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Original article

CYTOKINE DYNAMICS AND LONG-TERM OUTCOMES IN GERIATRIC HIP FRACTURE PATIENTS

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Abstract

Introduction: Hip fractures in the elderly are associated with high morbidity, mortality, and reduced quality of life. This study investigated the role of systemic inflammation, measured through serum levels of C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α), in predicting outcomes following operatively treated hip fractures in patients over 65 years of age.

Materials and Methods: A prospective, nonrandomized study was conducted involving 40 patients with hip fractures classified as 31A or 31B (AO classification). Blood samples were collected at four time points: within 10 hours post-injury, 48–60 hours post-surgery, on the seventh postoperative day, and on the 30th postoperative day. Serum levels of CRP and TNF-α were measured using ELISA. Functional outcomes, including quality of life (SF-12), mobility, and pain, were assessed at 12 months post-injury.

Results: Elevated serum levels of CRP and TNF-α were significantly associated with reduced quality of life, mobility, and survival. Deceased patients exhibited significantly higher cytokine levels compared to survivors at all time points. Multivariate regression analysis identified CRP ($p<0.0001$) and TNF-α ($p=0.017$) as independent predictors of quality of life, while TNF-α was significantly associated with mobility ($p=0.043$).

Conclusion: CRP and TNF-α may serve as valuable biomarkers for identifying high-risk patients and guiding postoperative care. Monitoring inflammatory markers could improve outcomes in geriatric hip fracture patients by enabling targeted interventions and rehabilitation programs.

Keywords: hip fracture, geriatrics, C-reactive protein, tumor necrosis factor-alpha, functional recovery

Introduction

Hip fractures represent a major public health challenge, particularly among the elderly population. As life expectancy increases globally, the incidence of hip fractures is projected to rise significantly, with estimates suggesting 4.5 million cases annually by 2050[1,2]. These injuries are associated with high morbidity and mortality, as well as a substantial decline in quality of life and functional independence[3,4].

The elderly population is particularly vulnerable to hip fractures due to age-related factors such as osteoporosis, reduced bone density, and an increased risk of falls[5]. Additionally, comorbidities such as cardiovascular disease, diabetes, and cognitive impairment further complicate recovery and contribute to poor outcomes[6,7]. Despite advances in surgical techniques and perioperative care, hip fractures remain a leading cause of disability and mortality in older adults[8].

The inflammatory response following trauma and surgery has been increasingly recognized as a key determinant of outcomes in hip fracture patients. Cytokines, such as CRP and TNF-α, play a central role in mediating the systemic inflammatory response, which can lead to complications such as delayed healing, infections, and organ dysfunction[9,10]. However, the relationship between serum cytokine levels and long-term outcomes in geriatric hip fracture patients remains poorly understood.

This study aimed to address this gap by analyzing the dynamics of serum cytokine levels in geriatric patients with operatively treated hip fractures and their association with functional outcomes, mobility, and survival. By identifying biomarkers that predict poor outcomes, this research seeks to inform targeted interventions and improve patient care.

Materials and Methods

Study Design and Participants

This prospective, nonrandomized study was conducted at the University Clinic for Traumatology in 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 enrolled 40 patients aged over 65 with hip fractures classified as 31A or 31B according to the AO classification[11]. Exclusion criteria were concomitant injuries, high-energy trauma, chronic inflammatory conditions, ongoing anti-inflammatory therapy, and an American Society of Anesthesiologists (ASA) score >3[12].

Data Collection

Demographic data, injury mechanism, fracture type, comorbidities, and pre-injury functional status (assessed using the Katz Index of Activities of Daily Living)[13] were recorded. Blood samples were collected at four time points: within 10 hours post-injury, 48-60 hours post-surgery, on the seventh postoperative day, and on the 30th postoperative day. Serum levels of CRP and TNF-α were measured using enzyme-linked immunosorbent assay (ELISA).

Follow-Up

Patients were followed for 12 months post-injury. Functional outcomes, including quality of life (assessed using the SF-12 questionnaire) [14], mobility, and pain, were evaluated at the final follow-up.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics 23.0. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR), while categorical variables were presented as frequencies. The Shapiro-Wilk test was used to assess normality. Differences in cytokine levels across time points were analyzed using the Friedman ANOVA and Repeated Measures ANOVA. Multivariate regression analysis was performed to identify independent predictors of quality of life and mobility. A p-value <0.05 was considered statistically significant.

Results

General Characteristics of the Study Population

The study included 40 participants, 60% of whom were female (n=24), with a median age of 78 years (range: 71-88 years). Pre-injury functional status, as assessed by the Katz Index of Activities of Daily Living, revealed that most patients (37.5%, n=15) had minimal limitations (grade 5), while 32.5% (n=13) had moderate limitations, 25% (n=10) had no limitations, and 5% (n=2) had significant limitations. According to the American Society of Anesthesiologists (ASA) scoring system, 45% (n=18) of patients were classified as ASA Score 2 (moderate systemic disease without significant functional limitations), 40% (n=16) as ASA Score 3 (serious systemic disease with functional repercussions), and 15% (n=6) as ASA Score 1 (healthy individuals). Fracture types, classified using the AO system, included 60% (n=24) type 31A (trochanteric fractures) and 40% (n=16) type 31B (femoral neck fractures)[11,12].
At the 12-month follow-up, 32 patients (80%) were alive, while 8 (20%) had died between 4 and 9 months after the injury. Pain levels, assessed on a scale of 0 to 10, were rated as 4 by the majority of participants (38%, n=12), with a mean pain score of 3.1±0.9. Quality of life, evaluated using the SF-12 questionnaire, had a median score of 56 points (maximum: 100). Self-reported mobility, expressed as a percentage of pre-injury levels, had a median value of 84%[13,14]. Table 1 summarizes the general characteristics of the study population.

Table 1. General characteristics of the study population

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(3 7 .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)

Serum Cytokine Levels Over Time

Serum levels of CRP and TNF-α were measured at four time points: within 10 hours post-injury (Sample A), 48-60 hours post-surgery (Sample B), on the seventh postoperative day (Sample C), and on the 30th postoperative day (Sample D).

CRP levels showed a significant increase from Sample A (median: 1.2 mg/dL, IQR: 0.9-2.3) to Sample B (median: 10 mg/dL, IQR: 5.6-26), followed by a gradual decline in Samples C (median: 7.9 mg/dL, IQR: 5.6-16) and D (median: 1.6 mg/dL, IQR: 1.1-3.2). Similarly, TNF-α levels peaked in Sample B (mean: 12.05±0.9 pg/mL) and remained elevated in Sample D (mean: 18.33±1.4 pg/mL). Statistical analysis revealed significant differences in CRP ($p<0.0001$, Friedman ANOVA) and TNF-α ($p<0.0001$, Repeated Measures ANOVA) levels across the four time points[15,16]. Table 2 provides an overview of the median serum cytokine levels at each time point.

Table 2. Median Serum Cytokine Levels at Four Time Points

	follow-up period				p-level
	A	B	C	D	
CRP mg/dL median (IQR)	1.2(0.9-2.3)	10(5.6-26)	7.9(5.6-16)	1.6(1.1-3.2)	[a] p<0.0001
TNF-α pg/mL mean ± SD	10.13±0.9	12.05±0.9	10.08±0.9	18.33±1.4	[b] p<0.0001

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

Comparison of Cytokine Levels Between Survivors and Non-Survivors

Deceased patients exhibited significantly higher serum levels of CRP and TNF-α compared to survivors at all four time points ($p<0.0001$). For example, in Sample B, the median CRP level in deceased patients was 100.5 mg/dL (IQR: 99.5-102), compared to 7.4 mg/dL (IQR: 5.05-17.5) in survivors. Similarly, TNF-α levels in deceased patients were consistently higher, with a mean of 13.11±0.005 pg/mL in Sample B compared to 11.79±0.75 pg/mL in survivors[17,18]. Table 3 presents the median cytokine levels in living *versus* deceased patients.

Table 3. Median Cytokine Levels in Living vs. Deceased Patients

	Follow-up period			
	A	B	C	D
CRP mg/dL				
live median (IQR)	1.05(0.752-1.75)	7.4(5.05-17.5)	6.1(4.1-12.05)	1.5(1.1-2.35)
dead median (IQR)	5.7(5.7-5.7)	100.5(99.5-102)	98(98-98)	68.3(67.7-69.95)
TNF-α pg/mL				
live mean ± SD	9.84±0.82	11.79±0.75	9.81±0.83	17.92±1.25
dead mean ± SD	11.27±0.022	13.11±0.005	11.18±0.02	19.98±0.007

Predictors of Quality of Life and Mobility

Multivariate regression analysis identified CRP ($p<0.0001$) and TNF-α ($p=0.017$) as independent predictors of quality of life, as measured by the SF-12 questionnaire. Similarly, TNF-α was significantly associated with self-reported mobility ($p=0.043$)[19,20]. Table 4 summarizes the results of the multivariate regression analysis for quality of life.

Table 4. Multivariate Regression Analysis for SF-12 Quality of Life

	B	Std.Error	Beta	T	Sig	95% Confidence Interval	
						Lower Bound	Upper Bound
CRP	-14.996	3.196	- 0.651	-4.692	0.000***	-21.566	-8.426
TNF-α	-26.157	10.270	-1.362	-2.547	0.017*	-47.267	-5.048

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

Table 5. Multivariate Regression Analysis for Mobility

	B	Std.Error	Beta	T	Sig	95% Confidence Interval	
						Lower Bound	Upper Bound
CRP	-10 . 309	9 . 642	- 0. 554	-1 . 069	0. 295	-30 . 128	9 . 509
TNF-α	-65 . 776	30 . 978	-4 . 238	-2 . 123	0.043 *	-129 . 453	-2 . 099)

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

Table 5 presents the results of the multivariate regression analysis for mobility.

Discussion

The findings of this study highlight the significant role of systemic inflammation in determining outcomes following geriatric hip fractures. Elevated serum levels of CRP and TNF-α were strongly associated with reduced quality of life, mobility, and survival. These results align with previous research demonstrating the detrimental effects of inflammation on recovery and long-term outcomes in trauma patients[21,22].

The observed increase in CRP and TNF-α levels immediately after injury and surgery reflects the body's acute inflammatory response to trauma. However, the sustained elevation of these markers in deceased patients suggests a dysregulated inflammatory response, which may contribute to complications such as infections, organ failure, and delayed healing[23,24]. This is consistent with studies showing that excessive inflammation can exacerbate tissue damage and impair healing processes[25,26].

The identification of CRP and TNF-α as independent predictors of quality of life and mobility underscores their potential utility as biomarkers for risk stratification. Patients with persistently elevated cytokine levels may benefit from targeted interventions, such as anti-inflammatory therapy or enhanced rehabilitation programs, to mitigate the adverse effects of systemic inflammation[27,28]. For example, Beloosesky *et al.*[29] demonstrated that elevated CRP levels were independently associated with complications and altered mental status in hip fracture patients, further supporting the clinical relevance of inflammatory markers.

This study also highlights the importance of early identification of high-risk patients. The significant differences in cytokine levels between survivors and non-survivors suggest that these markers could be used to predict mortality and guide clinical decision-making. Similar findings have been reported in other studies, where elevated CRP and TNF-α levels were associated with increased mortality and poor functional outcomes in elderly trauma patients[30,31].

However, this study has several limitations. The small sample size (n=40) and single-center design may limit the generalizability of the findings. Additionally, the lack of a control group makes it difficult to establish causality between cytokine levels and outcomes. Future studies with larger, multicenter cohorts are needed to validate these findings and explore the underlying mechanisms linking inflammation to poor outcomes in geriatric hip fracture patients[32,33].

Despite these limitations, the findings have important clinical implications. CRP, in particular, is routinely measured in clinical practice, making it a practical biomarker for identifying high-risk patients. By incorporating cytokine levels into clinical decision-making, healthcare providers can develop targeted interventions to improve outcomes in this vulnerable population[34,35].

The use of predictive scoring systems, such as the Nottingham Hip Fracture Score [36] and the Almelo Hip Fracture Score[37], has been shown to improve risk stratification and postoperative care in hip fracture patients. These tools, combined with inflammatory markers like CRP and TNF-α, could enhance the ability to identify patients at high risk for complications and mortality[38,39]. Furthermore, studies have demonstrated that early surgical intervention and multidisciplinary care pathways can significantly reduce mortality and improve functional outcomes in geriatric hip fracture patients[40,41].

Conclusion

This study demonstrated that elevated serum levels of CRP and TNF-α were associated with reduced quality of life, mobility, and survival in geriatric patients following hip fracture surgery. These findings highlight the importance of monitoring inflammatory markers to identify high-risk patients and guide postoperative care. By incorporating cytokine levels into clinical decision-making, healthcare providers can develop targeted interventions to improve outcomes in this vulnerable population. Future research should focus on validating these findings in larger cohorts and exploring the potential benefits of anti-inflammatory therapies in improving outcomes for geriatric hip fracture patients[42].

Conflict of interest statement. None declared.

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