



## Quality of life after pelvic ring fractures: Long-term outcomes. A multicentre study

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### ABSTRACT

**Aims:** This study was conducted to determine long-term (5–10 years) health-related quality of life (HRQOL) and ceiling effects in patients with a pelvic ring fracture.

**Patients and methods:** We identified all patients with pelvic ring fractures after high-energy trauma admitted at two level 1 trauma centres in the Netherlands from 2006 to 2011. Patients were asked to complete the Majeed Pelvic Score (MPS), EuroQol-5D (EQ-5D) and Short Musculoskeletal Function Assessment (SMFA) questionnaires. HRQOL analysis used a multiple linear regression model.

**Results:** In total, 136 patients returned the questionnaires. The median follow-up period was 8.7 years. The mean MPS and EQ-5D-VAS scores were 85.1 and 74, respectively. The mean EQ-5D index scores were 0.87, 0.81 and 0.82 in Tile B, A and C patients, respectively. The mean SMFA index was 24. A ceiling effect was observed for 1/3 of the patients. After multiple linear regression analysis, no differences were identified among the various fracture types for each questionnaire, with the exception of 2 subscales of the MPS.

**Conclusion:** Patients who suffer pelvic ring fractures generally have good HRQOL outcomes after 5–10 years. No significant differences were found among different fracture types. Long-term follow-up of patients with Tile C fractures is warranted.

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### Introduction

Pelvic fractures with disruption of the pelvic ring usually occur due to high-energy trauma (HET). [1] Patients with pelvic ring fractures often sustain multiple additional injuries [2]. Mortality and morbidity are significant, and the mortality rate can reach approximately 10–16%. [3] [4],

Numerous studies have been performed regarding the early management of pelvic fractures to improve functional outcomes. [2] [5], The results of the conservative management of unstable fractures are poor, with complications such as mal- or non-union and chronic pain [6]. Surgical therapy for unstable fractures is therefore currently an accepted treatment [7].

Few studies have focused on long-term health-related quality of life (HRQOL) evaluation and functional outcomes at 5–10 years after trauma. Oliver et al. [8] examined long-term HRQOL in patients with unstable pelvic fractures and found a 14% physical impairment and a 5.5% mental impairment compared to the American population, regardless of the type of management. Suzuki et al. [9] concluded that neurological impairment of the lower extremities was the main predictor of worsened quality of life and poor functional outcomes. Factors that contribute to poor outcomes identified in other studies include age, presence of a complex fracture type, surgery and chronic pain. [10] [11], Additionally, several authors have identified sexual and urological dysfunction as risk factors for decreased quality of life [12]. However, these studies included relatively small patient groups, with a follow-up period of only 2 years. [13] [14],

As a result, patient outcomes 5–10 years after trauma are not well understood. Furthermore, it is not clear how long the HRQOL of patients continues to improve. Several authors 15 have reported an improvement in HRQOL up to the fifth year after injury; however, other authors [16] have reported a significant decrease in HRQOL over time. The degree of increase or decrease in HRQOL can

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be measured using the maximum HRQOL score. Several studies have shown a large ceiling effect (>15% of patients with the highest score [17]) in follow-up analyses of patients with pelvic ring fractures. Brouwers et al. [18] and Lefaivre et al. [19] demonstrated ceiling effects at 29 and 56 months after injury, respectively. The present study was conducted to determine long-term (5–10 years) HRQOL and ceiling effects in pelvic ring fracture patients.

## Patients and methods

The study was reviewed by the medical ethics committee of the Radboudumc and was determined to fall outside the scope of the Medical Research Involving Human Subjects Act.

We identified all patients with a pelvic ring fracture who were admitted to two level 1 trauma centres in the Netherlands from 2006 to 2011 from our trauma registry. These trauma centres are both larger hospitals in the Netherlands, which treat >350 patients with an ISS > 16 per year. Patients were included if they were 18–80 years old, and their accident involved a HET, which was defined as an accident involving a moped travelling >30 km/h, a car accident at a high velocity, being thrown out of a vehicle/motorcycle, a collision with a pedestrian at >30 km/h, a fall from a high altitude (>5 m) or severe entrapment with long extrication.

Patients with osteoporotic fractures or a low-energy trauma (LET) were excluded. We also excluded patients who died and patients who did not demonstrate good command of the Dutch language.

Data concerning patient and trauma characteristics, fracture type (according to Tile category), Injury Severity Score (ISS), [20] concomitant injuries, acute and definitive treatment, complications and mortality were acquired from the relevant hospital databases.

All patients were asked to complete the Majeed Pelvis Score (MPS), [21] EuroQol-5D (EQ-5D) [22] and Short Musculoskeletal Function Assessment (SMFA) [23] questionnaires.

The MPS is widely used in research concerning quality of life of patients with pelvic injuries and is divided into 5 “subscales”: pain (30 points), work (20 points), sitting (10 points), standing (36 points total: walking aids, 12 points; gait unaided, 12 points; walking distance, 12 points), and sexual intercourse (4 points). If sexual intercourse was not attempted, for any reason, a score of four points was given [15].

The EQ-5D is a questionnaire with five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has three levels: no problem, moderate problem, or severe problem. The EQ Visual Analogue Scale (EQ-5D-VAS) records the patient’s self-rated state of health on an analogue scale between 0 (worst imaginable health state) and 100 (best imaginable health state). In addition, a scoring algorithm is available by which each health status (HS) description

can be expressed as a summary score. This summary score, the EQ-5D index, ranges from 1 for full health to 0 for death and can be interpreted as a judgement on the relative desirability of an HS compared to perfect health. A normal score on the EQ-5D index for the Dutch population is 0.87 (SD: 0.18) [24].

The SMFA is designed to assess the HS and HRQOL of patients with a broad range of musculoskeletal injuries and disorders. The Function index contains 39 items, and the Bother index contains 14 items. Both indices use a five-point Likert scale with scores ranging from 1 (not at all/never/none) to 5 (unable to do/always/extremely). The indices range from 0 to 100. Higher scores indicate a lower HS and lower HRQOL. The adapted Dutch version of the SMFA has been validated in patients with fractures of the upper or lower extremities [23]. In this study, only questions regarding the lower extremities were used.

## Data analysis

Patient characteristics were analysed with descriptive statistics. A multiple linear regression model was used for the HRQOL analysis. The following demographic and clinical characteristics and relevant adjustment factors for the present analysis were considered: the EQ-5D dimensions were dichotomized into “no problems” and “problems”, and multiple logistic regression was performed. The results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Continuous variables including the EQ-5D-VAS, EQ-5D index score and MPS were analysed using a multiple linear regression model with correction for the following confounders that were thought to have a significant impact on outcome: age, sex, ISS, fracture type (stable versus unstable), neurologic injury, urogenital injury, open fracture, injuries to the lower extremities and surgical treatment. The results are presented as  $\beta$ -coefficients (B) with 95% CIs. All statistical analyses were performed using SPSS, version 22 (SPSS Inc, Chicago, IL, USA), with consultation from biostatisticians. A p-value of  $\leq 0.05$  was considered statistically significant.

## Results

In total, 336 patients with a pelvic ring injury were identified. Of these 336 patients, 42 had died, 46 patients did not speak Dutch, and the contact addresses of 17 patients were not found. Therefore, 231 patients were ultimately eligible for this study. These patients were contacted and asked to complete the MPS, SMFA and EQ-5D questionnaires. One hundred thirty-six patients completed the questionnaires (59%). No significant differences were observed in age, gender, Tile classification and ISS between the included patients and patients who were not contacted.

The mean age of the included patients was 39 (SD 17) years, and the mean ISS was 22.8 (SD 14). Thirty-one patients (22.7%) were

**Table 1**  
Patient Characteristics.

Patient characteristics for the various Tile groups					
	Total (N=136)	Tile A (N=23)	Tile B (N=65)	Tile C (N=48)	p-value
Age (yrs)	39	38	36	43	NS
Male (%)	81	12 (52)	42 (65)	27 (56)	NS
ISS	29.9	16	28	33	p<0.01
Shock $\geq$ grade3 (%)	31 (23)	5 (22)	7 (11)	19 (40)	p=0.02
Open fracture (%)	10 (7)	2 (8)	4 (6)	4 (8)	NS
Surgical treatment (%)	75 (55)	0	34 (52)	41 (85)	p<0.01
Concomitant injuries (%)	119 (88)	19 (83)	57 (88)	43 (90)	NS
Lower extremity (%)	44 (32)	10 (43)	18 (28)	16 (33)	NS
Neurological injury (%)	47 (35)	7 (30)	23 (35)	17 (35)	NS
Urogenital injury (%)	5 (4)	1 (4)	1 (2)	3 (6)	NS

NS = not significant.

haemodynamically unstable upon presentation in the ER (shock class 3 or higher). Eighty-one patients were male (58.8%). Of the 136 patients returning the questionnaire, 23 had a Tile A fracture (16.9%), 65 had a Tile B fracture (47.7%), and 48 had a Tile C fracture (35.3%). Patient characteristics for the various Tile groups are listed in Table 1. Patients with a complex fracture type had a significantly higher ISS and shock class and were more often treated surgically.

Open fractures were observed in 10 patients (7.3%), of which seven were grade two or higher based on the scale reported by Gustilo and Anderson [25]. Seventy-five patients were treated operatively for the pelvic fracture (55.1%). Concomitant injuries were identified in 87% of patients. The majority of patients had concomitant injuries to the chest or extremities. Concomitant injuries to the lower extremities were observed in 44 patients (32.4%).

Neurological injury was observed in 47 patients (34.5%); of whom, 28 suffered severe head trauma (20.6%). Focal neurological deficits were observed in 9 patients (6.6%). Two patients exhibited complete paralysis due to spinal cord injury (1.5%).

Urogenital injuries were observed in five patients (4%); three patients had an urethral rupture, and two had a bladder rupture.

The median follow-up period was 8.7 years (range: 5–10 years).

## Outcome scores

### Mps

All 136 patients completed the MPS. The mean MPS score was 85.1 (SD 16.6). MPS scores are listed in Table 2. Almost 25% of patients reported significant sexual problems (fewer than 3 points on the MPS). No significant differences were found among the different fracture types. Return to work was reported in 57% of patients with a Tile A fractures, 63% with a Tile B fractures and 52% with a Tile C fractures. Regarding our follow-up period, 34% of patients had a maximal score of 100 points on the MPS, including 32% of Tile A, 36% of Tile B and 33% Tile C fracture patients.

### Eq-5d

The results of the EQ-5D are shown in Table 3. This questionnaire was completed by all included patients. The EQ-5D-VAS score was 74–76 of 100 and did not differ significantly among the Tile groups. The EQ-5D index score also did not differ significantly among the fracture types. A mean index score of 0.87 was observed in Tile B patients, while for Tile A and C patients, the mean index scores were 0.81 and 0.82, respectively. The average EQ-5D index score of the general Dutch population is 0.87 24.

**Table 2**  
MPS.

Mean MPS scores of all patients, divided into different Tile type groups					
MPS dimension	Description	MPS points	Tile A, % N=23	Tile B, % N=65	Tile C, % N=48
Pain	Intense, continuous at rest	5	0	0	2
	Intense with activity	10	4	2	2
	Tolerable, but limits activity	15	13	9	19
	Moderate activity, abolished by rest	20	9	8	10
	Mild, intermittent, normal activity	25	17	15	6
	Slight, occasional or no pain	30	57	66	60
Work	No regular work	4	39	29	38
	Light work	8	4	3	0
	Change of job	12	0	5	8
	Same job, reduced performance	16	4	12	8
	Same job, same performance	20	53	51	44
Sitting	Painful	4	0	0	0
	Painful if prolonged or awkward	6	26	23	25
	Uncomfortable	8	13	3	6
	Free	10	61	74	69
Sexual intercourse	Painful	1	4	2	0
	Painful if prolonged or awkward	2	9	8	10
	Uncomfortable	3	0	3	8
	Free	4	87	87	82
Standing A (walking aids)	Bedridden or almost bedridden	2	0	0	0
	Wheelchair	4	0	0	2
	Two crutches	6	13	3	10
	Two sticks	8	0	0	0
	One stick	10	4	0	6
	No sticks	12	83	97	82
Standing B (gait unaided)	Cannot walk or can barely walk	2	4	2	4
	Shuffling small steps	4	0	0	4
	Gross limp	6	0	2	0
	Moderate limp	8	0	6	10
	Slight limp	10	17	8	25
	Normal	12	78	82	57
Standing C (walking distance)	Bedridden or few metres	2	0	0	0
	Very limited time and distance	4	9	0	21
	Limited with sticks, difficult without prolonged standing possible	6	0	6	6
	One hour with a stick, limited without	8	4	2	0
	One hour without sticks, slight pain or limp	10	13	12	8
	Normal for age and general condition	12	74	80	65

**Table 3**  
EQ-5D.

The results of the EQ-5D for the different Tile type groups are shown. This questionnaire was completed by all included patients			
	Tile A	Tile B	Tile C
<b>N (%)</b>	23 (16.9)	65 (47.8)	48 (35.3)
Mean age, yrs (SD)	38 (19)	36 (16)	43 (17)
<b>EQ-5D</b>			
Mobility, %	61	77	48
Self-care, %	91	92	90
Usual activities, %	57	72	56
Pain, %	44	55	56
Anxiety/depression, %	78	88	81
EQ-5D-VAS score (SD)	74 (18)	76 (15)	76 (15)
<b>Average EQ-5D index (SD)</b>	0.81 (0.19)	0.87 (0.19)	0.82 (0.22)

#### SMFA (lower extremities)

The results of the SMFA are listed in Table 4. The Function questionnaire was completed by 126 patients (92.6%), and the Bother questionnaire was completed by 123 patients (90.4%). The mean score of the SMFA Function index was 24 (SD 19), and the mean score of the Bother index was 24 (SD 23).

#### Multiple linear analysis

Table 5 shows adjusted linear regression coefficients, after adjusting for age, sex, ISS, fracture type (stable versus unstable), neurologic injury, urogenital injury, open fracture, injuries to the lower extremities and surgical treatment.

Regarding the MPS, a significant difference was found in the dimension of standing (walking aids), with an OR of 0.26 (95% CI: 0.11–0.66),  $p=0.02$ . Patients with a Tile B fracture scored significantly higher than patients with a Tile C injury. The mean MPS scores did not differ significantly among the fracture types.

For the EQ-5D, a significant difference was found in the domain of mobility. Similar to the MPS, patients with type B fractures scored significantly higher than patients with type C fractures ( $\beta$ -coefficient: 0.73 (95% CI: 0.04–1.42)  $p=0.048$ ).

No differences were found among the fracture types for the EQ-5D-VAS and index scores.

For both the SMFA Bother and Function indices, no differences were found among the fracture types.

## Discussion

In this study, we evaluated the long-term HRQOL of pelvic ring fracture patients with a minimum follow-up period of 5 years. To our knowledge, our study is the first to describe a follow-up period of more than 5 years in a large patient group with pelvic ring fractures.

Recently, Brouwers et al. [18] reported the short and mid-term HRQOL of patients with pelvic ring fractures. They found that pain was increased in patients with a Tile C injury and observed significantly lower EQ-5D and MPS scores in patients with a Tile C injury than in patients with Tile A and B fractures.

In our study, no significant differences in pain and no large significant differences in functional outcomes and HRQOL were observed among the different Tile types. Significant differences were found in only 2 dimensions: mobility on the EQ-5D and standing on the MPS. In both dimensions, patients with Tile B fractures scored significantly better than those with Tile C fractures, while no significant difference between patients with Tile A and C fractures was found. The reason for this finding could be the relatively high percentage of Tile B2 fractures. Tile B2 fractures are lateral compression injuries with intact ligaments. Patients are normally allowed to mobilize within their pain limits and often do not require operative treatment. Patients with a Tile A fracture often suffer an isolated iliac wing fracture. The characteristics, ISS and concomitant injuries of patients with iliac wing fractures resemble those of patients with type C fractures [26]. This finding could explain why the scores for Tile B fracture patients are higher for certain dimensions than for those with other fractures.

Most studies report lower HRQOL values in patients with a pelvic ring fracture than in the normal population. [9, 10, 27, 28], Ayvaz et al. [29] reported SF-36 scores of patients treated with closed reduction and internal fixation that were comparable with the normal population. The results of the EQ-5D index score in our group were also comparable with those of the validated Dutch population. However, an analysis comparing the composition of our study population and that of Stolk et al. [24] was not performed. Therefore, we do not know whether both groups have comparable patient characteristics.

The mean MPS in our study was high compared to the studies of Suzuki [9] and van den Bosch [30] (85.1 versus 79.7 and 78.6, respectively). The EQ-5D index score in our group was 0.84, which was also higher than the results of Harvey-Kelly [12] (0.59) and Holstein [10] (0.78). The EQ-5D-VAS was 75.6 in our study, compared to 64.1 reported by Harvey Kelly [12] and 70.5 reported by Kerschbaum [28].

The ISS score in our group is higher than that found in previous studies. [9,12], Only in the study by van den Bosch [30] was the mean ISS higher (30.4). The follow-up periods in the above studies were all shorter than that in our study. Therefore, a possible explanation for these differences could be a change in the ability of patients to manage their present situation. Another hypothesis could be that more patients had fully recovered during the longer follow-up period of our study. We observed a maximal MPS score in 34% of patients, with a median follow-up of 8.7 years. Brouwers et al. [18] reported a maximal MPS score in 31% of Tile A, 28% of Tile B and 0% of Tile C fracture patients, with a median follow-up period of 2.5 years. Lefavre et al. [19] reported a maximum MPS score in 18.4% of patients, with a median follow-up period of 4.5 years. However, that study only included Tile B and C fractures.

Furthermore, no large differences were observed in our study among the Tile groups. Approximately one-third of the pelvic patients with Tile A (32%), Tile B (36%) and Tile C (33%) fractures were reportedly at the highest end of the MPS scale. Comparing these results with those of Brouwers et al. [18], it could be concluded that between 2.5 and 8.7 years of follow-up, no substantial increase in HRQOL was observed in patients with Tile A or B Fractures. However, the HRQOL of patients with Tile C fractures increased from 0 to 33%. This finding could illustrate that

**Table 4**  
SMFA.

The results of the SMFA are listed for the different Tile type fractures. The Function questionnaire was completed by 126 patients (92.6%), and the Bother questionnaire was completed by 123 patients (90.4%).				
	Tile A	Tile B	Tile C	p-value
SMFA_Bother, mean (SD)	21 (17)	24 (18)	25 (21)	0.695
SMFA_Function, mean (SD)	20 (22)	22 (21)	27 (25)	0.384

**Table 5**  
Multiple logistic regression model.

EQ-5D	Odds ratio	95% CI	Significance
Mobility			p = 0.02
Tile B-Tile A	0.50	0.17–1.46	
Tile C-Tile A	1.90	0.61–5.92	
Tile B-Tile C	0.26	0.11–0.66	
Self-care			p = 0.88
Tile B-Tile A	0.63	0.10–4.12	
Tile C-Tile A	0.79	0.12–5.42	
Tile B-Tile C	0.79	0.17–3.58	
Usual activities			p = 0.14
Tile B-Tile A	0.46	0.16–1.28	
Tile C-Tile A	0.98	0.33–2.90	
Tile B-Tile C	0.47	0.99–1.04	
Pain			p = 0.43
Tile B-Tile A	0.54	0.20–1.49	
Tile C-Tile A	0.52	0.17–1.53	
Tile B-Tile C	1.05	0.47–2.43	
Anxiety/Depression			p = 0.33
Tile B-Tile A	0.39	0.11–1.43	
Tile C-Tile A	0.69	0.18–2.58	
Tile B-Tile C	0.56	0.18–1.77	
	$\beta$ -coefficient	95% CI	
EQ-5D-VAS			p = 0.73
Tile B-Tile A	3.00	(–5.33–11.34)	
Tile C-Tile A	3.39	(–5.47k12.26)	
Tile C-Tile B	–0.39	(–6.93–6.15)	
EQ-5D index			p = 0.24
Tile B-Tile A	0.07	(–0.03–0.17)	
Tile C-Tile A	0.02	(–0.09–0.13)	
Tile B-Tile C	0.05	(–0.03–0.14)	
Majeed	$\beta$ -coefficient	95% CI	
Pain			p = 0.22
Tile B-Tile A	2.15	(–0.95–5.24)	
Tile C-Tile A	0.24	(–3.07–3.54)	
Tile B-Tile C	1.91	(–0.62–4.44)	
Work			p = 0.73
Tile B-Tile A	1.17	(–2.40–4.73)	
Tile C-Tile A	0.17	(–3.66–4.01)	
Tile C-Tile B	0.99	(–1.98–3.98)	
Sitting			p = 0.63
Tile B-Tile A	0.39	(–0.45–1.24)	
Tile C-Tile A	0.21	(–0.71–1.11)	
Tile C-Tile B	0.19	(–0.51–0.89)	
Sexual Intercourse			p = 0.83
Tile B-Tile A	0.09	(–0.25–0.43)	
Tile C-Tile A	0.03	(–0.34–0.39)	
Tile C-Tile B	0.07	(–0.22–0.35)	
Standing A (walking aids)			p = 0.048
Tile B-Tile A	0.84	(–0.03–1.72)	
Tile C-Tile A	0.11	(–0.82–1.05)	
Tile C-Tile B	0.73	(0.04–1.42)	
Standing B (gait unaided)			p = 0.11
Tile B-Tile A	0.34	(–0.79–1.46)	
Tile C-Tile A	–0.62	(–1.83–0.58)	
Tile C-Tile B	0.96	(0.07–1.85)	
Standing C (walking distance)			p = 0.06
Tile B-Tile A	0.42	(–0.94–1.78)	
Tile C-Tile A	–0.87	(–2.33–0.59)	
Tile C-Tile B	1.29	(0.22–2.37)	
Total MPS			p = 0.15
Tile B-Tile A	2.41	(–6.13–10.94)	
Tile C-Tile A	–4.23	(–13.40–4.95)	

**Table 5** (Continued)

Majeed	$\beta$ -coefficient	95% CI	
Tile C-Tile B	6.63	(−0.08–13.34)	
SMFA Function			p = 0.47
Tile B-Tile A	1.56	(−9.90–13.02)	
Tile C-Tile A	6.62	(−5.81–19.05)	
Tile C-Tile B	−5.06	(−14.40–4.28)	
SMFA Bother			p = 0.73
Tile B-Tile A	1.51	(−8.72–11.72)	
Tile C-Tile A	4.04	(−6.94–15.02)	
Tile C-Tile B	−2.54	(−10.70–5.63)	

the recovery of patients with Tile C fractures may be longer than previously assumed [2] and that long-term follow-up is warranted in these patients.

Previous studies have shown that age, injury severity, fracture type, neurological injury, urological injuries, sexual dysfunction and method of treatment could influence the functional and HRQOL outcomes. [9, 10, 12, 14, 31]. These factors, including open fractures, were identified as confounders in our linear regression model.

Chronic pain due to persistent neurological injury is a well-recognized factor that influences outcomes and is very difficult to treat. The prevalence of focal neurologic deficits was low in our group (6.6%). Additionally, the prevalence of urogenital disorders was low (4%). However, almost 25% of all patients reported sexual problems on the MPS. One possible explanation could be that sexual complaints are underreported by patients during follow-up because of the sensitive nature of these complaints. This hypothesis is supported by the findings of Harvey-Kelly et al. [12], who reported a high rate (28%) of patients who declined to complete the sexual questionnaires. Another explanation could be that, although there are no obvious injury to the urogenital systems, the lumbosacral plexus is damaged and causes severe problems. Pro-active evaluation by the treating physician should be mandatory in the follow-up of patients with a pelvic ring injury.

There are certain limitations to this study. The first is the cross-sectional nature of this study, which did not allow us to obtain baseline values of these patients for a comparison of our results. Hernefalk [32] reported that the pre-traumatic QOL in patients with surgically treated pelvic fractures is generally high and that pre-existing discomfort from the pelvic region is uncommon. Currently, we are performing a longitudinal designed study, which includes pre-injury assessment, short term outcomes [33].

Second, the possibility of selection bias exists. Of the 336 total patients with pelvic fractures identified in the study period, only 136 patients (40%) were ultimately included. This may have influenced the overall outcomes. However, of the 231 eligible patients who were contacted, no differences were found between the responders and non-responders in terms of age, gender, Tile classification and ISS.

## Conclusion

Patients who have suffered a pelvic ring fracture generally have good HRQOL outcomes after 5–10 years. With the exception of 2 subscales of the evaluated questionnaires, no significant differences were found among the different fracture types in these patients. Long-term follow-up of patients with Tile C fractures is warranted.

## Conflict of interest

Conflict of interest statement all authors must disclose any financial and personal relationships with other people, or

organisations, that could inappropriately influence (bias) their work, all within 3 years of the beginning the work submitted. If there are no conflicts of interest, authors should state that there are none. Please confirm that you have included your Conflict of Interest Statement as a separate file.

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