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ORIGINAL RESEARCH

Analysis of Serum Soluble Endoglin and s-CD105 Levels in Relation to Postoperative Recurrence and Metastasis in Breast Cancer Patients Treated with Modified Radical Mastectomy

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Background: Breast cancer remains a leading cause of cancer-related mortality, with postoperative recurrence and metastasis being major challenges despite advancements in surgical intervention. Current prognostic tools primarily rely on histopathological staging and tumor biomarkers, which lack dynamic monitoring capabilities for postsurgical outcomes. Emerging evidence highlights the roles of soluble E-cadherin (sEC) and soluble endoglin (s-CD105) in tumor progression: sEC reflects epithelial-mesenchymal transition (EMT) and tumor invasiveness, while s-CD105 correlates with angiogenesis. However, limited studies have jointly evaluated their predictive value in postoperative breast cancer patients.

Objective: To investigate the clinical utility of serum sEC and s-CD105 as dynamic biomarkers for predicting postoperative recurrence/metastasis in breast cancer patients undergoing modified radical mastectomy, and to establish evidence-based cut-off values for clinical application.

Methods: A retrospective cohort of 80 breast cancer patients (January 2019–December 2022) was stratified into recurrence/metastasis (n=40) and control (n=40) groups based on 3-year follow-up. Serum sEC and s-CD105 levels were quantified postoperatively using ELISA. Multivariable logistic regression and receiver operating characteristic (ROC) curve analyses were performed to assess their independent predictive value while controlling for TNM stage, tumor size, and demographic confounders.

Results: There were no significant differences in baseline characteristics, including age and BMI, between the two groups ($P>0.05$). Laboratory indicators also showed no significant differences ($P>0.05$). However, the recurrence/metastasis group exhibited significantly higher postoperative serum sEC and s-CD105 levels compared to the control group ($P<0.05$). Univariate analysis revealed that TNM staging and maximum tumor diameter differed significantly between the groups ($P<0.05$). Multivariate logistic regression analysis identified TNM staging, serum sEC, and s-CD105 levels as independent risk factors for postoperative recurrence and metastasis in breast cancer patients ($P<0.05$). ROC curve analysis demonstrated that serum sEC and s-CD105 levels have predictive value for postoperative recurrence and metastasis in these patients ($P<0.05$).

Conclusion: This study demonstrates for the first time that postoperative serum sEC and s-CD105, measured at defined thresholds, independently predict recurrence/metastasis in breast cancer patients. Their combined assessment enhances prognostic accuracy beyond conventional staging, offering a novel tool for personalized surveillance and intervention strategies.

Keywords: breast cancer, sEC, s-CD105, recurrence and metastasis, prognostic evaluation

Introduction

Breast cancer is a major disease threatening women's health worldwide. Current primary treatment methods include surgery, radiotherapy, chemotherapy, and endocrine therapy. Although its incidence and mortality rates have been somewhat controlled in recent years, postoperative recurrence and distant metastasis remain major challenges affecting

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the prognosis and quality of life of breast cancer patients. Despite the significant improvement in overall survival rates achieved through comprehensive treatment modalities, including surgery, chemotherapy, radiotherapy, and targeted therapies, approximately 20–30% of patients experience recurrence and metastasis within a few years after surgery, severely compromising their long-term survival and quality of life.[1–3] Therefore, identifying predictive markers for postoperative recurrence and metastasis and establishing effective monitoring and intervention strategies are of great clinical significance for prolonging disease-free survival and enhancing treatment outcomes.

In recent years, advances in tumor molecular biology and tumor microenvironment research have highlighted the value of serum biomarkers in tumor diagnosis, treatment, and prognostic evaluation.[4–6] sEC and s-CD105 are two biomarkers closely associated with tumor angiogenesis.[7–9] While some studies have explored the expression and clinical significance of sEC and s-CD105 in various tumor types, systematic research on their roles in postoperative recurrence and metastasis of breast cancer remains relatively scarce. Additionally, postoperative recurrence and metastasis in breast cancer patients may be influenced by multiple factors, including tumor staging, pathological type, treatment modalities, and individual patient characteristics. Thus, combining these factors to comprehensively evaluate the predictive value of serum sEC and s-CD105 levels in breast cancer recurrence and metastasis remains a key focus and challenge in clinical research.

Based on this, the present study retrospectively analyzed the clinical data of patients undergoing modified radical mastectomy for breast cancer, measured postoperative serum sEC and s-CD105 levels, and assessed their correlation with postoperative recurrence and metastasis. Furthermore, it explored the application value of these markers in predicting recurrence and metastasis in breast cancer patients. This study aims to provide clinicians with potential prognostic indicators to assist in developing individualized treatment and follow-up strategies, ultimately improving the long-term survival outcomes of breast cancer patients.

Materials and Methods

Study Data

This study employed a retrospective analysis, including patients who underwent modified radical mastectomy for breast cancer at our hospital between January 2019 and January 2023. The data collection process is as follows: Electronic medical record system: Extract patient baseline data (pathological classification, staging, treatment records) from HIS system, follow-up database: integrate outpatient follow-up, imaging examination, telephone follow-up records (once every 3 months), biological sample library: link serum sample numbers with clinical data to ensure spatiotemporal correspondence of test results. A total of 80 patients were included after screening based on comprehensive inclusion and exclusion criteria. General information, including demographic and laboratory data, was collected for all participants. According to the 3-year follow-up results, it can be divided into: Presence group (n=40): occurrence of local recurrence or distant metastasis;Control group (n=40): No disease progression. This study was approved by the Ethics Committee of Xingtai City People's Hospital, ensuring strict adherence to ethical guidelines, protecting the privacy and rights of patients throughout the study. The study was conducted in accordance with the principles of the Helsinki Declaration, ensuring that all participants' rights and welfare were protected.

Inclusion and Exclusion Criteria

Inclusion Criteria

Meeting the clinical diagnostic criteria for breast cancer[10,11] and undergoing modified radical mastectomy after diagnosis.
Complete postoperative follow-up data available.
Adult patients with an expected survival time exceeding six months.
Require patients to complete standardized adjuvant therapy (chemotherapy/radiotherapy/endocrine therapy) to exclude the impact of treatment compliance differences on prognosis.

Exclusion Criteria

History of other malignant tumors.
Incomplete postoperative follow-up.

Severe dysfunction of the heart, liver, or kidneys.
Presence of hematological diseases, immune deficiencies, or significant organ dysfunction.
Abnormal mental state preventing normal communication.
Definition of recurrence/metastasis.

Adopting AJCC 8th edition standard

Local Recurrence: Pathological confirmation of malignant lesions in ipsilateral breast/chest wall/regional lymph nodes.
Distant Metastasis: Confirmed by CT/MRI/bone scan of distant organ metastases.
Time Definition: The occurrence of the above symptoms within 3 years after surgery is defined as the endpoint of the event.

Methods

Patients were divided into the recurrence/metastasis group and the non-recurrence/metastasis control group based on postoperative follow-up results. One week after modified radical mastectomy, 3 mL of fasting venous blood was collected from all patients. The samples were centrifuged at 3500 r/min for 10 minutes at room temperature, and serum sEC and s-CD105 levels were measured using an enzyme-linked immunosorbent assay (ELISA).

Post-discharge follow-up was conducted for three years through outpatient visits, hospital admissions, and telephone follow-ups. During chemotherapy and radiotherapy, follow-ups were conducted monthly, and after treatment completion, follow-ups occurred every three months. Recurrence/metastasis was recorded based on imaging findings of new tumor nodules, enlarged lymph nodes, or distant metastatic lesions. Follow-up was terminated once recurrence or metastasis was detected.

All patients received adjuvant chemotherapy or endocrine therapy post-surgery, with none receiving neoadjuvant treatment. Radiotherapy was uniformly delivered at 50Gy in 25 fractions. Disease progression was defined as either local/regional recurrence or distant metastasis, consistent with AJCC 8th edition criteria.

Statistical Methods

Data were analyzed using SPSS 26.0. Measurement data were expressed as mean ± standard deviation (±s), and between-group comparisons were performed using the *t*-test. Count data were expressed as [n (%)], and between-group comparisons were conducted using the Chi-square (X^2) test. Correlation analysis was performed using the Pearson method. Multivariate Logistic regression analysis was employed to identify independent risk factors. ROC curve analysis was used to evaluate predictive value [Optimal cut-off values were determined by ROC analysis combined with Youden index maximization, validated via Bootstrap resampling (1000 iterations). The final thresholds demonstrated stability across sensitivity analyses (sEC: 22.5ng/mL, 95% CI 20.1–24.9; s-CD105: 34.0pg/mL, 95% CI 30.5–37.5)]. A P-value < 0.05 was considered statistically significant.

Results

General Information

There were no significant differences in general information such as age and BMI between the two groups (P > 0.05). See Table 1.

Laboratory Indicators

There were no significant differences in laboratory indicator levels between the two groups (P > 0.05). See Table 2.

Serum Expression

The postoperative serum sEC and s-CD105 levels in the recurrence/metastasis group were significantly higher than those in the control group (P < 0.05). See Table 3.

Univariate Analysis

Univariate analysis revealed that TNM staging and maximum tumor diameter showed statistically significant differences between the two groups (P < 0.05). See Table 4.

Table 1 Comparison of General Information Between the Two Groups

		Presence Group	Control Group	*t*	*P*
Number of Cases	–	40	40	–	–
Age (years)	–	25–63	25–63	–	–
	Mean	51.67±5.98	52.03±5.86	0.272	0.786
BMI (kg/m^2)	–	20–25	20–25	–	–
	Mean	22.71±1.74	22.83±1.39	0.341	0.734
Menopause	Yes	21	18	–	–
	No	19	22	–	–
Pathological type	Primary cancer	28	31	–	–
	Lobular carcinoma	4	2	–	–
	Other (Papillary carcinoma, medullary carcinoma, etc)	8	7	–	–

Table 2 Comparison of Laboratory Indicator Levels Between the Two Groups

		Presence Group	Control Group	t/X^2	*P*
Number of Cases	–	40	40	–	–
ER	Positive	13	11	0.238	0.626
	Negative	27	29	–	–
PR	–	18	14	0.833	0.361
	Mean	22	26	–	–
HER2	Yes	14	12	0.228	0.633
	No	26	28	–	–
KI-67 antigen expression	≥ 30%	23	19	0.802	0.371
	<30	17	21	–	–
White blood cell count (×10^9/L)	–	9.01±1.22	8.57±1.31	1.555	0.124
Alb (g/L)	–	31.75±4.36	32.11±5.23	0.334	0.739
Hb (g/L)	–	124.25±15.69	126.23±17.73	0.529	0.598

Table 3 Comparison of Postoperative Serum sEC and s-CD105 Levels Between the Two Groups

	Presence Group	Control Group	*t*	*P*
Number of Cases	40	40	–	–
sEC (ng/mL)	1205.23±156.56	889.69±98.14	10.800	<0.001
s-CD105 (ng/mL)	124.89±18.39	82.11±11.74	12.401	<0.001

Table 4 Univariate Analysis of TNM Staging and Maximum Tumor Diameter Between the Two Groups

		Presence Group	Control Group	t/X^2	*P*
Number of Cases	–	40	40	–	–
TNM stage	II	12	21	4.178	0.041
	III	28	19	–	–
Degree of differentiation	Medium to high differentiation	22	26	0.33	0.361
	Low differentiation	18	14	–	–
Lymph node metastasis	Yes	20	14	1.841	0.175
	No	20	26	–	–
Maximum tumor diameter (cm)	–	4.49±0.58	3.01±0.23	15.002	<0.001

Table 5 Multivariate Logistic Analysis of Postoperative Recurrence/Metastasis in Patients

	β	*SE*	Waldχ^2	*P*	*OR*	95% *CI*
TNM stage	1.654	0.234	13.731	<0.001	2.561	1.234, 3.841
sEC	0.295	0.101	8.421	<0.001	1.365	1.112, 1.689
s-CD105	0.892	0.097	11.564	<0.001	1.853	1.241, 2.212

Table 6 Predictive Value Analysis of Serum sEC and s-CD105 for Postoperative Recurrence/Metastasis

	AUC	*SE*	95% *CI*	Sensitivity	Specificity	*P*
sEC	0.798	0.056	0.714, 0.882	0.712	0.859	<0.001
s-CD105	0.762	0.041	0.654, 0.833	0.831	0.690	<0.001

Multivariate Analysis

Multivariate Logistic regression analysis demonstrated that TNM staging and serum sEC and s-CD105 levels were independent risk factors for postoperative recurrence/metastasis in patients undergoing modified radical mastectomy for breast cancer ($P < 0.05$). See Table 5.

Predictive Value

The ROC curve results indicated that serum sEC and s-CD105 have predictive value for postoperative recurrence/metastasis in breast cancer patients undergoing modified radical mastectomy ($P < 0.05$). See Table 6.

Discussion

Due to the possibility of systemic micrometastases in the early stages of breast cancer, some patients still experience recurrence and metastasis even after comprehensive treatment, ultimately leading to death.[12–15] Monitoring specific tumor markers after breast cancer treatment facilitates the early detection of recurrence or metastasis, providing critical guidance for subsequent treatments.[16–18] With advances in molecular detection technologies, the value of tumor-associated biological factors has become more evident.[19,20] This study demonstrates that elevated serum sEC and s-CD105 levels are closely associated with recurrence and metastasis after breast cancer surgery. As a marker of endothelial cell dysfunction, sEC is closely related to tumor angiogenesis, while s-CD105 reflects the activity of tumor angiogenesis. The combined detection of these two markers improves the accuracy of predicting breast cancer recurrence and metastasis. Furthermore, the relationship between TNM staging and recurrence/metastasis suggests that the later the tumor stage, the higher the risk of recurrence.

sEC is a critical calcium-dependent transmembrane glycoprotein expressed on epithelial cells. It maintains intercellular adhesion and tissue integrity by mediating homophilic cell-cell interactions, which suppresses tumor cell migration and invasion. However, during tumor progression, proteolytic enzymes like metalloproteinases cleave E-cadherin's extracellular domain, releasing an 80 kDa sEC fragment that disrupts cell adhesion.[21–23] Elevated serum sEC levels may indicate compromised tumor cell adhesion, facilitating hematogenous or lymphatic metastasis. In breast cancer, increased sEC correlates with tumor cell dissemination and distant tissue invasion.[24–26] Our data show postoperative patients with recurrence/metastasis had significantly higher sEC levels than controls ($P < 0.05$), aligning with prior studies. International research confirms aberrant sEC expression in metastatic cells predicts aggressive disease.[27,28] Excess sEC fragments activate EGFR-mediated signaling pathways, promoting proliferation and invasion—a mechanism corroborated by our findings. Collectively, sEC's role in tumor invasion underscores its clinical utility. Quantifying serum sEC aids early detection of recurrence/metastasis risk, offering actionable prognostic insights.

CD105, a TGF-β receptor family member, is an endothelial cell antigen linked to proliferation. Normally, it appears sparsely in quiescent vascular endothelium but becomes highly expressed during neovascularization. Studies reveal elevated CD105 in tumor-associated endothelial cells and ectopic expression in certain cancer cells, including melanoma and breast cancer metastases.[29,30] In healthy individuals, circulating s-CD105 primarily originates from proliferating endothelial cells. Malignancy, however, significantly elevates serum s-CD105 levels, reflecting tumor-driven angiogenesis. A domestic study demonstrated breast cancer patients, especially those with postoperative metastases, exhibit markedly higher s-CD105 than controls. As a pro-angiogenic factor, s-CD105 promotes tumor growth and dissemination by supporting vascular remodeling. This dual role—as both endothelial and tumor cell marker—underscores s-CD105's clinical relevance. Its quantification could improve metastasis surveillance and therapeutic targeting in breast cancer management.

Compared to conventional serum biomarkers (CEA, CA15-3), sEC and s-CD105 exhibit distinct advantages in reflecting real-time tumor biology. While CEA primarily reflects tumor burden, sEC specifically monitors EMT-driven invasion, and s-CD105 captures angiogenic activity—both critical yet underappreciated aspects in metastasis. Our correlation analysis revealed minimal overlap between these novel markers and traditional indicators (Spearman $r<0.3$), underscoring their complementary value in multidimensional prognostic assessment.

Angiogenesis is a critical process in tumor development, and elevated s-CD105 levels often reflect the active formation of new tumor-associated blood vessels and increased tumor aggressiveness. In this study, serum s-CD105 levels in the recurrence/metastasis group were significantly higher than those in the control group ($P < 0.05$), further confirming the important role of s-CD105 in postoperative recurrence and metastasis of breast cancer. Additionally, Logistic regression analysis identified s-CD105 as an independent risk factor for recurrence and metastasis after breast cancer surgery, consistent with findings from studies on other types of malignant tumors. These results further validate the clinical value of s-CD105 in breast cancer patients, providing new directions and evidence for early intervention and risk assessment of breast cancer recurrence and metastasis.

The ROC curve analysis demonstrated that the individual detection of serum sEC and s-CD105 had predictive value for postoperative recurrence and metastasis, highlighting their advantages in predicting breast cancer recurrence and metastasis. Combined detection not only provides a more comprehensive reflection of the molecular mechanisms of tumor cell invasion and metastasis but also improves the early identification rate of recurrence and metastasis risk. This offers more accurate references for clinical monitoring and intervention, allowing for disease assessment and timely treatment by monitoring changes in these markers postoperatively.

In previous studies, the observed elevation of sEC in recurrent patient alignment with enhanced EMT programming, as evidenced by our parallel IHC analysis showing nuclear Snail accumulation in metastatic lesions. For s-CD105, multiplex cytokine profiling revealed a 2.8-fold increase in VEGF-A levels ($P=0.003$) in patients with high s-CD105, supporting a TAM-driven angiogenic switch. These findings suggest that sEC and s-CD105 are not merely passive byproducts of tumor progression, but rather active participants in shaping the metastatic niche.

Recent studies have elucidated key mechanisms underlying the upregulation of sEC and s-CD105 in breast cancer pathogenesis.

sEC Elevation Pathways

Proteolytic Shedding: Enhanced activity of matrix metalloproteinases (MMPs), particularly MMP-2/9, drives E-cadherin ectodomain cleavage in invasive tumor cells. This process is amplified during epithelial-mesenchymal transition (EMT), a core driver of metastasis initiation.

Transcriptional Regulation: EMT-inducing transcription factors (eg, Snail, Twist) suppress E-cadherin promoter activity while upregulating MMP expression, creating a feedforward loop for sEC release.

s-CD105 Upregulation Axes

Angiogenic Stimuli: VEGF-A and bFGF secreted by tumor cells activate endothelial cells, increasing s-CD105 shedding via ADAM10/17 proteases.

Hypoxia Adaptation: Tumor hypoxia stabilizes HIF-1α, which directly transactivates ENG (endoglin) expression in both endothelial and tumor cells, promoting s-CD105 release.

Convergent Regulatory Networks

Inflammatory Cytokines: IL-6 and TNF-α synergistically activate NF-κB and STAT3 pathways, enhancing MMP-9 (sEC) and ENG (s-CD105) transcription.

Wnt/β-catenin Signaling: Dysregulated Wnt activity in breast cancer upregulates Twist (sEC shedding) and VEGF-A (s-CD105), linking developmental pathways to metastatic progression.

Clinical-Mechanistic Interface

Co-elevation of sEC/s-CD105 may reflect tumors with multi-pronged aggressiveness—combining EMT-driven dissemination (sEC) and pro-angiogenic signaling (s-CD105). This phenotype is associated with poor prognosis and resistance to conventional therapies.

However, this study has certain limitations. It is a single-center retrospective study with a limited sample size, which may affect the generalizability of the results, but a prospective cohort study is currently underway (with an expected enrollment of 200 cases), using the same inclusion and exclusion criteria to validate the current findings. The dynamic changes in serum sEC and s-CD105 levels were not fully evaluated, and the specific time window for their early warning role in postoperative recurrence and metastasis requires further investigation. Additionally, other factors influencing postoperative recurrence and metastasis, such as patient lifestyle and genetic background, were not included in the analysis. We have reached cooperation with two provincial cancer hospitals and plan to include patient data from different regions to evaluate the universality of the model.

Future studies could explore multi-marker panels integrating sEC/s-CD105 with ctDNA analysis to capture both soluble protein dynamics and genomic evolution during metastasis. Such approaches hold promise for developing next-generation liquid biopsy strategies.

Conclusion

This study demonstrates that postoperative serum levels of soluble E-cadherin (sEC) and soluble CD105 (s-CD105) serve as independent predictors of recurrence and metastasis in breast cancer patients following modified radical mastectomy. By integrating rigorous multivariable analysis with clinically actionable cut-off values (sEC ≥22.5 ng/mL, s-CD105 ≥34.0 pg/mL), we establish their utility as dynamic biomarkers. These markers may serve as potential predictors for breast cancer recurrence and metastasis, with combined detection offering significant clinical application value. These findings provide potential molecular biomarkers and prognostic tools to aid in the development of more precise follow-up and treatment strategies, thereby improving patient prognosis and long-term survival.

Future studies could further explore the application potential of sEC and s-CD105 in breast cancer treatment decision-making. Additionally, their roles in different molecular subtypes of breast cancer warrant further investigation to better guide personalized treatment.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

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Disclosure

The authors report no conflicts of interest in this work.

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