

Prognostic value of pretreatment skeletal muscle index in pancreatic carcinoma patients

A meta-analysis

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Abstract

Background: The association between pretreatment skeletal muscle index (SMI) and long-term survival of pancreatic carcinoma patients remains unclear up to now.

Methods: The PubMed, Web of Science and EMBASE databases were searched up to March 1, 2022 for relevant studies. The primary and secondary outcomes were overall survival and progression-free survival, respectively. The hazard ratios (HRs) and 95% confidence intervals (CIs) were combined to assess the relationship between pretreatment SMI and prognosis of pancreatic carcinoma patients. All statistical analysis was conducted by STATA 15.0 software.

Results: Twenty retrospective studies involving 3765 patients were included. The pooled results demonstrated that lower pretreatment SMI was significantly related to poorer overall survival (HR = 1.42, 95% CI: 1.25–1.62, $P < .001$) and progression-free survival (HR = 1.41, 95% CI: 1.08–1.84, $P = .012$). Besides subgroup analysis based on the treatment (non-surgery vs surgery) and tumor stage (advanced vs early stage) showed similar results.

Conclusion: Pretreatment SMI could serve as a promising and reliable prognostic factor for pancreatic carcinoma patients and lower pretreatment SMI predicted worse prognosis.

Abbreviations: CI = confidence interval, HR = hazard ratio, NOS = Newcastle Ottawa Scale, OS = overall survival, PFS = progression-free survival, SMI = skeletal muscle index.

Keywords: meta-analysis, pancreatic carcinoma, prognosis, skeletal muscle mass index

1. Introduction

Pancreatic carcinoma remains the fourth leading cause of cancer-related death over the world and a considerable number of patients are diagnosed with advanced stage.^[1,2] Despite great efforts in improving survival by developing more advanced treatment techniques in the systemic chemotherapy and operation, the prognosis of pancreatic carcinoma patients remains very poor with the 5-year survival rate of 9% at all tumor stages and 3% at advanced stage.^[2,3] The reasons for high mortality are that patients are frequently diagnosed with unresectable cancer and pancreatic carcinoma has a high risk of metastasis and recurrence.^[4,5]

Thus, it is a little hard to predict the survival of pancreatic carcinoma patients according to the tumor-node-metastasis stage. In recent years, a number of indexes which are easily obtained in clinics have been introduced and showed

relatively high prognostic value in pancreatic carcinoma patients such as the controlling systemic immune-inflammation index, modified Glasgow prognostic score (mGPS), lymphocyte to monocyte ratio, platelet to lymphocyte ratio, and C-reactive protein to albumin ratio.^[6–10] Unfortunately, these prognostic factors are limited in clinics due to the instability. On the other hand, growing evidence has indicated the close association between body composition and prognosis of cancer patients. Pancreatic carcinoma patients are frequently observed to experience body weight loss, especially skeletal muscle loss, which is related to the cancer progression.^[11–13] The loss of skeletal muscle mass is relatively objective and accurate. Meanwhile, a lot of studies have demonstrated that the nutritional status of the body is closely associated with disease progression and long-term survival of cancer patients.^[14–16] Besides, some studies revealed that pretreatment

The authors have no funding and conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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How to cite this article: Yang L, Liao X, Xie Z, Li H. Prognostic value of pretreatment skeletal muscle index in pancreatic carcinoma patients: A meta-analysis. *Medicine* 2023;102:19(e33663).

Received: 6 March 2023 / Received in final form: 7 April 2023 / Accepted: 10 April 2023

<http://dx.doi.org/10.1097/MD.00000000000033663>

skeletal muscle index (SMI) is significantly related to poor prognosis of cancer patients.^[17–21] However, the association between pretreatment SMI and survival of pancreatic cancer patients remains unclear up to now.

Thus, the aim of this meta-analysis was to further identify the prognostic role of pretreatment SMI in pancreatic carcinoma, which might help with the prediction of survival and formulation of treatment strategies for pancreatic cancer patients.

2. Materials and methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (2009) checklist.

2.1. Literature search

The PubMed, Web of Science and EMBASE databases were searched up to March 1, 2022 for studies which explored the prognostic value of pretreatment SMI in pancreatic carcinoma. The following key words were used during the literature search: pancreatic carcinoma, pancreatic cancer, skeletal muscle index, SMI, prognostic, survival and prognostic. The detailed search strategy was as follows: (pancreatic carcinoma OR pancreatic cancer) AND (skeletal muscle index OR SMI) AND (prognostic OR survival OR prognostic). Furthermore, the references of included studies were also reviewed for availability.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: patients were pathologically diagnosed with primary pancreatic carcinoma; the SMI was calculated through the computed tomography images before any anti-tumor treatment and association between pretreatment SMI and prognosis of pancreatic cancer patients was explored; the overall survival (OS) or progression-free survival (PFS) was defined as the clinical outcome and corresponding hazard ratios (HRs) and 95% confidence intervals (CIs) were directly reported.

The exclusion criteria were as follows: reviews, letters, editorials, meeting abstracts, or case reports; overlapped or duplicated data; the HRs with 95% CIs were not directly provided in the articles; low quality studies with the Newcastle Ottawa Scale (NOS) score of 5 or lower.^[22]

2.3. Data collection

The following data were collected from the included studies in this meta-analysis: the name of first author, publication year, country, tumor-node-metastasis stage, sample size, treatment (non-surgery vs surgery), cutoff value of SMI, endpoint (OS or PFS), HR and 95% CI.

2.4. Methodological quality assessment

As mentioned above, the methodological quality of included studies were evaluated according to the NOS score and only high-quality studies with a NOS score of 6 or higher were included in this meta-analysis.^[22]

The literature search, selection, data collection and quality assessment were all conducted by 2 authors independently. Any disagreement was resolved by team discussion.

2.5. Statistical analysis

The HRs with 95% CIs were combined to identify the association between pretreatment SMI and prognosis of pancreatic carcinoma patients. The heterogeneity among studies was

evaluated by Cochran's Q test and Higgins I^2 statistic. The $P < .10$ and/or $I^2 > 50\%$ was defined as significant heterogeneity and the random-effects model was applied for the pooled effect estimates; otherwise, the fixed-effects model was applied.^[23] Subgroup analyses stratified by the treatment (non-surgery vs surgery) and tumor stage (advanced vs early stage) were further conducted. Sensitivity analysis for OS was performed by excluding individual study from the meta-analysis each time. Begg's funnel plot and Egger's test were conducted to evaluate publication bias. Significant publication bias was defined as the $P < .05$, and then the trim-and-fill method was applied to assess the influence of potentially unpublished papers on the stability of the pooled results.^[24] All statistical analysis was conducted by STATA 15.0 software (College Station, TX).

3. Results

3.1. Literature search and selection

A total of 281 records were identified from 3 databases and 64 duplicated records were removed. Then 174 publications were removed after reading the titles. After screening the abstracts and full texts of remaining 43 publications, 23 records were excluded. Eventually, a total of 20 retrospective studies involving 3765 participants were enrolled in the current meta-analysis.^[25–44] The detailed literature searching and selection process is presented in Figure 1.

3.2. Basic characteristics of included studies

Among included studies, most studies were from Asian countries and the sample size ranged from 55 to 484. Half of included studies focused on advanced stage patients. The other detailed information is shown in Table 1.

3.3. The association between pretreatment SMI and OS of pancreatic cancer patients

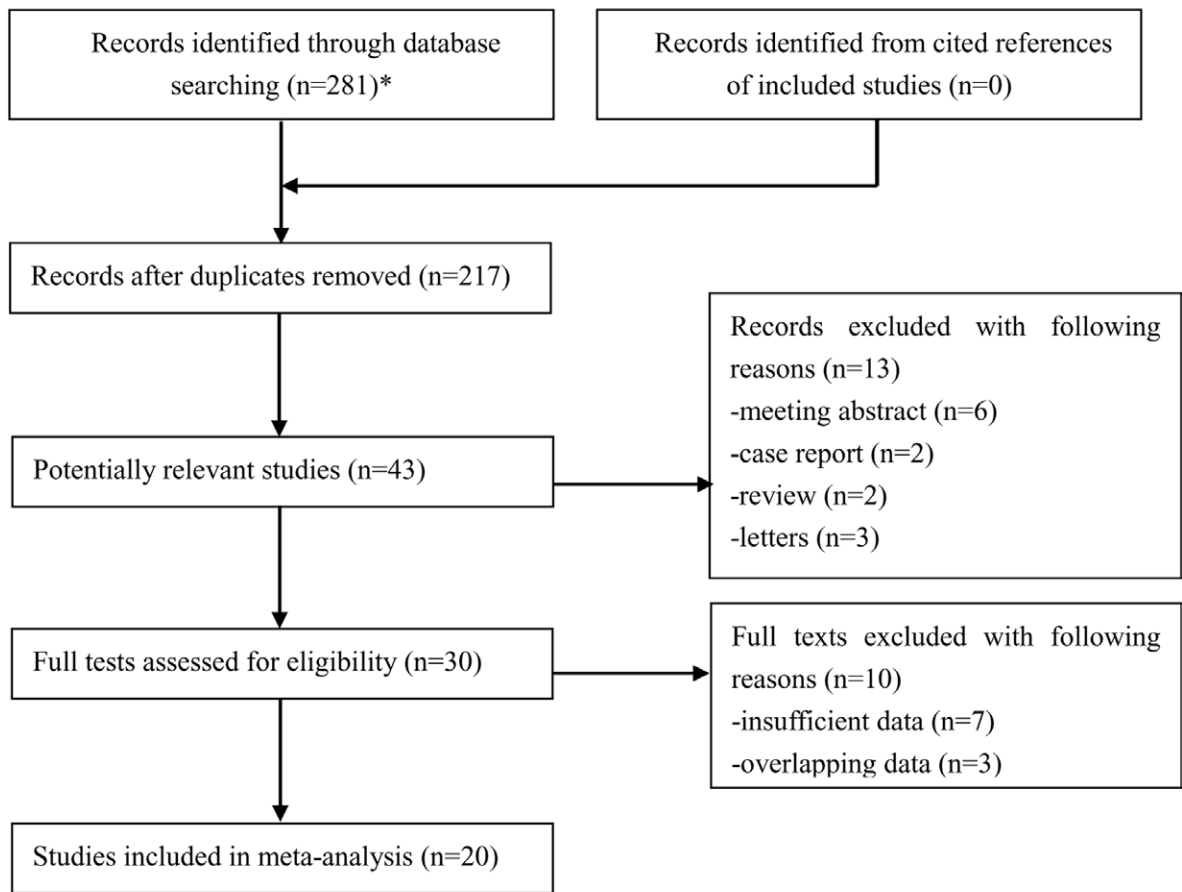
Nineteen studies explored the predictive role of pretreatment SMI for OS.^[25–43] The pooled results indicated that pretreatment SMI was significantly related to OS (HR = 1.42, 95% CI: 1.25–1.62, $P < .001$; $I^2 = 62.6\%$, $P < .001$) (Fig. 2). Subgroup analysis based on the treatment showed that lower pretreatment SMI was a prognostic risk factor in both operated (HR = 1.46, 95% CI: 1.16–1.84, $P = .001$; $I^2 = 50.8\%$, $P = .071$) and non-operated (HR = 1.41, 95% CI: 1.14–1.73, $P = .001$; $I^2 = 68.4\%$, $P = .001$) patients. Besides, subgroup analysis stratified by the tumor stage also indicated that lower pretreatment SMI was associated with poorer OS in both advanced stage (HR = 1.40, 95% CI: 1.16–1.69, $P = .001$; $I^2 = 65.8\%$, $P = .002$) and early stage (HR = 1.79, 95% CI: 1.24–2.58, $P = .002$) patients (Table 2).

3.4. The association between pretreatment SMI and PFS of pancreatic cancer patients

Only 5 studies explored the relationship between pretreatment SMI and PFS.^[28,31,35,38,44] The pooled demonstrated that lower pretreatment SMI was a risk factor of worse PFS in pancreatic carcinoma patients (HR = 1.41, 95% CI: 1.08–1.84, $P = .012$; $I^2 = 67.1\%$, $P = .016$) (Fig. 3; Table 2).

3.5. Sensitivity analysis

The sensitivity analysis showed that the results of the current meta-analysis were stable and reliable and none of included studies caused a significant impact on the overall results (Fig. 4).



*PubMed (n=91), EMBASE (n=65) and Web of Science (n=125).

Figure 1. The flow diagram of this meta-analysis.

Table 1

Basic characteristics of included studies.

Author	Year	Country	Sample size	TNM stage	Treatment	Cutoff of SMI	Endpoint	NOS
Choi ^[25]	2015	Korea	484	Advanced	Non-surgery	Male: <42.2 cm ² /m ² , female: <33.9 cm ² /m ²	OS	7
Park ^[26]	2016	Korea	88	Advanced	Non-surgery	Male: <49.18 cm ² /m ² , female: <31.09 cm ² /m ²	OS	7
Ninomiya ^[27]	2017	Japan	112	I-IV	Surgery	Male: <43.75 cm ² /m ² , female: <38.5 cm ² /m ²	OS	7
Okumura ^[28]	2017	Japan	301	I-II	Surgery	Male: <47.1 cm ² /m ² , female: <36.6 cm ² /m ²	OS, PFS	6
Bian ^[29]	2018	China	203	III-IV	Non-surgery	Male: <42.0 2c m ² /m ² , female: <36.55 cm ² /m ²	OS	6
El Amrani ^[30]	2018	France	107	NR	Surgery	Male: <52.4 cm ² /m ² , female: <38.5 cm ² /m ²	OS	7
Sugimoto ^[31]	2018	USA	323	NR	Surgery	Male: <55.4 cm ² /m ² , female: <38.9 cm ² /m ²	OS, PFS	6
Basile ^[32]	2019	Italy	162	Advanced	Non-surgery	Male: <53/43 cm ² /m ² , female: <41 cm ² /m ²	OS	6
Gruber ^[33]	2019	Austria	133	I-IV	Surgery	Male: <52.4 cm ² /m ² , female: <38.5 cm ² /m ²	OS	8
Kurita ^[34]	2019	Japan	82	Advanced	Non-surgery	Male: <45.3 cm ² /m ² , female: <37.1 cm ² /m ²	OS	8
Lee ^[35]	2019	Korea	57	Advanced	Non-surgery	NR	OS, PFS	6
Naumann ^[36]	2019	Germany	147	I-IV	Mixed	Male: <52.4 cm ² /m ² , female: <38.5 cm ² /m ²	OS	7
Wu ^[37]	2019	China	146	I-IV	Mixed	Male: <36.2 cm ² /m ² , female: <29.6 cm ² /m ²	OS	6
Cho ^[38]	2021	Korea	299	Advanced	Mixed	Male: <36.2 cm ² /m ² , female: <29.6 cm ² /m ²	OS, PFS	8
Hsu ^[39]	2021	USA	136	I-IV	NR	Male: <43.75 cm ² /m ² , female: <38.5 cm ² /m ²	OS	8
Kim ^[40]	2021	South Korea	330	Advanced	Non-surgery	Male: <53/43 cm ² /m ² , female: <41 cm ² /m ²	OS	7
Nakano ^[41]	2021	Japan	55	Advanced	Non-surgery	Male: <42.2 cm ² /m ² , female: <33.9 cm ² /m ²	OS	7
Peng ^[42]	2021	China	116	I-IV	Surgery	Male: <42.2 cm ² /m ² , female: <33.9 cm ² /m ²	OS, PFS	8
Uemura ^[43]	2021	Japan	69	Advanced	Non-surgery	Male: <42 cm ² /m ² , female: <38 cm ² /m ²	OS	8
Aziz ^[44]	2022	Netherlands	415	NR	Surgery	Male: <54.3/52.3 cm ² /m ² , female: <46.6/38.6 cm ² /m ²	PFS	6

NOS = Newcastle-Ottawa Scale, NR = not reported, OS = overall survival, PFS = progression-free survival, SMI = skeletal muscle index, TNM = tumor-node-metastasis.

3.6. Publication bias

Based on the asymmetric Begg’s funnel plot (Fig. 5) and $P < .001$ of Egger’s test, significant publication bias was detected. Thus,

the trim-and-fill method was applied. Five potentially unpublished articles were revealed (Fig. 6) and the pooled HRs in fixed-effects model and random-effects model were 1.149 (95%

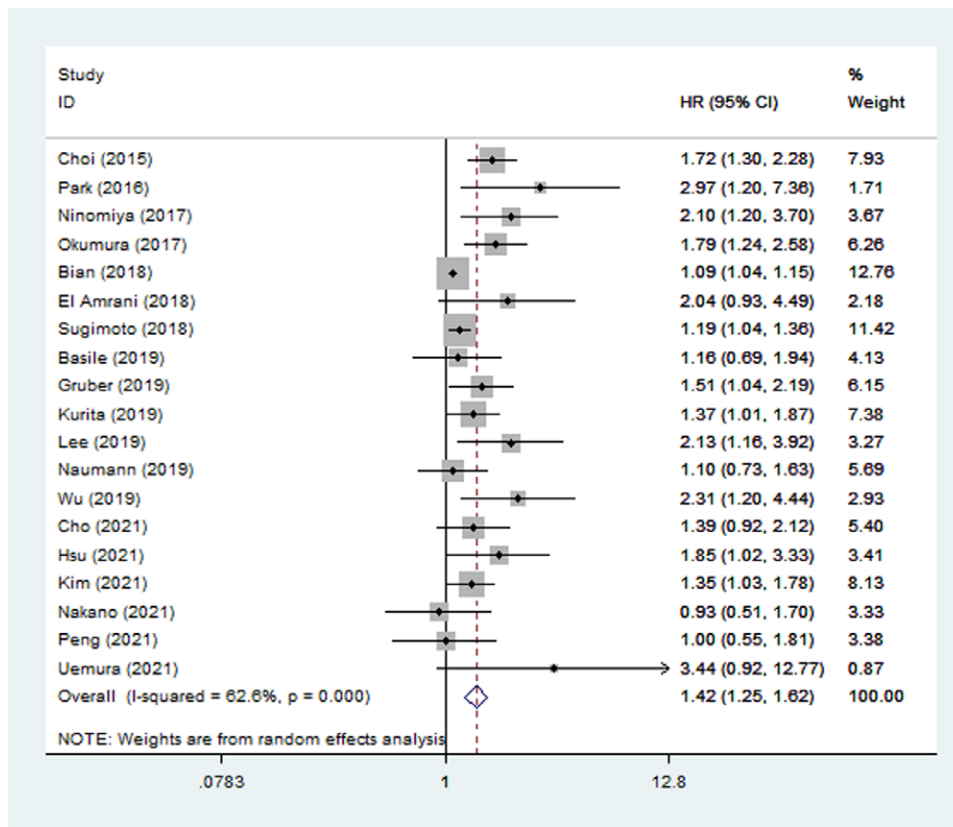


Figure 2. The association between pretreatment SMI and overall survival of pancreatic carcinoma patients. CI = confidence interval, HR = hazard ratio, SMI = skeletal muscle index.

Table 2
Results of meta-analysis.

	No. studies	HR	95% CI	P value	I ² (%)	P value
Overall survival	19	1.42	1.25–1.62	<.001	62.6	<.001
Treatment						
Non-surgery	9	1.41	1.14–1.73	.001	68.4	.001
Surgery	6	1.46	1.16–1.84	.001	50.8	.071
Tumor stage						
Advanced	10	1.40	1.16–1.69	.001	65.8	.002
Early	1	1.79	1.24–2.58	.002	–	–
Progression-free survival	5	1.41	1.08–1.84	.012	67.1	.016

CI = confidence interval, HR = hazard ratio.

CI: 1.101–1.199, *P* < .001) and 1.322 (95% CI: 1.171–1.493, *P* < .001) separately, which indicated that these 5 potentially unpublished studies did not have a significant impact on the overall results and our conclusions were still reliable.

4. Discussion

The current meta-analysis demonstrated that low pretreatment SMI was significantly associated with poor OS and PFS of pancreatic carcinoma patients after including 20 studies involving 3765 participants. Besides, the subgroup analysis based on the treatment and tumor stage showed similar findings. Thus, our study has indicated the high prognostic value of pretreatment SMI in pancreatic carcinoma patients. However, more prospective high-quality research is still needed to verify our findings.

SMI is usually applied to define the sarcopenia in clinics. Previous literatures have revealed that sarcopenia is a prognostic risk factor in several cancers including esophageal cancer, biliary tract cancer, head and neck cancer and gastric cancer.^[45–48]

Actually, sarcopenia is not only a decrease in muscle quantity or quality, but also a condition reflecting a disturbance of immunonutritional status, although its relationship with oncological microenvironment remains unclear up to now.^[49] A lot of studies have indicated that skeletal muscle plays an important role in the systematic inflammation.^[44,50] Besides, several inflammatory parameters such as the neutrophil to lymphocyte ratio, white blood cell count, C-reactive protein levels, erythrocyte sedimentation rate and systemic immune-inflammation index were found to be higher in sarcopenic patients.^[44,51] As mentioned above, most of these inflammatory indexes have a high prognostic value in cancer patients. Thus, overall, it is believed that SMI could show a high prognostic value in pancreatic carcinoma and our results have well certified this conjecture.

Furthermore, there are several meta-analyses which revealed the clinical role of SMI in cancer patients.^[52,53] Tranoulis et al included 21 studies and demonstrated that low SMI trended towards shorter OS (HR = 1.37, 95% CI: 0.99–1.90, *P* = .05) and was related to higher risk of postoperative complications

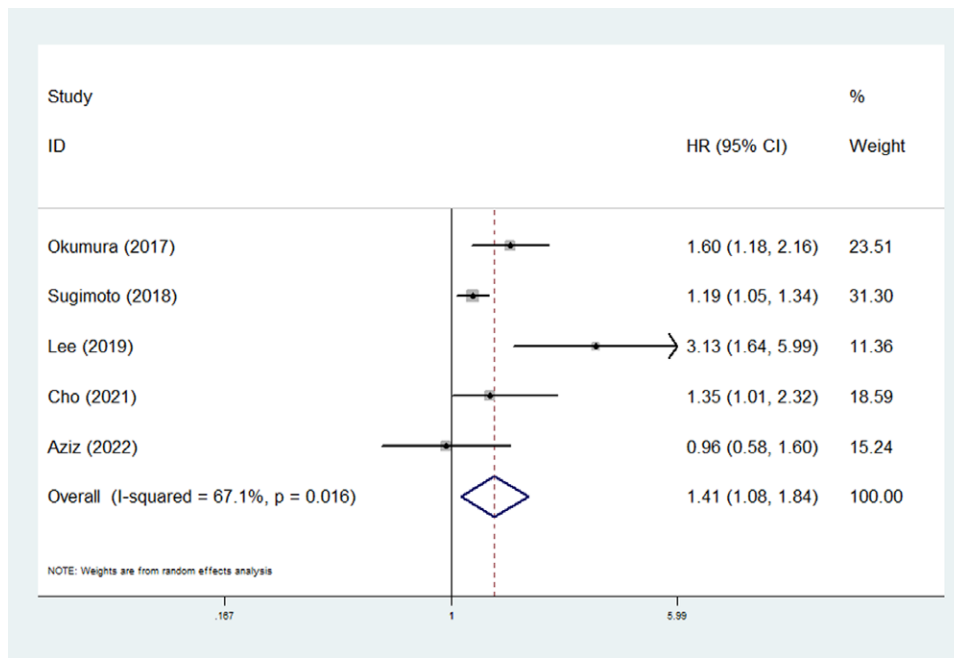


Figure 3. The association between pretreatment SMI and progression-free survival of pancreatic carcinoma patients. CI = confidence interval, HR = hazard ratio, SMI = skeletal muscle index.

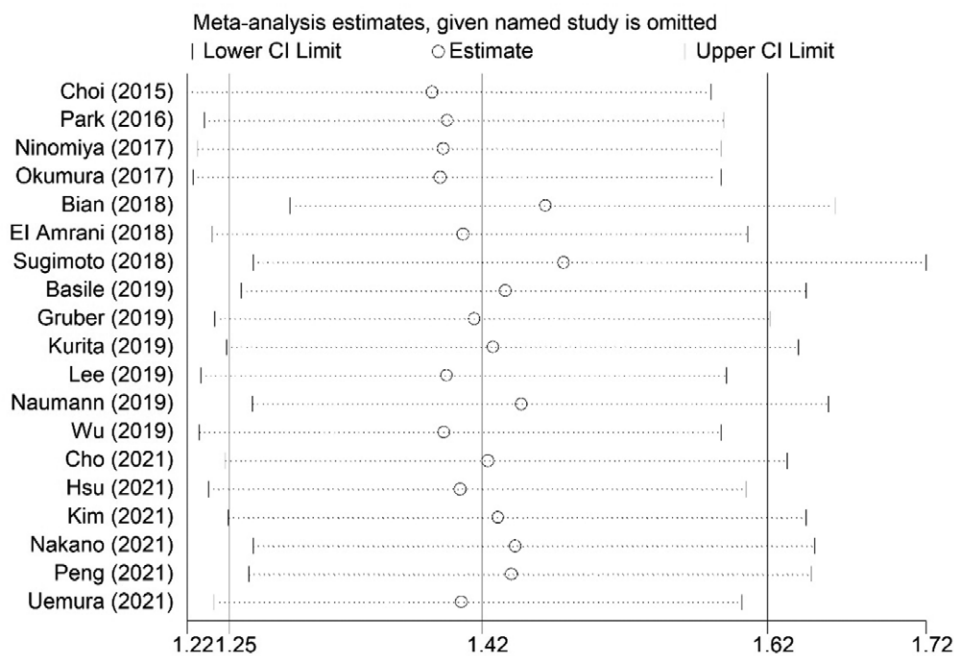


Figure 4. Sensitivity analysis about the association between pretreatment SMI and overall survival of pancreatic carcinoma patients. CI = confidence interval, SMI = skeletal muscle index.

[OR = 1.56, 95% CI: 1.16–2.11, $P = .004$] in women with epithelial ovarian malignancy.^[53] Besides, Di Giorgio et al indicated that low SMI was significantly associated with peritoneal metastases in colorectal cancer (OR = 1.45, 95% CI: 1.04–2.03, $P = .03$) after including 4 relevant studies involving 582 patients.^[52]

Although our meta-analysis demonstrated the significant association of pretreatment SMI with survival of pancreatic carcinoma patients, there are still some controversial fields worthy of more investigations. Only the prognostic role of pretreatment SMI in pancreatic carcinoma was identified in this meta-analysis. It is unclear that whether the change of SMI during the anti-tumor treatment could predict survival rates of

pancreatic cancer patients. Besides, it is necessary to explore whether it's possible to improve clinical outcomes of patients by increasing SMI values. In most included studies, sex-specific cutoff values of pretreatment SMI were applied. However, the baseline level of SMI could be affected by some parameters such as the disease stage and age. Thus, more specific thresholds of SMI should be determined, or subgroup analysis based on these parameters should be conducted in future research.

There are several limitations in this meta-analysis. First, all included studies were retrospectively conducted with relatively small sample sizes, which might cause some bias. Second, because of the lack of original data about the age, sex and other

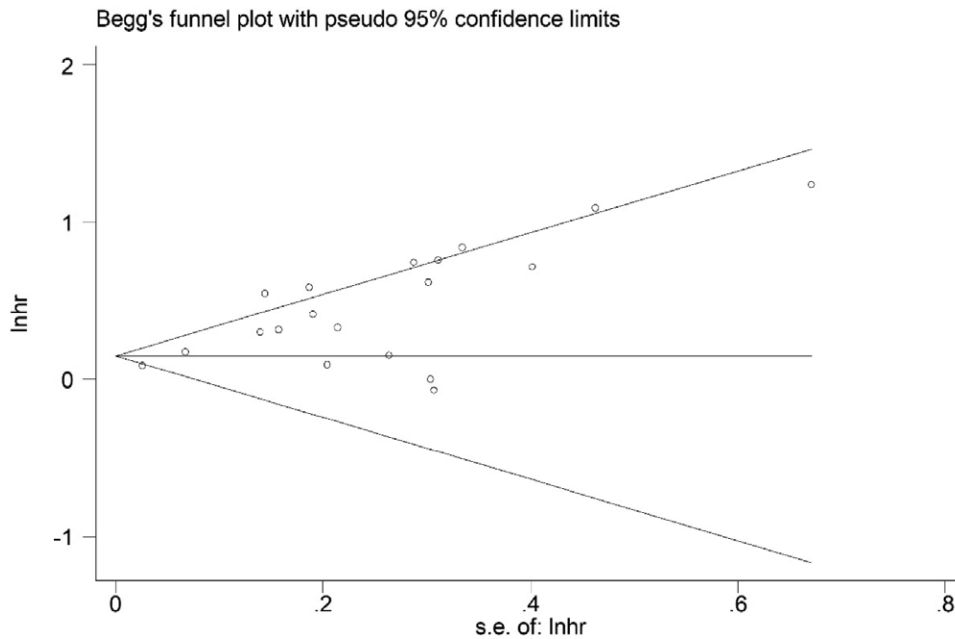


Figure 5. Begg's funnel plot.

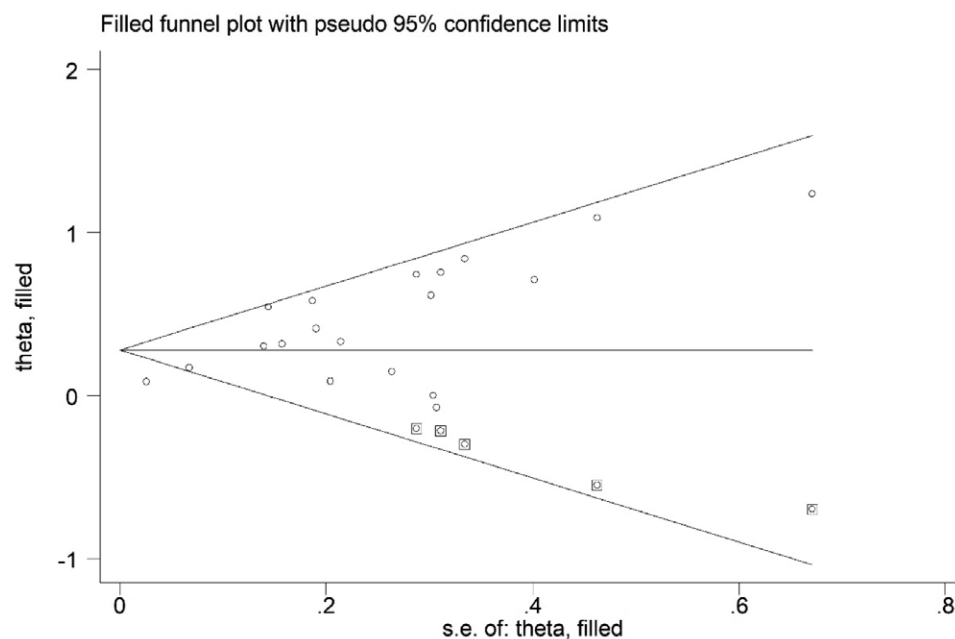


Figure 6. Trim Begg's funnel plot.

important parameters, we were unable to perform more subgroup analyses. Third, in this meta-analysis, we were unable to determine the optimal cutoff value of pretreatment SMI.

5. Conclusion

Pretreatment SMI could serve as a promising and reliable prognostic factor for pancreatic carcinoma patients and lower pretreatment SMI predicted worse prognosis. However, more prospective high-quality studies are still needed to further verify our findings.

Author contributions

Conceptualization: Li Yang, Haiwen Li.
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Validation: Zhong Xie.
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Writing – review & editing: Haiwen Li.

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