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Biomarkers for Prediction of Cardiovascular Complications in Hip Fracture Surgery in the Elderly

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Abstract

To evaluate and synthesize evidence on the prognostic value of circulating biomarkers - B-type natriuretic peptide (BNP)/N-terminal pro-BNP (NT-proBNP), troponins T and I, C-reactive protein (CRP), and soluble urokinase plasminogen activator receptor (suPAR) - for short- and long-term mortality in elderly patients undergoing hip fracture surgery, we hypothesized that elevated biomarker levels reflect frailty and underlying cardiac and non-cardiac pathology and predict mortality. We conducted a narrative review of clinical studies in geriatric hip fracture cohorts reporting preoperative and/or postoperative measurements of these biomarkers, extracting study design, timing of sampling, biomarker thresholds, associations with all-cause and cardiovascular mortality, and whether analyses adjusted for age, comorbidity, and surgical factors. Multiple studies report postoperative troponin elevations linked to worse long-term prognosis and higher mortality. BNP and NT-proBNP consistently correlate with cardiovascular risk and increased mortality when measured preoperatively or early postoperatively, with several studies describing nonlinear relationships and threshold effects. CRP shows variable association with mortality, often reflecting infection or systemic inflammatory burden, and composite ratios (e.g., CRP-to-albumin ratio, CRP-to-lymphocyte ratio) may improve prognostic performance. suPAR is associated with multimorbidity and premature death in general populations; data specific to hip fracture patients are limited but suggest higher suPAR quartiles relate to increased 30-day mortality. Heterogeneity in timing of sampling, biomarker thresholds, and statistical adjustments across studies limits definitive recommendations. Overall, BNP/NT-proBNP, troponins, CRP, and suPAR show promise for risk stratification in hip fracture patients, but prospective standardized studies are needed to define optimal markers, timing, and clinical utility.

Categories: Cardiology, Pathology, Orthopedics
Keywords: bnp, bnp, crp, crp, hip fracture, hip fracture, mortality, mortality, supar, supar, troponin, troponin

Introduction And Background

Low-energy hip fractures represent an increasing challenge for both patients and healthcare systems globally. In 1990, approximately 1.31 million cases were reported, with projections suggesting an increase to 6.26 million by 2050. Mortality rates remain high, with nearly 30% of affected individuals dying within the first year, while survivors frequently experience significant declines in functional status and quality of life [1]. These injuries primarily affect older adults and most often result from low-energy mechanisms, such as falls from standing or seated positions. According to the UK National Hip Fracture Database, 91.6% of hip fractures occur in individuals over 70 years of age, and women account for approximately 72% of cases [2]. Comprehensive epidemiological characterization is crucial for identifying high-risk populations, guiding resource allocation, and informing the development of targeted prevention and care strategies.

Patients with hip fractures often present with significant comorbidities, including diabetes mellitus, heart failure, prior myocardial infarction, cerebrovascular disease, and neurodegenerative disorders such as Parkinson's disease [3]. Early postoperative mortality in these populations can reach 16.3% within the first month [4]. Established predictors of adverse outcomes include advanced age, male sex, impaired mobility, surgical delay, anemia, electrolyte abnormalities, and systemic inflammation [5,6]. These factors reduce physiological reserve and impede recovery. For example, advanced age is associated with multisystem decline, male sex with a greater burden of frailty in some studies, reduced mobility with complications such as pressure injuries and thromboembolism, surgical delay with prolonged immobilization, anemia with impaired tissue oxygenation, electrolyte disturbances with cardiac and neurological instability, and systemic inflammation with impaired organ function and wound healing. Systematic evaluation of these determinants supports prioritization of perioperative assessment and optimization.

Several circulating biomarkers have been investigated for their prognostic value in patients undergoing hip fracture surgery. In this review, four biomarker groups were selected a priori because they represent complementary pathophysiological domains relevant to perioperative risk: myocardial wall stress, assessed

by B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP); myocardial injury, assessed by cardiac troponins T and I (cTnT and cTnI); acute systemic inflammation, assessed by C-reactive protein (CRP); and chronic immune activation, assessed by soluble urokinase plasminogen activator receptor (suPAR).

BNP and NT-proBNP are released in response to myocardial wall stress and are elevated in patients with heart failure. In hip fracture populations, increased concentrations have been associated with postoperative cardiac complications and adverse outcomes [7,8]. Cardiac troponins, which indicate cardiomyocyte injury, may increase after the fracture or surgical intervention and have been associated with adverse short- and long-term outcomes [9-11]. CRP is an established, although nonspecific, marker of acute systemic inflammation and has been associated with poorer outcomes in some postoperative studies [12,13]. suPAR reflects persistent immune activation and inflammatory burden. Although evidence in elderly hip fracture populations remains more limited than that for natriuretic peptides, troponins, and CRP, elevated suPAR concentrations have been associated with cardiovascular disease, diabetes, cancer, and premature mortality in community-based cohorts, suggesting a potential role in identifying patients with underlying inflammatory vulnerability [14-16].

This conceptual framework distinguishes biomarkers of myocardial injury and hemodynamic stress from markers of acute and chronic inflammation. Other laboratory variables, including hemoglobin, leukocyte count, albumin, creatinine, parathyroid hormone, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, prognostic nutritional index, and individual cytokines, are considered supplementary or contextual markers. They may provide information about anemia, renal dysfunction, nutritional status, systemic inflammation, or comorbidity, but they do not constitute the primary four-domain biomarker framework examined in this review.

Measuring these biomarkers may support perioperative risk stratification and inform clinical management, including monitoring intensity and optimizing cardiovascular and non-cardiovascular comorbidities. Nevertheless, the evidence supporting routine preoperative measurement and long-term prognostic use in elderly patients with hip fracture remains limited, and the clinical utility of these biomarkers beyond established clinical risk factors has not been fully established [16]. Accordingly, this review synthesizes the available evidence on biomarkers representing myocardial injury, myocardial wall stress, acute systemic inflammation, and chronic immune activation in hip fracture surgery. We hypothesize that elevated concentrations reflect a combination of frailty, cardiovascular stress or injury, and non-cardiac inflammatory pathology, thereby identifying patients at increased risk of postoperative complications and mortality.

Review

Materials and methods

We conducted a structured literature search in PubMed/MEDLINE, Scopus, and Google Scholar to identify studies investigating the prognostic value of BNP/NT-proBNP, cardiac troponins, CRP, and suPAR in older patients undergoing surgery for hip fracture. The search covered publications from January 1988 to 31 December 2025. We performed the final search on 31 December 2025.

The search strategy combined terms referring to hip fracture, femoral neck fracture, intertrochanteric fracture, proximal femoral fracture, older or geriatric patients, surgical treatment, postoperative outcomes, prognosis, mortality, complications, and the four biomarkers of interest. In PubMed, the search terms were combined using the Boolean operators “AND” and “OR.” We used equivalent database-specific combinations in Scopus and Google Scholar. The search also included manual screening of the reference lists of relevant primary studies and review articles in order to identify additional publications not retrieved through the electronic database search.

For this review, geriatric or older patients were defined as individuals aged 65 years or older. We considered studies using a different age threshold eligible when the study population was predominantly geriatric or when data for patients aged 65 years or older were reported separately. Eligible studies included patients with femoral neck, intertrochanteric, or other proximal femoral fractures who underwent operative treatment, including internal fixation, hemiarthroplasty, or total hip arthroplasty.

Studies involving mixed orthopedic populations were eligible only when they presented hip-fracture-specific results separately or when patients with hip fracture constituted the predominant study population. Studies conducted exclusively in patients with non-hip-fracture orthopedic conditions, such as isolated pelvic, vertebral, distal femoral, or lower-limb fractures, were excluded.

We included studies that evaluated at least one of the four primary biomarkers - BNP/NT-proBNP, cardiac troponins, CRP, or suPAR - and investigated at least one clinically relevant outcome. Eligible outcomes included short- or long-term mortality, postoperative cardiovascular complications, major medical complications, functional deterioration, readmission, and length of hospital stay. We considered prospective and retrospective cohort studies, case-control studies, and other observational studies reporting original

clinical data. Systematic reviews and meta-analyses were used for background information and for screening their reference lists, but they were not considered substitutes for original primary studies in the final qualitative synthesis.

We excluded studies that did not involve patients with hip fracture, did not assess any of the four primary biomarkers, did not report a relevant clinical or prognostic outcome, or lacked sufficient information on the study population, biomarker measurement, or outcome assessment. Non-human studies, editorials, commentaries, letters, study protocols, conference abstracts without adequate methodological or outcome data, and duplicate publications were also excluded. Only studies published in English were included because of resource and translation limitations.

After removing duplicate records, titles and abstracts were screened for relevance. We then assessed potentially eligible articles by full-text review. One reviewer performed the initial screening, while two authors independently reviewed all potentially eligible full-text articles. Disagreements were resolved through discussion and consensus; when consensus could not be reached, a senior author was consulted.

The database search identified 1,146 records. Manual screening of reference lists identified an additional 38 records. After removal of 267 duplicate records, 917 unique records remained for title and abstract screening. Of these, 842 records were excluded because they did not concern hip-fracture populations, did not evaluate one of the biomarkers of interest, or did not report a relevant clinical outcome. Seventy-five articles underwent full-text assessment. We excluded 39 articles at this stage, mainly because of an ineligible population, lack of biomarker-specific results, absence of relevant prognostic outcomes, duplicate reporting, or insufficient methodological information. A total of 36 studies were included in the final qualitative synthesis.

We selected the four primary biomarkers a priori based on a predefined pathophysiological framework. BNP and NT-proBNP were selected as markers of myocardial wall stress and hemodynamic overload. Cardiac troponins were selected as markers of myocardial injury or necrosis. We selected CRP as an indicator of acute systemic inflammation, whereas suPAR was selected as a marker of persistent immune activation and chronic inflammatory burden. Together, these biomarkers represent complementary biological processes that may contribute to adverse outcomes following hip fracture surgery.

We considered other laboratory and inflammatory parameters, including hemoglobin, creatinine, albumin, leukocyte count, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, prognostic nutritional indices, and individual cytokines, as supplementary or contextual markers. These variables provided clinical context, evaluated potential confounding, or compared alternative prognostic indicators. They were not considered part of the primary four-domain biomarker framework.

Because this study was a focused narrative review, we did not perform a quantitative meta-analysis. Nevertheless, we considered the methodological characteristics of the included studies when interpreting the findings. These characteristics included study design, sample size, timing of biomarker measurement, assay method, biomarker threshold, outcome definition, follow-up duration, adjustment for potential confounders, and completeness of outcome reporting.

Given the heterogeneity of study designs and clinical outcomes, we assessed the methodological quality and potential risk of bias of the included studies descriptively rather than using a single formal scoring system. We assigned greater evidentiary weight to prospective studies, studies with clearly defined biomarker measurements and clinically relevant endpoints, and studies using appropriate multivariable adjustment. We interpreted findings from small, retrospective, or insufficiently adjusted studies cautiously.

Troponin

Biological Rational

Cardiac troponins I and T are established markers of myocardial injury [9,17-19]. In older adults with hip fractures, troponin elevation may reflect acute myocardial injury, demand ischemia, perioperative myocardial injury, myocardial strain, or previously unrecognized cardiovascular disease. Hip-fracture surgery is performed in a population with substantial cardiovascular comorbidity and limited physiological reserve, making even modest troponin elevations potentially relevant for risk stratification.

High-sensitivity assays have increased the detection of low-level troponin elevations, including elevations occurring in the absence of clinically recognized myocardial infarction. Accordingly, troponin positivity should be interpreted as evidence of myocardial injury rather than as synonymous with acute myocardial infarction [9,19].

Timing of Measurement

Troponin concentrations have been evaluated on admission, preoperatively, within the first 24-72 hours

after surgery, and during later postoperative time points. Preoperative concentrations may reflect pre-existing myocardial injury and baseline cardiovascular vulnerability. In contrast, postoperative elevations may capture the physiological consequences of fracture, anesthesia, blood loss, surgical stress, hypoxia, anemia, and hemodynamic instability [10,17,18,20-22].

Comparisons between studies are therefore limited when sampling times and thresholds differ. Serial assessment may provide more clinically meaningful information than a single measurement, particularly when postoperative changes are considered alongside symptoms, electrocardiographic findings, and clinical events.

Prognostic Evidence

Several studies have reported an association between perioperative troponin elevation and adverse outcomes after hip-fracture surgery [11,17,20,22-24]. In a prospective cohort of 238 patients, elevated troponin I was detected in approximately one-quarter of patients preoperatively and postoperatively. Perioperative troponin elevation was associated with prolonged hospitalization and discharge to long-term care. In contrast, a substantial increase in troponin I was associated with markedly higher overall mortality after adjustment for clinical covariates [21,22].

In a longitudinal cohort of 148 patients, admission and peak troponin T concentrations were independently associated with mortality during long-term follow-up [25]. Higher troponin concentrations were also associated with longer hospital stay and subsequent cardiovascular events [25]. Similarly, in a cohort of 108 patients, troponin T elevation identified patients with higher one-year mortality, although significant differences in short-term mortality were not regularly observed [26].

Talsnes et al. reported that troponin T measured on postoperative day 4 was independently associated with three-month mortality after adjustment for relevant clinical factors [21]. Other hip-fracture cohorts have also reported comparable associations between postoperative troponin elevation and adverse cardiac outcomes [11,20,27,28].

Overall, the available evidence supports troponin elevation as a marker of increased perioperative and long-term risk. The association appears to be more consistent for mortality and general adverse outcomes than for adjudicated myocardial infarction alone (Table *1*).

Study	Study Design	Patients (no)	Age (years)	Troponin type , Assay and reported threshold	Results	Findings
Fisher et al. [22]	Prospective study	238	82	TnI; >0.06 µg/L	Within 72 h: 26.8% (≈64/238) had TnI >0.06 µg/L pre-op.; 29.7% (≈71/238) had TnI >0.06 µg/L within 72 h post-op.	Troponin I was independently associated with prolonged hospitalization and mortality after adjustment for age and other covariates.; TnI >1 µg/L associated with prolonged hospitalization, mortality
Izhaki et al. [25]	Prospective study	148	81	TnT; >0.1 ng/mL	On admission 22.9% (≈34/148) had elevated TnT (>0.1 ng/mL); proportion increased post-operatively	Admission TnT was associated with death; peak TnT >1.0 ng/mL linked to 1-year mortality; risk increases over 8 years
Spurrier et al. [26]	Prospective study	108	84	TnT; >0.03	26.8% (≈29/108) had elevated TnT (threshold >0.03) either pre-op or on postoperative day 1.	Higher 1-year mortality with elevated TnT; no significant difference in hospitalization or short-term mortality
Dawson-Bowling et al. [11]	Prospective study	108	>65	TnT; >0.03 ng/mL	Admission/pre-op: 11.1% (≈12/108) had elevated TnT (>0.03 ng/mL); post-op: 27.7% (≈30/108) had elevated TnT.	Elevated TnT linked to increased hospitalization, complications, higher mortality
Ausset et al. [28]	Prospective study	75	84	TnI; ≥0.08 and ≥0.1 ng/mL	26.7% (≈20/75) had TnI elevation on postoperative days 1–3 (thresholds reported as ≥0.08 and ≥0.1 ng/mL).	TnI elevation associated with major cardiac complications (6.6-fold) and mortality (3.6-fold) in 6 months
Talsnes et al. [21]	Prospective study	302	F: 85 M: 84	TnT; >0.01 µg/L	TnT measured pre-op, within 24 h post-op, and on days 1 and 4; elevated TnT (specifically >0.04 µg/L on day 4) correlated with increased mortality	Male sex, age, ASA score, TnT >0.04 µg/L on day 4 post-op correlated with mortality

TABLE 1: Prognostic Evidence for Cardiac Troponins in Older Adults Undergoing Hip-Fracture Surgery.

TnI: troponin I (cardiac troponin I), TnT: troponin T (cardiac troponin T), ASA: American Society of Anesthesiologists (physical status classification)

Heterogeneity and Confounding

Troponin interpretation is affected by age, pre-existing coronary artery disease, heart failure, renal dysfunction, anemia, hypoxia, sepsis, tachyarrhythmia, and perioperative hemodynamic changes [9,18,19]. Patients with elevated troponin are frequently older, less mobile, more frail, and more likely to have multiple comorbidities [17,29-31]. These factors may explain the observed association with mortality.

A further source of heterogeneity is the use of different troponin assays and thresholds. Conventional and high-sensitivity assays are not directly interchangeable, and the clinical meaning of a given concentration depends on the assay-specific reference range.

Limitations

A considerable proportion of troponin-positive patients do not meet diagnostic criteria for myocardial infarction. Reported rates of adjudicated myocardial infarction among troponin-positive patients have generally been substantially lower than the proportion with biochemical elevation [11,21,22,26,29,32,33]. Troponin elevation may therefore indicate myocardial strain or reduced cardiovascular reserve rather than an acute coronary occlusion.

Evidence specifically considering the incremental value of preoperative troponin testing remains limited.

Moreover, a raised preoperative troponin could prompt additional cardiac investigations or surgical delay. Because early surgery is generally associated with better outcomes after hip fracture, biomarker-guided delay warrants careful evaluation [34].

Clinical Utility

Troponins are widely available and familiar to clinicians. They may help identify patients who need closer perioperative surveillance, postoperative electrocardiographic monitoring, assessment for myocardial injury, and optimization of reversible risk factors [29,32,35]. However, clinicians should not use troponin alone to postpone surgery or diagnose myocardial infarction without clinical, electrocardiographic, and serial biochemical correlation.

B-type natriuretic peptide and N-terminal pro-BNP

Biological Rationale

BNP and NT-proBNP are released in response to myocardial wall stress, volume overload, and increased ventricular pressure [7,8,36,37]. They complement troponins because they primarily reflect hemodynamic stress and cardiac reserve rather than myocardial cell injury [7-9,36,37].

In older adults with hip fractures, elevated natriuretic peptide concentrations may identify occult heart failure, impaired ventricular function, pulmonary hypertension, atrial fibrillation, or limited ability to tolerate surgical and postoperative stress.

Timing of Measurement

BNP and NT-proBNP have been measured before surgery, within the first 24-48 hours after admission or injury, and postoperatively. Preoperative measurements may reflect baseline cardiovascular reserve and pre-existing heart failure. Postoperative values may additionally reflect fluid shifts, anesthesia, blood loss, renal impairment, hypoxia, and surgical stress.

Because natriuretic peptide concentrations may change rapidly during the perioperative period, report the timing of measurement precisely and consider it when comparing results between studies.

Prognostic Evidence

Evidence from hip-fracture and orthopedic populations suggests that elevated BNP or NT-proBNP is associated with postoperative cardiac events, morbidity, and mortality [36-44]. In a prospective orthopedic cohort, preoperative BNP was higher among patients who developed postoperative cardiac events and showed useful, although not definitive, sensitivity and specificity [40]. Preoperative BNP has also been associated with major echocardiographic abnormalities in elderly patients with traumatic hip fractures [43-45].

In a retrospective study of 455 patients undergoing hip-fracture repair, BNP measured within 48 hours of injury was associated with early morbidity, 30-day outcomes, and one- and two-year mortality [43]. Other studies have reported higher postoperative BNP concentrations among patients who died during the perioperative period [44,46].

Preoperative NT-proBNP has also demonstrated prognostic value [36,47]. In a cohort of 1,219 older adults undergoing surgery for hip fracture, NT-proBNP showed a nonlinear association with one-year all-cause mortality. Below an identified inflection point of approximately 1,099 ng/L, increasing NT-proBNP was associated with a progressive increase in mortality risk. In contrast, additional increases above this point were not associated with a statistically significant incremental rise in risk [47].

Collectively, these results indicate that natriuretic peptides may identify patients with limited cardiovascular reserve and increased risk of postoperative complications and mortality. However, variability in study designs, assay types, and thresholds limits the overall evidence, which should be considered when interpreting these associations (Table *2*).

Study	Study Design	Patients (no)	Age (years)	Biomarker and method of examination	Results	Findings
Villacorta et al. [46]	Prospective study	208	73 (65-82)	Pre-op BNP	8.0% cardiac events postop (median BNP higher in those patients); sensitivity 76.0%, specificity 79.0%	BNP independent predictor of cardiac events in orthopaedic surgery
Pili-Floury et al. [45]	Narrative review	75	85 (69-97)	Pre-op and 24h after admission BNP, and major echocardiographic abnormalities identification	Median pre-op BNP higher in patients with major echocardiographic abnormalities identification (527 vs. 119 pg/ml; p<0.0001)	Presence of major echocardiographic abnormalities or BNP ≥285 pg/ml associated with high mortality
Rodseth et al. [41]	Meta-analysis	2,179	69	Post-op BNP to enhance prediction of death and myocardial infarction	Elevated postop BNP strongest predictor at 30 days (OR: 3.7) and at ≥180 days (OR: 2.2)	Adding BNP improves risk stratification for death or myocardial infarction at 30 days and ≥180 days after surgery
Zhang et al. [47]	Prospective study	1,219	80 (72-88)	Pre-op NT-proBNP and 1-year mortality	Nonlinear association between NT-proBNP and mortality	NT-proBNP risk indicator of all-cause mortality
Zhao et al. [44]	Retrospective study	1,051	85 (80-90)	Postop 24h after admission BNP, and APACHE II score with mortality	Mean postop BNP: Death group-744.34; alive group-479.15 pg/ml	BNP and APACHE II score predict perioperative mortality in elderly patients with hip fracture and chronic diseases
Page et al. [43]	Retrospective study	455	82	BNP within 48h after injury, and complications identification	Mean BNP 221 pg/mL	Elevated BNP linked to increased complication risk and mortality at 1 and 2 years post-op

TABLE 2: Prognostic Evidence for BNP and NT-proBNP in Older Adults Undergoing Hip-Fracture Surgery.

BNP: B-type natriuretic peptide, NT-proBNP: N-terminal pro-B-type natriuretic peptide, OR: odds ratio, APACHE II: Acute Physiology and Chronic Health Evaluation II

Heterogeneity and Confounding

BNP and NT-proBNP concentrations are influenced by age, renal function, atrial fibrillation, left ventricular hypertrophy, pulmonary disease, sepsis, and body composition [7,8,36-42]. Concentrations are also generally higher in patients with established heart failure and chronic kidney disease, even in the absence of an acute cardiovascular event.

Differences in assay type, reporting units, thresholds, sampling time, and outcome definitions limit direct comparisons among studies. Evidence derived from vascular or broader non-cardiac surgical populations provides support [37,38,40-42]. Still, it cannot be assumed to apply fully to hip-fracture patients, who have different levels of frailty, surgery timing, and comorbidity.

Limitations

Although natriuretic peptides show a generally consistent prognostic association, few studies have shown that adding them improves discrimination, calibration, risk reclassification, or clinical decision-making beyond usual clinical risk factors [41,48]. The optimal threshold for older adults with hip fractures is still unknown.

Furthermore, elevated BNP or NT-proBNP does not identify a single specific risk mechanism. It may indicate chronic heart failure, acute hemodynamic stress, renal dysfunction, or global physiological vulnerability.

Clinical Utility

BNP and NT-proBNP may help identify patients who would benefit from targeted cardiovascular assessment, fluid-management review, echocardiography when clinically indicated, and enhanced postoperative monitoring. At present, they should be regarded as risk-refinement tools rather than stand-alone tests for determining whether surgery should proceed.

C-reactive protein

Biological Rationale

CRP is an acute-phase reactant that reflects systemic inflammation [49-55]. In hip-fracture patients, elevated CRP may represent the inflammatory response to tissue injury, infection, pre-existing disease, surgical trauma, or a combination of these causes [49,50,53,56-58]. Unlike cardiac troponins and natriuretic peptides, CRP is not specific to cardiovascular pathology.

Timing of Measurement

Preoperative CRP may reflect pre-existing inflammatory burden and the initial response to fracture. The inflammatory response to surgery and tissue injury strongly influences postoperative concentrations [49,50,53,58]. In one prospective study, CRP increased substantially during the first 48-60 hours after surgery and subsequently declined over the following days [53].

Consequently, preoperative and postoperative CRP values should not be interpreted interchangeably. Serial trajectories may be more informative than isolated values, but standardized sampling schedules are not consistently used.

Prognostic Evidence

The prognostic value of CRP in hip-fracture populations is suggestive but inconsistent [4,12,13,43,49,53,56]. In a retrospective cohort of 772 patients, elevated preoperative CRP was independently associated with higher one-year mortality [12]. Fakler et al. reported a stepwise increase in one-year mortality across increasing preoperative CRP categories, with mortality rising from 16% in patients with CRP below 10 mg/L to 40% in those with CRP of at least 40 mg/L [13].

In a smaller prospective cohort, postoperative CRP was higher among patients who developed infections, delirium, cardiovascular complications, and other postoperative complications [53]. However, postoperative CRP was not consistently associated with mortality in all analyses.

Composite inflammatory and nutritional indices may provide additional prognostic information. Higher preoperative CRP/lymphocyte and CRP/albumin ratios were associated with short-term mortality in a retrospective cohort of older adults with hip fractures [56]. These findings suggest that CRP may be more informative when interpreted alongside measures of nutritional status, lymphocyte count, anemia, and other indicators of physiological reserve. This integrated approach underscores the need to move toward a broader synthesis that evaluates how such composite indices can contribute to comprehensive risk assessment in hip-fracture populations (Table *3*).

Study	Study Design	Patients (no)	Age (years)	Method of examination	Results	Findings
Beloosesky et al. [53]	Prospective study	41	81.8 (68–97)	CRP and cytokines post fracture and postop	CRP: Preop 1.51 ± 0.44, 48-60h postop 17.06 ± 1.12, 7d postop 7.34 ± 1.03, 30d postop 3.34 ± 0.88	Postop CRP higher in patients with complications, infections, delirium, cardiovascular complications; no correlation to 6-month mortality
Fakler et al. [13]	Prospective study	209	81 (73-87)	Logistic regression for 1-year mortality	Mortality: Mild CRP (10–39.9 mg/l) 33%, active CRP (≥40 mg/l) 40%, no CRP (<10 mg/l) 16% (p = 0.002)	High preop CRP predicts 1-year mortality but not postop complications
Kim et al. [12]	Retrospective study	772	>65	CRP groups (high vs low) and 1-year mortality	1-year mortality: Overall 14.1%, High CRP 31.8%, Low CRP 12.5%	CRP >10.0 mg/dL preop independently predicts 1-year mortality after hip fracture surgery
Niessen et al. [4]	Retrospective study	782	84	ROC-curves for predictors of POSPOM	AUC for CRP: 0.49, CRP D0 did not improve POSPOM performance (AUC = 0.71)	Age, gender, neutrophil-to-lymphocyte ratio, and CRP not suitable for predicting postop mortality
Balta et al. [56]	Retrospective study	165	83 (75-91)	Association between CRP/CLR/CRP-ALB and survival	CRP/CLR and CRP/ALB higher in mortality group; age, preop Hb, CRP, and CRP/ALB significant predictors	Preop CRP and CRP/ALB ratio crucial in forecasting mortality within 30 days
Chen B, et al. (2023)	Meta-analysis	13 studies (total n=3,767)	Mean age range: 74.3–83.5	Systematic review of prospective/retrospective cohorts	High post-operative CRP was associated with higher mortality.	Elevated CRP levels significantly correlate with increased post-operative mortality risk.
Kaya O, et al. (2024)	Cross-sectional	154	Mean age: 80.4 ± 8.1	Preoperative blood sampling	High CAR (cutoff > 0.38) is a predictor of mortality.	Preoperative CAR is a robust, independent prognostic marker for short-term mortality.

TABLE 3: Prognostic Evidence for CRP and CRP-Derived Indices in Older Adults Undergoing Hip-Fracture Surgery.

CRP: C-reactive protein, ROC: receiver operating characteristic, POSPOM: Preoperative Score to Predict Postoperative Mortality, AUC: area under the curve, CLR: C-reactive protein-to-lymphocyte ratio, CRP-ALB: C-reactive protein-to-albumin ratio, Hb: hemoglobin, CAR: C-reactive protein-to-albumin ratio

Heterogeneity and Confounding

CRP is affected by infection, trauma severity, chronic inflammatory disease, malignancy, obesity, renal dysfunction, and postoperative tissue injury [49-53,55,56,58]. Thresholds vary considerably across studies, and some reports use mg/L whereas others use mg/dL. This increases the risk of misinterpretation and complicates comparisons.

Frailty, delayed presentation, pre-existing infection, malnutrition, and comorbidity burden may also confound the association between CRP and outcomes. In addition, an elevated postoperative CRP may represent an expected surgical response rather than a pathological complication.

Limitations

The ability of CRP alone to predict postoperative mortality is uncertain. Some studies have reported strong associations with mortality, whereas others have found limited discrimination or no improvement in established prediction models [4,12,13,53]. CRP is therefore unlikely to be sufficiently specific as an isolated

prognostic marker.

Evidence supporting high-sensitivity CRP as a marker of chronic low-grade inflammation largely comes from broader cardiovascular and general-population studies. It should not be directly extrapolated to the acute hip-fracture setting [54,55].

Clinical Utility

CRP is inexpensive, routinely available, and potentially useful as an aspect of a broader assessment of infection, inflammatory burden, and physiological vulnerability. Its greatest clinical value may lie in combination with clinical variables and related indices such as CRP/albumin or CRP/lymphocyte ratios. However, CRP should not be used alone to predict postoperative mortality or to determine surgical timing.

Soluble urokinase plasminogen activator receptor

Biological Rationale

suPAR is a circulating marker of immune activation and chronic inflammatory burden [15,57,59]. It is released from several immune and endothelial cell types in response to inflammatory stimuli and may reflect activation of both innate and adaptive immunological pathways [57-61].

Unlike CRP, which responds markedly to acute tissue injury, suPAR may reflect pre-existing vulnerability, chronic disease burden, frailty, and reduced physiological reserve [15,16,60-62]. This distinction may matter for older adults undergoing urgent surgery after hip fracture.

Timing of Measurement

The available hip-fracture evidence primarily concerns biomarker measurement around the time of admission or shortly after injury. The interpretation of suPAR may therefore reflect both chronic immune activation and the systemic response to fracture-related tissue injury.

Serial measurements and standardized sampling schedules have not been sufficiently evaluated. It remains unclear whether changes in suPAR after surgery provide additional prognostic information beyond a single baseline value.

Prognostic Evidence

Evidence specific to hip-fracture patients remains limited. In a regional hip-fracture registry and biobank, higher suPAR quartiles were associated with increased 30-day mortality. Higher CRP and ferritin concentrations and lower transferrin concentrations showed similar associations, suggesting that an amplified inflammatory and nutritional-risk profile may contribute to early mortality [14].

This evidence supports suPAR as a potential marker of global inflammatory vulnerability rather than a biomarker specific to cardiovascular complications. However, the available evidence comes from a limited number of cohorts and requires external validation.

Heterogeneity and Confounding

suPAR concentrations may be influenced by age, chronic kidney disease, infection, malignancy, diabetes, cardiovascular disease, and other chronic inflammatory conditions [15,16,60-62]. These factors are common among older adults with hip fractures and may confound the relationship between suPAR and mortality.

The lack of uniform thresholds and limited information on assay comparability further restrict interpretation of published results.

Limitations

The evidence base for suPAR in hip-fracture surgery is substantially smaller than that for troponins, BNP/NT-proBNP, or CRP. Its incremental value beyond age, frailty, comorbidities, renal function, albumin, CRP, and established clinical risk models still remains unclear.

Moreover, suPAR is a general marker of immune activation and should not be interpreted as a specific indicator of myocardial injury or cardiovascular disease.

Clinical Utility

suPAR is promising as a marker of systemic vulnerability and inflammatory risk, but it is not currently ready for routine clinical implementation in hip-fracture pathways. Prospective multicenter studies should evaluate its potential role using standardized assays, prespecified thresholds, serial sampling, and clinically relevant decision outcomes.

Comparative synthesis and clinical implications

Taken together, the four biomarkers reflect complementary pathophysiological domains relevant to perioperative risk in older adults with hip fractures. Cardiac troponins indicate myocardial injury, BNP and NT-proBNP reflect myocardial wall stress and hemodynamic overload, CRP represents acute systemic inflammation, and suPAR reflects persistent immune activation and chronic inflammatory burden [7-9,15,19,57,58,61]. Because these processes frequently coexist in hip-fracture patients, a multimarker framework may theoretically provide a more comprehensive risk assessment, although this approach has not yet been adequately validated in hip-fracture populations. Table *4* compares the main biological characteristics, timing considerations, prognostic evidence, confounders, limitations, and current clinical readiness of the four biomarkers.

Biomarker	Biological domain	Timing	Outcomes most consistently associated	Hip-fracture-specific evidence	Important confounders	Main limitation	Clinical readiness
Troponins	Myocardial injury	Preoperative and early postoperative	Mortality and cardiac complications	Associated with myocardial injury and short-term mortality	Renal dysfunction, chronic cardiac disease, assay type	Not specific for acute coronary syndrome	Moderate
BNP/NT-proBNP	Myocardial wall stress	Mainly preoperative	Mortality and cardiac complications	Associated with cardiovascular complications and mortality	Renal dysfunction, heart failure, age	Variable thresholds and influence of comorbidities	Moderate
CRP	Acute systemic inflammation	Preoperative and early postoperative	Infection, complications, and mortality	Associated inconsistently with infection, complications, hospitalization, and mortality	Trauma, infection, timing of measurement	Nonspecific inflammatory response	Limited
suPAR	Persistent immune activation	Mainly preoperative	Mortality and major complications	May identify patients with increased systemic vulnerability	Multimorbidity, renal dysfunction, inflammatory burden	Limited evidence and no standardized cut-off	Investigational

TABLE 4: Comparative Clinical and Pathophysiological Profile of the Four Primary Biomarkers in Older Adults Undergoing Hip-Fracture Surgery.

BNP: B-type natriuretic peptide, NT-proBNP: N-terminal pro-B-type natriuretic peptide, CRP: C-reactive protein, and suPAR: soluble urokinase plasminogen activator receptor

The timing of measurement is critical. Preoperative values may reflect baseline cardiovascular reserve, pre-existing myocardial injury, chronic inflammation, and physiological vulnerability. Postoperative values may additionally reflect anesthesia, blood loss, fluid shifts, tissue trauma, hypoxia, and surgical stress [10,20,27,49,53,58]. Therefore, preoperative and postoperative concentrations should not be treated as equivalent, and studies with different sampling schedules should be compared with caution.

A key comparative distinction among these biomarkers is their temporal and situational sensitivity. Preoperative troponin or natriuretic peptide levels may better indicate baseline cardiac reserve or unrecognized pathology, whereas postoperative elevations more directly reflect the acute stress response to surgery, anesthesia, and hemodynamic shifts. In contrast, CRP and suPAR values reflect both acute tissue injury and chronic disease burden, which may limit their specificity in the perioperative setting. Taken together, single-biomarker measurements are unlikely to provide comprehensive risk stratification, particularly when comorbidities and perioperative variables are highly heterogeneous.

The prognostic evidence for cardiac troponins and natriuretic peptides is stronger and more consistent in predicting perioperative cardiovascular risk and mortality, highlighting their value as cardiovascular risk indicators in this population. Nonetheless, several limitations affect the strength and clinical applicability of this evidence. Confounding factors such as renal dysfunction, chronic heart failure, and age may attenuate the predictive performance of these biomarkers, and heterogeneity in assay types, cut-off values, and sampling times across studies complicates direct comparison and generalizability [18,30,36,38,60,62]. For CRP, although its practical utility is supported by ease of measurement and low cost, its lack of specificity and substantial influence from surgical and non-cardiac inflammation limit its discriminatory value as a

prognostic tool. With suPAR, research is further limited by small sample sizes, variability in measurement protocols, and inconsistent threshold definitions, resulting in sparse, heterogeneous evidence that currently precludes robust conclusions about its clinical utility.

Direct comparison of prognostic performance across studies is hampered by methodological heterogeneity, including differences in assay types (for example, varying high-sensitivity versus standard troponin assays), thresholds for positivity (such as the use of different cut-off values for BNP or CRP), timing of measurement (preoperative versus postoperative sampling), and outcome definitions (for instance, all-cause versus cardiac-specific mortality). For example, one study may define postoperative troponin elevation based on a specific numerical threshold, while another may use a relative change or a different reference range, making findings difficult to reconcile. Furthermore, substantial overlap in the clinical correlates of biomarker elevations, such as frailty, renal dysfunction, and comorbidity, complicates determining each biomarker's incremental value. Notably, while associations between elevated biomarker levels and adverse outcomes persist after adjustment for some clinical variables, less evidence substantiates improvements in risk discrimination or changes in clinical management.

Collectively, this comparative analysis suggests that while each biomarker contributes distinct and complementary information, their greatest utility currently lies in refining, rather than replacing, clinical judgment. Troponins and BNP/NT-proBNP may facilitate more targeted perioperative cardiovascular assessment, whereas CRP and suPAR could augment the evaluation of inflammatory and systemic vulnerability. However, clinicians should avoid over-reliance on any single biomarker when making key management decisions. Future research should focus on standardized comparisons, multimarker strategies, and integrating biomarkers with clinical and functional assessments to improve risk stratification and guide perioperative care for hip-fracture patients.

The evidence is strongest for cardiac troponins and BNP/NT-proBNP as markers of perioperative cardiovascular risk and mortality. However, their concentrations are affected by renal dysfunction, chronic heart failure, atrial fibrillation, age, and other comorbidities. CRP is widely available and inexpensive but is nonspecific and strongly influenced by fracture-related and postoperative inflammation. suPAR may provide information regarding chronic inflammatory vulnerability, but evidence in hip-fracture populations remains limited.

Findings from broader non-cardiac surgical or vascular populations support the biological plausibility of these biomarkers but should not be assumed to be directly transferable to hip-fracture patients. Hip-fracture populations are characterized by advanced age, frailty, urgent surgery, high comorbidity burden, functional impairment, and substantial baseline mortality risk.

A key limitation of the current evidence is the uncertainty regarding whether incorporating biomarkers with established clinical variables meaningfully improves prognostic accuracy or alters management for hip-fracture patients. Many clinical predictors-such as age, frailty, cardiovascular disease, renal dysfunction, anemia, cognitive impairment, and surgical factors-already demonstrate substantial prognostic value. However, high-quality studies that demonstrate a significant incremental benefit from adding biomarkers remain scarce. Although some cohort studies have found independent associations between elevated troponin or NT-proBNP levels and adverse outcomes, few have thoroughly evaluated whether biomarkers enhance the predictive performance of multivariable models using rigorous metrics such as discrimination or calibration. Direct comparisons of model performance with and without biomarkers are rarely reported, limiting critical appraisal of their additive value beyond conventional risk factors. This heterogeneity and lack of robust comparative evidence undermine strong recommendations for biomarker use, and raise questions about the cost-effectiveness and practical implications of integrating biomarkers into clinical pathways. Consequently, it remains unclear when and how biomarker results should directly guide management decisions in hip-fracture care. Further research is needed to clarify these limitations and determine whether combining biomarkers with established clinical variables improves patient outcomes.

From a practical standpoint, clinicians should use these biomarkers to refine risk stratification and guide enhanced perioperative monitoring, rather than to dictate independent clinical decisions. Existing guidelines support this approach [32]. For example, the European Society of Cardiology (ESC) and European Society of Anaesthesiology (ESA) recommend that perioperative biomarkers such as troponins and natriuretic peptides inform cardiovascular risk estimation but should not be used as the sole basis for clinical decision-making [63]. Troponins and BNP/NT-proBNP should therefore prompt consideration of focused cardiovascular evaluation and closer hemodynamic surveillance in patients with elevated levels. Similarly, CRP and suPAR may indicate the need for additional assessment of inflammatory or systemic vulnerability, warranting multidisciplinary input or tailored postoperative care. Biomarker results should always be interpreted alongside thorough clinical assessment, and clinicians should avoid using biomarker elevations in isolation to delay surgical intervention, diagnose myocardial infarction, or determine postoperative resource allocation. Clear protocols, informed by published guidelines, should integrate biomarker information with clinical judgment, ensuring management decisions remain evidence-based and patient-centered.

To advance the field, future research should prioritize prospective multicenter trials that use standardized assays and sampling protocols to enable meaningful cohort comparisons and specifically test biomarker-guided interventions against current standard care in randomized controlled settings. Studies should be tasked with reporting clearly defined patient-centered outcomes-such as perioperative morbidity, mortality, functional recovery, and quality of life-and analyzing whether biomarker-informed strategies result in measurable improvements over traditional approaches. Furthermore, research should explicitly evaluate the added predictive value of multi-biomarker models when integrated with existing clinical risk tools, using robust statistical assessments of discrimination, reclassification, and calibration. Future studies should establish and validate clinically actionable biomarker thresholds and systematically assess implementation factors, including cost-effectiveness, reporting timeliness, and the impact on perioperative decision-making and resource allocation in hip-fracture care.

Conclusions

The findings of this review highlight the potential value of incorporating prognostic biomarkers into the care pathway for older adults with hip fractures. Biomarker assessment may facilitate the identification of patients at increased risk who could benefit from enhanced surveillance, individualized perioperative optimization, and targeted postoperative interventions. However, translating biomarker data into clinical decisions, such as determining the timing of surgery or allocating postoperative resources, requires rigorous evaluation of predictive performance and pragmatic studies that address implementation, cost-effectiveness, and impact on outcomes. Emerging biomarkers and composite indices, including the CRP/lymphocyte ratio, CRP/albumin ratio, and suPAR, show promise for improving risk stratification and informing management strategies.

In addition to biomarkers, demographic and clinical variables such as age, sex, comorbidity burden, and routine laboratory measures (including hemoglobin, leukocyte count, albumin, creatinine, and parathyroid hormone) remain significant determinants of prognosis following hip fracture. Future research should elucidate the biological mechanisms linking inflammation to adverse postoperative outcomes and validate the incremental value of biomarkers in large, multicenter cohorts. Studies that examine combinations of inflammatory markers (such as CRP, suPAR, and selected cytokines), assess serial biomarker trajectories, and incorporate biochemical data into established clinical risk models and decision-support tools may enhance individualized prognostication and support more precise perioperative care.

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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