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# Race-based differences in serum biomarkers for cancer-associated cachexia in a diverse cohort of patients with pancreatic ductal adenocarcinoma



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## Abstract

**Background** Pancreatic ductal adenocarcinoma is projected to become the second leading cause of cancer-related deaths by 2040, with the highest disease burden expected amongst Non-Hispanic Black patients. One of the most significant predictors of poor outcomes is the presence of cancer-associated cachexia (CCa). Yet, race- and ethnicity-specific biomarkers for early CCa diagnosis are lacking.

**Methods** We evaluated a panel of candidate biomarkers of CCa in a diverse cohort of patients with pre-treatment serum using multiplex ELISA-based methods.

**Results** We find that growth/differentiation factor-15 (GDF-15) is associated with cachexia severity, is superior to standard biomarkers at classifying cachexia, and differentiates between non-cachexia and pre-cachexia status, but only among Hispanic/Latinx and non-Hispanic White participants. Furthermore, high GDF-15 levels at diagnosis are associated with a greater weight loss from 3.3% (95%CI = -0.14–6.7) to 8.0% (CI = 5.9–10.1) over the 6 months post-diagnosis. Finally, both ENA-78/CXCL5 and GRO- $\alpha$ /CXCL1 are elevated in non-Hispanic Black individuals in a disease-independent manner ( $P < 0.001$  for both analytes).

**Conclusions** GDF-15 may be a potential biomarker for “pre-cachexia” in the non-Hispanic White and the Hispanic population, but not non-Hispanic Black individuals. These findings underscore the unmet need to enroll non-Hispanic Black participants in clinical trials for CCa.

## Plain language summary

Pancreatic cancer is projected to become the second leading cause of cancer-related deaths by 2040, with the highest burden expected amongst non-Hispanic Black patients. Cancer-associated cachexia, a multifactorial wasting condition, is the most significant predictor of poor treatment response and survival, but race-specific biomarkers for diagnosis of cachexia are lacking. In the current study, we evaluated blood-based biomarkers of cachexia while accounting for race and ethnicity. We found that growth/differentiation factor (GDF)–15 was better than standard biomarkers at classifying cachexia and cachexia severity in non-Hispanic White and Hispanic/Latinx patients, but not non-Hispanic Black patients. However, inflammatory markers ENA-78/CXCL5 and GRO- $\alpha$ /CXCL1 were specifically elevated amongst non-Hispanic Black participants. Our findings highlight the need to target non-Hispanic Black patients for enrollment in clinical trials studying cancer-associated cachexia.

Pancreatic ductal adenocarcinoma (PDAC) is increasing in incidence in the United States (US) and globally and is projected to be the second leading cause of cancer-related deaths in the US by 2040<sup>1</sup>. Up to 80% of PDAC cases develop cancer-associated cachexia (CCa), defined as a multifactorial wasting disorder characterized by loss of appetite, body weight, and/or lean body mass (i.e., skeletal muscle) leading to fatigue, functional impairment, treatment-related toxicities, poor quality of life, and reduced survival<sup>2–5</sup>. Properly detecting CCa in its earliest stage and intervening to maintain muscle mass remain key goals in the care of patients with PDAC.

Unfortunately, due to the lack of a well-established definition of CCa and heterogeneity of presentation, diagnosis of CCa typically does not occur until late in the disease course<sup>6–9</sup>.

Blood-based biomarkers of CCa have the potential to aid in earlier diagnosis and to monitor the effects of therapy on CCa. Laboratory values obtained as part of standard of care shown to have prognostic value for patients with CCa include serum C-reactive protein (CRP), albumin, hemoglobin (Hgb), white blood cell (WBC) count, CRP:albumin ratio or the Glasgow Prognostic Score, neutrophil to lymphocyte ratio, platelet

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count, and bilirubin<sup>10–18</sup>. Human studies conducted among patients with PDAC have also identified candidate circulating biomarkers of CCA which include: pro-inflammatory cytokines (e.g. interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor (TNF)- $\alpha$ , monocyte chemoattractant protein-1 (MCP-1)); transforming growth factor (TGF)- $\beta$  family members (e.g. activin A, growth/differentiation factor (GDF)–15); growth factors (e.g. Insulin-like growth factor binding protein 2 (IGFBP2)); adipokines (e.g. Leptin, Adiponectin); glycoproteins (Zinc- $\alpha$ -glycoprotein (ZAG)); glucagon-like-peptide-1 (GLP-1)) and branched chain amino acids<sup>19–24</sup>. Unfortunately, sample sizes in these studies were limited ranging from 60–99 PDAC cases, with most studies evaluating patients with metastatic disease at the time of blood collection.

Since prior associations with blood-based biomarkers were generally made in patients with advanced disease (who oftentimes were undergoing treatment), these associations may be linked to disease progression rather than CCA. Further, several of these studies were conducted in Asia and may not be racially diverse or generalizable to other racial/ethnic populations<sup>18,25,26</sup>. Of those conducted in the US<sup>21–23,27</sup>, all primarily were comprised of self-reported Non-Hispanic White (NHW) individuals, with only two of these studies<sup>23,27</sup> including self-reported Non-Hispanic Black (NHB) individuals ( $n = 7^{23}$  and  $n = 11^{27}$ ), and only one study<sup>27</sup> including self-reported Hispanic/Latinx (H/L) individuals ( $n = 5$ ).

Collectively, it is apparent that investigations of serum biomarkers of CCA in larger and more racially and ethnically diverse cohorts of newly-diagnosed PDAC cases are lacking. Given that PDAC incidence and mortality rates are highest in NHB participants followed by NHW and H/L participants<sup>28</sup>, it is prudent to focus research efforts on including historically underserved populations in studies of CCA. Thus, the goal of the current study is to investigate levels of candidate serum biomarkers in a diverse cohort of treatment-naïve (i.e., prior to receipt of cancer-related therapy) PDAC cases and determine their association with CCA status and survival by race and ethnicity. Importantly, we assess the added value of a race- and ethnicity-specific panel of biomarkers in predicting clinical outcomes above and beyond standard criteria obtained at the point of care. Our findings suggest that GDF-15 is a useful marker for early (prior to weight loss) cachexia but is racially-influenced.

## Methods

### Study participants

The Florida Pancreas Collaborative (FPC) is a multi-institutional prospective cohort study and biobanking initiative established to advance PDAC research in racially/ethnically diverse populations<sup>29</sup>. Participants in the FPC include 500 individuals with a suspected pancreatic mass presenting to one of the participating study sites. FPC participants meeting the following inclusion criteria were included in this analysis: 1) diagnosed with PDAC; 2) had available pre-treatment blood collection; and 3) were able to have their cachexia status ascertained. A total of 202 participants met these criteria (Supplementary Fig. 1). A subset of 69 participants who had alternative pancreas-associated diagnoses and who had baseline blood available are included in a supplemental analysis as a non-PDAC comparison group (Supplementary Fig. 1, see also supplemental methods). This study was approved by the Moffitt Cancer Center Scientific Review Committee (MCC19717, Pro00029598), and Advarra IRB (IRB00000971). All patients provided informed consent for participation<sup>29</sup>.

### Data collection and clinical outcomes

Demographic, clinical, and epidemiologic data were collected from participants at diagnosis and 6-month follow-up timepoints through: self-administered online- or teleform-based questionnaires; questions administered by the research coordinator at each participating study site; and abstraction from the electronic medical record<sup>29</sup>. Using available data, participant cachexia status was classified using two published categorization schemas. First, we used criteria by Vigano et al.<sup>30</sup>, which classifies the cachexia continuum into 4 stages (non-cachectic (NCA), pre-cachectic (PCA, i.e. those with abnormal labs (within 3 months of diagnosis) or appetite but

who have not lost a significant amount of weight in the last 6 months), cachectic (CA), and refractory cachectic (RCA)) based on clinical, laboratory, functional, and nutritional criteria (used in Fig. 1B). We also used a simplified method for CCA classification described by Fearon et al.<sup>31</sup> based on self-reported weight loss (WL) over the 6 months before PDAC diagnosis, with those having >5% WL or an underweight body mass index (BMI) plus WL > 2% categorized as cachectic, and those with  $\leq$ 5% WL as non-cachectic).

### Blood collection and processing

Blood was collected at diagnosis (pre-treatment) and follow-up timepoints via phlebotomy and processed into serum using previously described methods<sup>29</sup> and stored at  $-80^{\circ}\text{C}$ . Supplementary Table 1 lists all candidate biomarkers, the assay performance, and the percent of samples falling within the detectable range. Detailed methods for assays performed are found in Supplemental Materials. Mean percent coefficient of variation values (CV) (intra-assay variability) for all successful assays are found in Supplementary Table 2, ranging from 1.16% (ENA-78/CXCL5) to 40.02% (Angiotensin II).

### Statistics and reproducibility

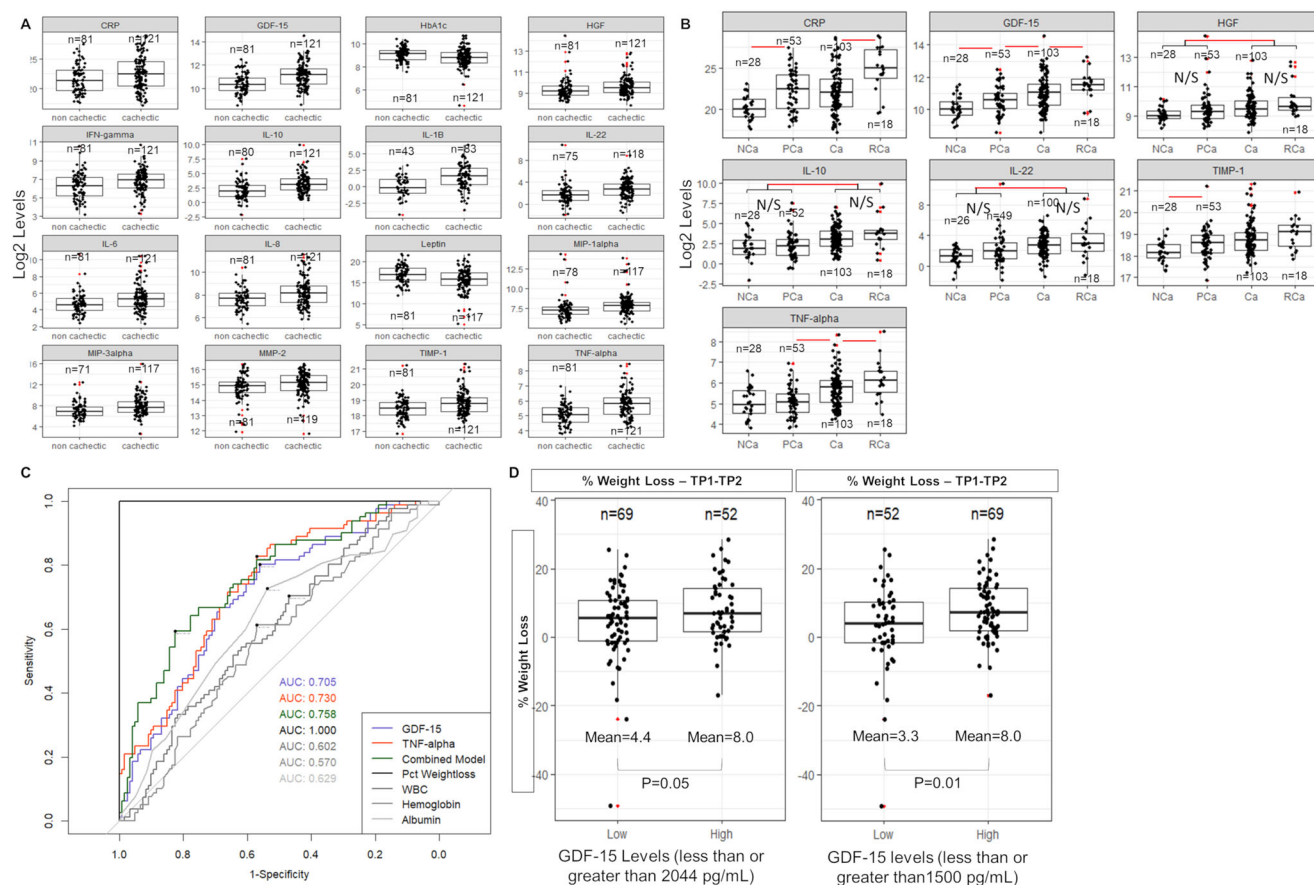
First, we tested for differences in clinicodemographic characteristics according to cachexia status<sup>31</sup>, race and ethnicity, and availability of serum at diagnosis (inclusion criterion) using Pearson's chi-squared test or Fisher's exact test for categorical variables and Wilcoxon rank sum test, analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables. Tukey's Honest Standard Differences or Dunn's test were used to test pairwise comparisons when ANOVA or Kruskal-Wallis tests were performed, respectively.

To test for differences in serum biomarkers according to dichotomous cachexia status<sup>31</sup>, we performed Wilcoxon rank sum tests or Kruskal Wallis tests in the overall study population ( $n = 202$ ) and in subgroups by tumor stage and gender. To understand differences in serum biomarkers across the CCA continuum, we used Kruskal Wallis tests, Cochran-Armitage trend tests and ordinal regression to test for differences across the four-stage and five-stage cachexia status classification systems defined by Vigano et al.<sup>30</sup> and Martin et al.<sup>32</sup>. We then dichotomized biomarkers that significantly differed by CCA status<sup>31</sup> at their medians and used multivariable logistic regression to assess the association of these biomarkers with CCA status<sup>31</sup>. To further test the ability of these biomarkers to identify cachectic patients, we examined their discriminatory capability by generating receiver operating characteristic (ROC) curves to assess the area under the curve (AUC), Youden's Index to identify optimal cut-points, sensitivity, and specificity using the 'pROC' R package<sup>33</sup>. We also performed this ROC analysis using common blood-based biomarkers associated with cachexia status (WBC count, albumin, hemoglobin)<sup>30</sup> and body composition metrics (BMI, waist circumference and waist to hip ratio) as comparisons, and percent WL was used as a positive control.

Considering that unintentional WL is a hallmark of CCA, we identified a subset of patients with body weight data collected at diagnosis and follow-up ( $n = 121$ ) to test for differences in percent WL across the 4-stage cachexia continuum<sup>34</sup> using a Kruskal-Wallis test with pairwise comparisons. Further, we explored differences in weight loss over time for select analytes that significantly differed by CCA status<sup>31</sup> using median splits and published cut-points<sup>35</sup>.

Next, to understand the mediating role of race and ethnicity on biomarkers of CCA, we tested for differences in serum biomarkers by CCA status<sup>31</sup> in subgroups by race and ethnicity using Kruskal Wallis tests. Further, to aid in our understanding of race-based differences in biomarkers of cachexia, we tested for differences in biomarkers by race and ethnicity, irrespective of cachexia status, using Kruskal Wallis tests and multivariable linear regression.

Finally, we examined the association of biomarkers that significantly differed by CCA status<sup>31</sup> with overall survival using Kaplan-Meier curves and log-rank tests. We also used Cox proportional hazards regression ('survival'



**Fig. 1 | Cachectic and pre-cachectic PDAC patients demonstrate significant differences in stress-related markers at baseline and GDF-15 can be used to classify patients into cachexia categories.** Boxplots showing a log-scale value of all significantly different serum biomarkers between cachectic and non-cachectic PDAC patients (A) and when stratified into 4 stages as in Vigano et al. B Nc = non cachectic, Pc = pre cachectic, Ca = cachectic, Rc = refractory cachectic. All plots in (A, B) are significant based on a Wilcoxon rank sum or Kruskal-Wallis test and BH-adjusted  $p$ -value (two-sided hypothesis). Significant differences in serum biomarkers between groups (BH-adjusted pairwise Dunn's test, two-sided hypothesis) are denoted with a red line in (B). Outliers are denoted by a red dot. C ROC curves for

percent self-reported weight loss (Pct Weightloss), GDF-15, TNF-alpha, white blood cell count (WBC), Hemoglobin and Albumin and a combined TNF-alpha \* GDF-15 model (Combined Model) using cachexia status at baseline as the "ground truth". Youden's optimal thresholds are denoted with a black dot. D Boxplot of percent weight loss (negative values indicate weight gain) from baseline to 6-month follow-up time point. Patients were dichotomized based on levels of GDF-15 (Low vs High based on the Youden's threshold values calculated by the ROC in Fig. 2C or by the values used in Groarke et al. (37).  $P$ -values represent a Wilcoxon rank sum test (two-sided hypothesis).

R package) to examine the association of several factors<sup>36</sup> with all-cause mortality. Overall survival time was calculated in months from the date of diagnosis to the date of last contact or death.

Benjamini-Hochberg (BH) method was used to adjust for multiple comparisons where appropriate. All analyses were performed in R version 4.4.0 (RRID:SCR\_000432). All tests were two-sided, and all  $p$ -values were calculated based on non-missing values and considered statistically significant at  $P < 0.05$ .

### Inclusion and ethics statement

This manuscript conforms to the Nature Journal reporting guidelines for reporting on Gender, Race and Ethnicity and other social constructs. Race and Ethnicity were self-reported for these studies due to genetic ancestry not being available for these participants. This research was conducted in the state of Florida and most participants were residents of this US state.

## Results

### Characteristics of the study population by cachexia status

Of 500 patients with a suspected pancreatic mass that were recruited to the FPC study, 318 were confirmed to have a diagnosis of PDAC<sup>29</sup>. Select sociodemographic and clinical characteristics of PDAC cases who donated

blood pre-treatment ( $n = 206$ ) are shown in Supplementary Table 3 (stratified by race and ethnicity). The final analytic dataset includes 202 of the 206 PDAC cases with blood for whom cachexia status could be determined using established criteria<sup>30,31</sup>, and comprised 132 NHW, 30 NHB, and 40 H/L cases (see Table 1 for a high-level overview of patient characteristics, Supplementary Fig. 1 for a flowchart of enrolled patients). At diagnosis, males were significantly more likely than females to be cachectic ( $P = 0.025$ ). Other predictors of CcA included lower BMI ( $P = 0.006$ ), diabetes ( $P = 0.027$ ), and a worse ECOG performance status ( $P < 0.001$ ) (Table 1). A higher proportion of patients with late-stage PDAC (tumor stage III/IV) were classified as cachectic (36.4%) than non-cachectic (32.1%). Cases classified as Ca ( $n = 121$ ) had significantly worse survival than those classified as Nc ( $n = 81$ ) (log-rank  $P = 0.009$ , Supplementary Fig. 2b, Table 1, see Supplementary Fig. 2c for survival stratified by cachectic stage as described by Vigano et al.<sup>30</sup>).

**Characteristics of the study population by race and ethnicity.** The prevalence of cachexia was highest in H/L cases (67.5%) followed by NHB (63.3%) and NHW (55.2%) individuals. H/L patients had lower BMI ( $P = 0.018$ ) than other racial and ethnic groups (Supplementary Table 3). NHB patients presented with more late-stage tumors ( $P = 0.039$ ) than their NHW and H/L counterparts (Table S3). Although NHB individuals

**Table 1 | Sociodemographic and clinical characteristics of Florida Pancreas Collaborative participants with known cachexia status and baseline blood<sup>b</sup> (*n* = 202)<sup>a</sup>**

		<b>NCa (<i>n</i> = 81)</b>	<b>NCa %</b>	<b>Ca (<i>n</i> = 121)</b>	<b>Ca %</b>	<b><i>p</i>-value<sup>c</sup></b>
Age at diagnosis, mean (SD) <sup>d</sup>		68.6 (11.1)		69.0 (10.2)		0.826
Gender <sup>e</sup>	Female	52	64.20%	57	47.11%	<b>0.025</b>
	Male	29	35.80%	64	52.89%	
Race and Ethnicity <sup>e</sup>	Non-Hispanic Black	11	13.58%	19	15.70%	0.442
	Hispanic/Latinx	13	16.05%	27	22.31%	
	Non-Hispanic White	57	70.37%	75	61.98%	
Education <sup>e</sup>	Post-graduate	19	23.46%	10	8.26%	<b>0.003</b>
	Up to college	29	35.80%	31	25.62%	
	Up to high school	9	11.11%	28	23.14%	
	Missing	24	29.63%	52	42.98%	
Income <sup>e</sup>	\$0-\$60,000	17	20.99%	33	27.27%	0.298
	\$60,000-\$100,000	15	18.52%	14	11.57%	
	Over \$100,000	9	11.11%	12	9.92%	
	Missing	40	49.38%	62	51.24%	
Insurance status <sup>e</sup>	Insured	52	64.20%	69	57.02%	0.618
	Uninsured	0	0.00%	2	1.65%	
	Missing	29	35.80%	50	41.32%	
Marital Status <sup>e</sup>	Married	42	51.85%	46	38.02%	0.138
	Unmarried	12	14.81%	26	21.49%	
	Missing	27	33.33%	49	40.50%	
Tumor Stage <sup>e</sup>	I/II	43	53.09%	50	41.32%	0.210
	III/IV	26	32.10%	44	36.36%	
	Missing	12	14.81%	27	22.31%	
Tumor Grade <sup>e</sup>	1 (well-diff)	3	3.70%	2	1.65%	0.759
	2 (moderately diff)	25	30.86%	32	26.45%	
	3 (poorly diff)	14	17.28%	19	15.70%	
	4 (undifferentiated)	0	0.00%	0	0.00%	
	Missing	39	48.15%	68	56.20%	
BMI Category <sup>e</sup>	Underweight	5	6.17%	16	13.22%	<b>0.021</b>
	Normal	20	24.69%	42	34.71%	
	Overweight	29	35.80%	43	35.54%	
	Obese	25	30.86%	18	14.88%	
	Missing	2	2.47%	2	1.65%	
BMI, mean (SD) <sup>d</sup>		27.8 (5.4)		25.7 (5.0)		<b>0.006</b>
Family history of pancreatic cancer <sup>e</sup>	No / Unknown	72	88.89%	119	98.35%	0.817
	Yes	9	11.11%	2	1.65%	
Smoking status <sup>e</sup>	Never	31	38.27%	36	29.75%	0.117
	Former	26	32.10%	37	30.58%	
	Current	2	2.47%	11	9.09%	
	Missing	22	27.16%	37	30.58%	
Age-adjusted CCI <sup>e</sup>	0-5	13	16.05%	15	12.40%	0.597
	>5	68	83.95%	106	87.60%	
	Missing	0	0.00%	0	0.00%	
Diabetes <sup>e</sup>	Yes	20	24.69%	46	38.02%	<b>0.027</b>
	No	35	43.21%	53	43.80%	
	Missing	26	32.10%	22	18.18%	
% Weight loss, median (SD) <sup>d</sup>		1.7 (2.8)		11.2 (5.3)		<b>&lt;0.0001</b>
Waist circumf, median (SD) <sup>d</sup>		36.56 (6.2)		37.80 (15.4)		0.731
Waist-Hip Ratio, median (SD) <sup>d</sup>		0.92 (0.11)		0.92 (0.07)		0.360



**Table 1 (continued) | Sociodemographic and clinical characteristics of Florida Pancreas Collaborative participants with known cachexia status and baseline blood<sup>b</sup> (n = 202)<sup>a</sup>**

		NcCa (n = 81)	NcCa %	Ca (n = 121)	Ca %	p-value <sup>c</sup>
ECOG performance status <sup>a</sup>	0	53	65.43%	38	31.40%	<b>&lt;0.0001</b>
	1	25	30.86%	70	57.85%	
	2	1	1.23%	6	4.96%	
	3-4	0	0.00%	3	2.48%	
	Missing	2	2.47%	4	3.31%	
Survival in days, median (LCL;UCL)	19.7 (15.1;38.8)		15.1 (13.3;17.8)		<b>0.009</b>	

P-values < 0.05 are in bold font.

BMI Body Mass Index, Ca Cachectic, CC/ Charlson Comorbidity Index, NcCa Non-cachectic, LCL/ Lower confidence interval, UCL/ Upper confidence interval, SD standard deviation, circumf circumference

<sup>a</sup>4 NHW patients with baseline blood (out of 206 total participants) could not be assessed for cachexia status due to missing weight values.

<sup>b</sup>Cachexia status according to Fearon et al. (31) with the following modification: skeletal mass index (SMI) was not assessed.

<sup>c</sup>p-values were calculated based on non-missing values/groups only.

<sup>d</sup>p-values represent a Wilcoxon ranked sum test (two-sided hypothesis).

<sup>e</sup>p-values represent a chi square test (two-sided hypothesis).

presented more frequently with late-stage tumors (50.0%) than NHW and H/L patients (37.5% and 29.4%, respectively), NHB patients did not have significantly poorer overall survival (OS) when compared to the NHW patients ( $P = 0.192$ , HR (95%CI):1.37(0.85–2.21) based on a pairwise comparison between group levels with adjustments for multiple testing). H/L PDAC patients in our cohort demonstrated a significantly longer OS time than other groups ( $P = 0.021$ , HR (95%CI): 0.58(0.35–0.97) when compared to NHW patients as a reference, Supplementary Table 3, Supplementary Fig. 2d). Finally, NHW patients were more likely to have a smoking history ( $P = 0.026$ ), and higher age-adjusted Charlson comorbidity index (ACCI) scores ( $P < 0.0001$ ) (Supplementary Table 3).

Importantly, we did not observe any unexpected systematic differences between characteristics of PDAC cases who did and did not have available pre-treatment blood (Supplementary Table 4<sup>29,37</sup>). Unsurprisingly, due to the observational nature of this study and the reliance upon blood collected at the time of standard of care, survival was shorter and ECOG performance score was worse in the group without pre-treatment blood available for research. All participants self-reported gender, race and ethnicity.

### Significant differences were observed between cachectic and non-cachectic PDAC cases overall for multiple serum biomarkers

**Univariate analysis:** Among PDAC cases with versus without CcCa based on weight loss (Fearon et al.)<sup>31</sup>, serum levels of 16 biomarkers were significantly altered (14 increased, 2 decreased) after adjustment for multiple comparisons (Table 2, Fig. 1A). The two most significantly increased markers in cachectic patients were TNF- $\alpha$  and GDF-15 (both ~1.4-fold increase;  $P_{adj} < 0.001$ ).

When stratified into subgroups according to tumor stage, three biomarkers emerged that were significantly elevated in cachectic patients with both early-stage (stage I/II) and late-stage (stage III/IV) tumors: TNF- $\alpha$  ( $P = 0.014$  (early) and  $P = 0.001$  (late)), GDF-15 ( $P = 0.003$  (early) and  $P = 0.018$  (late)), and IL-22 ( $P = 0.004$  (early) and  $P = 0.005$  (late)), see Supplementary Table 5 and Supplementary Fig. 3a). Additionally, we found that IL-6 ( $P = 0.001$ ), MIP3- $\alpha$  ( $P = 0.002$ ), and IL-8 ( $P = 0.009$ ) were significantly higher in cachectic versus non-cachectic PDAC patients with early-stage tumors, but not late-stage (Supplementary Table 5 and Supplementary Fig. 3b).

Further, when we stratified the PDAC cohort by gender, both males and females with Ca demonstrated significant increases in TNF- $\alpha$ , IL-10, IL-22, and GDF-15 compared to NcCa. A decrease in leptin was observed in Ca males compared to their non-cachectic counterparts (Supplementary Table 6, Supplementary Fig. 4a). Intriguingly, for several biomarkers (IL-1 $\beta$ ,

IL-6, IL-8, TIMP-1, and IFN- $\gamma$ ) only females demonstrated significantly increased levels in Ca vs. NcCa cases. In contrast, MIP-3 $\alpha$  was significantly increased in males with Ca but not females (Supplementary Table 6, Supplementary Fig. 4b).

**Exploratory analysis:** In an exploratory analysis using hierarchical clustering, biomarker clustering was not observed by CcCa status (cachectic versus non-cachectic based on Fearon et al.<sup>31</sup>; Supplementary Fig. 5). Analytes with >80% assay success were assessed due to the need for no missingness in the heatmap.

### Pre-cachexia stage can be differentiated by GDF-15 and TIMP-1 levels

**Analytes which differentiate “Pre-cachexia”:** When cachexia status was classified using a 4-stage system<sup>30</sup>, we found that patients with PCa can be differentiated from NcCa patients by CRP, TIMP-1, and GDF-15 (Fig. 1B, Supplementary Table 7). CRP was omitted from further analysis since it was used to stage cachexia<sup>30</sup>. When TIMP-1 and GDF-15 levels were dichotomized at the median, both TIMP-1 ( $P < 0.001$ ) and GDF-15 ( $P < 0.001$ ) were significantly increased over worsening cachexia stage, demonstrating a dose-dependent relationship between these biomarkers and the CcCa continuum. When ordinal regression was performed with TIMP-1 and GDF-15 as dichotomized predictor variables in the same model, GDF-15 remained a significant predictor of cachexia ( $P = 0.021$ ), but TIMP-1 did not. Indeed, GDF-15 remained significantly increased over all four cachexia stages even when adjusting for race and ethnicity, tumor stage, diabetes status, gender, age at diagnosis, and BMI ( $P < 0.001$ , Table 3).

We also assessed GDF-15 levels across the five grades of cachexia as described in Martin et al.<sup>32</sup> to assess the rigor and reproducibility of our findings using other cachexia classification systems. We found that GDF-15 increased over all 5 grades: stage 0 median (LCL-UCL): 1337.8 (1376.9–1972.6); stage 1 median (LCL-UCL): 1466.1 (1252.1–2537.3); stage 2 median (LCL-UCL): 1648.7 (1535.4–2638.8); stage 3 median (LCL-UCL): 2373.1 (2378.9–3646.7); stage 4 median (LCL-UCL): 2496.5 (1988.5–4332.6), though the increases were not statistically significant.

### GDF-15 and TNF- $\alpha$ can be used to predict cachexia status and perform better at cachexia classification than other commonly used classifiers of cachexia

**Regression models for cachexia status:** When dichotomized at the median, both GDF-15 ( $P < 0.001$ , OR = 4.81, 95%CI = 2.3–10.5) and TNF- $\alpha$  ( $P < 0.001$ , OR = 4.10, 95%CI = 1.89–9.34) were predictive of cachexia status when controlling for age at diagnosis, gender, tumor stage, BMI, R&E, and diabetes. Even when including all significant analytes as continuous variables in our model, GDF-15 remained significantly associated with cachexia status ( $P = 0.002$ )

**Table 2 | Medians and 95% confidence intervals for all biomarkers successfully tested, stratified by cancer cachexia status and sorted by adjusted P-value<sup>a</sup>**

Analyte	NcA Median (95% CI), N <sup>^</sup> = 81	Ca Median (95% CI), N <sup>^</sup> = 121	p-value	padj (BH)
TNF-α	33.4 (29.20–38.11)	56.28 (47.38–60.88)	<0.0001	<b>&lt;0.0001</b>
GDF-15	1271.59 (1089.15–1580.91)	2350.48 (1839.82–2584.06)	<0.0001	<b>&lt;0.0001</b>
IL-10	4.03 (2.76–5.80)	8.71 (6.68–10.02)	<0.0001	<b>&lt;0.0001</b>
IL-1β	0.9 (0.61–1.75)	3.2 (1.99–3.81)	<0.0001	<b>0.0001</b>
MIP-1α	152.67 (128.54–189.65)	221.93 (198.28–245.17)	<0.0001	<b>0.0001</b>
IL-22	3.2 (2.41–4.36)	6.73 (5.74–7.70)	<0.0001	<b>0.0001</b>
Leptin	121,996.73 (99,714.82–195,014.3)	53,078.42 (41,015.8–81,891.70)	0.0004	<b>0.002</b>
IL-8	204.15 (171.29–227.34)	289.36 (228.83–341.04)	0.001	<b>0.002</b>
MIP-3α	116.7 (80.70–167.97)	201.14 (145.62–289.25)	0.001	<b>0.002</b>
TIMP-1	35,984.5 (297,299–399,955.9)	44,094.3 (373,440.5–505,823.8)	0.0006	<b>0.002</b>
IL-6	23.69 (19.77–27.97)	38.72 (27.87–46.16)	0.001	<b>0.003</b>
HbA1c	572.02 (501.94–628.48)	452.93 (398.91–486.25)	0.004	<b>0.016</b>
HGF	589.49 (530.90–659.45)	738.63 (624.89–799.84)	0.005	<b>0.016</b>
IFN-γ	79.56 (58.79–103.74)	122.32 (91.13–130.87)	0.005	<b>0.016</b>
CRP	2,549,492 (1,540,626–5,169,510)	5,467,461 (3,175,698–7,392,241)	0.014	<b>0.038</b>
MMP-2	31,317.85 (26,768.12–33,330.05)	36,416.32 (32,430.30–39,551.80)	0.019	<b>0.05</b>
Albumin	2.605×10 <sup>11</sup> (2.51×10 <sup>11</sup> –2.88×10 <sup>11</sup> )	2.475×10 <sup>11</sup> (2.35×10 <sup>11</sup> –2.62)	0.04	0.1
TGF-β2	104.83 (91.51–148.52)	164.95 (120.30–186.15)	0.05	0.116
Glucose	85.98 (81.50–90.53)	96.24 (87.31–104.5)	0.058	0.129
GRO-α	3325.14 (2999.40–4245.34)	4118.13 (3349.83–4805.00)	0.128	0.245
HDL	660.42 (536.03–732.28)	575.99 (507.61–625.35)	0.124	0.245
LDL	21,891.72 (19,329.89–27064.01)	26,342.18 (23,425.72–29,175.56)	0.128	0.245
CCK	348.8 (317.63–400.53)	315.48 (282.10–356.31)	0.171	0.312
a-SMA	1.91 (1.67–2.49)	1.75 (1.59–2.05)	0.31	0.542
PPAR-γ	3.02 (2.51–3.48)	3.07 (2.74–3.80)	0.325	0.545
C-peptide	17,735.02 (13,956.45–21573.20)	20,946.29 (18,047.83–23,274.41)	0.38	0.614
ENA-78	9454.86 (8169.64–11186.14)	8900.89 (6987.64–10847.89)	0.582	0.876
MCP-1	2693.6 (2454.31–2870.71)	2750.78 (2599.75–2910.35)	0.584	0.876
Adiponectin	18,109,809 (15,615,568–22,137,548)	17,150,113 (15,053,026–19,449,897)	0.611	0.885
MDC	11,628.24 (10,809.04–12,579.34)	11,881.88 (11,068.23–12,589.69)	0.887	0.908
g-CSF	110.41 (99.57–133.17)	108.51 (98.73–133.92)	0.842	0.908
Insulin	47.2 (36.08–78.96)	61.29 (46.81–84.58)	0.83	0.908
TGF-β1	63,155.38 (56,232.94–69,420.71)	62,910.25 (56,638.54–69,333.16)	0.751	0.908
Activin A	1085.63 (698.86–1820.03)	1269.07 (870.62–1680.01)	0.677	0.908
Angiotensin II	0.98 (0.40–1.75)	0.46 (0.33–1.58)	0.833	0.908
HIF-1α	748.15 (544.27–1208.91)	759.61 (534.12–1031.64)	0.793	0.908
Laminin	1813.6 (1628.55–2136.06)	1851.53 (1698.74–2038.89)	0.869	0.908
Triglycerides	33.46 (28.99–38.94)	34.63 (29.58–41.86)	0.717	0.908
Fibronectin	193,128,820 (143,159,957–242,481,908)	211,750,040 (15,430,4079–261,156,220)	0.724	0.908
Lumican	1,928,639 (1,662,995–2,294,322)	2,049,788 (1,730,746–2,280,875)	0.716	0.908
ZAG	4,494,004 (4,126,555–5,165,083)	4,784,578 (4,336,660–5,289,872)	0.871	0.908
CA19-9	36.14 (17.89–53.02)	33.87 (21.56–81.78)	0.949	0.949

Adjusted P-values < 0.05 are in bold font and represent a Wilcoxon rank sum test (two-sided hypothesis) with BH adjustment for multiple hypothesis testing.

<sup>a</sup>Number of samples for analytes for which 100% of samples tested were in range.

BH Benjamini-Hochberg, Ca Cachectic, NcA Non-cachectic, p p-value, padj adjusted p-value, LCL lower confidence limit, UCL upper confidence limit.

<sup>a</sup>All values are given in pg/mL except for LDL, PPAR-γ and a-SMA (ng/mL); HbA1c and HDL (ug/mL); Glucose (mg/dL); Triglyceride (nmol/uL); and CA19-9 (U/mL).

**AUC results:** Both TNF-α and GDF-15 had AUC values of >0.7 and these analytes were used to generate a combined model by multiplying the two concentrations together (Fig. 1C). The combined model did have significantly higher AUC than GDF-15 alone ( $P = 0.009$ ) but not better than

TNF-α alone ( $P = 0.76$ ); AUCs for TNF-α and GDF-15 were not significantly different ( $P = 0.730$ ). Other markers such as white blood cell count, hemoglobin, and albumin did not perform better at classification (Fig. 1C, Supplementary Table 8)

**Table 3 | The association of serum biomarker, clinical, and demographic factors with cancer-associated cachexia stage<sup>a</sup>**

Characteristic	OR	95% CI	p-value
GDF-15 levels <sup>b</sup>			<b>0.0002</b>
GDF-15 <Median	—	—	
GDF-15 > Median	3.71	1.83, 7.68	
TIMP-1 levels <sup>b</sup>			0.4
TIMP-1 <Median	—	—	
TIMP-1 > Median	1.38	0.70, 2.73	
IL-6 levels <sup>b</sup>			0.2
IL-6 <Median	—	—	
IL-6 > Median	1.57	0.78, 3.19	
Gender			0.2
Female	—	—	
Male	1.51	0.80, 2.87	
Tumor Stage			0.09
1/2	—	—	
3/4	1.71	0.92, 3.21	
BMI			0.2
normal	—	—	
underweight	1.45	0.47, 4.57	
overweight	0.71	0.33, 1.51	
obese	0.49	0.20, 1.15	
Race/Ethnicity			0.1
NHW	—	—	
NHB	1.98	0.77, 5.16	
H/L	2.32	1.01, 5.46	
Diabetes			>0.9
no/no information	—	—	
yes	1	0.51, 1.93	
Age at Diagnosis <sup>c</sup>			0.3
<50	—	—	
≥50	2	0.53, 7.52	

OR Odds ratio, CI Confidence interval, NHW Non-Hispanic white, NHB Non-Hispanic black, H/L Hispanic/Latinx, BMI Body mass index.

<sup>a</sup>Ordinal regression was performed using cachexia stage (based on the Vignano et al. classification) as the response variable and GDF-15, IL-6, race/ethnicity, age, sex, diabetes, BMI or tumor stage as predictor variables. *P*-values < 0.05 are in bold font and represent ordinal linear regression model with a one-sided hypothesis.

<sup>b</sup>Patients were separated into two groups based on their analyte levels (via a median split).

<sup>c</sup>Patients were dichotomized into two age groups according to age at diagnosis.

### GDF-15 levels predict future weight loss

**Weight loss over time stratified by GDF-15 levels at baseline:** Patients with high GDF-15 levels at diagnosis (based on the optimal ROC threshold of 2044.7 pg/mL) lost a mean of 8.0% body weight and patients with low GDF-15 lost a mean of 4.4% body weight ( $P = 0.05$ , Fig. 1D) in the 6 months after GDF-15 assessment. Patients with high GDF-15 levels at diagnosis (defined by Groarke et al.<sup>35</sup>, 1500 pg/mL) lost a mean 8.0% body weight compared to patients with a low GDF-15 levels (3.3% body weight,  $P = 0.01$ , Fig. 1D) in the 6 months after GDF-15 assessment. TNF- $\alpha$  levels and combined levels of GDF-15 and TNF- $\alpha$  did not significantly predict weight loss over the same time period ( $P = 0.17$  and  $P = 0.06$  for TNF- $\alpha$  and combined model, respectively).

**Verification of weight loss for individuals classified as PCa:** As verification of the Vignano et al. cachexia classification, we compared weight loss in the 6 months post-diagnosis for participants classified as NCa or PCa.

Individuals classified as PCa lost more weight than individuals classified as NCa (median/SD = 2.2%/12.7 for non-cachectic individuals and 7.7%/9.7 for pre-cachectic individuals) in the 6 months post-diagnosis, though the difference is not significant ( $P = 0.10$ ). Furthermore, a greater proportion (70.8%, or 17 out of 24) of PCa individuals lost >5% of their body weight over the 6 months post-diagnosis as compared to the NCa group (40.0% or 8 out of 20) but this also did not achieve significance ( $P = 0.22$  via Fisher's Exact test).

### Stratification by race and ethnicity (R&E) reveals novel biomarkers of CCa for NHW and H/L participants, but not NHB participants

Of the serum biomarkers significantly deregulated in cachectic<sup>31</sup> PDAC cases overall (Table 2), several continued to show differences by R&E. For instance, GDF-15, IL-22, MIP-1 $\alpha$ , TIMP-1, and TNF- $\alpha$  levels were significantly higher in H/L and NHW PDAC cases with CCa than those without CCa. Although statistically significant differences were not observed for any of these biomarkers by CCa status among NHB cases (Fig. 2, Supplementary Table 9), TNF- $\alpha$  and IL-22 levels did trend upwards for NHB cachectic patients, similar to the other R&E groups (Fig. 2). In contrast to H/L and NHW cases, GDF-15 did not show any difference by cachexia status in NHB cases ( $P_{\text{adj}} = 0.95$ ). Intriguingly, we observed that NHW and H/L patients with cachexia had median GDF-15 levels that far exceeded 1500 pg/mL, but NHB patients with cachexia had a median GDF-15 level of 1488 pg/mL<sup>35</sup> (Supplementary Table 9).

### Racial and ethnic variation is apparent for neutrophil- and stress-linked cytokine biomarkers ENA-78/CXCL5 and GRO- $\alpha$ /CXCL1, independent of CCa or pancreas tumor type

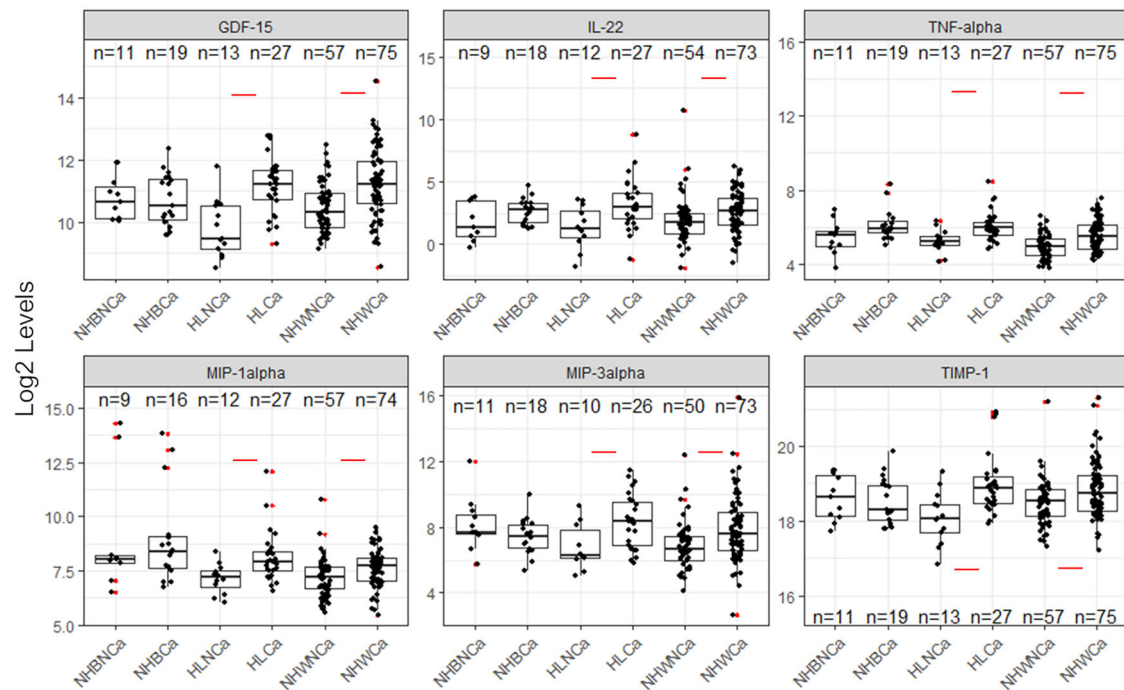
A total of 15 biomarkers had significantly different expression levels when comparing NHB, H/L, and NHW PDAC cases with baseline blood ( $n = 206$ ) (Supplementary Table 10). 2 of the 13 biomarkers were significantly elevated in NHB participants compared to both NHW and H/L cases and included GRO- $\alpha$ /CXCL1 ( $P < 0.001$ ) and ENA-78/CXCL5 ( $P < 0.001$ ) (Supplementary Table 10, Fig. 3A).

In response to finding higher ENA-78/CXCL5 and GRO- $\alpha$ /CXCL1 in NHB patients, we performed an *ad hoc* analysis further stratifying by cachexia status for ENA-78/CXCL5 and GRO- $\alpha$ /CXCL1. These analyses revealed that ENA-78/CXCL5 and GRO- $\alpha$ /CXCL1 levels were unchanged for any R&E group regardless of cachexia status<sup>31</sup> (Fig. 3B). When using linear regression with either ENA-78/CXCL5 or GRO- $\alpha$ /CXCL1 as response variables and R&E, cachexia status<sup>31</sup>, tumor stage, gender, and BMI as predictor variables, NHB patients demonstrated significantly increased ENA-78/CXCL5 and GRO- $\alpha$ /CXCL1 compared to other R&E groups (Supplementary Table 11). Furthermore, when ENA-78/CXCL5 and GRO- $\alpha$ /CXCL1 levels were compared by R&E in patients with other pancreatic conditions from the FPC cohort, NHB individuals continued to demonstrate significantly elevated baseline levels of these biomarkers compared to other R&E groups (Fig. 3C).

Since both GRO- $\alpha$ /CXCL1 and ENA-78/CXCL5 are linked to neutrophil function<sup>38,39</sup>, the serum neutrophil to lymphocyte ratio (NLR) was calculated using abstracted clinical data and tested for differences by R&E using a Kruskal-Wallis test. We found that NHB PDAC patients had significantly lower NLR than H/L and NHW patients ( $P < 0.001$  for both pairwise comparisons; Fig. 3D). Our data indicate that both higher levels in total lymphocyte count and lower levels in neutrophil count in NHB participants are responsible for this measure.

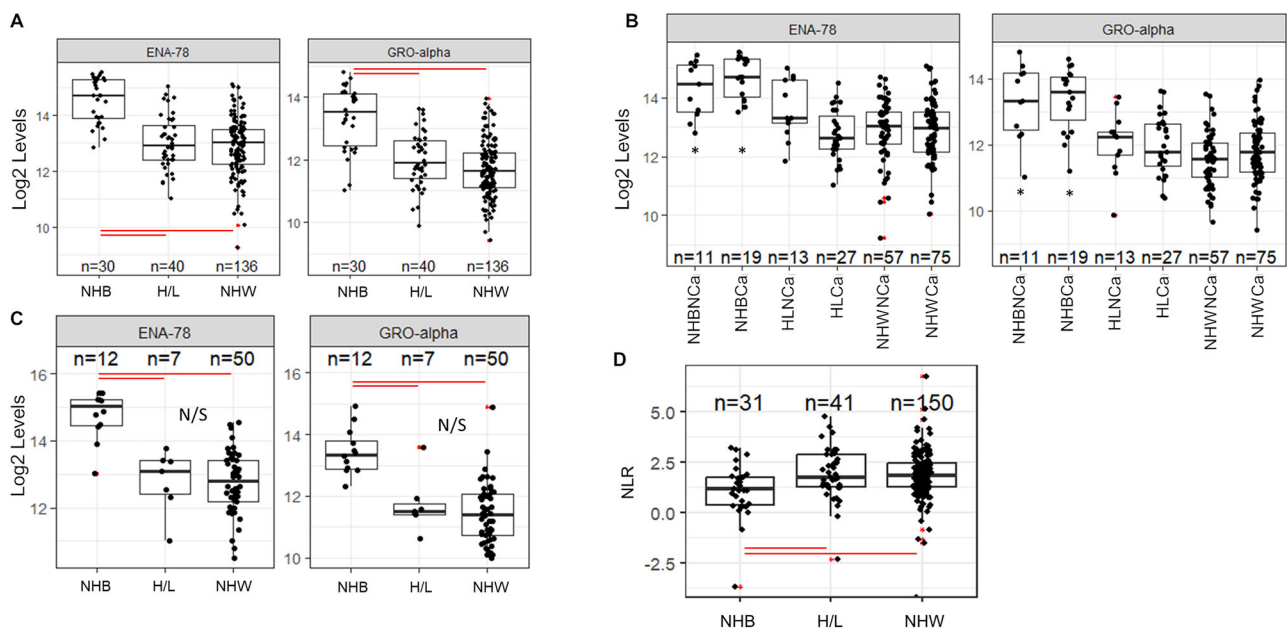
### Survival is predicted by inflammatory and proliferative cytokine levels

Among all biomarkers that were significantly different in Ca vs NCa PDAC patients (based on the Fearon criteria<sup>31</sup>), GRO- $\alpha$ , CRP, TNF- $\alpha$ , GDF-15, HGF, IL-10, IL-6, IL-8, and TIMP-1 were independent predictors of all-cause mortality in the PDAC cohort as continuous variables in univariate analyses (Supplementary Table 12). However, after dichotomizing these



**Fig. 2 | Both NHW and H/L participants demonstrate significant differences between non cachexia and cachexia status in stress-related markers at baseline.** Boxplots showing a log-scale value of serum biomarkers which are significantly different between cachectic and non-cachectic PDAC patients for at least two R/E's stratified into Non-Hispanic Black, Hispanic/Latinx and Non-Hispanic White

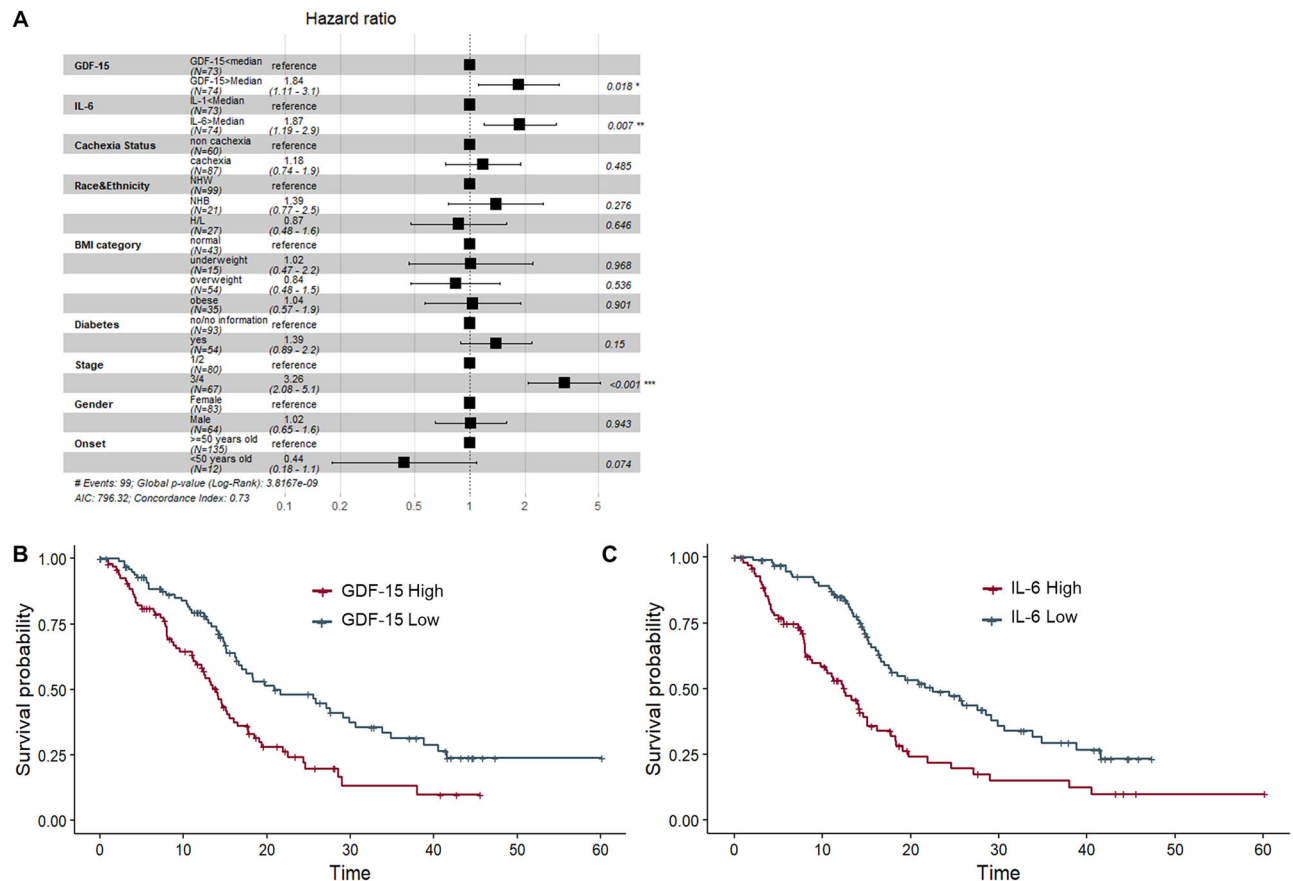
patients. Significance was determined by Kruskal-Wallis test (BH-adjusted) followed by a BH-adjusted Dunn's pairwise test (two-sided hypothesis). NHB Non-Hispanic Black, H/L Hispanic/Latinx, NHW Non-Hispanic White, Nc non cachectic, Ca cachectic. Significant differences in serum biomarkers between groups are denoted with a red line. Outliers are denoted by a red dot.



**Fig. 3 | PDAC and other patients demonstrate wide racial variation in select serum biomarkers at baseline.** A Boxplots showing a log-scale value of select significant biomarkers when PDAC R/E groups are compared (ENA-78/CXCL5 and GRO- $\alpha$ /CXCL1) and B when stratified into cachexia groups (NHB Non-Hispanic Black, HL Hispanic/Latino, NHW Non-Hispanic White, Nc non cachexia, Ca Cachexia). C Boxplots showing ENA-78 and GRO-alpha levels for non-PDAC

diagnoses. D Boxplot of neutrophil to lymphocyte ratio (NLR) for PDAC patients in the study. Significant differences between relevant groups are denoted with a red line. Significance between NHBnCa/NHBNCa and all other groups is denoted with a \*. Significance was determined by Kruskal-Wallis test (BH-adjusted) followed by a BH-adjusted Dunn's pairwise test (two-sided hypothesis). N/S not significant. Outliers are denoted by a red dot.





**Fig. 4 | GDF-15 and IL-6 are linked to overall survival in both CoxPH models and by Kaplan estimation.** A Forest plot of dichotomized analytes found to be associated with survival as continuous variables in a univariate analysis when controlled for demographic and patho-clinical variables. NHB Non-Hispanic Black, H/L Hispanic/Latinx, NHW Non-Hispanic White, NCa non cachectic, Ca Cachectic. P-values represent a pairwise comparison of the adjusted CoxPH model relative to

the reference group (two-sided hypothesis). Median levels of GDF-15 (B) or IL-6 (C) were calculated and participants were classed into either low (Low) or high (High) groups based on a median split. B, C represent Kaplan-Meier survival curves (Time = time to event in months) for GDF-15 ( $P = 0.003$ ) and IL-6 ( $P < 0.0001$ ), respectively. P-values represent global p-values of the survival analysis (two-sided hypothesis).

analytes via a median split and controlling for BMI, R&E, stage, cachexia status, gender, diabetes and age at diagnosis (Fig. 4A), GDF-15, IL-6 and tumor stage remained significant predictors of all-cause mortality. Furthermore, when dichotomized at the median, high GDF-15 and high IL-6 are associated with shorter overall survival (Log-rank  $P = 0.003$  and  $P < 0.001$  for GDF-15 and IL-6, respectively; Fig. 4B, C).

## Discussion

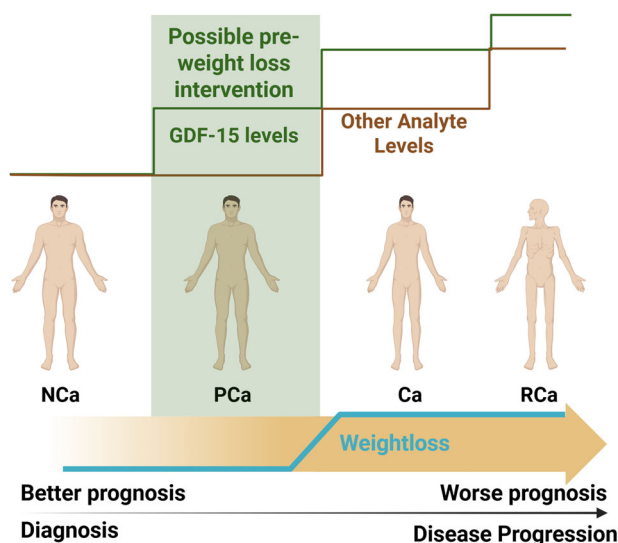
The FPC cohort represents one of the most racially and ethnically diverse group of PDAC and patients with other pancreatic-related conditions, with CCA status and available serum biomarker data analyzed to date<sup>18–25,40–44</sup>.

In the current investigation, GDF-15, also known as macrophage inhibitory cytokine 1 (MIC1), was identified as an important marker of pre-cachexia which continues to increase through the cachexia continuum, and which predicts survival among male and female H/L and NHW participants. GDF-15 is a pleiotropic molecule involved in the pathophysiology of cancers and other conditions and is tightly linked to stress pathways<sup>45–47</sup>. It is known as a key biomarker of stress, dysfunctional metabolism and energy production and has emerged as an attractive therapeutic target for obesity/metabolic disorders, cachexia, and immunotherapy<sup>35,48,49</sup>. Anti-GDF-15 monoclonal antibody treatment with ponesgromab is both well tolerated and may reverse anti-PD-L1 resistance in clinical trials<sup>50,51</sup>, thus this treatment modality may be useful in contexts other than CCA. In contrast to others<sup>52</sup>, we did not observe sexual dimorphism in cachexia-related GDF-15 upregulation<sup>53</sup>. Importantly, this molecule is found to be upregulated in the blood of patients with both early (I/II) and late (III/IV) stage tumors,

suggesting that increases in GDF-15 are not secondary to cancer progression. Furthermore, our findings suggest that GDF-15 levels should be interpreted with caution in the NHB population as this molecule may not be useful as a marker for cachexia due to the possibility of false negatives and given that GDF-15 did not significantly differ by cachexia status in NHB patients. Importantly, GDF-15 was one of only two markers which was predictive of “pre-cachexia” status.

Early identification and intervention for cancer-related cachexia is key to alleviating the negative outcomes associated with this condition<sup>5,21,30,34,52,54</sup>. Ponesgromab has shown great promise in clinical trials<sup>35,50</sup> but, notably, this trial did not include any NHB individuals. The Phase II trial of Ponesgromab used elevated GDF-15 ( $> 1500$  pg/mL) as an inclusion criteria. The observed difference in GDF-15 levels by R&E in cachectic patients may therefore explain the lack of inclusion of NHB individuals in this trial. Furthermore, our ROC results suggest that the Youden threshold for classification of cachexia with GDF-15 (2045 pg/mL) is somewhat higher than the inclusion cutoffs used in this trial. Importantly, in our PDAC cohort, patients with levels  $> 1500$  pg/mL at baseline are at greater risk for losing weight in the upcoming months. Thus, these findings not only underscore the importance of minority inclusion in clinical trials but are valuable from an interventional standpoint to identify H/L and NHW populations with pre-cachexia.

For non-NHB PDAC patients, our findings suggest that GDF-15 can be used to differentiate early cachexia from non-cachexia. Further cementing our findings, high levels of GDF-15 were found to predict greater weight loss in the 6 months after assessment. Collectively, our findings



**Fig. 5** | Overview of IL-6 and GDF-15 levels throughout the cancer-associated cachexia continuum.

suggest that GDF-15, while less predictive of survival outcomes (than e.g. IL-6), has utility as an *early* marker of metabolic stress and can be useful to predict weight loss. Thus, there may be a clinical benefit to evaluating GDF-15 levels as soon as possible after a probable PDAC diagnosis is made to alert clinicians of potential future weight loss and supportive care needs necessitating intervention (Fig. 5, created in biorender.com). However, this benefit would only be for NHW and H/L patients until a more reliable biomarker of cachexia can be discerned for NHB patients.

The role of GDF-15 and race is understudied. However, some studies, including a prostate cancer risk study by Rybicki et al.<sup>55</sup>, observed lower GDF-15 expression in male NHB participants. Contrary to these findings, a 2012 study identified Black race as being predictive of higher plasma GDF-15 levels in a study of atherosclerosis<sup>56</sup>. Hence, this work represents the first time that GDF-15 has been studied in the context of a response to metabolic stress (cachexia) and race. Collectively, these findings suggest that monitoring of weight/weight loss is paramount in the diagnosis of CCa in NHB patients, as biomarkers of CCa for this population remain elusive.

One intriguing finding that emerged from this study is that, although TNF- $\alpha$  and IL-22 did not reach significance for the smaller NHB group in our PDAC cohort, the means did trend upwards for these two markers in cachectic NHB patients, in stark contrast to GDF-15 and TIMP-1. Thus, these molecules may warrant further investigation as racially agnostic indicators of metabolic stress. TNF- $\alpha$  may be of special interest, as this molecule has long been studied as a metabolic stress and inflammatory cytokine<sup>57,58</sup>. Our data demonstrate that NHB and H/L participants have slightly higher circulating TNF- $\alpha$  levels than NHW participants, concordant with published literature and secondary to increased chronic or acute social stressors experienced by minority groups that increase inflammation<sup>59,60</sup>. Higher baseline levels of TNF- $\alpha$  in minorities may thus serve to blunt increases in this cytokine related to cachectic stress.

Another molecule we found to be predictive of PCa is the tissue inhibitor of metalloproteinases, TIMP-1<sup>61</sup>. TIMP-1 is a pro-inflammatory cytokine associated with proliferative processes<sup>61</sup>. Although TIMP-1 is not known to be associated with GDF-15 activity in cancer, TIMP-1 and GDF-15 were weakly correlated in a study of cardiovascular disease in aging patients, suggesting a prognostic use for these markers in a fingerprint<sup>62</sup> to better predict cachexia status.

Other main findings are the distinct racial differences in the aging/inflammatory biomarkers ENA-78/CXCL5 and GRO- $\alpha$ /CXCL1<sup>20,40,63</sup>. ENA-78/CXCL5 and GRO- $\alpha$ /CXCL1 are of particular interest, as they are upregulated in NHB patients *independent of CCa status and pancreas-related diagnosis*. ENA-78/CXCL5 is a member of the CXC chemokine

family and is involved in neutrophil signaling and recruitment<sup>64</sup>. Similarly, the chemokine CXCL1 is an angiogenic inflammatory marker which has been linked to neutrophil recruitment and migration of adipose stromal cells into the tumor microenvironment<sup>65</sup>. ENA-78/CXCL5 has been shown to promote pancreatic cancer cell growth, migration, and invasion, and to predict poor prognosis<sup>66–68</sup>. Other findings indicate that GRO- $\alpha$ /CXCL1 and ENA-78/CXCL5 are associated with stress due to social disruption, adult adversity and/or psychological comorbidity in chronic pain disorders<sup>69,70</sup>. Moreover, these signaling molecules have been associated with PDAC immune evasion<sup>67,71</sup>, lending credence to a racially unbalanced CXCL1/5-signaling “tumor-friendly” environment. We find that a higher circulating CXCL1/ENA-78/CXCL5 signature is associated with the NHB race, but *not* with higher circulating neutrophils in NHB patients in agreement with published literature<sup>72</sup>, suggesting that this minority group may be desensitized to cytokine-mediated neutrophil mobilization or signaling.

Interestingly, the cytokine in our panel with the strongest association with overall survival was IL-6. Consistent with other reports, IL-6 was *strongly* associated with worse survival in PDAC patients in our study<sup>73</sup>, suggesting a renewed interest in this prognostic marker may be warranted.

Our cohort of patients was recruited not only from academic centers, but also from community hospitals in the area<sup>29,74</sup> representing a more “real-world” scenario regarding choice of therapy, outcomes, and racial and ethnic diversity than many previous studies. Nevertheless, a limitation of the study is that none of the participants were “normal” healthy controls because all participants presented with a suspicion of a pancreatic mass. In addition, we note large variability in analyte levels (including GDF-15 levels)<sup>35</sup>, suggesting that GDF-15 is not universally upregulated during the cachectic state. Nevertheless, all reliably dysregulated biomarkers chosen for further evaluation from our panel, including GDF-15, had an intra assay variability of <20%. Furthermore, we note that decreased survival for patients with high IL-6 or high GDF-15 could plausibly be due to other tumor-related characteristics. Finally, although our PDAC cohort was more diverse than others, including clinical trials of cachexia therapies, there were only 30 NHB PDAC patients with baseline blood available. Thus, sample size is a limitation for this study, especially considering multiple stratification strategies, and larger follow-up studies are needed to validate these findings. We argue that trials aimed at specifically recruiting minority populations are crucial to fully understanding the nature of racial disparities in CCa and PDAC and that eligibility criteria may perpetuate these disparities due to lack of minority enrollment and participation<sup>75</sup>. Future studies by this group will investigate a possible link between adipose tissue deposition, cytokine signaling, race and PDAC progression.

## Conclusions

GDF-15 has emerged as a promising cachexia biomarker and is specifically increased prior to weight loss for *non-NHB* PDAC patients. Furthermore, although GDF-15 did not associate with cachexia status/weight loss in NHB patients, it was associated with survival even when controlled for R&E. Future work should endeavor to ensure that minority participants are well represented in PDAC cohorts so that the true biomarker landscape is evaluated from diverse populations. Furthermore, these studies suggest that gender should be included in any cachexia biomarker evaluation.

In addition to our GDF-15 findings, we report that the serum cytokine landscape for NHB PDAC patients is decidedly neutrophil-linked and pro-inflammatory compared to either other minorities (H/L participants) or NHW participants, but that circulating neutrophils are lower in the NHB individuals. Caution should be taken in interpreting these findings, however, to avoid over-simplifying the complex interplay between genetic background, social stressors, R&E, and the metabolic stress response resulting from cancer-associated WL.

## Data availability

A source file of all analyte levels, neutrophil and lymphocyte counts, longitudinal weight loss, cachexia status, diagnosis and survival data for all patients with baseline blood available for analysis (including non-PDAC

diagnoses) can be found in Supplementary Dataset 1. Source data for Figs. 1–4 can be accessed in Supplementary Dataset 1.

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J.B.P. conceived the study jointly with A.R.J. M.A.P. and E.W.D. designed and implemented the analyses and prepared the manuscript; Q.M. provided statistical support, A.B.M. and S.S. performed the cytokine assays, K.J. provided pathology analyses. M.A.P., E.W.D., S.A., J.P.A., T.L.B., M.B., T.L.C., T.B.deC., D.T.C., E.M.C., S.L.C., M.G.D. W.G.D., J.B.F., P.H., K.L.H., K.J., D.W.K., J.K., A.K.L., M.M., A.A.M., R.M., N.B.M., K.M., Q.M., M.A.M.-V., L.M.-U., K.D.O., N.P., J.M.P., G.R., K.A.R., L.M.S., P.S., A.F.T., J.K.T., D.V.T., J.G.T., V.V., C.J.W., D.J., S.M.J., A.R.J., and J.B.P. edited the manuscript.



## Competing Interests

J.M.P. is a consultant for ASTELLAS, J&J Worldwide, Ferranova, and ADVOCARE. All other authors noted that they have no conflicts or perceived conflicts of interest related to this work.

## Additional information

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