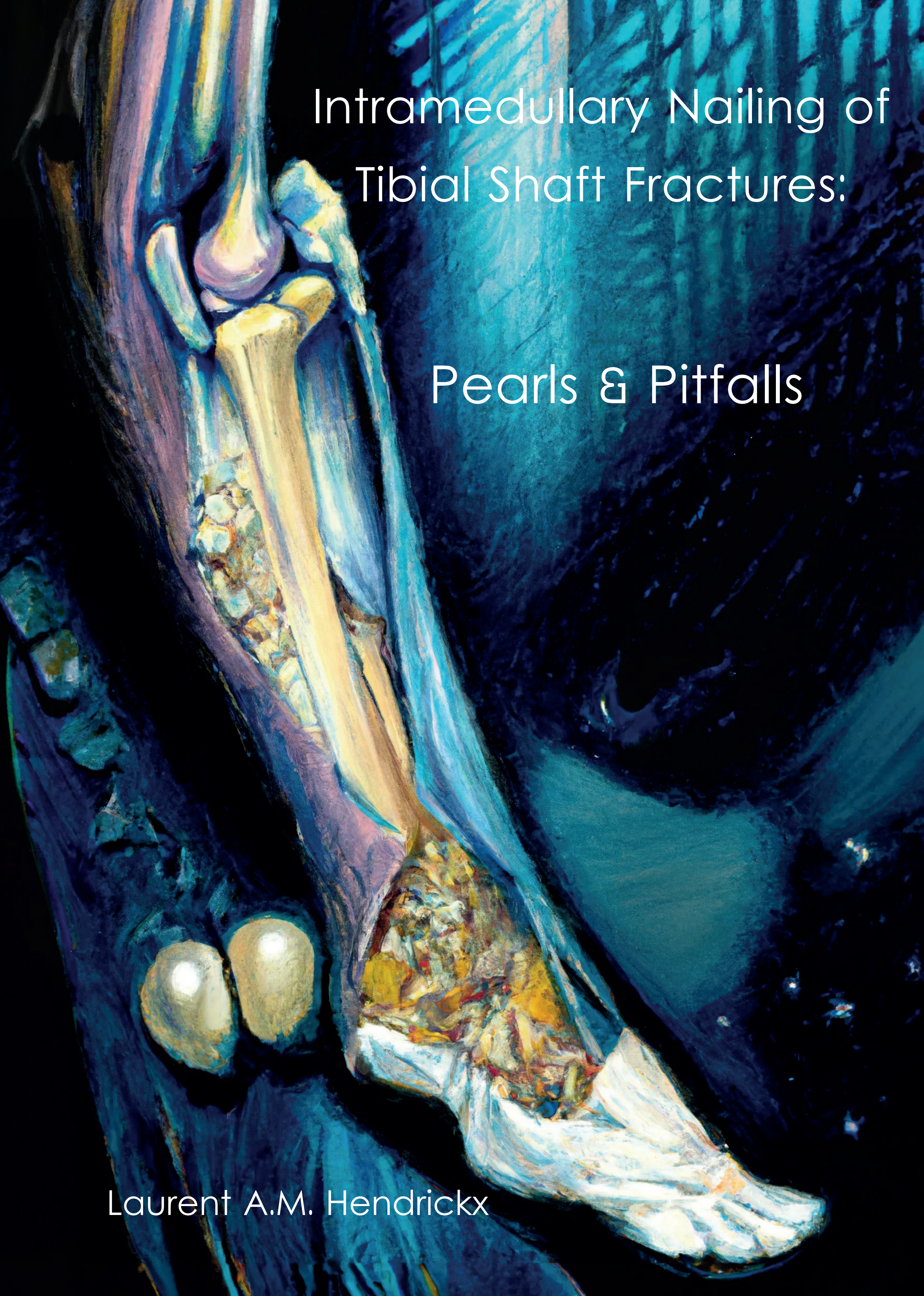
Intramedullary Nailing of Tibial Shaft Fractures: Pearls & Pitfalls

Laurent A.M. Hendrickx



Intramedullary Nailing of Tibial Shaft Fractures:

Pearls & Pitfalls

Laurent A.M. Hendrickx

Intramedullary Nailing of Tibial Shaft Fractures: Pearls & Pitfalls

Laurent A.M. Hendrickx

The research in this thesis was supported by grants from Flinders University, Michael van Vlooten Fonds, KNAW van Leersum Beurs, Traumaplatform, Prins Bernhard Cultuurfonds, Annafonds and Marti-Keuning Eckhardt Stichting.

Printing of this thesis was sponsored by Anna Fonds, Chipsoft, Nederlandse Orthopaedische Vereniging (NOV), Department of Orthopaedic Surgery Amsterdam UMC and Flinders University.

Layout & Design: Ridderprint

Printing: Ridderprint

Cover Design:

Cover by Ran × DALL·E

Prompt: “intramedullary nailing of tibial shaft fractures: pearls & pitfalls. Painting in van gogh style, dark blue tones. ”

Intramedullary nailing of tibial shaft fractures: pearls & pitfalls

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. P.P.C.C. Verbeek
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op vrijdag 9 februari 2024, te 13.00 uur

door Laurent Alexander Marijn Hendrickx
geboren te Amsterdam

Promotiecommissie

Promotores:	prof. dr. G.M.M.J. Kerkhoffs	AMC-UvA
	prof. dr. R.L. Jaarsma	Flinders University
Copromotores:	prof. dr. J.N. Doornberg	Rijksuniversiteit Groningen
Overige leden:	prof. dr. R.J. Oostra	AMC-UvA
	prof. dr. J.L. Tol	AMC-UvA
	prof. dr. M.H.J. Verhofstad	Erasmus Universiteit Rotterdam
	prof. dr. ir. N.J.J. Verdonschot	Radboud Universiteit
	prof. dr. M. Maas	AMC-UvA
	prof. dr. F.W. Bloemers	Vrije Universiteit Amsterdam

Faculteit der Geneeskunde

Dit proefschrift is tot stand gekomen binnen een samenwerkingsverband tussen de Universiteit van Amsterdam en Flinders University met als doel het behalen van een gezamenlijk doctoraat. Het proefschrift is voorbereid aan de Faculteit der Geneeskunde van de Universiteit van Amsterdam en aan het College of Medicine and Public Health van Flinders University.

This thesis was prepared within the partnership between the University of Amsterdam and Flinders University with the purpose of obtaining a joint doctorate degree. The thesis was prepared in the Faculty of Medicine of the University of Amsterdam and in the College of Medicine and Public Health of Flinders University.

INTRAMEDULLARY NAILING OF TIBIAL SHAFT FRACTURES:

PEARLS & PITFALLS

By

Laurent A.M. Hendrickx, MD MSc

Thesis
Submitted to Flinders University
for the degree of

Doctor of Philosophy
College of Medicine and Public Health
4th of November 2022

This thesis has been written within the framework of the Cotutelle Program, with the purpose of obtaining a joint doctorate degree. The thesis was prepared at the College of Medicine and Public Health of Flinders University and at the Faculty of Medicine of the University of Amsterdam.

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.
Laurent Hendrickx, 04-11-2022

Voor mijn ouders.

TABLE OF CONTENTS

Preface

Intramedullary nailing (IMN) is widely considered the primary operative treatment for tibial shaft fractures (TSF) [1,2]. The first use of intramedullary devices dates back to the Aztecs in the 16th century, who used wooden sticks in the intramedullary canal, as is described in the Florentine Codex [3,4] (Fig 1.) The method of tibial nailing on which our present-day technique is built, was first reported by Küntscher in 1940 [5]. The past century has seen a substantial evolution in techniques: reaming and interlocking screws were introduced in the 1950's, while the 1990's brought about the development of the titanium nail [6].

Figure 1. Page 226-227 of the Florentine Codex on the treatment of fractures. Source: General History of the Things of New Spain by Fray Bernardino de Sahagún: The Florentine Codex. Book X: The People, Their Virtues and Vices, and Other Nations; 1577. World Digital Library.

Even though the procedure has existed and advanced for several decades, complications still occur frequently due to the nature of the inflicted trauma as well as iatrogenic. Often subsequent surgery is required, which leaves with us opportunities for improvement.

Therefore, this thesis addresses the pearls and pitfalls of IMN for TSFs. The general introduction, Chapter 1, will identify the core contemporary issues of tibial intramedullary nailing by providing a systematic review of the incidence and nature of complications and subsequent surgical procedures. As such, it will provide an insight into the opportunities for research and improvement of care, thereby laying the foundation for the main body of this thesis which can be found in the outline provided hereafter.

Outline of thesis

THESIS AIM

The overall aim of this thesis is to contribute to individualizing the management of patients treated with IMN for a TSF in order to improve patient care after personal risk assessment (i.e. risk stratification). To achieve this, a more in-depth knowledge is required in regard to the various complications and subsequent surgical procedures that can occur. Particularly, a better insight into patient specific risks is essential to further individualize the management of patients with tibial shaft fractures, especially in our era of personalized medicine and data driven care. This may lead to an improvement of patient care and a prevention and reduction of complications.

Following the general introduction of Chapter 1, this thesis will consist of three parts. In **Part I** we aim to identify patient specific risks of subsequent surgery in order to individualize patient consent and anticipate peri-operative management. In **Part II** we aim to determine patient specific risks of complications in order to individualize diagnostic work-up and peri-operative treatment plans. In **Part III** we aim to define to what extent iatrogenic complications limit patients' functional performance, and to what extent these complications can be accepted to guide (post) operative management.

PART I. SUBSEQUENT SURGERY – RATE AND PATIENT SPECIFIC RISKS

Rates of re-operation after intramedullary nailing of tibial shaft fractures vary distinctly in literature. **Chapter 2** of this thesis provides a retrospective, single centre review of the subsequent surgery rate in patients undergoing intramedullary nailing of tibial shaft fractures. This chapter is furthermore set out to identify predictors of subsequent surgery for fracture and wound healing.

Chapter 3 aims to develop and validate a Machine Learning (ML) algorithm to predict these patient specific probabilities of subsequent surgery based on a large international multicentre database. This ML algorithm may aid clinicians in identifying which patients are at a high risk of unplanned subsequent surgery, allowing patients to be better informed and develop surgical strategies to address these risk that may be unique to one's individual patient.

PART II. COMPLICATIONS – RATE AND PATIENT SPECIFIC RISKS

Based on the literature review of Chapter 1, it appeared that rotational malalignment of the tibia often remains undiagnosed when diagnosis relies on clinical assessment alone. In **Chapter 4** we therefore assess the incidence of rotational malalignment on postoperative CT-scan imaging in order to gain a better insight in the true incidence of this complication. Predictors of tibial rotational malalignment are furthermore explored in this chapter.

Another diagnosis that should not be overlooked in tibial shaft fractures in order to prevent adverse sequelae is the potential presence of a concomitant posterior malleolar fracture (PMF). This fracture can be difficult to diagnose on radiographs and may often be missed [7–9]. When left undiagnosed preoperatively, patients are at risk of iatrogenic posterior malleolar displacement during intramedullary nailing of the tibia shaft fracture[10–12]. In **Chapter 5**, the true incidence of concomitant posterior malleolar fractures is assessed in a large series of CT-scan imaging. Furthermore, it aims to identify patient specific predictors of a PMF and develop a prediction rule that can aid surgeons in determining whether additional pre-operative CT imaging is warranted.

Chapter 6 aims to further build on this prediction rule. In this chapter, a ML prediction model to estimate the risk of PMF is developed and validated on a large multi-centre database. Implementation of accurate prediction models may improve diagnostic accuracy and facilitate the clinical decision-making process. For this model specific, it guides pre-op assessment with CT.

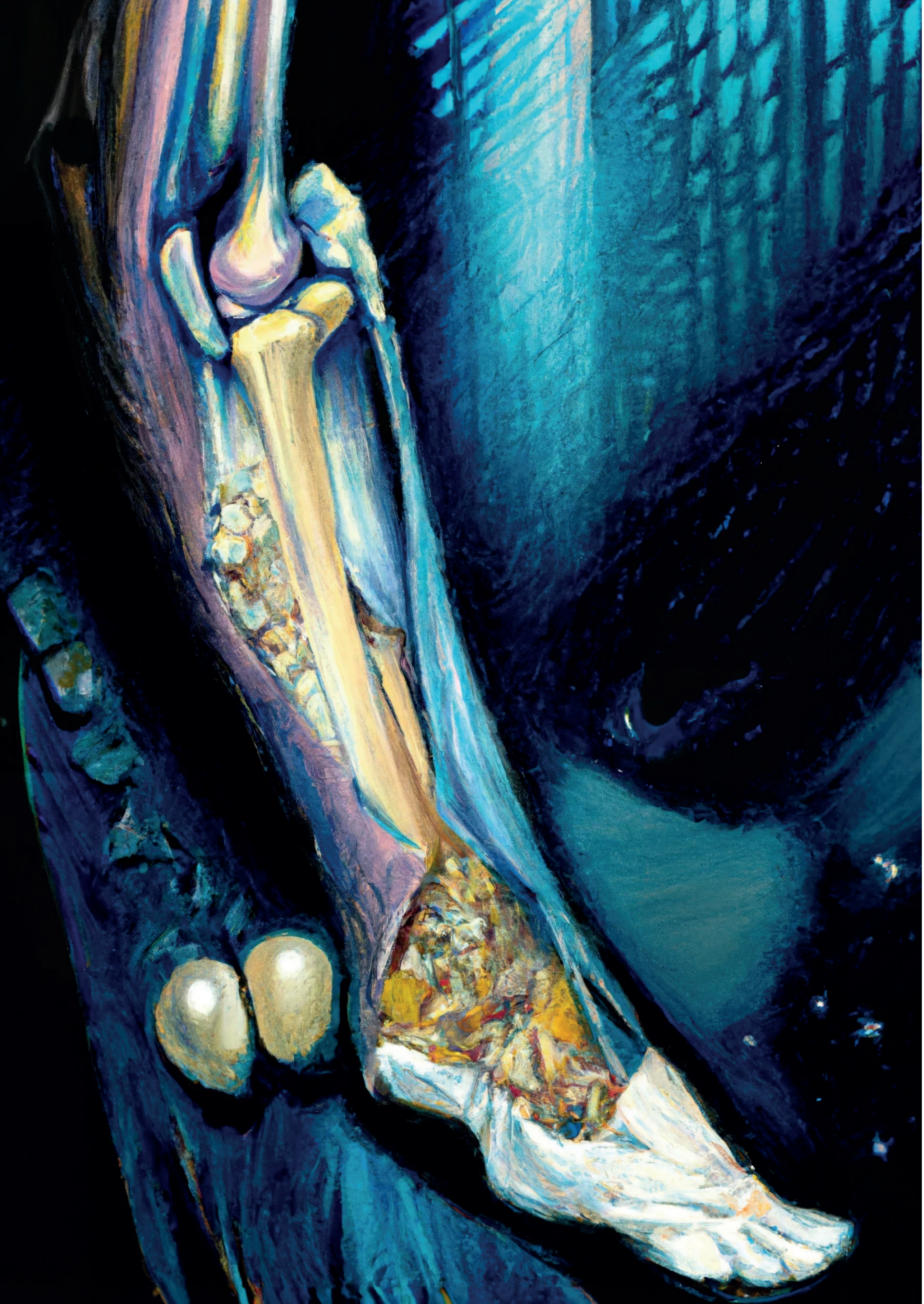
Chapter 7 addresses the risk of infection following operative treatment of tibial shaft fractures. In this chapter a ML model is developed to predict a patient's specific risk of postoperative infection based on variables that are directly available at hospital admission. This model may aid clinicians in determining the optimal peri-operative treatment plan for each individual patient.

PART III. WHAT OUTCOME IS ACCEPTABLE?

Rotational malalignment of the long bones is a common reason for litigation, and claims are commonly awarded [13]: The current definition of rotational malalignment of the tibia relies on an arbitrary cut-off value of >10 degrees. In the U.S, this value is used to determine whether patients are eligible for compensation based on the “Guides to the Evaluation of Permanent Impairment” [14]. **Chapter 8** is set out to quantify the effect of tibial rotational difference on the joint-biomechanics in vivo in a biomechanical 3D-motion-analysis study as well as on patient reported outcome. This may provide additional guidance in deciding to what extent rotational malalignment can be accepted postoperatively.

PART IV. CONCLUSIONS AND DISCUSSION

Part IV is the concluding part of the thesis. In **Chapter 9** the thesis is summarized. In **Chapter 10** the main findings are discussed and prospects for future research are provided.



1

CHAPTER 1

General Introduction

Complications and Subsequent Surgery after Intra-Medullary Nailing for Tibial Shaft Fractures: Review of 8110 patients

Laurent A.M. Hendrickx, James Virgin, Michel P.J. van den Bekerom, Job N. Doornberg, Gino M.M.J. Kerkhoffs, Ruurd L. Jaarsma

INJURY – JULY 2020
Elsevier - Injury. 2020 Jul;51(7):1647-1654.
https://www.injuryjournal.com/article/S0020-1383(20)30352-1/fulltext

ABSTRACT

Background

Intramedullary nailing of tibial shaft fractures has been common practice for decades. Nevertheless, complications occur frequently, and subsequent surgery is often required. To improve our understanding on how we may improve trauma care for patients with tibial shaft fractures, this study systematically reviewed all currently available evidence to assess the incidence of complications and rate of re-operations following intramedullary nailing of traumatic tibial fractures.

Methods

Trip Database, Medline, Scopus and Cochrane Library were searched on September 7th, 2018. Searches were limited to English studies published after January 1st, 1998. Studies were included if authors included more than 50 patients treated with intramedullary nailing for traumatic tibial fractures. Inclusion of studies and critical appraisal of the evidence was performed by two independent authors. Incidence of complications and rate of re-operations were reported with descriptive statistics.

Results

Fifty-one studies involving 8110 patients treated with intramedullary nailing for traumatic tibial fractures were included. Mean age of patients was 37.5 years. The most frequent complication was anterior knee pain (23%), followed by non-union (11%). Eighteen percent of patients required at least one subsequent surgery. The most frequent indication of subsequent surgery was screw removal due to pain or discomfort (9%). Dynamization of the nail to promote union was reported in 8% of the cases. Nail revision and bone-grafting to promote union were applied in 4% and 2% respectively.

Discussion & Conclusion

Patients treated with intramedullary nailing for tibial fractures need to be consented for high probability of adverse events as anterior knee pain, subsequent surgical procedures and bone healing problems are relatively common. However, based on current data it remains difficult to identify specifiers and determinants of an individual patient with specific fracture characteristics at risk for complications. Future studies should aim to establish patient specific risks models for complications and re-operations, such that clinicians can anticipate them and adjust and individualize treatment strategies.

Level of Evidence

Therapeutic Level III

Highlights

- One-in-five patients treated with intramedullary nailing of traumatic tibial fractures is affected by anterior knee pain.
- Non-union after intramedullary nailing of traumatic tibial fractures occurs in 11% of patients.
- 18% of patients treated with intramedullary nailing of traumatic tibial fractures undergoes one or more subsequent surgical procedures.

INTRODUCTION

Tibial shaft fractures are common long bone injuries with 16.9-21.5 cases per 100.000 per year [15,16]. Intramedullary nailing is widely considered the primary operative treatment for traumatic tibial shaft fractures [1,2]. The first use of the tibial nail on which the current technique is based was reported by Küntscher in 1940 [5]. The past century has seen a substantial evolution in technique: reaming and interlocking screws were introduced in the 1950's, with the 1990's bringing about the development of the titanium nail [6].

Despite the fact that the procedure has been in existence for several decades now, the nature of the traumatic tibial fractures and complications relating to intramedullary fixation allow opportunities for further improvement: patients frequently have to undergo subsequent surgical procedures; anterior knee pain has been reported in over half of the patients [17,18]; two-in-three patients have a screw penetrating in the proximal or distal tibiofibular joint [19]; and non-union has been reported in one-in-ten patients [20,21].

This study was set out to systematically review all currently available evidence to assess the incidence of complications and rate of re-operations following intramedullary nailing of traumatic tibial fractures. The knowledge derived from this systematic review can be used to educate both patients and clinicians. It may contribute to our understanding on how we can improve current techniques, so future treatment may result in fewer complications and lower rates of re-operation.

METHODS

Protocol

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22]. An unregistered review protocol was created prior to commencement of the study.

Selection Criteria

All studies assessing the outcome of tibial IMN were included provided they reported on at least fifty patients treated with intramedullary nailing for traumatic tibia fractures. Studies had to consist of a follow up of at least three months. The study cohorts had to be consistent on either surgical approach, the use of reaming or the type of intramedullary nail used. Studies not reporting on complications or use of reaming were excluded. Both inclusion and exclusion criteria are displayed in table 1.

TABLE 1. Inclusion and Exclusion Criteria

Inclusion Criteria	*Exclusion Criteria*
Studies assessing the outcome of intramedullary nailing in ≥ 50 patients with traumatic tibia fractures.	Follow-up of less than three months.
Studies must detail whether reamed/ unreamed nailing was applied.	No description of duration of follow-up.
Cohorts must be consistent on at least one of the following surgical characteristics: reamed/unreamed; surgical approach; type of nail.	Studies making use of atypical locking methods.
Studies must describe the incidence of at least one of the following complications: compartment syndrome, non-union, malunion, deep infection, rotational malalignment, anterior knee pain, nail breakage, screw breakage.	Studies assessing the outcome of intramedullary nailing in: floating knee injuries, pathological fractures, non-union, revision nailing.

Literature search strategy

In collaboration with a clinical librarian, ‘Trip Database’, ‘Medline’, ‘Scopus’ and ‘Cochrane Library’ were searched on 7 September 2018 to gather all available evidence. The searches were limited to English studies published after January 1st, 1998. This limitation in time was applied so only contemporary evidence was included. Search details are displayed in table 2.

TABLE 2. Literature search databases

Database(s)	Search terms
PubMed	*((("Fracture Fixation, Intramedullary"[Mesh]) OR "Bone Nails"[Mesh]) OR ((nail* [tiab]) OR (intramed* [tiab]))) AND (("Tibial Fractures"[Mesh]) OR (tibia* [tiab])) AND (complicat*)*
Trip Database	*(tibia*) AND ((nail*) OR (intramed*)) AND complic**
Scopus, Cochrane Database	*(TITLE-ABS-KEY ((tibia*) AND ((nail*) OR (intramed*))) AND ALL (complicat*))*

Screening for eligibility

Two authors (LH and JV) independently screened title, abstracts and full texts of the studies for eligibility. Disagreement was resolved by re-evaluation. If no agreement could be reached a senior author (JD) was consulted for a final decision.

Assessment of quality

Two authors (LH and JV) independently assessed the quality of the studies using a modified version of the ‘Coleman Methodology Score’ (Appendix A). The total score on the ‘‘Coleman Methodology Score’’ ranges from 0-100, corresponding to either poor (0-49 points), fair (50-69 points), good (70-84 points) or excellent (85-100 points) quality. Disagreement was resolved by discussion. If no agreement could be reached a senior author (JD) was consulted for a final decision.

Data extraction

The following data was extracted by one author (LH) and validated by a second author (JV): author names, title, publication year, journal, country, study design, length of follow up, sample size, type of approach, reamed/unreamed nailing, male/female ratio, age and ratio of open/closed fractures.

The rates of the following complications and subsequent surgeries were also extracted: postoperative compartment syndrome; non-union; malunion; deep infection; rotational malalignment; knee pain; nail breakage; screw breakage; fasciotomy; dynamization; revision malunion; revision non-union; revision deep infection; bone-grafting; removal or exchange of nail for other reasons; removal of screws only due to pain or irritation. The definitions of the complications are displayed in table 3.

TABLE 3. Definition Complications

Variable	Definition
Postoperative Compartment Syndrome	- *By index authors as postoperative compartment syndrome:* - *Clinical diagnosis* - *Absolute compartment pressures of >30 mmHg*105 *or differential compartment pressures of <30mmHg* 106
Non-union	- *No union and/or no signs of progressive healing at 6 months* - *By index authors using bone-grafting, dynamization or nail exchange or removal to promote union.* - *By index authors as non-union*
Malalignment/Malunion	- *>1 cm shortening* - *>5° angulation in coronal or sagittal plane* - *Indicated by index authors as malalignment/malunion*
Rotational Malalignment	- *Rotational difference of >10° diagnosed on CT-scan or clinically*
Deep infection	- *By index authors as deep infection*
Knee pain	- *By index authors as knee pain*
Nail breakage	- *By index authors as nail breakage*
Screw breakage	- *By index authors as screw breakage*

Statistical analysis

Descriptive statistics were calculated. Means were used for continuous variables and frequencies and percentages for categorical variables.

RESULTS

Study Selection

A total of 2891 unique records were identified of which 2678 were excluded based on title and abstract. The assessment of 213 full-texts resulted in the inclusion of 51 studies [23–73]. The flow chart of the selection process is displayed in figure 1.

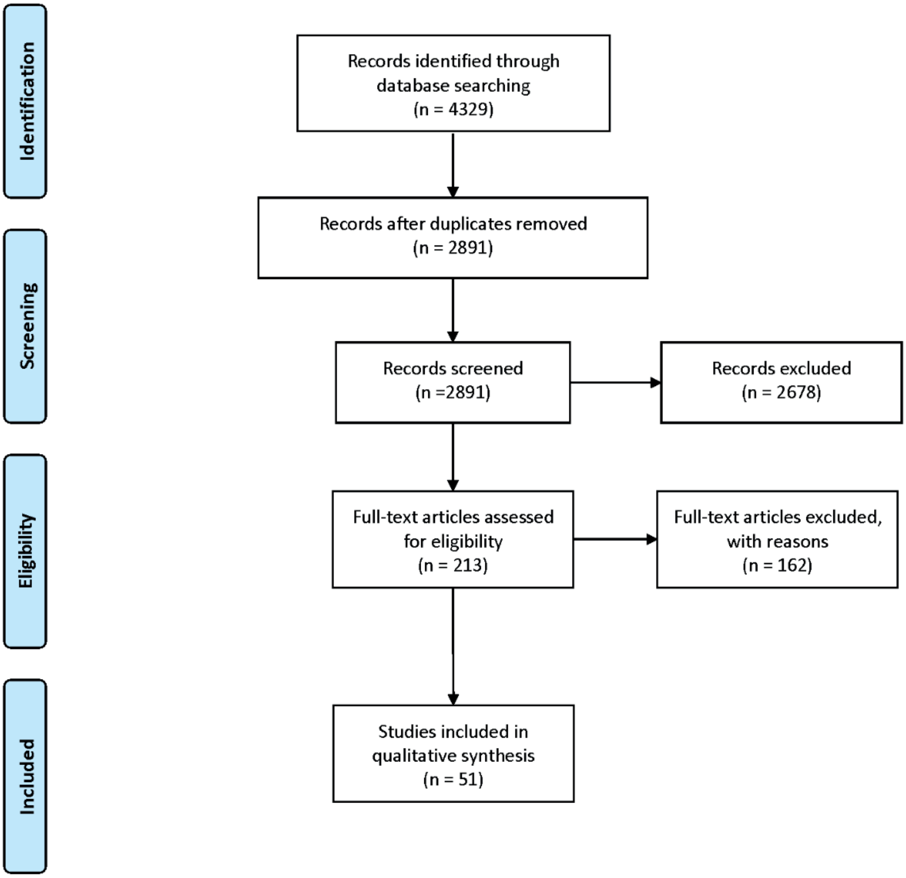


Figure 1. Flow chart of the selection process.

Critical appraisal

The mean Coleman score was 60.2 (range 32 -91), indicating a fair overall quality of included studies. Thirteen studies [23,31,32,41,46,52,53,55,57,60,62,63,73] ranked poor, 23 studies [24–27,29,33,34,36,38,40,44,47–50,54,56,59,61,64,70–72] ranked fair, 14 studies [28,35,37,39,42,43,45,51,58,65–69] were ranked good, and one study [30] ranked excellent.

Study characteristics

Eight randomized controlled trials[30,34,35,39,43,51,67,68], 9 prospective studies [28,33,37,49,58,59,65,66,70] and 34 retrospective studies[23–27,29,31,32,36,38,40–42,44–48,50,52–57,60–64,69,71–73] were included. Across studies there was a mean sample size of 161 patients (range 50-1226) and mean follow-up of 22 months (3-96). Nineteen studies were conducted in Europe[16,24,25,37–39,41,42,50,52–54,57,59–61,64,65,69], 16 studies in Asia [23,28,31,32,34–36,43,46,49,51,55,62,67,70,72], 13 studies in North-America[26,27,29,33,45,47,56,58,63,66,68,71,73] and one study in Africa [40]. Two studies were conducted across more than one continent [30,48].

Patient-, fracture- and surgery-characteristics (Table 4)

Combined the studies consisted of 8110 patients who had a total of 8174 traumatic tibial fractures treated with intramedullary nailing. The mean age of patients was 37.5 years with 74% being male. Follow-up ranged from 1-172 months, with a reported mean follow-up of 28 months. Sixty-seven percent of the fractures were closed. The fracture was located in the proximal-, middle- and distal-tibia in 9%, 37% and 54% of the cases respectively. Distribution according to AO/OTA-type [74,75] was 55% 42A, 31% 42B and 14% 42C.

Sixty percent of the fractures were treated with reamed intramedullary nailing whilst 40% were unreamed. Studies from North America (83%) more often used reamed intramedullary nailing when compared to studies from Europe (67%) and Asia (57%) (Table 5). Reaming was furthermore more frequently used in studies originating from 2009-2018 (73%) when compared to 1998-2008 (50%). There was no clear pattern with regards to fracture characteristics and the use of reamed or unreamed intramedullary nailing.

The parapatellar approach was used in 53% of the cases, the transpatellar approach in 38% and the suprapatellar/semi-extended approach in 9%.

TABLE 4. Patient Demographics, Fracture Characteristics & Surgery Characteristics - Total Sample Size N = 8110

		N*	**Studies**[α]
Age, years mean	37.5	5722	41[23–25,27–33,35–44,46–51,53–55,58,59,63–65,67–73]
	n (%)	**N***	**Studies**[α]
Gender			
Male	5030 (74%)	6830	44[23–25,27–51,53–55,57–59,62–65,67–69,71–73]
Female	1800 (26%)		
Fractures	8174	8110	51[23–73]
Fracture Characteristics	**n (%)**	**N****	**Studies**[α]
Open	2456 (33%)	7482	46[23–45,47–50,53–55,57–59,61–73]
Closed	5026 (67%)		
Location		3555	29[23,26–32,34–38,40,42,43,45,47–49,51,54,61,62,64,69,71–73]
Proximal 1/3rd	330 (9%)		
Middle 1/3rd	1305 (37%)		
Distal 1/3rd	1920 (54%)		
Type		5333	24[25,29,30,32,33,35,37–40,42,43,46,50,53–55,57,59,61,64,65,67,72]
42A	2934 (55%)		
42B	1630 (31%)		
42C	769 (14%)		
Surgery Characteristics	**n (%)**	**N****	**Studies**[α]
Reaming		8174	51[23–73]
Reamed	4939 (60%)		
Unreamed	3235 (40%)		
Approach		1815	19[24,25,28,31,32,35,37,38,42,43,45–47,51,54,65,66,71,72]
Transpatellar	690 (38%)		
Parapatellar	960 (53%)		
Suprapatellar/Semi extended	165 (9%)		

** Total number of patients for which a variable was reported*

*** Total number of fractures for which a variable was reported*

[α] *Number of studies in which a variable was reported*

TABLE 5. Reamed versus Unreamed Intramedullary Nailing.

	Reamed IMN	Unreamed IMN
Continent, number of studies (%)		
North America	10 (83%)	2 (17%)
Europe	12 (67%)	6 (33%)
Asia	8 (57%)	6 (43%)
Decade, number of studies (%)		
1998 - 2008	9 (50%)	9 (50%)
2009 - 2018	19 (73%)	7 (27%)
Fracture Location, number of fractures (%)		
Proximal	181 (55%)	147 (47%)
Middle	624 (49%)	643 (51%)
Distal	1085 (57%)	803 (43%)
Fracture Type, number of fractures (%)		
42A	1639 (57%)	1255 (43%)
42B	726 (45%)	881 (55%)
42C	348 (46%)	412 (54%)

Complications (Table 6)

The incidence of compartment syndrome was 3.8%. Deep infection occurred in 3.2% of the cases. The incidence of malunion and rotational malalignment were 7.5% and 1.3% respectively. The incidence of non-union was 10.7%. Anterior knee pain was reported in 22.9% of the cases. Screw breakage and nail breakage were reported in 7.1% and 0.7% of the cases respectively.

TABLE 6. Incidence Complications

	% (n)	**N***	**Studies**[α]
Early Complications			
Compartment syndrome	3.8% (145)	3858	20[25,30,32,39–41,44,49,50,52,60–66,68,72,73]
Deep infection	3.2% (196)	6067	36[23–35,37–40,43,48,49,51,54,56–59,61–67,71–73]
Late Complications			
Malunion	7.5% (251)	3351	30[23,25,28,29,31,33,34,36–40,43,45,47,48,51,53,54,58,61,64–70,72,73]
Rotational Malalignment	1.3% (22)	1699	12[25,35,39,40,43,45,53,54,61,64,65,68]
Non-union	10.7% (747)	6969	45[23–29,31–37,39–42,46–54,56–59,61–67,69–73]
Anterior knee pain	22.9% (427)	1862	17[24,25,32,37–39,42,45–47,51,55,62,65,70–72]
Implant failure			
Screw breakage	7.1% (288)	4041	23[23–25,28,30,32,35,39,40,48,54,58,59,61,62,64–66,68–70,72,73]
Nail breakage	0.7% (23)	3428	20[23–25,30,32,35,39,40,48,54,58,61,62,65–70,73]

** Total number of fractures for which a variable was reported*

[α] *Number of studies in which a variable was reported*

Subsequent surgery (Table 7)

Out of the 6088 patients in whom subsequent surgery was reported, a total of 1081 patients required subsequent surgery (17.8%, range 0-63%). One of the most frequent indications of subsequent surgery was dynamization of the nail, which was reported in 8.4% of the cases. Nail revision and bone-grafting to promote union were applied in 4.2% and 2.4% respectively.

Revision due to malunion and revision due to infection were seen in 1.3% and 1.2% respectively. In 3.8% of the cases, patients had to undergo fasciotomies due to compartment syndrome.

The most frequent indication of subsequent surgery was screw removal due to pain or discomfort (8.9%). Nail removal or nail exchange due to reasons other than failed union or infection occurred in 119 cases (8.2%): 108 nail removals due to pain and discomfort; 8 nail removals or exchanges due to implant failure or nail migration; and three removals or exchanges due to other reasons.

TABLE 7. Subsequent Surgery Rates

	% (n)	**N***	**Studies**[α]
Any subsequent surgery	17.8% (1081)	6088	43[23–25,27–42,44,46–51,53,54,56,58–67,69,71–73]
Fasciotomy	3.8% (145)	3858	20[25,30,32,39–41,44,49,50,52,60–66,68,72,73]
Dynamization	8.4% (296)	3515	23[23–25,27,29–31,34,35,38,40,42,49,54,56,61–64,66,67,69,71,72]
Bone grafting	2.4% (93)	3830	22[23–25,27,30–32,37–39,47,49,56,58,59,61–63,66,69,72,73]
Revision to promote union	4.2% (204)	4814	32[23–25,27–32,34–37,39,42,47,48,51,53,54,56,58,59,61–67,71,73]
Revision deep infection	1.2% (38)	3222	32[23–25,27,28,31,32,34–39,43,47–49,51,53,54,56,58,61,63–67,69,71–73]
Revision due to malunion	1.3% (23)	1724	14[23,25,36,39,45,47,48,50,61,65,67–69,72]
Nail exchange or removal other reasons	8.2% (119)	1446	12[27–29,32,33,38,46,61,63,67,71,73]
Screw removal pain or discomfort	8.9% (53)	598	7[27,29,33,38,63,71]

* *Total number of fractures for which a variable was reported*

[α] *Number of studies in which a variable was reported*

DISCUSSION

Although intramedullary nailing of tibial shaft fractures has been common practice for decades there is room for improvement: complications occur frequently, and subsequent surgery is often required [50]. This study systematically reviewed a total of 8110 patients in order to summarize contemporary evidence on the incidence of complications and re-operations following intramedullary nailing of traumatic tibial fractures. Patients treated with intramedullary nailing for tibial fractures need to be consented for high probability of adverse events as anterior knee pain, subsequent surgical procedures and bone healing problems, whilst surgeons may use this compiled information to manage expectations and improve shared decision making. However, based on current data it remains difficult to identify specifiers and determinants of individual patients at risk of complications. In order to individualize treatment, trauma care should focus on generating large (multicentre) datasets, or merge existing ones, to establish patient specific risk models to estimate probabilities of adverse events.

Limitations of this study include 1) fair overall methodological quality of included studies; and 2) heterogeneity of study designs, which did not allow for any quantitative analysis. Furthermore, one could argue that the inclusion of non-reamed intramedullary nailing may cause for ‘pollution’ of the results. However, when we compared the rates of complications and subsequent surgeries of the included studies that used non-reamed nailing to those that used reamed nailing, we could not demonstrate any beneficial effect of reamed intramedullary nailing. This is in line with the findings of the most recent Cochrane review on this matter [76]. Strengths of this study include 1) large number of studies and patients, making it the most comprehensive review of the literature on this subject to date; 2) strict inclusion and exclusion of studies and critical appraisal of the evidence by two independent authors; and 3) similarity of patient demographics and fracture characteristics to other epidemiological studies [77,78]. Given these strengths we believe that the incidences of complications and rates of subsequent surgical procedures we have reported are representative of true incidences in tibial fractures managed operatively with intramedullary nailing.

Anterior knee pain was the most prevalent complication occurring in 23% of cases. This incidence is only half of what has previously been described by Katsoulis and colleagues, reporting an incidence of 47% in their review of the literature published in 2006 [79]. Differences may be accounted for by ongoing improvements in operative technique and postoperative rehabilitation regimes over time: in this review the incidence of anterior knee pain declined from 27% (1998-2008) [24,25,55,62,65] to 21% (2009-2018) [32,37–39,42,45–47,51,70–72]. Recent adaptations of technique that are thought to result in a lower incidence of anterior knee pain include the suprapatellar approach [80], and oblique incisions for the infrapatellar approach [81]. In this review, two studies were included that compared a suprapatellar approach to an infrapatellar approach [45,51]. Sun and colleagues demonstrated significantly lower pain scores for the suprapatellar approach [51], whilst Ryan and colleagues found no significant difference in the incidence of anterior knee pain [45]. Other studies in literature are also contradictory on this matter: some suggest a lower incidence of anterior knee pain for the suprapatellar approach [80,82], whilst others did not find any difference compared to the infrapatellar approach [83–85]. Further research is required to assess whether the incidence of anterior knee pain can be reduced using a suprapatellar approach.

Non-union was found to be the second most prevalent complication with an incidence of 11%. This is in line with the 12% that Dailey and colleagues have recently demonstrated in a large retrospective series including 1003 patients treated with intramedullary nailing [57]. Various risk factors for non-union after intramedullary nailing of tibial fractures have been reported, including fracture gap, fracture type (open/closed) and fracture morphology (OA/OTA-classification) [21,57,86,87]. O’Halloran and colleagues have recently developed a non-union prediction score based on odds ratios of a multiple variable logistic regression model [86]. This score allows for the calculation of patient-specific non-union risks. Despite this, the clinical value of the score remains unclear as (external) validation of performance, by means of discrimination and calibration, is lacking [88,89]. Future studies should not only aim to develop, but also validate prediction scores. Machine learning algorithms may prove a valuable adjunct as has been demonstrated in previous orthopaedic studies [90,91]. Of the above-mentioned risk factors, fracture gapping is the only one that surgeons can potentially modify in order to avoid non-union. Avoiding non-union furthermore relies on surgeons remaining critical about issues like implant choice and surgical technique.

The rate of subsequent surgeries to promote union was relatively high as well, consisting of bone grafting in 2%, revision in 4% and dynamization in 8% of the cases. Eighteen percent of patients underwent at least one subsequent procedure. We believe this to be an underestimation, as various studies have not reported on each subsequent surgical procedure included in this rate. For instance, the SPRINT trial had a subsequent surgery rate of 15%, however, did not report on removal of screws or nail due to pain or irritation [20]. Stavrou and colleagues reported 21% of patients undergoing subsequent surgery in a retrospective analysis of 151 cases. They found AO/OTA type 42B-C fractures and alcohol abuse to be risk factors [50]. Prediction scores further identifying individual patients at risk of additional surgical procedures could aid clinicians in managing these patients' expectations, which may improve postoperative satisfaction [92–94].

Twelve studies [25,35,39,40,45,53,54,60,61,64,65,68] reported the incidence of rotational malalignment, with a weighted mean incidence of 1.3%. This is likely an underrepresentation of the true incidence of rotational malalignment, as all twelve studies based diagnosis on unreliable [95] clinical assessment. Studies using Computed-Tomography (CT) scanning to screen for rotational malalignment have reported much higher incidences ranging from 19-41% [95–99] (Table 8). These studies were excluded from this review on account of not meeting inclusion criteria because they were either based on small series [96,97,99], did not disclose reaming status [95] or made no report on duration of follow up [98]. The landmark paper on rotational malalignment after tibial intramedullary nailing, by Theriault and colleagues, reported an incidence as high as 41% [95]. We believe this to be a more accurate estimate of the true incidence. Future studies should further investigate the incidence of malrotation as well as the discrepancy between clinical and CT-based assessment of rotational malalignment. Various studies have demonstrated that malalignment in the coronal and sagittal plane may be avoided with certain surgical techniques such as Poller screws [100–102] or a suprapatellar approach [45,100,103]. It is less evident how rotational malalignment can be avoided. One study reported that by using an external tibial aiming device, commonly found in knee arthroplasty sets, they significantly reduced the incidence of rotational malalignment after tibial intramedullary nailing [104]. The personal experience from the authors is that the contralateral side should not be hidden under the drapes but also prepped and draped to serve as a reference during the operation. Whether this will indeed reduce the incidence of rotational malalignment will be subject of future study. As rotational malalignment is a common reason for litigation [13], research investigating the effect of rotational malalignment on functional outcome is also required.

In conclusion, this study reports a high incidence of adverse events and subsequent surgeries after nailing of tibial fractures. However, based on current data it remains difficult to identify specifiers and determinants of an individual patient, with specific fracture characteristics, at risk for complications. Future studies should aim to establish patient specific risk models for complications and re-operations, such that clinicians can anticipate these and individualize treatment strategies. To allow such studies in trauma care, multicentre collaborations are needed to generate large datasets or merge existing ones.

TABLE 8. Clinical Assessment versus CT Assessment of Rotational Malalignment

Clinical assessment of rotational malalignment

Study	*% (n)*	*N**
Djahangiri et al. [25]	2.1% (2)	96
Hapa et al. [35]	0% (0)	57
Ramos et al. [39]	0% (0)	86
Salem [40]	4.8% (7)	145
Prasad et al. [43]	16.7% (10)	60
Ryan et al. [45]	0% (0)	185
De Santos de la Fuente et al. [53]	0.6% (1)	167
Greitbauer et al. [54]	0% (0)	66
Gaebler et al. [61]	0% (0)	467
Drosos et al. [64]	0.6% (1)	161
Babis et al. [65]	0% (0)	115
Finkemeier et al. [68]	1.1% (1)	94
Total	*1.3% (22)*	*1699*

CT assessment of rotational malalignment

Study	*% (n)*	*N**
Say et al. [96]	19.2% (5)	26
Puloski et al.[97]	22.7% (5)	22
Jafarinejad et al. [98]	30.0% (18)	60
Theriault et al. [95]	41.4% (29)	70
Prasad et al. [99]	27.3% (6)	22
Total	*31.5% (63)*	*200*

** Total number of fractures for which a variable was reported*

REFERENCES

1. Busse JW, Morton E, Lacchetti C, Guyatt GH, Bhandari M. Current management of tibial shaft fractures: a survey of 450 Canadian orthopedic trauma surgeons. *Acta Orthop*. 2008;79(5):689-694.
2. Bhandari M, Guyatt GH, Swiontkowski MF, et al. Surgeons' preferences for the operative treatment of fractures of the tibial shaft. An international survey. *J Bone Joint Surg Am*. 2001;83-A(11):1746-1752.
3. Farill J. ORTHOPAEDICS IN MEXICO. *JBJS*. 1952;34(3):506.
4. *General History of the Things of New Spain by Fray Bernardino de Sahagún: The Florentine Codex. Book X: The People, Their Virtues and Vices, and Other Nations*. [publisher not identified]; 1577.
5. Küntscher G. The intramedullary nailing of fractures. *J Orthop Trauma*. 2014;28 Suppl 8:S3-S10.
6. Bong MR, Koval KJ, Egol KA. The history of intramedullary nailing. *Bull NYU Hosp Jt Dis*. 2006;64(3-4):94-97.
7. Stuermer EK, Stuermer KM. Tibial shaft fracture and ankle joint injury. *J Orthop Trauma*. 2008;22(2):107-112.
8. Marchand LS, Rane AA, Working ZM, et al. Radiographic Investigation of the Distal Extension of Fractures Into the Articular Surface of the Tibia (The RIDEFAST Study). *J Orthop Trauma*. 2017;31(12):668-674.
9. Sobol GL, Shaath MK, Reilly MC, Adams MR, Sirkin MS. The Incidence of Posterior Malleolar Involvement in Distal Spiral Tibia Fractures: Is it Higher than We Think? *J Orthop Trauma*. 2018;32(11):543-547.
10. Boraiah S, Gardner MJ, Helfet DL, Lorich DG. High association of posterior malleolus fractures with spiral distal tibial fractures. *Clin Orthop Relat Res*. 2008;466(7):1692-1698.
11. Georgiadis GM, Ebraheim NA, Hoeflinger MJ. Displacement of the posterior malleolus during intramedullary tibial nailing. *J Trauma*. 1996;41(6):1056-1058.
12. Zhang Y, Qin X, Song L, Li X. The risk of violating the posterior malleolar fracture when nailing the ipsilateral concomitant spiral distal tibial fracture. *BMC Musculoskelet Disord*. 2018;19(1):123.
13. Metcalfe CW, Harrison WD, Nayagam S, Narayan B. Negligence claims following non-union and malunion of long bone fractures: An analysis of 15 years of data. *Injury*. 2016;47(10):2312-2314.
14. Andersson GBJ, Cocchiarella L, eds. *Guides to the Evaluation of Permanent Impairment, Fifth Edition*. 5th ed. American Medical Association; 2000.
15. Court-Brown CM, Caesar B. Epidemiology of adult fractures: A review. *Injury*. 2006;37(8):691-697.
16. Larsen P, Elsoe R, Hansen SH, Graven-Nielsen T, Laessoe U, Rasmussen S. Incidence and epidemiology of tibial shaft fractures. *Injury*. 2015;46(4):746-750.

17. Toivanen JAK, Väistö O, Kannus P, Latvala K, Honkonen SE, Järvinen MJ. Anterior knee pain after intramedullary nailing of fractures of the tibial shaft. A prospective, randomized study comparing two different nail-insertion techniques. *J Bone Joint Surg Am*. 2002;84-A(4):580-585.

18. Court-Brown CM, Gustilo T, Shaw AD. Knee pain after intramedullary tibial nailing: its incidence, etiology, and outcome. *J Orthop Trauma*. 1997;11(2):103-105.

19. Cain ME, Doornberg JN, Duit R, Clarnette J, Jaarsma R, Jadav B. High incidence of screw penetration in the proximal and distal tibiofibular joints after intramedullary nailing of tibial fractures-A prospective cohort and mapping study. *Injury*. 2018;49(4):871-876.

20. Court-Brown CM. Reamed intramedullary tibial nailing: an overview and analysis of 1106 cases. *J Orthop Trauma*. 2004;18(2):96-101.

21. Metsemakers WJ, Handojo K, Reynders P, Sermon A, Vanderschot P, Nijs S. Individual risk factors for deep infection and compromised fracture healing after intramedullary nailing of tibial shaft fractures: a single centre experience of 480 patients. *Injury*. 2015;46(4):740-745.

22. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.

23. Mosheiff R, Safran O, Segal D, Liebergall M. The unreamed tibial nail in the treatment of distal metaphyseal fractures. *Injury*. 1999;30(2):83-90.

24. Dogra AS, Ruiz AL, Marsh DR. Late outcome of isolated tibial fractures treated by intramedullary nailing: the correlation between disease-specific and generic outcome measures. *J Orthop Trauma*. 2002;16(4):245-249.

25. Djahangiri A, Garofalo R, Chevalley F, et al. Closed and open grade I and II tibial shaft fractures treated by reamed intramedullary nailing. *Med Princ Pract*. 2006;15(4):293-298.

26. Reuss BL, Cole JD. Effect of delayed treatment on open tibial shaft fractures. *Am J Orthop* . 2007;36(4):215-220.

27. Sidky A, Buckley RE. Hardware removal after tibial fracture has healed. *Can J Surg*. 2008;51(4):263-268.

28. Lee YS, Lo TY, Huang HL. Intramedullary fixation of tibial shaft fractures: A comparison of the unlocked and interlocked nail. *Int Orthop*. 2008;32(1):69-74.

29. Vallier HA, Le TT, Bedi A. Radiographic and clinical comparisons of distal tibia shaft fractures (4 to 11 cm proximal to the plafond): plating versus intramedullary nailing. *J Orthop Trauma*. 2008;22(5):307-311.

30. Study to Prospectively Evaluate Reamed Intramedullary Nails in Patients with Tibial Fractures Investigators, Bhandari M, Guyatt G, et al. Randomized trial of reamed and unreamed intramedullary nailing of tibial shaft fractures. *J Bone Joint Surg Am*. 2008;90(12):2567-2578.

31. Giri SK, Adhikari BR, Gurung GB, Rc D, Bajracharya AR, Khatri K. Mini-open reduction and intramedullary interlocking nailing of fracture shaft of tibia without an image intensifier. *Nepal Med Coll J*. 2008;10(2):123-125.

32. Gadegone WM, Salphale YS. Dynamic osteosynthesis by modified Kuntscher nail for the treatment of tibial diaphyseal fractures. *Indian J Orthop*. 2009;43(2):182-188.

33. Ricci WM, Gallagher B, Brandt A, Schwappach J, Tucker M, Leighton R. Is after-hours orthopaedic surgery associated with adverse outcomes? A prospective comparative study. *J Bone Joint Surg Am*. 2009;91(9):2067-2072.

34. Tavakoli A, Tadi HM, Mahmoodian A. A comparison between unreamed locked intramedullary nailing and plate-Screw fixation in the treatment of tibial diaphyseal fractures. *Iran Red Crescent Med J*. 2010;12(6):640.

35. Hapa O, Muratli HH, Yüksel HY, Celebi L, Doğruyol D, Biçimoğlu A. Single or double distal locking in intramedullary nailing of tibial shaft fractures: a prospective randomized study. *Ulus Travma Acil Cerrahi Derg*. 2010;16(1):33-37.

36. Solooki S, Mesbahi SAR. Complex fractures of the tibia and femur treated with static interlocking intramedullary nail. *Iran Red Crescent Med J*. 2011;13(3):178-180.

37. Hernández-Vaquero D, Suárez-Vázquez A, Iglesias-Fernández S, García-García J, Cervero-Suárez J. Dynamisation and early weight-bearing in tibial reamed intramedullary nailing: its safety and effect on fracture union. *Injury*. 2012;43 Suppl 2(SUPPL. 2):S63-S67.

38. Leliveld MS, Verhofstad MHJ. Injury to the infrapatellar branch of the saphenous nerve, a possible cause for anterior knee pain after tibial nailing? *Injury*. 2012;43(6):779-783.

39. Ramos L, Bertrand ML, Benitez-Parejo N, Guerado E. How many distal bolts should be used in unreamed intramedullary nailing for diaphyseal tibial fractures? *Injury*. 2012;43 Suppl 2(SUPPL. 2):S59-S62.

40. Salem KH. Critical analysis of tibial fracture healing following unreamed nailing. *Int Orthop*. 2012;36(7):1471-1477.

41. Högel F, Gerber C, Bühren V, Augat P. Reamed intramedullary nailing of diaphyseal tibial fractures: comparison of compression and non-compression nailing. *Eur J Trauma Emerg Surg*. 2013;39(1):73-77.

42. Jankovic A, Korac Z, Bozic NB, Stedul I. Influence of knee flexion and atraumatic mobilisation of infrapatellar fat pad on incidence and severity of anterior knee pain after tibial nailing. *Injury*. 2013;44 Suppl 3(SUPPL.3):S33-S39.

43. Prasad M, Yadav S, Sud A, Arora NC, Kumar N, Singh S. Assessment of the role of fibular fixation in distal-third tibia-fibula fractures and its significance in decreasing malrotation and malalignment. *Injury*. 2013;44(12):1885-1891.

44. Larsen P, Lund H, Laessoe U, Graven-Nielsen T, Rasmussen S. Restrictions in quality of life after intramedullary nailing of tibial shaft fracture: a retrospective follow-up study of 223 cases. *J Orthop Trauma*. 2014;28(9):507-512.

45. Ryan SP, Steen B, Tornetta P 3rd. Semi-extended nailing of metaphyseal tibia fractures: alignment and incidence of postoperative knee pain. *J Orthop Trauma*. 2014;28(5):263-269.

46. Chen CY, Lin KC, Yang SW, Tarng YW, Hsu CJ, Renn JH. Influence of nail prominence and insertion point on anterior knee pain after tibial intramedullary nailing. *Orthopedics*. 2014;37(3):e221-e225.

47. Kruppa CG, Hoffmann MF, Sietsema DL, Mulder MB, Jones CB. Outcomes After Intramedullary Nailing of Distal Tibial Fractures. *J Orthop Trauma*. 2015;29(9):e309-e315.

48. Stephens KR, Shahab F, Galat D, et al. Management of Distal Tibial Metaphyseal Fractures With the SIGN Intramedullary Nail in 3 Developing Countries. *J Orthop Trauma*. 2015;29(12):e469-e475.

49. Balaji SM, Chandra PM, Devadoss S, Devadoss A. The effect of intact fibula on functional outcome of reamed intramedullary interlocking nail in open and closed isolated tibial shaft fractures: A prospective study. *Indian J Orthop*. 2016;50(2):201-205.

50. Stavrou PZ, Ciriello V, Theocharakis S, et al. Prevalence and risk factors for re-interventions following reamed intramedullary tibia nailing. *Injury*. 2016;47 Suppl 7:S49-S52.

51. Sun Q, Nie X, Gong J, et al. The outcome comparison of the suprapatellar approach and infrapatellar approach for tibia intramedullary nailing. *Int Orthop*. 2016;40(12):2611-2617.

52. Neumann MV, Strohm PC, Reising K, Zwingmann J, Hammer TO, Suedkamp NP. Complications after surgical management of distal lower leg fractures. *Scand J Trauma Resusc Emerg Med*. 2016;24(1):146.

53. De Santos De La Fuente FJ, Arévalo RL, Carrillo CT, Ramos Salguero JC, Fernández Medina JM. Intramedullary nailing and functional bracing of tibial shaft fractures. *Acta Orthop Scand*. 1998;69(5):493-497.

54. Greitbauer M, Heinz T, Gaebler C, Stoik W, Vécsei V. Unreamed nailing of tibial fractures with the solid tibial nail. *Clin Orthop Relat Res*. 1998;(350):105-114.

55. Fanian H, Dehghani M. Anterior knee pain after unreamed intramedullary nailing of the tibia. *J Res Med Sci*. 2008;13(5):260-263.

56. Collinge CA, Beltran MJ, Dollahite HA, Huber FG. Percutaneous clamping of spiral and oblique fractures of the tibial shaft: a safe and effective reduction aid during intramedullary nailing. *J Orthop Trauma*. 2015;29(6):e208-e212.

57. Dailey HL, Wu KA, Wu PS, McQueen MM, Court-Brown CM. Tibial Fracture Nonunion and Time to Healing After Reamed Intramedullary Nailing: Risk Factors Based on a Single-Center Review of 1003 Patients. *J Orthop Trauma*. 2018;32(7):e263-e269.

58. Henley MB, Chapman JR, Agel J, Harvey EJ, Whorton AM, Swiontkowski MF. Treatment of type II, IIIA, and IIIB open fractures of the tibial shaft: a prospective comparison of unreamed interlocking intramedullary nails and half-pin external fixators. *J Orthop Trauma*. 1998;12(1):1-7.

59. Markmiller M, Tjarksen M, Mayr E, Rüter A. The unreamed tibia nail Multicenter study of the AO/ASIF. *Langenbecks Arch Surg*. 2000;385(4):276-283.

60. Mullett H, Al-Abed K, Prasad CV, O'Sullivan M. Outcome of compartment syndrome following intramedullary nailing of tibial diaphyseal fractures. *Injury*. 2001;32(5):411-413.

61. Gaebler C, Berger U, Schandelmaier P, et al. Rates and odds ratios for complications in closed and open tibial fractures treated with unreamed, small diameter tibial nails: a multicenter analysis of 467 cases. *J Orthop Trauma*. 2001;15(6):415-423.

62. Joshi D, Ahmed A, Krishna L, Lal Y. Unreamed interlocking nailing in open fractures of tibia. *J Orthop Surg* . 2004;12(2):216-221.

63. Tang P, Gates C, Hawes J, Vogt M, Prayson MJ. Does Open Reduction Increase the Chance of Infection During Intramedullary Nailing of Closed Tibial Shaft Fractures? *J Orthop Trauma*. 2006;20(5):317-322.

64. Drosos GI, Bishay M, Karnezis IA, Alegakis AK. Factors affecting fracture healing after intramedullary nailing of the tibial diaphysis for closed and grade I open fractures. *J Bone Joint Surg Br*. 2006;88(2):227-231.

65. Babis GC, Benetos IS, Karachalios T, Soucacos PN. Eight years' clinical experience with the Orthofix tibial nailing system in the treatment of tibial shaft fractures. *Injury*. 2007;38(2):227-234.

66. Kakar S, Tornetta P 3rd. Segmental tibia fractures: a prospective evaluation. *Clin Orthop Relat Res*. 2007;460(460):196-201.

67. Bali K, Aggarwal S, Kumar V, et al. Operative management of type II and type IIIa open tibial fractures presenting from 6–24 hours after injury: an Indian experience. *Curr Orthop Pract*. 2011;22(3):262-266.

68. Finkemeier CG, Schmidt AH, Kyle RF, Templeman DC, Varecka TF. A prospective, randomized study of intramedullary nails inserted with and without reaming for the treatment of open and closed fractures of the tibial shaft. *J Orthop Trauma*. 2000;14(3):187-193.

69. Tyllianakis M, Megas P, Giannikas D, Lambiris E. Interlocking intramedullary nailing in distal tibial fractures. *Orthopedics*. 2000;23(8):805-808.

70. Mukhopadhyay AS, Mukherjee J, Sengupta A. The role of dynamisation vis-à-vis non-dynamisation after closed interlocking nailing in cases of closed tibial shaft fractures in adults. *J Indian Med Assoc*. 2010;108(6):361-362, 364.

71. Weil YA, Gardner MJ, Boraiah S, Helfet DL, Lorich DG. Anterior knee pain following the lateral parapatellar approach for tibial nailing. *Arch Orthop Trauma Surg*. 2009;129(6):773-777.

72. Burc H, Dursun M, Orhun H, Gurkan V, Bayhan I. Treatment of adult tibial diaphysis fractures with reamed and locked intramedullary nailing. *Acta Orthop Traumatol Turc*. 2009;43(1):7-13.

73. Obremskey WT, Medina M. Comparison of intramedullary nailing of distal third tibial shaft fractures: before and after traumatologists. *Orthopedics*. 2004;27(11):1180-1184.

74. Kellam JF, Meinberg EG, Agel J, Karam MD, Roberts CS. Introduction: Fracture and Dislocation Classification Compendium-2018: International Comprehensive Classification of Fractures and Dislocations Committee. *J Orthop Trauma*. 2018;32 Suppl 1:S1-S10.

75. Marsh JL, Slongo TF, Agel J, et al. Fracture and dislocation classification compendium - 2007: Orthopaedic Trauma Association classification, database and outcomes committee. *J Orthop Trauma*. 2007;21(10 Suppl):S1-S133.

76. Duan X, Al-Qwbani M, Zeng Y, Zhang W, Xiang Z. Intramedullary nailing for tibial shaft fractures in adults. *Cochrane Database Syst Rev*. 2012;1:CD008241.

77. Court-Brown CM, McBirnie J. The epidemiology of tibial fractures. *J Bone Joint Surg Br*. 1995;77(3):417-421.

78. Anandasivam NS, Russo GS, Swallow MS, et al. Tibial shaft fracture: A large-scale study defining the injured population and associated injuries. *J Clin Orthop Trauma*. 2017;8(3):225-231.

79. Katsoulis E, Court-Brown C, Giannoudis PV. Incidence and aetiology of anterior knee pain after intramedullary nailing of the femur and tibia. *J Bone Joint Surg Br*. 2006;88(5):576-580.

80. Sanders RW, DiPasquale TG, Jordan CJ, Arrington JA, Sagi HC. Semiextended intramedullary nailing of the tibia using a suprapatellar approach: radiographic results and clinical outcomes at a minimum of 12 months follow-up. *J Orthop Trauma*. 2014;28 Suppl 8(8 SUPPL):S29-S39.

81. Kerver ALA, Leliveld MS, den Hartog D, Verhofstad MHJ, Kleinrensink GJ. The surgical anatomy of the infrapatellar branch of the saphenous nerve in relation to incisions for anteromedial knee surgery. *J Bone Joint Surg Am*. 2013;95(23):2119-2125.

82. Serbest S, Tiftikçi U, Çoban M, Çirpar M, Dağlar B. Knee Pain and Functional Scores After Intramedullary Nailing of Tibial Shaft Fractures Using a Suprapatellar Approach. *J Orthop Trauma*. 2019;33(1):37-41.

83. Jones M, Parry M, Whitehouse M, Mitchell S. Radiologic outcome and patient-reported function after intramedullary nailing: a comparison of the retropatellar and infrapatellar approach. *J Orthop Trauma*. 2014;28(5):256-262.

84. Chan DS, Serrano-Riera R, Griffing R, et al. Suprapatellar Versus Infrapatellar Tibial Nail Insertion: A Prospective Randomized Control Pilot Study. *J Orthop Trauma*. 2016;30(3):130-134.

85. Isaac M, O'Toole RV, Udogwu U, et al. Incidence of Knee Pain Beyond 1-Year: Suprapatellar versus Infrapatellar Approach for Intramedullary Nailing of the Tibia. *J Orthop Trauma*. Published online May 8, 2019. doi:10.1097/BOT.0000000000001504

86. O'Halloran K, Coale M, Costales T, et al. Will My Tibial Fracture Heal? Predicting Nonunion at the Time of Definitive Fixation Based on Commonly Available Variables. *Clin Orthop Relat Res*. 2016;474(6):1385-1395.

87. Fong K, Truong V, Foote CJ, et al. Predictors of nonunion and reoperation in patients with fractures of the tibia: an observational study. *BMC Musculoskelet Disord*. 2013;14:103.

88. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. *Eur Heart J*. 2014;35(29):1925-1931.

89. Vergouwe Y, Steyerberg EW, Eijkemans MJC, Habbema JDF. Validity of prognostic models: when is a model clinically useful? *Semin Urol Oncol*. 2002;20(2):96-107.

90. Shah AA, Karhade AV, Bono CM, Harris MB, Nelson SB, Schwab JH. Development of a machine learning algorithm for prediction of failure of nonoperative management in spinal epidural abscess. *Spine J*. 2019;19(10):1657-1665.

91. Thio QCBS, Karhade AV, Ogink PT, et al. Can Machine-learning Techniques Be Used for 5-year Survival Prediction of Patients With Chondrosarcoma? *Clin Orthop Relat Res*. 2018;476(10):2040-2048.

92. Hamilton DF, Lane JV, Gaston P, et al. What determines patient satisfaction with surgery? A prospective cohort study of 4709 patients following total joint replacement. *BMJ Open*. 2013;3(4). doi:10.1136/bmjopen-2012-002525

93. Dunbar MJ, Richardson G, Robertsson O. I can't get no satisfaction after my total knee replacement: rhymes and reasons. *Bone Joint J*. 2013;95-B(11 Suppl A):148-152.

94. Noble PC, Conditt MA, Cook KF, Mathis KB. The John Insall Award: Patient expectations affect satisfaction with total knee arthroplasty. *Clin Orthop Relat Res*. 2006;452:35-43.

95. Theriault B, Turgeon AF, Pelet S. Functional impact of tibial malrotation following intramedullary nailing of tibial shaft fractures. *J Bone Joint Surg Am*. 2012;94(22):2033-2039.

96. Say F, Bülbül M. Findings related to rotational malalignment in tibial fractures treated with reamed intramedullary nailing. *Arch Orthop Trauma Surg*. 2014;134(10):1381-1386.

97. Puloski S, Romano C, Buckley R, Powell J. Rotational malalignment of the tibia following reamed intramedullary nail fixation. *J Orthop Trauma*. 2004;18(7):397-402.

98. Jafarinejad AE, Bakhshi H, Haghnegahdar M, Ghomeishi N. Malrotation following reamed intramedullary nailing of closed tibial fractures. *Indian J Orthop*. 2012;46(3):312-316.

99. Prasad CV, Khalid M, McCarthy P, O'Sullivan ME. CT assessment of torsion following locked intramedullary nailing of tibial fractures. *Injury*. 1999;30(7):467-470.

100. Hiesterman TG, Shafiq BX, Cole PA. Intramedullary nailing of extra-articular proximal tibia fractures. *J Am Acad Orthop Surg*. 2011;19(11):690-700.

101. Krettek C, Stephan C, Schandelmaier P, Richter M, Pape HC, Miclau T. The use of Poller screws as blocking screws in stabilising tibial fractures treated with small diameter intramedullary nails. *J Bone Joint Surg Br*. 1999;81(6):963-968.

102. Ricci WM, O'Boyle M, Borrelli J, Bellabarba C, Sanders R. Fractures of the proximal third of the tibial shaft treated with intramedullary nails and blocking screws. *J Orthop Trauma*. 2001;15(4):264-270.

103. Sanders RW, DiPasquale TG, Jordan CJ, Arrington JA, Sagi HC. Semiextended intramedullary nailing of the tibia using a suprapatellar approach: radiographic results and clinical outcomes at a minimum of 12 months follow-up. *J Orthop Trauma*. 2014;28(5):245-255.

104. Inci F, Yildirim AO, Ciliz DS, Kocak C, Ceyhan E, Öken ÖF. Intraoperative rotation control in closed intramedullary nailing in tibia diaphyseal fractures: a prospective, randomised study. *Acta Orthop Belg*. 2018;84(4):461-468.

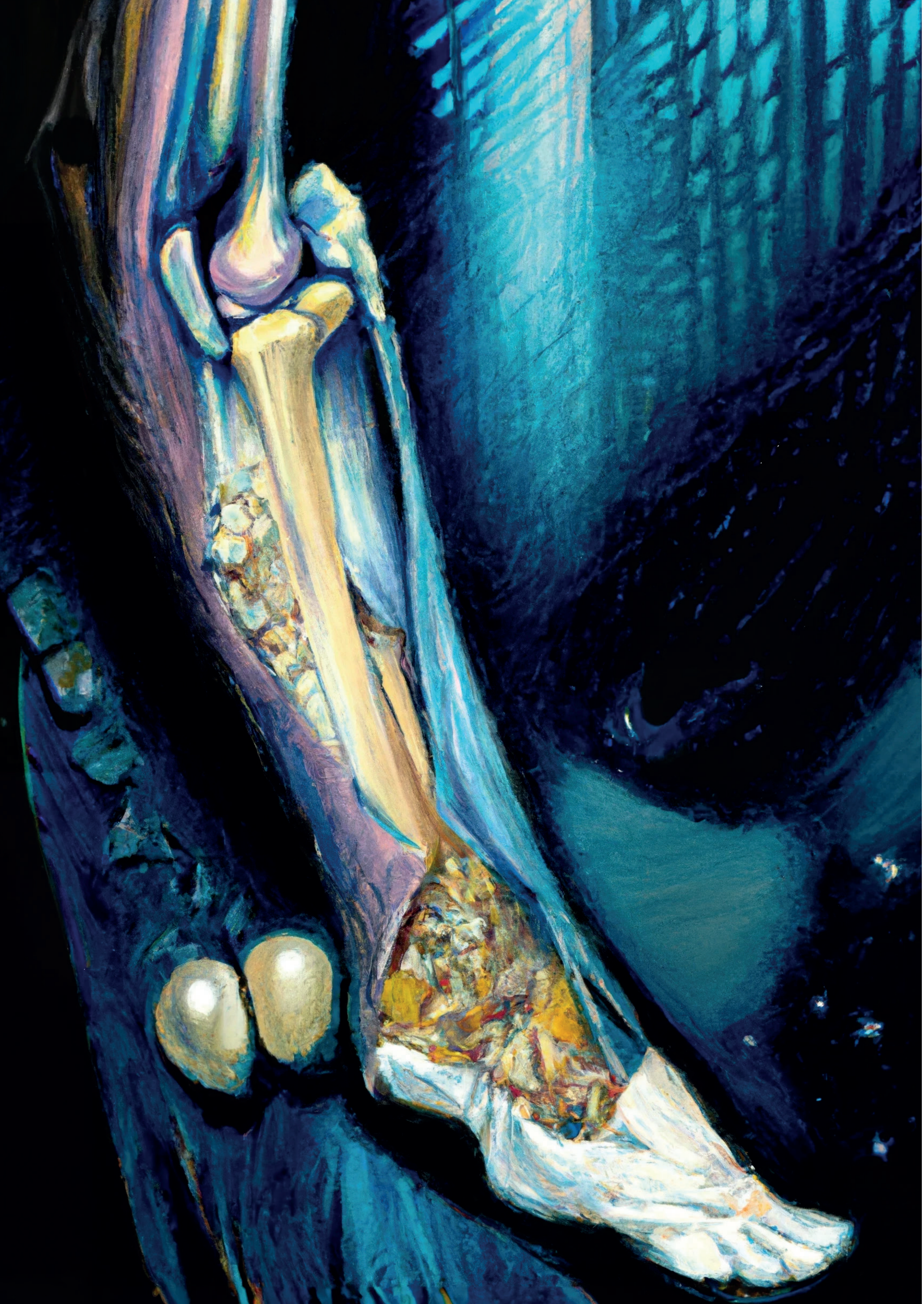
105. Mubarak SJ, Owen CA, Hargens AR, Garetto LP, Akeson WH. Acute compartment syndromes: diagnosis and treatment with the aid of the wick catheter. *J Bone Joint Surg Am*. 1978;60(8):1091-1095.

106. McQueen MM, Court-Brown CM. Compartment monitoring in tibial fractures. The pressure threshold for decompression. *J Bone Joint Surg Br*. 1996;78(1):99-104.

APPENDIX A

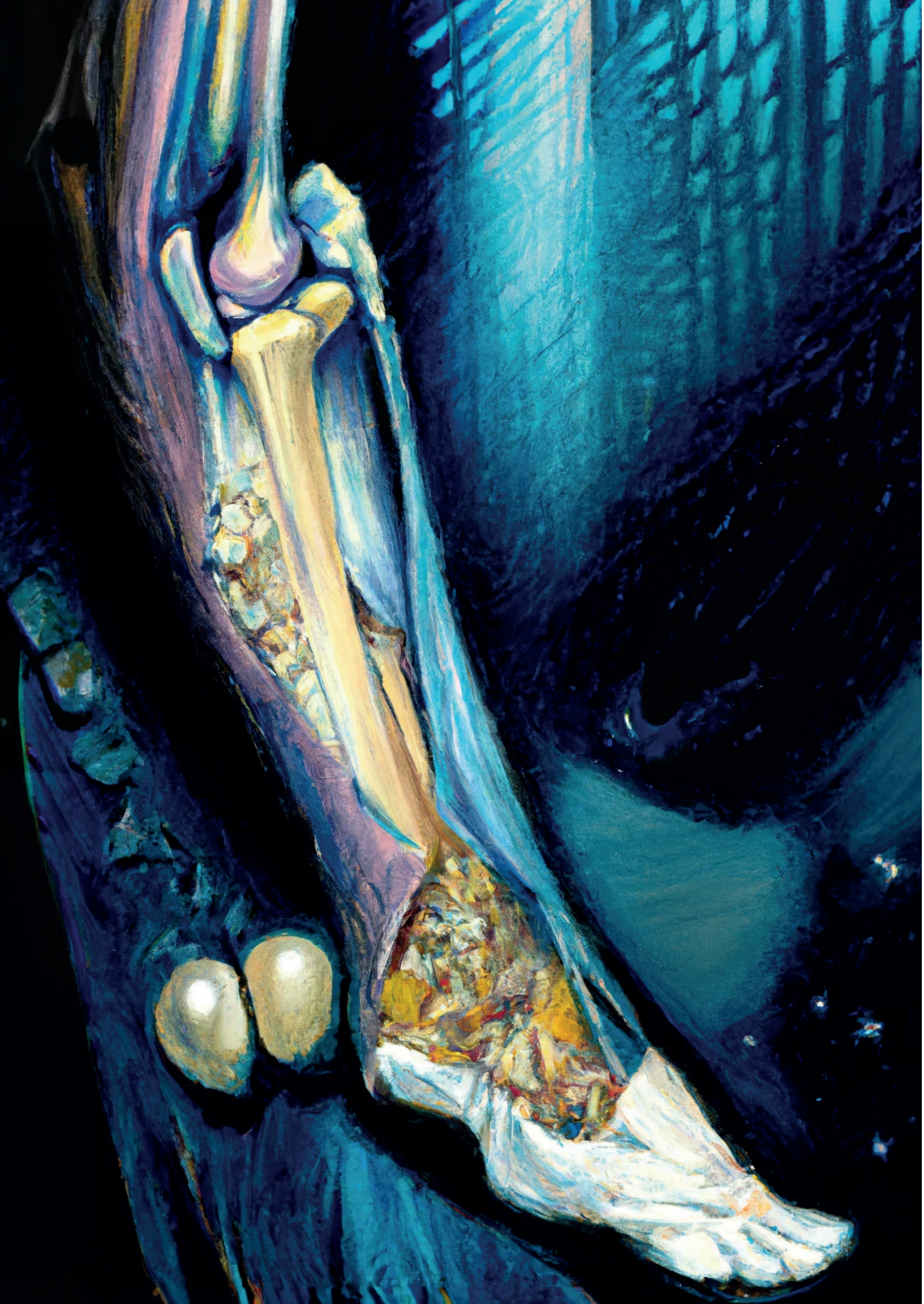
Modified Coleman Score

Section	Number or factor	Score
Part A. Only one score to be given for each section		
Study size – number of fractures (N)	> 60	10
	41-60	7
	20-40	4
	< 20, not stated	0
Mean follow-up	> 24 months	5
	12-24 months	2
	< 12 months	0
Number of different surgical procedures included in each reported outcome. More than one surgical technique may be assessed but separate outcomes should be reported undergoing the one procedure.	One surgical procedure only	10
	More than one surgical procedure, but >90% of subjects	7
	undergoing the one procedure, <10% concomitant procedures	0
	Not stated, unclear or <90% of subjects undergoing the one procedure	
Type of study	Randomized controlled trial	15
	Prospective cohort study	10
	Retrospective cohort study	0
Diagnostic certainty (type & location of fractures described)	Location and type of fractures described	5
	Location or type of fractures described	3
	None described	0
Description of surgical procedure given	Adequate (technique stated and necessary details of that type of procedure given)	5
		3
	Fair (technique only stated without elaboration)	
		0
	Inadequate, not stated, or unclear	
Description of postoperative rehabilitation	Inadequate description	0
	Well described	10
Part B. Scores may be given for each option in each of the 3 sections if applicable		
Outcome criteria	Outcome measures clearly defined	2
	Timing of outcome assessment clearly stated	2
	Use of outcome criteria that has reported good	3
	reliability	3
	Use of outcome with good sensitivity	
Procedure for assessing outcomes	Subjects recruited (results not taken from	5
	surgeons' files)	4
	Investigator independent of surgeon	3
	Written assessment	3
	Completion of assessment by subjects themselves with minimal investigator assistance	
Description of subject selection process	Selection criteria reported and unbiased	5
	Recruitment rate reported > 80% ; or	5
	<80%	3
	Eligible subjects not included in the study satisfactorily accounted for or 100% recruitment	5
Total score		100



Part I.

Subsequent Surgery – Rate and Patient Specific Risks



2

CHAPTER 2

Factors Associated with Subsequent Surgical Procedures after Intramedullary Nailing for Tibial Shaft Fractures

Laurent A.M. Hendrickx, James Virgin, Job N. Doornberg
Gino M.M.J. Kerkhoffs, Ruurd L. Jaarsma

EUROPEAN JOURNAL OF ORTHOPAEDIC SURGERY & TRAUMATOLOGY – JANUARY 2021

Springer - Eur J Orthop Surg Traumatol. 2021 Jan;31(1):43-50
https://link.springer.com/article/10.1007%2Fs00590-020-02733-z

ABSTRACT

Introduction

The reported rate of subsequent surgery after intramedullary nailing (IMN) of tibial shaft fractures (TSFs) is as high as 21%. However, most studies have not included the removal of symptomatic implant in these rates. The purpose of this study was to evaluate the subsequent surgery rate after IMN of TSFs, including the removal of symptomatic implants. Secondly, this study aimed to assess what factors are associated with subsequent surgery (1) to promote fracture and wound healing and (2) for the removal of symptomatic implants.

Methods

One-hundred and ninety-one patients treated with IMN for TSFs were retrospectively included. The rate of subsequent surgery was determined. Bi- and multivariable analysis was used to identify variables associated with subsequent surgery.

Results

Approximately half of patients (46%) underwent at least one subsequent surgical procedure. Forty-eight (25%) underwent a subsequent surgical procedure to promote fracture or wound healing. Age ($P < 0.01$), multi-trauma ($P < 0.01$), open fracture ($P < 0.001$) and index surgery during weekdays ($P < 0.05$) were associated with these procedures. Thirty-nine patients (20%) underwent a subsequent surgical procedure for removal of symptomatic implants. There was a significantly lower rate of implant removal in ASA II (11%) and ASA III–IV (14%) patients compared to ASA I patients (29%) ($P < 0.05$).

Conclusions

Patients treated with IMN for TSFs should be consented that about one-in-two patients will undergo an additional surgical procedure. Half of these procedures are required to promote wound or fracture healing; the other half are for symptomatic implant removal.

Level of Evidence

Therapeutic Level-IV

INTRODUCTION

Tibial shaft fractures (TSFs) are frequently occurring injuries [1]. Intramedullary nailing (IMN) is widely considered the best treatment for these injuries because it provides good direct relative fracture stability whilst being minimally invasive with regard to surrounding soft tissue [2]. Nevertheless, for many patients IMN is only the first operation in the process of achieving satisfactory operative outcomes, with (several) additional surgical procedures often required. Current literature reports on reoperation rates after operative treatment of TSFs ranging from 14 to 36%; however, few studies have directly investigated this study question (Table 1) [3–6]. Furthermore, the majority of these studies do not include or report on removal of implant due to local pain or irritation as a secondary procedure as these are considered discretionary. In a recent review of the literature, we found the average rate of symptomatic screw removal after IMN of TSFs to be 9% [7–12]. However, from the experience at our level-1 trauma centre we believe this to be an underestimation, hypothesizing that the true rate of screw removal, and therefore the true rate of subsequent surgery, is significantly higher.

Surgery for the removal of symptomatic implants can have a significant impact at a socio-economic level [13] and can increase the risk of additional complications [13,14]. Decreasing the rate of these procedures should therefore be considered an important goal. However, to the best of our knowledge, thus far, no factors associated with implant removal have been identified.

The primary aim of this study was to assess the total rate of subsequent surgery after IMN of TSFs, including symptomatic implant removals. The secondary aim was to assess what patient, trauma and fracture characteristics are associated with (1) subsequent surgery for wound and fracture healing and (2) subsequent surgery for implant removal. This knowledge will allow clinicians to better inform patients on expected outcomes following surgery. Additionally, it will allow for better insight into the total health economic costs associated with IMN of TSFs.

TABLE 1. Previous studies investigating factors associated with subsequent surgery after operative treatment of tibial shaft fractures.

Authors	Patients	Minimum follow-up	Subsequent surgery rate	Factors associated with subsequent surgery
Stavrou et al.[3]	151 treated with IMN	12 months	21%	42B or 42C AO/OTA Type Alcohol abuse
Fong et al.[4]	157 treated with IMN 36 treated with plate fixation	Unclear	13.5% overall	Open fractures Transverse fractures
Bhandari et al.[5]	80 treated with IMN 108 treated with plate fixation 4 treated with external fixator	12 months	16.3% for IMN 22.4% overall	Open fractures Cortical contact <50% Transverse fractures
Harris et al. [6]	124 treated with IMN 17 treated with external fixator 1 treated with plate fixation	6 months	35.8% overall	42B AO/OTA Type Gustilo-Anderson Grade II Gustilo-Anderson Grade III

MATERIALS & METHODS

Ethics

In accordance with the Declaration of Helsinki, our institutional review board granted approval for this study (Reference number: AUD/19/SAC/250).

Study Design, Setting, and Participants

As per protocol, all TSFs at our level-1 trauma centre are treated with reamed IMN with the TRIGEN Intramedullary Nailing System (Smith & Nephew, Andover, MA USA) with proximal and distal interlocking screws. Postoperatively, patients were allowed to weight bear as tolerated. Patients were routinely seen at 2, 6 and 12 weeks after surgery, or longer in case of an atypical recovery. Implant removal was not part of the standard treatment.

We included all skeletally mature patients with traumatic TSFs who were treated with IMN between January 2009 and September 2016, allowing for a minimum follow-up of 2.5 years. Patients treated for pathological fractures, patients with incomplete records and patients with inadequate follow-up (i.e. < 12 weeks) were excluded.

Variables, Outcome Measures, Data Sources, and Bias

Two authors not involved in patient care (LH and JV) assessed radiographs, patients' files, operation reports and CT scans to collect patient, trauma, fracture and treatment characteristics.

Independent variables included: (1) gender; (2) age; (3) multi-trauma; (4) trauma mechanism; (5) American Society of Anesthesiologists Physical Status (ASA-PS) [15]; (6) open fracture; (7) OTA/AO type of tibial fracture; (8) location of tibial fracture; (9) presence of fibula fracture; (10) the use > 2 proximal screws; (11) the use > 2 distal screws; (12) surgery during weekend or weekday; (13) after-hours surgery; and (14) level of surgeon. Fractures were classified into three groups according to the OTA/AO Fracture and Dislocation Classification Compendium: 42A1-3, 42B1-3 and 42C1-3. Trauma mechanism was classified as either low energy (< 30 km per hour or a fall from < 3 m) or high energy. After-hours surgery was defined as any surgery starting between 18.00 pm and 08.00 am. The cut-off for > 2 proximal or distal interlocking screws was chosen because, from our experience, the use of more locking screws is usually related to surgery for more complex fractures.

The primary outcome of this study was subsequent surgery, including elective procedures. It was recorded whether patients underwent one, two or more than two subsequent surgical procedures. Subsequent surgical procedures were also categorized into the following: (1) subsequent surgery to promote union (dynamization, nail exchange, bone graft); (2) wound closure (delayed primary wound closure, skin graft, flap or closure of fasciotomy wounds); (3) fasciotomies for postoperative compartment syndrome; (4) surgery to treat infection; (5) surgery to correct malunion or rotational malalignment; (6) surgery for wound healing (washout and debridement); (7) removal of interlocking screw due to irritation or pain; and (8) removal of tibial nail due to pain or irritation. Using these eight categories, two main groups were distinguished: (1) patients with a subsequent surgical procedure for fracture and wound healing (categories 1–6) and (2) and patients with a subsequent surgical procedure to remove symptomatic screws and/or tibial nail (categories 7 and 8).

Statistical analysis

Qualitative assessment of the data was performed. Descriptive statistics were calculated: means and standard deviations for normally distributed continuous variables, median and range for non-normally distributed continuous variables and frequencies and percentages for categorical variables.

Bivariable analysis was performed to assess whether any independent variables were associated with each respective group of subsequent surgical procedures. Binary logistic regression was used for continuous variables, and $\chi2$ test or Fisher exact was used for categorical and ordinal variables. Variables with a P value < 0.1 were subsequently entered in a multivariable binary logistic regression with a stepwise backward selection procedure. At each step, the variable with the largest P value was eliminated. This process was repeated until all variables in the equation reached a P value < 0.05. Multivariable binary logistic regression was limited to five events per variable.

Regarding subsequent surgery for symptomatic screws, we performed a subgroup analysis of patients who had undergone protocolled low-dose postoperative bilateral CT scans for the assessment of rotational malalignment [16]. his protocol was implemented at our institution in 2009 with an initial adherence rate of 43%. In 2018, the adherence rate of this protocol had increased to 83%. In a previous study, we analysed these postoperative CT scans to assess the incidence of iatrogenic screw penetration in the proximal and distal tibiofibular joint [17]. In the current study we re-used this data, to assess whether these types of screw penetration are associated with a higher rate of symptomatic screw removal.

RESULTS

From 2009 to 2016, 251 patients were treated with IMN for TSFs. Sixty patients (24%) were excluded: 36 patients (14%) had inadequate follow-up, 21 patients (8%) were followed up externally, one patient received palliative care after surgery, one patient had incomplete records and one patient had a pathological fracture.

A total of 191 patients were included. The majority of patients were male (71.2%) with a median age of 37 years (range, 14–90 years). Eighty patients (42%) sustained the fracture in a high-energy trauma, and 39 (20%) were polytrauma patients. Further patient and fracture characteristics are displayed in Table 2.

Eighty-seven patients (46%) underwent at least one subsequent surgical procedure. The most frequent indication for a first subsequent surgical procedure was screw removal due to irritation or pain (40%), followed by closure of wounds (25%) (Table 3). Twenty-nine patients (15%) underwent at least two subsequent surgical procedures. The most frequent second additional surgical procedures were performed for wound healing (31%), followed by closure of wounds (21%) (Table 3). Thirteen patients (7%) underwent more than two additional surgical procedures.

TABLE 2. Patient Demographics and Fracture Characteristics (n = 191)

Patient Characteristics	
Age, median years (range)	37 (14-90)
Gender, n (%)	
Male	55 (29%)
Female	136 (71%)
Multi-trauma, n (%)	
No	152 (80%)
Yes	39 (20%)
Trauma mechanism, n (%)	
Low energy	111 (58%)
High energy	80 (42%)
ASA-status, n (%)	
ASA I	92 (48%)
ASA II	64 (34%)
ASA III-IV	35 (18%)
Fracture Characteristics	
Open fracture, n (%)	
No	128 (67%)
Yes	63 (33%)
AO/OTA-type, n (%)	
42A1-3	119 (62%)
42B1-3	44 (23%)
42C1-3	28 (15%)
Location, n (%)	
Proximal	6 (3%)
Middle	58 (30%)
Distal	116 (61%)
Segmental	11 (6%)
Fibula fracture, n (%)	
No	27 (14%)
Yes	164 (86%)
Surgery Characteristics	
>2 proximal screws, n (%)	
No	175 (92%)
Yes	16 (8%)
>2 distal screws, n (%)	
No	145 (76%)
Yes	46 (24%)

Day of operation, n (%)	
Weekday	127 (66%)
Weekend	64 (34%)
After hours surgery, n (%)	
No	145 (76%)
Yes	46 (24%)
Level Primary Surgeon, n (%)	
Consultant	71 (37%)
Fellow	68 (36%)
Registrar	52 (27%)

TABLE 3. Overview of the First and Second Additional Subsequent Surgical Procedures Patients Underwent

Type of subsequent surgical procedure	First subsequent surgical procedure, n (%)	Second subsequent surgical procedure, n (%)
Surgery to promote union	9 (10%)	3 (10%)
Surgery to close wounds	22 (25%)	6 (21%)
Fasciotomy postoperative compartment syndrome	4 (5%)	2 (7%)
Surgery to treat infection	2 (2%)	1 (3%)
Surgery to correct malunion	5 (6%)	3 (10%)
Surgery to promote wound healing	6 (7%)	9 (31%)
Removal symptomatic screw	35 (40%)	5 (17%)
Removal symptomatic nail	4 (5%)	5 (17%)
Total	87 (100%)	29 (100%)

Subsequent surgery fracture & wound healing

Forty-eight patients (25%) underwent a first subsequent surgical procedure to promote fracture or wound healing. Bivariable analysis demonstrated that age ($P < 0.05$), multi-trauma ($P < 0.001$), trauma-mechanism ($P < 0.001$), open fracture ($P < 0.01$), AO/OTA type ($P < 0.01$), the use of more than 2 proximal interlocking screws ($P < 0.05$) and surgery during weekdays ($P < 0.05$) were associated with subsequent surgical procedures for fracture and wound healing (Table 4).

Multivariable analysis subsequently identified younger age ($P < 0.01$), multi-trauma ($P < 0.01$), open fracture ($P < 0.001$) and surgery during weekdays ($P < 0.05$) as independent predictors (Table 5).

TABLE 4. Bivariable Analysis of Patient-, Trauma-, Fracture- and Treatment Characteristics and Subsequent Surgery for Fracture and Wound Healing (n = 191)

Variable	Subsequent Surgery for Fracture & Wound healing		P-value
	No	*Yes*	
Gender, n (%)			0.30
Male	99 (73%)	37 (27%)	
Female	44 (80%)	11 (20%)	
Age, mean years (SD)	41.8 (17.4)	35.1 (16.8)	0.024*
Multi-trauma, n (%)			<0.001*
No	123 (81%)	29 (19%)	
Yes	20 (51%)	19 (49%)	
Trauma mechanism, n (%)			<0.001*
Low energy	94 (85%)	17 (15%)	
High energy	49 (61%)	31 (39%)	
ASA-status, n (%)			0.36
ASA I	71 (77%)	21 (23%)	
ASA II	44 (69%)	20 (31%)	
ASA III-IV	28 (80%)	7 (20%)	
Open fracture, n (%)			
No	105 (82%)	23 (18%)	0.001*
Yes	38 (60%)	25 (40%)	
AO/OTA-type, n (%)			0.003*
42A1-3	98 (82%)	21 (18%)	
42B1-3	30 (68%)	14 (32%)	
42C1-3	15 (54%)	13 (46%)	
Location, n (%)			0.16
Proximal	3 (50%)	3 (50%)	
Middle	43 (74%)	15 (26%)	
Distal	91 (78%)	25 (22%)	
Segmental	6 (55%)	5 (45%)	
Fibula fracture, n (%)			0.39
No	22 (81%)	5 (19%)	
Yes	121 (74%)	43 (26%)	
>2 proximal screws, n (%)			0.017*
No	135 (77%)	40 (23%)	
Yes	8 (50%)	8 (50%)	
>2 distal screws, n (%)			0.86
No	109 (75%)	36 (25%)	

Yes	34 (74%)	12 (26%)	
Day of operation, n (%)			0.012*
Weekday	88 (69%)	39 (31%)	
Weekend	55 (86%)	9 (14%)	
After hours surgery, n (%)			0.86
No	109 (75%)	36 (25%)	
Yes	34 (74%)	12 (26%)	
Level Surgeon, n (%)			0.68
Consultant	51 (72%)	20 (28%)	
Fellow	51 (75%)	17 (25%)	
Registrar	41 (79%)	11 (21%)	

* Binary logistic regression or χ2 test was significant at $P < 0.05$

TABLE 5. Multivariable Logistic Regression Analysis Subsequent Surgery Fracture & Wound Healing

Variable	Odds Ratio (95% Confidence Interval)	P-value
Age	0.96 (0.94-0.99) *	<0.01
Multi-trauma	3.20 (1.42 – 7.22)	<0.01
Open fracture	4.14 (1.89 – 9.05)	<0.001
Surgery on weekdays	2.96 (1.22 – 7.17)	0.02

*odds ratio per year increase in age

Subsequent surgery for removal of symptomatic screws and/or nail

Removal of symptomatic screws and/or nail occurred on average 578 days after the index procedure (range 94–1850 days). Thirty-nine patients (20%) underwent a first subsequent surgical procedure for removal of symptomatic screws or nails. Bivariable analysis indicated that only ASA-PS was associated with this type of subsequent surgery (Table 6). The rate of implant removal was significantly lower in ASA II and ASA III–IV patients as compared to ASA I patients ($P < 0.05$).

TABLE 6. Bivariable Analysis of Patient-, Trauma-, Fracture- and Treatment Characteristics and Subsequent Surgery for Symptomatic Screws or Nail

Variable	Surgery Symptomatic Screws or Nail		P-value
	No	*Yes*	
Gender, n (%)			0.63
Male	107 (79%)	29 (21%)	
Female	45 (82%)	10 (18%)	
Age, mean years (SD)	41.1 (18.1)	36.1 (14.3)	0.11
Multi-trauma, n (%)			0.38
No	119 (78%)	33 (22%)	
Yes	33 (85%)	6 (15%)	
Trauma mechanism, n (%)			0.90
Low energy	88 (79%)	23 (21%)	
High energy	64 (80%)	16 (20%)	
ASA-status, n (%)			0.01*
ASA I	65 (71%)	27 (29%)	
ASA II	57 (89%)	7 (11%)	
ASA III-IV	30 (86%)	5 (14%)	
Open fracture, n (%)			
No	97 (76%)	31 (24%)	0.06
Yes	55 (87%)	8 (13%)	
AO/OTA-type, n (%)			0.99
42A1-3	95 (80%)	24 (20%)	
42B1-3	35 (80%)	9 (20%)	
42C1-3	22 (79%)	6 (21%)	
Location, n (%)			0.55
Proximal	6 (100%)	0 (0%)	
Middle	44 (76%)	14 (24%)	
Distal	93 (80%)	23 (20%)	
Segmental	9 (82%)	2 (18%)	
Fibula fracture, n (%)			0.20
No	19 (70%)	8 (30%)	
Yes	133 (81%)	31 (19%)	
>2 proximal screws, n (%)			0.63
No	140 (80%)	35 (20%)	
Yes	12 (75%)	4 (25%)	
>2 distal screws, n (%)			0.50
No	117 (81%)	28 (19%)	
Yes	35 (76%)	11 (24%)	
Surgery in weekend, n (%)			0.46
No	103 (81%)	24 (19%)	
Yes	49 (77%)	15 (23%)	
After hours surgery, n (%)			0.87
No	115 (79%)	30 (21%)	
Yes	37 (80%)	9 (20%)	
Level Surgeon, n (%)			0.55
Consultant	59 (83%)	12 (17%)	
Fellow	54 (79%)	14 (21%)	
Registrar	39 (75%)	13 (25%)	

* $\chi 2$ test was significant at $P < 0.05$

Subgroup analysis of screw penetration

A total of 123 patients had undergone a low-dose postoperative CT scan to assess malalignment according to hospital protocol. Of these patients, 18 were excluded; in three patients, it was unclear which screw had been removed since no follow-up radiology was available; three patients had undergone dynamization to promote union; and in 12 patients, the tibial nail had been revised, removed or exchanged after the CT scan. In the remaining 105 patients, no association between proximal or distal tibiofibular screw penetration and screw removal could be demonstrated (Table 7).

TABLE 7. Bivariable Analysis of Tibiofibular Screw Penetration and Subsequent Surgery for Screw Removal.

		Screw Removal		
Tibiofibular Screw Penetration	*Total*	*Yes*	*No*	P-value
Proximal, n (%)				
No screw penetration	61	7 (11%)	54 (89%)	0.51
Screw penetration	44	7 (16%)	37 (84%)	
Distal, n (%)				
No screw penetration	63	10 (16%)	53 (84%)	0.57
Screw penetration	42	5 (12%)	37 (88%)	

DISCUSSION

Patients treated with IMN for TSFs should be consented that about one-in-two patients will undergo an additional surgical procedure. Approximately half of these additional surgical procedures are performed to promote fracture or wound healing. Age, multi-trauma, open fractures and index surgery during weekdays are predictors of this type of additional surgical procedures. The other half of procedures are discretionary: performed to remove interlocking screws and/or tibial nails causing pain or irritation. This type of procedures is less frequently performed in patients with higher ASA-PS and is not associated with tibiofibular screw penetration. These data support the consent of patients with TSFs: that IMN may not be a quick fix.

The findings of this study must be appreciated with an understanding of its limitations. Firstly, a substantial number (22%) of patients had to be excluded due to inadequate follow-up. Although loss to follow-up is a well-known problem in Orthopaedic Trauma [3] ould therefore not be included. Thirdly, this study was conducted at a single, level-1 trauma centre. This may have resulted in a slight overrepresentation of high-energy trauma and open fractures. However, since mono-trauma cases are also part of our daily routine practice and represented 80% of the entire cohort, we believe the current series is a good representation of the entire spectrum of tibial shaft fractures. Lastly, limited by the number of events per variable we were forced to group a number of independent variables. This may have concealed the effect of certain variables such as the previously documented effect of transverse fractures on the re-operation rate [4,5].

The one-in-two reoperation rate (46%) identified in this study is substantially higher than previously reported (14–36%) [3–6]. This is mainly due to the large number (n = 39) of surgical procedures carried out for symptomatic screw removal, which is not included in the majority of the previously reported studies, but very important in informed consent for our patients in the overall picture. It could be argued that the removal of symptomatic locking screws is a relatively minor surgical procedure; however, from a patients' perspective any type of surgery is often subjectively considered as major. With an estimated total procedural cost of $2000–2500 (AUD) at our institution, this type of surgery can furthermore have significant impact at a socio-economic level [13]. We therefore believe that it is important for clinicians and patients to be aware of this substantial number. It is important to note that the high rate of implant removal is not exclusive to IMN. In a randomized controlled trial comparing IMN and plate fixation of distal TSFs, the rate of subsequent surgery for implant removal was similar between both groups [18].

It is well known that open TSFs are at a higher risk of infection and non-union [19–22]. In the current study, open fractures were identified as an independent predictor of subsequent surgery. This is in line with what several previous studies have demonstrated [4–6] (Table 1). Both younger age and multi-trauma were also predictive of subsequent surgery for wound and fracture healing. Both of these variables may be considered indicative of injury severity. With regard to age, this can be explained by the bimodal distribution of TSFs: in younger patients, they are more often caused by traffic accidents, whereas in elderly patients they are most commonly caused by simple falls [23]. Lastly, surgery on weekdays was an independent predictor of subsequent surgery for wound and fracture healing. When initiating this study, we hypothesized the opposite to be true, as various studies have suggested outcome may be worse if patients are admitted or undergo surgery during the weekend [24–26]. A possible explanation for our finding could be that there may be a tendency to postpone non-acute, yet complex cases during the weekend to weekdays.

Only one variable was associated with subsequent discretionary surgery to remove symptomatic screws and/or nails: in patients with higher ASA-PS significantly less surgery was performed to remove implant. This is likely explained by surgeons and anaesthesiologists being more cautious with additional surgery in this patient group, rather than there being a causal relationship between ASA-PS and symptomatic screws. On the other hand, it may also indicate that we need to more critically review whether removal of screws and/or nails in patients with an ASA I status is necessary as one could argue that this is elective. Whilst it is suggested that screw penetration in the proximal and distal tibiofibular joint may lead to respective lateral sided knee-pain[17,27] and lateral sided ankle pain [17], there was no higher rate of removal of these screws in our study. Future studies should aim to assess whether screw penetration in the proximal or distal tibiofibular joint indeed causes pain or affects functional outcome. It is important to note that the interlocking screws which were used in this study have been modified in order to give the screw heads a lower profile. This modification was introduced in our hospital after our final inclusion. Future studies should be performed to assess whether this modification results in lower rates of screw removal.

Although we identified several predictors for subsequent surgery for fracture and wound healing, it remains difficult to extrapolate these findings to the individual patient: we present average results of an ‘extrapolated study population’. Moreover, these predictors have not been validated [28]. In orthopaedic surgery, various studies have recently been published that use a streamlined method for developing, validating and deploying prediction models [29,30]. The use of machine learning algorithms in these studies furthermore may allow for identifying nonlinear relations between variables [31]. Applying such methods could potentially aid in developing, validating and deploying a more practical prediction model to estimate the risk of subsequent surgery in individual patients with TSFs. This may require larger datasets and could be subject of future studies in our era of personalized care.

The current study could not identify any causal predictors of subsequent surgery for removal of implant. This might mostly be determined by type of implant used and local experiences and protocol. Given the high rate of these surgeries, future studies should aim to assess whether there are any other variables associated with these procedures. Identifying such variables may help modifying treatment in order to decrease the rate of these procedures.

In conclusion, nearly one-in-two patients treated with IMN for TSFs will undergo an additional surgical procedure. Approximately half of these procedures are required for wound and fracture healing, whilst the remaining half are discretionarily performed to remove symptomatic screws or nails. Age, open fractures and multi-trauma were independent predictors of the former, whilst a higher rate of symptomatic implant removal was seen in ASA I patients.

REFERENCES

1. Larsen P, Elsoe R, Hansen SH, Graven-Nielsen T, Laessoe U, Rasmussen S. Incidence and epidemiology of tibial shaft fractures. *Injury*. 2015;46(4):746-750.
2. Tornetta P III, Ricci W, McQueen MM, Others. *Rockwood and Green's Fractures in Adults*. Lippincott Williams & Wilkins; 2019.
3. Stavrou PZ, Ciriello V, Theocharakis S, et al. Prevalence and risk factors for re-interventions following reamed intramedullary tibia nailing. *Injury*. 2016;47 Suppl 7:S49-S52.
4. Fong K, Truong V, Foote CJ, et al. Predictors of nonunion and reoperation in patients with fractures of the tibia: an observational study. *BMC Musculoskelet Disord*. 2013;14:103.
5. Bhandari M, Tornetta P 3rd, Sprague S, et al. Predictors of reoperation following operative management of fractures of the tibial shaft. *J Orthop Trauma*. 2003;17(5):353-361.
6. Harris I, Lyons M. Reoperation rate in diaphyseal tibia fractures. *ANZ J Surg*. 2005;75(12):1041-1044.
7. Vallier HA, Le TT, Bedi A. Radiographic and clinical comparisons of distal tibia shaft fractures (4 to 11 cm proximal to the plafond): plating versus intramedullary nailing. *J Orthop Trauma*. 2008;22(5):307-311.
8. Leliveld MS, Verhofstad MHJ. Injury to the infrapatellar branch of the saphenous nerve, a possible cause for anterior knee pain after tibial nailing? *Injury*. 2012;43(6):779-783.
9. Sidky A, Buckley RE. Hardware removal after tibial fracture has healed. *Can J Surg*. 2008;51(4):263-268.
10. Weil YA, Gardner MJ, Boraiah S, Helfet DL, Lorich DG. Anterior knee pain following the lateral parapatellar approach for tibial nailing. *Arch Orthop Trauma Surg*. 2009;129(6):773-777.
11. Ricci WM, Gallagher B, Brandt A, Schwappach J, Tucker M, Leighton R. Is after-hours orthopaedic surgery associated with adverse outcomes? A prospective comparative study. *J Bone Joint Surg Am*. 2009;91(9):2067-2072.
12. Hendrickx LAM, Virgin J, van den Bekerom MPJ, Doornberg JN, Kerkhoffs GMMJ, Jaarsma RL. Complications and subsequent surgery after intra-medullary nailing for tibial shaft fractures: Review of 8110 patients. *Injury*. Published online April 22, 2020. doi:10.1016/j.injury.2020.04.021
13. Busam ML, Esther RJ, Obremskey WT. Hardware removal: indications and expectations. *J Am Acad Orthop Surg*. 2006;14(2):113-120.
14. Reith G, Schmitz-Greven V, Hensel KO, et al. Metal implant removal: benefits and drawbacks--a patient survey. *BMC Surg*. 2015;15:96.
15. Abouleish AE, Leib ML, Cohen NH. ASA Provides Examples to Each ASA Physical Status Class. *ASA Monitor*. 2015;79(6):38-49.
16. Cain ME, Hendrickx LAM, Bleeker NJ, Lambers KTA, Doornberg JN, Jaarsma RL. Prevalence of Rotational Malalignment After Intramedullary Nailing of Tibial Shaft Fractures: Can We Reliably Use the Contralateral Uninjured Side as the Reference Standard? *J Bone Joint Surg Am*. Published online January 20, 2020. doi:10.2106/JBJS.19.00731

17. Cain ME, Doornberg JN, Duit R, Clarnette J, Jaarsma R, Jadav B. High incidence of screw penetration in the proximal and distal tibiofibular joints after intramedullary nailing of tibial fractures-A prospective cohort and mapping study. *Injury*. 2018;49(4):871-876.

18. Vallier HA, Cureton BA, Patterson BM. Randomized, prospective comparison of plate versus intramedullary nail fixation for distal tibia shaft fractures. *J Orthop Trauma*. 2011;25(12):736-741.

19. O'Halloran K, Coale M, Costales T, et al. Will My Tibial Fracture Heal? Predicting Nonunion at the Time of Definitive Fixation Based on Commonly Available Variables. *Clin Orthop Relat Res*. 2016;474(6):1385-1395.

20. Dailey HL, Wu KA, Wu P-S, McQueen MM, Court-Brown CM. Tibial Fracture Nonunion and Time to Healing After Reamed Intramedullary Nailing: Risk Factors Based on a Single-Center Review of 1003 Patients. *J Orthop Trauma*. 2018;32(7):e263-e269.

21. Gaebler C, Berger U, Schandelmaier P, et al. Rates and odds ratios for complications in closed and open tibial fractures treated with unreamed, small diameter tibial nails: a multicenter analysis of 467 cases. *J Orthop Trauma*. 2001;15(6):415-423.

22. Metsemakers W-J, Handojo K, Reynders P, Sermon A, Vanderschot P, Nijs S. Individual risk factors for deep infection and compromised fracture healing after intramedullary nailing of tibial shaft fractures: a single centre experience of 480 patients. *Injury*. 2015;46(4):740-745.

23. Leliveld MS, Polinder S, Panneman MJM, Verhofstad MHJ, Van Lieshout EMM. Epidemiologic trends for isolated tibia shaft fracture admissions in The Netherlands between 1991 and 2012. *Eur J Trauma Emerg Surg*. Published online January 7, 2019. doi:10.1007/s00068-018-01072-3

24. Kostis WJ, Demissie K, Marcella SW, et al. Weekend versus weekday admission and mortality from myocardial infarction. *N Engl J Med*. 2007;356(11):1099-1109.

25. Bell CM, Redelmeier DA. Mortality among patients admitted to hospitals on weekends as compared with weekdays. *N Engl J Med*. 2001;345(9):663-668.

26. Honeyford K, Cecil E, Lo M, Bottle A, Aylin P. The weekend effect: does hospital mortality differ by day of the week? A systematic review and meta-analysis. *BMC Health Serv Res*. 2018;18(1):870.

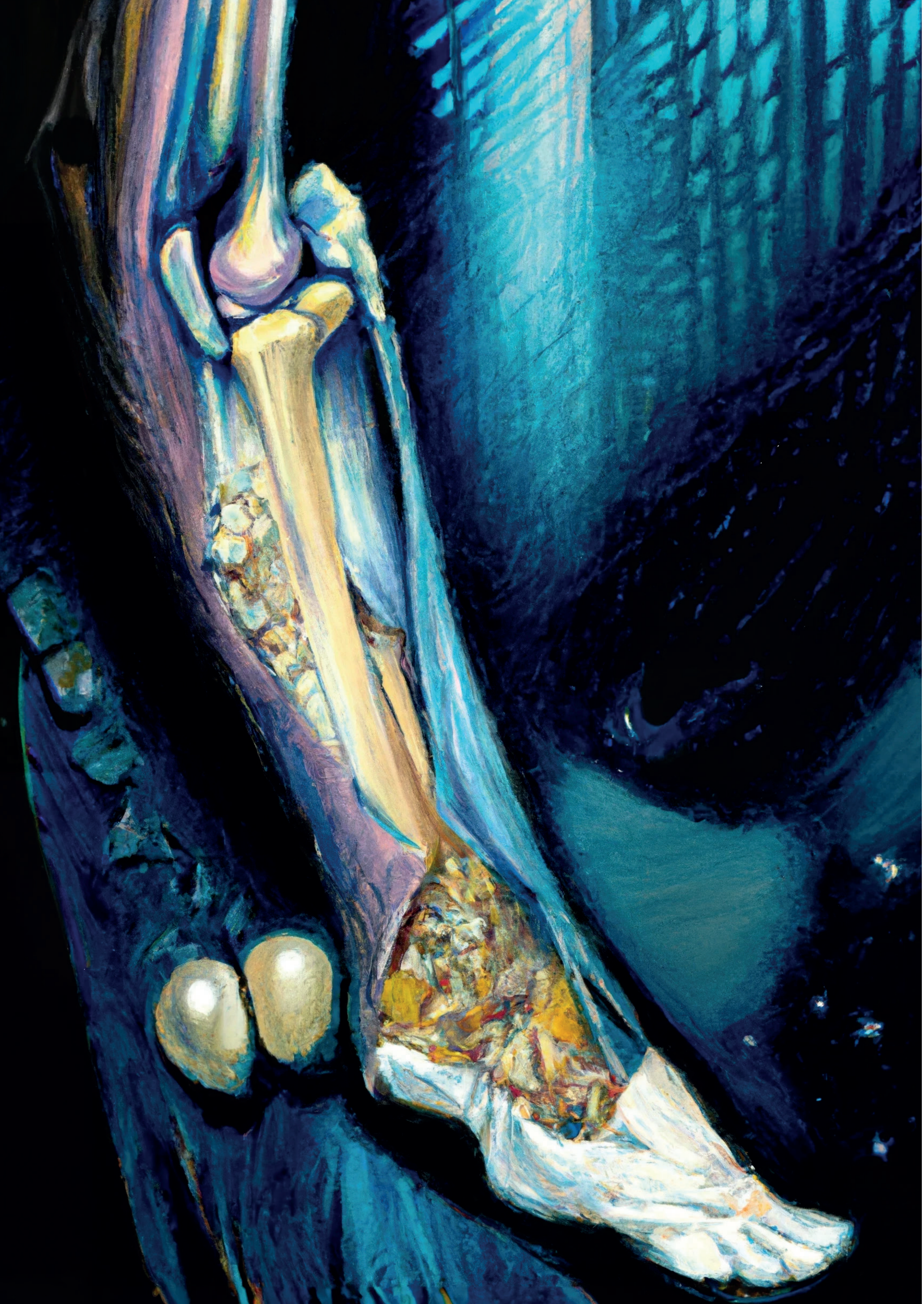
27. Labronici PJ, Santos Pires RE, Franco JS, Alvachian Fernandes HJ, Dos Reis FB. Recommendations for avoiding knee pain after intramedullary nailing of tibial shaft fractures. *Patient Saf Surg*. 2011;5(1):31.

28. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. *Eur Heart J*. 2014;35(29):1925-1931.

29. Thio QCBS, Karhade AV, Ogink PT, et al. Can Machine-learning Techniques Be Used for 5-year Survival Prediction of Patients With Chondrosarcoma? *Clin Orthop Relat Res*. 2018;476(10):2040-2048.

30. Hendrickx LAM, Sobol GL, Langerhuizen D, et al. A Machine Learning Algorithm to Predict the Probability of (Occult) Posterior Malleolar Fractures Associated with Tibial Shaft Fractures to Guide "Malleolus First" Fixation. *J Orthop Trauma*. 2019;Publish Ahead of Print. doi:10.1097/BOT.0000000000001663

31. Bertsimas D, Dunn J, Velmahos GC, Kaafarani HMA. Surgical Risk Is Not Linear: Derivation and Validation of a Novel, User-friendly, and Machine-learning-based Predictive OpTimal Trees in Emergency Surgery Risk (POTTER) Calculator. *Ann Surg*. 2018;268(4):574-583.



3

CHAPTER 3

A Machine Learning Algorithm to Identify Patients at Risk of Unplanned Subsequent Surgery After Intramedullary Nailing for Tibial Shaft Fractures.

Machine Learning Consortium on Behalf of SPRINT Investigators

Machine Learning Consortium

Laurent A.M. Hendrickx, Mohit Bhandari, Anne Eva J. Bulstra, Sofia Bzovsky, Job Doornberg; J. Carel Goslings, Ruurd L. Jaarsma, Kyle Jeray, Gino M.M.J. Kerkhoffs, Wouter H. Mallee, Brad Petrisor, David Ring, David Sanders, Emil H. Schemitsch, Inger B. Schipper, Sheila Sprague, Marc Swiontkowski, Paul Tornetta III, Stephen D. Walter

JOURNAL OF ORTHOPAEDIC TRAUMA – OCTOBER 2021

This is a non-final version of an article published in final form in: Wolters Kluwer – Journal of Orthopaedic Trauma. Oct 2021;35(10):e381-e388. https://journals.lww.com/jorthotrauma/Abstract/2021/10000/A_Machine_Learning_Algorithm_to_Identify_Patients.15.aspx

ABSTRACT

Objectives

In the SPRINT trial, 18% of patients with a tibial shaft fracture (TSF) treated with intramedullary nailing (IMN) had one or more unplanned subsequent surgical procedures. It is clinically relevant for surgeon and patient to anticipate unplanned secondary procedures, other than operations that can be readily expected such as reconstructive procedures for soft tissue defects.

Therefore, the objective of this study was to develop a machine learning (ML) prediction model using the SPRINT data, that can give individual patients and their care team an estimate of their particular probability of an unplanned second surgery.

Methods

Patients from the SPRINT trial with unilateral TSFs were randomly divided into a training-set (80%) and test-set (20%).

Five ML-algorithms were trained in recognizing patterns associated with subsequent surgery in the training-set based on a subset of variables identified by Random Forest algorithms.

Performance of each ML-algorithm was evaluated and compared based on 1) area under the ROC-curve (AUC); 2) Calibration slope and intercept; and 3) Brier-score.

Results

Total dataset comprised 1198 patients, of which 214 patients (18%) underwent subsequent surgery.

Seven variables were used to train ML-algorithms: 1) Gustilo-Anderson classification; 2) Tscherne-classification; 3) fracture location; 4) fracture gap; 5) polytrauma; 6) injury mechanism; 7) AO/OTA-classification.

The best-performing ML-algorithm had an AUC, calibration slope, calibration intercept and Brier-score of 0.766, 0.954, -0.002 and 0.120 in the training-set, and 0.773, 0.922, 0 and 0.119 in the test-set respectively.

Conclusions

A ML-algorithm was developed to predict the probability of subsequent surgery after IMN of TSFs. This ML-algorithm may assist surgeons to inform patients about the probability of subsequent surgery and might help to identify patients that need a different peri-op plan or a more intensive approach.

Level of Evidence

Level I, prognostic study

INTRODUCTION

Patients with tibial shaft fractures (TSFs) are prone to undergo multiple procedures: an average 21% of patients treated with intramedullary nailing will undergo one or more subsequent surgical procedures according to prospective- and retrospective cohort studies, with 23% reported in the SPRINT trial [1–3]. It is clinically relevant for surgeon and patient to anticipate unplanned secondary procedures, other than operations that can be readily expected such as closure of fasciotomy wounds, or reconstructive procedure for large soft tissue defects. Unplanned subsequent surgery includes a diversity of procedures, which amongst are re-operations in response to infection and subsequent surgery to promote union. Several factors associated with subsequent surgery have been identified in previous studies, including the presence of open fractures, transverse fractures, alcohol abuse, and lack of cortical continuity after fixation due to bone loss or inadequate reduction [1,4]. However, extrapolation of cohort averages is inadequate to estimate the probability of these adverse events and reoperations for an individual patient with unique fracture characteristics. In the era of data driven precision care there is a clinical need to establish patient specific risk stratification models in order for surgeons to give accurate surgical consent and allow for early intervention.

Prediction models in Orthopaedic Trauma have proven useful in risk stratification of injured patients in the diagnostic work-up process thereby optimizing workflow and more efficient use of resources [5–7]. Recent studies suggest that Artificial Intelligence (AI), in particular Machine Learning (ML) algorithms, may be a valuable adjunct to such prediction models [8–13]. In some datasets ML algorithms offer potential advantage of recognizing non-linear relationships [14]. Another, theoretical, advantage is the ability to improve accuracy of the model over time with an active feedback loop to allow for more accurate diagnosis, identification of new observations or patterns, and development of personalized diagnostics and treatment. However, no studies to date support this theoretical concept of this potential benefit of ML in Orthopaedic Trauma.

Prediction models applied to patients with a TSF undergoing intramedullary nailing may assist surgeons in accurate patient consent and facilitate early surgical decision making.

However from a methodological perspective, before implementation of such a prediction model; 1) subsequent studies are required for external validation, 2) then the model should be studied prospectively for diagnostic accuracy (i.e. “silent testing” in clinical practice) and 3) finally the model should be trained with a continuous feedback loop to continuously improve performance characteristics.

The purpose of this current study was to develop the initial ML prediction model using the SPRINT Trial database [15], to estimate the probability of unplanned subsequent surgery in patients undergoing intramedullary nailing for a TSF.

METHODS

Guidelines

This study was conducted according to the Guidelines for Developing and Reporting Machine Learning Predictive Models in Biomedical Research [16] and the Transparent Reporting of Multivariable Prediction Models for Individual Prognosis or Diagnosis (TRIPOD) guideline [17].

Data safety

For safe multicentre data exchange and analysis, our Consortium adhered to World Healthcare Organisation (WHO) regulations: "Policy on use and sharing of data collected in Member States by the World Health Organization (WHO) outside the context of public health emergencies" [18].

Data Source & Patient Selection

The SPRINT trial is an international multicentre randomized controlled trial that compared reamed intramedullary nailing of TSFs versus unreamed intramedullary nailing in patients with TSFs [15]. All patients with unilateral TSFs treated with intramedullary nailing from this database were included in the dataset for the current study.

Outcome of interest

The probability of an unplanned subsequent surgical procedure in patients treated with intramedullary nailing of TSFs was the primary outcome (of interest) for the ML algorithms to predict. Unplanned subsequent surgery included the following procedures: 1) re-operation in response to infection; 2) implant exchange to promote union; 3) implant removal to promote union; 4) dynamization of the fracture-implant construction in the operating room; 5) dynamization in the outpatient clinic; 6) subsequent surgery to correct (rotational) malunion; 7) subsequent surgery for wound healing problems; 8) bone grafting; 9) fasciotomy for postoperative compartment syndrome; 10) removal of locking screws because of breakage; and 11) incision and drainage of haematoma.

Planned subsequent surgical procedures included delayed primary wound closure and additional soft tissue reconstruction. These procedures were not used for the development of the ML prediction model.

In the protocol of the SPRINT trial, no surgery to promote union was allowed in the first six months, unless there was a fracture gap or bone-loss [19]. After six months, the criteria for the diagnosis of non-union was the combination of a persistent fracture line with no progress towards union and either tenderness at the fracture site, or pain with weight bearing [19].

Candidate Input Variables

Variables that were considered for model development are displayed in Table 1. The presence and size of postoperative fracture gap was assessed by the Central Adjudication Committee of the SPRINT trial [15,20]. In the SPRINT trial the location of fracture was recorded in five categories: proximal, proximal-middle, middle, distal-middle, distal. In the current study fractures were classified as proximal, middle or distal. Proximal-middle fractures were classified as proximal fractures and distal-middle fractures as distal fractures [20].

TABLE 1. Candidate Input Variables

Variable	Details
Age	Years
Diabetes	Yes/No
Mechanism of injury	Crush injury; Direct trauma (blunt); Direct trauma (penetrating); Fall; Twisting injury; Motor vehicle (driver/passenger); Motor vehicle (pedestrian); Motorcycle accident
Polytrauma	Yes/No
Smoking status	Non-smoker; Previous smoker; Current smoker
Use of NSAID's	Yes/No
Use of oral steroids	Yes/No
Gustillo-Anderson classification	Type I; Type II; Type IIIA; Type IIIB; Closed fracture
Tscherne classification	Type 0; Type 1; Type 2; Type 3; Open fracture
Location	Proximal; Middle; Distal
AO-classification	42A1; 42A2; 42A3; 42B1; 42B2; 42B3; 42C1; 42C2; 42C3
Reaming status	Reamed; Unreamed
Time from injury to surgery	<6 hours; 6 – 24 hours; >24 hours
Level of surgeon	Surgeon; Resident; Fellow
Nail material	Stainless steel; Titanium
Number of proximal screws used	
Number of distal screws used	
Reduction method	Manual reduction; Distractor; Fracture table; Other
Postoperative fracture gap	Yes/No

Missing data

Less than 0.5% of the data was missing. For only three variables more than 0.5% of the data was missing: multi-trauma (6.6%), fracture location (0.8%), and time from injury to surgery (0.7%). Missing data were imputed using the *MissForest* algorithm [21].

Model development.

The total dataset was randomly split into a training-set (80%) and test-set (20%), stratified on the outcome of interest: unplanned subsequent surgery.

Feature selection in the training-set using Random Forest algorithms [22] was used to select variables for algorithm training.

Because it is difficult to predict which ML algorithm provides the best prediction model [23], we trained and tested five different algorithms: 1) Bayes point machine; 2) boosted decision tree; 3) penalized logistic regression; 4) neural network; and 5) support vector machine. These algorithms were selected based on previous studies [12,24–27].

For each ML algorithm, ten-fold cross validation was repeated three times on the train-set, to train the algorithms and subsequently assess their predictive performance [12].

For each ML algorithm, the performance was evaluated by calculating the following performance measures: 1) discrimination; 2) calibration; and 3) overall model performance [28]. Discrimination can be assessed by calculating the area under the ROC curve (AUC). An AUC of 1 indicates perfect discriminative ability between patients that undergo subsequent surgery and patients that do not undergo subsequent surgery, whereas an AUC of 0.5 indicates that the model cannot discriminate at all [29]. A rule of thumb for interpreting the AUC is as follows: 0.5 – 0.7 is considered poor, 0.7 – 0.8 is considered acceptable, 0.8 – 0.9 is considered excellent and >0.9 is considered outstanding[30]. Calibration reflects the agreement between the observed outcome and predicted probability. It can be assessed by plotting the predicted probability versus the actual probability on the x-axis and y-axis respectively. The slope of this plotted curve should ideally equal 1, whereas the intercept should equal 0 [28,31]. The slope indicates whether predictions were too extreme, meaning that low predictions were too low, and high predictions too high, or, vice versa, not extreme enough. The intercept of the curve indicates whether the predictions are systematically too high (intercept < 0) or too low (intercept > 0) (36). Overall model performance can be assessed with the Brier score. This score reflects the squared difference between the actual and the predicted probability. It can range from 0 to 0.25, a lower score indicates a better model. The upper limit of the Brier score is dependent on the incidence of the outcome of interest [29].

The ML algorithms that performed best across all four performance measures were validated on the test-set by calculating the same performance measures. This was done to ensure similar performance of the trained model on 'new' data.

The following software was used for data analysis and web-app development: R-Studio Version 1.1.463 (R-studio, Boston, MA, USA), Excel Microsoft Office 2019 (Microsoft Corporation, Redmond, WA, USA), R version 3.5.2 (The R Foundation, Vienna, Austria), Microsoft Azure (Microsoft Corporation, Redmond, WA, USA), SPSS 25 (IBM SPSS Statistics, Armonk, NY, USA).

RESULTS

Patients

The total dataset included 1198 patients with unilateral TSFs treated with intramedullary nailing. Median age of the patients was 38 years, 74% was male. Sixty-eight percent of the patients had a closed fracture. Other patient and fracture characteristics are displayed in Table 2.

A total of 214 patients (18%) underwent one or more unplanned subsequent surgical procedures. Forty-five patients (3.8%) underwent two and 8 (0.7%) underwent more than two subsequent surgical procedures. Surgery for delayed or non-union (8.3%), wound-healing problems (7.8%) and infection (5.8%) were the most frequent subsequent surgical procedures.

TABLE 2. Patient Demographics & Fracture Characteristics

	N = 1198
Patient Characteristics	
Age, median (range)	38 (14-92)
Gender, n (%)	
Male	815 (68%)
Female	383 (32%)
Addition injury, n (%)	
Yes	319 (27%)
No	879 (%)
Mechanism of injury, n (%)	
Crush injury	64 (5%)
Direct trauma (blunt)	82 (7%)
Direct trauma (penetrating)	18 (2%)
Fall	353 (29%)
Twisting injury	57 (4.8%)
Motor vehicle (driver/passenger)	251 (21%)
Motor vehicle (pedestrian)	232 (19%)
Motorcycle accident	57 (5%)
Fracture Characteristics	
Fracture type	
Closed	815 (68%)
Open	383 (32%)
Location Tibia Fracture, n (%)	
Proximal 1/3rd	127 (11%)
Middle 1/3rd	286 (24%)
Distal 1/3rd	785 (65%)
Gustilo-Anderson classification, n (%)	
Closed	815 (68%)
Type I	104 (9%)
Type II	153 (13%)
Type IIIA	97 (8%)
Type IIIB	29 (2%)
Tscherne classification, n (%)	
Type 0	245 (20%)
Type 1	428 (36%)
Type 2	128 (11%)
Type 3	14 (1%)
Open fracture	383 (32%)
Bone loss, n (%)	
Yes	87 (7%)
No	1111 (93%)
Postoperative fracture gap, n (%)	
No fracture gap	1068 (89%)
Fracture gap <1cm	94 (8%)
Fracture gap >1cm	36 (3%)

Feature selection

Feature selection in the training-set using Random Forest algorithms resulted in seven variables for algorithm development: 1) Gustilo-Anderson classification; 2) Tscherne classification; 3) fracture location; 4) post-operative fracture gap; 5) polytrauma; 6) mechanism of injury; and 7) AO/OTA-classification. Importance of included variables are displayed in Figure 1.

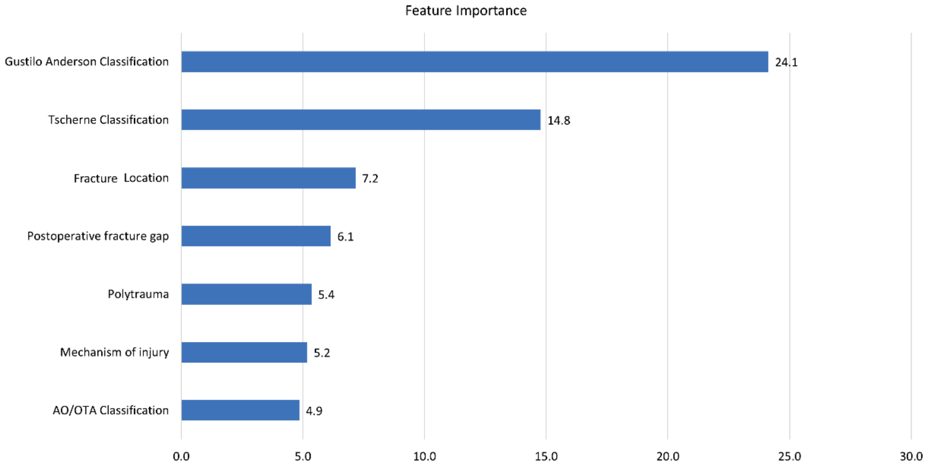


Figure 1. Variable importance based on feature selection using random forests.

Performance machine learning prediction models on training set

Discriminative performance of the five algorithms as quantified by the AUC ranged from 0.700 to 0.770 (Table 3) (Figure 2). Calibration slopes ranged from 0.796 to 0.954. Calibration intercepts ranged from –0.035 to 0.132 (Figure 3). Brier Score ranged from 0.118 to 0.132. The upper limit of the Brier score was 0.146, based on a subsequent surgery rate of 18%.

The penalized logistic regression- and boosted decision tree derived models showed the best performance in the training set. Therefore, the performance of these machine learning prediction models was further evaluated on the test-set.

TABLE 3. Performance of Machine Learning Algorithms in predicting subsequent surgery in training set (n=958) after 10-fold cross validation repeated three times.

	AUC	Calibration Slope	Calibration Intercept	Brier Score*
Bayes Point Machine	0.766	0.876	-0.035	0.119
Boosted Decision Tree	0.770	0.914	0.004	0.118
Penalized Logistic Regression	0.766	0.954	-0.002	0.120
Neural Network	0.769	0.796	0.132	0.119
Support Vector Machine	0.700	0.833	-0.002	0.132

**Upper Limit Brier Score = 0.146*

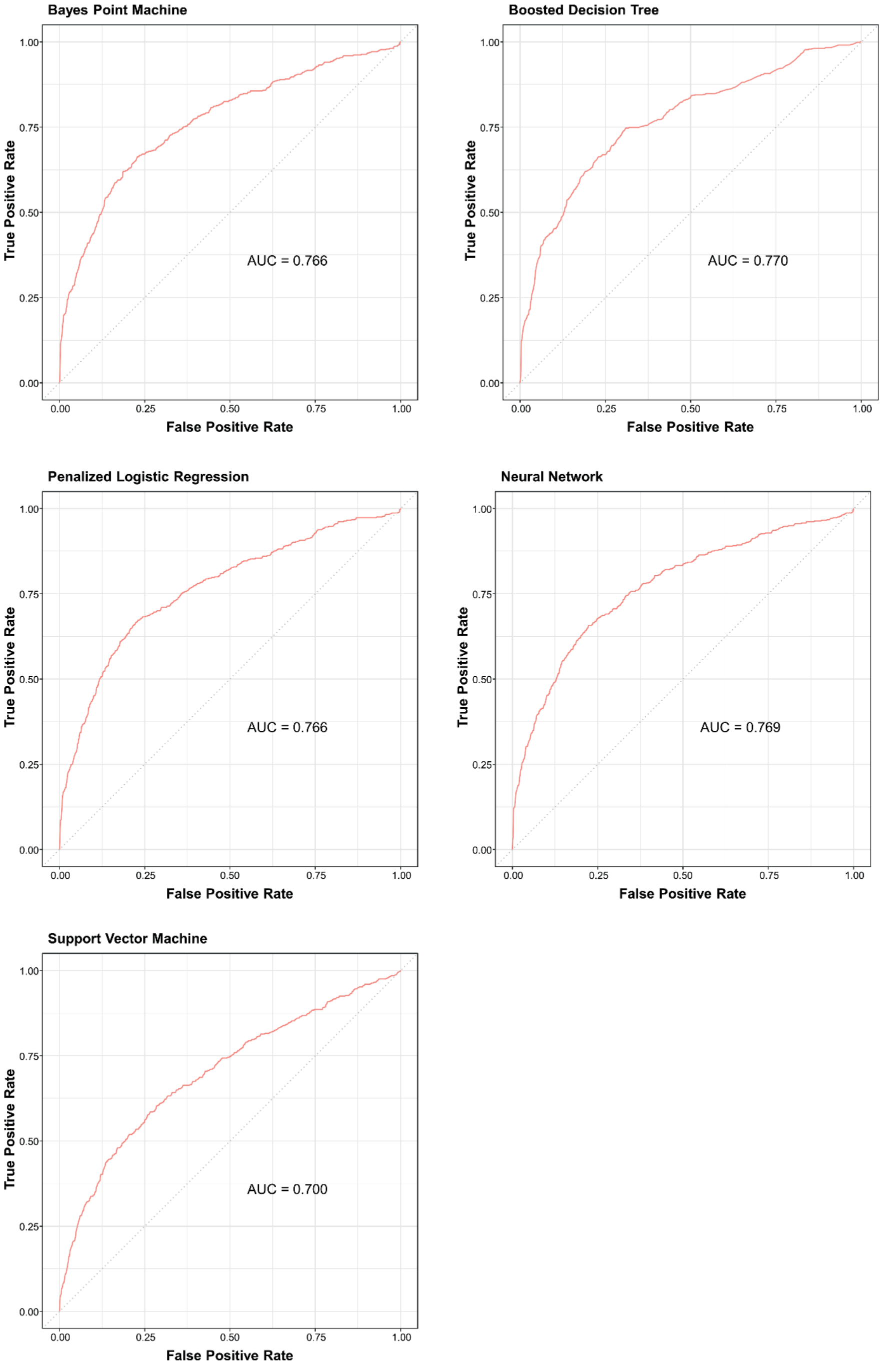


Figure 2. Receiver operating characteristic (ROC) curve and area under the curve (AUC) for each machine learning prediction model in the training set.

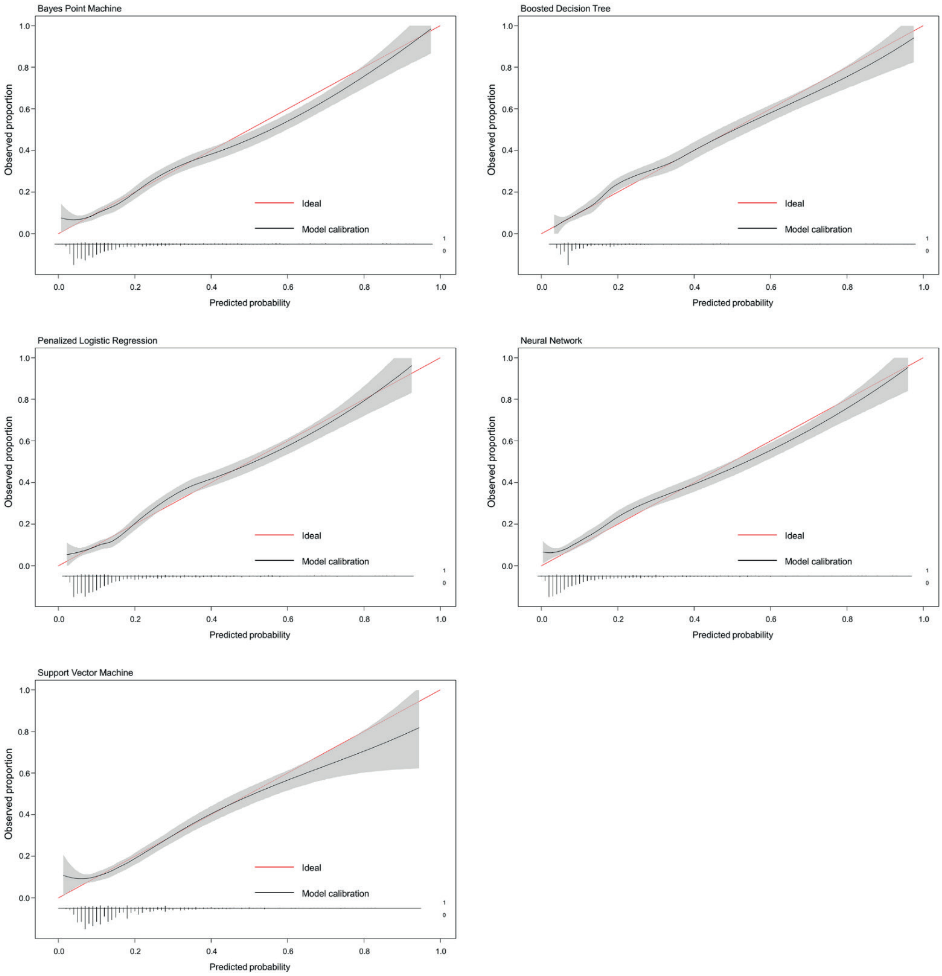


Figure 3. Calibration curves for each machine learning prediction model in the training set. The grey area around the calibration curves represents the 95% confidence interval.

Performance of best performing machine learning models on test-set

As assessed on the test-set, the penalized logistic regression derived model yielded a AUC of 0.773 calibration slope of 0.922, calibration intercept of 0 and Brier score of 0.119 (Table 4) (Figure 4) (Figure 5). This was superior to the performance of the boosted decision tree derived model with an AUC of 0.766, calibration slope of 0.854, calibration intercept of 0.015 and Brier score of 0.120.

The prediction model based on the penalized logistic regression algorithm was chosen as the final model. Gustilo Anderson Type IIIB, Tscherne Type 3 and AO/OTA Type 42C3 were the strongest predictors of unplanned subsequent surgery in this model (Figure 6).

TABLE 4. Performance of Machine Learning Algorithms in predicting subsequent surgery in test set (n=244).

	AUC	Calibration Slope	Calibration Intercept	Brier Score*
Boosted Decision Tree	0.766	0.854	0.015	0.120
Penalized Logistic Regression	0.773	0.922	0.000	0.119

**Upper Limit Brier Score = 0.146*

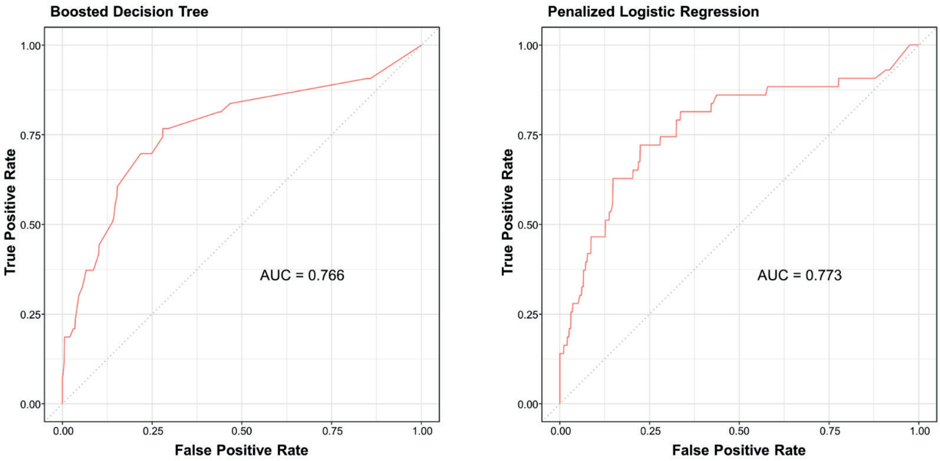


Figure 4. Receiver operating characteristic (ROC) curve and area under the curve (AUC) for the penalized logistic regression and the boosted decision tree in the test-set.

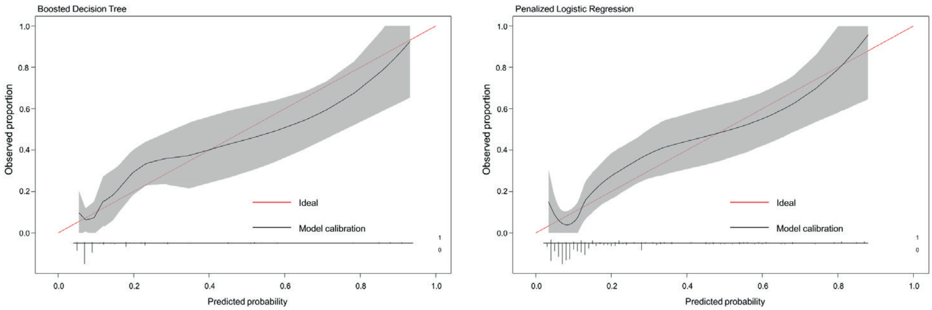


Figure 5. The calibration curves for the penalized logistic regression and the boosted decision tree in the test-set. The grey area around the calibration curves represents the 95% confidence interval.

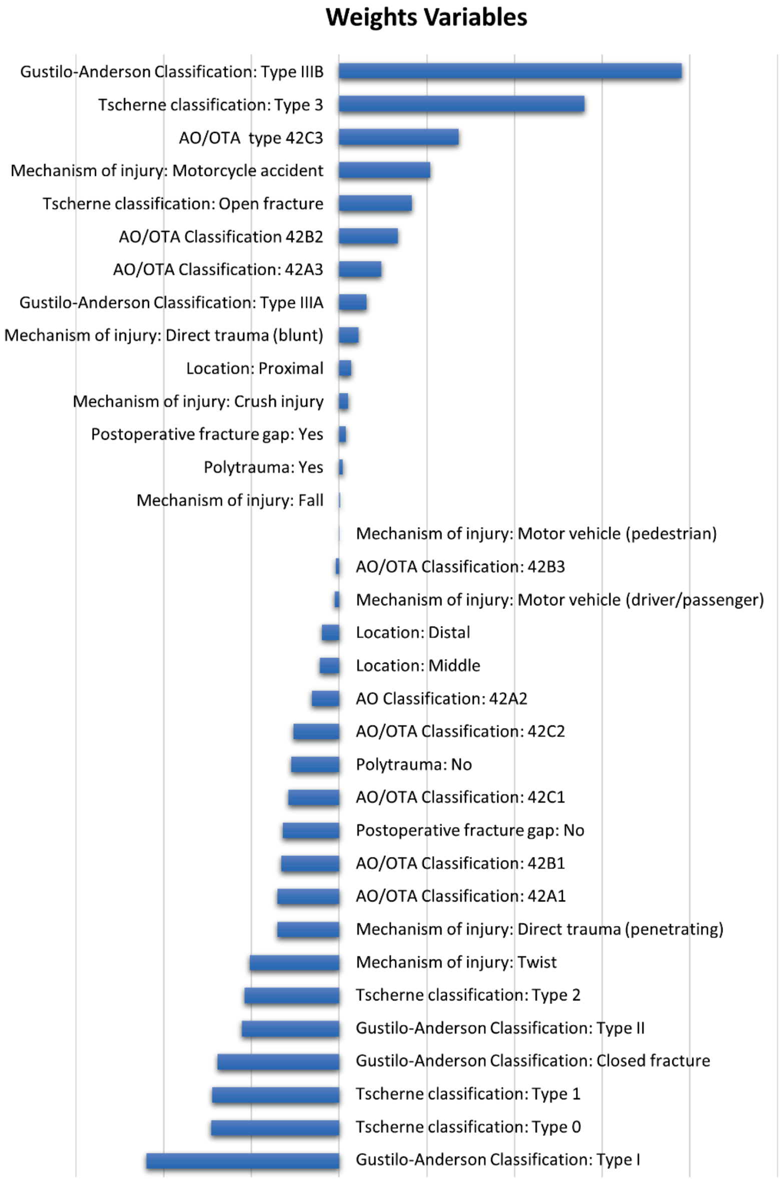
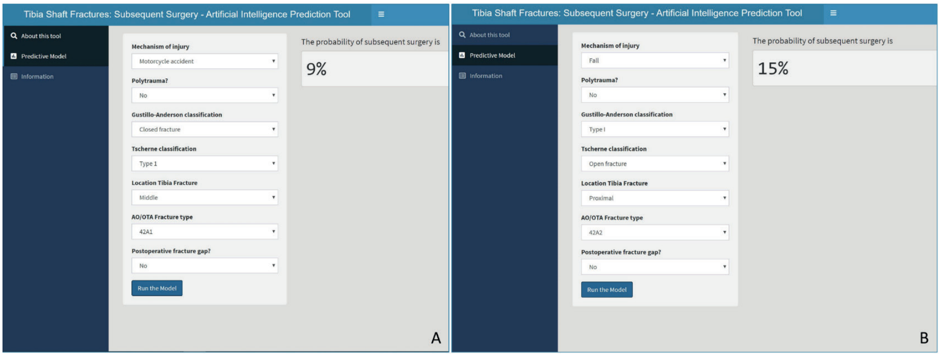


Figure 6. Weighted importance of the included variables in the final model.

Prediction Tool

We incorporated the penalized logistic regression derived model in an online open-access multi-platform prediction tool, allowing users to calculate the probability of unplanned subsequent surgery in patients treated with intramedullary nailing of TSFs: https://traumaplatform-ai-prediction-tools.shinyapps.io/Subsequent-Surgery-After-Tibial-IMN/

For a patient with a closed, middle third, spiral (42A1) TSF with minimal soft tissue injury (Tscherne type 1) after a motorcycle accident, without a postoperative fracture gap or other injuries the tool generates a 9% probability of unplanned subsequent surgery. For a patient with an open (Gustilo-Anderson Type I), proximal third, oblique (42A2) TSF after a fall without a postoperative fracture gap or other injuries, the tool generates a 15% probability (Figure 7)



Mechanism of injury: Motorcycle accident
Polytrauma?: No
Gustillo-Anderson classification: Closed fracture
Tscherne classification: Type 1
Location Tibia Fracture: Middle
AO/OTA Fracture type: 42A1
Postoperative fracture gap?: No
The probability of subsequent surgery is 9%

Mechanism of injury: Fall
Polytrauma?: No
Gustillo-Anderson classification: Type I
Tscherne classification: Open fracture
Location Tibia Fracture: Proximal
AO/OTA Fracture type: 42A2
Postoperative fracture gap?: No
The probability of subsequent surgery is 15%

Figure 7. Predicted probabilities for two fictitious case scenarios.

A. A patient with a closed, middle third, spiral (42A1) TSF with minimal soft tissue injury (Tscherne type 1) after a motorcycle accident, without a postoperative fracture gap or other injuries.

B. A patient with an open (Gustilo-Anderson Type I), proximal third, oblique (42A2) TSF after a fall without a postoperative fracture gap or other injuries (Figure 7B).

DISCUSSION

In the SPRINT trial a notable subset of patients (about 18%) had one or more additional, unplanned, surgical procedures after intramedullary rod fixation of a fracture of the tibial shaft [15]. Using this data, the current study developed a ML-algorithm that calculates an individual patient's probability of unplanned subsequent surgery after intramedullary nailing of a TSF.

Strengths of this study include the high-quality of data, which was collected in a prospective, randomized controlled setting with less than 0.5% missing data and the heterogeneity of the data (from 29 different hospitals across three countries and two continents) which enhances the external validity of the prediction model. Limitations include the lack of external validation of the model. Furthermore, various variables that have previously been considered detrimental for bone-healing such as alcohol consumption [1,32], chronic disease status [33] (e.g. hepatitis) and opioid use [34] were not available.

This investigation confirmed the ability to apply machine learning algorithms to a large data set to develop an algorithm that accurately estimates the probability of additional surgery in patients undergoing intramedullary nailing for TSFs. The ML prediction model estimates the probability of unplanned subsequent surgery based on seven fracture and patient specific characteristics. Various studies have previously identified fracture morphology [1,4,35–37], post-operative fracture gap [4,33,37–39], and open fracture [4,33,35,37] as prognostic factors that may indicate a higher risk of subsequent surgery in patients with TSFs. Mechanism of injury [33], multi-trauma [4], and location of fracture [38] are also reported on in previous studies. In addition, Tscherne classification was identified as important and used for model development in the current study.

As demonstrated on the independent test-set the best performing model had good discriminative performance, indicating the model was well able to differentiate high-risk patients from low-risk patients, and it was well calibrated, meaning that there was good correspondence between predicted probabilities and observed probabilities. Overall, model performance of the final model was similar to other machine learning predictive models that are recently developed for orthopaedic surgery [9,27,40,41].

Machine learning can be applied to large data sets to develop probability calculators to inform patients of their individual risk of a specific complication such as infection, or death [11,12,14]. Clinicians can use these calculators as clinical prediction rules helping to determine when specific tests or treatments might be helpful. The use of ML offers the potential benefit of identifying non-linear relations, where the presence of a specific variable may gain importance in patients with certain characteristics, but not in those with other characteristics [14,42]. Machine learning derived models may therefore further improve patient-specific risk estimations for patients with unique characteristics.

Before implementation in clinical practice, the ML model developed in the current study should be externally validated. External validation should be performed at an institution that did not contribute to the collection of data for the current model. This will indicate whether the model still performs well in different surgeon- and patient populations. Subsequently it should be prospectively evaluated in clinical practice (silent testing). Ultimately the model should be trained with a continuous feedback loop to continuously improve performance characteristics based on new data.

In conclusion, based on high quality multicentre data, we developed an accurate machine learning prediction model to identify patients at risk of unplanned subsequent surgery after intramedullary nailing of TSFs. This prediction model may assist surgeons to inform patients about their individual risk and might help to identify patients that need a different peri-op plan or a more intensive approach.

SPRINT Investigators

Mohit Bhandari, Gordon Guyatt, David W Sanders, Emil H Schemitsch, Marc Swiontkowski, Paul Tornetta 3rd, Stephen Walter, Sheila Sprague, Diane Heels-Ansdell, Lisa Buckingham, Pamela Leece, Helena Viveiros, Tashay Mignott, Natalie Ansell, Natalie Sidorkewicz, Julie Agel, Claire Bombardier, Jesse A Berlin, Michael Bosse, Bruce Browner, Brenda Gillespie, Alan Jones, Peter O'Brien, Rudolf Poolman, Mark D Macleod, Timothy Carey, Kellie Leitch, Stuart Bailey, Kevin Gurr, Ken Konito, Charlene Bartha, Isolina Low, Leila V MacBean, Mala Ramu, Susan Reiber, Ruth Strapp, Christina Tieszer, Hans J Kreder, David J G Stephen, Terry S Axelrod, Albert J M Yee, Robin R Richards, Joel Finkelstein, Wade Gofton, John Murnaghan, Joseph Schatztker, Michael Ford, Beverly Bulmer, Lisa Conlan, G Yves Laflamme, Gregory Berry, Pierre Beaumont, Pierre Ranger, Georges-Henri Laflamme, Sylvain Gagnon, Michel Malo, Julio Fernandes, Marie-France Poirier, Michael D McKee, James P Waddell, Earl R Bogoch, Timothy R Daniels, Robert R McBroom, Milena R Vicente, Wendy Storey, Lisa M Wild, Robert McCormack, Bertrand Perey, Thomas J Goetz, Graham Pate, Murray J Penner, Kostas Panagiotopoulos, Shafique Pirani, Ian G Dommisse, Richard L Loomer, Trevor Stone, Karyn Moon, Mauri Zomar, Lawrence X Webb, Robert D Teasdall, John Peter Birkedal, David Franklin Martin, David S Ruch, Douglas J Kilgus, David C Pollock, Mitchel Brion Harris, Ethan Ron Wiesler, William G Ward, Jeffrey Scott Shilt, Andrew L Koman,, Gary G Poehling, Brenda Kulp, William R Creevy, Andrew B Stein, Christopher T Bono, Thomas A Einhorn, T Desmond Brown, Donna

Pacicca, John B Sledge 3rd, Timothy E Foster, Ilva Voloshin, Jill Bolton, Hope Carlisle, Lisa Shaughnessy, William T Obremskey, C Michael LeCroy, Eric G Meinberg, Terry M Messer, William L Craig 3rd, Douglas R Dirschl, Robert Caudle, Tim Harris, Kurt Elhert, William Hage, Robert Jones, Luis Piedrahita, Paul O Schricker, Robin Driver, Jean Godwin, Philip James Kregor, Gregory Tennent, Lisa M Truchan, Marcus Sciadini, Franklin D Shuler, Robin E Driver, Mary Alice Nading, Jacky Neiderstadt, Alexander R Vap, Heather Vallier, Brendan M Patterson, John H Wilber, Roger G Wilber, John K Sontich, Timothy Alan Moore, Drew Brady, Daniel R Cooperman, John A Davis, Beth Ann Cureton, Scott Mandel, R Douglas Orr, John T S Sadler, Tousief Hussain, Krishan Rajaratnam, Bradley Petrisor, Brian Drew, Drew A Bednar, Desmond C H Kwok, Shirley Pettit, Jill Hancock, Peter A Cole, Joel J Smith, Gregory A Brown, Thomas A Lange, John G Stark, Bruce A Levy, Mary J Garaghty, Joshua G Salzman, Carol A Schutte, Linda Tastad, Sandy Vang, David Seligson, Craig S Roberts, Arthur L Malkani, Laura Sanders, Carmen Dyer, Jessica Heinsen, Langan Smith, Sudhakar Madanagopal, Linda Frantz-Bush, Kevin J Coupe, Jeffrey J Tucker, Allen R Criswell, Rosemary Buckle, Alan Jeffrey Rechter, Dhiren Shaskikant Sheth, Brad Urquart, Thea Trotscher, Mark J Anders,

Joseph M Kowalski, Marc S Fineberg, Lawrence B Bone, Matthew J Phillips, Bernard Rohrbacher, Philip Stegemann, William M Mihalko, Cathy Buyea, Stephen J Augustine, William Thomas Jackson, Gregory Solis, Sunday U Ero, Daniel N Segina, Hudson B Berrey, Samuel G Agnew, Michael Fitzpatrick, Lakina C Campbell, Lynn Derting, June McAdams, J Carel Goslings, Kees Jan Ponsen, Jan Luitse, Peter Kloen, Pieter Joosse, Jasper Winkelhagen, Raphaël Duivenvoorden, David C Teague, Joseph Davey, J Andy Sullivan,

William J J Ertl, Timothy A Puckett, Charles B Pasque, John F Tompkins 2nd, Curtis R Gruel, Paul Kammerlocher, Thomas P Lehman, William R Puffinbarger, Kathy L Carl, Donald W Weber, Nadr M Jomha, Gordon R Goplen, Edward Masson, Lauren A Beaupre, Karen E Greaves, Lori N Schaump, Kyle J Jeray, David R Goetz, David E Westberry, J Scott Broderick, Bryan S Moon, Stephanie L Tanner, James N Powell, Richard E Buckley, Leslie Elves, Stephen Connolly, Edward P Abraham, Trudy Steele, Thomas Ellis, Alex Herzberg, George A Brown, Dennis E Crawford, Robert Hart, James Hayden, Robert M Orfaly, Theodore Vigland, Maharani Vivekaraj, Gina L Bundy, Theodore Miclau 3rd, Amir Matityahu, R Richard Coughlin, Utku Kandemir, R Trigg McClellan, Cindy Hsin-Hua Lin, David Karges, Kathryn Cramer, J Tracy Watson, Berton Moed, Barbara Scott, Dennis J Beck, Carolyn Orth, David Puskas, Russell Clark, Jennifer Jones, Kenneth A Egol, Nader Paksima, Monet France, Eugene K Wai, Garth Johnson, Ross Wilkinson, Adam T Gruszczynski, Lisa Vexler.

REFERENCES

1. Stavrou PZ, Ciriello V, Theocharakis S, et al. Prevalence and risk factors for re-interventions following reamed intramedullary tibia nailing. *Injury*. 2016;47 Suppl 7:S49-S52.

2. Ricci WM, Gallagher B, Brandt A, Schwappach J, Tucker M, Leighton R. Is after-hours orthopaedic surgery associated with adverse outcomes? A prospective comparative study. *J Bone Joint Surg Am*. 2009;91(9):2067-2072.

3. Hernández-Vaquero D, Suárez-Vázquez A, Iglesias-Fernández S, García-García J, Cervero-Suárez J. Dynamisation and early weight-bearing in tibial reamed intramedullary nailing: its safety and effect on fracture union. *Injury*. 2012;43 Suppl 2(SUPPL. 2):S63-S67.

4. Bhandari M, Tornetta P 3rd, Sprague S, et al. Predictors of reoperation following operative management of fractures of the tibial shaft. *J Orthop Trauma*. 2003;17(5):353-361.

5. Stiell IG, Greenberg GH, McKnight RD, Nair RC, McDowell I, Worthington JR. A study to develop clinical decision rules for the use of radiography in acute ankle injuries. *Ann Emerg Med*. 1992;21(4):384-390.

6. Appelboam A, Reuben AD, Benger JR, et al. Elbow extension test to rule out elbow fracture: multicentre, prospective validation and observational study of diagnostic accuracy in adults and children. *BMJ*. 2008;337:a2428.

7. Walenkamp MMJ, Bentohami A, Slaar A, et al. The Amsterdam wrist rules: the multicenter prospective derivation and external validation of a clinical decision rule for the use of radiography in acute wrist trauma. *BMC Musculoskelet Disord*. 2015;16:389.

8. Bongers MER, Thio QCBS, Karhade AV, et al. Does the SORG Algorithm Predict 5-year Survival in Patients with Chondrosarcoma? An External Validation. *Clin Orthop Relat Res*. Published online April 27, 2019. doi:10.1097/CORR.0000000000000748

9. Shah AA, Karhade AV, Bono CM, Harris MB, Nelson SB, Schwab JH. Development of a machine learning algorithm for prediction of failure of nonoperative management in spinal epidural abscess. *Spine J*. Published online May 4, 2019. doi:10.1016/j.spinee.2019.04.022

10. Ogink PT, Karhade AV, Thio QCBS, et al. Predicting discharge placement after elective surgery for lumbar spinal stenosis using machine learning methods. *Eur Spine J*. Published online April 2, 2019. doi:10.1007/s00586-019-05928-z

11. Karhade AV, Thio QCBS, Ogink PT, et al. Predicting 90-Day and 1-Year Mortality in Spinal Metastatic Disease: Development and Internal Validation. *Neurosurgery*. Published online March 14, 2019. doi:10.1093/neuros/nyz070

12. Thio QCBS, Karhade AV, Ogink PT, et al. Can Machine-learning Techniques Be Used for 5-year Survival Prediction of Patients With Chondrosarcoma? *Clin Orthop Relat Res*. 2018;476(10):2040-2048.

13. Staartjes VE, de Wispelaere MP, Vandertop WP, Schröder ML. Deep learning-based preoperative predictive analytics for patient-reported outcomes following lumbar diskectomy: feasibility of center-specific modeling. *Spine J*. Published online November 16, 2018. doi:10.1016/j.spinee.2018.11.009

14. Bertsimas D, Dunn J, Velmahos GC, Kaafarani HMA. Surgical Risk Is Not Linear: Derivation and Validation of a Novel, User-friendly, and Machine-learning-based Predictive OpTimal Trees in Emergency Surgery Risk (POTTER) Calculator. *Ann Surg*. 2018;268(4):574-583.

15. Study to Prospectively Evaluate Reamed Intramedullary Nails in Patients with Tibial Fractures Investigators, Bhandari M, Guyatt G, et al. Randomized trial of reamed and unreamed intramedullary nailing of tibial shaft fractures. *J Bone Joint Surg Am*. 2008;90(12):2567-2578.

16. Luo W, Phung D, Tran T, et al. Guidelines for Developing and Reporting Machine Learning Predictive Models in Biomedical Research: A Multidisciplinary View. *J Med Internet Res*. 2016;18(12):e323.

17. Moons KGM, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med*. 2015;162(1):W1-W73.

18. WHO | WHO Data Policy. Published online May 29, 2018. Accessed August 7, 2019. https://www.who.int/publishing/datapolicy/en/

19. SPRINT Investigators, Bhandari M, Guyatt G, et al. Study to prospectively evaluate reamed intramedually nails in patients with tibial fractures (S.P.R.I.N.T.): study rationale and design. *BMC Musculoskelet Disord*. 2008;9:91.

20. Schemitsch EH, Bhandari M, Guyatt G, et al. Prognostic factors for predicting outcomes after intramedullary nailing of the tibia. *J Bone Joint Surg Am*. 2012;94(19):1786-1793.

21. Stekhoven DJ, Bühlmann P. MissForest--non-parametric missing value imputation for mixed-type data. *Bioinformatics*. 2012;28(1):112-118.

22. Kursa MB, Rudnicki WR, Others. Feature selection with the Boruta package. *J Stat Softw*. 2010;36(11):1-13.

23. Wolpert DH. The Lack of A Priori Distinctions Between Learning Algorithms. *Neural Comput*. 1996;8(7):1341-1390.

24. Maroco J, Silva D, Rodrigues A, Guerreiro M, Santana I, de Mendonça A. Data mining methods in the prediction of Dementia: A real-data comparison of the accuracy, sensitivity and specificity of linear discriminant analysis, logistic regression, neural networks, support vector machines, classification trees and random forests. *BMC Res Notes*. 2011;4:299.

25. Wainer J. Comparison of 14 different families of classification algorithms on 115 binary datasets. *arXiv [csLG]*. Published online June 2, 2016. http://arxiv.org/abs/1606.00930

26. Fernández-Delgado M, Cernadas E, Barro S. Do we need hundreds of classifiers to solve real world classification problems? *The Journal of Machine*. Published online 2014. http://www.jmlr.org/papers/volume15/delgado14a/delgado14a.pdf

27. Karhade AV, Thio QCBS, Ogink PT, et al. Development of Machine Learning Algorithms for Prediction of 30-Day Mortality After Surgery for Spinal Metastasis. *Neurosurgery*. Published online November 23, 2018. doi:10.1093/neuros/nyy469

28. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. *Eur Heart J*. 2014;35(29):1925-1931.

29. Steyerberg EW. *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating*. Springer Science & Business Media; 2008.

30. Hosmer DW, Lemeshow S, Sturdivant RX, Hosmer DW Jr. *Applied Logistic Regression*. John Wiley & Sons, Incorporated; 2013.

31. Vergouwe Y, Steyerberg EW, Eijkemans MJC, Habbema JDF. Validity of prognostic models: when is a model clinically useful? *Semin Urol Oncol*. 2002;20(2):96-107.

32. Gaston MS, Simpson AHRW. Inhibition of fracture healing. *J Bone Joint Surg Br*. 2007;89(12):1553-1560.

33. O'Halloran K, Coale M, Costales T, et al. Will My Tibial Fracture Heal? Predicting Nonunion at the Time of Definitive Fixation Based on Commonly Available Variables. *Clin Orthop Relat Res*. 2016;474(6):1385-1395.

34. Chrastil J, Sampson C, Jones KB, Higgins TF. Postoperative opioid administration inhibits bone healing in an animal model. *Clin Orthop Relat Res*. 2013;471(12):4076-4081.

35. Harris I, Lyons M. Reoperation rate in diaphyseal tibia fractures. *ANZ J Surg*. 2005;75(12):1041-1044.

36. Sarmiento A, Sharpe FE, Ebramzadeh E, Normand P, Shankwiler J. Factors influencing the outcome of closed tibial fractures treated with functional bracing. *Clin Orthop Relat Res*. 1995;(315):8-24.

37. Fong K, Truong V, Foote CJ, et al. Predictors of nonunion and reoperation in patients with fractures of the tibia: an observational study. *BMC Musculoskelet Disord*. 2013;14:103.

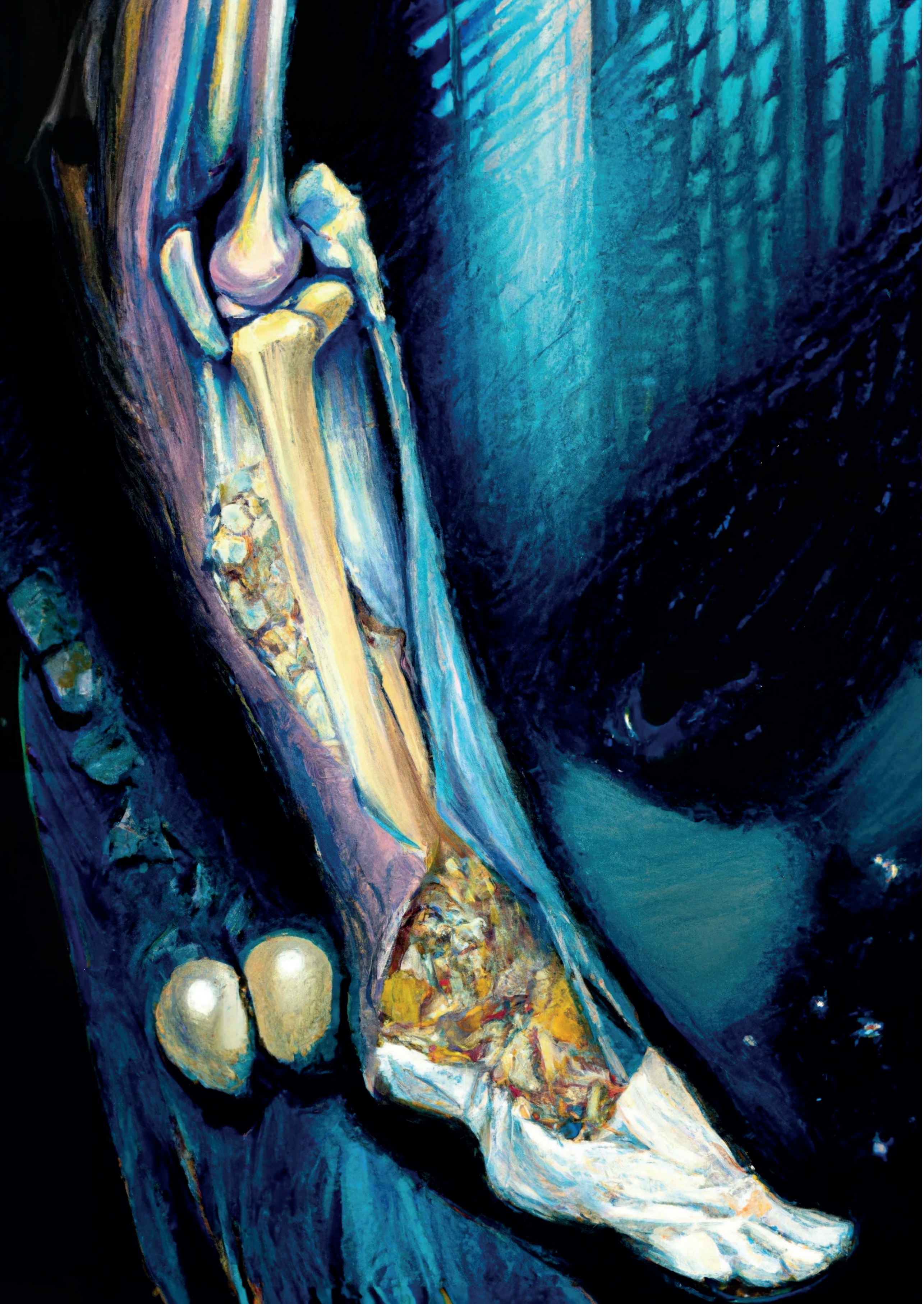
38. Audigé L, Griffin D, Bhandari M, Kellam J, Rüedi TP. Path analysis of factors for delayed healing and nonunion in 416 operatively treated tibial shaft fractures. *Clin Orthop Relat Res*. 2005;438:221-232.

39. Sanders DW, Bhandari M, Guyatt G, et al. Critical-sized defect in the tibia: is it critical? Results from the SPRINT trial. *J Orthop Trauma*. 2014;28(11):632-635.

40. Karhade AV, Ogink PT, Thio QCBS, et al. Machine learning for prediction of sustained opioid prescription after anterior cervical discectomy and fusion. *Spine J*. Published online January 30, 2019. doi:10.1016/j.spinee.2019.01.009

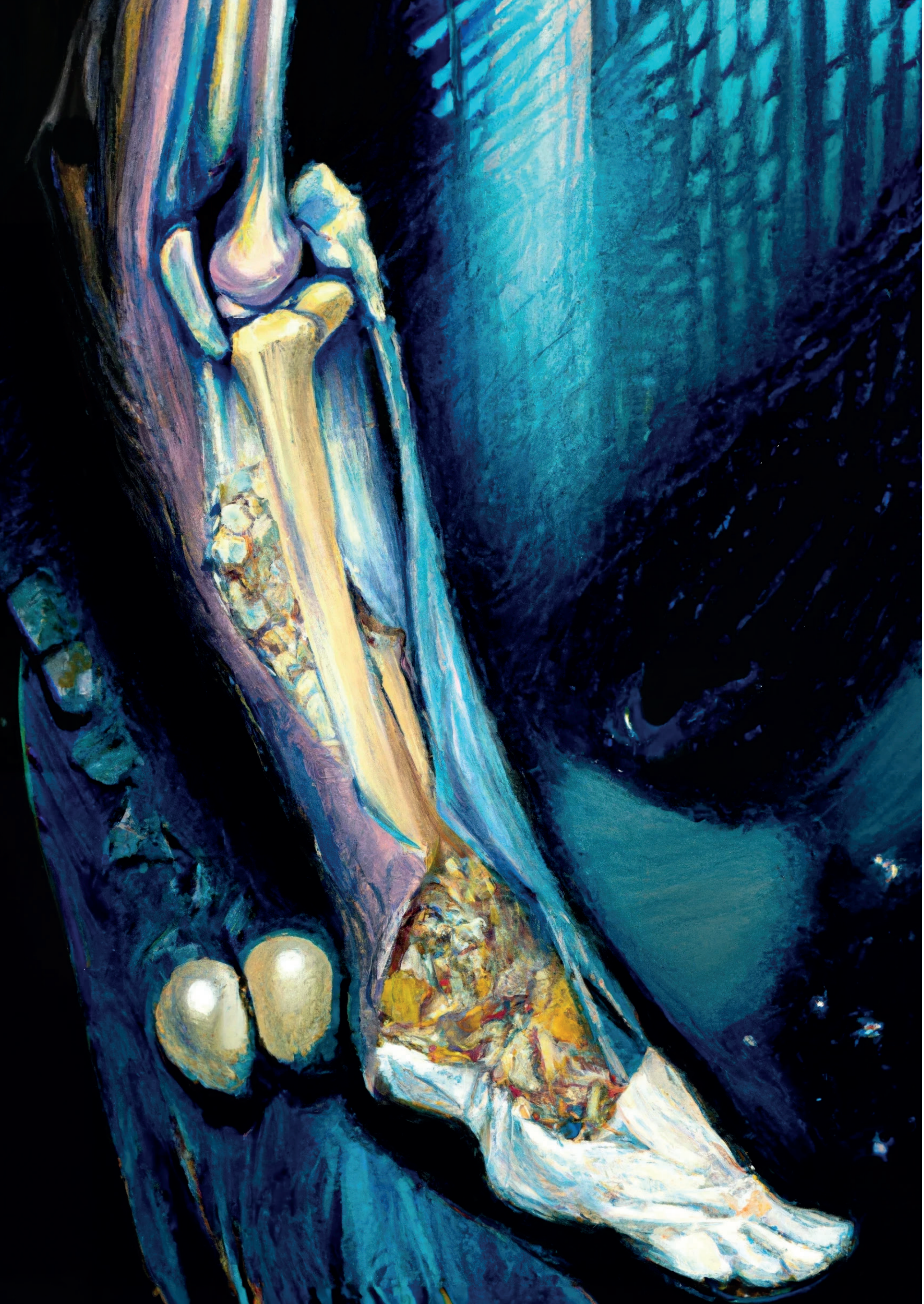
41. Karhade AV, Ogink P, Thio Q, et al. Development of machine learning algorithms for prediction of discharge disposition after elective inpatient surgery for lumbar degenerative disc disorders. *Neurosurg Focus*. 2018;45(5):E6.

42. Ouyang F-S, Guo B-L, Ouyang L-Z, et al. Comparison between linear and nonlinear machine-learning algorithms for the classification of thyroid nodules. *Eur J Radiol*. 2019;113:251-257.



Part II.

Complications – Rate and Patient Specific Risks



4

CHAPTER 4

Prevalence of Rotational Malalignment After Intramedullary Nailing of Tibial Shaft Fractures Can We Reliably Use the Contralateral Uninjured Side as the Reference Standard?

Megan E. Cain, Laurent A.M. Hendrickx, Nils Jan Bleeker, Kaj T.A. Lambers, Job N. Doornberg, Ruurd L. Jaarsma

THE JOURNAL OF BONE AND JOINT SURGERY – APRIL 2020

This is a non-final version of an article published in final form in:

Wolters Kluwer - J Bone Joint Surg Am. 2020 Apr;102(7):582-591. https://journals.lww.com/jbjsjournal/Abstract/2020/04010/Prevalence_of_Rotational_Malalignment_After.6.aspx

ABSTRACT

Background

Intramedullary nailing (IMN) is the treatment of choice for most tibial shaft fractures (TSF). However, an iatrogenic pitfall may be rotational malalignment (RM).

The aims of this retrospective analysis were to determine 1) incidence of RM using post-op Computed Tomography (CT) as the reference standard; 2) average baseline tibial torsion of uninjured tibiae; in order to answer 3) can we reliably use the contralateral uninjured limb as the reference standard?

Methods

Included were 154 patients (male/female - 71%/29%) median age 37 years. All patients were treated for a unilateral TSF with an IMN and underwent a low-dose bilateral post-op CT to assess RM.

Results

Over one-third of patients (n = 55; 36%) had post-operative RM >10º. Right-sided TSF were significantly more likely to display external RM; in contrast, left-sided fractures predisposed to internal RM.

Subsequently, we assessed the variability within the reference standard to determine if there was a left-right difference in baseline tibial torsion. This revealed a left-right rotational difference of 4° (right 41.1°± 8.0° *versus* left 37.0°± 8.2°; $p<0.01$), with the right tibia being on average 4° more externally rotated.

Applying this 4° correction to our cohort not only reduced the incidence of RM (n = 45; 29%); it equalized the internal- and external-RM distribution between left and right tibiae. Moreover, 20 patients (36%) previously classified as having RM >10º, no longer had RM after correction; and 11 patients (18%) previously categorized as normal, now had RM.

Conclusions

This study reveals apart from a high incidence of RM following IMN for TSF (36%), a pre-existing 4° left-right difference in tibial torsion which, sheds a different light on previous studies-, current clinical practice- and could have significant implications in the diagnosis and management of tibial RM. It should be considered when labelling our patients with a post-operative iatrogenic “RM”.

INTRODUCTION

Intramedullary nailing (IMN) is the treatment of choice for most patients with tibial shaft fractures (TSF). IMNs are recognised for their reproducibility, minimally invasive surgical technique, predictable fracture healing and rapid recovery[1–5]. However, IMN has been associated with higher rates of iatrogenic rotational malalignment (RM) when compared to open reduction and internal fixation[6–8].

RM is defined as a longitudinal internal- or external rotation of the injured tibiae compared to the uninjured contralateral side[4]. Most previous studies[2–5,9,10], have defined tibial RM as a rotational difference of >10˚ - similar to what has been reported for femoral malrotation -[1,11–13]. Computed tomography (CT) has been found to be the most reliable method for assessing RM[2,14,15]. Previous studies demonstrate a low rate of RM based on clinical examination (0%-7%)[2,4] whilst, with use of advanced imaging techniques such as CT, the reported incidence increases to 19%-41%[1–4,9,10,16].

Iatrogenic RM is correlated with patients' medicolegal reimbursement: in the United States patients with a RM of ≥10° are eligible for compensation in keeping with the "Guides to the Evaluation of Permanent Impairment"[17]. Thus identification of RM following IMN may have significant financial consequences[18], as well as potential functional impact[19–22]. Medico-legally long bone malrotation is a common reason for litigation, of which 90% of cases are proven to be based on negligence[18]. However, data on the correlation of post-op RM and patients' functional impairment or the presumption that the uninjured contralateral limb is the correct reference standard, are scarce.

The landmark paper by Theriault et al[10] in this Journal, currently provides the best evidence reporting a RM (>10°) incidence of 41% of patients with bilateral lower limb CT scanning, using the contralateral uninjured limb as the reference standard. No significant difference in 'lower extremity functional scale' was identified in this relatively small cohort study.

Therefore, the purpose of this study was to improve understanding of RM after IMN for TSF by addressing the following research questions: 1) what is the current incidence of RM; 2) what is the average baseline tibial torsion of uninjured limbs; and subsequently answer the overall research question: 3) can we reliably use the contralateral uninjured limb as the reference standard? The answers to these questions are clinically relevant for decision-making in patient care.

MATERIAL AND METHODS

Our Institutional Review Board waived the requirement for approval of this study in accordance to the Declaration of Helsinki, given post-operative rotational profiling with CT is part of the hospital protocol for patients undergoing IMN for TSF.

Study Subjects

We performed a retrospective review on a consecutive series of patients that underwent an IMN for a TSF between January 2009 and September 2016. To be included the 154 patients, were required to have undergone a protocolled low-dose postoperative CT for assessment of RM. This protocol was implemented in 2009, with an initial CT-scan rate of 43%, which has since improved to 83%. Included were 110 males (71%) and 44 females (29%), with a median age of 37 years. Patient and fracture characteristics are represented in Table 1.

Surgical Technique

All patients in this study were treated with the TRIGEN IMN system (Smith & Nephew, Andover, MA USA). IMN was performed as per routine and extensively published techniques[23–26]. Evaluation of fracture reduction was performed intra-operatively using simple fluoroscopy (assessment of cortical contact/continuity and mechanical axis) and clinical judgement (foot progression angle/alignment of second ray), though this was not standardised between surgeons. Protocolled postoperative low-dose CT-scans were undertaken an average of 2 days postoperatively.

CT Scanning Protocol

All 154 patients underwent postoperative bilateral short segment tibial CT-scanning as per institution protocol. The CT-scans were made in supine position with neutral hip rotation, knees extended, and ankles stabilized in a gutter in order to optimize reproducibility and reliability of scans. Plain CT-scans were then performed with helical blocks, through short segments of the proximal (including tibiofibular joint) and distal (including the tibiotalar joint) tibiae to minimize radiation exposure. The Total DLP was 94.6-144.3mGy.cm, which is an effective dose of 0.03784-0.05768mGy; equivalent to a plain chest radiograph (AP dose =0.02, lateral dose =0.04, totalling 0.06mGy).

TABLE 1 Demographic Data and Injury Details (N=154)

Variable	
Age*	41 ± 18.6 (14-90)
Sex†	
Male	110 (71%)
Female	44 (29%)
Polytrauma†	
Yes	29 (19%)
No	125 (81%)
Fracture Side†	
Right	82 (53%)
Left	72 (47%)
Open or Closed Fracture†	
Open	41 (27%)
Closed	113 (73%)
Fracture Classification†	
Simple	95 (62%)
Wedge	35 (23%)
Complex	24 (16%)
Fracture location†	
Proximal third	6 (4%)
Middle third	47 (31%)
Distal third	91 (59%)
Segmental fracture	10 (6%)
Fibula Fracture†	
Present	127 (82%)
Absent	27 (18%)
Fibula Fracture Location†¥	
Proximal third	30 (24%)
Middle third	43 (34%)
Distal third	38 (30%)
Segmental	16 (13%)

* Values are given as the mean and standard deviation with the range in parentheses.
† Values are given as the number, with the percentage in parentheses.
¥ The percentages are based on 127 fibula fractures.

CT Assessments of Tibial Rotational Torsion

Proximal angle measurements were made from CT-slices taken 2-3mm proximal to the tibiofibular joint. The angle determined by the horizontal reference and the line tangential to the dorsal tibia plateau[24] (Figure 1A and B). Distal angle measurements were made from CT-slices taken 2-3mm proximal to the tibiotalar joint. The angle determined by the horizontal reference and the line through the anatomic axis of distal tibia and the fibula (Figure 1C and D). Tibial torsion is the difference between the proximal and distal angle. We found excellent inter-observer and intra-observer reliability of this imaging method in a previous study (ICC = 0.92-0.97 and 0.87-0.92 respectively)[14].

RM was defined as the longitudinal rotational difference between the injured- and the non-injured limb[1–5,9,10,16,23–25,27]. A rotational difference of >10˚ was classified as "RM" as per previous studies[3–5,9,10,28]. According to this definition, one assumes there is no pre-existing baseline difference between the uninjured and now injured tibia in terms of rotational alignment. Puloski et al[4] and Johner et al[29] applied categorical ratings to RM and we adapted these adding a category of RM ≥ 30° (Table 2).

Mean tibial torsion of the contralateral (non-injured) tibiae in our cohort was also assessed to determine whether previous assumptions regarding left-right tibial rotation had been valid, given the contralateral limb serves as the reference standard in all studies on this subject to date (including ours)[2–4,10,16,27,30–33] as well as current malpractice lawsuits[17].

TABLE 2 Classification of Rotational Malalignment when comparing to contralateral limb using CT

Johner & Wruhs	Puloski	Our "Classic" Definition	Our "New" Definition	
			RIGHT	LEFT
Excellent (± 0-5°)				
Good (± 6-10°)	± <10°	± <10°	-6 to +14°	+4° to -16°
Fair (± 11-20°)	± 10-15°	± 10-19°	-16 to -7°, +15 to 24°	+5 to 14°, -17 to -26°
Poor (± >20°)	± >15°	± 20-29°	-26 to -17°, +25 to 34°	+15 to 24°, -27 to -36°
Unacceptable		± >30°	> -26°, > +34°	> +24°, > - 36°

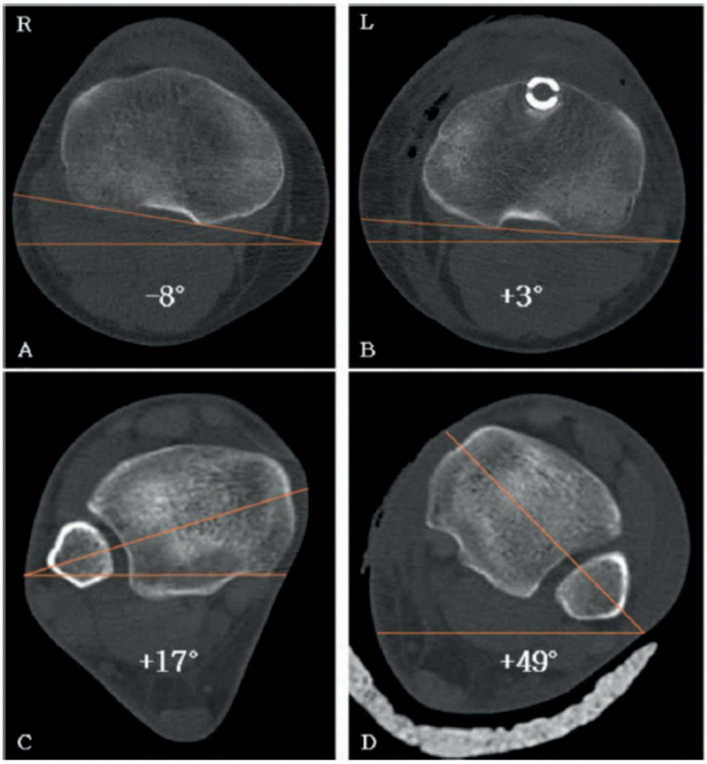


Figure 1. Assessment of post-operative Computed Tomography-slices taken 2-3 mm proximal the tibiofibular and tibiotalar joint of both the affected and unaffected limb. The proximal lines are drawn tangential of the dorsal tibia and the distal lines are drawn through the middle of the tibia and fibula. A and C are the angles of the healthy side and B and D are the angles of the injured side. The rotational difference of the healthy side is 25˚ (17˚(A) - -8˚(C)) and the rotational difference in the affected side is 46˚ (49˚(B) - 3˚ (D)). The rotational malalignment is calculated by taking the difference between the affected (+46˚) and unaffected side (+25˚). This means a rotational malalignment of +21˚ (46˚- 25˚), which is defined as an external rotational malalignment.

Statistical Analysis

Continuous data is presented as a mean when normally distributed; otherwise, the medians are reported. Baseline characteristics of study patients are summarized as frequencies and percentages for categorical variables and with means and standard deviations for continuous variables. Student's t-tests were performed to assess differences in RM between the injured and uninjured tibia, as well as comparison between uninjured tibiae to evaluate the value of the contralateral tibia to serve as the reference standard. The ordinal scores were compared by use of a Mann Whitney-U test. Pearson correlations coefficients were calculated to assess the association between continuous measurements and ordinal scores. A p-value ≤0.05 was considered statistically significant. Statistical analysis was performed by use of IBM SPSS Statistics for Macintosh, version 24.0 (Armonk, NY; IBM Corp).

Source of Funding

No external source of funding

RESULTS

Incidence of RM using the Uninjured (Contralateral) Limb as the Reference Standard (Table 3)

According to the 'classic' definition of RM[4,10,29]: 55 (36%) out of 154 patients were categorized as having RM (>10˚) after IMN. According to our categorical rating (Table 2): 46 patients (30%) had RM of 10-19°, 7 patients (5%) had RM of 20-29° and 2 patients (1%) had RM of ≥ 30°. The injured tibia was internally malrotated in 26 cases (47%) and externally malrotated in 29 (53%).

TABLE 3 Rotational Malalignment Data (N=154)

Variable	
Rotational Malalignment Degrees*	0.8° ±10.7° (-23.3°– 30.3°)
Rotational Malalignment Incidence†	
No rotational malalignment	99 (64%)
10-19° rotational malalignment	46 (30%)
20-29° rotational malalignment	7 (5%)
>30° rotational malalignment	2 (1%)
Internal and External Rotational Malalignment†¥	
Internal rotational malalignment	26 (47%)
External rotational malalignment	29 (53%)

† Values are given as the number, with the percentage in parentheses.
* Values are given as the mean and standard deviation with the range in parentheses.
¥ The percentages are based on 55 cases of rotational malalignment.

Distribution of RM According to Injury Side (Left versus Right) using the Contralateral Uninjured Limb as the Reference Standard (Table 4)

Assessment of RM distribution according to the side of the fracture revealed that IMN of left-sided TSF consistently resulted in a mean internal rotation (-4.5° ±9.5°), compared to the uninjured right limb. In contrast, IMN of right sided TSF resulted in a mean external rotation (5.5 ±9.4°) when compared to the uninjured left tibia. This mean rotational difference of 10° between the injured left tibia (-4.5°±9.5°) versus the injured right tibia (5.5° ±9.4°) was statistically significant (p<0.001).

More specifically, 28 (39%) of 72 patients with a left-sided TSF had RM, of which, 79% were internal oriented. RM for patients with a right-sided injury was the opposite: 27 (33%) of 82 patients with right-sided TSF had RM, of which, 85% were externally rotated (Figure 2).

TABLE 4 Left Right Distribution Rotational Malalignment (N=154)

Variable	Left-sided Fracture (n=72)	Right Sided Fracture (n=82)	P-value
Rotational Malalignment Degrees*	-4.5° ±9.5° (-23.3° – 18.5°)	5.5° ±9.4° (-15.1° – 30.3°)	<0.001$^{\text{ß}}$
Rotational Malalignment Incidence†			
No rotational malalignment	44 (61%)	55 (67%)	0.45$^{\phi}$
10-19° rotational malalignment	25 (34%)	21 (26%)	
20-29° rotational malalignment	3 (4%)	4 (5%)	
>30° rotational malalignment	0 (0%)	2 (2%)	
Internal and External Rotational Malalignment†			
No rotational malalignment	44 (61%)	55 (67%)	<0.001$^{\chi}$
Internal rotational malalignment	22 (31%)	4 (5%)	
External rotational malalignment	6 (8%)	23 (28%)	

* Values are given as the mean and standard deviation with the range in parentheses.
† Values are given as the number, the percentage in parentheses are based on the total number of left-sided or right-sided fractures.
ß Student's t-test
ϕ Fisher's Exact Test
χ Chi-square Test

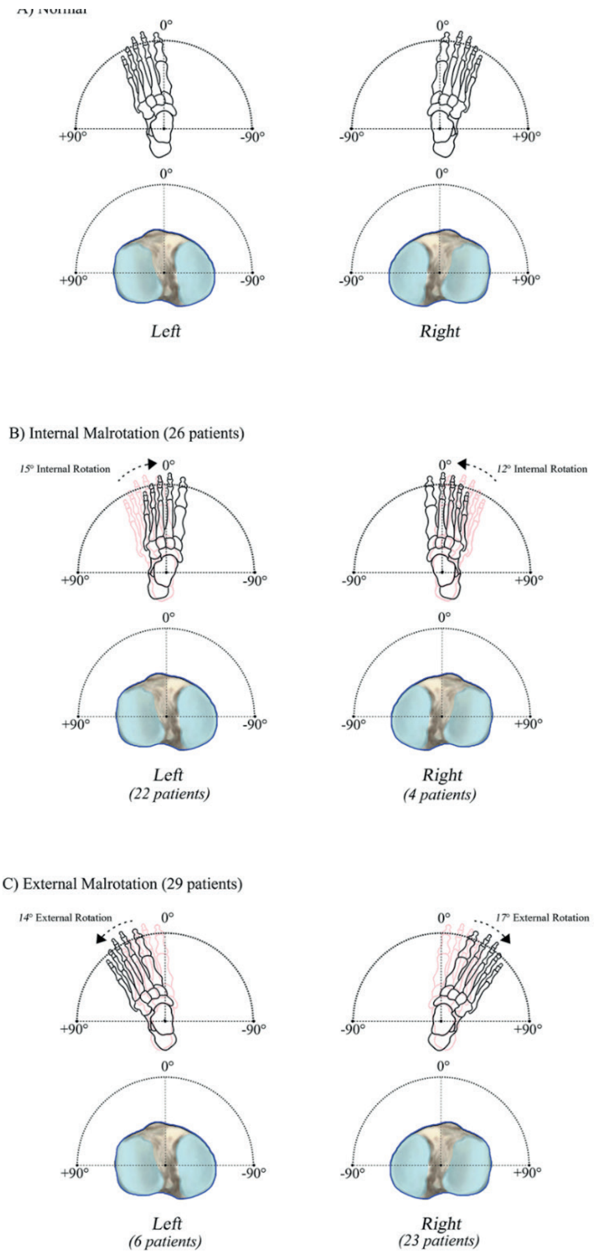


Figure 2. Representation of the average foot progression angle/rotational alignment in A) Normal individuals, B) in the 26 patients who sustained an internal RM following tibial IMN, and C) in the 29 patients who sustained an external RM following tibial IMN. In B) it can be seen of the 22 left sided TSF with internal RM they had an average RM of 15°, whilst in the 4 with an internal RM following a right sided fracture their average RM was 12°.

Significant Difference in -Baseline- Physiological Tibial Torsion of Contralateral Uninjured Left and Right Limbs (Table 5)

A significant left-right difference in terms of physiological tibial torsion of the uninjured limb was noted: the mean tibial torsion in 72 uninjured right tibiae was 41.1° ±8.0°, versus a mean tibial torsion of 37.0°±8.2° in 82 uninjured left tibiae (p<0.01). In other words, uninjured right tibiae were on average 4.1° more externally rotated than the uninjured left tibias. Given this, we “modified” our classification of RM – instead of ± <10°, the right would start at a baseline of +4, thus “good” would be -6 to +14°, whilst left starts as a baseline of -4, meaning “good” would be -14 to +6° and so on. A negative value representing internal rotation and positive external rotation.

TABLE 5 Tibial Torsion Data Injured and Non-injured side (N=154)

Variable	Left-sided Fracture (n=71)	Right-sided fracture (n=82)	P-value
Torsion Non-Injured Tibia*δ	41.1° ± 8.0° (25.7° – 59.4°)	37.0° ± 8.2° (19.7° – 57.5°)	<0.01ß
Torsion Injured Tibia*	36.4° ± 8.9° (14.0° – 60.0°)	42.5° ± 10.2° (17.7° – 67.0°)	<0.01ß

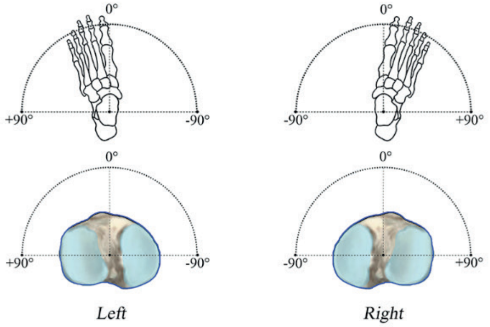
* Values are given as the mean and standard deviation with the range in parentheses.
ß Student’s t-test
δ Please be aware that the value displayed under the torsion of the non-injured tibia for left sided fractures refers to right tibias and vice versa for value displayed under the torsion of the non-injured tibias for right sided fractures.

Revised Incidence of RM accounting for average baseline difference of 4° (left vs right) in the Reference Standard (Table 6)

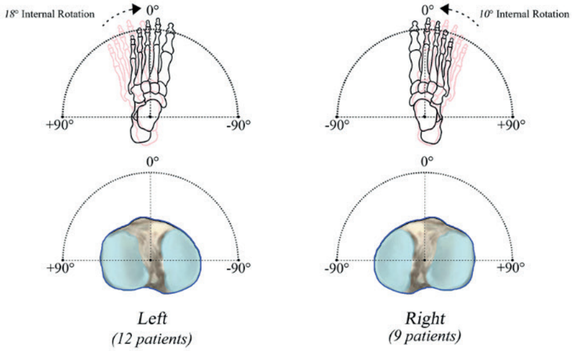
45 (29%) of 154 patients were now categorized as having RM. 23 (32%) out of 72 patients with left-sided TSF now had RM; 12 (52%) internally and 11(48%) externally malrotated. Of those with right-sided TSF, 22 (26%) out of 82 patients now had RM: 9 (41%) internally and 13 (57%) external malrotated (p=0.59) (Figure 3).

The revised calculations of RM in our cohort, utilizing the corrected baseline measures revealed that the mean rotational difference of left (-0.5 ±9.5°) and right (1.5 ±9.4°) TSF managed with IMN, no longer differed significantly.

A) Pre-existing 4° difference in tibial torsion



B) Adjusted internal malrotation (21 patients)



C) Adjusted external malrotation (24 patients)

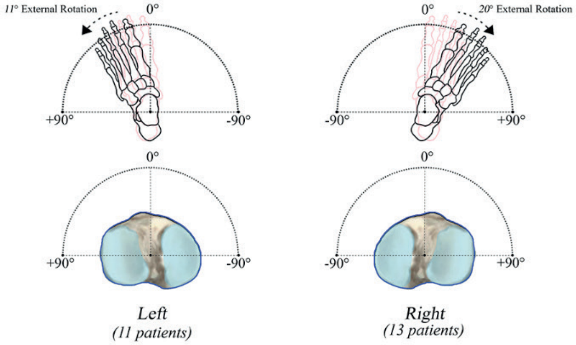


Figure 3. Representation of the average foot progression angle/rotational alignment when considering the right tibia is 4° more externally rotated than the left. A) The "adjusted normal" whereby the right foot is 4° more externally rotated than the left at baseline, B) The 21 patients now exhibiting internal RM following adjust for left-right difference. C) The 24 patients now exhibiting an external RM following adjustment for left-right differences.

TABLE 6 Left Right Distribution Rotational Malalignment According to Renewed Criteria π (N=154)

Variable	Left-sided Fracture (n=72)	Right Sided Fracture (n=82)	P-value
Rotational Malalignment Degrees* π	-0.5° ±9.5° (-19.3° – 22.5°)	1.5° ±9.4° (-19.1° – 26.3°)	0.75ß
Rotational Malalignment Incidence† π			
No rotational malalignment	49 (68%)	60 (73%)	0.84φ
10-19° rotational malalignment	21 (29%)	20 (24%)	
20-29° rotational malalignment	2 (3%)	2 (2%)	
>30° rotational malalignment	0 (0%)	0 (0%)	
Internal and External Rotational Malalignment† π			
No rotational malalignment	49 (68%)	60 (73%)	0.59χ
Internal rotational malalignment	12 (17%)	9 (11%)	
External rotational malalignment	11 (15%)	13 (16%)	

π Compared to a baseline of -4° for left sided tibial shaft fractures and +4° for right-sided tibial shaft fractures.
* Values are given as the mean and standard deviation with the range in parentheses.
† Values are given as the number, the percentage in parentheses are based on the total number of left-sided or right-sided fractures.
ß Student’s t-test
φ Fisher’s Exact Test
χ Chi-square Test

Alteration in Rotational Alignment Category (Table 7)

According to our modified classification of RM[4,29]: 20 patients who initially had RM using the assumption that left-right tibial torsion is equal no longer did when considering the 4° baseline rotational difference. Whilst, 11 patients initially classified as “normal”, on re-calculation, now fell outside the accepted 10° rotational difference. Thus, 20% of patients within our cohort changed category of rotational alignment following adjusting for this 4° rotational difference.

TABLE 7 Medicolegal perspective with 4° adjustment

	Number of Patients	Ramifications
No change in category of RM	124	
>10° External RM ◊ NORMAL	10	20 (36%) of those initially eligible for compensation no longer are
>10° Internal RM ◊ NORMAL	10	
NORMAL ◊ >10° External RM	5	11 (11%) of those initial not eligible for compensation now are
NORMAL ◊ >10° Internal RM	6	

DISCUSSION

This large retrospective review of a consecutive series of patients was developed to substantiate the incidence of RM following IMN for TSFs. We found a high incidence (36%) of RM after tibial IMN, but also showed that the side (left/right) of the TSF is associated with the direction of RM: left-sided TSFs are prone to internal RM whereas right-sided TSFs resulted in external RM. We hypothesized that a pre-existing 4° left-right difference in tibial torsion may account for this association. Re-analysis of our data considering this 4° difference drastically changed our results. It not only lowered overall incidence of RM (29%), but also lead to a similar distribution of internal/external RM for left- and right-sided TSFs. Importantly, cases previously labelled as significant RM were now found to have rotational alignment within normal ranges.

Our results should be interpreted in the light of their strengths and weaknesses. Strengths included: 1) a large series (154 patients), with cohort characteristics fitting those previously reported in the epidemiological study by Larsen et al[34] when looking at incidence and mechanism of TSF, making results generalizable. 2) The CT protocol for assessing RM has been found to be accurate, reliable and is associated with minimal radiation exposure[14]. 3) We were able to minimize bias by including all patients who had undergone an IMN for TSF with a post-operative CT scan. Weaknesses of the study included: 1) the study was limited to CT findings and hospital records. 2) The findings represent results of a single level 1 trauma centre, using a single implant. 3) There were multiple surgeons involved with varying levels of training. 4) We are unable to comment on the overall clinical implication of tibial RM >10°. 5) This remains a retrospective study subject to the potential bias and residual confounding from unmeasured or inadequately adjusted variables associated with such research designs.

In previous literature several different methods have been reported for measuring RM of the tibia[28,35–38]. However, CT is currently gold standard for radiologic assessment of tibial RM due to its ease of interpretation, imaging detail and reproducibility[3,4,23–25,27,39]. The CT protocol we utilised encapsulated a short segment only of the proximal and distal tibia limiting radiation dose to that equivalent to an antero-posterior and lateral chest radiograph. Having previously validated this protocol with an intra- and inter-reliability study[14], we feel it can be used confidently to determine RM of the tibia following an IMN.

Contradictory to the low incidence of RM determined by clinical measurements[2,4] various studies have reported high incidences (19%-41%) based on CT-assessments[1,4,9,10,16]. These studies had population sizes ranging from 22-81 patients, and each utilised a slightly different CT technique for determining RM. This study used a validated CT protocol[14] on a large cohort to confirm RM is indeed a serious iatrogenic complication of IMN affecting approximately 1 in 3 patients treated with an IMN for a TSF.

Alterations in lower extremity alignment have been associated with increased risk of both acute and chronic lower extremity injuries including stress fractures, patellofemoral maltracking[40,41], cruciate ligament injuries[42,43] and osteoarthritis[44]. None of these studies though, have been conducted on patients who have undergone an IMN for TSF. The main study assessing RM following tibial IMN, conducted by Theriault et al[10], reported 'lower extremity functional scale' scores to be similar in patients with RM or without RM, and subsequently concluded that RM does not have a significant short- to medium-term functional impact. They hypothesised this was due to a number of intrinsic compensatory mechanisms of the hip, knee and ankle joints, as has previously been demonstrated in RM of femoral shaft fractures[1]. Future studies could assess whether functional outcome of IMN indeed is not affected by tibial RM, and whether the compensation mechanisms of femoral RM (for example internal RM is better tolerated than external RM)[13] are the same for tibial RM.

The significant association between the side of the tibial fracture and the direction of RM came unexpected and has not been reported in literature before. We are aware that a more comprehensive study including other potential predictors of (the direction of) RM should be undertaken to assess whether the side of the fracture is an independent predictor.

In our large cohort the baseline rotation of all uninjured limbs had a ±8° range. Despite this fairly large individual variation, we felt that the large group size and for the purpose of this study, would allow averaging to a significant 4° difference in left-right rotation ($p<0.01$). This could explain the association between the side of fracture and direction of RM. This difference is in line with various other studies[31–33,45,46], reporting a left-right difference in tibial torsion in healthy subjects with the right-side being 2.1-4.9 degrees more externally rotated on average[33,45,47]. No translation of this reported anatomical left-right torsional difference into day-to-day clinical practice has been made. Our study aims to enable this, as it could imply that our current assessment of RM is inaccurate. It may explain the higher incidence of internal RM for left-sided TSFs and external RM for right TSFs.

This 4° difference in tibial torsion should be considered when assessing RM. Such analysis led to a marked reduction in the incidence of RM in this cohort. Moreover, many cases previously labelled as having RM were now within normal ranges of rotational alignment, and vice versa. Misdiagnosing RM could also have potential consequences when determining impairment ratings: in the USA, a RM of ≥10° may entitle the individual to a financial reimbursement under the "Guides to the

Evaluation of Permanent Impairment”[17]. This finding will not necessarily change nailing practises, though it is important to consider that left-sided TSFs are more likely to be mal-reduced internally where right-sided fractures are likely to be mal-reduced externally. This awareness on its own should reduce the incidence of iatrogenic RM. Conversely, changing the idea of “normal” (left = right) may have an impact on future whole body impairment rating calculations and claims.

CONCLUSION

This study reveals an overall high rate of RM (≥10°), in patients undergoing IMN of a TSF, as well as a pre-existing 4° difference in baseline tibial torsion (right more externally rotated). Applying this finding to our patient cohort not only reduced the incidence of RM (36% ◊ 29%), it also sheds a different light on results of previous studies, current clinical practice and could have significant consequences in the diagnosis and management of tibial RM.

REFERENCES

1. Jaarsma RL, Pakvis DFM, Verdonschot N, Biert J, van Kampen A. Rotational malalignment after intramedullary nailing of femoral fractures. *J Orthop Trauma*. 2004;18(7):403-409.
2. Say F, Bülbül M. Findings related to rotational malalignment in tibial fractures treated with reamed intramedullary nailing. *Arch Orthop Trauma Surg*. 2014;134(10):1381-1386.
3. Khan SB, Mohib Y, Rashid RH, Rashid H. Rotational Mal-Alignment after Reamed Intramedullary Nailing for tibial shaft fracture. *J Pak Med Assoc*. 2016;66(Suppl 3)(10):S106-S108.
4. Puloski S, Romano C, Buckley R, Powell J. Rotational malalignment of the tibia following reamed intramedullary nail fixation. *J Orthop Trauma*. 2004;18(7):397-402.
5. Polat A, Kose O, Canbora K, Yanık S, Guler F. Intramedullary nailing versus minimally invasive plate osteosynthesis for distal extra-articular tibial fractures: a prospective randomized clinical trial. *J Orthop Sci*. 2015;20(4):695-701.
6. Vallier HA, Cureton BA, Patterson BM. Randomized, prospective comparison of plate versus intramedullary nail fixation for distal tibia shaft fractures. *J Orthop Trauma*. 2011;25(12):736-741.
7. Janssen KW, Biert J, van Kampen A. Treatment of distal tibial fractures: plate versus nail. *Int Orthop*. 2007;31(5):709-714.
8. Im G-I, Tae S-K. Distal metaphyseal fractures of tibia: a prospective randomized trial of closed reduction and intramedullary nail versus open reduction and plate and screws fixation. *J Trauma*. 2005;59(5):1219-1223; discussion 1223.
9. Jafarinejad AE, Bakhshi H, Haghnegahdar M, Ghomeishi N. Malrotation following reamed intramedullary nailing of closed tibial fractures. *Indian J Orthop*. 2012;46(3):312-316.
10. Theriault B, Turgeon AF, Pelet S. Functional impact of tibial malrotation following intramedullary nailing of tibial shaft fractures. *J Bone Joint Surg Am*. 2012;94(22):2033-2039.
11. Jaarsma RL, Bruggeman AWA, Pakvis DFM, Verdonschot N, Lemmens JAM, van Kampen A. Computed tomography determined femoral torsion is not accurate. *Arch Orthop Trauma Surg*. 2004;124(8):552-554.
12. Jaarsma RL, van Kampen A. Rotational malalignment after fractures of the femur. *J Bone Joint Surg Br*. 2004;86(8):1100-1104.
13. Jaarsma RL, Ongkiehong BF, Grüneberg C, Verdonschot N, Duysens J, van Kampen A. Compensation for rotational malalignment after intramedullary nailing for femoral shaft fractures. An analysis by plantar pressure measurements during gait. *Injury*. 2004;35(12):1270-1278.
14. Bleeker NJ, Cain M, Rego M, et al. Bilateral Low-Dose Computed Tomography Assessment for Post-Operative Rotational Malalignment After Intramedullary Nailing for Tibial Shaft Fractures: Reliability of a Practical Imaging Technique. *Injury*. 2018;49(10):1895-1900.
15. Wissing H, Buddenbrock B. Determining rotational errors of the femur by axial computerized tomography in comparison with clinical and conventional radiologic determination. *Unfallchirurgie*. 1993;19(3):145-157.
16. Prasad CV, Khalid M, McCarthy P, O'Sullivan ME. CT assessment of torsion following locked intramedullary nailing of tibial fractures. *Injury*. 1999;30(7):467-470.

17. Andersson GBJ, Cocchiarella L, eds. *Guides to the Evaluation of Permanent Impairment, Fifth Edition*. 5th ed. American Medical Association; 2000.

18. Metcalfe CW, Harrison WD, Nayagam S, Narayan B. Negligence claims following non-union and malunion of long bone fractures: An analysis of 15 years of data. *Injury*. 2016;47(10):2312-2314.

19. Svoboda SJ, McHale K, Belkoff SM, Cohen KS, Klemme WR. The effects of tibial malrotation on the biomechanics of the tibiotalar joint. *Foot Ankle Int*. 2002;23(2):102-106.

20. van der Werken C, Marti RK. Post-traumatic rotational deformity of the lower leg. *Injury*. 1983;15(1):38-40.

21. Milner SA, Davis TRC, Muir KR, Greenwood DC, Doherty M. Long-term outcome after tibial shaft fracture: is malunion important? *J Bone Joint Surg Am*. 2002;84(6):971-980.

22. Puno RM, Vaughan JJ, Stetten ML, Johnson JR. Long-term effects of tibial angular malunion on the knee and ankle joints. *J Orthop Trauma*. 1991;5(3):247-254.

23. Jakob RP, Haertel M, Stüssi E. Tibial torsion calculated by computerised tomography and compared to other methods of measurement. *J Bone Joint Surg Br*. 1980;62-B(2):238-242.

24. Jend HH, Heller M, Dallek M, Schoettle H. Measurement of tibial torsion by computer tomography. *Acta Radiol Diagn* . 1981;22(3A):271-276.

25. Laasonen EM, Jokio P, Lindholm TS. Tibial torsion measured by computed tomography. *Acta Radiol Diagn* . 1984;25(4):325-329.

26. Zelle BA, Boni G. Safe surgical technique: intramedullary nail fixation of tibial shaft fractures. *Patient Saf Surg*. 2015;9(1):40.

27. Madadi F, Madadi F, Maleki A, Shamie AN, Washington ER 3rd, Yazdanshenas H. A new method for tibial torsion measurement by computerized tomography. *J Orthop*. 2016;13(1):43-47.

28. Clementz BG. Assessment of tibial torsion and rotational deformity with a new fluoroscopic technique. *Clin Orthop Relat Res*. 1989;(245):199-209.

29. Johner R, Wruhs O. Classification of tibial shaft fractures and correlation with results after rigid internal fixation. *Clin Orthop Relat Res*. 1983;(178):7-25.

30. Kahn KM, Beals RK. Malrotation after locked intramedullary tibial nailing: three case reports and review of the literature. *J Trauma*. 2002;53(3):549-552.

31. Reikerås O, Høiseth A. Torsion of the leg determined by computed tomography. *Acta Orthop Scand*. 1989;60(3):330-333.

32. Seber S, Hazer B, Köse N, Göktürk E, Günal I, Turgut A. Rotational profile of the lower extremity and foot progression angle: computerized tomographic examination of 50 male adults. *Arch Orthop Trauma Surg*. 2000;120(5-6):255-258.

33. Strecker W, Keppler P, Gebhard F, Kinzl L. Length and torsion of the lower limb. *J Bone Joint Surg Br*. 1997;79(6):1019-1023.

34. Larsen P, Elsoe R, Hansen SH, Graven-Nielsen T, Laessoe U, Rasmussen S. Incidence and epidemiology of tibial shaft fractures. *Injury*. 2015;46(4):746-750.

35. Staheli LT, Corbett M, Wyss C, King H. Lower-extremity rotational problems in children. Normal values to guide management. *J Bone Joint Surg Am*. 1985;67(1):39-47.

36. Stuberg W, Temme J, Kaplan P, Clarke A, Fuchs R. Measurement of tibial torsion and thigh-foot angle using goniometry and computed tomography. *Clin Orthop Relat Res*. 1991;(272):208-212.

37. Hudson D, Royer T, Richards J. Ultrasound measurements of torsions in the tibia and femur. *J Bone Joint Surg Am*. 2006;88(1):138-143.

38. Schneider B, Laubenberger J, Jemlich S, Groene K, Weber HM, Langer M. Measurement of femoral antetorsion and tibial torsion by magnetic resonance imaging. *Br J Radiol*. 1997;70(834):575-579.

39. Jeanmart L, Baert AL, Wackenheim A, Osteaux M, Balériaux D. *Atlas of Pathological Computer Tomography: Computer Tomography of Neck, Chest, Spine and Limbs*. Springer-Verlag; 1983.

40. Powers CM, Chen P-Y, Reischl SF, Perry J. Comparison of foot pronation and lower extremity rotation in persons with and without patellofemoral pain. *Foot Ankle Int*. 2002;23(7):634-640.

41. Powers CM, Maffucci R, Hampton S. Rearfoot Posture in Subjects With Patellofemoral Pain. *Journal of Orthopaedic & Sports Physical Therapy*. 1995;22(4):155-160. doi:10.2519/jospt.1995.22.4.155

42. Hertel J, Dorfman JH, Braham RA. Lower extremity malalignments and anterior cruciate ligament injury history. *J Sports Sci Med*. 2004;3(4):220-225.

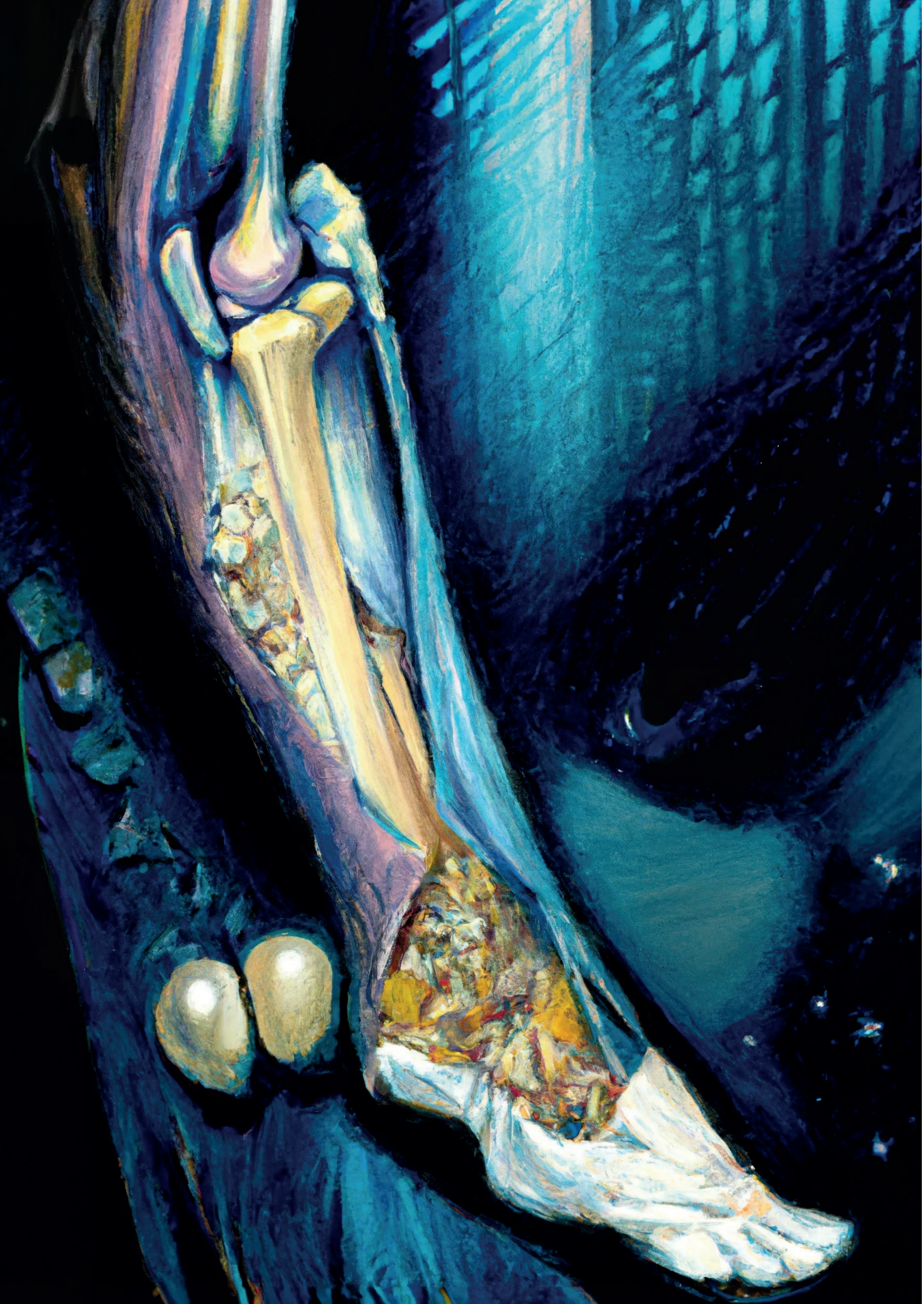
43. Loudon JK, Jenkins W, Loudon KL. The relationship between static posture and ACL injury in female athletes. *J Orthop Sports Phys Ther*. 1996;24(2):91-97.

44. Eckhoff DG. Effect of limb malrotation on malalignment and osteoarthritis. *Orthop Clin North Am*. 1994;25(3):405-414.

45. Clementz BG. Tibial torsion measured in normal adults. *Acta Orthop Scand*. 1988;59(4):441-442.

46. Nguyen A-D, Shultz SJ. Identifying relationships among lower extremity alignment characteristics. *J Athl Train*. 2009;44(5):511-518.

47. Schenk P, Vlachopoulos L, Hingsammer A, Fucentese SF, Fürnstahl P. Is the contralateral tibia a reliable template for reconstruction: a three-dimensional anatomy cadaveric study. *Knee Surg Sports Traumatol Arthrosc*. 2018;26(8):2324-2331.



5

CHAPTER 5

Incidence, Predictors, and Fracture Mapping of (Occult) Posterior Malleolar Fractures Associated with Tibial Shaft Fractures

Laurent A.M. Hendrickx, Megan. E. Cain, Inger N. Sierevelt, Bhavin Jadav, Gino M.M.J. Kerkhoffs, Ruurd L. Jaarsma, Job N. Doornberg

JOURNAL OF ORTHOPAEDIC TRAUMA– DECEMBER 2019

This is a non-final version of an article published in final form in:

Wolters Kluwer - Journal of Orthopaedic Trauma. 2019 Dec;33(12):e452-e458

https://journals.lww.com/jorthotrauma/FullText/2019/12000/Incidence,_Predictors,_and_Fracture_Mapping_of.14.aspx

ABSTRACT

Objectives

1) Evaluate the incidence of posterior malleolar fractures (PMF) in patients with tibial shaft fractures (TSF) using advanced imaging; 2) identify predictors for patients at risk for an (occult) PMF; and 3) describe PMF characteristics to guide “malleolus-first” fixation.

Design

Retrospective diagnostic imaging study.

Setting

Level-I trauma centre.

Patients

One-hundred sixty-four patients treated with intramedullary nailing for TSFs that underwent low-dose postoperative computed tomography (CT)-scans to assess (mal) rotational alignment

Intervention

Analysis of advanced imaging for presence of PMFs. Uni- and multivariate analyses to identify predictors. Qualitative analysis of PMFs by fracture mapping.

Main outcome measures

1) Incidence of PMFs in patients with TSFs as diagnosed on post-op CT-scans; 2) independent predictors for the presence of PMFs; and 3) PMF patterns.

Results

One-in-five patients with a TSF has an associated PMF (22%), increasing to one-in-two in patients with simple spiral fractures (56%). In 25% these fractures were occult.

Univariate analysis identified simple spiral and distal third TSFs, proximal third and spiral fibula fractures, and low energy trauma as predictors for PMFs. Multivariate analysis demonstrated that distal third and simple spiral TSFs were the only independent predictors.

Haraguchi Type I is the pattern specific to PMFs associated with TSF.

Conclusions

Half of patients presenting with a simple spiral TSF have an associated PMF. In one in four these are occult.

Additional preoperative CT-scan imaging may be considered in patients presenting with simple spiral distal third TSFs, despite negative lateral radiographs, so that PMFs can be identified and managed with “malleolus-first” fixation.

Level of Evidence

Level-III diagnostic.

INTRODUCTION

Kempegowda and colleagues make an argument for the importance of clinical suspicion- and recognition of posterior malleolar fractures (PMFs) in patients with tibial shaft fractures (TSFs) prior to intramedullary (IM) nailing allowing "malleolus first" fixation (Figure 1).[1] This technique results in better fracture reduction when compared to "tibia first" fixation.[1] A preoperative diagnosis of PMFs will theoretically prevent iatrogenic or secondary displacement of the posterior malleolar fragment (Figure, 2). [2-4] However, diagnosis has been challenging as PMFs may not be visible on plain radiographs, and computed tomography (CT) has not been routinely used for TSFs in the past. Therefore, it would be clinically useful to establish predictors to identify patients at risk for PMFs associated with their TSF, similar to the algorithm by Schottel and colleagues using predictive radiographic markers to identify concomitant ipsilateral ankle injuries[5]; as well as to improve our understanding of PMF pathoanatomy specific to PMFs associated with TSFs to guide "malleolus-first" fixation.

The reported incidence of PMFs associated with TSFs varies from 4 to 25%.[1,5–8] Most studies are based on radiographs[1,6–8], and one could argue that the reported incidence may be underestimated in these studies, because (occult) PMFs associated with TSFs can be difficult to diagnose on plain lateral radiographs.[7,9,10] Boraiah and colleagues previously reported on the association between distal third spiral fractures and PMFs: in their combined pro- and retrospective cohort of 62 consecutive patients with distal third TSFs they found an association of 48% in a selected subgroup of spiral shaft fractures.[2] Various other studies have reported on this increased incidence of PMFs associated with spiral TSFs. [1,5] However, the scarce data on this subject is limited by the retrospective nature of the studies[1,2,5], small sample sizes[2,5], or are based on plain radiographs that may not account for occult PMFs.[1,2]

Therefore, the purpose of this study is to: 1) report on the incidence of PMFs in a retrospective diagnostic imaging study of advanced imaging (CT) in a large series of 164 patients treated with IM-nailing for TSFs at our level-I trauma hospital; 2) identify predictors for an associated PMF in patients with TSFs and establish a practical clinical prediction rule; and 3) apply fracture mapping techniques to identify fracture characteristics specific to these PMFs. The clinical relevance of this Level III diagnostic imaging study is to improve our understanding of PMFs associated with TSFs by identifying patients with TSFs at risk for an (occult) PMF, as well as to describe the fracture patterns of PMFs to guide fracture specific "malleolus-first" fixation before nailing the tibia.

Figure 1. Example of reduction with “malleolus-first” fixation of an occult PMF: A 51-year-old man sustained a low-energy trauma resulting in a distal third spiral TSF (A–C). “Malleolus-first” fixation was applied with one AP partially threaded cancellous lag screw (D). Postoperative CT scans confirm maintained reduction (E and F), and 2-week plain radiographs show adequate fixation of the posterior malleolar fragment (G–I).

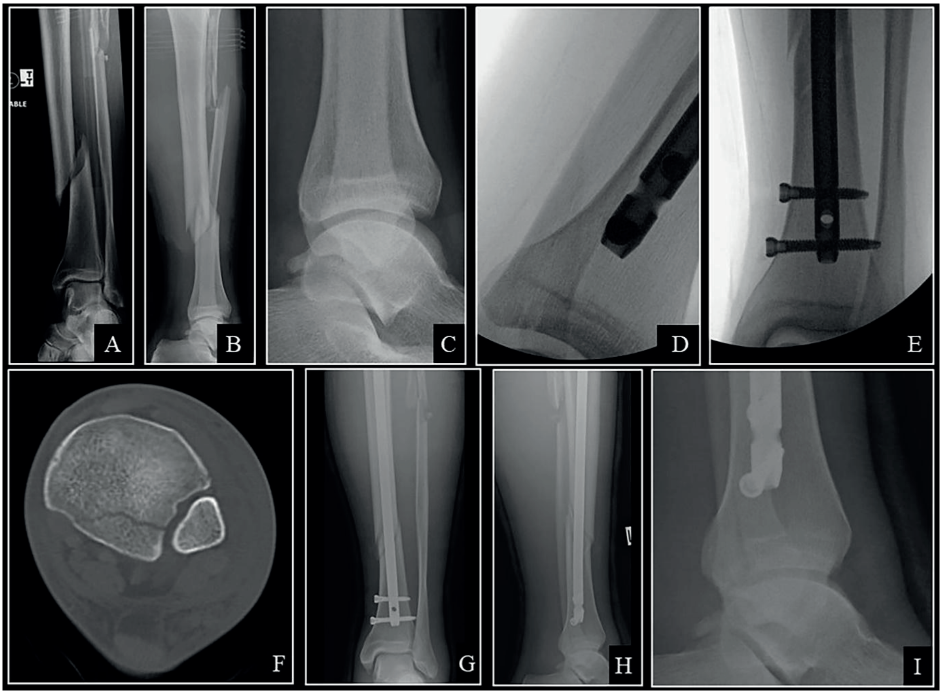


Figure 2. Example of a pre-operatively non-identified posterior malleolar fragment in a 34-year-old male with a spiral distal third tibia shaft fracture after a low-energy trauma (A-C), without intra-operative displacement due to – unintentionally - relatively high nail positioning with respect to the physeal scar (D, E). Postoperatively the posterior malleolar fracture was identified on protocolled low-dose rotational malalignment CT scans (F) and post-op plain radiographs (G-I), resulting in a change to non-weightbearing post-op rehab protocol to avoid secondary displacement.

MATERIALS & METHODS

Ethics

Our Institutional Review Board (IRB) waived requirement for approval of this retrospective diagnostic imaging study, in accordance to the Declaration of Helsinki.

Study design, setting and participants.

Patients treated with IM-nailing for TSFs at our level one trauma hospital were included from 2009 onwards, after undergoing a protocolled low-dose (i.e. effective dose of 0.03784–0.05768mGy; compares to chest radiograph as follows: AP dose is 0.02 and lateral is 0.04 = 0.06 mGy total) postoperative bilateral CT-scan for the assessment of rotational alignment of the tibia.[11] The trial of the protocol was implemented in 2009, with an initial CT-scan rate of 43%, while the adherence to post-op low-dose CT protocol improved to 83% in 2018 to date.

Variables, outcome measures, data sources and bias.

Two authors (LH and MC) not involved in patients' care independently assessed patients' files, preoperative radiographs and postoperative CT-scan images to obtain patient characteristics, trauma mechanism and fracture characteristics. Fracture type and location of the tibia and fibula fractures were classified according to the AO/OTA Fracture and Dislocation Classification Compendium.[12] Trauma mechanism was either classified as low-energy (<30 kilometres per hour or a fall from <3 metres) or high-energy. Postoperative CT-scans were used to determine the presence or absence of PMFs. In addition, the preoperative radiographs were retrospectively assessed by two independent authors (LH and MC) to determine whether the PMFs were occult (i.e. not visible on the preoperative radiograph). Disagreement was resolved with a third independent senior author (JND). PMFs were furthermore classified according to the Haraguchi[13] and Bartonicek classifications[14] (Figure 3) and qualitatively assessed using fracture mapping as described previously by our group.[15,16]

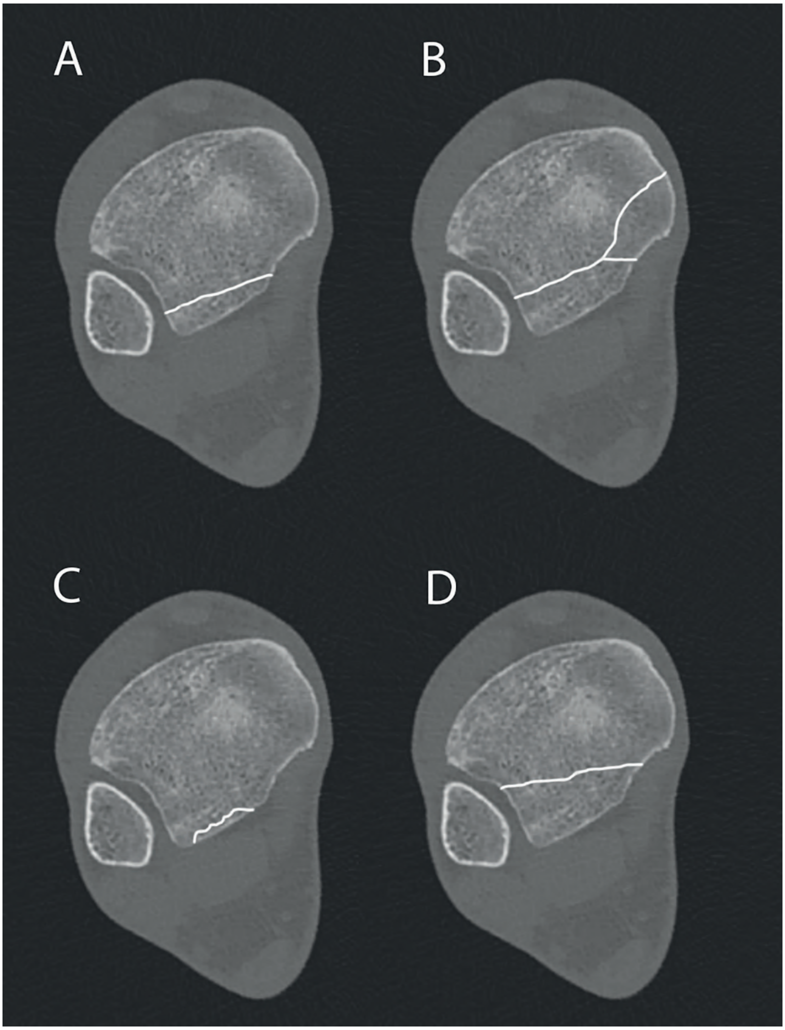


Figure 3. Posterior malleolar fractures according to the Haraguchi Classification and Bartoníček Classification. **1A.** Haraguchi Type I or Bartoníček type 2. Posterior malleolar fractures consisting of posterolateral fragments extending into the tibiofibular notch but involving less than one-third of the fibula incisura. **1B.** Haraguchi Type II or Bartoníček Type 3. Posterior malleolar fractures consisting of two fragments and extending into the posteromedial corner or into the medial malleolus. **1C.** Haraguchi Type III or Bartoníček Type 1. Extra-incisural posterior malleolar fractures consisting of small shell-shaped fragments at the posterior rim. **1D.** Haraguchi Type I or Bartoníček Type 4. Posterior malleolar fractures consisting of triangular fragments extending into the tibiofibular notch and involving more than one-third of the fibula incisura.

Statistical analysis to identify predictors

Descriptive statistics were presented: means and standard deviations for continuous variables (age) and frequencies and percentages for categorical variables (gender, trauma mechanism, location and type of tibia fracture, location and type of fibula fracture, presence of PMF).

First, univariate analysis (i.e. $\chi 2$-test or Fisher's exact test) was used to assess if any of the variables were associated with PMFs. P-values <0.05 were considered statistically significant. Subsequently multivariate binary logistic regression with a backward selection procedure was used to identify which of the predictive factors of the univariate analysis were independently associated with PMFs associated with TSFs. The number of variables tested in the binary logistic regression was limited by-, and dependent on- the total number of events (i.e. total number of PMFs) in the patient cohort: for every five events a degree of freedom could be added to the binary logistic regression analysis (e.g. 50 PMFs would allow for a multivariate analysis limited to 10 degrees of freedom).[17] The variables that proved to be the most significant in the univariate analysis were entered into the multivariate analysis first. Statistical analyses were performed in SPSS 25 (IBM SPSS Statistics).

Diagnostic Performance Characteristics Independent Variables

The independent predictive factors following from the multivariate analysis were evaluated in our patient cohort to demonstrate what the sensitivity and specificity for each combination of the factors would be. Firstly, we calculated in how many true positive, true negative, false positive and false negative cases the presence of these independent variables resulted. Subsequently sensitivity and specificity could be calculated.

Fracture mapping technique

Fracture mapping is a technique first described by Cole and colleagues that allows for the identification of recurring fracture patterns by superimposing a series of fracture lines onto a single template.[18] A single author (LH) used this fracture mapping technique, to map the fracture patterns of all PMFs that were identified on postoperative CT-scans. To create a template, an axial slice 3 mm above the apex of the tibial plafond of an unaffected tibia of a 28-year-old participant who suffered a contralateral TSF was used.

For each PMF, an axial slice within a 3mm range of the apex of the tibial plafond that allowed for the best visualization of the fracture pattern was selected and exported. These axial slices were then imported into Adobe Fireworks CS5 (Adobe, San Jose, California) so that they could be superimposed on the template and subsequently the fracture patterns could be drawn. A senior author (JND) with previous experience in the fracture mapping technique validated that the fracture patterns were mapped and superimposed correctly.[15,16]

RESULTS

Participants

Between 2009-2016 there were 245 patients with TSFs treated with IMN at our institution, of which 164 patients were included in the current study because they received a low-dose postoperative CT scan. The majority of the patients were male (n=118, 72%) and the average age was 41.7 years (SD 18.6 years, range 14-90 years) (Table 1).

TABLE 1. Patient Demographics & Fracture Characteristics

	Total sample size (n = 164)
Patient Characteristics	
Age, years mean (SD)	41.7 (18.6)
Gender, n (%)	
Male	118 (72%)
Female	46 (28%)
Trauma Characteristics, n (%)	
Multi Trauma	33 (20%)
Isolated Trauma	131 (80%)
High Energy Trauma	70 (43%)
Low Energy Trauma	94 (57%)
Fracture Characteristics	
Posterior Malleolar Fracture, n (%)	
Present	36 (22%)
Absent	128 (78%)
Location Tibia Fracture, n (%)	
Proximal 1/3rd	6 (4%)
Middle 1/3rd	49 (30%)
Distal 1/3rd	95 (58%)
Segmental	14 (9%)
Type Tibia Fracture, n (%)	
Spiral	48 (29%)
Oblique	31 (19%)
Transverse	23 (14%)
Comminuted not spiral	45 (27%)
Comminuted spiral	17 (10%)
Fibula fracture, n (%)	
Present	137 (84%)
Absent	27 (16%)
Location fibula fracture, n (%)	
No fibula fracture	27 (16%)
Proximal 1/3rd	30 (18%)
Middle 1/3rd	45 (27%)
Distal 1/3rd	43 (26%)

Segmental	19 (12%)
Type of fibula fracture, n (%)	
No fibula fracture	27 (16%)
Spiral	17 (10%)
Oblique	23 (14%)
Transverse	25 (15%)
Comminuted	57 (35%)
Segmental	15 (9%)

Incidence posterior malleolar fractures

Analysis of 164 postoperative low-dose CT-scans revealed a PMF in 36 patients with a TSF (22%). The incidence increased to one-in-two in patients with simple spiral fractures (56%). In 9 out of 36 patients (25%) the PMF could not be identified on preoperative radiograph.

Predictive factors for posterior malleolar fractures (Table 2)

Univariate analysis demonstrated that low energy trauma (p<0.01), AO/OTA fracture type -spiral- (p<0.0001) and -distal- location (p<0.0001) of tibia fractures, as well as the -spiral- fracture type (p<0.001) and the -proximal- location (p<0.001) of fibula fractures were associated with the presence of PMFs (Table 2). Due to the number of events in our cohort (36) multivariate analysis was limited to 7 degrees of freedom.

Univariate analysis revealed that the associations between location and type of tibia fracture and PMFs were the most significant. Multivariate analysis of these two variables with the 9 potential predictors allowed 7 degrees of freedom, and identified simple spiral TSFs (OR = 7.31 (reference category comminuted not spiral TSFs); 95% CI, 1.82 - 29.37, p<0.01) and distal third TSFs (OR = 9.46 (reference category middle third TSFs); 95% CI, 1.97 – 45.50 , p<0.01) as independent predictive factors for PMFs.

TABLE 2. Patient-, Trauma- and Fracture Characteristics and Posterior Malleolar Fractures

	Posterior malleolar fracture absent		**Posterior malleolar fracture present**		
	n	%	n	%	P-value
Gender					**0.65**
Female	37	80%	9	20%	
Male	91	77%	27	23%	
Trauma mechanism					**0.01***
High Energy	62	89%	8	11%	
Low Energy	66	70%	28	30%	
Type Tibia Fracture					**<0.0001***
Spiral	21	44%	27	56%	
Oblique	31	100%	0	0%	
Transverse	22	96%	1	4%	
Comminuted not spiral	42	93%	3	7%	
Comminuted spiral	12	71%	5	29%	
Location Tibia Fracture					**<0.0001** φ *
Proximal 1/3rd	6	100%	0	0%	
Middle 1/3rd	47	96%	2	4%	
Distal 1/3rd	61	64%	34	36%	
Segmental	14	100%	0	0%	
Type Fibula Fracture					**<0.001** *
Spiral	6	35%	11	65%	
Oblique	19	83%	4	17%	
Transverse	23	92%	2	8%	
Comminuted	43	75%	14	25%	
Segmental	13	87%	2	13%	
No Fibula Fracture	24	89%	3	11%	
Location Fibula Fracture					**<0.001** *
Proximal 1/3rd	14	47%	16	53%	
Middle 1/3rd	38	84%	7	16%	
Distal 1/3rd	35	81%	8	19%	
Segmental	17	89%	2	11%	
No Fibula Fracture	24	89%	3	11%	

* *χ2-test or Fisher's exact test was significant at $p<0.05$*
φ *Fisher Exact*

Diagnostic Performance Characteristics Independent Variables (Table 3)

The sensitivity and specificity of each of the combinations of the independent variables was evaluated. This revealed that the presence of both independent predictive factors (i.e. simple spiral and distal third TSFs) can predict a PMF with a sensitivity and a specificity of 75% (95% CI, 57.8% - 87.9%) and 85% (95% CI, 77.8% -90.8%) respectively. For the presence of at least one of both factors the sensitivity is 94% (95% CI, 81.3% - 99.3%) and the specificity 42% (95% CI, 33.5% - 51.2%). The presence of a distal third tibia fracture has a sensitivity of 94% (95% CI, 81.3%-99.3%) and specificity of 44% (95% CI, 35% - 52.8%). The presence of a simple spiral fracture has a sensitivity of 75% (95% CI, 57.8% - 87.9%) and specificity of 84%, (95% CI, 76.0% - 89.6%) (Table 3).

TABLE 3. Diagnostic Performance Characteristics Independent Variables

	Simple Spiral Tibia Shaft Fracture		Distal Third Tibia Shaft Fracture		Simple Spiral or Distal Third Tibia Shaft Fracture		Simple Spiral and Distal Third Tibia Shaft Fracture	
	Yes	No	Yes	No	Yes	No	Yes	No
Posterior Malleolar Fracture Present	27^{α}	9^{β}	34^{α}	2^{β}	34^{α}	2^{β}	27^{α}	9^{β}
Posterior Malleolar Fracture Absent	21^{γ}	107^{δ}	72^{γ}	56^{δ}	74^{γ}	54^{δ}	19^{γ}	109^{δ}
Sensitivity	75%		94%		94%		75%	
Specificity	84%		44%		42%		85%	

α true positives
β false negatives
γ false positives
δ true negatives

Fracture map of posterior malleolar fractures

The CT images of two patients proved to be of insufficient quality for accurate mapping of the PMF. Hence a total of 34 PMFs were mapped according to the earlier described fracture mapping technique (Figure 4)

According to the Haraguchi classification, 33 fractures could be classified as a Haraguchi type I fracture (97%) and 1 fracture could be classified as a Haraguchi type II fracture, there were no Haraguchi type III fractures. Fracture lines were also grouped together based on the entry points of the fracture lines into the tibiofibular joint. This revealed that of the 33 Haraguchi Type I fractures, twenty-one (64%) entered the tibiofibular joint in the middle third of the fibula incisura whereas twelve (36%) entered the tibiofibular joint in the posterior third of the fibula incisura, corresponding to Bartonicek type 4 and type 2 respectively (Figure 5).

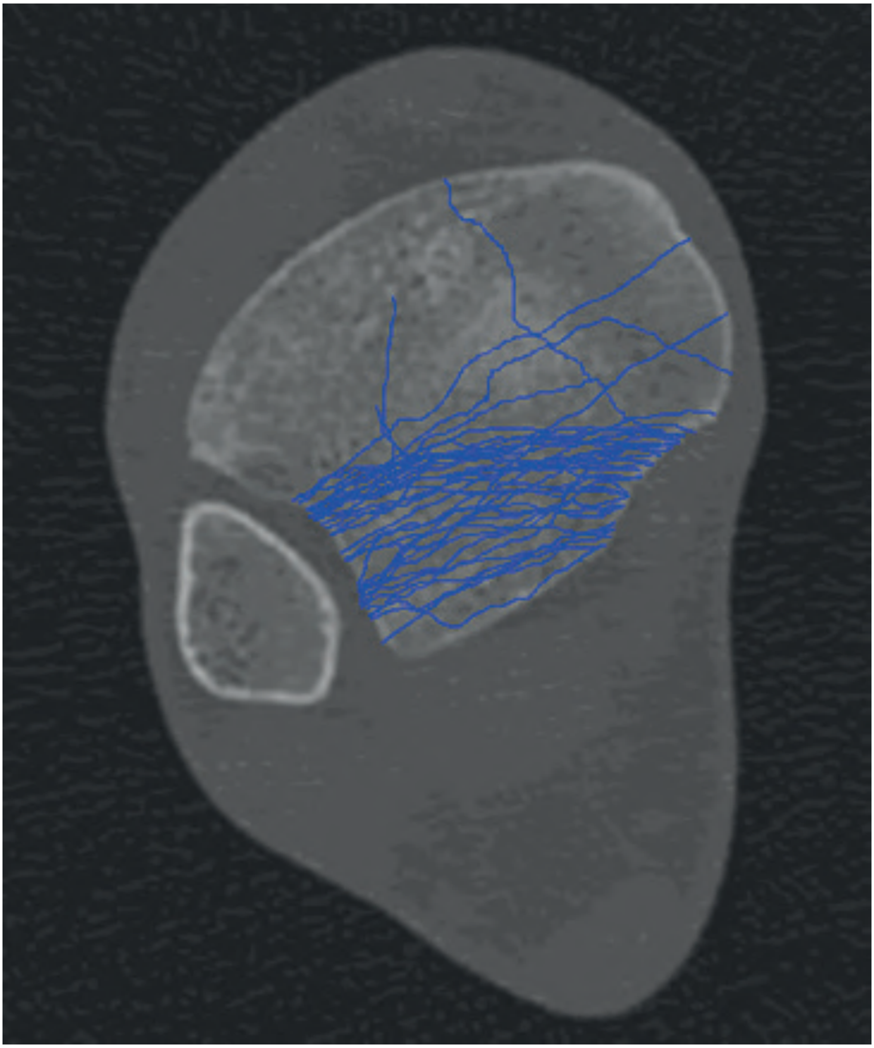


Figure 4. Fracture map of 34 posterior malleolar fractures.

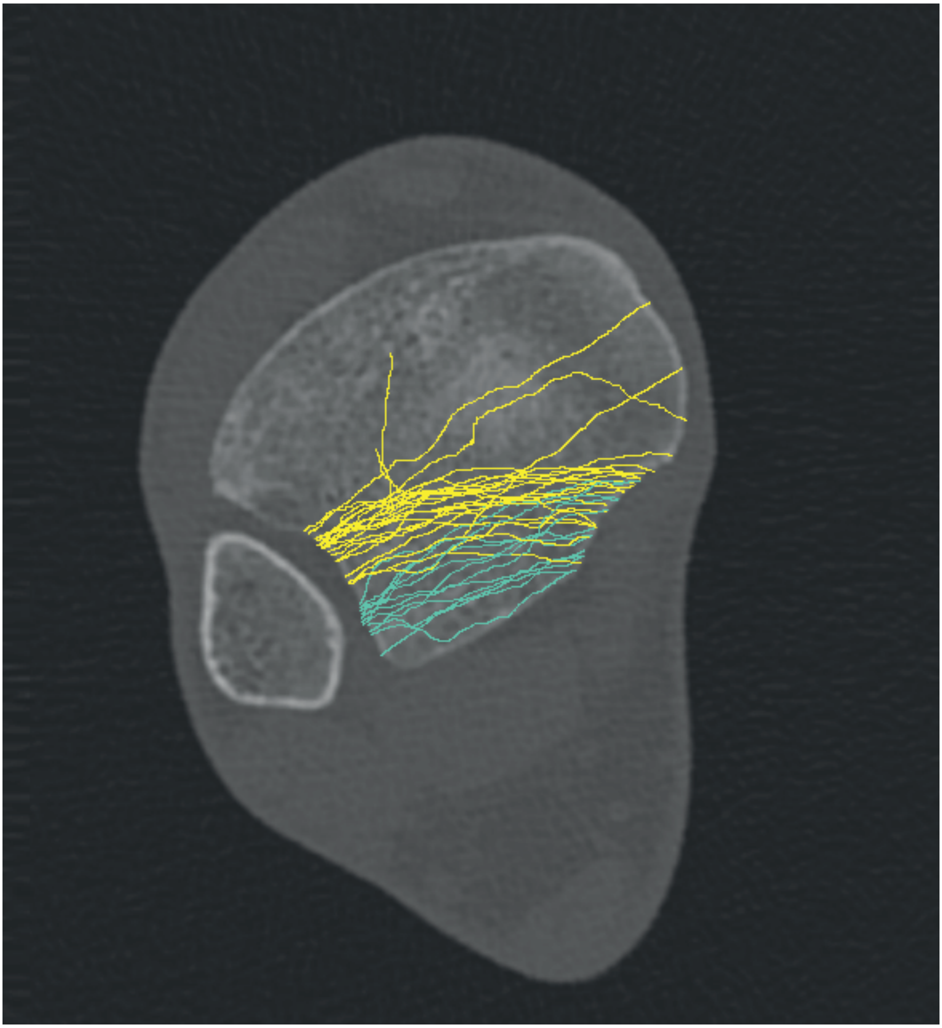


Figure 5. Fracture map of 33 Haraguchi type I PMFs: Twenty-one (64%) entered the tibiofibular joint in the middle third of the fibula incisura, corresponding to Bartoníček type 4 (yellow lines), and 12 (36%) entered the tibiofibular joint in the posterior third of the fibula incisura, corresponding to Bartoníček type 2 (blue lines).

Iatrogenic & Secondary Displacement

In our series there were two (6%) cases of iatrogenic displacement of the PMF due to the nailing. In both cases reduction was attempted, but postoperative CT-scan imaging demonstrated 4mm (Figure 6) and 5mm displacement respectively. There was one case (3%) of secondary displacement of the PMF. This case required revision surgery due to a loss of reduction of the TSF (Figure 7). All three cases were Haraguchi Type I fractures.

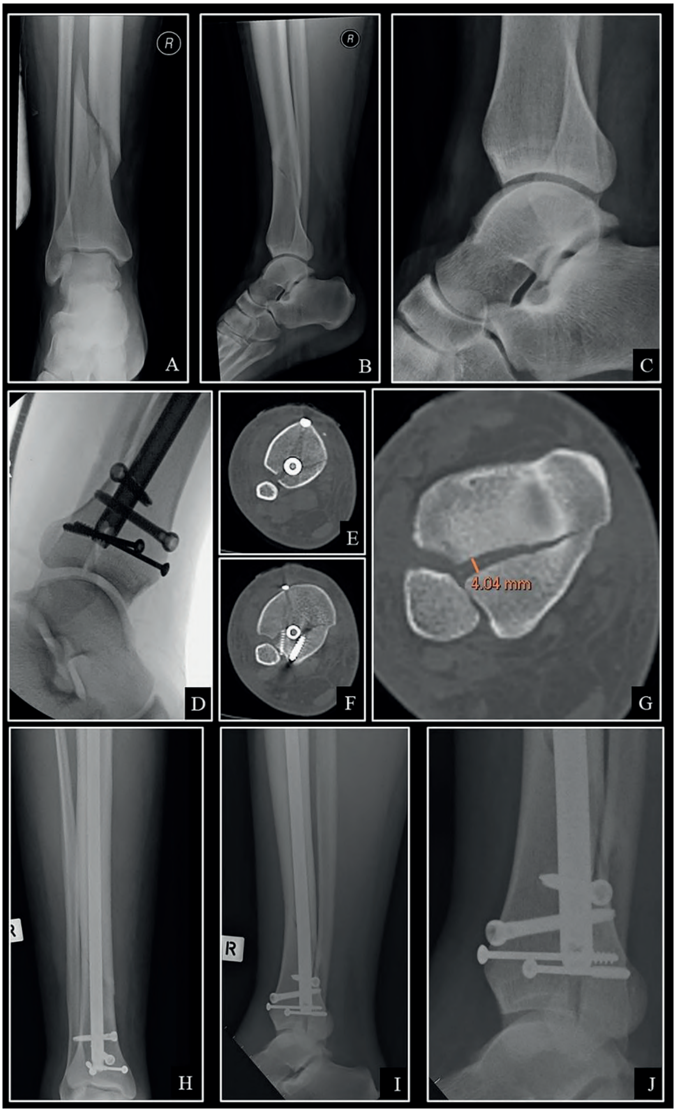


Figure 6. Example of iatrogenic displacement of PMF: A 36-year-old man with a distal third spiral TSF (A and B). One can appreciate the undisplaced PMF on plain lateral radiographs (C). Intraoperatively, decision was made to fix the tibia first resulting in secondary displacement of PMF, followed by malleolus fixation without proper reduction due to tibial nail interposition (D). Postoperative CT scans confirm iatrogenic displacement of PMF and show fracture gapping caused by tibial nail at 22 mm above the joint level (E), inability to reduce fragment with lag screws at 12 mm superior to the joint level (F), and resultant 4.0-mm fracture gap at the joint level (G). Two-week plain radiographs reveal persistent displacement with substantial gap of the tibial plafond, without significant step-off (H–J). Patient denied revision surgery to address poor reduction.

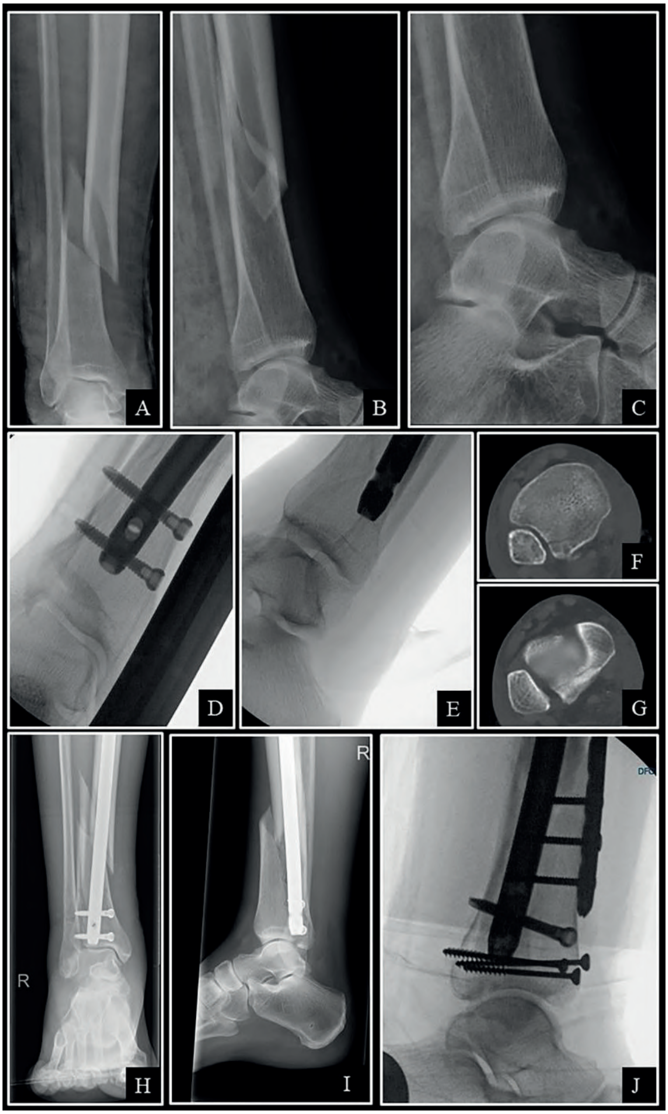


Figure 7. Example of secondary postoperative displacement of an occult posterior malleolar fragment, as well as complete loss of reduction in the occult spiral fracture plane.

A 57-year-old male sustained a distal third spiral tibia shaft fracture without a clear posterior malleolar fracture on plain radiographs (A-C). The position of the nail was relatively posterior (i.e. in the unidentified occult fracture plane), but without displacement of the posterior malleolar fracture on intra-operative fluoroscopy imaging (D, E). Postoperative CT-scans demonstrated a non-displaced posterior malleolar fracture (F, G). Two-week radiograph revealed complete loss of reduction due to posterior positioning of the tibial nail in the occult fracture plane extending into the posterior malleolar fracture (H, I). Patient underwent revision surgery of the tibial nail with additional plate fixation and lag screw fixation of the posterior malleolar fracture (J).

DISCUSSION

The incidence of PMFs in patients with TSFs found in this study on CT imaging was 22%, increasing to 56% in patients with simple spiral TSFs. In 25% of patients the PMFs were occult. Patients with a simple spiral TSF were 7 times more likely to have an associated PMF, and patients with a distal third TSF 9 times more likely to have a PMF. The presence of both these independent predictive factors can correctly detect 75% of the PMFs. Fracture mapping revealed that PMFs associated with TSFs are posterolateral oblique type fractures, amenable to AP or PA lag screw fixation.

The findings of this study should be appreciated in light of strengths and weaknesses: Strengths of this study include an analysis of the largest series of protocolled CT-scan images of PMFs associated with TSFs to date.[1,2,5,9,10,19] This study furthermore included all types and locations of TSFs to assess the incidence of PMFs, tested twenty-two predictors from six variables, and applied fracture mapping to characterise these particular PMFs making it one of the most comprehensive studies to contribute to our understanding of this common injury. Limitations include: firstly, a small group of fractures in the spectrum of high energy compound fractures that have been treated with frame in our institution. These outliers are not included in our series as this solely consisted of patients treated with IM-nailing. Secondly, all CT images were obtained postoperatively: one could argue that some of the occult fractures may have in fact been caused by intramedullary nailing, rather than being pre-existent. The authors believe that one particular case, a transverse middle third TSF and an associated PMF, may have in-fact been iatrogenic. On the preoperative radiograph there was no sign of a PMF and on the postoperative CT-scan the nail was protruding into the fracture site. The remainder PMFs however did fit the overall fracture patterns previously described.[1,5,7] Lastly, despite the large series, we were limited to two variables (i.e. location and type) which included nine possible predictors in our multivariate analysis.

The incidence of PMFs associated with TSFs in this study is in correspondence with the 25% previously reported by Kukkonen ($n^{TSF}=72$, $n^{PMF}=18$)[6] and Schottel ($n^{TSF}=71$, $n^{PMF}=18$)[5]. Various other studies reported either substantially lower (4 – 12%)[1,7,8] or higher incidences (38%)[19]. The difference (16%) in the latter may be caused by the potential introduction of selection bias in this study: patients without CT-scan imaging of the ankle were excluded.[19] The former studies assessing the incidence of PMFs demonstrated much lower incidences (4-12%).[1,7,8] However, these studies relied on radiographs[7,8] or made inconsistent use of CT-scan imaging[1], which may have led to an underestimation of the true incidence of PMFs. The low incidences found in these studies[1,7,8] do highlight however, that PMFs are difficult to diagnose on plain radiographs, which is also illustrated by the high percentage (25%) of occult PMFs in our study. This difficulty drove us to identify and confirm predictors and test these in a clinical prediction rule.

Various studies report a high incidence of PMFs in patients with distal third TSFs[1,6,7] and spiral TSFs.[1,2,6,7,10]. However, these series did not allow for testing additional predictors and variables to further quantify this association. Our study applied subsequent univariate and multivariate analyses to confirm what has previously been suspected: distal third TSFs and simple spiral TSFs are independent predictive factors for PMFs. This finding is supported by Huang and colleagues, who identified fracture location, fracture type and fracture length as independent predictors of PMF.[19]

In a recent study, Marchand and colleagues coined a simple radiographic predictor: a ratio that follows from the length of the TSF divided by the distance from the TSF to the tibial plafond.[9] The cut-off value (<0.224 on AP-radiographs) the authors propose for this ratio results in a sensitivity of 100%, however with a trade-off low specificity of 16%. In other words, the length of the fracture combined with distance of the fracture to the tibial plafond is good to rule an intra-articular component out, but not so useful to rule an intra-articular extension in. Our current study achieved a higher specificity combining two predictors to indicate which patients may require additional preoperative CT-scans in the presence of a potential occult PMF. In our opinion, the combination of the presence of both independent factors results in more clinically relevant diagnostic performance characteristics than length and distance to fracture site ratio, with the ability to detect 75%. We believe that especially the relatively high specificity (85%), resulting in few additional CT-scans, could justify the use of this prediction rule in clinical practice. Moreover, Sobol and colleagues recently published their pre-op CT protocol on distal third spiral TSF specifically and found an incidence of 92% of PMF in these specific types of TSF confirming the predictors of PMFs in this study.[10] Based on our presented data, and the study by Sobol and colleagues[10], we concur with a pre-op CT protocol only for patients with a distal third spiral TSF and a negative lateral radiograph, to confirm involvement of the posterior malleolus and have implemented this in our daily clinical practice in order to prevent iatrogenic and secondary displacement.

Fracture mapping revealed that PMFs associated with TSF may be considered a different entity than PMFs associated with rotational type ankle fractures, as these specific types (Haraguchi Types I – III) are evenly distributed among ankle fractures.[15,20] In our series, posterolateral oblique Haraguchi Type I was the pattern specific to PMF associated with TSF, similar to Huang et al.[19] According to Bartonicek's classification, type 4 was the dominant fracture pattern. This supports the findings of Zhang et al., who furthermore found these type 4 fractures to be at the highest risk of violation by distal locking screws.[4]

In our series, there were two cases in which iatrogenic and one case in which secondary displacement of PMFs could have been prevented with “malleolus-first” fixation. Because PMFs associated with TSFs consist of relatively large fragments, they seem excellently suitable for AP-fixation[1] or PA-fixation[21] with lag screws. These lag screws may be aimed slightly oblique with reference to the true sagittal plane, in order to lag perpendicular to the fracture line. This should be taken into account when ‘malleolus first’ fixation is applied.

Conclusion

One-in-five patients with a TSF has an associated PMF (22%), increasing to one-in-two in patients with simple spiral fractures (56%). In 25% of patients these fractures were occult. Additional preoperative CT-scan imaging may be considered in patients presenting with spiral distal third TSFs, despite negative lateral radiographs, so that PMFs can be identified and managed with “malleolus first” fixation.

REFERENCES

1. Kempegowda H, Maniar HH, Richard R, et al. Posterior Malleolar Fractures Associated With Tibial Shaft Fractures and Sequence of Fixation. J Orthop Trauma. 2016;30(10):568-571.
2. Boraiah S, Gardner MJ, Helfet DL, Lorich DG. High association of posterior malleolus fractures with spiral distal tibial fractures. Clin Orthop Relat Res. 2008;466(7):1692-1698.
3. Georgiadis GM, Ebraheim NA, Hoeflinger MJ. Displacement of the posterior malleolus during intramedullary tibial nailing. J Trauma. 1996;41(6):1056-1058.
4. Zhang Y, Qin X, Song L, Li X. The risk of violating the posterior malleolar fracture when nailing the ipsilateral concomitant spiral distal tibial fracture. BMC Musculoskelet Disord. 2018;19(1):123.
5. Schottel PC, Berkes MB, Little MTM, et al. Predictive radiographic markers for concomitant ipsilateral ankle injuries in tibial shaft fractures. J Orthop Trauma. 2014;28(2):103-107.
6. Kukkonen J, Heikkilä JT, Kyyrönen T, Mattila K, Gullichsen E. Posterior malleolar fracture is often associated with spiral tibial diaphyseal fracture: a retrospective study. J Trauma. 2006;60(5):1058-1060.
7. Stuermer EK, Stuermer KM. Tibial shaft fracture and ankle joint injury. J Orthop Trauma. 2008;22(2):107-112.
8. van der Werken C, Zeegers EV. Fracture of the lower leg with involvement of the posterior malleolus; a neglected combination? Injury. 1988;19(4):241-243.
9. Marchand LS, Rane AA, Working ZM, et al. Radiographic Investigation of the Distal Extension of Fractures Into the Articular Surface of the Tibia (The RIDEFAST Study). J Orthop Trauma. 2017;31(12):668-674.
10. Sobol GL, Shaath MK, Reilly MC, Adams MR, Sirkin MS. The Incidence of Posterior Malleolar Involvement in Distal Spiral Tibia Fractures: Is it Higher than We Think? J Orthop Trauma. 2018;32(11):543-547.
11. Bleeker NJ, Cain M, Rego M, et al. Bilateral Low-Dose Computed Tomography Assessment for Post-Operative Rotational Malalignment After Intramedullary Nailing for Tibial Shaft Fractures: Reliability of a Practical Imaging Technique. Injury. July 2018. doi:10.1016/j.injury.2018.07.031
12. Meinberg EG, Agel J, Roberts CS, et al. Fracture and Dislocation Classification Compendium - 2018. J Orthop Trauma. 2018;32 Supplement 1 pp: S1-S170.
13. Haraguchi N, Haruyama H, Toga H, Kato F. Pathoanatomy of posterior malleolar fractures of the ankle. J Bone Joint Surg Am. 2006;88(5):1085-1092.
14. Bartoníček J, Rammelt S, Kostlivý K, Vaněček V, Klika D, Trešl I. Anatomy and classification of the posterior tibial fragment in ankle fractures. Arch Orthop Trauma Surg. 2015;135(4):505-516.
15. Mangnus L, Meijer DT, Stufkens SA, et al. Posterior Malleolar Fracture Patterns. J Orthop Trauma. 2015;29(9):428-435.
16. Molenaars RJ, Mellema JJ, Doornberg JN, Kloen P. Tibial Plateau Fracture Characteristics: Computed Tomography Mapping of Lateral, Medial, and Bicondylar Fractures. J Bone Joint Surg Am. 2015;97(18):1512-1520.

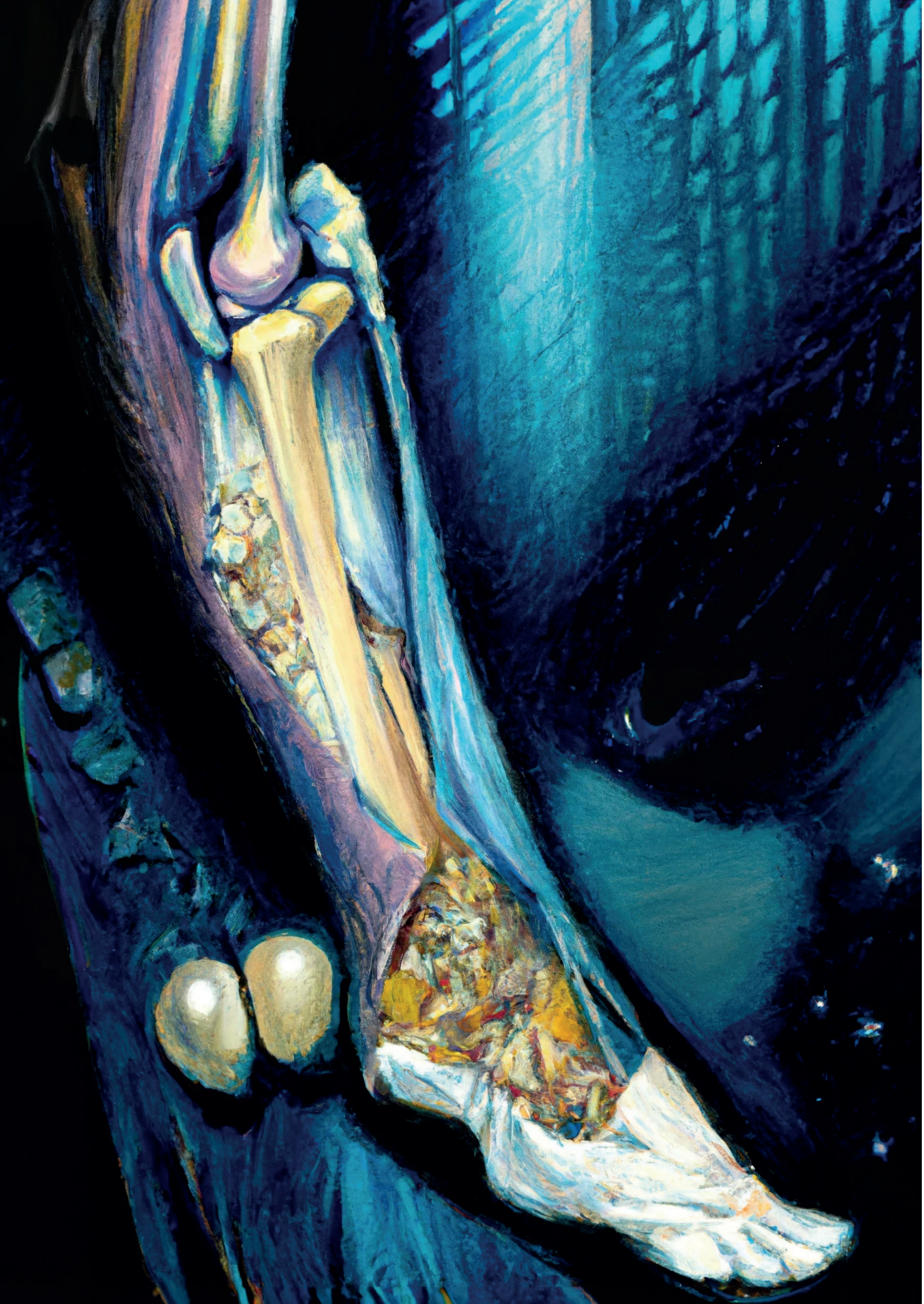
17. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol. 2007;165(6):710-718.

18. Cole PA, Mehrle RK, Bhandari M, Zlowodzki M. The pilon map: fracture lines and comminution zones in OTA/AO type 43C3 pilon fractures. J Orthop Trauma. 2013;27(7):e152-e156.

19. Huang Z, Liu Y, Xie W, Li X, Qin X, Hu J. Pre-operative radiographic findings predicting concomitant posterior malleolar fractures in tibial shaft fractures: a comparative retrospective study. BMC Musculoskelet Disord. 2018;19(1):86.

20. de Muinck Keizer R-JO, Meijer DT, van der Gronde BATD, et al. Articular Gap and Step-off Revisited: 3D Quantification of Operative Reduction for Posterior Malleolar Fragments. J Orthop Trauma. 2016;30(12):670-675.

21. Strenge KB, Idusuyi OB. Technique tip: percutaneous screw fixation of posterior malleolar fractures. Foot Ankle Int. 2006;27(8):650-652.



6

CHAPTER 6

A Machine Learning Algorithm to Predict the Probability of (Occult) Posterior Malleolar Fractures Associated with Tibial Shaft Fractures to Guide "Malleolus First" Fixation

Laurent A.M. Hendrickx, Garret L. Sobol, David Langerhuizen, Anne Eva J Bulstra, Jeremy Hreha, Sheila Sprague, Michael Sirkin, David Ring, Gino M.M.J. Kerkhoffs, Ruurd L. Jaarsma, Job N. Doornberg, Machine Learning Consortium

JOURNAL OF ORTHOPAEDIC TRAUMA – MARCH 2020

This is a non-final version of an article published in final form in:

Wolters Kluwer - Journal of Orthopaedic Trauma. 2020 Mar;34(3):131-138.

https://journals.lww.com/jorthotrauma/FullText/2020/03000/A_Machine_Learning_Algorithm_to_Predict_the.4.aspx

ABSTRACT

Objectives

The incidence of posterior malleolar fractures (PMFs) associated with tibial shaft fractures (TSFs) is higher than most assume, and 25% may go unrecognized on pre-operative plain radiographs.

The primary aim of this study was to develop an accurate Machine Learning (ML) predictive model incorporating patient-, fracture- and trauma-characteristics to identify individual patients at risk for an (occult) PMF.

Methods

Databases of two studies including patients with TSFs from two level-1 trauma-centres were combined for analysis. Using ten-fold cross validation, four supervised ML-algorithms were trained in recognizing patterns associated with PMFs: 1) Bayes point machine; 2) Support Vector Machine; 3) Neural Network; 4) Boosted decision tree.

Performance of each ML-algorithm was evaluated and compared based on 1) C-statistic; 2) Calibration slope and intercept; and 3) Brier-score. The best-performing ML-algorithm was incorporated into an online open-access prediction tool.

Results

Total dataset included 263 patients, of which 28% had a PMF. Training of the Bayes point machine resulted in the best-performing prediction model reflected by good C-statistic, calibration slope, calibration intercept and Brier-Score of 0.89, 1.02, -0.06 and 0.106 respectively. This prediction model was deployed as an open-access online prediction tool.

Conclusion

A ML based prediction model accurately predicted the probability of a (occult) PMF in patients with a TSF based on patient- and fracture- specific characteristics. This prediction model can guide surgeons in their diagnostic work-up and pre-operative planning. Further research is required to externally validate the model prior to implementation in clinical practice.

INTRODUCTION

It has been well established by Kempegowda and colleagues that posterior malleolar fractures (PMFs) associated with tibial shaft fractures (TSFs) benefit from "malleolus first" fixation prior to proceeding with intra-medullary nailing (IMN) [1]. This technique results in better fracture reduction and prevents secondary displacement of the PMFs -which are often non-displaced- compared to "tibia first" fixation [1].

Two recent studies report a high incidence of PMFs in patients with TSFs using CT-scan imaging as the reference standard [2,3]. While previous studies report an incidence of 4 up to 25% of PMFs associated with TSFs [4–7], these two new studies conducted by Sobol [2] and Hendrickx [3] demonstrated PMFs to occur in 56%-92% of the patients with distal spiral TSFs. Moreover, 25% of these PMFs were found to be occult as they could not be identified on pre-operative plain lateral radiographs [3].

In short, as the incidence of PMFs is higher than previously reported, and one quarter may go unrecognized on pre-o1erative plain radiographs risking iatrogenic secondary displacement intra-operatively; a clinical prediction tool to estimate the probability of a PMF in patients with TSFs may aid in the diagnostic work-up (i.e. obtaining a pre-operative CT) and surgical planning (i.e. malleolus first fixation) in patients with TSFs. Artificial intelligence (AI) and Machine Learning (ML) predictive models have recently been proven useful and accurate for clinical decision-making in other specialties [8–12], as well as in orthopaedic surgery in the recent months [13–21].

Therefore, the aim of our study is to develop- and evaluate four ML predictive models to identify patients with TSFs at risk of a PMF, taking into account both patient and fracture characteristics. The best-performing algorithm will be incorporated in an open-access web-based prediction tool. As such, we aim to apply ML predictive models to individualize patient care, by identifying which specific patients may benefit from a pre-operative CT scan and/or malleolus first fixation.

MATERIALS & METHODS

Guidelines

This study adhered to the Guidelines for Developing and Reporting Machine Learning Predictive Models in Biomedical Research [22] and the Transparent Reporting of Multivariable Prediction Models for Individual Prognosis or Diagnosis (TRIPOD) guideline [23].

Data Source & Patient Selection

Databases from two studies reporting on the incidence of PMFs in patients with TSFs [2,3] were combined to form one dataset. At Flinders Medical Centre (Adelaide, South-Australia, Australia), all patients treated with IM-nailing for tibial shaft fractures were included from 2009-2018 if they underwent protocolled low-dose post-operative bilateral CT-scans for the assessment of tibial rotational malalignment [24]. The adherence rate to this protocol increased from 43% in 2009 to 83% in 2018, which resulted in a database of 164 patients [3]. The database from Rutgers New Jersey Medical School (Newark, NJ, United States of America) consisted of all patients with TSFs treated with IM-nailing from 2013-2017 [2]. At this institution, preoperative CT-scans were routinely obtained in distal third spiral tibia shaft fractures, or if intraarticular involvement was suspected [2].

Patients from both databases were included in the dataset for the current study if 1) a concomitant PMF was present as confirmed on plain radiographs, CT-scan imaging or intraoperative fluoroscopy; or 2) the absence of a PMF was confirmed on CT-scan imaging. Pathological fractures, tibial pilon fractures, tibial plateau fractures and peri-prosthetic fractures were excluded. This resulted in the inclusion of all 164 patients from Flinders Medical Centre and 99 patients from Rutgers New Jersey Medical School.

Outcome

The probability of presence of a PMF in patients with a TSF was the primary outcome of interest for the ML algorithms to predict.

Input Variables

Based on previous studies [2,3], we obtained the following variables for algorithm training: trauma mechanism (i.e. high- or low-energy), age, type of tibia fracture (i.e. spiral, oblique, transverse, comminuted spiral, comminuted other), location of tibia fracture (proximal third, middle third, distal third, segmental), type of fibula fracture (spiral, oblique, transverse, segmental) and location of fibula fracture (proximal third, middle third, distal third, segmental). Tibia and fibula fractures were classified according to the AO/OTA Fracture and Dislocation Classification Compendium [25]. Trauma mechanism was either classified as low-energy (<30 kilometres per hour or a fall from <3 metres) or high-energy [26]. The data from Flinders Medical Centre was obtained by two independent observers (LH and MC). Cases of disagreement were resolved with a third independent senior author (JND)[3]. The data from Rutgers Medical School was obtained by one observer, who was a senior orthopaedic resident (PGY-4).

Model Development

Due to the relatively small sample size from a ML perspective, 10-fold cross validation was used for training and assessment of performance of the prediction models instead of a random split of the data into a training-set and a test-set [27]. Cross validation was repeated three times. Based on previous studies utilizing ML and reporting on a binary outcome [13,14,28–30], the following algorithms were selected for the current study: 1) support vector machine; 2) boosted decision tree models; 3) neural network; and 4) Bayes point machine. Each of these ML algorithms are supervised forms of ML, meaning their development relies on the training of the algorithm using labelled data: the presence or absence of a PMF.

Support vector machines are algorithms that can distinguish between two different outcomes by plotting and differentiating data-points in a multi-dimensional space (Figure 1). First, data is transformed and represented as points in space. These points are subsequently divided into two different classes drawing a “hyperplane”. The optimal hyperplane maximizes the distance between the two classes of data-points [31].

Decision trees are classification models in the form of a tree structure, in which the data is consecutively split into smaller subgroups based on data features (Figure 2). The decision tree splits the data to reach the highest degree of homogeneity between datapoints *within* each group and heterogeneity *between* each of the groups [32]. A boosted decision tree consists of multiple decision trees, in which each new tree corrects for the errors of the previous trees. The final prediction model is made on the entire ensemble of decision trees.

Neural networks are computational models mimicking the interconnected neurons of the human brain (Figure 3). They consist of an input layer containing input nodes (or variables); an output layer, representing the outcome; and one or more hidden layers of nodes (indirectly) connecting the input and output nodes. Within each connection, a specific weight is given to the values from the nodes in the previous layer to compute a value in the connected node in the next layer. The weights of the connections are altered and calibrated using forward- and back propagation, to compute an outcome that most accurately predicts the desired outcome in the output layer [33].

The Bayes point machine is a complex algorithm based on a Bayesian approach to linear classification. It is designed to approximate the theoretical optimal Bayesian average of various linear classifiers by identifying an average classifier [34–37].

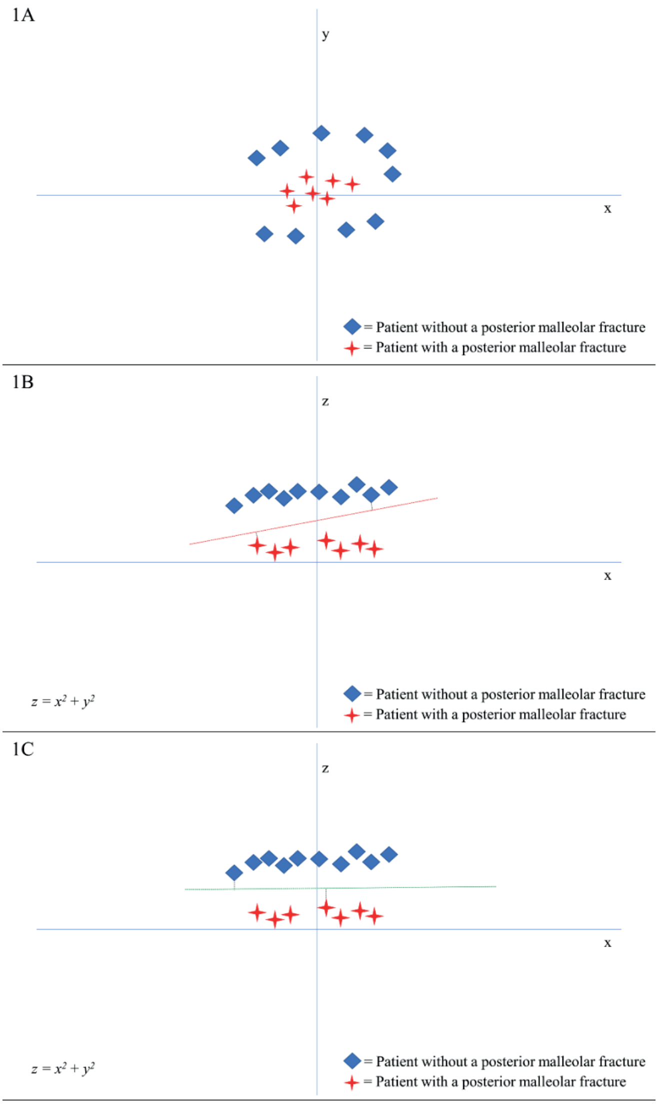


Figure 1A simplified example of a support vector machine.

1A. Differentiating between the two classes by drawing a hyperplane is not possible given the distribution of these datapoints. **1B.** Transformation of the data ($z = x^2 + y^2$) allows a hyperplane to separate the two classes. However, the distance to the closest datapoints from each class can be further optimized for the current hyperplane. **1C.** The optimal hyperplane, which 1) separates both classes; and 2) maximizes the distance to the closest datapoint of each class.

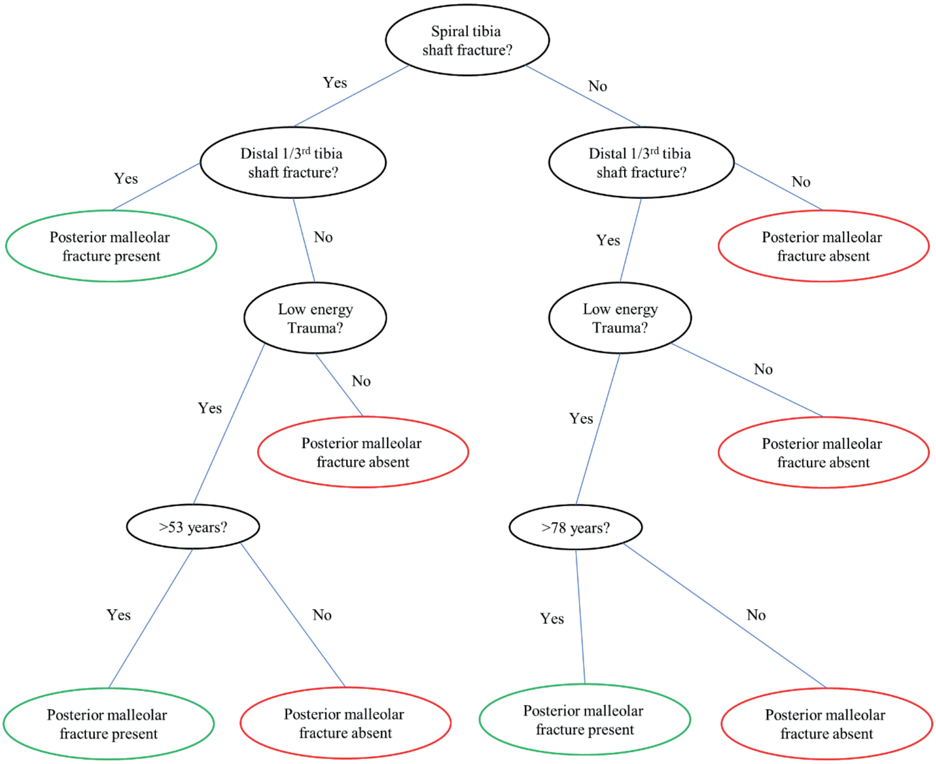


Figure 2. An example of a possible decision tree.

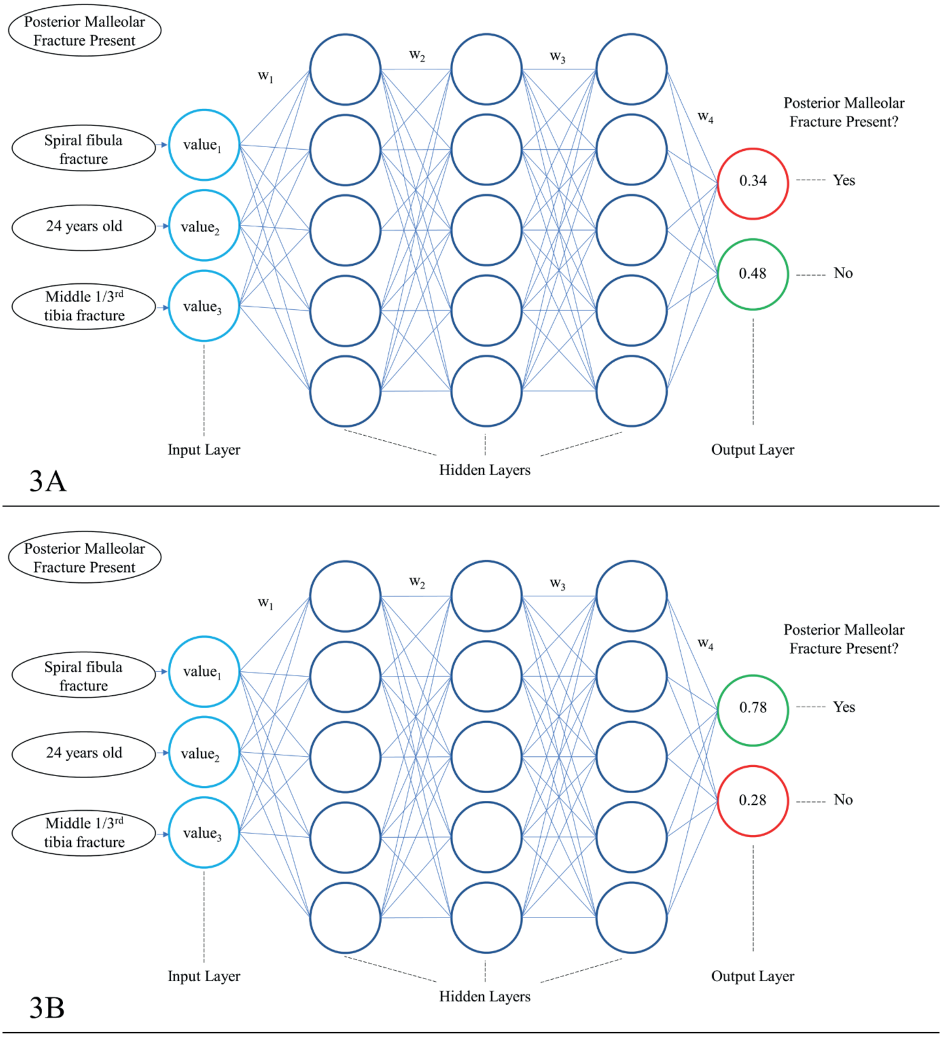


Figure 3 A simplified example of a neural network.

3A. The input variables (e.g. spiral fibula fracture, 24 years old, middle third tibia fracture) of a patient with a posterior malleolar fracture result in erroneous values in the output layer (i.e. a higher value for the node representing the prediction of ‘No posterior malleolar fracture’).

3B. Using forward- and back-propagation, the weights (w_1, w_2, w_3, w_4, (…), $w_{x)}$ within the neural network are calibrated to produce an outcome in the output layer that more accurately corresponds to the actual input.

Statistical Analysis

Baseline characteristics were calculated as frequencies and percentages for categorical variables, whereas mean and standard deviation (SD) were used for continuous variables.

The performance of each respective ML algorithm was assessed by measures of: 1) discrimination; 2) calibration; and 3) overall model performance [38]. First, the discriminative ability of the model can be assessed by calculating the C-statistic, also known as the area under the ROC curve (AUC) (Figure 4). A C-statistic of 1 indicates perfect discriminative ability between patients with a fracture and those without, whereas a C-statistic of 0.5 indicates a non-informative model [39]. Second, calibration reflects the agreement between the observed outcome and predicted probability. It can be assessed and visualized by plotting predicted probability (x-axis) *versus* the actual probability (y-axis) creating a calibration curve (Figure 5). The intercept of the calibration curve indicates whether the predictions are systematically too high (intercept < 0) or too low (intercept > 0) [38]. The slope of the calibration curve reflects whether the predictions were too extreme (i.e. low predictions too low, and high predictions too high), or not extreme enough (i.e. low predictions not low enough, and high predictions not high enough). A calibration slope smaller than 1 reflects the former, a calibration slope larger than 1 the latter [38,40]. Finally, overall model performance is assessed by calculating the squared differences between actual outcomes and predictions, also known as the Brier score. The score can range from 0, indicating a perfect model, to 0.25 for a non-informative model. The upper limit of the score depends on the incidence of the outcome. A maximum incidence of 50% results in an upper limit of 0.25 and an incidence of 10% results in an upper limit of 0.090. Hence, the upper limit for the Brier score was also calculated [39].

Application Development

The best-performing ML algorithm was incorporated into an online open-access multi-platform prediction tool. Orthopaedic Trauma Surgeons can enter patient specific- and fracture characteristic- input variables into the online prediction tool. These input variables are subsequently fed into the trained ML algorithm which returns the patient specific probability of a PMF.

We analysed the cross-validation results of the best-performing algorithm to identify three different threshold values of this prediction tool: 1) the threshold at which the sum of the sensitivity and specificity is the largest and the accuracy of the model the highest. This is equal to the point on the ROC-curve closest to the top-left corner; 2) the threshold at which the specificity is ≥ 95%; and 3) the threshold at which the sensitivity is ≥ 95%. For each threshold we also calculated true positives, false positives, true negatives, false negatives and accuracy. The accuracy is calculated by dividing the sum of the true positive and true negative cases by the total number of cases.

The following software was used for data analysis and web-app development: R-Studio Version 1.1.463 (R-studio, Boston, MA, USA), Excel Microsoft Office 2019 (Microsoft Corporation, Redmond, WA, USA), R version 3.5.2 (The R Foundation, Vienna, Austria), Microsoft Azure (Microsoft Corporation, Redmond, WA, USA), SPSS 25 (IBM SPSS Statistics, Armonk, NY, USA).

RESULTS

Patients

The combined data set consisted of 263 patients with a TSF, of which 75 patients had a PMF (29%). All 75 PMFs were verified on CT-scan imaging. The mean age of the patients in the training set was 41 years, 75% of the patients were male. The fractures were caused by a low energy trauma in 56% of the cases, and by a high energy trauma in 44% (Table 1).

TABLE 1. Patient Demographics & Fracture Characteristics

	Total sample size (n = 263)
Patient Characteristics	
Age, years mean (SD)	41.0 (18.0)
Gender, n (%)	
Male	196 (75%)
Female	67 (25%)
Trauma Characteristics, n (%)	
High Energy Trauma	116 (44%)
Low Energy Trauma	147 (56%)
Fracture Characteristics	
Posterior Malleolar Fracture, n (%)	
Present	75 (29%)
Absent	188 (71%)
Location Tibia Fracture, n (%)	
Proximal 1/3rd	13 (5%)
Middle 1/3rd	75 (29%)
Distal 1/3rd	161 (61%)
Segmental	14 (5%)
Type Tibia Fracture, n (%)	
Spiral	87 (33%)
Oblique	51 (19%)
Transverse	31 (12%)
Comminuted not spiral	73 (28%)
Comminuted spiral	21 (8%)
Fibula fracture, n (%)	
Present	231 (88%)
Absent	32 (12%)
Location fibula fracture, n (%)	
No fibula fracture	32 (12%)
Proximal 1/3rd	62 (24%)
Middle 1/3rd	66 (25%)
Distal 1/3rd	83 (32%)
Segmental	20 (8%)
Type of fibula fracture, n (%)	
No fibula fracture	32 (12%)
Spiral	30 (11%)
Oblique	57 (22%)
Transverse	40 (15%)
Comminuted	85 (32%)
Segmental	19 (7%)

Performance Machine Learning Algorithms (Table 2)

Discriminative performance as quantified by the C-statistic was good for all four ML algorithms ranging from 0.81 to 0.89 (Table 2) (Figure 4).

All four ML algorithms were well calibrated reflected by calibration slopes ranging from 0.94 to 1.26 and calibration intercepts ranging from -0.06 to 0.03 (Figure 5).

Overall model performance was good for all four ML algorithms, reflected by low Brier scores ranging from 0.106 to 0.114. The upper limit of the Brier score was 0.204, based on an incidence of PMFs of 28%.

The Bayes point machine was chosen as the final model, because it consisted of the highest C-statistic (0.89), lowest Brier-score (0.106), and calibration slope closest to 1 (1.02), whilst the calibration intercept was close to 0 (-0.06).

TABLE 2. Performance of Machine Learning Algorithms in predicting associated posterior malleolar fractures using 10-fold cross-validation repeated three times.

	C-statistic	Calibration Slope	Calibration Intercept	Brier Score*
Bayes Point Machine	0.89	1.02	-0.06	0.106
Boosted Decision Tree	0.81	1.02	0.01	0.114
Neural Network	0.89	1.26	0.03	0.108
Support Vector Machine	0.89	0.94	-0.02	0.108

**Upper Limit Brier Score = 0.20*

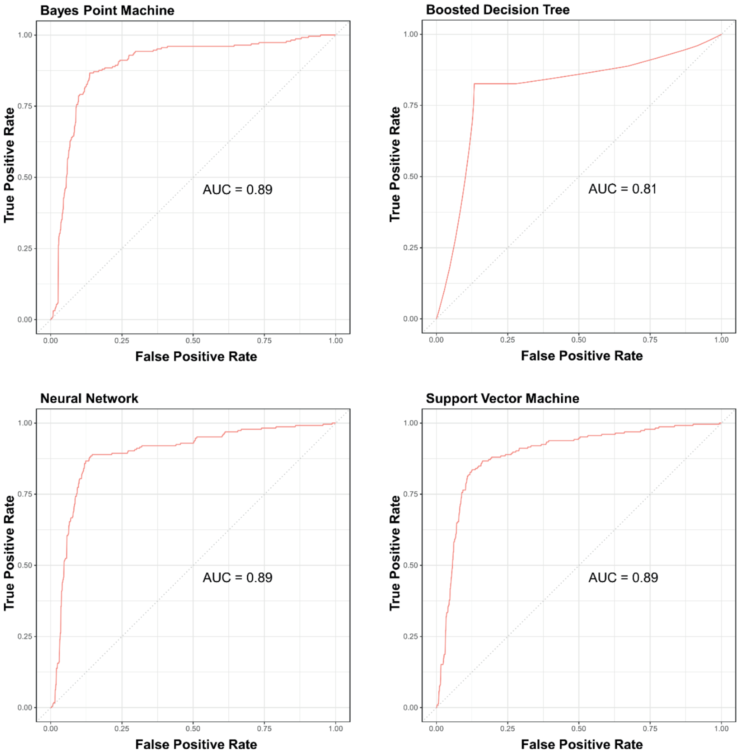


Figure 4. Receiver Operating Characteristic (ROC) curves for each respective ML algorithm.

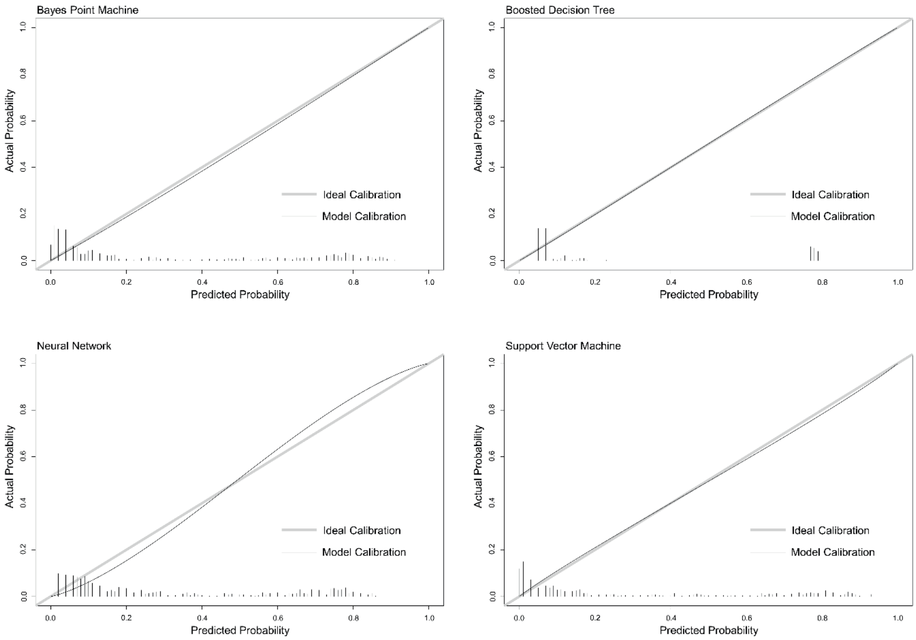


Figure 5. Calibration curves for each respective ML algorithm.

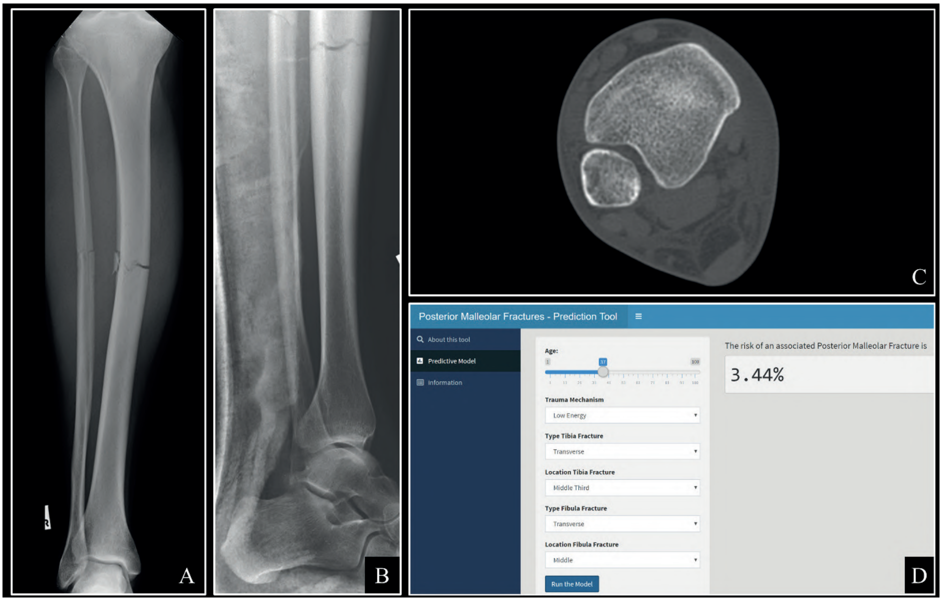
Online Prediction Tool

The prediction model based on the Bayes point machine was incorporated in an online open-access multi-platform prediction tool, allowing users to calculate the probability of a PMF after entering patient- and fracture specific input variables: https://traumaplatform.shinyapps.io/posteriormalleolar/ (Figures 6 and 7).

The threshold value corresponding to the largest sum of the sensitivity and specificity was 36.7%. The sensitivity and specificity were both 87% at this threshold. The threshold corresponding to a specificity of ≥ 95% was 74.5%. The sensitivity and specificity were 42.7% and 95.2% respectively at this threshold. The threshold corresponding to a sensitivity of ≥ 95% was 13%. The sensitivity and specificity were 96% and 72.3% respectively at this threshold. Corresponding true- and false positive rates, true- and false negative rates and accuracy rates for these probability thresholds are displayed in Table 3.

TABLE 3. Performance of Prediction Model for Various Thresholds.

Threshold	Sensitivity	Specificity	True positives	False positives	True negatives	False negatives	Accuracy
13%	96%	72.3%	72	52	136	3	79%
36.7%	87%	87%	65	24	164	10	87%
74.5%	42.7%	95.2%	32	9	179	43	80%



Age: 37

Trauma Mechanism: Low Energy

Type Tibia Fracture: Transverse

Location Tibia Fracture: Middle Third

Type Fibula Fracture: Transverse

Location Fibula Fracture: Middle

The risk of an associated Posterior Malleolar Fracture is

3.44%

Figure 6. A 37-year old male sustained a low-energy trauma resulting in a middle third transverse tibia shaft fracture and a middle third transverse fibula fracture, without an identifiable posterior malleolar fracture on pre-operative plain radiographs or postoperative CT-scan imaging (A-C). When the patient specific characteristics of this case were retrospectively fed into the prediction tool, it generated a 3% probability of a posterior malleolar fracture.

Age: 34

Trauma Mechanism: Low Energy

Type Tibia Fracture: Spiral

Location Tibia Fracture: Distal Third

Type Fibula Fracture: Comminuted

Location Fibula Fracture: Proximal

The risk of an associated Posterior Malleolar Fracture is

74.0%

Figure 7. A 34-year old male with a spiral, distal third tibia shaft fracture and a comminuted, proximal third fibula fracture after a low-energy trauma. Pre-operatively there was no posterior malleolar fracture identified on lateral plain radiographs (A-C), but postoperative CT-scan imaging demonstrated a posterior malleolar fracture. (D). When the patient specific characteristics of this case were retrospectively fed into the prediction tool it generated an 74% probability of a posterior malleolar fracture (E).

DISCUSSION

The incidence of (occult) PMFs associated with TSFs is higher than previously reported [2,3]. Identifying specific patients at risk for such fractures preoperatively can aid in improving surgical outcome by “malleolus first” fixation [1], thus preventing iatrogenic and secondary displacement of the posterior malleolus [1,41–43]. The current study developed an accurate ML predictive model to calculate the patient specific probability of an (occult) PMF in patients with a TSF. This may aid surgeons in requesting additional pre-operative CT imaging to guide intra-operative ‘malleolus first’ fixation (Figures 6 and 7).

Strengths of this study include: 1) good performance measures of the best-fit ML algorithm (i.e. C-statistic 0.89, Calibration slope 1.02, Calibration intercept -0.06 and Brier score 0.106); 2) the heterogeneity of the dataset - which consisted of patients from two level-1 trauma centres from two continents – enhancing the generalizability of the prediction model; and 3) deployment of an online open-access tool. This study includes several limitations. Firstly, the prediction model currently lacks a form of external validation. Secondly, the dataset was relatively small for ‘Big Data’ ML standards [14,19,44], even though it is the largest series to date on PMFs. Thirdly, TSFs treated with frames were not included in the dataset used for model development, potentially introducing small bias in the prediction model as these types of injuries are not associated with PMFs. Lastly, tibia and fibula fracture classification may be subject to interobserver variability. This may affect the accuracy of the prediction model.

The performance of the ML algorithms in this study was similar or even superior (i.e. quantified by C-statistic, Brier score, calibration slope and intercept) as compared to logistic regression based prediction models developed on much larger datasets in other studies [45–47]. In the current study, the small series for ML standards resulted in an accurate prediction model in terms of C-statistic, Brier score, calibration slope and intercept. This is likely to be attributable to the strength of the predictors of PMFs [2,3]. Nevertheless, we want to emphasize the cautiousness with which the probabilities generated by our prediction model should be interpreted, because external validation is yet to be performed. Ideally, external validation is performed at an institution that not contributed to the development of the current model (i.e. fully independent validation) because this will indicate the generalizability of the model to both different surgeon- and patient populations [39]. Validation of the algorithm on an external dataset provides the additional advantage of using this data to further train the algorithm, increasing the model’s robustness.

Three different probability thresholds were identified. These thresholds can be used to guide clinical decision making regarding additional preoperative CT-scans.

The highest accuracy of the model is reached at a threshold of 36.7%, indicating that at this threshold the largest number of patients is correctly classified. If it is deemed important not to miss a fracture, a low threshold should be maintained. In the current cohort, a threshold of 13% would have identified 72 out of 75 PMFs, however, as a trade-off many CT-scans would have been requested. If resources are scarce, a high threshold can be used. At a threshold of 74.5%, only 41 additional CT-scans would have been requested, of which 32 patients would have had a PMF.

Within the field of Orthopaedic Oncology and Spine, various studies have recently been published in which ML prediction models have been developed [13–17]. The prediction tool developed in the current study encourages us that these tools can be developed in Orthopaedic Trauma as well. They can be applied to clinically relevant questions to develop useful algorithms to aid patients and surgeons in decision-making and thus moving towards ‘personalized care’ in Trauma. This proof of concept is designed as the first step towards prediction tools build for continuous prospective data collection with implemented feedback loops that allows users to feedback the actual outcome of their cases. The ML algorithms incorporated in the prediction tools will continuously learn from the data that is prospectively fed into the tool, further improving reliability and increasing external validity.

An important limitation to date: ML models still lack the capacity to look beyond the borders of their input variables – the “supervised learning” concept. In contrast, physicians are able to combine patients’ preferences and objective parameters into careful clinical decision-making. In our opinion, the aim should be to let physicians and AI models act in synergy; instead of taking over clinical work, these tools should support physicians in their main tasks. In this case, it supports surgeons in allocating resources effectively (i.e. additional CT-scans) only to those patients at a high risk of PMFs. This minimizes additional costs and unnecessary radiation exposure, whilst it may improve patient outcome [1].

In conclusion, in this study an accurate ML prediction model was developed that can predict (occult) PMFs in patients with TSFs, based on patient-, fracture- and trauma-characteristics. This prediction model may aid surgeons in requesting additional pre-operative CT imaging to guide intra-operative ‘malleolus first’ fixation in patients with a confirmed PMF. Despite good performance measures of the final prediction model, we believe it should be considered a proof of concept rather than an actual tool to be used in clinical practice at this stage as external validation is still lacking. Future studies should aim to validate this ML algorithm on larger (multicentre) datasets and aim to incorporate feedback loops in their prediction tool to instantly improve its performance.

REFERENCES

1. Kempegowda H, Maniar HH, Richard R, et al. Posterior Malleolar Fractures Associated With Tibial Shaft Fractures and Sequence of Fixation. *J Orthop Trauma*. 2016;30(10):568-571.
2. Sobol GL, Shaath MK, Reilly MC, Adams MR, Sirkin MS. The Incidence of Posterior Malleolar Involvement in Distal Spiral Tibia Fractures: Is it Higher than We Think? *J Orthop Trauma*. 2018;32(11):543-547.
3. Hendrickx LAM, Cain ME, Sierevelt IN, et al. Incidence, Predictors and Fracture Mapping of (Occult) Posterior Malleolar Fractures Associated with Tibial Shaft Fractures. *J Orthop Trauma*. Published online August 13, 2019. doi:10.1097/BOT.0000000000001605
4. Schottel PC, Berkes MB, Little MTM, et al. Predictive radiographic markers for concomitant ipsilateral ankle injuries in tibial shaft fractures. *J Orthop Trauma*. 2014;28(2):103-107.
5. Kukkonen J, Heikkilä JT, Kyyrönen T, Mattila K, Gullichsen E. Posterior malleolar fracture is often associated with spiral tibial diaphyseal fracture: a retrospective study. *J Trauma*. 2006;60(5):1058-1060.
6. Stuermer EK, Stuermer KM. Tibial shaft fracture and ankle joint injury. *J Orthop Trauma*. 2008;22(2):107-112.
7. van der Werken C, Zeegers EV. Fracture of the lower leg with involvement of the posterior malleolus; a neglected combination? *Injury*. 1988;19(4):241-243.
8. Ting DSW, Cheung CY-L, Lim G, et al. Development and Validation of a Deep Learning System for Diabetic Retinopathy and Related Eye Diseases Using Retinal Images From Multiethnic Populations With Diabetes. *JAMA*. 2017;318(22):2211-2223.
9. Gulshan V, Peng L, Coram M, et al. Development and Validation of a Deep Learning Algorithm for Detection of Diabetic Retinopathy in Retinal Fundus Photographs. *JAMA*. 2016;316(22):2402-2410.
10. Chilamkurthy S, Ghosh R, Tanamala S, et al. Deep learning algorithms for detection of critical findings in head CT scans: a retrospective study. *Lancet*. 2018;392(10162):2388-2396.
11. Ehteshami Bejnordi B, Veta M, Johannes van Diest P, et al. Diagnostic Assessment of Deep Learning Algorithms for Detection of Lymph Node Metastases in Women With Breast Cancer. *JAMA*. 2017;318(22):2199-2210.
12. Esteva A, Kuprel B, Novoa RA, et al. Dermatologist-level classification of skin cancer with deep neural networks. *Nature*. 2017;542(7639):115-118.
13. Thio QCBS, Karhade AV, Ogink PT, et al. Can Machine-learning Techniques Be Used for 5-year Survival Prediction of Patients With Chondrosarcoma? *Clin Orthop Relat Res*. 2018;476(10):2040-2048.
14. Karhade AV, Thio QCBS, Ogink PT, et al. Development of Machine Learning Algorithms for Prediction of 30-Day Mortality After Surgery for Spinal Metastasis. *Neurosurgery*. Published online November 23, 2018. doi:10.1093/neuros/nyy469
15. Karhade AV, Thio Q, Ogink P, et al. Development of Machine Learning Algorithms for Prediction of 5-Year Spinal Chordoma Survival. *World Neurosurg*. 2018;119:e842-e847.

16. Karhade AV, Ogink P, Thio Q, et al. Development of machine learning algorithms for prediction of discharge disposition after elective inpatient surgery for lumbar degenerative disc disorders. *Neurosurg Focus*. 2018;45(5):E6.

17. Karhade AV, Ogink PT, Thio QCBS, et al. Machine learning for prediction of sustained opioid prescription after anterior cervical discectomy and fusion. *Spine J*. Published online January 30, 2019. doi:10.1016/j.spinee.2019.01.009

18. Staartjes VE, de Wispelaere MP, Vandertop WP, Schröder ML. Deep learning-based preoperative predictive analytics for patient-reported outcomes following lumbar diskectomy: feasibility of center-specific modeling. *Spine J*. Published online November 16, 2018. doi:10.1016/j.spinee.2018.11.009

19. Harris AHS, Kuo AC, Weng Y, Trickey AW, Bowe T, Giori NJ. Can Machine Learning Methods Produce Accurate and Easy-to-use Prediction Models of 30-day Complications and Mortality After Knee or Hip Arthroplasty? *Clin Orthop Relat Res*. 2019;477(2):452-460.

20. Langerhuizen DWG, Janssen SJ, Mallee WH, et al. What Are the Applications and Limitations of Artificial Intelligence for Fracture Detection and Classification in Orthopaedic Trauma Imaging? A Systematic Review. *Clin Orthop Relat Res*. Published online June 21, 2019. doi:10.1097/CORR.0000000000000848

21. Ramkumar PN, Haeberle HS, Bloomfield MR, et al. Artificial Intelligence and Arthroplasty at a Single Institution: Real-World Applications of Machine Learning to Big Data, Value-Based Care, Mobile Health, and Remote Patient Monitoring. *J Arthroplasty*. Published online June 17, 2019. doi:10.1016/j.arth.2019.06.018

22. Luo W, Phung D, Tran T, et al. Guidelines for Developing and Reporting Machine Learning Predictive Models in Biomedical Research: A Multidisciplinary View. *J Med Internet Res*. 2016;18(12):e323.

23. Moons KGM, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med*. 2015;162(1):W1-W73.

24. Bleeker NJ, Cain M, Rego M, et al. Bilateral Low-Dose Computed Tomography Assessment for Post-Operative Rotational Malalignment After Intramedullary Nailing for Tibial Shaft Fractures: Reliability of a Practical Imaging Technique. *Injury*. Published online July 29, 2018. doi:10.1016/j.injury.2018.07.031

25. Kellam JF, Meinberg EG, Agel J, Karam MD, Roberts CS. Introduction: Fracture and Dislocation Classification Compendium-2018: International Comprehensive Classification of Fractures and Dislocations Committee. *J Orthop Trauma*. 2018;32 Suppl 1:S1-S10.

26. ATLS Subcommittee, American College of Surgeons' Committee on Trauma, International ATLS working group. Advanced trauma life support (ATLS®): the ninth edition. *J Trauma Acute Care Surg*. 2013;74(5):1363-1366.

27. Steyerberg EW. Validation in prediction research: the waste by data splitting. *J Clin Epidemiol*. 2018;103:131-133.

28. Maroco J, Silva D, Rodrigues A, Guerreiro M, Santana I, de Mendonça A. Data mining methods in the prediction of Dementia: A real-data comparison of the accuracy, sensitivity and specificity of linear discriminant analysis, logistic regression, neural networks, support vector machines, classification trees and random forests. *BMC Res Notes*. 2011;4:299.

29. Wainer J. Comparison of 14 different families of classification algorithms on 115 binary datasets. *arXiv [csLG]*. Published online June 2, 2016. http://arxiv.org/abs/1606.00930

30. Fernández-Delgado M, Cernadas E, Barro S. Do we need hundreds of classifiers to solve real world classification problems? *The Journal of Machine*. Published online 2014. http://www.jmlr.org/papers/volume15/delgado14a/delgado14a.pdf

31. Noble WS. What is a support vector machine? *Nat Biotechnol*. 2006;24(12):1565-1567.

32. Kingsford C, Salzberg SL. What are decision trees? *Nat Biotechnol*. 2008;26(9):1011-1013.

33. Cross SS, Harrison RF, Kennedy RL. Introduction to neural networks. *Lancet*. 1995;346(8982):1075-1079.

34. Qi Y, Reynolds C, Picard RW. The Bayes Point Machine for Computer-user Frustration Detection via Pressuremouse. In: *Proceedings of the 2001 Workshop on Perceptive User Interfaces*. PUI '01. ACM; 2001:1-5.

35. Fontama V, Barga R, Tok WH. *Predictive Analytics with Microsoft Azure Machine Learning 2nd Edition*. Apress; 2015.

36. Herbrich R, Graepel T, Campbell C. Bayes Point Machines. *J Mach Learn Res*. 2001;1(Aug):245-279.

37. Ben-Assuli O, Padman R. Analysing repeated hospital readmissions using data mining techniques. *Health Syst (Basingstoke)*. 2018;7(3):166-180.

38. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. *Eur Heart J*. 2014;35(29):1925-1931.

39. Steyerberg EW. *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating*. Springer Science & Business Media; 2008.

40. Vergouwe Y, Steyerberg EW, Eijkemans MJC, Habbema JDF. Validity of prognostic models: when is a model clinically useful? *Semin Urol Oncol*. 2002;20(2):96-107.

41. Boraiah S, Gardner MJ, Helfet DL, Lorich DG. High association of posterior malleolus fractures with spiral distal tibial fractures. *Clin Orthop Relat Res*. 2008;466(7):1692-1698.

42. Georgiadis GM, Ebraheim NA, Hoeflinger MJ. Displacement of the posterior malleolus during intramedullary tibial nailing. *J Trauma*. 1996;41(6):1056-1058.

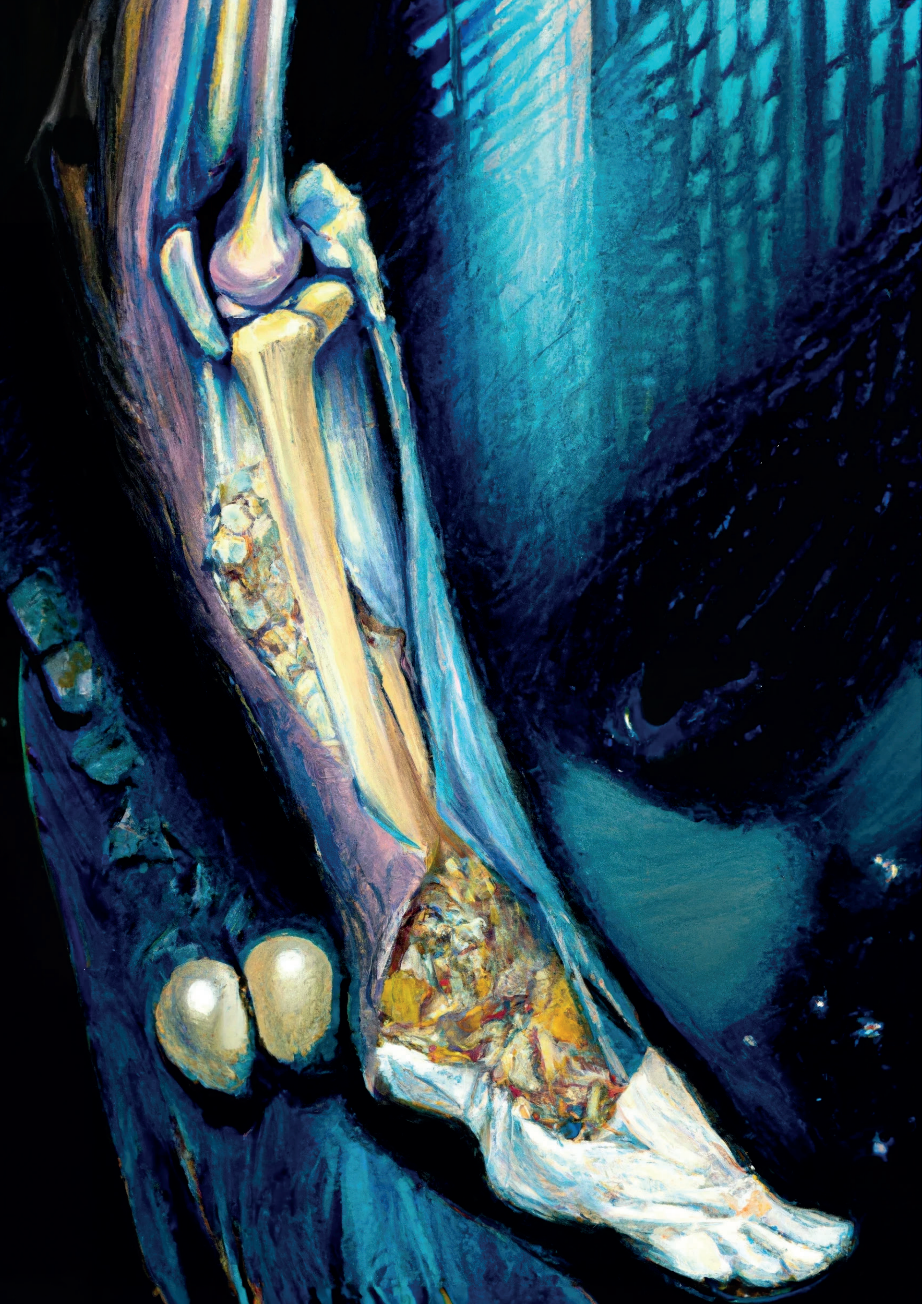
43. Zhang Y, Qin X, Song L, Li X. The risk of violating the posterior malleolar fracture when nailing the ipsilateral concomitant spiral distal tibial fracture. *BMC Musculoskelet Disord*. 2018;19(1):123.

44. Huber M, Kurz C, Leidl R. Predicting patient-reported outcomes following hip and knee replacement surgery using supervised machine learning. *BMC Med Inform Decis Mak*. 2019;19(1):3.

45. Jaja BNR, Saposnik G, Lingsma HF, et al. Development and validation of outcome prediction models for aneurysmal subarachnoid haemorrhage: the SAHIT multinational cohort study. *BMJ*. 2018;360:j5745.

46. Tammemägi MC, Katki HA, Hocking WG, et al. Selection criteria for lung-cancer screening. *N Engl J Med*. 2013;368(8):728-736.

47. Ratliff JK, Balise R, Veeravagu A, et al. Predicting Occurrence of Spine Surgery Complications Using "Big Data" Modeling of an Administrative Claims Database. *J Bone Joint Surg Am*. 2016;98(10):824-834.



7

CHAPTER 7

A Machine Learning Algorithm to Identify Patients with Tibial Shaft Fractures at Risk for Infection After Operative Treatment

Machine Learning Consortium, on behalf of the SPRINT and FLOW Investigators

Machine Learning Consortium

Laurent A M Hendrickx, Mohit Bhandari, Anne Eva J Bulstra, Sofia Bzovsky, Job N Doornberg, J Carel Goslings, Ruurd L Jaarsma, Kyle J Jeray, Gino M M J Kerkhoffs, Brad Petrisor, David Ring, Emil H Schemitsch, Marc Swiontkowski, David Sanders, Sheila Sprague, Paul Tornetta III, Stephen D Walter

JOURNAL OF BONE & JOINT SURGERY – MARCH 2021

This is a non-final version of an article published in final form in:

Wolters Kluwer - J Bone Joint Surg Am. Mar 2021;103(6):532-540. https://journals.lww.com/jbjsjournal/Abstract/2021/03170/A_Machine_Learning_Algorithm_to_Identify_Patients.11.aspx

ABSTRACT

Background

Risk stratification of individual patients prone to infection would allow surgeons to monitor high-risk patients more closely and intervene early when needed. This may reduce infection related consequences such as increased healthcare costs.

The purpose of this study was to develop a machine learning (ML) derived risk stratification tool using the SPRINT-Trial and FLOW-Trial databases to estimate the probability of infection in patients with operatively treated tibial shaft fractures (TSFs).

Methods

Patients with unilateral TSFs from the SPRINT-trial and FLOW-trial were randomly split into a derivation- (80%) and validation cohort (20%).

Random forests algorithms were used to select features relevant to predicting infection. These features were included for algorithm training.

Five ML-algorithms were trained in recognizing patterns associated with infection. Performance of each ML-algorithm was evaluated and compared based on 1) area under the ROC-curve (AUC); 2) Calibration slope and intercept; and 3) Brier-score.

Results

1822 patients were included, of which 170 patients (9%) developed an infection that required treatment: 62 patients (3%) received nonoperative treatment with oral or intravenous antibiotics and 108 patients (6%) underwent subsequent surgery in addition to antibiotics.

Random forests algorithms identified seven variables relevant for predicting infection: 1) Gustilo-Anderson classification or Tscherne classification; 2) bone loss; 3) mechanism of injury; 4) multi-trauma; 5) AO/OTA-fracture classification; 6) age; and 7) fracture location.

Training of the penalized logistic regression algorithm resulted in the best-performing prediction model with an AUC, calibration slope, calibration intercept and Brier score of 0.75, 0.94, 0.00 and 0.077 in the derivation cohort and 0.81, 1.07, 0.23 and 0.079 in the validation cohort respectively.

Conclusion

A ML prediction model was developed that can estimate the probability of infection for individual patients with TSFs based on patient- and fracture characteristics that are readily available at hospital admission.

Level of Evidence

Level III - Prognostic Study

INTRODUCTION

Infection after operative treatment of tibial shaft fractures (TSF) is reported in 3-9% of the patients [1–6]. Next to a higher risk of limb salvage procedures or amputation, these infections also result in significant reduction in health-related quality of life, prolonged hospital stay, higher rehospitalization rate and increased (healthcare) costs [7].

It is well known that the probability of infection rises with the complexity of the injury: Gustilo-Anderson Type IIIA, Type IIIB and Type IIIC fractures are recognised predictors of infection [1,2,8,9]. Complex fracture patterns (AO/OTA Type 42C) have also been associated with an increased risk of infection [2]. Other potential risk factors of infection include diabetes[5], smoking [10], time to first dose of antibiotics [11], increased time to surgery [1], timing of wound closure [12] and compartment syndrome [13]. These are well known general risk factors, derived from large cohorts of patients. However, it remains challenging for surgeons to translate these to one's specific patient to estimate individual risk. A more accurate estimate of the individual patient's-specific risk of infection (i.e. risk stratification) in patients with TSFs would allow surgeons to monitor high-risk patients more closely, intervene early when needed, or institute preventive measures.

Currently, there are no prediction models available to calculate patient specific probability of infection in patients with TSFs in order to stratify between high-risk and low-risk patients. Machine Learning (ML) derived algorithms may be a valuable adjunct in such models because they are able to identify non-linear relationships [14]. This may be one of the reasons why in orthopaedic surgery the development of these ML prediction models is getting more widespread [15–23]. Another, theoretical, advantage is the ability to improve accuracy of the model over time with an active feedback loop to allow for more accurate diagnosis and identification of new observations or patterns. Prior to clinical implementation of such a prediction model: 1) subsequent studies are required for external validation; 2) subsequently, the model should be studied prospectively for diagnostic accuracy (i.e. "silent testing" in clinical practice); and 3) finally the model should be analysed for clinical efficacy in a randomized controlled trial (RCT).

The purpose of this current study was to develop the initial ML prediction model using the SPRINT-Trial database [3] and FLOW-Trial database [24] to estimate the probability of infection in individual patients with operatively treated TSFs.

MATERIALS & METHODS

Guidelines

This study was conducted according to the Guidelines for Developing and Reporting Machine Learning Predictive Models in Biomedical Research [25] and the Transparent Reporting of Multivariable Prediction Models for Individual Prognosis or Diagnosis (TRIPOD) guideline [26].

Data safety

For safe multicentre data exchange and analysis, our Machine Learning Consortium adhered to World Healthcare Organisation (WHO) regulations: "Policy on use and sharing of data collected in Member States by the World Health Organization (WHO) outside the context of public health emergencies" [27].

Data Source & Patient Selection

The SPRINT-Trial, is an international multicentre randomized controlled trial, compared reamed intramedullary nailing (IMN) of TSFs versus unreamed IMN in patients with TSFs [3]. All patients with unilateral TSFs treated with IMN from this database were included in the dataset for the current study.

The FLOW-Trial is an international multicentre randomized controlled initiated to compare irrigations pressures as well as irrigations solutions in the treatment of open fractures [24]. All patients from this study with fractures of the tibial shaft were included in the dataset for the current study.

Treatment protocols of both studies included pre-operative administration of antibiotics. In eleven patients' antibiotics were not administered pre-operatively and in one patient it was not registered. None of these twelve patients eventually required treatment for infection.

Outcome of interest

The outcome of interest for the ML algorithm to predict was the probability of postoperative infection requiring operative or non-operative treatment in patients with TSFs.

Candidate Input Variables

Variables that could be used for model development had to be present in both the SPRINT [3] and FLOW [24] databases. Of the variables that were available, variables considered potentially important for predicting infections are displayed in Table 1.

In the SPRINT-trial the location of fracture was recorded in five categories: proximal, proximal-middle, middle, distal-middle, distal. In the current study fractures were classified as proximal, middle or distal. Proximal-middle fractures were classified as proximal fractures and distal-middle fractures as distal fractures [28]. In the SPRINT-trial, the degree of soft-tissue injury in open fractures was classified according to the Gustilo-Anderson Classification, and in closed fractures according to the Tscherne Classification. In the current study these variables were combined into one variable consisting of eight outcomes (Tscherne Type 0-3 and Gustilo-Anderson Type I-IIIB) ranging from Tscherne type 0 to Gustilo-Anderson Type IIIB. Multi-trauma was defined as any concomitant fracture or concomitant liver, bowel, splenic, lung, intracranial or axonal injury. In both the SPRINT and FLOW trial, the diagnosis of bone-loss was defined per the discretion of the treating surgeon.

TABLE 1. Candidate Input Variables

Variable	Details
Age	Years
Gender	Male/Female
Diabetes	Yes/No
Mechanism of injury	Crush injury; Direct trauma (blunt); Direct trauma (penetrating); Fall; Twisting injury; Motor vehicle (driver/passenger); Motor vehicle (pedestrian); Motorcycle accident
Multi-trauma	Yes/No
Smoking status	Non-smoker; Previous smoker; Current smoker
Use of NSAID’s	Yes/No
Gustilo-Anderson classification or Tscherne Classification	Gustilo-Anderson Type I; -Type II; -Type IIIA; -Type IIIB; Tscherne Classification Type 0; -Type 1; -Type 2; -Type 3
Location	Proximal; Middle; Distal
AO-classification	42A1; 42A2; 42A3; 42B1; 42B2; 42B3; 42C1; 42C2; 42C3
Bone loss	Yes/No
Level of surgeon	Surgeon; Resident; Fellow
Compartment syndrome	Yes/No

Missing data

0.4% of data was missing. For two variables more than 0.5% of the data was missing: multi-trauma (4.3%) and fracture location (0.55%). Missing data were imputed using the *MissForest* algorithm [29].

Model development.

The total dataset was randomly split into a derivation- (80%) and validation cohort (20%), stratified on the outcome of interest: infection.

Feature selection using Random forests algorithms was used to identify variables for algorithm training from the derivation cohort [30].

Because it is uncertain which ML algorithm allows for the development of the best prediction model, we trained and tested various ML algorithms. Based on previous studies [19,31–34] the following algorithms were chosen: 1) Bayes point machine; 2) boosted decision tree; 3) penalized logistic regression; 4) neural network; and 5) support vector machine.

For each ML algorithm, ten-fold cross validation was repeated three times on the derivation cohort to train the algorithms in recognizing patterns related to infection, and to subsequently assess their predictive performance.

For the assessment of the predictive performance of the algorithms, the following performance measures were used: 1) discrimination; 2) calibration; and 3) overall model performance [35]. The discriminative ability of a model can be assessed by calculating the area under the ROC-curve (AUC). The AUC can range from 0.5 to 1. An AUC of one indicates that the model has perfect discriminative ability. An AUC of 0.5 indicates that the model is non-informative [36]. The calibration of the model can be assessed by plotting a calibration curve. The slope of this curve should ideally be 1 whereas the intercept of this curve should ideally be 0 [35]. Finally, we also calculated the Brier score which is an indication of the overall model performance. The Brier score is obtained by calculating the squared differences between actual outcomes and predictions. The score can range from 0 to 0.25. A lower Brier score indicates a better model. The upper limit of the score is dependent on the incidence of the outcome in the dataset (e.g. infection). Therefore, the upper limit of the Brier score was also calculated and presented [36].

The ML algorithms that showed good performance across all four performance measures during cross-validation were further evaluated on the validation cohort. First the algorithms predicted the probability of infection for each case in the validation cohort. Subsequently, performance measures (e.g. AUC) could be calculated. The best-performing prediction model on the derivation- and validation cohort was incorporated into an online prediction tool.

The following software was used: Excel Microsoft Office 2019 (Microsoft Corporation, Redmond, WA, USA), R-Studio Version 1.1.463 (R-studio, Boston, MA, USA), R version 3.5.2 (The R Foundation, Vienna, Austria), SPSS 25 (IBM SPSS Statistics, Armonk, NY, USA), Microsoft Azure (Microsoft Corporation, Redmond, WA, USA).

RESULTS

Patients

The total dataset included 1822 patients with unilateral TSFs that were treated operatively. Median age of the patients was 38 years (14-92), 75% was male. Forty-five percent (45%) of the patients had a closed fracture. Other patient and fracture characteristics are displayed in Table 2.

A total of 170 patients (9%) developed an infection that required treatment: 62 patients (3%) were treated nonoperatively with intravenous antibiotics and 108 patients (6%) were treated operatively.

TABLE 2. Patient Demographics & Fracture Characteristics

	N = 1198
Patient Characteristics	
Age, median (range)	38 (14-92)
Gender, n (%)	
Male	1372 (75%)
Female	450 (25%)
Multi-trauma, n (%)	
Yes	786 (43%)
No	1036 (57%)
Mechanism of injury, n (%)	
Crush injury	103 (6%)
Direct trauma (blunt)	131 (7%)
Direct trauma (penetrating)	31 (2%)
Fall	426 (23%)
Twisting injury	67 (4%)
Motor vehicle (driver/passenger)	391 (21%)
Motor vehicle (pedestrian)	364 (20%)
Motorcycle accident	309 (17%)
Fracture Characteristics	
Fracture type	
Closed	815 (45%)
Open	1007 (55%)
Location Tibia Fracture, n (%)	
Proximal 1/3rd	172 (9%)

Middle 1/3rd	667 (37%)
Distal 1/3rd	983 (54%)
Gustilo-Anderson classification and Tscherne classification, n (%)	
Tscherne Type 0	245 (13%)
Tscherne Type 1	428 (23%)
Tscherne Type 2	128 (7%)
Tscherne Type 3	14 (1%)
Gustilo-Anderson Type I	214 (12%)
Gustilo-Anderson Type II	381 (21%)
Gustilo-Anderson Type IIIA	286 (16)
Gustilo-Anderson Type IIIB	126 (7%)

Feature selection

Feature selection in the derivation cohort using Random Forest algorithms identified seven variables relevant for algorithm development. In order of importance these variables were 1) Gustilo-Anderson classification or Tscherne classification; 2) bone loss; 3) mechanism of injury; 4) multi-trauma; 5) AO/OTA-classification; 6) age; and 7) location (Figure 1).

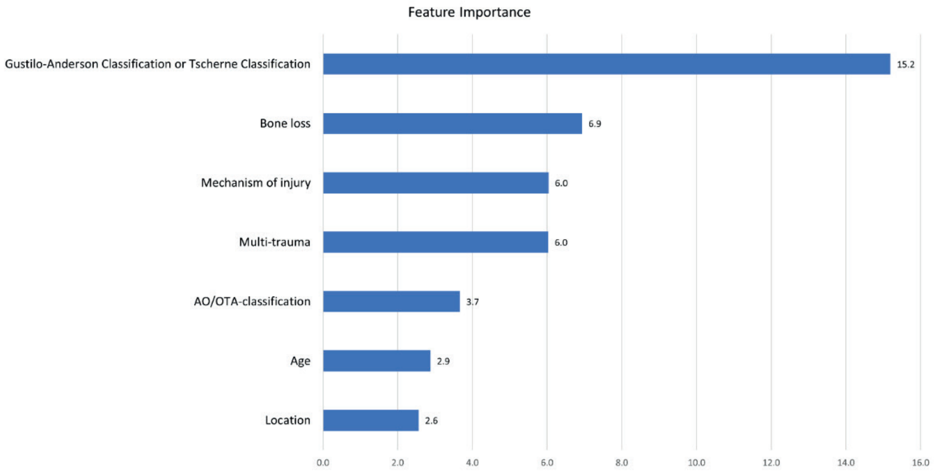


Figure 1. Variable importance based on feature selection using random forests.

Performance machine learning prediction models in the derivation cohort

Discriminative performance of the five algorithms as quantified by the AUC ranged from 0.67 to 0.75 (Table 3) (Figure 2). Calibration slopes ranged from 0.69 to 0.94.

Calibration intercepts ranged from –0.14 to 0.00 (Figure 3). Brier Score ranged from 0.076 to 0.080. The upper limit of the Brier score was 0.085, based on an incidence of infection of 9.3%.

Based on the numeric assessment of the four performance measures as well as on the graphical assessment of calibration curves the penalized logistic regression-, Bayes point machine- and boosted decision tree derived models were outperforming the neural network and support vector machine. The predictive performance of these three ML prediction models was further evaluated on the validation cohort.

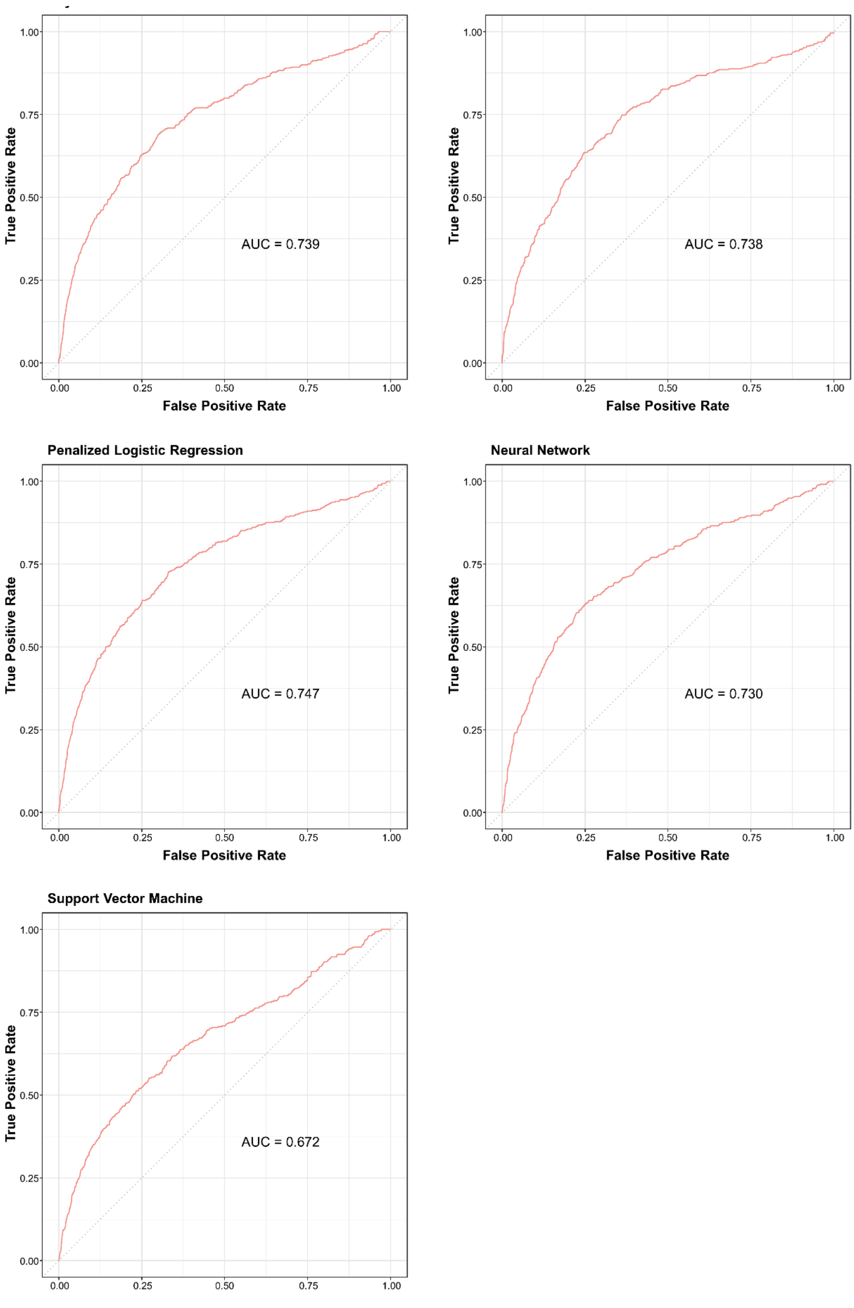


Figure 2. The receiver operating characteristic (ROC) curve and area under the curve (AUC) for each machine learning prediction model in the derivation-cohort.

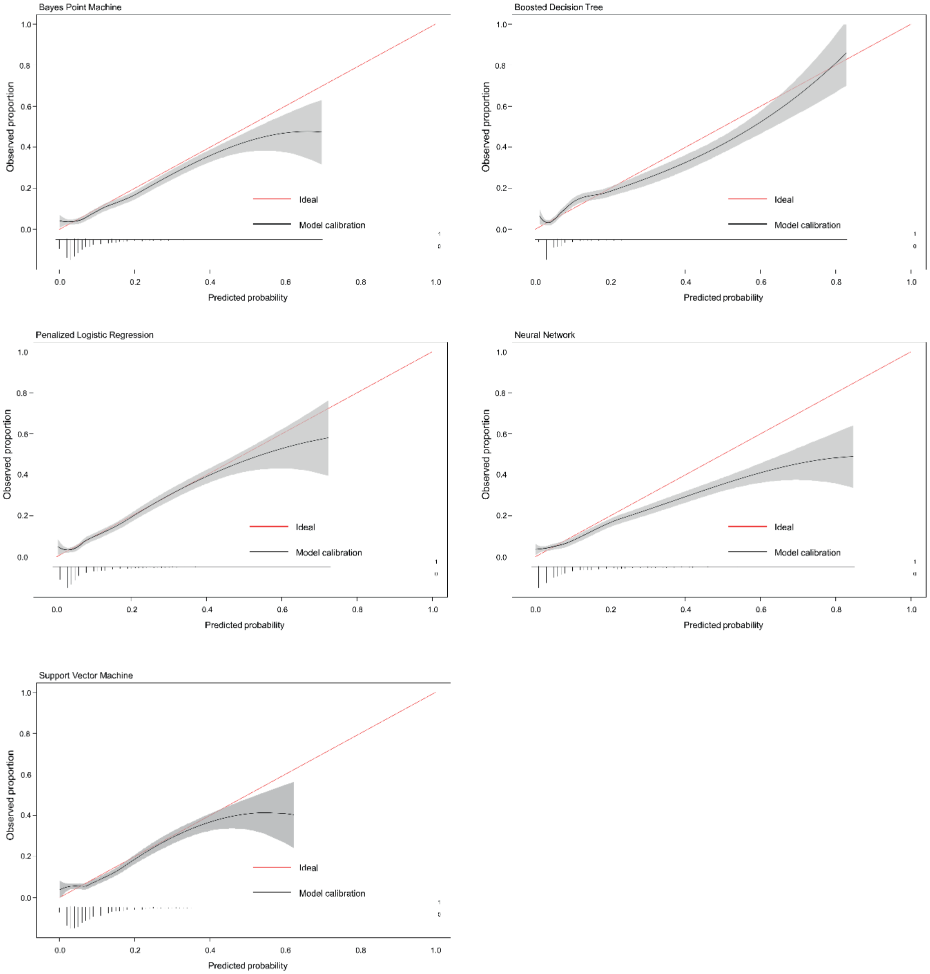


Figure 3. The calibration curves for each machine learning prediction model in the derivation-cohort. The grey area around the calibration curves represents the 95% confidence interval.

TABLE 3. Performance of Machine Learning Algorithms in predicting subsequent surgery in derivation cohort (n=1458) after 10-fold cross validation repeated three times.

	AUC	Calibration Slope	Calibration Intercept	Brier Score*
Bayes Point Machine	0.74 (0.71 – 0.77)	0.84 (0.74 – 0.94)	-0.06 (-0.17 – 0.05)	0.077
Boosted Decision Tree	0.74 (0.71 – 0.76)	0.83 (0.74 – 0.93)	-0.00 (-0.11 – 0.10)	0.077
Penalized Logistic Regression	0.75 (0.72 – 0.77)	0.94 (0.83 – 1.04)	0.00 (-0.10 – 0.11)	0.076
Neural Network	0.73 (0.70 -0.76)	0.69 (0.60 -0.78)	-0.14 (-0.26 - -0.03)	0.079
Support Vector Machine	0.67 (0.64 – 0.70)	0.76 (-0.64 – 0.70)	-0.00 (-0.11 – 0.10)	0.080

**Upper Limit Brier Score = 0.085*
( ) 95% Confidence Interval

Performance of best performing machine learning models on validation cohort

Discriminative performance of the three algorithms in the validation cohort as quantified by the AUC ranged from 0.80 to 0.82 (Table 4) (Figure 4). Calibration slopes ranged from 0.83 to 1.07. Calibration intercepts ranged from 0.04 to 0.11 (Figure 5). Brier Score ranged from 0.078 to 0.083, relative to the upper limit of 0.085. The Bayes point machine and penalized logistic regression showed similar performance, outperforming the boosted decision tree.

TABLE 4. Performance of Machine Learning Algorithms in predicting subsequent surgery in validation cohort (n=364)

	AUC	Calibration Slope	Calibration Intercept	Brier Score*
Bayes Point Machine	0.82	1.04	0.04	0.078
Boosted Decision Tree	0.80	0.83	0.11	0.083
Penalized Logistic Regression	0.81	1.07	0.09	0.079

**Upper Limit Brier Score = 0.085*

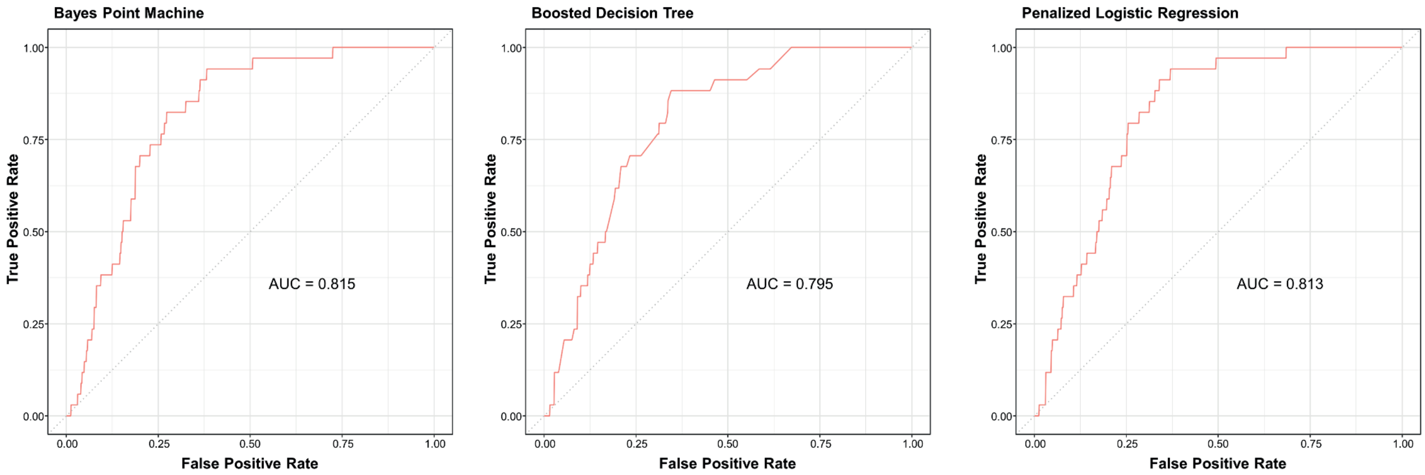


Figure 4. The receiver operating characteristic (ROC) curve and area under the curve (AUC) for Bayes point machine, boosted decision tree and penalized logistic regression in the validation-cohort.

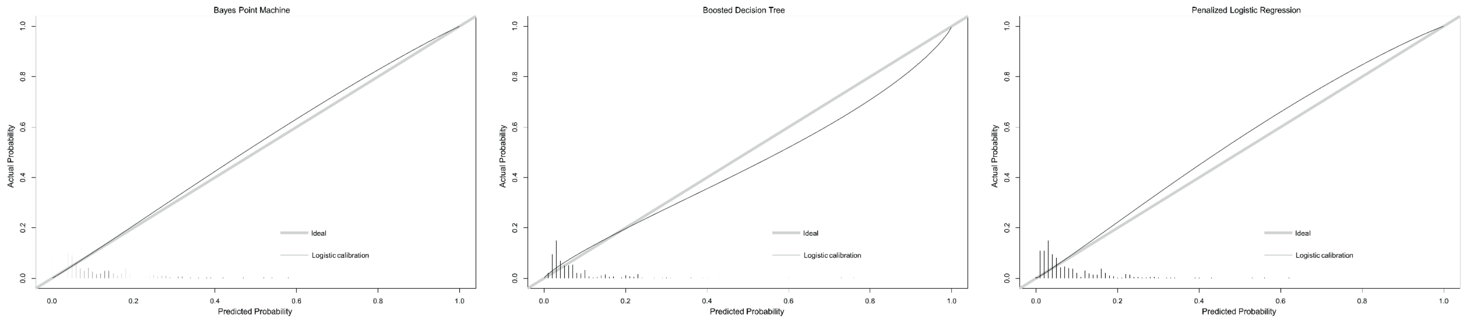


Figure 5. The calibration curves for the Bayes point machine, boosted decision tree and penalized logistic regression in the validation-cohort.

Final model

Based on better calibration in the derivation cohort (slope 0.94 vs. 0.84, intercept 0.00 vs. -0.06) and furthermore similar performance, the penalized logistic regression derived prediction model was deemed superior over the Bayes point machine and was therefore chosen as the final model. Gustilo-Anderson Type IIIA and Type IIIB, age, AO/OTA Type 42C3, crush injury and fall were the strongest predictors of infection in this model (Figure 6).

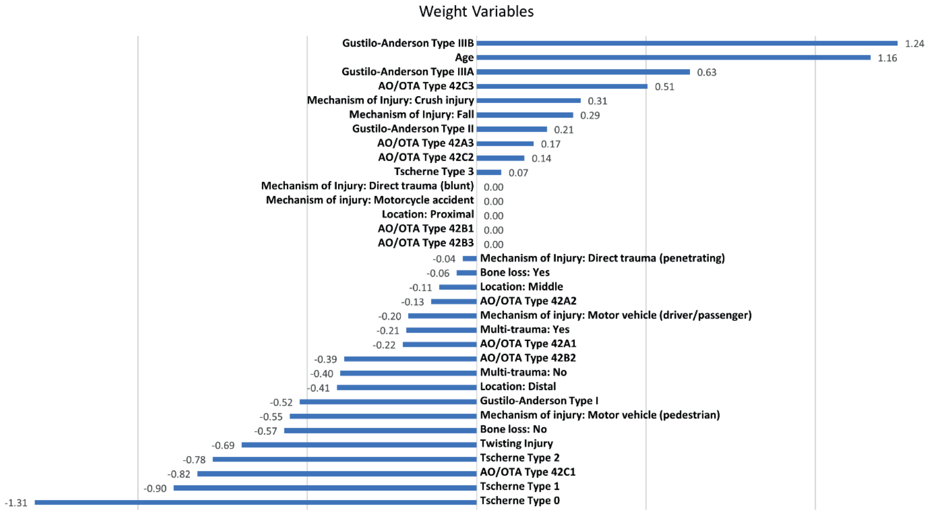
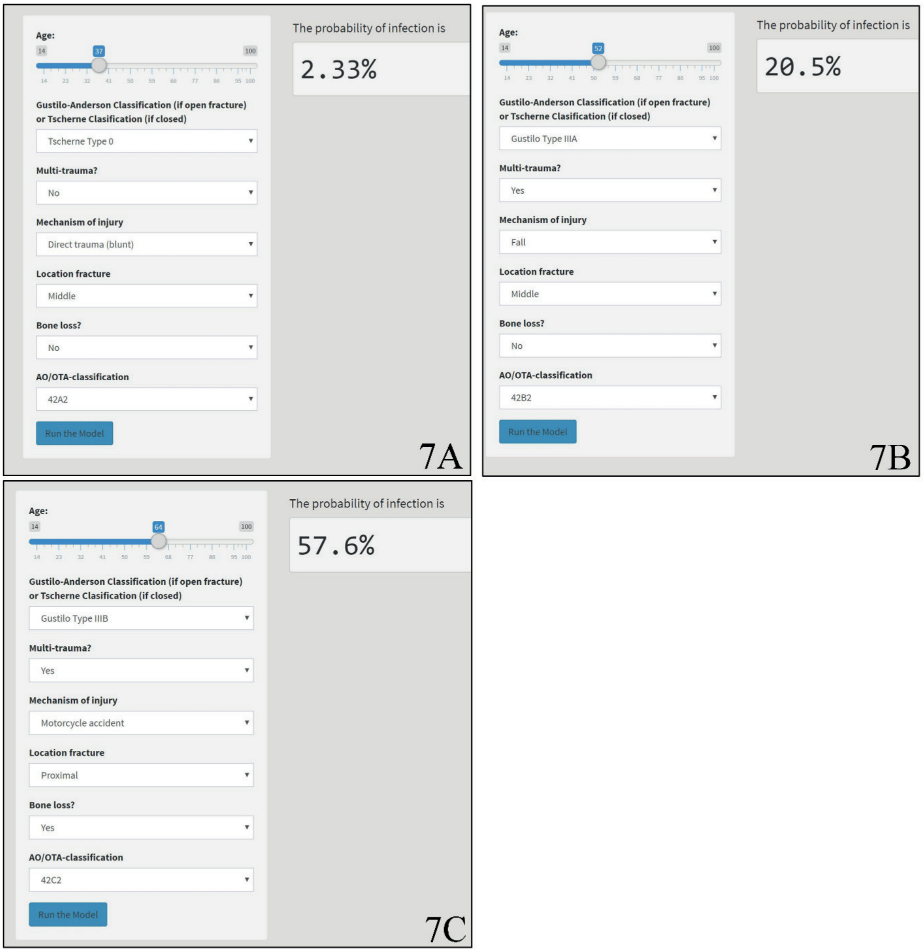


Figure 6. Importance of the variables in the final model based on the penalized logistic regression algorithm.

Online Prediction Tool

The final model was incorporated in an online open-access multi-platform prediction tool, allowing users to calculate the probability after operative treatment in patients with TSFs: *https://traumaplatform-ai-prediction-tools.shinyapps.io/tibia-shaft-infection*

Figure 7 displays the results the prediction tool generated for several case scenarios.



Age: 37

Gustilo-Anderson Classification (if open fracture) or Tscherne Clasification (if closed): Tscherne Type 0

Multi-trauma?: No

Mechanism of injury: Direct trauma (blunt)

Location fracture: Middle

Bone loss?: No

AO/OTA-classification: 42A2

The probability of infection is 2.33%

Age: 52

Gustilo-Anderson Classification (if open fracture) or Tscherne Clasification (if closed): Gustilo Type IIIA

Multi-trauma?: Yes

Mechanism of injury: Fall

Location fracture: Middle

Bone loss?: No

AO/OTA-classification: 42B2

The probability of infection is 20.5%

Age: 64

Gustilo-Anderson Classification (if open fracture) or Tscherne Clasification (if closed): Gustilo Type IIIB

Multi-trauma?: Yes

Mechanism of injury: Motorcycle accident

Location fracture: Proximal

Bone loss?: Yes

AO/OTA-classification: 42C2

The probability of infection is 57.6%

Figure 7. Probabilities generated by the prediction tool for three fictitious case scenarios. **7A.** For a 37-year old patient who sustained a blunt trauma resulting in a closed, Tscherne type 0, oblique, middle third tibia shaft fracture without bone-loss, the prediction tool generated a 2.3% probability of infection.**7B.** For a 52-year old multi-trauma patient with a complex (AO/OTA type 42B2), open (Gustilo-Anderson type IIIA), middle third tibia shaft fracture after a fall, without bone-loss, the prediction tool generates a 20.5% probability of infection. **7C.** For a 64-year old multi-trauma patient with a complex (AO/OTA type 42C), open (Gustilo-Anderson type IIIB), proximal third tibia shaft fracture after a motorcycle accident with bone loss, the prediction tool generates a 57.6% probability.

DISCUSSION

Infection is a common complication after operative treatment of TSFs affecting 3-9% of the patients [1–6]. This study developed a ML predictive model to identify individual patients at risk of infection after operative treatment of TSFs. The model is based on patient- and fracture characteristics that are available at hospital admission allowing clinicians to identify high-risk patients at a preoperative stage. Risk stratification of individual patients allows for close monitoring or early intervention with application of local antibiotics in those with open fractures at a high risk of infection. This may aid in averting infection or reduce infection related consequences including prolonged hospital stays, higher rehospitalization rates, costs associated with infection and reduced quality of life [7]. Before implementation, this model should be externally validated in subsequent (prospective) studies to evaluate diagnostic accuracy and clinical efficacy.

This study includes several strengths: 1) good performance of the best-fit ML algorithm with an AUC of 0.75 and 0.81 in the derivation and validation cohort, indicating acceptable and excellent discrimination respectively [37]; 2) large number of patients with a TSF included in the data-set; 3) high-quality of data, which was collected in an international prospective, randomized controlled setting and consisted of less than 0.5% missing data; and 4) heterogeneity of the data, which originated from 62 different hospitals across six countries and four continents, enhancing the external validity of the current prediction model.

Limitations to this study include the current lack of external validation. Furthermore, there is a potential risk of selection and indication bias, given the fact that the randomized controlled trials (i.e. SPRINT-trial and FLOW-trial) the data was derived from, were not designed to develop a prediction model for postoperative infection as for example operative debridement strategies were not protocolled. This also limited the variables available for model development. However, may on the other hand increase external validity as it represents daily practice in terms of respective surgical debridement techniques. Future external validity studies are needed. Other factors potentially related to infection, such as wound contamination [10], ASA status [38] and heart failure [5] were not included in the SPRINT-trial and FLOW-trial, and therefore not included in this study either, but may have improved the performance of the final prediction model. Also, the low prevalence of certain subsets of variables, such as Tscherne Grade III, may limit the capacity of the machine learning models to assess the true influence of these characteristics. Lastly, the dataset consisted of more open fractures, as this was the main inclusion criterium of the FLOW trial, than closed fractures, which may not be an accurate representation of the common distribution of open and closed fractures in patients with tibial fractures. It is unclear whether this affects the performance of the prediction model as external validity studies have yet to be performed.

It is well known that Gustilo-Anderson classification is highly predictive of infection [1,2,8,9]. In the current study this variable, together with Tscherne classification, formed the most important predictor of infection. We furthermore identified bone loss, mechanism of injury, multi-trauma, AO/OTA-classification, age and location as important variables. Diabetes [5,10], smoking-status [10] compartment syndrome [13] and male gender [10] have previously been identified as risk factors for infection in fracture surgery, however, were not identified to improve the performance characteristics of the model in the current cohort.

The penalized logistic regression derived prediction model was chosen as the final model. Based on better calibration in the derivation cohort (slope 0.938, intercept 0.004) this model was deemed superior over the other ML prediction models. The model yielded an AUC of 0.747 and 0.813 in the derivation and validation cohort respectively. This is similar to the model that Bachoura and colleagues previously developed to predict surgical site infection in orthopaedic trauma in general [5], consisting of an AUC of 0.81. A possible explanation as to why the AUC in the validation cohort was superior to that of the derivation cohort in the current study, may be that by chance the validation cohort may have consisted of more cases that were easy to predict.

The application of local antibiotics has been subject of debate in recent years [39–44]. Whilst prophylactic use of local antibiotics in patients with open fractures has been demonstrated to reduce infection rates [39], concerns about antimicrobial resistance remain [39–41]. Stratifying between high-risk and low-risk patients in order to determine what patients require prophylactic local antibiotics may prove to be a solution to these concerns. Therefore, subject of future studies should be to assess whether the prediction model can be effectively used to decrease infection rates whilst minimizing the number needed to treat.

In conclusion, we developed a ML prediction model that uses patient and fracture characteristics that are available at hospital admission to identify patients at risk of infection after operative treatment of TSFs. This model will allow future research into best practices surrounding intraoperative and postoperative management of patients with tibial shaft fractures based upon varied levels of predicted risk of infection.

REFERENCES

1. Metsemakers W-J, Handojo K, Reynders P, Sermon A, Vanderschot P, Nijs S. Individual risk factors for deep infection and compromised fracture healing after intramedullary nailing of tibial shaft fractures: a single centre experience of 480 patients. Injury. 2015;46(4):740-745.
2. Gaebler C, Berger U, Schandelmaier P, et al. Rates and odds ratios for complications in closed and open tibial fractures treated with unreamed, small diameter tibial nails: a multicenter analysis of 467 cases. J Orthop Trauma. 2001;15(6):415-423.
3. Study to Prospectively Evaluate Reamed Intramedullary Nails in Patients with Tibial Fractures Investigators, Bhandari M, Guyatt G, et al. Randomized trial of reamed and unreamed intramedullary nailing of tibial shaft fractures. J Bone Joint Surg Am. 2008;90(12):2567-2578.
4. Stavrou PZ, Ciriello V, Theocharakis S, et al. Prevalence and risk factors for re-interventions following reamed intramedullary tibia nailing. Injury. 2016;47 Suppl 7:S49-S52.
5. Bachoura A, Guitton TG, Smith RM, Vrahas MS, Zurakowski D, Ring D. Infirmity and injury complexity are risk factors for surgical-site infection after operative fracture care. Clin Orthop Relat Res. 2011;469(9):2621-2630.
6. Hendrickx LAM, Virgin J, van den Bekerom MPJ, Doornberg JN, Kerkhoffs GMMJ, Jaarsma RL. Complications and subsequent surgery after intra-medullary nailing for tibial shaft fractures: Review of 8110 patients. Injury. Published online April 22, 2020. doi:10.1016/j.injury.2020.04.021
7. Whitehouse JD, Friedman ND, Kirkland KB, Richardson WJ, Sexton DJ. The impact of surgical-site infections following orthopedic surgery at a community hospital and a university hospital: adverse quality of life, excess length of stay, and extra cost. Infect Control Hosp Epidemiol. 2002;23(4):183-189.
8. Whiting PS, Galat DD, Zirkle LG, Shaw MK, Galat JD. Risk Factors for Infection After Intramedullary Nailing of Open Tibial Shaft Fractures in Low- and Middle-Income Countries. J Orthop Trauma. 2019;33(6):e234-e239.
9. Thakore RV, Francois EL, Nwosu SK, et al. The Gustilo-Anderson classification system as predictor of nonunion and infection in open tibia fractures. Eur J Trauma Emerg Surg. 2017;43(5):651-656.
10. Kortram K, Bezstarosti H, Metsemakers W-J, Raschke MJ, Van Lieshout EMM, Verhofstad MHJ. Risk factors for infectious complications after open fractures; a systematic review and meta-analysis. Int Orthop. 2017;41(10):1965-1982.
11. Roddy E, Patterson JT, Kandemir U. Delay of Antibiotic Administration Greater than 2 Hours Predicts Surgical Site Infection in Open Fractures. Injury. 2020;51(9):1999-2003.
12. Lenarz CJ, Watson JT, Moed BR, Israel H, Mullen JD, Macdonald JB. Timing of wound closure in open fractures based on cultures obtained after debridement. J Bone Joint Surg Am. 2010;92(10):1921-1926.
13. Blair JA, Stoops TK, Doarn MC, et al. Infection and Nonunion After Fasciotomy for Compartment Syndrome Associated With Tibia Fractures: A Matched Cohort Comparison. J Orthop Trauma. 2016;30(7):392-396.

14. Bertsimas D, Dunn J, Velmahos GC, Kaafarani HMA. Surgical Risk Is Not Linear: Derivation and Validation of a Novel, User-friendly, and Machine-learning-based Predictive OpTimal Trees in Emergency Surgery Risk (POTTER) Calculator. Ann Surg. 2018;268(4):574-583.

15. Bongers MER, Thio QCBS, Karhade AV, et al. Does the SORG Algorithm Predict 5-year Survival in Patients with Chondrosarcoma? An External Validation. Clin Orthop Relat Res. Published online April 27, 2019. doi:10.1097/CORR.0000000000000748

16. Shah AA, Karhade AV, Bono CM, Harris MB, Nelson SB, Schwab JH. Development of a machine learning algorithm for prediction of failure of nonoperative management in spinal epidural abscess. Spine J. Published online May 4, 2019. doi:10.1016/j.spinee.2019.04.022

17. Ogink PT, Karhade AV, Thio QCBS, et al. Predicting discharge placement after elective surgery for lumbar spinal stenosis using machine learning methods. Eur Spine J. Published online April 2, 2019. doi:10.1007/s00586-019-05928-z

18. Karhade AV, Thio QCBS, Ogink PT, et al. Predicting 90-Day and 1-Year Mortality in Spinal Metastatic Disease: Development and Internal Validation. Neurosurgery. Published online March 14, 2019. doi:10.1093/neuros/nyz070

19. Thio QCBS, Karhade AV, Ogink PT, et al. Can Machine-learning Techniques Be Used for 5-year Survival Prediction of Patients With Chondrosarcoma? Clin Orthop Relat Res. 2018;476(10):2040-2048.

20. Staartjes VE, de Wispelaere MP, Vandertop WP, Schröder ML. Deep learning-based preoperative predictive analytics for patient-reported outcomes following lumbar discectomy: feasibility of center-specific modeling. Spine J. 2019;19(5):853-861.

21. Stopa BM, Robertson FC, Karhade AV, et al. Predicting nonroutine discharge after elective spine surgery: external validation of machine learning algorithms. J Neurosurg Spine. Published online July 26, 2019:1-6.

22. Ogink PT, Karhade AV, Thio QCBS, et al. Development of a machine learning algorithm predicting discharge placement after surgery for spondylolisthesis. Eur Spine J. Published online March 27, 2019. doi:10.1007/s00586-019-05936-z

23. Hendrickx LAM, Sobol GL, Langerhuizen D, et al. A Machine Learning Algorithm to Predict the Probability of (Occult) Posterior Malleolar Fractures Associated with Tibial Shaft Fractures to Guide “Malleolus First” Fixation. J Orthop Trauma. 2019;Publish Ahead of Print. doi:10.1097/BOT.0000000000001663

24. FLOW Investigators, Bhandari M, Jeray KJ, et al. A Trial of Wound Irrigation in the Initial Management of Open Fracture Wounds. N Engl J Med. 2015;373(27):2629-2641.

25. Luo W, Phung D, Tran T, et al. Guidelines for Developing and Reporting Machine Learning Predictive Models in Biomedical Research: A Multidisciplinary View. J Med Internet Res. 2016;18(12):e323.

26. Moons KGM, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med. 2015;162(1):W1-W73.

27. WHO | WHO Data Policy. Published online May 29, 2018. Accessed August 7, 2019. https://www.who.int/publishing/datapolicy/en/

28. Schemitsch EH, Bhandari M, Guyatt G, et al. Prognostic factors for predicting outcomes after intramedullary nailing of the tibia. J Bone Joint Surg Am. 2012;94(19):1786-1793.

29. Stekhoven DJ, Bühlmann P. MissForest--non-parametric missing value imputation for mixed-type data. Bioinformatics. 2012;28(1):112-118.

30. Kursa MB, Rudnicki WR, Others. Feature selection with the Boruta package. J Stat Softw. 2010;36(11):1-13.

31. Maroco J, Silva D, Rodrigues A, Guerreiro M, Santana I, de Mendonça A. Data mining methods in the prediction of Dementia: A real-data comparison of the accuracy, sensitivity and specificity of linear discriminant analysis, logistic regression, neural networks, support vector machines, classification trees and random forests. BMC Res Notes. 2011;4:299.

32. Wainer J. Comparison of 14 different families of classification algorithms on 115 binary datasets. arXiv [csLG]. Published online June 2, 2016. http://arxiv.org/abs/1606.00930

33. Fernández-Delgado M, Cernadas E, Barro S. Do we need hundreds of classifiers to solve real world classification problems? The Journal of Machine. Published online 2014. http://www.jmlr.org/papers/volume15/delgado14a/delgado14a.pdf

34. Karhade AV, Thio QCBS, Ogink PT, et al. Development of Machine Learning Algorithms for Prediction of 30-Day Mortality After Surgery for Spinal Metastasis. Neurosurgery. Published online November 23, 2018. doi:10.1093/neuros/nyy469

35. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J. 2014;35(29):1925-1931.

36. Steyerberg EW. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. Springer Science & Business Media; 2008.

37. Hosmer DW, Lemeshow S, Sturdivant RX, Hosmer DW Jr. Applied Logistic Regression. John Wiley & Sons, Incorporated; 2013.

38. Wang H, Pei H, Chen M, Wang H. Incidence and predictors of surgical site infection after ORIF in calcaneus fractures, a retrospective cohort study. J Orthop Surg Res. 2018;13(1):293.

39. Morgenstern M, Vallejo A, McNally MA, et al. The effect of local antibiotic prophylaxis when treating open limb fractures: A systematic review and meta-analysis. Bone Joint Res. 2018;7(7):447-456.

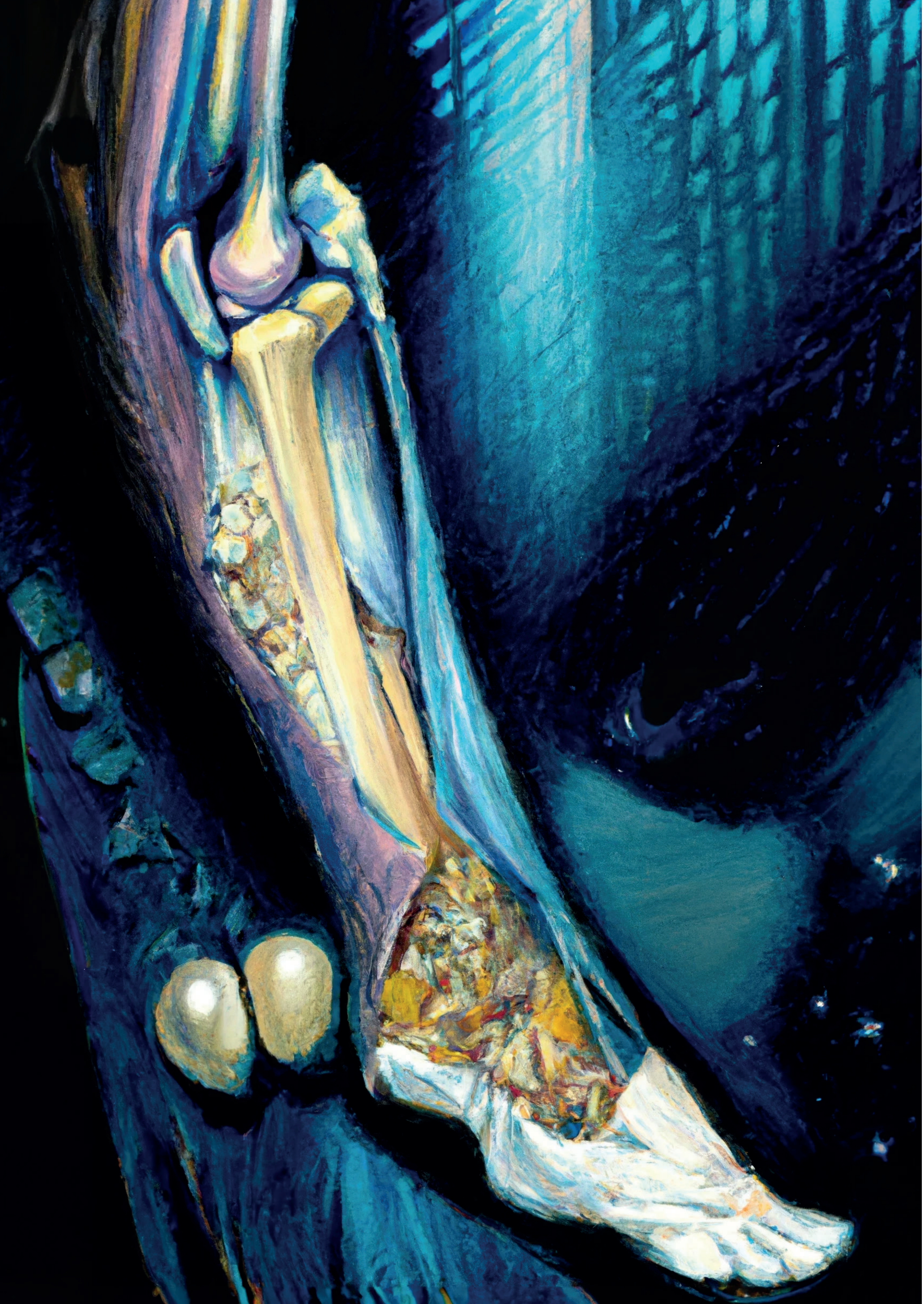
40. Lawing CR, Lin F-C, Dahners LE. Local Injection of Aminoglycosides for Prophylaxis Against Infection in Open Fractures. J Bone Joint Surg Am. 2015;97(22):1844-1851.

41. Bryson DJ, Morris DLJ, Shivji FS, Rollins KR, Snape S, Ollivere BJ. Antibiotic prophylaxis in orthopaedic surgery: difficult decisions in an era of evolving antibiotic resistance. Bone Joint J. 2016;98-B(8):1014-1019.

42. O'Toole RV, Joshi M, Carlini AR, et al. Local Antibiotic Therapy to Reduce Infection After Operative Treatment of Fractures at High Risk of Infection: A Multicenter, Randomized, Controlled Trial (VANCO Study). J Orthop Trauma. 2017;31 Suppl 1:S18-S24.

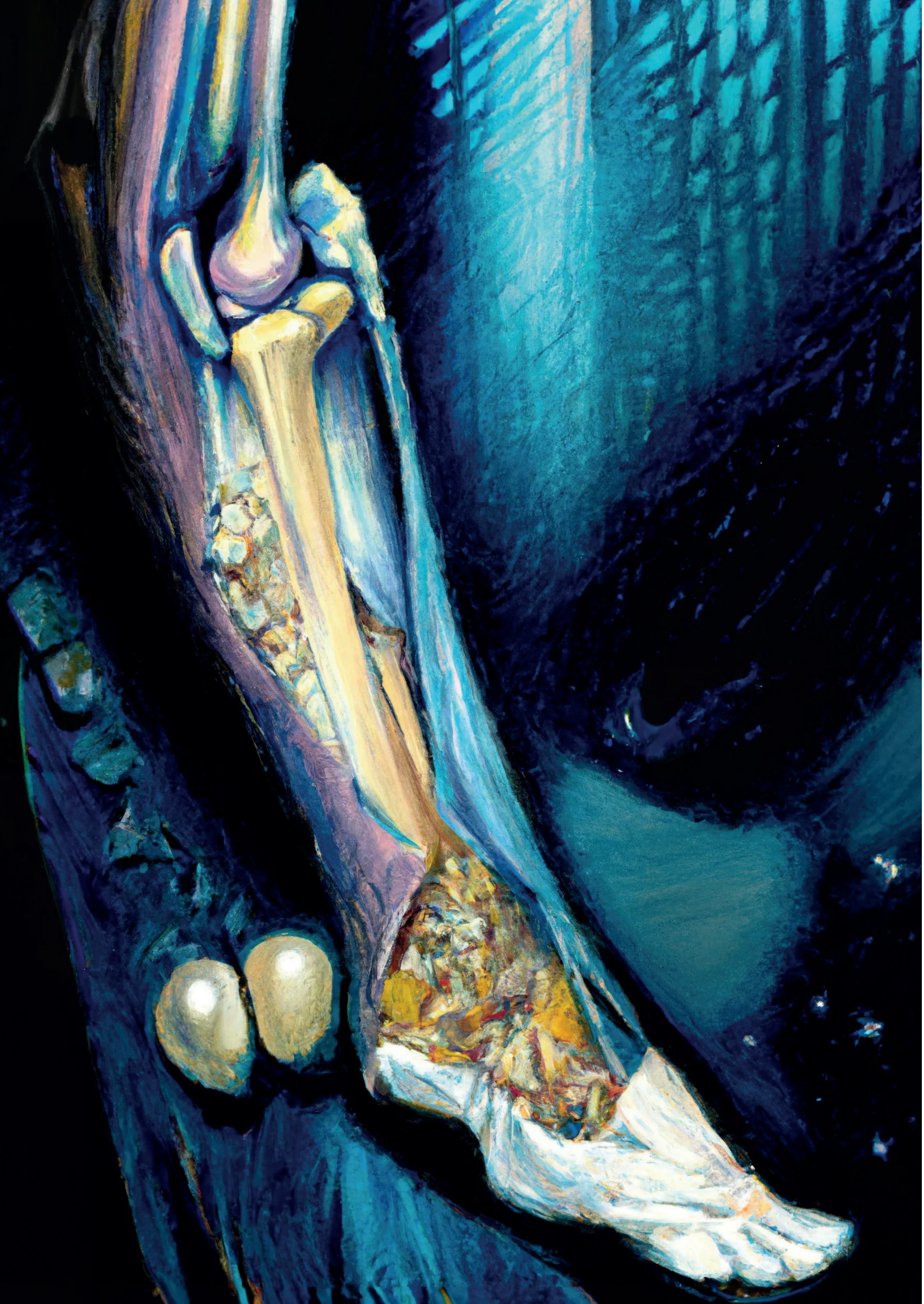
43. Shiels SM, Tennent DJ, Wenke JC. Topical rifampin powder for orthopedic trauma part I: Rifampin powder reduces recalcitrant infection in a delayed treatment musculoskeletal trauma model. J Orthop Res. 2018;36(12):3136-3141.

44. Singh K, Bauer JM, LaChaud GY, Bible JE, Mir HR. Surgical site infection in high-energy peri-articular tibia fractures with intra-wound vancomycin powder: a retrospective pilot study. J Orthop Traumatol. 2015;16(4):287-291.



Part III.

What Outcome is Acceptable?



8

CHAPTER 8

The Effect of Rotational Malalignment after Intramedullary Nailing of Tibial Shaft Fractures on Gait and Functional Outcome: A Prospective Study

Laurent A.M. Hendrickx, Jasvir S. Bahl, Job N. Doornberg, Inger N. Sierevelt, Leendert Blankevoort, Gino M.M.J. Kerkhoffs, Ruurd L. Jaarsma

ABSTRACT

Background

Despite the high incidence of iatrogenic tibial rotational malalignment after intramedullary nailing (IMN) of tibial shaft fractures (TSFs), evidence on its effects on functional outcome remains scarce.

Questions/Purposes

The purpose of this study was to investigate the effects of tibial rotational difference (TRD) between injured and contralateral lower limbs on gait kinematics of the hip-, knee- and ankle-joints; as well as to assess the association between TRD and self-reported function; pain and health related quality of life.

Methods

Patients treated with IMN for TSFs between January 2009 and September 2016 who underwent direct postoperative bilateral CT-scan imaging for assessment of rotational malalignment were invited to participate. All patients underwent overground gait analysis to assess kinematics of the hip-, knee- and ankle-joints. Furthermore, all patients completed the Knee-injury and Osteoarthritis Outcome Score, Foot and Ankle Outcome Score and PROMIS Global Health V1.2.

Results

Eighteen patients were included for analysis. Median time to follow up was 5.3 years (Range: 3.4 – 9.5). Mean tibial rotational difference was -1.3° (SD 10.9°; Range: -20.2°-15.8 °). A positive number indicates external TRD, a negative number internal TRD.

Peak hip flexion on the ipsilateral (*P* = 0.03, *coefficient* = -0.44) and contralateral side (*P* = 0.01, *coefficient* = -0.43); peak hip extension on the ipsilateral (*P* = <0.01, *coefficient* = -0.52) and contralateral side (*P* = <0.01, *coefficient* = -0.54); peak knee extension during stance phase on the ipsilateral (*P* = <0.01, *coefficient* = -0.28) and contralateral side (*P* = 0.02, *coefficient* = -0.28); mean internal hip rotation during stance phase on the ipsilateral (*P* = 0.01, *coefficient* = 0.31) and contralateral side (*P* = 0.03, *coefficient* = -0.36); and peak internal knee rotation during stance phase on the contralateral side (*P* = 0.02, *coefficient* = -0.22) were all associated with non-absolute TRD.

Only FAOS-Pain score was associated with absolute TRD (*P* = 0.02, *coefficient* = -0.86), indicating more pain with greater TRD. Other patient-reported outcomes were not associated with absolute TRD.

Conclusions

The direction and magnitude of TRD affects the gait kinematics in terms of peak extension and peak flexion of the hip- and knee-joint. Patients with greater TRD have worse long-term pain scores of the ipsilateral ankle joint.

Level of Evidence

Prognostic Level II.

INTRODUCTION

Rotational malalignment is a notorious complication of intramedullary nailing (IMN) of tibial shaft fractures (TSFs), partly due to medicolegal consequences. Patients are eligible for monetary compensation after iatrogenic malrotation of more than 10˚ according to the 5th Edition of the 'Guides to Evaluation of Permanent Impairment' [1,2]. In a recent study conducted by our research group, it was demonstrated that IMN of TSFs was complicated by postoperative rotational malalignment (>10˚) in approximately one-in-three patients [3]. This is largely in line with previous studies [4–8].

Despite this high incidence, evidence on the effect of rotational malalignment on functional outcomes remains scarce and comprises of only two studies [7,9], which both demonstrated no significant effects on patient reported outcome measures (PROMS). However, these studies were inherently limited by methodological design: Theriault et al. used an arbitrary cut-off value of 10° to differentiate between patients with and without rotational malalignment [7]. Categorizing patients in such groups may have concealed effects of increasing rotational difference. The study conducted by Boucher et al. made use of an experimental three-dimensional digital assessment technique to determine tibial rotational difference (TRD) [9]. Since authors did not verify their findings using CT-scan imaging, the most reliable method for assessing TRD [4,10,11], it remains unclear to what extent their findings are externally valid. Studies assessing tibial torsion suggest that decreased tibial torsion may be linked to osteoarthritis of the knee and ankle joint [12,13]. It has furthermore been demonstrated that excessive TRD results in significantly altered biomechanics of the knee-joint [14,15] and ankle-joint [16] in vitro.

Hence, more clarity on the effect of tibial rotational malalignment on 1) the joint biomechanics in vivo; as well as 2) on functional outcome, is needed. Therefore, the purpose of this study was to investigate the effect of TRD between injured and contralateral lower limbs on 1) gait kinematics of the hip-, knee- and ankle-joints using 3D-gait analysis; as well as to 2) assess the association between TRD and self-reported function, pain and health related quality of life. It was hypothesized that larger TRD between injured and contralateral limbs would have larger effects on 1) gait kinematics of the hip-, knee- and ankle-joint; and 2) self-reported function, pain and health related quality of life.

MATERIAL AND METHODS

This study was performed according to the STROBE guidelines [17].

Participants

Patients treated with IMN for TSFs between January 2009 and September 2016, who underwent postoperative bilateral CT-scan imaging for assessment of rotational malalignment, were contacted and invited to participate. Exclusion criteria are displayed in Table 1. All patients were treated with the TRIGEN IMN System (Smith & Nephew, Andover, MA USA). Intramedullary nailing was performed as per routine techniques [18]. Tibial rotational differences were established in a previous study using CT-scan imaging [3,10]. The technique used in this study to calculate TRD resulted in excellent inter-observer (ICC: 0.92-0.97) and intra-observer (ICC: 0.87-0.92) reliability [10].

In this assessment, an "external TRD" means the ipsilateral tibia is externally rotated compared to the contralateral tibia, i.e. the foot of the effected tibia is externally rotated relative to foot of the normal tibia. External TRD is defined as a positive number, internal TRD is defined as a negative number.

All patients underwent overground gait analysis and completed the Knee-injury and Osteoarthritis Outcome Score (KOOS) [19], Foot and Ankle Outcome Score (FAOS) [20] and PROMIS Global Health V1.2 [21,22].

Gait experiments

A single investigator (LH) placed reflective markers on patients according to standard lower-body marker set [23]. A static trial was captured for model scaling (see section musculoskeletal modelling below). Subsequently, subjects were asked to walk barefoot at a self-selected speed along an 8m walkway. A ten-camera motion analysis system (Vicon, Oxford Metrics) was used to capture marker trajectories at a sampling rate of 250 Hz. Ground reaction forces were captured simultaneously using four force platforms (Advanced Medical Technology [AMTI], Watertown, MA) sampling at 2000Hz. A minimum of three successful foot strikes were obtained per leg for each session.

Marker trajectories and ground reaction forces were processed using MOtoNMS [24] in MATLAB R2018b (The Mathworks Inc, MA, USA). Marker trajectories were low pass filtered with a second-order-zero-lag Butterworth filter (6Hz and 10Hz respectively).

Musculoskeletal modelling

Kinematics were calculated in OpenSim, using a generic lower limb model (Gait2392) [25], consisting of three Degrees of Freedom (DOF) at the hip and one DOF's at the knee joint. OpenSim allows one to analyse musculoskeletal models and dynamic simulations of movement. For the current study, Gait2392 model was adapted to allow for knee rotation ranging from −40° to 30°. Pelvic tilt was limited to from 0 to 6°. The ankle joint was partially locked allowing one DOF (i.e. dorsal and plantar flexion).

Musculoskeletal Atlas Project Client (MAPClient), containing shape models of the pelvis and lower limbs [26,27], was used to scale the generic Gait2392 model. The feet were linearly scaled using the experimental foot makers as the shape model does not contain feet. This method has previously been detailed by Bahl et al [23]. In short, it matches the embedded landmarks on the shape model to the reflective markers on the subject along 1-3 principal components, producing scale factors of a more anatomically realistic model, compared to linear scaling methods using experimental markers positions alone [23]

Inverse kinematics was used to reconstruct the motion of the model from the experimental markers. The joint angles were calculated as Tait-Bryan angles according to the ISB recommendations [28,29].

Gait outcome measures

From the gait kinematics, peak hip flexion and extension, peak hip abduction and adduction, mean hip rotation during stance phase, peak knee flexion and extension during stance and swing phase, peak knee internal rotation during stance phase, and peak ankle extension and flexion over the entire gait cycle were calculated. Temporospatial parameters included: 1) gait speed; 2) difference between the ipsilateral and contralateral side in step length, expressed in centimetres for easier interpretation; and 3) difference between the ipsilateral and contralateral side in single leg stance time, expressed as a proportion (%) of the total gait cycle.

Patient Reported Outcome Measures

To analyse the association between TRD and health related quality of life, pain and self-reported function, PROMIS Global Health V1.2 [21,22], FAOS [20] and KOOS [19] were administered.

With PROMIS Global Health V1.2 a score can be calculated for Global Physical Health and Global Mental Health, higher scores indicate better physical and mental health [21,22]. In orthopaedic patients, PROMIS Global Health has been reported to consist of adequate internal and external responsiveness to change [30].

FAOS and KOOS are questionnaires for adults measuring symptoms and functional limitations of the ankle and knee, respectively. They consist of five subscales: 1) pain; 2) other symptoms; 3) function in daily living; 4) function in sports; 5) ankle or knee related quality of life. FAOS has been reported to be a valid and reliable questionnaire for patients with foot and ankle symptoms [20,31–33]. KOOS has been reported to consist of adequate content validity, internal consistency, test-retest reliability, construct validity and responsiveness [34].

Statistical Analysis

Visual assessment of histograms was performed to assess whether data were normally distributed. Non-normally distributed data were presented as medians with ranges, normally distributed data were presented as means with standard deviations. Categorical data were presented as frequencies with percentages.

The association between absolute TRD and temporospatial parameters was assessed using bivariable linear regression. Effect of BMI on the outcomes was investigated. If BMI caused >10% difference in the beta-coefficient it was included as confounder in a multivariable linear regression model. The above process was repeated to assess the association between (non-absolute) TRD and kinematics.

The association between absolute TRD and PROMS was also assessed using bivariable linear regression. BMI and the score on the Center for Epidemiologic Studies Depression Scale Revised (CESD-R) were considered as potential confounders. An association was considered significant for P-values <0.05. All Statistical analyses were performed using IBM SPSS Statistics, version 24.0 (Armonk, NY; IBM Corp).

RESULTS

Participants

A total of 154 patients underwent postoperative CT-scan imaging after IMN between 2009 and 2016, of which 113 patients were excluded (Table 1). Of the remaining 42 patients, 13 declined to participate and 11 were lost to follow up. Eighteen patients were included for analysis (Male: 15; Female: 3; Mean age: 44.9 years [SD: 13.74]; BMI:26.0 kg/m² [SD: 4.4]). Median time to follow up was 5.3 years (Range: 3.4 – 9.5). Mean TRD was -1.3° (SD 10.9°; Range: -20.2°- 15.8 °). Individual patient characteristics are displayed in appendix I.

Captured gait data of one patient was of insufficient quality and was excluded from gait analysis results but included in analysis of PROMS.

TABLE 1. Exclusion Criteria

Exclusion Criteria	Excluded, n
<16 years at time of surgery	1
>75 years at time follow up	16
Deceased	3
Musculoskeletal- or neurological disorders or other trauma that may be associated with significant impaired functioning of the lower extremity	56
Removal or revision of tibial nail after CT-scan imaging was performed	9
Unable to speak English	0
Unable to give informed consent due to cognitive impairment	4
>2 hours of travel required	23

Kinematics

Regarding the first aim of this study to investigate the effect of iatrogenic (non-absolute) TRD on gait kinematics of the hip-, knee- and ankle-joints using 3D-gait analysis, it was observed that peak hip flexion on the ipsilateral (*P*=0.03) and contralateral side (*P*=0.01) and peak hip extension on the ipsilateral (*P*=<0.01) and contralateral side (*P*=<0.01) were significantly associated with TRD (Table 2) (Figure 1). The regression coefficients indicate that patients with larger external TRD have reduced peak hip flexion and increased peak hip extension on both the ipsilateral and contralateral side respectively. Meaning, that patients with larger external TRD on the injured side further extend their hips before they lift their feet, whilst there is less flexion in their hip before they strike their feet.

Also, TRD resulted in a significant difference in peak knee extension on the ipsilateral (*P*=<0.01) and contralateral side (*P*=0.02) during stance phase. The regression coefficients indicate that patients with larger external TRD have increased peak knee extension during stance phase on both the ipsilateral and contralateral side. Peak knee extension during swing phase and peak knee flexion were not significantly associated with TRD (Table 2) (Figure 2).

There were no significant associations between peak ankle flexion or extension on the ipsilateral or contralateral side and TRD (Figure 3). Peak hip adduction and peak hip abduction on the ipsilateral or contralateral side were also not significantly associated with TRD (Figure 4) (Table 3).

Mean internal hip rotation during stance phase was significantly associated with TRD for both the ipsilateral (*P*=0.01) and contralateral side (*P*=0.03) (Table 3) (Figure 5). The regression coefficients indicate that patients with larger external TRD have more internal rotation of the hip on the ipsilateral side, patients with internal TRD have more external rotation of the hip on the ipsilateral side. For the contralateral side external TRD is associated with more external rotation of the hip during stance phase, internal TRD is associated with internal rotation of the hip.

Peak internal knee rotation during stance phase on the contralateral side was significantly associated with TRD (*P*=0.02) (Table 3) (Figure 6). The regression coefficient indicates that patients with larger external TRD have more internal rotation of the knee on the contralateral side during stance phase. There was no significant association between peak internal knee rotation on the ipsilateral side and TRD.

TABLE 2. Bivariable analysis between Non-Absolute Rotational Difference and Peak Sagittal Plane Kinematics Using Linear Regression

Peak sagittal plane kinematics in degrees	Regression Coefficient	95% Confidence Interval	P-value	Corrected for	Crude β Coefficient
Peak hip flexion ipsilateral	-0.44	-0.84 – -0.05	0.03*	-	-
Peak hip flexion contralateral	-0.43	-0.76 – -0.01	0.01*	-	-
Peak hip extension ipsilateral	-0.52	-0.86 – -0.19	<0.01*	-	-
Peak hip extension contralateral	-0.54	-0.92 – -0.17	<0.01*	-	-
Peak knee flexion ipsilateral stance phase	-0.03	-0.24 – 0.17	0.73	-	-
Peak knee flexion contralateral stance phase	-0.04	-0.26 – 0.19	0.72	-	-
Peak knee extension ipsilateral stance phase	-0.28	-0.45 – -0.11	<0.01*	-	-
Peak knee extension contralateral stance phase	-0.28	-0.50 – -0.05	0.02*	-	-
Peak knee flexion ipsilateral swing phase	-0.15	-0.35 – 0.06	0.15	-	-
Peak knee flexion contralateral swing phase	-0.15	-0.32 – 0.01	0.06	-	-
Peak knee extension ipsilateral swing phase	<0.01	-0.21 – 0.21	1.0	-	-
Peak knee extension contralateral swing phase	<0.01	-0.13 – 0.13	0.99	-	-
Peak ankle flexion ipsilateral	0.06	-0.17 – 0.30	0.58	BMI	0.05
Peak ankle flexion contralateral	0.03	-0.21 – 0.28	0.78	BMI	0.02
Peak ankle extension ipsilateral	0.06	-0.34 – 0.47	0.74	BMI	0.04
Peak ankle extension contralateral	0.26	-0.08 – 0.60	0.12	BMI	0.23

External rotation was defined as a positive difference between the affected and unaffected limb and internal rotation is defined as a negative difference.

TABLE 3 Bivariable analysis between Non-Absolute Rotational Difference and Hip Abduction, Hip Rotation and Knee Rotation using Linear Regression

Variable	Regression Coefficient	95% Confidence Interval	P-value	Corrected for
Peak hip adduction ipsilateral end stance phase	0.11	-0.02 – 0.25	0.10	-
Peak hip adduction contralateral end stance phase	-0.01	-0.21 – 0.02	0.09	-
Peak hip abduction ipsilateral start swing phase	0.12	-0.03 – 0.28	0.12	-
Peak hip abduction contralateral start swing phase	-0.11	-0.28 – 0.066	0.21	-
Mean internal rotation hip ipsilateral stance phase	0.31	0.09 – 0.53	0.01*	-
Mean internal rotation hip contralateral stance phase	-0.36	-0.69 – -0.03	0.03*	-
Peak internal rotation knee ipsilateral stance phase	0.14	-0.03 – 0.31	0.10	-
Peak internal rotation knee contralateral stance phase	-0.22	-0.40 – -0.04	0.02*	

External rotation was defined as a positive difference between the affected and unaffected limb and internal rotation is defined as a negative difference.

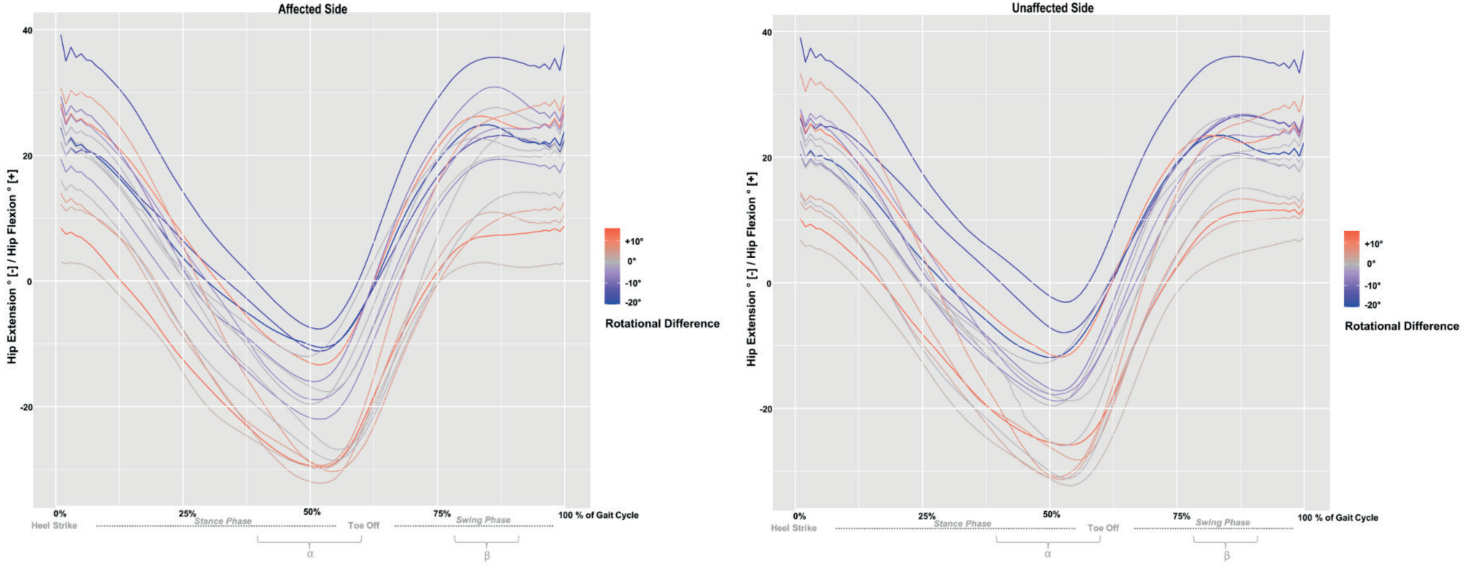


Figure 1. Hip flexion and extension curves for the ipsilateral (affected) and contralateral side (unaffected). Peak hip flexion was measured at 40-60% of gait cycle (α-interval). Peak hip extension was measured at 79-89% of gait cycle (β-interval). External TRD is defined as a positive number, internal TRD is defined as a negative number.

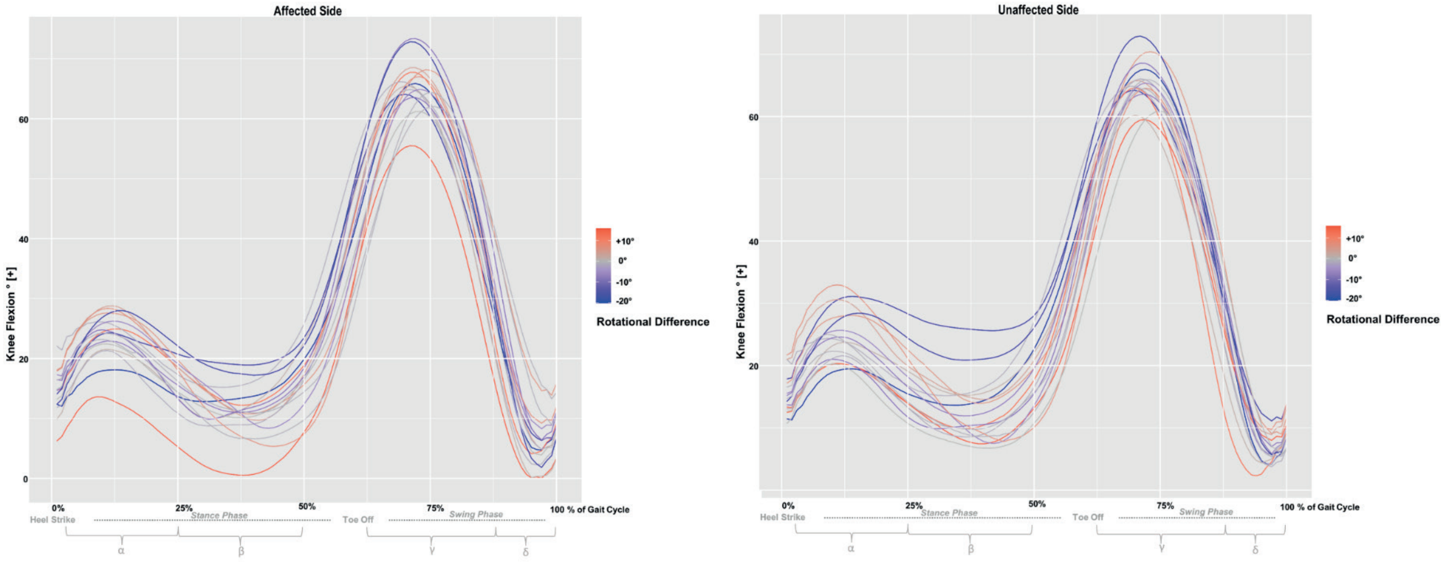


Figure 2. Knee flexion and extension curves for the ipsilateral and contralateral side.Peak knee flexion during stance phase was measured at 2-25% of gait cycle (α-interval). Peak knee extension during stance phase was measured at 25-50% of gait cycle (β-interval). Peak knee flexion during swing phase was measured at 62%-88% of gait cycle (γ-interval). Peak knee extension during swing phase was measured at 88-100% of gait cycle (δ-interval). External TRD is defined as a positive number, internal TRD is defined as a negative number.

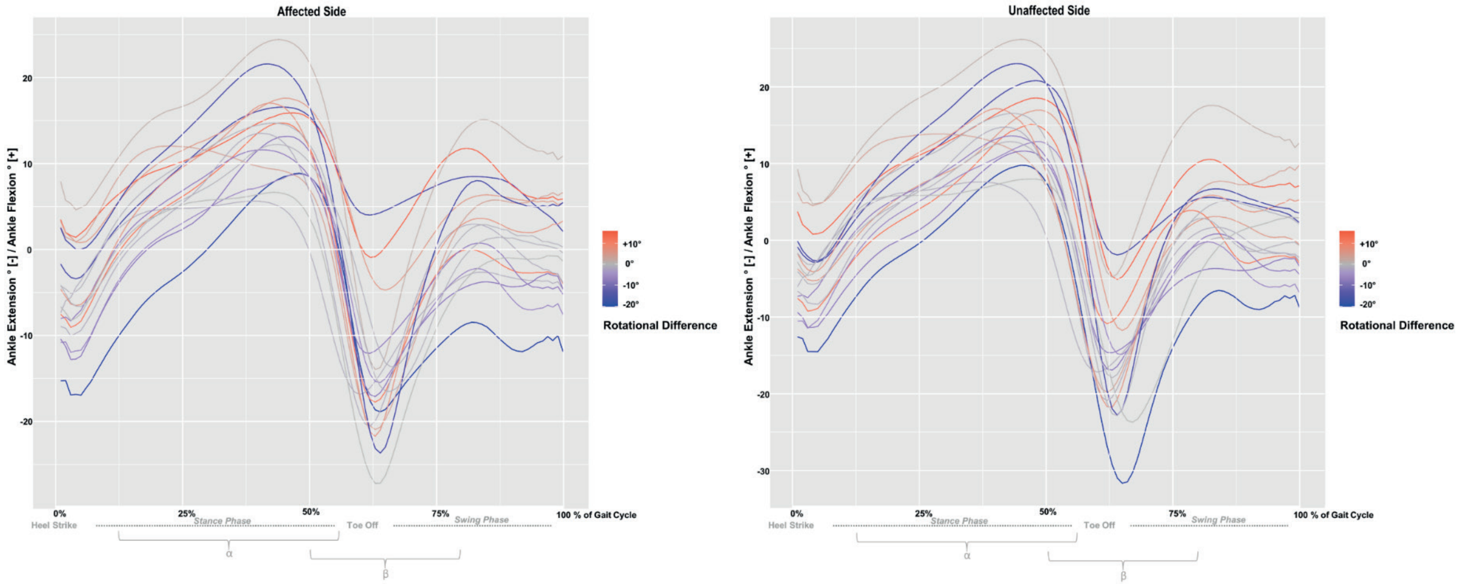


Figure 3. Ankle flexion and extension curves for the ipsilateral and contralateral side. Peak ankle flexion was measured at 12-55% of gait cycle (α-interval). Peak ankle extension was measured at 50-80% of gait cycle (β-interval). External TRD is defined as a positive number, internal TRD is defined as a negative number.

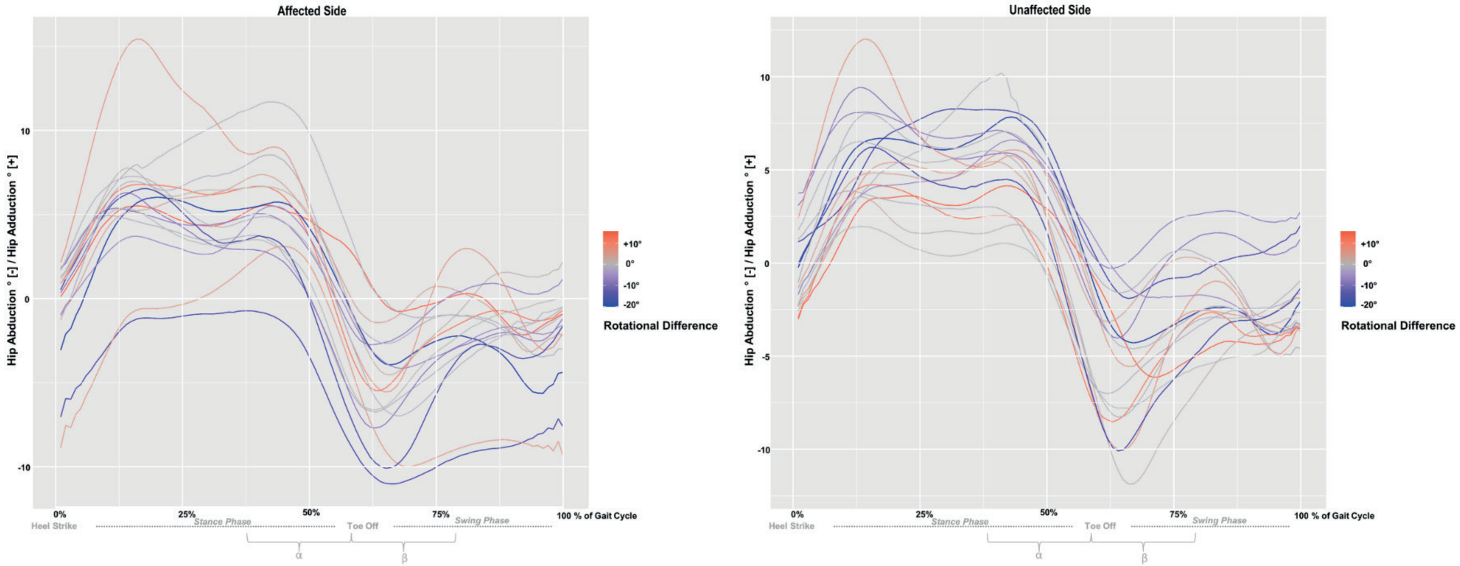


Figure 4. Hip Abduction and adduction curves for the ipsilateral and contralateral side. Peak hip adduction at the end of the stance phase was measured at 37-57% of gait cycle (α-interval). Peak hip abduction at the start of the swing phase was measured at 57-77% of gait cycle (β-interval). External TRD is defined as a positive number, internal TRD is defined as a negative number.

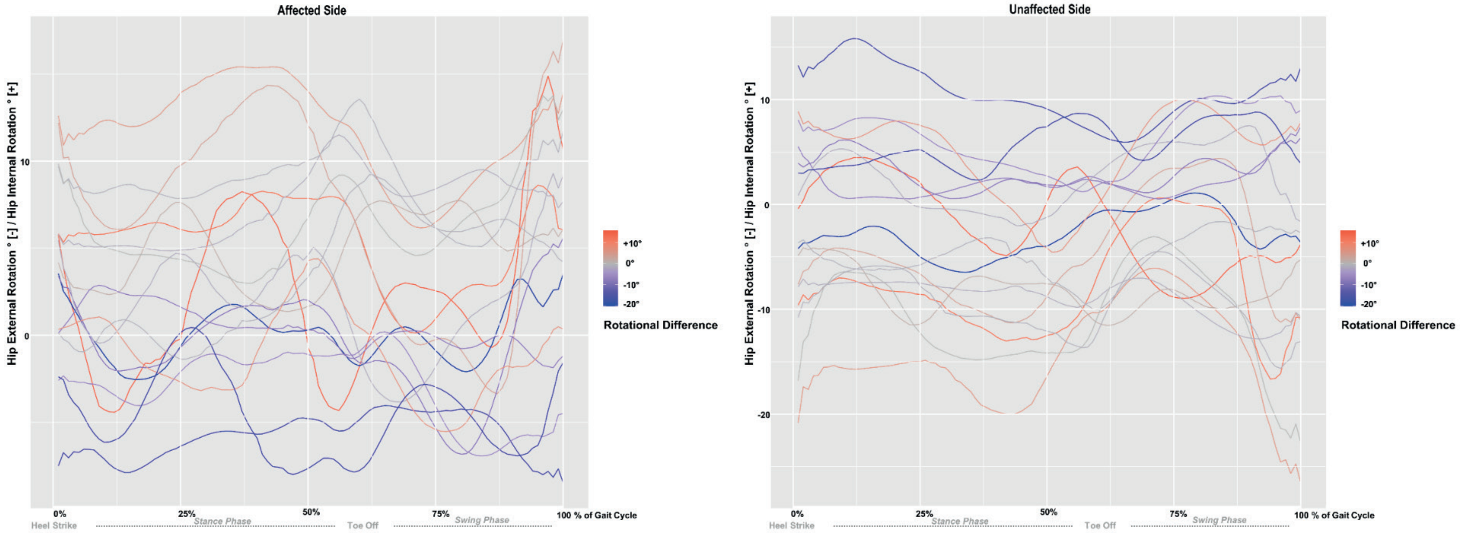


Figure 5. Hip rotation curves for the ipsilateral and contralateral side. Mean hip rotation was calculated over the entire gait cycle. External TRD is defined as a positive number, internal TRD is defined as a negative number.

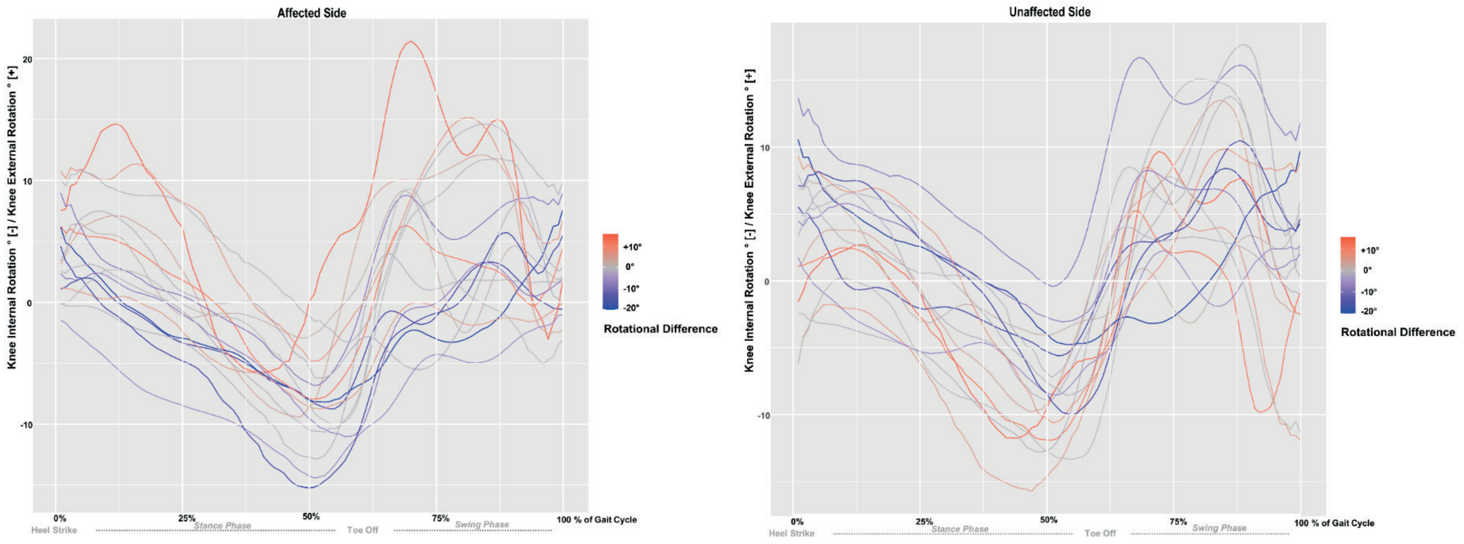


Figure 6. Knee rotation curves for the ipsilateral and contralateral side. Peak knee internal rotation during stance phase was measured at 25-60% of gait cycle (α-interval). External TRD is defined as a positive number, internal TRD is defined as a negative number.

Temporospatial Parameters

There was no significant association between (absolute) TRD and gait speed; difference in stance phase between the ipsilateral and contralateral side; or difference in step length between the ipsilateral and contralateral side (Table 4).

TABLE 4. Bivariable analysis between Absolute Rotational Difference and Spatiotemporal parameters using Linear Regression

Variable	Regression Coefficient	95% Confidence Interval	P-value	Corrected for
Gait speed, m/s	<-0.01	-0.01 – 0.01	0.69	-
Difference ipsilateral vs. contralateral side in % stance phase	0.07	-0.05 – 0.18	0.23	-
Difference step length ipsilateral vs. contralateral side, cm	0.11	-0.05 – 0.27	0.16	-

Functional Outcome Scores

To answer the secondary research question, whether there was an association between absolute TRD and self-reported function and health related quality of life, it was observed that FAOS-Pain was associated with (absolute) TRD (*P*=0.02). The regression coefficient, -0.86, indicated that patients with larger absolute TRD have worse FAOS-Pain scores. Post-hoc power analysis demonstrated that the regression analysis, in which TRD accounted for 28% of the variance in FAOS-Pain provided a power of 70%. The other domains of the FAOS were not associated with (absolute) TRD.

PROMIS Global-Health Mental and PROMIS Global Health Physical were not statistically significantly associated with (absolute) TRD (Table 5). There was also no statistically significant association between absolute TRD and any of the KOOS-domains. Mean and median PROM-scores for the entire cohort are displayed in Appendix II.

TABLE 5. Bivariable analysis between Absolute Rotational Difference and PROMIS, KOOS and FAOS using Linear Regression

Variable	Regression Coefficient	95% Confidence Interval	P-value	Adjusted for	Crude β Coefficient
PROMIS - Mental	0.34	-0.209 – 0.891	0.21	BMI, CESD-R	0.23
PROMIS - Physical	0.05	-0.17 – 0.28	0.63	BMI, CESD-R	-0.02
KOOS Pain	-0.48	-1.08 – 0.12	0.11	-	-
KOOS Symptoms	-0.16	-1.07 – 0.75	0.72	BMI, CESD-R	-0.26
KOOS ADL	-0.41	-0.95 – 0.12	0.12	-	-
KOOS Sports	0.24	-0.77 – 1.25	0.62	BMI, CESD-R	0.17
KOOS QOL	-0.68	-2.02 – 0.75	0.34	-	-
FAOS Pain	-0.86	-1.59 – -0.13	0.02*	-	-
FAOS Symptoms	-0.96	-1.95 – 0.03	0.06	-	-
FAOS ADL	-0.59	-1.21 – 0.02	0.06	-	-
FAOS Sports	-0.95	-2.14 – 0.23	0.11	-	-
FAOS QOL	-0.96	-2.37 – 0.45	0.17	-	-

DISCUSSION

The purposes of this study were to investigate the effect of TRD due to iatrogenic malalignment after IMN of TSFs on 1) gait biomechanics of the hip-, knee- and ankle-joints using 3D-gait analysis; and 2) to assess the association between absolute TRD and self-reported function, pain and health related quality of life. Contrary to what has thus far been reported, this study demonstrated that larger absolute TRD between the injured and non-injured tibia after IMN of TSFs are associated with higher pain in the ankle at the long-term. Tibial rotational difference affected sagittal plane and axial plane kinematics of the hip- and knee-joint.

This study has several limitations. Firstly, this study is limited by the small sample size. This is the result of the strict inclusion- and exclusion criteria, applied to prevent confounding factors from affecting gait analysis results. For example, polytrauma patients were excluded. Secondly, a substantial number of patients did not consent to participation. This may have resulted in selection bias. Another limitation is the use of skin-markers to track kinematics in the axial plane. Various studies have shown that it remains difficult to accurately track axial plane kinematics using this method [35,36]. This is reflected by the large variability in the axial plane kinematic curves. However, this limitation can only be overcome with the use of bone pin-based markers, which we believed to be a too invasive method and deemed unethical. This study also lacked radiographic imaging, as the hip-, knee- and ankle joints were not assessed radiographically for evidence of early onset osteoarthritic changes. Lastly, hip related PROMS were not collected. Strengths of this study include the first in-vivo analysis of the effect of iatrogenic TRD on the biomechanics of the joints of the lower extremity to date. Furthermore, this study made use of statistical shape modelling as part of the musculoskeletal modelling workflow [26]. This technique has recently been demonstrated to outperform conventional linear scaling methods, resulting in more reliable and accurate motion analysis data [23].

Several, in-vitro studies have assessed the effect of increased or decreased tibial torsion after operative fixation of tibial shaft fractures on the biomechanics of the knee- and ankle joint [14–16]. Although specific results differ between these studies, all concur that excessive internal or external tibial torsion results in altered kinematics and contact pressures of the knee- and ankle-joint [14–16]. To date, there have not been any in-vivo studies that studied the effect of iatrogenic malalignment after tibial shaft fractures. Thus, for comparative evidence on the effect of iatrogenic long-bone rotational differences on gait kinematics in vivo, one could review three studies investigating femoral rotational malalignment after IMN [37–39]. By analysing the foot progression line, two of these studies demonstrated that patients with femoral rotational malalignment compensate for their respective femoral rotational difference, since the foot progression line deviated less from the ipsilateral side than what was to be expected based on the femoral rotational difference [38,39]. A study by Ongkiehong et al. demonstrated that this compensation was predominantly established by hip rotation [37]. This compensation mechanism was also observed in the current study: patients with external TRD had on average more internal rotation in the hip during stance phase on the ipsilateral side, and patients with internal TRD vice versa: for every degree external TRD, mean internal rotation of the hip increased with 0.31°. Interestingly, hip rotation on the contralateral side was also associated with TRD, however, an opposite relationship was observed: for every degree external TRD of the ipsilateral side, external rotation of the hip increased with 0.36°. Other kinematics that were affected by TRD consisted of knee rotation on the contralateral side, hip extension on both the ipsilateral and contralateral side, and knee extension during stance phase on both the ipsilateral and contralateral side. Previous studies assessing the effect of iatrogenic femoral rotational malalignment on gait kinematics do not report on these associations.

This study also demonstrated that larger TRD is associated with higher pain as indicated by lower FAOS-pain scores. To the best of our knowledge, only two studies have previously assessed the effect of tibial rotational malalignment on long-term functional outcome based on PROMS [7,9]. In a prospective cohort study in this Journal, Theriault et al. could not demonstrate any difference between patients with and patients without rotational malalignment (i.e., >10° rotational difference) [7]. In a smaller study including 13 patients, conducted by Boucher et al. [9], no correlation could be demonstrated between TRD and lower extremity functional scale (LEFS) [40] or Western Ontario and McMaster University Osteoarthritis Index [41]. The findings of these studies contrast with the findings of the current study in which an increase of TRD was associated with worse scores on the FAOS-pain domain. This difference may be caused by Theriault et al. using a cut-off value of 10° to differentiate between patients with and without rotational malalignment, which may have concealed effects of larger degrees of rotational malalignment [7]. Boucher et al. used an experimental three-dimensional digital assessment technique to determine TRD, without subsequent verification of their results using CT-scan imaging [3,10]. Therefore, it remains unclear to what extent their findings are valid. Based on previously assessed minimally important changes of the Dutch FAOS-Pain (12.5 points) [42] we calculated that a TRD of 15° degrees results in a clinically important change in ankle pain. It is unclear whether these minimally important changes of the Dutch FAOS translate to the Australian population.

In conclusion, with the numbers available, this study demonstrated that the direction and amount of TRD affects the peak gait kinematics of the hip- and knee-joint, with compensation for TRD taking place at the hip and knee level. Furthermore, this study demonstrated that patients with larger absolute TRD have worse long-term pain scores of the ipsilateral ankle joint.

REFERENCES

1. Andersson GBJ, Cocchiarella L, eds. Guides to the Evaluation of Permanent Impairment, Fifth Edition. 5th ed. American Medical Association; 2000.
2. Metcalfe CW, Harrison WD, Nayagam S, Narayan B. Negligence claims following non-union and malunion of long bone fractures: An analysis of 15 years of data. Injury. 2016;47(10):2312-2314.
3. Cain ME, Hendrickx LAM, Bleeker NJ, Lambers KTA, Doornberg JN, Jaarsma RL. Prevalence of Rotational Malalignment After Intramedullary Nailing of Tibial Shaft Fractures: Can We Reliably Use the Contralateral Uninjured Side as the Reference Standard? J Bone Joint Surg Am. 2020;102(7):582-591.
4. Say F, Bülbül M. Findings related to rotational malalignment in tibial fractures treated with reamed intramedullary nailing. Arch Orthop Trauma Surg. 2014;134(10):1381-1386.
5. Puloski S, Romano C, Buckley R, Powell J. Rotational malalignment of the tibia following reamed intramedullary nail fixation. J Orthop Trauma. 2004;18(7):397-402.
6. Jafarinejad AE, Bakhshi H, Haghnegahdar M, Ghomeishi N. Malrotation following reamed intramedullary nailing of closed tibial fractures. Indian J Orthop. 2012;46(3):312-316.
7. Theriault B, Turgeon AF, Pelet S. Functional impact of tibial malrotation following intramedullary nailing of tibial shaft fractures. J Bone Joint Surg Am. 2012;94(22):2033-2039.
8. Prasad CV, Khalid M, McCarthy P, O’Sullivan ME. CT assessment of torsion following locked intramedullary nailing of tibial fractures. Injury. 1999;30(7):467-470.
9. Boucher M, Leone J, Pierrynowski M, Bhandari M. Three-dimensional assessment of tibial malunion after intramedullary nailing: a preliminary study. J Orthop Trauma. 2002;16(7):473-483.
10. Bleeker NJ, Cain M, Rego M, et al. Bilateral Low-Dose Computed Tomography Assessment for Post-Operative Rotational Malalignment After Intramedullary Nailing for Tibial Shaft Fractures: Reliability of a Practical Imaging Technique. Injury. 2018;49(10):1895-1900.
11. Wissing H, Buddenbrock B. Determining rotational errors of the femur by axial computerized tomography in comparison with clinical and conventional radiologic determination. Unfallchirurgie. 1993;19(3):145-157.
12. Yagi T, Sasaki T. Tibial torsion in patients with medial-type osteoarthritic knee. Clin Orthop Relat Res. 1986;(213):177-182.
13. Turner MS. The association between tibial torsion and knee joint pathology. Clin Orthop Relat Res. 1994;(302):47-51.
14. Yazdi H, Mallakzadeh M, Sadat Farshidfar S, Givehchian B, Daneshparvar H, Behensky H. The effect of tibial rotation on knee medial and lateral compartment contact pressure. Knee Surg Sports Traumatol Arthrosc. 2016;24(1):79-83.
15. Kenawey M, Liodakis E, Krettek C, Ostermeier S, Horn T, Hankemeier S. Effect of the lower limb rotational alignment on tibiofemoral contact pressure. Knee Surg Sports Traumatol Arthrosc. 2011;19(11):1851-1859.
16. Svoboda SJ, McHale K, Belkoff SM, Cohen KS, Klemme WR. The effects of tibial malrotation on the biomechanics of the tibiotalar joint. Foot Ankle Int. 2002;23(2):102-106.

17. Brand RA. Standards of reporting: the CONSORT, QUORUM, and STROBE guidelines. Clin Orthop Relat Res. 2009;467(6):1393-1394.

18. Zelle BA, Boni G. Safe surgical technique: intramedullary nail fixation of tibial shaft fractures. Patient Saf Surg. 2015;9(1):40.

19. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. J Orthop Sports Phys Ther. 1998;28(2):88-96.

20. Roos EM, Brandsson S, Karlsson J. Validation of the foot and ankle outcome score for ankle ligament reconstruction. Foot Ankle Int. 2001;22(10):788-794.

21. Rose M, Bjorner JB, Becker J, Fries JF, Ware JE. Evaluation of a preliminary physical function item bank supported the expected advantages of the Patient-Reported Outcomes Measurement Information System (PROMIS). J Clin Epidemiol. 2008;61(1):17-33.

22. Rose M, Bjorner JB, Gandek B, Bruce B, Fries JF, Ware JE Jr. The PROMIS Physical Function item bank was calibrated to a standardized metric and shown to improve measurement efficiency. J Clin Epidemiol. 2014;67(5):516-526.

23. Bahl JS, Zhang J, Killen BA, et al. Statistical shape modelling versus linear scaling: Effects on predictions of hip joint centre location and muscle moment arms in people with hip osteoarthritis. J Biomech. 2019;85:164-172.

24. Mantoan A, Pizzolato C, Sartori M, Sawacha Z, Cobelli C, Reggiani M. MOtoNMS: A MATLAB toolbox to process motion data for neuromusculoskeletal modeling and simulation. Source Code Biol Med. 2015;10:12.

25. Delp SL, Loan JP, Hoy MG, Zajac FE, Topp EL, Rosen JM. An interactive graphics-based model of the lower extremity to study orthopaedic surgical procedures. IEEE Trans Biomed Eng. 1990;37(8):757-767.

26. Zhang J, Sorby H, Clement J, et al. The MAP Client: User-Friendly Musculoskeletal Modelling Workflows. In: Biomedical Simulation. Springer International Publishing; 2014:182-192.

27. Zhang J, Fernandez J, Hislop-Jambrich J, Besier TF. Lower limb estimation from sparse landmarks using an articulated shape model. J Biomech. 2016;49(16):3875-3881.

28. Wu G, Siegler S, Allard P, et al. ISB recommendation on definitions of joint coordinate system of various joints for the reporting of human joint motion--part I: ankle, hip, and spine. International Society of Biomechanics. J Biomech. 2002;35(4):543-548.

29. Grood ES, Suntay WJ. A joint coordinate system for the clinical description of three-dimensional motions: application to the knee. J Biomech Eng. 1983;105(2):136-144.

30. Oak SR, Strnad GJ, Bena J, et al. Responsiveness Comparison of the EQ-5D, PROMIS Global Health, and VR-12 Questionnaires in Knee Arthroscopy. Orthop J Sports Med. 2016;4(12):2325967116674714.

31. Golightly YM, Devellis RF, Nelson AE, et al. Psychometric properties of the foot and ankle outcome score in a community-based study of adults with and without osteoarthritis. Arthritis Care Res . 2014;66(3):395-403.

32. Uimonen MM, Ponkilainen VT, Toom A, et al. Validity of five foot and ankle specific electronic patient-reported outcome (ePRO) instruments in patients undergoing elective orthopedic foot or ankle surgery. Foot Ankle Surg. Published online February 12, 2020. doi:10.1016/j.fas.2020.02.003

33. Sierevelt IN, Zwiers R, Schats W, et al. Measurement properties of the most commonly used Foot- and Ankle-Specific Questionnaires: the FFI, FAOS and FAAM. A systematic review. Knee Surg Sports Traumatol Arthrosc. 2018;26(7):2059-2073.

34. Collins NJ, Prinsen CAC, Christensen R, Bartels EM, Terwee CB, Roos EM. Knee Injury and Osteoarthritis Outcome Score (KOOS): systematic review and meta-analysis of measurement properties. Osteoarthritis Cartilage. 2016;24(8):1317-1329.

35. Reinschmidt C, van den Bogert AJ, Lundberg A, et al. Tibiofemoral and tibiocalcaneal motion during walking: external vs. skeletal markers. Gait Posture. 1997;6(2):98-109.

36. Benoit DL, Damsgaard M, Andersen MS. Surface marker cluster translation, rotation, scaling and deformation: Their contribution to soft tissue artefact and impact on knee joint kinematics. J Biomech. 2015;48(10):2124-2129.

37. Ongkiehong BF, Jaarsma RL, Blockhuis NTM, Verdonschot N, Duysens J, van Kampen A. Chapter 4. Compensation for post-traumatic rotational malalignment of the femur. A segmental rotational profile analysis. In: Rotational Malalignment after Fractures of the Femur. ; 2004:53-68.

38. Jaarsma RL, Ongkiehong BF, Grüneberg C, Verdonschot N, Duysens J, van Kampen A. Compensation for rotational malalignment after intramedullary nailing for femoral shaft fractures. An analysis by plantar pressure measurements during gait. Injury. 2004;35(12):1270-1278.

39. Tornetta P 3rd, Ritz G, Kantor A. Femoral torsion after interlocked nailing of unstable femoral fractures. J Trauma. 1995;38(2):213-219.

40. Binkley JM, Stratford PW, Lott SA, Riddle DL. The Lower Extremity Functional Scale (LEFS): Scale Development, Measurement Properties, and Clinical Application. Phys Ther. 1999;79(4):371-383.

41. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15(12):1833-1840.

42. Sierevelt IN, van Eekeren ICM, Haverkamp D, Reilingh ML, Terwee CB, Kerkhoffs GMMJ. Evaluation of the Dutch version of the Foot and Ankle Outcome Score (FAOS): Responsiveness and Minimally Important Change. Knee Surg Sports Traumatol Arthrosc. 2016;24(4):1339-1347.

APPENDIX I

TABLE. Individual Patient Characteristics

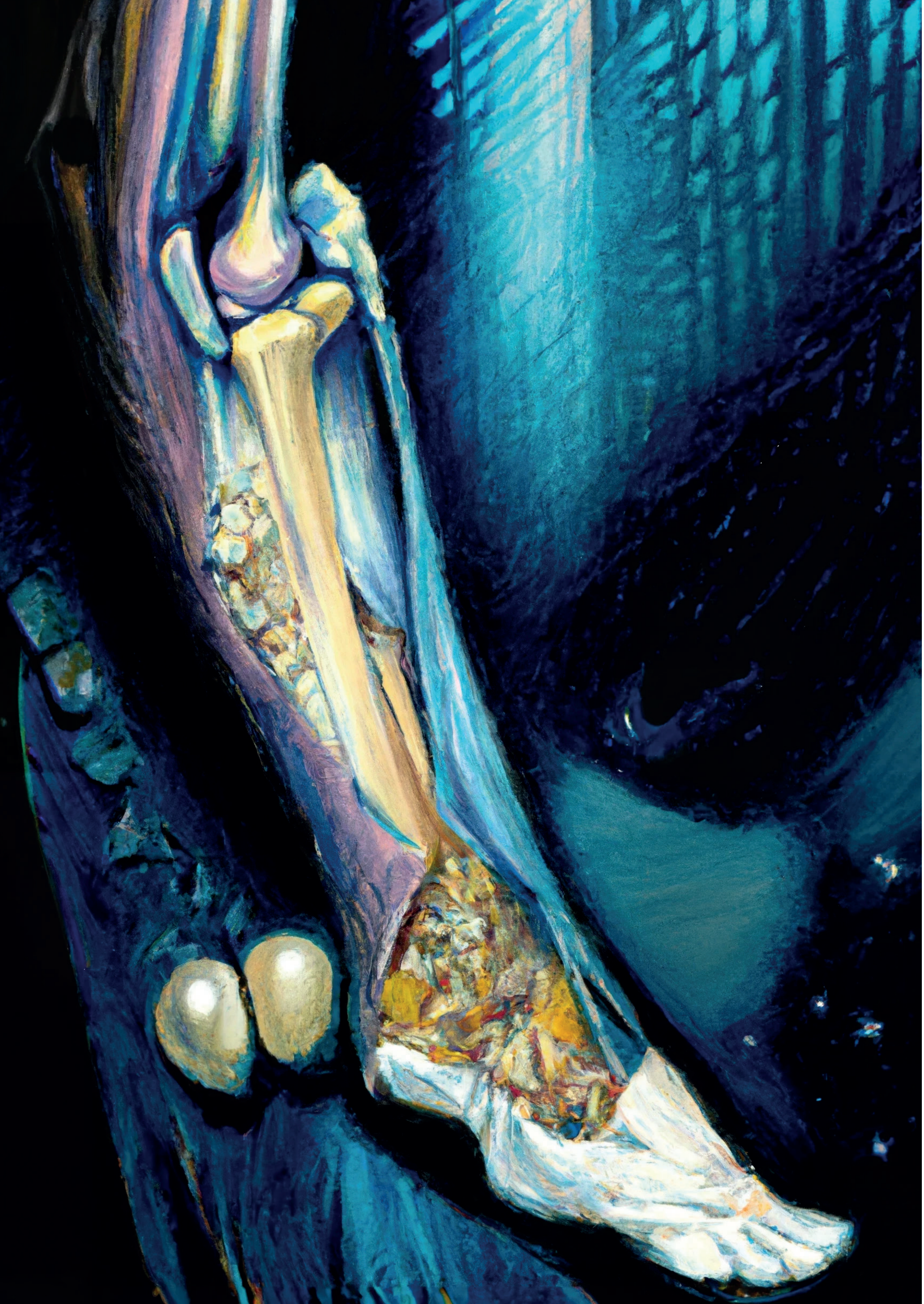
Patient	Gender	Age	BMI	Rotational Difference
1	Male	66	30.86	-18.2
2	Female	66	21.14	-1.5
3	Male	60	26.67	15.8
4	Male	54	27.08	-18.2
5	Male	64	24.31	-0.9
6	Male	31	25.71	0.0
7	Male	38	23.95	-0.9
8	Male	42	24.34	15.8
9	Male	25	25.72	-20.2
10	Male	46	26.15	12.6
11	Male	44	35.05	6.0
12	Male	55	26.87	-1.2
13	Female	47	36.47	1.6
14	Male	45	20.40	4.1
15	Male	39	26.20	-9.8
16	Male	37	20.87	-8.6
17	Male	25	24.13	-6.9
18	Female	25	21.23	6.9

APPENDIX II

TABLE. Mean and Median Values Cohort PROMS

	Mean* or Median**
PROMIS - Mental	52.26 (8.12)
PROMIS - Physical	52.82 (4.65)
KOOS Pain	95.5 [75 – 100]
KOOS Symptoms	91 [68 – 100]
KOOS ADL	98 [72 – 100]
KOOS Sports	87.5 [45 – 100]
KOOS QOL	88 [50 – 100]
FAOS Pain	95.5 [61 – 100]
FAOS Symptoms	82 [43 – 100]
FAOS ADL	98 [71 – 100]
FAOS Sports	87.5 [30 – 100]
FAOS QOL	75 [44 – 100]

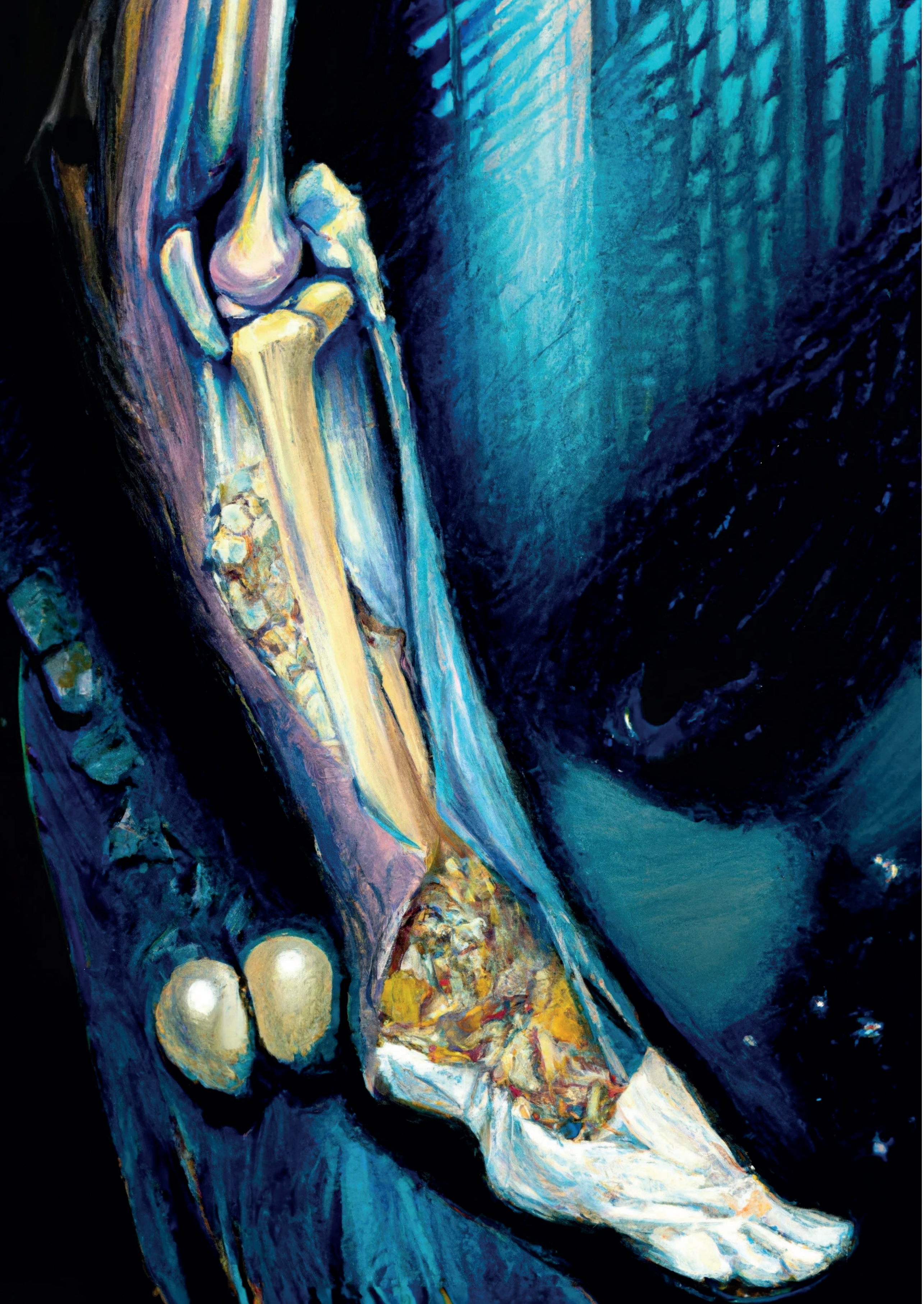
* Mean values are presented with standard deviations (sd).
** Median values are presented with ranges [range].



IV

Part IV.

Summary, Discussion and Conclusions



9

CHAPTER 9

Summary

The aim of this PhD Thesis was to contribute to individualizing the management of patients treated with intramedullary nailing for tibial shaft fractures to improve patient care. We aimed to achieve this by gaining a more in-depth knowledge regarding the various complications and subsequent surgical procedures that can occur, and by gaining a better insight in patient specific risks.

PART I. SUBSEQUENT SURGERY – RATE & PATIENT SPECIFIC RISKS

The first part of this thesis started with a retrospective study (**Chapter 2)** in which the rate of subsequent surgery, as well as predictors of subsequent surgery after intramedullary nailing of tibial shaft fractures were assessed. The study included 191 patients treated with intramedullary nailing for traumatic tibial shaft fractures, of which 87 patients (46%) underwent at least one subsequent surgical procedure. The most frequent indication for a first subsequent surgical procedure was screw removal due to irritation or pain (40%), followed by closure of wounds (25%). Predictors of subsequent surgery to promote fracture or wound healing consisted of age, multi-trauma, open fracture and surgery during weekdays. No causal predictors for subsequent surgery to remove symptomatic screws or nails were identified. Subgroup analysis furthermore demonstrated that there was no association between penetration of locking screws in the proximal- or distal tibiofibular joint and subsequent screw removal.

It remains difficult to estimate the risk of a subsequent surgical procedure for the individual patient based on the identified predictors from chapter 2. These limitations were overcome in **Chapter 3**, in which machine learning (ML) algorithms were used to develop a prediction model that calculates patient-specific probabilities of an unplanned subsequent surgical procedure. To develop this prediction model, a large database, including 1198 patients treated with intramedullary nailing of tibial shaft fractures, was used. This database was split in a derivation- and validation cohort. The derivation cohort was used to train five ML-algorithms in recognizing patterns associated with subsequent surgery. The validation cohort was subsequently used to assess each algorithm's predictive performance. This demonstrated that the best-performing ML-algorithm (boosted decision tree) was able to predict the probability of subsequent surgery. This was reflected by an area-under-the-ROC-curve of 0.862, calibration slope of 1.247, calibration intercept of 0.154 and Brier score of 0.105.

PART II. COMPLICATIONS - PATIENT SPECIFIC RISKS

In the second part of this thesis, the incidence and predictors of several complications were reviewed, in order to gain a better insight in the risks the individual patient is exposed to.

In **Chapter 4,** the incidence of rotational malalignment of the tibia was assessed in a consecutive series of 156 patients that underwent postoperative CT-scanning after tibial intramedullary nailing. Rotational malalignment is commonly defined as ≥10° rotational difference compared to the non-injured tibia. In this chapter we demonstrated that 55 out of 154 patients (36%) were affected by this complication. Twenty-six cases were affected by internal rotational malalignment (47%) and 29 cases by external rotational malalignment (53%). A more detailed analysis revealed that 22 out of the 26 cases (85%) of internal rotational malalignment occurred in left-sided tibia shaft fractures, whereas 23 out of 29 (79%) cases of external rotational malalignment occurred in right-sided fractures. This significant difference between left- and right-sided fractures may be attributable to the significant difference in physiological tibial torsion between left- (37.0°±8.2° and right-sided tibiae (41.1° ±8.0) that was furthermore identified in this chapter.

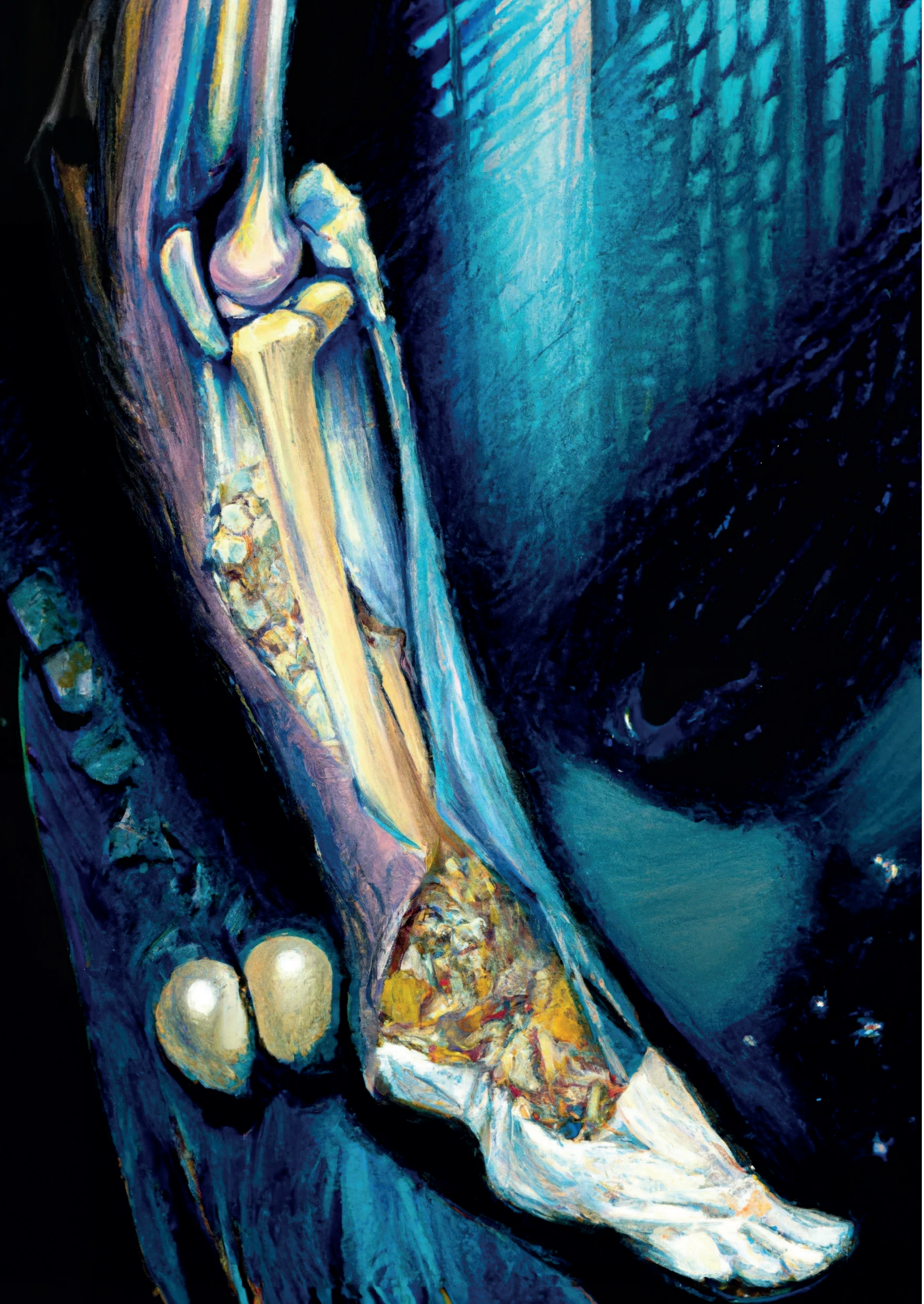
In **Chapter 5**, the incidence and predictors of posterior malleolar fractures associated with tibial shaft fractures was assessed in 164 patients. Because posterior malleolar fractures may be occult on radiographs, the true incidence of this concomitant injury remains unclear. Therefore, we based the diagnosis solely on CT-scan imaging. This demonstrated an incidence of posterior malleolar fractures associated with tibial shaft fractures of 22%. Twenty-five percent of these posterior malleolar fractures were occult on preoperative radiographs. Two independent predictors of posterior malleolar fractures were identified: 1) simple spiral tibia shaft fractures; and 2) distal third tibia shaft fractures. The presence of both these variables in a patient can correctly predict 75% of the posterior malleolar fractures. Fracture mapping revealed that posterior malleolar fractures associated with tibial shaft fractures consisted predominantly of Haraguchi Type I fractures (97%).

Chapter 6 further built on the predictors and prediction rule developed in the previous chapter. In this chapter, a large multicentre dataset consisting of 263 patients with a tibial shaft fracture was used to develop of a machine learning prediction model. Using repeated cross-validation, four different machine learning algorithms were trained in predicting posterior malleolar fractures. Subsequently, their predictive performance was assessed. The machine learning prediction model based on the Bayes point machine was superior to the other algorithms, and it could accurately predict posterior malleolar fractures. This was well reflected by an area-under-the-ROC-curve (AUC) of 0.89, calibration slope of 1.02, calibration intercept of -0.06 and Brier score of 0.106.

In **Chapter 7** we developed a machine learning prediction model to predict the risk of infection in patients operatively treated for tibial shaft fractures. To obtain an adequate sample size we combined databases from two large international multicentre randomized controlled trials, the SPRINT-trial and the FLOW-trial. This resulted in a dataset of 1822 patients with unilateral tibia shaft fractures, of which 170 patients (9%) developed an infection that required treatment. Seven variables were identified as important for predicting infection and included in model development: 1) Gustilo-Anderson classification or Tscherne classification; 2) bone loss; 3) mechanism of injury; 4) multi-trauma; 5) AO/OTA-classification; 6) age; and 7) fracture location. Five machine learning algorithms were trained and subsequently their performance was assessed. The prediction model based on the penalized logistic regression was superior based on better performance in the derivation-cohort (AUC 0.75, calibration slope 0.94, calibration intercept 0.00, Brier score 0.076) and validation-cohort (AUC 0.81, calibration slope 1.07, calibration intercept 0.09, Brier score 0.079).

PART III. WHAT OUTCOME IS ACCEPTABLE?

The third part of this thesis aimed to define to what extent iatrogenic complications limit patients' functional performance, and to what extent these complications can be accepted post-operatively to guide (post) operative management. **Chapter 8,** a prospective long-term follow-up of 18 patients treated with intramedullary nailing of tibial shaft fractures, demonstrated that patients with larger tibial rotational differences have worse long-term pain scores of the ipsilateral ankle joint. Based on minimally important changes of the Dutch FAOS-Pain (12.5 points) we calculated that a rotational difference of 14.53° results in a clinically important change in ankle pain. This chapter furthermore demonstrated that the direction and amount of tibial rotational difference affect peak gait kinematics of the hip- and knee-joint.



10

CHAPTER 10

Discussion

Implications for Clinical Practice, Opportunities for Future Research & Conclusions

Tibial shaft fractures are frequently occurring traumatic injuries (16.9-21.5 cases per 100.000 per year) [1,2] often affecting the young and active population. When these fractures are not treated adequately, they can result in chronic disability. Intramedullary nailing is widely considered the primary operative treatment for tibia shaft fractures [3,4], but even though the procedure has been in existence for several decades opportunities for further improvement remain. Especially in our era of "personalized" medicine and data driven care, it has become more important to differentiate between what is beneficial to the population and what is beneficial to the individual patient.

Therefore, the aim of this PhD Thesis was to contribute to individualizing the management of patients treated with intramedullary nailing for tibial shaft fractures in order to improve patient care.

PART I. SUBSEQUENT SURGERY – RATE AND PATIENT SPECIFIC RISKS

Over the years the technical aspects of intramedullary nailing of tibia shaft fractures have evolved substantially [5]. Nevertheless, subsequent surgery rates remain high. In a systematic review of the literature, we found that on average 1 in 5 patients will undergo more than 1 operation [5]. The re-operation rate we identified in a retrospective analysis of a consecutive series at our own level-1 trauma centre was even higher: almost 1 in 2 patients (46%) [6]. This large difference was mainly caused by 40% of subsequent surgical procedures performed to remove locking screws. It could be argued that this is a relatively minor surgical procedure, and this may be the reason why it is not commonly included in subsequent surgery rates reported in literature. However, from a patients' perspective any surgery is often considered major. Furthermore, with an estimated cost of $2000–2500 (AUD), this type of surgery can have significant impact at a socio-economic level [7]. Decreasing the rate of these procedures or the costs related to it should therefore be an aim for orthopaedic surgeons

This creates opportunity for future research: Since the final inclusion, the interlocking screws which were used at our trauma centre have been modified in order to give the screw heads a lower profile. Therefore, subject of future studies should firstly be to assess whether this modification has resulted in lower rates of screw removal. Furthermore, a recent study has shown that wide awake surgery can successfully be performed for open reduction and internal fixation of ankle fractures [8], a method that is already well known in hand surgery [9]. Future studies should assess whether wide awake surgery may also be performed to remove symptomatic locking screws and analyse how this affects costs.

The other half of subsequent surgical procedures in our series were performed to treat fracture or wound healing problems. As one may expect, these types of subsequent surgical procedures were more frequently seen in multi-trauma patients, open fractures, younger patients, and interestingly patients undergoing index surgery on a weekday [6]. Awareness of these risk factors allows clinicians to anticipate peri-operative management and better inform their patients about what they should expect. It is needless to state that good communication skills are paramount in establishing a good patient-clinician relationship. Providing patients with accurate information with individualized probabilities of outcomes may play an essential role in this. Studies have furthermore shown that more accurate expectation management results in better postoperative satisfaction rates [10,11]. To further tailor the provision of accurate information and managing expectations in patients with tibial shaft fractures, we used machine learning methods to develop a prediction model. With this prediction model, an individual estimation of the risk of subsequent surgery can be generated.

Machine learning can be applied to large data sets to develop prediction models that calculate the patient's individual risk of a specific complication or treatment outcome [12–14]. Clinicians can use these prediction models to create clinical prediction rules helping to determine when specific tests or treatments might be helpful. The use of ML offers the potential benefit of identifying non-linear relations, where the presence of a specific variable may gain importance in patients with certain characteristics, but not in those with other characteristics [12,15]. Such capabilities may give ML algorithms an advantage over traditional statistical methods in some datasets, especially when datasets grow larger and more complex. A recent study by our group demonstrated that for relatively small datasets, traditional logistic regression prediction models also suffice [16]. Nevertheless, we believe that prediction models, either ML or traditional statistical, are valuable adjuncts for clinical practice.

The development of the initial ML prediction model to predict the individual risk of subsequent surgery after tibial intramedullary nailing was the first step in a sequence of studies. The next step will consist of external validation of the ML prediction model. Subsequently, it should be prospectively evaluated in clinical practice. Ultimately the model should include a feedback loop to continuously improve diagnostic performance characteristics based on newly entered data.

Although development of ML prediction models in orthopaedic surgery is getting more widespread, relatively few of these models have been externally validated. External validation is an essential part in the cascade of developing and implementing clinical prediction models, and the absence of external validation should withhold clinicians from using such prediction models in clinical practice. Without external validation, it remains unclear whether models that have been trained on historical data, such as the SPRINT-data [17], are still valid in more recently treated patients [18,19]. Furthermore, external validation may indicate whether a prediction model remains valid in a different geographic region, or when the method of data collection is different from how the original data was collected [18,19].

After models have been externally validated, they may be utilized in clinical practice. Ideally, such models are implemented in electronic health record systems in such ways that they do not further enlarge the administrative burden clinicians already face. Natural language processing algorithms may prevent this by extracting input variables for prediction models from free text notes in patient medical records. Such algorithms have already been found to be effective and accurate in identifying surgical site infections in free-text notes [20].

Changes in patient demographics or treatment characteristics over time may affect performance of implemented prediction models. Therefore, similar to audits carried out to assure quality of care, performance of implemented prediction models needs to be periodically reviewed. Therefore, ideally, implemented prediction models consist of feedback loops that automate the above process, continuously monitoring the performance of the prediction models and automatically training algorithms on newly entered data.

Healthcare systems and hospitals have yet to adapt to the rapidly evolving machine learning and big-data analytic techniques. Awareness about the potential of these techniques amongst clinicians is increasing. This is an important first step in making this part of routine clinical care [21]. Clinicians should also have a basic understanding of how to interpret and assess prediction models if they were to use the generated advice on probability in clinically meaningful ways [21,22]. As datasets grow, including more data from the so-called ‘patient journey‘ and models become more complex, a more advanced understanding may be needed for the development, implementation, acceptance and maintenance of such models. Therefore, collaboration should be sought with data scientists to educate medical students and clinicians. Currently, few hospitals include a data analytics department involved in clinical decision making. However, it is likely that the importance of such expertise within healthcare systems and hospitals will grow. Since it is inefficient for hospitals, especially low-volume ones, to act alone in implementing this, collaboration is needed. This not only allows the development of bigger datasets resulting in more reliable prediction models but also makes the development and maintenance of prediction models more scalable and cost-efficient. Differences in healthcare systems, treatment characteristics, patient demographics or electronic health record systems may limit these collaborations on an international level, nonetheless, nationwide collaborations should be something that clinicians should strive for.

PART II. COMPLICATIONS - PATIENT SPECIFIC RISKS

Patients treated with intramedullary nailing of tibial shaft fractures are at risk for several complications. One of these complications is rotational malalignment of the tibia. In a retrospective study we not only found a high prevalence (36%) of rotational malalignment, but also showed that the laterality of the tibial shaft fracture is associated with the direction of rotational malalignment: left-sided tibial shaft fractures are prone to internal rotational malalignment whereas right-sided tibial shaft fractures result in external rotational malalignment [23]. Considerations as to why this association was found included: clockwise reaming of the intramedullary canal; the preferred handedness of the surgeon; and a pre-existent left-right difference in physiological tibial torsion. Studying the average torsion of the non-injured left- (37.0°±8.2) and right-sided tibiae (41.1° ±8.0) we found a mean left-right difference of 4°, thus we came to believe that this may play the most important role. This pre-existent difference implies that our current method of assessing RM, based on the premises of tibial symmetry, is inaccurate. This was well illustrated by reanalysis of our cohort taking the 4° difference into account: the overall prevalence of rotational malalignment decreased to 29%, and there now was a similar distribution of internal and external rotational malalignment for left and right-sided tibial shaft fractures. Although potentially being inaccurate, current best practice in assessing rotational malalignment postoperatively still relies on assuming symmetric torsion between the left and right tibia. As we are dealing with a mean value of 4° with a difference between the highest and lowest values for tibial torsion in our cohort of >30°, the only way to accurately determine the pre-existing difference in tibial torsion for the individual patient is to obtain pre-fracture CT scans of both legs. For obvious reasons, this is not possible. Nevertheless, it remains interesting to verify the hypothetical 4° difference in tibial torsion in a study of the normal population and to assess if there are any factors associated to a left-right or right-left difference. Several other opportunities for research on postoperative rotational malalignment of the tibia also remain. A more comprehensive study assessing if there are other predictors of the direction of rotational malalignment in patients treated with intramedullary nailing, such as fracture type, is currently being undertaken. Furthermore, a randomized controlled trial is being undertaken in which the prevalence of rotational malalignment after intramedullary nailing of tibia shaft fractures with draping of both legs versus draping of one leg is compared. Furthermore, an intra-operative imaging strategy is currently prospectively evaluated. In short: for the contralateral –intact- tibia, a reproducible anteroposterior (AP) radiographs with the image intensifier is obtained, and with this limb stabilized in the position with the perfect AP of the knee, a reproducible mortise view of the ankle is obtained by rotating the image intensifier (ii) until the perfect mortise is obtained. Subsequently, the rotation in degrees can be read from the ii machine. Finally, the perfect AP of the knee is obtained on the knee on the ipsilateral side of the fractured tibia fixed with IMN; then the ii is set in the degrees of rotation that was read from the contralateral side, and the distal end of the fractured limb is rotated and reduced on the –yet- unlocked nail so that a perfect mortise can be obtained. This strategy is reproducible and accurate in vitro, and is currently tested in vivo.

Also, Orthopaedic Trauma surgeons must be aware of the potential presence of an occult (i.e. not visible on plain lateral injury radiographs) posterior malleolar fracture (PMF) in the preoperative work-up of patients with tibial shaft fractures. In 22% of patients with a tibial shaft fracture, there is a PMF present. Moreover, 25% of these PMFs are occult [24]. If these fractures remain undiagnosed, they are at risk of iatrogenic displacement by the intramedullary nail or by early mobilization of the patient. Especially patients with a distal third and spiral tibial shaft fracture are at an increased risk of PMFs: the presence of both these variables could predict 75% of PMFs in our cohort. The presence of these fracture characteristics should therefore be a red flag for orthopaedic surgeons. By developing a ML prediction model, we aimed to further individualize the pre-operative diagnostic work-up of patients with a tibia shaft fractures. This model showed excellent performance in predicting PMFs [25]. Currently, we are undertaking a study to externally validate this ML prediction model. Also, the first steps are being undertaken to incorporate the model in a commonly used electronic health record system.

Infection is a common complication after operative treatment of tibia shaft fractures, affecting 3% to 9% of patients in the entire population, but surgeons' clinical experience tells us that some patients are prone and may have an individual risk of up to 50% or more [5,17,26–29]. However, for humans –surgeons- "it is difficult to make predictions, especially about the future (of our patients)". We developed a ML prediction model to identify individual patients who were at risk for infection after operative treatment of tibia shaft fractures and quantify such risks with a probability calculator. The model was based on patient and fracture characteristics that are available at hospital admission, allowing clinicians to identify high-risk patients at a preoperative stage. Clinical value of this prediction model may lie in closer monitoring of high-risk patients by acquiring additional blood tests or intensifying outpatient follow-up, this way infection can be detected earlier. Furthermore, early intervention with the application of local antibiotics in those with open fractures at a high risk of infection may aid in averting infection or in reducing infection-related consequences including prolonged hospital stays, higher rehospitalization rates, costs associated with infection, and lower quality of life [30]. The application of local antibiotics has been subject of debate in recent years [31–35], and may not be beneficial for the entire group of patients with tibial shaft fractures. Whilst prophylactic use of local antibiotics in patients with open fractures has been demonstrated to reduce infection rates [31], concerns about antimicrobial resistance remain [31–33]. Further stratifying between high-risk and low-risk patients with open fractures in order to determine which specific patients may benefit from prophylactic local antibiotics may prove to be a solution to these concerns. Therefore, after external validation of diagnostic accuracy, subject of future studies should be to assess whether the prediction model can be effectively used to decrease infection rates whilst minimizing the number needed to treat.

PART III. WHAT OUTCOME IS ACCEPTABLE?

Despite the high prevalence of 36%, evidence on the effect of rotational malalignment on functional outcome is scarce. Therefore, we initiated a study in which we evaluated the effect of rotational malalignment on gait and patient reported outcome measures (PROMS).

This demonstrated that several peak gait kinematics of the knee and hip joint are affected by the direction and the amount of rotational difference between the injured and non-injured tibia. Currently there are no studies available that can confirm these findings.

Furthermore, contrarily to what has thus far been reported, we demonstrated that larger rotational differences between the injured and non-injured tibia after intramedullary nailing of tibia shaft fractures are associated with increasingly worse, long-term, pain scores of the ankle. To the best of our knowledge, thus far only two studies have previously assessed the effect of rotational malalignment after tibial intramedullary nailing on long-term functional outcome based on PROMS [36,37]. In a prospective cohort study, Theriault and colleagues compared 29 patients with rotational malalignment (i.e., >10° rotational difference) to 41 patients without rotational malalignment after tibial intramedullary nailing. They could not demonstrate any differences in PROMS. In a smaller study including 13 patients conducted by Boucher and colleagues, no correlation could be demonstrated between rotational differences and PROMS [38].

These studies contrast with the findings of our study. This difference may be caused using different PROMS. Also, Theriault and colleagues used a cut-off value of 10° to distinguish between patients with and without rotational malalignment, rather than treating rotational difference as a continuous outcome [36]. This may have concealed effects of larger degrees of rotational difference. Given the fact that our study consisted of relatively small sample size, future studies assessing the association between tibial rotational difference and PROMS are needed. These studies should consist of larger sample sizes, and they should treat rotational difference as a continuous outcome rather than using a cut-off value to create a rotational malalignment group and a control group.

CONCLUSIONS

This thesis has increased our understanding about complications and subsequent surgical procedures that occur in patients treated with intramedullary nailing for tibial shaft fractures. Furthermore, patient specific risks have been identified and prediction models have been developed. This creates several opportunities for orthopaedic trauma surgeons to further individualize the pre-, intra-, and postoperative management of patients with tibial shaft fractures, thereby improving patient care (Table 1). Future studies building on this thesis should validate its findings and assess if the suggested opportunities for individualizing management result in improvement of patient outcome.

TABLE 1. Opportunities for individualizing management of patients with tibial shaft fractures.

Preoperative Setting
Individualizing patient consent based on the patient specific risk of subsequent surgery and infection.
Acquiring additional preoperative CT-scans in patients at an increased risk of a posterior malleolar fracture.
Intraoperative Setting
Preventing rotational malalignment by being aware of this frequently occurring pitfall, and apply an imaging strategy to prevent RM
Applying malleolus-first fixation in case of an associated posterior malleolar fracture.
Applying local antibiotics in patients with open fractures at a high risk of infection
Postoperative Setting
Adjusting postoperative management (e.g., additional blood tests or intensifying outpatient follow-up) in patients at an increased risk of subsequent surgery or infection.

REFERENCES

1. Court-Brown CM, Caesar B. Epidemiology of adult fractures: A review. Injury. 2006;37(8):691-697.
2. Larsen P, Elsoe R, Hansen SH, Graven-Nielsen T, Laessoe U, Rasmussen S. Incidence and epidemiology of tibial shaft fractures. Injury. 2015;46(4):746-750.
3. Busse JW, Morton E, Lacchetti C, Guyatt GH, Bhandari M. Current management of tibial shaft fractures: a survey of 450 Canadian orthopedic trauma surgeons. Acta Orthop. 2008;79(5):689-694.
4. Bhandari M, Guyatt GH, Swiontkowski MF, et al. Surgeons' preferences for the operative treatment of fractures of the tibial shaft. An international survey. J Bone Joint Surg Am. 2001;83-A(11):1746-1752.
5. Hendrickx LAM, Virgin J, van den Bekerom MPJ, Doornberg JN, Kerkhoffs GMMJ, Jaarsma RL. Complications and subsequent surgery after intra-medullary nailing for tibial shaft fractures: Review of 8110 patients. Injury. Published online April 22, 2020. doi:10.1016/j.injury.2020.04.021
6. Hendrickx LAM, Virgin J, Doornberg JN, Kerkhoffs GMMJ, Jaarsma RL. Factors associated with subsequent surgical procedures after intramedullary nailing for tibial shaft fractures. Eur J Orthop Surg Traumatol. 2021;31(1):43-50.
7. Busam ML, Esther RJ, Obremskey WT. Hardware removal: indications and expectations. J Am Acad Orthop Surg. 2006;14(2):113-120.
8. Tahir M, Chaudhry EA, Ahmed N, et al. Ankle Fracture Fixation with Use of WALANT (Wide Awake Local Anesthesia with No Tourniquet) Technique: An Attractive Alternative for the Austere Environment. J Bone Joint Surg Am. Published online January 12, 2021. doi:10.2106/JBJS.20.00196
9. Warrender WJ, Lucasti CJ, Ilyas AM. Wide-Awake Hand Surgery: Principles and Techniques. JBJS Rev. 2018;6(5):e8.
10. Trinh LN, Fortier MA, Kain ZN. Primer on adult patient satisfaction in perioperative settings. Perioper Med (Lond). 2019;8:11.
11. Hamilton DF, Lane JV, Gaston P, et al. What determines patient satisfaction with surgery? A prospective cohort study of 4709 patients following total joint replacement. BMJ Open. 2013;3(4). doi:10.1136/bmjopen-2012-002525
12. Bertsimas D, Dunn J, Velmahos GC, Kaafarani HMA. Surgical Risk Is Not Linear: Derivation and Validation of a Novel, User-friendly, and Machine-learning-based Predictive OpTimal Trees in Emergency Surgery Risk (POTTER) Calculator. Ann Surg. 2018;268(4):574-583.
13. Karhade AV, Thio QCBS, Ogink PT, et al. Predicting 90-Day and 1-Year Mortality in Spinal Metastatic Disease: Development and Internal Validation. Neurosurgery. Published online March 14, 2019. doi:10.1093/neuros/nyz070
14. Thio QCBS, Karhade AV, Ogink PT, et al. Can Machine-learning Techniques Be Used for 5-year Survival Prediction of Patients With Chondrosarcoma? Clin Orthop Relat Res. 2018;476(10):2040-2048.
15. Ouyang FS, Guo BL, Ouyang LZ, et al. Comparison between linear and nonlinear machine-learning algorithms for the classification of thyroid nodules. Eur J Radiol. 2019;113:251-257.

16. Oosterhoff JHF, Gravesteijn BY, Karhade AV, et al. Feasibility of Machine Learning and Logistic Regression Algorithms to Predict Outcome in Orthopaedic Trauma Surgery. JBJS. 2022;104(6):544.

17. Study to Prospectively Evaluate Reamed Intramedullary Nails in Patients with Tibial Fractures Investigators, Bhandari M, Guyatt G, et al. Randomized trial of reamed and unreamed intramedullary nailing of tibial shaft fractures. J Bone Joint Surg Am. 2008;90(12):2567-2578.

18. Steyerberg EW. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. Springer, Cham; 2019.

19. Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. Ann Intern Med. 1999;130(6):515-524.

20. Thirukumaran CP, Zaman A, Rubery PT, et al. Natural Language Processing for the Identification of Surgical Site Infections in Orthopaedics. J Bone Joint Surg Am. 2019;101(24):2167-2174.

21. Oosterhoff JHF, Doornberg JN, Machine Learning Consortium. Artificial intelligence in orthopaedics: false hope or not? A narrative review along the line of Gartner's hype cycle. EFORT Open Reviews. Published online October 26, 2020. doi:10.1302/2058-5241.5.190092

22. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J. 2014;35(29):1925-1931.

23. Cain ME, Hendrickx LAM, Bleeker NJ, Lambers KTA, Doornberg JN, Jaarsma RL. Prevalence of Rotational Malalignment After Intramedullary Nailing of Tibial Shaft Fractures: Can We Reliably Use the Contralateral Uninjured Side as the Reference Standard? J Bone Joint Surg Am. 2020;102(7):582-591.

24. Hendrickx LAM, Cain ME, Sierevelt IN, et al. Incidence, Predictors, and Fracture Mapping of (Occult) Posterior Malleolar Fractures Associated With Tibial Shaft Fractures. J Orthop Trauma. 2019;33(12):e452-e458.

25. Hendrickx LAM, Sobol GL, Langerhuizen D, et al. A Machine Learning Algorithm to Predict the Probability of (Occult) Posterior Malleolar Fractures Associated with Tibial Shaft Fractures to Guide "Malleolus First" Fixation. J Orthop Trauma. 2019;Publish Ahead of Print. doi:10.1097/BOT.0000000000001663

26. Metsemakers WJ, Handojo K, Reynders P, Sermon A, Vanderschot P, Nijs S. Individual risk factors for deep infection and compromised fracture healing after intramedullary nailing of tibial shaft fractures: a single centre experience of 480 patients. Injury. 2015;46(4):740-745.

27. Gaebler C, Berger U, Schandelmaier P, et al. Rates and odds ratios for complications in closed and open tibial fractures treated with unreamed, small diameter tibial nails: a multicenter analysis of 467 cases. J Orthop Trauma. 2001;15(6):415-423.

28. Stavrou PZ, Ciriello V, Theocharakis S, et al. Prevalence and risk factors for re-interventions following reamed intramedullary tibia nailing. Injury. 2016;47 Suppl 7:S49-S52.

29. Bachoura A, Guitton TG, Smith RM, Vrahas MS, Zurakowski D, Ring D. Infirmity and injury complexity are risk factors for surgical-site infection after operative fracture care. Clin Orthop Relat Res. 2011;469(9):2621-2630.

30. Whitehouse JD, Friedman ND, Kirkland KB, Richardson WJ, Sexton DJ. The impact of surgical-site infections following orthopedic surgery at a community hospital and a university hospital: adverse quality of life, excess length of stay, and extra cost. Infect Control Hosp Epidemiol. 2002;23(4):183-189.

31. Morgenstern M, Vallejo A, McNally MA, et al. The effect of local antibiotic prophylaxis when treating open limb fractures: A systematic review and meta-analysis. Bone Joint Res. 2018;7(7):447-456.

32. Lawing CR, Lin FC, Dahners LE. Local Injection of Aminoglycosides for Prophylaxis Against Infection in Open Fractures. J Bone Joint Surg Am. 2015;97(22):1844-1851.

33. Bryson DJ, Morris DLJ, Shivji FS, Rollins KR, Snape S, Ollivere BJ. Antibiotic prophylaxis in orthopaedic surgery: difficult decisions in an era of evolving antibiotic resistance. Bone Joint J. 2016;98-B(8):1014-1019.

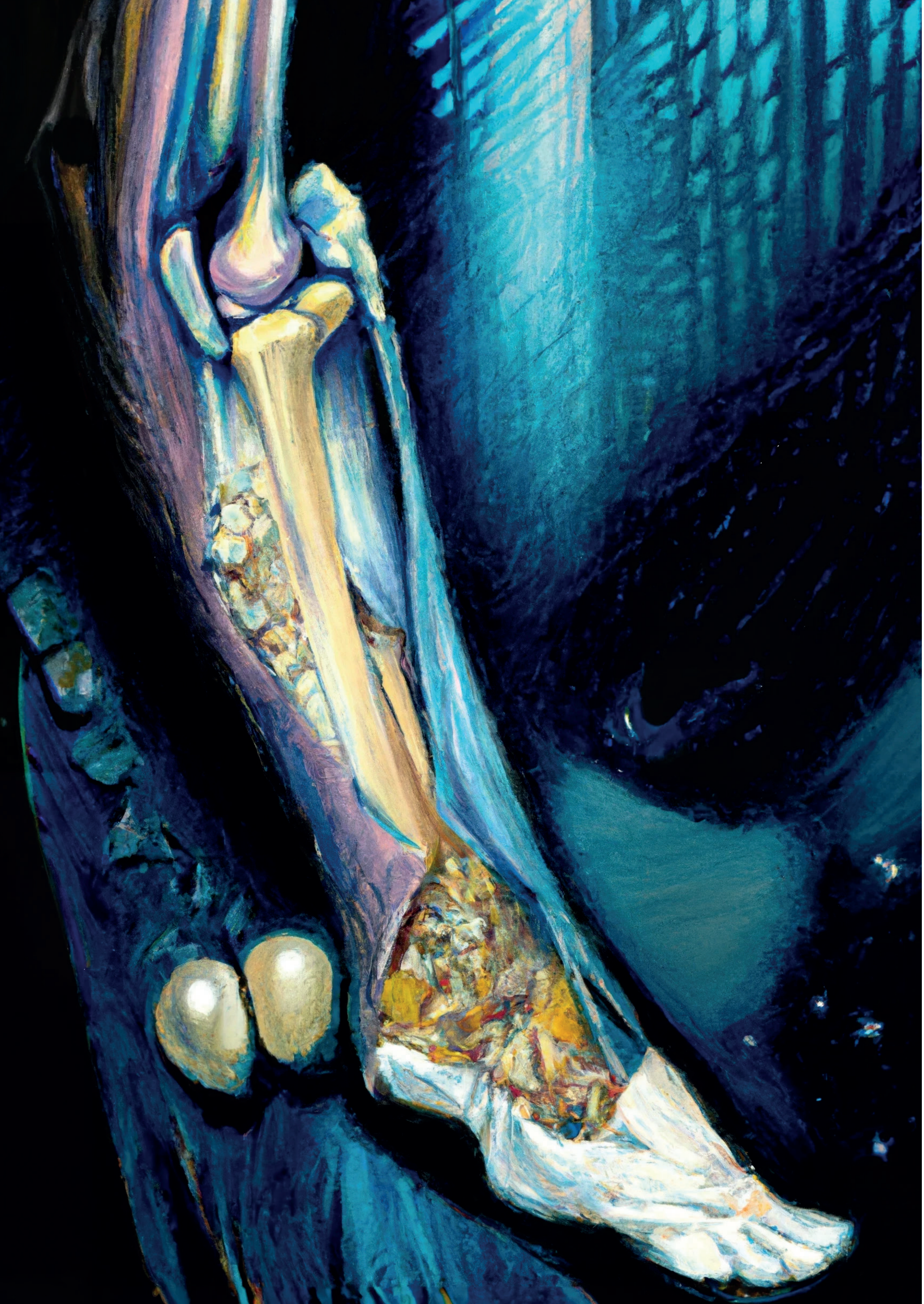
34. O'Toole RV, Joshi M, Carlini AR, et al. Local Antibiotic Therapy to Reduce Infection After Operative Treatment of Fractures at High Risk of Infection: A Multicenter, Randomized, Controlled Trial (VANCO Study). J Orthop Trauma. 2017;31 Suppl 1:S18-S24.

35. Shiels SM, Tennent DJ, Wenke JC. Topical rifampin powder for orthopedic trauma part I: Rifampin powder reduces recalcitrant infection in a delayed treatment musculoskeletal trauma model. J Orthop Res. 2018;36(12):3136-3141.

36. Theriault B, Turgeon AF, Pelet S. Functional impact of tibial malrotation following intramedullary nailing of tibial shaft fractures. J Bone Joint Surg Am. 2012;94(22):2033-2039.

37. Boucher M, Leone J, Pierrynowski M, Bhandari M. Three-dimensional assessment of tibial malunion after intramedullary nailing: a preliminary study. J Orthop Trauma. 2002;16(7):473-483.

38. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15(12):1833-1840.



11

CHAPTER 11

Nederlandse Samenvatting

Nederlandse Samenvatting

Dit proefschrift had ten doel de operatieve behandeling van tibiaschacht fracturen verder te individualiseren, om hiermee de kwaliteit van de patiëntenzorg en de uitkomsten te verbeteren. We hebben getracht dit te bewerkstelligen door een beter inzicht te verkrijgen in de verschillende complicaties en re-operaties die bij deze procedure op treden en door te analyseren wat de patiënt specifieke risico's hiervoor zijn.

DEEL I. RE-OPERATIES – INCIDENTIE & PATIËNT SPECIFIEKE RISICO'S

In Hoofdstuk 2 zijn de incidentie van re-operaties, en voorspellende factoren van re-operatie, na intramedullaire fixatie van tibiaschacht fracturen onderzocht. Deze studie bestond uit 191 patiënten die behandeld zijn met intramedullaire fixatie van tibiaschacht fracturen, waarvan 87 patiënten (46%) ten minste één re-operatie ondergingen. De meest voorkomende indicatie voor een eerste re-operatie was het verwijderen van schroeven die pijn veroorzaakten (40%), hierna was het sluiten van wonden de meest voorkomende indicatie (25%). Voorspellende factoren voor re-operatie ten behoeve van fractuurgenezing of wondgenezing waren: leeftijd, polytrauma, open fracturen en "index surgery" verricht op doordeweekse dagen. Er werden geen voorspellende factoren gevonden voor het verwijderen van symptomatische schroeven of pennen. Subgroep analyse toonde aan dat er geen verband was tussen het optreden van penetratie van schroeven in het proximale of distale tibiofibulaire gewricht en het verwijderen van schroeven.

Het blijft lastig om te voorspellen wat de individuele kans op een re-operatie is op basis van de risicofactoren uit Hoofdstuk 2. In Hoofdstuk 3 hebben we dit opgelost door een voorspelmodel te ontwikkelen met behulp van Machine Learning algoritmen. Met dit voorspelmodel kunnen patiënt-specifieke risico's op een ongeplande re-operatie worden berekend. Voor de ontwikkeling van het model hebben we gebruik gemaakt van een database die bestaat uit 1198 patiënten die behandeld zijn met intramedullaire fixatie van tibiaschacht fracturen. Deze database werd gesplitst in een training-cohort en een test-cohort. Het training-cohort werd gebruikt om vijf verschillende Machine Learning algoritmen te trainen in het voorspellen van de kans op een re-operatie. Het test-cohort werd vervolgens gebruikt om te bepalen welk Machine Learning algoritme het beste presteerde in het voorspellen van deze kans. Dit werd bepaald aan de hand van de Area-Under-the-ROC-curve, calibration-slope, calibration intercept en Brier-score. Het best presterende model was gebaseerd op een Boosted-Decision-Tree algoritme, met een area-under-the-ROC-curve van 0.862, calibration slope van 1.247, calibration intercept van 0.154 en Brier score van 0.105.

DEEL II. COMPLICATIES – PATIËNT SPECIFIEKE RISICO'S

In het tweede deel van deze thesis hebben we de incidentie en voorspellende factoren van verscheidene complicaties geanalyseerd, om een beter inzicht te krijgen in de risico's van de individuele patiënt.

In Hoofdstuk 4 hebben we de incidentie van malrotatie van de tibia bepaald bij 156 patiënten die na intramedullaire fixatie van de tibia een CT-scan ondergingen. Malrotatie wordt gedefinieerd als een rotatie deformiteit van ≥10 graden van de aangedane tibia vergeleken met de niet aangedane tibia. In de serie van 156 patiënten was er bij 55 patiënten (36%) sprake van malrotatie. Hiervan was er bij 26 patiënten (47%) sprake van interne malrotatie en bij 29 patiënten (53%) externe malrotatie. Verdere analyse toonde aan dat bij 22 van de 26 patiënten (85%) met interne malrotatie het linkerbeen intramedullaire fixatie had ondergaan, bij 23 van de 29 (79%) patiënten met externe malrotatie was dit het rechterbeen. Dit significante verschil in linkszijdige en rechtszijdige fracturen zou mogelijk verklaard kunnen worden door het (significante) fysiologische verschil in torsie van de tibia tussen linker (37.0 ±8.2) en rechter tibiae (41.1 ±8.0) dat eveneens in deze studie werd aangetoond.

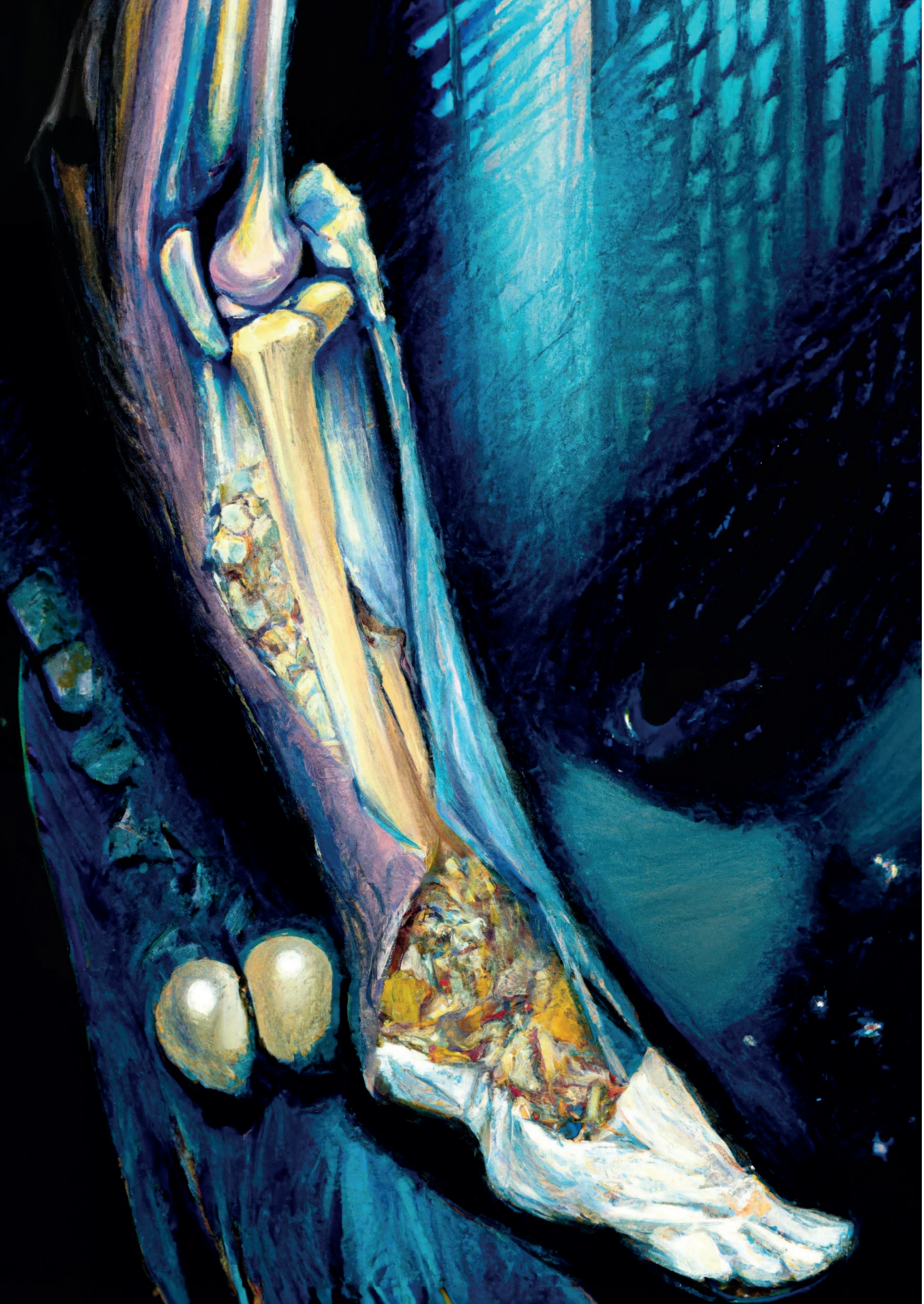
In Hoofdstuk 5 zijn de incidentie en voorspellers van fracturen van de posterieure malleolus bij tibiaschacht fracturen onderzocht in een serie van 164 patiënten. Omdat posterieure malleolus fracturen occult kunnen zijn op conventionele röntgenfoto's, is het onduidelijk wat de ware incidentie van deze bijkomende fractuur is. Daarom hebben we in deze studie de diagnose gebaseerd op CT-scans. Hiermee werd een incidentie van posterieure malleolus fracturen bij patiënten met tibia schacht fracturen van 22% aangetoond. Vijfentwintig procent (25%) van deze fracturen was occult op preoperatieve conventionele röntgenfoto's. Er werden twee onafhankelijke voorspellers voor posterieure malleolus fracturen gevonden: 1) niet communitieve spiraal fracturen van de tibiaschacht; en 2) fracturen in het distale 1/3 van de tibiaschacht. De aanwezigheid van beide variabelen bij een patiënt kan 75% van de posterieure malleolus fracturen voorspellen. Het "mappen" van alle fractuurpatronen toonde aan de posterieure malleolus fracturen bij tibiaschacht fracturen voornamelijk uit Haraguchi Type I fracturen bestaan (97%).

In Hoofdstuk 6 werd een multicenter dataset, die uit 263 patiënten met een tibiaschacht fractuur bestond, gebruikt om een Machine Learning voorspelmodel te ontwikkelen. Vier verschillende Machine Learning algoritmen werden middels cross validatie getraind in het voorspellen van posterieure malleolus fracturen bij patiënten met een tibiaschacht fractuur. Het Machine Learning algoritme dat hier het beste toe in staat was, was het Bayes point machine algoritme, met een area-under-the-ROC-curve (AUC) van 0.89, calibration slope van 1.02, calibration intercept van -0.06 en Brier score van 0.106.

In Hoofdstuk 7 hebben we een Machine Learning voorspelmodel ontwikkeld om het risico op infectie te voorspellen bij patiënten die geopereerd worden voor een tibiaschacht fractuur. Hiertoe hebben we twee grote internationale multicentre RCT's gecombineerd, respectievelijk de SPRINT-trial en FLOW-trial. Dit resulteerde in een dataset van 1822 patiënten met een unilaterale tibiaschacht fractuur, waarvan 170 patiënten (9%) een infectie ontwikkelde die behandeling behoefde. Zeven variabelen uit de dataset werden geïdentificeerd als voorspellende factoren voor infectie: 1) Gustilo-Anderson classificatie of Tscherne classificatie; 2) botverlies; 3) ongevalsmechanisme; 4) multi-trauma; 5) AO/OTA-classificatie; 6) leeftijd; en 7) locatie van de fractuur. Vijf verschillende Machine Learning algoritmen werden met behulp van deze variabelen getraind in het voorspellen van infectie. Het voorspelmodel gebaseerd op het "penalized logistic regression" algoritme was het beste in staat om infectie te voorspellen in zowel het train-cohort (AUC 0.75, calibration slope 0.94, calibration intercept 0.00, Brier score 0.076) als het test-cohort (AUC 0.81, calibration slope 1.07, calibration intercept 0.09, Brier score 0.079).

DEEL III. WELKE UITKOMST IS ACCEPTABEL?

Het derde deel van deze thesis had als doel om te definiëren in welke mate iatrogene complicaties de functie van patiënten limiteren en in welke mate deze complicaties postoperatief geaccepteerd kunnen worden. Hoofdstuk 8 betreft een prospectieve long-term follow-up van 18 patiënten behandeld met intramedullaire fixatie van tibiaschacht fracturen. In dit hoofdstuk werd aangetoond dat patiënten met grotere postoperatieve rotatieverschillen tussen de aangedane en niet-aangedane tibia, slechtere long-term pijn scores hebben van de enkel aan de geopereerde zijde. Op basis van "minimally important changes" van de "Nederlandse" FAOS-pijn score (12.5 punt) hebben we berekend dat een rotatieverschil van 14.53° resulteert in een klinisch relevant verschil van pijn in de enkel. In dit hoofdstuk werd verder aangetoond dat de richting en mate van rotatieverschil in de tibia effect heeft op de "peak gait kinematics" van de heup- en kniegewrichten.



Appendices

Portfolio

List of publications

Dankwoord

About the Author

PORTFOLIO

(Inter)national Conferences	Year	Workload (ECTS)
Australian Orthopaedic Association's Annual Scientific Meeting, Perth, Western Australia, Australia	2018	1.0
Australian Orthopaedic Association Annual Scientific Meeting SA/NT, Adelaide, South-Australia, Australia	2018	0.5
Australian Orthopaedic Trauma Society, Annual Scientific Meeting, Noosa, Queensland, Australia	2018	0.5
NOV Jaarcongres, Den Bosch, The Netherlands	2019	0.5
Traumadagen, Amsterdam, The Netherlands	2019	0.5
OTA Annual Meeting, Denver, Colorado, USA	2019	1.0
Symposium Experimenteel Onderzoek Heelkundige Specialismen, Amsterdam, The Netherlands	2019	0.5
Australian Orthopaedic Trauma Society Annual Scientific Meeting, Cairns, Queensland, Australia	2019	0.5
Australian Orthopaedic Association Annual Scientific Meeting SA/NT, Adelaide, South-Australia, Australia	2019	0.5
Australian Orthopaedic Association's Annual Scientific Meeting, Canberra, Australian Capital Territory, Australia	2019	1.0
Virtual EFORT Congress, Vienna, Austria	2020	0.5
NOV Jaarcongres, Utrecht, The Netherlands	2023	0.5

Presentations		
A Machine Learning Algorithm to Predict the Probability of (Occult) Posterior Malleolar Fractures Associated with Tibial Shaft Fractures to Guide "Malleolus First" Fixation.		
ORAL - Australian Orthopaedic Association, Annual Scientific Meeting SA/NT, Adelaide, South-Australia, Australia	2019	0.5
ORAL - Australian Orthopaedic Trauma Society, Annual Scientific Meeting, Cairns, Queensland, Australia	2019	0.7
ORAL - Australian Orthopaedic Association's Annual Scientific Meeting, Canberra, Australian Capital Territory, Australia	2019	0.7
POSTER - Virtual EFORT Congress, Vienna, Austria	2020	0.4
A Machine Learning Algorithm to Predict Infection After Operative Treatment of Tibial Shaft Fractures.		
ORAL - Symposium Experimenteel Onderzoek Heelkundige Specialismen, Amsterdam, The Netherlands	2019	0.5
POSTER - Virtual EFORT Congress, Vienna, Austria	2020	0.4

A Machine Learning Algorithm to Identify Patients at Risk of Subsequent Surgery After Intramedullary Nailing for Tibial Shaft Fractures.

ORAL - Virtual EFORT Congress, Vienna, Austria	2020	0.5
POSTER - Traumadagen, Amsterdam, The Netherlands	2019	0.4

Prevalence of Rotational Malalignment After Intramedullary Nailing of Tibial Shaft Fractures: Can We Reliably Use the Contralateral Uninjured Side as The Reference Standard?

ORAL - Virtual EFORT Congress, Vienna, Austria	2020	0.5
POSTER - Symposium Experimenteel Onderzoek Heelkundige Specialismen, Amsterdam, The Netherlands	2019	0.4

Incidence, Predictors and Fracture Mapping Of (Occult) Posterior Malleolar Fractures Associated with Tibial Shaft Fractures.

ORAL - Australian Orthopaedic Association Annual Scientific Meeting SA/NT, Adelaide, South-Australia, Australia	2018	0.5
ORAL - Australian Orthopaedic Association's Annual Scientific Meeting, Perth, Western Australia, Australia	2018	0.7
ORAL - Australian Orthopaedic Trauma Society Annual Scientific Meeting, Noosa, Queensland, Australia	2018	0.7
ORAL - NOV Jaarcongres, Den Bosch, The Netherlands	2019	1.0
ORAL - Traumadagen, Amsterdam, The Netherlands	2019	1.0
POSTER - OTA Annual Meeting, Denver, Colorado, USA	2019	0.4
POSTER - Virtual EFORT Congress, Vienna, Austria	2020	0.4

Radial Nerve Palsy Associated with Closed Humeral Shaft Fractures: A Systematic Review of 1221 Patients.

POSTER - 28th Congress SECEC-ESSSE, Geneva, Switzerland,	2018	0.4

A Machine Learning Algorithm to Identify Patients with Tibial Shaft Fractures at Risk for Infection After Operative Treatment

ORAL – Presented by J. Oosterhoff - AAOS Annual Meeting, San Diego, USA	2021	0.5

Courses

Practical Biostatistics Course, AMC Graduate School, Amsterdam, The	2019	1.0
Netherlands	2021	1.0
Tutoring/Supervising	2021	1.0
PhD-candidate Anouk van de Kuijt		
PhD-candidate Hidde Dijkstra		

Meetings

Weekly Research Meeting Adelaide Research Factory, Flinders University, Adelaide, South Australia, Australia	2018-2020	3.0
Weekly Research Meeting Department of Orthopaedic & Trauma Surgery, Flinders Medical Centre, Adelaide, South Australia, Australia	2018-2020	2.0

Parameters of Esteem

Flinders High Potential PhD Grant	2019	0.5
Michael van Vlooten Fonds	2019	0.5
KNAW van Leersum Beurs	2019	0.5
Traumaplatform Travel Grant	2019	0.5
Prins Bernhard Cultuurfonds	2019	1.0
Flinders University Student Association Travel Grant	2019	0.5
Traumaplatform Research Grant	2018	0.5
Annafonds Reisbeurs	2018	0.5
Marti-Keuning Eckhardt Stichting	2018	1.0
Finders High Potential PhD Grant	2018	0.5
Flinders University Student Association Travel Grant	2018	0.5

LIST OF PUBLICATIONS

1. Hendrickx, Laurent A. M., Megan E. Cain, Inger N. Sierevelt, Bhavin Jadav, Gino M. M. J. Kerkhoffs, Ruurd L. Jaarsma, and Job N. Doornberg. 2019. “Incidence, Predictors, and Fracture Mapping of (Occult) Posterior Malleolar Fractures Associated With Tibial Shaft Fractures.” Journal of Orthopaedic Trauma 33 (12): e452–58.
2. Hendrickx, Laurent A. M., Garret L. Sobol, David W. G. Langerhuizen, Anne Eva J. Bulstra, Jeremy Hreha, Sheila Sprague, Michael S. Sirkin, David Ring, Gino M. M. J. Kerkhoffs, Ruurd L. Jaarsma, Job N. Doornberg, and Machine Learning Consortium. 2020. “A Machine Learning Algorithm to Predict the Probability of (Occult) Posterior Malleolar Fractures Associated With Tibial Shaft Fractures to Guide ‘Malleolus First’ Fixation.” Journal of Orthopaedic Trauma 34 (3): 131–38.
3. Cain, Megan E., Laurent A. M. Hendrickx, Nils Jan Bleeker, Kaj T. A. Lambers, Job N. Doornberg, and Ruurd L. Jaarsma. 2020. “Prevalence of Rotational Malalignment After Intramedullary Nailing of Tibial Shaft Fractures: Can We Reliably Use the Contralateral Uninjured Side as the Reference Standard?” The Journal of Bone and Joint Surgery. American Volume 102 (7): 582–91.
4. Bergsma, Minke, Job N. Doornberg, Laurent Hendrickx, Batur Hayat, Gino M. M. J. Kerkhoffs, Bhavin Jhadav, Ruurd L. Jaarsma, and Gregory I. Bain. 2020. “Interpretations of the Term ‘Watershed Line’ Used as Reference for Volar Plating.” Journal of Wrist Surgery 9 (3): 268–74.
5. Hendrickx, Laurent A. M., James Virgin, Michel P. J. van den Bekerom, Job N. Doornberg, Gino M. M. J. Kerkhoffs, and Ruurd L. Jaarsma. 2020. “Complications and Subsequent Surgery after Intra-Medullary Nailing for Tibial Shaft Fractures: Review of 8110 Patients.” Injury 51 (7): 1647–54.
6. Hendrickx, Laurent A. M., James Virgin, Job N. Doornberg, Gino M. M. J. Kerkhoffs, and Ruurd L. Jaarsma. 2021. “Factors Associated with Subsequent Surgical Procedures after Intramedullary Nailing for Tibial Shaft Fractures.” European Journal of Orthopaedic Surgery & Traumatology: Orthopedie Traumatologie 31 (1): 43–50.
7. Machine Learning Consortium, on behalf of the SPRINT and FLOW Investigators. 2021. “A Machine Learning Algorithm to Identify Patients with Tibial Shaft Fractures at Risk for Infection After Operative Treatment.” The Journal of Bone and Joint Surgery. American Volume 103 (6): 532–40.
8. Machine Learning Consortium on behalf of the SPRINT Investigators. 2021. “A Machine Learning Algorithm to Identify Patients at Risk of Unplanned Subsequent Surgery After Intramedullary Nailing for Tibial Shaft Fractures.” Journal of Orthopaedic Trauma 35 (10): e381–88.
9. Hendrickx, Laurent A. M., Nick F. J. Hilgersom, Hassanin Alkaduhimi, Job N. Doornberg, and Michel P. J. van den Bekerom. 2020. “Radial Nerve Palsy Associated with Closed Humeral Shaft Fractures: A Systematic Review of 1758 Patients.” Archives of Orthopaedic and Traumatic Surgery. Archiv Fur Orthopadische Und Unfall-Chirurgie, April. doi:10.1007/s00402-020-03446-y.

10. Bulstra, Anne Eva J., Laurent A. M. Hendrickx, Inger N. Sierevelt, Geert A. Buijze, Gino M. M. J. Kerkhoffs, David Ring, Ruurd L. Jaarsma, and Job N. Doornberg. 2021. “Prospective Cohort Study to Investigate Factors Associated With Continued Immobilization of a Nondisplaced Scaphoid Waist Fracture.” The Journal of Hand Surgery 46 (8): 685–94.

11. Bleeker, Nils Jan, Inge H. F. Reininga, Bryan J. M. van de Wall, Laurent A. M. Hendrickx, Frank J. P. Beeres, Kaj Ten Duis, Job N. Doornberg, Ruurd L. Jaarsma, Gino M. M. J. Kerkhoffs, and Frank F. A. IJpma. 2021. “Difference in Pain, Complication Rates, and Clinical Outcomes After Suprapatellar Versus Infrapatellar Nailing for Tibia Fractures? A Systematic Review of 1447 Patients.” Journal of Orthopaedic Trauma 35 (8): 391–400.

12. Bulstra, Anne Eva J., and Machine Learning Consortium. 2022. “A Machine Learning Algorithm to Estimate the Probability of a True Scaphoid Fracture After Wrist Trauma.” The Journal of Hand Surgery 47 (8): 709–18.

13. Spanning, Sanne H. van, Lukas P. E. Verweij, Laurens J. H. Allaart, Laurent A. M. Hendrickx, Job N. Doornberg, George S. Athwal, Thibault Lafosse, Laurent Lafosse, Michel P. J. van den Bekerom, Geert Alexander Buijze, and Machine Learning Consortium. 2022. “Development and Training of a Machine Learning Algorithm to Identify Patients at Risk for Recurrence Following an Arthroscopic Bankart Repair (CLEARER): Protocol for a Retrospective, Multicentre, Cohort Study.” BMJ Open 12 (9): e055346.

14. Kuit, Anouk van de, Jacobien H. F. Oosterhoff, Hidde Dijkstra, Sheila Sprague, Sofia Bzovsky, Mohit Bhandari, Marc Swiontkowski, Emil H. Schemitsch, Frank F. A. IJpma, Rudolf W. Poolman, Job N. Doornberg, Laurent A. M. Hendrickx, and , the Machine Learning Consortium and FAITH Investigators. 2022. “Patients With Femoral Neck

15. Fractures Are at Risk for Conversion to Arthroplasty After Internal Fixation: A Machine-Learning Algorithm.” Clinical Orthopaedics and Related Research 480 (12): 2350–60.

16. Allaart, Laurens J. H., Sanne van Spanning, Laurent Lafosse, Thibault Lafosse, Alexandre Ladermann, George S. Athwal, Laurent A. M. Hendrickx, Job N. Doornberg, Michel P. J. van den Bekerom, Geert Alexander Buijze, and Machine Learning Consortium. 2023. Developing a Machine Learning Algorithm to Predict Probability of Retear and Functional Outcomes in Patients Undergoing Rotator Cuff Repair Surgery: Protocol for a Retrospective, Multicentre Study.” BMJ Open 13 (2): e063673.

17. Dijkstra, Hidde, Jacobien H. F. Oosterhoff, Anouk van de Kuit, Frank F. A. IJpma, Joseph H. Schwab, Rudolf W. Poolman, Sheila Sprague, Sofia Bzovsky, Mohit Bhandari, Marc Swiontkowski, Emil H. Schemitsch, Job N. Doornberg, Laurent A. M. Hendrickx, Machine Learning Consortium, HEALTH Investigators, and and the FAITH Investigators. 2023. “Development of Machine-Learning Algorithms for 90-Day and One-Year Mortality Prediction in the Elderly with Femoral Neck Fractures Based on the HEALTH and FAITH Trials.” Bone & Joint Open 4 (3): 168–81.

DANKWOORD

Bij dit proefschrift zijn veel verschillende mensen betrokken geweest. De totstandkoming was dan ook geen individuele-, maar een echte teamprestatie. Hierbij wil ik graag iedereen bedanken die betrokken is geweest voor de fijne samenwerking.

Een aantal mensen wil ik graag nog in het bijzonder bedanken:

Allereerst, prof. dr. J.N. Doornberg, beste Job, ik wil je ontzettend bedanken voor het prachtige avontuur! Jouw mentorship, enthousiasme en gezelligheid hebben ervoor gezorgd dat mijn PhD in Australië en Nederland een succesvolle ervaring is geworden met veel onvergetelijke herinneringen: fietsen in the Hills, bbq'en op shore CT, 1 op 1 research meetings met een spectaculair uitzicht, en vele congressen in binnen- en buitenland. Heel veel dank!

Prof. dr. R.L. Jaarsma, beste Ruurd, ik wil je enorm graag bedanken voor de fantastische tijd in Adelaide! Jouw klinische en academische ervaring en kennis van Australië waren onmisbaar voor het slagen van het onderzoek. Je hebt ons altijd met open armen ontvangen, zowel binnen het ziekenhuis als daarbuiten. De BBQ's en surfsessies in Middleton zijn daar prachtige herinneringen aan. Dank voor deze prachtige tijd!

Prof. dr. G.M.M.J. Kerkhoffs, beste Gino. Ik wil je heel graag bedanken voor de fijne samenwerking en support! Het was mooi om je tijdens de research trip te kunnen verwelkomen in Australië en je te kunnen rondleiden door Flinders en Adelaide. Ook al hebben we grotendeels in verschillende tijdzones gezeten, je was altijd direct bereikbaar voor overleg. Ook jouw ervaring en inzichten waren onmisbaar in de totstandkoming van dit proefschrift. Dank daarvoor!

Overige leden van de promotiecommissie, prof. dr. R.J. Oostra, prof. dr. J.L. Tol, prof. dr. M.H.J. Verhofstad, prof. dr. ir. N.J.J. Verdonschot, prof. dr. M. Maas en prof. dr. F.W. Bloemers, ik ben u zeer dankbaar voor uw interesse in dit proefschrift en de beoordeling daarvan.

Dear co-authors, thank you so much for all your help and support. Without you, finalizing this PhD-thesis would not have been possible. A special thanks to Megan, James, Jasvir, Nils-Jan and Inger with whom I collaborated on several studies.

Sylvia, Katharina and Taran. Thank you so much for your support and guidance in FMC, without you I would have been lost!

Ellen, dank voor alle organisatorische hulp in Amsterdam!

Cotutelle-team: Jetske, Annelise, David, Batur, Bram, Minke, Robin, Mads, Saskia, Pinky, Michiel en Aletta. Dank voor de samenwerking, Nederlandse gezelligheid en mooie herinneringen!

Berlino's en Mannschaft, jullie aanwezigheid en gezelligheid werden enorm gemist down-under, dank dat jullie mij na die jaren weer met open armen hebben ontvangen!

Reinier & Leo en Died & Dick, dank dat ik jullie (schoon)zusje mee mocht nemen naar Australie!

Robert & Marianne, veel dank voor jullie support en interesse in mijn PhD! Wat was het leuk om jullie op bezoek te hebben en rond te kunnen leiden door ons leven in Adelaide!

Merel & Misja en Joris & Tori, ook jullie werden enorm gemist in Australië! Wat is het enorm gezellig dat we weer dichter bij elkaar wonen en we elkaar weer meer kunnen zien!

Willem & Luuk, paranimfen en vrienden van het eerste uur! Wat hebben we al veel meegemaakt samen! Dank dat ik ook tijdens mijn verdediging op jullie kan rekenen!

Lieve pap & mam, dank voor jullie eeuwige support en liefde! Zonder jullie was dit proefschrift er niet geweest. Niet alleen gedurende mijn PhD, maar ook gedurende mijn jeugd en studie hebben jullie altijd en overal voor mij klaar gestaan. Daar wil ik jullie enorm voor bedanken!

Lieve Anne Eva, steun en toeverlaat! Jouw bijdrage aan dit proefschrift was echt van onschatbare waarde en daar wil ik je enorm voor bedanken! Sinds wij elkaar kennen bestaat het leven uit een aaneenschakeling van hoogtepunten, samen deze PhD reis afleggen was er zeker een van. Zowel binnen als buiten het ziekenhuis was het een prachtige tijd die ik nooit zal vergeten. Na onze verdediging wacht ons al snel een nieuw hoogtepunt, en ik kijk er enorm naar uit om met jou dit volgende avontuur aan te gaan!

ABOUT THE AUTHOR

Dr. Laurent Alexander Marijn "Ran" Hendrickx was born on January 17th, 1991, in Amsterdam, The Netherlands.

During his childhood he and his family moved to Nijmegen, where he completed his early education at Stedelijk Gymnasium Nijmegen. As a student he moved back to Amsterdam to pursue his medical degree at AMC-UvA. There, he distinguished himself as an Honours student with a special interest in orthopedic surgery.

His Master's Thesis on the "Incidence, Predictors, and Fracture Mapping of (Occult) Posterior Malleolar Fractures Associated with Tibial Shaft Fractures" laid the foundation for his continued contributions to the orthopedic field. This work paved the way for his selection into the prestigious "Cotutelle" Joint Doctorate PhD Program—a collaboration between the University of Amsterdam and Flinders University, Adelaide, Australia.

In Australia, he conducted his research on intramedullary nailing of tibial shaft fractures, under the esteemed guidance of Professor Gino Kerkhoffs, Professor Ruurd Jaarsma, and Professor Job Doornberg. He received multiple scholarships and grants to support his research. He furthermore presented his work at several conferences including the OTA Annual Meeting and NOV Annual Conference.

Ran is currently in training to become an orthopedic surgeon in ROGO Midden-West. Outside of work, he is an avid sports enthusiast who enjoys cycling, skiing, surfing, squash, padel and tennis. Ran currently lives in Amersfoort with his fiancée Anne-Eva.

Written by Luuk Giesen & Willem van Strien

Stellingen uit dit proefschrift

1. Patients treated with intramedullary nailing for tibial shaft afractures should be consented that one-in-two patients will undergo an additional surgical procedure. (Chapter 2)

2. Orthopaedic trauma surgeons should be aware that intramedullary nailing of tibial shaft fractures is complicated by postoperative rotational malalignment in 36% of patients. (Chapter 4)

3. The left-right difference seen in internal and external rotational malalignment after intramedullary nailing of tibial shaft fractures may be partially explained by a physiological left-right difference in tibial torsion. (Chapter 4)

4. Clinicians should be aware that in 22% of patients with a tibial shaft fracture, a posterior malleolar fracture is present, of which 25% may be occult on radiographs. (Chapter 4)

5. Patients with a spiral distal third tibial shaft fractures should undergo preoperative CT-scan imaging to rule out concomitant posterior malleolar fractures. (Chapter 5)

6. The use of (machine learning) prediction models can guide clinicians in individualizing treatment of patients with tibial shaft fractures. (Chapter 3, 4, 6 & 7)

7. Long term ankle pain in patients treated with intramedullary nailing in tibial shaft fractures is worsened by iatrogenic rotational malalignment. (Chapter 8)

Overige Stellingen

8. “Stay hungry, stay foolish” – Job Doornberg / Steve Jobs

9. “Twenty years from now you will be more disappointed by the things that you didn't do than by the ones you did do" – Mark Twain

10. "Don’t worry, be happy” – Bobby McFerrin