Original paper

The circulating inflammatory profile and tumour localisation in patients with pancreatic cancer

Krążący profil zapalny a lokalizacja guza u pacjentów z rakiem trzustki

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Słowa kluczowe: rak trzustki, odporność, nowotwór przewodu pokarmowego, biomarkery immunologiczne.

Abstract

Introduction: Pancreatic cancer represents one of the greatest challenges in oncology. It is often diagnosed at a stage when treatment options are already limited. Inflammation is one of the key factors influencing the dynamics of pancreatic cancer development and progression.
Aim of the research: The aim of this study is to assess the relationship between the location of pancreatic cancer and the levels of selected inflammatory cytokines, and to examine the differences in the concentration of these cytokines depending on the location of the tumour. We also assessed the diagnostic utility of inflammatory cytokines by conducting ROC curve analysis, as well as the correlations of cytokines with selected clinicopathological parameters and with the results of selected laboratory tests.
Material and methods: Concentrations of 37 cytokines: CTACK, eotaxin, basic FGF, G-CSF, GRO-α, HGF, IL-1β, IL-1ra, IL-2Rα, IL-4, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-16, IL-17, IL-18, IP-10, LIF, MCP-1, M-CSF, MIF, MIG, MIP-1α, MIP-1β, β-NGF, PDGF-BB, RANTES, SCF, SCGF-β, SDF-1α, TNF-α, TNF-β, and TRIAL was measured in the venous blood of 42 patients with pancreatic cancer.
Results: Eotaxin levels (p = 0.002), basic FGF (p = 0.316), G-CSF (p = 0.0408), IL-2Rα (p = 0.0487), IL-6 (p = 0.0001), IL-9 (p = 0.0002), IL-17 (p = 0.0153), IP-10 (p = 0.0228), MIP-1α (p = 0.0117), MIP-1β (p = 0.0021), RANTES (p = 0.0228), SCGF-β (p = 0.223), TNF-α (p = 0.0398), TNF-β (p = 0.002) was statistically significantly higher in the patient group with tumours located in the head compared to patients with tumours in the body and tail of the pancreas. ROC analysis demonstrated that cytokines may be useful in differentiating the location of pancreatic cancer. There is a correlation between cytokine concentrations and the location of pancreatic cancer.
Conclusions: Cytokines such as FGF, G-CSF, IL-2Rα, IL-6, IL-9, IL-17, IP-10, MIP-1α, MIP-1β, RANTES, SCGF-β, TNF-α, and TNF-β differentiate patients with cancer located in the head of the pancreas from patients with a distal location of this cancer with a high degree of sensitivity and specificity.

Streszczenie

Wprowadzenie: Rak trzustki stanowi jedno z największych wyzwań onkologii. Często diagnozowany jest w momencie, gdy możliwości leczenia są już ograniczone. Jednym z kluczowych czynników wpływających na dynamikę rozwoju i postęp raka trzustki jest stan zapalny.
Cel pracy: Ocena związku między lokalizacją raka trzustki i poziomem wybranych cytokin zapalnych oraz zbadanie różnic w stężeniu ocenianych cytokin w zależności od lokalizacji nowotworu. Ocena również przydatności diagnostycznej cytokin zapalnych za pomocą analizy krzywych ROC, jak również korelacji cytokin z wybranymi parametrami kliniczno-patologicznymi oraz wynikami wybranych badań laboratoryjnych.
Materiał i metody: Stężenia 37 cytokin: CTACK, *eotaxin*, *basic* FGF, G-CSF, GRO-α, HGF, IL-1β, IL-1ra, IL-2Rα, IL-4, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-16, IL-17, IL-18, IP-10, LIF, MCP-1, M-CSF, MIF, MIG, MIP-1α, MIP-1β, β-NGF, PDGF-BB, RANTES, SCF, SCGF-β, SDF-1α, TNF-α, TNF-β i TRIAL, były oznaczone we krwi żylnej u 42 pacjentów z rakiem trzustki.
Wyniki: Stężenia eotaxin (p = 0,002), basic FGF (p = 0,316), G-CSF (p = 0,0408), IL-2Rα (p = 0,0487), IL-6 (p = 0,0001), IL-9 (p = 0,0002), IL-17 (p = 0,0153), IP-10 (p = 0,0228), MIP-1α (p = 0,0117), MIP-1β (p = 0,0021), RANTES (p = 0,0228), SCGF-β (p = 0,223), TNF-α (p = 0,0398), TNF-β (p = 0,002) były statystycznie istotnie większe u chorych z nowotworem zlokalizowanym w głowie w porównaniu z chorymi z guzami występującymi w obrębie trzonu i ogona trzustki. Analiza ROC wykazała, że cytokiny mogą być przydatne w różnicowaniu lokalizacji raka trzustki. Stężenia cytokin są związane z lokalizacją raka trzustki.
Wnioski: Cytokiny, takie jak FGF, G-CSF, IL-2Rα, IL-6, IL-9, IL-17, IP-10, MIP-1α, MIP-1β, RANTES, SCGF-β, TNF-α, TNF-β, różnicują z wysoką czułością i swoistością chorych z rakiem zlokalizowanym w głowie trzustki od chorych z lokalizacją obwodową tego nowotworu.

Introduction

Globally, pancreatic cancer ranks as the seventh leading cause of death from cancer. It is 4 times more common in highly developed countries. Ninety per cent of malignant tumours in this organ are identified as ductal adenocarcinoma, making it the most prevalent type [1–3]. Unfortunately, pancreatic cancer is usually diagnosed when it is already unresectable locally or when distant metastases are present. At the time of diagnosis, only 10% of patients can undergo tumour resection [4]. All patients with pancreatic cancer, regardless of the stage, have a 5-year survival rate of approximately 8%. Surgical resection extends this rate to about 20%, and when postoperative chemotherapy is included, the rate reaches 30%. The most frequently occurring malignant tumour of this organ (90%) is ductal adenocarcinoma (PDAC) [5]. Surgery is the most effective method of treating pancreatic cancer. The extent of surgical resection is determined by the tumour's position. Pancreatoduodenectomy is the procedure of choice when a tumour is located within the head of the pancreas. Distal resections are performed in the body and tail of this organ. Pancreaticoduodenectomy is a procedure that involves the removal of the head of the pancreas, duodenum, and distal parts of the stomach as well as the gallbladder with the common bile duct (the Whipple procedure). Mortality following pancreatic surgery in reference units has decreased to 5%; however, it still poses a high risk of complications including pancreatic fistula [6]. In order to improve the unfavourable survival statistics of patients with pancreatic cancer, new diagnostic methods for pancreatic cancer ought to be researched and developed to enable an earlier diagnosis. Markers of the initial stage of carcinogenesis in pancreatic cancer are still being searched for. This requires in-depth research, which will help develop more targeted therapies in the future [7].

Persistent inflammation may result in the development of cancer, subsequently either promoting or hindering the proliferation of cancerous cells. The pro- and anticancer balance could be altered by the cells influenced by inflammation and inflammatory-responsive factors [8]. The anti-cancer impact of acute inflammation may stem from its ability to identify and eliminate cancer cells during the initial phase of the disease [9]. For certain cancers, including pancreatic, colorectal, and breast cancer, inducing a regulated acute inflammatory response may be utilised as a therapeutic strategy. On the other hand, during chronic inflammation, cells may facilitate carcinogenesis by promoting their own proliferation and fostering resistance [10]. Inflammation results in the stimulation of immune cells to secrete cytokines and chemokines. Cytokines in contact with pancreatic cells can activate inflammatory routes such as NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and JAK-STAT (janus kinase-signal transduction and transcription). This activation subsequently enhances the functionality of pro-inflammatory enzymes and leads to the generation of pro-inflammatory mediators, including interleukin 1β (IL-1β) and tumour necrosis factor α (TNF-α) [11, 12]. TNF-α, which originates from activated macrophages and T lymphocytes, has been observed to possess a proinflammatory impact that can lead the onset of cancer development by inflicting damage to DNA [13]. Understanding the principles that connect inflammation to cancer development could yield substantial benefits in oncology practice through the advancement of new diagnostic and treatment approaches for patients with pancreatic cancer.

Aim of the research

The main goal of our study was to assess the relationship between the location of pancreatic cancer and the levels of selected inflammatory cytokines, and to examine the differences in the concentration of the assessed cytokines depending on the location of the tumour. Additionally, we evaluated the diagnostic value of inflammatory cytokines by employing receiver operating characteristic (ROC) curve analysis. We also investigated the associations between cytokines and specific clinicopathological parameters, as well as the outcomes of chosen laboratory tests.

Material and methods

The Bioethics Committee of the Medical University of Bialystok gave their approval for the study to be conducted (authorisation number APK.002.237.2020). Upon receiving comprehensive disclosure regarding the objectives of our investigation and potential associated risks, all suitable participants furnished their written assent to partake in the research study.

Patients

The study group comprised 42 patients (22 women and 20 men) qualified for surgery due to PDAC in the 2nd Department of General and Gastroenterological Surgery of the University Teaching Hospital in Bialystok between 2020 and 2022. The patients, both men and women, did not undergo preoperative radiotherapy or chemotherapy. The criterion for exclusion of patients with pancreatic cancer were other coexisting neoplastic diseases. Material for research was collected from all patients before surgery.

The patients were divided into 2 groups depending on the location of the tumour: $n = 24$ pancreatic head, $n = 18$ body and tail. The histopathological examination determined the final diagnoses.

Histopathological examination

The tissue samples collected during the procedure were preserved in a 4% buffered formalin solution

and then embedded in paraffin at 56°C. The paraffin-embedded tissue blocks were sectioned into approximately 4-µm-thick slides using a Microm H340 microtome, followed by staining with haematoxylin and eosin. Then, 2 independent pathologists assessed the obtained sections using an Olympus CX22 microscope at magnifications of 200× and 400×.

Histopathological analysis were assessed in regards to the histological tumour type based on the World Health Organisation (WHO) grade for histological malignancy [14], and to stage the tumour based on the TNM classification system of the Union for International Cancer Control [15], which includes assessments of the tumour's depth of invasion (pT), the presence of lymph node metastases (pN), distant metastases (pM), and vascular infiltration.

Blood collection

Blood samples were taken from fasting patients, each providing 5.5 ml using the S-Monovette® serum collection system from Sarstedt, Germany. Following collection, the samples were subjected to centrifugation at 1500 × g for 10 min at a temperature of +4°C using the MPW 351 from MPW Med. Instruments in Warsaw, Poland, allowing for the isolation of serum from blood cells, with the serum being subsequently drawn off from the top. To inhibit oxidation of the samples, butylated hydroxytoluene at a concentration of roughly 0.5 M (20 µl for every 2 ml of plasma or serum) was introduced. The prepared samples were preserved at –80°C until analysed for inflammatory cytokines.

Inflammatory cytokines

Concentrations of 37 cytokines: cutaneous T cell-attracting chemokine (CTACK), eotaxin, basic fibroblast growth factor (basic FGF), granulocyte colony stimulating factor (G-CSF), growth related oncogene-α (GRO-α), hepatocyte growth factor (HGF), interleukin-1β, -1ra, -2Rα, -4, -6, -7, -8, -9, -10, -12, -16, -17, -18 (IL-1ra, -2Rα, -4, -6, -7, -8, -9, -10, -12, -16, -17, -18), inducible protein-10 (IP-10), leukaemia inhibitor factor (LIF), monocyte chemoattractant protein-1 (MCP-1); macrophage colony-stimulating factor (M-CSF), macrophage migration inhibitory factor (MIF), monokine induced by γ interferon (MIG), macrophage inflammatory protein-1α (MIP-1α), macrophage inflammatory protein-1β (MIP-1β), β-nerve growth factor (β-NGF), platelet-derived growth factor (PDGF-BB), regulated on activation normal T-cell expressed and secreted (RANTES), stem cell factor (SCF), stem cell growth factor β (SCGF-β), stromal cell-derived factor-1α (SDF-1α), TNF-α, tumour necrosis factor-β (TNF-β), and tumour necrosis factor-related apoptosis-inducing ligand (TRIAL) were measured using a customised Bio-Plex Pro Human Cytokine Screening Panel, 48-Plex (#12007283). Bio-Plex technology utilises a bead-based multiplex approach similar to an ELISA test. In this method, antibodies specific to the target biomarker are covalently attached to magnetic beads. When these particles are mixed with a specimen containing the target biomarker, they bind to form a compound. After a series of rinsing steps to purge non-specifically bound proteins, a secondary antibody tagged with biotin is added to establish a sandwich-like structure. This construction is finalised by the addition of streptavidin bound to phycoerythrin (SA-PE). The outcome is quantified using a dedicated instrument, like the Bio-Plex 200 system, offering efficacy comparable to traditional ELISA assays.

Statistical analysis

The analysis of the data was performed with GraphPad Prism version 8.4.3 (GraphPad Software, based in La Jolla, USA). To determine whether the data followed a normal distribution, the Shapiro-Wilk test was applied. Where data showed normal distribution, the difference between 2 groups was compared using Student's *t*-test. Conversely, the Mann-Whitney *U* test was applied for data that did not follow a normal distribution. The findings are expressed as the median along with the range from minimum to maximum values, and a *p*-value of less than 0.05 was considered to indicate statistical significance. The association between inflammatory cytokines and clinicopathological features of the subjects was investigated using Spearman's rank correlation coefficient. For assessing the diagnostic power of inflammatory cytokines, receiver operating characteristic (ROC) analysis was conducted, calculating the area under the curve (AUC) and establishing the best threshold values that achieve the highest sensitivity and specificity.

The determination of the study's sample size was informed by an earlier experiment that included 15 patients, utilising the online ClinCalc software for calculation. The sample size estimation took into account the concentration levels of IL-6 and TNF-α as key variables. A significance threshold was established at 0.05, with the study power set at 0.9. The ClinCalc software for calculating sample size yielded the required number of participants for one group, which was determined to be a minimum of 30 patients.

Results

Clinical findings

The study group consisted of 42 patients with pancreatic adenocarcinoma. The participants were divided into 2 groups (head, body, and tail) depending on the location of the tumour. Pancreatic head cancer was found in 57.1% of patients, and pancreatic body and tail cancer in 42.9% of patients. Normal body mass index (BMI) was found in 52.4% of patients, 34.7% were overweight, and 15.9% were in the Class 1 obesity range. Weight loss of more than

10 kg in the last 3 months was observed in 38.1% of the patients. The grade of tumour differentiation in the majority of patients (78.6%) was G2 (moderately differentiated). A pT3 and pT4 tumour were present in approximately 76.2% of the patients. Lymph node involvement (N1+N2) was present in 45% of the patients, and 35.7% had distant metastasis (M1). In the majority (90.5%) of patients, vascular infiltration was present. It is defined as ''tumour present within an lial-lined space either surrounded by a rim of muscle or containing red blood cells''. Detailed characteristics of the patients are presented in Tables 1 and 2.

Inflammatory cytokines

The levels of all analysed cytokines – CTACK, eotaxin, basic FGF, G-CSF, GRO-α, HGF, IL-1β, IL-1ra, IL-2Rα, IL-4, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-16, IL-17, IL-18, IP-10, LIF, MCP-1, M-CSF, MIF, MIG, MIP-1α, MIP-1β, β-NGF, PDGF-BB, RANTES, SCF, SCGF-β, SDF-1α, TNF-α, TNF-β, and TRIAL was higher in the group of patients with cancer located in the pancreatic head. The levels of eotaxin ($p = 0.002$), basic FGF ($p = 0.316$), G-CSF ($p = 0.0408$), IL-2Rα ($p = 0.0487$), IL-6 ($p = 0.0001$), IL-9 ($p = 0.0002$), IL-17 ($p = 0.0153$), IP-10 ($p = 0.0228$), MIP-1α ($p = 0.0117$), MIP-1β ($p = 0.0021$), RANTES ($p = 0.0228$), SCGF-β ($p = 0.223$), TNF-α ($p = 0.0398$), and TNF-β ($p = 0.002$) was statistically significantly higher in the group of patients with tumours located in the head in comparison to the patients with tumours in the body and tail of the pancreas (Table 3, Figure 1).

ROC analysis

ROC analysis revealed that every cytokine under study (eotaxin, basic FGF, G-CSF, IL-2Rα, IL-6, IL-9, IL-17, IP-10, MIP-1α, MIP-1β, RANTES, SCGF -β, TNF-α, TNF-β) may show usefulness in differentiating patients with cancer located in the head, body, and tail of the pancreas. The AUC for eotaxin was 0.7396, while the *p*-value was 0.0453; for basic FGF these values were 0.7552 and 0.0330, respectively; for G-CSF 0.7526 and 0.0348, for IL-2Rα 0.7266 and 0.0583; for IL-6, 0.9198 and 0.0005; for IL-9 0.8958 and 0.0009; for IL-17 0.7839 and 0.0177; for IP-10 0.7708 and 0.0236; and for MIP-1α the AUC was 0.7969 and the *p*-value was 0.0131. The AUC for MIP-1β was 0.8385 with a *p*-value of 0.0047, and for RANTES the AUC was 0.7708 with a *p*-value of 0.0236. The AUC for SCGF-β was 0.7857 while the *p*-value was 0.0233; for TNF-α these values were 0.7448 and 0.0408; for TNF-β the AUC was 0.9245 and the *p*-value was 0.0004 (Table 4).

Correlations

All statistically significant relationships are presented in Figures 2 and 3. Our analysis of clinical and other parameters revealed negative correlations between IL-1ra ($p = 0.027$, $R = -0.404$) and TNF-β ($p = 0.022$, $R = -0.403$) and tumour location. We observed a correlation between LIF ($p = 0.023$, $R = 0.481$) and TNF-β ($p = 0.037$, $R = 0.446$) and tumour size. TNF-β ($p = 0.037$, $R = -0.451$) and a negative correlation with tumour grade (G). Interestingly, we demonstrated a negative correlation between IL-16 ($p = 0.047$, $R = -0.401$) and the depth of tumour invasion (pT) and between IL-9 ($p = 0.011$, $R = -0.469$) and the presence of distant metastases (pM). Negative correlations were also present between IL-1 ra ($p = 0.006$, $R = -0.552$), IP-10 ($p = 0.047$, $R = -0.410$), β-NGF ($p = 0.033$, $R = -0.469$), and the presence of lymph node metastases (pN). Positive correlations were found between IL-16 ($p = 0.019$, $R = 0.400$), MIF ($p = 0.016$, $R = 0.404$), and weight loss (Figures 2 A, B). WBC was positively correlated with SDF-1α ($p = 0.0149$, $R = 0.427$), HGF ($p = 0.006$, $R = 0.472$), and with IL-6 ($p = 0.009$, $R = 0.571$). Neutrophil count was positively correlated with CTACK ($p = 0.023$, $R = 0.406$), HGF ($p = 0.009$, $R = 0.461$), IL-6 ($p = 0.003$, $R = 0.624$), MIF ($p = 0.0212$, $R = 0.412$), PDGF-BB ($p = 0.021$, $R = 0.412$), and SDF-1α ($p = 0.010$, $R = 0.458$). Moreover, HGF was also negatively correlated with RBC ($p = 0.021$, $R = -0.407$) and HCT ($p = 0.016$, $R = -0.424$). Significant associations were also found between Ca-19.9 and CTACK ($p = 0.039$, $R = 0.542$) and RANTES ($p = 0.017$, $R = 0.613$). β-NGF was negatively correlated with HGB ($p = 0.046$, $R = -0.430$) (Figures 3 A, B).

Discussion

Approximately 60% to 70% of PDAC originate in the pancreatic head, while the remaining 30% develop in the body (15%) and tail (15%) [16]. The severity and type of symptoms of the tumour strictly depend on its location. Tumours situated in the pancreatic head can lead to a constriction of the primary bile duct, resulting in mechanical jaundice or acute pancreatitis. Peripherally located tumours (pancreas body and tail) can reach significant sizes before causing severe pain or high obstruction of the gastrointestinal tract [17]. Cancerous changes in this location pose a very difficult diagnostic problem. Initially, the only symptoms are non-specific pain in the abdominal cavity, and in later stages diabetes, as well as weight loss may occur. These tumours are usually diagnosed belatedly when adjacent organs have already been affected or distant metastases have occurred [18].

Inflammation is crucial in the emergence and advancement of PDAC. Antigens specific to the tumour stimulate a reaction from the immune system. Within the pancreatic cancer microenvironment, a local immune reaction provokes inflammatory process, which is produced and sustained by cytokines, chemokines, reactive oxygen species, and small peptides. Cells involved in the inflammatory process have the potential to affect the metabolic processes of cancer cells,

Table 1. Demographic and clinical characteristics of pancreatic ductal adenocarcinoma (PDAC) patients

Parameter	All patients	Head	Corpus and tail
	***N* = 42**	***N* = 24**	***N* = 18**
Age [years] (mean ± SD):			
< 60	*n* = 13 (31.0%)	*n* = 7 (29.2%)	*n* = 6 (33.3%)
≥ 60	*n* = 29 (69.0 %)	*n* = 17 (70.8 %)	*n* = 12 (66.7 %)
Gender:			
Male	*n* = 20 (41.6%)	*n* = 10 (41.7%)	*n* = 10 (55.6%)
Female	*n* = 22 (58.4%)	*n* = 14 (58.3%)	*n* = 8 (44.4%)
BMI [kg/m^2] (mean ± SD)	25.55 (19.3–33.9)	25.75 (19.3–33.9)	24.94 (21.3–30.1)
18.5–24.9	*n* = 22 (52.4%)	*n* = 12 (50.0%)	*n* = 10 (55.6%)
25.0–29.9	*n* = 14 (31.7%)	*n* = 8 (33.3%)	*n* = 6 (37%)
30.0–34.9	*n* = 7 (15.9%)	*n* = 4 (16.7%)	*n* = 3 (18.4%)
Loss weight:			
< 10 kg	*n* = 26 (61.9%)	*n* = 15 (62.5%)	*n* = 11 (61.1%)
≥ 10 kg	*n* = 16 (38.1%)	*n* = 9 (37.5%)	*n* = 7 (38.9%)
Diabetes:			
Present	*n* = 12 (28.6%)	*n* = 8 (33.3%)	*n* = 4 (22.2%)
Absent	*n* = 30 (71.4%)	*n* = 16 (66.7%)	*n* = 12 (77.8%)
Pre-operative ERCP:			
Present	*n* = 15 (35.7%)	*n* = 15 (62.5%)	*n* = 0 (0.0%)
Absent	*n* = 27 (64.3%)	*n* = 9 (37.5%)	*n* = 18 (100%)
Tumour size:			
< 3 cm	*n* = 19 (45.2%)	*n* = 13 (54.2%)	*n* = 6 (33.3%)
≥ 3 cm	*n* = 23 (54.8%)	*n* = 11 (45.8%)	*n* = 12 (66.8%)
Histological differentiation grade:			
G1	*n* = 2 (4.8%)	*n* = 2 (8.3%)	*n* = 0 (0.0%)
G2	*n* = 33 (78.6%)	*n* = 19 (79.2%)	*n* = 14 (77.7%)
G3	*n* = 7 (16.6%)	*n* = 3 (12.5%)	*n* = 4 (22.3%)
Depth of tumour invasion (pT):			
T1+T2	*n* = 10 (23.8%)	*n* = 10 (41.7%)	*n* = 0 (0.0%)
T3+T4	*n* = 32 (76.2%)	*n* = 14 (58.3%)	*n* = 18 (100%)
Presence of lymph node metastasis (pN):			
Present	*n* = 19 (45.2%)	*n* = 10 (41.7%)	*n* = 9 (50.0%)
Absent	*n* = 23 (54.8%)	*n* = 14 (58.3%)	*n* = 9 (50.0%)
Presence of distant metastasis (pM):			
Present	*n* = 15 (35.7%)	*n* = 5 (20.8%)	*n* = 10 (55.6%)
Absent	*n* = 27 (64.3%)	*n* = 19 (79.2%)	*n* = 8 (44.4%)
Vascular infiltration:			
Present	*n* = 38 (90.5%)	*n* = 20 (66.8%)	*n* = 18 (100%)
Absent	*n* = 4 (9.5%)	*n* = 8 (33.3%)	*n* = 0 (0.0%)

ERCP – endoscopic retrograde cholangiopancreatography.

Table 2. Laboratory test results of pancreatic ductal adenocarcinoma (PDAC) patients

Parameter	All patients mean (min.–max.)	Head mean (min.–max.)	Corpus and tail mean (min.–max.)
White blood cell count [× 10^3/µl]	7.345 (2.95–18.34)	7.275 (4.58–18.34)	7.555 (2.95–16.01)
Neutrophil count [× 10^3/µl]	4.54 (1.27–14.69)	4.379 (2.08–14.69)	5.004 (1.27–13.6)
Lymphocyte count [× 10^3/µl]	2.053 (0.54–8)	2.045 (0.86–8)	2.078 (0.54–5)
RBC [× 106/µl]	4.078 (2.41–5.32)	4.089 (3.23–4.92)	4.045 (2.41–5.32)
HGB [g/dl]	12.39 (7.6–12.39)	12.45 (9.5–15)	12.19 (7.6–17.2)
HCT (%)	36.52 (22.5–46.9)	36.65 (28.3–43.1)	36.14 (22.5–46.9)
Platelets count [× 10^3/µl]	258.2 (82–562)	279.5 (148–562)	194.3 (82–313)
CEA [ng/ml]	0.4375 (0–1)	4.986 (1.5–39.5)	3.7 (3.7–3.7)
CA19-9 [U/ml]	198.2 (2.1–1200)	156.6 (2.1–1200)	780.8 (780.8–780.8)
CRP [mg/l]	29.4 (0–325.8)	28.78 (1–325.8)	31.19 (0–131)
Total protein [g/dl]	6.478 (5.3–7.6)	6.533 (5.3–7.6)	6.313 (5.7–7.4)
Albumins [g/dl]	3.282 (2.11–4.28)	3.233 (2.11–3.99)	3.441 (2.64–4.28)
Total bilirubin [mg/dl]	3.259 (0.32–11.74)	4.021 (0.44–11.74)	0.7543 (0.32–1.42)

particularly glucose metabolism, and by altering this metabolic route, they may promote tumour progression and evasion of immune surveillance [19, 20].

Cytokines, which are small proteins released by cells, play a crucial role as regulators of inflammation [21]. Numerous studies have demonstrated a variation in the expression of different cytokines in cases of pancreatic cancer [7, 22]. Cytokines can be stratified based on their functional mechanisms into pro-inflammatory (IL-1, IL-2, IL-6, IL-12, TNF-α, and chemokines such as IL-8 and MCP-1, and anti-inflammatory (e.g. IL-1ra, IL-4, IL-10) categories. Pro-inflammatory cytokines are synthesised and exert their effects on immunocompetent cells, initiating an inflammatory cascade. In contrast, anti-inflammatory cytokines modulate specific immune responses and curtail the propagation of inflammation [23]. Pro-inflammatory cytokines play a pivotal role in modulating the proliferation, activation, and differentiation of immune cells, in addition to directing immune cells to the loci of infection for the containment and eradication of intracellular pathogens, such as viruses [24]. As cancer develops and progresses, it has an impact on the cells of the immune system [25]. PDAC is characterised by elevated levels of inflammatory cytokines and angiogenic markers, which are integral to its pathogenesis and advancement [26]. Despite the immune system's initial recognition and elimination of aberrant or neoplastic cells through the activation of inflammatory pathways, malignant cells evolve defence mechanisms to circumvent host immune responses, a process termed immunoediting. Moreover, a pronounced desmoplastic reaction is emblematic of pancreatic ductal adenocarcinoma within the tumour microenvironment. This is indicative of the activation of pancreatic stellate cells, leading to the encapsulation of over 50% of the tumour with a dense fibrous stroma. The stromal barrier not only obstructs the entry of immune cells but also restricts the administration of anti-cancer drugs [27–29]. Numerous studies indicate that anti-inflammatory cytokines, i.e. TGF and IL-10, and pro-inflammatory cytokines – IL-1, IL-6, IL-17, and TNF-α, could be an essential factor in the progression of PDAC [30]. Our study demonstrates significantly higher levels of cytokines – eotaxin, basic FGF, G-CSF, IL-2Rα, IL-6, IL-9, IL-17, IP-10, MIP-1α, MIP-1β, RANTES, SCGF- β, TNF-α, and TNF-β – in patients with pancreatic cancer located in the pancreatic head compared to patients with tumours in the body and tail of the pancreas. This clearly indicates an increased inflammatory response in patients with tumours in the head of the pancreas, which may be caused by hyperbilirubinaemia. Mechanical jaundice in the course of cancer of the pancreatic head is an indication for endoscopic biliary stenting, which also results in the body's response and cytokine production. The prosthesis inserted during endoscopic retrograde cholangiopancreatography (ERCP) is a foreign body that can induce an inflammatory response [31].

Our study demonstrated that IL-1ra and TNF-β were closely correlated with tumour location, reaching higher values in patients with a tumour located in the pancreatic head. Increased circulating IL-1Ra levels have been linked to insulin resistance and the development of type 2 diabetes [32].

It is widely accepted that PDAC located peripherally are often accompanied by hyperbilirubinemia, which may additionally explain the observed relationships. Research conducted by Oldfield *et al.* corroborates the utility of circulating IL-1Ra as a potentially effica-

Table 3. Circulating levels of inflammatory cytokines and chemokines in pancreatic ductal adenocarcinoma (PDAC) patients

Parameter	All patients	Head	Corpus and tail	*P*-value
	N = 42	*N* = 24	*N* = 18	
CTACK [pg/ml]	1709 (583.9–3305)	1784 (583.9–3305)	1612 (1126–2452)	0.5292
Eotaxin [pg/ml]	147.1 (50.6–280.4)	158.9 (86.69–280.4)	122.8 (50.62–279.4)	0.0220
Basic FGF [pg/ml]	74.02 (30.76–165.4)	79.07 (41.25–165.4)	64.11 (44.8–118.8)	0.0316
G-CSF [pg/ml]	333.4 (105.2–753.9)	368.9 (129–753.9)	250.1 (105.2–533.4)	0.0408
GRO-α [pg/ml]	1320 (184.1–2095)	1386 (1071–2095)	1260 (1061–1564)	0.1108
HGF [pg/ml]	796.4 (241.4–5622)	829.2 (251.4–5622)	685.7 (324–1298)	0.9897
IL-1β [pg/ml]	2.489 (1.13–9.46)	2.677 (1.23–9.46)	1.964 (1.13–3)	0.2675
IL-1ra [pg/ml]	792.4 (175.8–4561)	903 (175.8–4561)	467.6 (175.8–1018)	0.2051
IL-2Rα [pg/ml]	97.16 (4337–425.6)	100.5 (43.37–425.6)	90.62 (56.76–178.9)	0.0487
IL-4 [pg/ml]	7.129 (2.415–13.97)	7.406 (4.56–13.97)	6.833 (4.17–13.22)	0.1625
IL-6 [pg/ml]	14.18 (1.07–88.68)	13.92 (1.07–88.68)	13.77 (1.54–39.19)	0.0001
IL-7 [pg/ml]	17.36 (20.75–52.52)	19.44 (11.07–52.52)	12.14 (11.07–15.35)	0.3691
IL-8 [pg/ml]	55.69 (12.03–415.7)	57.33 (12.38–415.7)	48.33 (12.03–204.5)	0.1983
IL-9 [pg/ml]	583.4 (69.51–740.2)	623.8 (519.8–740.2)	524.6 (431.6–604.9)	0.0002
IL-10 [pg/ml]	8.711 (4.6–24.66)	9.426 (4.6–24.66)	5.8 (5.8–5.8)	0.9907
IL-12 (p70) [pg/ml]	21.65 (9.65–33.72)	31.81 (29.89–33.72)	9.65 (9.65–9.65)	0.2199
IL-12 (p40) [pg/ml]	135.3 (48.96–528.2)	140.8 (48.96–528.2)	120.2 (72.91–200.2)	0.7463
IL-16 [pg/ml]	143.1 (29.22–742)	141.7 (29.22–742)	149.6 (50.98–361)	0.8674
IL-17 [pg/ml]	26.09 (11.47–69.54)	28.03 (11.47–69.54)	13.24 (13.24–13.24)	0.0153
IL-18 [pg/ml]	70.27 (12.25–264.2)	75.18 (12.25–264.2)	59.72 (33.75–99.35)	0.3912
IP-10 [pg/ml]	1296 (337.2–4540)	1405 (408.1–4540)	1021 (337.2–3133)	0.0228
LIF [pg/ml]	41.89 (15.95–99.48)	44.75 (15.95–99.48)	35.97 (18.12–62.48)	0.1981
MCP-1 [pg/ml]	61.05 (25.05–259.6)	64.64 (26.04–259.6)	52.56 (25.05–95)	0.4736
M-CSF [pg/ml]	23.04 (9.72–68.04)	25 (9.72–68.04)	18.52 (13.43–33.3)	0.1569
MIF [pg/ml]	1303 (395.1–6103)	1335 (395.1–6103)	1248 (747.9–1892)	0.5315
MIG [pg/ml]	1302 (401.7–3754)	1359 (407.3–3754)	1200 (401.7–2043)	0.6683
MIP-1α [pg/ml]	5.694 (1.73–14.23)	6.248 (1.73–14.23)	4.371 (2.5–10.82)	0.0117
MIP-1β [pg/ml]	321.6 (39.69–406)	328.3 (273.1–399.3)	299.1 (251.7–406)	0.0021
β-NGF [pg/ml]	18.05 (1.52–88.61)	19.87 (1.52–88.61)	13.09 (2.06–24.97)	0.3365
PDGF-BB [pg/ml]	4160 (1265–17421)	4116 (1265–18491)	4431 (1289–9843)	0.8394
RANTES [pg/ml]	10514 (3163–18491)	11389 (6443–18491)	8899 (3970–14197)	0.0228
SCF [pg/ml]	66.03 (19.25–129.6)	67.27 (40–129.6)	67.99 (51.56–90.08)	0.6773
SCGF-β [pg/ml]	169680 (51738–291580)	179188 (114004–291580)	155453 (106622–273793)	0.0223
SDF-1α [pg/ml]	2144 (547.5–4368)	2197 (1296–4368)	2177 (1519–2738)	0.8747
TNF-α [pg/ml]	63.36 (33.89–333.3)	68.29 (35–333.3)	49.95 (33.89–94.99)	0.0398
TNF-β [pg/ml]	792.8 (96.95–1021)	848.4 (672.8–1021)	710.2 (607.3–775.8)	0.0002
TRIAL [pg/ml]	76.33 (23.77–142.7)	81.17 (45.37–142.7)	68.17 (33.35–98.15)	0.4734

CTACK – cutaneous T cell-attracting chemokine, basic FGF – basic fibroblast growth factor, G-CSF – granulocyte colony stimulating factor, GRO-α – growth related oncogene-α, HGF – hepatocyte growth factor, IL – interleukin, IP-10 – inducible protein-10, LIF – leukaemia inhibitory factor, MCP-1 – monocyte chemoattractant protein-1, M-CSF – macrophage colony-stimulating factor, MIF – macrophage migration inhibitory factor, MIG – monokine induced by g interferon, MIP-1α – macrophage inflammatory protein-1α, MIP-1β – macrophage inflammatory protein-1β, β-NGF – β-NGF – β–nerve growth factor, PDGF-BB – platelet-derived growth factor-BB, RANTES – regulated on activation normal T-cell expressed and secreted, SCF – stem cell factor, SCGF-β, stem cell growth factor β, SDF-1α – stromal cell-derived factor-1α, TNF-α – tumour necrosis factor-α, TNF-β – tumour necrosis factor-β, TRIAL – tumour necrosis factor related apoptosis-inducing ligand.

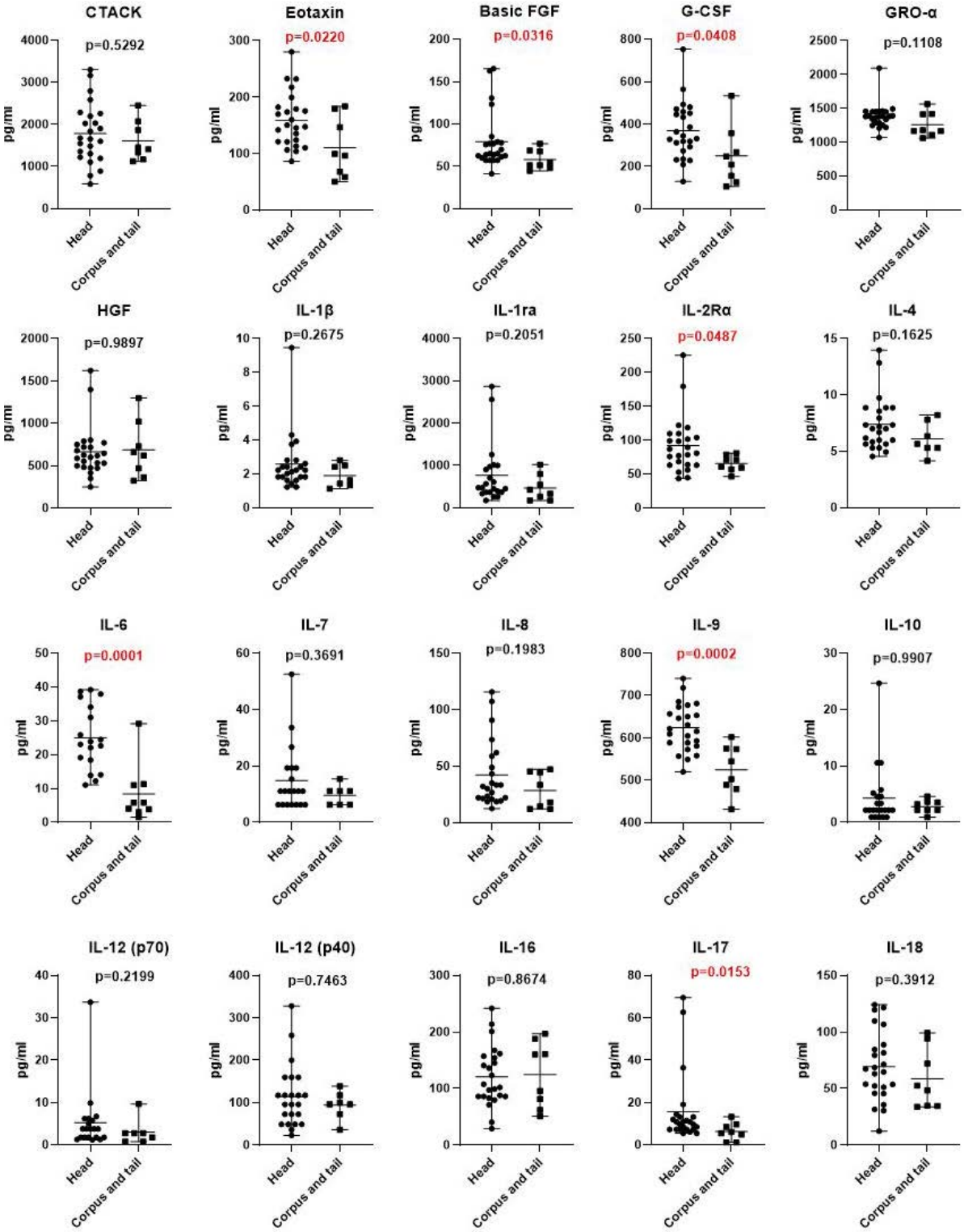

Figure 1. Comparison of cytokine levels between cancers located in the head vs. the body and tail of the pancreas

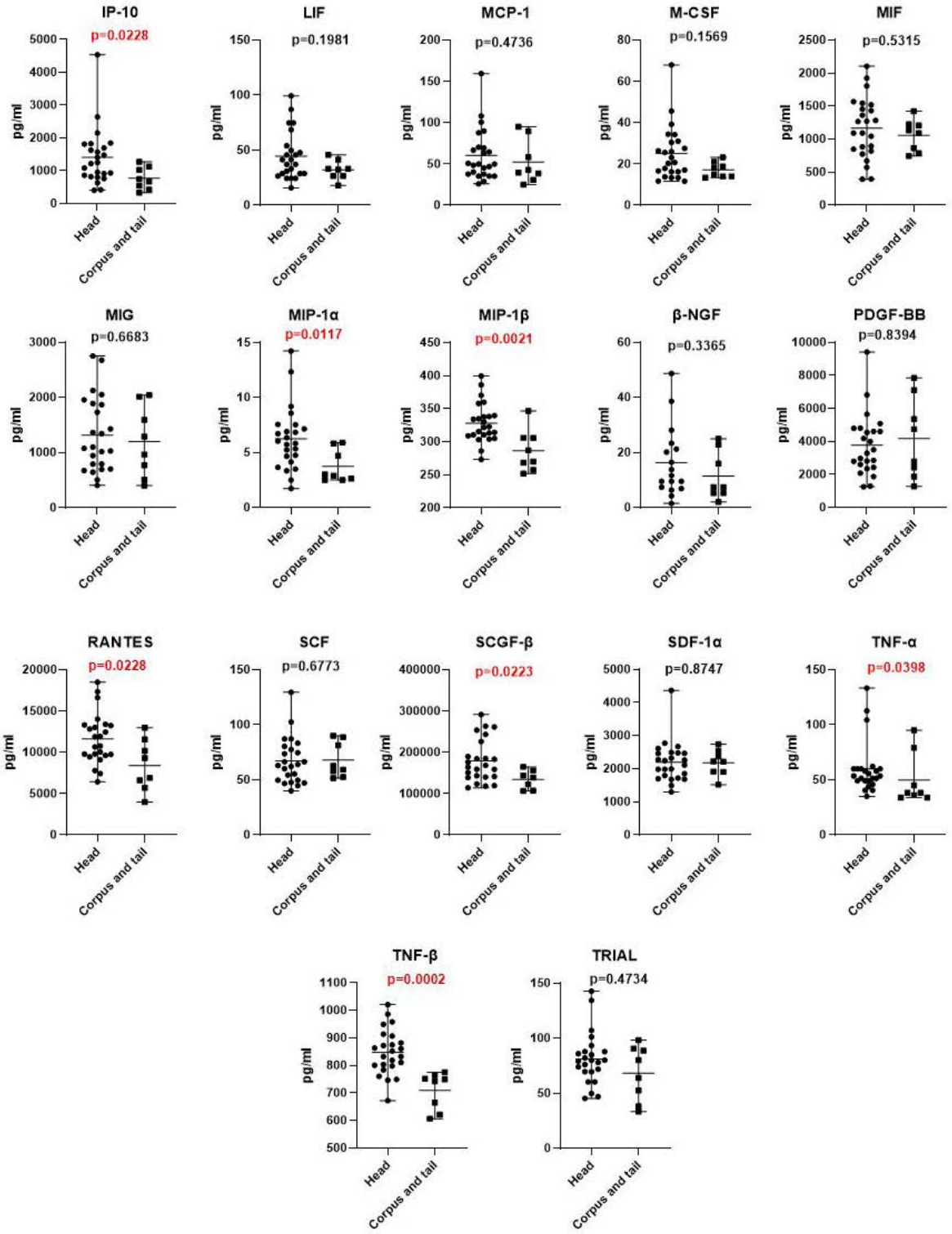

Figure 1. Cont.

Table 4. Receiver operating characteristic (ROC) analysis of inflammatory cytokines and chemokines of pancreatic ductal adenocarcinoma (PDAC) patients with tumours located in the head vs. corpus and tail

Parameter	AUC	*P*-value	Cut-off	Sensitivity (%)	Specificity (%)	95% confidence interval
CTACK [pg/ml]	0.5729	0.5423	< 1517	62.50	62.50	0.3574–0.7884
Eotaxin [pg/ml]	0.7396	0.0453	< 129.9	62.50	66.67	0.5009–0.9783
Basic FGF [pg/ml]	0.7552	0.0330	< 63.17	62.50	62.50	0.5466–0.9638
G-CSF [pg/ml]	0.7526	0.0348	< 270.5	75.00	79.17	0.5273–0.9779
GRO-α [pg/ml]	0.6927	0.1048	< 1341	62.50	66.67	0.4294–0.9561
HGF [pg/ml]	0.5026	0.9826	< 623.2	50.00	45.83	0.2422–0.7630
IL-1β [pg/ml]	0.6429	0.2568	< 2.180	57.14	54.17	0.3861–0.8996
IL-1ra [pg/ml]	0.6563	0.1972	< 437.6	62.50	63.64	0.4207–0.8918
IL-2Rα [pg/ml]	0.7266	0.0583	< 73.41	75.00	66.67	0.5535–0.8996
IL-4 [pg/ml]	0.6786	0.1564	< 6.265	57.14	58.33	0.4535–0.9036
IL-6 [pg/ml]	0.9198	0.0005	< 11.76	88.89	94.44	0.7786–1.000
IL-7 [pg/ml]	0.6143	0.3760	< 8.680	42.86	65.00	0.3938–0.8348
IL-8 [pg/ml]	0.6576	0.1905	< 31.06	50.00	52.17	0.4107–0.9045
IL-9 [pg/ml]	0.8958	0.0009	< 574.0	75.00	79.17	0.7790–1.000
IL-10 [pg/ml]	0.5028	0.9813	> 2.705	50.00	59.09	0.2891–0.7166
IL-12 (p70) [pg/ml]	0.6607	0.2132	< 3.275	85.71	60.00	0.4145–0.9070
IL-12 (p40) [pg/ml]	0.5435	0.7314	< 97.96	57.14	47.83	0.3262–0.7607
IL-16 [pg/ml]	0.5052	0.9653	> 115.5	50.00	54.17	0.2456–0.7649
IL-17 [pg/ml]	0.7839	0.0177	< 7.895	62.50	66.67	0.5844–0.9833
IL-18 [pg/ml]	0.6042	0.3841	< 53.14	62.50	66.67	0.3751–0.8332
IP-10 [pg/ml]	0.7708	0.0236	< 925.2	62.50	66.67	0.5946–0.9471
LIF [pg/ml]	0.6563	0.1917	< 35.25	75.00	58.33	0.4638–0.8487
MCP-1 [pg/ml]	0.5885	0.4594	< 44.20	62.50	66.67	0.3490–0.8281
M-CSF [pg/ml]	0.6719	0.1510	< 18.54	62.50	58.33	0.4876–0.8562
MIF [pg/ml]	0.5938	0.4334	< 1171	62.50	50.00	0.3990–0.7885
MIG [pg/ml]	0.5521	0.6634	< 1055	50.00	54.17	0.3121–0.7921
MIP-1α [pg/ml]	0.7969	0.0131	< 4.735	75.00	70.83	0.6311–0.9627
MIP-1β [pg/ml]	0.8385	0.0047	< 305.9	75.00	79.17	0.6510–1.000
β-NGF [pg/ml]	0.6250	0.3220	< 8.500	62.50	70.59	0.3821–0.8679
PDGF-BB [pg/ml]	0.5260	0.8277	> 3753	50.00	54.17	0.2529–0.7992
RANTES [pg/ml]	0.7708	0.0236	< 9926	62.50	62.50	0.5774–0.9643
SCF [pg/ml]	0.5521	0.6634	> 62.39	50.00	45.83	0.3268–0.7774
SCGF-β [pg/ml]	0.7857	0.0233	< 147502	71.43	66.67	0.6125–0.9589
SDF-1α [pg/ml]	0.5208	0.8618	> 2162	62.50	50.00	0.2962–0.7455
TNF-α [pg/ml]	0.7448	0.0408	< 47.61	75.00	79.17	0.4867–1.000
TNF-β [pg/ml]	0.9245	0.0004	< 770.5	87.50	83.33	0.8349–1.000
TRIAL [pg/ml]	0.5885	0.4594	< 79.58	50.00	50.00	0.3304–0.8467

CTACK – cutaneous T cell-attracting chemokine, basic FGF – basic fibroblast growth factor, G-CSF – granulocyte colony stimulating factor, GRO-α – growth related oncogene-α, HGF – hepatocyte growth factor, IL – interleukin, IP-10 – inducible protein-10, LIF – leukaemia inhibitory factor, MCP-1 – monocyte chemoattractant protein-1, M-CSF – macrophage colony-stimulating factor, MIF – macrophage migration inhibitory factor, MIG – monokine induced by g interferon, MIP-1α – macrophage inflammatory protein-1α, MIP-1β – macrophage inflammatory protein-1β, β-NGF – β-NGF – β-nerve growth factor, PDGF-BB – platelet-derived growth factor-BB, RANTES – regulated on activation normal T-cell expressed and secreted, SCF – stem cell factor, SCGF-β, stem cell growth factor β, SDF-1α – stromal cell-derived factor-1α, TNF-α – tumour necrosis factor-α, TNF-β – tumour necrosis factor-β, TRIAL – tumour necrosis factor related apoptosis-inducing ligand.

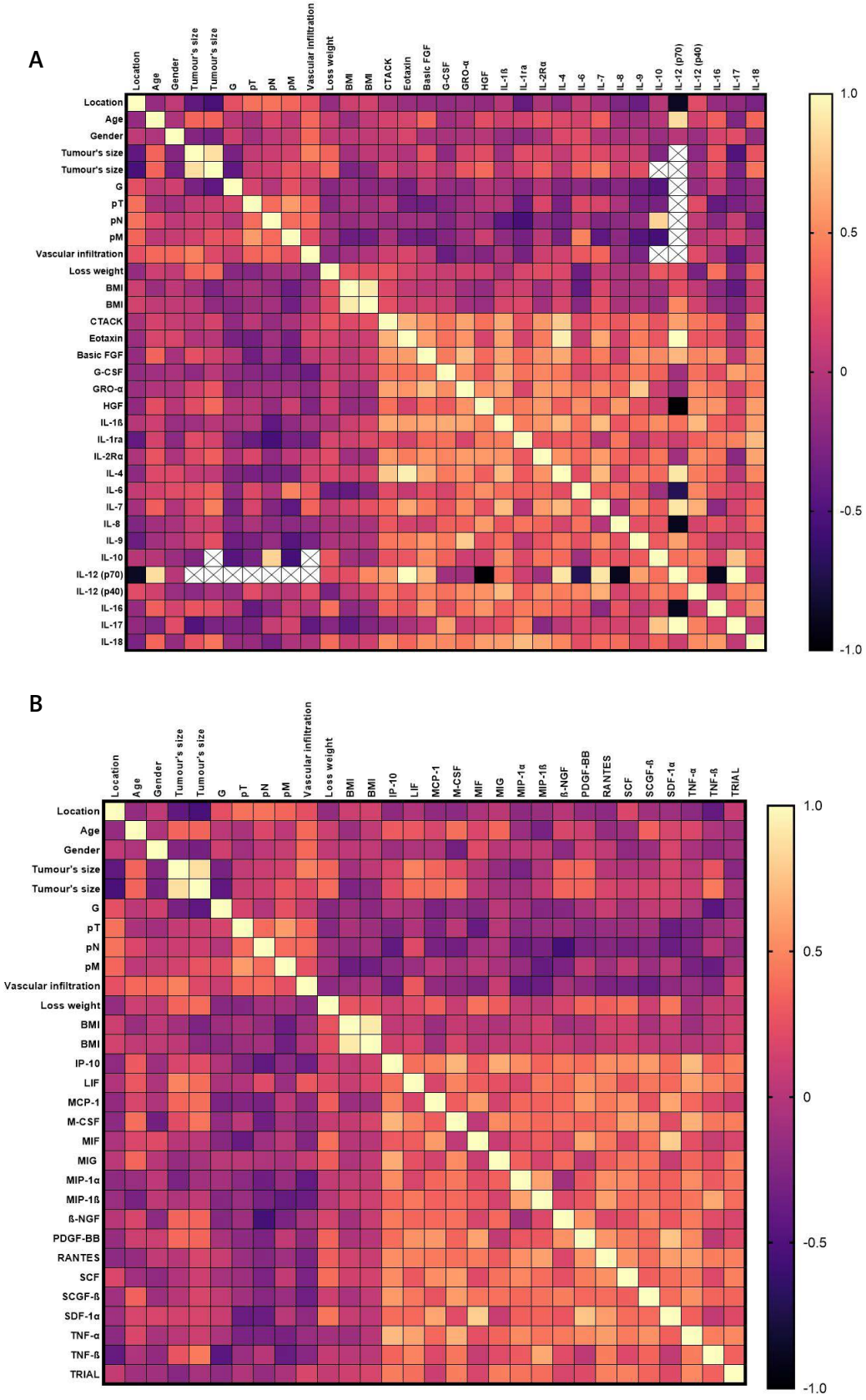

Figure 2. **A** – Correlation heat map of inflammatory cytokines with selected clinicopathological features. **B** – Correlation heat map of inflammatory cytokines with selected clinicopathological features

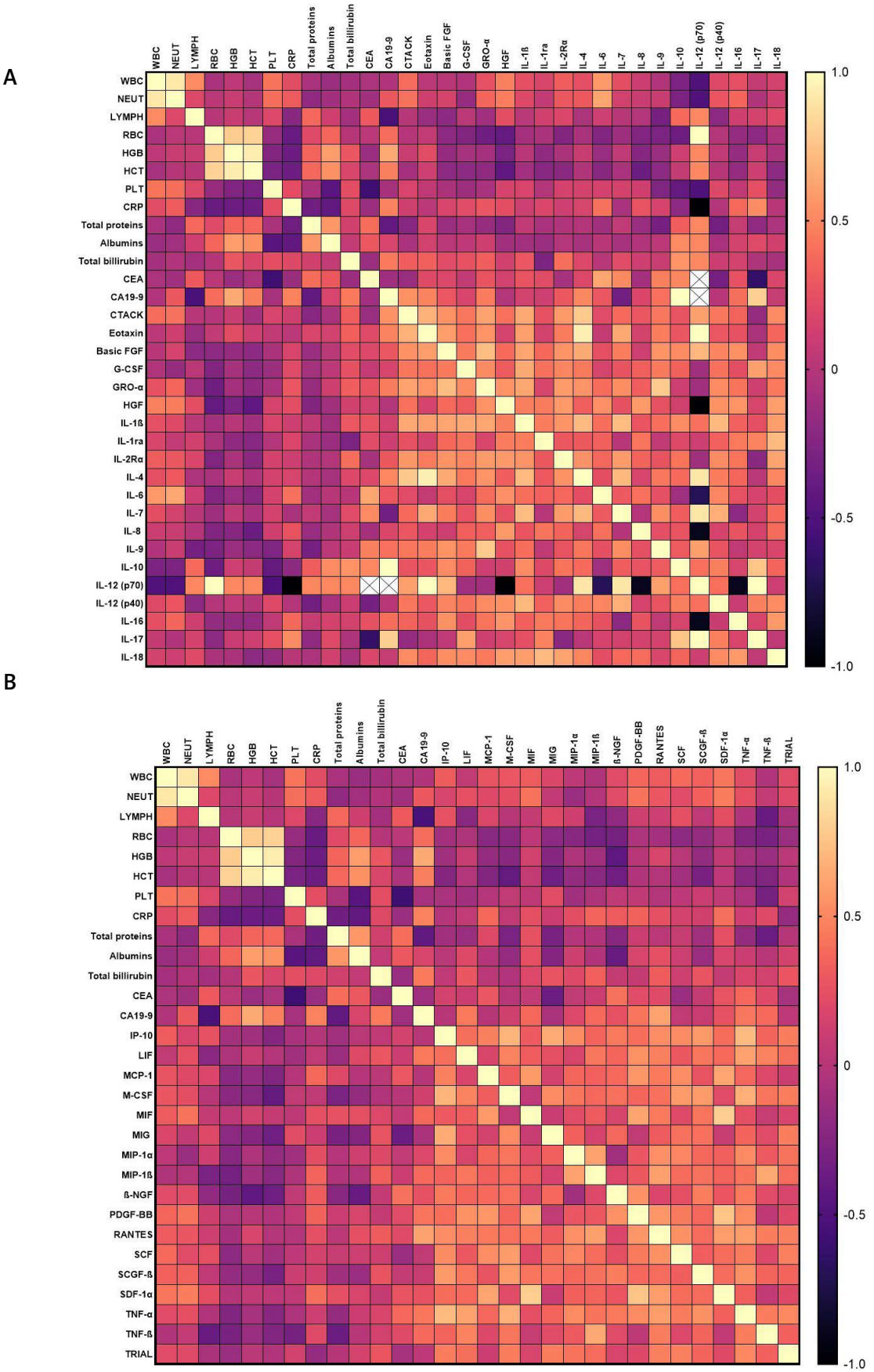

Figure 3. **A** – Correlation heat map of inflammatory cytokines and selected results of laboratory tests. **B** – Correlation heat map of inflammatory cytokines and selected results of laboratory tests

cious biomarker for the early identification of PDAC in individuals at elevated risk, particularly those who have recently received a diabetes diagnosis [33].

Research has confirmed that IL-6, which is a cytokine that promotes inflammation, also contributes to cancer progression [34, 35]. *In vitro* investigations have elucidated that pancreatic cancer cell lines and cancer-associated fibroblasts (CAF) synthesise IL-6. This cytokine can function in an autocrine and paracrine capacity, culminating in enhanced cancer cell motility and invasiveness, alongside the facilitation of epithelial-mesenchymal transition [36, 37]. In individuals diagnosed with PDAC, heightened concentrations of IL-6 detected in serum, pancreatic juice, and tissue samples have been associated with prognostic implications regarding tumour stage and patient survival. This observation substantiates the possible utility of this interleukin as a predictive biomarker for malignant tumours. However, the sensitivity and specificity of this method are extremely variable. A higher level of IL-6 in patients with a tumour located in the head of the pancreas may indicate the advanced stage of the neoplastic disease. Elevated serum IL-6 positively correlated with an increased risk of cancer development, weight loss, and metastases [30].

Th17 CD4+ cells produce IL-17, which plays a significant role in the onset and development of tumours. The presence of IL-17 receptors has been observed on cancer cells that are experiencing the epithelial-mesenchymal transition (EMT), with this expression reliant on the activity of the KRAS oncogene [38–40]. Our research noted increased levels of IL-17 in patients whose tumours were situated in the head of the pancreas, indicating that a tumour in this position might be associated with more intense chronic inflammation. It may also indicate its connection with mechanical jaundice or diabetes.

TNF-α serves as a principal modulatory protein integral to the orchestration of the host's immune response, and it is implicated in the mediation of systemic inflammation and pyrexia [41]. TNF-α, a type II transmembrane polypeptide, has transmission capabilities as a soluble factor following its liberation through proteolytic cleavage. Although TNF-α was originally classified as a cytokine that promotes inflammation, contemporary research lends support to its multifaceted role in carcinogenesis, underscoring its dual functionality in the process. TNF-α is involved in chronic inflammatory diseases. It has been suggested that this cytokine, at low concentrations, plays a foundational role in tumour promotion. Therefore, the tumour-promoting or inhibiting impact also depends on the regional levels and the site of manifestation [41]. TNF-α facilitates the activity of mast cells and fosters polar angiogenesis by inducing the production of pancreatic VEGF by stellate cell fibroblasts, further contributing to metastasis via the activation of NF-κB signalling pathways. In patients with PDAC, the presence of immune cells and human pancreatic tumour cells capable of synthesising and secreting TNF-α has been documented, indicating that cells changed by cancer are consistently subjected to endogenous autocrine stimulation [42].

Levels of CTACK and RANTES positively correlated with the number of neutrophils and carbohydrate antigen 19.9 (Ca 19.9), a recognised diagnostic tumour marker in PDAC [43]. Ca 19.9 antigen is one of the most frequently studied biomarkers in patients affected by pancreatic cancer. It is used for diagnostic and prognostic purposes [44, 45]. The sensitivity of Ca 19.9 in the early-stage of PCAC is low; in more advanced cancer lesions it is disturbed by the inflammatory response of the host and by obstructive jaundice [46]. Without a doubt, the potential of this biomarker has been weakened due to false-negative results in patients with pancreatic cancer and false-positive results in benign pancreatic and bile duct diseases [47]. CTACK may become a new, alternative, auxiliary marker. Cutaneous T-cell-attracting chemokine, also known as CCL27, is one of the chemokines that are key in the functioning of the immune system [48]. It is expressed strongly in both normal and inflamed skin. However, the number of clinical trials examining the association of CTAC with abdominal cancers is limited. A 2020 study found that adding CTACK, among other agents, to the reference models with Ca19-9 improved the survival rate for patients with PDAC [49]. In their study, Ceriolo *et al.* demonstrated that pancreatic islets in patients with pancreatic cancer are positive for CTACK expression [50]. A 2022 study provided evidence of a potential link between genetically determined CTACK levels and increased risk of prostate, kidney, and pancreatic cancer, as well as melanoma and non-Hodgkin's lymphoma [51].

In our study group, tumours resulted in jaundice in 65.2% of patients with pancreatic head cancer, while elevated bilirubin levels were rare in patients with peripheral tumours. It is a widely recognised phenomenon that bilirubin precipitates a systemic inflammatory response syndrome, potentially culminating in multiple organ dysfunction syndrome. The cardinal clinical presentations encompass haemodynamic instability, acute renal insufficiency, cardiovascular compromise, immunodeficiency, coagulopathies, metabolic derangements, and impairments in wound repair processes [52]. The compromised immune function observed in obstructive jaundice is a critical factor in the development of many complications. This occurrence is ascribed to the aforementioned perturbations in homeostasis within the enterohepatic axis and portal sequelae, in conjunction with systemic endotoxaemia [53]. The lack of bile in the intestines, disruption of the intestinal mucosa barrier, and increased endotoxin absorption, followed by endotoxaemia cause the production of pro-inflammatory cytokines

(including TNF-α or IL-6). Septic symptoms result mainly from the impairment of the immune system. Specifically, they stem from a deficiency in cell-mediated immunity (T cells) triggered by the secretion of cytokines (TNF-α, IL-1, IL-6, interferon-γ), prostaglandins, and various other inflammatory agents. Conjugated primary bile salts have been theorised to form micelles that bind endotoxins and reduce endotoxin permeability through intestinal epithelial cells [54]. A recent study demonstrated a decrease in LPS-responsive pro-inflammatory cytokines secreted by monocytes in obstructive jaundice. Biliary drainage reversed this effect. Patients with malignant tumours had a weaker response to LPS than patients with benign tumours [55]. Consequently, our observation showed a marked rise in inflammatory cytokines in patients with hyperbilirubinaemia associated with tumours in the pancreatic head.

Perioperative nutritional interventions, including immunonutrition, represent a significant therapeutic modality that enhances clinical outcomes following major surgical procedures, such as pancreatic resections [56]. Immunonutrition consisting of arginine, omega-3 fatty acids, and ribonucleic acid has demonstrated efficacy in modulating immune responses, attenuating inflammatory pathways, and optimising bowel function post-operatively [57]. Provision of nutritional support is essential for patients undergoing pancreatoduodenectomy, as a substantial proportion of these individuals exhibit malnourishment secondary to their underlying disease pathology. In patients exhibiting a catabolic state and experiencing stress attributable to both the disease itself and surgical trauma, there is a concomitant impairment of immune response. Modulation of this immune response is pivotal to enhancing patient prognosis, a claim substantiated by numerous clinical investigations [58–61]. In our study, IL-16 ($p = 0.019$, $R = 0.400$) and MIF ($p = 0.016$, $R = 0.404$) were positively correlated with weight loss. This suggests that the implementation of preoperative nutrition may improve the patient's condition and thus reduce inflammation and the occurrence of postoperative complications.

Conclusions

We demonstrated that the concentrations of cytokines (eotaxin, basic FGF, G-CSF, IL-2Rα, IL-6, IL-9, IL-17, IP-10, MIP-1α, MIP-1β, RANTES, SCGF-β, TNF-α, and TNF-β) were statistically significantly higher in patients with ductal carcinoma of the pancreatic head compared to patients with cancer located in the body and the tail. Cytokines such as FGF, G-CSF, IL-2Rα, IL-6, IL-9, IL-17, IP-10, MIP-1α, MIP-1β, RANTES, SCGF-β, TNF-α, and TNF-β differentiate, with high sensitivity and specificity, patients with cancer located in the head of the pancreas from patients with the peripheral location of this cancer.

The examination of clinical and chosen parameters showed negative correlations between IL-1ra and TNF-β and tumour location. Significant correlations were also found between Ca 19.9 and CTACK and RANTES.

It is important to acknowledge certain constraints of our study, including the small patient cohort size. Consequently, additional research involving a more extensive patient population with PDAC is necessary. Therefore, our study is the first step for future research purchased on the assessment of the diagnostic usefulness of inflammatory cytokines.

The concentration of selected parameters of inflammatory cytokines were performed exclusively on blood serum, which permits only an estimation of the results. Our evaluation was limited to a selection of cytokines; thus, we cannot provide a complete description of the inflammatory disorders of the PDAC patients. However, the carefully selected group of patients with PDAC constitutes an undeniable advantage of our study.

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Medical University of Bialystok.

Ethical approval

Approval number: APK.002.237.2020.

Conflict of interest

The authors declare no conflict of interest.

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