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Association of Serum Inflammatory Factors and Hip Joint Scores with Adverse Prognosis After Internal Fixation in Patients with Femoral Neck Fractures

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HW and LZ contributed equally to this work. They, as co-first authors, conducted the experiments in this study. ZM, MW and QX contributed to the design and interpretation of the current study and wrote the article. All authors read, revised, and approved the final manuscript.

Key words
Femoral neck fracture, Internal fixation, Serum inflammatory factors, Harris hip joint functional score, Adverse prognosis, Interlinks, Tumor necrosis factor, C reactive protein

ABSTRACT

The objective of this study was to explore the relationship between adverse postoperative outcomes, changes in serum inflammatory factor levels, and hip joint functional scores in patients undergoing internal fixation for femoral neck fractures (FNF). A total of 134 patients who underwent internal fixation surgery for FNFs were recruited. Based on their postoperative prognosis, patients were categorized into a control group (CG) (favorable FNF healing, n=100) and an observation group (OG) (non-union FNFs, n=34). Levels of interleukin (IL)-1, IL-6, IL-8, C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-α) were compared at preoperative (D0), postoperative day 1 (D1), postoperative day 7 (D7), postoperative month 1 (M1), postoperative month 3 (M3), and postoperative month 6 (M6). The Harris hip joint functional score was assessed preoperatively and 6 months postoperatively. At M1, M3, and M6, IL-1, IL-6, IL-8, CRP, and TNF-α levels were considerably elevated in the OG versus the CG (P<0.05). At 6 months postoperatively, the Harris total score increased in both groups, but the CG (86.94±5.06) had a greatly superior score to the OG (65.7±6.18) (P<0.05). Elevated levels of IL-1, IL-6, IL-8, CRP, and TNF-α along with decreased Harris hip joint functional scores following internal fixation surgery suggest the presence of adverse prognostic outcomes in FNFs.

INTRODUCTION

Femoral neck fracture (FNF) refers to a break occurring between the femoral head and the base of the femoral neck, and it can transpire across various age groups, although it is most prevalent among the elderly (Zhang *et al*., 2023; Sun *et al*., 2023). Clinical characteristic symptoms of FNFs encompass pain, restricted mobility, deformity of the lower limb, and limb shortening (Mishra *et al*., 2023). While the incidence of FNFs is relatively low, it has the potential to induce lifelong disabilities, thereby considerably impeding patients' daily lives (Bell *et al*., 2014).

With the increasing aging population and accelerated pace of life, the incidence of FNFs has been on the rise (Ahmed and Al-Dadah, 2023). Currently, the primary clinical approach to treating FNFs involves surgical interventions, including internal fixation (Chaudhuri *et al*., 2022) and total hip arthroplasty (Wu *et al*., 2021), wherein the choice of treatment method is determined by fracture type and the femoral blood supply condition (Jung and Park, 2012). Internal fixation has emerged as one of the most commonly utilized methods for clinical management of femoral fractures in recent years. It predominantly employs instruments such as hollow screws (Ge *et al*., 2023), femoral neck dynamic anti-rotation cross-pinning systems (FNS) (Park *et al*., 2023), and intramedullary nails (Georgiadis *et al*., 2022) to secure the fracture site, thereby facilitating fracture healing. Presently, internal fixation has garnered widespread recognition for enhancing treatment outcomes and patient comfort in FNF management (Kim *et al*., 2023). Nevertheless, instances of adverse prognosis persist among patients, primarily manifesting as femoral head avascular necrosis, functional impairment, and poor fracture healing (Yu *et al*., 2023).

FNF itself can be considered a stress response, and

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the pathological processes surrounding the perioperative period often trigger the involvement of various inflammatory factors. Relevant studies have indicated that surgery, trauma, and poor fracture healing can all lead to abnormal levels of serum inflammatory factors in patients (Golsorkhtabaramiri *et al*., 2023). Additionally, research has proposed that postoperative infection following internal fixation for fractures poses a great challenge in the treatment of fracture-related conditions (Ying *et al*., 2023), and there exists a close association between infection and the participation of serum inflammatory factors. Experts have previously suggested, through research, that serum inflammatory factors can be directly employed to assess the condition of patients with FNFs, thereby providing a basis for clinical treatment decisions (Chen *et al*., 2020). Nevertheless, there is a lack of specific research addressing the correlation between serum inflammatory factors and the postoperative prognosis of patients with FNFs undergoing internal fixation. Additionally, poor fracture prognosis may lead to localized avascular necrosis of the femoral head, subsequently resulting in hip joint functional impairments such as hip joint pain and restricted mobility (Barenius *et al*., 2018). Currently, the Harris hip score is a commonly used clinical standard for evaluating hip joint function (LeBrun *et al*., 2021). Nevertheless, there is currently no existing research examining the relationship between hip joint functional scores and adverse postoperative outcomes in patients with FNFs undergoing internal fixation.

To further elucidate the relationship between postoperative serum inflammatory factors, hip joint functional scores, and adverse outcomes such as femoral head avascular necrosis, functional impairment, and poor fracture healing in patients with FNFs after internal fixation surgery, patients who underwent internal fixation for FNFs were recruited as the research subjects of this study. A six-month follow-up was conducted to observe the patients' prognoses. Concurrently, changes in serum inflammatory factors and hip joint scores during the recovery period were documented for all patients. The relationship between serum inflammatory factors, hip joint scores, and patient prognosis was analyzed. This investigation aimed to provide research indicators for predicting the prognosis of patients undergoing internal fixation surgery for FNFs in clinical settings, with the goal of enhancing postoperative prognostic outcomes for these patients.

MATERIALS AND METHODS

Subjects

In this study, patients with FNFs who underwent internal fixation surgery at The People's Hospital of Qijiang District from April 2019 to April 2022 were recruited as the subjects. A total of 134 eligible patients were enrolled for subsequent research analysis. Patients were grouped according to their prognostic outcomes during the follow-up period, resulting in the formation of a control group (CG) and an observation group (OG). The CG comprised 100 patients who exhibited favorable prognoses, as confirmed by X-ray and CT examinations indicating successful healing of the FNF. Meanwhile, the OG consisted of 34 patients with adverse prognoses, identified by X-ray and CT assessments revealing non-union of the fracture.

Patients in both groups were eligible to join the study if they met the following inclusion criteria: (1) aged >18 years old; (2) patients with FNFs occurring within three weeks; (3) Patients with unilateral FNFs as confirmed by X-ray or CT scans; (4) Patients without concurrent fractures in other parts of the femur; (5) Patients with a follow-up period of ≥ 6 months and complete follow-up data. Exclusion criteria were as follows: (1) Patients on long-term corticosteroid therapy; (2) Patients with pre-existing hip or knee joint pain and restricted movement; (3) Patients with conditions like ankylosing spondylitis and rheumatoid arthritis; (4) Patients who experienced additional injuries postoperatively; (5) Patients with FNFs classified as pathological fractures; (6) Patients with psychological disorders.

The clinical data collected from patients included gender, age, body mass index (BMI), time of fracture occurrence, fracture cause, fracture Garden classification, degree of osteoporosis, underlying conditions upon admission, surgical duration, and method of internal fixation. A comparative analysis was conducted to ascertain whether drastic differences existed. Subsequent investigations were pursued in cases where no considerable differences were observed (P>0.05).

Determination of serum inflammatory factors

Blood samples of 5 ml were collected from patients in a fasting state at preoperative (D0), postoperative day 1 (D1), and day 7 (D7), postoperative month 1 (M1), postoperative month 3 (M3), and postoperative month 6 (M6). Enzyme-linked immunosorbent assay (ELISA) was utilized for the detection of serum inflammatory markers, including interleukin (IL)-1, IL-6, IL-8, C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-α). Serum levels of IL-1, IL-6, and IL-8 were measured using IL-1 ELISA kit, IL-6 ELISA kit, and IL-8 ELISA kit, respectively, all provided by Shanghai COIBO Bio-Engineering Co., Ltd. Serum CRP levels were determined using a CRP ELISA kit provided by Shanghai Enzyme-linked Bio Technology Co., Ltd. Serum TNF-α levels were assessed using a TNF-α ELISA kit provided by Shanghai Yenzhun Bio-Technology Co., Ltd.

Hip joint function score

In this study, the Harris hip score (HHS) methodology was employed to assess the functional status of the hip joint preoperatively and at 6 months postoperatively. The HHS encompasses four main aspects, namely, hip joint pain, range of motion, deformity, and functionality. The assessment of hip joint functionality encompasses various activities of daily living (stairs, transportation, sitting, footwear), gait, walking aids, and walking distance, each with distinct scoring values. The grading criteria for the hip joint functional score are as follows: scores between 90 and 100 are rated as excellent, scores between 80 and 89 as good, scores between 70 and 79 as fair, and scores below 70 as poor.

Statistical analysis

Statistical analysis of the research findings was conducted using SPSS 22.0. The measured data in the study were presented as mean ± standard deviation ($\bar{x}$±s). When comparing between the two groups, both groups exhibited normal distribution and homogeneity of variance. In cases where homogeneity of variance was met, a paired t-test (parametric test) was employed for group comparisons. When homogeneity of variance was not met, a Welch's t-test (t' test) was utilized. A significance level of $P<0.05$ indicated statistically significant differences.

RESULTS

Table I presents the statistical analysis of general clinical characteristics for patients in both the CG and the OG, including gender (male, female), age, BMI, time of fracture occurrence, fracture cause (including falls, vehicular accidents, impact injuries), fracture garden classification (including types I, II, III, IV), degree of osteoporosis (including mild, moderate, severe, none), underlying conditions upon admission (including hypertension, diabetes, none), surgical duration, and method of internal fixation (including closed reduction internal fixation, open reduction internal fixation). Upon comparison, no notable differences were observed between the two groups in terms of gender distribution, fracture cause, Garden classification, osteoporosis severity, underlying conditions upon admission, distribution of fixation methods, as well as average age, BMI, time of fracture occurrence, and surgical duration ($P > 0.05$). These results suggest the feasibility of subsequent research endeavors.

Table I. Statistics and comparison of general clinical data between CG and OG patients.

Index		CG (n=100)	OG (n=34)	P
Sex (n/%)	Male	68/68	23/67.65	0.212
	Female	32/32	11/32.35	0.182
Age (years old)		56.88±7.21	54.41±8.13	0.283
BMI (kg/m^2)		23.84±2.09	23.44±2.00	0.661
Fracture time (days)		4.71±1.62	4.55±1.39	1.212
Reason for fracture (n/%)	Fall injury	17/17	5/14.71	1.091
	Vehicular accident	56/56	20/58.82	0.222
	Impact injury	9/9.00	3/8.82	0.731
	Others	18/18	6/17.65	0.621
Garden classification (n/%)	I	0	0	-
	II	8/8.00	3/8.82	0.983
	III	58/58	20/58.82	1.093
	IV	34/34	11/32.35	1.009
Degree of osteoporosis (n/%)	Mild	12/12	5/14.71	1.001
	Moderate	29/29	10/29.41	0.982
	Severe	35/35	11/32.35	0.123
	None	24/24	8/23.53	1.772
Underlying disease (n/%)	Hypertension	44/44	16/47.06	0.761
	Diabetes	37/37	12/35.29	0.212
	None	25/25	9/26.47	1.652
Operation time (min)		96.84±12.41	93.65±11.65	1.209
Internal fixation method (n/%)	Closed reduction	57/57	18/52.94	1.092
	Open reduction	43/43	16/47.06	0.698

Table II. Serum inflammatory factor test results ($\bar{x}\pm s$).

		IL-1 (mg/L)	IL-6 (pg/mL)	IL-8 (pg/mL)	CRP (mg/L)	TNF-α (pg/mL)
CG	D0	12.4±0.81	7.3±0.24	32.6±0.93	27.6±0.87	1.18±0.37
	D1	13.6±0.96	144.3±0.62	70.1±0.37	122.6±0.71	2.75±0.24
	D7	15.2±0.87	13.2±0.22	36.4±0.27	68.6±0.64	2.26±0.66
	M1	8.7±0.74	10.2±0.44	34.4±0.73	39.7±0.45	1.72±0.56
	M3	7.5±0.55	5.4±0.12	27.1±0.55	27.3±0.45	1.35±0.47
	M6	7.2±0.33	7.3±0.22	26.8±0.88	25.2±0.77	1.15±0.76
OG	D0	11.8±0.93	7.2±0.32	32.2±0.44	26.1±0.49	1.1±0.42
	D1	13.9±0.87	144.4±0.53	72.2±0.34	122.5±0.75	2.61±0.29
	D7	14.7±0.95	15.1±0.11	37.2±0.45	72.4±0.84	2.39±0.71
	M1	13.7±0.64	50.2±0.23	58.2±0.71	92.1±0.67	3.01±0.91
	M3	16.9±0.48	78.2±0.14	145.4±0.33	101.2±0.88	3.65±0.82
	M6	23.8±0.65	129.1±2.83	168.1±0.77	112.3±0.61	5.11±0.85

D0, preoperative; D1, postoperative day 1; D7, postoperative day 7; M1, postoperative month 1; M3, postoperative month 3; M6, postoperative month 6.

Table III. Hip joint function scores of patients in the control and OGs before and 6 months after surgery (points).

	CG (n=100)		OG (n=34)	
	Preoperatively	6 months postoperatively	Preoperatively	6 months postoperatively
Pain	21.50±1.00	38.6±3.00	20.0±1.00	26.09±2.00
Activity level	2.53±0.51	4.53±1.01	2.64±0.55	3.08±1.08
Deformation	1.22±0.21	3.40±1.10	1.18±0.19	2.05±1.00
Function	25.88±2.33	40.38±3.56	24.10±2.09	34.48±4.05
Total score	51.13±3.49	86.94±5.06#	47.92±4.87	65.7±6.18#*

#, $P<0.05$ vs. preoperative; *, $P<0.05$ vs. CG.

Table II shows the statistical assessment of IL-1, IL-6, IL-8, CRP and TNF-α levels in both the CG and the OG of DO, D1, D7, M1, M3 and M6 patients. Upon comparison, IL-1 levels demonstrated inconsiderable differences between the two groups at the preoperative stage, as well as at postoperative day 1 and day 7 ($P>0.05$). Nevertheless, with the progression of follow-up duration, it was observed that patients in the OG exhibited progressively higher IL-1 levels M1, M3 and M6 versus the CG ($P<0.05$). Following comparative assessment, slight differences in IL-6 levels were discerned between the two groups at the preoperative stage, as well as at postoperative day 1 and day 7 ($P > 0.05$). Nevertheless, over the postoperative months 1, 3, and 6, patients in the OG exhibited a gradual escalation in IL-6 levels, which were notably superior to those observed in the CG ($P < 0.05$). Upon comparative analysis, no notable differences in IL-8 levels were evident between the two groups at the preoperative stage, as well as at postoperative day 1 and day 7 ($P > 0.05$). Nevertheless, over the postoperative months 1, 3, and 6, patients in the OG exhibited a gradual elevation in IL-8 levels, which were markedly superior to those observed in the CG ($P<0.05$). Upon comparison, no marked differences were observed in CRP levels between the two groups at the preoperative stage, as well as at postoperative day 1 and day 7 ($P>0.05$). Nevertheless, during the postoperative months 1, 3, and 6, patients in the OG demonstrated a rising trend in CRP levels, which were markedly superior to those in the CG ($P<0.05$). Upon comparison, inconsiderable differences were found in TNF-α levels were observed between the two groups at the preoperative stage, as well as at postoperative day 1 and day 7 ($P>0.05$). Nevertheless, over the postoperative months 1, 3, and 6, the TNF-α levels for patients in the OG exhibited an ascending trend and were notably superior to those in the CG ($P<0.05$).

Table III presents the statistical analysis of hip joint functional scores for patients in the CG and the OG before surgery and at 6 months postoperatively. Neglectable differences were indicated in hip joint pain, range of

motion, deformity, and functionality between the patients in the CG and the OG before surgery. The preoperative Harris total scores were (51.13±3.49) points in the CG and (47.92±4.87) points in the OG, and the differences were neglectable (P>0.05). At 6 months postoperatively, both the control and the OG exhibited increased Harris total scores versus their preoperative scores. Nevertheless, the Harris total score in the CG ((86.94±5.06) points) was markedly superior to that in the OG ((65.7±6.18) points) (P<0.05).

DISCUSSION

Surgical internal fixation techniques have found wide application in the clinical management of patients with FNFs. Although the therapeutic efficacy of this approach has garnered recognition from both clinicians and patients, a subset of patients continues to experience unfavorable prognoses (Cha *et al*., 2023; Yamada *et al*., 2022), notably including non-union of fractures. Previous investigations have proposed that the process of fracture healing involves the participation of various inflammatory factors, resulting in discernible fluctuations in the levels of inflammatory mediators during the period of fracture consolidation (Zhang *et al*., 2019). Based on clinical data, it has been observed that the healing process of FNFs tends to be protracted, with an average duration of 5-6 months, and a non-union rate of approximately 15% (Fjeld *et al*., 2022).

A six-month follow-up was performed on patients with FNFs who underwent internal fixation, thereby analyzing the variations in serum inflammatory factors among individuals with different prognoses. The results indicated that there were neglectable differences in the levels of serum inflammatory factors, including IL-1, IL-6, IL-8, CRP, and TNF-α, between the two groups at preoperative, postoperative day 1, and postoperative day 7. Nevertheless, with the progression of the follow-up period, it was observed that at postoperative months 1, 3, and 6, the levels of IL-1, IL-6, IL-8, CRP, and TNF-α in the OG were consistently elevated and markedly superior to those in the CG (P < 0.05). This suggests a relationship between unfavorable postoperative prognosis in FNF patients and the elevated levels of IL-1, IL-6, IL-8, CRP, and TNF-α. Fracture healing derives support from growth factors and nutrients obtained through the blood supply of the periosteum and soft tissues (Meesters *et al*., 2018). Nevertheless, fractures often elicit a series of inflammatory reactions due to the stimulus they impose on patients. TNF-α, as an early participant in the inflammatory response, can vasodilate and increase vascular permeability, thereby affecting tissue metabolism (Wu *et al*., 2022). Both IL-1 and IL-6 belong to pro-inflammatory cytokines. IL-1 can inflict damage on human tissues and incite local edema (Lee and Bae, 2015). During the process of fracture healing, IL-6 can be secreted by endothelial cells, monocytes, macrophages, T cells, fibroblasts, and others. It inhibits osteoblast synthesis, thereby influencing the healing of fractures (Kuroyanagi *et al*., 2023). IL-8 exerts stimulating effects on various critical cells in the human body, such as T cells and neutrophils. It promotes the secretion of proteases, which cause damage to endothelial cells, disrupt normal blood flow, and lead to tissue injury (Wu *et al*., 2019). Elevated levels of CRP often indicate the occurrence of infection in clinical settings, and postoperative infection following FNFs has long been a clinical challenge (Chen *et al*., 2021). Infections not only exacerbate the degree of bone necrosis but also facilitate the spread of inflammatory tissue and inhibit fracture healing (Jacob *et al*., 2023). Consequently, the elevation of serum inflammatory factors after internal fixation of FNFs can trigger unfavorable fracture prognosis, indicative of nonunion.

In this study, the Harris hip scoring system was employed to evaluate hip joint function in both patient groups before surgery and at six months postoperatively. The results indicated that, at the six-month postoperative mark, both the CG and the OG demonstrated increased Harris total scores relative to their respective preoperative scores. Notably, the CG exhibited a considerably higher Harris total score ((86.94±5.06) points) than the OG (65.7±6.18) points) (P<0.05). These findings suggest that patients with poor postoperative prognosis following internal fixation of FNFs tend to exhibit inferior hip joint function. Clinical observations substantiate that patients who experience nonunion of FNFs often manifest a spectrum of hip joint functional impairments, including localized muscle atrophy, hip joint pain, and restricted hip joint mobility. In severe cases, femoral head necrosis may ensue, further exacerbating damage to the hip joint (Pei *et al*., 2020; Li *et al*., 2020). As a consequence, lower hip joint scores are indicative of a higher likelihood of adverse prognosis associated with FNFs.

Nevertheless, it is important to note that this research focused solely on nonunion cases of FNFs, and adverse prognoses associated with FNFs encompass more than this particular phenomenon. Subsequent investigations will therefore address the specific adverse prognosis of femoral head necrosis, thus enhancing the comprehensiveness of the research content. Furthermore, it should be acknowledged that the sample size of patients with adverse prognosis in this study was limited to 34 cases, which is considered insufficient. Future studies should aim to expand the number of cases with adverse prognosis to enhance the accuracy and credibility of the research data.

CONCLUSION

The postoperative serum inflammatory cytokine levels and Harris hip function scores were investigated in patients with femoral neck fractures who underwent internal fixation. The results revealed elevated levels of inflammatory factors such as IL-1, IL-6, IL-8, CRP, and TNF-α, accompanied by a decrease in Harris hip function scores. These findings collectively suggest an unfavorable prognosis in femoral neck fractures.

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IRB approval

This study was approved by the People's Hospital of Qijiang District, Chongqing, 401420, China.

Ethical approval

The study was carried out in compliance with guidelines issued by ethical review board committee of The People's Hospital of Qijiang District, China. The official letter would be available on fair request to corresponding author.

Statement of conflict of interest

The authors have declared no conflict of interest.

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