Higher BMI Indicated Better Overall Survival Prognosis of Pancreatic Ductal Adenocarcinoma: A Real-World Study Based on 2,010 Cases

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Abstract

Background: Whether body mass index (BMI) was associated with the overall survival (OS) of pancreatic ductal adenocarcinoma (PDAC) remained controversial and uncertain.

Method: A total of 2,010 patients from single high-volume center were enrolled in the study. OS of PDAC patients was evaluated based on restricted cubic spline (RCS), propensity score (PS) and multivariable risk adjustment analyses.

Result: BMI was discovered linear related with OS (total $P=0.004$, non-linear $P=0.124$). BMI was analyzed as categorical data based on X-tile software defined cutoffs and World Health Organization (WHO) recommended cutoffs, respectively. Adjusted with confounding covariates, higher BMI manifested as a positive prognostic predictor. ($P_{\text{Xtile}}=0.003$, $P_{\text{WHO}}=0.002$) Furtherly, BMI was proven associated with OS in PS analysis. (Underweight_{Xtile} vs. Normal_{Xtile} $P=0.003$, Overweight_{Xtile} vs. Normal_{Xtile} $P=0.019$; Underweight_{WHO} vs. Normal_{WHO} $P<0.001$, Overweight_{WHO} vs. Normal_{WHO} $P=0.024$). It was also revealed that patients with higher BMI benefitted more from chemotherapy.(adjusted hazard ratio (aHR): Underweight_{Xtile}: 0.565 (0.389-0.819), Normal_{Xtile}: 0.474 (0.395-0.567), Overweight_{Xtile}: 0.409 (0.337-0.496); Underweight_{WHO}: 0.613 (0.401-0.940), Normal_{WHO}: 0.464 (0.387-0.557), Overweight_{WHO}: 0.425 (0.353-0.512)).

Conclusion: Among PDAC patients, higher BMI manifested as a favorable OS indicator, and the protective impact was probably based on chemotherapy administration. Patients with higher BMI were also observed with more chemotherapy administration and more OS benefits from chemotherapy.

Background

Pancreatic cancer, one of the most lethal malignancies, was estimated to cause 47,050 deaths in 2020.^[1] The 5-year survival rate is merely 9%.^[1] Pancreatic ductal adenocarcinoma (PDAC) is the main pattern of pancreatic cancer, taking approximately 85%.^[2] To improve and predict the overall survival (OS) of those patients was an everlasting hotspot for clinicians and researchers.

Body mass index (BMI), an easily accessible and inexpensive parameter, was ever reported associated with the incidence of pancreatic cancer.^[3] However, in our previous study, it was incidentally discovered that there existed a relevance between higher BMI and better OS among PDAC patients.^[4] And so far, the role of BMI in the long-term prognoses of PDAC patients still remained controversial.^[5-10] Limited by sample size and retrospective research nature, those studies could not convincingly elaborate the role of BMI. In this study, relying on propensity score (PS) analysis and multivariable risk adjustment analysis, we discussed the association between BMI and OS of among 2,010 PDAC patients. Based on our results, further researches could be designed and excavated aiming at the mechanism beneath and the relationship between metabolic status and the prognosis of PDAC.

Methods

Data Collection

All eligible patients pathologically diagnosed as PDAC treated according to National Comprehensive Cancer Network (NCCN) guideline were consecutively enrolled from Pancreatic Disease Center, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine during 2013.1 to 2019.12. The exclusive criteria included: 1) Without BMI data at diagnosis. 2) Without complete oncological data. 3) Without regular follow-up. 4) heterogenous carcinoma. Finally a total of 2,010 patients were admitted in our research. (Supp. Figure 1)

The study protocol was approved by the institutional review board at the authors' affiliated hospital. The local ethics committee waived the need for informed consent because the study was observational and retrospective. The study was undertaken according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines^[11] and in accordance with the latest version of the Declaration of Helsinki.

Definition

Height and weight information were recorded when diagnosed. Body mass index was calculated as weight in kilograms divided by the square of height in meters. The cutoffs defined by X-tile were 18.9 kg/m² & 23.3 kg/m² for trinomial categorizing. Also BMI was categorized in three groups based on the cutoffs (18.5 kg/m² and 23 kg/m²) defined by World Health Organization (WHO) for Asians.^[12] Patients below 18.9 kg/m², between 18.9-23.3 kg/m² and over 23.3 kg/m² were marked as Underweight, Normal and Overweight groups separately. Similar categorizing was performed based on WHO cut-offs. For better discrimination, different categorizing standards were marked as subscript. (γ_{Xtile} or γ_{WHO}) Disease was staged per the 8th American Joint Committee on Cancer (AJCC) using the TNM system. Radical surgeries were performed among patients without distant metastasis and arterial invasion (T1-3NxM0). For T4 patients, patients were treated with neoadjuvant therapy first and primary site surgeries secondly when evaluated as resectable. For M1 patients, patients were mainly treated with palliative and supportive cares. Biliary drainage included preoperative biliary stent placement, nasobiliary drainage and percutaneous transhepatic cholangial drainage. Overall survival (OS) in months was defined as the time from diagnosis to the date of death due to any cause.

Statistical Analysis

Normally distributed continuous variables were presented as mean $\pm$ SD, and analyzed using Student's t-test. Non-normally distributed continuous variables were presented as median (Q1-Q3), and analyzed using the Mann-Whitney U test. Kolmogorov-Smirnov test was utilized for normality tests of continuous variables. Categorical variables were presented as percentage, and analyzed using Pearson test. BMI was tested fitting proportional hazards assumption (PH assumption). OS was assessed using Kaplan-Meier curves and log-rank tests in univariable analyses and restricted cubic spline (RCS) curves (continuous BMI variable) and Cox proportional hazards models (continuous and categorical variables) in multivariable analyses, adjusting for clinically relevant factors identified in the univariable analyses. Cox-Mantel test were used for significance comparison. For better result presentation, in Cox regression models, CA199 was transferred into log(CA199). Moreover, due to the coherence of surgical intervention and TNM stages, surgical intervention was hided in multivariable Cox models and PS analyses. The knot number for RCS curves was set as 5 because of the sample size. X-tile was utilized for determining the cut-off value. Association between categorical data was assessed using c2 test, while association between continuous data using Spearman rank test, and association between categorical data and

continuous data using Kruskal-Wallis test. For interaction evaluation, product term in Cox model was utilized to assess the multiplicative interaction, while the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP) and the synergy index (S) were used for the assessment of additive interaction.

To eliminate the imbalance of chemotherapy administration among BMI categories, inverse probability of treatment weighting (IPTW) and standardized mortality ratio weighting (SMRW) were also introduced in for further analysis. The matching parameters included age, gender, ASA physical status, CA199, total bilirubin (TB), fasting blood glucose (FBG), albumin (ALB), biliary drainage, stage, differentiation and chemotherapy administration.

Statistical analysis of this study was performed by SPSS (IBM SPSS Statistics 26.0) , R Studio and X-Tile software. $P < 0.050$ was regarded statistically significant.

Results

Patients and Characteristics

A total of 2,010 patients were enrolled in this study. (Table 1, Supp. Table 1) The median age was 64 years old while the male proportion was 62.1%. The median BMI was 22.67 kg/m². 56.5% patients were treated with chemotherapy. The whole cohort consisted of 192 Ia (9.6%), 478 Ib (23.8%), 155 IIa (7.7%), 532 IIb (26.5%), 432 III (21.5%) and 221 IV (11%) stage patients. For Xtile categorizing, the Underweight, Normal and Overweight groups contained 216 (10.7%), 968 (48.2%) and 826 (41.1%) patients respectively. And for WHO categorizing, three categories included 157 (7.8%), 943 (46.9%) and 910 (45.3%) patients. Significant differences were observed in age, gender, FBG and chemotherapy administration among categories for both categorizing standards.

Table 1

Demographic and baseline characteristics of study cohort. (categorized by X-tile cutoffs.)

	Underweight (n=216)	Normal (n=968)	Overweight (n=826)	total	P value
Age	65 (59-72)	63 (57-69)	64 (57-69)	63 (58-69)	0.004
Male (%)	117 (54.2)	583 (60.3)	551 (66.7)	1251 (62.2)	0.001
ALB	38 (35-42)	39 (36-42)	40 (36-43)	39 (36-42)	0.001
FBG	5.68 (5.00-6.79)	6.04 (5.35-7.41)	6.10 (5.43-7.55)	6.03 (5.32-7.40)	<0.001
CA199	165.3 (37.1-766.9)	152.2 (39.0-484.6)	163.8 (41.7-563.7)	161.1 (40.2-552.2)	0.34
TB	16.9 (11.4-75.8)	17.0 (11.3-76.7)	16.6 (11.8-70.3)	16.8 (11.6-72.6)	0.935
Biliary drainage (%)	38 (24.5)	152 (20.8)	134 (21.8)	324 (21.6)	0.486
ASA Score (%)					0.394
1	130 (61.6)	530 (56.5)	433 (53.9)	1093 (56)	
2	65 (30.8)	334 (35.6)	297 (37)	696 (35.7)	
3	14 (6.6)	63 (6.7)	67 (8.4)	144 (7.4)	
4	2 (0.9)	11 (1.2)	6 (0.7)	19 (1)	
Tumor location (%)					0.495
Head	129 (59.7)	538 (55.6)	473 (57.2)	1140 (56.7)	
Body/Tail	87 (40.3)	430 (44.4)	353 (42.8)	870 (43.3)	
Diagnostic year (%)					0.758
2013	9 (4.2)	35 (3.6)	32 (3.9)	76 (3.8)	
2014	19 (8.8)	57 (5.9)	56 (6.8)	132 (6.6)	
2015	22 (10.2)	105 (10.8)	80 (9.7)	207 (10.3)	
2016	30 (13.4)	146 (15.1)	137 (16.6)	313 (15.6)	
2017	48 (22.7)	199 (20.6)	149 (18.0)	396 (19.7)	
2018	47 (21.8)	205 (21.3)	174 (21.1)	426 (21.2)	
2019	41 (19)	221 (22.8)	198 (24.0)	460 (22.9)	
Stage					0.162
Ia	17 (8.9)	88 (9.2)	87 (10.4)	192 (9.6)	
Ib	48 (22.2)	222 (22.9)	208 (25.2)	478 (23.8)	
IIa	19 (8.8)	72 (7.4)	64 (7.8)	155 (7.7)	
IIb	59 (27.3)	248 (25.6)	225 (27.3)	532 (26.5)	

III	48 (22.2)	238 (24.6)	146 (17.7)	432 (21.5)	
IV	25 (11.3)	100 (10.3)	96 (11.6)	221 (11)	
Differentiation (%)					0.252
I	0 (0)	6 (0.6)	1 (0.1)	7 (0.3)	
II	67 (31)	325 (33.6)	258 (31.2)	650 (32.3)	
III	149 (69)	633 (65.3)	567 (68.7)	1349 (67.1)	
IV	0 (0)	1 (0.1)	0 (0)	1 (0)	
Unknown	0 (0)	3 (0.3)	0 (0)	3 (0.1)	
Chemotherapy (%)	93 (43.1)	57 (56.9)	500 (60.5)	1144 (56.9)	<0.001
Surgical interventions (%)	152 (70.4)	669 (69.1)	598 (72.4)	1419 (70.6)	0.313
ALB, albumin; FBG, fasten blood glucose; TB, total bilirubin.					

Relationship of BMI with OS

The association of BMI at diagnosis and OS is depicted in RCS curves adjusted by Cox model. (Figure 1). The *P* value of total correlation and non-linear correlation were 0.004 and 0.124 respectively, suggesting that there existed a negatively correlated linear relationship between BMI and OS. The sharp slope was observed at the beginning of the curve, and the curve tends to be smooth when BMI exceeded around 23 kg/m².

BMI was a Positive Prognostic Predictor in Multivariable Risk Adjustment Analysis.

As a continuous data, BMI was tested fitting PH assumption with the Pearson relevance being 0.036 and significance being *P*=0.198. (Supp. Figure 2)

In univariate Cox survival analysis, BMI was analyzed as continuous data, Xtile categorical data and WHO categorical data separately. And they were all significantly related with OS. (continuous: hazard ratio (HR)=0.964, *P*<0.001; Xtile: HR (Normal vs. Underweight)= 0.745, *P*=0.001, HR (Overweight vs. Underweight)=0.664, *P*<0.001, HR (Overweight vs. Normal)=0.892, *P*=0.058; WHO: HR (Normal vs. Underweight)= 0.625, *P*<0.001, HR (Overweight vs. Underweight)=0.563, *P*<0.001, HR (Overweight vs. Normal)=0.901, *P*=0.076). (Table 2)

Table 2

Univariate analysis of risks of OS

Univariate		
	HR	P value
Age	1.012 (1.006-1.018)	≤0.001
Male	1.044 (0.932-1.170)	0.453
ALB	0.991 (0.981-1.002)	0.106
FBG	0.998 (0.992-1.004)	0.59
logCA199	1.318 (1.236-1.406)	≤0.001
TB	1.000 (1.000-1.001)	0.164
Biliary drainage	1.057 (0.929-1.203)	0.398
Body/tail	1.085 (0.971-1.212)	0.149
Diagnostic year		0.103
2013	Ref.	
2014	1.029 (0.762-1.389)	0.852
2015	1.204 (0.910-1.594)	0.194
2016	0.937 (0.715-1.228)	0.637
2017	1.120 (0.858-1.460)	0.405
2018	1.153 (0.880-1.512)	0.301
2019	0.960 (0.707-1.304)	0.795
ASA Score		0.798
1	Ref.	
2	0.977 (0.867-1.102)	0.709
3	0.926 (0.748-1.148)	0.485
4	1.180 (0.707-1.968)	0.527
Stage		≤0.001
Ia	Ref.	
Ib	1.168 (1.508-1.946)	0.002
IIa	1.618 (1.186-2.207)	0.002
IIb	2.197 (1.717-2.811)	≤0.001
III	3.213 (2.512-4.110)	≤0.001
IV	6.307 (4.831-8.235)	≤0.001
Differentiation		≤0.001

I	Ref.	
II	2.645 (0.372-18.835)	0.331
III	3.941 (0.554-28.008)	0.171
IV	41.974 (2.616-673.418)	0.008
Unknown	1.399 (0.127-15.446)	0.784
Chemotherapy	0.511 (0.458-0.570)	0.001
Surgical intervention	0.254 (0.207-0.309)	0.001
BMI	0.964 (0.946-0.983)	0.001
X-Tile categorizing		0.001
<18.9	Ref.	
18.9-23.3	0.745 (0.626-0.886)	0.001
≥23.3	0.665 (0.556-0.794)	0.001
WHO categorizing		0.001
<18.5	Ref.	
18.5-23	0.625 (0.514-0.759)	0.001
≥23	0.563 (0.462-0.685)	0.001
ALB, albumin; FBG, fasten blood glucose; TB, total bilirubin; HR, hazard ratio. Ref. reference.		

Multivariable Cox regression models were established based on continuous, Xtile categorical and WHO categorical BMI separately. (continuous: adjusted hazard ratio (aHR)=0.972, $P=0.004$; Xtile: aHR (Normal vs. Underweight)= 0.821, $P=0.038$, aHR (Overweight vs. Underweight)=0.723, $P=0.001$, aHR (Overweight vs. Normal)=0.880, $P=0.045$; WHO: aHR (Normal vs. Underweight)= 0.759, $P=0.010$, aHR (Overweight vs. Underweight)=0.685, $P<0.001$, aHR (Overweight vs. Normal)=0.903, $P=0.102$) (Figure 2, Table 3) AJCC stages, differentiation, CA199 and chemotherapy was discovered significantly relevant with OS in all Cox models. (Table 3) Both continuous and categorical BMI was discovered associated with chemotherapy (continuous BMI: association $P<0.001$, Xtile categorical BMI: association $P<0.001$, WHO categorical BMI: association $P<0.001$). Moreover, the product term of categorical BMI and chemotherapy manifested significantly relevant with OS (interaction $P_{Xtile}=0.004$; interaction $P_{WHO}=0.020$), suggesting the multiplicative interactions in models. The additive interaction between BMI and chemotherapy was explored and certified then. (RERI_{Xtile}: 0.50 (0.30-0.70), AP_{Xtile}: 0.58 (0.29-0.86), S_{Xtile}: 0.21 (0.06-0.75); RERI_{WHO}: 0.56 (0.37-0.74), AP_{WHO}: 0.70 (0.37-1.02), S_{WHO}: 0.26 (0.12-0.57)) Nevertheless, neither the association (Table 1, Supp. Table 1, $P_{Xtile}=0.162$, $P_{WHO}=0.099$), nor the interaction ($P_{Xtile}=0.699$, $P_{WHO}=0.966$) of categorical BMI and TNM stages was observed.

Patients with Higher BMI Was Discovered to Gain More OS Benefits from Chemotherapy

For different BMI categories, the ratio of patients receiving chemotherapy differed significantly. (Underweight_{Xtile}: 43.1%, Normal_{Xtile}: 57.0%, Overweight_{Xtile}: 60.5%, $P<0.001$; Underweight_{WHO}: 40.8%, Normal_{WHO}: 56.0%, Overweight_{WHO}: 60.7%, $P<0.001$). And in different Cox models stratified by categorical BMI, chemotherapy manifested different prognostic impact, indicating that patients with higher BMI probably gained more OS improvement from chemotherapy. (aHR: Underweight_{Xtile}: 0.565 (0.389-0.819), Normal_{Xtile}: 0.474 (0.395-0.567), Overweight_{Xtile}: 0.409 (0.337-0.496); Underweight_{WHO}: 0.613 (0.401-0.940), Normal_{WHO}: 0.464 (0.387-0.557), Overweight_{WHO}: 0.425 (0.353-0.512)). Stratified with chemotherapy administration, it was discovered that, in multivariable Cox models, categorical BMI was no longer associated with OS among chemotherapy-absence patients (Xtile: aHR (Normal vs. Underweight)= 0.911, $P=0.442$, aHR (Overweight vs. Underweight)=0.826, $P=0.133$, aHR (Overweight vs. Normal)=0.907, $P=0.287$; WHO: aHR (Normal vs. Underweight)= 0.835, $P=0.175$, aHR (Overweight vs. Underweight)=0.782, $P=0.071$, aHR (Overweight vs. Normal)=0.937, $P=0.463$), while was more significantly associated among chemotherapy patients (Xtile: aHR (Normal vs. Underweight)= 0.562, $P<0.001$, aHR (Overweight vs. Underweight)=0.458, $P<0.001$, aHR (Overweight vs. Normal)=0.815, $P=0.024$; WHO: aHR (Normal vs. Underweight)=0.488, $P<0.001$, aHR (Overweight vs. Underweight)=0.416, $P<0.001$, aHR (Overweight vs. Normal)=0.854, $P=0.076$). (Supp. Table 2, Supp. Table 3)

Table 3

Multivariate analyses of risks of OS

	Continuous BMI		WHO Model		X-tile Model	
	aHR	P value	aHR	P value	aHR	P value
Age	1.004 (0.998-1.011)	0.223	1.004 (0.997-1.01)	0.279	1.004 (0.997-1.011)	0.234
Male	1.120 (0.992-1.266)	0.068	1.124 (0.995-1.271)	0.060	1.122 (0.993-1.268)	0.064
ALB	1.004 (0.992-1.017)	0.51	1.004 (0.992-1.016)	0.541	1.005 (0.993-1.017)	0.43
FBG	1.018 (0.997-1.039)	0.086	1.017 (0.996-1.038)	0.111	1.018 (0.998-1.039)	0.084
logCA199	1.164 (1.093-1.240)	□ 0.001	1.161 (1.09-1.236)	□ 0.001	1.162 (1.091-1.237)	□ 0.001
TB	1.000 (0.999-1.001)	0.986	1 (0.999-1.001)	0.902	1 (0.999-1.001)	0.899
Biliary drainage	1.113 (0.941-1.316)	0.213	1.109 (0.938-1.311)	0.227	1.114 (0.942-1.318)	0.205
ASA Score		0.142		0.163		0.151
1	Ref.		Ref.		Ref.	
2	0.926 (0.817-1.050)	0.231	0.926 (0.817-1.05)	0.231	0.927 (0.818-1.051)	0.239
3	1.182 (0.934-1.495)	0.164	1.179 (0.931-1.493)	0.171	1.184 (0.935-1.498)	0.16
4	1.317 (0.753-2.305)	0.334	1.272 (0.727-2.228)	0.400	1.298 (0.742-2.271)	0.36
Stage		□ 0.001		□ 0.001		□ 0.001
Ia	Ref.		Ref.		Ref.	
Ib	1.587 (1.210-2.080)	0.001	1.58 (1.205-2.072)	0.001	1.574 (1.2-2.064)	0.001
Ila	1.704 (1.226-2.370)	0.002	1.681 (1.209-2.337)	0.002	1.691 (1.216-2.351)	0.002
Ilb	2.399 (1.846-3.117)	□ 0.001	2.384 (1.834-3.098)	□ 0.001	2.391 (1.84-3.107)	□ 0.001
III	3.568 (2.744-4.640)	□ 0.001	3.542 (2.724-4.607)	□ 0.001	3.558 (2.736-4.627)	□ 0.001
IV	6.478 (4.856-8.641)	□ 0.001	6.442 (4.831-8.591)	□ 0.001	6.501 (4.874-8.671)	□ 0.001
Differentiation		□ 0.001		□ 0.001		□ 0.001

I	Ref.		Ref.		Ref.	
II	4.642 (0.649-33.205)	0.126	4.725 (0.66-33.815)	0.122	4.762 (0.665-34.092)	0.12
III	6.444 (0.903-46.008)	0.063	6.562 (0.918-46.882)	0.061	6.637 (0.929-47.436)	0.059
IV	\		\		\	\
Unknown	1.652 (0.147-18.599)	0.684	1.744 (0.155-19.613)	0.652	1.744 (0.155-19.61)	0.652
Chemotherapy	0.458 (0.405-0.518)	□ 0.001	0.462 (0.408-0.522)	□ 0.001	0.462 (0.408-0.522)	□ 0.001
BMI	0.972 (0.953-0.991)	0.004				
BMI Stage				0.002		0.003
Underweight			Ref.		Ref.	
Normal			0.759 (0.617-0.935)	0.010	0.821 (0.682-0.989)	0.038
Overweight			0.685 (0.555-0.847)	0.000	0.723 (0.597-0.875)	0.001
ALB, albumin; FBG, fasten blood glucose; TB, total bilirubin. aHR, adjusted hazard ratio. Ref., reference.						

Propensity Score Analysis Revealed the Role of BMI Additionally

Not only between Underweight category and Normal category, IPTW and SMRW analyses were performed between Overweight category and Normal category as well. The characteristics of weighted cohorts were shown. (Table 4, Supp. Table 4, Supp. Table 5, Supp. Table 6) It was discovered that BMI was still an independent prognostic predictor with chemotherapy factor balanced. (Figure 3, Figure 4, Underweight_{Xtile} vs. Normal_{Xtile} P=0.003, Overweight_{Xtile} vs. Normal_{Xtile} P=0.019; Underweight_{WHO} vs. Normal_{WHO} P<0.001, Overweight_{WHO} vs. Normal_{WHO} P=0.024)

Table 4

Baseline data comparisons after IPTW analysis. (categorized by X-tile cutoffs)

	Underweight (1089.88)	Normal (1091.45)	P value	SMD	Normal (1672.01)	Overweight (1668.85)	P value	SMD
Age	64 (58-70)	63 (58-70)	0.534	0.055	63.00 (57.77-69.00)	64.00 (57.00-69.00)	0.982	0.001
Female (%)	463.5 (42.5)	451.5 (41.4)	0.783	0.023	615.5 (36.8)	613.3 (36.7)	0.978	0.001
Asa (%)			1	0.01			1	0.003
1	631.8 (58.0)	635.6 (58.2)			934.9 (55.9)	934.5 (56.0)		
2	383.3 (35.2)	379.3 (34.8)			599.6 (35.9)	597.6 (35.8)		
3	65.0 (6.0)	66.5 (6.1)			123.3 (7.4)	122.3 (7.3)		
4	9.8 (0.9)	10.0 (0.9)			14.3 (0.9)	14.5 (0.9)		
Differentiation (%)			0.266	0.109			0.985	0.009
I	0.0 (0.0)	6.0 (0.5)			7.0 (0.4)	6.1 (0.4)		
II	345.2 (31.7)	358.7 (32.9)			534.5 (32.0)	531.6 (31.9)		
III	744.7 (68.3)	726.7 (66.6)			1130.5 (67.6)	1131.2 (67.8)		
Stage (%)			0.989	0.064			1	0.003
Ia	97.7 (9.0)	98.4 (9.0)			162.2 (9.7)	162.6 (9.7)		
Ib	237.0 (21.7)	247.4 (22.7)			401.2 (24.0)	401.3 (24.0)		
IIa	86.1 (7.9)	85.2 (7.8)			128.6 (7.7)	128.6 (7.7)		
IIb	256.9 (23.6)	272.3 (24.9)			431.5 (25.8)	431.3 (25.8)		
III	269.5 (24.7)	265.5 (24.3)			359.5 (21.5)	357.6 (21.4)		
IV	142.7 (13.1)	122.6 (11.2)			188.9 (11.3)	187.5 (11.2)		
Biliary drainage (%)	188.1 (17.3)	179.0 (16.4)	0.785	0.023	275.4 (16.5)	274.0 (16.4)	0.978	0.001
TB	17.10 (11.36-65.50)	16.60 (11.20-66.31)	0.675	0.018	16.70 (11.22-65.63)	16.33 (11.70-66.45)	0.989	0.001

AIB	39.00 (36.00-42.00)	39.00 (36.00-42.00)	0.711	0.011	39.00 (37.00-42.00)	39.00 (36.00-43.00)	0.958	0.003
FBG	5.82 (5.08-7.26)	5.99 (5.30-7.35)	0.489	0.065	6.06 (5.36-7.43)	6.14 (5.45-7.55)	1	<0.001
chemotherapy (%)	587.3 (53.9)	598.8 (54.9)	0.816	0.02	989.8 (59.2)	990.0 (59.3)	0.959	0.003
CA199	167.53 (41.57-736.56)	152.50 (39.30-481.59)	0.225	0.016	149.90 (39.30-465.31)	164.78 (41.49-561.24)	0.925	0.005
ALB, albumin; FBG, fasten blood glucose; TB, total bilirubin; SMD, standard deviation mean difference.								

Discussion

BMI, a simple, inexpensive and readily available parameter, was broadly applied in the evaluation of metabolic diseases, endocrinal diseases, oncological diseases and so on.^[13-17] The role of BMI in pancreatic cancer oncogenesis was studied and discussed in previous studies. Higher BMI was ever discovered related with increased incidence of pancreatic cancer.^[3] However, for patients diagnosed as pancreatic cancer already, how BMI influenced their prognoses was still unclear and controversial.

In RCS analysis, a negative linear relationship between BMI and OS was observed. There was a strong association with higher risk of death in underweight patients when compared to Normal group individuals. The curve tends to be smooth when BMI above around 23 kg/m².

Because the included patients were treated according to NCCN guideline, the surgical intervention was closely associated with TNM stages. Therefore we hid the surgical intervention in multivariable Cox models and PS analyses. With univariate analysis, the tumor location and the diagnostic year were filtered out for multivariable analysis. In multivariable risk adjustment analysis, TNM stages and differentiation were significantly related with OS as expected. Both categorical BMI were also observed significantly related with OS. FBG and ALB were additional 2 parameters to evaluate the nutrition condition as the supplementation of BMI, whereas neither significant impact on the OS (Table 3) nor correlation with BMI (FBG: $P=0.087$, ALB: $P=0.060$) was observed in this study.

Chemotherapy administration was discovered related with both continuous BMI and categorical BMI. No significant association or interaction was observed between TNM stages and BMI. More patients were treated with chemotherapy in higher BMI groups. Stratified with BMI level, we compared the impact of chemotherapy in different categories. And chemotherapy was discovered with more positive impact on OS in higher BMI categories. Stratified with chemotherapy administration, the protective impact of BMI was only observed in the chemotherapy subcategory, indicating that BMI might prolong the OS via the administration of chemotherapy.

Given that there existed interaction and association between BMI and chemotherapy, IPTW analysis was introduced for further certification of BMI's role. With pairwise comparisons, compared with normal weight patients, underweight was discovered a risk factor while overweight a protective factor on OS. The consistence

of IPTW and SMRW analysis results indicated that no significant confounding/interacting factor was excluded. No significant differences of chemotherapy administration were observed anymore in different pairs.

Some limitations in this study should be stressed out. First, though with PS analysis and multivariable risk adjustment, the nature of retrospective single center data still limited the reliability and extrapolation of this study. A multi-center prospective study containing BMI analysis could help well facilitate the results. Secondly, given that all enrolled subjects were Chinese Han population, more researches aiming at patients from different districts and with different races should be planned.

In this study, we studied and elaborated the relationship between BMI and OS of PDAC patients based on IPTW, RCS and multivariable risk adjustment analyses. Higher BMI generally indicated better OS among PDAC patients. More patients were treated with chemotherapy in higher BMI groups. And for different BMI categories, higher BMI indicated better OS benefits from chemotherapy, which could be the possible mechanism of higher BMI indicating better OS. The relevance between BMI and chemotherapy demanded further studies. We are also curious of the association among BMI changes, chemotherapy and OS. And further researches targeting the mechanism beneath and the relations between metabolic status and malignant diseases could be organized and performed.

Declarations

Ethics approval and consent to participate:

All clinical decisions or interventions were in accordance with National Comprehensive Cancer Network (NCCN) guideline for pancreatic cancer. The ethics committee of Shanghai Jiao Tong University School of Medicine affiliated Ruijin Hospital waived the need for informed consent because the study was observational and retrospective. The ethics committee of Shanghai Jiao Tong University School of Medicine affiliated Ruijin Hospital approved this retrospective study including patients from Pancreatic Disease Center .

Consent for publication:

All co-authors declared no conflicts on publication.

Availability of data and materials:

The raw data should be inaccessible to public. The statistic data and results could be available. Anyone requesting data could contact fnz01b74@rjh.com.cn.

Competing interests:

All co-authors declared no conflicts of interests.

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Figures

Figure 1

The relationship between BMI and OS was explored using RCS function based on Cox model over 5 knots. 95% confidence bands are displayed.

A

B

Figure 2

A)The adjusted survivorship curves of Cox model with X-tile categorical BMI. B) The adjusted survivorship curves of Cox model with WHO categorical BMI.

Figure 3

A)The Kaplan-Meier curves of UnderweightXtile group and NormalXtile group in IPTW cohort. B) The Kaplan-Meier curves of OverweightXtile group and NormalXtile group in IPTW cohort. C) The Kaplan-Meier curves of UnderweightXtile group and NormalXtile group in SMRW cohort. D) The Kaplan-Meier curves of OverweightXtile group and NormalXtile group in SMRW cohort.

Figure 4

A) The Kaplan-Meier curves of UnderweightWHO group and NormalWHO group in IPTW cohort. B) The Kaplan-Meier curves of OverweightWHO group and NormalWHO group in IPTW cohort. C) The Kaplan-Meier curves of UnderweightWHO group and NormalWHO group in SMRW cohort. D) The Kaplan-Meier curves of OverweightWHO group and NormalWHO group in SMRW cohort.

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