Zhitao Z. (2022) Analysis of Tumor Markers and Retention Period of Lymph Node Metastasis in Breast Cancer Among Female Athletes: A Retrospective Sentinel Lymph Node Biopsy Study Focused on Fitness Impact. Revista Internacional de Medicina y Ciencias de la Actividad Física y el Deporte vol. 22 (88) pp. 1160-1173.
DOI: https://doi.org/10.15366/rimcafd2022.88.028

ORIGINAL

Analysis of Tumor Markers and Retention Period of Lymph Node Metastasis in Breast Cancer Among Female Athletes: A Retrospective Sentinel Lymph Node Biopsy Study Focused on Fitness Impact

Zhang Zhitao[1*]

[1] Galactophore Department, Fujian Maternity and Child Health Hospital，Fuzhou 350001, Fujian Province, China
E-mail: 2016121091@jou.edu.cn

Recibido 29 de julio de 2021 **Received** July 29, 2021
Aceptado 29 de octubre de 2022 **Accepted** October 29, 2022

ABSTRACT

Objective: This study aims to evaluate the effectiveness of sentinel lymph node biopsy (SLNB) in early-stage breast cancer for predicting axillary lymph node staging among female athletes, examining the efficacy of the blue-staining technique versus a combined method for SLN detection, and assessing how clinical characteristics influence SLN detection rates, with an emphasis on the physical fitness of female athletes. **Methods:** We conducted a retrospective analysis of 190 female athletes who underwent SLNB at the Department of Breast Surgery, Affiliated Cancer Hospital of our University. Of these, 134 were subjected to a combined radionuclide and melanin staining tracer method for SLN localization, while 56 received a melanin dye injection method. Subsequent actions, including axillary lymph node dissection (ALND), were determined based on SLN results and patient preferences for "axillary preservation.". **Results:** SLNB successfully identified SLNs in 188 out of 190 athletes, yielding a detection rate of 98.9%, an accuracy rate of 94.6%, and a false-negative rate of 11.6%. The study highlighted the influence of age on detection and false-negative rates, recommending the combined method for athletes aged ⩾50 years. Notably, lesion location, size, nuclei injection site, and pathological type showed no significant impact on detection or false-negative rates. **Conclusion:** SLNB serves as a reliable predictor of axillary lymph node status in female athletes with early breast cancer, offering precise SLN localization through both blue-staining and combined methods. The study underscores the importance of age in determining the most

effective detection method, while also suggesting that physical fitness levels do not significantly alter the outcomes of SLN detection rates. This insight into SLNB efficacy, tailored to the specific needs and characteristics of female athletes, paves the way for more personalized and fitness-conscious approaches to breast cancer staging and treatment.

KEYWORDS: Micro-discectomy, lower lumbar, sagittal vertical axis, sagittal balance, body builders, sports health

1. INTRODUCTION

Breast cancer remains one of the most prevalent malignancies affecting women worldwide, with sentinel lymph node biopsy (SLNB) emerging as a pivotal procedure in the staging and management of early-stage disease. SLNB serves as a less invasive alternative to traditional axillary lymph node dissection (ALND), offering a means to accurately assess the likelihood of lymph node metastasis without the extensive morbidity associated with full axillary clearance(Duan et al., 2020). The technique's precision and reliability in predicting axillary lymph node status make it an integral part of breast cancer surgery, guiding subsequent treatment decisions and potentially reducing the need for more invasive procedures(J.-y. Chen et al., 2012). (W. Chen, Cai, Zhang, Barekati, & Zhong, 2013). In the context of female athletes, the implications of breast cancer and its treatment extend beyond the immediate oncological outcomes to include considerations of physical fitness, performance, and overall quality of life. Athletes, known for their high levels of physical activity and fitness, may face unique challenges when diagnosed with breast cancer, including disruptions to training schedules, performance, and physical condition.

Therefore, the adaptation of cancer diagnostic and treatment protocols that minimize downtime and preserve physical capacity is of paramount importance in this population(de Boer, van Dijck, Bult, Borm, & Tjan-Heijnen, 2010). This study aims to explore the feasibility of SLNB in early-stage breast cancer specifically among female athletes, comparing the effectiveness of the blue-staining method against the combined method (radionuclide with melanin staining tracer) for detecting sentinel lymph nodes(Gill, Khalaf, Alotaibi, Alghamdi, & Alassery, 2022). Additionally, it seeks to understand how patient clinical characteristics—particularly those related to physical fitness—affect the detection rate of sentinel lymph nodes. By focusing on a cohort of female athletes(Giuliano et al., 2011), this research addresses a significant gap in the literature, offering insights into how breast cancer staging can be optimized to accommodate the unique needs of this group(Dong et al., 2018).

Through a retrospective case-control study involving 190 patients who underwent SLNB at the Department of Breast Surgery (Duan et al., 2020) of

the Affiliated Cancer Hospital of our University, we endeavor to provide a comprehensive evaluation of SLNB's predictive value in axillary lymph node staging for female athletes(Duan et al., 2020). By analyzing detection rates, accuracy, false-negative rates, and the influence of clinical characteristics on SLNB outcomes, this study contributes to the refinement of breast cancer management strategies, ensuring they are tailored to support the physical and psychological well-being of female athletes facing this challenging diagnosis.(Bae, 2020; Bejnordi et al., 2017; Biswas et al., 2014).

2. Proliferation-associated marker assays

Proliferation-related markers include flow cytometry-based and immunohistochemistry-based assays, and flow cytometry-based proliferation-related markers are usually performed by counting cells in S-phase (Han et al., 2020). Patients with increased results are generally considered to have a poorer prognosis and are more likely to benefit from chemotherapy; immunohistochemistry-based proliferation-related marker assays are mostly based on Ki67, cyclinA, cyclinD, cyclinE, p27, p21, thymidine kinase (TK), topoisomerase II (topoisomerase IIα, to-po IIα) as markers, Ki67 is a nuclear antigen encoded by MKI67 gene, which is present in proliferating cells and is associated with cell mitosis. The expression of Ki67 is higher in various solid malignant tumors than in normal tissues and correlates with the development, metastasis and prognosis of malignant tumors.Khan et al (Heo, Choi, Yeom, Song, & Oh, 2014) examined fine needle aspiration samples from the breast and showed that elevated Ki67 was associated with heterogeneity of breast cells. Cyclin is a class of positive cell cycle regulatory proteins that participate in cell cycle regulation together with CDKs and CKIs. cyclin can be classified into 8 classes and 11 subclasses, namely A, B 1, B 2, C, D 1, D 2, D 3, E, F, G and H, and their levels vary with the cell cycle, CyclinC, D and E reach their maximum activity in G 1 phase and regulate the transition from G 1 to S phase (Huang et al., 2020). Their increased expression is seen in many primary malignant tumors.

P27 is a member of the cip/kip of CDKIs, i.e., p21, and can be detected by complexes with CyclinE-CDK 2, CyclinA-CDK 2 and CyclinD TK is a key enzyme for DNA synthesis from thymidine nucleosides and has two isozymes, cytoplasmic TK1 and mitochondrial TK2, which are associated with cytokinesis and are present at low levels during G 1 phase of cytokinesis (Jiang et al., 2021). TK 1 is associated with cell division, and the level of TK 1 is low in the G 1 phase of cell division, but gradually increases in the S phase and reaches a peak in the G 2 phase. Topoisomerase II is a nuclear enzyme that catalyzes the topoisomeric transformation of DNA and regulates the three-dimensional structure of DNA (Kawada & Taketo, 2011). It is closely related to chromatin or chromosome assembly, DNA recombination, gene transcription and DNA repair after damage. Overexpression of topoisomerase

II has been observed in a variety of solid malignancies (Khalaf & Abdulsahib, 2021). However, it has also been pointed out that proliferation-related marker assays lack uniform standards and are less convincing in guiding clinical practice (Liang et al., 2019).

3. Information and methods

3.1 General data

The clinical data of 190 patients with breast cancer who underwent SLNB in our breast surgery department were retrospectively analyzed. All cases were diagnosed by preoperative puncture or postoperative pathological examination, and the clinical stage was $T_{1\sim2}N_0M_0$. All patients were female, aged 28 to 80 years, with a median age of 48 years. The clinical characteristics of the 190 patients are shown in Table 1. The above patients underwent both SLNB and ALND except for 31 cases of breast-conserving axillary surgery, 4 cases of nipple-areola preserving complex + axillary surgery, and 5 cases of single incision with a total of 40 patients undergoing SLNB only (no ALND was performed after the SLN was determined to be negative by rapid pathological examination). Patients with SLNB were divided into a blue dye group (n = 56) and a combined group (n = 134) according to the tracer used.

Table 1(a): Clinical characteristics of 190 patients with SLNB breast cancer

Clinical features	**n**
Age	
< 50 years old	109
≥ 50 years old	81
Clinical stage	
T_1 (maximum diameter ≤ 2cm)	111
T_2 (2cm < maximum diameter ≤ 5cm)	79
Location of lesion	
Outer upper quadrant	112
Outer lower quadrant	27
Inner upper quadrant	21
Inner lower quadrant	11
Areola area	19
Nuclide injection site	
Peri-lesion	149
Areola area	41
Surgical procedure	
Radical breast-conserving surgery	31
Modified radical surgery	111
Breast-conserving axillary surgery	30

Table 1(b): Clinical characteristics of 190 patients with SLNB breast cancer

Clinical features	**n**
Modified radical surgery with preserved nipple-areola complex	5
Preserved nipple-areola complex + preserved axillary surgery	4
Single incision	5
Radical surgery	2
Pathological type	
Non-invasive carcinoma	19
Invasive carcinoma	171

3.2 Determination criteria of SLN

①The main methods of SLN detection are radionuclide method, dye method and combined method. In the present study, the SLN was localized by the method of melanin dye injection and the injection of radionuclide $[^{99m}TC]$ sulfated colloid mixture combined with melanin dye injection. ②After the injection of sulfated colloid, lymphatic scintigraphy was performed, and the location of the "hot spot" outside the injection site was marked on the body surface. ③All lymph nodes that exceeded 10% of the maximum lymph node count were measured before surgery. ④ The first blue-stained lymph node/group of blue-stained lymph nodes into which all the blue-stained lymphatic vessels entered after US blue dye injection. The combined method locates the suspected lymph nodes by palpation of the above methods and selects the cut as the SLN; the merocyanine staining method looks for the first lymph node/group of lymph nodes entered by blue-stained lymph vessels under direct vision as the SLN.

3.3 Operation method of SLNB

The patients and their families were firstly informed about the blue dye tracing method of SLN, and the patients signed the informed consent form and voluntarily chose this method. A total of 56 of the 190 patients in this group were traced by the blue dye injection method, and the blue injection ($2ml$: 20 mg/stem) was injected around the lump or the areola area 15 min before the operation, in four points: internal, external, upper, and lower, each point injected with $0.5ml$.

Among them, 36 cases were injected around the lump and 20 cases were injected in the areola area. If the patient was to undergo radical breast-conserving surgery, a transverse incision was made in the axillary fold in the direction of lymphatic drainage. If the patient was to undergo modified radical surgery, no additional incision was required, and the skin flap was freed at the same time. The day before the operation, the patient and family members were informed about the SLNB, and after the patient and family members understood the situation, they signed the SLNB consent form, and an

experienced senior physician from the breast surgery department marked the location of the lesion and the injection site according to the patient's condition, and then went to the nuclear medicine department for injection of technetium $[^{99m}TC]$ sulfide colloid mixture (produced by Beijing Shihong Drug Development Center).

The injection site: if the patient can palpate the lump, three injection points are chosen around the lump at 3, 6 and 9 points; if the lump cannot be palpated after biopsy, such as nipple overflow or calcified foci, three injection points are chosen in the areola area at 3, 6 and 9 points. Among the 190 patients in this group, 134 patients were localized with the combined tracer method of SLN, of which 112 were injected around the mass and 22 were injected in the areola area. The injection volume was 0.5 ml per site, totaling $1.5ml$. Some studies have shown that 0.5 ml to 2 $ml$of sulfur colloid can better visualize the lymph nodes in the majority of breast cancer patients. Lymphatic scintigraphy was performed under the Symbia SPECT (single-photon emission computed tomography) system from SIEMENS at 15 min and 30 min after injection of $[^{99m}TC]$ vulcanized colloids (Figure 1).

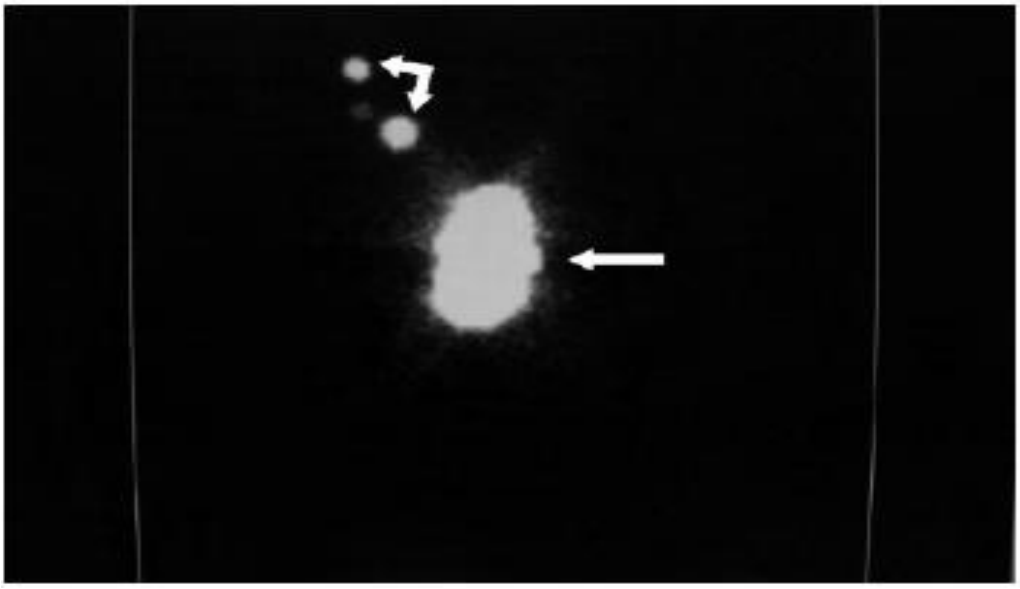

Figure 1: Lymphatic scintigraphy

Note: *SLN shown by right-angled arrow at the top, injection site shown by arrow at the bottom*

Preoperatively, the physician used a handheld λ -ray detector (Neoprobe 2000, Johnson & Johnson, USA) to first detect the background count, and then slid back and forth in an orderly manner toward the axilla to detect the "hot spot" location, marking all lymph nodes that exceeded 10% of the maximum lymph node count on the body surface. The primary surgeon injected $2ml$ of melanin around the lump or the areola area approximately 15 min before the procedure, with four injections of $0.5ml$ each at the internal, external, superior, and inferior sites. The injection site of melanin in the

combined method was the same as that of the $[^{99m}TC]$ sulfide colloid injection site, i.e., around the lump or into the areola area at the same time.

4. Results

In the combined group, 134 patients underwent SLNB by radionuclide combined with methylene blue dye tracing method, and all 134 cases were detected, with a detection rate of 100% (134/134) and 5 false negatives (SLN was negative and non-SLN was positive on routine histological section). 39 cases of axillary lymph node metastases were detected in this group, with a false negative rate of 12.8% (5/39). Among them, 31 cases did not undergo SLNB after negative SLN, and the remaining 103 cases underwent both SLNB and ALND.

In the blue-stained group, among the 56 patients who underwent SLNB using the Mebane dye injection tracer method, 54 cases were detected, and 2 cases were not detected, with a detection rate of 96.4% (54/56) and 3 false-negative patients. 30 patients in this group had axillary lymph node metastases, with a false-negative rate of 10.0% (3/30). Among them, 9 patients had SLNB only, and the rest had both SLNB and ALND in 47 cases.

The detection rates of the two groups were 100% (134/134) and 96.4% (54/56), respectively, and the differences were not statistically significant (p = 0.086, Table 2); the differences were not statistically significant when comparing the false-negative rates of the two groups by Fisher's exact probability test (p = 0.717, Table 2).

Table 2: Comparison of the results of the two tracer methods

Group	n	SLN			Detection rate (%)	p	ALN		False negative rate (%)	p
		Number of detections	+	-			+	-		
Joint group	134	134	34	100	100		39	64	5(12.8)	
Blue dye group	56	54	27	27	96.4	0.086	30	17	3(10.0)	0.717

In this study, a total of 505 SLNs were detected in 188 cases with an average of 2.7 SLNs, including 49 cases with 1 SLN, 56 cases with 2 SLNs, 38 cases with 3 SLNs, and 45 cases with ≥4 SLNs. In 150 patients who underwent SLNB, a total of 2378 axillary lymph nodes were cleared, with 5 to 44 lymph nodes detected in each case and an average of 15.9 lymph nodes detected in each case. In this study, 150 patients underwent both SLNB and ALND. Among the 148 patients with SLN detected, 69 patients had positive axillary lymph nodes, of which 8 had false negatives, and the false negative

rate in this study was 8/69×100% = 11.6%. Two cases were not detected in the blue-stained group, and the influence of the clinical characteristics of the patients in this group on the detection rate was analyzed.

The results showed that the effect of the patient's age on the detection rate was statistically significant (p = 0.042 < 0.05), while the other clinical characteristics such as lesion size, number of lymph nodes taken, pathological type, lesion site and injection site had no statistically significant effect on the detection rate of SLN (p > 0.05, Table 3).

Table 3: Effect of clinical characteristics on the detection rate of patients in the blue-stained group

Clinical features	**SLN**			P
	Number of detections	**Number of undetected cases**	**Detection rate (%)**	
Age				
< 50 years old	44	0	100	
≥ 50 years old	10	2	83.3	0.042
Clinical stage				
T_1	41	1	97.5	
T_2	13	1	93.4	0.472
Number of biopsies (SIN)				
1~2	29	2	92.9	
≥3	25	0	100	0.502
Pathological type				
Non-invasive carcinoma	7	0	100	
Invasive carcinoma	47	2	95.8	1.000
Lesion site				
Lateral quadrant	33	2	96.9	
Medial and areolar area	20	1	95.2	1.000
Injection site				
Peri-lesion	34	2	94.4	
Areola area	20	2	100	0.533

Among 190 patients in this study, 69 patients with axillary lymph node metastasis were detected, of which 8 cases were false negative for SLNB, that is, SLN was negative, but the results of routine pathological examination confirmed that axillary lymph nodes were positive. The relationship between clinical characteristics and false negative rate was analyzed as shown in table 4. The influence of age factors on false negative rate was statistically significant (p = 0.021 < 0.05). The false negative rate in the group aged < 50

years was significantly lower than that in the group aged ≥ 50 years, while there was no significant difference in the effects of other clinical features, such as mass size. Number of SLN biopsies, histopathological classification, lesion location and tracer injection site on the false negative rate (p > 0.05, table 4)

Table 4: Relationship between clinical characteristics and false-negative rate

Clinical features	**Number of axillary lymph node metastases**	**Number of false-negative cases**	**False-negative rate (%)**	P
Age				
< 50 years old	39	1	2.6	
≥ 50 years old	30	7	23.3	0.021
Clinical stage				
T_1	27	2	7.0	
T_2	42	6	14.8	0.578
Number of biopsies (SIN)				
1~2	39	4	10.3	
≥3	30	4	13.3	
Pathological type				
Non-invasive carcinoma	1	0	0	
Invasive carcinoma	68	8	11.8	1.000
Lesion site				
Lateral quadrant	52	5	9.6	
Medial and areolar area	17	3	17.8	0.644
Injection site				
Peri-lesion	62	8	12.6	
Areola area	7	0	0	1.000

5. Discussion

SLNB has been regarded as the standard treatment modality for surgical axillary management of invasive breast cancer because of its role in guiding the clinical stage and prognosis of patients, but it has many complications due to the blockage of lymphatic return to the upper extremity. Statistics show that among the complications of ALND, 15%-33% are pain, 70%-80% are numbness, 10%-20% are limited range of motion, 20%-30% are lymphedema, and 15%-30% are breast edema, and ALND has no therapeutic significance for patients with negative axillary lymph nodes, causing

unnecessary suffering to patients. Currently, most of the patients facing breast surgeons are early-stage breast cancer, and about 70% of early-stage breast cancer patients do not have axillary lymph node metastasis, and more and more data suggest that in early-stage breast cancer patients without SLN metastasis, SLN resection alone can achieve the same results as total axillary lymph node dissection, and its advantages of low complications, low trauma, and high quality of life are the goals of patients and surgeons.

The goal of SLN resection alone is the same as total axillary lymphatic dissection. Randomized trial studies have shown that there is no difference in disease-free survival in patients with negative SLN who are exempted from ALND compared to conventional ALND. The results of a foreign study showed that there was no statistically significant difference between the 5-year overall survival rate of patients in the group without ALND and the group with ALND, and there was no statistically significant difference in the cumulative breast cancer-related events in the two groups, while patients in the group without ALND had less postoperative surgical site and affected limb pain, shorter recovery time, and better function than those in the ALND group. Some studies have shown that the detection rate of SLNB can exceed that of ALND. As an important component of conventional breast cancer surgery (Mori et al., 2019; Qiu, Shao, Yang, Shen, & Zhang, 2011), the detection rate of SLNB can exceed 97%, with a false-positive rate of less than 10%. However, there was no significant difference in the survival time and overall survival time of SLNB in patients with local control, disease-free early-stage breast cancer with and without ALND. The results of another foreign study showed that the chance of axillary lymph node recurrence after SL-NB alone was only 0.25%-1%, and the resulting patient benefit was much greater than the chance of recurrence and metastasis. SLNB has gradually replaced ALND in the evaluation of axillary lymph nodes with fewer complications, and the accurate localization of SLN has naturally become the core of the whole biopsy procedure. Multiparametric gene expression profiling is a method of measuring multiple genes expressed in tumor tissue to estimate tumor biological behavior. The measurement of these genes may help in the diagnosis of breast cancer, the development of individualized treatment plans, and the estimation of prognosis. Multiparametric gene analysis attempts to further classify breast cancers based on the existing ER, PR, and HER 2-based staging with the aim of obtaining more homogeneous groupings to guide individualized treatment. Multi-parametric gene expression profiling is mainly performed by cDNA libraries, oligonucleotide microarrays, and multiplexPCR.

Onco-typeDX is an RT-PCR-based test that calculates the RS score by measuring 21 genes, and a high RS score is associated with recurrence. It has been reported that breast cancer patients with high RS scores are more likely to benefit from adjuvant chemotherapy (CMF regimens)(Rajendran, Khalaf, Alotaibi, & Alghamdi, 2021).The MammaPrint test is based on 70

genes associated with distant breast cancer metastasis screened by the Netherlands Cancer Institute and its collaborating institutions. These 70 genes include genes related to the regulation of cell proliferation as well as genes involved in tumor invasion, metastasis, and angiogenesis. However, the high requirements of MammaPrint test specimen processing have limited its wide application to some extent (Song, Kim, & Won, 2017; Takada et al., 2012). Bone marrow micrometastasis detection is performed by IHC or PCR, RT-PCR, or flow cytometry on bone marrow aspiration specimens from breast cancer patients to detect normal glandular epithelial cells as a positive result. It has been suggested in the literature that this method can be used as a complement to axillary lymph node biopsy or even as an alternative to the former to some extent(Zhang, Wu, & Zhang, 2021; Zhao et al., 2012).

Bone marrow micro metastases usually indicate a higher risk of recurrence and a poorer prognosis. However, it has been noted that epithelial cells can occasionally be detected in the bone marrow of healthy volunteers, and it is unclear whether the small number of epithelial cells found in the bone marrow is a normal physiological phenomenon; secondly, it is difficult to distinguish hematopoietic stem cells from hypo fractionated epithelial cells in the bone marrow, both morphologically and in terms of markers; again, patients with positive axillary lymph node biopsies, even without adjuvant chemotherapy, do not recur during a 20-year follow-up. The results of the study showed that 25% of the patients with positive axillary lymph node biopsy did not recur even without adjuvant chemotherapy. Whether the epithelial cells found in the bone marrow of breast cancer patients have the same biological characteristics as the glandular epithelium found in the axillary lymph nodes is unclear (Weissenbacher et al., 2010; Yu et al., 2013).

6. Conclusion

Our study provides compelling evidence that sentinel lymph node biopsy (SLNB) is a highly effective and reliable method for predicting axillary lymph node status in female athletes with early-stage breast cancer. Through the retrospective analysis of 190 cases, we have demonstrated that both the blue-staining method and the combined radionuclide and melanin staining tracer method are capable of accurately locating sentinel lymph nodes (SLNs), with a notable detection rate of 98.9%, an accuracy rate of 94.6%, and a false-negative rate of 11.6%. These findings underscore the utility of SLNB as a critical tool in the staging and treatment planning for breast cancer among physically active women. The study further highlights the significant effect of age on the detection and false-negative rates of SLN, advocating for the combined method as the preferred approach for athletes aged 50 years and above. Conversely, variables such as lesion location, size, nuclei injection site, and pathological type were found to have no substantial impact on the outcomes of SLN detection, suggesting that the efficacy of SLNB transcends

these clinical characteristics.

Importantly, this investigation into the feasibility and precision of SLNB within a cohort of female athletes opens new avenues for integrating considerations of physical fitness and athletic activity into breast cancer care. By acknowledging the unique physiological and lifestyle factors of this population, our study paves the way for more personalized, fitness-conscious cancer treatment strategies that not only aim to optimize oncological outcomes but also preserve the quality of life and athletic performance. In sentinel lymph node biopsy stands as a cornerstone technique in the axillary staging of breast cancer for female athletes, offering a balance between thorough cancer care and the maintenance of physical fitness. Future research should continue to explore and refine SLNB methodologies, ensuring that the evolving needs of active women are met with precision, empathy, and respect for their athletic commitments.

Data Availability

The experimental data used to support the findings of this study are av ailable from the corresponding author upon request.

Conflicts of Interest

The authors declared that they have no conflicts of interest regarding this work.

Funding Statement

There is no specific funding to support this research.

References

Bae, M. S. (2020). Using deep learning to predict axillary lymph node metastasis from US images of breast cancer. In (Vol. 294, pp. 29-30): Radiological Society of North America.

Bejnordi, B. E., Veta, M., Van Diest, P. J., Van Ginneken, B., Karssemeijer, N., Litjens, G., . . . Balkenhol, M. (2017). Diagnostic assessment of deep learning algorithms for detection of lymph node metastases in women with breast cancer. *Jama, 318*(22), 2199-2210.

Biswas, S., Sengupta, S., Roy Chowdhury, S., Jana, S., Mandal, G., Mandal, P. K., . . . Kuprash, D. V. (2014). CXCL13–CXCR5 co-expression regulates epithelial to mesenchymal transition of breast cancer cells during lymph node metastasis. *Breast cancer research and treatment, 143*, 265-276.

Chen, J.-y., Chen, J.-j., Yang, B.-l., Liu, Z.-b., Huang, X.-y., Liu, G.-y., . . . Shao, Z.-m. (2012). Predicting sentinel lymph node metastasis in a

Chinese breast cancer population: assessment of an existing nomogram and a new predictive nomogram. *Breast cancer research and treatment, 135*, 839-848.

Chen, W., Cai, F., Zhang, B., Barekati, Z., & Zhong, X. Y. (2013). The level of circulating miRNA-10b and miRNA-373 in detecting lymph node metastasis of breast cancer: potential biomarkers. *Tumor Biology, 34*, 455-462.

de Boer, M., van Dijck, J. A., Bult, P., Borm, G. F., & Tjan-Heijnen, V. C. (2010). Breast cancer prognosis and occult lymph node metastases, isolated tumor cells, and micrometastases. *Journal of the National Cancer Institute, 102*(6), 410-425.

Dong, Y., Feng, Q., Yang, W., Lu, Z., Deng, C., Zhang, L., . . . Pei, S. (2018). Preoperative prediction of sentinel lymph node metastasis in breast cancer based on radiomics of T2-weighted fat-suppression and diffusion-weighted MRI. *European radiology, 28*(2), 582-591.

Duan, W., Gu, J., Wen, M., Zhang, G., Ji, Y., & Mumtaz, S. (2020). Emerging technologies for 5G-IoV networks: applications, trends and opportunities. *IEEE Network, 34*(5), 283-289.

Gill, H. S., Khalaf, O. I., Alotaibi, Y., Alghamdi, S., & Alassery, F. (2022). Multi-Model CNN-RNN-LSTM Based Fruit Recognition and Classification. *Intelligent Automation & Soft Computing, 33*(1).

Giuliano, A. E., Hunt, K. K., Ballman, K. V., Beitsch, P. D., Whitworth, P. W., Blumencranz, P. W., . . . Morrow, M. (2011). Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *Jama, 305*(6), 569-575.

Han, P., Yang, H., Liu, M., Cheng, L., Wang, S., Tong, F., . . . Liu, H. (2020). Lymph node predictive model with in vitro ultrasound features for breast cancer lymph node metastasis. *Ultrasound in Medicine & Biology, 46*(6), 1395-1402.

Heo, D. S., Choi, H., Yeom, M. Y., Song, B. J., & Oh, S. J. (2014). Serum levels of matrix metalloproteinase-9 predict lymph node metastasis in breast cancer patients. *Oncology reports, 31*(4), 1567-1572.

Huang, Y., Li, J., Chen, Y., Jiang, P., Wang, L., & Hu, J. (2020). Identification of early recurrence factors in childhood and adolescent B-cell acute lymphoblastic leukemia based on integrated bioinformatics analysis. *Frontiers in Oncology, 10*, 565455.

Jiang, D., Wang, F., Lv, Z., Mumtaz, S., Al-Rubaye, S., Tsourdos, A., & Dobre, O. (2021). QoE-aware efficient content distribution scheme for satellite-terrestrial networks. *IEEE Transactions on Mobile Computing, 22*(1), 443-458.

Kawada, K., & Taketo, M. M. (2011). Significance and mechanism of lymph node metastasis in cancer progression. *Cancer research, 71*(4), 1214-1218.

Khalaf, O. I., & Abdulsahib, G. M. (2021). Design and Performance Analysis of

Wireless IPv6 for Data Exchange. *Journal of Information Science & Engineering, 37*(6).

Liang, Y., Chen, X., Tong, Y., Zhan, W., Zhu, Y., Wu, J., . . . Li, Y. (2019). Higher axillary lymph node metastasis burden in breast cancer patients with positive preoperative node biopsy: may not be appropriate to receive sentinel lymph node biopsy in the post-ACOSOG Z0011 trial era. *World Journal of Surgical Oncology, 17*, 1-9.

Mori, N., Mugikura, S., Miyashita, M., Kudo, Y., Suzuki, M., Li, L., . . . Takase, K. (2019). Perfusion contrast-enhanced ultrasound to predict early lymph-node metastasis in breast cancer. *Japanese Journal of Radiology, 37*, 145-153.

Qiu, J., Shao, S., Yang, G., Shen, Z., & Zhang, Y. (2011). Association of Toll like receptor 9 expression with lymph node metastasis in human breast cancer. *Neoplasma, 58*(3), 251-255.

Rajendran, S., Khalaf, O. I., Alotaibi, Y., & Alghamdi, S. (2021). MapReduce-based big data classification model using feature subset selection and hyperparameter tuned deep belief network. *Scientific reports, 11*(1), 24138.

Song, B.-I., Kim, H. W., & Won, K. S. (2017). Predictive value of 18 F-FDG PET/CT for axillary lymph node metastasis in invasive ductal breast cancer. *Annals of surgical oncology, 24*, 2174-2181.

Takada, M., Sugimoto, M., Naito, Y., Moon, H.-G., Han, W., Noh, D.-Y., . . . Inamoto, T. (2012). Prediction of axillary lymph node metastasis in primary breast cancer patients using a decision tree-based model. *BMC medical informatics and decision making, 12*, 1-10.

Weissenbacher, T. M., Zschage, M., Janni, W., Jeschke, U., Dimpfl, T., Mayr, D., . . . Dian, D. (2010). Multicentric and multifocal versus unifocal breast cancer: is the tumor-node-metastasis classification justified? *Breast cancer research and treatment, 122*, 27-34.

Yu, J., Du, W., Yan, F., Wang, Y., Li, H., Cao, S., . . . Ren, X. (2013). Myeloid-derived suppressor cells suppress antitumor immune responses through IDO expression and correlate with lymph node metastasis in patients with breast cancer. *The Journal of immunology, 190*(7), 3783-3797.

Zhang, Z., Wu, D., & Zhang, C. (2021). Study of cellular traffic prediction based on multi-channel sparse LSTM. *Computer Science, 48*(6), 296-300.

Zhao, Y.-C., Ni, X.-J., Li, Y., Dai, M., Yuan, Z.-X., Zhu, Y.-Y., & Luo, C.-Y. (2012). Peritumoral lymphangiogenesis induced by vascular endothelial growth factor C and D promotes lymph node metastasis in breast cancer patients. *World journal of surgical oncology, 10*(1), 1-9.