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ORIGINAL ARTICLE

The prognostic value of CA19-9 response after neoadjuvant therapy in patients with pancreatic cancer: a systematic review and pooled analysis

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Abstract

Background Pancreatic cancer (PC) is a highly aggressive and refractory disease, with disappointing 5-year survival rates. Regarding the wide application of neoadjuvant treatment in patients with PC, how the post-neoadjuvant Carbohydrate antigen 19-9 (CA19-9) response could translate into a survival benefit is not clearly understood. We aimed to evaluate the correlation of the CA19-9 response with overall survival (OS) in patients with PC receiving neoadjuvant therapy.

Methods An extensive electronic search in PubMed, Embase, and the Cochrane Library was performed to identify relevant articles, from which data relevant to independent correlations of the CA19-9 response with overall survival (OS) were extracted for analysis. A random-effects model was used to calculate the pooled hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs).

Results Altogether, 17 eligible studies were identified in the systematic review. Pooled analysis showed that CA19-9 response > 50% (HR, 0.43; 95% CI 0.29–0.56; $P < 0.001$) and normalization of CA19-9 (HR, 0.52; 95% CI 0.42–0.63; $P < 0.001$) after neoadjuvant treatment are significantly associated with promising overall survival. The results also showed that optimal CA19-9 response after neoadjuvant treatment was significantly related to a favorable prognosis (HR = 0.49, 95% CI 0.42–0.55, $P < 0.001$; I2 = 45.1%, $P = 0.04$). Subgroup analysis revealed there were no prognostic difference between CA19-9 > 50% and normalization of CA19-9 after neoadjuvant treatment ($P = 0.338$), but the duration of neoadjuvant chemotherapy over 4 months was significantly associated with expanded postoperative survival ($P = 0.013$).

Conclusions Serum CA19-9 is valuable in determining the effect of neoadjuvant treatment in patients with PC. Post-neoadjuvant CA19-9 response > 50% or CA19-9 normalization was related to a more promising overall survival, suggesting that optimal CA19-9 response may be a suitable prognostic index to guide treatment decisions.

Abbreviations

PC	Pancreatic cancer
NCCN	National comprehensive cancer network
BRPC	Borderline resectable pancreatic cancer
CA19-9	Carbohydrate antigen
NAT	Neoadjuvant therapy
OS	Overall survival
NCT	Neoadjuvant chemotherapy
NCRT	Neoadjuvant chemoradiotherapy
FOLFIRINOX	The combination of 5-fluorouracil, oxaliplatin, and irinotecan
HR	Hazard ratio
PRISMA	Preferred reporting items for systematic reviews and meta-analyses

Introduction

Pancreatic cancer (PC) is a highly aggressive and refractory disease, with a 5-year survival rate of less than 10%. Recent studies have revealed that pancreatic cancer has become the third leading cause of cancer-related death in the United States [1, 2]. Radical surgical resection remains the only potential cure; however, more than half of patients were not suitable for curative resection due to metastatic or locally advanced

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disease. Moreover, the survival benefit after resection is more likely to be hampered by the biological behavior of PC [3]. With the development of systematic therapy, there were the compelling evidences from the prospective studies which revealed that neoadjuvant treatment has emerged as an alternative to a surgery-first approach which presented several advantages, including downstaging local disease, systematic control of occult micrometastasis, and increasing the R0 resection rate [4–6]. The efficacy and safety of neoadjuvant therapy in borderline resectable and locally advanced PC have been well demonstrated, such that in the newest National Comprehensive Cancer Network (NCCN) guidelines, neoadjuvant treatment was highly recommended for the management of BRPC, as well as high-risk resectable PC [7, 8].

With the growing acceptance of a neoadjuvant treatment strategy for patients with PC, the necessity of precise evaluation of the treatment response has been increasingly emphasized. Although a variety of approaches are used to assess the post-neoadjuvant therapy response, including radiographical changes and changes in tumor marker levels, it is still difficult to estimate the total tumor burden accurately before proceeding with surgery [4, 9]. The heterogeneity of neoadjuvant treatment regimens, inconsistent relationship between tumor response and imaging findings, and lack of a gold standard post-treatment evaluation are the current primary obstacles to the accurate evaluation and treatment of PC patients. Carbohydrate antigen 19-9 (CA19-9) is the most widely used tumor marker in patients with PC. Its utility in determining prognosis and the response to treatment for patients undergoing surgery and chemotherapy has been acknowledged in previous studies. Patients with high levels of CA19-9 at baseline are usually associated with an advanced stage of disease and poor survival [10, 11]. A massive decline or normalization of the CA19-9 level following surgery is a favorable prognostic factor for survival [12]. However, the predictive value of decreasing CA19-9 levels during neoadjuvant treatment for the assessment of the treatment response and survival remains unclear. Numerous studies have reported the beneficial effects of the CA19-9 response after neoadjuvant treatment on survival, but these findings have been limited to retrospective studies in most institutions and there is still insufficient high-level clinical evidence. Therefore, we performed a systematic review and pooled analysis to investigate the association between the change in CA19-9 after neoadjuvant treatment and the prognostic characterization of patients who completed the intended therapy.

Materials and methods

Literature search

A systematic search was undertaken using the PubMed and Embase databases for articles published from March 2010 to March 2020. Two authors independently searched the relevant literature. Combinations of "Pancreatic Cancer", "Pancreatic Neoplasm", "Neoadjuvant Therapy", Neoadjuvant Treatment", "CA19-9", and "Carbohydrate Antigen 19-9″ were used as search terms and only articles published in English were included.

Criteria for inclusion and exclusion

Studies eligible for selection had to meet the following inclusion criteria: 1. patients diagnosed with pancreatic cancer were treated with neoadjuvant therapy; and 2. studies with complete information on CA19-9 response and survival for the assessment of hazard ratios (HRs) and their 95% confidence intervals (95% CIs) or provided sufficient data for calculating HRs and 95% CIs from Kaplan–Meier survival curves or using Tierney's method [13].

The exclusion criteria were as follows: 1. duplicate publications; 2. insufficient data to estimate hazard ratios and 95% CIs; and 3. letters, editorials, case reports, reviews, comments, or meeting abstracts.

Data extraction

Two researchers independently reviewed all selected studies and extracted detailed information, including the first author's name, publication year, number of patients, resectability of cancer, type of NAT, change in CA19-9 after NAT, number or percentage of surgical patients, follow-up, and survival statistics using a predefined data extraction form. We extracted survival outcome data directly from the studies if the HR and 95% CI were presented or calculated them from the Kaplan–Meier curves using Tierney's method.

Statistical analysis

Stata software (version 16.0, Stata Corporation, College Station, TX, USA) was used to analyze the extracted data. In this pooled analysis, the prognostic value of the change in CA19-9 after neoadjuvant treatment was evaluated using the pooled HR and corresponding 95% CI. When the HR and its 95% CI did not overlap with 1, the change in CA19-9 after neoadjuvant treatment had a statistically significant effect on survival.

The I^2 test was applied to evaluate the interstudy heterogeneity of the HRs. A fixed-effects model (Mantel–Haenszel method) was used when there was minimal heterogeneity among the eligible studies. Otherwise, a random-effects model was applied to calculate the pooled HR when they demonstrated significant heterogeneity. A funnel plot with Begg and Egger tests would be produced to evaluate potential publication bias if sufficient studies were identified.

Quality assessment

Considering that all eligible studies were non-randomized controlled trials, study quality assessment was guided by the Newcastle–Ottawa Scale. Studies with scores ≥ 7 were considered of high quality. Any disagreement was resolved by discussion and consensus agreement.

Results

Study selection and patient characteristics

Retrieved by the aforementioned search strategy, a total of 2478 studies were included initially. After preliminary elimination and secondary further screening, 17 studies met the inclusion and exclusion criteria and were determined accessible for the pooled analysis. These 17 articles, comprised 16 retrospective studies and 1 prospective study. Moderate overall research quality was assessed by the Newcastle–Ottawa Scale with mean score 6.8. The subject number of studies varied from 66 to 419, with a mean size of 131. In total sum, there are 2242 patients receiving neoadjuvant therapy and the therapeutic strategy were various in each institution, including FOLFIRINOX-based systematic chemotherapy, gemcitabine-based chemotherapy (Gemcitabine alone or combined with albumin-bound paclitaxel, S-1), and 5-fluorouracil-based chemotherapy with or without radiotherapy. Preoperative chemotherapy alone was used in 5 studies (Table 1). The literature search process was summarized in a flow diagram based on PRISMA statement (Fig. 1).

CA19-9 response and survival

The degree of CA19-9 response was characterized in six studies, and among those studies, a decrease of 50% is the most studied change. A pooled analysis showed that CA19-9 response > 50% after neoadjuvant treatment is significantly associated with promising overall survival in PDAC patients (HR = 0.47, 95% CI 0.33–0.61, $P < 0.001$; $I^2 = 64.0\%$, $P = 0.02$) (Fig. 2).

A cutoff value of a normal CA19-9 level was widely studied for survival analysis in patients with neoadjuvant treatment and nine studies were included in the following pooled analysis. Successful normalization of CA19-9 after neoadjuvant treatment was significantly associated with favorable overall survival in patients who completed the preoperative treatment and radical surgery (HR = 0.56, 95% CI 0.45–0.67, $P < 0.001$; $I^2 = 43.2\%$, $P = 0.08$) (Fig. 3).

Considering both the response > 50% and normalization were optimal indicator of reduction of CA19-9 after neoadjuvant treatment, we did the pooled analysis with this combination. The results showed that optimal CA19-9 response was also promising factors related with prolonged overall survival (HR = 0.49, 95% CI 0.42–0.55, $P < 0.001$; $I^2 = 45.1\%$, $P = 0.04$) (Fig. 4).

Subgroup analyses

We performed three subgroup analyses based on neoadjuvant sequence with or without radiotherapy, chemotherapy duration, and the method of achieving optimal CA19-9 response (CA19-9 > 50% or CA19-9 normalization). No significant deviations from the main results were found in the subgroup analysis of sequence with radiotherapy and the method of achieving optimal CA19-9 response (Figs. 4, 5). Further subgroup analyses regarding the chemotherapy duration showed that patients who received duration of neoadjuvant chemotherapy over 4 months had a survival benefit over those within 4 months (heterogeneity between the groups, $P = 0.013$) (Fig. 6).

Sensitivity analysis and publication bias assessment

Given that heterogeneity was observed in the pooled analysis, a sensitivity analysis was performed for the studies included in this study. Sensitivity analysis after excluding the study by Shimpei et al. showed that the trend supporting the survival benefit of NAT was maintained.

Discussion

To date, surgical resection remains the only curative treatment for PC. However, more than 80% of patients are ineligible for curative surgery and the benefit gained from radical resection of PC is frequently compromised by local tumor recurrence and distant metastases, even in the case of R0 resection. To improve resectability and overall prognosis, neoadjuvant therapy, an emerging therapeutic strategy that has been well-received by patients with breast cancer and colorectal cancer, demonstrated great potential in the systemic control of local disease and occult micrometastasis prior to surgery. Numerous studies have reported significant advantages of neoadjuvant treatment with respect to surgical resectability, R0 resection rate, and overall survival

Table 1 Characteristics of included studies

Study, year, country	Center	Study design	Case	Tumor resectability	Resectability criteria	Neoadjuvant therapy	Neoadjuvant regimen	Post-neoadjuvant CA199 response	NOS
Tzeng [14] 2013, USA	MDACC	Retro	141	BR	AHPBA/SSO/SSAT MDACC	NCT	Gem based or 5-Fu	47 normalized	7
Boone [15] 2014, USA	UPMC	Retro	78	BR, LA	AHPBA/SSO/SSAT	NCT, NCRT	Gem based; FOLFIRINOX	24 normalized; 54 > 50% response	7
Kobayashi [16] 2014, Japan	Mie University	Prosp	100	R, BR, LA	NCCN 2010	NCRT	Gem based	40 > 50% response	8
Aldakkak [17] 2015, USA	MCW	Retro	235	R, BR	MCW	NCT + NCRT	NR	95 normalized	7
Williams [18] 2016, USA	UCLA	Retro	109	BR, LA	AHPBA/SSO/SSAT	NCT	5-FU based and others	40 normalized	5
Murakami [19] 2017, Japan	Hiroshima University Hospital	Retro	66	BR	NCCN 2016	NCT	Gem based or FOLFIRINOX	29 normalized	6
Rajamanickam [20] 2017, USA	MCW	Retro	123	R, BR	NCCN 2016	NCT, NCRT NCT + NCRT	NR	63 normalized	7
Reni [21] 2017, Italy	IRCCS Ospedale San Raffaele	Retro	223	BR, LA	NCCN 2014	NCT	Gem based	37 > 50% response	7
Tsai [22] 2018, USA	MCW	Retro	131	R, BR	MCW	NCT, NCRT NCT + NCRT	NR	58 normalized	8
Dhir [23] 2018, USA	UPMC	Retro	193	R, BR	NCCN 2017	NCT or NCRT	Gem based or FOLFIRINOX	142 normalized; 90 > 80% response	7
Truty [24] 2019, USA	Mayo Clinic	Retro	194	BR/LA	NR	NCT + NCRT	FOLFIRINOX or GA	101 normalized	8
Yoo [25] 2019, Korea	AMC	Retro	135	BR,LA	NCCN 2016	NCT	Gem based or FOLFIRINOX	58 normalized	7
Macedo [26] 2019, USA	CPC	Retro	274	BR,LA	Alliance classification	NCT or NCRT	FOLFIRINOX or GA	75 > 50% response	7
Aoki [27] 2020, Japan	Multicenter Study	Retro	240	R, BR	NCCN 2016	NCT or NCRT	NR	33 normalized	7
Maeda [28] 2020, USA	Mayo Clinic Rochester, University of California, and Tohoku University	Retro	305	R, BR	NCCN 2017	NCT or NCRT	GS or GA; FOLFIRINOX-FOLFOX S-1 or 5-FU based	146 normalized	7
Al Abbas [29] 2020, USA	UPMC	Retro	369	R, BR, LA	SSO/AHPBA/SSAT/NCCN	NCT or NCRT	Gem based or 5-Fu based	98 normalized; 91 > 85% response	6
Murthy [30] 2020, USA	UPMC	Retro	419	R, BR	SSO/AHPBA/SSAT/NCCN	NCT or NCRT	Gem based or 5-Fu based others	261 > 50% response	6

MDACC MD Anderson cancer center, *UPMC* university of Pittsburgh medical center, *MCW* medical college of Wisconsin, *UCLA* university of California-Los Angeles, *AMC* asan medical center, *CPC* central pancreas consortium. R, resectable, *BR* borderline resectable, *LA* local advanced, *AHPBA/SSO/SSAT* Americas hepatopancreato-biliary association/ society of surgical oncology/society for surgery of the alimentary tract, *NCCN* national comprehensive cancer network, *NCT* neoadjuvant chemotherapy, *NCRT* neoadjuvant chemoradiotherapy, *GA* gemcitabine and albumin-bound paclitaxel, *GS* gemcitabine and S-1, Gem based, gemcitabine-based chemotherapy, *5-Fu based* 5-fluorouracil-based chemotherapy, *NOS* Newcastle–Ottawa scale; *NR* not reported

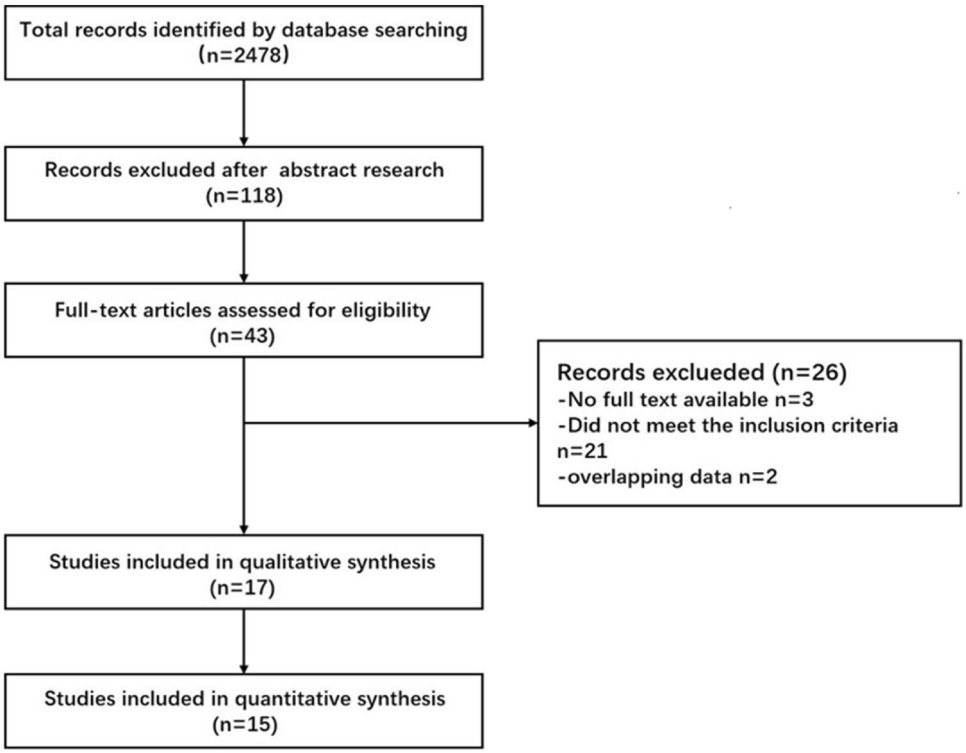

Fig. 1 Flow diagram of the inclusion and exclusion of studies

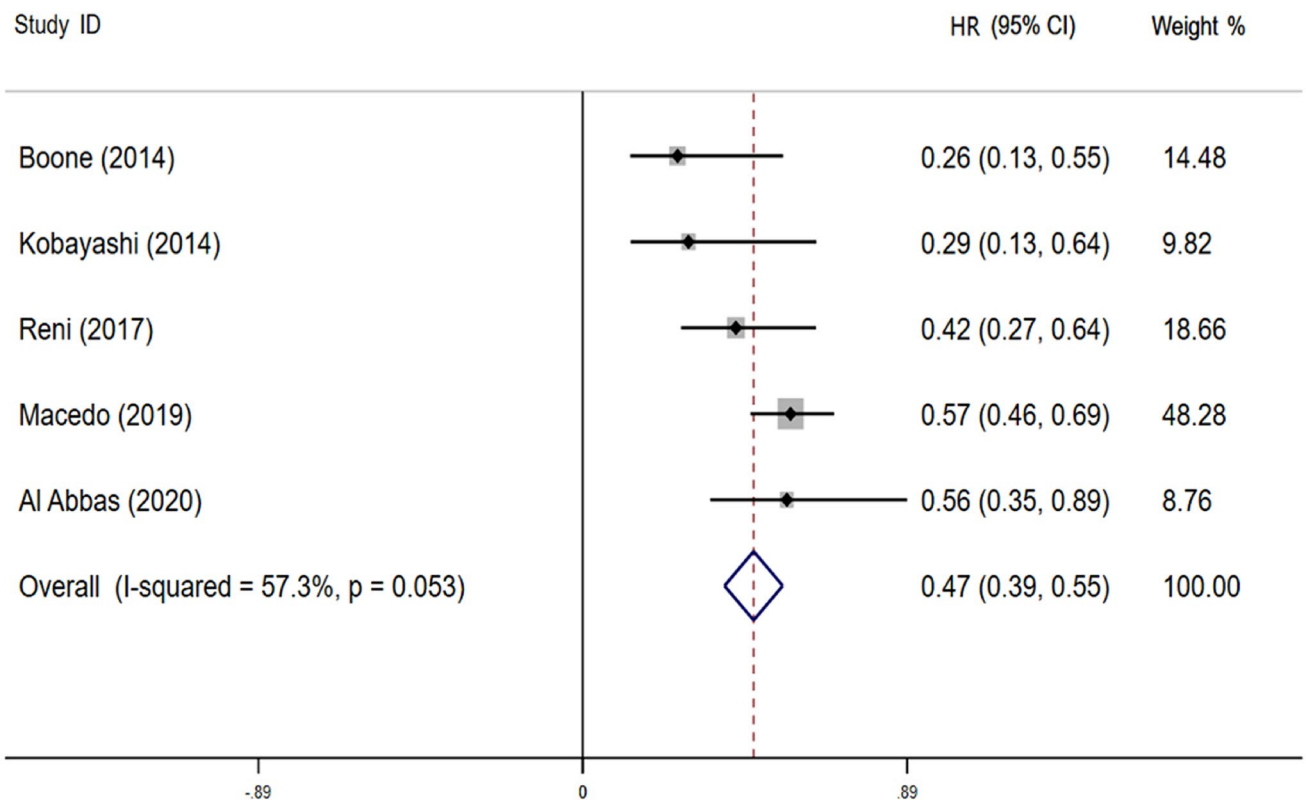

Fig. 2 Overall survival with post-neoadjuvant CA19-9 Response > 50% for patients receiving neoadjuvant therapy

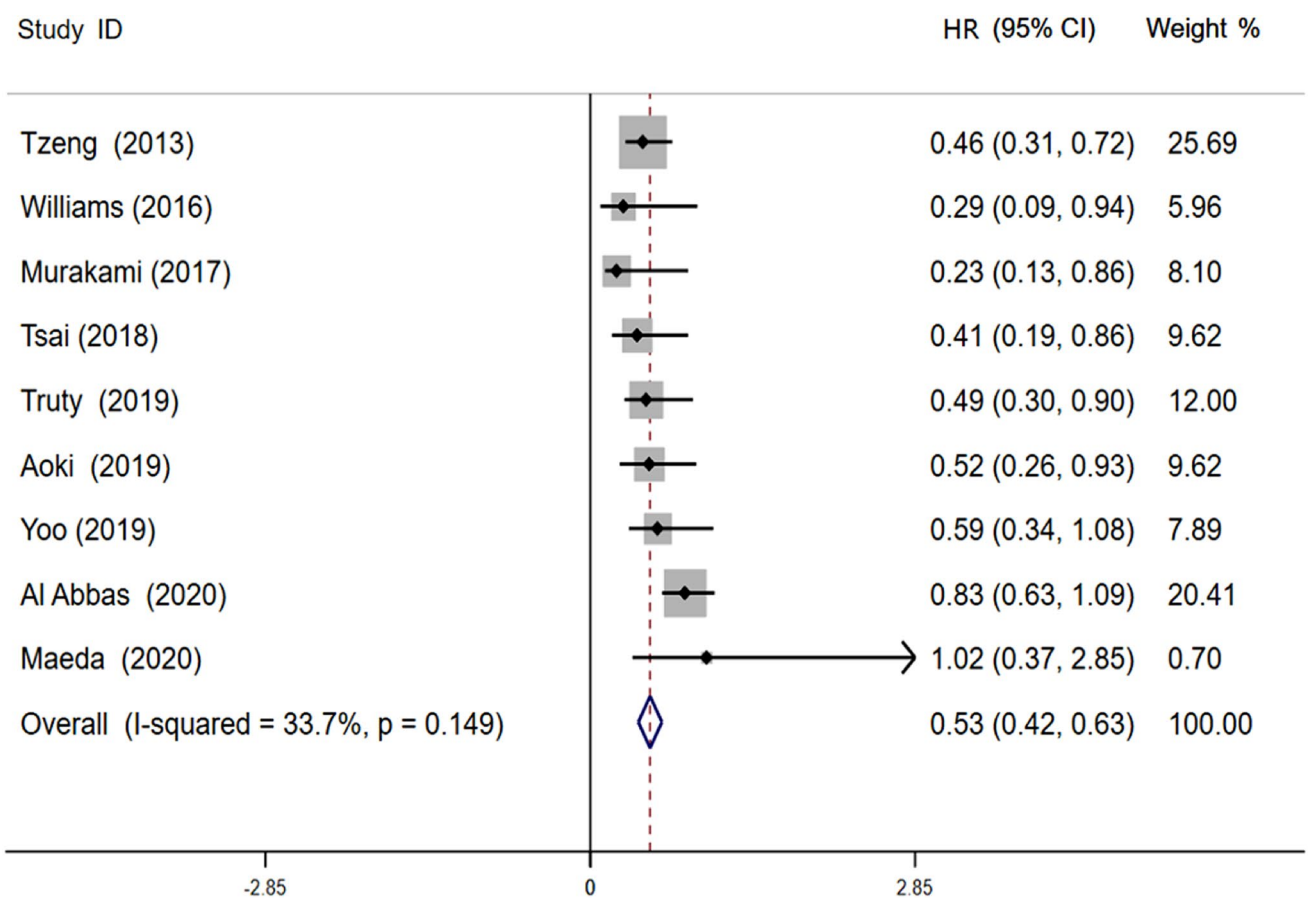

Fig. 3 Overall survival with post-neoadjuvant CA19-9 normalization for patients receiving neoadjuvant therapy

[31]. Restaging evaluation followed by neoadjuvant treatment could identify patients with highly aggressive disease who would not benefit from surgical resection. Imaging examinations and tumor markers are the most commonly used evaluation tools, and CA19-9 is the most commonly used tumor marker in PC. CA19-9 has provided useful information regarding tumor remission and recurrence in operative and metastatic cases; however, it is still unclear how the response of CA19-9 after neoadjuvant treatment would affect the prognosis of patients.

In the present pooled analysis, we found that a CA19-9 response > 50% and normalization of CA19-9 after neoadjuvant treatment were significantly associated with increased OS. Combined analysis revealed that response > 50% and normalization were optimal indicator of CA19-9 reduction to predict the post-neoadjuvant overall survival and potentially guide clinical strategies after treatment. In subgroup analysis, we also found that there was no significant effect on OS whether magnitude of CA19-9 response > 50% or normalization as long as optimal response is achieved. In addition, the duration of neoadjuvant treatment over 4 months was also remarkably associated with favorable prognosis. Previous studies demonstrated that increased or insufficient decrease in CA19-9 usually represented unsatisfactory control of the total tumor burden and probable presence of progressing disease. Research from Takahashi highlighted the poor prognosis in patients with evident chemoresistance and aggressive malignancy [32]. Therefore, concerns about the optimal response of CA19-9 have been raised, when aiming to select appropriate treatment strategies and maximize the patient's survival. Our work confirmed the use of CA19-9 as a single tool to indicate treatment response after neoadjuvant procedure, and the optimal CA 19-9 reduction would be determined to guide future treatment decisions due to their survival benefit.

Research concerning the magnitude of the proportional change in CA19-9 after neoadjuvant therapy differed between the included studies. Although a reduction of > 50% was the most commonly evaluated, other magnitudes of change were also taken into consideration in the survival analysis. Van et al. reported that a CA19-9 decrease of over 30% was associated with improved survival [33]. Al Abbas et al. indicated that a CA19-9 response of 85% or higher was the optimal threshold for predicting survival and could be

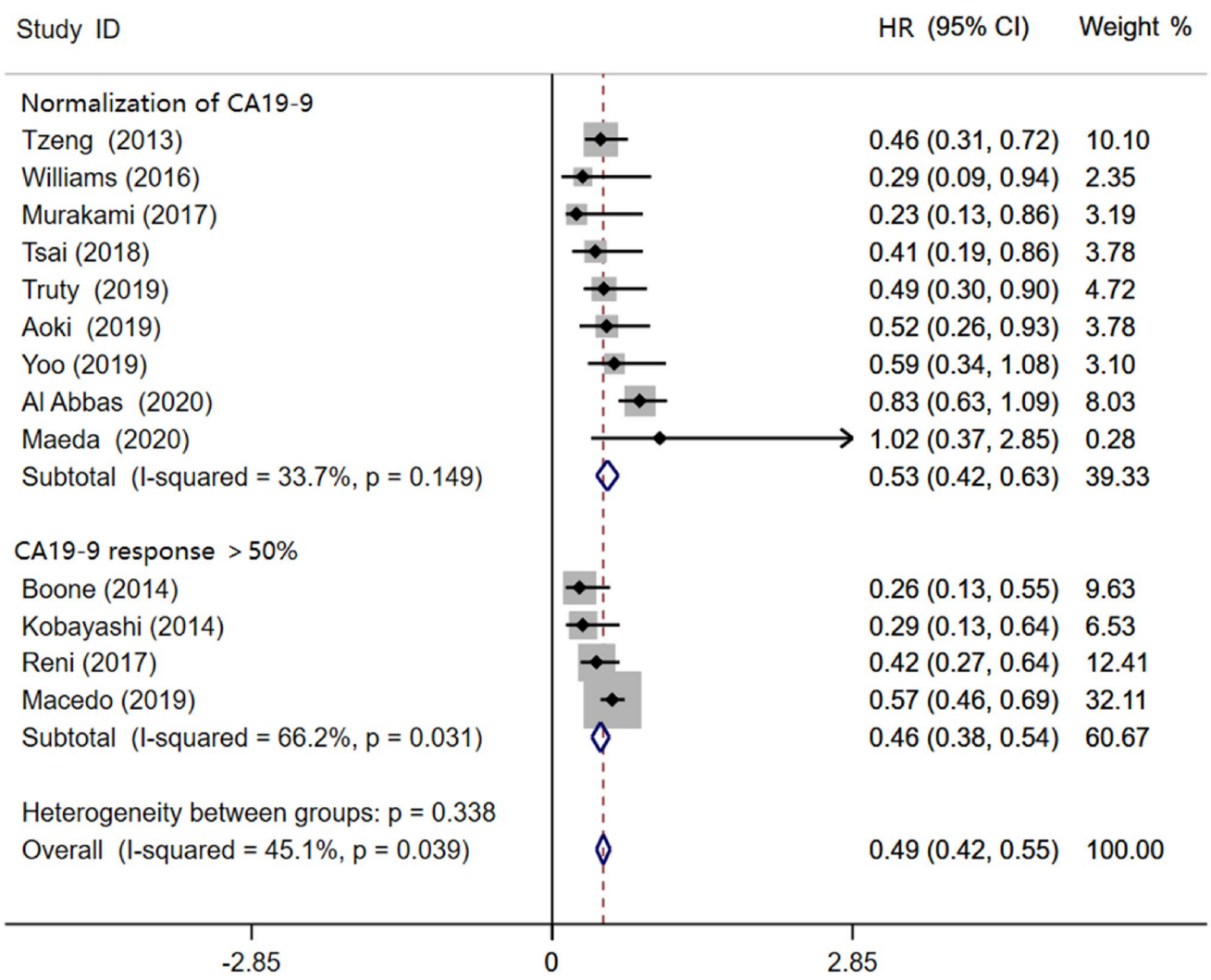

Fig. 4 Subgroup analysis of prognostic impact on different method to achieve optimal CA19-9 response

incorporated as an endpoint for neoadjuvant therapy [29]. Those studies inspired our further exploration; however, limited as we were to incomplete data, the presented data were not adequate for pooled analysis in this work. Interestingly, we found that the more significant the decrease in CA19-9, the lower the hazard ratio in the survival analysis study, which may lead to the conclusion that patients could benefit more from a greater reduction in CA19-9. However, it is difficult to predict the maximum magnitude of the CA19-9 response during neoadjuvant treatment in clinical practice. Combined our result of impact of long duration of preoperative treatment on CA19-9 response, we hypothesize that maybe prolongation of the chemotherapy cycles or treatment duration to maintain the ideal response level of CA19-9 for a period of time may improve the prognosis of patients [34].

Our work reinforced the CA19-9 as a reliable indicator of the response to NAT in patients with an elevated CA19-9 level at baseline. A massive decrease of > 50% or normalization of the CA19-9 level after neoadjuvant therapy is an effective method for evaluating the treatment response and post-neoadjuvant and postoperative prognosis because the change in CA19-9 is rooted in the tumor biology of PC [35, 36]. Consistent with the research of Hao Liu, the optimal NAT response as evaluated based on the magnitude of the CA19-9 response may predict survival benefit regardless of the regimen [37]. Nonetheless, it may not be suitable for patients who are non-secretors of CA19-9 or have comorbid obstructive cholangitis. For these patients, the change in CA19-9 is disrupted in the restaging evaluation and other markers, such as anatomical changes in radiographic images or inflammatory indices, may be potential

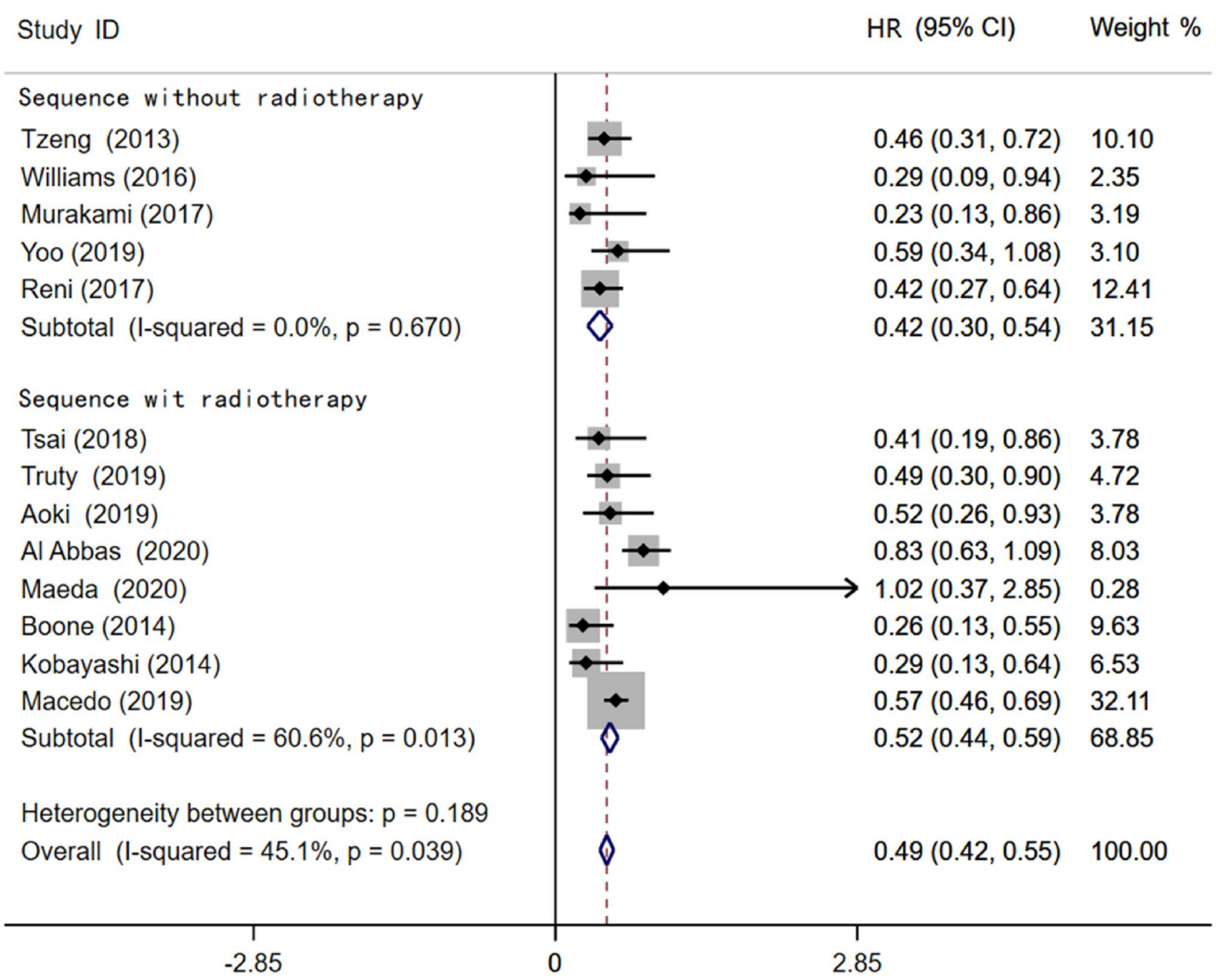

Fig. 5 Subgroup analysis of prognostic impact on sequence of radiotherapy in patients with optimal CA19-9 response

replacements. Murthy pointed out that the post-neoadjuvant immune-inflammation index closely paralleled changes in CA19-9 and that its combination with CA19-9 may improve prognostic prediction. Moreover, changes in the standard uptake value on 18fluoro-2-deoxy-d-glucose positron emission tomography–computed tomography could reflect the change in tumor burden and facilitate the indicative function of CA19-9 during neoadjuvant treatment.

To the best of our knowledge, our work is the first systematic review reporting the prognostic value of the CA19-9 response to neoadjuvant treatment; however, there are still some limitations to the current study. First, the majority of analyzed findings were from retrospective studies. A potential imbalance in patient characteristics (performance status and comorbidities) is likely, and findings from more fit patients who potentially received and completed all intended treatment with negative results may exist unpublished. This could be the main reason for the publication bias. Second, heterogeneity may exist in the staging of different tumors resectability and the follow-up duration; therefore, the conclusions may not be generalized to different tumor stages, especially with respect to long-term outcomes. Third, given the insufficient data on the delivered chemotherapy regimens or radiotherapy, the findings did not show the potential effects of different chemotherapy or radiotherapy regimens on survival outcomes between patients with a CA19-9 response. Fourth, the limited available literature suggests that optimal CA 19-9 response after neoadjuvant therapy could be significantly associated with R0 resection rate, negative lymph node metastases, and histopathologic response, but this conclusion cannot be reached due to inadequate data for aggregated analysis in this work.

In summary, serum CA19-9 values are useful in determining the treatment effect after NAT. The findings of our pooled analysis substantiate the favorable prognostic value

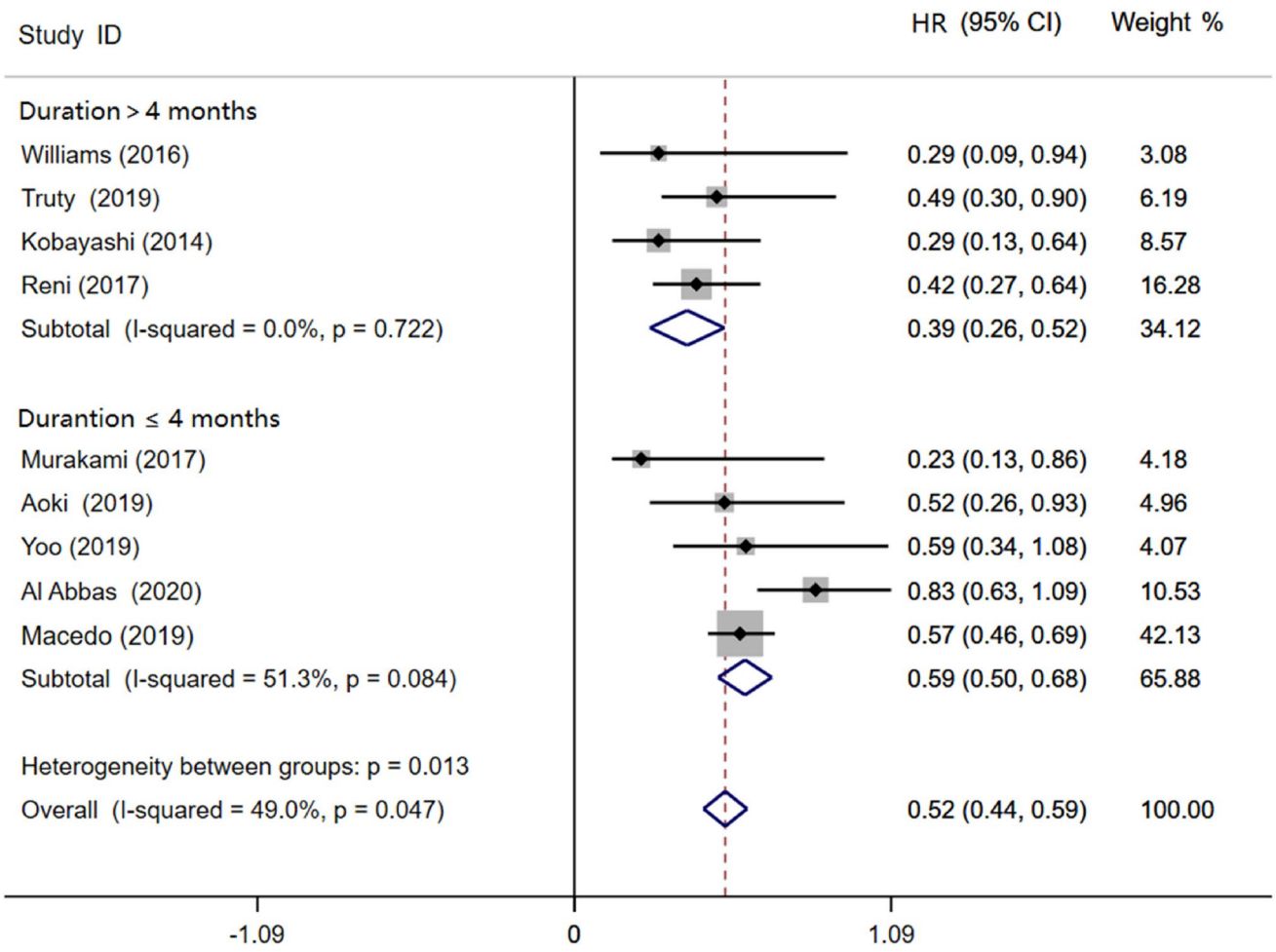

Fig. 6 Subgroup analysis of prognostic impact on duration of neoadjuvant treatment in patients with optimal CA19-9 response

of the optimal CA19-9 response in patients with pancreatic cancer receiving neoadjuvant treatment and radical surgery. In the future, the optimal CA19-9 response can be used to guide clinical decision after neoadjuvant therapy according to our research. And we hope the future prospective studies may explore the prognostic impact of long-period maintenance of optimal CA19-9 response through prolonged treatment or more aggressive management.

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Compliance with ethical standards

Conflict of interest No potential conflicts of interest were disclosed.

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