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An Overview of LDH, Calcium, and CRP Levels in Bone Metastasis Due to Primary Cancer: Breast, Lung, Thyroid, Prostate, and Liver Cancer at Prof. Dr. I.G.N.G. Ngoerah Hospital in January-March 2024

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ABSTRACT

Background: Bone metastasis is a disease that occurs when cancer cells began to spread from their original site to bone tissue. These cancer cells are able to reach bones due to osteomimicry, the ability to express genetic profiles that resemble the target location of metastasis. The most common primary cancers that cause bone metastases included lung cancer, breast cancer, and prostate cancer. Based on previous research, some factors that may influenced the likelihood of bone metastasis are such as: LDH, calcium, and CRP levels.
Method: The purpose of this study is to give an overview of the distribution of LDH levels, calcium levels and CRP levels in bone metastasis due to primary cancer: breast, lung, thyroid, prostate, and liver cancer at Prof. Dr. I.G.N.G Ngoerah General Hospital in January-March 2024. This study used a quantitative descriptive epidemiological study with a cross-sectional design. The study's dependent variable was bone metastasis, while the independent variable was primary cancer of: breast, lung, thyroid, prostate, and liver cancer, LDH level, calcium level, and CRP level. A total of 53 medical records were taken out of 186 patients with bone metastasis. The research lasted for 3 months, starting in January 2024 and ending in March 2024.
Results: This research found an abnormality in LDH and CRP levels on bone metastasis due to breast cancer; abnormality in LDH, calcium, and CRP levels on bone metastasis due to lung cancer abnormality in CRP levels on bone metastasis due to thyroid cancer; abnormality in LDH levels on bone metastasis due to prostate cancer; and abnormality in LDH and calcium levels on bone metastasis due to liver cancer.
Conclusion: In this study, it can be concluded that there are mostly abnormalities in LDH and CRP, but mostly normal calcium levels in patients with bone metastasis due to primary cancer: breast, lung, thyroid, prostate, and liver cancer at Prof. Dr. I.G.N.G Ngoerah General Hospital in January-March 2024.

***Key words*:** Bone metastasis, LDH, calcium, CRP, breast cancer, lung cancer, thyroid cancer, prostate cancer, and liver cancer

INTRODUCTION

Bone metastasis is a disease that occurs when cancer cells begin to spread from their original site to bone tissue. These cancer cells are able to reach the bone due to their osteomimicry ability, by expressing a genetic profile that resembles the target site of metastasis[18]. Bone metastasis usually spreads to bones that contain a lot of myeloid tissue and trabecular bone such as ribs, vertebrae and pelvic bones[9]. Trabecular bone has a higher likelihood of metastasis due to more frequent vascularization and bone remodeling, while myeloid tissue has a higher likelihood of metastasis due to high vascularization. Bone metastasis is divided into osteolytic and osteoblastic based on bone resorption and formation type[23]. According to some previous studies the most common primary cancers that caused bone metastasis included lung cancer (18.05%) followed by liver cancer (6.63%), thyroid cancer (4%), breast cancer (3.66%) and prostate cancer (4.61%)[29]. Bone metastasis can have few factors, several factors that are suspected to influence the occurrence of bone metastasis are LDH, calcium, and CRP[10,12,24].

LDH is an enzyme that catalyzes the conversion of lactate to pyruvate. This conversion is an essential step in cell's energy productions. When cells die, LDH is released and flows into the blood, which was a response to cell damage, this causes LDH levels to increase in the bloodstream or other body fluids. Thus LDH can be used as a general marker of cell / tissue damage. Changes in LDH levels in cells can be associated with changes in tissue metabolic function[10].

Calcium is an essential molecule involved in many biochemical processes throughout the body, playing a critical role in proper heart function, bone structural integrity, muscle contraction and act as an enzymatic signal in biochemical pathways. The ubiquitous second messenger Ca2+ is an important regulator of cell migration[25].

C-reactive protein (CRP) is a plasma protein that can increase up to 1000-fold during inflammation. Conditions that can cause changes in CRP concentrations are such as: infections, traumatic injuries, surgery, burns, inflammatory conditions, and advanced cancer.[24]

This study aimed in finding the distribution of LDH, calcium, and CRP levels in patients with bone metastasis due to to primary cancer: breast, lung, thyroid, prostate, and liver cancer at Prof. Dr. I.G.N.G Ngoerah General Hospital in January-March 2024.

MATERIALS & METHODS

This research used a quantitative descriptive epidemiological study with a cross-sectional design to observe the distribution of LDH, calcium, and CRP levels in patients with bone metastasis due to primary cancer: breast, lung, thyroid, prostate, and liver cancer at Prof. Dr. I.G.N.G Ngoerah General Hospital in January-March 2024. This research used retrospective chart review to collect 53 medical records from 186 bone patients of which meet the study exclusion and inclusion criteria.

Research inclusion criteria: patients with bone metastasis due to to primary cancer: breast, lung, thyroid, prostate, and liver cancer at Prof. Dr. I.G.N.G Ngoerah General Hospital in January-March 2024. The study exclusion criteria are incomplete medical record data, that lacks either LDH, calcium, or CRP levels.

The independent variables in this study are primary cancer of: breast, lung, thyroid, prostate, liver cancer, and LDH, calcium, and CRP levels. While the dependent variable is bone metastasis.

In this research, after getting the ethical clearance and permission to do retrospective chart review at Prof. Dr. I.G.N.G Ngoerah General Hospital in January-March 2024. The obtained data then would be collected and processed on excel.

This research has received ethical clearance from the Research Ethics Commission of the Faculty of Medicine, Udayana University,

with number 1095/UN14.2.2.VII.14/LT/2024.

RESULTS

This study was a cross-sectional study with 53 patients with bone metastasis due to primary cancer: breast, lung, thyroid, prostate, and liver cancer at Prof. Dr. I.G.N.G Ngoerah General Hospital in January-March 2024 that met the research criteria as research subjects.

Table 1: Bone metastasis disease based on the primary cancer

Primary Cancer	Number (n)	Percentage (%)
Breast	27	45.8%
Lung	13	27.08%
Thyroid	6	12.5%
Prostate	4	8.3%
Liver	3	6.25%

Table 2: LDH, calcium, CRP levels on Primary Breast Cancer

Variable	Mean	Min	Max	±SD
LDH	509 U/L	94 U/L	1473 U/L	±427.4
Calcium	8.94 mg/dL	6.7 mg/dL	11.5 mg/dL	±1.44
CRP	50.18 mg/L	7.3 mg/L	160.2 mg/L	±44.2

Normal LDH levels are 125-220 U/L, normal CRP levels are below 5 mg, while normal calcium levels are 8.8-10.2 mg/dL. Table 2 shows that the average LDH levels in patients with primary breast cancer are high, the average calcium levels are normal, and the average CRP levels are high.

Table 3: LDH, calcium, CRP levels on Primary Lung Cancer

Variable	Mean	Min	Max	±SD
LDH	510.6 U/L	254 U/L	784 U/L	±155.91
Calcium	8.1 mg/dL	6. 3 mg/dL	15.5 mg/dL	±2.35
CRP	26.07 mg/L	0 mg/L	214.6 mg/L	±59.64

Table 3 shows that the average LDH levels in patients with primary lung cancer are high, the average calcium levels are low, and the average CRP levels are high.

Table 4: LDH, calcium, CRP levels on Primary Thyroid Cancer

Variable	Mean	Min	Max	±SD
LDH	144 U/L	117 U/L	177 U/L	±20.6
Calcium	8.83 mg/dL	7.8 mg/dL	9.9 mg/dL	±0.84
CRP	15.86 mg/L	6.1 mg/L	32.6 mg/L	±11.26

Table 4 shows that the average LDH levels in patients with primary thyroid cancer are high, the average calcium levels are low, and the average CRP levels are high.

Table 5: LDH, calcium, CRP levels on Primary Prostate Cancer

Variable	Mean	Min	Max	±SD
LDH	387 U/L	239 U/L	560 U/L	±152.34
Calcium	10.1 mg/dL	7.9 mg/dL	12.5 mg/dL	±2.08
CRP	0 mg/L	0 mg/L	0 mg/L	±0

Table 5 shows that the average LDH levels in patients with primary prostate cancer are high, the average calcium levels are normal, and the average CRP levels are normal.

Table 6: LDH, calcium, CRP levels on Primary Liver Cancer

Variable	Mean	Min	Max	±SD
LDH	99 U/L	91 U/L	107 U/L	±8
Calcium	8.3 mg/dL	7.5 mg/dL	9.9 mg/dL	±1.38
CRP	0 mg/L	0 mg/L	0 mg/L	±0

Table 6 shows that the average LDH levels in patients with primary liver cancer are low, the average calcium levels are low, and the average CRP levels are normal.

DISCUSSION

In the study that was conducted at Prof. Dr. I.G.N.G Ngoerah, about the overall distribution of LDH, calcium, and CRP levels in bone metastatic disease based on primary cancer, it was found that based on it's primary cancer, namely primary cancer

originating from the breast had 27 patients (45.8%), followed by lung cancer that had 13 patients (27.08%%), thyroid cancer had 6 patients (12.5%), prostate cancer had 4 patients (8.3%), and liver cancer had 3 patients (6.25%). Compared with the overall distribution of bone metastatic disease based on primary cancer in the SEER database of 113,317 patients, lung cancer came in 44.69%, prostate cancer in 5.69%, liver cancer in 4.42%, breast cancer in 3.73% and thyroid cancer in 0.77%3. This study also found high LDH levels in 35 patients (72.9%), low calcium levels in 31 patients (64.5%), and high CRP levels in patients (58.3%). These results are in line with statements of lung cancer[27], prostate cancer[22], breast cancer[17], thyroid cancer[13], and of liver cancer[29], which may prove that abnormalities in LDH levels may influence the occurrence of metastasis, especially bone metastasis[1]

High LDH levels are caused by glycolysis that occurs in bone metastases, the main regulator of the glycolytic response is the transcription factor of hypoxia-inducible factor-1α (HIF1α)58. This factor mediates a pleiotropic response to hypoxic stress by inducing survival genes, including glucose transporters, which increase glycolysis and resistance to extracellular acidosis in adaptation to conditions in early pre-malignant tumors and in the evolution of invasive primary cancers[5]. The association of abnormal CRP levels with the occurrence of bone metastases has also been described in studies[21] in lung cancer, prostate cancer[22], breast cancer[15], thyroid cancer[28], and in liver cancer[16]. High CRP levels can be an indicator of bone metastatic disease[6]. When trauma or inflammation occurs in a tissue and the injury continues, an inflammatory mediator (such as IL-6 and IL-1β) would signal hepatocytes to continue to synthesize acute phase proteins, so there will be a measurable increase in pCRP levels.

Elevated pCRP levels indicate pCRP levles getting reduced and converted to mCRP, and any condition that limits mCRP production will result in decreased natural defense responses. Higher pCRP levels in blood reflect the persistence and severity of tissue damage associated with metastatic cancer[11]. Other studies have also suggested that abnormal calcium levels may be an indicator of bone metastatic disease, as in a study[11] that states that osteoblastic bone metastases can cause hypocalcemia due to excessive calcium uptake (hungry bone syndrome). Hungry bone syndrome occurs in the postoperative period after parathyroidectomy for primary hyperparathyroidism or secondary to total thyroidectomy for thyrotoxicosis, and can also occur in cases of metastatic prostate cancer. Parathyroid hormone is released from parathyroid principal cells when the calcium-sensing receptor (CaSR) registers low calcium levels and thus initiates a cascade of reactions leading to bone resorption and bone formation, to increase calcium levels. There were statistically significant changes in bone markers with all formation markers increasing (osteocalcin, calcitonin, and c-terminal peptide) and resorption markers decreasing (TRAP-5b) in post parathyroidectomy. During this process, a shift in bone metabolism from resorption to net formation causes an influx of minerals into the bone with reduced blood calcium and phosphate levels[4].

In the primary cancers that caused bone metastasis, The distribution of LDH levels in breast cancer shows an average of high LDH levels, an average of normal calcium levels, and an average of high CRP levels. The distribution of the average LDH levels in patients with primary lung cancer is that they are of on a higher level, the average calcium levels is low, and the average CRP levels is high. Compared with several studies where it was found that metastatic breast and lung cancer tends to have higher LDH levels. In [11] different studies[17] such as; a study conducted by Medical News Today it was found that metastatic breast cancer tends to have higher calcium levels[19], in 242 patients in the Malwa area it was found that metastatic breast

cancer tends to have higher CRP levels[15].

The distribution of average LDH levels in patients with primary thyroid cancer is that they are of on a higher level, the average calcium levels is low, and the average CRP levels is high. Compared with several studies conducted such as; in a 2021 study of metastatic thyroid cancer patients, high LDH levels were found[13], in a study of metastatic thyroid cancer patients, at a cancer center in 2013, calcium levels tend to be low[8], in a study of several thyroid diseases, high CRP levels were found[2].

The distribution of average LDH levels in patients with primary prostate cancer is that of on a higher level, the average calcium levels is normal, and the average CRP levels is normal. Compared with several studies conducted such as; in studies based on PubMed, Embase, Web of Science, and libraries and studies before January 2020 on patients with metastatic prostate cancer found high LDH levels[26], in studies on metastatic prostate cancer with the use of bone resorption inhibitors[3], low calcium levels were found, in a 2021 study on metastatic prostate cancer found high CRP levels[20].

The distribution of average LDH levels in patients with primary liver cancer is low, the average calcium level is low, and the average CRP level is normal. Compared with several studies conducted such as; in a 2016 study on metastatic liver cancer that founds high LDH levels[7], in a 2022 study on liver disease found low calcium levels[14], in a 2023 study on liver cancer which found high CRP levels[16].

CONCLUSION

It can be concluded that in this study there is mostly abnormal distribution in LDH and CRP, but mostly normal calcium levels in patients with bone metastasis due to primary cancer: breast, lung, thyroid, prostate, and liver cancer.

SUGGESTION

Building on the discussion and conclusions of this study, it is recommended that future research explore the relationship of other bone metastasis factors and variables with bone metastasis.

Declaration by Authors

Ethical Approval: Approved by the Research Ethics Commission of the Faculty of Medicine, Udayana University with number 1095/UN14.2.2.VII.14/LT/2024.

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