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Body composition parameters predict survival in pancreatic cancer—A retrospective multicenter analysis

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Abstract

Background: Parameters to adapt individual treatment strategies for patients with pancreatic ductal adenocarcinoma (PDAC) are urgently needed. The present study aimed to evaluate body composition parameters as predictors of overall survival (OS) in PDAC patients.

Methods: Measurements of body composition parameters were performed on computed tomography scans at diagnosis. Height-standardized and Body Mass Index- and sex-adjusted regression formulas deriving cut-offs from a healthy population were used. The Kaplan-Meier method with the log-rank test was performed for survival analysis. Independent prognostic factors were identified with uni- and multivariable Cox regression analyses.

Results: In total, 354 patients were analyzed. In a multivariable Cox model, besides tumor stage and resection status, only myosteatosis (HR 1.53; 95% CI 1.10–2.14, $p = 0.01$) was an independent prognostic factor of OS among body composition parameters. Subgroup analyses revealed that the prognostic impact of myosteatosis was higher in patients ≤68 years of age, with advanced tumor stages and patients without curative intended resection.

Conclusions: The analysis of one of the largest Caucasian cohorts to date, demonstrated myosteatosis to be an independent prognostic factor of OS in PDAC. To improve outcomes, prospective trials aiming to investigate the utility of an early assessment of myosteatosis with subsequent intervention by dieticians, sports medicine physicians, and physiotherapists are warranted.

KEYWORDS
body composition, CT, diagnosis, myosteatosis, pancreatic cancer, pancreatic ductal adenocarcinoma, prediction, survival

Marko Damm, Ljupcho Efremov, Sebastian Krug, and Jonas Rosendahl contributed equally to this study.

INTRODUCTION

Despite improvements in surgical and medical therapies, pancreatic ductal adenocarcinoma (PDAC) still has the worst survival rate among solid tumors.[1] Due to an increasing incidence, PDAC is predicted to be the second-leading cause of cancer-related death by 2030.[2] The dismal prognosis of PDAC is, amongst others, determined by tumor-dependent factors, such as diagnosis at an advanced stage and comparatively low response rates to chemotherapy. Recent studies revealed that patient-dependent anthropometric factors, including weight loss and reduction of muscular tissue due to nutritional derangements, such as exocrine pancreatic insufficiency, appear to have prognostic relevance.[3] Such parameters are rarely assessed in daily clinical practice, even though they could be easily obtained from computed tomographies (CTs) used for tumor staging.[4]

In the past, several body composition parameters have been examined, with contradicting results regarding their prognostic relevance. This was most likely due to heterogeneity of study populations, methods employed to analyze the data, cut-offs used and clinical settings examined[5–21] Sarcopenia—a term used for low muscle mass—was associated with frailty, immobility and worse overall survival (OS) in PDAC patients.[8–11,15–18,20,22] The combination of sarcopenia with obesity (sarcopenic obesity) or visceral obesity (sarcopenic visceral obesity) demonstrated potential prognostic relevance in other types of cancer.[23] Both conditions were investigated in PDAC patients and were related to unfavorable outcomes.[16,18,21] Furthermore, myosteatosis, a state of increased fat content in the muscular tissue, which can be determined on the CT scan using reduced radiodensity values of the muscular compartment, has been identified as a putative cause of decreased muscle strength and quality as well as a predictor of worse survival.[5,9,14,16,17]

However, the transferability of the findings to other cohorts is unclear as most of the mentioned studies were monocentric and comprised limited patient numbers. In addition, almost half of the published studies have only included patients from Asia. Given the different values of body composition parameters between Asian and Caucasian populations, the generalizability of these results remains elusive.[24]

The aim of the present study was to evaluate various body composition parameters as predictors of survival in a large European multicenter cohort. The identification of patients at risk offers the potential to facilitate a more targeted and patient-focused therapy. Early detection of prognostic factors allows immediate intervention and potentially improves the prognosis and quality of life (QoL).

Key summary

Summarize the established knowledge on this subject

- Body composition parameters appear to play a prognostic role in patients with pancreatic carcinoma, but data among studies are inconsistent, methods vary, and analyses of larger cohorts are lacking.

What are the significant and/or new findings of this study?

- The analysis of this large Caucasian cohort showed that, among body composition parameters, only myosteatosis was an independent prognostic factor of overall survival in multivariable Cox regression analysis.
- The prognostic impact of myosteatosis was relevant especially for patients ≤68 years of age, patients with advanced tumor stages and patients without curative intended resection.
- Age-, sex-, and Body Mass Index-adjusted cut offs where used to enable a personalized analysis approach paving the way for a precision medicine-based treatment approach.

METHODS

Data collection

In this multicenter retrospective study, data were collected from PDAC patients diagnosed between 2011 and 2019 at the Sheffield teaching Hospital NHS trust, Sheffield, UK and the University Hospital Halle, Halle (Saale), Germany. Inclusion criteria were histological confirmation of PDAC, abdominal CT with sufficient image quality at the time of diagnosis and a minimum follow-up of 12 months. Comorbidities were assessed by calculation of the Charlson Comorbidity Index (CCI).[25] Patients with incomplete clinical data and/or active second cancer were excluded from the analysis. The primary end-point of the analysis was OS, as defined by the time of diagnosis until death. Patients with missing values for the following selected variables were removed: Body Mass Index (BMI; $n = 21$), CCI ($n = 5$) and skeletal muscle index (SMI; $n = 27$), no information on resection margin ($n = 2$) and 3 patients who had only available non-contrast CT. The total analyzed sample size was 354 PDAC patients.

Measurements of primary body composition parameters

Measurements of muscle and fat compartments were performed on a single axial CT slice at the longitudinal center of the third lumbar vertebra (L3) by experienced radiology specialists in the two institutions separately. Analyzed CT scans were retrieved at the time of PDAC diagnosis. The segmentation of the different abdominal tissues was performed semiautomatically by the use of the analysis software SliceOMatic V5.0 (Tomovision) based on characteristic radiodensity ranges (Figure 1). According to previous studies, the attenuation range of −29 to +150 Hounsfield units (HU) was defined for muscle tissue (skeletal muscle area, SMA), −190 to −30 HU for subcutaneous (SAT) and intermuscular adipose tissue, and −150

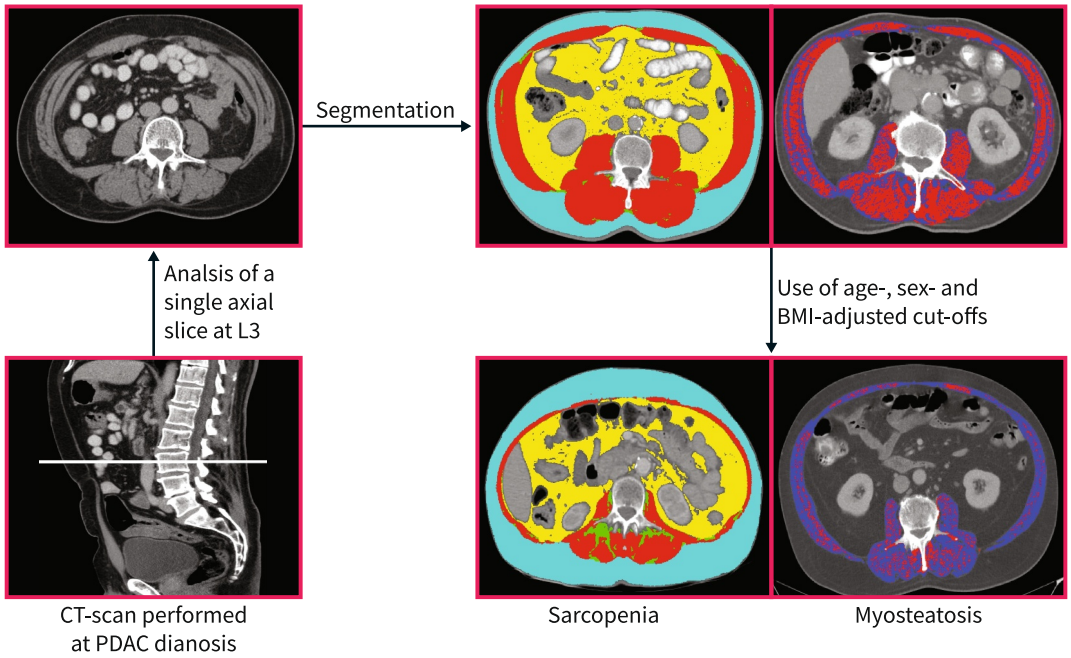

FIGURE 1 Measurements of body composition parameters. Measurements of muscle and fat compartments were performed on a single axial computed tomography (CT) slice at the longitudinal center of the third lumbar vertebra (L3) (left, bottom, and top). Analyzed CT scans were retrieved at the time of PDAC diagnosis. The segmentation of the different abdominal tissues was performed based on characteristic density ranges. The muscle tissue (muscle mass, MM) is displayed in red (middle, top). Subcutaneous (SAT), intermuscular (IMAT), and visceral adipose tissue (VAT) in turquoise, green, and yellow. To visualize the intramuscular fat, muscular tissue with low density (−29 to 50 HU) is displayed in blue (right, top). Shown are exemplary patients with sarcopenia (middle, bottom) and myosteatosis (right, bottom). PDAC, pancreatic ductal adenocarcinoma.

to −50 HU for visceral adipose tissue (VAT).[26,27] The mean HU of the muscle area (MMA, mean muscle attenuation), also referred to as muscle radiodensity, served as a proxy for the extent of intramuscular fat infiltration, that is, myosteatosis.

Secondary body composition parameters

Secondary parameters were not directly measured but were derived from primary body composition parameters. The SMI was calculated by correcting SMA at L3 for the patient's height: SMA (cm^2)/height squared (m^2). For the definition of sarcopenia, a *z*-score was calculated, with height-standardized and BMI- and sex-adjusted regression formula derived from a healthy population, using −2 *z*-score cut-off value for diagnosis.[28] The approach used to define myosteatosis was similar, using cut-offs for MMA adjusted for age, sex and BMI.[29] The total adipose tissue equaled the SAT and VAT added together. Visceral adiposity was defined as a ratio of visceral to subcutaneous fat area (VSR, visceral to subcutaneous adipose tissue area ratio = VAT/SAT) above 0.96 for women, and above 1.41 for men.[16] The size of muscle area relative to the area of the visceral fat was determined as visceral to muscle ratio (VMR = SMA/VAT). Obesity was present if the BMI was ≥30 kg/m^2 and visceral obesity if the area of visceral fat (VAT) was >100 cm^2. Sarcopenic obesity and sarcopenic visceral obesity were combinations of these parameters with concomitant prevalent sarcopenia.

Statistical analysis

Continuous variables were investigated with Kruskal-Wallis test and reported as median with interquartile range (IQR). Categorical variables are presented as frequencies with percentages, analyzed with the Chi-square or Fisher exact tests. The median overall survival (mOS) was calculated using the Kaplan-Meier method and the log-rank test was used to assess the differences between the curves. All patients were censored after a follow-up of 24 months. To evaluate prognostic factors among body composition parameters, variables were dichotomized and uni- and multivariable Cox proportional hazards regression analyses were performed. Results from the univariable models guided the selection, with promising variables ($p \leq 0.10$), subsequently included in the multivariable analysis. All analyses were performed using SAS software version 9.4 (SAS Institute).

RESULTS

Characteristics of study population

In total, 354 patients were analyzed (Table 1). The median age (IQR) was 68 (60–75) years, of which 40% of patients were women. The median BMI (IQR) was 25.1 (22.9–28.0) kg/m^2. In our dataset, 43% of the patients were tumor stage UICC I/II, while 30% and

TABLE 1 General characteristics of PDAC patients.

Characteristics	Overall cohort (n = 354)
Age, years (median, IQR)	68 (60–75)
<60 years, *n* (%)	85 (24.0%)
60–70 years, *n* (%)	114 (32.2%)
>70 years, *n* (%)	155 (43.8%)
Sex, *n* (%)	
Women	142 (40.1%)
Men	212 (59.9%)
BMI (median and IQR)	25.1 (22.9–28.0)
BMI <30 kg/m^2, *n* (%)	292 (82.5%)
BMI ≥30 kg/m^2, *n* (%)	62 (17.5%)
CCI, *n* (%)	
0	119 (33.6%)
1	117 (33.1%)
2+	118 (33.3%)
UICC, *n* (%)	
Stadium IA/IB/IIA/IIB	153 (43.2%)
Stadium III	106 (30.0%)
Stadium IV	95 (26.8%)
Resection, *n* (%)	
No resection	233 (65.8%)
R0	81 (22.9%)
R1/R2[a]	40 (11.3%)
Survival	
Median follow-up, months (IQR)	11.2 (5.3–19.7)
Median OS, months (95% CI)	11.2 (10.0–12.7)
2-year survival (95% CI)	22% (18%–27%)
Body composition	
MM, cm^2, median (IQR)	129.6 (107.5–153.7)
SMI, cm^2/m^2, median (IQR)	44.5 (39.4–50.7)
MMA, HU, median (IQR)	34.3 (28.9–40.2)
TAT, cm^2, median (IQR)	310.6 (203.1–416.8)
SAT, cm^2, median (IQR)	157.3 (103.9–216.5)
VAT, cm^2, median (IQR)	139.8 (68.4–214.7)
IMAT, cm^2, median (IQR)	11.1 (6.5–17.0)
VMR, median (IQR)	0.94 (0.65–1.70)
VSR, median (IQR)	0.77 (0.46–1.29)
Sarcopenia, yes, *n* (%)	114 (32.2%)
Myosteatosis, yes, *n* (%)	61 (17.2%)
Visceral obesity, yes, *n* (%)	222 (62.7%)
Sarcopenic visceral obesity, yes, *n* (%)	78 (22.0%)
Sarcopenic obesity, yes, *n* (%)	25 (7.0%)
Visceral adiposity, yes, *n* (%)	75 (21.2%)

Abbreviations: BMI, Body Mass Index; CCI, Charlson Comorbidity Index; IMAT, intermuscular adipose tissue; IQR, interquartile range; MM, muscle mass; MMA, mean muscle attenuation; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; SAT, subcutaneous adipose tissue; SMI, skeletal muscle index; TAT, total adipose tissue; UICC, Union Internationale Contre le Cancer; VAT, visceral adipose tissue; VMR, visceral to muscle ratio; VSR, visceral to subcutaneous adipose tissue area ratio.

[a]R2 margin was combined with R1 due to a very low number of patients in the R2 resection group.

27% were UICC III and IV, respectively. Approximately one-third (32%) of the patients were sarcopenic, whereas 17% showed myosteatosis. Obesity, visceral obesity, sarcopenic obesity, sarcopenic visceral obesity, and visceral adiposity were prevalent in 18%, 63%, 7%, 22%, and 21% of patients. The median follow-up was 11.2 months (IQR 5.3–19.7 months) and the mOS was 11.2 months (95% CI 10.0–12.7). The 2-year survival rate was 22% (95% CI 18%–27%).

Body composition characteristics

Supplemental Table S1 summarizes the differences in patients with or without sarcopenia, myosteatosis and sarcopenic visceral obesity. The group of patients with sarcopenia was older (71 years vs. 65 years, $p < 0.001$) and had a higher proportion of men (74% vs. 53%, $p < 0.001$). There were fewer R0 resections in sarcopenic patients (15% vs. 27%), although more than half of these patients were in an earlier stage than patients without sarcopenia.

In the myosteatosis group, there was also a similar difference with regard to sex distribution but not with age. Of note, the distribution of the tumor stages did not differ between the groups.

The height, BMI and sex-adjusted median cut-offs of the whole study population for sarcopenia and myosteatosis were 40.8 (IQR 35.5–44.8) cm/m^2 (men: 43.1 (IQR 39.5–46.7) cm/m^2; women: 34.0 (IQR 31.2–35.7) cm/m^2) for the SMI and 22.6 (IQR 16.7–27.9) HU (men: 25.2 (IQR 18.3–28.1) HU, women: 16.6 (IQR 13.5–17.7)) HU for the MMA.

Survival analysis

Kaplan-Meier analysis showed a tendency toward, but not significant, worse mOS for patients with sarcopenia (10.3 (95% CI 8.7–13.9) versus 11.3 (95% CI 9.9–13.0) months, $p = 0.09$), myosteatosis (8.2 (95% CI 4.7–13.9) versus 11.3 (95% CI 10.3–13.0), $p = 0.07$), sarcopenic obesity (10.3 (95% CI 4.7–15.3) versus 11.2 (95% CI

10.0–12.8), $p = 0.15$) and sarcopenic visceral obesity (10.0 (95% CI 5.5–13.9) versus 11.3 (95% CI 10.2–13.0), $p = 0.1$) (Figure 2).

The stratified analysis by subgroups showed significantly poorer survival in patients with tumor stage I/II and sarcopenia ($p = 0.02$), but not in the group of patients with stage III/IV ($p = 0.08$) (Figure 3; Supplemental Figure S1).

Interestingly, the same subgroup analysis showed an inverted prognostic impact of myosteatosis. There was a difference in mOS in patients with stage III/IV when myosteatosis was present ($p = 0.001$) (Supplemental Figure S2). Similarly, there was also a worse prognosis in patients without curative intended resection in the presence of myosteatosis ($p = 0.02$) (Figure 4). Regarding subgrouping by age,

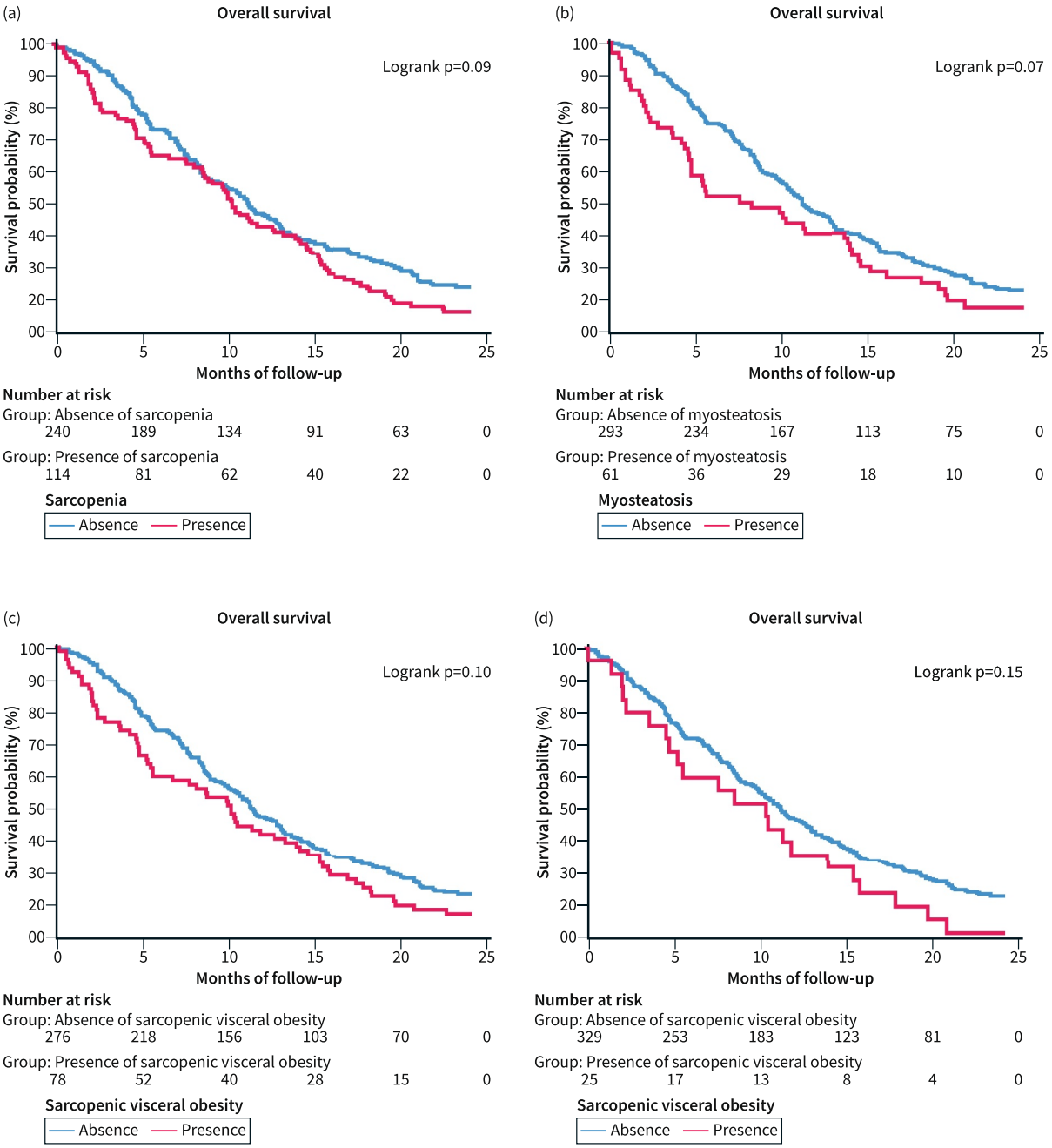

FIGURE 2 Survival of PDAC patients in presence or absence of body composition characteristics. Kaplan-Meier curves of PDAC patients with the presence or absence of sarcopenia (a), myosteatosis (b), sarcopenic visceral obesity (c), and sarcopenic obesity (d). The analysis showed a tendency toward, but not significant, worse mOS for patients with sarcopenia (10.3 (95% CI 8.7–13.9) versus 11.3 (95% CI 9.9–13.0) months, $p = 0.09$), myosteatosis (8.2 (95% CI 4.7–13.9) versus 11.3 (95% CI 10.3–13.0), $p = 0.07$), sarcopenic obesity (10.3 (95% CI 4.7–15.3) versus 11.2 (95% CI 10.0–12.8), $p = 0.15$), and sarcopenic visceral obesity (10.0 (95% CI 5.5–13.9) versus 11.3 (95% CI 10.2–13.0), $p = 0.10$). mOS, median overall survival; PDAC, pancreatic ductal adenocarcinoma.

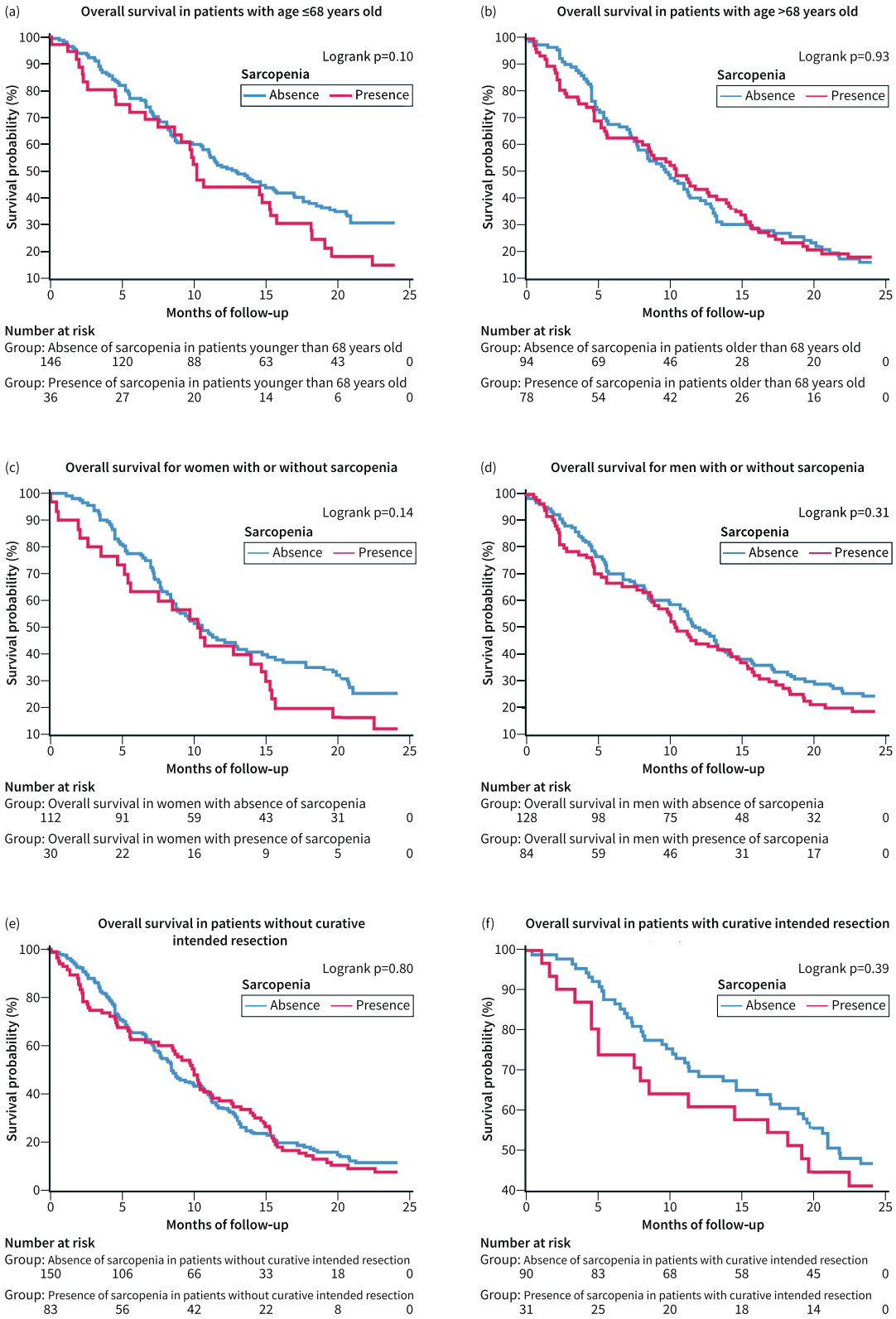

FIGURE 3 Subgroup analysis of PDAC patients in the presence or absence of sarcopenia. Different prognostic relevance of sarcopenia in subgroups defined by different ages (a and b), gender (c and d) and resection status (e and f) in PDAC patients. There was no prognostic difference in sarcopenia in different age groups, gender, or resection status. PDAC, pancreatic ductal adenocarcinoma.

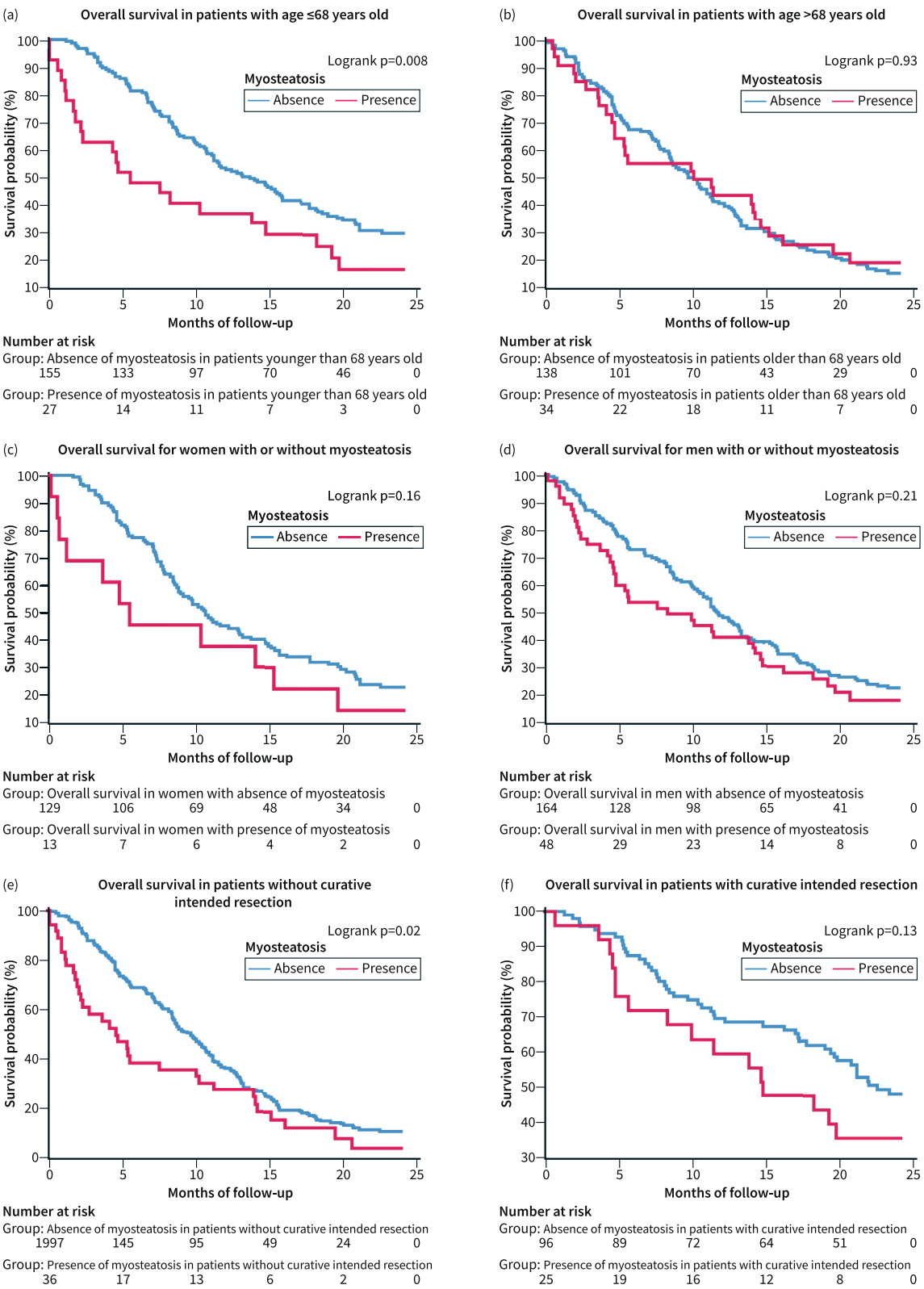

FIGURE 4 Subgroup analysis of PDAC patients in the presence or absence of myosteatosis. Different prognostic relevance of myosteatosis in subgroups defined by different ages (a and b), gender (c and d) and resection status (e and f) in PDAC patients. Myosteatosis was associated with significantly poorer survival in patients with age ≤68 years ($p = 0.008$), but not in the group of older patients ($p = 0.84$). There was no difference in the prognostic impact of myosteatosis based on gender. The worse prognosis with the presence of myosteatosis was in patients without curative intended resection status ($p = 0.02$). PDAC, pancreatic ductal adenocarcinoma.

unfavorable prognosis was seen for myosteatosis in younger age (≤68 years) in comparison to older patients (>68 years) ($p = 0.008$). Subgroup formation according to different ranges of BMI or CCI did not lead to any survival differences (results not shown).

Regression analysis

The univariable and multivariable regression analysis is shown in Table 2. Only categorical variables were analyzed.

All body composition parameters, that showed a tendency toward worse survival in univariable analysis ($p \leq 0.10$) and other prognostically important variables such as stage and resection status were included in the multivariable model together with age and sex.

Myosteatosis (HR: 1.53 (95% CI 1.10–2.14), $p = 0.01$), but not sarcopenia or sarcopenic visceral obesity had an independent impact on OS in PDAC patients. Curative-intent resection and higher tumor stage (UICC III/IV) were also significantly associated with better (0.37 (95% CI 0.27–0.52), $p < 0.001$) and worse (1.35 (1.02–1.80), $p = 0.03$) prognosis.

DISCUSSION

In the present retrospective study of pooled data from two specialized centers, we demonstrated that among body composition parameters only myosteatosis was an independent prognostic factor leading to a reduced mOS in PDAC patients in a multivariable model. Subgroup analysis revealed that the prognostic impact of myosteatosis was significant in younger patients (≤68 years), patients without curative intended resection and patients with advanced tumor stages (UICC III/IV).

TABLE 2 Survival analyses with Cox proportional hazards models.

	Univariable model		Multivariable model	
Variable	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Age				
≤68 years	Reference		Reference	
>68 years	**1.37 (1.08–1.74)**	***0.009***	1.19 (0.92–1.53)	*0.17*
Men	Reference		Reference	
Women	0.97 (0.76–1.25)	*0.97*	1.11 (0.86–1.43)	*0.40*
BMI				
<30	Reference		-	-
≥30	1.21 (0.89–1.64)	*0.22*	-	-
CCI, *n* (%)				
0	Reference		-	-
1	0.84 (0.59–1.20)	*0.35*	-	-
2+	1.07 (0.82–1.40)	*0.59*	-	-
UICC, *n* (%)				
Stadium IA/IB/IIA/IIB	Reference		Reference	
Stadium III/IV	**1.81 (1.42–2.32)**	***<0.0001***	**1.35 (1.02–1.80)**	***0.03***
Curative resection				
No	Reference		Reference	
Yes	**0.33 (0.25–0.44)**	***<0.001***	**0.37 (0.27–0.52)**	***<0.0001***
Sarcopenia, yes	**1.23 (0.96–1.59)**	***0.09***	1.02 (0.68–1.54)	*0.89*
Myosteatosis, yes	**1.32 (0.97–1.80)**	***0.07***	**1.53 (1.10–2.14)**	***0.01***
Visceral adiposity, yes	1.14 (0.85–1.52)	*0.35*	-	-
Sarcopenic obesity, yes	1.37 (0.88–2.12)	*0.15*	-	-
Sarcopenic visceral obesity, yes	**1.26 (0.95–1.66)**	***0.10***	1.04 (0.67–1.62)	*0.85*

Note: All *p*-values are in italics. In bold we marked promising variables in the univariable model (promising variables ($p \leq 0.10$)) and significant variables in the multivariable model. ($p < 0.05$).

Abbreviations: BMI, Body Mass Index; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; UICC, Union Internationale Contre le Cancer.

Myosteatosis

Myosteatosis is a condition that increases with aging, is associated with insulin resistance and diabetes and is negatively correlated with muscle mass, strength, and mobility.[30] Furthermore, it has been associated with systemic inflammation in PDAC and colorectal cancer patients.[31] It has been hypothesized that the fat infiltration of the muscle mediates toxic effects, which exacerbate systemic inflammation and insulin resistance.[32,33] However, reverse causality is also conceivable, such that cancer-induced inflammation triggers myosteatosis. In a mouse xenograft model with human PDAC cells, it was shown that PDAC-derived interleukin-6 signaling resulted in myosteatosis, adipocyte lipolysis and systemic inflammation.[34] This crosstalk between tumor, muscle and fat led to cachexia and was associated with increased mortality. Interestingly, removal of IL-6 led to reversed effects, indicating that this is a potential therapeutic approach.

However, there is no generally accepted definition of myosteatosis. The European Working Group on Sarcopenia in Older People (EWGSOP) recommended that, if possible, cut-offs should be derived from reference values of healthy young adults.[35] In line with these recommendations, we used cut-offs for myosteatosis, which have been defined in a healthy Caucasian population.[29] Moreover, these cut-offs were adjusted for age, sex, and BMI. This individual adjustment is particularly important in view of the fact that myosteatosis correlates with these parameters. This method has the most accurate reproducibility and can therefore be implemented in clinical practice for use on individual patients in terms of precision medicine. ROC-curve derived cut-offs from previous studies lack this individual adjustment and therefore the accuracy seems insufficient.

While most of the previous studies that examined the prognostic impact of body composition parameters in PDAC patients did not assess myosteatosis, several smaller studies with Asian PDAC patients showed comparable results.[5,14,16] Conversely, two studies failed to demonstrate the independent prognostic relevance of myosteatosis[18,19]. In the study of Rollins et al., 228 patients with unresectable PDAC or distal cholangiocarcinoma treated in the United Kingdom were investigated.[19] In univariable analysis myosteatosis was associated with reduced OS, in contrast to sarcopenia. Myosteatosis was associated with systemic inflammation and anemia. Furthermore, myosteatosis correlated with worse performance status. However, this relationship did not persist in an age- and sex-adjusted multivariable Cox regression model. In the study of Peng et al., 116 patients with resectable PDAC from Taiwan were analyzed.[18] Here, myosteatosis was neither associated with OS in univariable nor in multivariable analysis, whereas sarcopenia was the only significant prognostic factor for OS among all variables analyzed.

One explanation for these differences may be the definition of the cut-offs for myosteatosis used in the distinct studies. Of note, the mentioned studies had a 2, 5–3-fold higher prevalence of myosteatosis compared with our data. Thus, the reported myosteatosis prevalence of up to 55% was significantly higher than in our study with 17%.

The previously used cut-offs were determined in a ROC curve analysis of a population with various cancers and not only PDAC patients.[36] They were much higher than the cut-off used in the present study (<33–41 HU vs. <22.6 HU (median)). Nonetheless, the different cut-offs do not seem to be the sole explanation for the divergent results. For instance, in the study of Griffin et al., the same cut-offs as in our study were used. In this study, patients with borderline resectable PDAC receiving neoadjuvant chemotherapy were investigated and muscle attenuation influenced prognosis in the multivariable model.[14] Consistent with these results, Okumura et al. performed a ROC curve analysis in patients with localized PDAC who underwent resection. The cut-offs were <30.7 (for females) and <34.6 (for males) HU and the prevalence of myosteatosis was higher compared to our data (48%). Here, myosteatosis was associated with worse OS in multivariable analysis and with higher age, lower albumin level and a lower completion rate of adjuvant chemotherapy.[16]

Based on the retrospective nature of our study, several confounders may be present that potentially influence the results. In addition to differences in ethnic or demographic characteristics and the methodology used, discrepancies could be explained by varying prevalence of tumor stages in the populations or different tumor therapies used.

Sarcopenia

Our data did not confirm the independent influence of sarcopenia on survival in PDAC patients as seen by others.[8,10,11,16,18,20] As stated above, differences in methodology and study populations are most likely responsible for these discrepancies.

While this study followed the EWGSOP recommendations, none of the previously mentioned studies used cut-offs determined in a healthy population. Because of the different methodology in these analyses, with cut-offs ranging from <34 to <52 cm^2, wide variability of sarcopenia prevalence in PDAC populations has been reported, ranging from approximately 17% to 63%. Moreover, they were conducted almost exclusively in Asian cohorts. With our approach, we had a prevalence of 32.2%, which almost corresponded to the prevalence of a meta-analysis of >4400 patients with PDAC (40%).[37] Interestingly, the studies that did not find an independent association between sarcopenia and survival comprised exclusively Caucasian PDAC patients.[14,19,38] Of note is a recently published Italian study of 371 PDAC patients who underwent surgery. Although there was an association between sarcopenic obesity and postoperative complications, the disease-free survival was not affected.[39] To further clarify the influence of ethnicity on sarcopenia, comparative studies are needed. Finally, a systematic review of sarcopenia in approximately 2000 different advanced cancer patients also concluded that sarcopenia did not impact the prognosis.[40]

Parameters that describe distribution of fat tissue

Previous studies identified high VSR as prognostically relevant in resectable and advanced PDAC.[9,16] Visceral fat is recognized to be

more bioactive than subcutaneous fat, promoting systemic inflammation and oncogenesis via proinflammatory cytokines.[41] In the present study, body composition parameters related to the quantity or distribution of fat did not show a significant association with survival. This might be partially explained by the fact that we had to use cut-offs for VSR determined by Okumura et al. in a Japanese cohort as cut-offs from a healthy Caucasian population are lacking. However, such cut-offs are urgently needed for the analysis of Caucasian patients since Asian populations are characterized by a high visceral fat content for a given body weight compared with matched Caucasian populations.[24] This assumption can be transferable to PDAC patients, because in the study by Okumura et al., visceral adiposity was significantly more often observed compared to our study (54% vs. 28% of the patients).

Limitations

Despite the large sample size and compliance with methodological recommendations as published using expert guidelines, this study has some limitations. Because of the retrospective nature, patient selection bias might be present. The multi-center design could be another source of bias due to possible regional differences in patient characteristics and treatment protocols. In addition, potential confounders that may affect survival, such as the administration of chemotherapy or performance status, were not included in the analysis.

To keep the representativeness of the study population as high as possible, patients with any stage and therapy were included. However, even with this increased sample size a stratified analysis proved challenging due to a small number of patients with the respective characteristics.

Furthermore, although patients with obvious anasarca or fluid collections were excluded from the analyses, reduced attenuation values from fluid accumulation in the muscle cannot be completely ruled out. Finally, this study only analyzed morphological criteria of the muscles and cannot provide information about the actual clinical muscle function, which can only be obtained via clinical tests such as hand grip strength.

Future perspectives and conclusion

Prospective data on PDAC patients providing evidence for physical or nutritional interventions in specific high-risk patients are scarce. Some authors support the implementation of a routinely conducted "Nutritional Oncology Board" with the aim of performing systematic screening to facilitate early and sustained implementation of nutritional support.[3]

In general, to support muscle anabolism and reduce catabolism, the early and proactive combination of both nutritional and exercise interventions as a multimodal approach is recommended.[42] Dietary interventions should include adequate provision of energy and protein, possibly supported by oral nutritional supplements. In addition, certain nutrients such as amino acids (leucine), vitamin D, n-3 polyunsaturated fatty acids, and beta-hydroxy-beta-methylbutyrate can enhance the anabolic potential.

In a small study, home-based moderate-intensity aerobic exercises and resistance training of 33 PDAC patients during neoadjuvant therapy prevented a decrease in SMI and resulted in a small but not significant increase in muscle density.[43] However, there was no nutritional intervention and outcomes such as survival or QoL were not investigated.

Interestingly, a recently published study showed that a 12-week intervention consisting of exercises and protein supplementation increased lean soft tissue by an average of 0.9 kg in elderly patients diagnosed with advanced pancreatic cancer compared to controls.[44] In addition, QoL, symptom burden, and physical performance improved in the intervention group, but there was no significant effect on survival.

These results show that favorable effects for the patients can be achieved even with a relatively short period of the intervention and that despite the limited life expectancy of these patients, it should be implemented more widely. However, there is an urgent need for prospective evidence in this field.

In the present study, we showed that myosteatosis, but not sarcopenia, is an independent prognostic factor of mOS in PDAC patients. Data from this large Caucasian study could help to identify high-risk patients and enable early targeted therapy to improve their outcome. Since CT imaging is routinely performed as part of the diagnostic algorithm for PDAC patients, such data could be easily implemented into the work-up. The cut-offs chosen in our study seem applicable, although prospective validation is still required.

AUTHOR CONTRIBUTIONS

Conceptualization: Marko Damm, Ljupcho Efremov, and Johannes Dober. *Methodology*: Marko Damm, Ljupcho Efremov, and Johannes Dober. *Formal analysis*: Ljupcho Efremov. *Data curation*: Marko Damm, Ljupcho Efremov, Mustafa Jalal, Nabeegh Nadeem, Johannes Dober, and Jonathan Wadsley. *Writing—original draft preparation*: Marko Damm, Ljupcho Efremov, and Johannes Dober. *Writing—review and editing*: Marko Damm, Ljupcho Efremov, Mustafa Jalal, Nabeegh Nadeem, Johannes Dober, Patrick Michl, Walter A. Wohlgemuth, Jonathan Wadsley, Andrew D. Hopper, Sebastian Krug, and Jonas Rosendahl. *Visualization*: Marko Damm and Ljupcho Efremov. *Supervision*: Jonas Rosendahl and Sebastian Krug. *Project administration*: Marko Damm. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

Anonymized datasets with the removal of potentially identifying variables can be requested from the corresponding author.

ETHICS APPROVAL

The study was performed in accordance with the Declaration of Helsinki. The ethics committee of the Martin-Luther-University Halle-Wittenberg provided ethical approval on the 24th of July 2020 (Number: 2020-115). The study was also approved previously by the local institutional review board of Sheffield Teaching Hospitals (REC-reference: 21/HRA/2546). According to their decisions, gaining informed consent was not required due to the retrospective nature of this study. Clinical data were collected from patient files at each center, coded and transferred as fully anonymized data for analysis.

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