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Original Article

Characterizing the Acute Phase Response in Hip Fracture Patients

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SUMMARY

Background: The acute phase response (APR) is systemic body reaction to tissue injury, and its dysregulation leads to poor outcomes. Acute phase reactants exhibit a lot of variation, which makes differential diagnosis difficult – especially in fragile patients. The aim of the present study is to describe the perioperative acute phase response kinematics in hip fracture patients.
Materials and methods: 431 hip fracture patients over 65 years old who underwent surgical treatment were included in a prospective study. Pre-operative C reactive protein, albumin, vitamin D, and fibrinogen concentrations and C reactive protein of the 3–4th day post-operatively were obtained. Patients were followed up for 30 days and all infectious complications were removed.
Results: The admission C-reactive protein (CRP) levels exhibited a statistically significant negative correlation with both albumin ($p = .038$) and vitamin D ($p = .021$). On the first post-operative day, patients with femoral neck fractures showed statistically significantly lower CRP levels compared to those with intertrochanteric ($p = .046$) and subtrochanteric ($p = .007$). This pattern persisted on the 3rd–4th post-operative days ($p < .001$). Hemiarthroplasty, total hip arthroplasty, and cannulated screws groups demonstrated statistically lower post-operative CRP values compared to the dynamic hip screw ($p < .001$, $p < .001$, $p = .024$) and proximal femoral nail groups ($p < .001$, $p < .001$, $p = .024$).
Conclusions: Surgeries for extracapsular hip fractures are associated with a greater acute phase response compared to surgeries for intracapsular fractures. Vitamin D was found as possible negative acute phase reactant.

1. Background

The acute phase response (APR) is a vital systemic reaction to tissue injury, playing a crucial role in the organism ability to heal after trauma through various physiological, biochemical, and nutritional changes.[1–3] Literature indicates that both hyperactivity and hypoactivity of the APR can lead to adverse outcomes.[1,2] Biomarkers associated with the APR, such as C-reactive protein (CRP), are non-specific and exhibit significant variability, complicating differential diagnosis.[4–7] This issue is particularly important in geriatric patients with hip fractures (HF), who face complications in up to 40% of cases following surgery.[8–16] In these patients, fluctuations in APR reactants can occur due to multiple factors, including the fracture itself, surgical interventions, age related organ changes, and potential infectious complications.[4,15–21] While some studies have suggested a decrease in incidence of HP in Northern countries and a stabilization in Central Europe, the prevalence and significance of hip fractures are expected to rise as the population ages and individuals become more polymorbid. This demographic shift is likely to lead to higher complication and mortality rates among these patients.[8,10,11,22,23] Identifying alterations in APR biomarkers in hip fracture patients could facilitate more intensive monitoring, prompt early interventions, and the establishment of specialized care pathways, ultimately improving patient outcomes.

The aim of the present study was to describe perioperative APR kinematics in HF patients, considering fracture types (femoral neck, intertrochanteric, and subtrochanteric) and surgery types (hemiarthroplasty (HA), total hip arthroplasty (THA), osteosynthesis by proximal femoral nail (PFN), dynamic hip screw (DHS), and cannulated screws (CS)) during in-hospital stay. The authors propose that the APR of HF patients may differ based on the type of fracture and the specific surgical procedure performed.

2. Materials and methods

The prospective study was conducted at a tertiary orthopaedic trauma centre from December 1, 2022, to December 31, 2023. All patients or their proxies provided informed consent to participate, and the study received approval from both the Institutional Review Board of our hospital and "Vilnius Regional Biomedical Research Ethics Committee" (2022/11-1473-941). Following were the inclusion criteria: ≥ 65 years patients; intertrochanteric fracture; subtrochanteric fracture; femoral neck fracture; patients who underwent surgical treatment; low energy trauma (simple fall); closed fractures; isolated trauma; acute trauma (no more than 72 hours). Exclusion criteria were patients who had infectious complications

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(urinary infection, pneumonia, superficial or deep surgical site infection), pathological fractures, fractures without trauma, old trauma, trauma with neurovascular damage, concomitant trauma, unknown time of trauma. All patients were followed up for 30 days post-surgery. On the 30th day, the patient or their proxy was contacted to collect information regarding their condition. The final sample size consisted of 431 patients, as depicted in the flow chart (Figure 1). All surgical interventions were either performed or supervised by a consultant orthopaedic surgeon.

We routinely evaluated pre-operative white blood cell count (WBC), CRP, fibrinogen, albumin, vitamin D (25(OH)D), and fibrinogen on the day of hospitalization. Furthermore, all patients were obtained and checked on the first and 3-4th post-operative days for CRP levels. Following laboratory markers were used to evaluate the APR: CRP, fibrinogen, albumin, vitamin D. The first two are positive reactants (increases with the APR) and the last two are negative (decreases when APR is increasing). Furthermore, CRP/albumin ratio (CAR) was calculated from the pre-operative values. Previous studies have identified the CAR as a predictor of adverse outcomes across various pathologies.[20,21] Given that CAR is a ratio of positive and negative acute phase reactants, it may offer greater sensitivity within patient groups than measuring these reactants independently. To further investigate this, we included CAR in the present study. The patients were categorized based on the type of hip fracture – femoral neck (intracapsular), intertrochanteric (extracapsular), and subtrochanteric (extracapsular) – as well as the type of surgical intervention performed. Surgical interventions included hemiarthroplasty, total hip arthroplasty, osteosynthesis via proximal femoral nail, osteosynthesis via dynamic hip screw, and osteosynthesis via cannulated screws.

Pre-operative values for C-reactive protein (CRP), fibrinogen, vitamin D, and albumin were not stratified according to the type of surgery, as these biochemical markers are not influenced by the surgical procedure itself.

All analyses were performed by IBM SPSS version 26.0 software (SPSS Inc., Chicago, IL) for Windows. Normally distributed data is presented as mean (± standard deviation). Non-normally distributed data is presented as median (25–75th interquartile range (IQR)). For comparison of normally distributed data ANOVA test was used. Shapiro-Wilk test was used to evaluate the normality of data distribution. To compare non-normally distributed variables, Kruskal-Wallis test was used. In case of normally distributed data in one group and non-normally distributed data in the other, Kruskal-Wallis test was used. Furthermore, we used pairwise comparison to compare multiple groups. Pearson correlation coefficient was used to correlate scale variables and is presented in brackets with p value. Level of significance α was set as $p < 0.05$.

3. Results

General information on patients is presented in Table 1.

Table 1
Descriptive statistics of the general information on the patients and the groups.

Variables	
Gender (female/male)	333 (77.3%)/98 (22.7%)
Age	82 ± 8
Number of comorbidities	6 ± 3
Fracture type	
Femoral neck	208 (48.3%)
Pertrochanteric	199 (46.2 %)
Subtrochanteric	24 (5.6 %)
Surgery type	
Hip hemiarthroplasty (HA)	126 (29.2%)
Total hip arthroplasty (THA)	61 (14.2%)
Dynamic hip screw (DHS)	48 (11.1%)
Proximal femoral nail (PFN)	183 (42.5%)
Cannulated screws (CS)	13 (3.0%)

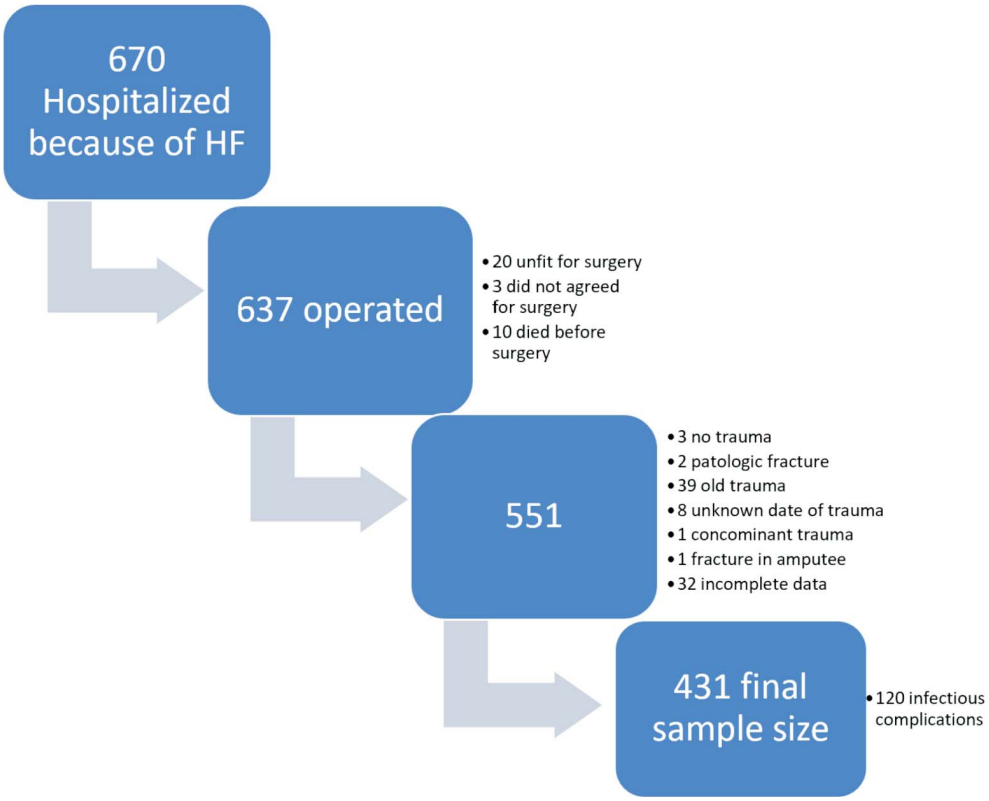

Figure 1. Flow chart of the final sample size.

Among all the patients, on admission, CRP and albumin concentration had statistically significant negative correlation (p = 0.038, Pearson coefficient = -0.108). The same statistically significant negative correlation was observed between pre-op CRP and vitamin D (p = 0.021, Pearson coefficient = -0.116). Descriptive statistics of the variables within the groups are presented in Table 2 and Table 3.

On admission, fracture type did not significantly affect CRP levels (p = 0.083). By the first post-operative day, femoral neck fractures had lower CRP than intertrochanteric (p = 0.046) and subtrochanteric fractures (p = 0.007); there was no significant difference among extracapsular fractures (p = 0.077). On days 3–4 post-op, femoral neck fractures continued to show lower CRP (p < 0.001), and intertrochanteric fractures had lower CRP than subtrochanteric fractures (p = 0.034). Intracapsular fractures had higher pre-operative fibrinogen than intertrochanteric (p = 0.025) and subtrochanteric fractures (p = 0.039), with no difference between extracapsular fractures (p = 0.308). Femoral neck fractures also showed higher albumin than intertrochanteric (p < 0.001) and subtrochanteric fractures (p = 0.020); no difference was found among extracapsular fractures (p = 0.729). Vitamin D levels did not differ significantly by fracture type (p = 0.112).

On the first post-operative day, only the THA group had significantly lower CRP levels compared to PFN (p = 0.002) and DHS (p = 0.017). This difference increased by days 3–4 (p < 0.001). At days 3–4, HA and CS also showed significantly lower CRP values than PFN (p < 0.001 and p = 0.018) and DHS (p < 0.001 and p = 0.024). Subtrochanteric fractures had significantly lower CAR than intertrochanteric (p = 0.017) and femoral neck fractures (p = 0.011).

4. Discussion

In HF patients, APR is understudied and at the time of writing, literature was spare on data. The findings of this study indicate the need for physicians to maintain a high level of awareness regarding the postoperative inflammatory response, particularly in patients with subtrochanteric fractures. These fractures are associated with significantly elevated postoperative CRP levels compared to femoral neck and intertrochanteric fractures, which is a notable and unique observation of this research. The surgical management of subtrochanteric fractures typically involves long proximal nails and open reduction, while intertrochanteric fractures are generally treated with closed reduction and short proximal nails. This difference in surgical technique necessitates a "fracture-specific" approach, which likely impacts the APR following surgery. This inherent link between fracture type and surgical approach introduces a potential bias in the study: not only subtrochanteric fracture itself, but its specific surgical approach alters APR, but in this case fracture and surgery type are inseparable. Surgical approaches for intracapsular fractures (THA, HA, CS) were associated with lower CRP values compared to those for extracapsular fractures (PFN, DHS). As there was no significant difference in baseline CRP between fracture patterns, these results suggest that the type of surgery has a greater influence on postoperative APR than the type of fracture.

We developed multivariable regression models to examine potential confounding factors influencing CRP values. Models incorporating fracture type, age, and comorbidities indicated that THA and HA were significant predictors of CRP on the first post-operative day, but this significance was reduced after adjusting for age. This trend did not persist for CRP measured on days 3–4, and number of comorbidities had no impact. Fracture type remained a statistically significant predictor of CRP on both the first and 3rd–4th postoperative days, unaffected by adjustment for age or comorbidities. Our findings suggest that age confounds the relationship between surgical procedure (THA/HA) and early post-operative CRP, which aligns with the fact that THA is typically performed on younger, more active patients than HA.

Clinically, it is important to recognize that normal CRP values should not be anticipated in patients with HF, as demonstrated by our study findings: 1. Upon admission, 48.3% of patients exhibited CRP levels exceeding 5 mg/l, with 35.3% surpassing 10 mg/l; 2. On the first postoperative day, 83.5% of patients had CRP levels above 5 mg/l, 80.5% above 10 mg/l, and 18.8% exceeded 100 mg/l. 3. By the 3rd to 4th postoperative day, 82.8% of patients still had CRP levels above 5 mg/l, while 81.7% remained above 10 mg/l. To ensure a more accurate assessment of the normal APR in HF patients, we specifically excluded all individuals with infectious complications from our analysis.

In general, we have observed that extracapsular hip fractures

Table 2
Descriptive statistics of the variables within the fracture types.

Variable	All groups (N = 431)	Fracture type		
		Femoral neck (N = 208)	Pertrochanteric (N = 199)	Subtrochanteric (N = 24)
WBC ($\times 10^{12}$/l) pre-op	9.9 (8–12)	9.7 (7.8–11.9)	10.1 (8.1–12.2)	9.8 (8.8–13.3)
WBC ($\times 10^{12}$/l) first day after surgery	8.9 (7.1–11.1)	10 (7.7–11.9)	8.4 (6.9–10.1)	8.2 (6.7–10.5)
WBC ($\times 10^{12}$/l) 3rd–4th day after surgery	7.1 (5.7–8.5)	7.2 (5.8–8.4)	7 (5.6–8.6)	5.7 (6.8–9.4)
CRP (mg/l) pre-op	4 (1.4–20.8)	4.3 (1.6–21.7)	5 (1.3–23.7)	1.7 (.65–11)
CRP (mg/l) first day after surgery	60.3 (36.5–63)	58.3 (34.1–85.4)	69.5 (41.8–101.5)	98.9 ± 58.2
CRP (mg/l) 3rd–4th day after surgery	65.9 (32.1–65.5)	45 (27.9–72.9)	77 (52.7–111.4)	110.8 ± 55.1
Fibrinogen (g/l) pre-op	3.7 ± 0.9	3.7 ± 0.9	3.6 ± 0.9	3.5 ± 8
Albumin (g/l) pre-op	39.3 ± 6.7	40.5 ± 10.2	38.2 ± 4.1	38.1 ± 3.6
Vitamin D (nmol/l) pre-op	48.5 ± 33	54 ± 35	45.3 ± 33	58.2 ± 41.4
CRP/albumin ratio	.1 (.03–.5)	.1 (.04–.6)	.1 (.03–.6)	.03 (.02–.2)

CRP, C reactive protein; WBC, white blood cell count.

Table 3
Descriptive statistics of the variables within the fracture types.

Variable	Surgery type				
	HA (N = 126)	THA (N = 61)	PFN (N = 183)	DHS (N = 48)	CS (N = 13)
CRP (mg/l) first day after	59.8 (34.6–93.8)	48.4 (22.7–78.2)	69.9 (43–101.2)	72.2 ± 24.9	70.8 ± 51
CRP (mg/l) 3rd–4th day after surgery	50.5 (28.8–72.3)	40.7 ± 24.2	80.4 (57.6–111.9)	86.3 ± 39.4	50.9 ± 29.7

CRP, C reactive protein; CS, cannulated screws; DHS, dynamic hip screw; HA, hemiarthroplasty; PFN, proximal femoral nail; THA, total hip arthroplasty.

yield higher APR than compared to intracapsular, which was unique at the time of writing. It is observed not only in CRP values, but in negative APR reactant albumin values too – intracapsular fractures had significantly higher concentration than compared to extracapsular fractures. However, it should be taken in mind that hypoalbuminemia is common in the elderly.[4,19,24] We found it to be 14.4% (albumin lower than 35 g/l). In our case all our patients were 65 and older, we assumed that our sample was affected by this matter equally and difference between groups is present because of the APR. At the time of the writing, the CAR was previously found to predict 30 day and 1 year mortality after hip fracture surgery.[20,21] As CAR represents the ratio between positive APR reactant (CRP) and negative reactant (albumin) it is logical, that the index represents the dysregulation of APR which was found previously to represent poor patient outcomes.[1,2] The aim of this study was not to evaluate the outcomes of hip fracture patients, but we observed a pattern those patients with subtrochanteric fractures had the significant hypoalbuminemia pre-operatively and significantly higher CRP values post-operatively compared with other fracture types. Our calculated CAR was combined from admission values, and we did not find statistically significant differences, but pre-operative hypoalbuminemia and post-operative CRP elevation might show that patients with subtrochanteric fractures are prone to APR dysregulation and poor outcomes. However, this hypothesis needs to be proven in further studies.

The findings of our study align with previous research that highlights the interplay between various APR reactants, particularly the negative correlation between pre-operative CRP and albumin concentrations.[7,17–19] Our investigation extends this understanding by demonstrating a significant negative correlation between CRP and vitamin D levels, a relationship that has garnered increasing attention in recent studies. Previous literature has posited that vitamin D may function as a negative APR reactant, and our results lend support to this hypothesis.[3] For instance, Zhao et al. reported higher vitamin D levels in patients with simple fracture patterns compared to those with more complex fractures, suggesting a potential link between vitamin D status and injury severity.[25] In our study, vitamin D levels did not differ significantly between fracture groups, nor did they correlate with albumin concentration. Thus, while there are limitations, we can only suggest that vitamin D may be a negative APR reactant. Notably, we identified a concerning prevalence of vitamin D deficiency, with 75.4% of patients exhibiting insufficient levels. This finding underscores the importance of vitamin D supplementation in the elderly population.

The observed significantly higher fibrinogen concentrations in intracapsular fractures compared to extracapsular fractures in this study may not be primarily linked to the APR. A more plausible explanation lies in the role of fibrinogen in the coagulation process. Notably, we found that patients with extracapsular fractures exhibited significantly lower haemoglobin levels compared to those with intracapsular fractures ($p < 0.001$). This suggests a potential higher use of fibrinogen for coagulation process in subtrochanteric fractures. Moreover, it is important to consider that fibrinogen levels typically peak at least two days following the initiation of the APR. Since our study did not assess postoperative fibrinogen levels, it becomes one of the limitations of present study.

As with all studies, ours has certain limitations. First, it is a single centre study, which means that the findings may not be generalizable to other hospitals or settings. The patient population examined is limited to those admitted to our institution, potentially affecting the external validity of the results. Moreover, we did not analyse complications, as this was beyond the scope of our study. This omission is a notable shortcoming, as understanding complications could provide valuable insights into patient outcomes. We excluded all patients with infectious complications to minimize their impact on the APR. However, it would be beneficial to assess the comorbidities of the patients using a standardized tool, such as the Charlson Comorbidity Index, to ensure comparability and to better understand the influence of underlying conditions on APR.

5. Conclusions

Extracapsular hip fractures trigger a higher acute phase response than intracapsular one's post-surgery. Fracture morphology impacts APR more than surgery type. Vitamin D was found as a negative acute phase reactant. Normal CRP and vitamin D levels should not be expected in HF patients.

Conflicts of interest

The authors declare no conflicts of interest.

Author contributions

PM conceptualized the present study, collected, analysed and interpreted the data, performed statistical analysis, interpreted the results and drafted manuscript; RB, SU, RM, VU and IŠ collected, analysed and interpreted the data, interpreted the results. The manuscript was reviewed by all authors. Finally, all authors read and approved the final manuscript for publication.

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