CANCER DIAGNOSIS & PROGNOSIS *5*: 855-861 (2025)
doi: 10.21873/cdp.10500

Podoplanin – Related Lymphatic Micro Vessel Density Digital Analysis in Breast Adenocarcinoma

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Abstract

Background/Aim: Neo-lymphangiogenesis induces lymphatic invasion of cancer cells, significantly increasing the metastatic potential of breast carcinomas (BCs). Among the molecules that are implicated in lymphangiogenesis, podoplanin (PDPN, gene locus: 1p36.21) – a transmembrane receptor glycoprotein – is expressed exclusively in lymphatic vessels. The current study explored the impact of PDPN-dependent mean lymphatic micro-vessel density (mLMVD) in invasive ductal (inDBC) and invasive lobular breast adenocarcinomas (inLBC).

Materials and Methods: A set of thirty (n=30) paraffin-embedded invasive BC tissue sections (22 inDBCs and 8 inLBCs, respectively) were analyzed by applying a combination of immunocytochemistry (IHC) and digital image analysis (DIA) assays.

Results: High and moderate mLMVD rates (defined by the mean number of lymphatic domains with emboli in five optical fields under 400X magnification) were detected in 5/30 (16.6%) and 6/30 (20%) cases (total 11/30 (36.6%),

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Received June 11, 2025 | Revised July 8, 2025 | Accepted July 11, 2025

respectively. In these cases, PDPN demonstrated strong cytoplasmic/membranous staining intensity. The remaining 19 cases (63.4%) demonstrated low levels of mLMVD. mLMVD was significantly correlated with the stage of the examined malignancies (p=0.019), whereas a marginal association with the grade of differentiation was identified (p=0.042). No significant correlation was observed with histological subtype (p=0.234) or tumor size (p=0.085).
Conclusion: Neo-lymphangiogenesis in BCs is a critical histological feature in the progression of the malignancy and is correlated with an aggressive phenotype (advanced stage). PDPN expression in lymphatic micro vessels is a reliable biomarker for evaluating lymphangiogenic activity in BCs, independently of their histotype, especially when assessed with precise DIA techniques.

Keywords: Podoplanin, breast, carcinoma, immunohistochemistry, biomarkers, lymphangiogenesis, digital analysis.

Introduction

Lymphangiogenesis is a significant physiological procedure leading to the formation of new lymphatic vessels, the appropriate stromal substrate for the development and functionality of the human lymphatic system (1). In contrast, the neo-lymphangiogenesis-mediated lymphatic vessel invasion induces the metastatic potential of malignancies, affecting the survival rates and prognosis of patients (2-6). Among the molecules that are considered reliable biomarkers for estimating the levels of lymphangiogenesis, podoplanin (PDPN) is one of the most prominent (7). The PDPN gene (gene locus: 1p36.21) encodes for a transmembrane receptor, a mucin – type glycosylated glycoprotein. It consists of three domains: an extracellular, a transmembrane and an intracellular tail (8). PDPN plays a key role in normal lymphatic development and functional homeostasis of the immune system, whereas its abnormal expression leads to excessive lymphatic infiltration and spread of malignant tumors (9-12). Concerning breast adenocarcinoma, PDNP expression detects neo-lymphatic domains that include cancerous emboli. This histological element serves as absolute evidence of high metastatic potential (advance tumor stage) in the corresponding patients (13, 14). In the current experimental study –based on a combination of immunohistochemistry (IHC) and digital image analysis (DIA), we focused on podoplanin - based mean lymphatic micro-vessel density (mLMVD) measurement in invasive ductal (inDBC) and invasive lobular breast adenocarcinomas (inLBC). We also explored its impact on the clinic-pathological parameters of the examined patients.

Materials and Methods

Study group. We used a pool of thirty (n=30) archival, formalin-fixed and paraffin-embedded inDBC (n=22) and inLBC (n=8) tissue specimens obtained during breast cancer surgical resection. The First Department of Obstetrics and Gynaecology, Medical School, National and Kapodistrian University of Athens, "Alexandra" General Hospital, Athens, Greece and the corresponding Ethics Committee of the National and Kapodistrian University of Athens consented to the use of these tissues for research purposes (Reference ID research protocol: 51/KM77/2022 Medical School/MSc Program: Breast Lesions), according to World Medical Association Declaration of Helsinki guidelines (2008, revised 2014). The prepared tissue sections were fixed in 10% neutral-buffered formalin. Hematoxylin and eosin (H&E)-stained slides were evaluated by two independent pathologists for the histo-categorization, grading and staging of the examined malignant cases according to the World Health Organization (WHO) pathology guidelines (15).

Antibodies and immunohistochemistry assay (IHC). PDPN protein expression analysis was performed using an IHC assay. We applied the ready-to-use anti-PDPN mouse

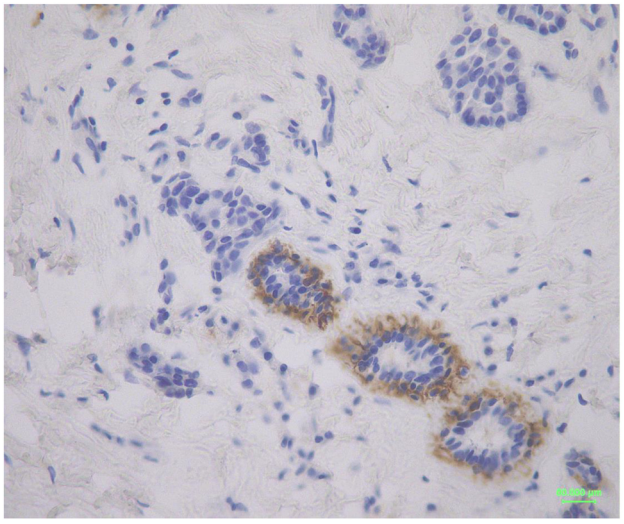

Figure 1. *Podoplanin expression pattern in breast adenocarcinoma. A case of invasive ductal breast adenocarcinoma demonstrating novel lymphatic vessels with cancer-infiltrated lumen. Note the strong cytoplasmic/membranous, brown endothelial ring-like staining expression of the marker. Additionally, the mLMVD demonstrated a value of 3,5 lymphatic domains per optical field (original magnification 400×, DAB brown chromogen).*

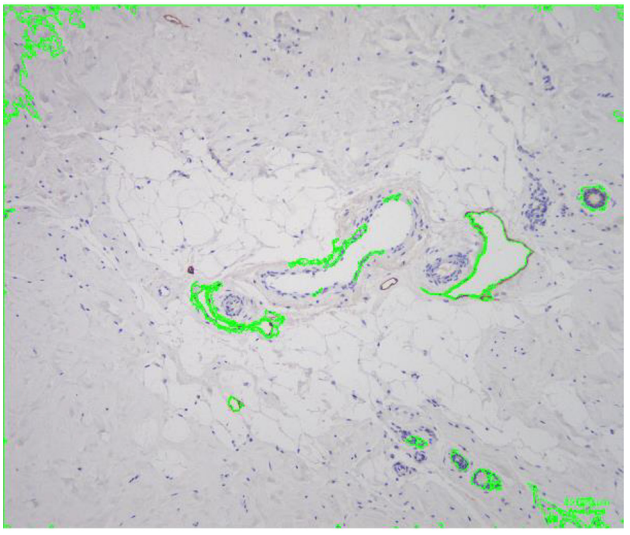

Figure 2. *Implementation of a digital image analysis algorithm for combined podoplanin protein expression and lymphatic microvessel density measurements. Green encircled areas represent different expression levels on the immunostained slide and detect the absolute number of lymphatic domains per optical field (DAB brown chromogen, original magnification 100×).*

monoclonal antibody (clone D-240, Dako/Agilent, Santa Clara, CA, USA; dilution 1:150). The IHC protocol was implemented on 3-4 μm thick serial tissue sections, according to our previous published methodology (16). For negative control, the primary antibody was omitted. Cytoplasmic mainly and marginally membrane staining pattern was considered acceptable and specific according to antibody manufacturer's instructions (Figure 1). Normal lymphatic endothelium tissue sections demonstrating PDPN expression were used as a positive control.

Digital Image Analysis assay (DIA). PDNP protein expression levels and mLMVD rates were estimated quantitatively by measuring the corresponding protein staining intensity levels (densitometry calculation) in the lymphatic endothelium cells and their number, respectively. A DIA assay was performed by applying a semi- automated system (hardware: Microscope CX-31, Olympus, Melville, NY, USA; Digital camera, Sony, Tokyo, Japan; Windows 10.0/ImageProPlus v 6.0, Media Cybernetics Inc., Rockville, MD, USA). According to the digitized algorithm, PDPN- stained areas were detected (5 optical fields at ×400 magnification) and a digital database including the corresponding snapshots was constructed. A specific macro (cytoplasmic/membranous expression profile) was assessed as a matrix for the measurements. A broad spectrum of continuous grey scale values (0-255) at the RedGreenBlue (RGB) color band combination was used for calculating different protein expression levels (Figure 2). Staining intensity values decreasing to 0 corresponded to a progressive protein over-expression. In contrast, higher values approaching 255 indicated a progressive loss of staining intensity. mLMVD rates were calculated based on the number of distinct, isolated PDPN-stained endothelial ring-like structures (vessels) per high-power optical field (400× original magnification). The current methodology has been previously described by our team for the calculation of CD34-based MVDs (17). The complete results for PDPN/mLMVD, DIA values, and statistical analysis are demonstrated in Table I.

Table I. *Clinicopathological parameters of the examined inDBC/inLBC (n=30) cases and podoplanin (PDPN) DIA-based immunohistochemistry results.*

Clinicopathological parameters		PDPN		*p*-Value
		High/Moderate mLMVD	Low mLMVD	
BC cases	n=30 (%)	11/30 (36.6%)	19/30 (63.4%)	
Histotype				0.234
inDBC	22/30 (73.3%)	8/30 (26.7%)	14/30 (46.6%)	
inLBC	8/30 (26.7%)	3/30 (10%)	5/30 (16.6%)	
Grade				**0.042**
I	8/30 (26.7%)	2/30 (6.66%)	6/30 (20%)	
II	19/30 (63.3%)	7/30 (23.3%)	12/30 (40%)	
III	3/30 (10%)	2/30 (6.66%)	1/30 (3.33%)	
Stage				**0.019**
I	19/30 (63.3%)	6/30 (20%)	13/30 (43.3%)	
II	8/30 (26.7%)	2/30 (6.66%)	6/30 (20%)	
III	3/30 (10%)	3/30 (10%)	0/30 (0%)	
Max tumor diameter				0.085
<10 cm	23/30 (76.6%)	7/30 (23.4%)	16/30 (53.3%)	
≥10 cm	7/30 (23.4%)	4/30 (13%)	3/30 (10%)	

BC: Breast adenocarcinoma; inDBC: invasive ductal breast adenocarcinoma; inLBC: invasive lobular breast adenocarcinoma; DIA: Digital Image Analysis assay; mLMVD: mean lymphatic micro-vessel density; High: ≥4 lymphatic domains per optical field 400× original magnification; Moderate mLMVD: ≥3<4 lymphatic domains per optical field 400× original magnification; Low: mLMVD: <3 lymphatic domains per optical field 400× original magnification. Statistically significant values are shown in bold.

Statistical analysis. Descriptive statistics were carried out using the statistical package SPSS vr 21.00 (IBM Corporation, Somers, NY, USA). The Kolmogorov – Smirnov test was utilized for normality analysis of the quantitative variables. Unifactorial analyses were made by using the Student's *t*-test. All tests were two-sided, statistical significance was set at $p<0.05$.

Results

According to the measurements extracted by DIA assay implementation, the examined cases demonstrated differences regarding PDPN expression levels and the corresponding LMVD values. High and moderate mLMVD rates (mean number of lymphatic domains with emboli in five optical fields under 400× magnification) were detected in 5/30 (16.6%) and 6/30 (20%) cases [total 11/30 (36.6%)], respectively. In these cases, PDPN demonstrated strong cytoplasmic/membranous staining intensity expression levels. The rest of them (n=19, 63.4%) demonstrated low levels of mLMVD. mLMVD was significantly correlated with the stage of the examined malignancies ($p=0.019$), whereas a marginal association with the grade of differentiation was identified ($p=0.042$), but not with the size (max diameter) of them ($p=0.085$) or with their histotype ($p=0.234$).

Discussion

Infiltration and migration of cancer cells into the vascular and lymphatic circulation is a severe clinicopathological event that enhances the aggressive biological behavior of malignant tumors (18). Lymph node metastasis is mediated by the development of neo-lymphatic structures that provide the critical substrate for cancer cell invasion and spreading. Specific molecules produced by lymphatic endothelia, along with associated mechanisms, are implicated in increasing the metastatic potential of cancers, including BC. Among them, vascular endothelial growth factor receptor 3 (VEGFR3) and its vascular endothelial growth factor C/D (VEGF-C/D) ligands are considered as key factors in lymphangiogenesis in BC (19,

20). In addition, PDPN, angiopoietins, and Platelet-Derived Growth Factor-BB (PDGFBB) are described as most critical for this procedure (21).

In the current experimental study, we explored the role of PDPN-dependent mLMVD in both inDBCs and inLBCs. We applied a digital algorithm to accurately identify and measure the neo-lymphatic domains in PDPN-immunostained slides. We observed that neo-lymphangiogenesis was correlated with an aggressive phenotype (advanced stage), independently of the histo-type. Interestingly, PDPN expression was found to be denser in the endothelial cytoplasm of the most aggressive cases characterized by obvious cancerous emboli (High: ≥4 lymphatic domains per optical field 400× original magnification). The combination of increased mLMVD and PDPN strong immunoexpression -that corresponds to increased functional activity- seems to be associated with poor prognosis in BC cases. Similarly, another study group concluded that the combination of increased m LMVD, PDPN immunoexpression and also increased expression rates of the platelet endothelial cell adhesion molecule-1 (PECAM-1)/CD31 protein is correlated with advance disease and poor survival prognosis (22). In support, another study also revealed the crucial relation between the lymphatic emboli in neo-lymphatic structures and axillary lymph node metastasis in patients with BC (23). Similarly, another study –focused on the intra- and peri-tumoral lymphangiogenesis and angiogenesis – concluded that both were increased in cases with a high lymph node ratio (defined as the ratio of positive to the total number of lymph nodes) (24). Interestingly, PDPN over-expression in the subareolar Sappey's plexus has been correlated with lymphogenous metastasis to the axillary lymph nodes, especially in triple-negative BC cases (25). Concerning inflammatory BC cases, a combination of over-expressed neo-lymphoangiogenic markers (PDPN, VEGF C-D) has been associated with an increased number of tumor emboli (26). Finally, the role of disialoganglioside GD2 in cancer stem cell activation, epithelial-mesenchymal transition (EMT), lympho-vascular invasion and its interaction with specific molecules, including PDPN, is under investigation in BC (27). Similarly, combined PDPN, platelet-derived growth factor receptor-β (PDGFR-β) and matrix metalloproteinase (MMPs) over-expression is frequently detected in poorly differentiated BC cases that demonstrate elevated EMT (28). The same study has also revealed an unexplored correlation between PDPN and human epidermal growth factor receptor-2 (HER-2). Moreover, the combined over-expression of PDPN and Twist – a key transcriptional factor implicated in EMT–in inDBC has been correlated with an aggressive phenotype in the corresponding patients (29).

In conclusion, PDPN over-expression is a sensitive, specific, and reliable biomarker for estimating neo-lympangiogenic activity in BCs independently of their inDBC or inLBC histological subtypes. Increased PDPN-related mLMVDs are associated with aggressive BC phenotypes (increased lymph invasion, advanced stage). Understanding the mechanisms that lead to PDPN over-expression is a crucial step for designing and developing novel anti-PDPN inhibition strategies with molecules that block its expression (30).

Conflicts of Interest

The Authors confirm that there are no conflicts of interest in regard to this study.

Authors' Contributions

All Authors contributed to the study. GIM, ET, SM: Conceptualization and design; KG, IKP, SM, EP, PF: Materials preparation, data collection and statistical analysis; ET: DIA analysis; Statistical Analysis: GT; GIM, ET, MA, AN: Draft writing; Draft reviewing, academic advisors: CD, SK. All Authors read and approved the final manuscript.

Funding

The Authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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