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Foot and Ankle Forklift Injuries; Diagnosis to Treatment Options, Return to Work and Functional Outcomes

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ABSTRACT

As our tertiary-level trauma center is close to an industrial zone and associated international port, industrial injuries are seen more often than is expected in routine practice. The aim of this study was to present the demographic data, treatment options, and changes in work-life of patients with foot and ankle injuries due to a forklift accident, and to determine the factors affecting the clinical outcome. The study was conducted in our university hospital and included patients who presented with a foot and ankle injury resulting from a forklift accident. Data were collected including age, sex, dominant extremity, history of trauma, presence of fracture, management (surgical or conservative), complications, time of return to work, workforce loss, and the American Orthopaedic Foot and Ankle Society (AOFAS) and Short Form Health Survey (SF-36) scores at the final follow-up examination. Evaluation was made of 132 patients, comprising 113 (85.6%) males and 19 (14.4%) females with a mean age of 32 years (range 16-65 years). The most frequently recorded occupational group was shipyard workers (50%). The most common mechanism of injury was crushing under the forklift wheel (n = 63, 47.7%). The most frequently injured foot region was the forefoot (47%). A total of 90 (68.1%) patients continued to work in the same position on return to work. The lowest mean AOFAS score (73.4) and SF-36 (physical component) score (37.3) were determined in cases with mixed region injuries ($p = .0001$, $p = .0001$). The wearing of protective footwear had no effect on the rate of return to work ($p = .195$), workforce loss ($p = .34$) and AOFAS score ($p = .166$). This study is the largest series of patients with foot and ankle injuries related to forklift accidents. Forklift injuries can be treated conservatively or surgically according to the clinical condition of the patient. The main indicators of return to work and functional outcome are which foot region is injured and whether or not the injury causes a fracture.

With developments in industry, there is increasing use of industrial machinery such as forklifts. This increasing use necessitates close contact of workers, constituting a risk of injury for both those using a forklift and those working around it. Forklift accidents cause both fatal and nonfatal occupational injuries. Of all industrial machinery, forklifts are the most frequent cause of fatal injuries (1,2). A large proportion of these injuries are penetrating injuries of the foot and ankle. Forklift-related foot and ankle injuries constitute <3% of all foot and ankle injuries (3).

As our tertiary-level trauma center is close to an industrial zone and associated international port, industrial and port-related injuries are seen more often than is expected in routine practice. Proportionally, injuries involving forklifts are more severe than those injuries originating from other industrial accidents (4), and should therefore be evaluated as a different group. In the current literature, there is a limited amount of data on the epidemiology and treatment modalities of foot and ankle injuries related to forklifts (3), and there are no long-term clinical results (return to work, functional score).

The aim of this study was to present the demographic data, treatment options, and changes in work-life of patients with foot and ankle injuries due to a forklift accident, and to determine the factors affecting the clinical outcome.

Materials and Methods

Approval for the study was granted by the ethics committee of the institution to which the authors were affiliated. The study was conducted in a tertiary-level trauma

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center of a university hospital. The study included a total of 132 patients who presented at the hospital between 2012 and 2022 with a foot and/or ankle injury resulting from a forklift accident. Patients were excluded from the study if the injuries resulted from a traffic accident (motorcycle or any other vehicle accident), other industrial accidents, or were forklift injuries without foot and ankle injuries.

At the time of first presentation, that was collected for each patient including demographic data (age, gender), the dominant and injured extremity side, the work conditions (industry sector, shift worked at the time of the accident, time of presentation, nationality, use of protective footwear), mechanism of injury (forklift- patient position in 5 subgroups), the injured region of the extremity (1 = forefoot, 2 = midfoot, 3 = hindfoot or ankle, 4 = mixed region) (Fig. 1*A-E*), fracture or soft tissue injury without fracture, open-closed fracture status, soft tissue defect (degloving), and the presence of compartment syndrome (Fig. 2).

The treatments applied to patients (surgery, conservative, fasciotomy, amputation), and the rates and duration of hospitalization were documented (Fig. 3*A-F*). The basic principles of treatment are conservative treatment of small nonarticular and nondisplaced fractures, and surgical treatment of intra-articular, open fractures, multifractures, and displaced fractures.

Complications that developed and the rates and time (days) of return to work in the same position were documented from the follow-up notes of the patients. At the final follow-up examination, all the patients were evaluated by an experienced (board-certified associated professor) foot and ankle surgeon, and the American Orthopaedic Foot and Ankle Society (AOFAS) and Short Form Health Survey (SF-36) (physical) scores were completed. The dependent and independent variables affecting the time of return to work (same work position), functional scores, and SF-36 scores of the patients were investigated.

All the patients with open fractures were administered tetanus prophylaxis intravenously (iv) and antitetanus intramuscularly (im). The Gustilo-Anderson (GA) classification was used to classify the open fractures (5). Antibiotics were administered within the first 30 minutes of presentation to patients with an open fracture. All the patients received antibiotics within the first 2 hours of the initial trauma. Type I and II fractures were treated with 2 gr iv cefazolin every 8 hours (total 3 doses) following the first antibiotics. Type III fractures were administered 2 gr iv ceftriaxone (single dose) immediately, and 1 gr iv vancomycin every 12 hours for 24 hours (total 2 doses) (6). Dose adjustments were made for pediatric patients and obese patients. In accordance with the institutional policy, when there was no documented infection, all the antibiotics were terminated 24 hours after definitive wound closure. Finally, the lower leg was immobilized with a foot and ankle splint.

Data entry and data analysis were performed using Statistical Package for the Social Sciences software (SPSS version 18.0, Chicago, IL). Descriptive statistics were stated in the tables as number and percentage for discrete random variables and as mean ± standard deviation, or median and range values as appropriate for continuous random variables. The chi-square test was used in the comparisons between categorical variables, and the unpaired *t*-test and one-way ANOVA test were applied to continuous variables. The level of statistical significance was set at 0.05.

Results

Evaluation was made of 132 patients, comprising 113 (85.6%) males and 19 (14.4%) females with a mean age of 32 years (range 16-65 years), and 50% of the patients were aged <30 years. The dominant extremity was affected in 104 (78.7%) cases. The injury occurred during daytime working hours (8 AM-4 PM) in 60.6% of the patients. Protective footwear was worn by 33 (25%) patients at the time of the injury. Work experience of <3 years was determined in 73% of the patients. The most frequently recorded occupational group was shipyard workers (50%). The most common mechanism of injury was crushing under the forklift wheel (n = 63, 47.7%). The most frequently injured foot region was the forefoot (47%). The demographic data of the patients and injury characteristics are shown in Table 1.

A fracture was diagnosed in 60 (45%) patients and only soft tissue injury in 72 (55%). Mixed region injuries had the highest rate of fracture (100%) (p = .008). An open fracture was determined in 19 (14.3%) patients, as GA Type I open fracture in 1 patient, GA Type II in 12, GA Type IIIa in 3, GA Type IIIb in 2, and GA Type IIIc in 1. The patient with GA Type IIIc open fracture was an 18-year-old female, and first and second metatarsophalangeal joint amputation was performed (Fig. 3*F*). In a 65-year-old male with Type IIIb open fracture (Fig. 4*A-C*), open reduction internal fixation and vacuum-assisted closure was performed, but the patient died because of a massive pulmonary embolism in the first 24 hours postoperatively. Only 1 patient had severe pain with passive toes movement, and compartment syndrome was determined both clinically and compartmental pressure measurements (Fig. 2*A*). Treatment was applied because of degloving injury in 6 patients. Apart from the patient with GA Type IIIb fracture and degloving injury, debridement was performed in the first session for 5 other patients. Split-thickness skin grafting was performed in the second session. The patient group at greatest risk of developing degloving injury was the group with mixed region injury (p = .002). A total of 113 (85.6%) patients were treated conservatively, and the highest rate of requiring surgery (57.1%) was in the mixed region injury group (p = .007).

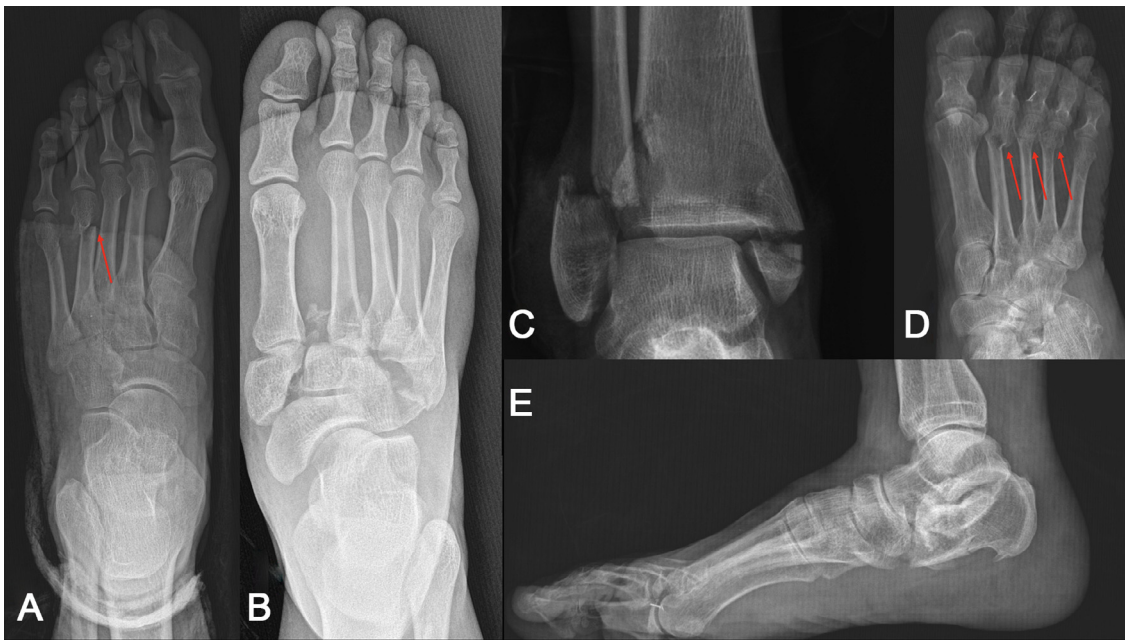

Fig. 1. (*A*) A patient with an isolated metatarsal fracture was evaluated as a forefoot region injury. (*B*) A patient with a Lisfranc injury was evaluated as a midfoot region injury. (*C*) A patient with ankle bimalleolar fracture was evaluated as a hindfoot or ankle region injury. (*D* and *E*) = A patient with calcaneus and second, third, and fourth metatarsal fractures was evaluated as a mixed region injury.

Fig. 2. (*A*) A patient with acute compartment syndrome. The photograph shows the clinical situation before the fasciotomy. (*B*) First evaluation in the emergency department of a patient with degloving injury.

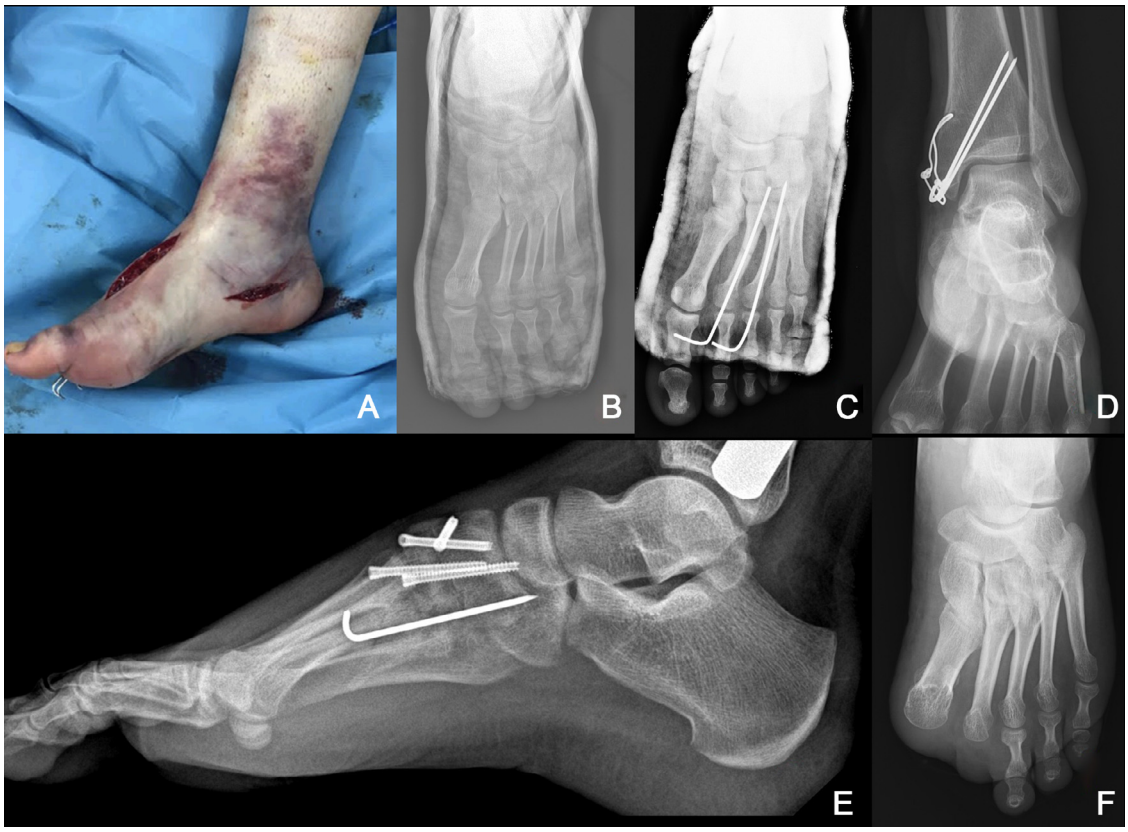

Fig. 3. (*A*) Perioperative clinical image of a patient who underwent fasciatomy surgery. (*B*) Short-leg cast treatment of a patient with a nondisplaced fracture in the proximal of the second metatarsal bone. (*C*) Treatment of second and third metatarsal displaced shaft fracture with closed reduction percutaneous pinning and short-leg splint. (*D*) Treatment of a patient with a medial malleolus fracture with the Zugurtung technique. (*E*) Surgical treatment of a patient with Lisfranc injury. (*F*) X-ray showing first and second metatarsophalangeal joint amputation after first and second toe crush injury.

Table 1
Patient demographics and injury information

All Patients		Number (%)
Age	<30	66 (50%)
	30-50	57 (43.2%)
	>50	9 (6.8%)
Gender	Male	113 (85.6%)
	Female	19 (14.4%)
Injury side	Right	77 (58.3%)
	Left	55 (41.7%)
Dominant side injury		104 (78.7%)
Time of presentation	12 AM-8 AM	27 (20.4%)
	8 AM-4 PM	80 (60.6%)
	4 PM-12 AM	25 (18.9%)
Protective footwear	Using	33 (25%)
	No	99 (75%)
Nationality	Citizen	130 (98.5%)
	Immigrants	2 (1.5%)
Shift worked at the time of the accident	First 4 hours	76 (57.6%)
	Second 4 hours	53 (42.4%)
Years of experience	3>	96 (72.7%)
	>3	36 (27.3%)
Industry sector	Shipyard	66 (50%)
	Textile	28 (21.2%)
	Cargo	23 (17.4%)
	Other	15 (11.3%)
Mechanism of injury	Crush under a forklift wheel	63 (47.7%)
	Stuck between a forklift and an object	36 (27.3%)
	Crash of the forklift directly to the casualty/victim	7 (5.3%)
	Crush under a material falling from forklift	22 (16.7%)
	Fall of the forklift driver off the forklift	4 (3%)
Trauma Compartment	Forefoot	62 (47%)
	Midfoot	14 (10.6%)
	Hind foot and ankle	49 (37.1%)
	Mixed compartment	7 (5.3%)
Total		132 (100%)

Other = raw material industry, catering.

Of the total patients, 24 (18.1%) were hospitalized in the orthopedics and traumatology clinic, and 102 were observed for several hours in the short stay unit and then discharged. The highest rate of hospitalization was in the group with mixed region injury (57%) (p = .0001). No difference was determined in the duration of hospitalization according to foot regions (p = .375; Table 2).

Complications developed in 20 (15.1%) patients and there was more than one complication in 6 patients. The most common complication was persistent pain, followed by joint arthrosis. Other complications seen were pes planus, Sudeck atrophy, talus osteochondral lesion, and infection. A 49-year-old female patient developed skin necrosis, and full layer skin grafting was performed on this patient (Fig. 5*A-D*). Patients with mixed region injury had the highest complication rate (42%) (p = .0059; Table 3).

A total of 90 (68.1%) patients continued to work in the same position on return to work. The patient who died and the patient who underwent amputation did not return to work. The position at work was changed on return by 40 patients (transfer to a desk job). Thus a total of 130 patients returned to work with a mean workforce loss of 44 days. The patients with mixed region injury had the lowest return to work rate (28%) and the highest workforce loss (119 days) (p = .039, p = .0001), followed by those with midfoot injuries (50%, 62.1 days). The wearing of protective footwear had no effect on the rate of return to work (p = .195) and workforce loss (p = .34). The mechanism of injury and type of industry sector had no effect on the rate of return to work and workforce loss. The loss of workforce was significantly greater in cases with fracture compared to those with only soft tissue injury (p = .001). When there were findings of high-energy injury, such as open fracture, compartment syndrome, or degloving injury, the loss of workforce hours was significantly higher than for foot injuries in a single location (p = .0001; Table 4).

The mean follow-up period was 4.7 years (range 6 months-12 years). The mean AOFAS score at final follow-up of 131 patients was 90 ± 8.9, and the mean SF-36 score was 50.5 ± 9.3. The lowest mean AOFAS score (73.4) and SF-36 score (37.3) were determined in cases with mixed region injuries (p = .0001, p = .0001). Cases with fracture or

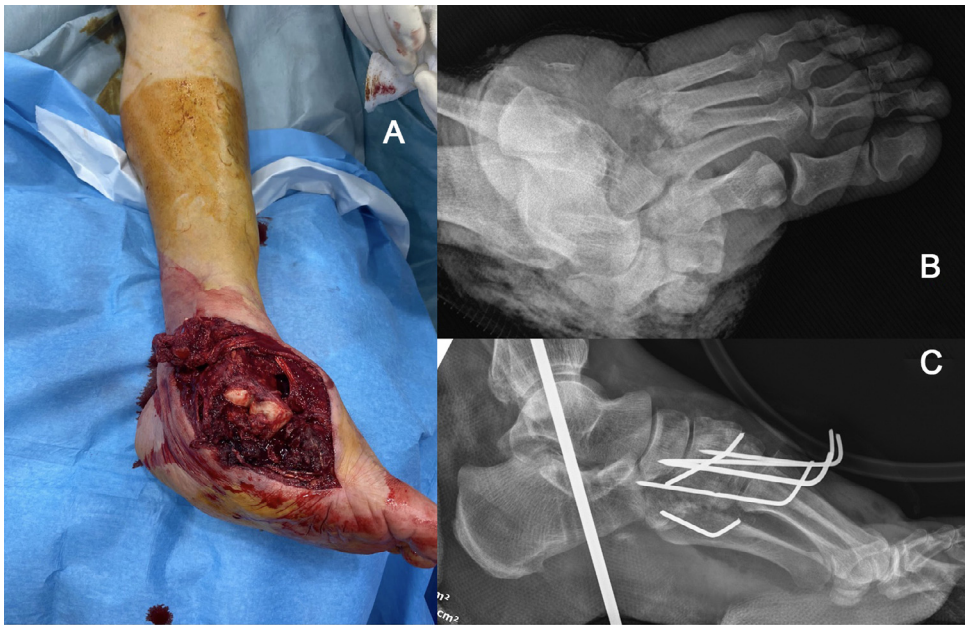

Fig. 4. (*A*) Mixed region injury accompanying Type IIIb open fracture. (*B*) Anterior posterior foot X-ray showing mid- and hindfoot injury and multiple dislocations. (*C*) Postoperative lateral foot X-ray of a patient applied with open reduction and percutaneous pinning.

Table 2
Diagnosis and treatment modalities by foot compartment

		Forefoot	Midfoot	Hind Foot and Ankle	Mixed Compartment	*p* Value
Injury severity	Fracture	24 (38.7%)	9 (64.2%)	20 (40.9%)	7 (100%)	.008
	Only soft tissue injury	38 (61.3%)	5 (35.8%)	29 (59.1%)	0 (0%)	
	Total	62 (100%)	14 (100%)	49 (100%)	7 (100%)	
Treatment modality	Operation (ORIF-CRIF)	3 (4.8%)	3 (21.5%)	8 (16.4%)	4 (57.1%)	.007
	Conservative treatment	58 (93.5%)	11 (78.5%)	41 (83.6)	3 (42.9%)	
	Amputation	1 (1.6%)	0	0	0	
	Total	62 (100%)	14 (100%)	49 (100%)	7 (100%)	
Open fracture	Yes	5 (8%)	3 (21%)	9 (13.8%)	2 (28.5%)	.226
	Total	62 (100%)	14 (100%)	49 (100%)	7 (100%)	
Compartment syndrome	Yes	0	1 (7%)	0	0	.037
	Total	62 (100%)	14 (100%)	49 (100%)	7 (100%)	
Degloving injury	Yes	0	0	4 (8.1%)	2 (28.5%)	.002
	Total	62 (100%)	14 (100%)	49 (100%)	7 (100%)	
Hospitalization	Inpatient clinic	4 (18.4%)	5 (35.7%)	11 (22.4%)	4 (57.1%)	.0001
	Total	62 (100%)	14 (100%)	49 (100%)	7 (100%)	
Hospitalization day	Mean value	6	9.4	5.73	6.75	.375

Abbreviations: CRIF, close reduction internal fixation; ORIF, open reduction internal fixation.

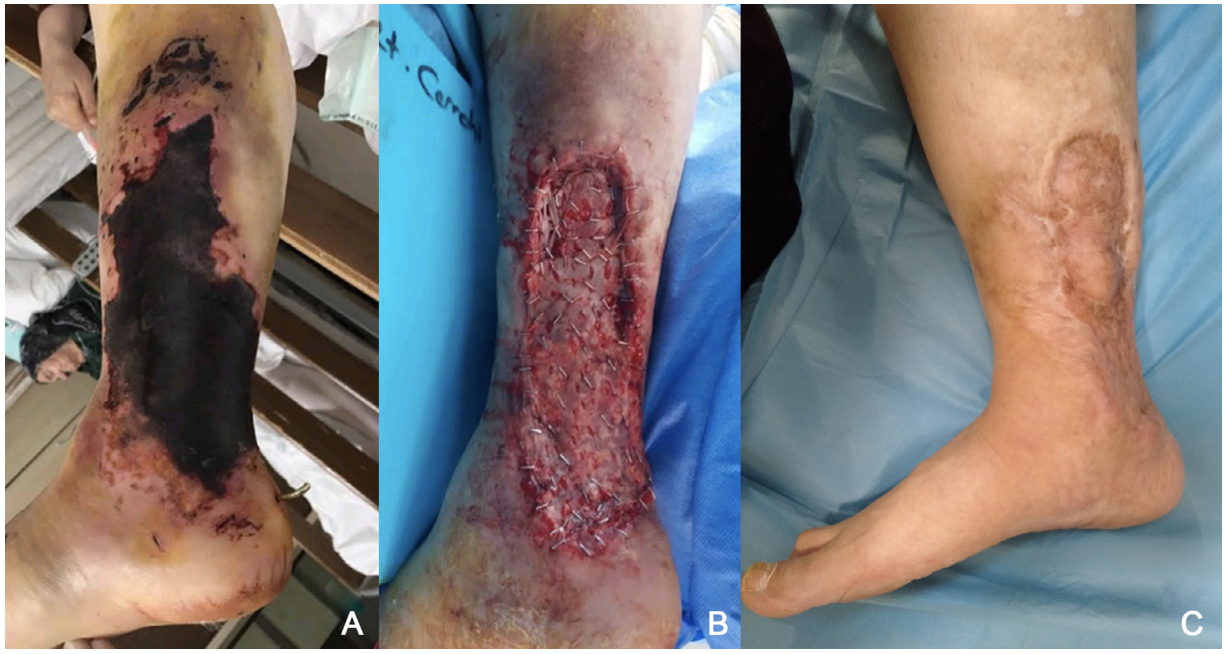

Fig. 5. (*A*) Photograph of ankle necrosis of a patient who underwent surgery for multiple metatarsal and calcaneal fractures after crush injury. (*B*) Perioperative photograph of applying skin graft to necrosis of the ankle. (*C*) Postoperative third year photograph of the patient who underwent skin grafting on the ankle.

Table 3
Complications and some unpredictable findings

	Forefoot (62 Patients)	Midfoot (14 Patients)	Hind Foot and Ankle (49 Patients)	Mix Region (7 Patient)	*p* Value
Persistent pain	4	4	5	1	
Sudeck atrophy	0	1	0	1	
Arthrosis	0	0	1	2	
Nonunion	0	0	1	0	
Pes planus	0	0	1	1	
Talus osteochondral lesion	0	0	1	1	
Infection	0	0	1	0	
Skin necrosis	0	0	0	1	
Total	4 (6.4%)	5 (35.7%)	8 (16.3%)	3 (42.8%)	.0059

Some cases have multi complication.

Table 4
Clinical outcomes and return to work

		Return to Same Work Position		Workforce Loss		AOFAS Score		SF 36 Score	
	All Patients (132 Number)	Number (Percentage)	*p* Value	Loss of Labor Force Mean (Std. D.)	*p* Value	Mean (Std. D.)	*p* Value	Mean (SD)	*p* Value
Trauma compartment	Forefoot	45 (72.5%)	.039	28.8 (4.4)	.0001	95.6 (3.5)	.0001	56.3 (8.8)	.0001
	Midfoot	7 (50%)		62.1 (11.7)		83.2 (10.3)		43.9 (6.3)	
	Hind foot and Ankle	36 (73.4%)		48.8 (7.2)		86.6 (8.5)		46.5 (5.4)	
	Mixed compartment	2 (28.5%)		119.1 (18.9)		74.3 (5.3)		37.3 (2.7)	
Protective footwear	Using (33 N)	26 (78.7%)	.195	37.2 (6.9)	.34	91.8 (8.4)	.166	51.7 (9.2)	.363
	No (99 N)	64 (64.6%)		46.3 (4.9)		89.3 (9.09)		50 (9.3)	
Mechanism of injury	Crush under a forklift wheel	40 (63.4%)	.277	52.5 (6.3)	.327	88.4 (9.8)	.182	50.1 (9.9)	.956
	Stuck between a forklift and an object	27 (75%)		32.6 (5.8)		90.1 (8.4)		50.8 (9.4)	
	Crash of the forklift directly to the casualty/victim	6 (85.7%)		38.5 (14)		90.5 (9.3)		50.1 (7.5)	
	Crush under a material falling from forklift	13 (59%)		38.8 (11.8)		93.9 (6.8)		51.3 (8.9)	
	Fall of the forklift driver off the forklift	4 (100%)		53.75 (23.5)		90 (2.1)		47.7 (4.6)	
Injury severity	Fracture (60 N)	33 (55%)	.005	83.1 (5.9)	.0001	83.7 (9.4)	.0001	43.1 (5.3)	.0001
	Only soft tissue injury (72 N)	57 (79.1%)		12 (0.8)		95 (4.01)		56.5 (7.3)	
Industry sector	Shipyard (66 N)	45 (68.1%)	.97	54.3 (6.1)	.073	89 (9.8)	.444	48.6 (9.3)	.049
	Textile (28 N)	20 (71.4%)		33.3 (7.7)		90.2 (7.4)		51.1 (8.1)	
	Cargo (23 N)	15 (65.2%)		38.4 (11)		89.4 (8.2)		52.5 (7.7)	
	Other (15 N)	10 (66.6%)		26.9 (6.02)		94.3 (6.7)		54.4 (5.3)	
High-energy injury (open fracture, compartment send. or degloving)	Yes (21 N)	11 (52.3%)	.15	116.5 (9.6)	.0001	78.1 (8.3)	.0001	39.8 (4.3)	.0001
	No (111 N)	79 (71.8%)		30.9 (3.2)		92.1 (7.2)		52.4 (8.6)	
Total		90 (68.1%)		44.04 (7.2)		90 (8.9)		50.5 (9.3)	

the presence of high-energy injury were determined to have worse AOFAS and SF-36 scores. The relationships between the use of protective footwear, the mechanism of injury, industry sector, and the AOFAS and SF-36 scores are shown in Table 4.

Discussion

For the first time in literature, this study presents the clinical outcomes, measure of quality of life, and return to work rate after foot and/or ankle forklift injuries, and highlights the problems inherent and specific to the industrial setting. A thorough understanding of the risk factors, pathophysiology, treatment modalities, and clinical outcomes of these injuries is important to help the treating surgeon coordinate appropriate treatments, for patients and employers to implement protective measures, and for optimal worker management after injury. To the best of our knowledge, this study of 132 patients with foot and ankle injuries as a result of forklift accidents is the largest case series on this subject in the literature. After a forklift accident, foot and ankle fractures, degloving injuries, compartment syndrome, amputations, or solely soft tissue injuries may be observed, and these may require surgical treatment or can be managed conservatively, especially in selected patients, particularly in the forefoot region.

Only one study could be found in recent literature that has evaluated foot and ankle injuries directly related to forklift accidents. In that study of 113 patients by Hong et al (3), the forefoot was the most commonly injured foot region, as in the current study. The probable reason for the predominance of forefoot injuries may be the realization of the trauma and withdrawing the foot at the last minute. In the current series, the group that could be treated conservatively at the highest rate (93.5%) were the patients with forefoot injuries. This was probably due to the greater number of fractures that are suitable for conservative treatment, such as isolated phalanx fractures with single fragment metatarsal fractures. Hong et al (3) observed complications in 20% of cases, while complications were determined at the rate of 15% in the current study. This high rate of complications is most likely due to the injury causing severe soft tissue injury whether fracture develops or not, degloving injury and the greater rate of open fractures, especially in the hind foot and ankle (7). Moreover, the follow-up period of the current study was a mean 4.7 years, but possible complications such as arthritis and pes planus may be noticed more often when the follow-up period is longer.

Crush injury is the most common reason for compartment syndrome (8). Although it has been stated in the literature that of all the regions, forefoot injuries are at the greatest risk of compartment syndrome, in the current study, compartment syndrome was determined in only 1 patient and that was in the midfoot region (9). Patients in the current study at risk of compartment syndrome were examined frequently, and diagnosis was based on clinical examination. In suspicious cases such as severe pain and passive toe motion, intracompartmental pressure was measured. There were no untreated patients, but the development of persistent pain and Sudeck atrophy were believed to be related to the crushing at the time of the initial trauma and the delayed weightbearing after treatment. When the crush injury is so severe that the compartment bursts open, it becomes an open fracture or degloving. This was considered to be the reason why compartment syndrome was encountered less in this study. Degloving injuries are the most destructive form of forklift-related soft tissue injuries, and sometimes when primary closure is not sufficient, flap, graft, or vacuum-assisted closure is performed (10,11). Vacuum-assisted closure was applied to 1 patient of the current series, but mortality occurred because of postoperative pulmonary emboli, and for the other 5 patients, a second surgery was required for split-thickness skin graft.

The factors most affecting the clinical and functional results (AOFAS and SF-36) seem to be whether or not the injury causes the development of fracture and which foot region is injured. Although mixed region injuries were associated with a poor clinical outcome, hindfoot and ankle injuries also had poor results, although there was no statistically significant difference between the groups. Contrary to expectations, according to the current study data, the use of metal protective footwear remained ineffective in high-energy injuries. This was

supported by a model prepared by Kwon et al (12). In this cadaver model, it was stated that steel toe-cap boots were protective against forefoot injuries but did not provide excellent protection (12). Forklift injuries differ from other workplace injuries in that the trauma does not come directly from above and there is a high probability of it coming from the lateral or medial side of the foot as the wheel turns over the foot. This then creates rotational torque force on the foot. Surprisingly, the type of industry sector had no effect on the AOFAS score but was found to have an effect on the SF-36 score. This was thought to be due to the workplace conditions and employer's attitude. Trauma may have a mental effect, but there are no data to support this.

Based on the data of this study, some recommendations can be made to employers because economic losses associated with industrial accidents are a problem throughout the world in general (13). Only 50% of all patients with forklift injuries return to work (14). In the current series, 32% of the patients could not return to work. This rate is most probably higher for patients with foot and ankle injuries. Vora et al (4) claimed that the treatment outcomes of patients with industrial crush injuries were much worse than those of exposure to other foot and ankle injuries. One of the most common problems following crush injuries is morbidity associated with chronic pain, nerve dysfunction, foot and ankle stiffness and pain, and sympathetic-mediated pain syndromes (4). In addition, the patient is not only affected by the physical score following foot and ankle crush injury, but the social health perception of the patient is also impaired (15,16). Previous recommendations have been made to try decrease forklift injuries in the industrial setting, such as these individuals can be transferred to a calmer working area after injury, for example a desk job. Most forklift accidents occur in the form of striking a pedestrian, which is probably due to the narrow working area of forklifts and that people do not take sufficient care in this narrow area (1). Forklift working areas could be expanded. The foot heals and the patient returns to work but reduced productivity because of chronic pain is a difficult situation for employers. The sick leave period of those returning to work after recovery could be extended. Of all reported accidents, 50% occur to workers aged <30 years, and 65% of the accidents involve workers with less than 5 years of experience (4,17). The findings of the current study support these data. Young and less experienced workers should be given more intense training.

There were some limitations to this study, primarily the retrospective design. There were subjective complaints such as pain and residual swelling on examination and documentation. It is important to note that this study was conducted in a single center, and although this is the largest hospital in the region, it is possible that patients without complications may not have sought treatment at our facility.

Due to developing industries, there is increasing use of forklifts in industry, and in parallel with this, forklift injuries are seen more often. This study is the largest patient series presenting patients with foot and ankle injuries related to forklift accidents. It is important in which region of the foot and/or ankle the injury is located. Forklift injuries can be treated conservatively or surgically depending on the clinical condition of the patient's foot and ankle. The vast majority of injuries are in the forefoot region and this region has higher return-to-work rates and AOFAS scores. The clinical results of patients with mixed region injuries and hindfoot injuries seem to be worse. The currently available protective footwear is not sufficient to protect workers against forklift injuries. The main indicators of return to work and functional outcome are which foot region is injured and whether or not the injury causes a fracture.

Author Contribution

All authors contributed to the study design, data collection, data analysis, and reporting for this manuscript. All authors have read and approved the final submitted manuscript.

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