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Original article

INCREASE IN SERUM CYTOKINE CONCENTRATION FOLLOWING GERIATRIC HIP FRACTURE – CLINICAL RELEVANCE

Spasov Marko[1,2], Krstevski Stefan[1], Arsovski Oliver[1,2], Eftimov Ivan[3], Hajradinovikj Dino[1], Gavrilovski Andreja[1,2]

[1]University Clinic for Traumatology, Orthopaedic Diseases, Anaesthesia, Reanimation, Intensive Care and Emergency Centre - Skopje, Republic of North Macedonia
[2]Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia
[3]Public General Hospital - Department for Orthopedics and Traumatology, Strumica, Republic of North Macedonia
e-mail: marko.spasov@medf.ukim.edu.mk

Abstract

Introduction: Hip fractures are the most common operatively treated skeletal injuries, predominantly affecting individuals over 65 years of age who often have multiple comorbidities. A global increase in hip fracture incidence has been observed, accompanied by unfavorable outcomes, including reduced life expectancy. This study aimed to analyze the inflammatory response after hip fracture and surgery in patients aged over 65 years, and its association with functional outcomes.

Methods: This prospective, non-randomized study included patients with AO type 31A and 31B hip fractures admitted for surgical treatment. Eligible participants had demographic and clinical parameters recorded, including ASA scores, pharmacological therapy, and Katz Index scores. Blood samples were collected at four time points: within 10 hours post-injury, 48-60 hours post-surgery, on postoperative day seven, and day 30. Laboratory analyses included IL-1β, IL-6, and IL-10 levels. Follow-up data, including survival, mobility, pain, and quality of life (SF-12), were collected at 12 months.

Results: The study included 40 patients (median age: 78 years; 60% female). By the 12-month follow-up, 32 participants survived, while 8 died within 4-9 months. Deceased patients had significantly higher serum levels of IL-1β, IL-6, and IL-10 at all time-points. IL-6 was identified as an independent predictor of reduced mobility (p=0.013) and quality of life (p=0.009).

Conclusion: Elevated serum inflammatory markers were associated with poorer quality of life, mobility, and survival. These findings suggest potential for targeted rehabilitation programs and preventive strategies to improve outcomes in geriatric hip fracture patients.

Keywords: hip, geriatrics, surgery, cytokine, survival

Introduction

Hip fractures represent the most common injury in operative traumatology. The incidence of this injury increases sharply in the population over 65 years of age. Modern healthcare systems face several thousand patients with this injury each year; according to published data, it ranges from 20 per 100,000 inhabitants in Africa to 574 per 100,000 inhabitants in advanced social systems such as Denmark. Globally, about 1.6 million hip

fractures were registered in 2000[1]. It is estimated that in 2040 the incidence of hip fractures will double compared to the second decade of the twentieth century[2,3]. In other words, the number of hip fractures by 2050 would be 4.5 million globally[4]. The expected increase in the incidence of hip fractures will have a reflection on modern healthcare systems, especially considering that the population older than 65 years usually suffers from multiple comorbidities such as dementia and delirium, which further increase the dependency of these individuals and increase the rate of morbidity[5-10].

To date, several studies have indicated poor functional outcome after hip fracture in individuals older than 65 years. This is primarily due to reduced mobility, dependence on other people to fulfill daily needs and, in general, a reduction in the quality of life[11-15]. Along with a decrease in functional level, the daily routine and quality of life of these individuals also change. According to one study, 9% of individuals with a hip fracture who did not suffer from dementia and as many as 69% of those who suffered from dementia were unable to live independently following this injury[16]. According to data from Denmark for 2012, only 49% of those with a hip injury continued to live in their usual living environment, 37% went to a nursing home, 10% to a sanatorium, and even 4% died during hospital stay[2]. So far, no data has been published on the long-term status regarding living conditions.

Hip fracture in adults is also associated with shortened life expectancy. According to data from a recently published meta-analysis, the risk ratio of death is 5.75 for women and 7.95 for men during the first 3 months after a hip fracture[17]. Studies investigating the long-term effect of mortality after this injury are still rare.

During the last decades, various instruments have been developed to predict the outcome after geriatric hip fracture. For this purpose, the Nottingham scale for hip fractures[18,19], the POSUM score[20,21], and the Almelo score for hip fractures[22] are commonly used, but none of these systems showed good discrimination[23]. Numerous studies show that hip fractures, especially intertrochanteric fractures, continue to be a significant source of mortality and morbidity. It is considered that the high rate of mortality and morbidity is due to a combination of factors, first of all, trauma, surgical intervention as an additional trauma, already present comorbidities and reduced physiological reserve[241].

With this type of injuries, the mortality rates were determined at different time points: during hospitalization - 3%[25], two months postoperatively - 6%[26], six months postoperatively - 16%[27], and one year postoperatively - 29%[28]. Various conditions have been identified, which are considered to be a risk factor for mortality after hip fracture; among them are usually included: gender, place of residence, previous myocardial infarction, chronic obstructive pulmonary disease and timing of the surgical intervention[29-32].

Identifying patients at risk of developing complications and death after a geriatric hip fracture is a key step in treatment

In patients who have experienced multiple trauma, the development of multiple organ failure and acute respiratory distress syndrome is due to an imbalance in the systemic inflammatory response[33-35]. Therefore, for a long term, certain cytokines, whose serum concentrations can be easily measured, have been proposed as potential markers for identifying patients at high risk of developing complications[36-39].

Several recent studies have highlighted the role of so-called chronic inflammation in the aging process and age-related diseases. However, we still do not have much knowledge about the cytokine response in adult patients with hip fracture and its role in the occurrence of complications and death after this injury.

The aim of this prospective study was to analyze the inflammatory response to injury and surgery in patients older than 65 years with operatively treated hip fracture and its association with functional outcome and mortality one year after injury and surgery.

Material and methods

This prospective non-randomized study was conducted at the University Clinic for Traumatology Skopje, and the laboratory analyses were performed at the biochemical laboratory of the Institute of Biology, part of the Faculty of Natural Sciences and Mathematics in Skopje.

The study included patients who were admitted to the Clinic for operative treatment of hip fractures of type 31A and 31B according to the AO classification[40] and were older than 65 years.

Exclusion criteria were:

- presence of concomitant injury;
- injury sustained by a high-energy mechanism;
- patients suffering from chronic inflammatory conditions;
- patients who continuously receive anti-inflammatory drugs;
- patients who at admission have a score greater than 3 according to the scoring system of the American Society of Anesthesiology (ASA score) [41].

The study was approved by the Ethics Committee of the Faculty of Medicine in Skopje. After admission to the hospital, patients who met the inclusion and exclusion criteria were visited by the researcher. On that occasion, they were informed about the study being conducted at the hospital. It was explained to them that they were candidates for participation in the study, along with the nature and purpose of the study. It was also explained to them that the possible participation in the study was voluntary; it would not affect their treatment in any way, and they would not be exposed to additional interventions. Also, they were informed that they could leave the study at any time, but also that they could be excluded by the principal investigator. In addition, it was explained to them how the data related to their health would be handled, stored and used. They were provided with an Information Form describing the relevant aspects of their participation in the study and were asked to read it or have it read to them, and were given the opportunity to discuss it with family members or others close to them. Finally, by asking questions, the researcher checked that potential participants understood the nature of the study and their expectations from it. If the patient agreed to participate in the study, he was asked to sign the Informed Consent.

The following parameters of the study participants were initially recorded:

- gender;
- age;
- the mechanism of injury;
- the type of fracture according to the AO classification;
- the present comorbidities;
- the pharmacological therapy they were receiving;
- Katz's index for determining the level of performance of daily activities before the injury[42]. This instrument evaluates the level of performance of basic daily activities. It contains questions from 6 areas: bathing, dressing, toileting, transferring, continence and feeding. The maximum score is 6 points, and the minimum score is 0 points.

Sampling protocol

During the venipuncture, where a blood sample was taken for routine biochemical analysis necessary for patient's treatment, one additional vacutainer of blood was taken, analyzed and stored in a chamber according to the principles of the laboratory work. This sample was taken within the first ten hours post-injury.

The second sample was taken within 48 to 60 hours postoperatively.

The third sample was taken on the seventh postoperative day.

The fourth sample was taken on the thirtieth postoperative day.

All samples were processed and stored in an identical manner as the first one, with strict adherence to the principles of the laboratory work. Blood samples taken at the same time intervals, the results of which were used in treatment of patients, were also analyzed in the study. These analyses included basic biochemical markers (serum levels of glucose, triglycerides, cholesterol, total proteins, enzyme activity of ALT, AST, CK, LDH, ϒGT). We also registered hematological parameters from differential blood count and C-reactive protein values.

Follow-up

The follow-up period was 12 months. At the control, conducted at this time-point, definitive data/parameters for the study were collected/determined and registered in a checklist by the researcher:

- Mobility - self-evaluation of mobility expressed in percentages, compared to that before the injury. The patient was asked to answer the question: "What percentage is your mobility, i.e., walking, compared to that before the injury and surgery?";
- Pain - the respondent was asked on a scale from 0 to 10 to evaluate the level of pain associated with the injury - 0 indicated no pain, and 10 - worst possible pain;
- SF-12 - short form for quality of life-12. This form consists of 12 questions from 8 different domains. Maximum number of points is 100, which indicates maximum quality of life; zero indicates the worst possible quality of life[43].

Once sample collection was completed, laboratory analysis of serum cytokine levels was performed from the four samples collected for each participant individually. In doing so, the following cytokines were analyzed:

- IL-1β;
- IL-6;
- IL-10.

These analyses were carried out using the ELISA method. The obtained data were statistically analyzed using the statistical software IBM SPSS Statistics 21. and SPS S 23.0. Shapiro-Wilks W test was used to test the normality of data distribution.

Statistical characteristics of the categorical variables are shown with absolute and relative numbers, while quantitative variables are shown by average, standard deviation, minimum and maximum values, median value and interquartile range.

Correlation between variables was analyzed with the Spearman's rank correlation coefficient and Pearson's linear correlation coefficient.

Friedman ANOVA and ANOVA repeated measures were used to compare the values of the analyzed parameters at the 4 measurement points, as well as to compare values between alive and deceased patients at the 4 measurement points.

Linear multivariate regression analysis was used to determine independent significant predictors of quality of life and mobility.

Statistical data significance was defined if $p<0.05$.

Results

General characteristics of the study population

A total of 40 patients were included in the present study. The majority of them were female (24 examinees - 60%). The average age of patients was 78 years, ranging from 71 to 88 years.

Patients' health status before injury was evaluated. According to the Katz index for the level of performance of daily activities, the largest number of patients had a minimal limitation

(grade 5; 15 patients - 37.5%), followed by 13 patients who had a moderate limitation in the performance of daily activities (32.5%), ten patients who had no limitation (25%) and two patients who had a significant limitation (5%).

According to the scoring system of the American Society of Anesthesiology (ASA score), the largest number of patients were classified as Score 2 - moderate systemic disease without significant functional limitations (18 patients - 45%), 16 patients belonged to Score 3 - serious systemic disease with functional repercussions (40%). Six patients (15%) belonged to Score 1.

AO classification was used for the preoperative classification of the fractures' character[40]. According to this classification system, 24 patients (60%) had a 31A type fracture - a fracture of the trochanteric part, while the remaining 16 patients had a fracture of the neck of the femur.

By the end of the study, 32 out of the 40 patients included in the study were alive, and in these patients several parameters for evaluating functionality were determined. The remaining 8 patients (20%) died within the period 4-9 months after the injury.

At the final examination, patients were asked to rate the level of pain they felt on a scale from 0 to 10. According to their answers, the majority rated their pain as 4 (12 respondents - 38%), followed by those who rated the pain as 2 and 3 (9 respondents - 28%). One respondent (3%) rated the pain as 1, and another rated it as 5. The average pain rating score in the examined group was 3.1.

Table 1. General characteristics of the studied group

Variable	
Gender n (%)	
Male	16(40)
Female	24(60)
Age (mean ± SD) (min – max)	(78.45 ± 5.6) (71 - 88)
Katz ADI n (%)	
3	2(5)
4	13(32.5)
5	15(37.5)
6	10(25)
ASA scoring system n (%)	
1	6(15)
2	18(45)
3	16(40)
Fracture type n (%)	
31 A	16(40)
31 B	24(60)
Pain n (%)	
1	1(3)
2	9(28)
3	9(28)
4	12(38)
5	1(3)
Pain (mean ± SD)	3.12 ± 0.9
SF- 12 (mean ± SD)	56.47 ± 15.7
Mobility (mean ± SD)	84.69 ± 12.7
Outcome n (%)	
Alive	32(80)
Dead	8(20)

In addition to pain, patients were also asked to rate their quality of life at the final examination. For this purpose, the short form for evaluating the quality of life - SF12 was used.

The average score of the quality of life was 56 points. The maximum sum of points in this scoring system is 100, and it indicates an excellent quality of life.
A subjective instrument was also used to determine post-injury mobility. Patients were asked to estimate their current mobility as a percentage compared to the that before the injury. The average rating score for the entire group of respondents was 84. The above results are summarized in Table 1.

Results of the analyzed cytokines serum levels

In this study, the following cytokines were analyzed: IL-1β, IL-6, IL-10 at four time points. The first sample that was labeled as A was the serum cytokine levels examined during the first 10 hours after the injury. The second sample was labeled as B and it represented the serum cytokine levels analyzed in the period 48-60 hours after the injury. The third sample labeled as C referred to serum cytokine levels analyzed on the seventh postoperative day, and the last sample was taken on the thirtieth postoperative day.

Table 2. Overview of median values of serum cytokine levels analyzed at the four defined time points. Values are expressed in mg/dl for C-reactive protein, and in pg /dl for the other cytokines

	follow-up period				p-level
	A	**B**	**C**	**D**	
IL - 1β pg/mL mean ±SD	0.66 ± 0.077	0.71 ± 0.068	0.68 ± 0.05	0.71 ± 0.074	[b]p=0.004
IL - 6 pg/mL mean ±SD	39.53 ± 3.5	46.84 ± 4.9	20.30 ± 3.2	14.55 ± 1.7	[b]p<0.0001
IL - 10 pg/mL mean ± SD	7.52 ± 0.6	6.42 ± 0.71	4.22 ± 0.2	4.38 ± 0.4	[b]p<0.0001

[a] p (Friedman ANOVA) [b] p (Repeated measures ANOVA)

The obtained results are summarized in Table 2. A statistically significant difference was registered at the 4 time points for IL-1β (p=0.004), IL-6 (p<0.0001), IL-10 (p<0.0001).

Table 3. Median levels of analyzed cytokines in alive versus deceased patients

	follow-up period			
	A	**B**	**C**	**D**
IL - 1β pg/mL				
Alive median ±SD	0.68 ± 0.075	0.7 ± 0.071	0.67 ± 0.05	0.7 ± 0.08
Dead median ±SD	0.58 ± 0.0075	0.76 ± 0.00	0.69 ± 0.00	0.71± 0.014
IL - 6 pg/mL				
Alive mean ± SD	38.95 ± 3.7	45.26 ± 4.15	19.42 ±2.93	13.99 ± 1.5
Dead mean ± SD	41.84 ± 0.11	53.17 ± 0.09	23.82 ± 0.19	16.79 ± 0.18
IL - 10 pg/mL				
Alive mean ± SD	7.33 ± 0.5	6.21 ± 0.63	4.16 ± 0.23	4.24 ± 0.35
Dead mean ± SD	8.27 ± 0.012	7.25 ± 0.011	4.43 ± 0.014	4.92 ± 0.014

Table 3 presents the serum concentrations of IL-1β, IL-6 and IL-10 in surviving and deceased patients at all time points. In the analyzed period, surviving and deceased patients had significantly different dynamics of serum levels of IL-1β (p=0.0023), IL-6 (p<0.0001), IL-10 (p=0.000005). Deceased patients had significantly higher serum levels of IL-6 and IL-10 at all time points, as well as higher levels of IL-1β at time points A and B, compared to alive patients.

According to the results of the multivariate regression analysis, to determine the impact of the analyzed markers on the SF-12, IL-6 was confirmed as independent significant marker affecting quality of life (p=0.009). These results are shown in Table 4.

Table 4. Results of the multivariate regression analysis for SF-12 quality of life short form

	B	Std. error	Beta	T	sig	95% Confidence Interval	
						Lower Bound	Upper Bound
IL - 1β	-9.194	6.436	-0.044	-1.429	0.165	-22.422	4.035
IL - 6	4.907	1.727	1.166	2.842	0.009**	1.357	8.456
IL - 10	-4.133	2.035	-0.131	-2.031	0.053	-8.317	0.050

dependent variable: SF-12r ^{2} =0.994,*** p< 0.0001 * *p<0.01 *p<0.05

The results of the multivariate regression analysis employed to determine the independent predictive markers for mobility showed that IL-6 was significantly associated with mobility (p=0.013) **(**Table 5).

Table 5. Results of the multivariate regression analysis for mobility

	B	Std. error	Beta	T	sig	95% Confidence Interval	
						Lower Bound	Upper Bound
IL – 1β	7.551	19.413	0.045	0.389	0.70	-32.353	47.456
IL – 6	13.920	5.209	4.092	2.672	0.013*	3.213	24.626
IL – 10	-2.239	6.139	-0.088	-0.365	0.718	-14.858	10.381

dependent variable: mobility r ^{2} =0.916, *p<0.05

Discussion

Hip fractures in the geriatric population represent a serious injury that is associated with osteoporosis and results in significant post-traumatic mortality and morbidity during the first year after injury[44]. To date, several studies have demonstrated the association of osteoporosis and hip fractures with increased serum levels of cytokines[45,46].

A total of 32 patients with type 31A and 31B hip fractures according to the AO classification system were analyzed in this study. All patients were over 65 years of age and had no lower American Society of Anesthesiology score than 3. Analysis of serum levels of defined cytokines at four time points during the first thirty postoperative days showed an increase in serum cytokine levels immediately after injury, followed by a drop, with significant differences in the values at the defined time points.

Of particular interest to us was to analyze the correlation of mortality during the first year after injury and its possible association with serum cytokine levels during the first month after injury. Overall, the mortality in this study was 20%. The results showed that in deceased patients, significantly higher jumps in the serum values of all tested cytokines (IL-1β, IL-6 и IL-10) were registered.

To determine whether any of the analyzed serum markers had an impact on quality of life, a multivariate regression analysis was used. According to the obtained results, IL-6 (p=0.009) was shown to be a marker that independently, significantly affected the quality of life.

Multivariate logistic regression analysis was also performed on self-assessed mobility. In this case, it was shown that serum levels of IL-6 were significantly associated with mobility (p=0.013).

Although the idea that there is an association between serum levels of cytokines after injury and outcome after injury in general is well established, the correlation between serum

levels of cytokines and mortality, quality of life and mobility in the geriatric group of patients has not been investigated in detail. The results of Belooseski *et al.*, and Stojanovic *et al.*, who analyzed the correlation between the kinetics of pro- and anti-inflammatory cytokines on postoperative complications and cognitive status of adult patients with hip fracture[47,48], demonstrated a significant increase in serum levels of IL-6.

For participants who had changes in mental status, higher kinetic curves for IL-6 were observed when compared to those patients who had normal mental status and were without cognitive impairment. Analyzing the mutual effect of complications and altered mental status, studies have shown that patients with altered mental status had higher values of IL-6, IL-8 and IL-10 in comparison to those with normal mental status. It has been emphasized that serum levels of cytokines increase dramatically in patients after hip fracture.

The current study has several limitations. Firstly, it included a small number of participants. In addition, the control group was not formed and analyzed, and the rise in serum levels of cytokines was concluded based on the established reference values. On the other hand, this study is the first in our country that has focused on these laboratory parameters in the geriatric population in our country, and is among the few studies in the world on this topic.

Conclusion

The practical applicability of the findings that emerged from this study is aimed at identifying patients at high risk for postoperative mortality during the first year after injury, as well as those at risk of a significant reduction in mobility and, in general, a decline in quality of life after injury. A drastic increase in these values may indicate the need for additional examinations and interventions in order to reduce postoperative mortality, and to design rehabilitation programs that would allow satisfactory mobility and quality of life after this frequent, and for many, fatal injury.

Conflict of interest statement. None declared.

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