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Prognostic values of abdominal body compositions on survival in advanced pancreatic cancer

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Abstract

To investigate the clinical impact of body composition on outcomes in advanced pancreatic cancer (APC), we performed a retrospective analysis of patients diagnosed with APC between 2010 and 2016. The extent of visceral fat, subcutaneous fat, and skeletal muscle was measured using computed tomography (CT) images, together with visceral to subcutaneous adipose tissue area ratio (VSR) and skeletal muscle index (SMI). The effects of these body composition parameters on survival in APC were explored. In total 203 APC patients were enrolled in this study, with a median age of 65 years (range: 31–80 years). The median overall survival (OS) was 9.5 months (95% confidence interval, 7.6–12.4 months). The survival analysis showed that OS in patients with high SMI was significantly longer than those in patients with low SMI (11.1 vs 8.0 months, $P < .001$). However, when analyzed with VSR, the OS in patients with high VSR was significantly shorter than those in patients with low VSR (8.3 vs 9.4 months, $P < .001$). Multivariate analyses revealed that ECOG performance status (hazard ratio [HR]: 1.56; $P < .001$), stage III (HR: 0.63; $P = .039$), SMI (HR: 0.92; $P = .019$), VSR (HR: 1.38; $P = .005$), and skeletal muscle area (HR: 0.95; $P = .049$) were independent risk factors for mortality. In conclusion, visceral adiposity, as well as low muscle mass and quality, was closely associated with OS of APC. Therefore, evaluating body compositions may be a practical approach for predicting patient prognosis.

Abbreviations: 95% CI = 95% confidence interval, APC = advanced pancreatic cancer, BMI = body mass index, CT = computed tomography, ECOG PS = Eastern Cooperative Oncology Group performance status, HR = hazard ratio, HU = Hounsfield unit, MA = muscle area, OS = overall survival, ROC = receiver-operating characteristic, SD = standard deviation, SFA = subcutaneous fat area, SMI = skeletal muscle index, VFA = visceral fat area, VSR = tissue area ratio.

Keywords: adiposity, advanced pancreatic cancer, sarcopenia, survival analysis

1. Introduction

Pancreatic cancer is a common and highly aggressive type of malignancy, for which the 5-year overall survival (OS) rate is <6%.[1,2] In recent years, the incidence of pancreatic cancer has continuously increased. During 2000 to 2011, the incidence of pancreatic cancer in mainland China increased 1.3-fold and the mortality rate increased 1.2-fold.[3] Although surgery and systemic chemotherapy have been demonstrated to improve patient survival in resectable pancreatic cancers, the prognosis remains poor. In unresectable pancreatic cancer, the prognosis is even worse. In addition to tumor-related prognostic factors, patients' body compositions, such as obesity and muscularity, are considered to be associated with prognosis.[4]

Obesity is a major risk factor for diseases such as cardiovascular disease and type 2 diabetes. Recent evidence suggests that obesity is positively correlated with the risk of cancer and negatively correlated with prognosis.[5] Human adipose tissue is distributed in 2 main areas which have different structural and functional characteristics: the visceral fat area (VFA) and the subcutaneous fat area (SFA). Research shows that visceral fat is more bioactive in altering lipid metabolism, regulating many adipokines and promoting chronic inflammation.[6] VFA, SFA, and muscle area (MA) can be measured directly using computed tomography (CT) imaging, and visceral adiposity is determined by the measured parameters.[7] Recent studies have shown that central obesity in visceral to subcutaneous fat area ratio (VSR) is a poor prognostic factor for esophageal squamous cell carcinoma and hepatocellular carcinoma.[8,9]

Skeletal muscle loss and adipose tissue accumulation may occur simultaneously, a case usually defined as sarcopenic obesity. Skeletal muscle depletion is a powerful prognostic factor independent of body mass index (BMI). Muscle-reduced obesity has also been shown to correlate with poor prognosis of malignant tumors. Muscle reduction features include decreased muscle mass and infiltration of intramuscular fat, leading to decreased muscle strength and quality.[4] Different proportions and degrees of obesity among eastern and western populations

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due to differences in dietary habits between eastern and western populations.[10] We are unsure whether cutoff values of visceral obesity and muscle loss in western studies are applicable to study population and assessment efficacy in China. In this study, the relationship between the distribution of abdominal body composition parameters, such as VFA, SFA, MA, VSR, and skeletal muscle index (SMI), and the prognosis of advanced pancreatic cancer (APC) patients in eastern China was investigated. The purpose was to explore the value of evaluating APC patient prognosis using clinical indicators.

2. Methods

2.1. Patients characteristics

Between 2010 and 2016, a patient cohort with evidence of APC from the Department of Oncology at the First Affiliated Hospital of Soochow University was included in the study, including patients with locally advanced disease and distant metastases. Among the evaluated cases, patients were excluded who did not undergo a CT examination that included the third lumbar vertebra within the first 30 days before the first cycle of chemotherapy. The clinical and imaging parameters of patients were retrospectively collected. The main end point of this analysis was OS, as defined by the time from enrolment to death. Patients who were alive as of the cutoff date were administratively censored, whereas patients lost to follow-up were censored at the time of the last follow-up. An approved and signed Institutional Review Board informed consent form was obtained from all participants.

2.2. CT image analysis

Cross-sectional CT images of the third lumbar vertebra were analyzed using ImageJ software (version 1.44p; National Institutes of Health, USA), and the abdominal muscular fat boundaries were manually sketched at the level of the lower part of the third lumbar vertebra (Fig. 1). Two clinicians measured these images independently, and the mean of the 2 measurements was calculated for each patient. Tissue Hounsfield unit (HU) thresholds were used as follows: −150 to −50 for visceral fat, −190 to −30 for subcutaneous fat, and −29 to 150 for skeletal muscle.[7] To investigate the distribution of abdominal adipose tissue, VSR was calculated as follows: VSR = VFA (cm^2)/SFA (cm^2). A high VSR was regarded as a proxy for visceral adipose tissue accumulation. The area of the skeletal muscle was normalized for height; then, SMI was calculated as follows: SMI = MA (cm^2)/height squared (m^2). Low MA was regarded as a proxy for low muscle quality.

2.3. Statistical analysis

Continuous variables are expressed as mean ± standard deviation, and categorical variables are presented as frequency. Continuous variables were nonparametrically analyzed using the Mann–Whitney *U* test, whereas categorical variables were compared using either the χ^2 test or the Fisher exact test. Gender-specific cutoff values for each body composition parameter were explored using receiver-operating characteristic (ROC) curves. The cutoff values were calculated based on the best accuracy in relation to 1-year mortality. Cox proportional hazards assumptions were measured with Schoenfeld residual analysis for univariate and multivariate analysis at a level of significance of 0.05, and the 95% confidence interval (95% CI) was used to characterize the distribution of variables. The cumulative OS was calculated using the Kaplan–Meier method and log-rank test was used to assess the differences between the curves. All statistical analyses were performed using SPSS software (version 20.0; IBM Corporation, Somers, NY), with $P < .05$ being deemed statistically significant.

3. Results

3.1. General situation of patients

In our study, 203 APC patients who were treated with palliative chemotherapy from 2010 to 2016 were included. The patient's clinical characteristics are grouped by sex in Table 1. The median age at enrolment was 65 years (range, 31–80 years). Twenty-seven (13.3%) had local APC, and 186 (86.7%) had metastatic disease. One hundred eighty-three (90.1%) patients received gemcitabine-based chemotherapy; the rest received fluoropyrimidine-based chemotherapy (Table 1).

3.2. Body composition analysis

In this study, VFA (137.12 vs 109.52 cm^2), SFA (109.64 vs 95.31 cm^2), and MA (118.06 vs 91.32 cm^2) were significantly different between male and female patients ($P < .05$). For the standardized muscle index SMI, there was a significant difference between the male and female subgroups (42.02 vs 36.55 cm^2/m^2, $P = .029$). Further analysis of the distribution of abdominal fat in the cohort showed significant differences in VSR between the male and female subgroups (1.25 vs 1.15, $P = .033$) (Table 1).

3.3. Survival analysis

At last follow-up in June 2017, the median follow-up time was 13.0 months (95% CI, 8.1–16.9 months), with a total of 176

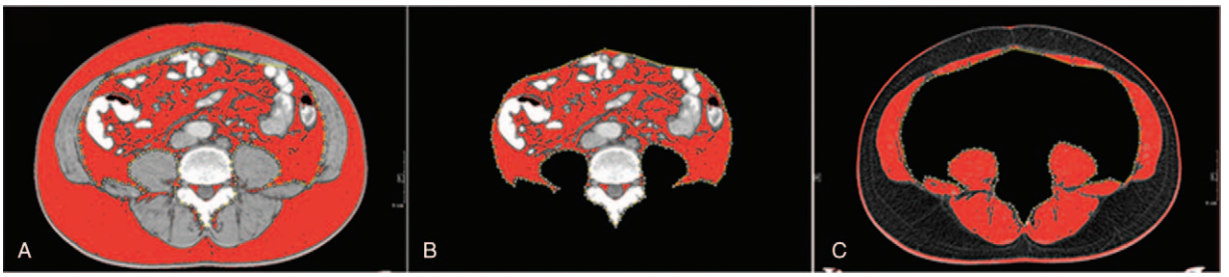

Figure 1. Measurement of body composition variables at the level of the third lumbar vertebra with CT images. (A) The areas of visceral fat and subcutaneous fat (red); (B) the areas of visceral fat (red); and (C) the areas of total skeletal muscle (red).

Table 1

Demographic and clinicopathological characteristics of the 203 patients included in our study.

	Male (n = 121)	Female (n = 82)	*P*
Age (mean ± SD), y	66 ± 32	65 ± 27	.382
ECOG PS (0–1/≥2)	97/24	56/16	.694
TNM stage (III/IV)	17/104	10/72	.703
Primary tumor location (head/body and tail)	91/30	61/21	.896
Primary tumor size ≥ 2 cm	88	63	.646
Poor differentiation	15	10	.830
CA19–9, U/mL	157.86 ± 22.32	171.65 ± 26.18	.254
Hemoglobin, g/L	124.71 ± 17.03	120.17 ± 13.62	.139
Serum albumin, g/L	39.11 ± 7.07	38.22 ± 6.96	.301
Prior chemotherapy	35	21	.605
Prior pancreatectomy	51	33	.923
BMI (mean ± SD), kg/m^2	21.17 ± 5.08	20.49 ± 4.31	.405
SMI (mean ± SD), cm^2/m^2	42.02 ± 18.01	36.55 ± 16.17	.029
VSR (mean ± SD)	1.25 ± 1.56	1.15 ± 1.34	.033
VFA (mean ± SD), cm^2	137.12 ± 67.43	109.52 ± 54.68	<.001
SFA (mean ± SD), cm^2	109.64 ± 43.02	95.31 ± 40.26	<.001
MA (mean ± SD), cm^2	118.06 ± 50.92	91.32 ± 40.36	<.001

BMI = body mass index, ECOG PS = Eastern Cooperative Oncology Group performance status, MA = muscle area, SD = standard deviation, SFA = subcutaneous fat area, SMI = skeletal muscle index, VFA = visceral fat area, VSR = tissue area ratio.

deaths during follow-up. The median OS was 9.5 months (95% CI, 7.6–12.4 months).

In the univariate analysis, the mortality-related variables included the Eastern Cooperative Oncology Group performance status (ECOG PS) (hazard ratio [HR]: 1.51; $P = .002$), tumor stage III (HR: 0.56; $P = .008$), serum albumin (HR: 0.45; $P = .039$), SMI (HR: 0.95; $P = .036$), VSR (HR: 1.49; $P < .001$), VFA (HR: 1.34; $P = .043$), SFA (HR: 1.31; $P = .046$), and MA (HR: 0.97; $P = .047$). In multivariate Cox regression analysis, the following scores were screened as independent prognostic factors: ECOG (HR: 1.56; $P < .001$), tumor stage III (HR: 0.63; $P = .039$), SMI (HR: 0.92; $P = .019$), VSR (HR: 1.38; $P = .005$), and MA (HR: 0.95; $P = .049$). Because of a weaker prognostic ability, baseline serum albumin, VFA, and SFA were dropped from the multivariate model. Additional factors were not entered because of lack of a significant prognostic effect (Table 2). The cutoff values of SMI and VSR were determined by ROC curve according to 1-year mortality rate. The cutoff value for SMI in the male subgroup is 43.62 cm^2/m^2 (sensitivity = 0.51; specificity = 0.72). The cutoff value for SMI in the female subgroup is 38.57 cm^2/m^2 (sensitivity = 0.38; specificity = 0.74). The cutoff values for VSR are 1.27 (sensitivity = 0.51; specificity = 0.67) in the male subgroup and 1.12 (sensitivity = 0.55; specificity = 0.63) in the female subgroup (Fig. 2), respectively. Study cohorts were grouped by SMI and VSR cutoffs. The survival analysis showed that the median OS was 11.1 versus 8.0 months ($P < .001$) in the high SMI and low SMI subgroups, respectively (Fig. 3A), whereas the median OS was 8.3 versus 9.4 months ($P < .001$) in the low VSR and high VSR subgroups, respectively (Fig. 3D). In male patients the median OS was 11.0 versus 8.0 months ($P < .001$) in the high SMI and low SMI subgroups, respectively (Fig. 3B). Furthermore, in female patients the high SMI subgroup had longer median OS than the low SMI subgroup (13.0 vs 6.7 months, $P < .001$) (Fig. 3C). Further analysis of the survival of VSR subgroups in different sex cases showed that the median OS in male patients was 8.4 versus 9.2 months for those categorized as high VSR and low VSR ($P = .007$), respectively (Fig. 3E). The median OS of female with high VSR or low VSR was 7.6 versus 10.6 months ($P < .001$), respectively (Fig. 3F).

4. Discussion

This study explored the influence of muscle fat composition distribution on the prognosis of APC. The results showed that SMI and VSR were associated with the OS of patients with APC. The prognosis was worse for APC patients with low SMI and high VSR.

For a pancreatic cancer patient who is overweight or obese (BMI ≥ 22 kg/m^2) combined with reduced muscle mass, OS is shorter

Table 2

Univariate and multivariate analysis for evaluation of the associations between tested parameters and overall survival.

	Univariate analysis		Multivariate analysis	
	HR(95% CI)	*P* value	HR(95% CI)	*P* value
Gender(male)	0.96(0.75-1.15)	0.871		
Age (≥60year)	1.03(0.88-1.29)	0.803		
ECOG PS (≥2)	1.51(1.16-1.96)	0.002	1.56(1.24-1.98)	<0.001
Stage III	0.56(0.36-0.86)	0.008	0.63(0.40-0.98)	0.039
Tumor location (head)	1.09(0.45-2.65)	0.852		
Tumor size ≥ 2 cm	0.94(0.38-2.28)	0.884		
CA19-9	1.83(0.96-2.98)	0.079		
Hemoglobin	0.86(0.66-1.05)	0.354		
Serum albumin	0.45(0.26-0.93)	0.039		
BMI	1.06(0.62-1.84)	0.826		
SMI	0.95(0.89-0.98)	0.036	0.92(0.87-0.96)	0.019
VSR	1.49(0.95-0.99)	<0.001	1.38(1.10-1.74)	0.005
VFA(cm^2)	1.34(1.03-1.73)	0.043		
SFA (cm^2)	1.31(1.01-1.69)	0.046		
MA (cm^2)	0.97(0.95-0.99)	0.047	0.95(0.92-1.00)	0.049

95% CI = 95% confidence interval, BMI = body mass index, ECOG PS = Eastern Cooperative Oncology Group performance status, HR = hazard ratio, MA = muscle area, SD = standard deviation, SFA = subcutaneous fat area, SMI = skeletal muscle index, VFA = visceral fat area, VSR = tissue area ratio.

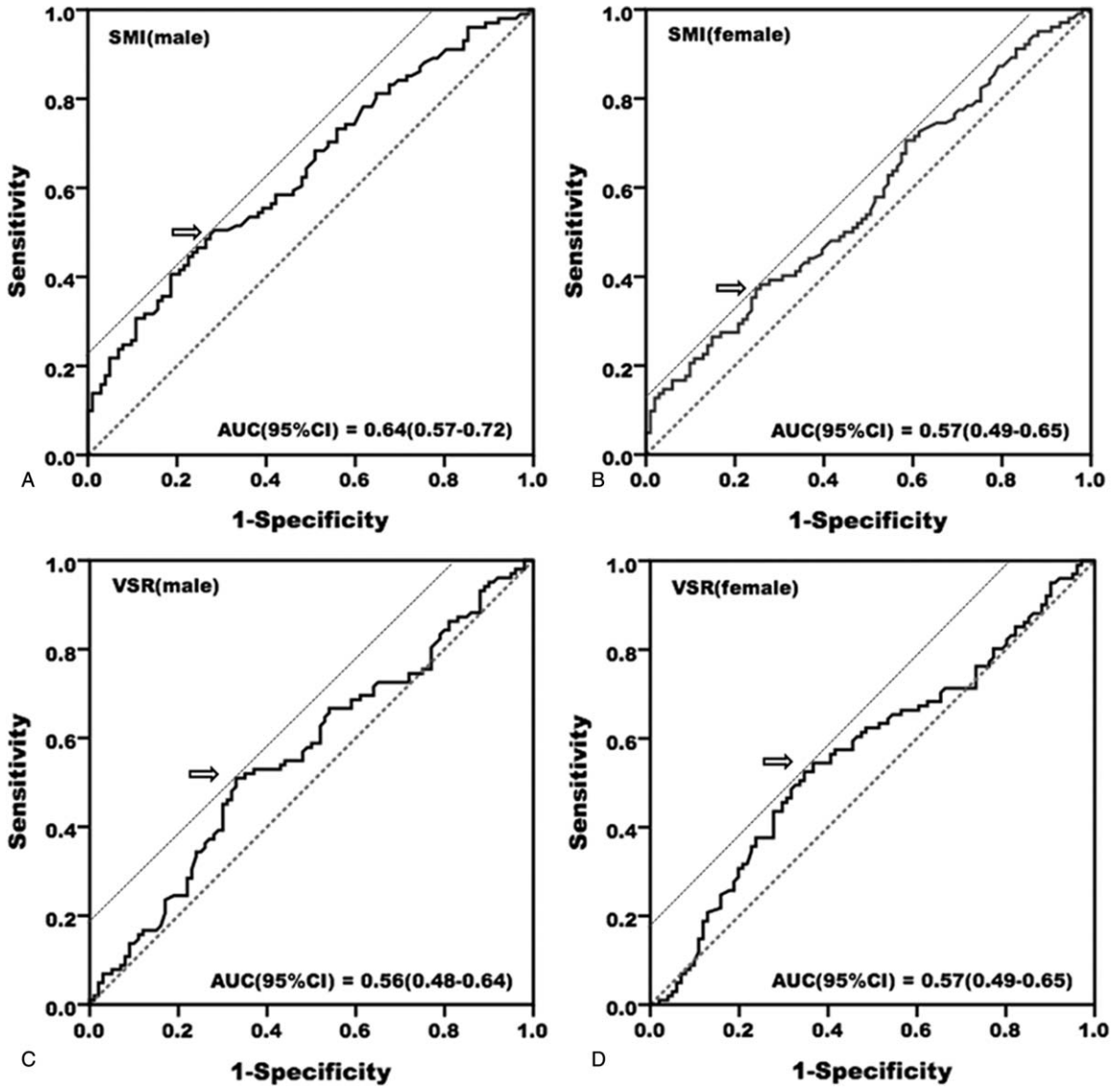

Figure 2. ROC curves of SMI and VSR. (A) ROC curve of SMI in the male subgroup with a cutoff of 43.62 cm^2/m^2; (B) ROC curve of SMI in the female subgroup with a cutoff of 38.57 cm^2/m^2; (C) ROC curve of VSR in the male subgroup with a cutoff of 1.27; and (D) ROC curve of VSR in the female subgroup with a cutoff of 1.12.

than that for a patient who has muscle mass reduction only.[11] Unlike the classic BMI obesity index, there is no clear definition of the cutoff value for muscle-reduced obesity and visceral obesity. In this study, the SMI cutoff value calculated by ROC curve was 43.62 cm^2/m^2 in the male subgroup and 38.57 cm^2/m^2 in the female subgroup, whereas the cutoff for VSR was 1.27 in the male subgroup and 1.12 in the female subgroup. Our study has some differences with the previous literature.[4,12,13] Nishigori et al presented SMIs, as assessed by CT images, for their male subgroup of 52.4 cm^2/m^2 and female subgroup of 38.5 cm^2/m^2 in Japanese population. There were significant differences in SMI among different sexes.[13] In another study carried out in a different Japanese population, the SMI parameter values were generally lower than those in Nishigori et al's work. Furthermore, the differences between male and female subgroups were also dissimilar.[4] The reason for this phenomenon may be that different ethnic groups and different dietary habits led to differences in the proportion of obesity in different regions.[14] Inflammation, decreased activity, low protein intake, and age-related factors are considered to be the major causes of muscle stenosis.[15] However, the exact mechanism by which muscle reduction increases the risk of mortality is still under investigation.

Previous studies have demonstrated a positive correlation between the degree of obesity and the risk of serious complications after radical resection in patients with early resectable pancreatic cancer, and that the risk of death increases with the accumulation of visceral fat.[9] In APC, obesity is also associated with patient survival, with a corresponding decrease in survival as the patient's BMI increases.[16] In our study, SMI and VSR were screened as independent prognostic factors, with an increased risk of death and an overall shorter survival in patients with low SMI and high VSR. Existing research suggests that both skeletal muscle and adipose tissue can be considered secretory organs.[17] However, in the case of skeletal muscle atrophy, myocyte energy expenditure decreases and the rate of fat deposition tends to increase.[18] Muscle reduction causes muscular contractile dysfunction leading to abnormal cellular energy states while also affecting a series of physiological

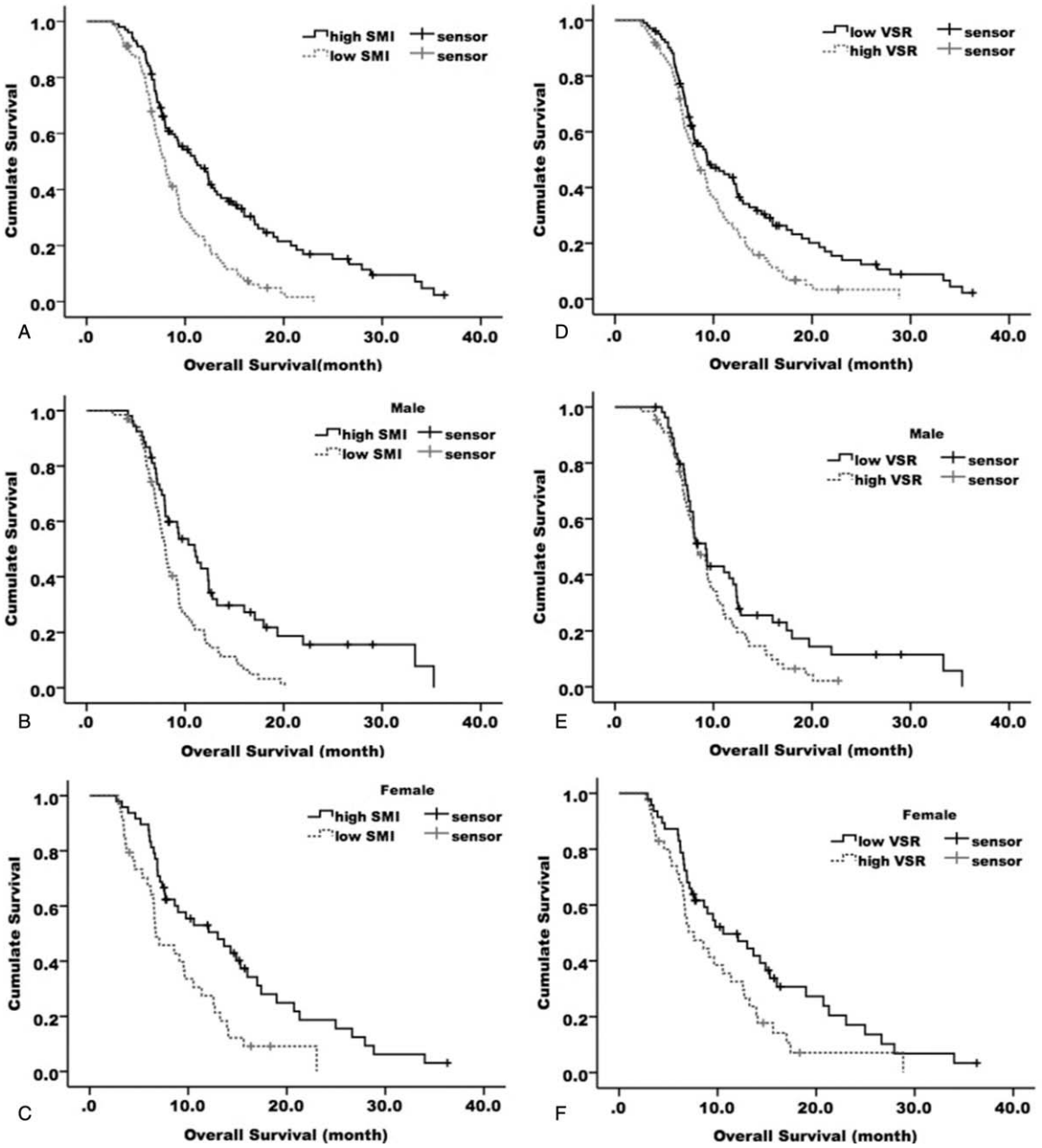

Figure 3. OS of patients with advanced pancreatic cancer based on SMI and VSR. (A) OS by SMI in study cohorts; (B) OS by SMI in male cohorts; (C) OS by SMI in female cohorts; (D) OS by VSR in study cohorts; (E) OS by VSR in male cohorts; and (F) OS by VSR in female cohorts.

processes such as impairments of cell growth, nutrient metabolism, insulin resistance, and cellular immunity.[13] Besides having different cytokine secretion profiles, the functions of visceral fat and subcutaneous fat are different.[19] Visceral fat is more bioactive in altering lipid metabolism, regulating many adipokines and thereby promoting chronic inflammation. Visceral and intramuscular fat accumulation increases the expression of proinflammatory cytokines, which are associated with chronic inflammation and oncogenesis. Therefore, visceral obesity, muscle mass loss, and intramuscular accumulation of adipose tissue are considered indicators of poor prognosis for survival.[20,21]

In clinical practice, visceral obesity and muscle loss are closely related to increased postoperative complications.[22] In patients with early-stage resectable pancreatic cancer, the risk of death was significantly increased and the survival was significantly shorter if preoperative BMI was $>22\,kg/m^2$, and the imaging findings suggested muscle-reduced obesity.[11] In patients receiving palliative chemotherapy, the dose of chemotherapeutic drugs is usually determined by body surface area or body weight. Patients with severe muscle-reduced obesity who are overweight are more likely to have chemotherapeutic toxicity than those with low weight, the proportion of premature termination of treatment rises due to increased toxicity of chemotherapy.[12] Furthermore, obesity-induced inflammation and tumor-associated neutrophil infiltration lead to the proliferation of adjacent tissues in the tumor microenvironment. On the one hand, this promotes tumor growth directly. On the other hand, it reduces

the response of tumor cells to chemotherapy agents through the blockage of chemotherapeutic drug dispersion.[23] Because our results were addressed in a dataset of a small Chinese community, and because cohorts enrolled were retrospectively collected at a single tertiary center, the sample size is still far from perfect, and results may therefore have been influenced by selection bias. Consequently, earlier reception of chemotherapy, which could extend the survival time from the beginning of enrollment, would result in a leading bias in the case of this study. Finally, the sensitivity and specificity of the test would be affected by the chosen classification standard. According to routine surveillance in clinical practice, our dichotomous analysis of ROC was based on survival status at 1 year. The optimal cutoff point of observation needs further exploration. Furthermore, it is important to consider whether our cutoff values are adequate for defining visceral adiposity in most areas of mainland China. Further work to evaluate the prognosis of APC should include validation with a larger cohort, initiation of multicenter collaborations, and exploration of further indicators of visceral obesity and low muscular obesity in China's population.

5. Conclusion

Visceral fat obesity and muscle loss are closely related to the risk of APC death. Therefore, evaluating body compositions may be a novel and accessible approach for predicting the prognosis of patients with APC.

Author contributions

Data curation: H.-J. Dai, H.-X. Ji, Y.-T. Fang.
Formal analysis: H.-J. Dai.
Funding acquisition: X.-J. Bian.
Methodology: X.-J. Bian, H.-J. Dai., W. Li.
Visualization: J. Nan, J. Feng.
Writing – original draft: H.-J. Dai.
Writing – review and editing: X.-J. Bian.

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