Serum amyloid A protein in cancer prognosis: a meta-analysis and systematic review

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Background: Published studies showed divergent results of the prognostic value of serum amyloid A protein (SAA) in patients with different cancers. Therefore, we conducted this meta-analysis so as to assess the association between SAA and cancer prognosis.

Methods: A comprehensive search was conducted to identify the literatures working over SAA and survival in patients with cancers published until January 2020. Sufficient data for assessing overall survival in cancers were extracted descriptively and quantitatively from the studies and a pooled odds ratio was calculated using the Mantel-Haenszel fixed-effect or random-effect model.

Results: Ten eligible papers were identified by two reviewers independently, including 4 studies that evaluated renal cell carcinoma (RCC), 2 studies evaluated lung cancer and the other 3 studies evaluated melanoma, gastric cancer and different cancers. Elevated SAA expression and shorter overall survival (OS) had a statistically significant relation [pooled 1-year OR was 5.07, 95% confidence interval (CI), 3.71–6.94, Q=9.15, I^2=0%; pooled 3-year OR was 4.21, 95% CI, 3.18–5.56, Q=14.94, I^2=46%; pooled 5-year OR was 5.69, 95% CI, 2.66–12.18, Q=24.83, I^2=80%]. Subgroup analysis of RCC patients showed remarkable association between SAA and shorter OS (pooled 1-year OR =4.76, 95% CI, 3.00–7.56, Q=4.18, I^2=4%; pooled 3-year OR =4.89, 95% CI, 3.06–7.81, Q=2.88, I^2=0%).

Conclusions: High SAA status is correlated with an unfavorable OS in different cancers, especially in RCC, and digestive cancer.

Keywords: Serum amyloid A proteins (SAA); cancer; prognostic factor; overall survival (OS); tumor marker

Introduction

Serum amyloid A protein (SAA), also known as serum amyloid protein A, is a 600-nucleotide long (1) and 122 amino acids protein and the encoding gene is located on chromosome 11p15.1 (2). In the human, SAA gene family contains the highly homologue SAA1, SAA2, SAA3 and SAA4 (3). SAA is an acute phase reactive protein as well as a high-density lipoprotein (HDL)-related protein (4,5). Meanwhile, SAA is expressed principally in hepar and extrahepatic cells or tissues such as epithelial cells, lymphocytes, and cancer cells (6) while occurring trauma,

Table 1 Study eligibility criteria table

Study eligibility criteria	Detail
SAA definition	Serum amyloid a protein as defined by each study (no restriction regarding laboratory method, immunity method)
Outcome measure	Overall survival
Study design	Prospective or retrospective cohort studies
Patient age	Any
Anatomical site	Any
Study tissue	Any
Stage	Any
Therapy	Any
Length of follow-up	Any

inflammation, infection, and oncogenesis (6,7).

SAA modulates cell adhesion, migration (8) in inflammation by inducing cytokines [IL-8 (9), G-CSF (10), etc.] expression and plays an important role in metabolism and transport of HDL and cholesterol (11). In addition, in the oncogenesis and tumor progression of various malignancies, chronic and lasting inflammation was considered as a crucial factor (12-15). But the function of SAA in oncogenesis still remains not clearly explained, and published studies suggest that SAA could become a biomarker to evaluate the growth of tumor and host response activity (16).

Following the explosive growth of knowledge of cancer biology, prognostic biomarker searching has been the most important fields of clinical oncology. A growing number of publications stated that chronic inflammation plays a prognostic role in many different cancers (17,18) and SAA status has been suggested as a prognostic biomarker for several tumors, such as renal cell carcinoma (RCC) (19), breast carcinoma (20), melanoma (21), lung cancer (22) and gastric carcinoma (23). The aim of this systematic review and meta-analysis was to clearly and comprehensively understand the prognostic value of SAA in different cancers with a standardized meta-analysis technique.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-3417).

Methods

### Search strategy and study eligibility

Published studies were comprehensively searched on two

independent databases PubMed and EBSCO till January 2020 using the MeSH words: "serum amyloid A protein" AND "Neoplasms". SAA levels were determined by each author of the studies with immunity method value. Overall survival (OS), which is defined as the length of time that patients were still alive from initial cancer diagnosis, was the primary outcome. Prospective cohort studies and retrospective ones were both included. Articles were ruled out following the criteria: (I) non-abstract or non-English article; (II) case reports or review articles; (III) duplicate ones. The other respects of the studies like patient ethnicity, type and stage of tumor, length of follow up, and therapeutic schedule was not restricted (study eligibility criteria outlined in *Table 1*).

Publication identification and data extraction

To identify the eligibility of the studies, every publication was examined by two authors independently according to Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guideline (24). To exclude the unrelated articles, the titles and abstracts of each study were read carefully with a unified standard. The remaining relevant studies were deeply examined to check their relevance. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (25) to present the flow chart of study identification in *Figure 1*.

Two reviewers used the Newcastle-Ottawa Quality Assessment Scales to conduct the quality assessment independently for each study. And all differences between the two reviewers' assessment were solved by consensus.
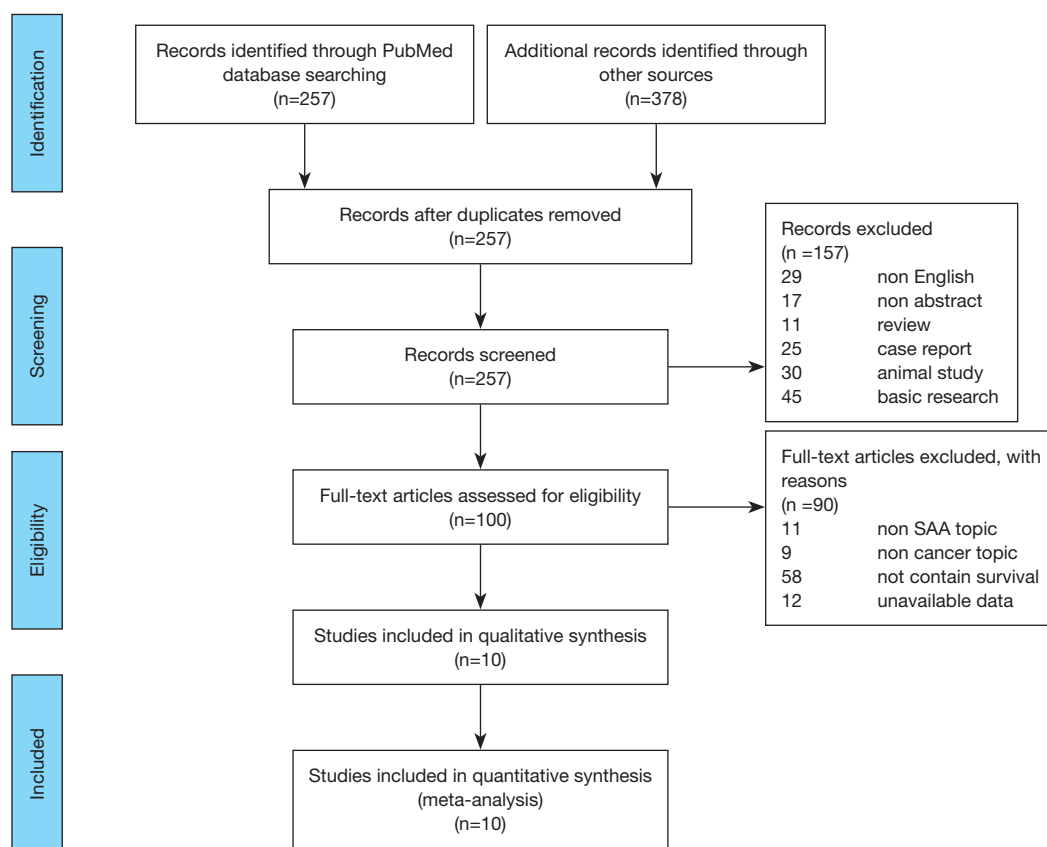
Figure 1 Study identification flowchart. Using standardized protocol for a comprehensive search through two electronic databases, a total of 10 studies were included in this review for qualitative or quantitative analysis.

Statistical analysis

We used Review Manager 5 to conduct the statistical analysis. The patients were divided into two constitutive groups according to SAA levels (SAA-high, SAA-low) by each study. Heterogeneity of clinical factors and methodological sources between studies were taken into consideration to assess whether it is appropriate to complete such a statistical synthesis. We calculated the heterogeneity using Q test, and measured the discordance of pooled OR by I^2 statistics (26). For this meta-analysis, we defined an I^2 statistic of <50% as an indication of acceptable heterogeneity. Funnel plots were drew to evaluate the publication bias.

For the meta-analysis, OS was defined as the primary outcome. We used the weighted average of ORs to get a summary of the relationship between OS and SAA expression, which can partially correct the variance of OR in each publication. Mantel-Haenszel Fixed-effects (27) model was used to complete the synthesis when P<0.1, I^2<50%, in

the opposite, Random-effects (26) model used when P>0.1, I^2>50%. In order to show the result of synthesis more clearly, forest plots presenting ORs of each study and pooled OR were completed. In the forest plots, the horizontal line segments indicated 95% confidence intervals (CIs), and the box in the middle of each line segment represented OR of each study. The vertical line was the reference line representing OR =1.0. At the bottom of the forest plots, the diamond represented the pooled OR, and the width represented the CIs. In order to evaluate the effect of cancer type of the result, subgroup analyses (RCC, lung cancer, digestive cancer, other or mixed) were conducted.

Results

Eligible studies

The 635 initially identified records were searched from two database (PubMed and EBSCO) with the MeSH words: "serum amyloid A protein" AND "Neoplasms" (flow chart

of study identification summarized in *Figure 1*). Then, 424 records were excluded for the reason of duplication, non-English and non-abstract. While conducting the initial title/abstract screen, we excluded 111 publications just because they were reviewed, case report, animal study or basic research; 100 studies remained for full-text inspection after title/abstract screening. The remained 100 records were carefully assessed for the eligible studies (*Figure 1*). During this procedure, 90 full-text articles were excluded for unavailable data or unrelated to the main topic (SAA, cancer and survival) and ten publications (21,28-36), published from 1986 to 2020, were qualified for the meta-analysis for the success to extract the necessary data.

Study characteristics

The characteristics of these ten publications were presented in *Table 2*. The total included patient number of all the publications was 1496, ranging from 58 to 379 per study (median =150). Four studies assessed RCC (21,28,30,36), two evaluated lung cancer (29,31), and one each assessed melanoma (21), esophageal carcinoma (33), gastric cancer (34), and different cancer (35). Almost all studies included different disease stages except one study not reported such relevant information. However, one study (32) examined only stage IIb or IIIa cancers, one (31) examined only stage I and II cancers, and one (28) examined only stage IV cancers.

Heterogeneity in SAA definition

The lab methods extracted from each included studies were presented in *Table 2*. Different lab methods were used for evaluating the SAA status, including two studies (32,36) used ELISA, two (31,34) LATI (latex agglutination turbid metric immunoassay), two (21,29) immunohistochemistry assay, one (28) conventional antibody-directed enumeration assays, one (35) used radioimmunoassay, one (33) poly-clonal antibody and another one (30) was not reported. Different method and the staining score decided the different cutoff for elevated SAA status in each study. The total mean percentage of elevated SAA status patients was 45.3%. Melanoma and ESCC showed the highest percentage (far over 50%) of elevated SAA among the patients. The percentage of SAA overexpression in lung, gastric and renal cancer ranged 17.25% to 54.3%. Significant statistical heterogeneity was absent in 1-year survival ($Q=9.15$, $I^2=0\%$) (*Figure 2*), 3-year survival

($Q=14.94$, $I^2=46\%$) (*Figure 3*), but present in 5-year survival ($Q=24.83$, $I^2=80\%$) (*Figure 4*).

Meta-analysis

Total OS

The combined analysis for the included ten studies showed that SAA status had a strong correlation with a shorter OS (1-year survival OR for death =5.07, 95% CI, 3.71–6.94, P<0.00001) (*Figure 2*), while no study indicated that SAA was correlated with a longer OS. We can also draw a similar conclusion for the 3-year OS (OR for death =4.21, 95% CI, 3.18 to 5.56, P<0.00001) (*Figure 3*) and 5-year OS (OR for death =5.69, 95% CI, 2.66–12.18, P<0.00001) (*Figure 4*).

OS for different cancers

In renal carcinoma (21,28,30,36), a high SAA status showed an unfavorable OS (OR for death at 1 year =4.76, 95% CI, 3.00–7.56; OR for death at 3 years = 4.89, 95% CI, 3.06–7.81; OR for death at 5 years =6.82, 95% CI, 2.63–17.68) (*Figures 2-4*). The two studies of digestive carcinoma (33,34) indicated that elevated SAA status correlated with a worse OS than that in RCC (OR for death at 1 years =12.99, 95% CI, 2.43–69.61, P<0.0001; OR for death at 3 years =9.15, 95% CI, 4.87–17.18, P<0.00001; OR for death at 5 years =8.63, 95% CI, 4.88–15.26, P<0.00001) (*Figures 2-4*). However, there was no statistical difference between digestive and non-digestive cancers. High status of SAA reported in another two studies of lung cancer was also associated with an unfavorable 1-year OS (OR for death =6.81, 95% CI, 2.21–20.92) (*Figure 2*).

Publication bias

Publication bias analysis of the ten studies were presented as funnel plots (*Figure 5*) and the results indicate negligible publication bias

Discussion

A systematic review was carried out to evaluate the effect of SAA status on OS of patients with different kind of tumors. This meta-analysis showed a remarkable role of SAA in diverse cancer prognosis as well as in the subgroup of RCC, lung cancer and digestive carcinoma. No matter in early and locally advanced diseases (stages I–III) or in metastasis carcinoma (stage IV), our analysis showed an essential effect. Therefore, SAA could be included as one of the prognostic biomarker factors for cancers especially for RCC

Table 2 Summary of included study characteristics

Study	Year	Country (region)	Patient number	Type of tumor	Stage	Male gender (N, %)	Median age (range)	Lab method	SAA classification	Definition of SAA (+)	SAA (+) prevalence (N, %)	NOS score	OS/PFS
Findeisen P, et al. (21)	2009	Germany	379	Melanoma	I–IV	208, 54.9%	54.7 (6.8–87.8)	Immunonephelometric assay	Low/high	SAA >10 mg/L	203, 53.6%	8	OS
Vermaat JS, et al. (I) (28)	2012	The Netherlands	114	mRCC	IV	76, 67%	60 (49.9–70.1)	Conventional antibody-directed enumeration assays	Low/high	SAA >71 ng/mL	52, 45.6%	8	PFS, OS
Vermaat JS, et al. (II) (28)	2012	The Netherlands	151	mRCC	IV	107, 71%	60.2 (50.1–70.3)	Conventional antibody-directed enumeration assays	Low/high	SAA >72 ng/mL	82, 54.3%		PFS, OS
Paret C, et al. (29)	2010	Germany	87	RCC	NR	NR	NR	Immunohistochemistry assay	Negative/positive	NR	15, 17.2%	7	OS
Liu YS, et al. (30)	2012	China	106	Lung cancer	IIb, IIIa	NR	NR [41–73]	NR	Low/high	SAA >17.05	56, 52.8%	7	OS, RFS
Wang JY, et al. (33)	2012	China	165	Esophageal squamous cell carcinoma	I–IV	129, 78.2%	58.5 [40–70]	Poly-clonal antibody	Non-elevated/elevated	SAA >8.0 mg/L	91, 55.2%	7	OS
Kwon HC, et al. (34)	2012	South Korea	115	Gastric cancer	I–IV	68, 59.1%	NR	Latex agglutination turbidoimmunometric assays	Low/high	SAA >4.2 mg/mL	57, 49.6%	8	DFS, OS
Biran H, et al. (35)	1986	Israel	151	Cancer	I–IV	48, 31.8%	NR	Radioimmunoassay	Low/high	SAA >10 µg/mL	39, 25.8%	5	OS
Kimura M, et al. (31)	2001	Japan	72	RCC	I–II	NR	60.4 [34–81]	Latex agglutination turbidimetric immunoassay	Normal/elevated	SAA >8 mg/L	38, 52.8%	6	OS
Ramankulov A, et al. (36)	2008	Germany	98	RCC	I–IV	66, 67.3%	60.0 [55–65]	ELISA	Low/high	SAA >27.7 mg/L	30, 30.6%	8	OS
Wang YS, et al. (32)	2013	Taiwan	58	Lung cancer	I–IV	42, 72.4%	53.4% <70 years	ELISA	Low/high	SAA >670 µg/mL	15, 25.9%	8	OS

mRCC, metastatic renal cell carcinoma; RCC, renal cell carcinoma; SAA, serum amyloid A protein; PFS, progression-free survival; OS, overall survival.
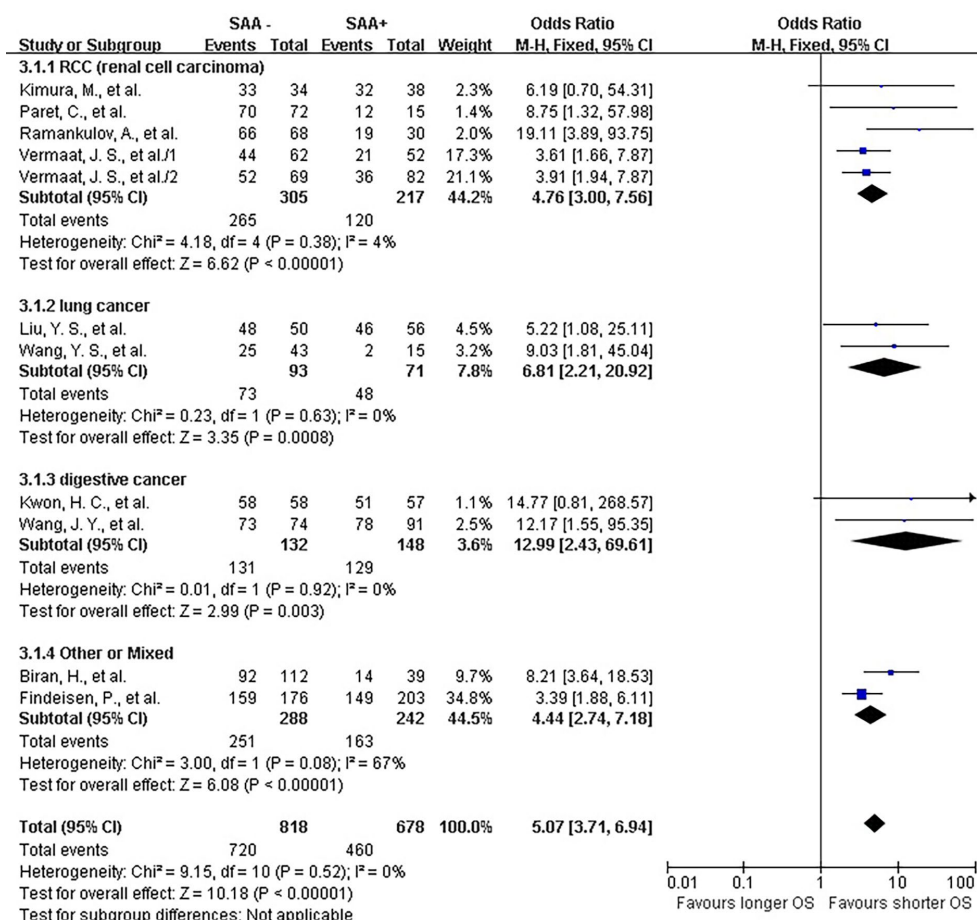
Figure 2 Forrest plot of ORs for the association of SAA expression with 1-year overall survival (OS). It showed that SAA could be an independent prognostic factor for OS in different cancer patients. SAA, serum amyloid A protein.

and digestive carcinoma. And should be selected with or for a further prospective study with our previous results CD 166 and CD 133 expressions.

Plenty of prognostic factors for different cancers existed in current references, such as breast cancer (37,38), bladder cancer (39,40), RCC (41), colorectal cancer (42), lung cancer and so on. The researchers have proved some clinical prognostic factors, mainly tumor staging and performance status (PS) (43). However, some clinical prognostic factors are not homogeneous, so that clinical oncologists cannot easily predict the survival for individual patients, such as tumor staging. Consequently, meta-analyses to evaluate the prognostic value of a new biological marker are urgent needed to solve the limitation statistical power of small size studies and to indicate more new prognostic factors, as our group published these years (44,45).

Heterogeneity is a significant problem that can influence

the result of meta-analysis. Therefore, to avoid selection biases, we carried a methodological assessment as we implemented in prior studies (44,45). There was no obvious difference between the 10 eligible studies. However, it was hard to perform credible statistical comparisons with a limited study number of each subgroup.

Several limitations of our meta-analysis need to be taken into account while discussing our results. Primarily, potential confounding factors would not be corrected for the reason of the unavailable individual patient data such as age, gender or TNM. Such a literature-based analysis was unlikely to gain adequate information. Secondly, publication bias, selection bias, difference in lab method of detecting SAA and definition of SAA (+) between each study, and method of extrapolation of OR, were also factors that would directly influence our result.

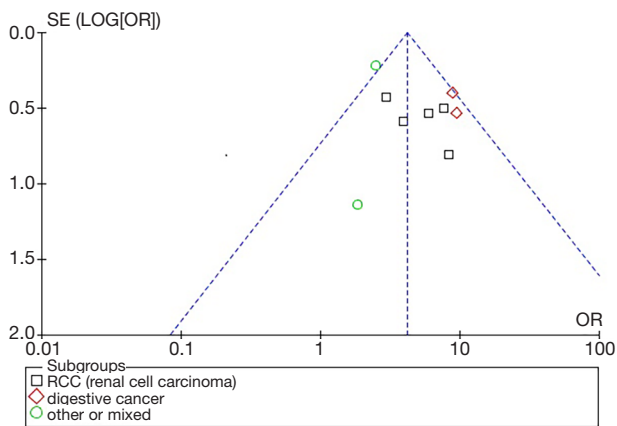In conclusion, our meta-analysis indicates that high SAA
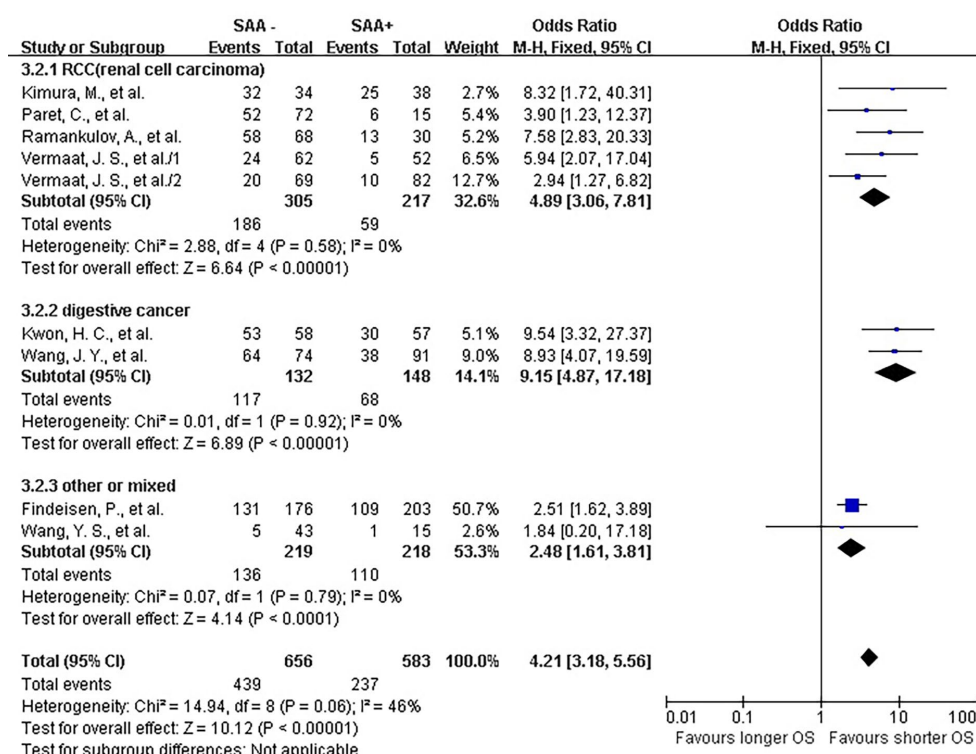
Figure 3 Forrest plot of ORs stratified on cancer type for the association of SAA expression with 3-year overall survival (OS). SAA, serum amyloid A protein.
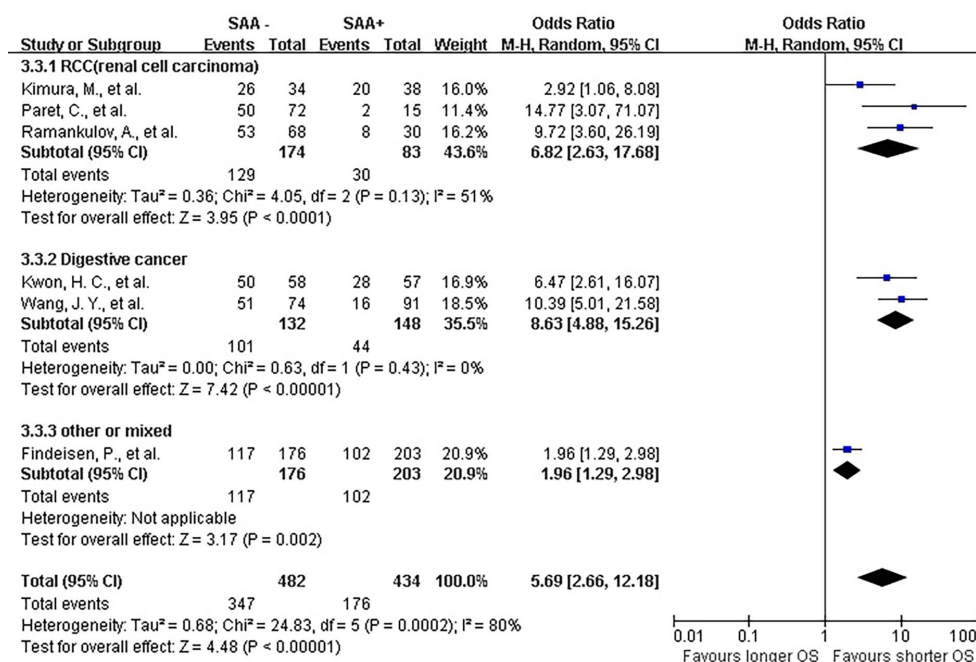
Figure 4 Forrest plot of ORs stratified on cancer type for the association of SAA expression with 5-year overall survival (OS). SAA, serum amyloid A protein.

Figure 5 Funnel plot of ORs for stratified on cancer type the association of SAA expression with 3-year overall survival (OS). SAA, serum amyloid A protein.

status is correlated with an unfavorable OS in different cancers, especially in RCC, and digestive cancer. Our present and prior results from meta-analyses serve to carry out a prospective multivariate trial aiming to observe which combination of classical and new prognostic biomarkers or which biomarkers will play a more important role in the prognosis of cancer patients.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/tcr-20-3417

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-3417). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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