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Use of negative pressure wound therapy in patients with fracture-related infection more than doubles the risk of recurrence

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ABSTRACT

Purpose: Fracture-related infection (FRI) is one of the most serious complications in orthopedic trauma surgery. Despite its widespread use, the role of Negative Pressure Wound Therapy (NPWT) remains controversial in the management pathway of FRI. The aim of this study was to assess the relationship between the application of NPWT and its duration and recurrence of infection in operatively treated FRI patients.

Patients and Methods: This is a retrospective cohort study based on the FRI database of three level 1 Trauma Centres. Included patients had to be at least 16 years of age and surgically treated for FRI between January 1st 2015 and September 1st 2020. Patients were subdivided in either the NPWT group, when NPWT was applied as part of the FRI treatment, or in the control group, when no NPWT had been applied. To limit confounding, patients were excluded if they (also) underwent NPWT prior to the diagnosis of FRI. The relation between the duration of NPWT during FRI treatment and the recurrence rate of infection was analyzed using a multivariable logistic regression model.

Results: A total of 263 patients were included, 99 in the NPWT group and 164 in the control group. The median duration of NPWT was 18.0 (IQR 15.8) days. In the NPWT group, 28 patients (28.3%) developed a recurrent FRI. In the control group, 19 patients (11.6%) had a recurrent FRI ($p = 0.001$, 95% CI [0.174 – 0.635]). In the NPWT group there were no significant differences in baseline characteristics between the recurrence and non-recurrence group. The duration of NPWT was associated with a higher risk of recurrence of infection ($p = 0.013$, OR 1.036, 95% CI [1.008 – 1.066]).

Conclusion: Delayed wound closure with the application of NPWT increased the risk of recurrence of infection in patients with soft tissue defects after FRI treatment. Therefore, it is advised to consider NPWT only as a short-term (e.g. few days) necessity to bridge the period until definitive wound closure can be established.

Introduction

Fracture-related infection (FRI) remains one of the most serious complications in orthopedic trauma surgery [1,2]. Standardized treatment strategies have been developed over the years, which can be summarized as the execution of surgical debridement, tissue sampling for microbiological culturing, dead space management, fracture stabilization and adequate soft tissue coverage followed by appropriate antimicrobial therapy [3]. Although the fact that the important role for soft tissue management has increasingly been acknowledged over the past decades, there remains controversy on how this should be achieved [4]. With respect to wounds that cannot be primarily closed, several reconstructive options can be applied, such as aiming for the formation of granulation tissue that in a later stage can be covered with a split skin graft (SSG) or a more direct approach by carrying out a robust tissue-based reconstruction (a so-called local or free-flap). Also, negative pressure wound therapy (NPWT) has been gaining

Abbreviations: FRI, Fracture-Related Infection; NPWT, Negative Wound Pressure Therapy.

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popularity as a (temporarily) wound coverage option in FRI patients. Two reasons that are often put forward for the application of NPWT in FRI patients are 1) the need for bridging wound coverage until final reconstruction can be performed and 2) its use as a method to promote tissue granulation aiming to achieve a situation where delayed primary closure can be performed, whether or not with an SSG [5].

Although the term 'therapy' suggests otherwise, the general use of NPWT is merely as a wound dressing method for non-closable wounds. The negative pressure creates a vacuum via a foam dressing causing mechanical forces to the wound that are claimed to stimulate wound healing and form granulation tissue [6]. Another oft-stated advancement is that NPWT pulls the wound edges together and removes exudate and infectious materials [7,8]. Due to the simplicity of the application and bed-side care, NPWT is widely used as dressing and management method for all kinds of complex wounds. Nevertheless, there are still serious downsides and reported complications [9,10]. The necessity of exposing the wound each time a foam change is required creates subsequent opportunities for pathogens to contaminate the wound with associated risks of secondary infection. To reduce this risk, especially in the presence of exposed implants, NPWT procedures are often carried out in the operating theatre, where general or regional anesthesia can be required. These additional surgical procedures are costly, time consuming, potentially hazardous and cause discomfort to the patient. The same burden applies for home-care situations. Regular dressing changes and device malfunctions, results in persisting dependency on health care professionals. Another downside is the fact that constantly being hooked up to an (at times noisy) electronical device hinders the patient's freedom of movement. From a medical point of view, the alleged positive effects are subject of debate. Despite the claimed positive effect of NPWT on wound healing [11], others report reduced oxygen perfusion of intact skin of the dorsum of the foot in healthy volunteers after application of NPWT [12]. The influence of this phenomenon on bone vitality, but also fracture and wound healing, is unknown. As mentioned above, NPWT devices may malfunction and thus interrupt wound drainage which can result in undesirable fluid accumulation or air and fluid leakage. As a consequence, more unplanned surgeries for debridement and re-application of the NPWT need to be carried out leading to a potential cascade of increasing soft tissue problems and infection complexity [13].

Currently, as scientific evidence is lacking, most recommendations for NPWT with respect to the treatment of FRI are based on expert opinions [14,15]. Therefore, there is a need to clarify the role of NPWT in FRI patients. We hypothesized that the application of NPWT will result in a higher recurrence rate of infection, and that the risk of recurrence increases as duration of NPWT application is longer. For this reason, the aim of this study is to assess the relationship between the use (and duration) of NPWT and recurrence of infection in operatively treated FRI patients.

Patients and methods

Study design

This study is a multicentre, international, retrospective cohort study involving data of patients from three level 1 trauma centres: the University Medical Centre Utrecht (UMCU), the University Medical Centre Groningen (UMCG) , both in The Netherlands and the University Hospitals Leuven (UZ Leuven) in Belgium.

Patient population

Patients were eligible for inclusion if they: 1) were diagnosed with an FRI between January 1st 2015 and September 1st 2020; 2) were at least 16 years of age at time of infection diagnosis; 3) had a minimum of three surgically obtained deep tissue cultures taken at the time of the FRI diagnosis and 4) had at least one year follow-up after the cessation of (both surgical and antibiotic) therapy. Patients were subdivided into a group where NPWT had been applied (from the UMCU, UMCG and UZ Leuven) as part of FRI treatment and a control group of patients to whom no NPWT had been applied (from the UMCU and UMCG). All three centres applied isolated NPWT exclusively, no concomitant NPWT instillation methods were used. The diagnosis of FRI had to be confirmed according to the FRI consensus criteria [16]. To limit confounding, patients were excluded if they had NPWT at any time point in their fracture treatment prior to the diagnosis of FRI (e.g. for management of open fractures). Furthermore, FRIs of the skull and spine were excluded.

Overall, there were two main indications for applying NPWT. Firstly, part of our study population had NPWT as a short bridging solution to planned, definitive soft tissue reconstruction (a planned local or free flap that could not be carried out immediately). Secondly, patients had NPWT as an intended way to stimulate granulation tissue only for later SSG.

Collected data

Information was retrieved from the retrospective FRI databases of the three participating centres. Data was collected on patient demographics (i.e., sex, age, Body Mass Index(BMI), smoking status, and diabetes), fracture characteristics (i.e., location, type of implant and soft tissue status) and FRI characteristics (i.e., outcome of microbiological cultures and days between index surgery and FRI,). The use of local antibiotics (defined as any to the bone or wound applied antibiotics, whether in a resorbing or non-resorbing carrier), was also noted. Open fractures were classified by the Gustilo-Anderson Classification [17]. An FRI was confirmed based on the criteria of the FRI consensus definition: the presence of two or more identical pathogens identified by at least two separate tissue cultures, purulent drainage or the presence of pus and/or the presence of a fistula, a sinus or wound breakdown [16]. Furthermore, data on NPWT duration (in days), definitive wound closure methods and recurrence of infection were collected. Recurrence of infection was defined as re-occurrence of at least one confirmatory criterion according to the consensus criteria after cessation of surgical and antimicrobial treatment. Additionally, data on the pathogens causing FRI (and recurrence of FRI) were gathered. Definitive wound closure methods were subdivided into two categories: wound healing by primary intention (either delayed primary suture or tissue-based reconstruction) and wound healing by secondary intention (granulation of the wound, possibly combined with SSG).

Statistical analysis

Baseline patient, fracture and FRI characteristics were descriptively analyzed. If normally distributed, continuous variables were described using mean and standard deviation (SD). Median and interquartile range (IQR) were used if data was not normally distributed. Categorical variables were described with frequencies and percentages.

Patient characteristics were compared by using the Fisher's exact test for categorical data. The independent students t-test was used if continuous data was normally distributed and the Mann-Whitney U test if the distribution of continuous data was not normal. Two-tailed p-values were used. If $p < 0.1$, the variable was considered as confounder and included in the logistic regression model. A multivariable logistic regression was performed to evaluate the impact of NPWT duration on infection recurrence. Results

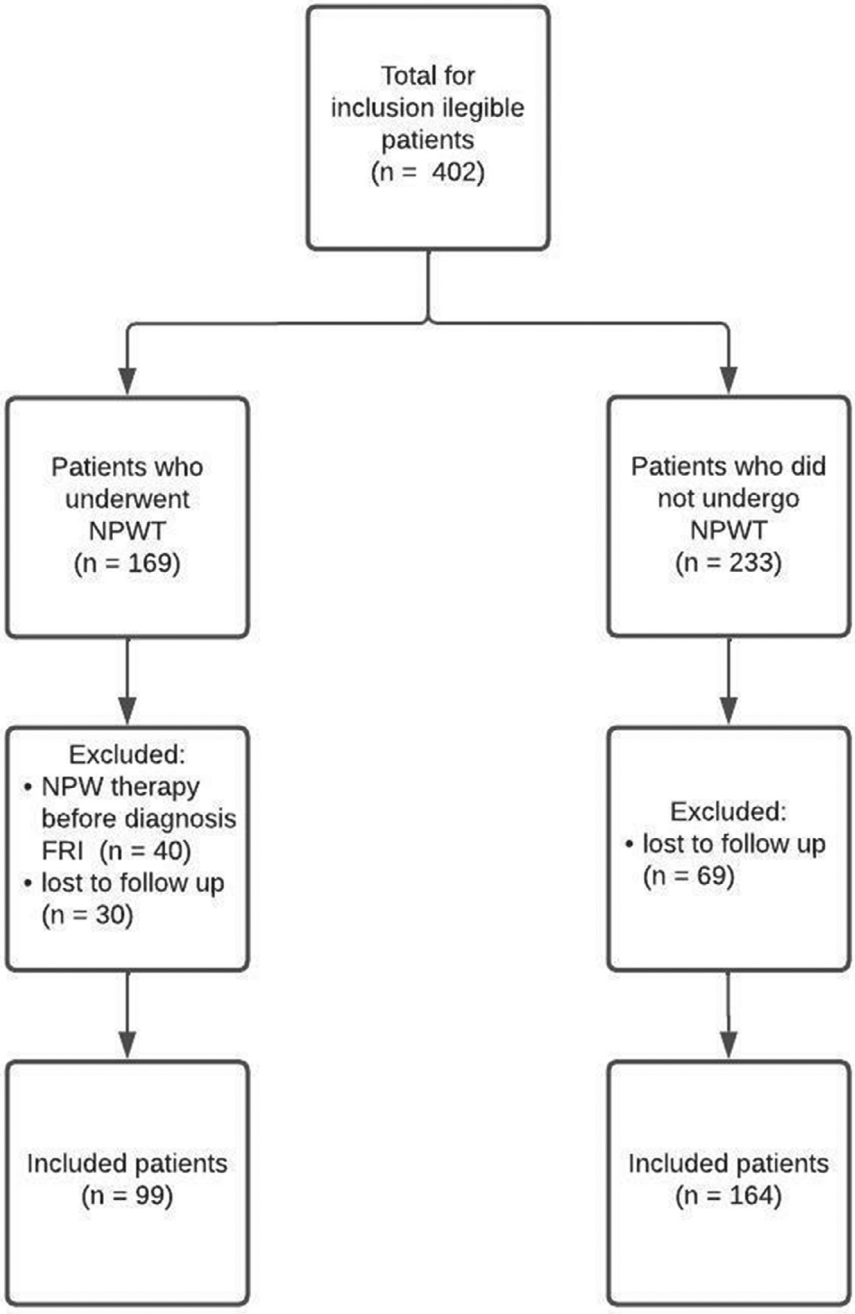

Fig. 1. Flow diagram of patient inclusion.

were described with the p-value, odds ratio (OR) and 95% confidence interval (CI).

The FRI databases of the UMCU and UMCG were composed using the Data Capturing program CASTOR, the UZ Leuven database was composed in Microsoft Excel. Analyses were conducted using SPSS Statistics version 25.0 (IBM Corp, Armonk, NY). The level of statistical significance was set at $p<0.05$.

Results

Patient demographics and fracture characteristics

A total of 99 patients were eligible for inclusion in the NPWT group (Fig. 1), the majority of whom were male (n = 66, 66.7%). The mean age was 51.4 ± 17.0 years. The average BMI was 25.9 ± 4.6 kg/m^2, 37 patients (37.4%) were active smokers and 11 patients (11.1%) had diabetes mellitus. Tibia/fibula was the most frequently affected bone (n = 68, 68.7%), followed by fractures of the foot (n = 10, 10.1%). Plate and screw osteosynthesis were the most commonly used implants at index operation for fracture stabilization (n = 68, 68.7%). At time of injury, 33 patients (33.3%) had an open fracture. Most of those open injuries were classified as a type III (n = 19, 57.6%) according to the Gustilo-Anderson classification [17].

The control group consisted of 164 patients with a mean age of 50.2 ± 17.1 years. Most patients were male (n = 123, 75.0%). Also in this group, the most frequently involved fracture locations were the tibia/fibula (n = 64, 39.0%), but then followed by the femur (n = 42, 25.6%). There were significantly more tibia/fibula fractures in the study group compared to the control group (p< 0.001). In

Table 1
patient demographics and fracture characteristics.

Variable	Description	NPWT group (n = 99)	no-NPWT group (n = 164)	p-value
Patient demographics				
Gender, n (%)	Male	66 (66.7)	123 (75.0)	0.159
	Female	33 (33.3)	41 (25.0)	
Age, years (SD)		51.4 (±17.0)	50.2 (±17.1)	0.607
BMI, kg/m^2 (SD)		26.0 (± 4.8)	27.1 (± 5.5)	0.077
Smoking, n (%)	Yes	37 (38.1)	49 (30.4)	0.221
	No	60 (61.9)	112 (69.6)	
Diabetes, n (%)	Yes	11 (11.1)	21 (12.8)	0.846
	No	88 (88.9)	143 (87.2)	
Fracture characteristics				
Fracture location, n (%)	Humerus	4 (4.0)	15 (9.1)	<0.001*
	Forearm	5 (5.1)	15 (9.1)	
	Pelvis	4 (4.0)	23 (14.0)	
	Femur	4 (4.0)	42 (25.6)	
	Patella	3 (3.0)	0 (0.0)	
	Tibia/fibula	68 (68.7)	64 (39.0)	
	Foot	10 (10.1)	5 (3.0)	
Type of implant used at index operation, n (%)	Plate	67 (67.7)	104 (63.4)	0.752
	Screw(s)	8 (8.1)	9 (5.5)	
	Nail	17 (17.2)	34 (20.7)	
	External fixation	3 (3.0)	7 (4.3)	
	Index operation was removal of implant only	4 (4.0)	10 (6.1)	
Soft tissue status, n (%)	Closed	66 (66.7)	120 (73.2)	0.267
	Open	33 (33.3)	44 (26.8)	
Gustilo classification open fractures, n (%)	Type I	7 (21.2)	6 (13.6)	0.143
	Type II	7 (21.2)	19 (43.2)	
	Type III	19 (57.6)	19 (43.2)	

SD: standard deviation *: significantly more tibia/fibula fractures in study group compared to control group ($p < 0.05$).

Table 2
FRI characteristics and outcome.

Variable	Description	NPWT group (n = 99)	no-NPWT group(n = 164)	p-value
FRI characteristics				
Polymicrobial infection, n (%)	Yes	50 (50.5)	60 (36.6)	0.227
	No	41 (41.4)	79 (48.2)	
	Culture negative	8 (8.1)	25 (15.2)	
NPWT duration days, median days (IQR)		18.0 (15.8)	-	
Definitive wound closure method, n (%)	Primary intention	56 (56.6)	164 (100.0)	
	Secondary intention	43 (43.4)	0 (0.0)	
FRI outcome				
Recurrence, n (%)	Yes	28 (28.3)	19 (11.6)	0.001
	No	71 (71.7)	145 (88.4)	

IQR: interquartile range.

the control group, 44 patients (26.8%) had an open fracture, these were mostly classified as Gustilo-Anderson type II or type III (each n = 19, combined 86.4%). The patient and fracture characteristics of the NPWT group and the control group are displayed in Table 1.

FRI characteristics

As per study protocol, none of the patients underwent NPWT before the time of FRI diagnosis. At time of inclusion, in the NPWT group, 50 infections (50.5%) were polymicrobial, 41 (41.1%) were monomicrobial and in the remaining eight patients (8.1%) no pathogen was detected. In the latter group of so-called culture negative FRIs the infection was confirmed based on the other clinical confirmative criteria (i.e., exposed implant (n = 1), wound dehiscence (n = 3), fistula (n = 3) and purulent discharge (n = 1)). The median duration of NPWT was 18.0 days (IQR 15.8). After the period of NPWT, in 56 patients (56.6%) the wound was closed by primary intention (suturing or tissue-based reconstruction). The other wounds healed by secondary intention (granulation possibly combined with a SSG procedure). Overall, 28 patients in the study group (28.3%) developed a recurrent FRI.

In the control group 60 infections (36.6%) were polymicrobial, 79 (48.2%) were monomicrobial and 25 (15.2%) were culture negative. All wounds were closed by primary intention (whether or not with a local or free flap). Overall,19 patients (11.6%) developed a recurrent FRI which is significantly lower compared to the group treated with NPWT (p = 0.001, 95% CI [0.174 – 0.635]). The FRI characteristics and outcome are presented in Table 2.

Recurrence of FRI in the NPWT group

Patients treated with NPWT were subdivided into two groups: with and without recurrence of FRI. These groups were compared on patient demographics, fracture characteristics and FRI characteristics in a univariable analysis, as displayed in Table 3. Although not significantly different, there were relatively more smokers (n = 15, 53.6%) in the recurrence group than in the non-recurrence group (n = 22, 31.9%) (p = 0.065). With p < 0.1, smoking status was identified as a potential confounder and taken into

Table 3
Univariable analysis of patients with and without FRI recurrence.

Variable	Description	Patients (n = 99)	FRI Recurrence (n = 28)	No FRI recurrence (n = 71)	p-value
Patient demographics					
Gender, n (%)	Male	66 (66.7)	21 (75.0)	45 (63.4)	0.346
	Female	33 (33.3)	7 (25.0)	26 (36.4)	
Age, years (SD)		51.4 (±17.0)	47.4 (±17.8)	52.8 (± 16.6)	0.177
BMI, kg/m^2 (SD)		25.9 (± 4.6)	26.8 (± 4.6)	25.7 (± 4.8)	0.281
Smoking, n (%)	Yes	37 (38.1)	15 (53.6)	22 (31.9)	0.065
	No	60 (61.9)	13 (46.4)	47 (68.1)	
Diabetes, n (%)	Yes	11 (11.1)	2 (7.1)	9 (12.7)	0.799
	No	88 (88.9)	26 (92.9)	62 (87.3)	
Fracture characteristics					
Soft tissue status, n (%)	Closed	66 (66.7)	18 (64.3)	48 (67.6)	0.458
	Open	33 (33.3)	10 (35.7)	23 (32.4)	
Type of implant used at index operation, n (%)	Plate	67 (67.7)	19 (67.9)	48 (67.6)	0.535
	Screw(s)	8 (8.1)	1 (3.6)	7 (9.9)	
	Nail	17 (17.2)	5 (17.9)	12 (16.9)	
	External fixation	3 (3.0)	2 (7.1)	1 (1.4)	
	Index operation was removal of implant only	4 (4.0)	1 (3.6)	3 (4.2)	
FRI characteristics					
Days between index surgery and FRI, median (IQR)		19.5 (46.3)	15.5 (25.3)	23.0 (56.5)	0.217
Polymicrobial infection, n (%)	Yes	50 (50.5)	13 (46.4)	28 (39.4)	0.643
	No	41 (41.4)	13 (46.4)	37 (52.1)	
	Culture negative	8 (8.1)	2 (7.1)	6 (10.5)	
Local antibiotics used, n (%)	Yes	32 (32.3)	6 (21.4)	26 (36.6)	0.162
	No	67 (67.7)	22 (78.6)	45 (63.4)	
Definitive wound closure method, n (%)	Primary intention	56 (56.6)	14 (50.0)	42 (59.2)	0.501
	Secondary intention	43 (43.4)	14 (50.0)	29 (40.8)	

SD: standard deviation IQR: interquartile range.

Table 4
Multivariable logistic regression analysis.

	β	OR	95% CI	p-value
NPWT duration	0.036	1.036	1.008 – 1.066	0.013*
Smoking status	0.838	2.312	0.901 – 5.934	0.081*
Baseline risk	-2.081	0.125	-	-

*Statistically significant at p<0.05; OR: odds ratio; 95% CI: 95% confidence interval.

account in the logistic regression model. No other statistically significant differences between the groups were identified.

Duration of NPWT

The multivariable logistic regression model, which was adjusted for smoking status as a potential confounder, demonstrated that the duration of NPWT is an independent risk factor for recurrence of FRI with an OR of 1.036 (p = 0.013, 95% CI [1.008 – 1.066]) (Table 4).

Figure 2 shows a graphic overview of the relation between the duration of NPWT and the probability of recurrence of infection.

Microbiological epidemiology of FRI and recurrence of FRI

The identified pathogens causing the (recurrent) FRI are presented in Appendix 1 and Appendix 2. In the NPWT group, ten patients (36.6%) had identical pathogens in both the primary FRI and the recurrent FRI. In three patients (10.7 %) additional pathogens were detected in the recurrent FRI, and in 16 patients (57.1%) no pathogens at all matched between primary and recurrent infection. In the control group, six patients (31.5%) had identical pathogens in both the primary FRI and the recurrent FRI. In three patients (15.8%) additional pathogens were detected in the recurrent FRI and in 12 patients (63.2%) there were all new pathogens in the recurrent FRI. There were three (10.7%) culture negative cases in the NPWT group and three cases in the non-NPWT group (15.8%).

Discussion

This study showed that the risk of recurrence more than doubles in FRI patients with soft tissue defects who are treated with NPWT compared to immediate primary closure (28.3% vs. 11.6%, p = 0.001, 95% CI [0.174 – 0.635]). It is the first large study where this relation is described, in particular with a well-defined patient cohort with exclusion of patients with NPWT prior to the FRI diagnosis. The only significant difference between the groups is the fracture location. There are relatively more patients with a tibia/fibula fracture in the study group. This is probably due to the fact that most soft tissue issues in FRI occur in the lower limb [18]. Moreover, delayed wound closure (in other words, longer duration of NPWT) is also associated with an increased risk of FRI recurrence (p = 0.013, OR = 1.036, 95% CI [1.008 – 1.066]). Our results confirm the conclusions of two recent systematic reviews, in which the lack of scientific evidence for the use of NPWT in FRI patients was noted [14,15]. Based on these results, clinicians involved in the care of FRI patients are advised to be very cautious when considering application of NPWT as a treatment strategy for soft tissue defects in FRI patients.

Although, there are studies that describe positive effects of NPWT in FRI management such as a reduced bacterial load and a diminished amount of (re)infections [18–20], the literature remains controversial and many critical papers have been published [21–23,25–27]. Assadian *et al.* (2010) demonstrated in an *in vitro* model using *Staphylococcus aureus,* the incapability of NPWT to reduce bacterial load in non-viable tissue [21]. Therefore, they concluded that the apparent bacterial reduction after several days of NPWT, as described in other studies, can be attributed to immune-

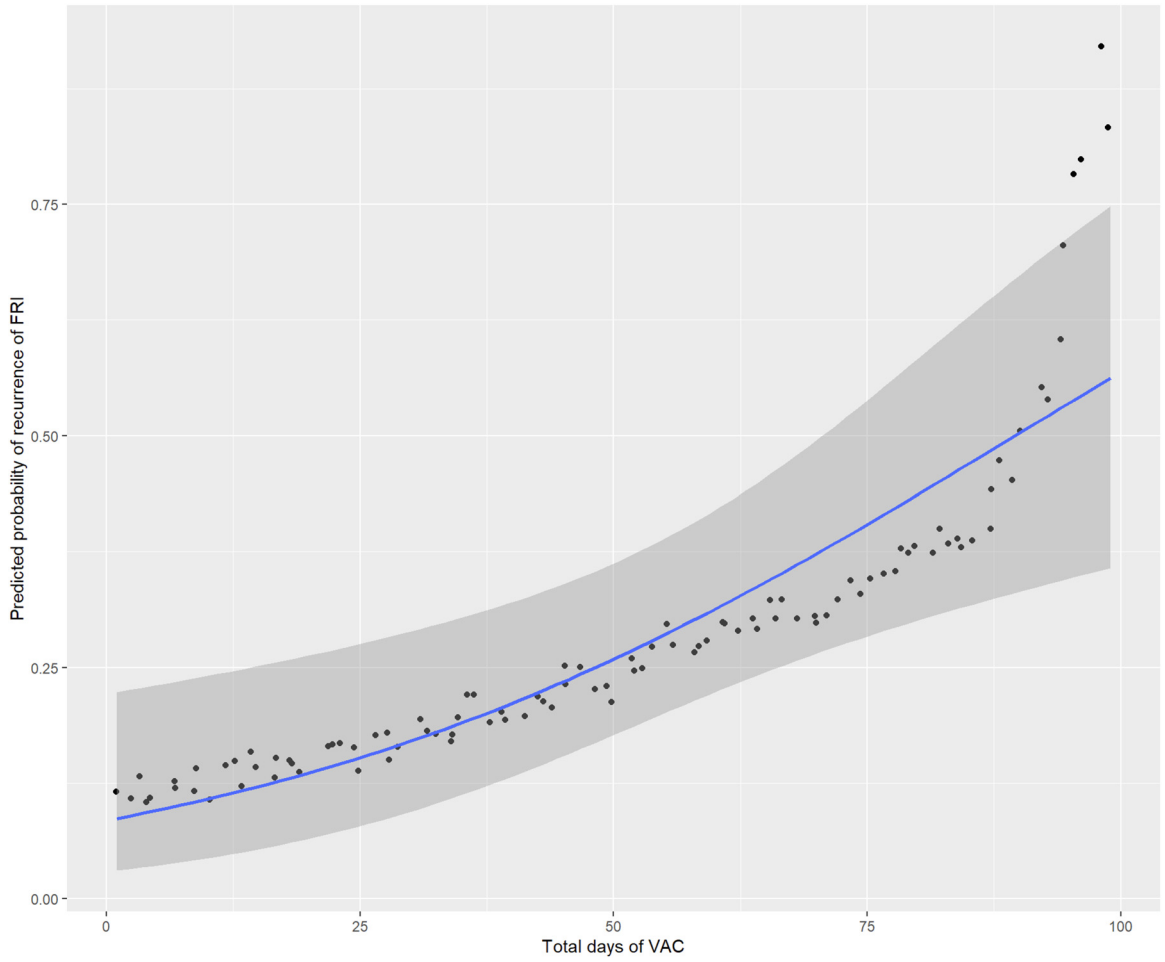

Fig. 2. Relation between time of NPWT application and probability of recurrence of infection.

modulating factors (the body's immune system or other antibacterial effects) rather than the direct physical effect induced by negative pressure. Furthermore, other authors stated that the application of NPWT in combination with the use of a local antibiotic depot reduced the antibiotic effectiveness [22]. Lalliss *et al.* (2010), described that the effect of NPWT on bacterial load reduction differs between pathogen types. In this study, the authors presented an animal model with a complex wound that was inoculated with *Pseudomonas aeruginosa* or *S. aureus* followed by NPWT. A clear load reduction of *P. aeruginosa* was seen, but no reduction in *S. aureus* concentrations were observed. Therefore, they concluded that (prolonged) NPWT use might not decrease the bacterial load in all patients, and bacterial selection and subsequent development of antibiotic resistance of certain pathogens may occur [23]. This is in particular relevant because *S. aureus* is the most common pathogen causing FRI [24]. In our study there was a shift in micro-organisms causing the recurrence of FRI in both groups. In the NPWT group it was slightly more often the same pathogen that was causing both the initial FRI as the recurrence compared to the control group (36,6% vs 31,5%). One could hypothesize that maybe the elimination of primarily causative bacteria is less successful when NPWT is applied since intravenously administered antibiotics will not be able to be transported to the site of infection when a synthetic foam is covering the fracture.

There are more reported downsides of NPWT in FRI patients. A recent large randomized controlled trial by Costa *et al.* (2018) demonstrated that there is no benefit of applying NPWT in comparison to standard, non-vacuum dressings in open fractures of the lower limb with regard to the risks of developing an FRI [25]. Another study on open fractures stated that (prolonged) NPWT usage results in a higher risk of developing infection and need of amputation [26]. It has to be acknowledged that sufficiently powered, prospective clinical studies on the use of NPWT in FRI management are lacking to date [14,15]. However, there are published expert opinions (level 5 evidence) stating that the longer NPWT is applied, the more wound edges will become negatively affected with more rigid and scarred soft tissues [3,27]. Typically, at the time of final reconstruction, granulation tissue resulting from NPWT application has an unhealthy appearance and needs to be removed entirely before a robust tissue-based reconstruction can be carried out, thereby nullifying the entire NPWT treatment duration.

Furthermore, it is likely that at least in a subgroup of patients who underwent NPWT as part of their treatment for FRI, the NPWT was applied to bridge the time to soft tissue reconstruction surgery. Unfortunately, as many surgeons will recognize, theatre slots are scarce, in particular when they are semi-urgent. This means that modern time FRI management faces logistical challenges that have an impact on treatment outcome. From a socio-economic point of view, it is likely that it is much more cost-effective to invest in a solution for these health care shortcomings. The fact that immediate soft tissue reconstructions cannot be

performed in a timely manner affects the long-term morbidity for FRI patients and comes with associated, assumedly higher, overall costs.

Limitations

The main limitation of our study was the relatively small number of patients in the NPWT group, mainly due to our strict inclusion criteria. Therefore, it was not possible to perform a more extensive multivariable logistic regression adjusting for more confounders. Secondly, no distinction could be made regarding the choices in indication and duration of the NPWT. This was inherent to the retrospective study design. Thirdly, we constructed our cohort based on a minimum of three deep tissue cultures, this is not in line with a later published recommendation were a minimum of five is advised [28]**.** Fourthly, the reported incidence of FRI recurrence in the control group (11.6%) might be an underestimation since this group consisted of less tibia/fibula fractures ($p < 0.001$) in comparison with the study group, which are more prone to FRI. ([29]) Lastly, because the recurrence groups are small, and due to the retrospective nature of this study where we cannot be sure that appropriate cultures were collected at all times, we cannot draw any definite conclusions from the observation we did according the micro-organisms. More in depth research addressing this phenomenon has to be conducted to gain insight into the effect of NPWT application on pathogen evolution in FRI patients.

Conclusion

Delayed wound closure with the application of NPWT increased the risk of recurrence of infection in patients with soft tissue defects after FRI treatment. Therefore, it is advised to consider NPWT only as a short-term (e.g. few days) necessity to bridge the period until definitive wound closure can be established.

Ethical approval

The ethical committee of the University Medical Centre Utrecht confirmed that ethical approval was not required for this study (reference METC 20-004/C).

Declaration of Competing Interest

The authors of this study have no conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.injury.2022.10.014.

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