

Lactate dehydrogenase (LDH) and C-reactive protein (CRP) as a potential prognostic factor in metastatic bone disease (MBD) of proximal femur based on Harris hip score (HHS) underwent cephalomedullary nailing and bipolar hemiarthroplasty

I Gede Eka Wiratnaya^{1*}, Sri Mahadhana², Andrew Sutheno²,
Leonardus William Kuswara², Nyoman Gede Grenata Nanda Ustriyana²

ABSTRACT

Introduction: Pathological fractures in the proximal femur are common, often caused by metastatic bone disease (MBD). Treatment options include resection, reconstruction, or fixation. This study explores the prognostic value of C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels in the Harris Hip Score (HHS) for patients with pathological fractures due to MBD.

Methods: Forty patients with pathological fractures were divided into cephalomedullary nail (CM) and bipolar hemiarthroplasty (BHA) groups. CRP and LDH levels were measured. The correlation between CRP, LDH, and HHS was assessed using Pearson's and Spearman's correlation. Multiple linear regression was used to predict HHS from CRP and LDH.

Results: The mean age of patients was 59 years, with 95% having poor HHS. CRP and LDH levels were significantly correlated with HHS (CRP: $r = -0.47$, $p = 0.002$; LDH: $r = 0.59$, $p < 0.001$). Multiple linear regression showed CRP and LDH as predictors of HHS ($R^2 = 0.36$, $p < 0.001$), with the fitted model: "HHS = 95.76 - 0.317*(CRP) - 0.232*(LDH)". Elevated CRP and LDH levels indicate ongoing inflammation and cellular stress, potentially hindering recovery and impacting HHS. CRP's association with adverse prognoses in various cancers is highlighted. LDH's role in cellular stress and metabolism is emphasized. Combining CRP and LDH evaluations enhances the prognostic assessment of MBD and HHS outcomes.

Conclusion: CRP and LDH levels significantly correlate with HHS in patients with MBD-related pathological fractures. Higher levels of CRP and LDH indicate worse functional outcomes. Evaluating these biomarkers aids in assessing disease severity and treatment effectiveness, assisting in informed clinical decisions. This study sheds light on the prognostic potential of CRP and LDH in the context of metastatic bone disease and its impact on hip function and recovery.

Keywords: CRP, LDH, Metastatic Bone Disease, Pathological Fracture, Proximal Femur.

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¹Consultant at Department of Orthopedic and Traumatology, Faculty of Medicine, Universitas Udayana, Denpasar, Bali

²Resident at Department of Orthopedic and Traumatology, Faculty of Medicine, Universitas Udayana, Denpasar, Bali

*Corresponding to:

I Gede Eka Wiratnaya; Department of Orthopedics and Traumatology, Faculty of Medicine, Universitas Udayana—General Hospital Prof. IGNG Ngoerah Denpasar, Indonesia.

wiratnayaigedeeka@gmail.com

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INTRODUCTION

Pathological fractures occur frequently in the proximal femur.¹ Treatment of the metastatic disease of the proximal femur consists of tumor resection and reconstruction, or fixation.² Pathological fractures often result from metastatic bone disease (MBD). One study showed that approximately 4-7% of patients with MBD had pathological fractures. MBD itself is a bone cancer that originates from the spread of cancer from other organs.³⁻⁶ Metastatic bone disease is a significant source of illness and death.⁷ The extensive

interactions between tumor and bone cells drive the occurrence of metastatic bone disease, disrupting normal bone metabolism.⁴ In a study analyzing cases of femoral metastases, fractures occurred in 33 of a total of 428 patients (7.7%). Of all cases of fractures obtained, fractures in the proximal part of the femur are 5 times more frequent than fractures in the shaft.⁸

The Harris hip score (HHS) is a joint-specific score that is completed by both the clinician and the patient and consists of 10 items covering domains of pain, function, functional activities, deformity, and hip

range of motion. The HHS has been used to evaluate functional outcomes after per trochanteric hip fracture and intracapsular fracture neck of the femur. Construct validity of an outcome instrument shows that all the domains of the instrument are indeed measuring what they are supposed to measure. Responsiveness of an outcome instrument is defined as the sensitivity of the instrument to detect clinically relevant change over some time. Validity and responsiveness are context-specific terms and the evidence applies to a particular condition and specific intervention only.

The HHS is a valid and reliable outcome instrument to assess functional outcomes after total hip replacement.⁹

LDH is found in almost every cell in the body, converting lactate to pyruvate in the glycolysis process. When a cell dies, it becomes extracellular and can be detected in the blood. Thus, dead cell increase reflects a proportional number of tissue injuries and could be caused by various diseases one of which is cancer.^{10,11} A worse prognosis related to the high serum LDH level was found statistically significant in the study. Another significant outcome in that study that can be used to predict poor prognosis is CRP levels. CRP is a common acute-phase serum protein and is used as a marker of inflammation associated with tissue damage.¹²⁻¹⁴ CRP has been proven to be strongly associated with various cancers, exhibiting diagnostic or prognostic value.¹⁵ They conclude that CRP is statistically significant in predicting the survival rate in patients with bone tumors, patients with pre-operative CRP levels > 1.0 mg/dL had a lower survival rate than patients with CRP levels < 1 mg/dL ($p = 0.026$).¹⁵ A study also concluded that the increase in CRP levels 12 hours after surgery for Bipolar Hemiarthroplasty was significantly higher compared to Cephalomedullary Nailing.¹⁶ In a recent study, pathological CRP was also found to be a negative independent prognostic factor in patients with long bone metastases, along with types of primary tumors.¹⁷ In addition, several studies discuss prognostic factors regarding LDH and CRP simultaneously. In an analysis conducted in one study showed that high levels of LDH and CRP were associated with the worst prognosis.¹⁸ This study aims to identify the role of CRP and LDH as prognostic factors of HHS in patients with pathological fracture of metastatic bone disease to assess the functional outcomes after CM nailing and long-stem hemiarthroplasty bipolar.

METHODS

This study is a cross-sectional study conducted in Prof. IGNG Ngerah General Hospital from August 2022 until January 2023. The inclusion criteria in this study are patients who suffered pathological fractures and underwent surgery. Patients

with incomplete data were excluded from this study. Then, the patients were divided into the cephalomedullary nail group ($n = 20$) and the bipolar hemiarthroplasty group ($n = 20$) based on the surgery undergone by the patient. Harris Hip Score, C-reactive protein (CRP), and lactate dehydrogenase (LDH) levels in serum were measured from all patients and collected from the hospital registry. The correlation between each predictor variable and Harris Hip Score was assessed using Pearson's correlation if the data is normally distributed. Spearman's correlation was used instead if the normality assumption was not met. Multivariate analysis using multiple linear regression was used to calculate HHS from both CRP and LDH values. A p -value below 0.05 was considered statistically significant.

RESULTS

In this study, a sample of 40 patients was

obtained from August 2019 to August 2022. The mean age of the patients was 59 years. There were 22 male patients and 18 female patients, each had an average age of 60.5 years and 58.4 years respectively. The overwhelming majority of patients in this study (95%) have a poor Harris Hip Score (**Table 1**).

Table 2 describes the baseline characteristics between the two groups of intervention (cephalomedullary nail and bipolar hemiarthroplasty). The cephalomedullary nail group had a higher female patient proportion, compared with the bipolar hemiarthroplasty group which had a higher male patient proportion. The bipolar hemiarthroplasty group had a significantly higher Harris Hip Score compared with the cephalomedullary nail group ($p = 0.001$) (**Figure 1**).

Bivariate analysis was performed between the predictor variables (CRP and LDH) and HHS (**Table 3**). Both predictor variables have a significant inverse

Table 1. Distribution of the characteristics of the research subjects

Variable	N (%)	Mean ± SD
Age		59 ± 10
Gender		
Male	22 (55%)	
Female	18 (45%)	
Harris Hip Score		
Excellent (90-100)	0 (0%)	
Good (80-89)	0 (0%)	49.9 ± 10.3
Fair (70-79)	2 (5%)	
Poor (<70)	38 (95%)	
Intervention		
Cephalomedullary nail	20 (50%)	
Bipolar hemiarthroplasty	20 (50%)	

Table 2. Subgroup analysis of baseline characteristics of the subjects

Variable	Cephalomedullary Nail	Bipolar Hemiarthroplasty
Age (mean ± SD, years)	58.1 ± 9.8	60 ± 10.1
Gender (n, %)		
Male	8 (40%)	14 (70%)
Female	12 (60%)	6 (30%)
Harris Hip Score (mean ± STD)	44.9 ± 6.4	54.9 ± 11.2
Harris Hip Score (n, %)		
Excellent (90-100)	0 (0%)	0 (0%)
Good (80-89)	0 (0%)	0 (0%)
Fair (70-79)	0 (0%)	2 (10%)
Poor (<70)	20 (100%)	18 (90%)

correlation with HHS. The correlations between CRP and HHS ($r = -0.47$; $p = 0.002$), and LDH and HHS ($r = 0.59$, $p < 0.001$) are notable.

Further multivariate analysis was performed as shown in **Table 4**. Multiple linear regression was used to test if CRP and LDH significantly predicted HHS. These variables statistically significantly predicted HHS, explaining 36% of the variability of HHS in this study ($R^2 = 0.36$; $F(2, 37) = 10.21$, $p < 0.001$). The fitted regression model was: "Harris Hip Score = $95.76 - 0.317 \times (\text{CRP in mg/dL}) - 0.232 \times (\text{LDH in units/L})$ "

DISCUSSION

The limited investigation of the prognostic value of biomarkers such as CRP and LDH in MBD is in contrast to their extensive utilization, cost-effectiveness, and established standardization. CRP, a non-specific measure of inflammation, has the potential to demonstrate increased levels of malignancies. The verification of its involvement as a prognostic biomarker for survival has been demonstrated in several types of adult malignancies. It is worth noting that an increased level of CRP has been associated with adverse prognoses in various types of cancers, such as renal

cell carcinoma, gastric cancer, lung cancer, breast cancer, and bone sarcoma.¹⁹

LDH serves as a pyridine-linked enzyme that plays a crucial role in the conversion of pyruvate to lactate during the process of glycolysis, as well as the oxidation of L-lactate to pyruvate in the setting of gluconeogenesis. Due to the increased use of glucose observed in cancer cells, hematological malignancies and certain solid tumors affecting adults have been found to exhibit elevated levels of LDH.²⁰ Moreover, it has been observed that LDH exhibits extensive expression in numerous human tissues and is produced as a response to tissue injury in a range of disorders. Previous studies have established associations between the serum concentration of LDH and several factors such as tumor load, growth patterns, survival rates, and invasive potential. Several investigations have suggested that serum LDH could serve as a possible prognostic predictor in bone tumors. Nevertheless, there are still inconsistent results. The current body of literature lacks sufficient evaluation of the potential of serum LDH levels as a prognostic indicator for survival in patients diagnosed with MBD. Moreover, the reported data on this matter thus far exhibit significant variation and do not provide clear evidence. Within the domain of soft-tissue sarcomas, CRP has consistently retained its importance as a prognostic biomarker.²¹

Elevated levels of CRP and lactate dehydrogenase LDH not only serve as markers of inflammation and cellular stress but also signify a persistent state of physiological imbalance that can potentially impede the recovery process and compromise the outcomes assessed by the HHS. The Harris Hip Score, a comprehensive tool widely used to evaluate hip function and post-operative recovery, becomes an important indicator of an individual's ability to regain optimal mobility and quality of life following hip interventions.²²

CRP, as a sensitive marker of systemic inflammation, provides valuable insights into the body's immune response. Elevated CRP levels often correlate with ongoing inflammation, indicating that the body's defense mechanisms are still actively

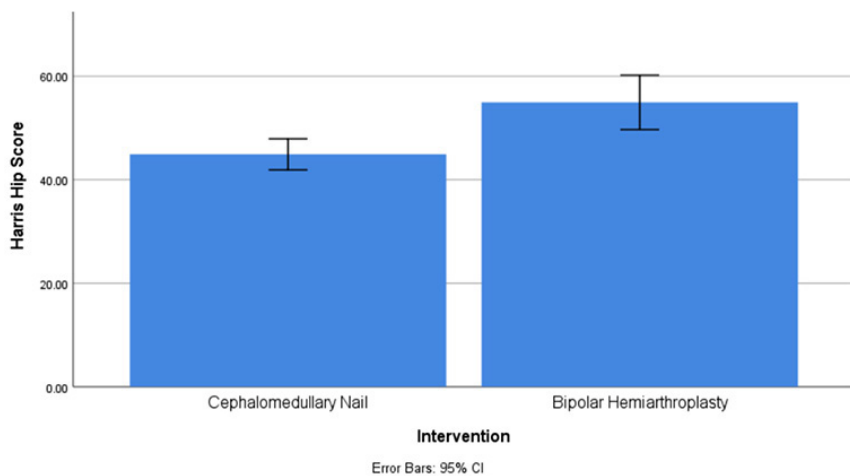


Figure 1. Harris Hip Score between both types of intervention

Table 3. Correlation matrix between Harris Hip Score and the predictor variables

Variables	HHS
CRP	
r	-0.47
p	0.002
LDH	
r	-0.59
p	< 0.001

CRP = C-reactive protein, LDH = lactate dehydrogenase, r = Pearson's correlation, p = P-value

Table 4. Multiple linear regression model of predictors of Harris Hip Score (HHS)

Variables	B	SE	t	P
(Constant)	95.76	13.12	7.298	0.000
CRP	-0.317	1.208	-0.262	0.004
LDH	-0.232	0.084	-2.762	0.009

CRP = C-reactive protein; LDH = lactate dehydrogenase; SE = standard error; t = t-value; p = p-value; $R^2 = 0.36$; $p < 0.001$

engaged. In the context of hip surgery or interventions, sustained inflammation can interfere with the healing process. It can hinder the formation of new tissue, delay the repair of damaged structures, and contribute to persistent pain and discomfort. These factors collectively impede the restoration of normal hip function, leading to a poorer Harris Hip Score. Inflammatory processes might also lead to the accumulation of fluid and tissue swelling, limiting joint mobility and causing discomfort that affects the patient's ability to perform the activities assessed by the HHS.²³

Similarly, heightened LDH levels reflect ongoing cellular stress and metabolic dysregulation. Elevated LDH suggests that cells are experiencing increased demand for energy and resources, potentially due to the ongoing tissue repair and remodeling processes post-surgery. When cellular stress persists, it can divert resources away from the intricate healing mechanisms required for optimal hip recovery. This diversion can result in delayed tissue regeneration, compromised structural integrity, and less efficient functional restoration, all of which contribute to a lower Harris Hip Score.²⁴

The combination of high CRP and LDH levels indicates that the body's response to surgery or intervention remains imbalanced and possibly exaggerated. This prolonged state of inflammation and cellular stress impedes the body's ability to efficiently rebuild and remodel the hip joint. Consequently, patients with elevated CRP and LDH levels may experience more pain, reduced range of motion, and slower progress in rehabilitation exercises—all factors that negatively impact the Harris Hip Score.^{25,26}

The integration of LDH and CRP evaluations into the prognostic assessment of MBD, in conjunction with the examination of the benefits associated with Bipolar Hemiarthroplasty, establishes a comprehensive framework for clinical decision-making and the development of individualized treatment approaches. Additional investigation and rigorous clinical trials are necessary to substantiate and build upon these findings, ultimately augmenting the management and provision of care for those afflicted with Metastatic Bone Disease.²⁷

According to the surgical data, it was shown that proximal femoral nail anti-rotation (PFNA) exhibited a higher level of effectiveness compared to Bipolar Hemiarthroplasty (BHA) in older patients. However, no significant differences were noted in terms of functional outcomes. It is worth mentioning that PFNA offers some advantages, such as a small incision size, easy implant insertion, and reliable stability. However, it may have limitations in promoting immediate weight-bearing. On the other hand, BHA presents certain benefits regarding the duration of the operation and the ability to bear weight early on, rendering it a feasible alternative surgical method for older patients.²⁷

In a theoretical context, it is postulated that persons who undergo hemiarthroplasty as a result of a pathological fracture of the proximal femur, particularly induced by MBD, may experience a comparatively more advantageous functional recovery in the initial months following the surgical intervention, as compared to those who receive treatment with PFNA. However, several additional characteristics have a major impact on functional outcomes, including age, gender, pre-fracture health state, social reliance, and post-operative complications. In a study conducted by Luo et al.²⁷ at the one-year follow-up assessment, there was no statistically significant difference found between the two groups regarding the Harris Hip Score. The mean Harris Hip Score was 81.3 ± 8.2 for the PFNA group and 79.1 ± 10.2 for the hemiarthroplasty group, with a p-value of 0.240. The lack of a statistically significant difference in HHS between the PFNA and hemiarthroplasty groups at one year could be influenced by a combination of factors such as well-matched sample characteristics, disease progression, surgical technique, post-operative care, and the potential impact of loss to follow-up. In a separate investigation conducted by Tang et al.²⁸ it was found that there was no statistically significant disparity in the Harris Hip Score between the PFNA and hemiarthroplasty groups after a three-year follow-up (83.0 ± 12.2 for PFNA and 80.2 ± 10.9 for hemiarthroplasty, $P = 0.09$). However, a notable distinction arose in the percentage of favorable functional outcomes, with 90.2% for PFNA and 79.6% for hemiarthroplasty. In a prospective

randomized study conducted by Özkayın et al.²⁹, a comparison was made between the use of PFNA and hemiarthroplasty for the treatment of intertrochanteric fractures in elderly patients. The study found that at the three-month follow-up, the average Harris Hip Score was 45.24 for the PFNA group and 63.38 for the hemiarthroplasty group, indicating a significant difference between the two treatment approaches. Hemiarthroplasty involves replacing the femoral head with a prosthetic implant, which could provide immediate relief from pain and improved joint stability shortly after the surgery. This may lead to a faster initial recovery and better early functional outcomes compared to the PFNA, which focuses on internal fixation. provides an artificial joint surface that can potentially offer more stability and immediate weight-bearing, enabling patients to put more weight on the affected leg sooner after the procedure. This early mobility and reduced pain may contribute to improved functional scores in the early recovery phase. Similarly, the Harris Hip Score averages at the twelve-month mark were found to be 68.44 for the group treated with PFNA and 75.95 for the group treated with hemiarthroplasty, indicating a notable difference between the two treatment approaches. The results of this study indicate that there is a possibility of achieving better functional outcomes in the intermediate to long term for intertrochanteric fractures treated with hemiarthroplasty. However, it is necessary to conduct other studies with longer follow-up periods to validate this conclusion.²⁷⁻³¹

CONCLUSION

This study proved a statistically significant correlation between CRP and LDH levels with the Harris Hip Score HHS in the context of MBD affecting the Proximal Femur. The observed negative correlation, where higher CRP and LDH levels are associated with lower HHS scores, suggests that elevated CRP and LDH levels may serve as indicative markers of greater disease severity and diminished functional outcomes. The evaluation of LDH and CRP concentrations has become a valuable predictive instrument in the setting of MBD impacting

the Proximal Femur. This research investigation centers on individuals who have undergone Cephalomedullary Nailing and Bipolar Hemiarthroplasty procedures, emphasizing the importance of biomarkers in forecasting patient outcomes. The results emphasize the significance of LDH and CRP in assessing the severity of disease and evaluating the effectiveness of treatment, hence assisting healthcare professionals in making well-informed judgments.

CONFLICT OF INTEREST

None

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ETHICAL CONSIDERATION

This research was approved by the Research Ethics Commission Unit of the Faculty of Medicine, Universitas Udayana with the letter number: 1745/UN14.2.2.VII.14/LT/2022.

AUTHOR CONTRIBUTION

All authors contributed equally to this study.

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