Plasma Matrilysins MMP-7 and MMP-26 Concentrations as Diagnostic Biomarkers for Breast Cancer Patients

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Abstract

Background: Metalloproteinases (MMPs) are a group of proteolytic enzymes involved in the maintenance of a proper structure of extracellular matrix (ECM). Matrilysins (MMP-7 and MMP-26) are the one of the group of MMPs that could represent potential breast cancer (BC) markers. The aim of the study was to evaluate plasma levels of MMP-7, MMP-26 and CA 15-3 individually and in combination and assess the a diagnostic utility of studied matrilysins in BC patients.

Methods: The study group consisted of 120 patients with BC, the control group consisted of 40 patients with benign breast cancer and 40 healthy women. Concentrations of MMP-7 and MMP-26 were determined by Enzyme-Linked Immunosorbent Assay, CA 15-3 by Chemiluminescent Microparticle Immunoassay.

Results: The plasma levels of MMP-7 were significantly higher in the entire BC group than in the control group. Concentrations of MMP-26 and CA 15-3 were the highest in the III and IV stage of disease. The highest diagnostic sensitivity was observed in the III and IV stage of cancer for set of all tested markers (92.5%). The highest diagnostic specificity was noted for all tested parameters in all studied BC group (95.0%). The area under the receiver operating characteristic (ROC) curve (AUC) set of markers (MMP-7+MMP-26+CA 15-3) was the largest (0.9138) in III and IV stage. Also individual marker analysis showed that MMP-7 had the highest AUC (0.8894) in advanced stages of disease.

Conclusions: Data suggested that MMP-7 can be considered as additional marker improving diagnostic utility of CA 15-3 in early stages of BC patients. Therefore, combined analysis of MMP-7 and MMP-26 with CA 15-3 might be useful in detection of disease progression. Future investigation is needed to evaluate whether matrilysins might be a potential markers improving diagnosis of BC.

Background

Breast cancer (BC) is the most often diagnosed cancer in female around the world. It mainly originates from the lactiferous ducts as a result of uncontrolled proliferation in epithelial cells (1). Studies of pathological processes associated with tumour growth and the occurrence of lymph node metastases and distant metastases revealed matrix metalloproteinases (MMPs) as pivotal proteins involved in shaping the tumour microenvironment and thus, cancer progression and metastases (2, 3). MMPs are the family of a proteolytic enzymes responsible for the remodelling of the extracellular matrix (ECM). Most of MMPs consist of a propeptide, a catalytic metalloproteinase domain, a linker peptide of variable lengths and a hemopexin (Hpx) domain. MMPs include matrilysins: MMP-7 and MMP-26, which do not have the linker peptide and the Hpx domain (4). MMP-7 may affect the structure of casein, laminin, fibronectin, collagen III/IV/V/IX/X/XI, type I/II/IV/ V gelatins, elastin and proteoglycans inducing their degradation (5). MMP-7 also regulates several biochemical processes such as activation, degradation, and shedding of non-ECM proteins. Heparin-binding epidermal growth factor precursor (proHB-EGF), membrane-bound Fas ligand (FasL), tumour necrosis factor (TNF) alpha precursor, E-cadherin are cleaved by MMP-7 into

mature HB-EGF, soluble FasL, TNF-alpha and E-cadherin which promote cellular proliferation and invasion (6). MMP-7 is secreted specifically by epithelial cells and the tumour cells themselves, which is opposite to the other MMPs, which are mostly produced by macrophages, endothelial cells or fibroblasts (5, 6). MMP-26 cleaves of not only ECM components e.g. vitronectin, fibrinogen, type IV collagen and gelatins, but also non-ECM proteins such as insulin-like growth factor-binding protein-1 (IGFBP-1) and α-1 protease inhibitor (7, 8). Expression of MMP-26 in healthy tissues is reduced, whereas its expression increases in cancerous tissue of epithelial origin (9, 10). Data performed by Marchenko et al. have shown increased *MMP-26* gene expression in various tumour cell lines including MCF-7 breast carcinoma cells. In addition, they speculated that MMP-26 is probably involved in destruction of necrotic tissue of oxygen deficiency tumours and may participate in neovascularization and angiogenesis (10).

Available literature data most often described increased matrilysins expression in breast cancer cells, but there are few reports connected with their plasma concentration in breast cancer patients. Therefore, the aim of the current study was was to determine the plasma levels of MMP-7 and MMP-26 in comparison to the commonly accepted tumour marker (CA 15 – 3) at various stages of BC.

Methods

Enrolled patients

Table 1 shows the study and control groups. The study group comprised 120 patients with BC referred to the Department of Oncology, Medical University of Bialystok, Poland, between 2015 and 2018. Classification and assessment of the stage of the tumour were established in accordance with the International Union against Cancer Tumour-Node-Metastasis (UICC-TNM) classification. Histopathology of breast cancer was assessed in all cases by biopsy of mammary tumour tissue before or after surgery (all patients with ductal adenocarcinoma). Written consent, including participants' own statements about their medical history (i.e. data related to reproductive history, personal or family history of cancer, general health problems: hospitalization or surgery and the use of drugs) and lifestyle habits, including smoking, were obtained. None of the patients received chemotherapy or radiation therapy before taking blood samples. Initial assessment procedures had included physical examination and blood tests, mammography, breast ultrasound, breast core biopsy and chest x-ray. In addition, radioisotope bone scans, bone marrow aspiration and examination, and brain and chest tomography scans were performed as needed.

Table 1
Characteristic of examined groups: BC patients and control groups.

Study group			Number of cases
Study groups:	Ductal adenocarcinoma		120
breast cancer patients	**Median age (range)**		54 (21–85)
	Tumour stage	I	40
		II	40
		III + IV	40
	Menopausal status		
	Premenopausal		38
	Postmenopausal		82
Control groups	**Benign breast tumour lesions patients**		40
	adenoma		18
	fibroadenoma		22
	Median age (range)		44 (33–63)
	Menopausal status		
	Premenopausal		17
	Postmenopausal		23
	Healthy women		40
	Median age (range)		46 (25–64)
	Menopausal status		
	Premenopausal		18
	Postmenopausal		22

The control group consisted of 80 cases divided into 2 groups: 40 patients with benign breast lesions and 40 healthy patients. All patients in the control group underwent mammary gland examination by a gynaecologist and breast ultrasound. The benign mammary lesions were confirmed by histopathological examination. In addition, women with inflammation and associated diseases such as circulatory disorders were excluded from the study.

The study was approved by the local Ethics Committee (R-I-002/51/2015) and all patients agreed to participate in the study.

Plasma Collection And Storage

Venous blood samples were taken from all patient classified to the study. Blood was collected in EDTA tubes (S-Monovette, SARSTEDT, Germany). Plasma samples were obtained by centrifugation in 1000xg for 15 minutes at 2–8 °C and stored at -85 °C until assay.

Measurement of MMP-7, MMP-26 and CA 15-3

The tested parameters (MMP-7 and MMP-26) were measured with enzymelinked immunosorbent assay (ELISA) (MMP-7-R&D systems, Abingdon, United Kingdom; MMP-26-EIAab Science, Wuhan, China), according to the manufacturer's instructions. Plasma concentrations of CA 15 − 3 were measured by chemiluminescent microparticle immunoassay (CMIA) (Abbott,Chicago, IL, USA). The intra and inter-assay coefficient were checked by manufacturer of diagnostic kits to comply standards.

Statistical analysis

Statistical analysis was based on program STATISTICA 12.0 (StatSoft, Tulsa, OK, USA). The Shapiro-Wilk test showed lack of normal distribution in received data. Therefore, the Mann Whitney U test, the Kruskal–Wallis test, and a multivariate analysis of various data by the post hoc Dwass–Steel–Critchlow–Fligner were used to determine differences between the groups. The value $p < 0.05$ was regarded as statistically significant. Diagnostic sensitivity (SE), specificity (SP), predictive value of a positive test result (PPV) and predictive value of a negative test result (NPV) were calculated. The cut-off values were based on the 95th percentile.

Comparison of the diagnostic power of all studied markers was assessed using the areas under the receiver operating characteristic (ROC) curve (AUC) which were performed using the GraphRoc program for Windows (Windows, Royal, AR, USA). Healthy patients and benign breast tumour groups represented the control group in analyses of diagnostic performance (SE, SP) and ROC curves.

Results

Table 2 presents the median and the range of plasma levels of the investigated MMPs and CA 15 − 3. In case of BC patients the concentrations of MMP-7, MMP-26 and CA 15 − 3 were significantly higher when compared to healthy patients (for MMP-7 and MMP-26 $p < 0.001$; for CA 15 − 3 $p = 0.002$). Moreover, the median levels of MMP-7 in all BC stages were higher than in healthy group (for stage I $p = 0.003$; for stages II, III and IV $p < 0.001$). Interestingly, only in stage III and IV the median levels of MMP-26 and CA 15 − 3 were significantly higher in comparison to the healthy subjects ($p < 0.001$).

Table 2
Plasma levels of tested parameters in patients with BC, benign breast tumour and healthy patients.

	MMP-7 (ng/ml)	MMP-26 (ng/ml)	CA 15 – 3 (U/ml)
Breast cancer group (median, range)			
Stage I	2.2 (0.0–6.0)[a]	9.0 (2.8–19.6)	17.2 (6.2–50.3)
Stage II	2.0 (0.6–7.4)[a, f]	12.4 (2.7–23.2)	18.2 (4.4–48.1)
Stage III + IV	5.5 (0.3–10.4)[a, b, c, d, f]	17.4 (5.8–27.2)[a, b, c, d, f]	23.9 (8.9–251.0)[a, b, c, d, f]
Total group	3.2 (0.0-10.4)[a, b, f]	12.6 (2.7–27.2)[a, b, f]	19.4 (4.4–251.0)[a, b, f]
Control groups (median, range)			
Benign breast tumour	2.3 (0.3–7.2)[e]	9.9 (2.7–15.3)	15.0 (5.2–45.4)
Healthy patients	0.9 (0.3–5.2)	8.3 (3.4–15.2)	16.2 (6.7–29.2)
Total group	1.3 (0.3–7.2)	9.0 (2.7–15.3)	15.5 (5.2–45.4)
Notes:			
[a] Statistically significant when patients with BC compared with healthy women.			
[b] Statistically significant when patients with BC compared with benign breast tumour group.			
[c] Statistically significant when patients with BC stages III and IV compared with patients with BC stage I.			
[d] Statistically significant when patients with BC stages III and IV compared with patients with BC stage II.			
[e] Statistically significant when patients with benign breast tumour compared with healthy women.			
[f] Statistically significant when patients with BC compared with total control group.			

When compared BC patients and benign breast tumour group similar relationship was observed. The median levels of MMP-7, MMP-26 and CA 15 – 3 in total BC group were higher than in benign breast tumour group ($p = 0.013$; $p = 0.015$; $p = 0.003$ respectively). Also, the concentrations of all tested parameters were significantly higher in stage III and IV in comparison to benign breast tumour patients ($p < 0.001$). However, regarding benign breast tumour patients the concentration of MMP-7 was higher in comparison to healthy subjects ($p = 0.03$).

Concentrations of tested parameters in BC patients were tumour stage dependent. The median levels of MMP-7, MMP-26 and CA 15 – 3 in stage III and IV were significantly higher in comparison to stage I (for

MMPs $p < 0.001$; for CA 15 − 3 $p = 0.003$) and stage II ($p < 0.001$; $p = 0.001$; CA 15 − 3 $p = 0.043$, respectively).

The concentrations of MMP-7, MMP-26 and CA 15 − 3 in BC group were significantly higher than in total control group (benign breast tumour and healthy patients) ($p < 0.001$). The median levels of all tested parameters in stage III and IV were increased in comparison to control group ($p < 0.001$). Moreover, the concentrations of MMP-7 in stage II were statistically higher than in control group ($p = 0.013$).

Table 3 presents the diagnostic criteria: sensitivity (SE), specificity (SP), predictive value of a positive test result (PPV), and predictive value of a negative test result (NPV) in BC patients. The SE in the total BC group for MMP-7 and MMP-26 was the same for both enzymes (45.0%), and simultaneously was higher when compared to CA 15 − 3. The greatest SE was observed for combination of all investigated markers (MMP-7 + MMP-26 + CA 15 − 3) (63.6%).

Table 3
The diagnostic criteria of tested parameters in BC patients.

Tested parameters	Diagnostic criteria (%)	Breast cancer			
		Stage I	**Stage II**	**Stage III + IV**	**Total group**
MMP-7	SE	27.5	32.5	75.0	45.0
	SP	95.0	95.0	95.0	95.0
	PPV	84.6	86.7	93.7	96.4
	NPV	56.7	58.5	79.2	36.5
MMP-26	SE	20.0	37.5	77.5	45.0
	SP	95.0	95.0	95.0	95.0
	PPV	80.0	88.2	93.9	96.4
	NPV	54.3	60.3	80.9	36.5
CA 15 – 3	SE	12.5	27.5	57.5	32.5
	SP	95.0	95.0	95.0	95.0
	PPV	71.4	84.6	92.0	95.1
	NPV	52.1	56.7	69.1	31.9
MMP-7 + CA 15 – 3	SE	35.0	45.0	90.0	56.7
	SP	90.0	90.0	90.0	90.0
	PPV	77.8	81.8	92.3	94.4
	NPV	58.1	62.1	90.0	40.9
MMP-26 + CA 15 – 3	SE	27.5	50.0	87.5	55.0
	SP	90.0	90.0	90.0	90.0
	PPV	73.3	83.3	89.7	94.3
	NPV	55.4	64.3	87.8	40.0
MMP-7 + MMP-26 + CA 15 – 3	SE	40.0	57.5	92.5	63.3
	SP	85.0	85.0	85.0	85.0
	PPV	72.7	79.3	86.1	92.7
	NPV	58.6	66.7	87.2	43.6

The SE of the all tested parameters increased with the progression of the cancer. The SE of the tested parameters in stage I was the highest for MMP-7 (27.5%). Interestingly, in the stage II the highest SE was

observed for MMP-26 (37.5%). In stage III and IV also higher SE was noticed for MMPs (for MMP-7 75.0%; for MMP-26 77.5%) than for CA 15 − 3 (57.5%). Moreover, increasing SE was observed in every stage of the cancer for combination of markers: MMP-7 + CA 15 − 3 (stage I: 35.0%; stage II: 45.0%; stage III + IV: 90.0%); MMP-26 + CA 15 − 3 (stage I: 27.5%; stage II: 50.0%; stage III + IV: 87.5%); MMP-7 + MMP-26 + CA 15 − 3 (stage I: 40.0%; stage II: 57.5%; stage III + IV: 92.5%).

The diagnostic SP for all tested parameters was very high in total group of cancer patients and in all stages of cancer (95.0%). The SP for the combination of MMPs with CA 15 − 3 was lower (85.0%) than for sets MMP-7 + CA 15 − 3 and MMP-26 + CA 15 − 3, where SP values was the same in both cases (90.0%).

The predictive value of a positive test result (PPV) in the group of BC patients, among tested parameters was slightly higher for MMPs (96.4% for MMP-7 and MMP-26) than for CA 15 − 3 (95.1%). The PPV in stage I was the highest for MMP-7 (84.6%), but for stage II was the highest for MMP-26 (88.2%). In stage III and IV the PPV were similar for both enzymes (MMP-7: 93.7%; MMP-26: 93.9%). Among all tested markers PPV was increased with the advanced stage of BC. The combined use of the tested parameters with CA15-3 resulted in an increase of PPV in every stage of tumour.

The predictive value of a negative test result (NPV) in the group of BC was higher for MMPs than for CA 15 − 3 (36.5%; 31.9% respectively). The NPV was the highest in stage II and IV for all tested parameters (MMP-7: 79.2%; MMP-26: 80.9%; CA 15 − 3: 69.1%). In stage I the highest NPV values was represented by MMP-7 (56.7%), in stage II MMP-26 (60.3%). The combined use of the tested parameters with CA15-3 resulted in an increase of NPV in every stage of tumour, but in stage III and IV the values of NPV were the highest (MMP-7 + CA 15 − 3: 90.0%; MMP-26 + CA 15 − 3: 87.8%; MMP-7 + MMP-26 + CA 15 − 3: 87.2%).

The relationship between the diagnostic SE and SP is illustrated by the ROC curve in Table 4. The AUC indicates the possible clinical usefulness of a tumour marker and therefore, its diagnostic power. In the total group of BC AUCs for all parameters were significantly higher in comparison to AUC = 0.5 ($p < 0.001$). The AUC for MMP-7 (0.7306) in entire group of BC was larger than for MMP-26 (0.6720) and CA 15 − 3 (0.6743). Using the set of markers, e.g. CA 15 − 3 with MMP-7 or MMP-26 resulted in an increase in AUC (0.7464; 0.7157 respectively). We have noticed that the AUC for set of markers CA 15 − 3 with MMP-7 was slightly larger than for combination CA15-3 with MMP-7 and MMP-26 (Fig. 1.).

Table 4
Diagnostic criteria of ROC curve for tested parameters in BC.

Tested parameters	AUC	SE	95% C.I. (AUC)	P (AUC = 0.5)
ROC criteria in breast cancer (total group)				
MMP-7	0.7306	0.0355	(0.661-0.800)	< 0.001
MMP-26	0.6720	0.0375	(0.599–0.745)	< 0.001
CA 15 – 3	0.6743	0.0378	(0.600-0.748)	< 0.001
MMP-7 + CA 15 – 3	0.7464	0.0341	(0.680–0.813)	< 0.001
MMP-26 + CA 15 – 3	0.7157	0.0357	(0.646–0.786)	< 0.001
MMP-7 + MMP-26 + CA 15 – 3	0.7461	0.0339	(0.680–0.813)	< 0.001
ROC criteria in breast cancer (I stage)				
MMP-7	0.6328	0.0538	(0.527–0.738)	0.0136
MMP-26	0.5259	0.0597	(0.409–0.643)	0.6638
CA 15 – 3	0.5988	0.0556	(0.490–0.708)	0.0755
MMP-7 + CA 15 – 3	0.6538	0.0535	(0.549–0.759)	0.0040
MMP-26 + CA 15 – 3	0.5856	0.0565	(0.475–0.696)	0.1297
MMP-7 + MMP-26 + CA 15 – 3	0.6413	0.0540	(0.535–0.747)	0.0090
ROC criteria in breast cancer (II stage)				
MMP-7	0.6697	0.0500	(0.572–0.768)	0.0007
MMP-26	0.6216	0.0620	(0.500-0.743)	0.0499
CA 15 – 3	0.6270	0.0568	(0.516–0.738)	0.0252
MMP-7 + CA 15 – 3	0.6745	0.0541	(0.568–0.781)	0.0013
MMP-26 + CA 15 – 3	0.6711	0.0599	(0.554–0.788)	0.0043
MMP-7 + MMP-26 + CA 15 – 3	0.6834	0.0551	(0.575–0.791)	0.0009
ROC criteria in breast cancer (III + IV stage)				
MMP-7	0.8894	0.0361	(0.819–0.960)	< 0.001
MMP-26	0.8684	0.0419	(0.786–0.951)	< 0.001
CA 15 – 3	0.7970	0.0433	(0.712–0.882)	< 0.001
MMP-7 + CA 15 – 3	0.9109	0.0320	(0.848–0.974)	< 0.001
MMP-26 + CA 15 – 3	0.8905	0.0375	(0.817–0.964)	< 0.001

Tested parameters	AUC	SE	95% C.I. (AUC)	P (AUC = 0.5)
MMP-7 + MMP-26 + CA 15 − 3	0.9138	0.0325	(0.850–0.977)	< 0.001

In stage I of BC the highest AUC value was noticed for combination of CA 15 − 3 with MMP-7 (0.6538; p = 0.004), and it was higher in comparison to set of CA 15 − 3, MMP7 and MMP-26 (0.6413; p = 0.009). Considering single markers, the highest AUC was observed for MMP-7 (0.6328; p = 0.0136) (Fig. 2.). In stage II of BC the highest AUC was for set of all tested parameters (0.6834; p = 0.0009). Slightly marked differences in areas under ROC curves were observed for combination of CA 15 − 3 with MMP-7 and MMP-26 (0.6745; p = 0.0013 and 0.6711; p = 0043, respectively). Regarding all tested parameters the highest AUC was presented by MMP-7 (0.6697; p = 0.0007), for MMP-26 and CA 15 − 3 values of AUC was very similar (0.6216; p = 0.0499 and 0.6270; p = 0.0252 respectively) (Fig. 3.). In stage III and IV of BC the AUC for MMP-7 (0.8894) was larger than for MMP-26 (0.8684) and CA 15 − 3 (0.7970). We have also observed that the AUC for combination of all studied parameters (0.9138) was the highest in comparison to the combination of CA 15 − 3 with MMP-7 and MMP-26 (0.9109; 0.8905, respectively). AUCs for all parameters were significantly larger in comparison to AUC = 0.5 (p < 0.001 in all cases) (Fig. 4.).

Discussion

MMPs have proven role in BC progression. They participate in the modulation of the immune system, angiogenesis and development of the tumour microenvironment, leading to the progression of cancer. Their ability to disintegrate ECM components is considered as key factor leading to disease progression (11). Among MMPs, the most extensive studies to date have been conducted on MMP-2 and MMP-9, which are considered to have a significant impact on the development of BC (12–14). Nevertheless, is essential to search the functions of other MMPs that may further explain their role in BC progression. In this paper we focused our attention on serum levels of MMP-7 and MMP-26 in BC patients. In addition, we compared the tested enzymes with the commonly marked protein CA 15 − 3 in BC patients and assessed whether combining the enzymes with each other or with CA 15 − 3 demonstrated promising diagnostic value. To our best knowledge, our research team is the first, which performed analysis of plasma concentrations of MMP-7 and MMP-26 with CA 15 − 3 in BC patients. However, circulating levels of MMP-7 and MMP-26 have still uncertain role in cancer progression and development.

The data presented here revealed that BC patients demonstrate a significantly higher concentrations of plasma levels MMP-7, MMP-26 and CA 15 − 3 than healthy patients. Moreover, concentration of MMP-7 was increased in patients with benign breast tumour in comparison to healthy subjects. We hypothesize that serum concentrations of studied parameters may be predictive factors when distinguishing between healthy and BC patients or even benign breast changes. Consequently, patients with III and IV stage of disease had a significantly higher MMP-7, MMP-26 and CA 15 − 3 levels when compared to I stage of BC and control group. Literature data provided no reports on plasma concentrations of matrilysins in patients with BC. Clinical studies suggest that circulating MMPs may indicate early signs of BC (15, 16). Nevertheless, clinical-control cohort studies regarding the relationship between the concentration of

MMPs include MMP-7 in plasma and the subsequent risk of postmenopausal breast cancer showed no dependence. No difference between concentration in the study group and control was observed. There was also no difference between the concentration of MMPs and the occurrence of mammary cancer (16). Consistent with data cited above is study performed by Aroner et al. (17). They also performed 10 years follow-up study associating plasma MMPs, e.g. MMP-7 witch BC risk. Additionally, no significant association of these MMPs with BC subtypes was found, although a positive association with node metastases for MMP7 was suggested. This indicates that MMP-7 is not suitable to be a marker for detection of early stages of BC; however, it seems to be an appropriate marker for diagnostic and therapy monitoring in advanced stages of BC (17).

Katunina et al. performed analysis of MMPs (including MMP-7) in tumour tissue, adjacent histologically intact tissue and serum of patients with BC (18). Enzyme immunoassay test showed higher MMP-7 levels in cancer than in healthy tissue. There was no correlation between concentration MMP-7 in tissue and serum. Serum analysis did not show a significant increase in MMP-7 concentration in BC subjects compared to the control group (18). Their results are oppose with our observations. Nevertheless, it is worth noting that the researchers conducted analysis in serum not in plasma as we did. In addition, they had a small study group – 45 women with breast cancer and 8 patients in the control group. Therefore, due to study limitations, the results they received may explain no significant relationships between the tested groups.

It is known that MMP-26 is involved in the development of estrogen-dependent cancers, including breast cancer (19, 20). BC cells expressing MMP-26 were characterized by an increase in the number of mitotic figures, atypia, the presence of glycogen fields and atypical lysosomes in the cytoplasm. The ability of these cells to migrate significantly increased when compared to the control group, and significantly decreased in the presence of anti-MMP-26 antibodies. The number and length of blood vessels produced as a result of induction by cells expressing MMP-26 was higher than those induced by tumour cells not expressing MMP-26. Expression of MMP-26 increased the malignant phenotype of these cells in vivo (20). However, literature lack data regarding plasma level of MMP-26 in BC patients. Research on plasma levels of both matrilysins we found in paper of Galewska et al. They evaluated concentrations of MMP-7 and MMP-26 in plasma and serum of the umbilical cord blood (21). However, work of Galewska is not associated with breast cancer, so we are unable to compare our findings regarding MMP-26 or both enzymes since no reports on the subject are available.

Sensitivity, specificity and area under ROC curve characterise the diagnostic usefulness for tumour markers. Considering our data higher values of SE for all tested parameters were observed. The SP for individual matrilysin and CA 15 – 3 was the same in all studied group (95%). Similar results were received for MMP-7 by Będkowska et al. who analysed

MMP-7 concentration in epithelial ovarian cancers (22). They observed higher concentrations of MMP-7 compared to the healthy group. Moreover they noted higher SE values associated with tumour progression. The SP was the same in all disease stages (95%). Considering AUC values, they showed

significantly higher AUCs when compared to AUC = 0.5 in all studied ovarian cancer group (22). In our work the AUCs of all compared markers were significantly higher compared to AUC = 0.5 in II, III and IV stage of cancer. In I stage of advancement only single analysis of MMP-7 or in conjunction with MMP-26 and CA 15 − 3 demonstrated diagnostic usefulness. Work of Leelawat et al. described diagnostic utility of MMP-7 in cholangiocarcinoma (23). They noted increased concentration of MMP-7 in serum of cholangiocarcinoma patients and SE and SP values were higher for matrilysin than for commonly used marker in diagnosis of cancers of digestive tract CA 19 − 9. Interestingly, analysis of AUC showed that MMP-7 was more accurate than CA 19 − 9 in diagnosis of cholangiocarcinoma (23). Vocka et al. studied accuracy of MMP-7 in diagnosing patients with metastatic colorectal cancer and compared serum levels of MMP-7 with CEA and CA 19 − 9 (24). Concentration of MMP-7 was significantly higher in patients with colorectal cancer compared to healthy controls. MMP-7 had very similar SE and SP as CEA, but had higher SE than CA 19 − 9. Serum level of MMP-7 correlated with worse disease outcome and had prognostic value (24). All results presented above described different types of cancer than BC, but showed similar trend e.g. elevated levels of MMP-7 in cancer patients, high values of SE and SP and higher values of AUC compared to AUC = 0.5. Unfortunately, we could not compare our data regarding MMP-26 or combination of MMP-7 and MMP-26 with each other and with CA 15 − 3, because no reports corresponding with subject are available. Our work is innovative as is the first report about the diagnostic usefulness of set of markers MMP-7 and MMP-26 in combination with CA 15 − 3 in BC diagnosis.

Conclusions

Our results indicate that MMP-7 and MMP-26 are promising marker for BC diagnostic. Furthermore, the results presented here suggest that combined analysis of MMP-7 and MMP-26 with CA 15-3 might be useful in detection of disease progression. Moreover, MMP-7 may be introduced as breast tumour biomarker, especially in diagnosis of early stages of BC.

Abbreviations

BC: Breast cancer;

MMPs: Metalloproteinases;

ECM: Extracellular matrix;

MMP-7: Metalloproteinase 7;

MMP-26: Metalloproteinase 26;

IGFBP-1: Insulin-like growth factor-binding protein-1;

Hpx: Hemopexin;

proHB-EGF: Heparin-binding epidermal growth factor precursor;

FasL: Membrane-bound Fas ligand;

TNF: Tumour necrosis factor;

SE: Sensitivity,

SP: Specificity;

AUC: Area under ROC curve.

Declarations

Ethics approval and consent to participate

The study was approved by the Bioethics Committee of the Medical University of Bialystok (R-I-002/51/2015) and all patients agreed to participate in the study.

Consent for publication

Not applicable.

Availability of data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing of interests

All authors declare no conflict of interests.

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Authors' contributions

BMP: conceptualization, sample collection, perform the research, analyzed the data, writing the original draft. AP: conceptualization, review and editing. ED: sample collection, perform the research. IS: sample collection, perform the research. MN: analyzed the data, review and editing. SŁ: conceptualization, analyzed the data, review and editing. All authors had read and approved this manuscript.

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Not applicable.

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Figures

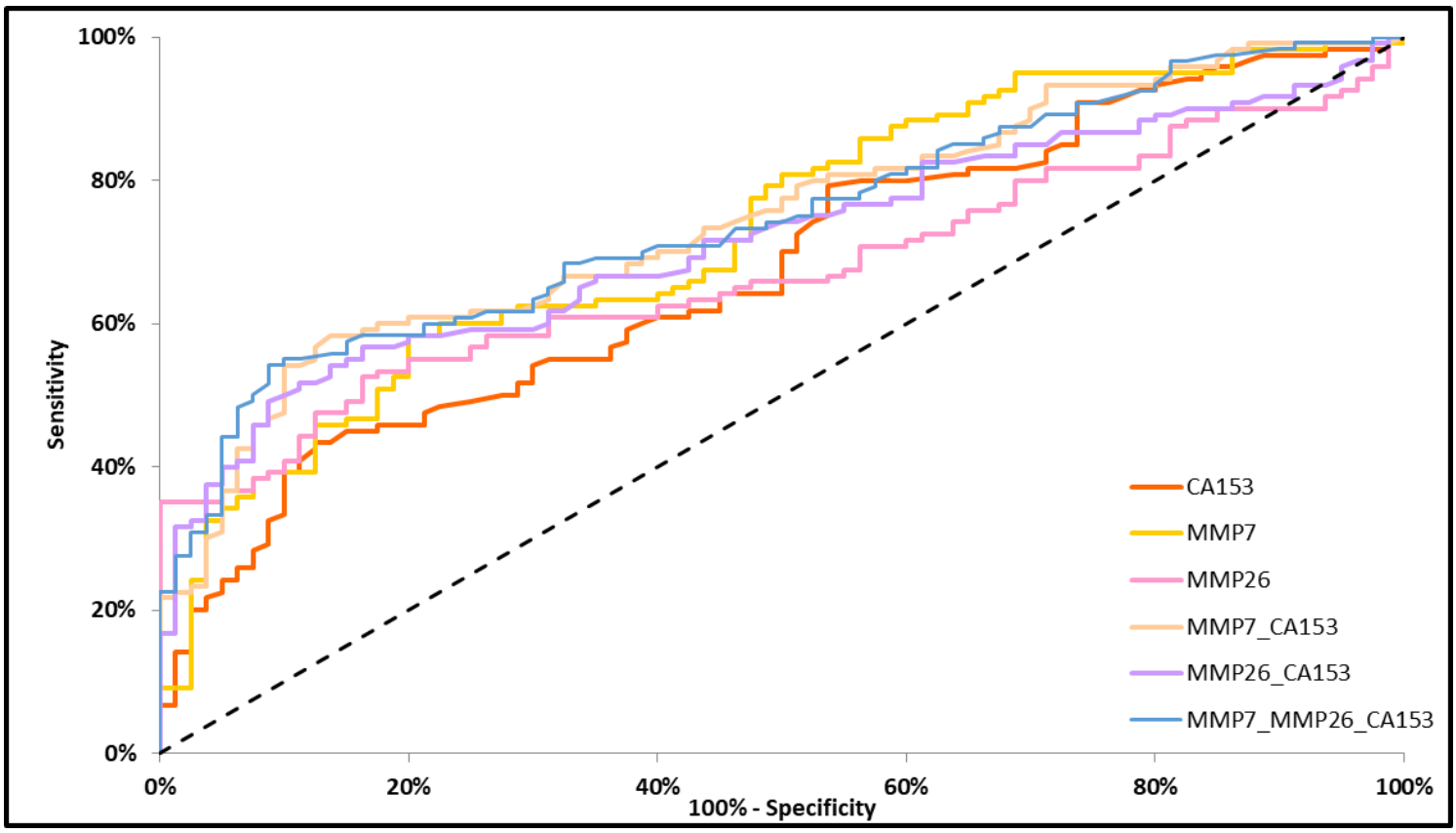

Figure 1

Diagnostic criteria of ROC curve in entire BC group.

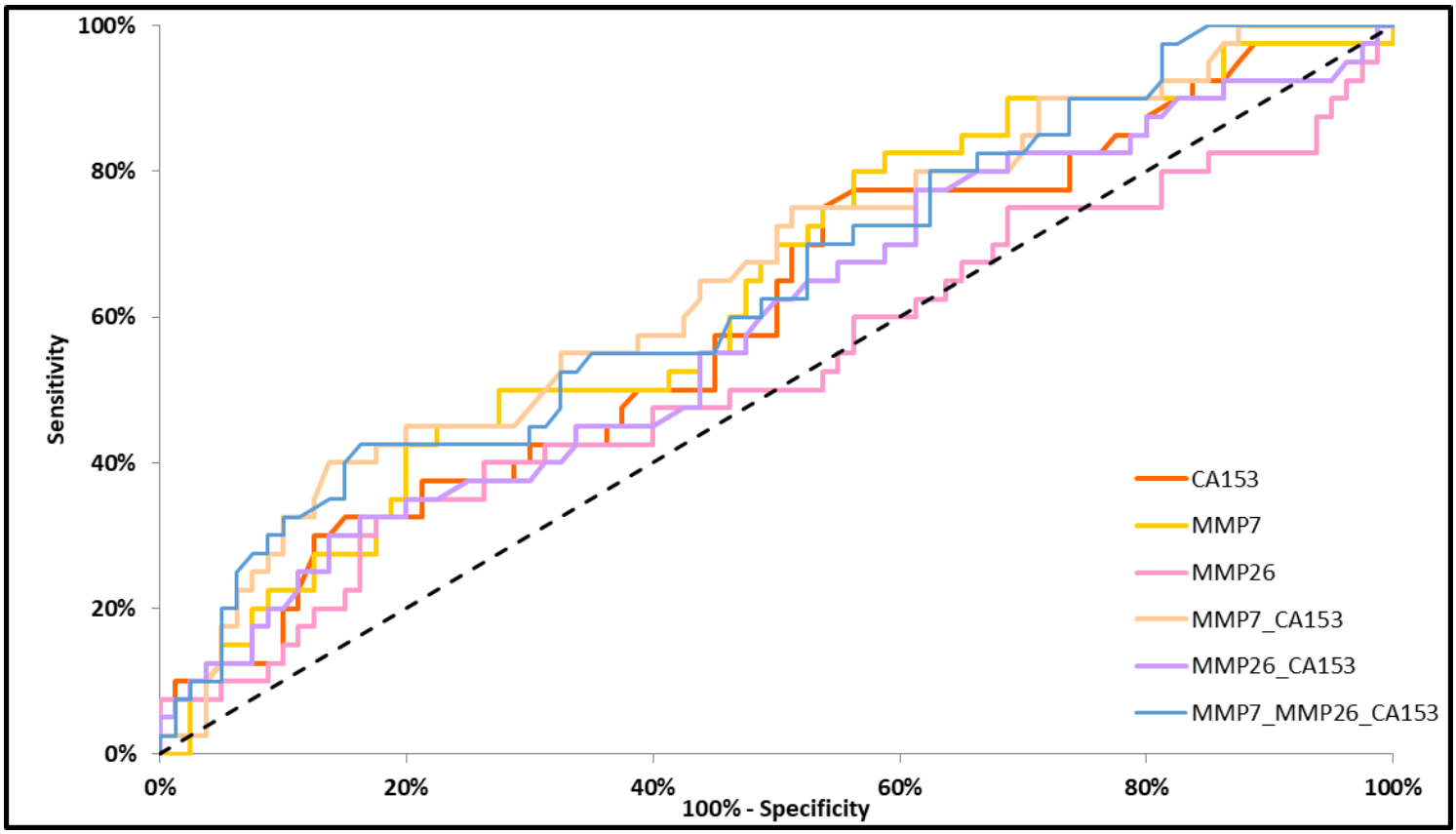

Figure 2

Diagnostic criteria of ROC curve in stage I of BC.

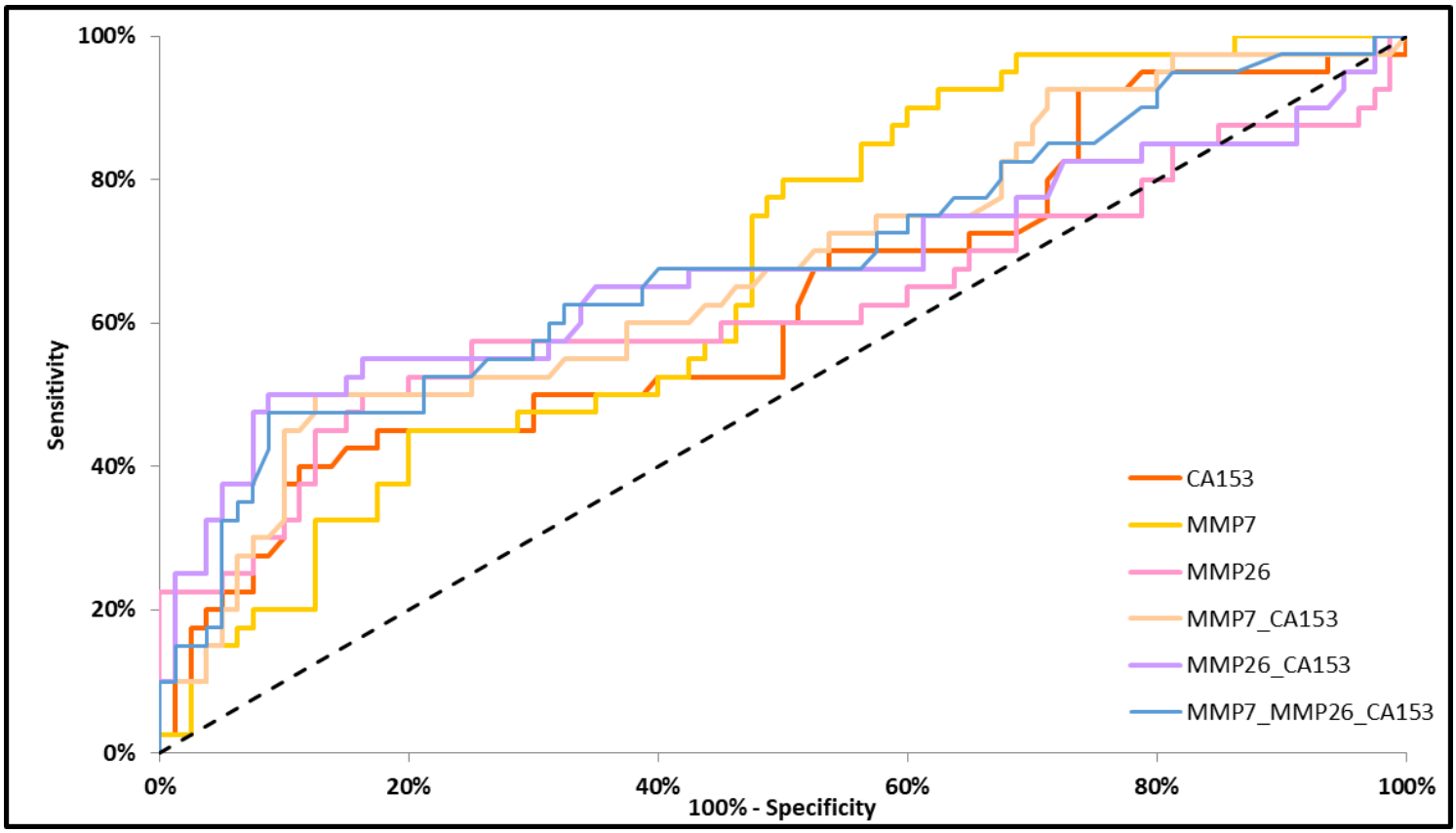

Figure 3

Diagnostic criteria of ROC curve in stage II of BC.

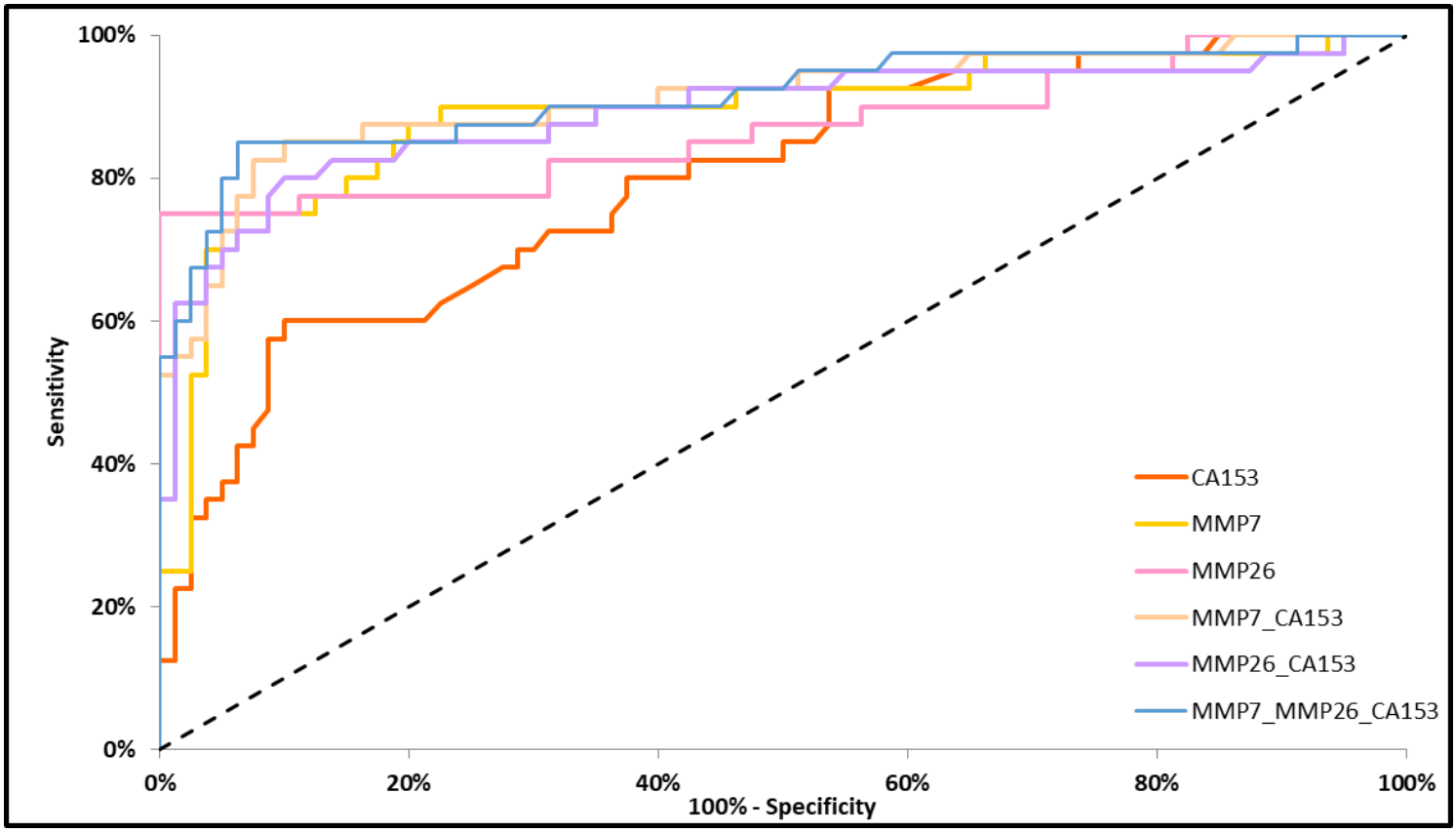

Figure 4

Diagnostic criteria of ROC curve in stage III and IV of BC.