



Article

Association of *SLC7A5*/*LAT1* Expression with Clinicopathological Parameters and Molecular Subtypes: Could It Be Considered in the Management of Breast Cancer?

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Abstract

Introduction: Breast cancer is a heterogeneous malignancy influenced by diverse molecular profiles. The L-type amino acid transporter 1 (*LAT1*), encoded by the *SLC7A5* gene, plays a key role in tumor metabolism, growth, and angiogenesis. Through its role in amino acid transport and activation of the mTORC1 signaling pathway, *LAT1* has emerged as a potential therapeutic target. **Objective:** To evaluate *SLC7A5*/*LAT1* expression and its association with clinicopathological parameters and molecular subtypes of invasive carcinoma of no special type (NST) in a Pakistani cohort. **Methods:** Eighty-three patients who underwent mastectomy or modified radical mastectomy for histologically confirmed primary invasive carcinoma of no special type were included. Immunohistochemistry was used to assess *SLC7A5*/*LAT1* expression. Associations with clinicopathological features and molecular groups were analyzed using the Chi-square test. **Results:** The mean age of *SLC7A5*-positive patients was 48.4 ± 10.8 years. Overall, 24.1% of patients demonstrated *SLC7A5* positivity. Although *SLC7A5* expression was more frequent in cases categorized as having moderate or poor prognosis based on the Nottingham Prognostic Index (NPI), this trend was not statistically significant. Similarly, no significant associations were observed between *SLC7A5* expression and other clinicopathological or molecular variables. **Conclusions:** *SLC7A5*/*LAT1* expression was identified in approximately one-quarter of invasive breast carcinoma cases. Its expression appeared more common in tumors with poorer NPI categories, but without statistically verified associations. These findings suggest that *SLC7A5* may act independently of conventional clinicopathological parameters. Larger, longitudinal studies with survival follow-up are required to clarify its prognostic and therapeutic significance.

Keywords: breast cancer; *SLC7A5* protein; *LAT1* protein; prognostic index; lymph node; tumor biomarker



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1. Introduction

Breast cancer (BC) remains one of the most heterogeneous malignancies, characterized by marked molecular, biological, and clinical diversity. Classification based on molecular markers such as the human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER), and progesterone receptor (PR) has been instrumental in defining subtypes—luminal A, luminal B, HER2-enriched, and triple-negative breast cancer (TNBC)—each with unique prognostic and therapeutic implications [1]. These molecular distinctions have guided the era of precision oncology, enabling targeted treatments and improved patient outcomes. Yet, even within defined subtypes, variability in clinical behavior and therapeutic response persists, underscoring the existence of additional molecular factors that influence disease progression and treatment resistance. Identifying such factors is critical for refining prognostic tools and expanding therapeutic options, especially in the face of adaptive tumor metabolism and evolving resistance mechanisms.

One of the emerging molecular regulators at this intersection of metabolism and oncogenesis is solute carrier family 7 member 5 (*SLC7A5*), which encodes the L-type amino acid transporter 1 (LAT1). LAT1 is a sodium-independent transmembrane transporter responsible for the uptake of large neutral amino acids—particularly leucine, phenylalanine, and valine—required for protein synthesis and cellular growth [2]. Beyond its primary transport function, LAT1 plays a pivotal role in cancer cell metabolism by modulating the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway. Through leucine-mediated activation of mTORC1, LAT1 contributes to nutrient sensing, metabolic adaptation, and survival under nutrient stress conditions—hallmarks of aggressive tumors [3]. This coupling of amino acid transport to growth signaling places LAT1 at a strategic metabolic checkpoint linking nutrient availability to oncogenic signaling, proliferation, and therapy resistance.

Recent advances in cancer therapeutics increasingly recognize metabolic reprogramming as a defining feature of tumor evolution. As described in reviews such as “Cancer Treatments: Past, Present, and Future”, metabolic and transport-related mechanisms have progressively shifted from being ancillary processes to becoming central targets of therapeutic intervention. Inhibitors of metabolic pathways—including amino acid transporters like LAT1—are now viewed as potential adjuncts to overcome resistance to conventional therapies and to enhance biomarker-driven patient selection. Within this paradigm, LAT1’s dual function—as both a metabolic enabler and a signaling modulator—renders it a compelling biomarker and therapeutic target, especially in tumors that thrive under metabolic stress, such as TNBC.

In breast cancer, elevated LAT1 expression has been linked to enhanced proliferation, angiogenesis, and poor differentiation, all of which correlate with aggressive clinical behavior and adverse outcomes [4]. LAT1 facilitates sustained amino acid influx, ensuring the biosynthetic and energetic demands of rapidly dividing tumor cells are met. By maintaining intracellular leucine levels, LAT1 not only drives protein synthesis but also activates nutrient-sensing pathways that promote anabolic metabolism and suppress apoptosis [5]. Moreover, the interplay between LAT1 and the AKT/mTORC1 axis has been observed in hormone receptor-positive cell lines such as MCF-7, where its upregulation augments proliferative signaling [6,7]. Collectively, these findings suggest that *SLC7A5* is not merely a metabolic transporter but a dynamic participant in oncogenic signaling and cellular adaptation—key processes that underpin therapeutic resistance and disease recurrence.

Clinically, high *SLC7A5* expression has been correlated with poor histological differentiation, higher tumor grade, and advanced stage, indicating its potential as a prognostic indicator. However, despite extensive research across diverse populations, there remains a paucity of data from South Asian cohorts, where distinct genetic, environmental, and dietary factors may shape tumor metabolism differently. Understanding LAT1 expression

in this regional context is crucial for building a more globally inclusive molecular landscape of breast cancer biology.

Therefore, this study examined the LAT1 (*SLC7A5*) expression in a cohort of Pakistani patients with invasive breast carcinoma, aiming to determine its prevalence and its association with clinicopathological parameters such as tumor grade, size, nodal status, molecular subtype, and the Nottingham Prognostic Index. By correlating LAT1 expression with established prognostic markers, this research sought to clarify its role in breast tumor biology and assessed its potential as a biomarker for disease aggressiveness and therapeutic targeting. Grounding this investigation within the broader continuum of cancer metabolism and therapeutic evolution highlights how understanding nutrient transporters like LAT1 can inform the next generation of precision oncology strategies—where targeting cellular metabolism may complement and enhance traditional receptor- and gene-driven treatments.

2. Materials and Methods

This was a prospective study. The samples were collected from two tertiary care hospitals in Lahore, Pakistan: Mayo Hospital and Shaikh Zayed Hospital.

Ethical considerations

The study was conducted as part of a Ph.D. research project and was approved by the Advanced Studies and Research Board of the University of Health Sciences (UHS), Pakistan, with ethical approval number: UHS/Education/126-16/215.

Inclusion and Exclusion criteria

Included samples were taken from mastectomy or modified radical mastectomy specimens, from patients with microscopically confirmed primary invasive carcinoma of no special type (ductal).

Patients who had received neoadjuvant therapy were excluded. Neoadjuvant therapy in cancer is primarily administered before the surgery to downstage the tumor, making previously inoperable or borderline resectable tumors amenable to surgical removal. To avoid treatment-induced alterations in histological and molecular features, these specimens were excluded.

Histopathological Assessment

All tissue samples underwent a standard fixation and paraffin embedding, followed by sectioning and staining with hematoxylin and eosin (H&E). Tumors were graded histologically using the Nottingham Histological Grading System, in accordance with the College of American Pathologists (CAP) Cancer Protocol of resection specimens from patients with invasive carcinoma of the breast (June 2024).

The Nottingham Prognostic Index (NPI) was calculated for each case using the following formula: $NPI = (0.2 \times \text{tumor diameter in cm}) + \text{lymph node stage} + \text{tumor grade}$. Lymph node stage and tumor grade were categorized as shown in the Table 1 below:

Table 1. Lymph node stage and tumor stage used to calculate the Nottingham Prognostic index.

Lymph Node Stage	Tumor Grade
1: No node metastasis	1: Grade 1
2: 1–3 node metastasis	2: Grade 2
3: >3 nodes metastasis	3: Grade 3

The NPI-based prognostic groups were classified as follows:

Good outcome: $NPI < 3.4$, Moderate risk: $NPI 3.4–5.3$, Poor outcome: $NPI \geq 5.4$.

Immunohistochemistry (IHC)

For biomarker analysis, immunohistochemical staining was performed on 4 μm sections from two representative paraffin blocks of each tumor. Expressions of estrogen

receptor (ER), progesterone receptor (PR), HER2/neu, and Ki-67 were assessed based on College of American Pathologists (CAP) Guidelines (March 2023). *SLC7A5* protein expression was evaluated using a recombinant rabbit monoclonal antibody (Anti-*SLC7A5*/LAT1, Abcam, Code: ab208776, dilution 1:300). Testis tissue was used as a positive control, following manufacturer recommendations. Expression was considered positive when strong membranous and/or cytoplasmic staining was observed in >10% of tumor cells; negative if staining was seen in <10% of cells [8].

Three independent consultant histopathologists evaluated the IHC slides. In cases of interpretational variance, the majority consensus (2 out of 3 pathologists) was considered final. In order to assess scoring reproducibility, inter-observer variability was analyzed using Cohen's kappa (κ) statistic, which demonstrated substantial agreement ($\kappa = 0.78$) among pathologists, confirming consistency of LAT1 scoring. The localization of LAT1 staining (membranous versus cytoplasmic) was specifically documented, as LAT1 can exhibit mixed localization depending on the quality of fixation and the performance of the antibody batch. Representative photomicrographs (Figure 1) have been relabeled to clearly indicate staining intensity and localization, ensuring the distinction between membranous and cytoplasmic expression is visually evident.

Statistical Analysis

Data were compiled and analyzed using IBM SPSS Statistics, version 27. Frequencies and percentages were calculated for categorical variables like age of the patient, side of the tumor (left/right breast), nodal stage (stages N0, N1, N2, N3), tumor stage (T2, T3, T4), Nottingham grade (I, II, III), and the molecular classifications. The Pearson chi-square test was applied to evaluate associations between clinicopathological variables. A p -value < 0.05 was considered statistically significant.

3. Results

A total of 83 patients with invasive ductal carcinoma meeting the criteria were included in this study. The expression of *SLC7A5* was evaluated, and a comparative analysis was conducted between positive and negative cases. Among these patients, 63 (75.9%) were *SLC7A5*-negative, while 20 patients (24.1%) were *SLC7A5*-positive. This difference in expression was statistically significant ($p < 0.001$), indicating a relatively lower rate of *SLC7A5* positivity in the study cohort.

The mean age of *SLC7A5*-positive patients was 48.4 ± 10.8 years. When grouped by age, patients ≤ 50 years showed a non-significantly higher frequency of *SLC7A5* positivity compared to those > 50 years, suggesting a potential trend without statistical support. Regarding tumor laterality, 14 of the 20 *SLC7A5*-positive tumors (70%) were located on the right side, while 6 (30%) were on the left. Although *SLC7A5* positivity appeared more common in right-sided tumors, this difference was not statistically significant.

The association of *SLC7A5* expression with lymph node status showed that most positive cases were in the N1–N2 category (4–9 metastatic nodes). Specifically, 9 patients (45%) were N1 and 7 (35%) were N2, whereas only 4 (20%) had no nodal involvement (N0). This pattern suggests a tendency for *SLC7A5* positivity in patients with lymph node involvement, although statistical significance was not reached (Table 2).

Table 2. Association of *SLC7A5* expression with clinicopathological parameters in women with invasive carcinoma of no-special type.

Parameters		Negative, n (%)	Positive, n (%)	Total, n (%)	Chi Square (p-Value)
Total	83	63 (75.9)	20 (24.1)	83	<0.001 *
Age	<50	43 (51.8)	15 (18)	58 (69.9)	$\chi^2 = 0.33, p = 0.57$
	>50	20 (24.1)	5 (6)	25 (30.1)	
Laterality	Right	37 (44.6)	14 (16.9)	51 (61.4)	$\chi^2 = 0.81, p = 0.37$
	Left	26 (31.3)	6 (7.2)	32 (38.6)	
Nodal stage	No	20 (24.1)	4 (4.8)	24 (28.9)	$\chi^2 = 4.74, p = 0.19$
	N1	20 (24.1)	9 (10.8)	29 (34.9)	
	N2	15 (18.1)	7 (8.4)	22 (26.5)	
	N3	8 (9.6)	0	8 (9.6)	
Tumor stage	T2	30 (36.1)	10 (12)	40 (48.2)	$\chi^2 = 4.97, p = 0.08$
	T3	23 (27.7)	3 (3.6)	26 (31.3)	
	T4	10 (12)	7 (8.4)	17 (20.5)	
Nottingham grade	I	4 (4.8)	0	4 (4.8)	$\chi^2 = 4.096, p = 0.129$
	II	27 (32.5)	5 (6)	32 (38.6)	
	III	32 (38.6)	15 (18.1)	47 (56.6)	
Molecular classification	Luminal A	25 (30.1)	6 (7.2)	31 (37.3)	$\chi^2 = 1.638, p = 0.651$
	Luminal B	8 (9.6)	2 (2.4)	10 (12)	
	HER2	11 (13.3)	6 (7.2)	17 (20.5)	
	Triple negative (TN)	19 (22.9)	6 (7.2)	25 (30.1)	
NPI	Good	5 (6)	0	5 (6)	$\chi^2 = 3.932, p = 0.140$
	Moderate	22 (26.5)	4 (4.8)	26 (31.3)	
	Poor	36 (43.4)	16 (19.3)	52 (62.7)	

NPI thresholds: Good < 3.4, Moderate 3.4–5.3, Poor ≥ 5.4 . * Shows the statistically significant value

Table 3 summarizes the key outcomes. *SLC7A5* expression was more frequently observed in tumors with higher histological grade (Grade III) compared to Grade I/II, indicating a trend toward association with aggressive tumor phenotype, though the difference was not statistically significant ($p = 0.129$). Similarly, patients with poor Nottingham Prognostic Index (NPI) scores showed a higher frequency of *SLC7A5* positivity ($p = 0.14$), suggesting a potential link to worse clinical outcomes. However, no significant association with age was found ($p = 0.567$), indicating that *SLC7A5* expression is independent of patient age.

Furthermore, associations between *SLC7A5* expression and common breast cancer biomarkers—estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki67—were assessed. As summarized in Table 4, no statistically significant associations were observed between *SLC7A5* and any of these biomarkers.

Overall, the reactivity of *SLC7A5* does not significantly correlate with age, tumor laterality, lymph node stage, tumor grade, molecular subtype, or biomarker profile. These findings suggest that *SLC7A5* may function independently of conventional clinicopathological parameters and could potentially serve as an independent prognostic or diagnostic marker in invasive ductal breast carcinoma.

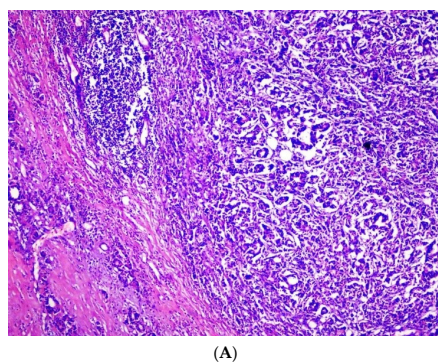
Table 3. Summary table with effect sizes and interpretation.

Variable	Key Association	Direction	Strength	p-Value	Clinical Interpretation
Tumor Grade III vs. I/II	Higher <i>SLC7A5</i> positivity	↑	Moderate	0.129	Suggests aggressive phenotype
NPI Poor	More positive cases	↑	Moderate	0.14	May predict poor outcome
Age	Not significant	–	Weak	0.567	No age association

Table 4. Association of *SLC7A5* with biochemical parameters of invasive carcinoma of no special type.

		<i>SLC7A5</i> Negative, <i>n</i> (%)	<i>SLC7A5</i> Positive, <i>n</i> (%)	Total, <i>n</i> (%)	Chi Square (<i>p</i> Value)
ER	Negative	28 (33.7)	10 (12)	38 (45.8)	0.189, 0.664
	Positive	35 (42.2)	10 (12)	45 (54.2)	
PR	Negative	29 (34.9)	11 (13.3)	40 (48.2)	0.489, 0.484
	Positive	34 (41)	9 (10.8)	43 (51.8)	
HER2	Negative	44 (53)	12 (14.5)	56 (67.5)	0.670, 0.413
	Positive	19 (22.9)	8 (9.6)	27 (32.5)	
Ki67	<15%	17 (20.5)	5 (6)	22 (26.5)	0.031, 0.861
	>15%	46 (55.4)	15 (18.1)	61 (73.5)	

The following Figure 1A–D show standard Nottingham grading system. Figure 1A shows tubule formation of 10–75%, with mitosis of 10–19/HPF and moderate nuclear pleomorphism, graded as moderately differentiated invasive ductal carcinoma, NST based on standard Nottingham grading system. Figure 1B shows complete negative staining of *SLC7A5*, whereas Figure 1C,D show complete and strong membranous staining of *SLC7A5* in more than 10% tumor cells in invasive ductal carcinoma, NST.

**Figure 1.** Cont.

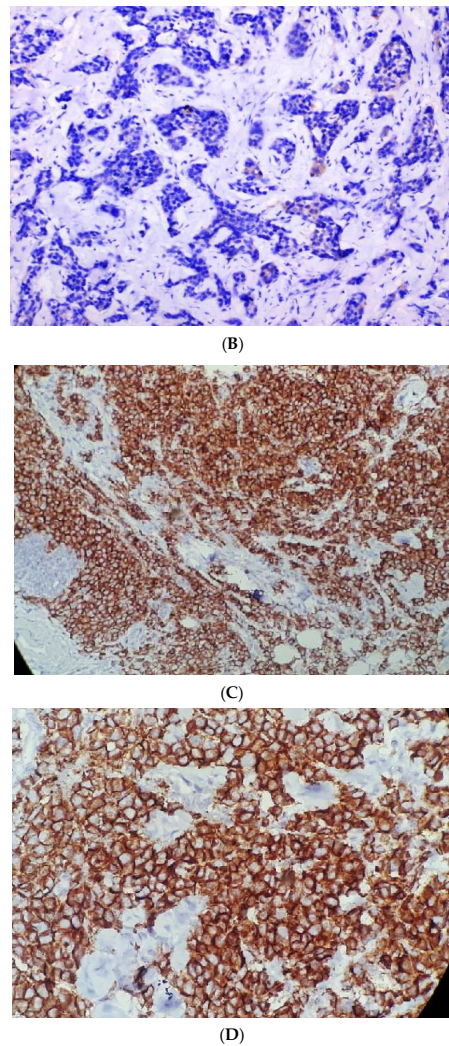


Figure 1. (A) Moderately differentiated invasive carcinoma, NST (H&E, 40 $\times$), showing tubule formation (10–75%), mitoses (10–19/HPF), and moderate nuclear pleomorphism. (B) Complete negative staining for *SLC7A5* (100 $\times$). (C) Strong membranous and cytoplasmic *SLC7A5* positivity in >10% of tumor cells (100 $\times$). (D) Intense membranous and cytoplasmic staining for *SLC7A5* (400 $\times$).

4. Discussion

Breast cancer is a highly heterogeneous malignancy that exhibits considerable molecular, cellular, and biological variability, influencing treatment responses and clinical outcomes. The molecular subtypes of BC—luminal A, luminal B, HER2-enriched, and triple-negative breast cancer (TNBC)—each exhibit distinct biological behaviors, prognoses, and therapeutic responses. This inherent diversity emphasizes the urgent need for novel biomarkers that can better inform prognosis, aid in risk stratification, and identify potential therapeutic targets in BC patients [7,8].

In this study, we investigated the expression of the solute carrier family 7, member 5 (*SLC7A5*), which encodes the L-type amino acid transporter 1 (LAT1), in invasive ductal carcinoma (IDC) samples from Pakistani breast cancer patients. Our findings did not reveal statistically significant correlations between *SLC7A5* expression and key clinicopathological parameters such as tumor grade, stage, lymph node involvement, or molecular subtype. While these observations may initially suggest that *SLC7A5* expression is regulated independently of these clinical variables, this interpretation must be made cautiously. Several of the observed associations were descriptive trends with non-significant *p*-values (0.1–0.5), indicating insufficient strong evidence of definitive biological relevance. The relatively

small sample size ($n = 83$) limits the statistical power of the study, reducing the ability to detect weak-to-moderate associations. Therefore, the absence of significant correlations should not be viewed as proof of independence but rather as a reflection of limited sample resolution or potential random variation [9]. Future studies with larger, multi-institutional cohorts are warranted to clarify whether these trends represent true biological effects or statistical noise.

Interestingly, previous studies have reported significant associations between *SLC7A5* expression and adverse clinical outcomes, such as poor survival and metastatic progression, in various cancers, including breast cancer. Elevated levels of *SLC7A5* have been linked to more aggressive tumor phenotypes—higher tumor grade, advanced stage, and hormone receptor negativity—suggesting a role in disease aggressiveness and poor prognosis [10,11]. Mechanistically, *SLC7A5* facilitates amino acid transport and activates the mTORC1 signaling pathway, thereby promoting tumor cell proliferation and metabolic adaptation under stress conditions. In contrast, the absence of statistically significant associations in our cohort may reflect the study's preliminary nature, sample size limitations, or population-specific variability rather than a genuine lack of biological significance [12,13]. Hence, the potential of *SLC7A5* as an independent prognostic biomarker requires validation through studies with greater statistical power and extended clinical follow-up.

In this cohort, *SLC7A5* was expressed in 24.1% of patients, with relatively higher expression levels observed in certain molecular subtypes such as luminal, HER2-positive, and TNBC, though these differences did not reach statistical significance. This aligns with studies conducted in other populations, such as a Japanese cohort that reported higher *SLC7A5* expression in HER2-positive and TNBC subtypes [14]. The variability in expression across ethnic and demographic groups emphasizes the importance of considering regional, genetic, and environmental factors when evaluating biomarker utility. Conducting region-specific studies can therefore provide critical insight into population-based tumor biology and improve the applicability of molecular markers in diverse clinical settings.

Our findings also indicated that *SLC7A5* expression tended to be higher among patients in the moderate and poor prognostic categories based on the Nottingham Prognostic Index (NPI), although this trend did not reach statistical significance. These observations are consistent with regional studies reporting associations between high *SLC7A5* expression and worse outcomes, particularly in advanced-stage disease [15,16]. Given that the NPI integrates tumor size, lymph node status, and histological grade, incorporating molecular markers like *SLC7A5* into this framework may improve predictive accuracy—especially in populations where traditional prognostic models may have reduced discriminative power. Nevertheless, such integration requires validation through studies with larger cohorts to confirm the consistency and magnitude of these effects.

The biological role of *SLC7A5* in tumor metabolism further highlights its potential as a therapeutic target. By transporting essential amino acids, particularly leucine, *SLC7A5* supports protein synthesis and activates the mTORC1 pathway, fostering anabolic metabolism, cell proliferation, and survival—all critical processes in cancer progression. Inhibition of LAT1 has emerged as a promising therapeutic approach, especially in aggressive subtypes like TNBC, where metabolic dependency on amino acid transport is high [17,18]. Current clinical trials on LAT1 inhibitors aim to exploit these vulnerabilities by restricting nutrient supply to tumor cells, thereby impeding their growth and survival [19,20]. Such approaches could complement existing targeted and immunotherapeutic strategies, contributing to a broader shift toward metabolism-directed cancer therapy.

While survival data and Kaplan–Meier analyses were not included in this study due to the limited sample size, their inclusion in future work would significantly strengthen the evaluation of *SLC7A5*'s prognostic impact. Longitudinal studies with larger and more

diverse cohorts will be essential to determine whether *SLC7A5* expression correlates with overall or disease-free survival outcomes. Future research should also consider integrating transcriptomic and proteomic analyses to better understand *SLC7A5*'s regulatory mechanisms and its interactions with other oncogenic pathways [21].

Although *SLC7A5* expression was detected in 24% of cases, the current data only describe its distribution and clinicopathological correlations rather than its prognostic or predictive impact. As this study did not include survival outcomes, any suggestion of *SLC7A5* functioning as an independent prognostic factor would be premature. Its potential prognostic value should instead be explored in longitudinal studies that incorporate survival endpoints to establish its true predictive relevance.

Finally, it is important to acknowledge that this study's conclusions are limited by the relatively small sample size and single-region design. While several descriptive patterns were observed, these should not be over interpreted as biologically meaningful until verified in larger, multi-institutional cohorts. The observed non-significant trends highlight the inherent complexity of biomarker interpretation in small studies and underscore the need for collaborative, statistically powered research to produce clinically translatable evidence.

5. Conclusions

SLC7A5 (LAT1) expression was detected in approximately one-quarter of invasive ductal carcinoma samples from Pakistani breast cancer patients. Although minor trends toward higher expression were observed in certain molecular subtypes and prognostic categories, these did not reach statistical significance. The findings suggest that *SLC7A5* participates in tumor metabolic processes but, based on current data, cannot yet be considered a prognostic biomarker.

This study provides foundational insight into LAT1 expression patterns within an underrepresented population and underscores the importance of conducting larger, longitudinal studies that integrate clinical outcomes, molecular profiling, and therapeutic response. Such efforts will be essential to clarify whether *SLC7A5* serves as a meaningful prognostic indicator or a viable target for metabolic intervention in breast cancer.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data generated during this study are part of this manuscript. The detailed data is unavailable due to privacy or ethical restrictions, but can be obtained from the corresponding author with a reasonable request. Data is not deposited in any registry.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

LAT 1	L-type amino acid transporter
SLC7A5	solute carrier family 7, member 5
AA	Amino acids
BC	Breast Cancer
NST	No Specific Type

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