Original Article

OPEN ACCESS

Liver Function Indicators Before and After Detection of Hepatic Metastases in Patients with Breast Cancer: A Retrospective Analysis Over Time

Biswajit Pradhan [1], Snigdharani Choudhury [2], Satyajit Behera [3], Jyotiranjan Mohapatra *[4], Diptish Kumar Sahoo [5], Sashibhushan Dash [6]

[1]Department of Biochemistry, A. H. Post-graduate Institute of Cancer, Cuttack, Odisha, India.
[2]Department of Microbiology, A. H. Post-graduate Institute of Cancer, Cuttack, Odisha, India.
[3]Department of General Surgery, Dharanidhar Medical College and Hospital, Keonjhar, Odisha.
[4]Department of General Surgery, Shri Jagannath Medical College and Hospital, Puri, Odisha, India.
[5]Department of Orthopedics, Shri Jagannath Medical College and Hospital, Puri, Odisha, India.
[6]Scientist C, Multidisciplinary Research Unit, Pandit Raghunath Murmu Medical College and Hospital, Baripada, Mayurbhanj, Odisha, India.

*Corresponding Author: Dr. Jyotiranjan Mohapatra; *drjrm.mkcg@gmail.com*

Received: 15 January 2025; **Revised:** 21 February 2025; **Accepted:** 09 March 2025; **Published:** 20 March 2025

Abstract

Background: Hepatic metastases represent a significant clinical challenge in breast cancer management, underscoring the importance of identifying predictive factors to optimize patient care. As the longitudinal patterns of liver function protein levels surrounding hepatic metastasis development remain poorly characterized, this study prospectively analyzed protein level trajectories over an 18-month period, spanning six months prior to and twelve months following metastasis diagnosis. ***Methods:*** This retrospective cohort study examined 104 patients with breast cancer-derived hepatic metastases, who received treatment at A.H. Post-Graduate Institute of Cancer, Cuttack, between 2022 and 2024. Data were retrospectively extracted from patient medical records. ***Results:*** Six months preceding the diagnosis of hepatic metastases, statistically significant deviations from established reference intervals were observed in hepatic function biomarkers. Specifically, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), and alkaline phosphatase (ALP) exhibited elevations ($p<0.001$), while albumin levels demonstrated a concomitant decrease ($p<0.001$). At the time of metastatic diagnosis, further statistically significant increases in AST, GGT, and LDH were noted relative to the six-month pre-diagnosis levels ($p<0.001$). These hepatic function indicator changes were independent of patient or tumor-specific parameters. Notably, increased AST and decreased albumin at the time of diagnosis were associated with reduced overall survival. ***Conclusion:*** Evaluation of hepatic function protein levels is warranted to determine their clinical utility as biomarkers for the early identification of liver metastasis in breast cancer patients. Implementation of such screening protocols, in conjunction with advanced therapeutic interventions, may positively impact patient survival.

Keywords: ***Breast Cancer, Hepatic Metastases, Liver Function Indicators, Retrospective Analysis.***

Introduction

Breast cancer remains the leading malignancy in women, comprising 30% of all female cancers and ranking second in cancer-related mortality after lung cancer [1]. It is the primary cause of cancer death among women globally [2]. While therapeutic advancements have enhanced overall prognosis, 20-30% of breast cancer patients develop metastatic disease [3-5]. The rising incidence of metastasis significantly diminishes patient survival, with a reduction in the 5-year survival rate from 80% to 23% upon metastatic progression [6-8].

Metastatic dissemination significantly impacts patient survival, emphasizing the necessity of early detection to facilitate timely therapeutic intervention and improve clinical outcomes. Hepatic metastasis, a common complication of breast cancer, is associated with a poor prognosis, characterized by a 5-year survival rate of 8.5% [9,10]. However, surgical resection of liver metastases has demonstrated survival benefits [11,12], underscoring the critical role of prompt diagnosis.

Hepatic dysfunction is a common finding in breast cancer liver metastasis (BCLM), with previous studies reporting a 92% prevalence and strong positive correlations observed between gamma-glutamyl transferase (GGT) and alkaline phosphatase (AP) levels [13]. Stage III cancer and c-erbB-2-positivity have been identified as independent predictors of liver metastasis [14]. Compared to patients without hepatic involvement, those with BCLM demonstrate significantly elevated serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), GGT, AP, lactate dehydrogenase (LDH), and cancer antigen 15-3 [10,11]. Therefore, the integrated analysis of tumor markers and liver

function tests may offer a valuable screening modality for BCLM. Additionally, serum albumin and total bilirubin levels have been shown to possess prognostic utility in predicting survival in patients with liver metastases [14,15].

This retrospective study sought to evaluate the predictive capacity of serum liver function-associated protein levels, as determined by standard screening assays, for the development of breast cancer liver metastases (BCLM) prior to clinical or radiological identification. Uniquely within our institution, this research investigated these protein levels across a defined 18-month temporal window, encompassing six months preceding and twelve months following BCLM diagnosis, thereby extending beyond traditional post-diagnostic analyses.

Methods

Patient selection

This retrospective analysis utilized prospectively collected data to investigate liver function protein levels in breast cancer patients aged 20 to 80 years, treated at A.H. Post-Graduate Institute of Cancer, Cuttack, between January 2022 and December 2024. Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase (AP), albumin, and bilirubin were extracted at three distinct time points: six months prior to, at the time of, and twelve months following the diagnosis of breast cancer liver metastases (BCLM).

Normal ranges of liver function proteins as used in the University of Vienna.AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase, AP, alkaline phosphatise (Table 1).

Table 1: Normal ranges of liver function proteins

Liver Enzyme	Normal range
ASTU/L	<35
ALTU/L	<35
GGTU/L	<40
LDHU/L	<250
APU/L	<105
Albumin g/L	35–52
Bilirubin mg/dL	<1.2

Clinical and pathological data were retrospectively extracted, encompassing tumor molecular subtype (luminal A, luminal B, HER2-positive, triple-negative), histological type (invasive ductal carcinoma, invasive lobular carcinoma), and grade (I-III). Additionally, demographic and lifestyle factors, including age, body mass index (BMI), smoking history, alcohol consumption, and exposure to potentially hepatotoxic medications, were recorded. Institutional standard reference ranges were utilized for data normalization (Table 1).

Statistical analysis

This study evaluated the prevalence of elevated liver function parameters six months prior to breast cancer liver metastases (BCLM) diagnosis. A chi-square test was utilized to compare observed percentages of values exceeding upper normal limits against expected rates, based on the assumption of a normal distribution and corresponding percentile cutoffs. Temporal changes in liver function parameters were assessed using Mann-Whitney U-tests, comparing values at BCLM diagnosis and 12 months post-diagnosis to baseline levels. Due to non-normality, this non-parametric approach was selected. To mitigate type I errors from multiple comparisons (n=21), a Bonferroni correction was applied, adjusting the significance threshold to $\alpha = 0.0023$. Exploratory analyses, employing Pearson or Spearman correlation coefficients for continuous or ordinal variables, and Mann-Whitney U-tests for nominal variables, were conducted to investigate potential associations between liver function parameters and other factors, utilizing a significance level of $\alpha = 0.05$.

Results

A retrospective cohort analysis was conducted on 286 patients with metastatic breast cancer. Initial screening identified 82 patients with breast cancer liver metastases (BCLM), excluding 204 patients without hepatic involvement. Within the BCLM cohort, 54 patients (66.85%) exhibited complete serum liver protein data at two time points: six months prior to and at the time of BCLM diagnosis. Longitudinal laboratory data, encompassing BCLM diagnosis and twelve months post-diagnosis, were available for 58 patients (70.73%). A subset of 31 patients (37.80%) possessed complete data across all three time points. Two patients were excluded due to data insufficiency. Analysis of potential risk factors for elevated liver function proteins revealed that 77 patients (93.90%) were receiving at least one medication with documented hepatotoxic potential, with a mean of one such medication per patient.

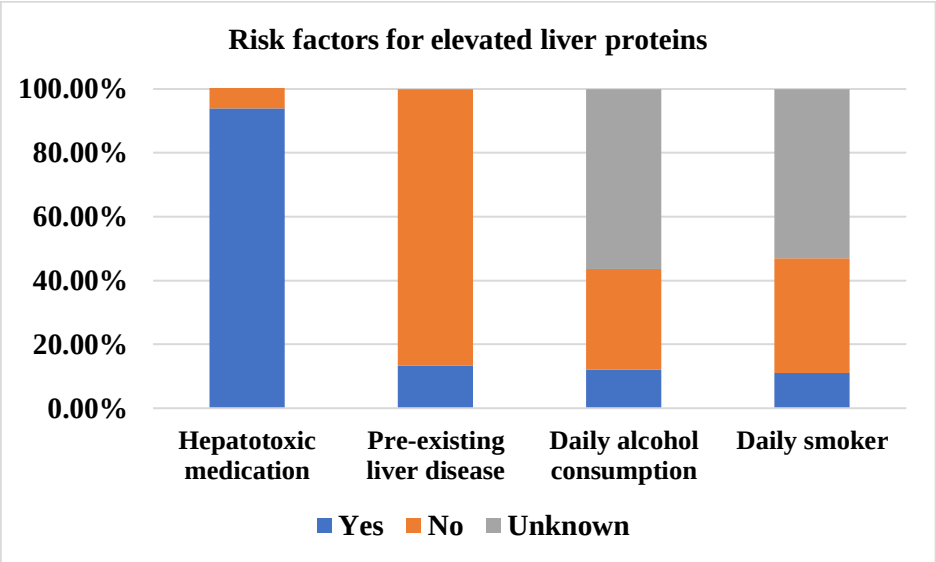

Fig1. Risk factors for elevated liver proteins.

A significant proportion of the patient cohort (93.90%) were exposed to at least one potentially hepatotoxic medication, with a mean of 4.3 such agents administered concurrently. Pre-existing hepatic comorbidities were identified in 13.41% of patients, including a spectrum of conditions such as hepatic cirrhosis, hepatomegaly, hepatitis, cholangitis, steatohepatitis, cholestasis, hepatic tissue injury, and Hodgkin's lymphoma. Lifestyle risk factors included daily alcohol consumption in 12% of patients and daily tobacco use in 11%.

Tumor characteristics

The study cohort comprised patients with a mean age of 52.5 years (range: 25–80 years) at initial breast cancer diagnosis, with a mean latency of 5 years to the subsequent detection of breast cancer liver metastases (BCLM). Immunohistochemical subtyping of metastatic tissue, performed on 93.90% (n=77) of patients, demonstrated the following distribution: luminal A (15.58%), luminal B (31.16%), HER-2 positive (32.46%), and triple-negative (20.77%). Subtype data were not available for 6.10% (n=5) of patients. Histological confirmation of the primary tumor type was achieved in 95.12% (n=78) of cases, revealing a predominance of invasive ductal carcinoma (80.51%, n=63), followed by invasive lobular carcinoma (18.18%, n=14) and mixed carcinoma (2.43%, n=2).

In this cohort, 80.4% (n=66) of patients exhibited extrahepatic metastatic dissemination. The most common sites of extrahepatic involvement were bone (77.27%, n=51), followed by lung (46.96%, n=31), brain (16.66%, n=11), skin (13.63%, n=9), peritoneum (4.54%, n=3), and ovary (1.51%, n=1). Isolated hepatic metastases were observed in 19.51% (n=16) of patients. Multiorgan metastases, excluding the liver, were present in 37.80% (n=31) of the study population. The median maximum diameter of intrahepatic lesions was 21 mm. Solitary hepatic metastases were documented in 14.63% (n=12) of patients. The distribution of intrahepatic lesion multiplicity was as follows: 2–4 metastases in 34.14% (n=28), 5–8 metastases in 10.97% (n=9), and a miliary pattern in 40.24% (n=33).

Liver function indicator values

In a cohort of 55 patients subsequently diagnosed with breast cancer liver metastases (BCLM), 27.77% (n=15) demonstrated elevated aspartate aminotransferase (AST) levels six months prior to diagnosis, a statistically significant increase compared to an expected 5% prevalence ($p<0.001$). The median AST level within this subset was 25.9 U/L (mean 34.1 U/L). At the time of BCLM diagnosis, AST levels were significantly elevated relative to the six-month pre-diagnosis values (median 36.1 U/L, mean 65.5 U/L; $p<0.001$). Twelve months post-diagnosis, while AST levels remained elevated compared to the six-month pre-diagnosis values (median 34.9 U/L, mean 77.6 U/L), the observed difference did not maintain statistical significance after correction for multiple comparisons ($p < 0.05$) (Fig 2).

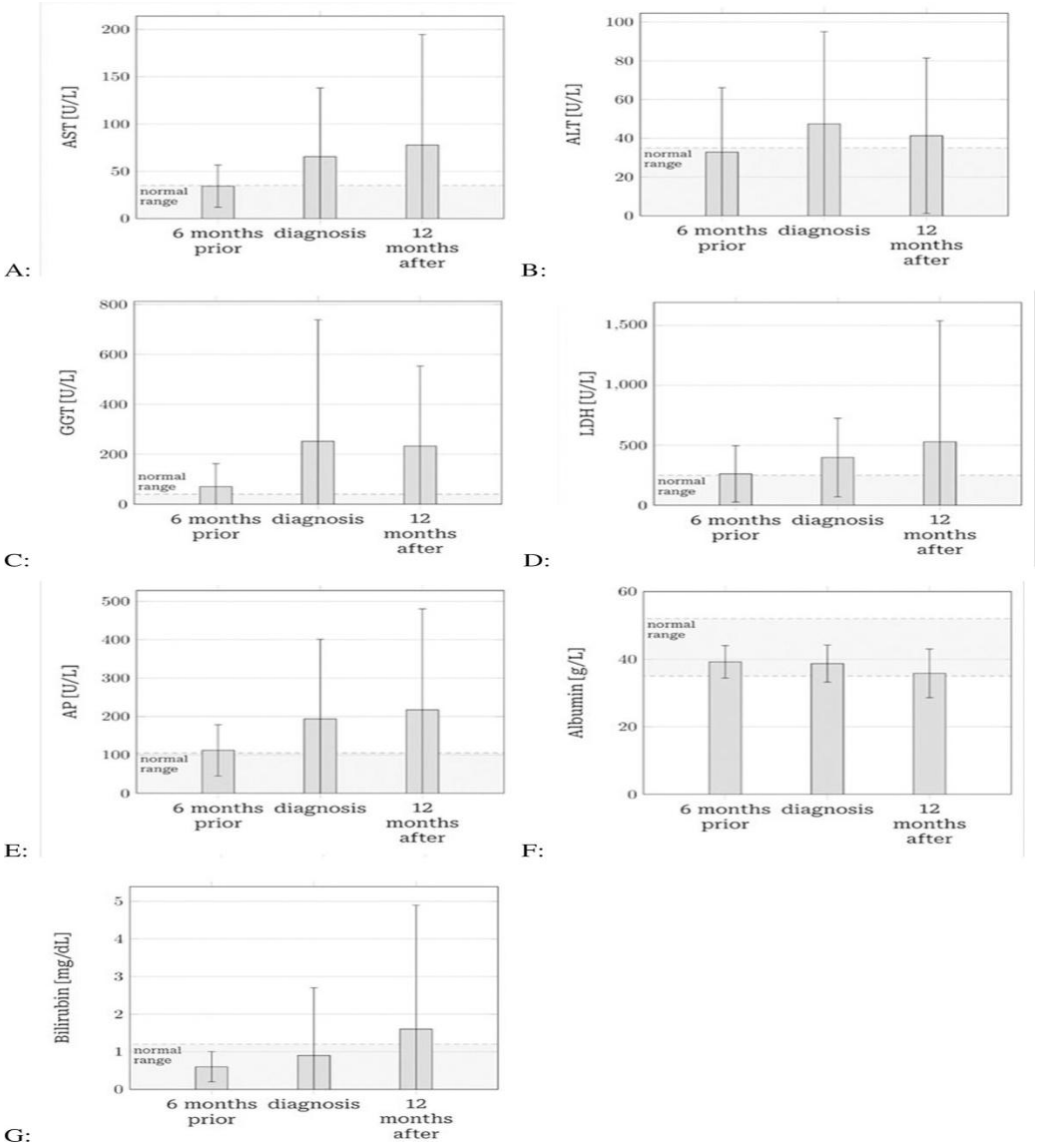

Fig 2. Mean liver function protein level changes over time.

The concentrations (Y-axis) of each enzyme, including AST (A), ALT (B), GGT(C), LDH (D), AP (E), and proteins, including Albumin (F), and Bilirubin (G), are plotted as bar graph, showing values 6-month prior, at the time of diagnosis, and 12-month post-diagnosis, represented on X-axis. The light grey belt shows normal ranges of protein level. Statistical analysis was performed using SPSS software and the p-values are represented as significant with a level of 0.05. After corrected by the Bonferroni method given the number of 21 tests, yielding a significance level of α=0.0024.

A significant positive correlation was established between the ordinal severity of hepatic metastases and aspartate aminotransferase (AST) concentrations at the time of breast cancer liver metastases (BCLM) diagnosis (Spearman's rho = 0.524, $p < 0.001$). Additionally, elevated AST levels at BCLM diagnosis were independently associated with a statistically significant increase in 12-month mortality ($p = 0.001$). Notably, AST levels demonstrated no significant associations with molecular subtypes, primary tumor histology, tumor grade, alcohol consumption, smoking status, body mass index, age at initial breast cancer diagnosis, or age at BCLM diagnosis.

In the six-month period preceding the diagnosis of breast cancer liver metastases (BCLM), median alanine aminotransferase (ALT) levels were 21 U/L (mean 32.7 U/L), with 27.77% of patients demonstrating values above the established normal range. This proportion represented a statistically significant increase compared to the expected 5% ($p < 0.001$). At the time of BCLM diagnosis, the median ALT was 30.1 U/L (mean 47.5 U/L), which, after multiple comparisons correction, did not significantly differ from the pre-diagnostic levels ($p = 0.007$). Twelve months post-diagnosis, median ALT increased to 28.1 U/L (mean 41.4 U/L), exceeding the levels observed six months prior. Furthermore, a statistically significant positive correlation was established between the number of hepatic metastatic lesions and ALT levels at the time of diagnosis (Spearman $r = 0.417$, $p < 0.001$).

In these study patients who developed breast cancer liver metastases (BCLM), a statistically significant elevation of gamma-glutamyl transferase (GGT) levels was observed six months prior to diagnosis. Specifically, 41.81% of patients presented with GGT levels exceeding the established normal range (median 36.1 U/L, mean 70.4 U/L; $p < 0.001$ compared to an expected 5% in healthy individuals). At the time of BCLM diagnosis, a further increase in GGT levels was noted, with 63.2% of patients exhibiting elevated values (median 52.9 U/L, mean 251.8 U/L). Twelve months post-diagnosis, while a marginal reduction in mean GGT levels was observed (median 83.1 U/L, mean 232.8 U/L), levels remained significantly higher than those recorded six months pre-diagnosis ($p < 0.001$). Furthermore, a significant positive correlation was established between GGT levels at diagnosis and the number of hepatic metastatic lesions (Spearman $r = 0.493$, $p < 0.001$).

In patients subsequently diagnosed with bone and/or central nervous system leptomeningeal metastases (BCLM), lactate dehydrogenase (LDH) levels demonstrated a significant temporal pattern. Six months prior to BCLM diagnosis, the median LDH was 198.1 U/L (mean 261.3 U/L), with 27.27% of patients exhibiting levels exceeding the normal reference range, a proportion significantly greater than the expected 5% ($p < 0.001$, implied). At the time of BCLM diagnosis, the median LDH increased to 265.9 U/L (mean 397.9 U/L), and twelve months post-diagnosis, the median was 237.4 U/L (mean 529.4 U/L). A statistically significant elevation in LDH was observed at BCLM diagnosis compared to levels six months prior ($p < 0.001$). However, no significant difference was found between LDH levels at BCLM diagnosis and twelve months post-diagnosis ($p = 0.16$). Furthermore, a statistically significant positive correlation was established between LDH levels at BCLM diagnosis and the number of metastatic lesions, as evidenced by a Spearman's rank correlation coefficient of 0.267 ($p = 0.011$).

In the six months preceding the diagnosis of breast cancer liver metastases (BCLM), 16.36% of patients (9/55) exhibited hypoalbuminemia, a proportion significantly elevated compared to the expected 2.5% (median: 39.5 U/L, mean: 39.1 U/L). While median and mean albumin levels demonstrated a downward trend at BCLM diagnosis and 12 months post-diagnosis, the reduction at 12 months did not reach statistical significance after correction for multiple comparisons ($p = 0.016$) when compared to the 6-month pre-diagnosis baseline. Notably, patients with a post-BCLM diagnosis survival of less than 12 months presented with significantly lower albumin levels at the time of diagnosis compared to those with a survival exceeding 12 months ($p = 0.001$).

In this retrospective cohort of 55 patients with breast cancer, 40% (n=22) presented with elevated alkaline phosphatase (AP) levels six months prior to the diagnosis of breast cancer liver metastases (BCLM), significantly exceeding the expected 5% prevalence in a healthy population ($p < 0.001$). The median AP level at six months pre-diagnosis was 92.9 U/L (mean 111.8 U/L). At the time of BCLM diagnosis and 12 months post-diagnosis, median AP levels were 112.9 U/L (mean 193.6 U/L) and 116.2 U/L (mean 217.6 U/L), respectively. While a numerical increase in AP levels was observed across these time points, statistical significance was not maintained after multiple comparison correction ($p = 0.18$ and $p = 0.009$, respectively). However, a statistically significant positive correlation was demonstrated between AP levels at the time of BCLM diagnosis and the number of hepatic metastatic lesions (Spearman's rho = 0.404, $p < 0.001$).

Within a cohort of 55 patients, 7.27% (n=4) presented with hyperbilirubinemia, a prevalence not statistically dissimilar from a hypothesized 5% threshold ($p = 0.372$). Although the proportion of patients with elevated bilirubin did not significantly deviate from the expected 5%, a statistically significant temporal increase in mean bilirubin concentrations was observed ($p = 0.011$), despite the absence of significant changes in median values ($p = 0.581$). Specifically, median bilirubin levels remained relatively stable at 0.46 U/L six months pre-diagnosis and at diagnosis, increasing minimally to 0.48 U/L twelve months post-diagnosis. Conversely, mean bilirubin levels demonstrated a progressive elevation from 0.5 U/L to 0.8 U/L and 1.5 U/L across the respective time points. Additionally, a statistically significant positive correlation was established between bilirubin levels at the time of diagnosis and the number of metastatic lesions (Spearman $r = 0.254$, $p = 0.011$).

Discussion

In this retrospective cohort study, 40.4% of patients demonstrated significant gamma-glutamyl transferase (GGT) elevation six months preceding the diagnosis of biliary carcinoma with liver metastases (BCLM). GGT levels showed a progressive increase coinciding with BCLM diagnosis, and a direct correlation was observed between GGT levels and metastatic burden. The simultaneous elevation of GGT and alkaline phosphatase (ALP) at diagnosis is indicative of heightened biliary tract compromise in BCLM.

Although gamma-glutamyl transferase (GGT) is acknowledged for its high sensitivity in hepatic enzyme assessment, its diagnostic specificity is constrained [16]. Given that non-alcoholic fatty liver disease (NAFLD) and cholestasis, both recognized causes of GGT elevation, share risk factors with breast cancer [17], the documented association between NAFLD and breast cancer in non-

obese women, as reported by Kwak et al., may explain the observed GGT elevation in this cohort, potentially acting as a significant confounder.

While confined to the liver, hepatic metastasis in breast cancer significantly compromises patient prognosis [18]. This study, consistent with prior reports of a median survival of 11.2 months [14], demonstrated significant associations between biochemical markers and survival outcomes. Specifically, elevated aspartate aminotransferase (AST) levels were associated with increased mortality, corroborating findings by O'Reilly et al. [13]. Similarly, hypoalbuminemia correlated with reduced survival, as previously reported by Cheung et al. [19]. Notably, patients within this cohort experiencing survival durations of less than 12 months post-diagnosis of breast cancer liver metastasis (BCLM) exhibited significantly lower albumin levels ($p = 0.001$), underscoring its prognostic value alongside AST.

The finding of a baseline normal bilirubin concentration, despite concurrent elevations in other liver function tests (LFTs), six months prior to breast cancer liver metastasis (BCLM) diagnosis, raises significant clinical considerations. This observation suggests a potential predominance of hepatocellular injury over cholestatic processes. Given the established utility of liver enzyme profiles in BCLM detection, we recommend proactive screening for hepatic metastases in breast cancer patients presenting with abnormal LFTs. This approach facilitates timely implementation of optimal treatment strategies, including emerging therapies such as selective internal radiation therapy [20], thereby potentially improving long-term patient outcomes. Furthermore, the subsequent temporal pattern of increased aspartate aminotransferase (AST), lactate dehydrogenase (LDH), alkaline phosphatase (AP), and bilirubin, coupled with a decrease in albumin, observed twelve months post-BCLM diagnosis, may reflect either progressive disease burden or iatrogenic hepatotoxicity.

The current retrospective analysis is limited by its small sample size and the potential for confounding factors. Specifically, the study did not fully control for hepatotoxic medication exposure, pre-existing hepatic comorbidities such as hepatitis B infection [21] and non-alcoholic fatty liver disease (NAFLD), or the presence of bone lesions, which may independently influence alkaline phosphatase (AP) levels. To mitigate these limitations, a prospective, large-scale cohort study is planned, focusing on breast cancer patients with liver metastases. This future investigation will incorporate AP isoenzyme analysis to differentiate skeletal and hepatic contributions to AP elevation. Despite these limitations, this study provides a preliminary analysis of alterations in liver protein levels preceding the diagnosis of breast cancer liver metastases (BCLM).

Conclusion

Considering the clinical risk of breast cancer liver metastasis (BCLM), the utilization of liver function tests as a screening tool is advocated for female breast cancer patients. To optimize patient management in the context of emerging survival-prolonging therapies, a prospective, multicenter trial is necessary to validate the diagnostic accuracy of these tests and to determine the optimal frequency of liver function protein level monitoring during extended follow-up.

Declarations

Ethical Approval and Consent to participate

Not applicable as retrospective nature of study. Consent for publication: Not applicable as retrospective nature of study.

Availability of supporting data

Upon request to the corresponding author.

Competing interests

Nil

Funding Statement

Nil

Authors contributions

All authors made substantial contributions to the reported work, including in the areas of conception, study design, execution, data collection, analysis, and interpretation. They participated in drafting, revising, and critically reviewing the article, gave final approval for the version to be published, agreed on the journal for submission, and accepted responsibility for all aspects of the work.

References

[1] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin. 2021 Jan; 71(1):7–33. https://doi.org/10.3322/caac.21654. Epub 2021 Jan 12. Erratum in: CA Cancer J Clin. 2021; 71(4):359. 10.3322/caac.21654.

[2] Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, et al. Cancer statistics for the year 2020: An overview. Int J Cancer. 2021. https://doi.org/10.1002/ijc.33588.

[3] Wu Q, Li J, Zhu S, Wu J, Chen C, Liu Q, et al. Breast cancer subtypes predict the preferential site of dis- tant metastases: A SEER based study. Oncotarget. 2017; 8(17):27990–27996. https://doi.org/10. 18632/oncotarget.

[4] Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, Andre´ F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020; 31(12):1623– 1649. https://doi.org/10.1016/j.annonc.2020.09.010

[5] AlSendi M O'Reilly D, Zeidan YH, Kelly CM. Oligometastatic breast cancer: Are we there yet? Int J Cancer. 2021; 149(8):1520–1528. https://doi.org/10.1002/ijc.33693

[6] Ma R, Feng Y, Lin S, Chen J, Lin H, Liang X, et al. Mechanisms involved in breast cancer liver metasta- sis. J Transl Med. 2015; 13:64. https://doi.org/10.1186/s12967-015-0425-0.

[7] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012; 62(1):10–29. https://doi.org/10.3322/caac.20138.

[8] Liang Y, Zhang H, Song X, Yang Q. Metastatic heterogeneity of breast cancer: Molecular mechanism and potential therapeutic targets. Semin Cancer Biol. 2020; 60: 14–27. https://doi.org/10.1016/j. semcancer.2019.08.012.

[9] Tsilimigras DI, Brodt P, Clavien PA, Muschel RJ, D'Angelica MI, Endo I, et al. Liver metastases. Nat Rev Dis Primers. 2021; 7(1):27. https://doi.org/10.1038/s41572-021-00261-6.

[10] Abbott DE, Brouquet A, Mittendorf EA, Andreou A, Meric-Bernstam F, Valero V, et al. Resection of liver metastases from breast cancer: estrogen receptor status and response to chemotherapy before metastasectomy define outcome. Surgery. 2012; 151(5):710–6. https://doi.org/10.1016/j.surg.2011.12.017.

[11] Nesbit EG, Donnelly ED, Strauss JB. Treatment Strategies for Oligometastatic Breast Cancer. Curr Treat Options Oncol. 2021; 22(10):94. https://doi.org/10.1007/s11864-021-00889-2.

[12] Charalampoudis P, Mantas D, Sotiropoulos GC, Dimitroulis D, Kouraklis G, Markopoulos C. Surgery for liver metastases from breast cancer. Future Oncol. 2015; 11(10):1519–1530. https://doi.org/10.2217/ fon.15.43.

[13] Mogrovejo E, Manickam P, Amin M, Cappell MS. Characterization of the syndrome of acute liver failure caused by metastases from breast carcinoma. Dig Dis Sci. 2014 Apr; 59(4):724-36. doi: 10.1007/s10620-013-2943-z.

[14] Cao R, Wang LP. Serological diagnosis of liver metastasis in patients with breast cancer. Cancer Biol Med. 2012; 9(1):57–62. https://doi.org/10.3969/j.issn.2095-3941.2012.01.011.

[15] i, L., Cheng, L., Zhu, X. *et al.* Risk and prognostic factors of breast cancer with liver metastases. *BMC Cancer* 21, 238 (2021). https://doi.org/10.1186/s12885-021-07968-5

[16] Kuntz E, Kuntz H-D. Hepatology: Principles and practice; history, morphology, biochemistry, diagnos- tics, clinic, therapy. 2nd ed. Heidelberg: Springer; 2006.

[17] Kwak MS, Yim JY, Yi A, Chung GE, Yang JI, Kim D, et al. Nonalcoholic fatty liver disease is associated with breast cancer in nonobese women. Dig Liver Dis. 2019; 51(7):1030–1035. https://doi.org/10.1016/ j.dld.2018.12.024.

[18] Er O, Frye DK, Kau SW, Broglio K, Valero V, Hortobagyi GN, Arun B. Clinical course of breast cancer patients with metastases limited to the liver treated with chemotherapy. Cancer J. 2008 Jan-Feb;14(1):62-8. doi: 10.1097/PPO.0b013e3181629a7b.

[19] Luo J, Xiao J, Yang Y, Chen G, Hu D, Zeng J. Strategies for five tumour markers in the screening and diagnosis of female breast cancer. Front Oncol. 2023 Jan 23; 12:1055855. doi: 10.3389/fonc.2022.1055855.

[20] Schatka I, Tschernig M, Rogasch JMM, Bluemel S, Graef J, Furth C, et al. Selective Internal Radiation Therapy in Breast Cancer Liver Metastases: Outcome Assessment Applying a Prognostic Score. Can- cers (Basel). 2021; 13(15):3777. https://doi.org/10.3390/cancers13153777.

[21] Yu P, Liu P, Li N, Xie X, Tang H, Wu J, et al. Hepatitis B virus infection specially increases risk of liver metastasis in breast cancer patients: a propensity-matched analysis. Transl Cancer Res. 2020; 9 (3):1506–1517. https://doi.org/10.21037/tcr.2020.01.63.