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Risk factors for fracture-related infection after ankle fracture surgery

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A R T I C L E I N F O

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A B S T R A C T

Introduction: Ankle fracture surgery comes with a risk of fracture-related infection (FRI). Identifying risk factors are important in preoperative planning, in management of patients, and for information to the individual patient about their risk of complications. In addition, modifiable factors can be addressed prior to surgery. The aim of the current paper was to identify risk factors for FRI in patients operated for ankle fractures.
Methods: A cohort of 1004 patients surgically treated for ankle fractures at Haukeland University Hospital in the period of 2015–2019 was studied retrospectively. Patient charts and radiographs were assessed for the diagnosis of FRI. Binary logistic regression was used in analyses of risk factors. Regression coefficients were used to calculate the probability for FRI based on the patients' age and presence of one or more risk factors.
Results: FRI was confirmed in 87 (9%) of 1004 patients. Higher age at operation ($p < .001$), congestive heart failure (CHF), $p = 0.006$), peripheral artery disease (PAD, $p = 0.001$), and current smoking ($p = .006$) were identified as risk factors for FRI. PAD and CHF were the risk factors displaying the strongest association with FRI with an adjusted odds ratio of 4.2 (95% CI 1.8–10.1) and 4.7 (95% CI 1.6–14.1) respectively.
Conclusion: The prevalence of FRI was 9% after surgical treatment of ankle fractures. The combination of risk factors found in this study demonstrate the need for a thorough, multidisciplinary, and careful approach when faced with an elderly or frail patient with an ankle fracture. The results of this study help the treating surgeons to inform their patients of the risk of FRI prior to ankle fracture surgery.
Level of evidence: Level III retrospective case-control study

Introduction

Ankle fractures are the third most common surgically treated fracture type after hip fractures and distal radius fractures, and constitutes 10% of all fractures [1,2]. Operative treatment of ankle fractures comes with a risk of complications [3]. The most common complications are fracture-related infection (FRI, prevalence of 1.44–16%) and iatrogenic injury to the superficial peroneal nerve occurring in up to 21% of patients surgically treated for ankle fractures [3–7]. Other perioperative complications are malreduction of the fractures or the syndesmosis (0.82–2%) [3,4,8]. Ovaska found malreduced syndesmosis to be the most frequent reason for reoperation [8]. Less frequent are prolonged fracture healing or pseudarthrosis (1%), posttraumatic osteoarthritis (0.5%), and pulmonary embolism (0.34%) [3,4]. Hardware removal due to pain or stiffness is common (23–50%) [3,9], but one may argue that those complaints may be expected due to the injury or surgery itself. It may therefore not be classified as a complication.

FRI might have severe consequences for patients - spanning from temporary reduced ankle function to below-knee amputation [7–9]. Identification of risk factors are important in the evaluation of surgical treatment, and for prevention and treatment of such infections [10,11]. Potential risk factors can be patient-related, injury-related and treatment-related [11,12,14–17]. Patient-related factors include age at operation, diabetes mellitus, peripheral artery disease (PAD), or smoking [7,18–20]. Injury related risk factors may be open fractures and dislocation fractures [21]. Treatment factors include preoperative management, time to operation, choice of surgical approach, type of osteosynthesis, and duration of surgery [11]. A common definition of FRI is important to improve comparisons across studies, assessment of patients with possible infection, and treatment of patients with infection after fracture treatment [22,23]. Such a definition was reached through a consensus agreement [22,23]. The consensus of the FRI definition

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includes *confirmatory* and *suggestive* criteria of FRI (Fig. 1). The clinical c*onfirmatory criteria* are the presence of fistulas, sinus formation, or wound breakdown with communication to bone or implant. Purulent drainage or pus also confirms an infection. These clinical signs are considered pathognomonic of FRI [24].

Few studies have examined the risk of FRI after ankle fracture surgery, applying consensus-based criteria. Therefore, the aim of the current paper was to identify risk factors for developing FRI in patients operated for ankle fractures at a level 1 trauma hospital in Bergen, Norway. Secondary aims were to calculate the probabilities for a given patient of developing FRI based on the presence of one or several of the identified risk factors.

Patients and methods

This was a retrospective study identifying risk factors for the development of FRI in all operated ankle fractures at Haukeland University Hospital in the period January 2015 through December 2019. All patients operated for ankle fractures were included. Exclusion criteria were patients under 18 years of age at time of primary surgery, bilateral injuries, and patients with follow-up at another hospital. A flow-chart for patient inclusion is presented in Fig. 2.

The current study is a secondary analysis of a previously published patient cohort [25]. Patients were identified through a selective search in the operation planning system, Orbit version 5.11.2, based on ICD-10 codes and Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (NCSP) codes for uni-, bi- and trimalleolar fractures and infection complication diagnosis. Codes used in the initial search were S82.4–9, T81.3–4, T81.9, T84.6–7, T84.9, NHJ60–63, NHS19, NHS29, NHS39, NHS49, NHS59, and NHS99.

Plain radiographs of all potential patients were examined by the main author for fracture classification. Patient charts were reviewed for information concerning trauma, treatment, comorbidity, and complications. The charts were thoroughly examined for information concerning trauma mechanism, treatment given, comorbidities, and complications and postoperative signs of FRI. Patients were diagnosed with FRI following the consensus definition flow-chart [5,6,20]. Information on comorbidity such as diabetes mellitus, chronic renal failure, congestive heart failure (CHF), dementia, polyneuropathies, and connective tissue disease (I.e. Rheumatoid arthritis, ankylosing spondylitis) were sought in the prior medical history and registered only if they had a confirmed diagnosis prior to admission. PAD was registered when the patients were admitted to the hospital for primary surgery or if confirmed after investigation due to poor wound healing and suspicion of poor blood supply to the lower extremity. A sub-analysis of association to FRI for patients with dislocation fractures were performed, as these have formerly been shown to have a poor outcome [11]. Sectra software version 22.1 (Sectra AB, Linköping, Sweden) was used for examination of radiographs and images of computer tomography (CT).

Surgical technique

Most patients treated with screw and plate osteosyntheses had open reduction and internal fixation (ORIF) via a direct lateral or medial surgical approach to the malleoli. A posterior approach midway between the Achilles tendon and the lateral malleolus was also applied at the treating orthopedic surgeon's choice. A fibula nail, Taylor spatial frame or a hindfoot nail were used in certain patients (Table 1). These devices were used if the soft tissue was compromised with blisters, the patient was considered non-compliant (i.e., mental- or cognitive impairment, and/or alcohol- or drug abuse), had poorly controlled diabetes mellitus, or were found to have PAD.

Statistics

Categorical variables were analyzed with Pearson's chi-squared test and continuous variables by Mann-Whitney U test. Continuous variables are presented with the median and interquartile range (IQR) in parenthesis. Binary logistic regression was performed to identify risk factors for development of FRI between those patients who developed FRI and those who did not. A primary logistic regression analysis included variables that were statistically more frequent among patients with FRI and that also were considered clinically relevant (Table 1). The logistic regression analysis was performed controlling for the effects of the *patient related* risk factors sex, age, ASA classification, current smoking status, diabetes mellitus, chronic kidney disease, PAD, dementia, CHF, alcohol or drug abuse, and current smoking status. *Injury related* risk factors such as open fractures and high-energy mechanism of injury, and the *treatment related* risk factors use of temporary external fixation, hindfoot nail, and hardware removal were also included in the analysis. After a primary regression analysis, in addition to sex, only the statistically significant variables were included in the final model. Sex was included in the model as the risk of developing FRI is known to be associated with male sex [26]. The logistic regression model was found to be statistically significant, $p < 0.001$, and had a Nagelkerke R squared of 0.12.

Also, an assessment of the probability for developing FRI was performed for different types of patient groups based on the presence or absence of the identified risk factors [27,28].

A priori level of significance was set to $p =< 0.05$. IBM SPSS v.26 (SPSS Inc., Chicago, IL) was used for analyses.

Ethical considerations

The project has approval of the Helse Bergen data protection officer and regional committee for medical and health research ethics (REC ID 328,437).

Results

A total of 1004 patients with surgically treated ankle fractures were included in the study (Fig. 2). Sixty percent were women and median age at time of primary ankle fracture surgery was 53 (IQR 38–66) years. Mean body mass index (BMI) was 26.9 (IQR 24.2–30.2), and 891 (89%) of the patients had an ASA score (American Society of Anesthesiologist classification) of 1–2.

Fracture-related infection

Eighty-seven (9%) of the 1004 included patients were diagnosed with FRI – as defined by the FRI consensus definition. Patient demographics, injury- and fracture characteristics, and treatment variables are presented in Table 1. The group of patients with FRI was older, had a higher ASA score, smoked more often, suffered more from alcohol or drug abuse, and were diagnosed more often with PAD, compared with patients without FRI (Table 1). Patients who underwent hardware removal due to stiffness or discomfort, or as part of planned syndesmotic screw removal did not have an increased rate of FRI (Table 2). Time from injury to definitive surgery was not associated with FRI, neither in the whole study population ($p = .95$) nor in sub-analysis of patients with dislocation fractures ($p = .73$).

Results of the binary logistic regression to identify risk factors associated with FRI are presented in Table 2. Age at operation ($p < .001$), CHF ($p = 0.006$), PAD ($p = 0.001$), and current smoking ($p = 0.006$) were associated with increased risk of FRI.

Dementia was found to have a p-value of 0.06 with an adjusted odds ratio (aOR) of 2.9 (95% Confidence interval (C.I.) 0.96–8.8). It was not included in the regression model.

The different probabilities of developing FRI based on one or more of the risk factors are presented in Table 3. Healthy young patients (18 years of age) had low probability (1%) of developing FRI, 50-year-old patients without any risk factors had a 3% probability of developing

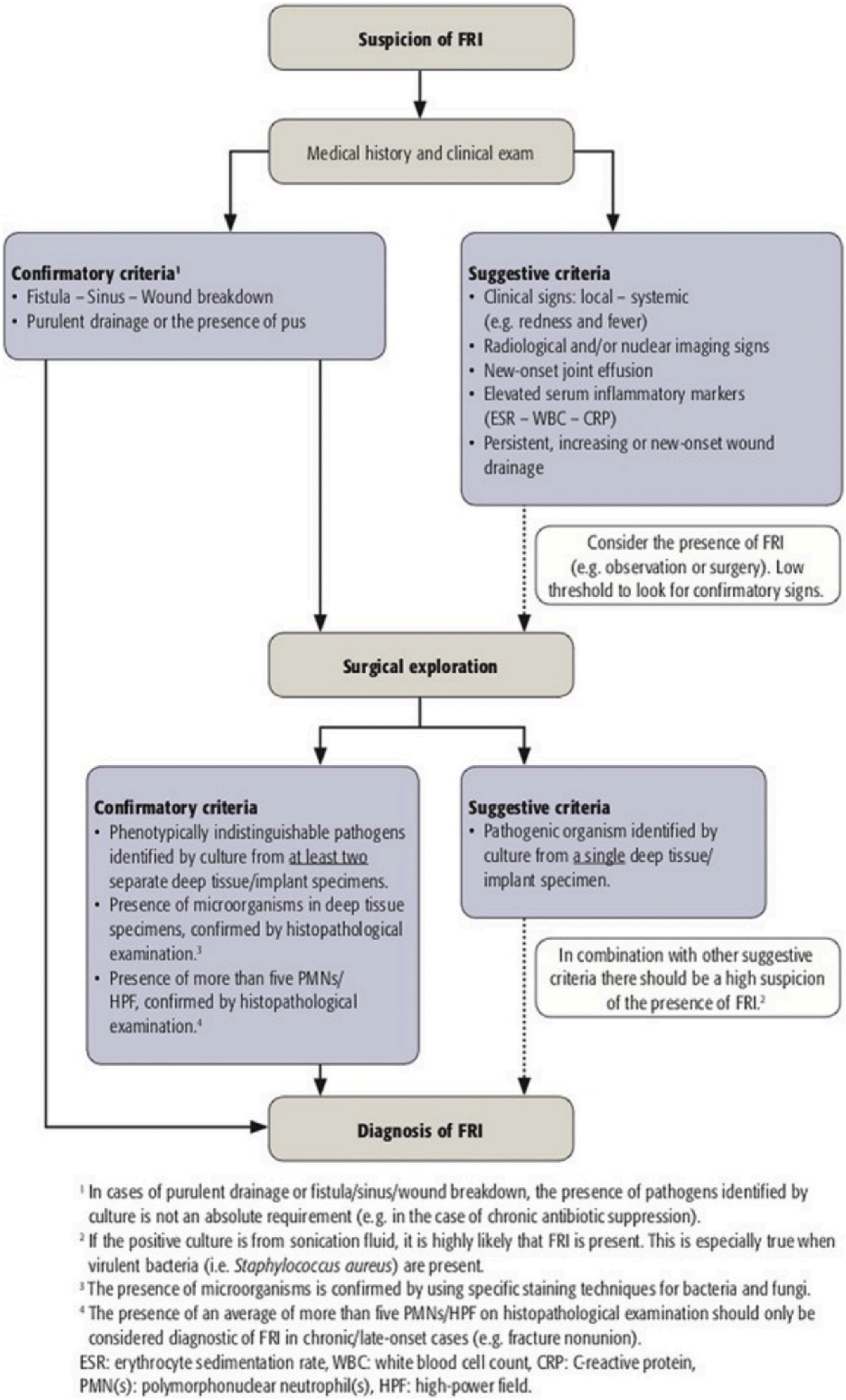

Fig. 1. Definition and flow-chart for diagnosis of Fracture-related infection. Figure from "Diagnosing Fracture-related Infection: Current Consepts and Recommendations",
Govaert GAM, Kuehl R, Atkins BL, Trampuz A, Morgenstern M, Obremskey WT, Verhofstad MHJ, McNally MA, Metsemakers WJ; Fracture-Related Infection (FRI) Consensus Group. J Orthop Trauma. 2020 Jan;34(1):8–17
The figure is adapted from:
Fracture-related infection: A consensus on definition from an international expert group.
Metsemakers WJ, Morgenstern M, McNally MA, Moriarty TF, McFadyen I, Scarborough M, Athanasou NA, Ochsner PE, Kuehl R, Raschke M, Borens O, Xie Z, Velkes S, Hungerer S, Kates SL, Zalavras C, Giannoudis PV, Richards RG, Verhofstad MHJ. Injury. 2018 Mar;49(3):505–510.

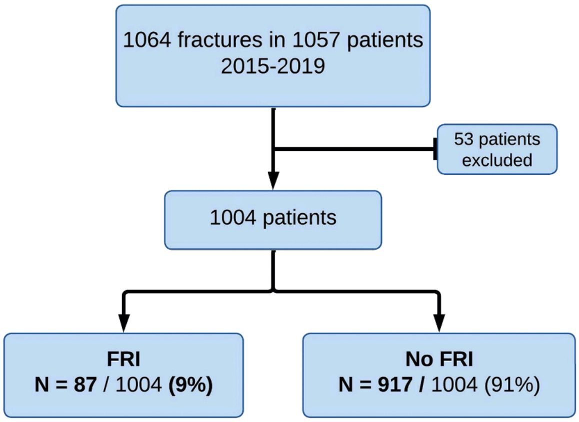

Fig. 2. . Patient inclusion and number of patients with fracture-related infection (FRI).

FRI, but this risk doubled if the patient was a smoker (7%). Eighty-year-old patients had an 6% risk of developing FRI, while old comorbid patients (>80 years of age with PAD) had a very high probability (> 26%) of developing FRI after surgical treatment for ankle fractures (Table 3).

Discussion

In this retrospective cohort follow-up study of 1004 patients with surgically treated ankle fractures the *risk factors* associated with development FRI were advanced age at operation, peripheral artery disease (PAD), congestive heart failure (CHF), and current smoking. Young healthy patients had a low risk of FRI, while the risk of FRI was very high in old and comorbid patients.

Recent publications have presented a new definition of FRI to improve diagnosis, treatment, and future research of infection after fracture surgery [22,23]. In concordance with correctly defining the diagnosis, the identification of risk factors associated with FRI is important. The patients may then be informed of the risk of FRI and patients at risk can be identified and measures for prevention of modifiable factors may be performed. Knowing the risk factors for development FRI helps the surgeon in choice and timing of surgery. Unfortunately, only a few of the risk factors may be modifiable. However, optimizing patients with congestive heart failure may reduce edema and reduce the risk of wound dehiscence. Probably, all measures that optimize blood flow and improve oxygenation of the soft tissue will be beneficial. If the state of the patient and the stability of the fracture allows it, one may delay surgery and perform a percutaneous transluminal angioplasty in patients with critical ischemia [29]. Namgoong et al. found a significantly increased toe pressure after angioplasty in diabetic patients with severe ischemic PAD (Systolic toe pressure <20 mm Hg) [29]. The best effect was found weeks after the intervention. Still, it may increase blood flow and give better circumstances for the wound healing.

Several risk factors for FRI were identified in the current study. First, *higher age* was found to have 30% increased odds ratio (O.R.) per 10-year interval. The results were similar to previous studies [7,13]. A Finnish study found more than a threefold increase from 1970 to 2000 in the incidence of ankle fractures among patients older than 65 years of age [30]. Soohoo found an odds ratio for development of FRI of 1.73 (C.I. 1.49–2.01) in patients 75 years or older compared to patients under 75 years of age [4]. In the current study a 75-year-old patient would have an O.R. of 2.95 for developing FRI, similar to the O.R. of 3.14 Sun and colleagues found in their study from 2018. Spek et al. also found a high infection rate of 15.9% among 282 patients older than 65 years who were surgically treated for ankle fractures. They argue that due to the known high risk of FRI the patients must be informed adequately and according to their risk of postoperative infection [7]. With increasing

Table 1
Patient demographics and injury characteristics for patients with and without Fracture Related Infection (FRI).

		No FRI (N = 917)	FRI (N = 87)	P - Value
Patient characteristics				
Age (years)		52 (37–65)	61 (48–73)	<0.001
Sex				
	Female	557 (61)	47 (54)	0.2
	Male	360 (39)	40 (46)	
Deceased		37 (4)	16 (18)	<0.001
BMI (kg/m2)		26.7 (24.2–30.1)	27.7 (24.7–30.8)	0.3
ASA classification				
	ASA 1	357 (39)	19 (22)	0.002
	ASA 2	467 (51)	48 (55)	0.4
	ASA 3	90 (10)	19 (22)	<0.001
	ASA 4	3 (0.3)	1 (1)	0.2
Alcohol or drug abuse		34 (4)	10 (12)	0.001
Current smoker		155 (17)	24 (28)	0.01
Diabetes mellitus		43 (5)	6 (7)	0.4
Peripheral Arterial Disease		17 (2)	10 (12)	<0.001
Congestive Heart Failure		9 (1)	7 (8)	<0.001
Chronic Kidney Disease		5 (0.5)	3 (3)	0.004
Dementia		14 (2)	5 (6)	0.006
Polyneuropathy		17 (2)	3 (3)	0.3
Connective tissue disease		37 (4)	5 (6)	0.5
Fracture and injury characteristics				
AO/OTA classification				
	No fibula fracture	47 (5)	0	0.03
	44A	15 (2)	1 (1)	0.7
	44B	594 (65)	52 (60)	0.4
	44C	208 (23)	26 (30)	0.1
	Proximal fibula fracture	53 (6)	8 (9)	0.2
Malleolar involvement				
	Isolated proximal fibula fracture	19 (2)	3 (3)	0.4
	Unimalleolar	325 (35)	19 (22)	0.01
	Bimalleolar	243 (27)	31 (36)	0.07
	Trimalleolar	327 (36)	34 (39)	0.5
	Chaput-Tillaux	3 (0.3)	0	0.6
Dislocation fracture		214 (23)	26 (30)	0.2
Open fracture		16 (2)	4 (5)	0.07
Multitrauma		5 (0.5)	1 (1)	0.5
High energy trauma		26 (3)	6 (7)	0.04
Treatment characteristics				
Attempted non-op. treatment		20 (2)	4 (5)	0.2
Direct lateral and/or medial appraoch		732 (80)	65 (75)	0.3
Posterior surgical approach		174 (19)	16 (18)	0.9
Plate and/or screw osteosynthesis		906 (99)	81 (93)	<0.001
Fibula nail (Total N = 10)		8 (1)	2 (2)	0.2
Hindfoot nail (Total N = 5)		2 (0.2)	3 (3)	<0.001
Taylor spatial frame (Total N = 2)		1 (0.1)	1 (1)	0.04
Reoperation		44 (5)	3 (3)	0.6
External fixator prior to definitive surgery		136 (15)	19 (22)	0.08
Syndesmosis fixation		369 (40)	38 (44)	0.5
Planned removal of syndesmosis fixation (Total N = 52)		47 (5)	5 (6)	0.8
Removed hardware due to mechanical irritation (Total N = 155)		153 (17)	2 (2)	<0.001
Time from injury to definitive operation (days)		5 (3–8)	6 (3–10)	0.3
Length of stay (days)		6 (4–10)	8 (5–16)	<0.001
Postoperative length of stay (days)		2 (1–3)	3 (1–7)	<0.001
Duration of operation (minutes)		72 (50–98)	74 (54–107)	0.5

Demographics of patient-, fracture and injury-, and treatment characteristics for patients with and without fracture-related infection (FRI). Number of patients with percentages in parenthesis for cathegorical variables, and median values with interquartily range in parenthesis for continuous variables. P-values calculated with Pearson X2 test for categorical variables and with mann-Whitney U test for contiuous variables. BMI = Body Mass Index, ASA = American Society of Anesthesiologists.

Table 2
Logistic regression model of risk factors for Fracture-related infection.

	aOR (95% C.I.)	P-value
Female Sex	0.7 (0.4–1.1)	0.1
Age by 10 year interval	1.3 (1.1–1.5)	<0.001
Current smoking status	2.1 (1.2–3.5)	0.006
Congestive heart failure	4.7 (1.6–14.1)	0.006
Peripheral arterial disease	4.2 (1.8–10.1)	0.001

Logistic model of risk factors for Fracture Related infection. aOR - adjusted Odds Ratio. C.I. - Confidence interval.

Table 3
Probability of developing FRI based on the identified risk factors.

	Probability in%
18 year old patient, no risk factors	1
50 year old patient, no risk factors	3
50 year old patient, current smoker	7
70 year old patient, no risk factors	5
80 year old patient, no risk factors	6
80 year old patient, current smoker	12
80 year old patient with heart failure	24
80 year old patient with PAD	26
80 year old patient with PAD and current smoker	37
80 year old patient with heart failure and current smoker	39
80 year old patient with PAD and heart failure	57
80 year old patient with PAD, current smoking and heart failure	73

Calculation of probabilty of developing FRI based on the identified risk factors from Table 2. PAD: Peripheral Artery Disease.

age in the general population, patients with comorbidities will be more frequent. Several studies therefore recommend a multidisciplinary approach to patients with ankle fractures above the age of 65 years [31, 32]. This may include optimizing the vascular status of the lower extremities, correcting serum glucose levels in diabetic patients, and reducing lower extremity edema in patients with CHF. The incidence of CHF and PAD increases with age [33]. Both the presence of CHF and PAD showed a 4-fold increased risk of FRI in the current study. Patients with heart failure may be more frail, more immobile – and prone to falling, and may have poorer peripheral vascular status [33,34]. In a study on comorbidities among 558 patients with heart failure, 60% of the patients had 3 or more comorbidities – underlining the frailty of this group of patients [34]. Heart failure was recently shown to be a risk factor for FRI in a large study by Szymski et al. [35]. They found a relative risk (R.R). of 3.8 for the development of FRI in patients with CHF compared to the general population. *CHF and PAD* were the strongest predictor for development of FRI in the current study. Several studies have shown similar results [15,35,36]. Richardson found an O.R. of 2.16 in patients with PAD for development of FRI compared O.R. of 4.2 in the current study. Aigner underlines the importance of identification of peripheral perfusion status and optimalization prior to surgery [37]. In the outpatient clinic or emergency department a Buerger test - elevation and subsequent lowering of the foot outside the examination bench - is a quick and easy assessment of the foot's arterial status [38]. Ankle-Brachial Pressure Index is another feasible examination but may be misleading in the case of stiff vessels or microangiopathy [38]. A clinical assessment of vascular status preoperatively should, in our opinion, always be performed. With signs of vascular impairment, a vascular surgeon should be consulted, and proper measures performed.

Bauersachs and Steg emphasizes that PAD and coronary artery disease often coexists, 48–68% of patients with PAD also have coronary artery disease [33,39]. Having disease in one vascular bed is a marker for diffuse atherosclerosis elsewhere [33]. PAD is underdiagnosed, as illustrated in the current study where some of the patients were diagnosed with PAD after the occurrence of wound problems or signs of FRI [33].

Smoking was found to double the risk for development of FRI in the current study, in concordance with former studies [19]. Smoking exposes the body to toxins including carbon monoxide (CO) which binds hemoglobin and shifts the oxyhemoglobin dissociation curve to the left [40,41]. This reduces the soft tissue oxygenation with increased risk of postoperative infection as a result. In elective surgery a four week of abstinence is recommended [40]. One expect a brief preoperative abstinence to increase tissue oxygenation, but the true association of a short pause from smoking and FRI is currently unknown [40]. Perioperative abstinence is a modifiable risk factor and must be addressed while the patient is admitted. Smoking is closely associated with both cardiovascular disease, heart failure and PAD [42–45]. Therefore, the current results and the literature underline the important role of helping patients with cessation of smoking. Bullen argues that all doctors in contact with patients who are current smokers should offer advice on cessation, counseling, and nicotine replacement therapy [42].

The use of a tibio-talar-calcaneal hindfoot nail was used in the current study population with the intention to reduce the risk of FRI. However, three of five patients treated with a hindfoot nail developed FRI. A hindfoot nail was used in patients with high comorbidity. According to the calculations in Table 3 the patients would have a probability of FRI in the range of 26–73%. Although not statistically significant as a risk factor it demonstrates the challenge of treating high risk patients – by any surgical approach. The overarching theme of the vascular status of the patient warrants a thorough examination and preoperative optimalization [45].

Dementia is known to be an important determinant of deteriorating physical status [46]. However, dementia was not found to have a significant association with FRI in the current study. The low number of patients with dementia may have influenced the result. Shivarathre et al. also described dementia as a risk factor of postoperative wound problems in addition to diabetes mellitus, peripheral vascular disease, and smoking [47]. They found an odds ratio of 5.1 for wound problems in case of dementia.

Surprisingly, and in contrast with several studies, diabetes mellitus (DM) did not have a higher prevalence in the FRI group of the current study [17,35]. Several studies have found DM to be a major risk factors for postoperative infection, especially in case of diabetes with hyperglycemia or complications such as neuropathy, retinopathy, and angiopathy [16,17,47,48]. There were a low number of patients with diabetes mellitus in the present study, and even fewer with poor glycemic control (as measured by HbA1c and serum glucoses), resulting in poor statistical power of the analyses.

ASA class 3 or higher is a known risk factor for postoperative infections [16]. It was not significant in our regression analysis. We expect the reason being the strong associations of other individual risk factors to FRI. Patients with PAD, heart failure, and patients who were current smokers would have been given a higher ASA class.

Strengths of the current study are the high number of patients included and a transparent report of FRI from a level 1 trauma hospital - and the potential to examine a broad specter of potential risk factors for FRI. Also, as the ankle is the most frequent location for FRI, the number of patients with FRI is relatively high [24]. The retrospective study design, however, has inherent limitations. Information from patient charts may be imprecise regarding the degree of PAD, on smoking habits, clinical state regarding heart failure, and management of the patient's diabetes mellitus. The formula for the probability of FRI cannot account for the variation in degree of PAD among patients or the variation of how many cigarettes the patients smoke per day. This information is not included in the patient charts, and we are therefore not able to do calculations or assumption on this matter. Three of ten patients were diagnosed with PAD after the wound problems occurred which also highlights a weakness of retrospective studies.

Identifying risk factors are important for information to the individual patient about their risk of complications, in preoperative planning, and the management of the patients. In preparation to surgery the risk of FRI must be weighed against the indication for the procedure. In addition, modifiable factors and optimalization of patients must be addressed prior to surgery. The combination of risk factors found in this study demonstrates the need for a thorough, multidisciplinary, and careful approach when faced with ankle fractures in elderly patients.

Conclusion

The current study found an FRI-rate of 9% after surgically treated ankle fractures. Advanced age, congestive heart failure, peripheral artery disease, and current smoking were found to be risk factors for the development of FRI. Peripheral artery disease and congestive heart failure yielded the highest risk of FRI, while current smoking was the only modifiable risk factor. The results of this study help the treating surgeons to inform their patients of the risk of FRI prior to ankle fracture surgery.

Declaration of Competing Interest

None.

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