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https://doi.org/10.31925/farmacia.2026.2.4 **ORIGINAL ARTICLE**

COMPARTMENT-SPECIFIC ADIPOKINE AND INFLAMMATORY SIGNATURES IN BREAST AND PANCREATIC CANCER: A CLINICAL-TRANSLATIONAL PILOT STUDY

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Abstract

This study aimed to investigate the profiles of adipokines and cytokines found in urine, peritumoral adipose tissue, and subcutaneous adipose tissue from patients with breast and pancreatic cancer. We also wanted to understand their clinical and translational significance in relation to body mass index (BMI), systemic inflammation, and tumor markers. To achieve this, we measured levels of adiponectin, adipsin, RPB-4, MCP-1, IL-1β, IP-10, IL-10, IL-8, leptin, IL-6, IFN-γ, resistin, and TNF-α in urine and the two types of adipose tissue using a LEGENDplex multiplex assay for flow cytometry. We observed notable differences across biological compartments for all mediators we examined, with urinary concentrations significantly higher than those in adipose tissue. The urinary leptin-to-adiponectin (L/A) ratio showed a significant positive correlation with body mass index and emerged as a more robust indicator of metabolic imbalance than either leptin or adiponectin alone. Tumor-infiltrating T-cell analysis, available for a small subset of patients, revealed marked inter-individual variability without permitting statistical inference.

Rezumat

Acest studiu și-a propus să investigheze profilurile adipokinelor și citokinelor identificate în urină, în țesut adipos peritumoral și în țesut adipos subcutanat la pacienți cu cancer de sân și cancer pancreatic, precum și relevanța lor clinică și translațională în raport cu indicele de masă corporală (IMC), inflamația sistemică și markerii tumorali. În acest scop, au fost determinate nivelurile de adiponectină, adipsină, RBP-4, MCP-1, IL-1β, IP-10, IL-10, IL-8, leptină, IL-6, IFN-γ, rezistină și TNF-α în urină și în cele două tipuri de țesut adipos, utilizând un test multiplex LEGENDplex pentru citometrie în flux. Au fost observate diferențe notabile între compartimentele biologice pentru toți mediatorii analizați, concentrațiile urinare fiind semnificativ mai ridicate decât cele din țesutul adipos. Raportul leptină/adiponectină (L/A) determinat în urină a prezentat o corelație pozitivă semnificativă cu indicele de masă corporală și s-a dovedit a fi un indicator mai robust al dezechilibrului metabolic comparativ cu leptina sau adiponectina analizate separat. Analiza limfocitelor T infiltrante tumorale, disponibilă pentru un subset restrâns de pacienți, a evidențiat o variabilitate inter-individuală marcată, fără a permite efectuarea inferențelor statistice.

Keywords: secretome, adipokines, breast cancer, pancreatic cancer, flow cytometry

Introduction

Inflammation is a vital biological process necessary for host defence and tissue homeostasis; however, when dysregulated, it is a major driver of tumour initiation and progression. Growing evidence shows that many solid tumours grow and change in an environment that is always inflamed. This is characterized by ongoing activation of innate immune pathways, significant stromal remodelling and alterations in immune surveillance (1). Pancreatic cancer exemplifies an inflammation-driven malignancy, whereas breast cancer demonstrates the complex interactions of inflammatory signals influenced by metabolic and hormonal factors.

Inflammasomes are cytosolic protein complexes that are essential for the innate immune response, as they recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) (1). When activated, inflammasomes break

down pro-caspase-1 into its active form. This causes interleukin-1β (IL-1β) and interleukin-18 (IL-18), which are pro-inflammatory cytokines, to mature and be released. It also causes pyroptosis, a type of programmed cell death that is both lytic and very inflammatory, and is caused by gasdermin D (2).

Inflammasomes have a significant impact on cancer, as they can promote or inhibit tumour progression, depending on cell type, tumour type and microenvironmental signals.

Recent studies around pancreatic cancer have increasingly focused on inflammasome signalling as a key connection between chronic inflammation and pancreatic neoplasms development. Pancreatic cancer is characterized by the presence of chemokines such as IL-6, IL-8, TNF-α and IFN-γ, as well as cytokines from inflammasomes, which play an important role in disease development and therapy response. When activated, the NLRP3 axis creates a pro-inflammatory environment, in which cancer cells evade the immune system and spread to nearby tissues (3). This is not a one-step process. Instead, it involves a complex network of signals, such as IL-6, TNF-α and various chemokines, that work together to make the disease more aggressive and treatment-resistant. For example, IL-1β and IL-18 may alter tumour cells and stromal components by promoting angiogenesis, fibrosis and immune cell recruitment in the tumour microenvironment. All these interconnected networks of signals provide insight into why pancreatic cancers are frequently resistant to treatment and marked by an aggressive evolution.

Breast cancer arises within a multifaceted inflammatory microenvironment, where the consequences of inflammasome activation are context dependent. Under specific conditions, inflammasome signalling can promote tumour progression by stimulating angiogenesis, driving epithelial-mesenchymal transition and facilitating invasion and metastatic dissemination.

Conversely, there are instances in which inflammasome activation restricts tumour growth by inducing pyroptotic cell death and supporting anti-tumour immune responses. This dual function of inflammasome biology within breast cancer highlights the complex interaction between tumour and immune environment (1).

We now understand that adipose tissue is far more than just a passive site for energy storage. We've come to realize that adipose tissue is much more than just a place where the body stores energy. It is a complex endocrine organ that plays an important role in both metabolism and cancer biology. This fat tissue actively alters the tumour microenvironment by releasing a variety of bioactive molecules known as adipokines. When this tissue doesn't function properly, which is common in people who are overweight, it can cause a long-lasting, low-level inflammatory state. This state might help tumours grow and spread, and it could also make tumours less responsive to standard treatments. This is especially important in breast cancer, where tumours are often surrounded by a microenvironment with many fat cells (4).

Leptin and adiponectin are two important adipokines that influence this inflammatory and metabolic signalling. Leptin levels, which tend to be higher in individuals with higher body fat, promote tumour growth by activating survival pathways such as PI3K/AKT and MAPK, thereby stimulating tumour cell proliferation, survival, migration and angiogenesis (5, 6). This signalling pathway not only supports the growth and longevity of cancer cells but is also linked to increased tumour aggressiveness and a weakened immune response in both breast and pancreatic cancers (7, 8). On the other hand, adiponectin usually has a protective and anti-inflammatory role. Still, its levels often decrease in obese individuals, making them more prone to insulin resistance and at a higher risk for cancer progression (9).

Beyond these well-known adipokines, other adipokines, such as resistin and adipsin, further modulate the inflammatory landscape. They play a role in immune cell recruitment, cytokine production and in shaping the interaction between the tumour and its surrounding stroma, creating a complex network that links systemic metabolic health to localized inflammation at the tumour site (10-14).

As we advance our clinical strategies for breast cancer to include more personalized genetic screenings and preventive surgeries, it is important to consider these intricate relationships. As our clinical approach to breast cancer evo-lves to incorporate more personalized genetic scree-nings and prophylactic surgeries for high-risk individuals (15, 16), a substantial gap in our knowledge persists. We presently do not possess a detailed map illustrating the distribution of these inflammatory mediators across various biological compartments. A better understanding of these patterns could be key to understanding how tumours interact with their hosts, potentially leading to novel therapies.

In this context, the current study aimed to investigate compartment-specific adipokine profiles in urine, subcutaneous adipose tissue and peritumoral adipose tissue from patients with breast and pancreatic cancer, and to explore their potential clinical and translational relevance in relation to inflammatory status and selected clinical parameters.

Materials and Methods

Patient's cohort and study design

All samples were obtained from 15 patients recruited and surgically treated for pancreatic or breast cancer at "Prof. dr. Al. Trestioreanu" Oncologic Institute of Bucharest. As shown in Figure 1, the study was conducted using four distinct types of biological specimens: (i) preoperative urine, (ii) tumour tissue, (iii)

peritumoral adipose tissue and (iv) subcutaneous adipose tissue.

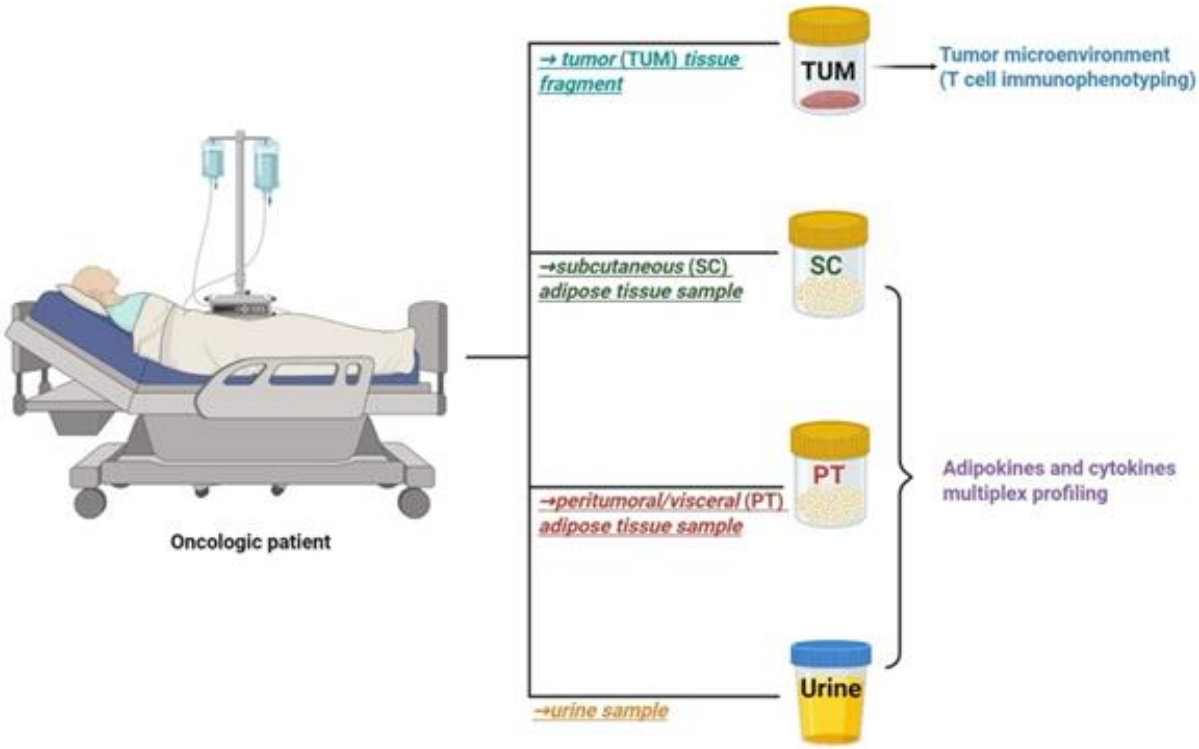

Figure 1.
Experimental design

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of "Prof. dr. Al. Trestioreanu" Oncologic Institute of Bucharest (protocol code 12/28.03.2025). Informed consent was obtained from all subjects involved in the study.

Sample collection and pre-processing

Spontaneous first-morning void urine samples were collected in sterile, designated containers. To maintain the stability of the cytokine profile, the urine samples were centrifuged at 1500 rpm for 5 minutes to remove cellular debris. The supernatant was stored at -20°C until analysis.

All three tissue specimens: (i) the primary tumour mass, (ii) the peritumoral adipose tissue samples and (iii) the subcutaneous adipose tissue samples, were harvested during the surgical intervention. After resection, the tissue samples were weighed and then placed in three different storage containers with MACS® Tissue Storage Solution (Cat. Nr. 130-100-008, Miltenyi Biotec, Bergisch Gladbach, Germany). After 24 h of incubation at 37°C, the samples were centrifuged at 1500 rpm for 5 min, and the supernatants containing secreted cytokines were stored at -20°C until analysis. The primary tumour mass was submitted to the institute's pathology department for diagnostic validation. The pathologist examined the tumour sample and dissected a representative fragment, which was placed in the same storage tissue solution described above.

Tumour tissue dissociation

Single-cell suspensions were prepared using the Tumor Dissociation Kit, human (Cat. Nr. 130-095-929, Miltenyi Biotec, Bergisch Gladbach, Germany) according to the manufacturer's instructions. Briefly, as shown in Figure 2, the tumour sample were subjected to mechanical dissociation by cutting the tumour fragment into 2 - 4 mm pieces and followed by placing the minced tissue into specialized gentleMACS™ C tubes (Cat. Nr. 130-093-237, Miltenyi Biotec, Bergisch Gladbach, Germany) with the enzymatic dissociation cocktail on gentleMACS™ Dissociator (Cat. Nr. 130-093-235, Miltenyi Biotec, Bergisch Gladbach, Germany). The automated tissue homogenization was performed at room temperature, following the manufacturer's preset programs. Subsequently, enzymatic digestion for tumour-infiltrating lymphocytes (TILs) was performed by incubating the C tube at 37°C for 30 minutes with constant agitation. The resulting suspension was filtered through a 70 µm cell strainer to remove remaining connective tissue and cell aggregates. The single-cell suspension was centrifuged at 3000 rpm for 10 minutes, and the pellet was collected.

T cell immunophenotyping

The characterization of T cell subpopulations was performed using the DuraClone IM T cell subsets kit (Cat. Nr. B53328, Beckman Coulter, Brea, CA, USA). This dry reagent assay contains the following pre-formulated fluorochrome-conjugated antibodies: CD45RA, CD197 (CCR7), CD28, CD279 (PD-1), CD27, CD3, CD4, CD8, CD45 and CD57. The previously obtained cell pellet was resuspended in 100 µL phosphate-buffered saline (PBS) and added to the bottom of the tube, avoiding contact with the dried reagent. The tube was vortexed for 8 seconds and incubated in the dark at room temperature for 15 minutes. After a PBS wash, the samples were fixed according to the manufacturer's recommendations and acquired on a Beckman Coulter Gallios Flow Cytometer (Figure 2). Prior to the acquisition, a quality check (QC) was performed, and the protocol was optimized and enrolled using single-stained DuraClone tubes for compensation. The data was analysed using Kaluza Software.

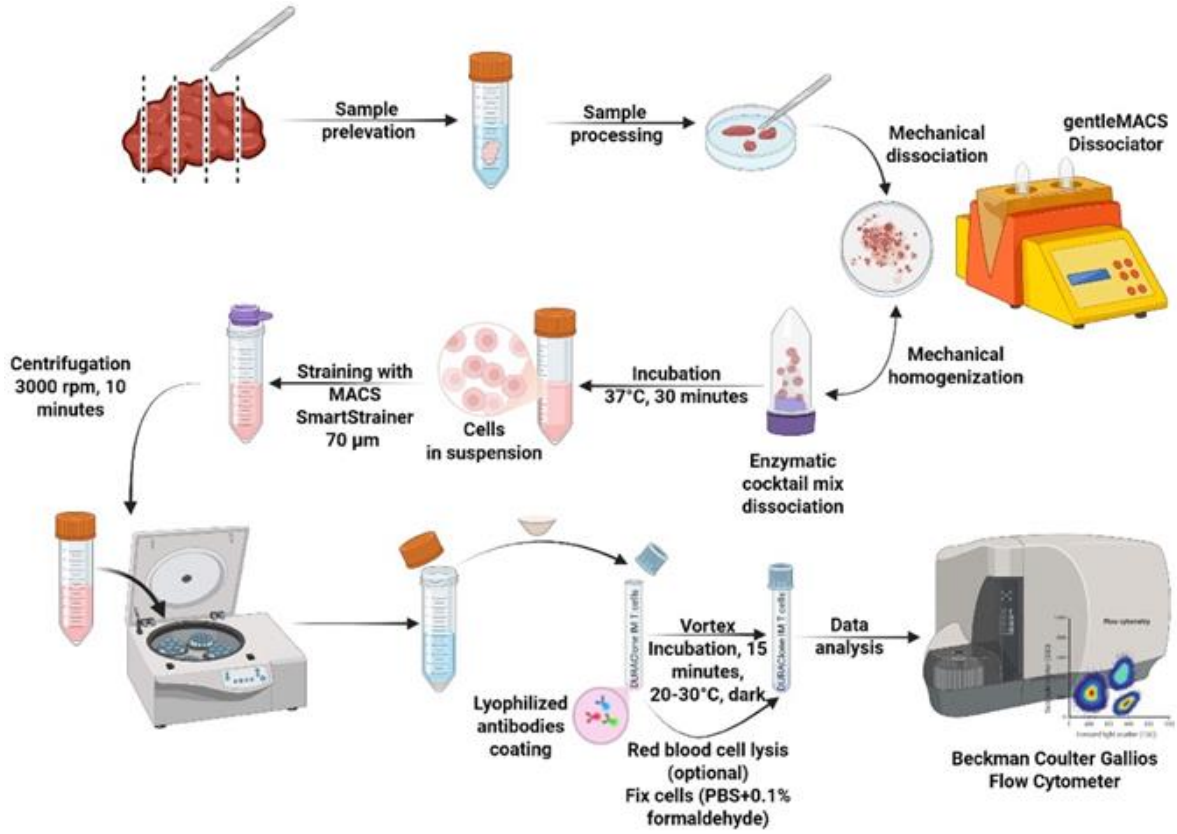

Figure 2.
Complete workflow for T cell immunophenotyping from solid tissue samples

Adipokines and cytokines multiplex profiling

The multiplex profiling of the following 13 adipokines and cytokines: adiponectin, adipsin, RBP-4, MCP-1, IL-1β, IP-10, IL-10, IL-8, leptin, IL-6, IFN-γ, resistin and TNF-α was performed using the LEGEND-plex Human Adipokine Panel (13-plex) (Cat. Nr. 740196, BioLegend, San Diego, CA, USA). As mentioned before, following the initial centrifugation step to remove the cellular debris, the urine and adipose tissues supernatants were partitioned into aliquots and stored at -20°C until the day of analysis. The samples were thawed and subjected to a secondary centrifugation step at the same parameters to remove any potential protein precipitates formed during the freeze-thaw cycle. Prior to analysis, urine samples were diluted 2X as recommended by the producer, and peritumoral and subcutaneous adipose tissues were diluted 4X. The protocol was performed according to the manufacturer's indications and is illustrated in Figure 3. Briefly, 25 µL of the diluted sample was incubated with premixed beads provided in the kit for 2 hours at room temperature on a plate shaker (800 rpm) in the dark. Following a step wash, 25 µL of biotinylated detection antibodies was added and incubated for an hour in the same conditions, followed by the addition of 25 µL of Strepavidin-PE (SA-PE) for 30 minutes. Data acquisition was performed on a Beckman Coulter Gallios Flow Cytometer. The final concentrations were calculated in pg/mL using a 7-parameter standard logistic curve, as described in the manufacturer's instructions.

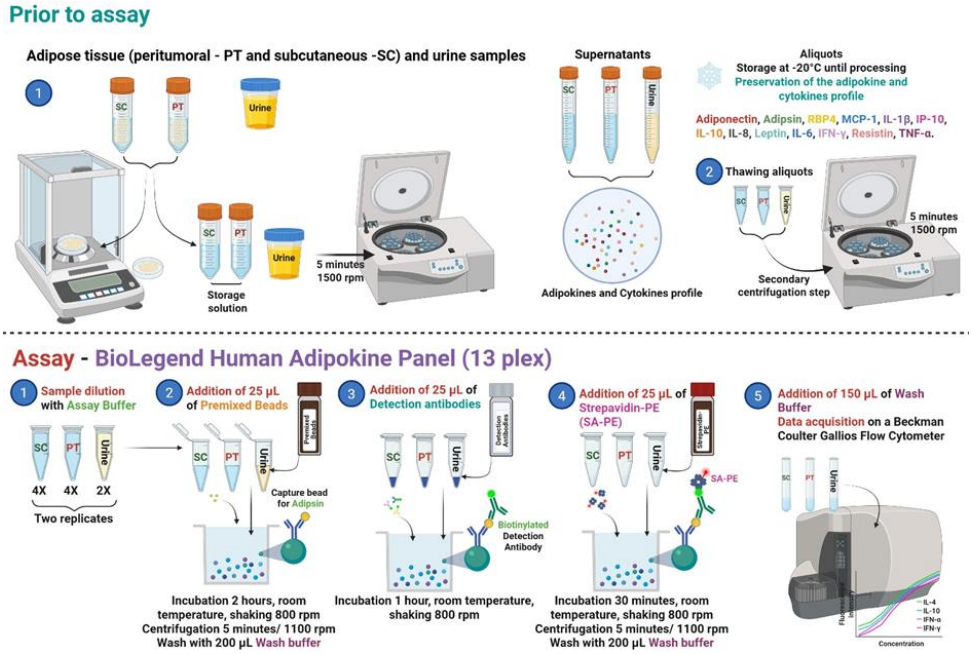

Figure 3.
Complete workflow for the multiplex quantification of adipokines and cytokines from peritumoral adipose tissues, subcutaneous adipose tissues and urine samples

Statistical analysis

Raw data from the LEGENDplex multiplex assay were acquired by flow cytometry and analysed with Kaluza Analysis 2.1 software (Beckman Colter), with median fluorescence intensity (MFI) values extracted for each analyte. Standard curves were generated using manufacturer-provided standards and fitted using a logistic regression model. Analyte concentrations (pg/mL) were calculated by interpolation of sample MFI values within the dynamic range of the standard curves. To ensure biological relevance, analyte concentrations were normalized according to sample type. Urinary concentrations were normalized to creatinine levels and expressed as pg/mg creatinine. Adipokine and cytokine concentrations derived from adipose tissue supernatants were normalized to tissue weight and expressed as pg/g of tissue. After normalization, values below the limit of quantification (LLOQ) were replaced with half of the detection limit (LLOQ/2), while values exceeding the upper limit of quantification (ULOQ) were set to the highest measurable concentration for subsequent analyses. In all patients and all compartments, Il-1β, IP-10 and TNF-α values were LLOQ, therefore, these analytes were excluded for further analysis.

Due to the skewed distribution and wide dynamic range of the data, a log10 transformation was applied to improve data visualization and reduce the impact of extreme values. Nonparametric statistical methods were used for all statistical analyses, given the sample size and distribution characteristics.

Adipokine and cytokine levels across biological compartments (urine, peritumoral adipose tissue and subcutaneous adipose tissue) were compared using the Friedman test for repeated measures, followed by Dunn's multiple comparisons test. Associations between body mass index (BMI) and analyte levels were assessed using Spearman's rank correlation coefficient. Correlations were evaluated separately for each biological compartment. The leptin-to-adiponectin ratio was calculated using raw normalized concentrations. Values below LLOQ were imputed prior to ratio calculation. The resulting ratios were log transformed and analysed as an integrative marker of adipose tissue dysfunction in correlation with BMI, CRP and tumour markers.

Additional exploratory analyses were conducted to assess associations between adipokines, systemic inflammatory markers (C-reactive protein, CRP) and tumour markers (CA 19-9 in pancreatic cancer; CA 15-3 and CEA in breast cancer), with stratification by cancer type where applicable.

In parallel, immunophenotyping raw data obtained using the DuraClone IM T Cell panel (Beckman Coulter) were analysed using Kaluza software. For each sample, cell populations were identified and quantified based on marker expression, and the frequency of each immune cell subset was extracted for downstream analysis. The gating strategy was performed according to the manufacturer's recommendations and consisted of a sequential approach: initial exclusion of debris based on forward and side scatter (FSC/SSC), followed by doublet discrimination using FSC-A *versus* FSC-H parameters. Viable leukocytes were identified within the $CD45^+$ population, after which T lymphocytes were gated as $CD3^+$ cells.

Subsequent subsetting was performed to distinguish $CD4^+$ and $CD8^+$ T-cell populations. Further phenotypic characterization included the identification of naive and memory subsets based on CD27 and CD28 expression, as well as markers of activation and senescence/exhaustion, including PD-1 and CD57. Only patients with more than 1000 events in the gate $CD3^+$ were further considered.

All statistical analyses were performed using GraphPad Prism (version 6.0; GraphPad Software, San Diego, CA, USA). All samples were analysed in duplicate, and data are presented as the mean of duplicate measurements. All tests were two-tailed, and a p-value < 0.05 was considered statistically significant. Given the exploratory nature of this study, results were interpreted in the context of effect size, directionality and biological plausibility.

Results and Discussion

Clinical and demographic characteristics of the study cohort

The study cohort comprised 15 patients (Table I) undergoing surgical treatment, including 9 patients with breast cancer and 6 patients with pancreatic cancer.

Table I

Clinicopathological characteristics, treatment details and serum biomarker levels of patients with breast and pancreatic neoplasms

No.	Age	Sex	BMI	Neoplasm type	Pathological staging	Neoadjuvant treatment	CRP	CEA	CA19.9	CA15-3
1.	52	F	20.6	Invasive lobular breast carcinoma (G1), ER+, PR+, HER2low	pT2(m2) pN0	No	0.10 mg/dL	4.64 ng/mL	n/a	15.73 U/mL
2.	77	F	33.59	Invasive ductal breast carcinoma(G2), ER+, PR+, HER2 negative	pT1c pN0(sn)	No	1.55 mg/dL	< 1.73 ng/mL	n/a	10.03 U/mL
3.	62	F	31.6	Invasive ductal breast carcinoma (G2), ER+, PR+, HER2 negative	pT1cpN0	No	0.80 mg/dL	< 1.73 ng/mL	n/a	17.06 U/mL
4.	80	F	36.85	Invasive breast apocrine carcinoma (G2), triple negative (ER-, PR-, HER2-)	ypT3 ypN0	Yes	0.20 mg/dL	2.13 ng/mL	n/a	34.17 U/mL
5.	72	F	35.76	Invasive lobular carcinoma (G2), ER+, PR+, HER2-	pT1c pN0 (sn)	No	0.25 mg/dL	< 1.73 ng/mL	n/a	6.09 U/mL
6.	65	F	26.71	Invasive ductal breast carcinoma (G1), ER+, PR-, HER2-	pT2 pN0 (sn)	No	< 0.10 mg/dL	4.02 ng/mL	n/a	9.86 U/mL
7.	68	F	20.83	Invasive ductal breast carcinoma(G1), ER+, PR+, HER2 negative	pT1c pN0 (sn)	No	0.26 mg/dL	3.10 ng/mL	n/a	13.01 U/mL
8.	67	F	31.25	Invasive ductal breast carcinoma (G2), ER+, PR+, HER2 negative	ypT1b ypN0	Yes	0.16 mg/dL	3.03 ng/mL	3.58 U/mL	19.08 U/mL
9.	66	F	34.22	Invasive ductal breast carcinoma (G2), ER+, PR+, HER2 negative	ypT2 (m2) pN1a(sn)	Yes	0.42 mg/dL	3.02 ng/mL	n/a	11.53 U/mL
10.	75	F	19.10	Ductal adenocarcinoma of the pancreatic head (NOS)-G1	ypT1c ypN1	Yes	0.74 mg/dL	9.75 ng/mL	< 2.06 U/mL	n/a
11.	20	F	29	Pancreatic cystic acinar transformation	n/a	No	10 mg/dL	44 ng/mL	7.3 U/mL	44 U/mL
12.	64	M	21	Ductal adenocarcinoma of the pancreatic head (NOS)-G2	ypT3 ypN2	Yes	0.32 mg/dL	4.54 ng/mL	157.34 U/mL	n/a
13.	42	M	30.8	Pancreatic neuroendocrine tumour (NET-G1)/(insulinoma), located in the body and tail of the pancreas	pT1 pN0	No	0.99 mg/dL	4.97 ng/mL	2.21 U/mL	n/a
14.	54	M	31.38	Well-differentiated ampullary adenocarcinoma (G1)	pT3b pN1;	No	0.34 mg/dL	< 1.73 ng/mL	5.21 U/mL	n/a
15	75	M	24.69	Pancreatic intraductal papillary mucinous neoplasm (IPMN) with low-grade dysplasia	n/a	N0	0.15 mg/dL	2.43 ng/mL	28.11 U/mL	n/a

F/M – Female/Male; BMI – Body Mass Index (kg/m²); ER – Oestrogen Receptor; PR – Progesterone Receptor; HER2 – Human Epidermal Growth Factor Receptor 2; HER2 low – Low HER2 expression (IHC 1+ or 2+ without amplification); Triple negative – ER−, PR−, HER2−; G1/G2 – Tumour grade (well/moderately differentiated); NOS – Not Otherwise Specified; NET – Neuroendocrine Tumour; IPMN – Intraductal Papillary Mucinous Neoplas

The cohort included 11 females and 4 males, with a median age of 66 years (range 20 - 80 years; mean ± SD: 62.6 ± 15.6 years).

Patients exhibited heterogeneous metabolic profiles, with a median body mass index (BMI) of 30.8 kg/m² (range 19.1 - 36.9 kg/m²; mean ± SD: 28.5 ± 5.9 kg/m²), indicating a predominance of overweight and obese individuals within the cohort. Systemic inflammatory status, assessed by C-reactive protein (CRP), showed marked inter-individual variability,

with a median value of 0.26 mg/dL (range 0.1 - 10 mg/dL; mean ± SD: 1.07 ± 2.41 mg/dL), reflecting heterogeneous inflammatory activity.

Tumour marker measurements were available for a subset of patients. In breast cancer patients, CA 15-3 levels (n = 9) showed a median of 15.7 U/mL (range 6.1 - 34.2 U/mL; mean ± SD: 16.0 ± 8.1 U/mL). In pancreatic cancer patients (n = 6), CA 19-9 levels showed pronounced variability, with a median of 6.25 U/mL (range 2.21 - 157.3 U/mL; mean ± SD: 33.7 ± 61.3 U/mL). Carcinoembryonic antigen (CEA) values had a median of 3.0 ng/mL (range 1.7 - 44 ng/mL; mean ± SD: 6.17 ± 10.66 ng/mL).

Neoadjuvant treatment was not administered to most patients (10 out of 15), while the remaining patients received heterogeneous neoadjuvant regimens. All patients originated from an urban environment.

In conclusion, this pilot cohort includes patients with heterogeneous clinical and metabolic characteristics, allowing exploratory assessment of compartment-specific inflammatory and adipokine signatures.

Compartment-specific adipokine and cytokine profiles across urine, peritumoral adipose tissue and subcutaneous adipose tissue

To investigate compartment-specific adipokine and cytokine signatures, levels of the following 13 mediators: adiponectin, adipsin, RBP-4, MCP-1, IL-1β, IP-10, IL-10, IL-8, leptin, IL-6, IFN-γ, resistin and TNF-α were compared across urine, peritumoral adipose tissue and subcutaneous adipose tissue using Friedman tests on paired samples. Statistically significant differences across compartments were observed for all analytes ($p < 0.05$ for all; most $p < 0.001$), supporting the presence of distinct compartment- specific secretory profiles (Figure 4).

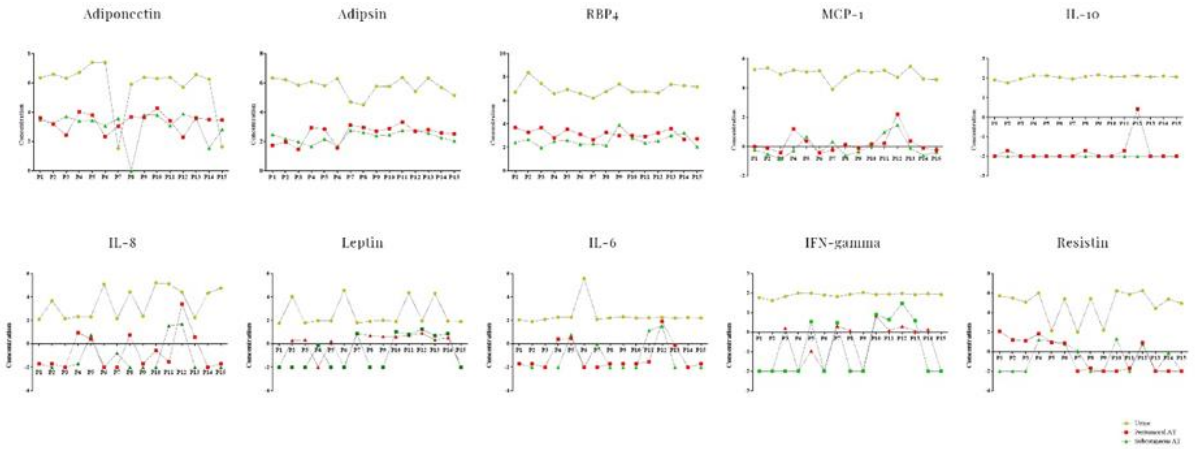

Figure 4.

Levels (normalized concentration: urinary - pg/mg creatinine; tissue - pg/g of adipose tissue) of adiponectin, adipsin, RBP-4, MCP-1, IL-10, IL-8, leptin, IL-6, IFN-γ and resistin in urine, peritumoral adipose tissue and subcutaneous adipose tissue

Across all 10 remaining analytes, urinary concentrations were several orders of magnitude higher than those measured in adipose tissue supernatants, indicating that urine integrates systemic and tissue-derived inflammatory and metabolic signals. In contrast, both adipose tissue compartments exhibited substantially lower absolute concentrations, consistent with localized, tightly regulated paracrine signalling.

Post-hoc pairwise analyses revealed that while urinary levels differed uniformly from both adipose tissue compartments for all mediators, differences between peritumoral and subcutaneous adipose tissue were analyte-specific. Notably, adipsin, RBP4 and IL-10 displayed significantly different levels between peritumoral and subcutaneous adipose tissue ($p < 0.05$). In contrast, other adipokines and cytokines, including adiponectin, leptin, IL-8, TNF-α and MCP-1, did not show significant differences between the two adipose depots.

These findings indicate that urine represents a highly sensitive compartment that reflects cumulative systemic inflammatory and metabolic activity, whereas adipose tissue compartments capture localized signalling dynamics. The relatively limited number of mediators differentiating peritumoral from subcutaneous adipose tissue suggests that tumour proximity induces selective, rather than global, reprogramming of adjacent adipose tissue. Mediators such as IL-10 and IP-10 may therefore represent key candidates involved in tumour-associated immune modulation at the adipose–tumour interface.

These data support the interpretation that systemic and local compartments capture different layers of tumour-associated inflammatory and metabolic signalling, and that tumour proximity may induce

selective rather than diffuse adipose tissue changes. This interpretation aligns with the background literature cited in our manuscript, which describes adipose tissue as an active endocrine and inflammatory organ and emphasizes that adipokines and cytokines participate in complex tumour-stroma interactions in both breast and pancreatic cancer (4, 5, 13).

Associations between adipokines, BMI and systemic inflammation

BMI–adipokine associations. The relationship between adiposity and adipokine levels was explored using Spearman's rank correlation analysis. Body mass index (BMI) showed substantial inter-individual variability in this cohort (median 30.8 kg/m², range 19.1 - 36.9 kg/m²; mean ± SD 28.5 ± 5.9 kg/m²; n = 15). Among individual adipokines, BMI demonstrated weak to moderate inverse correlations with urinary adiponectin (r = - 0.33, p = 0.23), IL-6 (r = - 0.49, p = 0.064), IL-10 (r = - 0.47, p = 0.078) and IFN-γ (r = - 0.47, p = 0.078), while a positive trend was observed with creatinine (r = 0.47, p = 0.08). However, none of these associations were statistically significant. Classical adipokines exhibited limited associations with BMI; leptin showed no meaningful correlation, and RBP4 showed only a weak, non-statistically significant positive association. These findings suggest that individual adipokine levels are only partially influenced by adiposity in this heterogeneous cancer cohort. In contrast, the leptin-to-adiponectin (L/A) ratio emerged as a more robust marker of adiposity-related metabolic imbalance, particularly in urine (Figure 5), where it showed a significant positive correlation with BMI (r = 0.63, p* = 0.014), whereas only moderate, non-significant associations were observed in subcutaneous and peritumoral adipose tissue. This finding supports the use of urinary L/A as an integrative, non-invasive marker of adiposity-related metabolic dysregulation.

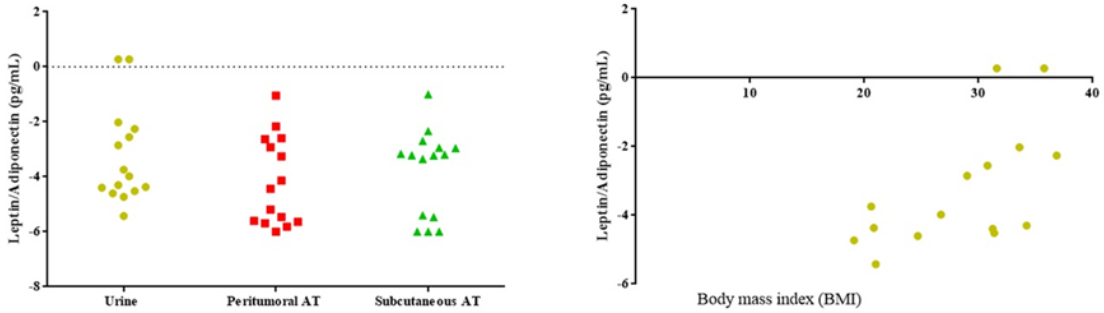

Figure 5.

Left: Leptin-to-adiponectin ratio across compartments; Right: Urinary leptin-to-adiponectin ratio correlates with BMI

The L/A ratio was chosen because it integrates the pro-inflammatory effects of leptin and the anti-inflammatory properties of adiponectin, making it a more robust and clinically relevant indicator of adipose tissue dysfunction than either hormone alone. Previous studies have shown that L/A is a superior bio-marker of metabolic imbalance and cardiovascular risk compared with individual adipokines, and emerging evidence highlights its value in oncologic contexts, where it more accurately reflects obesity-related changes in tumour biology than leptin or adiponectin alone (17, 18). This observation that the L/A ratio integrates opposing biological signals and may better reflect adipose dysfunction than single adipokines is consistent with the literature already cited in the manuscript, which supports leptin as predominantly pro-tumorigenic and adiponectin as generally anti-inflammatory and anti-tumoral, especially in obesity-associated cancer biology (5, 8). At the same time, because the significant association was predominantly observed in urine and not in adipose tissue compartments, our data may suggest that urinary L/A may better reflect global adiposity-related dysregulation in this setting than tissue-derived measurements.

Systemic inflammation: CRP in relation to adipokine-based markers and IL-8. Systemic inflammatory status was assessed using C-reactive protein (CRP), which exhibited pronounced variability across patients (median 0.26 mg/dL; range 0.1 - 10 mg/dL; mean ± SD: 1.07 ± 2.41 mg/dL). Spearman correlation analyses revealed weak, non-significant positive associations between CRP and the leptin-to-adiponectin ratio, and between CRP and IL-8 levels, in all three studied compartments. These findings indicate that, within this pilot cohort, metabolic adipokine imbalance and chemokine-mediated inflammatory signalling are not tightly coupled to systemic acute-phase inflammation (Table II).

The absence of strong correlations between CRP and adipokine-based markers underscores the biological distinction between chronic metabolic dysregulation and acute-phase inflammatory responses in cancer patients. Based on our data, this suggests that systemic acute-phase inflammation, as measured by CRP, was not tightly aligned with the adipokine-based and chemokine-based patterns observed in urine and

adipose tissue. This interpretation remains cautious, but it aligns with the framework outlined in the introduction, in which chronic inflammatory signalling, inflammasome-related pathways, and adipokine dys-regulation are presented as interconnected yet biologically complex processes in cancer (1, 3).

Table II

r and p values for CRP correlation with L/A ratio and IL-8

CRP correlated with L/A					
urine		**peritumoral adipose tissue**		**subcutaneous adipose tissue**	
r	p	r	p	r	p
0.2556	0.3551	-0.1573	0.5686	-0.05919	0.8341
CRP correlated with IL-8					
urine		**peritumoral adipose tissue**		**subcutaneous adipose tissue**	
r	p	r	p	r	p
0.2719	0.3235	-0.4459	0.0819	-0.01453	0.33

Associations between adipokines, cytokines and tumour markers

Pancreatic cancer (CA 19-9, n = 6). In patients with pancreatic cancer (n = 6), exploratory Spearman correlation analyses were performed to assess the relationship between CA 19-9 levels and selected adipokines and cytokines across urine, peritumoral adipose tissue and subcutaneous adipose tissue. Overall, most associations between CA 19-9 and inflammatory mediators were weak and did not reach statistical significance. However, a notable inverse association was observed between CA 19-9 and leptin levels in peritumoral adipose tissue ($r = -0.65$, $p^{****} < 0.001$), suggesting that higher tumour antigen burden may be associated with reduced leptin expression in adipose tissue adjacent to the tumour. Additional inverse trends were observed between CA 19-9 and the leptin-to-adiponectin ratio in peritumoral adipose tissue ($r = -0.77$, $p = 0.10$), although these did not reach statistical significance. No consistent associations were identified between CA 19-9 and IL-8 levels across compartments, highlighting the complexity of inflammatory signalling in pancreatic cancer.

Breast cancer (CA 15-3 and CEA, n = 9). In breast cancer patients (n = 9), tumour marker levels (CA 15-3 and CEA) were evaluated in relation to adipokines and cytokines across biological compartments. CA 15-3 levels exhibited an inverse correlation with leptin concentrations in subcutaneous adipose tissue ($r = -0.6$, $p = 0.09$), as well as inverse trends with IL-8 ($r = -0.346$, $p = 0.14$) and IL-10 ($r = -0.28$, $p = 0.194$) in peritumoral adipose tissue compartments. CEA levels demonstrated a distinct pattern, showing a significant inverse association with the urinary leptin-to-adiponectin ratio ($r = -0.695$, $p^{*} = 0.04$) and positive trends with IL-8 ($r = 0.61$, $p = 0.08$) and IL-10 ($r = 0.44$, $p = 0.23$) in peritumoral adipose tissue. This compartment-specific behaviour underscores the heterogeneous biological processes reflected by different tumour markers. Taken together, these exploratory analyses indicate that tumour marker levels may be linked to selective alterations in adipokine and cytokine profiles, particularly within adipose tissue compartments. The compartment-specific nature of these associations reinforces the concept that tumour-adipose interactions are spatially regulated and may differ between breast and pancreatic cancer. Given the limited sample size and exploratory design, these findings should be interpreted cautiously; nevertheless, they generate testable hypotheses regarding the interplay between tumour burden, metabolic signalling and local inflammatory regulation. Based on our data, the most appropriate interpretation is that tumour-marker relationships were selective, compartment-dependent and not uniform across all analytes. This selective pattern is compatible with the literature already summarized in the manuscript, which describes leptin as involved in tumour-promoting signalling and adipokine networks as modulators of tumour–stroma interactions, but also highlights that these relationships are complex and context-dependent in both breast and pancreatic cancer (8, 11, 13).

Exploratory analysis of adipokines and tumour immune microenvironment

Tumour-infiltrating T-cell subsets were assessed by flow cytometry for all the patients, but only two patients with pancreatic cancer and four patients with breast cancer displayed $CD3^{+}$ expression over the threshold. Given the very small number of available samples, no inferential statistical analyses were performed, and the results are reported descriptively.

Marked inter-individual variability in T-cell composition was observed across these cases. In pancreatic cancer patients, $CD3^{+}$ T-cell proportions ranged from approximately 25% to 54%, with a predominance of $CD4^{+}$ cells and relatively low $CD8^{+}$ representation. In breast cancer patients, $CD3^{+}$ T-cell levels ranged from approximately 20% to 50%, with a broader distribution of $CD8^{+}$ T-cell proportions.

Although no statistical associations can be inferred, these preliminary observations are consistent with the concept that metabolic and inflammatory signals derived from adipose tissue may influence the tumour immune microenvironment. In particular, the

variability observed in T-cell subsets across patients aligns with the heterogeneous adipokine and cytokine profiles described in earlier sections of this study.

Taken together, these exploratory findings highlight the need for future studies that incorporate larger patient cohorts and systematic immune profiling to elucidate the interplay among adipokine imbalance, inflammatory signalling and antitumor immunity.

In this clinical-translational pilot study, we identified compartment-specific differences in adipokine and inflammatory mediator profiles across urine, peritumoral tissue and subcutaneous adipose tissue in patients with breast and pancreatic neoplasms. Overall, the results of our study support the concept that systemic and local compartments capture different, complementary layers of tumour-associated metabolic and inflammatory signalling rather than a single uniform process. This interpretation is biologically plausible because adipose tissue is now recognized as an active endocrine and immunomodulatory organ, and tumour-associated adipocytes can undergo selective phenotypic reprogramming that influences tumoral cell behaviour, stromal remodelling and immune responses in both breast and pancreatic malignancies. These insights are in line with the increasing evidence that cancer therapies are becoming more personalized and dynamic, and besides being influenced by molecular profiling and adaptive molecular subtyping under treatments, we should also rethink our therapeutic strategies to more effectively address the interactions between tumours and their surrounding stroma (19, 20).

A notable and potentially novel finding of the present study is that urine was the most sensitive compartment, consistently displaying higher concentrations of adipokines and cytokines than adipose tissue. The fact that urinary concentrations were consistently higher than those measured in adipose tissue suggests that the urine might be amenable to use as a biomarker. Most published adipokine work in breast and pancreatic cancer has focused so far on serum, plasma, tumour tissue, not urine. Recent studies have emphasized that adipokines can be measured in urine and may provide clinically useful information precisely because urine sampling is non-invasive and can capture systemic perturbations that are not easily appreciated in single tissue compartments. A systematic review by Tews *et al*. reported that urinary adipokines reflect disease activity in metabolic and inflammatory conditions and highlighted their diagnostic potential due to non-invasive sampling and their ability to capture systemic perturbations (21).

In breast cancer, Gnerlich *et al*. reported that peritumoral adipokine expression is altered by both obesity and tumour aggressiveness, supporting the concept that the peritumoral adipose tissue is biologically distinct (22). More recent reviews of cancer-associated adipocytes in breast cancer similarly emphasize selective reprogramming of peritumoral adipose tissue rather than a diffuse inflammatory switch (23).

Another finding of our study is that RBP-4 and IL-10 differed between peritumoral and subcutaneous adipose tissue, which is particularly noteworthy considering recent literature. RBP4, the literature is limited but supports a role in metabolic regulation and cancer- related pathways (24). While direct evidence in breast cancer is limited, our findings suggest that RBP4 may also reflect differences between peritumoral adipose tissue *versus* subcutaneous adipose tissue, suggesting its potential involvement in tumour-metabolic interactions. The IL-10 observed in our data also aligns with findings from breast cancer microenvironment studies, where adipose-derived stromal cells and tumour-associated adipose tissue have been shown to express immunoregulatory mediators such as IL-10 and TGF-β, contributing to local immune modulation (25). This supports the concept that adipose tissue adjacent to tumours can acquire a tolerogenic phenotype and immunomodulatory phenotype, influencing tumour progression and immune evasion, rather than being purely pro-inflammatory.

Our BMI analyses are consistent with recent literature. Contemporary studies confirm that leptin levels increase with obesity, while adiponectin decreases, shifting the adipokine balance toward a pro-tumorigenic state (26). Accordingly, the leptin-to-adiponectin (L/A) ratio has been proposed as a robust indicator of adipose tissue dysfunction and metabolic risk (27). In cancer contexts, adipokine imbalance, characterized by elevated leptin and reduced adiponectin-has been implicated in tumour progression through effects on proliferation, angiogenesis and immune modulation (28). In line with this framework, individual adipokines in our cohort showed only weak associations with BMI, whereas the urinary L/A ratio showed a stronger association. This association was stronger in urine rather than adipose tissue, suggesting that urinary L/A may better capture systemic adiposity-related dysregulation.

The lack of a strong association between CRP and adipokine-based markers in your cohort is not surprising when compared to the literature. Broad inflammatory-cancer frameworks show that CRP is a marker of systemic acute-phase response, whereas leptin, adiponectin, IL-8 and related mediators participate in more metabolic, stromal and chronic inflammatory circuits (29).

Overall, in the breast cancer subgroup, the inverse associations observed between CA 15-3, leptin and the urinary L/A ratio should be interpreted as exploratory The literature on leptin in breast cancer is heterogeneous: while meta-analyses generally report elevated circulating leptin and support its role in promoting epithelial-mesenchymal transition, migration

and metastasis, clinical studies have shown inconsistent associations with prognosis, with some reporting no clear relationship and others suggesting subtype-specific effects (30, 31). Within this context, the inverse CA 15-3-leptin relationship observed in our study does not contradict existing evidence but likely reflects the small sample size and the compartment analysed, as our data derive from postoperative tissue and urine rather than large serum-based cohorts. These findings therefore support the interpretation that tumour marker–adipokine relationships are context- and compartment-dependent, rather than uniform across biological matrices. Within this context, the inverse CA 15-3-leptin relationship in our cohort does not contradict existing evidence but likely reflects the small sample size and compartment-specific nature of our data. These findings support the interpretation that tumour marker-adipokine relationships are context- and compartment-dependent, rather than uniform across biological matrices.

In the pancreatic cancer subgroup, our data show an inverse association between CA 19-9. Prior studies in the literature have revealed that circulating leptin and adiponectin levels are altered in pancreatic cancer, and adipokines are increasingly recognized as contributors to tumour growth, stromal remodelling and obesity-related risk (32, 33). Another study reported that higher prediagnostic leptin levels were associated with increased risk of pancreatic cancer in men (34), while earlier clinical studies have described abnormal leptin/adiponectin profiles in pancreatic cancer patients and explored their relationship with tumour characteristics (35). In contrast to these primarily serum-based findings, our data suggest that peritumoral adipose leptin may decrease as CA 19-9 increases, potentially reflecting local adipose reprogramming or tumour-driven suppression.

While leptin and adiponectin have been extensively studied, increasing attention has been directed toward less-characterized mediators such as adipsin, which appears to play roles beyond general metabolic regulation (36). Experimental studies in breast cancer have demonstrated that adipocytes can promote tumour cell invasiveness through metabolic and paracrine mechanisms, including hepatocyte growth factor–related signalling pathways (37), while cancer-associated adipocytes exhibit a distinct activated phenotype that contributes to tumour progression. In addition, translational studies have reported altered adipokine expression in adipose tissue associated with breast tumours, supporting its involvement in tumour-adipose crosstalk (25). Although the present study is limited in size, our findings are consistent with these reports, suggesting that adipsin may represent a subset of adipokines that are particularly sensitive to remodelling of tumour-adjacent adipose tissue. The involvement of RBP-4 and IL-10 is also consistent with literature linking metabolic signalling and immune regulation to tumour-stroma interactions (24).

Our findings have several potential therapeutic and translational implications. The identification of the compartment-specific adipokine signatures suggests that systemic and local tumour-stroma interactions may require distinct therapeutic approaches, with urine reflecting global metabolic dysregulation and adipose tissue representing a localized therapeutic target within the tumour microenvironment.

The observation that the urinary leptin-to-adiponectin (L/A) ratio reflects adiposity-related imbalance supports its potential utility as a non-invasive biomarker for patient stratification and monitoring. This aligns with clinical and experimental evidence demonstrating that adipokine imbalance is associated with cancer biology and progression. Clinical studies in pancreatic cancer have reported reduced circulating leptin and altered adiponectin/leptin ratios (32, 33) while studies about leptin, adiponectin and CA 19-9 together suggest that adipokine profiles may be linked to tumour characteristics (34).

In the context of breast cancer, randomized controlled trials (RCTs) have consistently shown that weight loss interventions lead to significant drops in circulating leptin levels. In fact, these reductions often exceed 30% among participants who lose at least 10% of their body weight. (38). Combining calorie restriction with exercise seems to yield the greatest weight loss, suggesting that these two approaches might have a complementary effect on our metabolism (39).

Metformin-based breast cancer trials have shown reductions in circulating leptin, and more recent data suggest that this decrease may be greater when metformin is paired with lifestyle intervention. This pattern is consistent with improvements in insulin resistance and related metabolic pathways (40).

Our study indicates a weak relationship between CRP and adipokine-based markers, suggesting that conventional inflammatory markers may not be sufficient to guide these strategies. This sustains the potential value of adipokine-based profiling. From a clinical standpoint, increased circulating resistin has been associated with more severe characteristics of breast cancer: larger tumours, advanced stages of the disease, lymph node metastasis and poorer survival rates in certain groups of patients, supporting the potential role of resistin as a prognostic biomarker (11).

Conclusions

This clinical translational pilot study, which focuses on clinical applications, shows that adipokine and cytokine levels differ significantly between breast and pancreatic cancer, depending on the tissue type examined: urine, subcutaneous adipose tissue and peritumoral adipose tissue. In our data, urine was the most sensitive for detecting systemic metabolic and

inflammatory activity. Notably, the urinary leptin-to-adiponectin (L/A) ratio was strongly associated with BMI, suggesting its potential as a non-invasive marker of metabolic dysregulation. In contrast, the poor correlations with CRP suggest that acute-phase inflammation is not directly associated with adipokine-driven metabolic signalling. Altogether, these findings support a model in which urine reflects systemic dysregulation, while adipose tissue shows local interactions among breast and pancreatic cancers and their surrounding stroma. Future research with larger groups is needed to validate these results and investigate their potential for diagnosis, prognosis and treatment.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Ethics approval and consent to participate

All experimental procedures were approved by the Ethics Committee of "Prof. dr. Al. Trestioreanu" Oncologic Institute of Bucharest (approval No. 12/ 28.03.2025). Informed consent was obtained from all patients included in the study.

AI use disclosure

During the preparation of this manuscript, the author(s) used Grammarly AI for editing assistance and language improvement, specifically to improve spelling, grammar, word choice, readability and clarity. The author(s) reviewed and revised all outputs from these tools and take(s) full responsibility for the final content of the work.

Conflict of interest

Burcea-Dragomiroiu GTA is a Managing Editor of the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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