Indonesian Journal of Global Health Research
Volume 8 Number 1, February 2026
e-ISSN 2715-1972; p-ISSN 2714-9749
http://jurnal.globalhealthsciencegroup.com/index.php/IJGHR

ASSOCIATION OF LACTATE DEHYDROGENASE AND PREDICTIVE BIOMARKERS IN PRIMARY LUNG AND BREAST TUMORS WITH METASTATIC BONE DISEASE

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ABSTRACT
Metastatic Bone Disease (MBD) is one of the most aggressive forms of tumor spread, reshaping the tumor microenvironment into a hypoxic and acidic state that enhances lactate dehydrogenase (LDH) activity. Primary lung and breast tumors possess distinct predictive biomarkers, EGFR and HER2, which drive the Warburg effect and further elevate LDH levels. MBD often leads to skeletal-related events that impair quality of life and require prompt, comprehensive management. This study aimed to examine the the association between LDH levels and EGFR/HER2 expression, and evaluate LDH's potential as an early, efficient indicator for clinical decision-making in MBD patients. Method: A cross-sectional study was conducted through medical record reviews at Dr. Moewardi General Hospital, Surakarta. Samples included patients with primary lung and breast tumors diagnosed with MBD from 2023–2024, selected using total sampling. Serum LDH, EGFR, and HER2 data were then retrieved from the electronic medical record. Associations between LDH and EGFR/HER2 were analyzed using binary logistic regression. LDH showed a positive but statistically non-significant association with EGFR mutation status in lung cancer patients with MBD (OR=0.999, 95% CI=0.994–1.004, p=0.713) and with HER2 status in breast cancer patients with MBD (OR=1.750, 95% CI=0.084–36.287, p=0.718). LDH was positively associated with EGFR and HER2 expression in MBD patients, though the associations were not statistically significant.

Keywords: biomarkers; lactate dehydrogenase; metastatic bone disease; primary lung tumor; primary breast tumor

How to cite (in APA style)
Yunus, M. A. S., Saputra, R. D., & Idulhaq, M. (2026). Association of Lactate Dehydrogenase and Predictive Biomarkers in Primary Lung and Breast Tumors with Metastatic Bone Disease. *Indonesian Journal of Global Health Research*, *8*(1), 745–752. https://doi.org/10.37287/ijghr.v8i1.672.

INTRODUCTION

The Annual Report to the Nation on the Status of Cancer (ARN) 2021 reported an increase in newly diagnosed cancer cases in the United States, from 1.4 million in 2001 to 1.7 million in 2016. Among these, approximately 0.8% were Metastatic Bone Disease (MBD) (Christ et al., 2023), a secondary malignancy arising from the spread of primary tumors to the bone. MBD represents a late-stage cancer complication resulting from hematogenous or lymphatic dissemination and ranks as the third most aggressive metastatic site after lung and liver metastases, leading to Skeletal-Related Events (SREs). These complications include pain, spinal cord compression, and pathological fractures, which significantly impair quality of life (QoL) and survival (Dalkir et al., 2024; Morris & LiBrizzi, 2021).

SREs also impose a substantial economic burden on both patients and healthcare systems, being associated with higher rates of hospitalization, invasive procedures, and outpatient care visits. In the United States, SREs are estimated to account for approximately 17% of total cancer-related healthcare costs. MBD is a complex, multidisciplinary disease requiring an integrated approach to management. Optimal treatment aims to prevent fractures, preserve mobility, minimize pain, and

improve QoL. However, the lack of an integrated musculoskeletal care team often results in uncoordinated management and less optimal clinical outcomes. Patients with pathological fractures secondary to MBD present unique perioperative and intraoperative considerations, underscoring the critical need for coordinated multidisciplinary management (Morris & LiBrizzi, 2021).

At the cellular level, MBD alters cancer cell metabolism and the Tumor Microenvironment (TME). Under hypoxic or semi-hypoxic conditions, tumor cells increase lactate production through glucose and glutamine metabolism. Lactate export, mediated by Lactate Dehydrogenase (LDH), helps maintain intracellular pH homeostasis but acidifies the TME, thereby promoting angiogenesis, metastasis, and immune evasion. LDH catalyzes the conversion of pyruvate to lactate during anaerobic glycolysis, a process known as the Warburg effect, which sustains cancer cell proliferation. Elevated serum LDH levels are correlated with tumor aggressiveness, resistance to therapy, and poor prognosis. Although LDH represents a promising prognostic biomarker, it lacks specificity, necessitating the use of additional molecular markers for accurate cancer characterization (Pérez-Tomás & Pérez-Guillén, 2020).

Lung and breast tumors—two major primary tumors responsible for MBD—are often driven by mutations and overexpression of Epidermal Growth Factor Receptor (EGFR) and Human Epidermal Growth Factor Receptor 2 (HER2), respectively. These biomarkers play vital roles in tumor progression and patient survival. According to Feng et al. (2022), EGFR and HER2 dysregulation enhances glycolysis and the Warburg effect, subsequently elevating LDH activity. However, molecular testing for EGFR and HER2 remains costly and time-consuming, posing challenges for timely decision-making in musculoskeletal oncology teams managing advanced MBD cases. Therefore, investigating the associations of LDH levels, EGFR mutation status, and HER2 expression offers potential for developing a simpler prognostic indicator. This study aimed to analyze the association between serum LDH levels and EGFR mutation status in primary lung tumor patients, as well as HER2 status in primary breast tumor patients with MBD in Surakarta, to explore their potential as efficient alternative biomarkers for prognosis assessment, appropriate procedure selection, and rapid clinical decision-making, as no previous research has examined these associations in this population.

METHOD

This study was a cross-sectional study conducted at Dr. Moewardi General Hospital (RSDM), Surakarta. Data collection was carried out in June 2025 using secondary data from electronic medical records of patients diagnosed with Metastatic Bone Disease (MBD) between 2023 and 2024. The study population included patients with MBD in Surakarta, while the accessible population consisted of patients diagnosed and treated at RSDM during the study period. Adult patients (≥18 years) with histopathological and/or imaging-confirmed MBD who had complete records of serum LDH levels measured within one month after primary tumor confirmation and before definitive therapy were included. Patients were also required to have EGFR mutation status (for primary lung tumor cases) or HER2 expression results (for primary breast tumor cases) recorded in their medical files. Exclusion criteria included systemic diseases known to affect LDH levels, double primary malignancies, and incomplete or inconsistent medical records. Sampling was performed using a total sampling method, and the minimum required sample size of 13 was determined using OpenEpi version 3 www.openepi.com (Dean et al., 2013) with an estimated population frequency of 0.8% from Christ et al. (2023). The research protocol was approved by the Research Ethics Committee of Dr. Moewardi General Hospital (No. S932108003-7850).

The independent variable in this study was serum LDH level, categorized as normal (240‑480 U/L) or high (≥480 U/L). The dependent variables were EGFR mutation status (mutant or wild type) and HER2 expression (positive or negative). Statistical analysis was performed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA). Descriptive data were presented as means

with standard deviations for continuous variables and as proportions for categorical variables. Associations of LDH levels and EGFR/HER2 status were analyzed using binary logistic regression. A p-value of <0.05 was considered statistically significant, and 95% confidence intervals were reported.

RESULT

A total of 26 subjects participated in this study, consisting of 13 patients with primary lung tumors with MBD, and 13 patients with primary breast tumors with MBD.

Table 1.
Subject Characteristics (n=26)

Characteristics	f	%	Mean±SD
Sex			
- Male	9	34.6	
- Female	17	65.4	
Age (years)			57.9±2.5
Primary Tumor			
- Lung	13	50.0	
- Breast	13	50.0	
Pathological Fracture			
- Femur	14	53.8	
- Humerus	9	34.6	
- Pelvic	3	11.5	
Procedure			
- Biopsy	8	30.8	
- Marginal excision	3	11.5	
- Wide excision	7	26.9	
- Radical excision	8	30.8	
LDH levels (U/L)*			420.6±55.1
- High (≥480)	8	30.8	
- Normal (240–480)	18		

*LDH levels cutoff were based on Pelizzari et al. (2019).

Table 1 presents the general characteristics of the study participants. The majority of MBD patients at RSDM were female (17 patients; 65.4%), with a mean age of 57.9 ± 2.5 years. Most respondents experienced pathological fractures of the femur (14 patients; 53.8%) and had undergone definitive treatment (18 patients; 69.2%). The majority of participants had normal LDH levels (18 patients; 69.2%), with a mean value of 420.6 ± 55.1 U/L.

Table 2.
Subject Characteristics based on Primary Tumor (n=26)

Characteristics	Primary Lung Tumor (n=13)			Primary Breast Tumor (n=13)			p-value[a]
	f	%	Mean±SD	f	%	Mean±SD	
Sex							0.006*
- Male	8	61.5		1	7.7		
- Female	5	38.5		12	92.3		
Age (years)			62.2±2.9			53.6±3.7	0.072
Pathological Fracture							0.110
- Femur	5	38.5		9	69.2		
- Humerus	5	38.5		4	30.8		
- Pelvic	3	23.1		-	-		
Procedure							0.101
- Biopsy	6	46.2		2	15.4		
- Marginal excision	2	15.4		1	7.7		
- Wide excision	3	23.1		4	30.8		
- Radical excision	2	15.4		6	46.2		
LDH levels (U/L)**							
- High (≥480)	6	46.2	523.5±95.9	2	15.4	317.6±41.3	0.101
- Normal (240–480)	7	53.8		11	84.6		
EGFR							

- Mutant	1	7.7		-			-
- Wild-type	12	92.3		-			
HER2***			-				
- Positive (+2 to +3)	-			5	38.5	1.08±0.4	-
- Negative (0 to +1)	-			8	61.5		

[a] p-values for differences in categorical variables were derived using the Chi-Square test. p-values for continuous variables were derived from Independent T-test for normally distributed data, and from the Mann-Whitney U test for non-normally distributed data.
*Statistically significant (p<0.05).
*LDH levels cutoff were based on Pelizzari et al. (2019).
***HER2 levels cutoff were based on American Society of Clinical Oncology (ASCO) / College of American Pathologists (CAP) guideline (Wróbel et al., 2025).

Table 2 shows the characteristics of respondents based on the primary tumor site. Patients with primary lung tumors with MBD were predominantly male (8 patients; 61.5%), whereas those with primary breast tumors with MBD were mostly female (12 patients; 92.3%), showing a significant difference (p = 0.006). The mean age of patients with primary lung tumors with MBD was higher than that of patients with primary breast tumors and MBD (62.2 ± 2.9 vs. 53.6 ± 3.7 years), although the difference was not statistically significant (p = 0.072). Most respondents experienced pathological fractures in the extremities (p = 0.110), and the majority had received definitive treatment (p = 0.101), both among patients with primary lung and breast tumors with MBD. Elevated LDH levels were more common among patients with primary lung tumors with MBD (6 patients; 46.2%), whereas most patients with primary breast tumors with MBD had normal LDH levels (11 patients; 84.6%), though this difference was not statistically significant (p = 0.101). The mean LDH level was higher in patients with primary lung tumors with MBD compared to those with primary breast tumors with MBD (523.5 ± 95.9 vs. 317.6 ± 41.3 U/L). Most patients with primary lung tumors with MBD had wild-type EGFR (12 patients; 92.3%), while most patients with primary breast tumors with MBD were HER2-negative (8 patients; 61.5%), with a mean value of 1.08 ± 0.4.

Table 3.
Association of LDH and EGFR Mutation Status in Primary Lung Tumor Patients with MBD

Variable	EGFR				Beta	OR	95%CI	p-value[a]
	Mutant		Wild-type					
	f	%	f	%				
LDH					0.001	0.999	0.994-	0.713
- High	1	100.0	5	41.7			1.004	
- Normal	-	-	7	58.3				

[a] p-values for associative analyses were obtained from Binary Logistic Regression.
Table 3 presents the association between LDH levels and EGFR status in patients with primary lung tumors with MBD. Patients with primary lung tumors with MBD who had elevated LDH levels were 0.999 times more likely to have EGFR mutation status. However, this association was not statistically significant (p = 0.713).

Table 4.
Association of LDH and HER2 Status in Primary Breast Tumor Patients with MBD

Variable	HER2				Beta	OR	95%CI	p-value[a]
	Positive		Negative					
	f	%	f	%				
LDH*					0.560	1.750	0.084-	0.718
- High	1	20.0	1	12.5			36.287	
- Normal	4	80.0	7	87.5				

[a] p-values for associative analyses were obtained from Binary Logistic Regression.
Table 4 shows the association between LDH levels and HER2 status in patients with primary breast tumors with MBD. Patients with primary breast tumors and MBD who had elevated LDH levels were 1.750 times more likely to have positive HER2 status. However, this association was also not statistically significant (p = 0.718).

DISCUSSION

The majority of patients with primary lung and breast tumors with MBD at RSDM were female (17 patients; 65.4%), with a mean age of 57.9 ± 2.5 years, and most experienced pathological fractures in the femur (14 patients; 53.8%). This finding is consistent with previous research by Armando et al. (2023) in Surabaya, which reported that 34 out of 51 MBD patients at Dr. Soetomo Hospital were female, with the peak incidence observed in patients aged 56–60 years (29.4%). Armando et al. (2023) also found that lung and breast tumors were among the top five primary tumors that metastasized to bone, with the femur ranking as the second most common site of pathological fractures. Estrogen facilitates metastasis of primary tumors to bone by creating a supportive TME and activating estrogen receptor alpha, which explains the higher incidence of MBD in women (Oprea-Lager et al., 2021). Increasing age can lead to genomic instability, telomere shortening, proteostasis disruption, mitochondrial dysfunction, cellular senescence, and stem cell exhaustion, making individuals more susceptible to genetic errors and mutations that increase the risk of cancer and metastasis (Terracina et al., 2023). In both lung adenocarcinoma and breast cancer, exosomal miR-214 is highly expressed and promotes osteoclast differentiation, playing a critical role in the development of MBD (Zhang & Wu, 2021). The pattern of bone metastasis correlates with the distribution of red bone marrow, making vertebrae, femur, pelvis, and ribs more vulnerable to metastasis (Onken et al., 2019).

Patients with primary lung tumors with MBD were predominantly male (8 patients; 61.5%), whereas those with primary breast tumors with MBD were mostly female (12 patients; 92.3%), showing a significant difference ($p = 0.006$). This finding aligns with the study by Astrayana & Astawa (2024) in Bali, which reported that 12 out of 21 patients with primary lung tumors and MBD were male. Primary lung tumors with MBD are more common in males due to epithelial–mesenchymal transition (EMT) triggered by activation of AKT and MEK-ERK signaling pathways. These activations result from EGFR mutations and amplifications caused by epigenetic alterations that inactivate tumor suppressor genes, often induced by high carcinogen exposure from smoking habits (Astrayana & Astawa, 2024). Similarly, Armando et al. (2023) in Surabaya reported that most patients with breast cancer and MBD were female (66.67%). Breast tumors with MBD are more prevalent among females because estrogen and ER expression help modulate the TME to favor cancer cell progression (Cheng et al., 2024).

Patients with primary lung tumors with MBD who had elevated LDH levels were 0.999 times more likely to have EGFR mutations. However, this finding was not statistically significant ($p = 0.713$). This result is consistent with Azuma et al. (2014) in Japan, who reported a significant association between PD-L1 expression and EGFR mutation status in lung cancer patients (OR = 25.4; 95% CI = 2.9–47.9; $p = 0.027$). PD-L1 is a protein expressed on the surface of cancer cells that enables immune evasion by suppressing T-cell activity (Lin et al., 2024). Both PD-L1 and LDH levels are elevated in immunosuppressive and hypoxic TMEs (Han et al., 2020). The discrepancy between the current study and Azuma et al. (2014) may be attributed to differences in study design. Azuma et al. (2014) conducted a retrospective cohort using resected tumor tissue (in vitro) and applied multivariate analysis controlling for tumor stage, age, sex, smoking history, and histopathology. The lack of a significant association between LDH and EGFR mutation status in this study might be due to uncontrolled confounding variables in the statistical analysis. In patients with primary lung tumors harboring EGFR mutations, increased LDH levels indicate enhanced anaerobic glycolytic metabolism, characteristic of the Warburg effect, where cancer cells preferentially utilize anaerobic glycolysis despite adequate oxygen availability. EGFR mutations promote cell proliferation and pro-survival signaling, heightening metabolic demands and accelerating glucose conversion to lactate via LDH. Elevated LDH reflects intratumoral hypoxia, which subsequently activates the transcription factor HIF-1α. HIF-1α activation not only upregulates LDH-A expression but also supports angiogenesis, tissue invasion, and metastatic dissemination, including to the bone (Chan et al., 2021; Todd & Johnson, 2020).

Patients with primary breast tumors with MBD who had elevated LDH levels were 1.750 times more likely to be HER2-positive, although this association was not statistically significant (p = 0.718). These findings are similar to Masruroh et al. (2019) in Surabaya, who reported a significant relationship between LDH levels in pleural fluid and HER2 positivity in breast cancer patients with pleural metastases (OR = 42.0; 95% CI = 4.351–405.402; p = 0.004). The discrepancy between this study and Masruroh et al. (2019) may be explained by differences in sample characteristics and LDH measurement sites. The non-significant association between LDH and HER2 in this study could be due to uncontrolled confounding variables in the analysis. In HER2-positive breast cancer patients with MBD, elevated LDH levels reflect an aggressive and hypoxic tumor metabolic state. HER2-positive breast cancers exhibit enhanced glycolytic and glutaminolytic metabolism, leading to increased lactate production and LDH-A activation, which confer proliferative and invasive advantages to cancer cells. This hypoxic environment upregulates HIF-1α expression, which transcriptionally regulates glycolytic genes, including LDH-A, and promotes angiogenesis and bone invasion (Huang et al., 2023; Zhi et al., 2024). This study provides a comprehensive analysis of the clinical characteristics, primary tumor profiles, and metabolic markers associated with MBD in lung and breast cancer patients. Further research using primary data with a prospective multicenter design and multivariate statistical modeling is needed to validate these findings and elucidate the underlying causal relationships among LDH, EGFR mutation, and HER2 status.

CONCLUSION

LDH was positively associated with EGFR and HER2 expression in patients with metastatic bone disease (MBD), although these associations were not statistically significant in this study. This finding suggests the potential role of LDH as a predictive biomarker in patients with primary lung and breast tumors presenting with MBD. Further analysis of the relationship between LDH levels, molecular characteristics, and clinical outcomes may contribute to improved decision-making in diagnostic evaluation, prognosis, and therapeutic strategies for primary lung and breast tumors patients with MBD.

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