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ORIGINAL RESEARCH

Prognostic value of deep learning-derived body composition in advanced pancreatic cancer—a retrospective multicenter study

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Background: Despite the prognostic relevance of cachexia in pancreatic cancer, individual body composition has not been routinely integrated into treatment planning. In this multicenter study, we investigated the prognostic value of sarcopenia and myosteatosis automatically extracted from routine computed tomography (CT) scans of patients with advanced pancreatic ductal adenocarcinoma (PDAC).

Patients and methods: We retrospectively analyzed clinical imaging data of 601 patients from three German cancer centers. We applied a deep learning approach to assess sarcopenia by the abdominal muscle-to-bone ratio (MBR) and myosteatosis by the ratio of abdominal inter- and intramuscular fat to muscle volume. In the pooled cohort, univariable and multivariable analyses were carried out to analyze the association between body composition markers and overall survival (OS). We analyzed the relationship between body composition markers and laboratory values during the first year of therapy in a subgroup using linear regression analysis adjusted for age, sex, and American Joint Committee on Cancer (AJCC) stage.

Results: Deep learning-derived MBR [hazard ratio (HR) 0.60, 95% confidence interval (CI) 0.47-0.77, $P < 0.005$] and myosteatosis (HR 3.73, 95% CI 1.66-8.39, $P < 0.005$) were significantly associated with OS in univariable analysis. In multivariable analysis, MBR ($P = 0.019$) and myosteatosis ($P = 0.02$) were associated with OS independent of age, sex, and AJCC stage. In a subgroup, MBR and myosteatosis were associated with albumin and C-reactive protein levels after initiation of therapy. Additionally, MBR was also associated with hemoglobin and total protein levels.

Conclusions: Our work demonstrates that deep learning can be applied across cancer centers to automatically assess sarcopenia and myosteatosis from routine CT scans. We highlight the prognostic role of our proposed markers and show a strong relationship with protein levels, inflammation, and anemia. In clinical practice, automated body composition analysis holds the potential to further personalize cancer treatment.

Key words: body composition, deep learning, pancreatic cancer, prognosis, computed tomography

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the most common subtype of pancreatic cancer (90%) and remains a highly fatal disease. More than 80% of patients are diagnosed at an unresectable stage, with a 5-year overall survival (OS) rate of <10%.[1,2] First symptoms often occur at an advanced stage, including cachexia-related symptoms such as weight and appetite loss.[2,3] Besides pancreatic cancer,

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cachexia occurs in many other cancers and is closely related to inflammation.[4-6] A hallmark of cancer-associated cachexia is the presence of sarcopenia, which is strongly associated with OS.[7-14] In this context, sarcopenia is defined not only by the quantity of muscle but also by its qualitative characteristics, such as the extent of myosteatosis, which is also related to poor survival in pancreatic cancer.[15-18] Previous studies have measured body composition markers by segmenting computed tomography (CT) scans at the third lumbar vertebra level. This approach only yields an estimate and does not capture the exact individual body composition of patients. In addition, the lack of automation makes these approaches impractical for routine clinical care. As a result, the potential of capturing accurate body composition for individual prognostication and treatment planning has yet to be realized. In the absence of alternatives, body mass index (BMI) is often used instead in clinical practice. However, BMI does not distinguish between different tissue types and therefore does not capture specific pathological conditions such as sarcopenia.[7] Our previous work demonstrated that muscle-to-bone ratio (MBR) automatically derived from abdominal CT images was a significant prognostic marker in advanced colorectal cancer patients. In contrast, BMI showed no association with OS.[19] In this work, we build on our previous findings to demonstrate the prognostic value of CT-derived sarcopenia, as measured by MBR, and myosteatosis as indicators of cachexia. Due to the close association of cachexia with metabolic and inflammatory processes, we also investigated the changes in various laboratory values during therapy in a subgroup of patients.[4,6,16]

With the increasing use of personalized therapy approaches in oncology, it is critical to accurately assess the patient's disease state, including body composition. In this retrospective multicenter study, we demonstrated the potential of comprehensive body composition markers automatically extracted from CT images for the stratification of advanced pancreatic cancer patients.

PATIENTS AND METHODS

Study design

Deidentified medical data were collected from three participating cancer centers in Germany. A total of 601 patients were included in the final analysis after the exclusion of patients due to curative treatment or missing data. All of the patients included in the study were diagnosed with histologically confirmed PDAC and were not eligible for curative resection. OS was defined as the time from initiation of systemic treatment to date of death from any cause. Patients for whom no date of death was available at the time of the last follow-up were censored. The study was approved by the Ethics Committee of the Medical Faculty of the University Duisburg-Essen (No. 21-10347). The requirement for written informed consent was waived due to the retrospective design of the study.

Assessments

Abdominal CT images obtained before initiation of systemic treatment were used to carry out deep learning-based segmentation of body composition. Before extracting body composition markers, CT images were resampled to 5-mm slice thickness to ensure they met the requirements for the following extraction process. Body composition markers were assessed using a fully automated extraction pipeline that identifies the abdominal cavity and computes the corresponding body composition volumes in this area.[20] The analysis included abdominal muscle, bone, and inter- and intramuscular adipose tissue (IMAT) volumes. To assess sarcopenia, we calculated the MBR by dividing abdominal muscle volume by bone volume as previously described.[19] Myosteatosis was assessed by dividing the abdominal volume of IMAT by abdominal muscle volume. Skeletal muscle density (SMD) was defined as the mean muscle attenuation in Hounsfield units at the third lumbar vertebra level and was automatically assessed by our model. Additional patient information used in this study was obtained from the patient's electronic health records. For the Essen cohort, all data were retrieved from the smart hospital information platform (SHIP) of University Hospital Essen. In SHIP, medical data are stored in FHIR format, allowing for specific, query-driven data collection.

Statistical analysis

Univariable and multivariable Cox proportional hazards analyses were used to analyze the association of MBR and myosteatosis with OS. We created subgroups based on MBR and myosteatosis and compared OS using Kaplan—Meier survival curves and a log-rank test. The associations between markers and mean laboratory values during treatment were examined using linear regression analysis corrected for age, sex, and American Joint Committee on Cancer (AJCC) stage. Locally weighted linear regression was used to visualize the progression of laboratory values after the initiation of treatment. The correlation between markers and age was analyzed using the Pearson correlation coefficient (r). Differences between markers by sex were assessed using a two-tailed t-test. Differences between markers by cohort were evaluated using a one-way analysis of variance test. P values ≤ 0.05 were regarded as statistically significant. All statistical analyses and visualizations were carried out using Python 3.8 and the packages lifelines, matplotlib, scipy, seaborn, and statsmodels.[21-25]

RESULTS

Patient characteristics

A total of 601 patients from three German cancer centers were included in the study. The participating centers were University Hospital Essen ($n = 155$), Goethe University Frankfurt ($n = 146$), and Technical University of Munich ($n = 300$). Inclusion criteria were: (i) histologically confirmed diagnosis of PDAC; (ii) no eligibility for curative resection; (iii) abdominal CT image available before

Table 1. Patient characteristics in the pooled cohort ($n = 601$)

Patient characteristics	
Age, years	
Median	66.0
Range	32.6-90.7
Sex, *n* (%)	
Male	334 (55.6)
Female	267 (44.4)
AJCC stage, *n* (%)	
IV	470 (78.2)
III	105 (17.5)
II	20 (3.3)
I	6 (1.0)
Chemotherapy regimen, *n* (%)	
Gemcitabine-based	323 (53.7)
FOLFIRINOX	218 (36.3)
Other	15 (2.5)
Unknown	45 (7.5)
MBR	
Median	2.36
Range	1.16-3.69
Myosteatosis	
Median	0.17
Range	0.01-0.78
Median survival time, months (95% CI)	8.8 (8.1-9.5)
Censored, *n* (%)	139 (23.1)

AJCC, American Joint Committee on Cancer; CI, confidence interval; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, oxaliplatin; MBR, muscle-to-bone ratio.

initiation of palliative therapy. The distribution of CT-derived MBR and myosteatosis is shown in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2023.102219. The median age of the pooled cohort was 66.0 years, and 55.6% of patients were male. At the time of analyses, 462 (67.9%) patients had died, and 139 (23.1%) patients were censored. Median survival time from the start of palliative chemotherapy was 8.8 months [95% confidence interval (CI) 8.1-9.5 months, see Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2023.102219]. Patient characteristics are described in Table 1.

Association of body composition markers with age and sex

Across cohorts, we saw comparable levels of body composition markers in relation to age and sex (Figure 1). In the pooled cohort ($n = 601$), we observed a strong correlation between age and MBR ($r = -0.47$, $P < 0.005$) and moderate correlations between age and myosteatosis ($r = 0.27$, $P < 0.005$, see Figure 1A). We observed significant differences in MBR ($P < 0.005$) and myosteatosis ($P < 0.005$) between male and female patients (Figure 1B). While MBR was higher in male patients, there was more myosteatosis in female patients. These results were consistent with literature findings regarding age- and sex-specific muscle differences.[26,27]

Sarcopenia and myosteatosis are independent prognostic markers in advanced PDAC

In univariable Cox proportional hazards analysis, MBR [hazard ratio (HR) 0.60, 95% CI 0.47-0.77, $P < 0.005$] and myosteatosis (HR 3.73, 95% CI 1.66-8.39, $P < 0.005$) were significantly associated with OS (Table 2). In addition, age (HR 1.01, 95% CI 1.01-1.02, $P < 0.005$) and AJCC stage (HR 1.22, 95% CI 1.02-1.46, $P = 0.03$) were found to be significantly associated with OS. In multivariable analysis, MBR

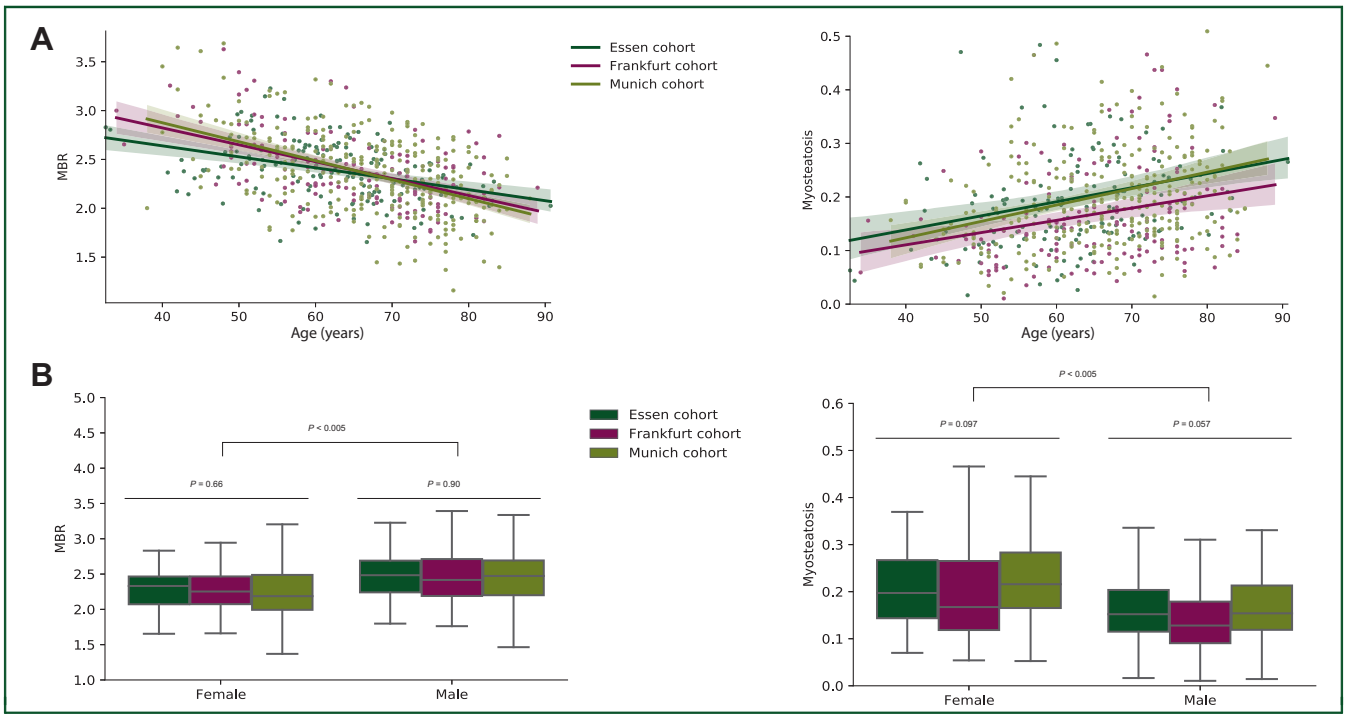

Figure 1. Body composition markers in relation to age and sex. (A) Association between MBR or myosteatosis and age. (B) Association between MBR or myosteatosis and sex.
MBR, muscle-to-bone ratio.

Table 2. Results of univariable and multivariable analyses in the pooled cohort ($n = 601$)

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.01 (1.01-1.02)	**<0.005**	1.01 (1.00-1.02)	0.062
Sex (male)	0.89 (0.74-1.07)	0.226	1.03 (0.84-1.27)	0.764
AJCC stage	1.22 (1.02-1.46)	**0.03**	1.33 (1.11-1.60)	**<0.005**
MBR	0.60 (0.47-0.77)	**<0.005**	0.70 (0.52-0.94)	**0.019**
Myosteatosis	3.73 (1.66-8.39)	**<0.005**	3.11 (1.20-8.06)	**0.02**

P-values ≤ 0.05 in bold.
AJCC, American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio; MBR, muscle-to-bone ratio.

(HR 0.70, 95% CI 0.52-0.94, $P = 0.019$), myosteatosis (HR 3.11, 95% CI 1.20-8.06, $P = 0.02$), and AJCC stage (HR 1.33, 95% CI 1.11-1.60, $P < 0.005$) were independently associated with OS.

In a subgroup treated with 5-fluorouracil or gemcitabine-based chemotherapy ($n = 555$), MBR (HR 0.66, 95% CI 0.49-0.90, $P = 0.008$) and myosteatosis (HR 2.76, 95% CI 1.05-7.27, $P = 0.04$) were associated with OS independent of treatment regimen (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.102219). We then compared subgroups with the highest (highest 25%) or lowest (lowest 25%) MBR (Figure 2A) or myosteatosis (Figure 2B) in the pooled cohort. Using Kaplan–Meier plots and a log-rank test, we observed significantly different OS of the high and low MBR ($P < 0.005$) or myosteatosis ($P = 0.008$) subgroups. Kaplan–Meier plots by AJCC stage are provided in Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2023.102219. Here, we saw the strongest prognostic effect at higher disease stages, which also comprised the largest proportion of our cohort.

In 523 patients, our model was also able to automatically assess SMD. In multivariable analysis, SMD was independently associated with OS (HR 0.98, 95% CI 0.97-0.99, $P = 0.009$, see Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102219).

Association between sarcopenia or myosteatosis and blood-based markers during therapy

In the Essen cohort, laboratory values were available for patients after therapy initiation. To further investigate the pathophysiological relationships of cachexia, we examined the association between MBR or myosteatosis and mean values of available laboratory markers in this subgroup ($n = 155$) over 1 year after treatment initiation. Using linear regression analysis adjusted for age, sex, and AJCC stage, we found a significant association between body composition markers and inflammatory as well as metabolic biomarkers (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.102219). For MBR, we observed a significant association with mean levels of albumin [coefficient (β) $= 0.78$, $P < 0.005$], C-reactive protein (CRP, $\beta = -4.45$, $P = 0.015$), hemoglobin ($\beta = 1.39$, $P < 0.005$), and total protein ($\beta = 0.68$, $P < 0.005$). For myosteatosis, we found a significant association with mean levels of albumin ($\beta = -0.89$, $P = 0.042$) and CRP ($\beta = 11.56$, $P = 0.014$). None of the other markers examined showed a statistically significant association with MBR or myosteatosis. Figure 3 illustrates the marked differences in laboratory values between the subgroups with high (highest 25%) and low (lowest 25%) MBR (Figure 3A) or myosteatosis (Figure 3B).

In a subgroup with available information at baseline ($n = 96$), MBR (HR 0.29, 95% CI 0.11-0.78, $P = 0.014$) and myosteatosis (HR 1.36, 95% CI 1.05-1.77, $P = 0.019$) were associated with OS independent of CRP and albumin levels (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2023.102219).

DISCUSSION

Cachexia is a major prognostic factor in pancreatic cancer, underscoring the critical need to incorporate a thorough analysis of a patient's unique body composition into treatment planning.[4,7] In this retrospective multicenter study, we

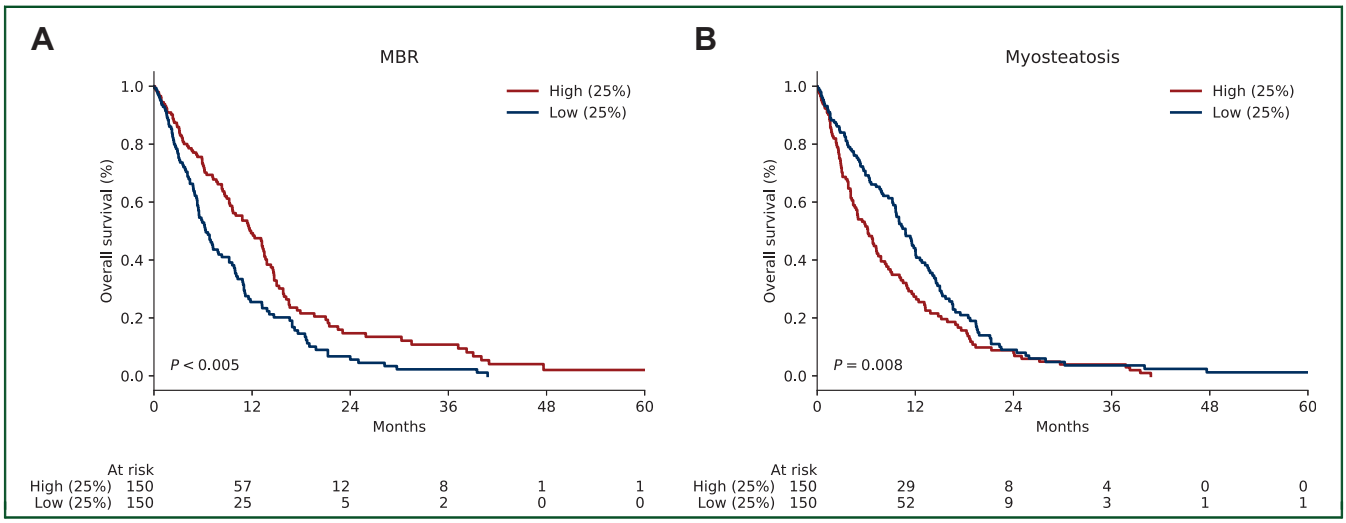

Figure 2. Kaplan–Meier plot showing overall survival according to MBR and myosteatosis in the pooled cohort. (A) Overall survival of patients with high and low MBR. (B) Overall survival of patients with high and low myosteatosis.
MBR, muscle-to-bone ratio.

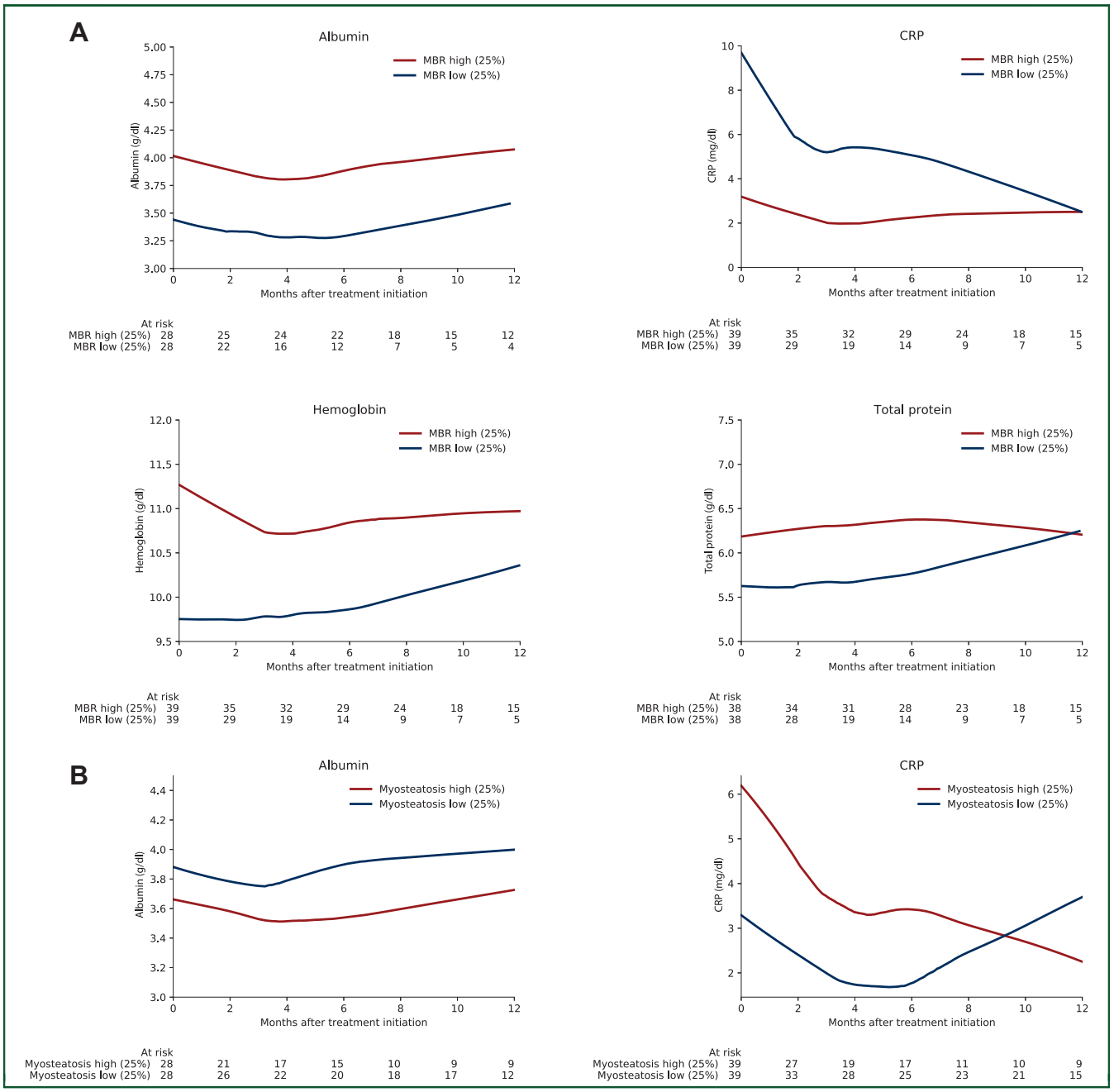

Figure 3. Development of laboratory values in high (highest 25%) and low (lowest 25%) MBR and myosteatosis subgroups. (A) MBR. (B) Myosteatosis. Only laboratory markers significant in linear regression analysis are shown.
CRP, C-reactive protein; MBR, muscle-to-bone ratio.

demonstrated the cross-site applicability of an automated workflow to extract body composition markers from routine CT images. We identified sarcopenia, defined by MBR, and myosteatosis as independent predictors of OS, which could be used for clinical risk stratification. To further elucidate the underlying pathophysiological processes, we analyzed the development of blood parameters from the start of therapy in a subgroup. We found a strong relationship between the proposed muscle markers and blood-based metabolic as well as inflammatory markers.

Sarcopenia is considered a key indicator of cachexia and is a well-established prognostic factor in pancreatic cancer.[4,6] As CT scans are part of the clinical routine for initial staging and disease progression, body composition assessment directly from CT images holds great potential. Previous studies have assessed sarcopenia mostly as a quantitative marker, e.g. as skeletal muscle index.[7-14] However, the European Working Group on Sarcopenia in the Elderly (EWGSOP) describes sarcopenia in the current definition as a combination of muscle quantity and quality.[15] We used the abdominal MBR to describe muscle quantity, whose potential we demonstrated in our previous work in advanced colorectal cancer patients.[19] Myosteatosis, the degree of fat infiltration into muscle tissue,

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has been proposed to describe muscle quality.[15,28,29] To measure the extent of myosteatosis, we used the abdominal ratio of IMAT to muscle volume, which has been previously described and found to correlate closely with muscular function.[30,31]

In contrast to previous studies in unresectable pancreatic cancer, we used a fully automated deep learning approach to capture comprehensive body composition markers from CT images of the entire abdomen.[20] Compared to manual measurement at the third lumbar vertebra level, our approach provides a more accurate assessment of body composition. It can be applied in routine clinical care without additional burden on medical staff or concern for interobserver variability. Across centers, we saw comparable values of MBR and myosteatosis and similar associations with respect to sex and age, which are also described in the literature.[26,27] This demonstrates the generalizability of our approach and the potential for cross-center applicability in routine clinical practice.

At University Hospital Essen, clinical data are stored in FHIR format and can thus be used for comprehensive data analyses.[19,32] To investigate how cachexia affects the course of treatment, we analyzed the evolution of laboratory markers from the start of therapy in the Essen subgroup. We observed an association between MBR and myosteatosis with inflammatory markers and between MBR and hemoglobin as a marker of anemia. This finding is consistent with previous results and highlights the close relationship between body composition markers and underlying systemic processes during cancer-associated cachexia.[6,16] We also saw an association between our body composition markers and the levels of albumin and total protein, which may underscore the presence of nutritional deficiencies. As both CRP and albumin are recommended prognostic markers in pancreatic cancer trials, our body composition markers may provide additional guidance for patient management.[33]

The limitations of our study are mainly due to the retrospective design. While we used large datasets from three major German university hospitals, future studies will need to include more geographically diverse datasets to validate our findings further. As our cohort was mainly composed of patients with late-stage disease, the prognostic role of the proposed markers needs to be further investigated in early unresectable and resectable disease stages. Considering the major importance of cachexia in many other diseases apart from pancreatic cancer, future studies should also investigate the value of automatically derived MBR and myosteatosis in other malignant and nonmalignant diseases.[6,34]

In conclusion, this multicenter study demonstrates the prognostic value of deep learning-derived sarcopenia and myosteatosis in advanced pancreatic cancer. Given the increasing importance of personalized treatment approaches, our findings have the potential to be seamlessly integrated into routine clinical care for patients with pancreatic cancer.

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DISCLOSURE

JTS receives honoraria as consultant or for continuing medical education presentations from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Immunocore, MSD Sharp Dohme, Novartis, Roche/Genentech, and Servier. His institution receives research funding from Abalos Therapeutics, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eisbach Bio, and Roche/Genentech; he holds ownership and serves on the Board of Directors of Pharma15, all outside the submitted work. All other authors have declared no conflicts of interest related to this study.

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