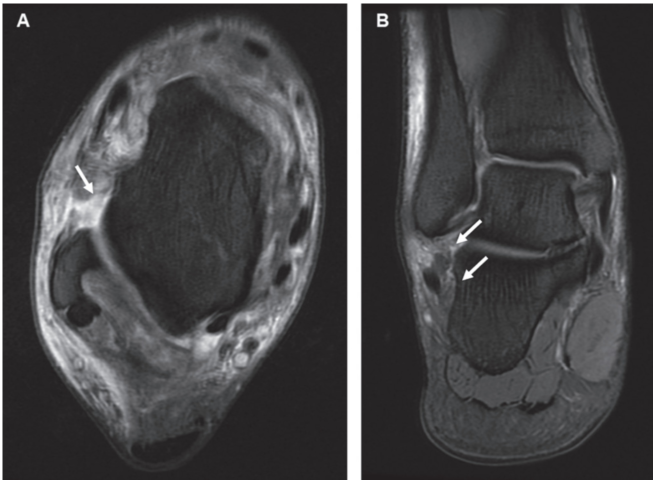
The three major ligamentous complexes (lateral ankle complex, deltoid complex (subdivided in deep deltoid and superficial deltoid) and syndesmosis complex) were graded according the four-grade Schneck grading system.

Grading of individual ligaments

The following individual ankle ligaments were graded according to the four grade Schneck grading system:

- Lateral ligaments; including the anterior talofibular ligament (ATFL), calcaneofibular ligament (CFL) and posterior talofibular ligament (PTFL) (figure 1).
- Syndesmosis ligaments; including the anteroinferior tibiofibular ligament (AITFL), interosseous ligament (IOL), interosseous membrane (IOM), posteroinferior tibiofibular ligament (PITFL) and transverse tibiofibular ligament (TTFL) (figure 2).
- Medial ligaments; subdivided in the superficial deltoid ligaments (tibionavicular (TN), tibiospring (TS), tibiocalcaneal (TC) and posterior tibiotalar (PT), respectively) and the ligaments comprising the deep portion of the deltoid (anterior tibiotalar (ATT) and posterior tibiotalar (PTT)) (figure 3).

Figure 1 Acute lateral ankle ligament injury.



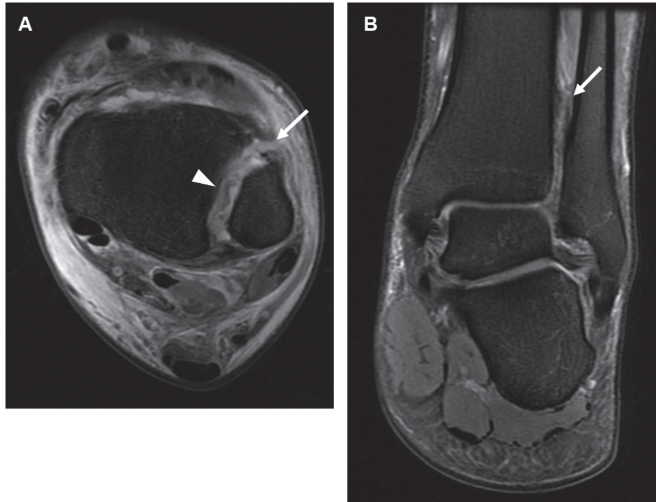
(**A**) Axial PD-FS image showing complete discontinuity (Schneck grade III) of the anterior talofibular ligament (ATFL; arrow). (**B**) Coronal PD-FS image showing complete discontinuity (Schneck grade III) of the calcaneofibular ligament (CFL; arrows). Proton density fat saturated (PD-FS)

Presence versus absence of acute ligamentous lesions

To assess the intrarater and interrater reliability for the presence or absence of acute ligamentous lesions in the ligamentous complexes and individual ligaments, the MRI grading system was evaluated as dichotomous outcomes;

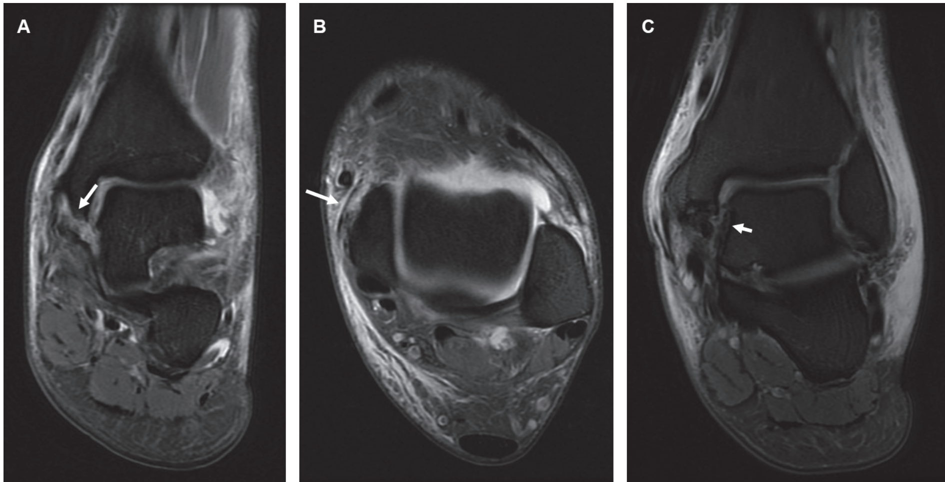
- Grade 0: was considered absence of an acute lesion.
- Grade 1-3: was considered presence of an acute lesion.

Figure 2 Acute syndesmosis injury.



(**A**) Axial PD-FS image showing complete discontinuity (Schneck grade III) of the anteroinferior tibiofibular ligament (AITFL; arrow) and waviness of the interosseous ligament (IOL; arrowhead) consistent with complete discontinuity (Schneck grade III) (**B**) Coronal PD-FS image showing complete discontinuity of the interosseous membrane (IOM; arrow). Proton density fat saturated (PD-FS)

Figure 3 Acute deltoid injury.



(**A**) Coronal PD-FS image showing complete discontinuity (Schneck grade III) of the tibiocalcaneal ligament (TC) (**B**) Axial PD-FS image showing tibionavicular ligament (TN; arrow) detachment (Schneck grade III)) (**C**) Coronal PD-FS image showing complete discontinuity (Schneck grade III) of the posterior tibiotalar ligament (PTT; arrow). Proton density fat saturated (PD-FS)

Presence versus absence of complete discontinuity:
To assess the intrarater and interrater reliability for the presence or absence of complete discontinuity in the ligamentous complexes and individual ligaments, the MRI grading system was evaluated as dichotomous outcomes;

- Grade 0-2: was considered absence of complete discontinuity.
- Grade 3: was considered as presence of complete discontinuity.

Statistical analysis
Descriptive statistics was used to present patient demographics (age, time to MRI, sports) and the number and distribution of lesions graded by the individual observers. Continuous variables were presented as mean with standard deviation (SD) for data with a normal distribution and as median with interquartile range (IQR) in case of non-normal distribution. Categorical data were presented as frequencies and proportions.

Intrarater and interrater reliability of the Schneck grading system[11] (ligamentous lesions; grade 0-3) and Sikka classification system[10] (syndesmosis injury; grade I-IV) were determined using linear weighted kappa statistics on an ordinal scale (K). Intrarater and interrater reliability for dichotomised data were determined using unweighted kappa statistics.

Overall agreement was calculated for dichotomous observations and weighted agreement was calculated for ordinal variables. We calculated prevalence (P) and bias index (BI) from cross tabulations for the dichotomous variables. Prevalence was defined as percentage (%) of included ankle injuries with positive findings. Bias index was defined as the extent to which the radiologists disagreed on the proportion of positive (or negative) findings.[12]

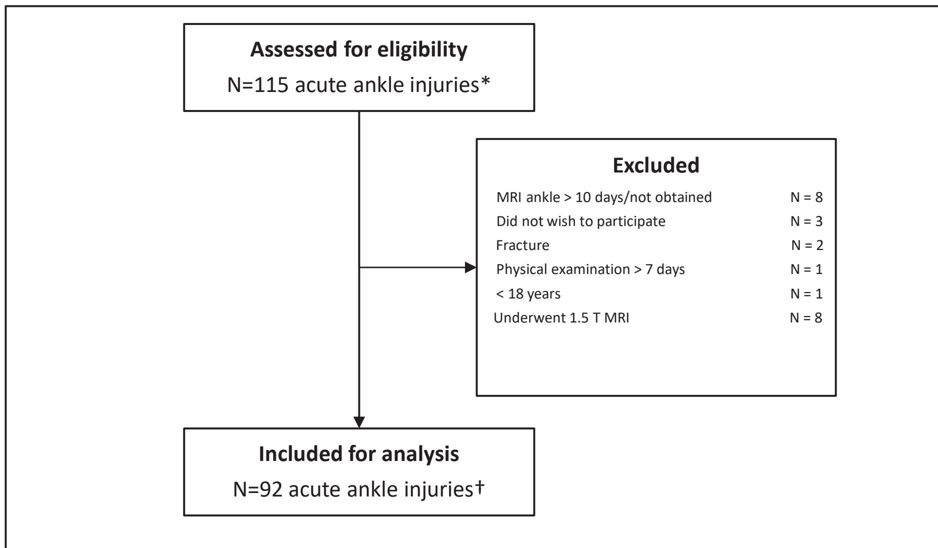
Reliability was considered poor if <0, slight 0–0.20, fair 0.21–0.40, moderate 0.41–0.60, substantial 0.61–0.80 and almost perfect if 0.81–1.00.[13] Statistical analysis was performed using Statistical Package for Social Sciences (SPSS version 21.0, Chicago, IL). Weighted agreement was calculated using Stata Statistical Software, Release 11 (College Station, TX; StataCorp LP).

RESULTS

Baseline characteristics

Between September 2016 and September 2018, a total of 115 acute ankle injuries (110 athletes) were assessed for eligibility. (figure 4) Ninety-two ankles were included. Of these 92 imaged acute ankle injuries, 4 were subsequent contra-lateral ankle injuries and 1 case of re-injury (>1 year). The median age at time of injury was 23 years (IQR 20-27), with a range from 18 to 42 years. The median time from injury to MRI was 3 days (IQR 1-5). Of the 87 included athletes, 47% played football, 14% volleyball, 14% basketball, 11% futsal, 5% athletics and 7% participated in other sports.

Figure 4 Flowchart



*In 110 athletes; † In 87 athletes

Grading of ligamentous complexes

The distribution of acute ligamentous complex lesions (Schneck grades 1-3) as graded by both radiologists, ranged from: lateral complex 72.8&-87.0%; syndesmosis complex 18.5&-68.5%; deep deltoid complex 4.4%-62.0%; superficial deltoid complex 5.4%-43.5%. (Table 2; Supplementary appendix) Intrarater and interrater reliability of the Schneck grading system for the three ligamentous complexes was, respectively, moderate to almost perfect (K= 0.51-0.89) and slight to moderate (K = 0.14-0.47).

Table 2 Intrarater and interrater reliability of grading ligamentous complexes and individual ligaments according the four grade Schneck grading system and classification of syndesmosis injury according the four grade Sikka classification system.

	Intrarater					Interrater				
	N (lesions)		***Kappa (95% CI)***	***Landis & Koch***	***Weighted Agreement***	***N (lesions)***		***Kappa (95% CI)***	***Landis & Koch***	***Weighted Agreement***
	R1a	R1b				R1a	R2			
Schneck grading of ligamentous complexes										
Lateral complex	67	67	0.76 (0.65-0.86)	Substantial	88.77%	67	80	0.47 (0.34-0.60)	Moderate	76.81%
Deltoid complex	10	8	0.51 (0.18-0.84)	Moderate	94.57%	10	63	0.14 (0.04-0.24)	Slight	68.84%
- Superficial	5	6	0.65 (0.30-1.00)	Substantial	97.83%	5	40	0.19 (0.03-0.35)	Slight	80.80%
- Deep	6	4	0.42 (-0.03-0.87)	Moderate	96.38%	6	57	0.07 (-0.03-0.16)	Slight	72.83%
Syndesmosis complex	18	17	0.89 (0.80-0.99)	Almost perfect	97.10%	18	63	0.37 (0.23-0.50)	Fair	71.74%
Sikka classification										
Syndesmosis	16	14	0.95 (0.90-1.00)	Almost perfect	99.18%	16	42	0.51 (0.37-0.66)	Moderate	89.40%
Scheck grading of individual ligaments										
Lateral ankle ligaments										
- ATFL	66	67	0.73 (0.62-0.84)	Substantial	87.68%	66	77	0.55 (0.43-0.68)	Moderate	80.07%
- CFL	46	46	0.62 (0.49-0.75)	Substantial	84.78%	46	76	0.31 (0.20-0.41)	Fair	63.41%
- PTFL	2	0	N/A	N/A	97.83%	2	25	0.14 (-0.05-0.33)	Slight	84.78%
Superficial deltoid ligaments										
- TN	4	5	0.56 (0.10-1.00)	Moderate	97.83%	4	33	0.16 (0.02-0.30)	Slight	83.70%
- TS	5	5	0.69 (0.35-1.00)	Substantial	98.19%	5	32	0.24 (0.06-0.42)	Fair	86.59%
- TC	3	2	0.32 (-0.19-0.83)	Fair	97.83%	3	35	0.07 (-0.05-0.19)	Slight	82.97%
- PT	3	2	0.38 (-0.17-0.94)	Fair	96.74%	3	25	0.01 (-0.08-0.10)	Slight	80.98%

Table 2 Continued

	Intrarater					Interrater				
	N (lesions)		***Kappa (95% CI)***	***Landis & Koch***	***Weighted Agreement***	***N (lesions)***		***Kappa (95% CI)***	***Landis & Koch***	***Weighted Agreement***
	R1a	R1b				R1a	R2			
Deep deltoid ligaments										
- ATT	6	3	0.48 (0.02-0.95)	Moderate	97.10%	6	54	0.07 (-0.02-0.17)	Slight	73.91%
- PTT	2	3	0.27 (-0.20-0.74))	Fair	97.28%	2	31	0.06 (-0.02-0.14)	Slight	85.87%
Syndesmosis ligaments										
- AITFL	18	17	0.89 (0.80-0.99)	Almost perfect	97.10%	18	63	0.36 (0.22-0.49)	Fair	71.74%
- IOL	12	10	0.64 (0.43-0.86)	Substantial	93.48%	12	26	0.56 (0.39-0.73)	Moderate	89.13%
- IOM	7	13	0.63 (0.40-0.87)	Substantial	93.48%	7	17	0.53 (0.32-0.73)	Moderate	92.93%
- PITFL	10	9	0.94 (0.87-1.00)	Almost perfect	99.28%	10	4	0.45 (0.16-0.75)	Moderate	92.93%
- TTFL	2	0	N/A	N/A	98.55%	2	2	-0.02 (-0.04-0.00)	Poor	96.74%

The total valid lesions for both radiologists (R1a, R1b R2) out of an overall total of 92 MR scans are presented (*N*). Reliability for grading (Schneck) and classification (Sikka) are presented as weighted-kappa (K) and weighted agreement. All values are presented with 95% confidence interval (95%CI); anterior talofibular ligament (ATFL); calcaneofibular ligament (CFL); posterior talofibular ligament (PTFL); tibionavicular (TN); tibiospring (TS); tibiocalcaneal (TC); posterior tibiotalar (PT); deep anterior tibiotalar (ATT); deep posterior tibiotalar (PTT); anteroinferior tibiofibular ligament (AITFL); interosseous ligament (IOL); interosseous membrane (IOM); posteroinferior tibiofibular ligament (PITFL); transverse tibiofibular ligament (TTFL); not applicable (N/A)

Table 3 Dichotomisation of Schneck grading system for (1) presence vs absence of acute lesions and (2) presence vs absence of complete dicontinuity of the individual ankle ligaments.

	Intrarater					*Interrater*				
	N (lesions)		***Kappa (95% CI)***	***Landis & Koch***	***Agreement***	***N (lesions)***		***Kappa (95% CI)***	***Landis & Koch***	***Agreement***
	R1a	R1b				R1a	R2			
Presence of acute ligamentous lesions										
Lateral ankle complex	67	67	0.73 (0.57-0.89)	Substantial	89.10%	67	80	0.31 (0.10-0.53)	Fair	77.20%
- ATFL	66	67	0.70 (0.54-0.87)	Substantial	88.00%	66	77	0.35 (0.14-0.57)	Fair	77.20%
- CFL	46	46	0.61 (0.45-0.77)	Substantial	80.40%	46	76	0.26 (0.11-0.41)	Fair	63.00%
- PTFL	2	0	N/A	N/A	97.80%	2	25	0.11 (-0.03-0.26)	Slight	75.00%
Superficial deltoid complex	5	6	0.52 (0.15-0.89)	Moderate	94.60%	5	40	0.14 (0.03-0.25)	Slight	62.00%
- TN	4	5	0.42 (0.00-0.83)	Moderate	94.60%	4	33	0.15 (0.02-0.29)	Slight	68.50%
- TS	5	5	0.58 (0.20-0.95)	Moderate	95.70%	5	32	0.20 (0.04-0.35)	Slight	70.70%
- TC	3	2	0.38 (‘-0.17-0.94)	Fair	96.70%	3	35	0.05 (-0.05-0.15)	Slight	63.00%
- PT	3	2	0.38 (-0.17-0.94)	Fair	96.70%	3	25	0.01 (-0.11-0.13)	Slight	71.70%
Deep deltoid complex	6	4	0.37 (-0.03-0.76)	Fair	93.50%	6	57	0.05 (-0.03-0.12)	Slight	42.40%
- ATT	6	3	0.42 (0.01-0.83)	Moderate	94.60%	6	54	0.06 (-0.02-0.14)	Slight	45.70%
- PTT	2	3	0.38 (-0.17-0.94)	Moderate	96.70%	2	31	0.08 (-0.03-0.19)	Slight	68.50%
Syndesmosis complex	18	17	0.82 (0.67-0.97)	Almost perfect	94.60%	18	63	0.17 (0.06-0.27)	Slight	48.90%
- AITFL	18	17	0.82 (0.67-0.97)	Almost perfect	94.60%	18	63	0.17 (0.06-0.27)	Slight	48.90%
- IOL	12	10	0.69 (0.46-0.92)	Substantial	93.50%	12	26	0.49 (0.29-0.69)	Moderate	82.60%
- IOM	7	13	0.67 (0.42-0.91)	Substantial	93.50%	7	17	0.53 (0.29-0.78)	Moderate	89.10%
- PITFL	10	9	0.94 (0.83-1.00)	Almost perfect	98.90%	10	4	0.54 (0.23-0.86)	Moderate	93.50%
- TTFL	2	0	N/A	N/A	97.80%	2	2	-0.02 (-0.04-0.00)	Poor	95.70%
Presence of complete discontinuity										
Lateral ankle complex	39	36	0.71 (0.56-0.85)	Substantial	85.90%	39	55	0.49 (0.33-0.66)	Moderate	73.90%

Table 3 Continued

	Intrarater					Interrater				
	N (lesions)		***Kappa (95% CI)***	***Landis & Koch***	***Agreement***	***N (lesions)***		***Kappa (95% CI)***	***Landis & Koch***	***Agreement***
	R1a	R1b				R1a	R2			
- ATFL	38	36	0.68 (0.53-0.84)	Substantial	84.80%	38	45	0.63 (0.47-0.79)	Substantial	81.50%
- CFL	17	9	0.56 (0.32-0.80)	Moderate	89.10%	17	49	0.29 (0.15-0.43)	Fair	63.00%
- PTFL	0	0	N/A	N/A	100.00%	0	0	N/A	N/A	100.00%
Superficial deltoid complex	1	1	1.00 (1.00-1.00)	Almost perfect	100.00%	1	5	0.32 (-0.16-0.80)	Fair	95.70%
- TN	1	1	1.00 (1.00-1.00)	Almost perfect	100.00%	1	3	-0.02 (-0.04-0.01)	Poor	95.70%
- TS	1	1	1.00 (1.00-1.00)	Almost perfect	100%	1	2	-0.02 (-0.04-0.01)	Poor	96.70%
- TC	0	0	N/A	N/A	100.00%	0	2	N/A	N/A	97.80%
- PT	0	0	N/A	N/A	100.00%	0	0	N/A	N/A	100.00%
Deep deltoid complex	2	1	0.66 (0.04-1.00)	Substantial	98.90%	2	5	-0.03 (-0.07-0.00)	Poor	92.40%
- ATT	2	1	0.66 (0.04-1.00)	Substantial	98.90%	2	5	-0.03 (-0.07-0.00)	Poor	92.40%
- PTT	0	0	N/A	N/A	100.00%	0	3	N/A	N/A	96.70%
Syndesmosis complex	13	12	0.95 (0.86-1.00)	Almost perfect	98.90%	13	14	0.87 (0.73-1.00)	Almost perfect	96.70%
- AITFL	13	12	0.95 (0.86-1.00)	Almost perfect	98.90%	13	13	0.91 (0.79-1.00)	Almost perfect	97.80%
- IOL	5	9	0.39 (0.05-0.72)	Fair	91.30%	5	12	0.43 (0.13-0.73)	Moderate	90.20%
- IOM	4	11	0.50 (0.19-0.81)	Moderate	92.40%	4	1	-0.02 (-0.05-0.01)	Poor	94.60%
- PITFL	0	1	N/A	N/A	98.90%	0	0	N/A	N/A	100.00%
- TTFL	1	0	N/A	N/A	98.90%	1	1	-0.01 (-0.03-0.00)	Poor	97.80%

The total valid lesions for both radiologists (R1a, R1b R2) out of an overall total of 92 MR scans are presented (*N*). Reliability for grading (Schneck) dichotomised for the presence of acute lesions or complete discontinuity are presented as unweighted-kappa (K) and overall agreement. All values are presented with 95% confidence interval (CI); anterior talofibular ligament (ATFL); calcaneofibular ligament (CFL); posterior talofibular ligament (PTFL); tibionavicular (TN); tibiospring (TS); tibiocalcaneal (TC); posterior tibiotalar (PT); deep anterior tibiotalar (ATT); deep posterior tibiotalar (PTT); anteroinferior tibiofibular ligament (AITFL); interosseous ligament (IOL); interosseous membrane (IOM); posteroinferior tibiofibular ligament (PITFL); transverse tibiofibular ligament (TTFL); not applicable (N/A)

Classification of syndesmotic injury

The distribution of the Sikka classification for both radiologists is reported in the supplementary appendix. (Table 2; supplementary appendix) Use of this classification system in patients with syndesmosis injury resulted in almost perfect intrarater reliability (k=0.95) and moderate interrater reliability (K=0.51).

Grading of individual ligaments

The distribution of acute ligamentous lesions (Schneck grades 1-3) per individual ligament, as graded by both radiologists, is detailed in the supplementary appendix. (Table 2, Supplementary appendix) Grading of the individual lateral ankle ligaments resulted in substantial intrarater reliability (K=0.62-0.73) and slight to moderate interrater reliability (K=0.14-0.55). For the individual syndesmosis ligaments intrarater reliability ranged from substantial to almost perfect (K= 0.63-0.94) and interrater reliability ranged from poor to moderate (K=-0.02-0.56). Intrarater reliability for the deltoid ligaments ranged from fair to substantial (K= 0.27-0.69) and interrater reliability ranged from slight to fair (K=0.01-0.24).

Presence versus absence of acute ligamentous lesions

Acute ligamentous lesions (Schneck grades 1-3) were most frequently scored in the ATFL (71.7%-83.7%), CFL (50.0%-82.6%) and AITFL (18.5%-68.5%). (Table 3, Supplementary appendix) Grading of the ATFL and CFL for acute lesions of the individual ligaments resulted in substantial intrarater reliability (K=0.61-0.70) and fair interrater reliability (K=0.26-35), respectively. Almost perfect intrarater reliability (K=0.82) and slight interrater reliability was observed for acute lesions of the AITFL (K=0.17). Intrarater and interrater reliability of the ligamentous complexes ranged from fair to almost perfect (K=0.37-0.82) and slight to fair (K=0.05-0.31).

Presence versus absence of complete discontinuity:

Complete ligamentous discontinuity (Schneck grade 3) was scored most frequently in the ATFL (39.1%-48.9%), CFL (9.8%-53.3%) and AITFL (13.0%-14.1%). (Table 3; supplementary appendix) Moderate to substantial intrarater reliability was established for complete discontinuity of the ATFL and CFL (K=0.56-0.68) and interrater reliability ranged from fair to substantial (K=0.29-0.63). Almost perfect intrarater and interrater reliability was observed for the AITFL (K=0.91-0.95). Intrarater and interrater reliability of the ligamentous complexes ranged from substantial to almost perfect (K=0.66-1.00) and poor to moderate (K=-0.03-0.87).

DISCUSSION

In this study we reported the reliability of the Schneck grading system and the Sikka classification for acute ligamentous ankle injuries on 3T MRI. Grading of the ligamentous complexes according the Schneck grading system and classification of syndesmosis injury according the Sikka classification resulted in slight to almost perfect reliability. Grading of the individual ankle ligaments according the Schneck grading system resulted in limited reliability. When dichotomised for the presence or absence of complete discontinuity, the interrater reliability of the ATFL and AITFL improved to substantial and almost perfect, respectively.

Grading of ligamentous complexes; comparison with previous literature

For grading of acute ligamentous complex injuries, only two previous studies have reported on the diagnostic reliability of a standardised grading approach.[6,9] In a prospective study Gaebler et al. presented the diagnostic reliability of a grading approach to acute injury of the lateral ligamentous complex. Applied on 0.5 T and 1.0 T MRI, grading resulted in good intrarater reliability ($\kappa = 0.65$) and fair interrater reliability ($\kappa = 0.40$).[6] A more recent study by Roemer et al. reported almost perfect intrarater reliability ($\kappa = 0.88$, $\kappa = 0.94$, $\kappa = 0.81$, respectively) and moderate to almost perfect interrater reliability ($\kappa = 0.85$, $\kappa = 0.90$, $\kappa = 0.41$, respectively) for grading of acute and chronic injury of the three ligamentous complexes, which is comparable to our findings.[9]

Grading of individual ligaments; comparison with previous literature

For grading of all the individual ankle ligaments, no comparable study on acute ankle injuries has been published. For the individual lateral ankle ligaments, one study investigated the reliability of 3T MRI for acute injury of the ATFL.[14] In this study the diagnostic accuracy and diagnostic reliability for addition of the 'bright-rim sign' to the standard diagnostic criteria of ATFL injury were determined. Interrater reliability for acute injury of the ATFL varied widely, depending on the applied definition ($\kappa = 0.48$–0.93).

In chronic lateral ankle ligament injuries, two studies have investigated the reliability of scoring injury to the ATFL.[15,16] Kim et al reported excellent rater reliability (Intraclass Correlation Coefficient (ICC)=0.915) for detection of presence or absence of injury to the ATFL.[15] In contrast to our study, no grading of injury severity was applied. In another study, grading of chronic injury was reported in a cohort of patients with chronic lateral ankle instability.[16] Grading on a four-grade scale for chronic injury resulted in substantial intrarater reliability (K 0.68-0.75) and moderate to almost perfect interrater reliability (K 0.55-0.87).

For acute deltoid injury the interrater reliability on 3T MRI has been reported in one study.[8] In this study, diagnostic reliability of MRI was investigated in a cohort of patients with lateral malleolar fractures secondary to a Supination-External Rotation trauma. The interrater reliability for partial and complete discontinuity of the deep deltoid ligaments ranged from fair to moderate (k = 0.46; k = 0.22), which is better than that observed in our cohort. In addition, the increased prevalence of deltoid injury in this cohort could potentially have decreased the reported kappa-values.[12]

For syndesmotic injuries, three previous studies have reported on diagnostic reliability of MRI.[7,17,18] The main difference with our population is that these studies only included patients with MRI-confirmed syndesmosis injury or with acute ankle fractures and thus an increased prevalence. As increased prevalence comes with high chance agreement, the reported kappa values for syndesmotic injury might be lower than the true kappa value in a non-selected population.[12]

In the study by Hermans et al. patients with an acute ankle fracture underwent 1.5 T MRI.[17] Grading of acute syndesmosis injury demonstrated substantial and almost perfect interobserver reliability for the AITFL (K=0.61) and PITFL (K=0.83). Addition of a 45° oblique MRI-plane improved the interrater reliability for the AITFL to almost perfect (K=0.92). As our multi-plane MRI-sequence lacked such a plane, the addition could hypothetically further improve the diagnostic reliability for low-grade injuries of the AITFL.

Presence versus absence of complete discontinuity:

In daily clinical practice, the presence of peri-ligamentous oedema or partial discontinuity is less consequential, as the decision for surgical intervention is based on the presence of complete ligamentous discontinuity.[19,20] Simplified scoring for the presence of complete discontinuity or acute lesions might therefore be more clinically relevant in this setting. Therefore, the four-grade Schneck grading was dichotomised for presence of acute lesions and presence of complete discontinuity. This resulted in improved interrater reliability for complete discontinuity of the ATFL (substantial) and AITFL (almost perfect). As complete discontinuity of these two ligaments has major ramifications in selected patients (e.g. athletes), the improved reliability of dichotomised grading might be preferential in the clinical setting.

Strength and Limitations

To our knowledge, this study is the largest prospective cohort study on diagnostic reliability of grading acute injuries of all three ligamentous complexes. Its strength lies in its prospective design, broad inclusion criteria (all acute ankle injuries) and use of 3T MRI. Despite these facts, the study has some limitations. First, the reported

reliability of the deltoid ligaments and posterior syndesmosis ligaments (PITFL and TTFL) should be interpreted with caution as the low prevalence of injury potentially influenced the k-values and corresponding confidence intervals.[12] An even larger cohort of athletes might improve the obtained k-values and narrow the confidence interval further. Secondarily, although discrepancies in MRI grading are inherent, considerable bias was observed for the dichotomisation strategy in which ligaments were graded either normal (grade 0) or as having an acute lesion (grade 1-3). The bias indices normalised for the dichotomisation strategy in which ligaments were either not completely discontinuous (grade 0-2) or completely discontinuous (grade 3). This suggests a bias of the second radiologist towards scoring low-grade injuries. Potentially, increased interrater reliability could have been achieved with a more elaborate calibration session. However, the limited calibration of both radiologists should be considered a strength of this study, as it represents daily clinical practice.

Future research should aim to correlate grading of injury severity with return to play prognosis after acute ligamentous ankle injuries. Application of the current available grading systems on 3T MRI is insufficiently reliable for this purpose. Dichotomised scoring for complete discontinuity of ankle ligaments and additional (angulated) MR-planes could potentially improve interrater reliability; however, additional research is required to substantiate these claims.

Implications for clinical practice

Dichotomised grading (absence or presence of complete discontinuity) of the ATFL and AITFL resulted in substantial to almost perfect interrater reliability. Therefore, when interpreting MRI results of an acute ligamentous ankle injury, reported presence of complete discontinuity of the ATFL and AITFL can be considered reliable. Dichotomised grading (absence or presence of complete discontinuity) of the CFL, resulted in fair interrater reliability. Thus, reported discontinuity of the CFL should be interpreted with caution. In clinical practice this means that MRI can guide treatment of ligamentous ankle injuries, based on the presence of complete discontinuity of the ATFL and AITLF only. In clinical practice this means that MR grading can guide treatment based on complete discontinuity of the ATFL and AITFL. This implies that MR imaging can reliably differentiate acute ankle injuries with and without syndesmotic involvement. Since the AITFL is the first syndesmotic ligament to be injured, a prerequisite for syndesmotic instability is complete discontinuity of the AITFL.[21] MR imaging could therefore aid the identification of patients, with an increased probability of syndesmotic instability (e.g. torn AITFL) for further diagnostic work-up (e.g. arthroscopy).[22] The use of MR imaging in the diagnosis of acute ligamentous ankle injuries can therefore be considered most useful in those patients with increased probability of syndesmosis injury.

Conclusion

In athletes, grading of the three major ligamentous complexes and the individual ankle ligaments according the Schneck grading system using 3T MRI resulted in limited reliability. When dichotomised for the presence of complete discontinuity, the interrater reliability of the Schneck grading system improved to substantial and almost perfect for the ATFL and AITFL, respectively. Classification of syndesmosis injury according the Sikka classification resulted in moderate interrater reliability.

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Supplementary appendix Intrarater and interrater reliability of (1) grading ligamentous complexes and individual ligaments according the four grade Schneck grading system, (2) classification of syndesmosis injury according the four grade Sikka classification system, dichotomisation of Schneck grading system for (3) presence vs absence of acute lesions and (4) presence vs absence of complete dicontinuity of the individual ankle ligaments.

	Intrarater								*Interrater*							
	N (lesions)		***Kappa (95% CI)***	***Landis & Koch***	***Weighted Agreement***	***Agree-ment***	***PI***	***BI***	***N (lesions)***		***Kappa (95% CI)***	***Landis & Koch***	***Weighted Agreement***	***Agree-ment***	***PI***	***BI***
	R1a	R1b							R1a	R2						
Schneck grading of ligamentous complexes																
Lateral complex	67	67	0.76 (0.65-0.86)	Substantial	88.77%				67	80	0.47 (0.34-0.60)	Moderate	76.81%			
- Grade 1	15	17							15	9						
- Grade 2	13	14							13	16						
- Grade 3	39	36							39	55						
Deltoid complex	10	8	0.51 (0.18-0.84)	Moderate	94.57%				10	63	0.14 (0.04-0.24)	Slight	68.84%			
- Superficial	5	6	0.65 (0.30-1.00)	Substantial	97.83%				5	40	0.19 (0.03-0.35)	Slight	80.80%			
- Grade 1	2	4							2	23						
- Grade 2	2	1							2	12						
- Grade 3	1	1							1	5						
- Deep	6	4	0.42 (-0.03-0.87)	Moderate	96.38%				6	57	0.07 (-0.03-0.16)	Slight	72.83%			
- Grade 1	3	2							3	41						
- Grade 2	1	1							1	11						
- Grade 3	2	1							2	5						
Syndesmosis complex	18	17	0.89 (0.80-0.99)	Almost perfect	97.10%				18	63	0.37 (0.23-0.50)	Fair	71.74%			
- Grade 1	2	3							2	21						
- Grade 2	3	2							3	28						
- Grade 3	13	12							13	14						

Supplementary appendix Continued

	Intrarater								Interrater							
	***N* (lesions)**		***Kappa* (95% CI)**	***Landis & Koch***	***Weighted Agreement***	***Agree-ment***	***PI***	***BI***	***N* (lesions)**		***Kappa* (95% CI)**	***Landis & Koch***	***Weighted Agreement***	***Agree-ment***	***PI***	***BI***
	R1a	R1b							R1a	R2						
Sikka classification of syndesmotic injury																
Syndesmosis	16	14	0.95 (0.90-1.00)	Almost perfect	99.18%				16	42	0.51 (0.37-0.66)	Moderate	89.40%			
- Grade I	5	2							5	26						
- Grade II	2	3							2	13						
- Grade III	8	8							8	2						
- Grade IV	1	1							1	1						
Scheck grading of individual ligaments																
Lateral ankle ligaments																
- ATFL	66	67	0.73 (0.62-0.84)	Substantial	87.68%				66	77	0.55 (0.43-0.68)	Moderate	80.07%			
- Grade 1	16	22							16	14						
- Grade 2	12	9							12	18						
- Grade 3	38	36							38	45						
- CFL	46	46	0.62 (0.49-0.75)	Substantial	84.78%				46	76	0.31 (0.20-0.41)	Fair	63.41%			
- Grade 1	12	14							12	9						
- Grade 2	17	23							17	18						
- Grade 3	17	9							17	49						
- PTFL	2	0	N/A	N/A	97.83%				2	25	0.14 (-0.05-0.33)	Slight	84.78%			
- Grade 1	0	0							0	20						
- Grade 2	2	0							2	5						
- Grade 3	0	0							0	0						

Supplementary appendix Continued

	Intrarater								Interrater							
	N (lesions)		***Kappa (95% CI)***	***Landis & Koch***	***Weighted Agreement***	***Agree-ment***	***PI***	***BI***	***N (lesions)***		***Kappa (95% CI)***	***Landis & Koch***	***Weighted Agreement***	***Agree-ment***	***PI***	***BI***
	R1a	R1b							R1a	R2						
Superficial deltoid ligaments																
- TN	4	5	0.56 (0.10-1.00)	Moderate	97.83%				4	33	0.16 (0.02-0.30)	Slight	83.70%			
- Grade 1	2	4							2	19						
- Grade 2	1	0							1	11						
- Grade 3	1	1							1	3						
- TS	5	5	0.69 (0.35-1.00)	Substantial	98.19%				5	32	0.24 (0.06-0.42)	Fair	86.59%			
- Grade 1	2	3							2	22						
- Grade 2	2	1							2	8						
- Grade 3	1	1							1	2						
- TC	3	2	0.32 (-0.19-0.83)	Fair	97.83%				3	35	0.07 (-0.05-0.19)	Slight	82.97%			
- Grade 1	2	2							2	23						
- Grade 2	1	0							1	10						
- Grade 3	0	0							0	2						
- PT	3	2	0.38 (-0.17-0.94)	Fair	96.74%				3	25	0.01 (-0.08-0.10)	Slight	80.98%			
- Grade 1	3	2							3	16						
- Grade 2	0	0							0	9						
- Grade 3	0	0							0	0						
Deep deltoid ligaments																
- ATT	6	3	0.48 (0.02-0.95)	Moderate	97.10%				6	54	0.07 (-0.02-0.17)	Slight	73.91%			
- Grade 1	3	2							3	38						
- Grade 2	1	0							1	11						
- Grade 3	2	1							2	5						

Supplementary appendix Continued

	Intrarater								Interrater							
	***N* (lesions)**		***Kappa* (95% CI)**	***Landis & Koch***	***Weighted Agreement***	***Agree-ment***	***PI***	***BI***	***N* (lesions)**		***Kappa* (95% CI)**	***Landis & Koch***	***Weighted Agreement***	***Agree-ment***	***PI***	***BI***
	R1a	R1b							R1a	R2						
- PTT	2	3	0.27 (-0.20-0.74)	Fair	97.28%				2	31	0.06 (-0.02-0.14)	Slight	85.87%			
- Grade 1	1	2							1	25						
- Grade 2	1	1							1	3						
- Grade 3	0	0							0	3						
Syndesmosis ligaments																
- AITFL	18	17	0.89 (0.80-0.99)	Almost perfect	97.10%				18	63	0.36 (0.22-0.49)	Fair	71.74%			
- Grade 1	2	3							2	22						
- Grade 2	3	2							3	28						
- Grade 3	13	12							13	13						
- IOL	12	10	0.64 (0.43-0.86)	Substantial	93.48%				12	26	0.56 (0.39-0.73)	Moderate	89.13%			
- Grade 1	2	0							2	11						
- Grade 2	5	1							5	3						
- Grade 3	5	9							5	12						
- IOM	7	13	0.63 (0.40-0.87)	Substantial	93.48%				7	17	0.53 (0.32-0.73)	Moderate	92.39%			
- Grade 1	0	1							0	4						
- Grade 2	3	1							3	12						
- Grade 3	4	11							4	1						
- PITFL	10	9	0.94 (0.87-1.00)	Almost perfect	99.28%				10	4	0.45 (0.16-0.75)	Moderate	92.93%			
- Grade 1	1	0							1	2						
- Grade 2	9	8							9	2						
- Grade 3	0	1							0	0						

Supplementary appendix Continued

	Intrarater								Interrater							
	***N* (lesions)**		***Kappa* (95% CI)**	***Landis & Koch***	***Weighted Agreement***	***Agree-ment***	***PI***	***BI***	***N* (lesions)**		***Kappa* (95% CI)**	***Landis & Koch***	***Weighted Agreement***	***Agree-ment***	***PI***	***BI***
	R1a	R1b							R1a	R2						
- TTFL	2	0	N/A	N/A	98.55%				2	2	-0.02 (-0.04-0.00)	Poor	96.74%			
- Grade 1	1	0							1	0						
- Grade 2	0	0							0	1						
- Grade 3	1	0							1	1						
Presence of acute ligamentous lesions																
Lateral ankle ligaments	67	67	0.73 (0.57-0.89)	Substantial		89.10%	0.46	0.00	67	80	0.31 (0.10-0.53)	Fair		77.20%	0.60	0.14
- ATFL	66	67	0.70 (0.54-0.87)	Substantial		88.00%	0.45	0.01	66	77	0.35 (0.14-0.57)	Fair		77.20%	0.55	0.12
- CFL	46	46	0.61 (0.45-0.77)	Substantial		80.40%	0.00	0.00	46	76	0.26 (0.11-0.41)	Fair		63.00%	0.33	0.33
- PTFL	2	0	N/A	N/A		97.80%	0.98	-0.02	2	25	0.11 (-0.03-0.26)	Slight		75.00%	0.71	0.25
Superficial deltoid ligaments	5	6	0.52 (0.15-0.89)	Moderate		94.60%	0.88	0.01	5	40	0.14 (0.03-0.25)	Slight		62.00%	0.51	0.38
- TN	4	5	0.42 (0.00-0.83)	Moderate		94.60%	0.90	0.01	4	33	0.15 (0.02-0.29)	Slight		68.50%	0.60	0.32
- TS	5	5	0.58 (0.20-0.95)	Moderate		95.70%	0.89	0.00	5	32	0.20 (0.04-0.35)	Slight		70.70%	0.60	0.29
- TC	3	2	0.38 (-0.17-0.94)	Fair		96.70%	0.95	-0.01	3	35	0.05 (-0.05-0.15)	Slight		63.00%	0.59	0.35
- PT	3	2	0.38 (-0.17-0.94)	Fair		96.70%	0.95	-0.01	3	25	0.01 (-0.11-0.13)	Slight		71.70%	0.70	0.24
Deep deltoid ligaments	6	4	0.37 (-0.03-0.76)	Fair		93.50%	0.89	-0.02	6	57	0.05(-0.03-0.12)	Slight		42.40%	0.32	0.55
- ATT	6	3	0.42 (0.01-0.83)	Moderate		94.60%	0.90	-0.03	6	54	0.06 (-0.02-0.14)	Slight		45.70%	0.35	0.52
- PTT	2	3	0.38 (-0.17-0.94)	Fair		96.70%	0.95	0.01	2	31	0.08 (-0.03-0.19)	Slight		68.50%	0.64	0.32
Syndesmosis ligaments	18	17	0.82 (0.67-0.97)	Almost perfect		94.60%	0.62	-0.01	18	63	0.17 (0.06-0.27)	Slight		48.90%	0.12	0.49

Supplementary appendix Continued

	Intrarater								Interrater							
	***N* (lesions)**		***Kappa* (95% CI)**	**Landis & Koch**	**Weighted Agreement**	**Agree-ment**	**PI**	**BI**	***N* (lesions)**		***Kappa* (95% CI)**	**Landis & Koch**	**Weighted Agreement**	**Agree-ment**	**PI**	**BI**
	R1a	R1b							R1a	R2						
- AITFL	18	17	0.82 (0.67-0.97)	Almost perfect		94.60%	0.62	-0.01	18	63	0.17 (0.06-0.27)	Slight		48.90%	0.12	0.49
- IOL	12	10	0.69 (0.46-0.92)	Substantial		93.50%	0.76	-0.02	12	26	0.49 (0.29-0.69)	Moderate		82.60%	0.59	0.15
- IOM	7	13	0.67 (0.42-0.91)	Substantial		93.50%	0.78	0.07	7	17	0.53 (0.29-0.78)	Moderate		89.10%	0.74	0.11
- PITFL	10	9	0.94 (0.83-1.00)	Almost perfect		98.90%	0.79	-0.01	10	4	0.54 (0.23-0.86)	Moderate		93.50%	0.85	-0.07
- TTFL	2	0	N/A	N/A		97.80%	0.98	-0.02	2	2	-0.02 (-0.04-0.00)	Poor		95.70%	0.96	0.00
Presence of complete discontinuity																
Lateral ankle ligaments	39	36	0.71 (0.56-0.85)	Substantial		85.90%	0.18	-0.03	39	55	0.49 (0.33-0.66)	Moderate		73.90%	0.02	0.17
- ATFL	38	36	0.68 (0.53-0.84)	Substantial		84.80%	0.20	-0.02	38	45	0.63 (0.47-0.79)	Substantial		81.50%	0.10	0.08
- CFL	17	9	0.56 (0.32-0.80)	Moderate		89.10%	0.72	-0.09	17	49	0.29 (0.15-0.43)	Fair		63.00%	0.28	0.35
- PTFL	0	0	N/A	N/A		100.00%	1.00	0.00	0	0	N/A	N/A		100.00%	1.00	0.00
Superficial deltoid ligaments	1	1	1.00 (1.00-1.00)	Almost perfect		100.00%	0.98	0.00	1	5	0.32 (-0.16-0.80)	Fair		95.70%	0.93	0.04
- TN	1	1	1.00 (1.00-1.00)	Almost perfect		100.00%	0.98	0.00	1	3	-0.02 (-0.04-0.01)	Poor		95.70%	0.96	0.02
- TS	1	1	1.00 (1.00-1.00)	Almost perfect		100%	0.98	0.00	1	2	-0.02 (-0.04-0.01)	Poor		96.70%	0.97	0.01
- TC	0	0	N/A	N/A		100.00%	1.00	0.00	0	2	N/A	N/A		97.80%	0.98	0.02
- PT	0	0	N/A	N/A		100.00%	1.00	0.00	0	0	N/A	N/A		100.00%	1.00	0.00
Deep deltoid ligaments	2	1	0.66 (0.04-1.00)	Substantial		98.90%	0.97	-0.01	2	5	-0.03 (-0.07-0.00)	Poor		92.40%	0.92	0.03
- ATT	2	1	0.66 (0.04-1.00)	Substantial		98.90%	0.97	-0.01	2	5	-0.03 (-0.07-0.00)	Poor		92.40%	0.92	0.03
- PTT	0	0	N/A	N/A		100.00%	1.00	0.00	0	3	N/A	N/A		96.70%	0.97	0.03

Supplementary appendix Continued

	Intrarater								Interrater							
	***N* (lesions)**		***Kappa* (95% CI)**	***Landis & Koch***	***Weighted Agreement***	***Agree-ment***	***PI***	***BI***	***N* (lesions)**		***Kappa* (95% CI)**	***Landis & Koch***	***Weighted Agreement***	***Agree-ment***	***PI***	***BI***
	R1a	R1b							R1a	R2						
Syndesmosis ligaments	13	12	0.95 (0.86-1.00)	Almost perfect		98.90%	0.73	-0.01	13	14	0.87 (0.73-1.00)	Almost perfect		96.70%	0.71	0.01
- *AITFL*	13	12	0.95 (0.86-1.00)	Almost perfect		98.90%	0.73	-0.01	13	13	0.91 (0.79-1.00)	Almost perfect		97.80%	0.72	0.00
- *IOL*	5	9	0.39 (0.05-0.72)	Fair		91.30%	0.85	0.04	5	12	0.43 (0.13-0.73)	Moderate		90.20%	0.82	0.08
- *IOM*	4	11	0.50 (0.19-0.81)	Moderate		92.40%	0.84	0.08	4	1	-0.02 (-0.05-0.01)	Poor		94.60%	0.95	-0.03
- *PITFL*	0	1	N/A	N/A		98.90%	0.99	0.01	0	0	N/A	N/A		100.00%	1.00	0.00
- *TTFL*	1	0	N/A	N/A		98.90%	0.99	-0.01	1	1	-0.01 (-0.03-0.00)	Poor		97.80%	0.98	0.00

The total valid lesions for both radiologists (R1a, R1b R2) out of an overall total of 92 MR scans are presented (*N*). Reliability for grading (Schneck) and classification (Sikka) are presented as weighted-kappa (K) and weighted agreement. Reliability for grading (Schneck) dichotomised for the presence of acute lesions or complete discontinuity are presented as unweighted-kappa (K) and overall agreement. All values are presented with 95% confidence interval (CI); Prevalence Index (PI); Bias Index (BI) anterior talofibular ligament (ATFL); calcaneofibular ligament (CFL); posterior talofibular ligament (PTFL); tibionavicular (TN); tibiospring (TS); tibiocalcaneal (TC); posterior tibiotalar (PT); deep anterior tibiotalar (ATT); deep posterior tibiotalar (PTT); anteroinferior tibiofibular ligament (AITFL); interosseous ligament (IOL); interosseous membrane (IOM); posteroinferior tibiofibular ligament (PITFL); transverse tibiofibular ligament (TTFL); not applicable (N/A)

5

CHAPTER 6

Does involvement of the anterior syndesmosis affect the functional outcome of acute ligamentous ankle injuries?

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ABSTRACT

Objectives: to compare patient reported outcomes between acute ligamentous ankle injuries 1) without involvement of the anterior syndesmosis and 2) with involvement of the anterior syndesmosis (without clinical instability).

Methods: between September 2016 and December 2020 all athletes (≥18 years) with an acute ankle injury presenting within 7 days post-injury were screened for eligibility. Athletes with a frank fracture or unable to acquire 3T magnetic resonance imaging (MRI) within 10 days post-injury were excluded. Athletes with syndesmosis injuries classified as unstable or athletes who underwent surgery of the injured ankle within 1-year post-injury were excluded. After completing the diagnostic pathway, athletes were referred for criteria-based rehabilitation. Functional outcome questionnaires (Karlsson & Peterson and Foot and Ankle Outcome Score [FAOS]) were administered at 6 weeks, 6 months and 1-year post-injury.

Results: a total of 94 athletes were included. In 28 athletes (30%) the anterior syndesmosis was injured. In the first six weeks post-injury, median Karlsson & Peterson score improved from 37 (IQR 20.5-49) to 80 (IQR 70-90) for the group without involvement versus 35 (IQR 25-62) to 82 (IQR 72-87) for the group with involvement. FAOS sports improved similarly in both groups. During follow-up no statistically significant between group differences in functional outcome scores were observed at six weeks, six months and 1 year follow-up.

Conclusions: In athletes, acute ligamentous ankle injuries with involvement of the anterior syndesmosis ligament (MRI confirmed and without signs of clinical instability) are not associated with worse functional outcome at 6 weeks, 6 months, and 1-year post-injury compared to injuries without involvement

INTRODUCTION

Ankle ligament injuries are among the most common sports injuries.[1] Depending on the trauma mechanism, the lateral ankle ligaments, syndesmosis, medial ankle ligaments (or a combination thereof) may be injured. When the syndesmosis complex is involved, the anterior inferior tibiofibular ligament (AITFL) is the first to be injured.[2] Pain on palpation over the AITFL is observed in up to 40% of athletes presenting with an acute ankle sprain.[3] Magnetic Resonance Imaging (MRI) may reveal interstitial injury, partial discontinuity, or complete discontinuity of the AITFL.[4] Currently it is unknown whether involvement of the AITFL affects the prognosis of acute ligamentous ankle injuries.

Involvement of the AITFL often goes unrecognized as clinical examination in the acute setting can be challenging.[5,6] Management of injuries involving the AITFL is therefore often suggested to be comparable to that of other ligamentous ankle injuries (e.g. lateral ankle sprain). Rehabilitation typically consists of progressive weightbearing with the use of external support (e.g. brace or taping) and a supervised exercise program addressing strength, proprioception and functional deficits.[7–9] Despite comparable treatment it remains unknown whether the functional outcome of acute ligamentous ankle injuries is affected by interstitial injury, partial discontinuity, or complete discontinuity of the AITFL. Therefore, a study comparing patient reported outcome of acute ligamentous ankle injuries without AITFL involvement and with interstitial injury, partial discontinuity, or complete discontinuity of the AITFL confirmed with MRI is required.

The aim of this study was to compare the patient reported outcome between acute ligamentous ankle injuries 1) without involvement of the anterior syndesmosis ligament (AITFL) and 2) with interstitial injury, partial discontinuity, or complete discontinuity of the AITFL at baseline, 6 weeks, 6 months, and 1-year follow-up. Our hypothesis is that acute ligamentous ankle injuries involving the AITFL are associated with worse patient reported functional outcome than without AITFL involvement.

METHODS

Patients

In this prospective cohort study all adult athletes (≥18 years) presenting to the walk-in clinic of Aspetar Orthopaedic and Sports Medicine Hospital within 7 days after an acute ankle injury were included. For this study the term athlete was defined as a person who participated in sports at a professional or recreational level. Patients with a fracture or the inability to obtain a MR scan within 10 days post-injury were excluded. For this specific study patients who underwent surgery (including syndesmotic stabilization) of the injured ankle within 1-year post-injury were excluded. Thus, acute ankle injuries involving the AITFL (modified West Point I) and subsequent IOL/IOM (modified West Point IIa), without signs of clinical instability (e.g. normal deltoid ligament and negative squeeze test) were included.[2,10] Syndesmosis injuries involving the AITFL, IOL/IOM and classified as unstable (modified West Point ≥IIb) by a senior Orthopaedic Sports Medicine Surgeon (Pd'H) were excluded (e.g. deltoid injury and/or positive squeeze test and/or PITFL injury). Patients who did not respond to at least one of the follow-up questionnaires were excluded from analysis. All athletes provided written informed consent at time of inclusion. Ethical approval was obtained from the Anti-Doping Lab Qatar (IRB No. F2016000153).

Reference standard

All MR scans were obtained within 10 days post-injury using a 3.0 T MRI system (GE Discovery, GE Healthcare). The patient was positioned supine with their ankle placed in an 8-channel Foot & Ankle array. The imaging protocol has been described previously, but in short T1 weighted and Proton-Density Fat-Saturated [PD-FS] sequences were obtained in the sagittal plane, T2-weighted and PD-FS sequences in the transverse plane and PD-FS sequences in the coronal plane.[11]

MR grading

Blinded to clinical information two radiologists independently graded the four syndesmosis ligaments; (Anterior Tibiofibular ligament [AITFL], Interosseous ligament [IOL], Interosseous Membrane [IOM] and Posterior Tibiofibular ligament [PITFL]) using a previously described scoring form.[11] Ligaments were graded according the Schneck grading system; grade 0 normal, grade 1 interstitial injury (increased proton density and T2 signal inside the ligament without visualized fiber disruption); grade 2 partial discontinuity (partial discontinuity but preserved remnant fibers) and grade 3 complete discontinuity.[4] Due to fair to moderate interrater reliability, disagreement between radiologists regarding grading of individual ligaments was settled by discussion during a consensus meeting.[11]

Rehabilitation

Athletes underwent criteria-based rehabilitation at the Aspetar Department of Rehabilitation. The rehabilitation protocol constitutes four phases. (Supplementary rehabilitation protocol) Professional athletes were allowed to complete rehabilitation at their club under supervision of a National Sports Medicine Programme (NSMP) physiotherapist if they preferred.

Functional outcome questionnaire

At baseline (time of inclusion) a standardized questionnaire, containing an Arabic or English version of the Foot and Ankle Outcome Score (FAOS) and the Karlsson & Peterson scoring system was administered. Both the FAOS and Karlsson & Peterson questionnaires were translated by a bilingual speaker (O.A.). Before administration the hospital's Medical Translation Committee (consisting of three bilingual medical healthcare providers) evaluated the translation integrity, quality, and cultural adaptation of the questionnaire. The same questionnaire was administered at 6 weeks, 6 months, and 12 months post-injury. The FAOS is a 42-items questionnaire intended to evaluate symptoms and functional limitations of the foot and ankle using five subscales.[12] The total FAOS outcome score ranges from 0 (extreme problems) to 100 (no problems). The FAOS has previously been validated in patients undergoing lateral ligament reconstruction.[12] Construct validity demonstrated a moderate correlation with the Karlsson & Peterson score (r=0.58-0.67). High internal consistency (Crohnbach's alpha ≥0.88) and test-retest reliability (Spearman's correlation coefficient ≥0.85) were reported for the five FAOS subscales. For ankle and hindfoot surgery a Minimally Important Change (MIC) of 7 (symptoms subscale) to 38 points (sports subscale) has been reported.[13] The Karlsson & Peterson is a questionnaire intended to evaluate ankle joint function after lateral ligament injury. Points are given for eight different categories including functional stability, pain, swelling and stiffness. The total K&P score ranges from 0 (extreme problems) to a total maximum score of 90 (no problems). The K&P score has demonstrated a strong inverse correlation with ankle joint stability in the sagittal (r= -0.72) and frontal plane (r= -0.84).[14] Return to play was recorded in the questionnaire battery administered at 6 weeks, 6 months and 12 months (whichever questionnaire battery was closest to the time of return to play). Return to play (in days) was defined as when the athlete had completed full rehabilitation and was cleared to return to sport.

Statistical analysis

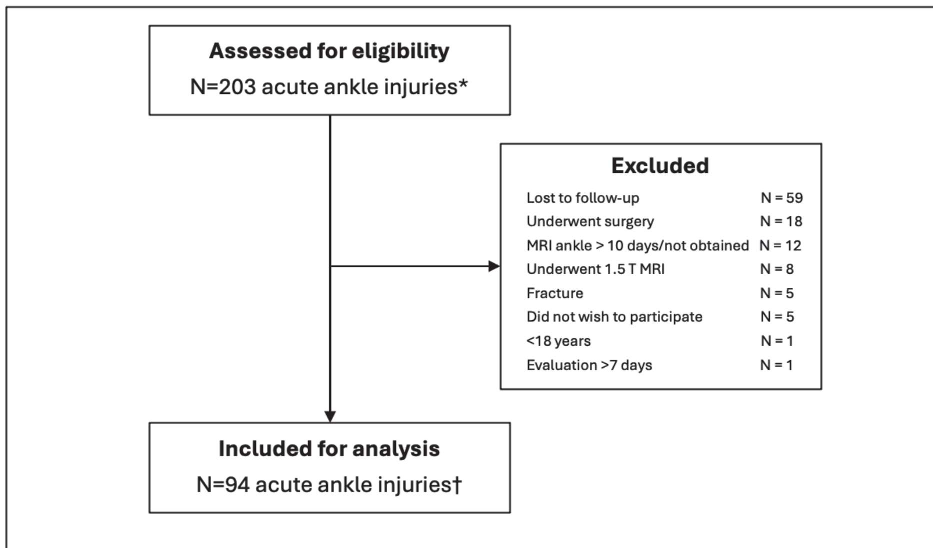
Statistical analysis was performed using SPSS software (V.21; IBM Corp). Descriptive statistics were used to report patient characteristics and injury distribution. Data distribution was assessed by visual inspection and the Shapiro-Wilk test. Included

patients were categorized into two groups 1A) acute ligamentous ankle injuries without injury of the AITFL and 1B) acute ligamentous ankle injuries with interstitial injury, partial discontinuity, or complete discontinuity of the AITFL. Two subset analyses were performed comparing ligamentous ankle injuries 2A) without involvement of the AITFL and 2B) with interstitial injury or partial discontinuity of the AITFL and 3A) without involvement of the AITFL and 3B) with interstitial injury of the AITFL. To compare FAOS and Karlsson & Peterson scores between groups at baseline, 6 weeks, 6 months and at 1 year the unpaired t-test or Mann-Whitney U test was used as appropriate. A linear mixed model was used to compare between group differences in FAOS and Karlsson & Peterson scores during the 1-year follow-up. Significance was set at $p<0.05$.

RESULTS

Between September 2016 and December 2020, a total of 203 acute ankle injuries were screened for eligibility. (Figure 1) For this analysis a total of 94 acute ankle injuries in 94 athletes were included. Of the 109 excluded ankle injuries a total of 18 patients were excluded for undergoing ankle surgery within one year after surgery. (Supplementary appendix 1) Most athletes were male (87%). The left ankle was involved in 54% of athletes. Of the included athletes 45% participated in football, 12% in volleyball, 11% in basketball, 9% in handball, 9% in futsal, 4% in athletics and 11% in other sports. Of the included athletes 63 (67%) participated in sports at a professional level. The median age at time of injury was 24 (IQR 20-29). Baseline clinical evaluation was performed a median 2 days (IQR 1-3) post-injury. MR scans were obtained after a median 3 days (IQR 2-5). Injury of the AITFL was observed in 28 patients (30%; 17 interstitial injury, 6 partial discontinuity, 5 complete discontinuity). (Supplementary appendix 2)

Figure 1 Flowchart for in-/exclusion



*In 194 athletes; † in 94 athletes

Baseline characteristics

Patient demographics at baseline and concomitant MR findings are reported in table 1. No statistically significant between group differences in demographics were observed. Lateral ligament injuries were present in 74% of the patients without injury

of the AITFL and 79% (p=0.80) of patients with injury of the AITFL. Medial ligament injury was observed more frequently in patients with injury of the AITFL (5% vs 21%; p=0.02). No injury of the lateral ankle ligaments or AITFL was observed in 18% of patients.

Table 1 Patient demographics and concomitant injuries at baseline.

	AITFL intact (N=66)	AITFL involvement (N=28)	P-value
Baseline characteristics			
Age (years)	23 (IQR 20-28)	26 (IQR 21.25-30)	0.16
Gender (male)	56/66 (85%)	26/28 (93%)	0.50
New/recurrent (recurrent)	18/66 (27%)	6/28 (21%)	0.62
Time to evaluation (days)	2 (IQR 1-3)	1.5 (IQR 1-2.75)	0.39
Time to MRI (days)	3 (IQR 2-5)	2.5 (IQR 1-4)	0.09
Concomitant injuries			
Lateral ankle ligaments	49/66 (74%)	22/28 (79%)	0.80
Medial ankle ligaments	3/66 (5%)	6/28 (21%)	**0.02**
Osteochondral injuries	1/66 (1.5%)	3/28 (11%)	0.08

Involvement of the anterior inferior tibiofibular ligament (AITFL) was defined as interstitial edema, partial discontinuity, or complete discontinuity; N total number of athletes.

Functional outcome at follow-up

Median Karlsson & Peterson and FAOS subscale scores at baseline, 6 weeks, 6 months and 1 year are detailed in table 2 and figure 2. Loss to follow-up was 22% at six weeks, 51% at six months and 55% at one year. No statistically significant between group difference in functional outcome scores were observed at each time-point when comparing the group with intact AITFL and the group with interstitial edema, partial discontinuity, or complete discontinuity of the AITFL. Mixed model analysis demonstrated no statistically significant difference between groups or any difference in improvement of functional outcome during the 1-year follow-up. (Table 3) Sub-analyses 1) excluding complete discontinuity of the AITFL and 2) excluding partial and complete discontinuity of the AITFL demonstrated similar results. (Supplementary appendix 3 and 4) The median return to play duration was 36 days (IQR 14-51; N=27/66) for athletes without involvement of the anterior syndesmosis and 41.5 days (IQR 32.3-54; N=10/28) in athletes with involvement of the anterior syndesmosis. There was no statistically significant difference between both groups (table 4).

Table 2 Median patient reported functional outcome scores at baseline, six weeks, six months and one year follow-up.

	N	AITFL intact	N	AITFL involvement	P-value
Baseline					
K&P score	60	37 (IQR 20.5-49)	25	35 (IQR 25-62)	0.44
FAOS symptoms	62	54 (IQR 39-71)	27	57 (IQR 43-86)	0.27
FAOS pain	62	47 (IQR 28-64.75)	26	59.5 (IQR 39.25-72.5)	0.14
FAOS ADL	61	62 (IQR 35-73.5)	26	65.5 (IQR 46.25-86.5)	0.14
FAOS sports	62	30 (IQR 5-47.5)	25	25 (IQR 5-77.5)	0.83
FAOS QOL	62	50 (IQR 29.5-69)	27	56 (IQR 31-81)	0.17
6 weeks					
K&P score	47	80 (IQR 70-90)	23	82 (IQR 72-87)	0.61
FAOS symptoms	50	89 (IQR 79-100)	23	93 (IQR 79-100)	0.97
FAOS pain	50	94 (IQR 86-100)	23	94 (IQR 89-100)	0.64
FAOS ADL	50	100 (IQR 97-100)	23	100 (IQR 99-100)	0.68
FAOS sports	50	90 (IQR 85-100)	23	90 (IQR 85-100)	0.95
FAOS QOL	50	88 (IQR 69-100)	23	88 (IQR 69-100)	0.87
6 months					
K&P score	33	90 (IQR 81-90)	12	86 (IQR 80.5-90)	0.30
FAOS symptoms	33	96 (IQR 84-100)	13	96 (IQR 87.5-100)	0.76
FAOS pain	33	100 (IQR 95.5-100)	13	100 (IQR 94-100)	0.94
FAOS ADL	33	100 (IQR 96.5-100)	13	100 (IQR 100-100)	0.15
FAOS sports	33	100 (IQR 90-100)	13	100 (IQR 92.5-100)	0.66
FAOS QOL	32	100 (IQR 88-100)	13	100 (IQR 84.5-100)	0.94
1 year					
K&P score	29	90 (IQR 85-90)	11	90 (IQR 85-90)	0.77
FAOS symptoms	31	100 (IQR 93-100)	11	100 (IQR 93-100)	0.96
FAOS pain	31	100 (IQR 97-100)	11	100 (IQR 97-100)	0.87
FAOS ADL	31	100 (IQR 100-100)	11	100 (IQR 99-100)	0.80
FAOS sports	31	100 (IQR 90-100)	11	95 (IQR 85-100)	0.32
FAOS QOL	31	100 (IQR 88-100)	11	100 (IQR 75-100)	0.59

AITFL involvement is defined as interstitial edema, partial discontinuity, or complete discontinuity. N total number of athletes, AITFL anterior inferior tibiofibular ligament, K&P Karlsson & Peterson, FAOS Foot and Ankle Outcome Score, ADL Activities of Daily Living, QOL Quality of Life, IQR Interquartile Range. The total K&P score ranges from 0 (extreme problems) to 90 (no problems). The FAOS subscale scores range from 0 (extreme problems) to 100 (no problems).

Figure 2 Boxplot of the median Karlsson & Peterson score and Foot and Ankle Outcome Score at 6 weeks, 6 months and 1 year follow-up.

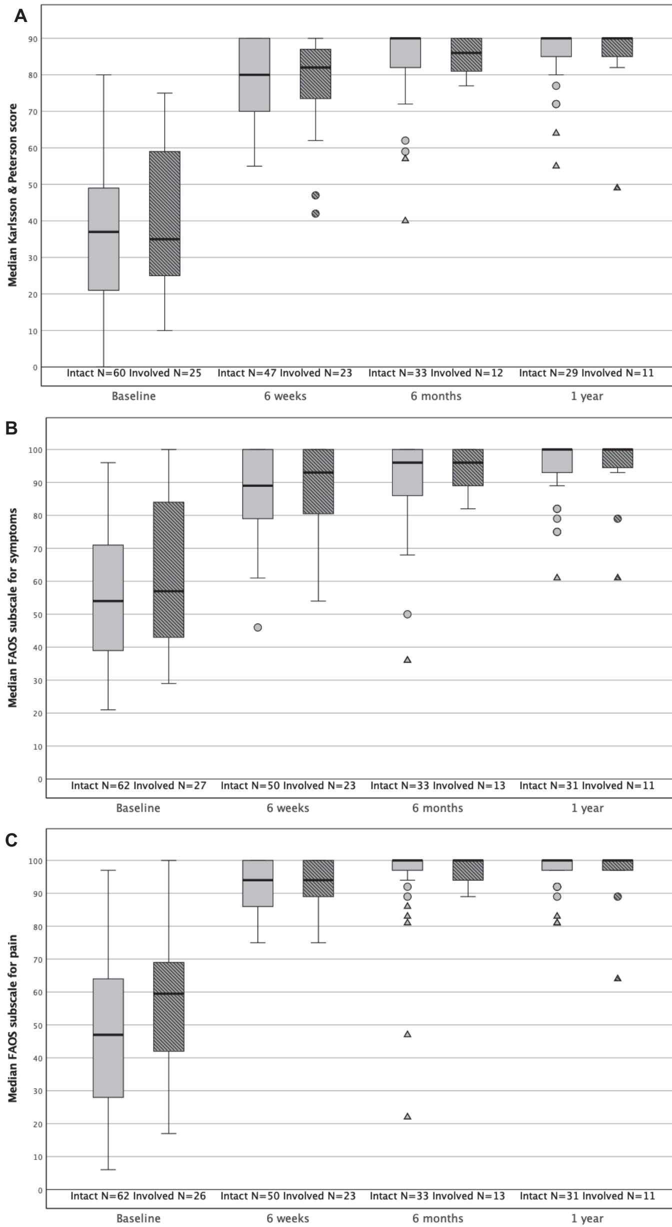
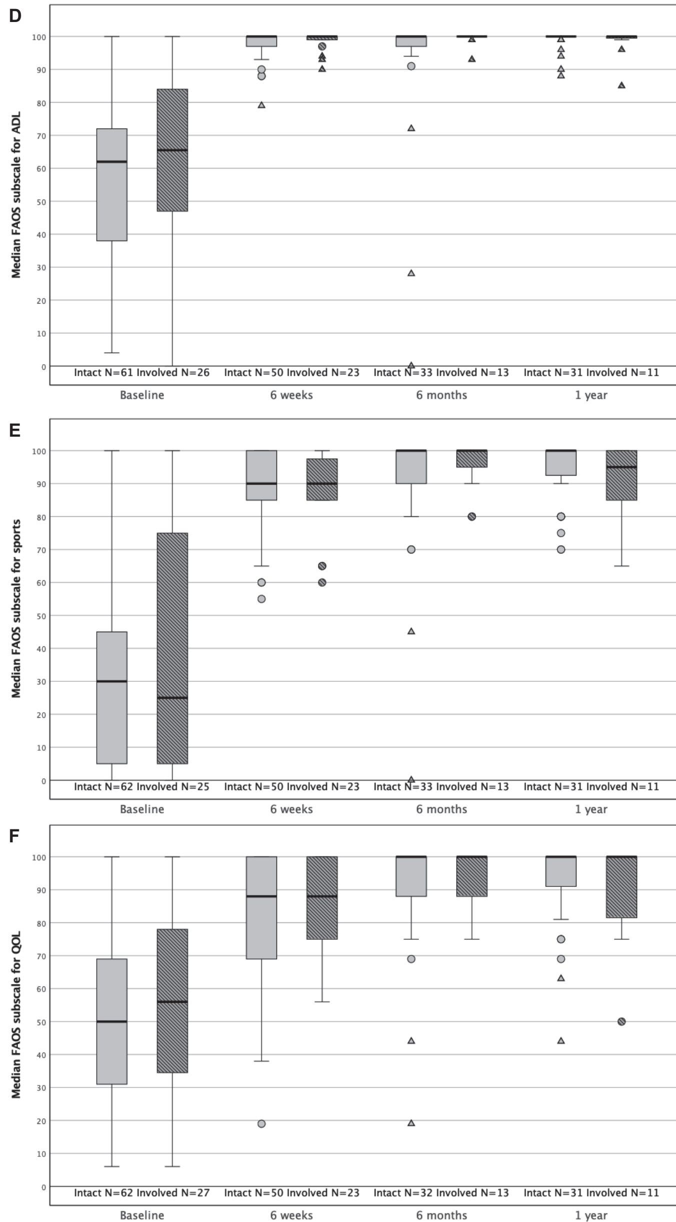


Figure 2 Continued



A) Karlsson & Peterson score (IQR) and Foot and Ankle Outcome Score (IQR); B) subscale for symptoms; C) subscale for pain; D) subscale for activities of daily living; E) subscale for sports, F) subscale for quality of life at 6 weeks, 6 months and 1 year follow-up for acute ligamentous ankle injuries with intact Anterior Inferior Tibiofibular Ligament (AITFL; light grey) compared to acute ankle injuries with interstitial edema, partial discontinuity, or complete discontinuity of the AITFL (diagonal lines in dark grey).

Table 3 Outcome of the linear mixed model for patient reported functional outcome during 1-year follow-up reported as beta-coefficient with corresponding 95% confidence interval.

	B-coefficient (CI 95%)	**P-value**
K&P score	-1.18 (-4.78-2.43)	0.52
FAOS symptoms	-1.23 (-5.18-2.72)	0.54
FAOS pain	-1.06 (-3.90-1.79)	0.46
FAOS ADL	-0.47 (-1.91-0.98)	0.52
FAOS sports	-0.18 (-4.29-3.93)	0.93
FAOS QOL	-2.12 (-7.08-2.84)	0.40

AITFL involvement is defined as interstitial edema, partial discontinuity, or complete discontinuity. N total number of athletes, AITFL anterior inferior tibiofibular ligament, K&P Karlsson & Peterson, FAOS Foot and Ankle Outcome Score, ADL Activities of Daily Living, QOL Quality of Life, CI 95% confidence interval. The total K&P score ranges from 0 (extreme problems) to 90 (no problems). The FAOS subscale scores range from 0 (extreme problems) to 100 (no problems).

Table 4 Median return to play duration (in days; with corresponding IQR) in athletes with an acute ankle injury with and without involvement of the anterior syndesmosis

AITFL intact (N=27/66)	**AITFL involvement (N=10/28)**	**P-value**
36 (IQR 14-51)	41.5 (IQR 32.3-54)	0.25

AITFL involvement is defined as interstitial edema, partial discontinuity, or complete discontinuity. N total number of athletes per group, AITFL anterior inferior tibiofibular ligament, IQR interquartile range

DISCUSSION

The most important finding in this study is that in athletes with an acute ligamentous ankle injury, involvement of the AITFL (modified West Point I-IIa) without signs of clinical instability (based on physical examination) yielded comparable functional outcomes at 6 weeks, 6 months, and 1-year compared to injuries without involvement when managed with the same criteria-based rehabilitation approach. When treated like a lateral ligament injury (e.g. supervised exercise program) involvement of the anterior syndesmosis did not affect functional outcome.

Functional outcome of anterior syndesmosis injury

Functional outcome of supervised rehabilitation for syndesmosis injury has only been described in one study.[15] In this prospective cohort study, including 96 West Point cadets with an acute ankle injury, 55% reported loss of function or presence of intermittent pain at 6 weeks and 40% reported residual symptoms at 6 months. The presence of syndesmosis injury was established to be the best predictor of chronic ankle dysfunction at 6 weeks and 6 months. These findings are in contrast with our study, as injury of the anterior syndesmosis did not seem to affect functional outcome during follow-up. This can possibly be attributed to the exclusion of syndesmosis injuries with clinical instability (modified West Point >IIB) in our cohort.[2] As current literature suggests a prolonged return to play for injuries of the anterior syndesmosis, future studies should focus on the functional outcome during the first six weeks post-injury.

6

Return to play after syndesmosis injury

Return to play after syndesmosis injury was evaluated in a recent systematic review.[16] In a sub-analysis, including a total of five studies (305 patients), conservative treatment of acute ligamentous ankle injuries demonstrated a prolonged return to play for syndesmotic injuries compared to lateral ligament injuries (40 days vs 4 days). These results are in stark contrast with our findings (42 days vs 36 days). A possible explanation could be the large within group variance observed in the current study, which might reflect a bias created by our clinical setting (secondary referral center). In a previous prospective cohort study including a total of 60 athletes, athletes with a lateral ligament injury (N=30) returned to play after a median of 15 days compared to a median 62 days for athletes with a syndesmosis injury (N=30).[17] However, this study did not explore the association between syndesmotic stability and time to return to play. In a retrospective cohort study of 36 NFL players an association between MR graded syndesmosis injury severity and increased number of missed games was observed.[18] Depending on injury severity, athletes missed between 0.25

games (isolated injury of the AITFL) up to ≥3 games (injury of the AITFL, IOL, PITFL and/or deltoid ligament). However, in this study there was no standardization of the rehabilitation protocol and three of the included players underwent surgery. Return to play after surgical treatment of unstable syndesmosis injuries (modified West Point ≥IIb) has been evaluated in previous studies and is usually prolonged compared to that of stable syndesmosis injuries.[2,10] We recommend future studies to examine the association between injury severity and time to return to play for stable syndesmosis injuries to enable better prediction of return to play.

Strength and limitations

This is the first study to compare patient reported functional outcome of acute ligamentous ankle injuries involving the anterior syndesmosis ligament (AITFL). Our prospective design, large cohort of recreational and professional athletes and use of MRI as reference standard contribute to the strength of this study as it allowed us to accurately differentiate between injury patterns and compare patient reported outcome in a population with high physical demands. A limitation of this study is the relatively high loss to follow-up with the risk of introducing selection bias. Furthermore, the modified West Point classification was used as an exclusion criterion. Although commonly used in daily clinical practice it has not been validated and was subject to the interpretation of clinical and MR findings by the senior Orthopaedic Sports Medicine Surgeon. In addition, the use of patient reported outcome measures which have not been validated for the current setting and patient group introduces the risk of bias by compromising validity and reliability. Finally, athletes were often unable to recall their exact return to play date which might have resulted in selection bias.

Clinical implications

The current pragmatic trial demonstrates that when the same criteria-based rehabilitation approach is applied in athletes with acute ligamentous ankle injuries, irrespective of involvement of the anterior syndesmosis (modified West Point I-IIa), comparable outcome at 6 weeks, 6 months and 1 year are reported. This information can be used in clinical practice to inform athletes and their medical support team on what to expect from the rehabilitation process after an injury of the anterior syndesmosis ligament. Future research may consider if a different rehabilitation approach in the presence of anterior syndesmosis injury can result in better outcomes. It is important to note that we did not compare the functional outcome of anterior syndesmosis injuries after conservative treatment with surgical stabilization of the syndesmosis.[10] This should be taken into consideration when extrapolating our results to a shared decision-making situation.

Conclusion

This study demonstrates that in athletes, acute ligamentous ankle injuries involving the anterior syndesmosis ligament (MR confirmed and without signs of clinical instability) are not associated with worse functional outcome at 6 weeks, 6 months, and 1-year post-injury compared to acute ligamentous ankle injuries without involvement when managed with the same criteria-based rehabilitation approach.

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Supplementary appendix 1 Patients excluded for undergoing surgery within 1-year post-injury.

ID	Injury mechanism	Physical examination	MRI syndesmosis	MRI Deltoid	Type of surgery
#8	Unknown	Sq pos; Tend 4 cm	AITFL/IOL gr 3; IOM/PITFL gr 2	Superficial gr 0; Deep gr 0	Syndesmotic fixation
#24	Eversion	Sq neg; Tend 3 cm	AITFL/IOL gr 3; PITFL gr 2	Superficial gr 0; Deep gr 0	Syndesmotic fixation
#34	Inversion	Sq pos; Tend 2 cm	AITFL gr 3; IOL/IOM gr 2	Superficial gr 0; Deep gr 0	Syndesmotic fixation
#53	Inversion	Sq pos; Tend 15 cm	-	Superficial gr 0; Deep gr 0	Broström + Deltoid repair
#57	Eversion/ER	Sq pos; Tend 8 cm	AITFL gr 3; IOL gr 2; IOM gr 3	Superficial gr 0; Deep gr 0	Syndesmotic fixation + Broström
#64	Inversion	Sq neg; Tend 20 cm	-	Superficial gr 0; Deep gr 0	Broström
#67	IR	Sq neg; Tend pos	-	Superficial gr 0; Deep gr 2	Broström
#71	Inversion	Sq pos; Tend 3 cm	AITFL/IOL gr 3; IOM gr 1; PITFL gr 2	Superficial gr 0; Deep gr 0	Syndesmotic fixation + Broström
#74	Inversion	Sq neg; Tend 2 cm	-	Superficial gr 0; Deep gr 0	Treatment of osteochondral defect
#80	Inversion	Sq neg; Tend neg	AITFL gr 3	Superficial gr 0; Deep gr 0	Syndesmotic fixation
#92	Inversion	Sq neg; Tend 10 cm	AITFL gr 3; IOL/IOM/PITFL gr 2	Superficial gr 0; Deep gr 0	Syndesmotic fixation
#94	Inversion/HPF	Sq pos; Tend 10 cm	AITFL gr 3; IOL/IOM gr 2	Superficial gr 0; Deep gr 0	Syndesmotic fixation
#99	Inversion	Sq neg; Tend 3 cm	AITFL/IOL gr 3; IOM/PITFL gr 2	Superficial gr 0; Deep gr 0	Syndesmotic fixation
#109	Eversion	Sq pos; Tend 5 cm	AITFL/IOL/IOM/PITFL gr 2	Superficial gr 0; Deep gr 0	Syndesmotic fixation + Broström
#112	Eversion/ER	Sq pos; Tend 5 cm	AITFL/IOL/IOM gr 3; PITFL gr 2	Superficial gr 3; Deep gr 0	Syndesmotic fixation + Broström
#130	Inversion	Sq neg; Tend 5 cm	AITFL gr 3; IOL/PITFL gr 1	Superficial gr 0; Deep gr 0	Excision of os trigonum
#141	Unknown	Sq pos; Tend neg	AITFL/IOM/IOL gr 3; PITFL gr 1	Superficial gr 0; Deep gr 0	Syndesmotic fixation
#165	Inversion	Sq pos; Tend 3 cm	AITFL/IOL gr 3; IOM gr 2; PITFL gr 3	Superficial gr 0; Deep gr 0	Syndesmotic fixation + Broström

Clinical description of patients who were excluded for undergoing surgery within 1-year post-injury; MRI Magnetic Resonance Imaging; Sq Squeeze test; Tend Tenderness over the syndesmosis; ER/IR external/internal rotation; HPF hyper plantar flexion; AITFL anterior inferior tibiofibular ligament; IOL/IOM Interosseous Ligament/Membrane; PITFL Posterior inferior Tibiofibular Ligament;

Supplementary appendix 2 Clinical description of the included acute ankle injuries with involvement (interstitial edema, partial discontinuity of complete discontinuity) of the Anterior Inferior Tibiofibular ligament.

ID	Injury mechanism	Physical Examination	MRI syndesmosis	MRI lateral	MRI deltoid	Treatment
#2	Inversion	Sq neg; Tend neg	AITFL gr 1	ATFL/CFL gr 3; PTFL gr 2	Superficial gr 0; Deep gr 0	Rehabilitation
#10	Inversion/IR/HPF	Sq pos; Tend 4 cm	AITFL gr 2	ATFL/CFL gr 3	Superficial gr 0; Deep gr 0	Ankle boot + Rehabilitation
#13	Inversion/Eversion	Sq pos; Tend 1 cm	AITFL gr 1	ATFL/CFL gr 1;	Superficial gr 0; Deep gr 0	Rehabilitation
#32	Inversion	Sq neg; Tend 1 cm	AITFL/IOL gr 2	ATFL gr 3; CFL gr 2;	Superficial gr 0; Deep gr 0	Ankle boot + Rehabilitation
#36	Inversion	Sq neg; Tend neg	AITFL/IOL gr 3; IOM/PITFL gr 2	ATFL/CFL gr 3;	Superficial gr 0; Deep gr 0	Rehabilitation
#39	Eversion	Sq pos; Tend neg	AITFL gr 2; IOL gr 1	ATFL gr 3; CFL gr 0;	Superficial gr 1; Deep gr 0	Rehabilitation
#41	Eversion	Sq neg; Tend neg	AITFL gr 1	ATFL/CFL gr 3; PTFL gr 2	Superficial gr 0; Deep gr 0	Rehabilitation
#43	Inversion	Sq neg; Tend neg	AITFL gr 1	ATFL: gr 1; CFL: gr 1;	Superficial gr 0; Deep gr 1	Rehabilitation
#44	Inversion/ER/HPF	Sq neg; Tend pos	AITFL gr 2	-	Superficial gr 0; Deep gr 0	Rehabilitation
#45	Inversion/Eversion	Sq neg; Tend 5 cm	AITFL gr 1	ATFL gr 1	Superficial gr 2; Deep gr 0	Ankle boot + Rehabilitation
#47	ER	Sq neg; Tend neg	AITFL gr 1	ATFL gr 1; CFL gr 2	Superficial gr 2; Deep gr 0	Ankle boot + Rehabilitation
#68	Inversion	Sq neg; Tend neg	AITFL gr 1	ATFL gr 2	Superficial gr 0; Deep gr 0	Rehabilitation
#72	Inversion	Sq neg; Tend neg	AITFL gr 2	ATFL/CFL gr 2	Superficial gr 0; Deep gr 0	Bracing + Rehabilitation
#85	Inversion	Sq neg; Tend neg	AITFL gr 1	ATFL gr 1	Superficial gr 1; Deep gr 1	Rehabilitation
#103	HPF	Sq neg; Tend 4 cm	AITFL gr 1	ATFL gr 3; CFL gr 1	Superficial gr 0; Deep gr 0	Ankle boot + Rehabilitation
#105	Inversion	Sq neg; Tend neg	AITFL gr 1	ATFL/CFL gr 3	Superficial gr 0; Deep gr 0	Taping + Rehabilitation

Supplementary appendix 2 Continued

ID	Injury mechanism	Physical Examination	MRI syndesmosis	MRI lateral	MRI deltoid	Treatment
#127	Inversion	Sq neg; Tend neg	AITFL gr 3; IOL/ PITFL gr 1	-	Superficial gr 0; Deep gr 0	Ankle boot + Rehabilitation
#134	Inversion	Sq neg; Tend 4 cm	AITFL gr 2	ATFL gr 3	Superficial gr 0; Deep gr 0	Brace + Rehabilitation
#135	Inversion	Sq neg; Tend 1 cm	AITFL gr 1	ATFL/CFL gr 2	Superficial gr 0; Deep gr 0	Ankle boot + Rehabilitation
#138	Unknown	Sq neg; Tend 11 cm	AITFL gr 1	ATFL gr 3; CFL gr 2	Superficial gr 0; Deep gr 0	Ankle boot + Rehabilitation
#145	HPF	Sq pos; Tend neg	AITFL gr 1	-	Superficial gr 0; Deep gr 0	Brace + Rehabilitation
#146	Unknown	Sq neg; Tend 5 cm	AITFL gr 1	ATFL gr 3; CFL gr 2	Superficial gr 0; Deep gr 0	Taping + Rehabilitation
#147	Inversion	Sq neg: Tend 1cm	AITFL gr 1	ATFL gr 2	Superficial gr 0; Deep gr 0	Rehabilitation
#156	Eversion	Sq neg; Tend 9 cm	AITFL/IOL gr 3; IOM/PITFL gr 2	-	Superficial gr 0; Deep gr 0	Ankle clamp + Rehabilitation
#157	Eversion	Sq pos; Tend 15 cm	AITFL/IOL gr 3; IOM gr 2; PITFL gr 1	-	Superficial gr 3; Deep gr 0	Ankle boot + Rehabilitation
#158	Inversion	Sq neg; Tend neg	AITFL gr 1	ATFL gr 3; CFL gr 2	Superficial gr 0; Deep gr 0	Ankle boot + Rehabilitation
# 168	Inversion/HPF	Sq neg; Tend neg	AITFL/IOL gr 3; IOM/PITFL gr 2	-	Superficial gr 0; Deep gr 0	Ankle boot + Rehabilitation
# 173	Inversion	Sq neg; Tend neg	AITFL gr 1	ATFL gr 3; CFL gr 2	Superficial gr 0; Deep gr 0	Ankle boot + Rehabilitation

Clinical description of patients with involvement of the syndesmosis; MRI Magnetic Resonance Imaging; Sq Squeeze test; Tend Tenderness over the syndesmosis; ER/ IR external/internal rotation; HPF hyper plantar flexion; AITFL anterior inferior tibiofibular ligament; IOL/IOM Interosseous Ligament/Membrane; PITFL Posterior inferior Tibiofibular Ligament; ATFL anterior talofibular ligament; CFL calcaneofibular ligament; PTFL posterior talofibular ligament; L lateral ankle ligaments; S syndesmosis.

Supplementary appendix 3A Subset analysis comparing functional outcome of acute ankle injuries without involvement of the AITFL and acute ankle injuries with interstitial injury or partial discontinuity of the AITFL.

	N	AITFL intact	N	AITFL involvement	P-value
Baseline					
K&P score	60	37 (IQR 20.5-49)	20	38.5 (22.75-63.50)	0.37
FAOS symptoms	62	54 (IQR 39-71)	22	60.5 (42-86)	0.27
FAOS pain	62	47 (IQR 28-64.75)	21	64 (36.5-76)	0.12
FAOS ADL	61	62 (IQR 35-73.5)	21	74 (45.5-95)	0.06
FAOS sports	62	30 (IQR 5-47.5)	20	27.5 (6.25-80)	0.47
FAOS QOL	62	50 (IQR 29.5-69)	22	47 (29.5-85.75)	0.35
6 weeks					
K&P score	47	80 (IQR 70-90)	18	82 (74.25-100)	0.53
FAOS symptoms	50	89 (IQR 79-100)	18	93 (78-100)	0.85
FAOS pain	50	94 (IQR 86-100)	18	94 (86-100)	0.85
FAOS ADL	50	100 (IQR 97-100)	18	100 (98.5-100)	0.86
FAOS sports	50	90 (IQR 85-100)	18	90 (85-96.25)	0.74
FAOS QOL	50	88 (IQR 69-100)	18	84.5 (67.5-100)	0.82
6 months					
K&P score	33	90 (IQR 81-90)	10	86 (81.5-90)	0.43
FAOS symptoms	33	96 (IQR 84-100)	11	100 (89-100)	0.45
FAOS pain	33	100 (IQR 95.5-100)	11	100 (94-100)	0.77
FAOS_ADL	33	100 (IQR 96.5-100)	11	100 (100-100)	0.24
FAOS sports	33	100 (IQR 90-100)	11	100 (90-100)	0.91
FAOS QOL	32	100 (IQR 88-100)	11	100 (81-100)	0.72
1 year					
K&P score	29	90 (IQR 85-90)	11	90 (IQR 85-90)	0.73
FAOS symptoms	31	100 (IQR 93-100)	11	100 (IQR 93-100)	0.94
FAOS pain	31	100 (IQR 97-100)	11	100 (IQR 97-100)	0.82
FAOS ADL	31	100 (IQR 100-100)	11	100 (IQR 99-100)	0.72
FAOS sports	31	100 (IQR 90-100)	11	95 (IQR 85-100)	0.24
FAOS QOL	31	100 (IQR 88-100)	11	100 (IQR 75-100)	0.53

For this subset analysis AITFL involvement is defined as interstitial edema or partial discontinuity. Patients with complete discontinuity were excluded from this analysis. N total number of athletes, AITFL anterior inferior tibiofibular ligament, K&P Karlsson & Peterson, FAOS Foot and Ankle Outcome Score, ADL Activities of Daily Living, QOL Quality of Life, IQR Interquartile Range. The total K&P score ranges from 0 (extreme problems) to 90 (no problems). The FAOS subscale scores range from 0 (extreme problems) to 100 (no problems).

Supplementary appendix 3B Outcome of the linear mixed model for patient reported functional outcome during 1-year follow-up reported as beta-coefficient with corresponding 95% confidence interval.

	B-coefficient (CI 95%)	**P-value**
K&P score	-1.33 (-5.17-2.51)	0.50
FAOS symptoms	-1.20 (-5.41-3.00)	0.57
FAOS pain	-0.64 (-3.68-2.41)	0.68
FAOS ADL	-0.28 (-1.83-1.27)	0.72
FAOS sports	0.39 (-4.00-4.78)	0.86
FAOS QOL	-0.82 (-6.12-4.48)	0.76

For this subset analysis AITFL involvement is defined as interstitial edema or partial discontinuity. Patients with complete discontinuity were excluded from this analysis. N total number of athletes, AITFL anterior inferior tibiofibular ligament, K&P Karlsson & Peterson, FAOS Foot and Ankle Outcome Score, ADL Activities of Daily Living, QOL Quality of Life, CI 95% confidence interval. The total K&P score ranges from 0 (extreme problems) to 90 (no problems). The FAOS subscale scores range from 0 (extreme problems) to 100 (no problems).

Supplementary appendix 4A Subset analysis comparing functional outcome of acute ankle injuries without involvement of the AITFL and acute ankle injuries with interstitial injury of the AITFL.

	N	AITFL intact	N	AITFL involvement	P-value
Baseline					
K&P score	60	37 (IQR 20.5-49)	15	32 (IQR 20-59)	0.82
FAOS symptoms	62	54 (IQR 39-71)	17	57 (IQR 35.5-76.5)	0.67
FAOS pain	62	47 (IQR 28-64.75)	16	59.5 (IQR 33.75-69)	0.29
FAOS ADL	61	62 (IQR 35-73.5)	16	60 (IQR 44-92.5)	0.27
FAOS sports	62	30 (IQR 5-47.5)	15	20 (IQR 5-80)	0.89
FAOS QOL	62	50 (IQR 29.5-69)	17	69 (IQR 25-100)	0.14
6 weeks					
K&P score	47	80 (IQR 70-90)	14	82 (IQR 69.5-87.75)	0.86
FAOS symptoms	50	89 (IQR 79-100)	14	94.5 (IQR 72.25-100)	0.73
FAOS pain	50	94 (IQR 86-100)	14	95.5 (IQR 85.25-100)	0.67
FAOS ADL	50	100 (IQR 97-100)	14	99.5 (IQR 96.25-100)	0.79
FAOS sports	50	90 (IQR 85-100)	14	92.50 (IQR 80-100)	0.93
FAOS QOL	50	88 (IQR 69-100)	14	84.5 (IQR 67.5-95.5)	0.77
6 months					
K&P score	33	90 (IQR 81-90)	7	85 (IQR 80-90)	0.23
FAOS symptoms	33	96 (IQR 84-100)	8	98 (IQR 86.75-100)	0.63
FAOS pain	33	100 (IQR 95.5-100)	8	98.5 (IQR 92.5-100)	0.64
FAOS_ADL	33	100 (IQR 96.5-100)	8	100 (IQR 100-100)	0.24
FAOS sports	33	100 (IQR 90-100)	8	100 (IQR 83.75-100)	1.00
FAOS QOL	32	100 (IQR 88-100)	8	88 (IQR 81-100)	0.23
1 year					
K&P score	29	90 (IQR 85-90)	7	90 (IQR 82-90)	0.70
FAOS symptoms	31	100 (IQR 93-100)	7	100 (IQR 93-100)	0.88
FAOS pain	31	100 (IQR 97-100)	7	100 (IQR 97-100)	0.67
FAOS ADL	31	100 (IQR 100-100)	7	100 (IQR 99-100)	0.69
FAOS sports	31	100 (IQR 90-100)	7	95 (IQR 85-100)	0.26
FAOS QOL	31	100 (IQR 88-100)	7	94 (IQR 75-100)	0.25

For this subset analysis AITFL involvement is defined as interstitial edema. Patients with partial or complete discontinuity were excluded from this analysis. N total number of athletes, AITFL anterior inferior tibiofibular ligament, K&P Karlsson & Peterson, FAOS Foot and Ankle Outcome Score, ADL Activities of Daily Living, QOL Quality of Life, IQR Interquartile Range. The total K&P score ranges from 0 (extreme problems) to 90 (no problems). The FAOS subscale scores range from 0 (extreme problems) to 100 (no problems).

Supplementary appendix 4B Outcome of the linear mixed model for patient reported functional outcome during 1-year follow-up reported as beta-coefficient with corresponding 95% confidence interval.

	B-coefficient (CI 95%)	P-value
K&P score	0.65 (-3.83-5.14)	0.78
FAOS symptoms	0.09 (-4.73-4.90)	0.97
FAOS pain	-0.41 (-3.95-3.14)	0.82
FAOS ADL	0.13 (-1.68-1.94)	0.88
FAOS sports	0.82 (-4.27-5.92)	0.75
FAOS QOL	-0.04 (-6.16-6.08)	0.99

For this subset analysis AITFL involvement is defined as interstitial edema. Patients with partial or complete discontinuity were excluded from this analysis. N total number of athletes, AITFL anterior inferior tibiofibular ligament, K&P Karlsson & Peterson, FAOS Foot and Ankle Outcome Score, ADL Activities of Daily Living, QOL Quality of Life, CI 95% confidence interval. The total K&P score ranges from 0 (extreme problems) to 90 (no problems). The FAOS subscale scores range from 0 (extreme problems) to 100 (no problems).

Supplementary rehabilitation protocol

CHAPTER 7

The prevalence, size and anatomic location of cartilage and osteochondral lesions in athletes with an acute ligamentous ankle injury

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ABSTRACT

Background: in athletes with an acute ligamentous ankle injury, cartilage and osteochondral lesions ((O)CLs) have been reported in 8% using 1.5T MRI. Visualization of cartilage injuries improves with the use of higher field-strenghts.

Purpose: to evaluate the prevalence, size and anatomic location of (O)CLs in athletes with an acute ligamentous ankle injury using 3T MRI, as well as was to determine the association of (O)CLs with injury of 1) the lateral ankle ligaments and 2) anterior syndesmosis.

Study design: cohort study; level of evidence 3.

Methods: for this prospective cohort study, all acute ligamentous ankle injuries in athletes (≥18 years of age) evaluated in the outpatient department of a specialized Orthopaedic and Sports Medicine Hospital within 7 days post-injury were assed for eligibility. Acute ankle injuries were excluded if 3T MRI could not be obtained within 10 days after injury or if imaging demonstrated a frank fracture. A musculoskeletal radiologist assessed MR scans for the presence, location and size of (O)CLs. Morphology was graded using the modified Berndt and Harty score, Griffith MRI score and International Cartilage Regeneration & Joint Preservation Society (ICRS) score. In addition, injuries of the lateral ankle ligaments and anterior syndesmosis were graded. A multivariate logistic regression analysis was performed to evaluate the association between (O)CLs and injury of the 1) lateral ankle ligaments and 2) anterior syndesmosis.

Results: between September 2016 and February 2020, a total of 171 acute ankle injuries in 166 athletes were included in this study. The overall prevalence of (O)CLs was 14%. (O)CLs of the talus and tibia were observed in 24 (14%) and 9 (5%) acute ankle injuries, respectively. Of 33 (O)CLs, 28 (85%) were classified as cartilage lesions. Lateral ligament injury was observed in 73% of acute ankle injuries, and anterior syndesmosis injury in 38%. Multivariate logistic regression analysis did not show significantly higher odds of (O)CLs in the presence of anterior syndesmosis injury (OR 2.16; 95% CI 0.90-5.16).

Conclusion: In athletes with an acute ligamentous ankle injury, a prevalence for (O)CLs of 14% was established using 3T MRI. The majority were cartilage lesions. No statistically significant association between (O)CLs and lateral ligament or syndesmosis injury was established.

INTRODUCTION

Concomitant pathology of the ankle is frequently observed after acute ligamentous ankle injuries.[1,2]. Concomitant pathology may include; (avulsion-) fractures, ligamentous injuries (e.g. syndesmosis), tendon injuries, and osteochondral lesions. Osteochondral lesions are hypothesized to be part of a degenerative cascade, beginning with (1) partial-thickness cartilage surface lesions, then progressing to (2) osteochondral lesions and finally (3) end-stage osteoarthritis.[3] Early detection of cartilage and osteochondral lesions ([O]CLs) might mitigate the risk of osteoarthritis. Understanding the prevalence (including size and anatomic location) of (O)CLs could aid in the identification of athletes at risk of developing osteoarthritis.

In a recent meta-analysis, the prevalence of (O)CLs in chronic ankle instability was investigated.[4] In this meta-analysis of twelve studies (including 2145 patients), a prevalence of 32% was reported using intra-operative findings. In athletes with an acute ligamentous ankle injury, one previous study has evaluated the prevalence of osteochondral lesions only.[1] In this cohort study of 261 athletes who underwent 1.5T magnetic resonance imaging (MRI) after an acute ligamentous ankle injury, a prevalence of 8% was reported for osteochondral lesions. As visualization of cartilage lesions improves with the use of higher field strengths, the prevalence of (O)CLs could be higher than the previously reported 8% for osteochondral lesions only.[5] A prospective cohort study using a 3.0T MRI in athletes with an acute ligamentous ankle injury is therefore warranted.[6]

For athletes with syndesmosis injuries, the prevalence of (O)CLs was also reported in a recent meta-analysis.[7] In this meta-analysis of 9 studies (including 402 syndesmotic injuries) a prevalence of 21% was reported using MRI and arthroscopic findings. This is higher than the previously reported prevalence of 8% in athletes with an acute ligamentous ankle injury.[1] Therefore, exploring the association between (O)CLs, lateral ligament and anterior syndesmosis injuries could help decide which athletes need referral for additional MR imaging.

Considering the lack of consensus on the prevalence of (O)CLs and the potential for 3.0T MRI to improve detection, the primary aim of this study was to describe the prevalence, size and anatomic location of (O)CLs in athletes with an acute ligamentous ankle injury. The secondary aim was to determine the association of (O)CLs with injury of the 1) lateral ankle ligaments and 2) anterior syndesmosis.

METHODS

Participants

Data used in this cross-sectional study were collected in the context of a prospective cohort study on the diagnosis and outcome of acute ligamentous ankle injuries in athletes.[8–12] For this study, all acute ligamentous ankle injuries in athletes (≥18 years of age) evaluated in the outpatient department of a specialized Orthopaedic and Sports Medicine Hospital within 7 days after injury, were assessed for eligibility. Acute ankle injuries were excluded if 3T MRI could not be obtained within 10 days after injury or if imaging demonstrated a frank fracture. Written informed consent was obtained from all athletes at the time of inclusion. Ethics approval was obtained from the Institutional Review Board. (Anti-Doping Lab Qatar; IRB No. F2016000153).

Imaging

All athletes underwent a 3T MR scan (GE Discovery; GE Healthcare) with an 8-channel receive-only Foot & Ankle array (Invivo; Philips Healthcare). The imaging protocol has been described previously.[10]

Grading of ligamentous injury

The MR scans (≤10 days after injury) were evaluated for ligamentous ankle injuries by a musculoskeletal radiologists (M.R.A.N.) with 10 years of experience. The radiologist graded the ligamentous lesions of the lateral ankle ligaments (anterior talofibular ligament [ATFL], calcaneofibular ligament [CFL], and posterior talofibular ligament [PTFL]) and syndesmotic ligaments (anterior inferior tibiofibular ligament [AITFL], interosseous ligament [IOL], interosseous membrane [IOM], and posterior inferior tibiofibular ligament [PITFL]) according the Schneck grading system[13]: normal (grade 0), low-grade sprain (grade 1: peri-ligamentous high signal/edema on proton density-weighted sequences and no discontinuity of fibers), partial discontinuity (grade 2: partial discontinuity but preserved remnant fibers) and complete discontinuity (grade 3).

Grading of (O)CLs

The presence of (O)CLs of the talus and tibia was evaluated by a senior musculoskeletal radiologist (M.B.) with 24 years of experience. A previous study demonstrated almost perfect interrater reliability for the detection of osteochondral lesions in the acute setting.[1] Cartilage lesions were defined as injury of the superficial cartilage with or without subsequent involvement of the subchondral bone.[3,14] Osteochondral lesions were defined as compressed areas of trabecular bone with or without damage of the overlying cartilage (transchondral fracture) or an avulsion of an osteocartilaginous

flake.[15] When an (O)CL was observed, the size (in mm) was measured in 3 directions (anteroposterior, mediolateral, superoinferior) (interobserver reliability k = 0.87).[16] The anatomic location was recorded using the 9-grid scales developed by Elias and Raikin et al [17,18] (interobserver reliability k = 0.55).[19] Cartilage lesions were graded using the International Cartilage Regeneration & Joint Preservation Society (ICRS) score.[20] Morphology of osteochondral lesions was graded using the modified Berndt & Harty score, Griffith MRI score and ICRS score.[20–22] (Supplementary appendix 1-3) When multiple lesions were observed, the largest measurement was reported.

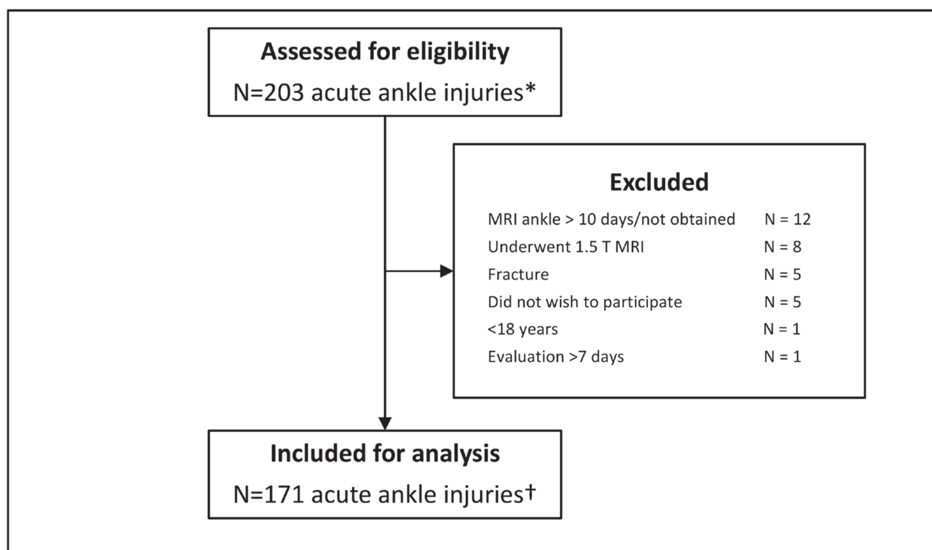
Statistical analysis

Demographics, prevalence, size and anatomic location of (O)CLs were reported using descriptive statistics. To determine the association between the presence of (O)CLs and 1) lateral ligament and 2) anterior syndesmosis injury, a multivariate logistic regression analysis (enter method) was performed. For this analysis, lateral ligament injury was defined as a partial or complete discontinuity of the ATFL and/or CFL. Injury of the syndesmosis ligaments was defined as a partial or complete tear of the AITFL. Athletes were considered to have an (O)CL if they had a ICRS grade ≥1A (cartilage lesion) or a modified Berndt & Harty grade ≥1 (osteochondral lesion). Statistical analysis was performed using SPSS software (Version 27; IBM Corp).

RESULTS

A total of 171 acute ankle injuries in 166 athletes were included in this study. (Figure 1) Of the 171 included acute ankle injuries, 4 were subsequent contralateral ankle injuries and one was a re-injury (>1 year). Patient characteristics are shown in table 1.

Figure 1 Flowchart for study inclusion



*In 194 athletes; † in 166 athletes

Overall prevalence of (O)CLs

The overall prevalence of cartilage and osteochondral lesions ((O)CLs) was 14% (*N=24/171*). (Table 2) (O)CLs of the talus and tibia were observed in 24 (14%) and 9 (5%) acute ankle injuries, respectively. (Figure 2A & 2B)

Prevalence, size and location of cartilage lesions

The prevalence of cartilage lesions was 12% (*N=20/171*). (Table 2) Cartilage lesions of the talus and tibia were observed in 20 (12%) and 8 (5%) acute ankle injuries, respectively. The median size of the talar cartilage lesions was 22 mm^3 (IQR 8-68). Talar cartilage lesions were primarily located lateral (25%), medial (25%) and anteromedial (20%). Tibial cartilage lesions were a median 18 mm^3 (IQR 4-84) and primarily located on the posteromedial (37.5%) and anteromedial (25%) aspect. (Figure 2C & 2D)

Prevalence, size and location of osteochondral lesions

The prevalence of osteochondral lesions was 2% (*N=4/171*). (Table 2) Osteochondral lesions of the talus and tibia were observed in 4 (2%) and 1 (1%) acute ankle injuries, respectively. The median size of talar osteochondral lesions was 96 mm^3 (IQR 11-242). Talar osteochondral lesions were located on the posteromedial (50%), lateral (25%) and anterior aspect (25%). (Figure 2E & 2F)

Association between (O)CLs and ligamentous injury

Injury of the lateral ankle ligaments was observed in 73% of acute ankle injuries. Injury of the anterior syndesmosis was observed in 38% of acute ankle injuries. Results of the analysis for the association between (O)CLs and location of ligamentous injury are reported in table 3. Multivariate logistic regression analysis demonstrated non statistically significant higher odds of (O)CLs in the presence of syndesmosis injury (OR 2.16; 95% CI 0.90-5.16; *p=0.08*) compared to lateral ligament injury.

Table 1 Demographics of included ankle injuries

Time to clinical evaluation (days)	2 (IQR 1-3)
Time to MRI (days)	3 (IQR 2-5)
Age at time of injury (years)	24 (IQR 20-28)
Side (right)	85 (50%)
History of ipsilateral ankle sprains	43 (25%)
Sports	
- Football	75 (44%)
- Volleyball	26 (15%)
- Futsal	15 (9%)
- Basketball	12 (7%)
- Handball	12 (7%)
- Athletics	5 (3%)
- Other sports	26 (15%)

Data are presented as n (%) or median (IQR). MRI, magnetic resonance imaging.

Table 2 Size, location and grading of cartilage and osteochondral lesions ((O)CLs) according to the Modified Berndt & Harty, Griffith, and ICRS Classification Systems

ID	Type	Location	Size AP	Size ML	Depth	Modified B&H	Griffith	ICRS
Talus								
#2	Cartilage	Central	4	1	1	N/a	N/a	Grade 1B
#8	Cartilage	Anteromedial	5	3	1	N/a	N/a	Grade 2
#9	Cartilage	Posterolateral	4	3	1	N/a	N/a	Grade 3A
#16	Osteochondral	Posteromedial	16	11	1	Grade 2	Grade 4B	Grade 4
#25	Cartilage	Lateral	6	2	1	N/a	N/a	Grade 3B
#28	Cartilage	Lateral	8	6	1	N/a	N/a	Grade 4
#38	Cartilage	Medial	1	1	1	N/a	N/a	Grade 3C
#39	Cartilage	Posterolateral	15	12	1	N/a	N/a	Grade 3C
#68	Cartilage	Anteromedial	2	3	1	N/a	N/a	Grade 3A
#74	Cartilage	Medial	10	7	2	N/a	N/a	Grade 4
#85	Cartilage	Posteromedial	10	9	1	N/a	N/a	Grade 3A
#86	Cartilage	Posterolateral	4	5	1	N/a	N/a	Grade 3C
#93	Osteochondral	Anterior	3	3	1	Grade 1	Grade 2B	Grade 4
#94	Cartilage	Medial	4	2	1	N/a	N/a	Grade 4
#112	Cartilage	Medial	2	3	1	N/a	N/a	Grade 3D
#116	Osteochondral	Posteromedial	4	4	1	Grade 1	Grade 2B	Grade 4
#120	Cartilage	Central	19	3	1	N/a	N/a	Grade 4
#130	Osteochondral	Lateral	11	8	3	Grade 2	Grade 3B	Grade 4
#145	Cartilage	Lateral	8	5	2	N/a	N/a	Grade 4
#147	Cartilage	Anteromedial	8	9	1	N/a	N/a	Grade 2
#153	Cartilage	Anteromedial	5	6	1	N/a	N/a	Grade 3C

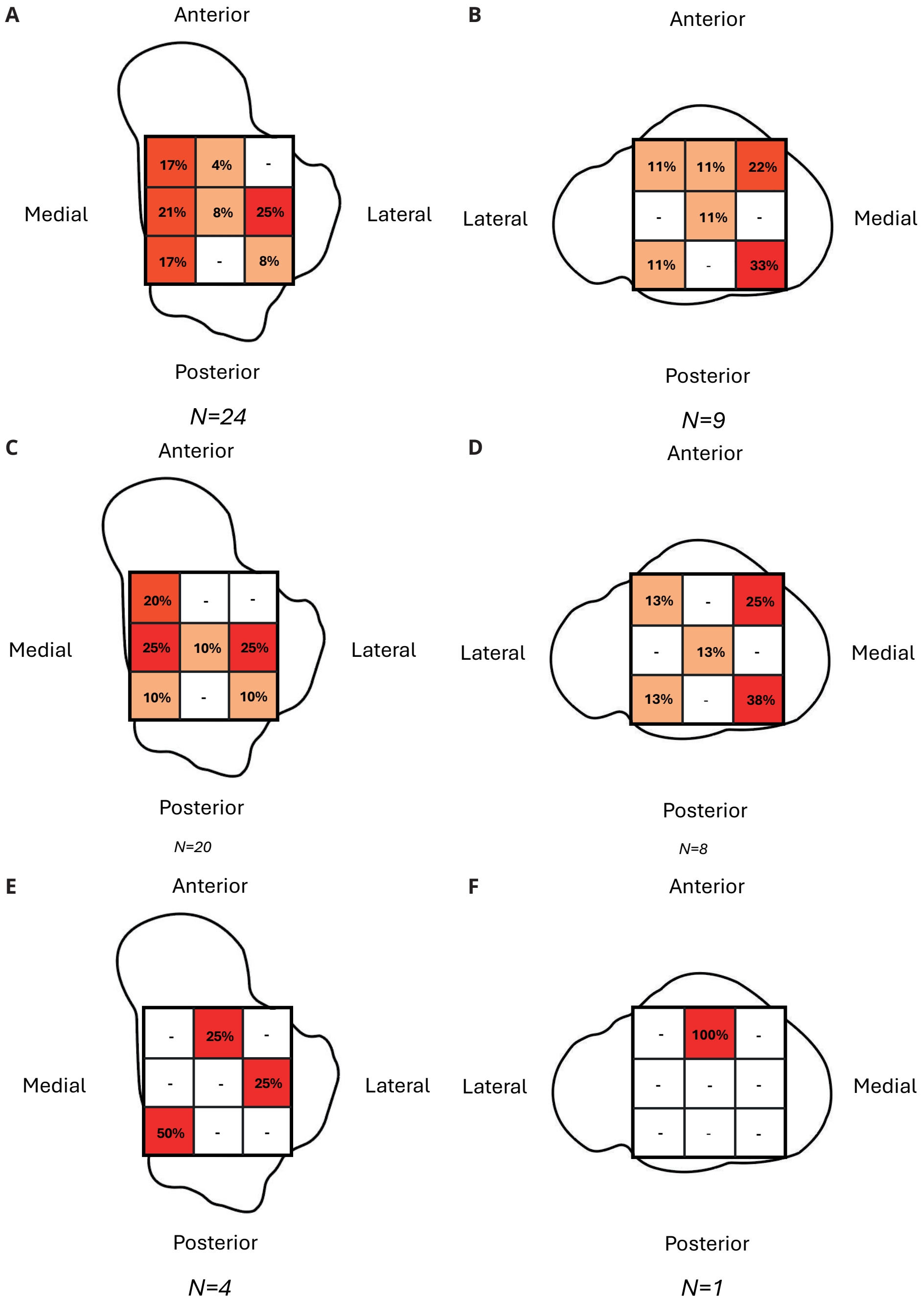
Table 2 Continued

ID	Type	Location	Size AP	Size ML	Depth	Modified B&H	Griffith	ICRS
#157	Cartilage	Lateral	8	3	1	N/a	N/a	Grade 4
#164	Cartilage	Medial	5	3	2	N/a	N/a	Grade 3A
#194	Cartilage	Lateral	4	2	1	N/a	N/a	Grade 3C
Tibia								
#16	Cartilage	Posteromedial	13	7	1	N/a	N/a	Grade 4
#28	Cartilage	Anterolateral	4	4	1	N/a	N/a	Grade 3B
#39	Cartilage	Posterolateral	8	8	1	N/a	N/a	Grade 3C
#68	Cartilage	Anteromedial	3	1	1	N/a	N/a	Grade 2
#85	Cartilage	Posteromedial	1	1	1	N/a	N/a	Grade 3C
#93	Osteochondral	Anterior	5	9	1	Grade 1	Grade 2B	Grade 4
#120	Cartilage	Central	12	9	1	N/a	N/a	Grade 4
#147	Cartilage	Anteromedial	4	5	1	N/a	N/a	Grade 4
#164	Cartilage	Posteromedial	2	3	1	N/a	N/a	Grade 1B

Description of included acute ankle injuries with cartilage and osteochondral lesions ((O)CLs); AP Anteroposterior; B&H Berndt & Harty; International Cartilage Regeneration & Joint Preservation Society; ML Mediolateral; N/a Not applicable.

7

Figure 2 Distribution of cartilage and osteochondral lesions ([O]CLs) on talus and tibia



Distribution of cartilage and osteochondral lesions ([O]CLs) expressed as percentage of total lesions present on talus or tibia. Distribution of (O)CLs on A) talus and B) tibia; distribution of cartilage lesions on C) talus and D) tibita; distribution of osteochondral lesions on E) talus and F) tibia.

Table 3 Multivariate logistic regression analysis for the association between (O)CLs and ligamentous injury location.

	N	OR (95%CI)	SE	P-value
Cartilage injury (including osteochondral lesions)				
- Lateral ligament injury	124	0.91 (0.35-2.38)	0.49	0.85
- Syndesmosis injury	65	2.16 (0.90-5.16)	0.45	0.08

The odds ratio for the independent predictor associated with cartilage and osteochondral lesions ([O]CLs) is presented. Lateral ligament injury was defined as partial or complete discontinuity of the ATFL and/or CFL. Syndesmosis injury was defined as partial or complete discontinuity of the AITFL. Odds ratio (OR) are presented with corresponding 95% confidence interval (95% CI) and standard error (SE).

DISCUSSION

The most important finding in this prospective cohort study of 171 acute ankle injuries (166 athletes) is the relatively high prevalence of (O)CLs (14%) as determined by MRI. (O)CLs of the talus and tibia were observed in 24 (14%) and 9 (5%) acute ligamentous ankle injuries, respectively. The majority (85%) of (O)CLs were classified as cartilage lesions. Syndesmosis injury demonstrated non statistically significant higher odds of (O)CLs (OR 2.16; 95% CI 0.90-5.16) compared with lateral ligament injury. The finding of this study suggest that (O)CLs are more prevalent in acute ligamentous ankle injuries than previously reported.

Comparison to previous literature – prevalence

The overall prevalence of cartilage and osteochondral lesions ((O)CLs) in this study was 14%. A previous study of 261 athletes with an acute ligamentous ankle injury, from the same specialized Orthopaedic and Sports Medicine Hospital, established a prevalence of 8% using 1.5 T MRI.[1] A possible explanation for the higher prevalence in the current study is the use of a high field-strength (3T) MRI, which improves the visualization of superficial cartilage lesions. These findings are consistent with the literature on the use of MRI for the detection of cartilage injuries of the knee. In a meta-analysis of sixteen studies (including 1886 patients) 3T MRI demonstrated higher diagnostic accuracy for the detection of cartilage lesions of the knee in comparison with 1.5 T MRI.[5]

In patients with a syndesmosis injury, a recent meta-analysis reported a prevalence of (O)CLs in up to 21% using both MRI and arthroscopic findings.[7] Despite the hypothesis of the current study, no statistically significant association between (O)CLs and syndesmosis injury was established. A possible explanation might be that in the current study partial and/or complete discontinuity of the anterior syndesmosis (AITFL) was considered disease positive. Thus, clinically stable syndesmosis injuries (West Point ≤IIA) were included, whereas in the literature most studies include patients with unstable syndesmosis injuries requiring surgical stabilization (West Point ≥IIB).[7,23] Future prospective cohort studies should therefore aim to investigate the correlation of clinical stability (stress test assessment) with the prevalence of (O)CLs.

Comparison to previous literature – anatomic location

The primary anatomic location of (O)CLs was the talus (14%). (O)CLS of the tibia were observed in 5% and only in the presence of (O)CLs of the talus. (O)CLs of the talus were located on the lateral (25%), medial (21%) and posteromedial aspect (17%). These findings are in line with the findings of a recent meta-analysis on the distribution of (O)CLs of the talus. In this study the posteromedial (28%) and medial (31%) zones of the talus had the

highest prevalence of (O)CLs.[24] The distribution pattern of (O)CLs in the current study suggest that a subset of athletes sustained an inversion injury of the ankle, with either a plantarflexed ankle (medial talar (O)CLS) or dorsiflexed ankle (lateral talar (O)CLS).[15] Previous studies reporting on the anatomic location of (O)CLs in patients with isolated syndesmosis injuries have reported the highest prevalence at the anterolateral and lateral aspect of the talus.[25,26] Although in the current study a prevalence of 25% was reported for the lateral aspect of the talus, no (O)CLs were observed at the anterolateral aspect of the talus. The findings in the current study warrant further research to elucidate the association between trauma mechanism, injured ligamentous complexes, and location of (O)CLs.

The development of osteoarthritis

Osteoarthritis is characterized by the degradation of joint cartilage and underlying bone, leading to pain, swelling, and reduced motion. In acute ligamentous ankle injuries, (O)CLS are hypothesized to be either 1) asymptomatic superficial cartilage lesions which will remain asymptomatic; 2) post-traumatic cartilage cracks that, with involvement of the subchondral bone might become symptomatic; and 3) large acute symptomatic lesion with involvement of the subchondral bone plate. It is important to note that not all cartilage injuries become symptomatic and lead to end-stage ankle osteoarthritis. However, no prognostic factors to determine which (O)CLs will become symptomatic or progress to end-stage ankle osteoarthritis have been identified. In the current study the majority of talar (58%) and tibial (56%) (O)CLS were classified as superficial cartilage injuries (ICRS grades 1-3), supporting the theory that a subset of superficial cartilage injuries remains asymptomatic. However, a large prospective cohort study identifying prognostic factors for the development of symptomatic (O)CLs and end-stage osteoarthritis in athletes with an acute ligamentous ankle injury is warranted.

Strength and Limitations

The main strengths of this study is the use of a high-field strength MRI (3T) in a large prospective cohort of athletes with acute ligamentous ankle injuries to determine the prevalence of (O)CLs. Despite the use of a high-field strength MRI, the diagnostic accuracy of (O)CLs remains inferior to the use of (needle) arthroscopy.[25] Furthermore, selection bias may have occurred, as athletes with a mild acute ligamentous ankle injury might not have presented for clinical and radiological evaluation and completed rehabilitation at their club. Finally, only the ICRS grading system was applied to cartilage lesions. This is because of the composition of the modified Berndt & Harty and Griffith grading system (bone marrow edema precedes transchondral fracture), which is consistent with the definition used for osteochondral lesions. The ICRS classification system is more suitable to grade cartilage injuries (cartilage injury precedes involvement of the subchondral bone).

Clinical implications

The most important finding in this study is that 3T MRI-determined (O)CLs are more common than previously reported. The study should raise awareness amongst clinicians of the prevalence of concomitant (O)CLS in athletes with an acute ligamentous ankle injury. In clinical practice, early diagnosis and appropriate management of ligamentous injuries (e.g. unstable syndesmosis injury) using physical examination or ultrasound should be paramount.[8,9] If physical rehabilitation for an athlete fails despite adequate treatment, referral for MRI to rule out (O)CLs should be considered. When an (O)CL is present, MRI may provide valuable information on size, location, and grading of the (O)CL and can be used to guide treatment.[27] Future large prospective cohort studies should aim to identify clinical predictors (e.g., age, history of ipsilateral ankle sprain, and stress instability) associated with the presence of (O)CLs.

CONCLUSION

In athletes undergoing 3T MRI for an acute ligamentous ankle injury, the prevalence of (O)CLs is 14%. The majority of these injuries were cartilage lesions. The findings of this study suggest that (O)CLs are more prevalent in athletes with an acute ligamentous ankle injury than reported previously in studies utilizing 1.5T MRI.

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Supplementary appendix 1 Modified Berndt & Harty

Grade	Description
1	Subchondral bone compression; marrow edema
2	Chip avulsed, but attached
3	Detached chip, but undisplaced
4	Detached and displaced chip
5	Talar cyst, with adjacent edema of the talar body

Supplementary appendix 2 Griffith MRI-score

Grade	Description
1a	Bone marrow change (edema, cystic change) with no collapse of subchondral bone area, no osteochondral junction separation and intact cartilage.
1b	Grade 1a + cartilage fracture present.
2a	Variable collapse of subchondral bone area with osteochondral separation though intact Cartilage.
2b	Grade 2a + cartilage fracture present. This is an unstable lesion with level of instability related to extent of cartilage fracture.
3a	Variable collapse of subchondral bone area with no osteochondral separation +/- variable cartilage hypertrophy
3b	Grade 3a + cartilage fracture present
4a	Separation within or at edge of bone component with intact overlying cartilage
4b	Grade 4a + cartilage fracture present. This is an unstable lesion with level of instability related to extent of cartilage fracture
5	Complete detachment of osteochondral lesion. This is an unstable lesion.

Supplementary appendix 3 ICRS-classification

Grade	Description
0	Macroscopically normal cartilage without notable defects
1A	Intact surface but fibrillation and/or slight softening is present
1B	ICRS 1a + superficial lacerations and fissures are found
2	Defects that extend deeper but involve <50% of the cartilage thickness
3A	Deep defects that extend through >50% of the cartilage depth but not to the calcified layer
3B	Deep defects that extend through >50% of the cartilage depth to the calcified layer
3C	Defects that extend down to but not through the subchondral bone plate
3D	Blisters
4	Cartilage defects that extend into the subchondral bone

CHAPTER 8

General discussion

GENERAL DISCUSSION

The primary aim of this thesis was to evaluate the use of clinical evaluation and ultrasound in the diagnosis of acute ligamentous ankle ligament injuries. The secondary aims were to determine 1) the prognosis of clinically stable syndesmosis injuries and 2) the association of syndesmosis injury with cartilage and osteochondral lesions ((O)CLs). This general discussion will reflect on the methodology and findings of the included studies and their scientific and clinical implications.

Reflections on methods and results

To reflect on the methodology and findings of included studies three statements were included.

Statement 1: acute clinical evaluation of ligamentous ankle injuries; unloved and underappreciated

Clinical evaluation of acute ankle injuries in athletes is the cornerstone of diagnosing ligamentous ankle injuries. For lateral ligament injury, the diagnostic value of clinical evaluation has been evaluated in various (historic) publications.[1,2] Since the landmark study by van Dijk et al., delayed clinical evaluation for lateral ligament injury has become the standard of care.[3,4] In this study it was demonstrated that in the acute setting (0-2 days post-injury), the combination of lateral hematoma, tenderness over the ATFL and a positive anterior drawer test had a 71% sensitivity and 33% specificity. When performed in the delayed setting (4-7 days post-injury) diagnostic value improved to 96% sensitivity and 84% specificity. Current clinical guidelines therefore recommend delayed physical examination 4–7 days post-injury.[5] However, in this study only the combination of lateral hematoma, tenderness over the ATFL and a positive anterior drawer test was evaluated. In clinical practice this may have translated to an underappreciation of the diagnostic value of acute clinical evaluation. In **chapter 2** we therefore appraised the diagnostic value of clinical evaluation for the diagnosis of lateral ligament injury in the acute (0-2 days post-injury) and delayed setting (5-8 days injury). In this study it was demonstrated that absent lateral swelling in the acute setting had a high negative predictive value. A positive anterior drawer test and presence of hematoma had a high positive predictive value. Furthermore, sensitivity of common clinical findings improved when performed in the delayed setting.

For syndesmosis injury, two large prospective cohort studies have reported conflicting results regarding the diagnostic value of clinical evaluation.[6,7] In a prospective cohort study of 96 patients who underwent clinical evaluation within 24 hours post-injury, sensitivity (14–56%) and specificity (48–83%) were reported as insufficient.[6] In another multi-centre

prospective cohort study of 87 athletes, examined within 7 days post-injury tenderness of the anterior syndesmosis had 92% sensitivity and a positive squeeze test had 88% specificity.[7] In **chapter 3** we therefore evaluated the diagnostic value of clinical evaluation for the diagnosis of syndesmosis injury in the acute setting (0-7 days post-injury). It was demonstrated that despite patients reporting high levels of pain, eversion mechanism of injury and a positive squeeze test were associated with the presence of syndesmosis injury. Furthermore, overall clinical suspicion had a high negative predictive value.

When interpreting the results of both chapters it should be considered that MRI was used as reference standard. Despite MRI having high diagnostic accuracy for ligamentous lesions, it does not directly correlate with clinical ankle instability.

Both chapters underline the importance of meticulous clinical evaluation of athletes with an acute ligamentous ankle injury. In elite athletes where there are important time constraints, thorough clinical evaluation in the acute setting can expedite accurate diagnosis, appropriate management and therefore potentially return to play. Non-athletes or recreational athletes visiting an A&E department (staffed by less experienced doctors under the supervision of senior A&E consultants) will probably still be referred for delayed physical examination as sensitivity of clinical findings improves when swelling and pain have subsided.

Statement 2: imaging of acute ankle injuries; is ultrasound the new stethoscope?
In **chapter 4** the diagnostic value of ultrasound for the diagnosis of ligamentous ankle injuries was evaluated. This study demonstrated that ultrasound had 100% sensitivity and 100% specificity for complete discontinuity of the AITFL. For complete discontinuity of the lateral ankle ligaments (ATFL, CFL), ultrasound had lower diagnostic value. Sensitivity and specificity for complete discontinuity of the ATFL was 87% and 69%, respectively. Discontinuity of the CFL was diagnosed with 29% sensitivity and 92% specificity. Ultrasound is cheap and readily available, making it the perfect screening modality for syndesmosis injuries in elite athletes. With recent innovations making ultrasound handheld portable, it can be performed pitch-side by a Team Physician or in the A&E department by an Emergency Physician, making it the stethoscope of the future. This will improve the detection of acute syndesmosis injuries which can be notoriously difficult to diagnose. Dynamic manoeuvres did not improve the diagnostic value of ultrasound for the diagnosis of complete discontinuity of the AITFL. The diagnostic manoeuvres with the highest diagnostic value (side-to-side difference in external rotation) had a sensitivity of 82% and specificity of 86%. This could perhaps be explained by the fact that stable syndesmosis injuries (West Point I-IIa) were considered disease positive.[8] In these patients, widening of the syndesmosis will not occur when

undergoing dynamic manoeuvres. The findings of this study should therefore be interpreted in the light of using a static diagnostic method (MRI) as reference standard. Furthermore, it could be that performing the dynamic manoeuvres in the sagittal plane instead of the coronal plane will further improve diagnostic accuracy.[9,10] Despite a limited number of shortcomings, this study was the first large prospective cohort study underlining the potential of ultrasound in the diagnosis of ligamentous ankle injuries.

Statement 3: prognosis of acute ankle injuries and prevalence of (O)CLs; the good, the bad and the ugly

Functional outcome of syndesmosis injuries has been described in one study.[11] In this study the best predictor for chronic ankle dysfunction at six weeks and six months was syndesmosis injury. However, this study did not differentiate stable (modified West Point I-IIa) from unstable injuries (modified West Point IIb-III) injuries. In elite athletes with an acute ligamentous ankle injury, MRI often demonstrates edema or partial discontinuity of the AITFL (West Point I). It remains unknown whether these clinically stable injuries of the anterior syndesmosis affect the outcome of acute ligamentous ankle injuries. Therefore, in **chapter 6** the patient reported functional outcome of acute ligamentous ankle injuries with or without (clinically stable) anterior syndesmosis injury was evaluated. It was found that conservatively treated (e.g. supervised rehabilitation) clinically stable anterior syndesmosis injuries (AITFL) do not affect the functional outcome at 6 weeks, 6 months and 1-year post-injury. A possible explanation for these findings is that clinically unstable syndesmosis injuries were excluded. A limitation of this study was that stability of the syndesmosis was assessed by clinical evaluation of a senior Orthopaedic Sports Medicine Surgeon. Future studies evaluating conservative treatment of stable syndesmosis injuries (West Point I-IIa) should use a non-invasive, or minimally invasive, dichotomous method to determine syndesmotic stability. Doing so would further improve the validity of the study. In addition, the current study only reported return to play for a small subset of athletes as many were lost to follow-up or unable to recall their exact return to play date. A study evaluating return to play of clinically stable syndesmosis injuries is therefore warranted. This should preferably be done in a prospective comparative study with physiotherapists blinded to MR findings. Despite minor shortcoming, this study might justify more aggressive rehabilitation of elite athletes with edema or partial discontinuity of the anterior syndesmosis.

The prevalence of cartilage and osteochondral lesions ((O)CLs) in athletes with an acute ligamentous ankle injury was investigated in one previous study.[12] In this retrospective cohort study of 261 athletes with a prevalence of 8% was established using 1.5T MRI. In **chapter 7** the prevalence of (O)CLs was evaluated using 3.0 T MRI, as the visualization of cartilage injuries improves with higher field-strength. In this

study a prevalence of 14% was established. The findings in this study demonstrate that (O)CLS are more common than previously reported. In addition, the association between (O)CLs and syndesmosis injury was evaluated. Although higher odds were observed for (O)CLs in the presence of syndesmosis injury, it did not reach statistical significance. A possible explanation might be the relatively small sample size. Furthermore, stable syndesmosis injuries (West Point I-IIa) were also considered disease positive. As demonstrated in unstable injuries the presence of (O)CLs increases from 12% with West Point grade IIB injury to 40% with West Point grade III injury.[13] It is likely that considering stable syndesmosis injuries as disease positive will have impacted the association with (O)CLs. Recent studies have demonstrated that not all (O)CLs are visualized using MRI.[14] Using MRI might therefore have resulted in an underreporting in our study. Future studies should therefore aim to use minimally invasive alternatives (e.g. nanoscope) to determine the true prevalence of (O)CLs in a large prospective cohort study of athletes with acute ligamentous ankle injuries. Gathered data might be used to determine prognostic factors for the development of end-stage osteo-arthritis. Findings from the current study should raise awareness on the high prevalence of (O)CLs in patients with an acute ligamentous ankle injury. Athletes who fail to progress during rehabilitation of an acute ligamentous ankle injury should therefore be evaluated to rule out the presence of (O)CLs.

Clinical and scientific implications

Clinical implications

Elite athletes who sustain an acute ligamentous ankle injury should be clinically evaluated as soon as possible. In the acute setting it is imperative to determine the mechanism of injury (e.g. eversion). When tenderness over the lateral ankle ligaments is absent, complete discontinuity is unlikely. When there is lateral swelling, hematoma or a positive anterior drawer test, complete discontinuity of the lateral ankle ligaments is likely. When based on the mechanism of injury (eversion) and clinical evaluation (squeeze test) syndesmosis injury is suspected, ultrasound can be used to rule out syndesmosis injury. If injury of the lateral ankle ligaments is suspected or ultrasound is positive for syndesmosis injury, elite athlete should be referred to an experienced Sports Medicine Surgeon. In elite athletes a MR scan will often be obtained to determine which ligamentous complexes are injured and rule out concomitant (O)CLs. Elite athletes with partial discontinuity of the lateral ankle ligaments or anterior syndesmosis (West Point I-IIa) can be referred for supervised rehabilitation. To prevent long term-sequela and improve return to sports, elite athletes with complete discontinuity of the lateral ankle ligaments or with clinically unstable syndesmosis injuries (West Point IIb-III) should be counselled for surgical intervention (e.g. Tightrope fixation).

Recreational athletes who sustain an acute ligamentous ankle injury will often present to their General Practitioner or local A&E department. In a hectic A&E department or General Practitioners office, it might not be feasible to rule out ligamentous ankle injuries in the acute setting, due to high levels of pain and swelling. The aim should therefore be to rule out any fractures. In recreational athletes, proper clinical evaluation in the delayed setting improves sensitivity of common clinical findings. Recreational athletes with hematoma or a positive anterior drawer test, consistent with complete discontinuity of the lateral ankle ligaments, can be referred for supervised rehabilitation. When during delayed clinical evaluation a syndesmosis injury is suspected ultrasound can be used to detect syndesmosis injury. Patients with stable syndesmosis injuries (West Point I-IIa) can be referred for a supervised rehabilitation program. Patients who are undergoing supervised rehabilitation but fail to progress should undergo MRI to rule out concomitant (O)CLS. Patients with chronic ankle instability or unstable syndesmosis injuries (West Point IIb-III) should be referred to a specialized Foot & Ankle surgeon.

Scientific implications

Diagnostic accuracy of dynamic ultrasound for the diagnosis of syndesmosis injury was evaluated in **chapter 4.** The use of internal and external torque did not improve diagnostic accuracy. A possible explanation might be the inclusion of stable syndesmosis injuries as disease positive. However, recent studies suggest we should evaluate instability of the syndesmosis in the sagittal plane. Future clinical studies evaluating the use of dynamic ultrasound should therefore compare the application of internal and external torque with translation in the sagittal plane.[15]

Diagnostic reliability of MR injury grading of the ligamentous ankle complexes was evaluated in **chapter 5.** As demonstrated the Schneck grading system, which is the most used grading system in daily clinical practice, demonstrated limited inter- and intrarater reliability. The outcome of this study reflects the difficulties with interpreting MRI scans, experienced in daily clinical practice. Future studies using MR grading as a reference standard could benefit from using a dichotomous grading system (e.g. normal vs. complete discontinuity) as this demonstrated to improve diagnostic reliability.

Strengths and limitations

The strength of this thesis is that we prospectively recruited a large cohort of athletes with acute ligamentous ankle injuries and used high-field strength MRI (3T) as reference standard. However, the use of 3T MRI as reference standard is also the main limitation of this thesis. MRI has demonstrated high diagnostic accuracy for injuries of the lateral ankle ligaments and syndesmosis.[16,17] Although potential

instability can be delineated from MRI findings, instability is a dynamic finding. (e.g. West Point IIa/IIb) In **chapter 3** and **chapter 4** it would have been of value if dynamic (in-)stability of the syndesmosis had been quantified using non-invasive (e.g. dynamic ultrasound) or minimally invasive techniques. (e.g. nanoscope) Only considering unstable syndesmosis injuries as disease positive might improve the diagnostic value of clinical evaluation and dynamic ultrasound.

Another limitation of this thesis is its external validity. Aspetar is a specialized Orthopaedic and Sports Medicine hospital which organizes daily walk-in-clinics for athletes with acute musculoskeletal injuries. These clinics are attended by senior sports medicine physician with extensive experience in diagnosing musculoskeletal injuries, subsequent imaging studies are analysed by specialized Musculoskeletal Radiologist and rehabilitation is performed under supervision of physiotherapist with extensive experience in treating acute ligamentous ankle injuries. In daily clinical practice athletes are often seen by healthcare practitioners who are less experienced in diagnosing and treating musculoskeletal injuries. This affects the external validity of our findings and should be considered when interpreting the results of this thesis.

Finally, a relatively high loss to follow-up occurred in **chapter 6**. Most athletes were willing to participate in the studies as it included extensive imaging studies of which the outcome was provided to the patient and their support team. Several athletes were lost to follow-up after imaging studies had been completed, as they did not want to participate in the further rehabilitation process.

Future prospects

Future studies investigating the diagnostic accuracy of clinical evaluation or (dynamic-) ultrasound for the diagnosis of syndesmosis injuries should aim to differentiate stable (West Point I-IIa) from unstable (West Point IIb-III) syndesmosis injuries. Options include the use of non-invasive (weight-bearing CT) or minimally invasive techniques (e.g. nanoscope) to determine stability. Clinical tests (e.g. squeeze test) and dynamic ultrasound might demonstrate improved diagnostic accuracy when only unstable syndesmosis injuries are considered disease positive. With the advance of artificial intelligence, large multi-centre datasets might be used to explore the development of a diagnostic algorithm for syndesmosis injury and cartilage lesions.

Return to play times for acute ligamentous ankle injuries with and without syndesmosis involvement were reported for a subset of athletes included in **chapter 6**. No statistically significant difference between both groups was observed. This is in contrast with current literature where athletes with syndesmosis injuries

demonstrate a prolonged return to play compared to athletes with injury of the lateral ankle ligaments. Therefore, a large prospective cohort study evaluating the time to return to play, return to performance and re-injury rates is warranted. Future studies should aim to 1) use high-quality reference standards (e.g. 3T MRI), 2) quantify stability of the syndesmosis (e.g. weight-bearing CT), 3) apply blinding of the treating physiotherapist. To identify risk factors for re-injury, a test battery for strength, balance and proprioception may be administered when athletes are cleared to return to play.

Osteoarthritis may develop in athletes after an acute ligamentous ankle injury. Osteoarthritis is understood to be the result of a degenerative cascade, starting with partial-thickness cartilage surface lesions followed by osteochondral lesions and finally end-stage osteoarthritis. However, not all athletes develop end-stage osteoarthritis after an acute ligamentous ankle injury. A hypothetical risk factor for the development of ankle osteoarthritis is the presence of syndesmosis injury and concomitant cartilage lesions. A large prospective cohort study using a high-quality reference standard (e.g. 3T MRI, nanoscopy) to assess the ankle cartilage of athletes with an acute ligamentous ankle injury is therefore required. Long-term follow-up of this cohort could help to determine which athletes are at increased risk of developing osteoarthritis.

Conclusion

This thesis underlines the importance of clinical evaluation of athletes with an acute ligamentous ankle injury. In the acute setting, understanding the mechanism of injury and thorough physical examination can be useful to determine involvement of the lateral ankle ligaments (lateral hematoma or positive anterior drawer test) and syndesmosis (eversion mechanism or squeeze test). In the delayed setting, sensitivity of common clinical findings for injury of the lateral ankle ligaments improves. When based on clinical evaluation a syndesmosis injury is suspected, ultrasound can be used to confirm the diagnosis.

When compared to acute ligamentous ankle injuries without involvement of the syndesmosis, clinically stable anterior syndesmosis injuries do not affect functional outcome at 6 weeks, 6 months and 1-year post-injury. Finally, the findings of this thesis should raise awareness amongst clinicians on the high prevalence of concomitant (O)CLs in athletes with an acute ligamentous ankle injury.

APPENDIX

Summary

SUMMARY

Acute ligamentous ankle injuries are among the most prevalent injuries in sports. In clinical practice, the diagnostic work-up of athletes with an acute ligamentous ankle injury often focuses on the lateral ankle ligaments, which are affected most commonly. However, a subset of athletes will incur a syndesmosis or other concomitant injury (e.g. osteochondral injury). Research on the diagnostic work-up and outcome of these injuries is lacking. The aim of this thesis is to investigate the diagnostic work-up and prognosis of acute ligamentous ankle injuries, specifically including syndesmosis and other concomitant injuries, such as chondral injuries.

Part 1. Introduction

In **chapter 1** an introduction to this thesis is provided with an overview of current knowledge of anatomy, injury mechanism, clinical evaluation, imaging, grading, management, and prognosis of acute ligamentous ankle injuries.

Part 2. Clinical evaluation of acute ligamentous ankle injuries

Clinical evaluation is the mainstay for the diagnosis of acute ligamentous ankle injuries. In **chapter 2** the diagnostic value of clinical evaluation using common clinical findings was evaluated in the acute and delayed setting. For this study 43 athletes with an acute ligamentous ankle injury underwent clinical evaluation in the acute (0-2 days post-injury) and delayed setting (5-8 days post-injury). 3 Tesla (T) MRI was used as reference standard. This study concluded that in the acute setting, clinical findings with high sensitivity were useful to exclude complete discontinuity of the lateral ankle ligaments (absent lateral swelling). Within the acute setting, clinical findings with a high specificity (e.g. haematoma, anterior drawer test and talar tilt test) are useful to identify athletes with high probability of complete discontinuity. In addition, the study demonstrated that sensitivity of common clinical findings improves when evaluated in the delayed setting (5-8 days post-injury).

In **chapter 3** the acute clinical evaluation (0-7 days post-injury) for syndesmosis injury was evaluated. In this study a total of 145 athletes, with 150 acute ankle injuries, underwent physical examination for syndesmosis injury. 3T MRI was used as reference standard. This study established that in the acute setting (0-7 days post-injury) an eversion mechanism of injury and a positive squeeze test were associated with the presence of syndesmosis injury. When the examining physician had a negative overall clinical suspicion, the probability of syndesmosis injury reduced considerably.

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Part 3. Imaging of acute ligamentous ankle injuries

The diagnostic value of (dynamic-) ultrasound was evaluated in **chapter 4**. In this study 91 athletes, with 92 acute ankle injuries, were evaluated. Patients underwent (dynamic-) ultrasound of the lateral ankle ligaments (ATFL, CFL) and anterior syndesmosis (AITFL) within 10 days post-injury. 3T MRI was used as reference standard. For injury of the ATFL and CFL ultrasound demonstrated 87% and 29% sensitivity and 69% and 92% specificity, respectively. Ultrasound demonstrated a 100% diagnostic accuracy for injury of the anterior syndesmosis (AITFL). Dynamic measurement did not improve diagnostic accuracy of anterior syndesmosis injury, with a side-to-side difference in external rotation having the highest diagnostic accuracy (82% sensitivity and 86% specificity).

As 3T MRI was used as reference standard in all studies incorporated into this thesis, it was imperative to determine its inter- and intra-rater reliability. In **chapter 5** the diagnostic reliability for injury of the lateral ankle ligaments (ATFL, CFL, PTFL), syndesmosis ligaments (AITFL, IOL, IOM, PITFL, TTFL) and medial ankle ligaments (TN, TS, TC, PT, ATT, PTT) was evaluated. Two musculoskeletal radiologists graded 92 MR scans of athletes with an acute ankle injury. All scans were obtained within 10 days post-injury. Ligamentous ankle injuries were graded using the Schneck grading system and Sikka classification for syndesmosis injury. One radiologist repeated the MR grading after 30 days to determine intra-rater reliability. The Schneck grading system had limited inter- and intra-rater reliability for grading of the individual ankle ligaments. Reliability for grading of the ATFL and AITFL improved when dichotomized for the presence of complete discontinuity. The Sikka classification demonstrated moderate to almost perfect inter and intra-rater reliability.

Part 4. Prognosis of acute ligamentous ankle injuries and associated injuries

The functional outcome of stable anterior syndesmosis injuries was evaluated in **chapter 6**. For this study a total of 94 athletes with an acute ankle injury were prospectively followed-up at 6 weeks, 6 months and 1 year. Anterior syndesmosis injury was diagnosed using 3T MRI. Based on clinical evaluation a senior Orthopaedic Sports Medicine Surgeon confirmed syndesmotic stability. Athletes requiring surgical stabilization of the syndesmosis were excluded. Of the 94 included athletes, 28 were diagnosed with a stable syndesmosis injury. Athletes underwent rehabilitation at the in-house rehabilitation facility or in case of professional athletes at their club. At follow-up the Foot and Ankle Outcome score (FAOS) and modified Karlsson & Peterson questionnaires were administered. No between group difference in FAOS subscores or modified Karlsson & Peterson outcome scores were observed. This study concluded that when comparing acute ligamentous ankle injuries with and without involvement of the anterior syndesmosis, no statistically significant between group differences in functional outcome scores were observed at six weeks, six months and 1 year.

The size, prevalence and anatomic location of cartilage and osteochondral injuries ((O)CLs) in athletes with an acute ligamentous ankle injury was evaluated in **chapter 7.** Using 3T MRI in a total of 171 athletes, (O)CLs were observed in 14%. No statistically significant association between (O)CLs and syndesmosis injury was observed.

Part 5. Discussion & Summary
In **chapter 8** a general discussion and summary of this thesis is provided.

APPENDIX

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Acuut enkelbandletsel is een van de meest voorkomende sportblessures. In de klinische praktijk richt de diagnostiek bij atleten met acuut enkelbandletsel zich met name op de laterale enkelbanden, welke het meest frequent zijn aangedaan. Bij een deel van de atleten met een acuut enkelbandletsel is er echter sprake van syndesmoseletsel en/of letsel van geassocieerde anatomische structuren (bijv. kraakbeenschade). Tot op heden is er weinig onderzoek verricht naar de diagnostiek en prognose van deze specifieke letsels. Het primaire doel van dit proefschrift is daarom het onderzoeken van het diagnostisch proces en de prognose van acuut enkelbandletsels, waaronder specifiek syndesmoseletsel en geassocieerd letsel, zoals bijvoorbeeld kraakbeen letsels.

Deel 1. Introductie

In **hoofdstuk 1** wordt een inleiding gegeven op dit proefschrift, met een overzicht van de huidige kennis over anatomie, trauma-mechanismen, klinische evaluatie, radiologische beeldvorming, classificatie, behandeling en prognose van acuut enkelbandletsel.

Deel 2. Klinische evaluatie van acute enkelbandletsels

Klinische evaluatie is de hoeksteen in de diagnostiek van acuut enkelbandletsel. In **hoofdstuk 2** werd de diagnostische waarde van klinische evaluatie voor lateraal enkelbandletsel, met behulp van veelvoorkomende klinische bevindingen, geëvalueerd in zowel de acute als de uitgestelde setting. Voor deze studie ondergingen 43 atleten met een acuut enkelbandletsel een klinische evaluatie in de acute (0-2 dagen na het letsel) en de uitgestelde setting (5-8 dagen na het letsel). 3 Tesla (T) MRI werd gebruikt als referentiestandaard. De conclusie van deze studie is dat in de acute setting, klinische bevindingen met een hoge sensitiviteit nuttig zijn om een volledige discontinuïteit van de laterale enkelbanden uit te sluiten (afwezigheid van laterale zwelling). In de acute setting zijn klinische bevindingen met een hoge specificiteit (bijv. hematoom, voorste schuiflade test en talar tilt test) nuttig om atleten met een grote kans op volledige discontinuïteit te identificeren. Bovendien toonde deze studie aan dat de sensitiviteit van veelvoorkomende klinische bevindingen verbeterde wanneer zij werden geëvalueerd in de uitgestelde setting (5-8 dagen na het letsel).

In **hoofdstuk 3** werd de diagnostische waarde van acute klinische evaluatie (0-7 dagen na het letsel) voor syndesmoseletsel onderzocht. In deze studie ondergingen 145 atleten, met in het totaal 150 acute enkelbandletsels, een klinische evaluatie voor syndesmoseletsel. 3T MRI werd gebruikt als referentiestandaard. In deze

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studie werd vastgesteld dat in de acute setting (0-7 dagen na het letsel) een eversie-mechanisme en een positieve squeeze-test geassocieerd zijn met de aanwezigheid van syndesmoseletsel. Wanneer de onderzoekende arts een negatieve algehele klinische verdenking had, nam de kans op syndesmoseletsel statistisch significant af.

Deel 3. Radiologisch onderzoek van enkelbandletsel

De diagnostische waarde van (dynamische) echografie werd onderzocht in **hoofdstuk 4**. In deze studie werden 91 atleten, met in het totaal 92 acute enkelbandletsels, geïncludeerd. Atleten ondergingen binnen 10 dagen na het trauma (dynamische) echografie van de laterale enkelbanden (ATFL, CFL) en de anterieure syndesmose (AITFL). 3T MRI werd gebruikt als referentiestandaard. Echografie had voor complete rupturen van de ATFL en CFL, een sensitiviteit van 87% en 29% en specificiteit van 69% en 92%. Echografie had een diagnostische accuraatheid van 100% voor complete rupturen van de anterieure syndesmose (AITFL). Dynamische metingen verbeterden de diagnostische accuraatheid voor anterieur syndesmoseletsel niet. Van de dynamische tests had de meting in exorotatie, vergeleken met de contra-laterale zijde, de hoogste diagnostische accuraatheid (82% sensitiviteit en 86% specificiteit).

Omdat alle studies in dit proefschrift gebruik maken van 3T MRI als referentiestandaard, was het noodzakelijk de inter- en intra-beoordeelaars betrouwbaarheid hiervan te bepalen. In **hoofdstuk 5** werd daarom de diagnostische betrouwbaarheid van letselgradering van de laterale enkelbanden (ATFL, CFL, PTFL), syndesmose (AITFL, IOL, IOM, PITFL, TTFL) en mediale enkelbanden (TN, TS, TC, PT, ATT, PTT) geëvalueerd. Twee musculoskeletale radiologen beoordeelden 92 MRI-scans van atleten met een acuut enkelbandletsel. Alle MRI-scans werden binnen 10 dagen na het trauma verkregen. Enkelbandletsel werd gegradeerd met behulp van het Schneck-gradatiesysteem en de Sikka-classificatie voor syndesmoseletsel. Eén radioloog herhaalde de MRI-beoordeling na 30 dagen om de intra-beoordelaars betrouwbaarheid te bepalen. Het Schneck-gradatiesysteem had beperkte inter- en intra-beoordelaars betrouwbaarheid voor de beoordeling van de afzonderlijke enkelbanden. De betrouwbaarheid voor de beoordeling van de ATFL en AITFL verbeterde wanneer dichotomisatie werd toegepast voor de aanwezigheid van complete discontinuïteit. De Sikka-classificatie toonde een matige tot bijna perfecte inter- en intra-beoordelaars betrouwbaarheid.

Deel 4. Prognose van acuut enkelbandletsel en geassocieerd letsels

De functionele uitkomst van stabiel anterieur syndesmoseletsel werd geëvalueerd in **hoofdstuk 6**. Voor deze studie werden 94 atleten met een acuut enkelbandletsel prospectief vervolgd na 6 weken, 6 maanden en 1 jaar. De aanwezigheid van anterieur syndesmoseletsel werd bepaald met behulp van 3 T MRI. Indien er sprake

was van syndesmoseletsel werd de stabiliteit van de syndesmose beoordeeld door een ervaren orthopaedisch chirurg. Atleten waarbij een indicatie bestond voor chirurgische stabilisatie van de syndesmose, werden geëxcludeerd. Van de 94 geïncludeerde atleten werd bij 28 een stabiel anterieur syndesmosesletsel vastgesteld. De geïncludeerde atleten ondergingen revalidatie bij de afdeling fysiotherapie van het ziekenhuis. In het geval van professionele atleten werd revalidatie bij hun club ook toegestaan. Ten tijde van follow-up werd de Foot and Ankle Outcome Score (FAOS) en de gemodificeerde Karlsson & Peterson vragenlijsten afgenomen. Op de verschillende tijdspunten werd er geen significant groepsverschil waargenomen in de FAOS-subscores of de gemodificeerde Karlsson & Peterson uitkomstscores. De studie concludeerde dat bij atleten met een acuut enkelbandletsel, betrokkenheid van de anterieure syndesmose geen statistisch significante slechtere functionele uitkomst gaf na 6 weken, 6 maanden en 1 jaar.

Tenslotte werd in **hoofdstuk 7** de omvang, prevalentie en anatomische locatie van kraakbeen- en osteochondrale letsels ([O]CL's) bij atleten met een acuut enkelbandletsel geëvalueerd. Met behulp van 3T MRI werden bij 14% van de 171 geïncludeerde atleten een (O)CL's geconstateerd. Er werd geen statistisch significante associatie gevonden tussen syndesmoseletsel en (O)CL's.

Deel 5. Discussie & Samenvatting

Hoofdstuk 8 bevat een algemene discussie en samenvatting van dit proefschrift.

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APPENDIX

PhD portfolio

PHD PORTFOLIO

Name: T.P.A. Baltes
PhD period: June 2017-May 2026
PhD supervisors: Prof. Dr. J.L. Tol, Prof. Dr. G.M.M.J. Kerkhoffs
PhD co-supervisor: Prof. Dr. P. D'Hooghe

PhD training

General courses	**Year**	**ECTS**
Collaborative Institutional Training Initiative (CITI) for research on human subjects or research involving animals	2017	0.3
BROK-course ('Basiscursus Regelgeving Klinisch Onderzoek')	2021	1.5
BROK-course refresher	2025	1.5
Seminars, workshops and masterclasses		
Aspetar Tuesday lecture (weekly)	2017-2020	2
Aspetar Journal club 2x/month	2017-2020	1.6
AO Basic Principles of Fracture Management	2019	0.5
Amsterdam UMC Friday lectures	2020-2025	0.2
DFAS Starter and Advanced course	2023	0.5
NVA Knee/Shoulder Arthroscopy Course	2024	0.5
EFAS Specimen Lab Course in Barcelona (Spain)	2025	0.5
EFAS Specimen Lab Course in Vienna (Austria)	2025	0.5
AO Advanced Principles of Fracture Management	2025	0.5
AO Approaches and Fracture Care in Practice	2025	0.5
Oral Presentations		
Aspetar Tuesday lecture, Doha (Qatar)	2020	0.5
AFC Medical conference, Doha (Qatar)	2023	1.5
ISOKINETIC, London (United Kingdom)	2023	0.5
IOC Research Meeting, Amsterdam (The Netherlands)	2023	0.5
Sportmedisch Wetenschappelijk Jaarcongres, Vianen (The Netherlands)	2023	0.5
ISAKOS 15th Biennial Congress, Munich (Germany)	2025	0.5
NVA Anniversary Meeting 2025, Noordwijk (The Netherlands)	2025	0.5

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	Year	ECTS
Poster Presentations		
ESSKA Congress, Paris (France)	2022	0.5
(Inter)national conferences – Attendance		
Northern Orthopedic Federation (NOF)/Dutch Orthopedic Society (NOV) Annual Congress, Rotterdam (The Netherlands)	2024	0.2
NVA Annual Meeting 2024, Amsterdam (The Netherlands)	2024	0.2
Edinburgh Trauma Symposium, Edinburgh (United Kingdom)	2025	0.2
Other		
Reviewer for Injury	2023-2024	3.0
Reviewer for Knee Surgery, Sports Traumatology, Arthroscopy	2023-2024	1.0
Reviewer for Journal of Experimental Orthopaedics	2024	0.2
Reviewer for BMC Musculoskeletal Disorders	2024	0.2
Tutoring, Mentoring, Supervising		
Anouk Schmidt, BSc thesis, Medicine	2020	1.0
Jesper Smit, BSc thesis, Medicine	2022	1.0
Michael Does, BSc thesis, Medicine	2025	1.0
Daan van Steijn, MSc thesis, Medicine	2025	1.5
Grants		
Marti-Keuning Eckhardt Foundation personal grant	2021	1.0
IOC International Visiting Trainee grant	2025/2026	3.0
Awards and Prizes		
NVOT Traveling Fellowship, Royal Infirmary Edinburgh (United Kingdom)	2025	2.0

APPENDIX

List of publications
(peer reviewed)

LIST OF PUBLICATIONS (PEER REVIEWED)

1. **Baltes TPA**, Zwiers R, Wiegerinck JI, van Dijk CN. Surgical treatment for midportion Achilles tendinopathy: a systematic review. Knee Surg Sports Traumatol Arthrosc. 2017 25:1817-1838

2. **Baltes TPA**, Donders JCE, Kloen P. What is the hardware removal rate after anteroinferior plating of the clavicle? A retrospective cohort study. J Shoulder Elbow Surg. 2017 26:1838-1843

3. Opdam KTM, **Baltes TPA**, Zwiers R, Wiegerinck JI, van Dijk CN. A 2-8 year follow-up study of patient satisfaction and functional outcome in the endoscopic treatment of midportion Achilles Tendinopathy. Arthroscopy. 2017 34:264-269

4. Zwiers R, **Baltes TPA**, Opdam KTM, Wiegerinck JI, van Dijk CN. Prevalence of Os Trigonum on CT Imaging. Foot Ankle Int. 2017 39:338-342

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6. D'Hooghe P, Grassi A, Alkhelaifi K, Calder J, **Baltes TPA**, Zaffagnini S, Ekstrand J. Return to play after surgery for isolated unstable syndesmotic ankle injuries (West Point grade IIB and III) in 110 male professional football players: a retrospective cohort study. Br J Sports Med. 2020 54:1168-1173

7. **Baltes TPA**, Arnaiz J, Geertsema L, Geertsema C, D'Hooghe P, Kerkhoffs GMMJ, Tol JL. Diagnostic value of ultrasonography in acute lateral and syndesmotic ligamentous ankle injuries. Eur Radiol. 2020 31:2610-2620

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9. **Baltes TPA**, van der Veen AJ, Blankevoort L, Donders JCE, Kloen P. Locking plate constructs in subtrochanteric fixation; a biomechanical comparison of LCP screws and AO-nuts. Clin J Orthop Trauma. 2020 31:1-6

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10. Van der Burg FAE, **Baltes TPA**, Kloen P. Large segmental defects in midshaft clavicle nonunion treated with autologous tricortical iliac crest bone graft. Shoulder Elbow. 2023 15: 45-53

11. Grewal S, **Baltes TPA**, Wiegerinck EMA, Kloen P. Recalcitrant nonunion of the clavicle. Strategies Trauma Limb Reconstr. 2022 17:1-6

12. **Baltes TPA**, Al Sayrafi O, Arnaiz J, Al-Naimi M, Geertsema C, Geertsema L, Holtzhausen L, D'Hooghe P, Kerkhoffs G, Tol JL. Acute clinical evaluation for syndesmosis injury has high diagnostic value. Knee Surg Sports Traumatol Arthrosc. 2022 30:3871-3880

13. **Baltes TPA**, Geertsema C, Geertsema L, Holtzhausen L, Arnaiz J, Al-Naimi M, Al-Sayrafi O, Whiteley R, Slim M, D'Hooge P, Kerkhoffs GM, Tol JL. Acute clinical evaluation for the diagnosis of lateral ankle ligament injuries is useful: A comparison between the acute and delayed settings. Knee Surg Sports Traumatol Arthrosc. 2024 32:550-561

14. **Baltes TPA,** Al Sayrafi O, Al-Naimi M, Anadani M, Abassi M, Whiteley R, D'Hooghe P, Kerkhoffs GMMJ, Tol J.L. Does involvement of the anterior syndesmosis affect the functional outcome of acute ligamentous ankle injuries? J Sci Med Sport 2024 28:305-312

15. Hagemeijer NC, **Baltes TPA**, Wallinga AG, Guss D, Kerkhoffs G. Diagnosis of syndesmotic instability: clinical evaluation, radiographs, ultrasound, (weightbearing) CT scan, MRI and arthroscopy. Tech Foot Ankle 2025 DOI: 10.1097/BTF.0000000000000445

16. **Baltes TPA**, Dalansi F, Al-Naimi M, Bordalo M, Holtzhausen LJ, Whiteley R, Cardinale M, D'Hooghe P, Kerkhoffs GM, Tol JL. The Prevalence, Size, and Anatomic Location of Cartilage and Osteochondral Lesions in Athletes With an Acute Ligamentous Ankle Injury. Am J Sports Med 2025 53:2173-2180

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1. D'Hooghe P, Bouri F, Eleftheriou A, **Baltes TPA**, Alkhelaifi K. Ankle fractures and return to sports in Athletes; Does Arthroscopy add value to the treatment? In: Sport Injuries of the Foot and Ankle - A Focus on Advanced Surgical Techniques. Editors: Canata GL, D'Hooghe P, Hunt K, Kerkhoffs GMMJ, Longo UG. Springer 1e ed 2018. Chapter 16.

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APPENDIX

Curriculum Vitae

CURRICULUM VITAE

Thomas Baltes was born in Baarn on the 3th of March 1993. After graduating Griftland College high school Soest in 2011, he commenced his study Medicine at the University of Amsterdam.

During his study he got the opportunity to participate in research projects on hindfoot pathology (prof. dr. C.N. van Dijk) and orthopaedic traumatology (prof. dr. P. Kloen) at the department of Orthopaedic Surgery and Sports Medicine of the Amsterdam UMC. After completing his senior internship at the department of Orthopaedic Surgery and Traumatology of the Tergooi Medical Center Hilversum (dr. A.M.J.S. Vervest) he graduated from the University of Amsterdam in 2017.

From 2017 until 2020 he worked as a post-graduate Researcher at Aspetar Orthopaedic and Sports Medicine Hospital in Doha (Qatar). During his period as post-graduate researcher he managed the prospective Aspetar Ankle study which would form the basis of his PhD-thesis. (prof. dr. P. D'Hooghe; prof. dr. J.L. Tol; prof. dr. G.M.M.J. Kerkhoffs)

After working as a resident not in training at the Amphia Hospital Breda (prof. dr. D. Eygendaal) he was accepted for orthopaedic surgery residency in 2021. He continued his research on ligamentous ankle injuries during his residency in general surgery (common trunk) at the Noordwest Ziekenhuis Alkmaar (dr. K.J. Ponsen) and in orthopaedic surgery at the Spaarne Gasthuis Hoofddorp (dr. A. van Noort) and Amsterdam UMC (dr. M.U. Schafroth). This culminated in the defence of his PhD-thesis in 2026.

Currently Thomas works as a resident at the department of Orthopaedic Surgery and Traumatology of the Tergooi Medical Center Hilversum (dr. R.A.W. Verhagen). He happily lives in Amsterdam with his wife Lisa Malipaard. After completion of his residency in Orthopaedic Surgery his aim is to become an orthopaedic (trauma) surgeon with a focus on (sports-) injuries of the lower extremities.

APPENDIX

Acknowledgements

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First and foremost, I would like to extend my gratitude to all the athletes who participated in the Aspetar ankle study. Despite facing injury, you embraced the demanding diagnostic and rehabilitation process that was part of the study. Your invaluable contribution made this research, and the completion of this thesis, possible.

Prof. dr. G.M.M.J. Kerkhoffs, Gino, onze eerste kennismaking kan ik mij nog goed herinneren. Je kwam meteen to-the-point en dwong mij om duidelijk mijn doelen aan te geven: 1) promoveren, 2) een opleidingsplek orthopedie. Je hebt mij gesteund, gepusht en af en toe de juiste richting gewezen. Daar ben ik je ontzettend dankbaar voor. Ik kijk er naar uit om in de kliniek van je te mogen leren.

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