Early detection of pancreatic cancer in high-risk individuals

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Temporal Trends in Body Composition and Metabolic Markers Prior to Diagnosis of Pancreatic Ductal Adenocarcinoma

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ABSTRACT

Background and aims

Changes in body composition and metabolic factors may serve as biomarkers for the early detection of pancreatic ductal adenocarcinoma (PDAC). The aim of this study was to capture the longitudinal changes in body composition and metabolic factors prior to diagnosis of PDAC.

Methods

We performed a retrospective cohort study in which all patients (≥18 years) diagnosed with PDAC from 2002 to 2021 were identified. We collected all abdominal CT scans and 10 different blood-based biomarkers up to 36 months prior to diagnosis. We applied a fully automated abdominal segmentation algorithm previously developed by our group for three-dimensional quantification of body composition on CT scans. Longitudinal trends of body composition and blood-based biomarkers prior to PDAC diagnosis were estimated using linear mixed models, compared across different time windows, and visualized using spline regression.

Results

We included 1,690 patients in body composition analysis, of whom 516 (30.5%) had ≥ 2 prediagnostic CT scans. For analysis of longitudinal trends of blood-based biomarkers, 3,332 individuals were included. As an early manifestation of PDAC, we observed a significant decrease in visceral and subcutaneous adipose tissue, accompanied by a decrease in serum lipids (e.g., LDL, total cholesterol, and triglycerides), and an increase in blood glucose levels. Loss of muscle tissue and bone volume was predominantly observed in the last 6 months prior to diagnosis.

Conclusion

This study identified significant alterations in a variety of soft tissue and metabolic markers that occur in the development of PDAC. Early recognition of these metabolic changes may provide an opportunity for early detection.

Keywords: pancreatic cancer, early detection, biomarkers, body composition

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis and is currently the third leading cause of cancer related mortality in the United States.[1] Early detection is critical for improving survival rates but is difficult due to the lack of specific symptoms in the early stages of the disease.[2] One of the challenges in early detection is identifying individuals at increased risk from the general population, who could potentially benefit from longitudinal surveillance programs.[3-7] Although individuals with specific PDAC predisposing germline pathogenic variants are well-defined high-risk subgroups, they only represent 10% of cases.[8] Therefore, it is important to understand the metabolic and physiological changes associated with sporadic PDAC development to distinguish high-risk subgroups from the general population.

Studies have shown that as PDAC progresses, cancer cells promote a wide range of metabolic changes, including upregulation of glycolysis and induction of lipolysis.[9-11] The most notable manifestation of these changes is recognized as cancer-induced cachexia, defined as a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass.[12] This phenomenon is commonly observed in patients with terminal cancer.[13] However, subtle signs of cachexia may be present even when only neoplastic precursor lesions are present.[14] In fact, elevated plasma branched-chain amino acid levels several years before diagnosis suggest that whole-body protein breakdown is an early event in the development of PDAC.[15] Similarly, new-onset diabetes (NOD) accompanied by weight loss has been observed with a significant lead time of more than 6 months in patients developing PDAC. This has been used to differentiate between those at high and low risk of developing the disease.[16] However, since 1.4 million Americans are diagnosed with diabetes each year,[17] more sensitive metabolic and physiological markers need to be identified to further guide risk stratification. Various metabolic and body composition parameters have been described in patients prior to diagnosis of PDAC, some occurring several years before diagnosis, providing a promising avenue for identifying markers for early detection.[15, 18-20]

Therefore, the aim of this study was to comprehensively investigate the longitudinal changes in body composition and biochemical markers related to nutrition, metabolism, and inflammation leading up to PDAC diagnosis in a large cohort of patients. We hypothesized that significant alterations in both body composition and biochemical markers could be observed up to three years before the clinical diagnosis of PDAC.

METHODS

Study Population

This retrospective cohort study used the Mayo Clinic Cancer Registry to identify patients ≥ 18 years of age with a diagnosis of PDAC from January 1, 2002 to September 9, 2020. Details of patient selection are provided in the **Supplementary Methods**. This study was approved by the Mayo Clinic Institutional Review Board (21–011051).

Collection of Body Composition Biomarkers

Patients with PDAC who underwent abdominal computed tomography (CT) scans within 36 months prior to diagnosis were selected. A validated deep learning-based algorithm was used to determine subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), skeletal muscle area (SMA) and density (SMD), and vertebral bone area (VBA) and density (VBD) from a 20 cm section of the abdomen centered at the midpoint of L3.[18, 21-25] A detailed description the CT scan acquisition and body composition analyses is provided in the **Supplementary Methods**.

Collection of Blood-Based Biomarkers

We identified patients with PDAC who had received at least one of ten commonly used blood-based biomarker tests in the 36 months prior to diagnosis. These markers were selected based on their relationship to nutrition, metabolism and/or (systemic) inflammation and included: albumin, C-reactive protein (CRP), fasting blood glucose (FBG), hemoglobin (Hb), hemoglobin A1c (HbA1c), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, triglycerides, and white blood cell count (WBC). To avoid the potential effects of chemotherapy and surgical treatment on these blood-based markers, those acquired after the date of diagnosis were excluded.

Blood-based biomarkers may be affected by other conditions unrelated to PDAC (e.g., a WBC count exceeding 30×109 / L may be observed in the case of hospitalization for pneumonia); therefore, we excluded values less than 1.5 interquartile range (IQR) below the first quartile, or greater than 1.5 IQR above the third quartile.

Statistical Methods

Overall Trend Analysis

Overall changes in biomarkers for the entire study population during the 36 month study period were visualized by conditional mean smoothed with locally estimated scatterplot smoothing (LOESS), available in the *ggplot* function of R. A smoothing factor of 0.3, corresponding to a 12 month moving average, was applied.

To estimate of the overall change in biomarkers over the 36 month period, a linear mixed model (LMM) was applied; regression coefficients (denoted as β) with 95% confidence intervals (CIs) were estimated and interpreted as the difference in mean of biomarkers corresponding to time in months closer to diagnosis. In addition, LMM estimates within different time windows were determined to indicate the time at which biomarker alterations begin to occur.

Pairwise Trend Analysis

To capture biomarker changes relative to a person's own earlier, baseline exam, we included individuals who had multiple observations during the study period. Changes in body composition and blood-based biomarkers were estimated over 3 time windows: 36-12 months vs 12-6 months, 12-6 months vs 6-3 months, and 6-3 vs 3-0 months prior diagnosis. Patients with ≥1 observations in both timeframes were included and the change between time windows was estimated. In case of ≥1 observations within each timeframe, the intra-timeframe observation values were averaged. The change for each individual was plotted using boxplots with paired lines for visual comparison.

One-way ANOVA test was used to determine if there was a significant change in the means between two specific time windows. All statistical tests were two-tailed and P-values less than 0.05 were considered statistically significant. Statistical analysis was performed using R Statistical Software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 9,221 patients with PDAC were identified from the Mayo Clinic Cancer Registry. Of these, 1,990 individuals (21%) had ≥ 1 CT scans within 3 years prior to diagnosis (**Figure 1**). After applying exclusion criteria, 1,690 (18%) individuals were eligible for body composition biomarker analysis, of whom 516 (30.5% of the analysis cohort) had ≥ 2 prediagnostic CT scans. We identified 3,306 (36%) patients with ≥1 blood-based biomarkers within 3 years prior to diagnosis. Detailed demographic and clinical characteristics of the two cohorts are shown in **Table 1**. No relevant differences were observed between the study population and source population.

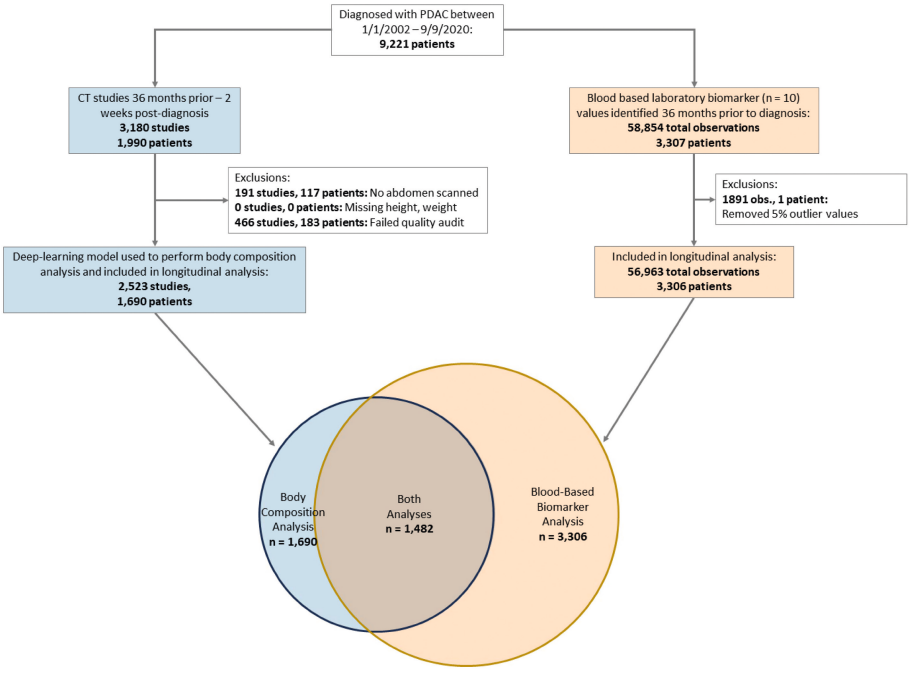


Figure 1. Flowchart of Inclusion, Exclusion, and Data Collection of Patients Diagnosed with Pancreatic Ductal Adenocarcinoma and Venn diagram showing the number of patients included only in body composition biomarker analysis (n = 1,690), only in blood-based biomarker analysis (n = 3,306), or in both types of analyses (n = 1,482). During the quality audit of body composition analysis, we excluded CT series that lacked a 20 cm section of the abdomen containing the third lumbar spine vertebra (L3) and non-axial reconstructions based on several fields provided in the DICOM metadata.

Table 1. Patient Demographics and Clinical Characteristics at Time of PDAC Diagnosis

		Study Population	
Characteristics	**Source population (N = 9,221)**	**Body composition biomarker cohort (N = 1,690)**	**Blood-based biomarker cohort (N = 3,306)**
Demographics			
Age, median (IQR)	68 (60-76)	69 (60-77)	70 (62-77)
Male	5038 (54.6%)	962 (56.9%)	1860 (56.3%)
BMI, median (IQR)	26.6 (23.4-30.3)	26.9 (23.3-29.8)	26.5 (23.4-30.1)
Normal (< 25)	2218 (37.4%)	575 (38.0%)	1098 (37.9%)
Overweight (25-29)	2113 (35.6%)	575 (38.0%)	1056 (36.5%)
Obese (≥ 30)	1603 (27.0%)	364 (24.0%)	743 (25.6%)
Missing, n	3287	176	409
Race			
White	8349 (90.9%)	1515 (89.6%)	2991 (90.5%)
Black	240 (2.6%)	22 (1.3%)	70 (2.1%)
Asian	85 (0.9%)	12 (0.7%)	32 (1.0%)
Other/Unknown	514 (5.6%)	141 (8.3%)	213 (6.4%)
Hispanic	97 (1.1%)	6 (0.4%)	42 (1.3%)
Comorbidities			
Diabetes mellitus	1441 (26.7%)	501 (29.6%)	1009 (30.5%)
Chronic kidney disease	178 (3.3%)	62 (3.7%)	152 (4.6%)
Congestive heart failure	451 (8.4%)	145 (8.6%)	334 (10.1%)
Chronic pulmonary disease	855 (15.9%)	261 (15.4%)	553 (16.7%)
Moderate/severe liver disease	365 (6.8%)	103 (6.1%)	221 (6.7%)
PDAC characteristics			
Stage			
I	1339 (15.7%)	213 (12.8%)	408 (12.3%)
II	2657 (31.2%)	541 (32.5%)	1091 (33.0%)
III	1293 (15.2%)	327 (19.6%)	592 (17.9%)
IV	3235 (38.0%)	585 (35.1%)	1215 (36.8%)
Missing, n	697	24	0
Resectable	3447 (37.4%)	502 (29.7%)	1070 (32.4%)
Tumor location			
Head	4720 (51.3%)	929 (55.0%)	1836 (55.5%)
Body/Tail	2666 (29.0%)	389 (23.0%)	816 (24.7%)
Overlapping	805 (8.7%)	193 (11.4%)	301 (9.1%)
Other	1014 (11.0%)	179 (10.6%)	353 (10.7%)

NOTE. Data are n (%) unless indicated otherwise.
Abbreviations: IQR, interquartile range. PDAC, pancreatic ductal adenocarcinoma.

Temporal Trends of Body Composition Markers

Overall trends of body composition over 36 months prior to diagnosis of PDAC are visualized in **Figure 2** and corresponding LMM estimations are provided in **Table 2**. The original data distribution is provided in **Supplementary Figures 1** and **2**. LMM estimations for different time windows are provided in **Supplementary Table 1.** The most pronounced and sustained changes were observed in VAT area and SAT area indices, with decreases of -1.94 (95% CI, -2.39, -1.48) and -2.59 (95% CI, -3.17, -2.02; **Table 2**) in area (cm^2)/height (m^2) per 6 months closer to diagnosis, respectively. Loss of SMA was less pronounced and mainly observed in the last 6 months before diagnosis. The observed trends in body composition were similar in individuals who were diagnosed with stage I/II disease and stage III/IV disease (**Supplementary Figure 5**).

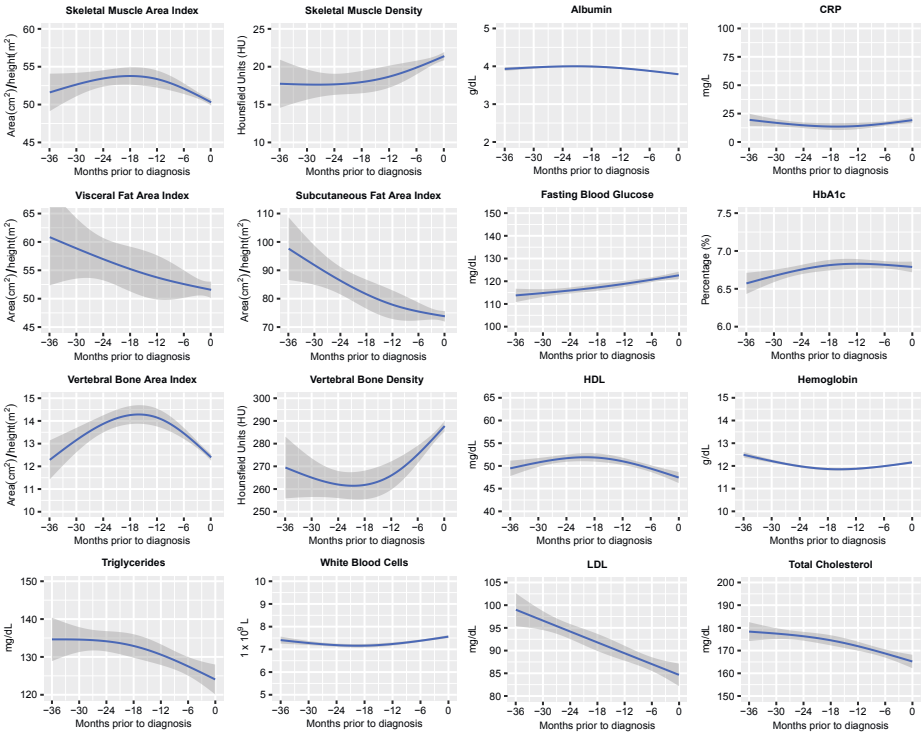


Figure 2. Longitudinal trends for body composition biomarkers (part A) and blood-based biomarkers (part B) over 36 months prior to diagnosis of PDAC. The blue lines indicate the mean with the 95% confidence interval in grey.

Table 2. Linear Mixed Model Estimations for Biomarkers Over the 36 Month Study Period Prior to Diagnosis of PDAC

Body composition biomarkers	n	β (95% CI)	*P*
Skeletal muscle area (cm^2/m^2)	1,690	-0.40 (-0.60, -0.19)	<0.001
Skeletal muscle density (HU)	1,690	-0.14 (-0.38, 0.09)	0.235
Visceral adipose tissue area (cm^2/m^2)	1,690	-1.94 (-2.39, -1.48)	<0.001
Subcutaneous adipose tissue area (cm^2/m^2)	1,690	-2.59 (-3.17, -2.02)	<0.001
Vertebral bone area (cm^2/m^2)	1,690	-0.23 (-0.33, -0.13)	<0.001
Vertebral bone density (HU)	1,690	2.96 (1.82, 4.10)	<0.001
Blood-based biomarkers			
Albumin (g/dl)	2,236	-0.03 (-0.03, -0.02)	<0.001
C-reactive protein	312	0.51 (-0.33, 1.35)	0.232
Fasting blood glucose (mg/dl)	928	1.23 (0.79, 1.68)	<0.001
HbA1c (%)	1,042	0.08 (0.07, 0.09)	<0.001
High-density lipoprotein (mg/dl)	1,321	-0.22 (-0.41, -0.03)	0.022
Hemoglobin (g/dl)	3,254	-0.09 (-0.10, -0.08)	<0.001
Low-density lipoprotein (mg/dl)	1,170	-2.83 (-3.31, -2.34)	<0.001
Total cholesterol (mg/dl)	1,359	-2.69 (-3.18, -2.20)	<0.001
Triglycerides (mg/dl)	1,370	-1.86 (-2.61, -1.11)	<0.001
White blood cells ($x10^9/l$)	3,198	0.04 (0.02, 0.06)	<0.001

NOTE. N = Sample size; β = regression coefficient; CI = confidence interval; β values, 95% CIs, and p-values (*P*) result from linear mixed models. β values and 95% CIs are interpreted as the difference in means of the given biomarker per 6 months closer to diagnosis of PDAC. Body composition area measurements were normalized by dividing by patients' height squared.

These findings were consistent in the pairwise trend analysis. The most notable changes were observed in the last 6 months prior to diagnosis, where VAT decreased 12.9% (n = 81; $P < .001$), SAT decreased 14.7% (n = 81; $P < .001$), and SMA decreased 6.3% (n = 81; $P < .001$; **Supplementary Figure 3** and **Supplementary Table 2**). Interestingly, similar to the mean temporal trend analysis, VBA decreased (a loss of 10.1%; $P < .001$), while VBD increased 5.6% ($P < .001$) in the last 6 months.

Figure 3 demonstrates progression of body composition over time in a sample case. In this 65-year-old man, a 15% decrease in SAT area, a 36% decrease in VAT area (26% combined loss), and a 6% decrease in SMA were observed over a 20-month period. He was ultimately diagnosed with stage IIB PDAC. Using the known density of human fat tissue (0.92 g/cm^3) and fat-free tissue (1.10 g/cm^3),[26, 27] the combined loss of mass corresponding to the anatomic region included in analysis (colored region) is approximately 0.8 kilograms (1.7 pounds).

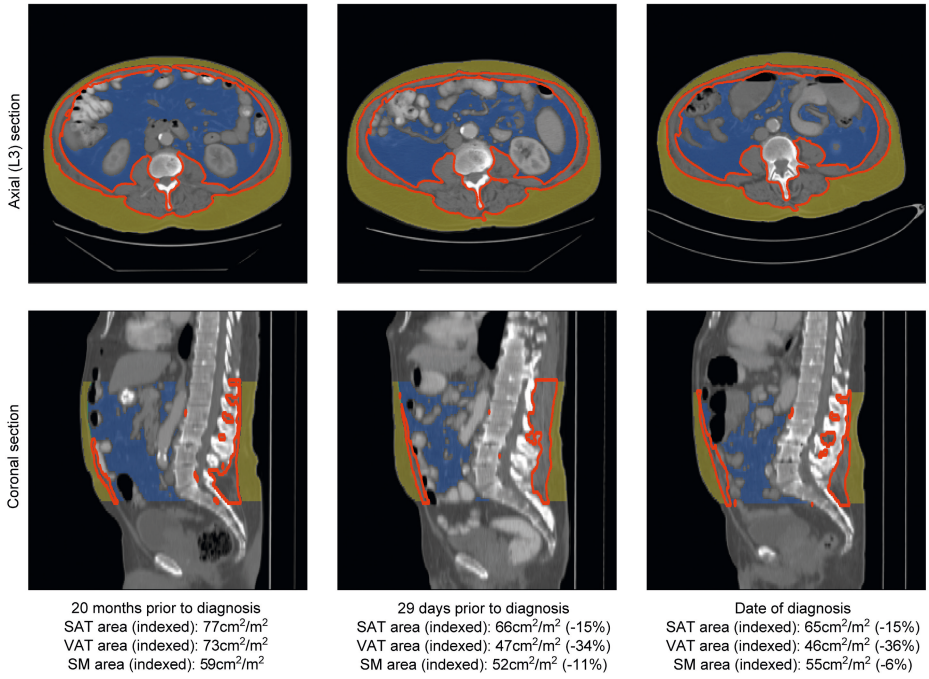


Figure 3. Example case of a 65-year-old man diagnosed with stage IIB PDAC. Images are axial (top) and coronal (bottom) sections of CT scans with automated segmentation of SAT (yellow), SMA (red), and VAT (blue). A 15% decrease in SAT area, a 36% decrease in VAT area (26% combined loss), and a 6% decrease in SMA were observed over a 20-month period before this patient was diagnosed with PDAC.

Temporal Trends of Blood-Based Biomarkers

Overall, similar to VAT and SAT, a sustained decreasing trend was observed over the 3-year study period for LDL (β = -2.83; 95% CI, -3.31, -2.34; $P < .001$), total cholesterol (β = -2.69; 95% CI, -3.18, -2.20; $P < .001$) and triglycerides (β = -1.86; 95% CI, -2.61, -1.11; $P < .001$; **Figure 2** and **Table 2**). HDL levels remained more stable over time. On a group level, FBG increased prior to diagnosis, although occurrence of hyperglycemia was less clearly reflected in HbA1c. The other markers (albumin, CRP, hemoglobin, and white blood cells) showed no distinct changes towards diagnosis of PDAC. The observed trends were consistent across early and late disease stages (**Supplementary Figure 6**).

Pairwise analysis also showed significant reductions in serum lipids (**Supplementary Figure 4; Supplementary Table 2**). An 8.2% (n = 318; $P < .001$) reduction in LDL was evident up to 3 years before diagnosis and persisted throughout the observation period. Similar deviations were observed for total cholesterol (-8.3% in the last 6 months) and triglycerides (-11.7% in the last 6 months).

DISCUSSION

In this large cohort of individuals, we examined longitudinal changes in body composition and biochemical markers related to nutrition, metabolism, and inflammation over a period of 36 months

prior to PDAC diagnosis. The comprehensive analysis of 16 markers was designed to provide insights into the pathophysiological changes of the disease and to identify potential biomarkers that could aid in the early detection of PDAC.

One of the most notable findings is that there was a consistent decrease in VAT and SAT during PDAC development, well before diagnosis. Interestingly, in parallel, serum lipids also showed a steady decrease over this 36-month period. Collectively, this may reflect the effects of tumor progression, inducing expansion of brown adipose tissue and reduction of white adipose tissue, inflammation, and lipolysis.[28, 29] Another hallmark of cancer-associated cachexia is the observed loss of SMA (sarcopenia), although less pronounced and mostly visible in the last 6 months before diagnosis, which is associated with poor outcomes.[30, 31] This is consistent with observations by Sah et al.,[18] who demonstrated similar temporal profiles, with a change in lipids and SAT as an early manifestation (1.5 years prior to diagnosis of an overt clinical diagnosis of PDAC), followed by a decrease in VAT and muscle in the last 6 months prior to diagnosis. Taken together, these findings suggest that in the pathophysiological changes that occur during the development of PDAC, muscle mass is initially preserved and loss of adipose tissue may be among the first identifiable systemic manifestations of disease. In addition, the paradoxically increasing blood glucose levels (1.23 mg/dL per month) in combination with decreasing adipose tissue and serum lipids may be an early indicator of pancreatic endocrine insufficiency (e.g., pancreatogenic (type 3c) diabetes)[32], in contrast to what would be expected in the context of decreased insulin sensitivity and metabolic syndrome. These could serve as useful markers for identification of subpopulations at high-risk of developing PDAC in the midst of the diabetes epidemic. A significant finding is that the observed trends in both body composition and blood-based biomarkers were consistent in patients diagnosed with early versus late stage disease, underscoring the potential for early detection.

Another recently identified facet of systemic wasting in patients with PDAC is osteopenia, characterized by loss of bone mass, which has been linked to worse outcomes.[33, 34] This condition is related to sarcopenia (together known as osteosarcopenia)[35] which is also thought to be driven by a combination of endocrine factors arising from the interplay of inflammation, nutritional deficiencies, and decreased physical activity.[36] Our findings, although modest, may indicate early signs of osteopenia through loss of vertebral bone area (volume) in the months leading up to diagnosis, as observed in both the overall trend and the pairwise trend analysis (10% decrease). Surprisingly, we observed a concomitant increase in bone density. This seemingly paradoxical finding of diminishing bone volume and increasing bone density may be due to the presence of osteoblastic bone metastases in some individuals. Such metastases, characterized by abnormal bone growth and increased bone density,[37] are commonly observed in prostate cancer[38], though in PDAC, the predominant nature of skeletal metastases has been variably reported as being osteoblastic or osteolytic.[39-41] Bone metastases in PDAC most often present in the vertebrae, where they could potentially manifest as areas of increased bone density alongside the reduction in bone volume. Alternatively, we must consider the possibility that measurement artifacts may contribute to these relatively subtle changes observed. As we are the first to describe such a phenomenon in the pre-diagnostic phase of PDAC, we hope that future studies will re-examine and elucidate these findings.

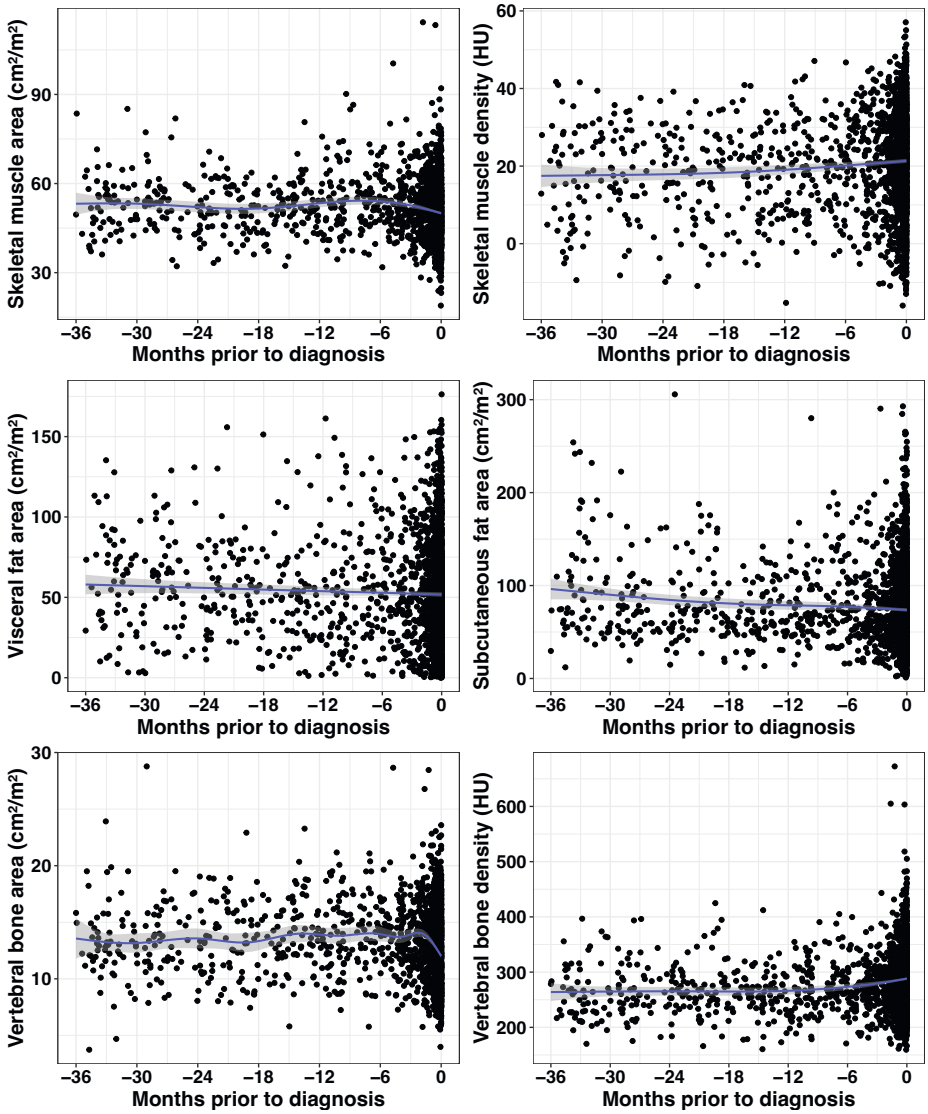
The present study is the largest longitudinal study to date of changes in body composition and biochemical markers in the pre-diagnostic stages of PDAC. While our goal was to gain a comprehensive picture of biomarker changes that occur in the development of PDAC, one perceived

limitation of our approach is the lack of a control cohort. However, in our study, an individual's prior measurement served as a reference and indicated whether relevant biomarker changes occurred. For body composition, this approach is also supported by the fact that in the absence of significant pathology or deliberate lifestyle intervention, fat composition is relatively stable and tends to increase with age.[42] Another factor to consider is the inherent limitation of the clinical indications (i.e. selection bias) that guide the determination of blood-based biomarkers and CT scans. This is intrinsic to the hospital setting in which our study was conducted and may be particularly relevant for markers associated with inflammation (e.g., CRP and leukocytes), which are typically assessed in the context of suspected infection. Consequently, their applicability as markers for early detection may be limited. Conversely, markers such as HDL, LDL, and total cholesterol, which are commonly assessed in cardiovascular risk management, are less likely to be influenced by concurrent symptoms and thus have greater potential for utility in this context. Other limitations are the absence of information regarding medications used for treatment of dyslipidemia and diabetes, and the predominantly White study population. To increase the robustness of our findings, validating our observations in alternative settings with a more diverse population, such as a primary care, would be of considerable interest to assess the broader generalizability and utility of the identified biomarker patterns.

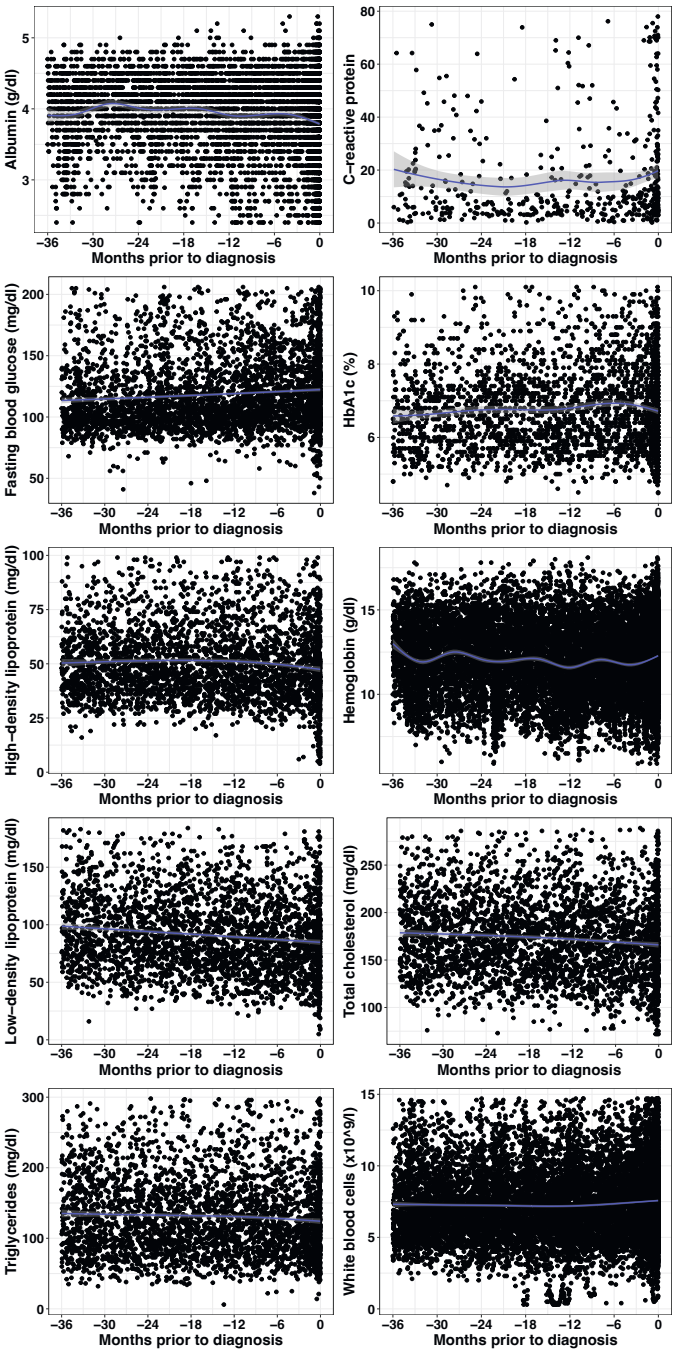
Our next step is to establish a case-control study to evaluate the discriminative power of the most promising biomarkers in distinguishing cases from controls. Subsequently, we envision that these markers could be used to develop an algorithm that captures subtle changes over time and predicts which patients are at increased risk of PDAC. By flagging patients with evolving metabolic and body composition patterns, the tool will prompt radiologists to examine the pancreas more closely for features indicative of malignancy that warrant further investigation. In addition, the use of these markers could potentially expand and refine existing prediction models, such as the Enriching New-Onset Diabetes for Pancreatic Cancer (ENDPAC) model[16], which has shown a promise for predicting PDAC risk in patients with NOD.[43] In addition, investigations into the precise mechanistic underpinnings of the observed biomarker changes are warranted, which may lead to the discovery of urgently-needed biomarkers more specific to PDAC development.[44]

In summary, we have collected extensive data on body composition and blood-based biomarkers to investigate the pathophysiological changes that occur in the prediagnostic stages of PDAC. Over a 36-month period, the earliest and most predominant changes were observed in adipose tissue and related serum lipid markers. In addition, the onset of sarcopenia and osteopenia in the months prior to diagnosis highlights the broad systemic impact of PDAC on body composition. By unravelling the temporal sequence of these changes, we have taken a step toward identifying biomarkers that may aid in the detection of PDAC at its earliest stages. Further research is warranted to validate and extend these findings to PDAC risk prediction models, ultimately paving the way for improved risk assessment and selective screening of individuals at high risk for this devastating malignancy.

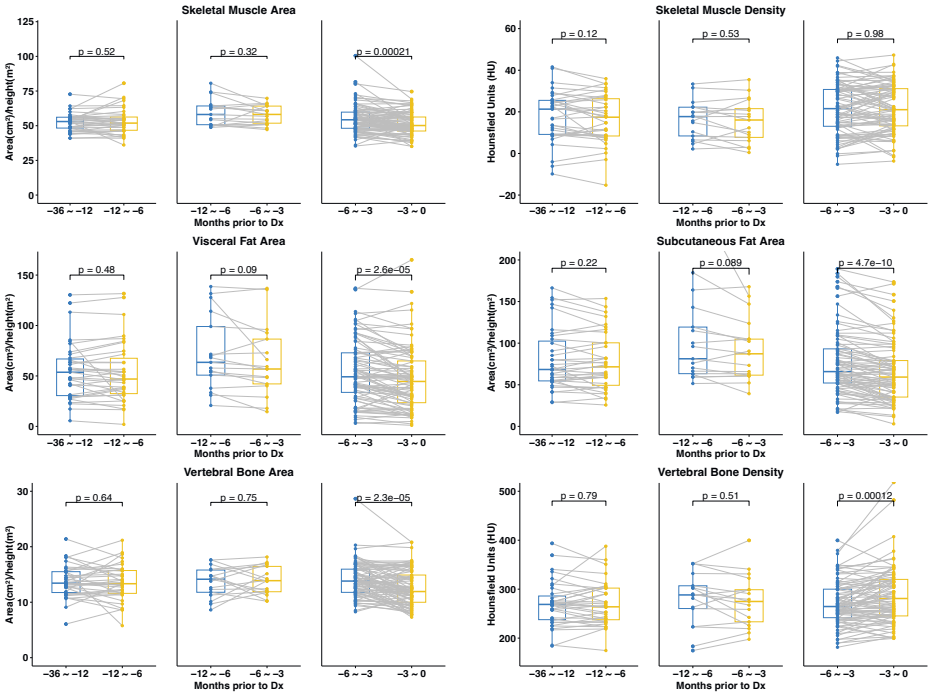
SUPPLEMENTARY MATERIALS



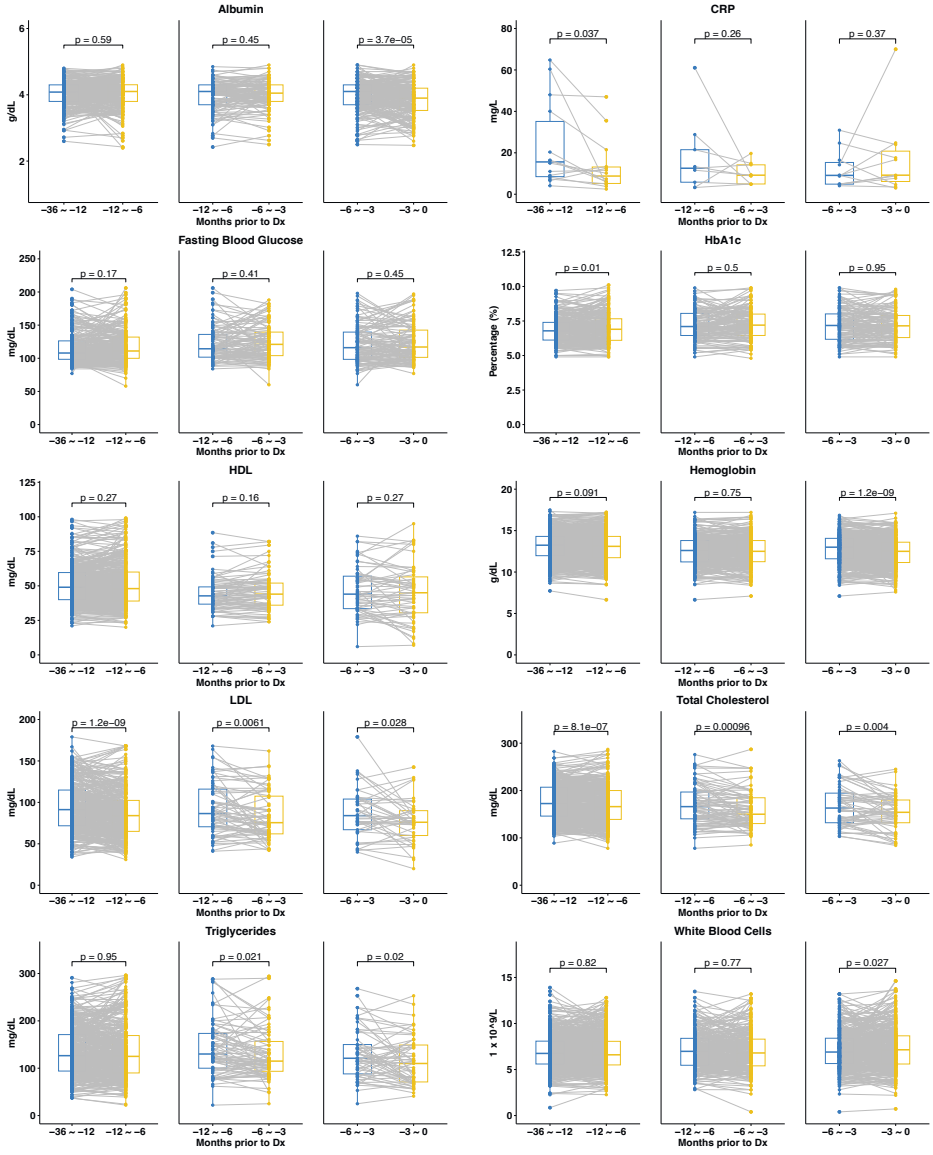
Supplementary Figure 1. Scatterplot with spline regression line to show the original data distribution for body composition biomarkers. The blue lines indicate the mean with the 95% confidence interval in grey.



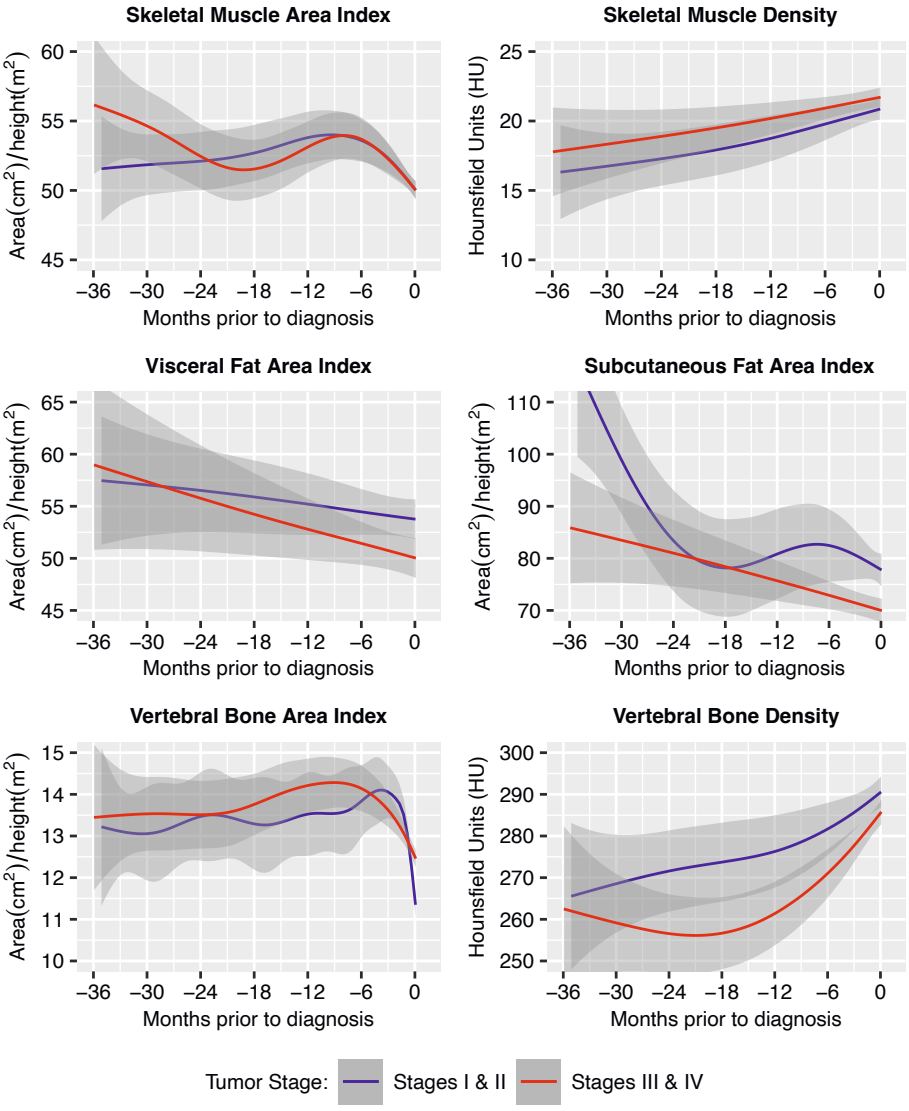
Supplementary Figure 2. Scatterplot with spline regression line to show the original data distribution for blood-based biomarkers. The blue lines indicate the mean with the 95% confidence interval in grey.



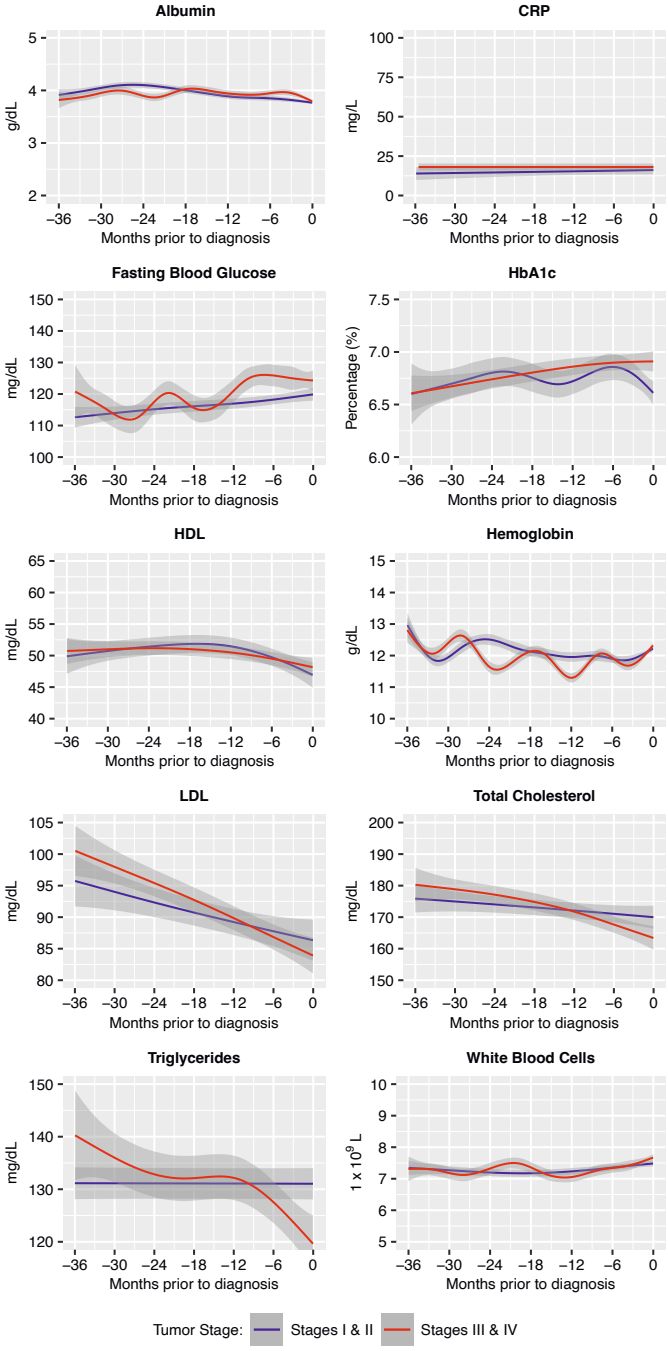
Supplementary Figure 3. Paired box plots comparing body composition biomarkers within different time windows prior to diagnosis of PDAC. Gray lines indicate trend lines for individual patients over the time intervals. Box plots indicate the median with lower and upper quartile.



Supplementary Figure 4. Paired box plots comparing blood-based biomarkers within different time windows prior to diagnosis of PDAC. Gray lines indicate trend lines for individual patients over the time intervals. Box plots indicate the median with lower and upper quartile.



Supplementary Figure 5. Longitudinal trends for body composition biomarkers over 36 months prior to diagnosis of PDAC, subdivided by patients diagnosed with stage I and II disease (*blue*) and stage III and IV disease (*red*). The blue or red lines indicate the mean with the 95% confidence interval in grey.



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Supplementary Table 1. Linear Mixed Model Estimations for Biomarkers for Different Time Windows Prior to Diagnosis of PDAC: 36 to 12 Months Prior, 12 to 6 Months prior and 6 Months to Time of Diagnosis.

	-36 to -12 months			-12 to -6 months			-6 months to diagnosis		
Body composition metrics	n	β (95% CI)	*P*	n	β (95% CI)	*P*	n	β (95% CI)	*P*
Skeletal muscle area (cm^2/m^2)	172	-0.01 (-0.10, 0.08)	0.827	94	0.36 (-0.57, 1.29)	0.447	1,646	-0.85 (-1.11, -0.60)	0.000
Skeletal muscle density (HU)	172	-0.02 (-0.16, 0.13)	0.786	94	-0.09 (-1.02, 0.82)	0.842	1,646	-0.18 (-0.49, 0.13)	0.250
Visceral adipose tissue area (cm^2/m^2)	172	-0.15 (-0.38, 0.08)	0.196	94	0.32 (-0.93, 1.60)	0.621	1,646	-1.79 (-2.27, -1.31)	0.000
Subcutaneous adipose tissue area (cm^2/m^2)	172	-0.27 (-0.63, 0.08)	0.136	94	-0.21 (-2.81, 2.60)	0.873	1,646	-2.81 (-3.39, -2.24)	0.000
Vertebral bone area (cm^2/m^2)	172	0.02 (-0.03, 0.07)	0.461	94	0.07 (-0.27, 0.41)	0.686	1,646	-0.58 (-0.71, -0.46)	0.000
Vertebral bone density (HU)	172	0.03 (-0.52, 0.57)	0.919	94	4.81 (0.64, 8.98)	0.026	1,646	5.02 (3.51, 6.52)	0.000
Laboratory markers									
Albumin (g/dl)	619	0.00 (0.00, 0.01)	0.004	346	0.02 (0.01, 0.04)	0.007	2,024	-0.04 (-0.05, -0.03)	0.000
C-reactive protein	119	-0.26 (-0.53, 0.02)	0.068	47	-2.51 (-6.53, 1.46)	0.211	200	1.14 (-0.84, 3.12)	0.261
Fasting blood glucose (mg/dl)	510	0.10 (-0.04, 0.23)	0.180	280	-0.03 (-1.43, 1.38)	0.968	686	1.03 (-0.02, 2.07)	0.055
HbA1c (%)	450	0.01 (0.00, 0.01)	0.000	288	0.02 (-0.02, 0.05)	0.394	852	-0.01 (-0.04, 0.02)	0.540
High-density lipoprotein (mg/dl)	929	0.02 (-0.03, 0.07)	0.350	436	0.09 (-0.79, 0.98)	0.836	759	-0.66 (-1.27, -0.05)	0.034
Hemoglobin (g/dl)	1,184	-0.01 (-0.01, -0.00)	0.002	683	0.06 (0.02, 0.10)	0.005	3,037	-0.06 (-0.08, -0.04)	0.000
Low-density lipoprotein (mg/dl)	825	-0.41 (-0.57, -0.26)	0.000	389	-1.15 (-2.81, 0.53)	0.178	660	-0.39 (-1.61, 0.82)	0.525
Total cholesterol (mg/dl)	959	-0.36 (-0.52, -0.21)	0.000	454	-2.72 (-4.40, -1.01)	0.002	796	-0.59 (-1.93, 0.76)	0.387
Triglycerides (mg/dl)	937	-0.27 (-0.52, -0.02)	0.036	442	-3.35 (-5.97, -0.68)	0.011	809	-1.78 (-3.47, -0.07)	0.040
White blood cells (x10^9/l)	1,143	0.00 (-0.01, 0.01)	0.971	645	-0.09 (-0.15, -0.03)	0.002	2,978	0.01 (-0.03, 0.05)	0.542

NOTE. N = Sample size; β = regression coefficient; CI = confidence interval; β values, 95% CIs, and p-values (*P*) result from linear mixed models. β values and 95% CIs are interpreted as the difference in means of the given biomarker per 1 month closer to diagnosis of PDAC. Body composition area measurements were normalized by dividing by patients' height squared.

Supplementary Table 2. Pairwise Trend Analysis of Biomarkers Across Different Time Windows Prior toDiagnosis of PDAC

Body composition biomarkers	Comparison	n	Mean (SD), reference	Change rate (%)	Mean difference (95% CI)	*P*
Skeletal muscle area (cm^2/m^2)	-36 ~ -12 vs -12 ~ -6	35	53.22 (9.45)	1.32	0.69 (-1.49, 2.87)	0.523
	-12 ~ -6 vs -6 ~ -3	17	57.90 (6.85)	-2.91	-1.73 (-5.29, 1.83)	0.318
	-6 ~ -3 vs -3 ~ 0	81	51.56 (8.42)	-6.31	-3.48 (-5.25, -1.7)	<0.001
Skeletal muscle density (HU)	-36 ~ -12 vs -12 ~ -6	35	16.35 (11.82)	-8.09	-1.44 (-3.26, 0.38)	0.118
	-12 ~ -6 vs -6 ~ -3	17	15.57 (10.38)	-4.81	-0.79 (-3.4, 1.83)	0.533
	-6 ~ -3 vs -3 ~ 0	81	21.52 (11.59)	0.08	0.02 (-1.47, 1.5)	0.983
Visceral adipose	-36 ~ -12 vs -12 ~ -6	35	53.39 (30.5)	-2.69	-1.48 (-5.72, 2.76)	0.484
tissue area (cm^2/m^2)	-12 ~ -6 vs -6 ~ -3	17	64.77 (35.63)	-10.09	-7.27 (-15.8, 1.26)	0.090
	-6 ~ -3 vs -3 ~ 0	81	47.16 (31.76)	-12.90	-6.99 (-10.1, -3.87)	<0.001
Subcutaneous adipose	-36 ~ -12 vs -12 ~ -6	35	77.6 (34.64)	-2.94	-2.35 (-6.18, 1.48)	0.220
tissue area (cm^2/m^2)	-12 ~ -6 vs -6 ~ -3	17	91.84 (38.35)	-12.88	-13.58 (-29.51, 2.34)	0.089
	-6 ~ -3 vs -3 ~ 0	81	65.79 (37.68)	-14.70	-11.33 (-14.52, -8.15)	<0.001
Vertebral bone area (cm^2/m^2)	-36 ~ -12 vs -12 ~ -6	35	13.53 (3.28)	-1.72	-0.24 (-1.25, 0.78)	0.639
	-12 ~ -6 vs -6 ~ -3	17	13.91 (2.53)	1.70	0.23 (-1.27, 1.73)	0.746
	-6 ~ -3 vs -3 ~ 0	81	12.60 (3.27)	-10.06	-1.41 (-2.03, -0.79)	<0.001
Vertebral bone density (HU)	-36 ~ -12 vs -12 ~ -6	35	270.71 (45.07)	0.39	1.06 (-7.11, 9.24)	0.793
	-12 ~ -6 vs -6 ~ -3	17	276.00 (53.29)	-1.74	-4.88 (-20.08, 10.32)	0.506
	-6 ~ -3 vs -3 ~ 0	81	286.49 (58.35)	5.57	15.13 (7.7, 22.55)	<0.001
Blood-based biomarkers						
Albumin	-36 ~ -12 vs -12 ~ -6	236	4.04 (0.44)	0.37	0.01 (-0.04, 0.07)	0.588
	-12 ~ -6 vs -6 ~ -3	112	4.00 (0.44)	0.69	0.03 (-0.04, 0.1)	0.449
	-6 ~ -3 vs -3 ~ 0	194	3.84 (0.50)	-3.47	-0.14 (-0.2, -0.07)	<0.001
CRP	-36 ~ -12 vs -12 ~ -6	14	13.35 (13.02)	-42.95	-10.05 (-19.38, -0.72)	0.037
	-12 ~ -6 vs -6 ~ -3	9	10.08 (5.22)	-43.73	-7.83 (-22.81, 7.15)	0.262
	-6 ~ -3 vs -3 ~ 0	11	17.26 (19.14)	43.91	5.27 (-7.19, 17.73)	0.368
Fasting Glucose	-36 ~ -12 vs -12 ~ -6	220	117.18 (26.01)	1.78	2.05 (-0.88, 4.99)	0.170
	-12 ~ -6 vs -6 ~ -3	95	124.53(26.84)	1.79	2.19 (-3.11, 7.49)	0.414
	-6 ~ -3 vs -3 ~ 0	107	123.92 (28.34)	1.55	1.89 (-3.01, 6.79)	0.445
Hba1c	-36 ~ -12 vs -12 ~ -6	220	6.99 (1.1)	1.87	0.13 (0.03, 0.23)	0.010
	-12 ~ -6 vs -6 ~ -3	119	7.29 (1.14)	0.83	0.06 (-0.12, 0.24)	0.501
	-6 ~ -3 vs -3 ~ 0	116	7.2 (1.16)	-0.09	-0.01 (-0.19, 0.18)	0.946
HDL	-36 ~ -12 vs -12 ~ -6	356	51.17 (16.21)	1.05	0.53 (-0.41, 1.47)	0.266

Supplementary Table 2. continued.

Body composition biomarkers	Comparison	n	Mean (SD), reference	Change rate (%)	Mean difference (95% CI)	*P*
	-12 ~ -6 vs -6 ~ -3	76	45.76 (13.43)	2.58	1.15 (-0.45, 2.75)	0.156
	-6 ~ -3 vs -3 ~ 0	55	44.92 (20.67)	-4.19	-1.96 (-5.46, 1.54)	0.266
Hemoglobin	-36 ~ -12 vs -12 ~ -6	552	13.05 (1.78)	-0.71	-0.09 (-0.2, 0.01)	0.091
	-12 ~ -6 vs -6 ~ -3	265	12.49 (1.81)	-0.18	-0.02 (-0.16, 0.12)	0.749
	-6 ~ -3 vs -3 ~ 0	403	12.42 (1.72)	-2.85	-0.36 (-0.48, -0.25)	<0.001
LDL	-36 ~ -12 vs -12 ~ -6	318	86.62 (29.66)	-8.21	-7.74 (-10.17, -5.31)	<0.001
	-12 ~ -6 vs -6 ~ -3	66	84.01 (29)	-9.13	-8.44 (-14.39, -2.49)	0.006
	-6 ~ -3 vs -3 ~ 0	41	77.05 (26.58)	-11.61	-10.12 (-19.12, -1.12)	0.028
Total Cholesterol	-36 ~ -12 vs -12 ~ -6	377	169.55 (40.23)	-3.79	-6.67 (-9.29, -4.06)	<0.001
	-12 ~ -6 vs -6 ~ -3	78	159.06 (39.64)	-6.30	-10.7 (-16.9, -4.5)	<0.001
	-6 ~ -3 vs -3 ~ 0	55	153.84 (37.65)	-8.30	-13.93 (-23.21, -4.64)	0.004
Triglycerides	-36 ~ -12 vs -12 ~ -6	365	135.00 (57.95)	-0.10	-0.14 (-4.68, 4.41)	0.953
	-12 ~ -6 vs -6 ~ -3	75	129.60 (54.58)	-8.61	-12.21 (-22.55, -1.87)	0.021
	-6 ~ -3 vs -3 ~ 0	57	114.34 (51.19)	-11.72	-15.18 (-27.86, -2.49)	0.020
White Blood Cells	-36 ~ -12 vs -12 ~ -6	517	6.90 (1.98)	0.23	0.02 (-0.12, 0.15)	0.816
	-12 ~ -6 vs -6 ~ -3	243	7.02 (2.15)	-0.49	-0.03 (-0.26, 0.19)	0.766
	-6 ~ -3 vs -3 ~ 0	372	7.33 (2.33)	3.32	0.24 (0.03, 0.44)	0.027

NOTE. Comparison: A vs B (ref=A); Change rate = (B-A)/A*100%, where a negative change rate indicates a decrease; Mean difference: Mean B – Mean A; n = group sample size; 95% CI = 95% confidence interval; *P* = *P*-value; SD = standard deviation.

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