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Serum MMP-11 Reflects Tumor Progression While MMP-7 Predicts Survival in Pancreatic Cancer

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Abstract

Background

Pancreatic ductal adenocarcinoma (PDAC) remains a highly aggressive malignancy with limited reliable biomarkers for diagnosis and prognosis. Matrix metalloproteinases (MMPs), particularly MMP-11 and MMP-7, have been implicated in tumor progression and metastasis and may represent clinically relevant circulating biomarkers.

Aim

To evaluate the diagnostic and prognostic significance of MMP-11 and MMP-7 levels in serum and pancreatic tissue of patients with PDAC and to assess their association with tumor stage, metastatic spread, and overall survival.

Methods

This prospective observational study included 154 patients undergoing pancreatic surgery between 2022 and 2024. Serum and tissue concentrations of MMP-11 and MMP-7 were measured using ELISA. Statistical analyses included group comparisons, ROC curve analysis, correlation analysis, and Kaplan–Meier survival analysis.

Results

MMP-11 concentrations were significantly higher in patients with malignant tumors compared to benign pancreatic diseases in both tissue and serum and increased with advancing disease stage and metastatic spread. ROC analysis demonstrated good diagnostic performance of serum MMP-11. Elevated serum MMP-7 levels were significantly associated with reduced overall survival.

Conclusion

MMP-11 and MMP-7 represent complementary biomarkers in PDAC. MMP-11 reflects tumor progression and metastatic disease, whereas MMP-7 is associated with survival outcomes. Combined assessment of these markers may improve diagnostic and prognostic stratification in pancreatic cancer.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignancies, characterized by late diagnosis and poor survival [1]. Current biomarkers, particularly CA19-9 and CEA, have limited diagnostic specificity and sensitivity, especially in inflammatory pancreatic diseases [2, 3]. Therefore, the identification of novel biomarkers capable of improving early detection, disease stratification, and prognostic assessment remains a clinical priority.

Tumor progression in PDAC is closely associated with remodeling of the extracellular matrix (ECM), a process mediated largely by matrix metalloproteinases (MMPs), a family of zinc-dependent endopeptidases involved in tissue invasion, metastasis, and tumor microenvironment modulation [4, 5]. Among them, matrix MMP-11 and MMP-7 have emerged as biologically relevant candidates. MMP-11 is primarily associated with stromal components and tumor–stroma interactions, while MMP-7 is produced mainly by epithelial tumor cells and contributes to invasion, metastasis, and resistance to apoptosis.

Previous studies have demonstrated altered expression of both MMP-11 and MMP-7 in several malignancies, including pancreatic cancer, and suggested their potential role as circulating biomarkers [4, 5, 6]. However, their combined diagnostic and prognostic significance in PDAC remains insufficiently characterized.

Therefore, the aim of this study was to evaluate the diagnostic and prognostic value of MMP-11 and MMP-7 in serum and pancreatic tissue of patients with pancreatic cancer. We further assessed their association with tumor stage, metastatic spread, and overall survival, and compared their performance with established biomarkers CA19-9 and CEA.

Material and Method

Study Design and Ethical Approval

This prospective observational study was conducted at the I. Department of Surgery, Faculty of Medicine, Pavol Jozef Šafárik University in Košice, in cooperation with the Deparment of Medical and Clinical Biochemistry, University Hospital L. Pasteur in Košice. The study protocol was approved by the institutional Ethics Committee of University Hospital L. Pasteur in Košice and performed in accordance with the principles of the Declaration of Helsinki and Act No. 576/2004 Coll. on healthcare.

All participants were informed about the study objectives and procedures and provided written informed consent prior to inclusion.

Study Population

Patients indicated for pancreatic surgery between 09/2022-12/2024 were consecutively enrolled. A total of 154 subjects were included in the final analysis and divided into two groups:
(i) malignant tumor group (MTG; n = 108), comprising patients with histologically confirmed pancreatic ductal adenocarcinoma,

(ii) benign tumor group (BTG; n = 46), including patients with non-malignant pancreatic diseases (e.g., chronic pancreatitis or benign lesions).

No statistically significant difference in sex distribution was observed between groups (MTG: 48.1% female, 51.9% male; BTG: 34.8% female, 65.2% male; χ^2 test, p = 0.117).

A significant difference in age was identified, with a higher median age in the MTG group (68 years) compared to the BTG group (63 years) (Mann–Whitney U test, p = 0.001). Patients older than 50 years were more prevalent in the MTG group (94.5%) than in the BTG group (73.9%).

Inclusion and Exclusion Criteria

Inclusion criteria were:

- age ≥ 18 years,
- indication for pancreatic surgery,
- availability of preoperative blood samples,
- provision of written informed consent.

Exclusion criteria included:

- previous oncological treatment (chemotherapy or radiotherapy),
- presence of other active malignancies,
- incomplete clinical or laboratory data,
- refusal to participate in the study.

Sample Collection

Peripheral venous blood samples were collected preoperatively in the morning after an overnight fast. Blood was drawn into BD Vacutainer tubes containing a separation gel.

Pancreatic tissue samples were obtained intraoperatively during surgical resection in a subset of patients. All collected samples were immediately transported to the Department of Medical and Clinical Biochemistry under controlled conditions for further processing.

Sample Processing

Blood samples were centrifuged at 3,500 × g for 10 minutes at room temperature to obtain serum, which was subsequently aliquoted and stored at −80 °C until analysis.

Pancreatic tissue samples were rinsed in phosphate-buffered saline (PBS) to remove residual blood and debris. Tissue homogenization was performed in an appropriate lysis buffer on ice. The homogenates were centrifuged at 18,000 × g for 20 minutes at 4 °C, and the resulting supernatants were collected and stored for biochemical analysis.

Quantification of MMP-11 and MMP-7

Serum and tissue concentrations of MMP-11 were determined using a commercially available ELISA kit (Human MMP-11 ELISA Kit, NBP3-06887, Novus Biologicals), in accordance with the manufacturer's instructions.

Serum and tissue concentrations of MMP-7 were measured using a Human MMP-7 ELISA Kit (EH328RB, Invitrogen), following the recommended protocol.

All samples were analyzed in duplicate, and mean values were used for statistical evaluation.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics and GraphPad Prism. Descriptive statistics were calculated for all variables.

Normality of data distribution was assessed using the Shapiro–Wilk test. As the data did not follow a normal distribution, non-parametric methods were applied. Differences between two independent groups were evaluated using the Mann–Whitney U test, while comparisons among multiple groups were conducted using Dunn's multiple comparison test.

Correlations between variables were assessed using Pearson's correlation coefficient.

Receiver operating characteristic (ROC) curve analysis was performed for selected parameters to evaluate their diagnostic performance, including calculation of the area under the curve (AUC), sensitivity, and specificity. The optimal cut-off value was determined using the Youden index derived from ROC curve analysis.

Tumor Classification and Staging

Tumor staging was performed according to the Tumor–Node–Metastasis (TNM) classification system of the American Joint Committee on Cancer, based on the 8th edition guidelines.

Pathological staging (pTNM) was determined using postoperative histopathological examination of resected pancreatic tissue specimens. Tumor size and extent (T category), regional lymph node involvement (N category), and the presence of distant metastases (M category) were assessed according to standardized criteria.

Tumors were further stratified into clinical stages (I–IV) based on TNM combinations. For analytical purposes, patients were additionally grouped into early-stage disease (stages I–II) and advanced-stage disease (stages III–IV).

Histopathological evaluation included assessment of tumor differentiation grade (G1–G3), lymphovascular invasion, and perineural invasion, when available. All pathological analyses were performed by experienced pathologists in accordance with institutional standards.

For correlation analyses, MMP11 and MMP7 levels were evaluated in relation to individual TNM parameters (T stage, nodal status, and metastatic spread), as well as overall clinical stage.

Results

Initial analyses were primarily aimed at characterizing the expression of MMP-11 and MMP-7 in pancreatic tissue samples, providing insight into local pathological processes. To explore their potential as minimally invasive biomarkers, the analysis was subsequently extended to preoperative serum samples. We hypothesized that tumor-associated alterations would also be reflected systemically.

Table 1 summarizes the distribution of MMP-7 and MMP-11 concentrations in tissue and serum samples from patients stratified into BTG and MTG.

Table 1

Tissue and serum concentrations (median, 25th and 75th percentile) of MMP-7 and MMP-11 in BTG and MTG and serum concentrations of MMP-7 and MMP-11 with and without distant metastases

Tissue MMP-7	***Median (ng/mL)***	***25% Percentile***	***75% Percentile***	***Sig.***
BTG	**50.44**	**35.74**	**74.27**	**ns**
MTG	**62.35**	**39.32**	**93.33**	**ns**
Serum MMP-7	**17.87**	**17.87**	**22.64**	
BTG	**21.84**	**18.67**	**25.81**	
MTG				
Tissue MMP-11	0.93	0.77	1.53	**0.0194**
BTG	2.67	2.30	3.60	**0.0161**
MTG	0.99	0.25	2.05	
Serum MMP-11	2.47	1.02	5.75	
BTG				
MTG				

Comparison between BTG and MTG

Although median tissue MMP-7 levels were higher in the MTG group (62.35 vs. 50.44 ng/mL), and serum levels were also slightly elevated (21.84 vs. 17.87 ng/mL), these differences did not reach statistical significance ($p > 0.05$).

In contrast, MMP-11 concentrations were significantly higher in the MTG group compared to BTG, both in tissue (median: 2.67 vs. 0.93 ng/mL; $p = 0.0194$; Fig. 1:A1) and serum (median: 2.47 vs. 0.99 ng/mL; $p = 0.0161$; Fig. 1:A2).

ROC Analysis

To further evaluate the diagnostic performance of the analyzed biomarkers, ROCs were generated.

MMP-11 demonstrated significant discriminative ability in both tissue (AUC = 0.8485, $p = 0.0208$; Table 2; Fig. 1:B1) and serum samples (AUC = 0.7430, $p = 0.0175$; Table 2; Fig. 1:B2). Optimal cut-off value was 2.04 ng/mL (sensitivity 69.19%, specificity 98.0%; J = 61.27%) for serum, and 1.95 ng/mL (sensitivity 68.11%, specificity 88.4%; J = 49.24%) for tissue.

Table 2
Results of ROC curve analysis for the diagnostic accuracy of tissue and serum MMP-11 in BTG vs MTG patients and of serum MMP-11 in patients without and with distant metastases

Tissue MMP-11	***AUC***	***Std. Error***	***95% CI***	***Sig.***
	0.8485	**0.1023**	**0.6479-1.000**	**0.0208**
Serum MMP-11	0.7430	0.0728	0.6002–0.8859	**0.0175**
*Serum MMP-11**	0.7708	0.1028	0.5694–0.9723	**0.0061**
*Results from patients with and without distant metastases				

Association with Metastases

Further analysis focused on the association selected MMP concentrations with presence of distant metastases in serum samples. Serum levels of both MMP-11 and MMP-7 were higher in patients with metastases compared to those without metastases. While MMP-11 showed a statistically significant increase (median: 1.491 vs. 6.873 ng/mL; $p = 0.0051$; Fig. 2A), MMP-7 demonstrated a similar increasing trend; however, this difference did not reach statistical significance. ROC analysis confirmed that serum MMP-11 could reliably distinguish between patients with and without metastases (AUC = 0.7708, $p = 0.0061$; Fig. 2B). Optimal cut-off value was 1.15 ng/mL (sensitivity 74.11%, specificity 100.0%; J = 57.92%).

Correlation Analysis

Spearman's rank correlation analysis identified several statistically significant associations between circulating biomarkers and clinicopathological parameters (Table 3). Disease stage showed moderate to strong positive correlations with all evaluated tumor markers, including MMP-7 ($\rho = 0.600$, $p < 0.001$), MMP-11 ($\rho = 0.460$, $p = 0.001$), CEA ($\rho = 0.635$, $p < 0.001$), CA19.9 ($\rho = 0.767$, $p < 0.001$), and AFP ($\rho = 0.455$, $p = 0.003$). The strongest association was observed between CA19.9 and disease stage, indicating its close relationship with tumor progression.

Significant correlations were also found among individual tumor markers. CEA demonstrated strong positive correlations with CA19.9 ($\rho = 0.638$, $p < 0.001$) and AFP ($\rho = 0.556$, $p < 0.001$). MMP-7 was moderately correlated with both CEA ($\rho = 0.508$, $p < 0.001$) and CA19.9 ($\rho = 0.505$, $p < 0.001$), suggesting its association with tumor burden and

biological activity. MMP-11 showed weaker correlations overall, reaching statistical significance only in relation to CA19.9 ($\rho = 0.355$, $p = 0.012$).

No significant correlations were observed between age and tumor markers or disease stage. Similarly, gender was not significantly associated with biomarker levels or stage. However, a weak but statistically significant inverse correlation between gender and age was identified ($\rho = -0.269$, $p = 0.020$), indicating that male patients were younger compared to female patients within the cohort.

Table 3: Spearman's rank correlation with MMP-11 and MMP-7, CEA, CA19-9, AFP, stage, gender and age

			MMP-7	MMP-11	CEA	CA19.9	AFP	Stage	Gender	Age
Spearman's rho	MMP-7	Correlation Coefficient	1,000	,147	**,508****	**,505****	,231	**,600****	-,125	-,057
		Sig. (2-tailed)	.	,324	**,000**	**,000**	,196	**,000**	,358	,682
		N	56	47	**52**	**53**	33	**56**	56	55
	MMP-11	Correlation Coefficient	,147	1,000	,222	**,355***	,308	**,460****	,085	,140
		Sig. (2-tailed)	,324	.	,129	**,012**	,098	**,001**	,544	,322
		N	47	53	48	**49**	30	**53**	53	52
	CEA	Correlation Coefficient	**,508****	,222	1,000	**,638****	**,556****	**,635****	-,186	,092
		Sig. (2-tailed)	**,000**	,129	.	**,000**	**,000**	**,000**	,126	,458
		N	**52**	48	69	**67**	**41**	**69**	69	68
	CA19.9	Correlation Coefficient	**,505****	**,355***	**,638****	1,000	**,456****	**,767****	-,095	,010
		Sig. (2-tailed)	**,000**	**,012**	**,000**	.	**,003**	**,000**	,439	,938
		N	**53**	**49**	**67**	68	**41**	**68**	68	67
	AFP	Correlation Coefficient	,231	,308	**,556****	**,456****	1,000	**,455****	-,288	,198
		Sig. (2-tailed)	,196	,098	**,000**	**,003**	.	**,003**	,068	,214
		N	33	30	**41**	**41**	41	**41**	41	41
	Stage	Correlation Coefficient	**,600****	**,460****	**,635****	**,767****	**,455****	1,000	-,119	,090
		Sig. (2-tailed)	**,000**	**,001**	**,000**	**,000**	**,003**	.	,311	,447
		N	**56**	**53**	**69**	**68**	**41**	75	75	74
	Gender	Correlation Coefficient	-,125	,085	-,186	-,095	-,288	-,119	1,000	**-,269***
		Sig. (2-tailed)	,358	,544	,126	,439	,068	,311	.	**,020**
		N	56	53	69	68	41	75	75	**74**
	Age	Correlation Coefficient	-,057	,140	,092	,010	,198	,090	**-,269***	1,000
		Sig. (2-tailed)	,682	,322	,458	,938	,214	,447	**,020**	.

N	55	52	68	67	41	74	**74**	81
**. Correlation is significant at the 0.01 level (2-tailed).								
*. Correlation is significant at the 0.05 level (2-tailed).								

Survival Analysis

Kaplan–Meier survival analysis was performed to evaluate the prognostic significance of MMP-7 and MMP-11 expression levels. Patients were stratified according to predefined cut-off values.

Elevated MMP-7 levels (> 21 ng/mL) were significantly associated with poorer overall survival compared to patients with lower levels (< 21 ng/mL) (log-rank test, p = 0.010; Fig. 3).

In contrast, no statistically significant difference in overall survival was observed between patients with high (> 2 ng/mL) and low (< 2 ng/mL) MMP-11 levels (p = 0.521; Fig. 4). Despite its correlation with disease stage, MMP-11 does not appear to have prognostic value in terms of survival in this cohort.

Discussion

In this study, we evaluated the diagnostic and prognostic relevance of MMP-11 and MMP-7 in patients with PDAC and demonstrated distinct biological and clinical roles of these biomarkers. The most consistent finding was the significant elevation of MMP-11 levels in malignant disease, accompanied by a clear association with advanced tumor stage and metastatic spread, consistent with previous reports describing its role in tumor progression and microenvironment modulation [6, 7]. These results support the concept that MMP-11 reflects tumor progression and systemic disease burden, likely through its involvement in tumor–stroma interactions and microenvironment remodeling.

On the other hand, the elevated MMP-7 levels were significantly associated with reduced overall survival, suggesting that this biomarker may capture aspects of tumor aggressiveness not fully reflected by anatomical staging alone, in line with previous observations linking MMP-7 expressions to aggressive tumor behavior and unfavorable prognosis [4, 5].

The identified cut-off values provide a potential clinically applicable threshold for risk stratification and may support individualized patient management in pancreatic cancer. However, these values should be interpreted cautiously and require validation in independent cohorts before routine clinical implementation.

The differential behavior of MMP-11 and MMP-7 likely reflects their distinct biological origins. MMP-11 is predominantly linked to stromal activation and disease extent, whereas MMP-7 is associated with epithelial tumor activity and clinical outcomes. This functional divergence may explain why MMP-11 is more closely related to tumor stage and metastasis, while MMP-7 demonstrates stronger prognostic value for survival.

From a clinical perspective, serum-based biomarkers offer practical advantages over tissue-based analyses, as they are minimally invasive and suitable for repeated monitoring, a concept supported by recent studies evaluating circulating biomarker panels in pancreatic cancer [3]. Our findings suggest that the combined assessment of MMP-11 and MMP-7, particularly in conjunction with established markers such as CA19-9 and CEA, may improve diagnostic accuracy and risk stratification in patients with pancreatic cancer.

Several limitations should be acknowledged. Potential confounding factors, including tumor burden and systemic inflammation, may have influenced biomarker levels and should be considered in future studies. The study cohort was relatively modest in size, and the absence of an independent validation cohort limits generalizability. Future studies should focus on validation in larger, multicenter populations and on integrating MMP-based biomarkers into multivariable predictive models. For now, the findings should be interpreted as hypothesis-generating.

Overall, our results indicate that MMP-11 and MMP-7 represent complementary biomarkers in PDAC, reflecting different aspects of tumor biology and clinical behavior. Their combined use may contribute to improved diagnostic and prognostic assessment in pancreatic cancer.

Conclusion

This study demonstrates that matrix metalloproteinases MMP-11 and MMP-7 represent promising and complementary biomarkers in PDAC. MMP-11 was significantly associated with malignant disease, advanced tumor stage, and metastatic spread, indicating its value as a marker of tumor progression and disease burden. In contrast, MMP-7, despite showing no significant differences in median levels between groups, was significantly associated with overall survival, suggesting its relevance as a prognostic indicator of biologically aggressive disease.

Importantly, these findings highlight a functional divergence between stromal-associated and epithelial-derived MMPs, reflecting distinct aspects of tumor biology. While MMP-11 appears to capture tumor microenvironment remodeling and disease extent, MMP-7 may better reflect tumor aggressiveness and patient outcomes.

The superior performance of serum-based measurements underscores their clinical applicability as non-invasive and repeatable biomarkers. The combined assessment of MMP-11 and MMP-7, particularly in conjunction with established markers such as CA19-9 and CEA, may improve diagnostic accuracy and enable more refined risk stratification in patients with pancreatic cancer.

Further validation in larger, multicenter cohorts is warranted to confirm these findings and to establish the clinical utility of MMP-based biomarker panels in routine practice.

Declarations

Statement Regarding Absence of a Conflict of Interests

The authors declare having no conflict of interest for this article.

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

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Figures

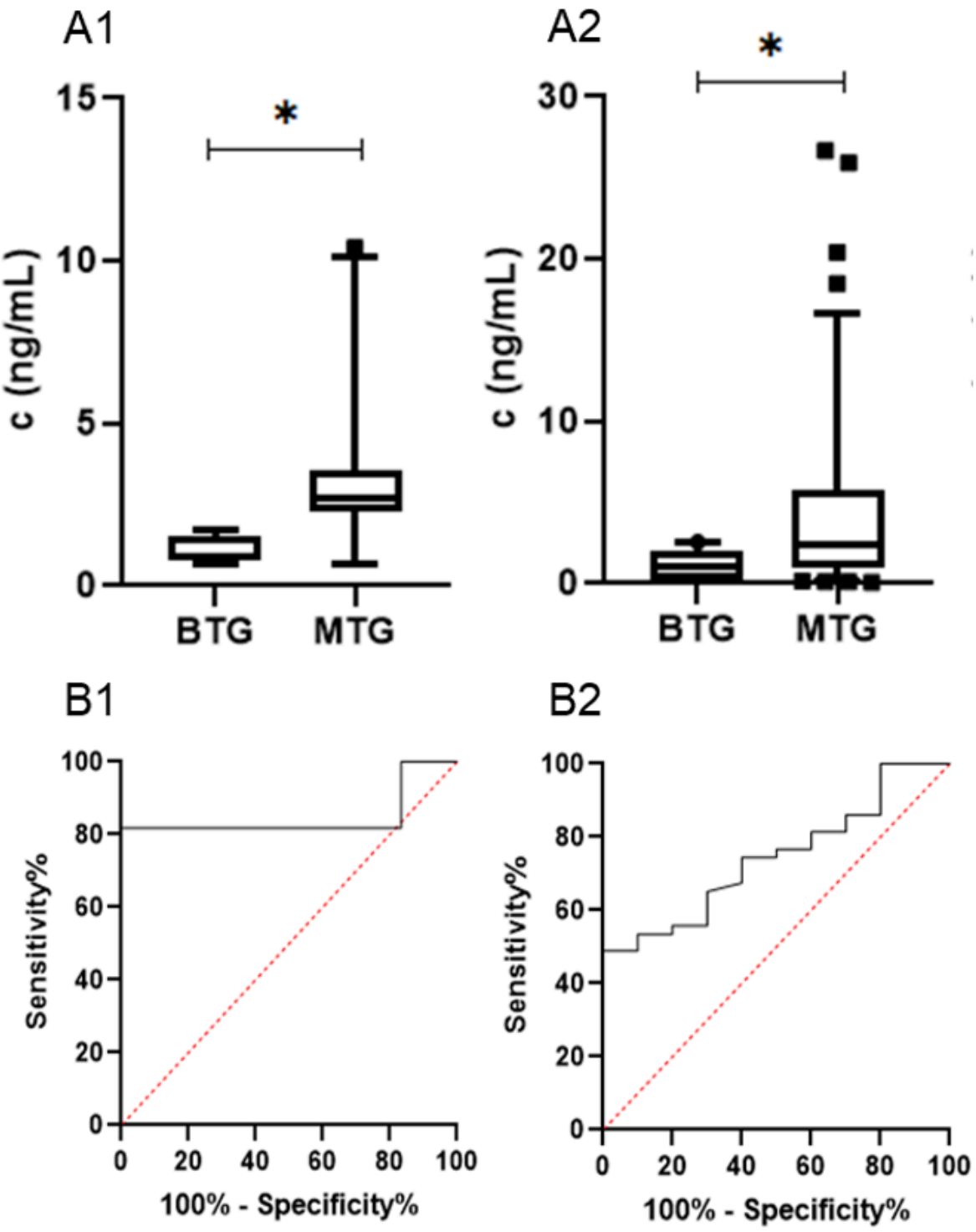


Figure 1

Boxplots for MMP-11 in tissue (A1), and in serum (A2). ROC curves for MMP-11 in tissue (B1), and in serum (B2) for patients in BTG and MTG

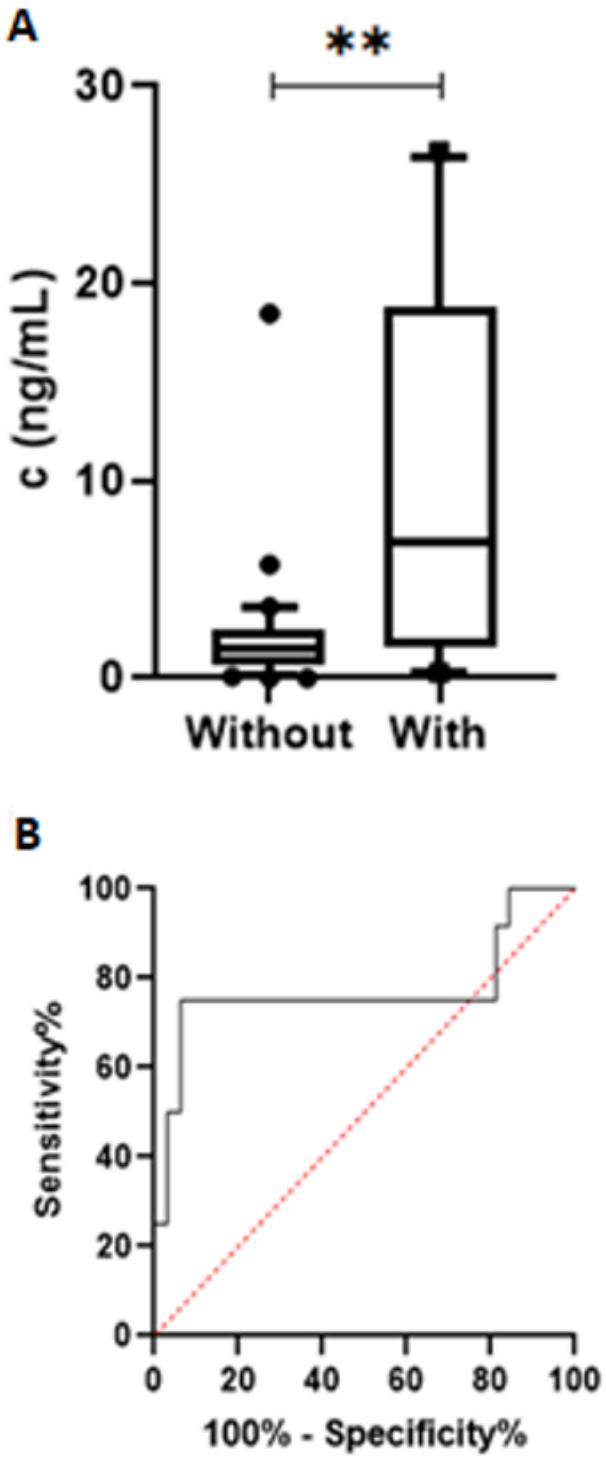


Figure 2

Boxplots for serum MMP-11 (A) for patients without and with distant metastases. ROC curves for MMP-11 (B) for patients without or with distant metastases

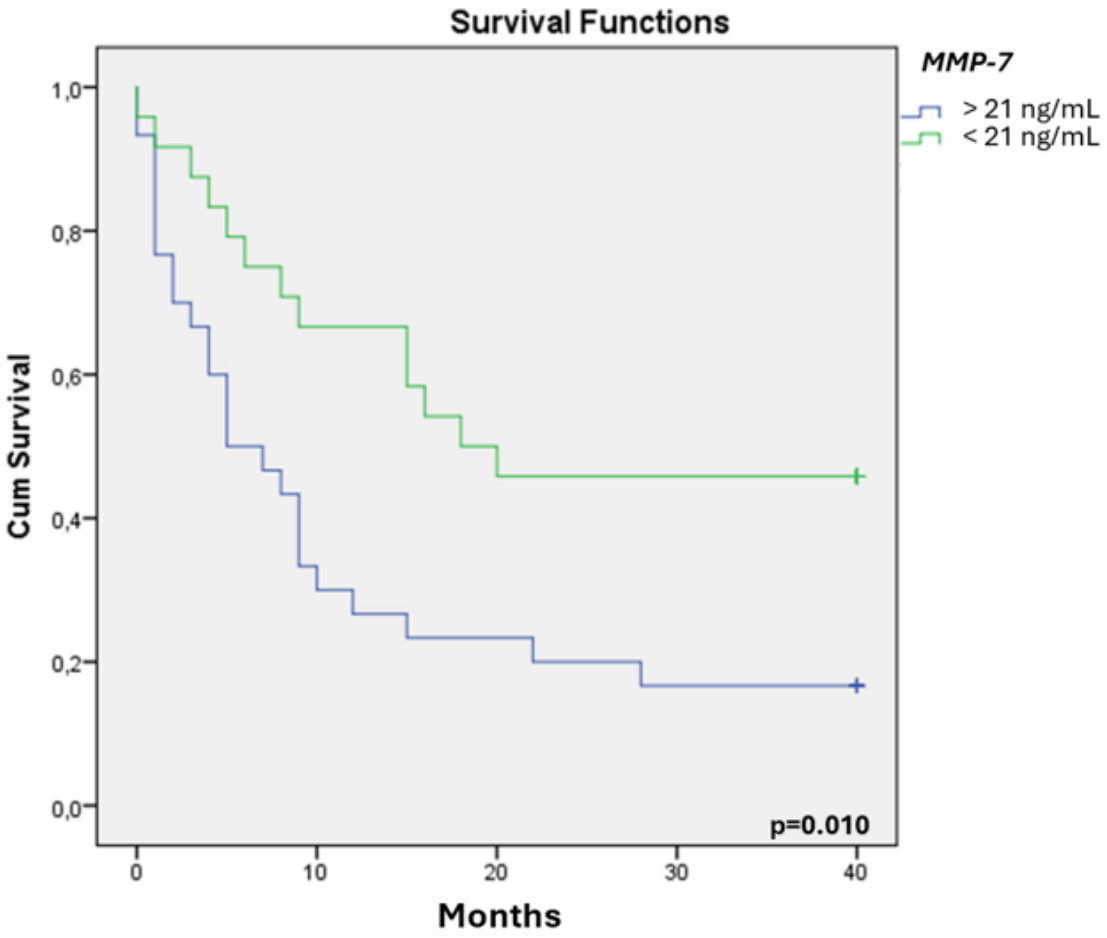


Figure 3

Kaplan-Meier analysis based on serum MMP-7 concentrations

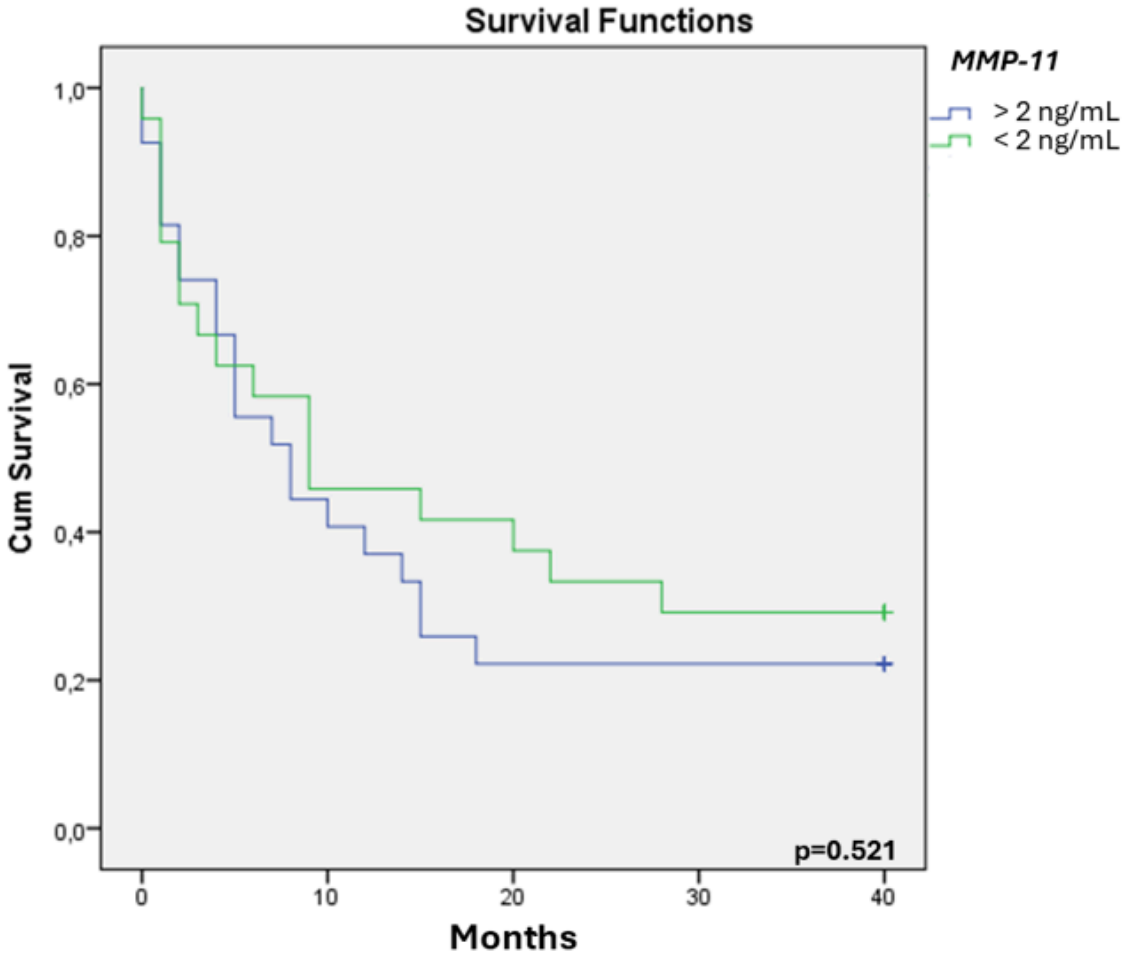


Figure 4

Kaplan-Meier analysis based on serum MMP-11 concentrations