# *Postdiagnosis Loss of Skeletal Muscle, but Not Adipose Tissue, Is Associated with Shorter Survival of Patients with Advanced Pancreatic Cancer*

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# Post diagnosis loss of skeletal muscle, but not adipose tissue, is associated with shorter survival of patients with advanced pancreatic cancer

**Ana Babic**[1,*], **Michael H. Rosenthal**[1,2,*], **William R. Bamlet**[3], **Naoki Takahashi**[3], **Motokazu Sugimoto**[3], **Laura V. Danai**[4], **Vicente Morales-Oyarvide**[1], **Natalia Khalaf**[5], **Richard F. Dunne**[6], **Lauren K. Brais**[1], **Marisa W. Welch**[1], **Caitlin L. Zellers**[1], **Courtney Dennis**[7], **Nader Rifai**[8], **Carla M. Prado**[9], **Bette Caan**[10], **Tilak K. Sundaresan**[11], **Jeffrey A. Meyerhardt**[1], **Matthew H. Kulke**[1,12], **Clary B. Clish**[7], **Kimmie Ng**[1], **Matthew G. Vander Heiden**[1,13], **Gloria M. Petersen**[3,#], **Brian M. Wolpin**[1,#]

[1]Dana-Farber Cancer Institute, Boston, MA

[2]Department of Radiology, Brigham and Women's Hospital, Boston, MA

[3]Mayo Clinic Cancer Center, Rochester, MN

[4]Department of Biochemistry and Molecular Biology, University of Massachusetts Amherst, Amherst, MA

[5]Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, Boston, MA

[6]Division of Hematology/Oncology, University of Rochester Medical Center, Rochester, NY

[7]Broad Institute of MIT and Harvard University, Cambridge, MA

[8]Department of Pathology, Boston Children's Hospital, Boston, MA

[9]Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Canada

[10]Kaiser Permanente Division of Research, Oakland, CA

[11]Kaiser Permanente San Francisco, San Francisco, CA

[12]Boston University and Boston Medical Center, Section of Hematology/Oncology, Boston, MA

[13]Koch Institute for Integrative Cancer Research and Department of Biology, Massachusetts Institute of Technology, Cambridge, MA

## Abstract

**Background:** Pancreatic cancer is associated with development of cachexia, a wasting syndrome thought to limit survival. Few studies have longitudinally quantified peripheral tissues or identified biomarkers predictive of future tissue wasting.

**Corresponding author:** Dr. Ana Babic, 450 Brookline Avenue, Boston, MA 02215, Phone: +1-617-582-9983, ababic1@partners.org.
*Authors share co-first authorship
#Authors share co-last authorship

**Methods:** Adipose and muscle tissue were measured by computed tomography at diagnosis and 50–120 days later in 164 patients with advanced pancreatic cancer. Tissue changes and survival were evaluated by Cox proportional hazards regression. Baseline levels of circulating markers were examined in relation to future tissue wasting.

**Results:** Compared to patients in the bottom quartile of muscle change per 30 days (average gain of 0.8 ± 2.0 cm2), those in the top quartile (average loss of 12.9 ± 4.9 cm2) had a hazard ratio (HR) for death of 2.01 (95% CI, 1.12–3.62). Patients in the top quartile of muscle attenuation change (average decrease of 4.9 ± 2.4 Hounsfield units) had a HR of 2.19 (95% CI, 1.18–4.04) compared to those in the bottom quartile (average increase of 2.4 ± 1.6 Hounsfield units). Changes in adipose tissue were not associated with survival. Higher plasma branched chain amino acids (BCAAs; P=0.004) and lower monocyte chemoattractant protein-1 (MCP-1; P=0.005) at diagnosis were associated with greater future muscle loss.

**Conclusions:** In patients with advanced pancreatic cancer, muscle loss and decrease in muscle density in two to four months after diagnosis were associated with reduced survival. BCAAs and MCP-1 levels at diagnosis were associated with subsequent muscle loss.

**Impact:** BCAAs and MCP-1 levels at diagnosis could identify a high-risk group for future tissue wasting.

### Keywords

Pancreatic cancer; patient survival; cancer cachexia; muscle loss; adipose tissue loss; biomarkers

## Introduction

Patients with advanced pancreatic cancer have particularly poor survival, with overall 5-year survival less than 10% (1). Several factors are thought to limit patient survival, including a tissue wasting syndrome commonly referred to as cachexia (2). An international expert consensus defined cachexia as >5% weight loss over past 6 months, >2% weight loss in patients with body mass index (BMI)<20, or appendicular skeletal mass consistent with sarcopenia (2).

Nevertheless, studies have examined pancreatic cancer associated cachexia and patient outcomes with differing results, likely due to differing definitions of cachexia, measurement approaches, and study designs (3–5). In most studies, body composition was measured only at diagnosis. These static pre-treatment measurements may not capture the dynamic nature of tissue wasting and its relationship with patient survival.

Cachexia is thought to occur in up to 80% of patients with advanced pancreatic cancer during the course of their disease (6). While several biomarkers for detecting cachexia in newly diagnosed patients have been described (7), there are currently no validated biomarkers that predict the severity of future wasting in the period following diagnosis. Among the most studied candidates are inflammatory cytokines interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) (7), and monocyte chemoattractant protein-1 (MCP-1) (8). We have previously demonstrated that circulating branched chain amino acids (BCAAs; isoleucine, leucine, and valine) are liberated from tissues in mouse models and patients with

early pancreatic cancer (9). However, the ability of these circulating markers to predict future tissue wasting is not known.

We measured tissue compartments using CT imaging, a precise and reproducible method for tissue quantification in cancer patients (10), before treatment and at restaging in patients with advanced pancreatic cancer. Using these imaging studies, we examined whether changes in tissue compartments predicted patient survival, and whether circulating markers measured at the time of cancer diagnosis could identify patients at higher risk of future tissue wasting.

## Methods

### Study population

This study included patients from Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC) (N=117) and Mayo Clinic (N=47) with the following requirements: (1) diagnosed with advanced pancreatic ductal adenocarcinoma between 2000–2015, (2) available CT scan prior to receiving any cancer-directed treatment, including surgery, chemotherapy or radiation, (3) available follow-up CT scan 50–120 days after the baseline scan, which is the common time interval of the first restaging scan to evaluate treatment efficacy, and (4) stored pre-treatment plasma sample obtained within 30 days before to 60 days after cancer diagnosis. From a population of patients previously evaluated in a cross-sectional study of tissue compartments and patient outcomes (11), 164 patients met the four requirements (Figure 1). The study was approved by Institutional Review Boards of Dana-Farber/Harvard Cancer Center and Mayo Clinic. All patients provided informed consent.

### Computed tomography analysis of body composition

CT scans were acquired as part of regular clinical care using imaging hardware and acquisition protocols from multiple institutions. Reconstructed slice thicknesses were 5 mm in 92% of patients, 3 mm in 5% and other values 1–5 mm in 2%. Skeletal muscle, visceral adipose tissue, and subcutaneous adipose tissue areas were measured on axial CT images at the level of the L3 vertebral body, as previously described (11). Skeletal muscle index (SMI) was calculated as the ratio of muscle area ($cm^2$) to squared height ($m^2$). We also measured muscle attenuation, a marker of muscle density, which can capture the intramuscular accumulation of lipid droplets (12). Mean muscle attenuation was calculated as the average CT attenuation in Hounsfield units across all pixels in the labeled muscle region. Pretreatment and restaging scans were concordant for intravenous (IV) contrast administration in 97% of patients, with 97% of scans performed with IV contrast. Since administration of IV contrast may affect muscle attenuation measurements on CT imaging (13), the five patients with discordant IV contrast use were excluded from the analyses of muscle attenuation with patient survival and biomarker levels. Scans from DF/BWCC were analyzed by manual segmentation using Slice-O-Matic software (v4.3; Tomovision, Montreal, Canada) (11). Images were analyzed by trained image analysts blinded to study question, study design and image order (baseline vs. follow-up scan). Aggregate intra-analyst coefficients of variation (CV) were 0.53% for muscle (individual reader range: 0.48–1.14%), 0.44% for subcutaneous adipose (0.19–0.55%), and 0.66% (0.41–0.97%) for

visceral adipose tissue. Final data verification was performed by a board-certified radiologist. Scans from Mayo Clinic were analyzed using software developed at the Mayo Clinic with manual review by radiologists at that site. A version of this software was described by Weston *et al* (14). To calculate the variation between analysis methods used at the two study sites, we analyzed scans from 20 patients using both methods, and obtained similar results, with CV of 2.4% for muscle, 3.8% for visceral adipose tissue, and 1.7% for subcutaneous adipose tissue.

### Plasma marker measurements

Plasma isoleucine, leucine and valine were measured by liquid chromatography tandem mass spectrometry (LC-MS) as previously described (11). The mean CVs were 7.6% for isoleucine, 8.0% for leucine, and 7.3% for valine. Total plasma BCAAs were derived by summing the concentrations of individual BCAAs. We previously measured plasma IL-6, MCP-1, and soluble tumor necrosis factor receptor type II (sTNF-RII) in a subset of 92 patients (15). sTNF-RII is an established surrogate for TNF-α due to its lower diurnal variation and higher stability in frozen samples (16). CVs were calculated using blinded duplicate samples, and were 3.6% for IL-6, 10.5% for MCP-1, and 6.1% for sTNF-RII.

### Covariate data

Patient demographic, clinical, and treatment data were obtained from medical records and patient questionnaires, including age, sex, height, weight at the time of diagnosis, race/ethnicity, smoking status, history of diabetes, year of diagnosis, cancer stage, cancer treatment type and duration, and date of death or last follow-up visit.

### Statistical analysis

To evaluate the association between change in body composition and patient survival, we used multivariate Cox proportional hazards regression models and calculated hazards ratios (HR) and 95% confidence intervals (CI). Overall survival was defined as time from diagnosis to death from any cause or end of follow-up, whichever came first. In an initial multivariate model, we adjusted for age at diagnosis (years), study site (DF/BWCC, Mayo Clinic), race (white, non-white), baseline body composition measurement (continuous), sex, year of diagnosis (2000–2010, 2011–2015), and disease stage (locally advanced, metastatic). In the second multivariate model, we additionally adjusted for BMI (continuous), smoking history (never, past, current, unknown), history of diabetes (no diabetes, diabetes duration ≤4 years, diabetes duration >4 years, unknown), and type of treatment (FOLFIRINOX/FOLFOX/FOLFIRI, gemcitabine/ gemcitabine combination, chemoradiation, no treatment/ unknown). We calculated median survival times for patents in each quartile of body composition change using direct adjusted survival estimation (17). Change in body composition was expressed as the difference per 30 days in tissue measurements between the follow-up and baseline CT scans. Due to differences in body composition change by sex, we calculated sex-specific quartiles of change for each measurement. The bottom quartile (*i.e.*, patients with the least change) was taken as the reference group, and a *P*-value for trend was evaluated by entering the median value of sex-specific quartiles in Cox proportional hazards models. Similarly, the association between baseline body composition and patient survival was examined using sex-specific quartiles of baseline measurements. Muscle wasting was

also categorized by the presence of sarcopenia using established cut-points of SMI (BMI ≤24.9 kg/m$^2$: <43 cm$^2$/m$^2$ for men and <41 cm$^2$/m$^2$ for women; BMI ≥25 kg/m$^2$: <53 cm$^2$/m$^2$ for men and <41 cm$^2$/m$^2$ for women) (18). Heterogeneity of the association across the two study sites was assessed using Cochran's Q-statistic (19). We performed stratified analyses by sex, cancer stage, and treatment type, and evaluated the statistical interaction using the Wald test of the cross-product term of change in body composition and stratification variables.

Differences in body composition change across quartiles of plasma markers were evaluated using the Kruskal-Wallis test. The association between BCAAs and MCP-1 with change in muscle area was further modeled using multivariate linear regression. All *P*-values were 2-sided. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

## Results

Patient characteristics overall and by study site are shown in Table 1. All patients had advanced disease at diagnosis, with 106 (65%) having metastatic disease and 58 (35%) having locally advanced disease. Median overall survival times were 14.8 months for patients with locally advanced disease and 10.2 months for metastatic disease. Median time between pathological diagnosis and baseline scans was 1 day (Interquartile range (IQR): 26 days), and the median time between baseline and follow-up scans was 80 days (IQR: 28 days). By the end of follow-up, 140 (85%) patients had died.

Between the baseline and follow-up scans, patients lost an average of 9.9% of muscle, 14.7% of subcutaneous adipose tissue, and 7.5% of visceral adipose tissue (Table 2). Muscle attenuation declined on average 3.2 HU between the two scans, reflecting decreasing muscle density. Changes were similar in patients from the two study sites (Supplementary Table S1). Muscle and visceral adipose loss per 30 days was greater among men (Table 2 and Supplementary Table S2). At baseline, 86 (52%) of patients were sarcopenic, and 113 (69%) were sarcopenic at follow-up scan. Correlation coefficients for clinical characteristics and body composition measurements are shown in Supplementary Table S3.

Compared to patients in the bottom quartile of muscle change per 30 days (*i.e.* those that lost the least muscle), patients in the top quartile experienced a 2-fold increase in the hazards for mortality (HR, 2.01; 95% CI, 1.12–3.62; *P*-trend=0.01) (Table 3). Similarly, patients in the top quartile of muscle density change per 30 days (*i.e.* those with the greatest reduction in muscle density) had a 2.2-fold increased mortality (HR, 2.19; 95% CI, 1.18–4.04; *P*-trend=0.02) compared to those in the bottom quartile. No association was identified between patient survival and change in subcutaneous (*P*-trend=0.52) or visceral (*P*-trend=0.20) adipose tissue. The associations were similar across the two study sites (all *P*-heterogeneity>0.15). Mean duration of cancer treatment was similar across quartiles of muscle area (*P*=0.16), or muscle density (*P*=0.77) change (Supplementary Table S4).

In stratified analyses by sex, disease stage, and treatment type, no statistically significant interactions were identified for change in muscle or adipose areas (all P-interaction ≥ 0.16). In contrast, the association between change in muscle density and survival was more

pronounced among women (per sex-specific standard deviation HR, 2.27; 95% CI, 1.35–3.84) than men (HR,1.16; 95% CI, 0.80–1.69; *P*-interaction=0.05). However, interaction tests were limited by modest sample sizes within strata.

We analyzed four circulating biomarkers from baseline plasma samples to identify patients at risk of developing tissue wasting after diagnosis. Patients in the top quartiles of BCAAs had a greater loss of muscle per 30 days ($P$=0.004) (Table 4), but a similar change in other tissue measurements. Loss of muscle or adipose tissues was similar across quartiles of IL-6 and sTNF-RII (all $P \geq 0.11$), while patients in the highest quartile of MCP-1 experienced significantly less muscle loss ($P$=0.005) (Table 4). In multivariate adjusted models, the association of higher BCAA levels with greater loss of muscle was attenuated, while the association of higher MCP-1 levels with lower loss of muscle was similar (Supplementary Table S5).

## Discussion

In this study of patients with advanced pancreatic cancer treated at two academic cancer centers, loss of muscle area and decrease in muscle density as assessed by CT imaging in the two to four months after diagnosis were associated with a significant reduction in patient survival. Specifically, patients in the top quartile of muscle loss or decrease in muscle density had an adjusted median overall survival 4–5 months shorter than those in the bottom quartile of these measurements. In contrast, changes in adipose tissues were not associated with patient survival even though large losses were also identified for these tissues, suggesting that muscle and adipose tissue wasting may mark biologically distinct processes, a finding supported by data in preclinical models (11). Circulating levels of BCAAs and MCP-1 at diagnosis were associated with future muscle loss.

Previous studies of post-diagnosis body composition change reported no significant association between patient survival and muscle loss (5,20), and either no association (5) or shorter survival in patients with greater visceral adipose tissue loss (20). While both studies included patients with advanced disease and identified similar rates of change in body composition, patient outcomes were evaluated using unadjusted Kaplan-Meier survival curves. Given the association of tissue changes with patient characteristics such as age, sex, and BMI, multivariate modeling is necessary to evaluate independent associations between body composition change and patient survival. Dalal *et al.* observed shorter survival in patients with locally advanced disease receiving chemoradiation with higher loss of visceral adipose tissue (21), and we cannot rule out that body composition change might be differentially associated with patient survival depending on stage and type of treatment.

Several studies have examined muscle area measured at diagnosis in pancreatic cancer patients with advanced disease and observed either no difference (4,5,20,21) or worse survival in patients with sarcopenia (3) or lower muscle density (4). Our recent study of baseline body composition among 682 patients with previously untreated pancreatic cancer included the patients analyzed here, and baseline body composition measurements were not associated with patient survival (11). These data suggest that the rate of change in body

composition measurements in these patients may better reflect the adverse biology of tissue wasting, rather than the static measurements taken at the time of diagnosis.

Loss of muscle mass and muscle density may reflect a more aggressive disease biology, whereby muscle is reactive to a rapidly growing malignancy without contributing to either the specific growth of the tumor or compromise of the host (22). Alternatively, muscle loss might have a causal effect leading to reduced patient survival. Reversal of cancer-associated muscle loss in animal models has been shown to increase survival in some cancer types (23,24). In patients, muscle wasting can result in generalized weakness and poor tolerance of cancer-directed treatments, which may contribute to worsened survival (25). Furthermore, nutritional starvation could lead to muscle catabolism and less effective anti-tumoral immune response (26), which may also have an adverse impact on patient survival.

No biomarkers are currently used in the clinic to identify cancer patients at increased risk of muscle wasting. The majority of studies examining potential cachexia biomarkers have used a cross-sectional design, comparing levels of biomarkers between patients with and without cachexia at the time of diagnosis (7). While cross-sectional studies can identify biomarkers differentiating patients with or without cachexia, longitudinal studies are needed to identify biomarkers associated with future tissue depletion. Using a retrospective, longitudinal cohort study design, we have shown that higher levels of baseline BCAAs are associated with accelerated loss of muscle in the two to four months after diagnosis and thus may reflect higher ongoing rates of muscle degradation. These data are consistent with a previous study in mouse models of pancreatic cancer showing that circulating levels of BCAAs are increased early in the development of pancreatic cancer as a consequence of muscle wasting (9).

We observed no association between plasma IL-6 and sTNF-RII levels at diagnosis and subsequent tissue wasting. In some, but not all prior cross-sectional studies, IL-6 and TNF-α levels were higher in pancreatic cancer patients with cachexia compared to patients without cachexia defined as weight loss (7,27). Our results suggest that IL-6 and sTNF-RII at diagnosis do not predict subsequent tissue loss as quantified on CT images. Interestingly, we observed less future muscle loss in patients with higher circulating levels of MCP-1, which is not consistent with a prior cross-sectional study in which higher circulating MCP-1 levels were seen in patients with cachexia defined by weight loss (8). In animal models of acute (28) and chronic (29) muscle injury, MCP-1 was shown to facilitate muscle repair and regeneration. Thus, one might speculate that patients with higher MCP-1 levels may have greater ability to repair muscle damage induced by pancreatic cancer.

An important strength of the current study was the precise tissue quantification at two time points during disease using CT imaging. Thus, the dynamics of body composition change over time could be evaluated in relation to both patient outcomes and circulating biomarkers. Importantly, baseline CT imaging and blood collection were performed prior to any cancer-directed treatment, reducing confounding by treatment status. Furthermore, we collected data for multiple potential confounding covariates, allowing for determination of the independent association of body composition changes and patient survival.

Our study has several limitations. Muscle attenuation is widely used as a proxy for intramuscular fat accumulation and area-preserving atrophy (12), but attenuation values can also be decreased by fluid accumulation from anasarca. Further work is required to differentiate the aspects of altered muscle attenuation most related to poor patient survival. Body composition change was followed for 50–120 days after diagnosis, rather than for the patient's entire treatment course. However, a previous study that evaluated body composition changes for up to four consecutive CT scans (419 days after diagnosis) found little difference in rate of change in muscle or adipose tissue across study intervals (20). Furthermore, the initial several months after diagnosis are critical for identification of cachexia, as this period provides a window of opportunity for interventions to reduce tissue wasting and improve patient outcomes. Additionally, patients must have undergone repeat imaging at least 50 days after the baseline scan, such that patients with extremely rapid progression of their cancer may not have been included in our study population. Information on use of nutritional supplements such as L-carnitine or omega-3 polyunsaturated fatty acids (PUFA) (30) was not available in our study population, so their impact on skeletal muscle or adipose tissue changes could not be assessed. Lastly, most patients were white; therefore, these observations need to be validated in additional, more diverse populations.

In conclusion, in this large study of patients with advanced pancreatic cancer and serial quantification of body composition using CT imaging, post-diagnosis loss of muscle, but not of adipose tissue was associated with reduced patient survival. Furthermore, baseline plasma levels of BCAAs and MCP-1 were associated with future muscle loss, potentially marking a patient group at high risk for future complications due to cancer cachexia.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67(1):7–30. [PubMed: 28055103]
2. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12(5):489–95. [PubMed: 21296615]

3. Choi Y, Oh DY, Kim TY, Lee KH, Han SW, Im SA, et al. Skeletal Muscle Depletion Predicts the Prognosis of Patients with Advanced Pancreatic Cancer Undergoing Palliative Chemotherapy, Independent of Body Mass Index. PLoS One 2015;10(10):e0139749. [PubMed: 26437072]
4. Rollins KE, Tewari N, Ackner A, Awwad A, Madhusudan S, Macdonald IA, et al. The impact of sarcopenia and myosteatosis on outcomes of unresectable pancreatic cancer or distal cholangiocarcinoma. Clin Nutr 2016;35(5):1103–9. [PubMed: 26411749]
5. Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res 2009;15(22):6973–9. [PubMed: 19887488]
6. Bachmann J, Buchler MW, Friess H, Martignoni ME. Cachexia in patients with chronic pancreatitis and pancreatic cancer: impact on survival and outcome. Nutr Cancer 2013;65(6):827–33. [PubMed: 23909726]
7. Loumaye A, Thissen JP. Biomarkers of cancer cachexia. Clin Biochem 2017;50(18):1281–8. [PubMed: 28739222]
8. Talbert EE, Lewis HL, Farren MR, Ramsey ML, Chakedis JM, Rajasekera P, et al. Circulating monocyte chemoattractant protein-1 (MCP-1) is associated with cachexia in treatment-naive pancreatic cancer patients. J Cachexia Sarcopenia Muscle 2018;9(2):358–68. [PubMed: 29316343]
9. Mayers JR, Wu C, Clish CB, Kraft P, Torrence ME, Fiske BP, et al. Elevation of circulating branched-chain amino acids is an early event in human pancreatic adenocarcinoma development. Nat Med 2014;20(10):1193–8. [PubMed: 25261994]
10. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab 2008;33(5):997–1006. [PubMed: 18923576]
11. Danai LV, Babic A, Rosenthal MH, Dennstedt EA, Muir A, Lien EC, et al. Altered exocrine function can drive adipose wasting in early pancreatic cancer. Nature 2018;558(7711):600–4. [PubMed: 29925948]
12. Aubrey J, Esfandiari N, Baracos VE, Buteau FA, Frenette J, Putman CT, et al. Measurement of skeletal muscle radiation attenuation and basis of its biological variation. Acta Physiol (Oxf) 2014;210(3):489–97. [PubMed: 24393306]
13. van Vugt JLA, Coebergh van den Braak RRJ, Schippers HJW, Veen KM, Levolger S, de Bruin RWF, et al. Contrast-enhancement influences skeletal muscle density, but not skeletal muscle mass, measurements on computed tomography. Clin Nutr 2018;37(5):1707–14. [PubMed: 28743427]
14. Weston AD, Korfiatis P, Kline TL, Philbrick KA, Kostandy P, Sakinis T, et al. Automated Abdominal Segmentation of CT Scans for Body Composition Analysis Using Deep Learning. Radiology 2018:181432.
15. Babic A, Schnure N, Neupane NP, Zaman MM, Rifai N, Welch MW, et al. Plasma inflammatory cytokines and survival of pancreatic cancer patients. Clin Transl Gastroenterol 2018;9(4):145. [PubMed: 29691365]
16. Diez-Ruiz A, Tilz GP, Zangerle R, Baier-Bitterlich G, Wachter H, Fuchs D. Soluble receptors for tumour necrosis factor in clinical laboratory diagnosis. European journal of haematology 1995;54(1):1–8. [PubMed: 7859870]
17. Makuch RW. Adjusted survival curve estimation using covariates. J Chronic Dis 1982;35(6):437–43. [PubMed: 7042727]
18. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol 2013;31(12):1539–47. [PubMed: 23530101]
19. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7(3):177–88. [PubMed: 3802833]
20. Di Sebastiano KM, Yang L, Zbuk K, Wong RK, Chow T, Koff D, et al. Accelerated muscle and adipose tissue loss may predict survival in pancreatic cancer patients: the relationship with diabetes and anaemia. Br J Nutr 2013;109(2):302–12. [PubMed: 23021109]

21. Dalal S, Hui D, Bidaut L, Lem K, Del Fabbro E, Crane C, et al. Relationships among body mass index, longitudinal body composition alterations, and survival in patients with locally advanced pancreatic cancer receiving chemoradiation: a pilot study. J Pain Symptom Manage 2012;44(2): 181–91. [PubMed: 22695045]
22. Dodson S, Baracos VE, Jatoi A, Evans WJ, Cella D, Dalton JT, et al. Muscle wasting in cancer cachexia: clinical implications, diagnosis, and emerging treatment strategies. Annu Rev Med 2011;62:265–79. [PubMed: 20731602]
23. Toledo M, Busquets S, Penna F, Zhou X, Marmonti E, Betancourt A, et al. Complete reversal of muscle wasting in experimental cancer cachexia: Additive effects of activin type II receptor inhibition and beta-2 agonist. Int J Cancer 2016;138(8):2021–9. [PubMed: 26595367]
24. Zhou X, Wang JL, Lu J, Song Y, Kwak KS, Jiao Q, et al. Reversal of cancer cachexia and muscle wasting by ActRIIB antagonism leads to prolonged survival. Cell 2010;142(4):531–43. [PubMed: 20723755]
25. Ongaro E, Buoro V, Cinausero M, Caccialanza R, Turri A, Fanotto V, et al. Sarcopenia in gastric cancer: when the loss costs too much. Gastric Cancer 2017;20(4):563–72. [PubMed: 28477106]
26. Flint TR, Fearon DT, Janowitz T. Connecting the Metabolic and Immune Responses to Cancer. Trends Mol Med 2017;23(5):451–64. [PubMed: 28396056]
27. Tan CR, Yaffee PM, Jamil LH, Lo SK, Nissen N, Pandol SJ, et al. Pancreatic cancer cachexia: a review of mechanisms and therapeutics. Front Physiol 2014;5:88. [PubMed: 24624094]
28. Lu H, Huang D, Ransohoff RM, Zhou L. Acute skeletal muscle injury: CCL2 expression by both monocytes and injured muscle is required for repair. FASEB J 2011;25(10):3344–55. [PubMed: 21697550]
29. Fang J, Shi GP, Vaghy PL. Identification of the increased expression of monocyte chemoattractant protein-1, cathepsin S, UPIX-1, and other genes in dystrophin-deficient mouse muscles by suppression subtractive hybridization. J Cell Biochem 2000;79(1):164–72. [PubMed: 10906764]
30. Gartner S, Kruger J, Aghdassi AA, Steveling A, Simon P, Lerch MM, et al. Nutrition in Pancreatic Cancer: A Review. Gastrointest Tumors 2016;2(4):195–202. [PubMed: 27403414]

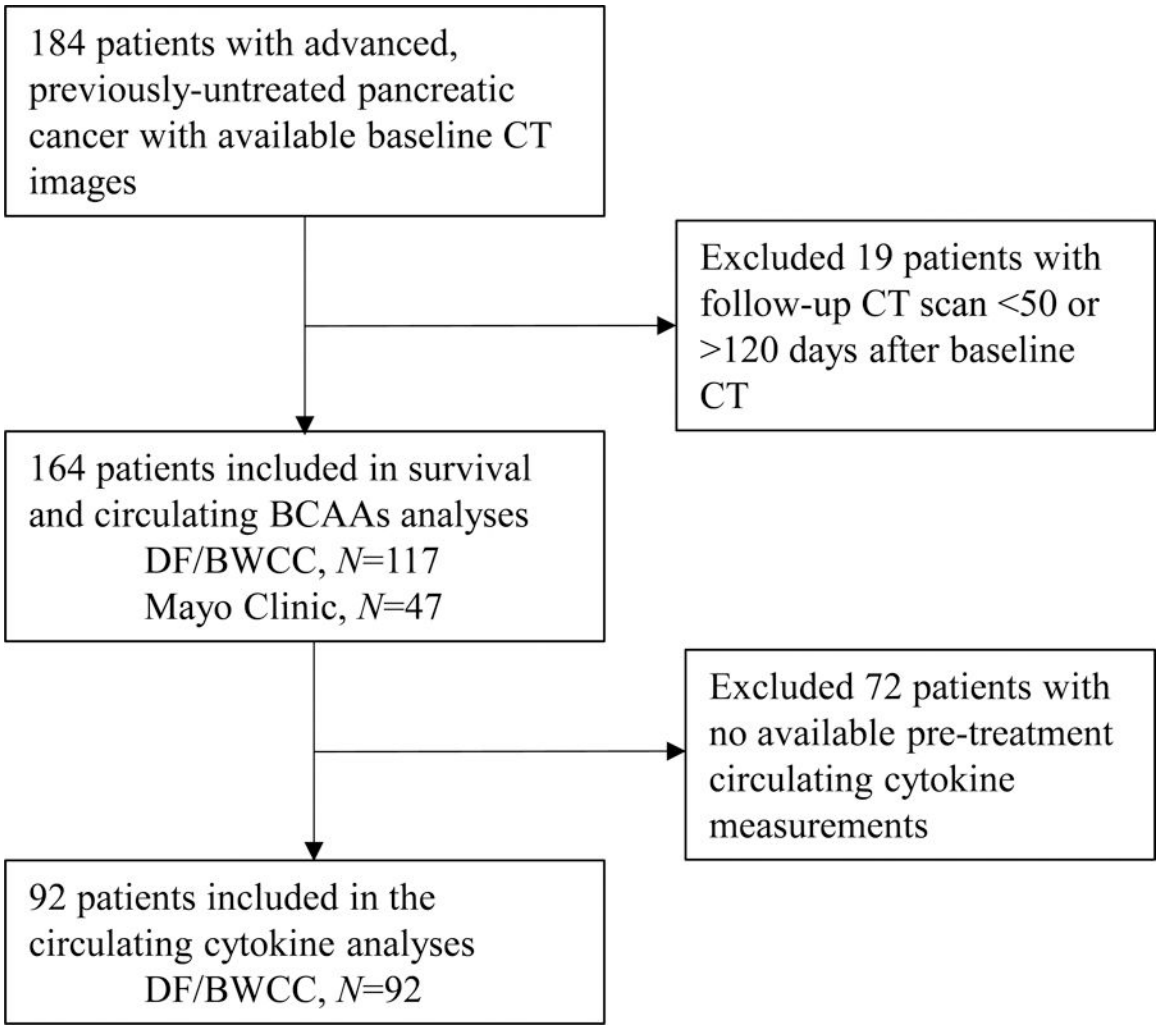


**Figure 1. Selection of pancreatic cancer patients included in the study of post-diagnosis body composition change**

Figure 1 shows the criteria used for selection of pancreatic cancer patients included in this study. Patients were selected based on the availability of pretreatment CT images, CT images obtained 50–120 days after diagnosis, and pretreatment plasma samples (N=164). A subset of those patients (N=92) had cytokine measurements in pretreatment plasma samples. Abbreviations: BCAAs, branched chain amino acids; CT, computed tomography; DF/BWCC, Dana-Farber/Brigham and Women's Cancer Center

**Table 1.**

Baseline characteristics of pancreatic cancer patients

| **Patient characteristics**[a] | **DF/BWCC (*N*=117)** | **Mayo Clinic (*N*=47)** | **Overall (*N*=164)** |
|---|---|---|---|
| Age at diagnosis, years | 63.6 (9.5) | 62.9 (10.3) | 63.4 (9.7) |
| Female sex | 52 (44) | 17 (36) | 69 (42) |
| Race/ethnicity | | | |
| White | 106 (91) | 47 (100) | 153 (93) |
| Black | 7 (6) | 0 (0) | 7 (4) |
| Other | 3 (3) | 0 (0) | 3 (2) |
| Unknown | 1 (1) | 0 (0) | 1 (1) |
| Body-mass index, kg/m$^2$ | 26.5 (5.4) | 29.1 (5.7) | 27.2 (5.6) |
| Diabetes history | | | |
| No diabetes | 78 (67) | 36 (77) | 114 (70) |
| Diabetes ≤4 years | 19 (16) | 7 (15) | 26 (16) |
| Diabetes >4 years | 9 (8) | 2 (4) | 11 (7) |
| Unknown | 11 (9) | 2 (4) | 13 (8) |
| Smoking history | | | |
| Never | 54 (46) | 16 (34) | 70 (43) |
| Past | 53 (45) | 20 (43) | 73 (45) |
| Current | 10 (9) | 2 (4) | 12 (7) |
| Unknown | 0 (0) | 9 (19) | 9 (5) |
| Year of diagnosis | | | |
| 2000–2010 | 32 (27) | 25 (53) | 57 (35) |
| 2011–2015 | 85 (73) | 22 (47) | 107 (65) |
| Cancer stage | | | |
| Locally advanced | 30 (26) | 28 (60) | 58 (35) |
| Metastatic | 87 (74) | 19 (40) | 106 (65) |
| Median survival time, months | | | |
| All patients | 11.0 | 13.9 | 11.4 |
| By stage | | | |
| Locally advanced | 13.3 | 16.0 | 14.8 |
| Metastatic | 10.2 | 10.8 | 10.2 |
| Initial treatment program | | | |
| FOLFIRINOX / FOLFOX / FOLFIRI[b] | 56 (48) | 15 (32) | 71 (43) |
| Gemcitabine or Gemcitabine combination[c] | 53 (45) | 17 (36) | 70 (43) |
| Chemoradiation (RT with 5-FU or Capecitabine) | 7 (6) | 9 (19) | 16 (10) |
| No treatment / Unknown | 1 (1) | 6 (13) | 7 (4) |
| Median time (IQR) between histologic diagnosis and baseline CT scan (days) | 2 (28) | 1 (14) | 1 (26) |
| Median time (IQR) between baseline and follow-up CT scan (days) | 80 (28) | 84 (27) | 80 (28) |
| Median time (IQR) between baseline CT scan and blood draw (days) | 12 (21) | 1 (8) | 8 (19) |

[a] Continuous variables are reported as mean (standard deviation), and categorical variables are reported as number (percent), unless noted otherwise.

[b] FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, oxaliplatin; N=61), FOLFOX (5-fluorouracil, leucovorin, oxaliplatin; N=9) or FOLFIRI (5-fluorouracil, leucovorin, irinotecan; N=1)

[c] Gemcitabine (N=41) or Gemcitabine combinations (N=29), including Gemcitabine plus: bevacizumab/erlotinib (N=2), capecitabine (N=3), cisplatin (N=3), erlotinib (N=2), nab-paclitaxel/momelotinib (N=2), nab-paclitaxel (N=4), panitumumab/erlotinib (N=1), temsirolimus (N=1), AGS-1C4D4 (N=1), AMG-479 (N=2), IPI-926 (N=6), or TH-302 (N=2)

Abbreviations: 5-FU, 5-fluorouracil; CT, computed tomography; DF/BWCC, Dana-Farber/Brigham and Women's Cancer Center; IQR, interquartile range; RT, radiotherapy

**Table 2.**

Body composition changes between baseline and follow-up computed tomography scans in patients with advanced pancreatic cancer

| | *N* | Baseline measurement[a] | Change between baseline and follow-up CT scan[a] | % change between baseline and follow-up CT scan[a] | Change per 30 days[a] | % change per 30 days[a] |
|---|---|---|---|---|---|---|
| **Overall** | | | | | | |
| Skeletal muscle area ($cm^2$) | 164 | 136.5 (36.3) | −14.6 (16.4) | −9.9 (11.0) | −5.4 (5.9) | −3.7 (3.9) |
| Skeletal muscle attenuation (HU) | 159 | 36.8 (9.2) | −3.2 (7.6) | N/A[b] | −1.1 (3.0) | N/A[b] |
| Subcutaneous adipose tissue area ($cm^2$) | 164 | 190.2 (103.0) | −27.5 (35.4) | −14.7 (19.7) | −9.8 (13.2) | −5.3 (8.0) |
| Visceral adipose tissue area ($cm^2$) | 164 | 162.1 (104.6) | −24.5 (39.4) | −7.5 (58.3) | −9.2 (14.8) | −2.5 (23.1) |
| **Women** | | | | | | |
| Skeletal muscle area ($cm^2$) | 69 | 104.1 (19.1) | −8.5 (14.4) | −7.8 (12.9) | −3.3 (4.9) | −2.9 (4.5) |
| Skeletal muscle attenuation (HU) | 66 | 35.4 (9.8) | −3.1 (6.7) | N/A[b] | −1.2 (2.9) | N/A[b] |
| Subcutaneous adipose tissue area ($cm^2$) | 69 | 211.0 (118.4) | −28.9 (43.6) | −12.7 (22.3) | −9.8 (16.3) | −4.2 (9.3) |
| Visceral adipose tissue area ($cm^2$) | 69 | 101.6 (76.1) | −8.3 (23.9) | 5.6 (85.0) | −3.0 (9.1) | 3.0 (33.8) |
| **Men** | | | | | | |
| Skeletal muscle area ($cm^2$) | 95 | 160.6 (25.7) | −19.0 (16.5) | −11.4 (9.2) | −7.0 (6.0) | −4.2 (3.3) |
| Skeletal muscle attenuation (HU) | 93 | 37.8 (8.7) | −3.3 (8.2) | N/A[b] | −1.1 (3.1) | N/A[b] |
| Subcutaneous adipose tissue area ($cm^2$) | 95 | 175.1 (87.9) | −26.5 (28.3) | −16.2 (17.6) | −9.8 (10.5) | −6.1 (7.0) |
| Visceral adipose tissue area ($cm^2$) | 95 | 206.0 (100.7) | −36.2 (44.1) | −17.0 (21.1) | −13.7 (16.5) | −6.6 (8.0) |

[a] Mean (standard deviation)

[b] The Hounsfield unit scale has a zero value set in the middle of its range, so percent calculations relative to the arbitrary zero are not meaningful.

Abbreviations: CT, computed tomography; HU, Hounsfield unit

**Table 3.**

Hazard ratios for mortality by quartiles of body composition change per 30 days in patients with advanced pancreatic cancer

| | Quartile of body composition change per 30 days | | | | |
|---|---|---|---|---|---|
| | **1** **Less loss of tissue area** | **2** | **3** | **4** **More loss of tissue area** | ***P*-trend[c]** |
| **Skeletal muscle area** | | | | | |
| Mean (SD) change per 30 days ($cm^2$) | 0.8 (2.0) | −3.0 (1.7) | −6.8 (2.7) | −12.9 (4.9) | |
| Person-months | 552.2 | 578.5 | 511.4 | 399.8 | |
| Deaths/Cases | 35/41 | 36/42 | 36/41 | 33/40 | |
| Median survival, months | 13.9 | 12.8 | 10.2 | 9.8 | |
| Model I[a] | Ref | 1.29 (0.78–2.12) | 1.53 (0.92–2.56) | 1.84 (1.06–3.20) | 0.03 |
| Model II[b] | Ref | 1.25 (0.73–2.14) | 1.83 (1.07–3.15) | 2.01 (1.12–3.62) | 0.01 |
| **Visceral adipose tissue area** | | | | | |
| Mean (SD) change per 30 days ($cm^2$) | 6.4 (7.8) | −4.4 (5.1) | −12.6 (6.2) | −26.5 (13.6) | |
| Person-months | 558.6 | 579.2 | 444.0 | 401.8 | |
| Deaths/Cases | 32/40 | 35/40 | 38/40 | 31/39 | |
| Median survival, months | 11.3 | 13.3 | 11.0 | 10.2 | |
| Model I[a] | Ref | 0.79 (0.47–1.33) | 1.20 (0.71–2.01) | 1.29 (0.74–2.27) | 0.13 |
| Model II[b] | Ref | 0.76 (0.44–1.28) | 1.04 (0.59–1.83) | 1.31 (0.72–2.39) | 0.20 |
| **Subcutaneous adipose tissue area** | | | | | |
| Mean (SD) change per 30 days ($cm^2$) | 5.6 (7.2) | −5.4 (3.1) | −13.9 (3.0) | −26.1 (9.5) | |
| Person-months | 569.4 | 487.1 | 434.6 | 492.6 | |
| Deaths/Cases | 3¾0 | 32/40 | 36/40 | 35/39 | |
| Median survival, months | 11.3 | 12.9 | 10.2 | 11.3 | |
| Model I[a] | Ref | 0.78 (0.46–1.32) | 1.26 (0.75–2.12) | 0.97 (0.57–1.65) | 0.45 |
| Model II[b] | Ref | 0.85 (0.49–1.49) | 1.27 (0.72–2.23) | 1.00 (0.57–1.75) | 0.52 |
| | **1** **Less decrease in muscle attenuation** | **2** | **3** | **4** **More decrease in muscle attenuation** | ***P*-trend[c]** |
| **Skeletal muscle attenuation** | | | | | |

| | Quartile of body composition change per 30 days | | | | |
|---|---|---|---|---|---|
| | **1 Less loss of tissue area** | **2** | **3** | **4 More loss of tissue area** | ***P*-trend[c]** |
| Mean (SD) change per 30 days (HU) | 2.4 (1.6) | −0.3 (0.5) | −1.7 (0.5) | −4.9 (2.4) | |
| Person-months | 528.8 | 524.0 | 506.0 | 419.4 | |
| Deaths/Cases | 34/39 | 35/41 | 34/40 | 33/39 | |
| Median survival, months | 13.9 | 12.9 | 10.8 | 8.8 | |
| Model I[a] | Ref | 1.30 (0.79–2.13) | 1.72 (1.02–2.90) | 2.51 (1.42–4.43) | 0.002 |
| Model II[b] | Ref | 1.27 (0.75–2.14) | 1.69 (0.97–2.94) | 2.19 (1.18–4.04) | 0.02 |

[a]Adjusted for age (continuous), baseline body composition measurement (continuous), sex, years of diagnosis (2000–2010, 2011–2015), race (white, non-white), stage (locally advanced, metastatic) and study site (DF/BWCC, Mayo Clinic)

[b]Additionally adjusted for BMI (continuous), diabetes (no diabetes, diabetes duration ≤4 years, diabetes duration >4 years), smoking (never, past, current), and treatment type (FOLFIRINOX / FOLFOX / FOLFIRI, Gemcitabine / Gemcitabine doublet, Chemoradiation, No treatment / Unknown)

[c]Calculated using sex-specific quartile median as a continuous variable

Abbreviations: DF/BWCC, Dana-Farber/Brigham and Women's Cancer Center; FOLFIRINOX: 5-fluorouracil, leucovorin, irinotecan, oxaliplatin; FOLFOX: 5-fluorouracil, leucovorin, oxaliplatin; FOLFIRI: 5-fluorouracil, leucovorin, irinotecan; HU, Hounsfield unit; SD, standard deviation

**Table 4.**

Baseline circulating markers and subsequent body composition changes between baseline and follow-up computed tomography scans in patients with advanced pancreatic cancer

| | Circulating Total BCAAs | | | | |
|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | *P*-value[a] |
| *N* | 40 | 41 | 42 | 41 | |
| Range (μM) | 83.8–275.1 | 275.7–322.1 | 323.3–388.2 | 390.1–673.8 | |
| Skeletal muscle area ($cm^2$) | −2.6 (5.4) | −6.2 (5.5) | −6.4 (6.5) | −6.2 (5.2) | 0.004 |
| Skeletal muscle attenuation (HU) | −0.3 (2.6) | −2.1 (3.2) | −1.4 (3.2) | −0.7 (2.8) | 0.06 |
| Visceral adipose tissue area ($cm^2$) | −6.0 (9.9) | −9.2 (17.3) | −10.6 (14.2) | −10.8 (16.6) | 0.24 |
| Subcutaneous adipose tissue area ($cm^2$) | −13.1 (13.6) | −7.8 (13.7) | −8.5 (13.7) | −10.0 (11.4) | 0.23 |
| | **Circulating IL-6** | | | | |
| | Q1 | Q2 | Q3 | Q4 | *P*-value[a] |
| *N* | 23 | 23 | 23 | 22 | |
| Range (pg/ml) | 0.2–1.5 | 1.5–2.5 | 2.6–3.3 | 3.6–33.2 | |
| Skeletal muscle area ($cm^2$) | −5.8 (6.0) | −6.9 (6.1) | −5.2 (4.5) | −6.2 (7.2) | 0.91 |
| Skeletal muscle attenuation (HU) | −1.3 (3.5) | −1.2 (4.0) | −1.7 (2.6) | −1.5 (4.2) | 0.89 |
| Visceral adipose tissue area ($cm^2$) | −7.4 (11.0) | −11.2 (16.7) | −9.2 (18.2) | −11.5 (18.1) | 0.75 |
| Subcutaneous adipose tissue area ($cm^2$) | −10.5 (11.8) | −9.1 (15.0) | −14.0 (15.9) | −8.5 (15.0) | 0.57 |
| | **Circulating sTNF-RII** | | | | |
| | Q1 | Q2 | Q3 | Q4 | *P*-value[a] |
| *N* | 23 | 23 | 24 | 22 | |
| Range (pg/ml) | 1397.2–2316.8 | 2318.2–3228.9 | 3244.0–4899.7 | 4910.9–10000.0 | |
| Skeletal muscle area ($cm^2$) | −7.2 (4.7) | −7.7 (6.5) | −5.8 (5.5) | −4.0 (6.9) | 0.11 |
| Skeletal muscle attenuation (HU) | −0.6 (2.5) | −2.6 (4.0) | −1.6 (3.3) | −1.6 (4.0) | 0.32 |
| Visceral adipose tissue area ($cm^2$) | −8.6 (14.3) | −12.3 (17.3) | −6.0 (15.3) | −11.5 (13.9) | 0.59 |
| Subcutaneous adipose tissue area ($cm^2$) | −10.4 (10.6) | −10.5 (13.9) | −9.1 (12.7) | −11.5 (17.5) | 0.58 |
| | **Circulating MCP-1** | | | | |
| | Q1 | Q2 | Q3 | Q4 | *P*-value[a] |
| *N* | 21 | 24 | 23 | 23 | |
| Range (pg/ml) | 4.3–41.5 | 41.6–77.7 | 91.2–176.8 | 181.7–448.3 | |
| Skeletal muscle area ($cm^2$) | −9.7 (5.7) | −6.3 (4.9) | −5.0 (6.3) | −3.4 (5.3) | 0.005 |
| Skeletal muscle attenuation (HU) | −1.8 (3.7) | −1.0 (3.3) | −1.2 (3.3) | −1.8 (4.0) | 0.94 |
| Visceral adipose tissue area ($cm^2$) | −12.9 (13.4) | −7.0 (11.2) | −7.7 (21.1) | −12.3 (16.9) | 0.39 |
| Subcutaneous adipose tissue area ($cm^2$) | −11.0 (9.0) | −12.4 (14.0) | −10.0 (15.6) | −9.0 (17.9) | 0.72 |

[a] *P*-value is calculated using Kruskal Wallis test

Abbreviations: BCAAs, branched chain amino acids; HU, Hounsfield unit; IL-6, interleukine-6; MCP-1, monocyte chemoattractant protein-1; sTNF-RII, soluble tumor necrosis factor receptor type II