

Association between baseline C-reactive protein level and survival outcomes for cancer patients treated with immunotherapy: A meta-analysis

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Abstract. The prognostic impact of baseline C-reactive protein (CRP) in patients with cancer receiving immune checkpoint inhibitors (ICIs) is unclear. The present meta-analysis aimed to review the prognostic value of baseline C-reactive protein (CRP) levels for patients with cancer receiving immunotherapy. Electronic databases, including PubMed, EMbase, Cochrane Library, Web of Science, Chinese National Knowledge Infrastructure, WanFang, Chinese Literature Biomedical Database and Weipu Database, were used to identify cohort studies on the relationship between the baseline CRP levels and ICI survival outcomes from inception to November 2020. Literature screening, data extraction and quality evaluation of studies were independently performed by two reviewers. Subsequently, a meta-analysis was performed using STATA 14.0. A total of 13 cohort studies comprising 2,387 patients with cancer were included in the present meta-analysis. The results indicated that high baseline CRP levels (serum CRP measured within 2 weeks before ICI treatment) were associated with low overall survival (OS) and progression-free survival (PFS) rate among patients treated with ICIs. The subgroup analysis based on cancer type showed that high baseline CRP levels were associated with poor survival outcomes of multiple types of cancer, such as non-small cell lung cancer (6/13; 46.2%), melanoma (2/13; 15.4%), renal cell (3/13; 23.0%) and urothelial carcinoma (2/13; 15.4%). Similar results were observed in subgroup analysis based on the CRP cut-off value

of 10 mg/l. In addition, a higher mortality risk was reported in patients with cancer and CRP ≥ 10 mg/l (hazard ratio, 2.76; 95% CI, 1.70-4.48; $P < 0.001$). Compared with patients with low baseline CRP levels, increased baseline CRP levels were associated with low OS and PFS rate in patients with cancer receiving ICIs. Furthermore, CRP ≥ 10 mg/l indicated a worse prognosis. Therefore, baseline CRP levels may serve as a marker for the prognosis of patients with certain types of solid tumor treated with ICIs. Due to the limited quality and quantity of included studies, more prospective well-designed studies are required to verify the present findings.

Introduction

Cancer seriously affects health and is responsible for the death of most people worldwide; there were an estimated 19.3 million new cases and 10 million cancer deaths worldwide in 2020 (1). In recent years, immunotherapy has emerged as a novel treatment option for advanced tumors (2). Current research hotspots include immune checkpoint inhibitors (ICIs) and multiple ICIs have shown clinical benefits for treatment of certain advanced cancers. However, factors such as low response rate, disease pseudoprogression and immune-associated adverse events require the identification of predictive and prognostic biomarkers to determine which patients may benefit from cancer immunotherapy (3). Histological markers such as programmed death-ligand 1 (PD-L1) expression, tumor mutation burden (TMB), microsatellite instability (MSI) and T cell receptors (TCRs) are currently well-known predictive biomarkers but they still present some limitations in clinical application and in predicting the efficacy of ICIs (4).

There are several cut-off criteria and antibodies for the PD-L1 expression analysis. For example, in cohort studies on PD-L1 inhibitors, such as durvalumab (5) and atezolizumab (6) SP163 and SP142 antibodies were used to evaluate the expression of PD-L1. However, in cohort studies on PD-1 inhibitors, such as nivolumab (7) and pembrolizumab (8), 28-8 and 22C3 antibodies were used (9). On the other hand, bias in defining positivity for PD-L1 expression could be observed among different cohort studies because of different

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cut-off values ranging from 1-50% (10). Secondly, several limitations exist on the clinical application of TMB for predicting the efficacy of ICIs. For example, different cohort studies use different TMB cut-off values (11-14). Although pembrolizumab was approved by the US Food and Drugs Administration (FDA) for use in patients with high TMB (TMB-H) solid tumors (≥ 10 mutations/megabase), contradictory results are observed in clinical practice (15). A previous study showed that patients with TMB-H had a low response rate to ICIs, while patients with low TMB values benefit from ICI therapies (16). Thirdly, although high MSI (MSI-H) is approved by FDA as a biomarker for predicting the efficacy of pembrolizumab in the treatment of solid tumors regardless of tumor histology, a contradictory phenomenon remains observable in clinical practice: For example, several studies suggest that patients with colorectal cancer with microsatellite stability (MSS) can also have a notable clinical response to PD-1 inhibitors (17,18).

By contrast, hematological markers are a focus of clinical research due to their several advantages including affordability, convenience and non-invasiveness. However, hematological markers have some limitations. For example, TCR plays important role in recognizing neoantigens, a prerequisite of T cell antitumor response. It was demonstrated that increased richness of TCR clonotypes is correlated with increased overall survival (OS) time in patients with melanoma treated with ipilimumab (19). This beneficial phenomenon could also be observed in patients with urothelial carcinoma treated with atezolizumab, in which long-term clinical benefits were significantly correlated with expansion of TCR (20). However, contradictory results were observed with anti-PD-1 therapy (21). Due to the heterogeneity of TCRs and the need for complicated analytical techniques, such as high-throughput sequencing and single-cell sequencing techniques, the clinical application for predicting the efficacy of ICIs is premature. Therefore, exploring other clinically available and accessible hematological markers is important. It was reported that inflammatory responses are associated with apoptosis inhibition, angiogenesis promotion and DNA damage, which result in tumor progression (22). Routine detection of multiple indicators in peripheral blood can reflect the inflammatory status of patients with cancer. C-reactive protein (CRP), as a marker of systemic inflammation, can predict the survival outcomes of patients with cancer treated with ICIs. A previous report showed that increased CRP was a marker of poor prognosis in patients with cancer who were treated with ICIs, which was associated with shortened progression-free survival (PFS) and OS times (23). Although several studies investigated the association between CRP levels and ICI therapy survival outcomes, different conclusions were found in these studies: For example, among patients with advanced melanoma who were treated with nivolumab, increased CRP levels were significantly associated with poor OS and PFS (24). By contrast, in patients with non-small cell lung cancer (NSCLC) who were treated with nivolumab, CRP was not correlated with PFS or OS (25). For ICIs other than nivolumab, the association between CRP and ICI therapy survival outcomes remains contradictory. For example, Muto *et al* (26) found that in patients with advanced melanoma, CRP is not associated with the efficacy of ipilimumab and OS; however, Shibata *et al* (27) found that in

patients with advanced NSCLC, increased serum CRP levels at 6 weeks of treatment could predict longer survival when pembrolizumab was given as first-line treatment.

Therefore, the present meta-analysis aimed to explore the association between baseline CRP levels and survival outcomes of patients with cancer who were treated with ICIs to provide a basis for improved evaluation of the prognosis.

Materials and methods

Literature search. Electronic databases, including PubMed, EMBase, Cochrane Library, Web of Science, Chinese National Knowledge Infrastructure, WanFang, Chinese Literature Biomedical Database and Weipu Database (28) were searched to identify cohort studies on the relationship between baseline CRP levels and ICI survival outcomes from inception to November 2020. The key words used for the literature search were: 'C-reactive protein', 'C reactive protein', 'CRP', 'neoplasms', 'tumors', 'cancers', 'carcinoma', 'immunotherapy', 'immune checkpoint inhibitor', 'PD-1 inhibitor', 'PD-L1 inhibitor', 'CTLA-4 inhibitor', 'nivolumab', 'pembrolizumab', 'atezolizumab', 'durvalumab' and 'ipilimumab'. In addition, the references of relevant articles were reviewed to identify potentially eligible studies.

Eligibility criteria. The inclusion criteria were as follows: i) Eligible patients were pathologically diagnosed with solid tumor and treated with ICIs alone or ICIs combined with systemic chemotherapy; ii) reported baseline CRP levels before treatment; iii) provided hazard ratios (HRs) and 95% CIs for baseline CRP levels and OS or PFS analysis or the data necessary to calculate them. When duplicated data were reported in different studies, only the most recent or highest quality were included.

The exclusion criteria were as follows: i) Reviews, comment letters, meeting abstracts or case reports; ii) *in vivo* or *in vitro* studies; iii) studies published in a language other than Chinese or English; iv) immunotherapy regimens other than ICIs; v) full text was not available or did not provide all necessary data mentioned in the inclusion criteria above; vi) provided post-treatment CRP levels or dynamic changes in CRP levels only.

Data extraction. A total of two authors independently reviewed and extracted data from the included studies. Any discrepancy was resolved through discussion with a third author. The data extracted from the eligible studies included the following items: i) Name of the first author(s) and year of publication; ii) patient median age and sex ratio; iii) sample size and types of cancer and ICI drug; iv) CRP cut-off values; v) HR and 95% CI associated with OS and PFS. The HRs from multivariate Cox analysis were top-priority for use when reported.

Quality assessment. The quality assessment of studies was conducted by two independent researchers according to the Newcastle-Ottawa Scale (NOS) (29), which assesses the quality based on three aspects: i) Selection of study subjects; ii) comparability between groups; and iii) measurement of outcomes. The maximum score was 9 points and studies scoring ≥ 6 points were regarded as high-quality studies.

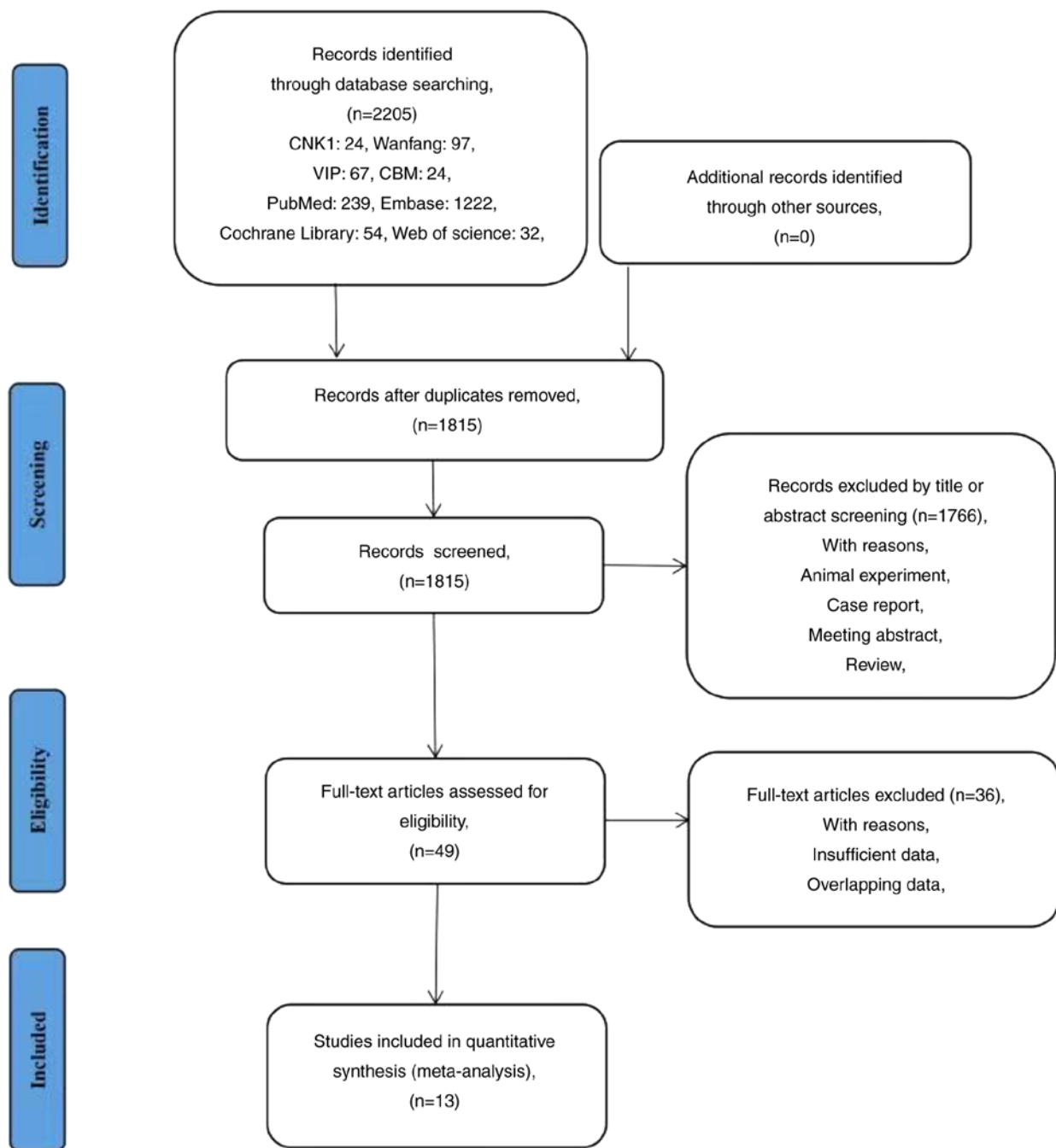


Figure 1. Literature screening workflow. CNKI, Chinese National Knowledge Infrastructure; VIP, Chongqing Weipu Database for Chinese Technical Periodicals; CBM, Chinese Biomedical database.

Statistical analysis. Meta-analysis was conducted using STATA software (version 14.0; StataCorp.). The HR and corresponding 95% CI were used to evaluate the association between CRP and ICI survival outcomes in patients with cancer. Q test was performed to assess heterogeneity of included studies and the I^2 statistic was calculated to evaluate the total observed variability due to study heterogeneity. $I^2 > 50\%$ and/or $P < 0.1$ was considered to indicate statistically significant heterogeneity (30). Subgroup analysis was performed to identify the source of heterogeneity. A random-effects model was chosen for the meta-analysis if there was significant heterogeneity between studies; otherwise, a fixed-effects model was selected (31). Sensitivity analysis was performed by excluding

each study individually to assess the stability of the results (32). Publication bias was assessed using Egger's and Begg's tests, and $P < 0.05$ was considered to indicate a significant publication bias (33,34). When significant publication bias was found, Duval and Tweedie's trim and fill method was used to calculate the effect of potential data censoring or publication bias on the outcomes of the meta-analysis (35).

Results

Characteristics of the included studies. A total of 2,205 relevant studies were identified through a systematic literature search. Firstly, 390 duplicate publications were excluded, while

Table I. Baseline characteristics of included studies.

First author/s, year	Median age, years	Sex, male/female	Cancer type	Sample size, n	Treatment	CRP cut-off level, mg/l	Outcome	Newcastle-Ottawa Scale	(Refs.)
Nakamura <i>et al</i> , 2016	67	52/46	Melanoma	98	Nivolumab	3	OS	6	(36)
Oya <i>et al</i> , 2017	66	87/37	NSCLC	124	Nivolumab	10	PFS	7	(37)
Naqash <i>et al</i> , 2018	64	56/31	NSCLC	87	Nivolumab	50	OS	6	(38)
Tanizaki <i>et al</i> , 2018	68	90/44	NSCLC	134	Nivolumab	4.1	PFS and OS	6	(25)
Ishihara <i>et al</i> , 2019	NA	45/13	RCC	58	Nivolumab	10	PFS and OS	5	(39)
Yasuoka <i>et al</i> , 2019	69	32/8	UC	40	Pembrolizumab	5	OS	7	(40)
Laino <i>et al</i> , 2020									(41)
Cohort 1	64	121/89	Melanoma	206	Nivolumab	5.3	OS	7	
Cohort 2	59	202/114	Melanoma	313	Nivolumab	5.75	OS	7	
Cohort 3	61	202/113	Melanoma	311	Ipilimumab	5.75	OS	7	
Cohort 4	59	206/108	Melanoma	313	Nivolumab + ipilimumab	5.75	OS	7	
Tamura <i>et al</i> , 2020	70	29/12	UC	41	Pembrolizumab	10.6	OS	6	(42)
Adachi <i>et al</i> , 2019	70	206/90	NSCLC	296	Nivolumab	10	PFS	7	(43)
Suzuki <i>et al</i> , 2019	68	47/18	RCC	65	Nivolumab	21	PFS and OS	7	(44)
Inomata <i>et al</i> , 2018	NA	54/18	NSCLC	36	Nivolumab/Pembrolizumab	10	PFS	6	(45)
Noguchi <i>et al</i> , 2020	68.5	51/13	RCC	64	Nivolumab	15	PFS	7	(46)
Taniguchi <i>et al</i> , 2017	68	135/66	NSCLC	201	Nivolumab	3	PFS	6	(47)

NA, not available; NSCLC, non-small cell lung cancer; RCC, renal cell cancer; UC, urothelial carcinoma; OS, overall survival; PFS, progression-free survival.

Table II. Subgroup analysis of overall survival.

Subgroup	Number of studies	Heterogeneity test		Effect model	Meta-analysis		(Refs.)
		P-value	I ² , %		Hazard ratio (95% CI)	P-value	
NSCLC	2	0.470	0	Fixed	2.19 (1.21-3.97)	0.010	(39,29)
RCC	2	0.815	0	Fixed	4.32 (1.55-12.01)	0.005	(40,45)
UC	2	0.655	0	Fixed	4.69 (2.04-10.79)	<0.001	(41,43)
Melanoma	2	0.555	0	Fixed	1.35 (1.15-1.59)	<0.001	(37,42)
CRP cut-off, mg/ml							
<10	4	0.168	34.1	Fixed	1.40 (1.13-1.74)	0.003	(37,29,41,42)
≥10	4	0.516	0	Fixed	2.76 (1.70-4.48)	<0.001	(39,40,43,45)

NSCLC, non-small cell lung cancer; RCC, renal cell cancer; UC, urothelial carcinoma; CRP, C-reactive protein.

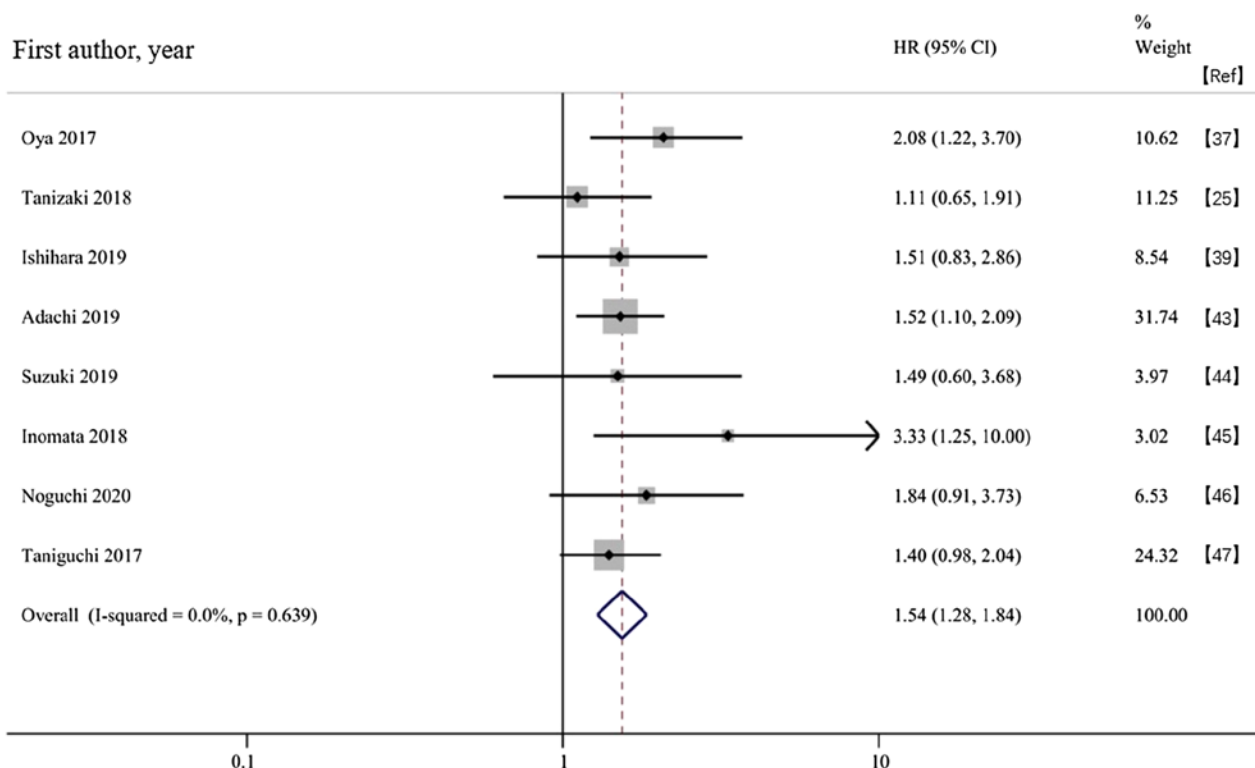


Figure 2. Forest plot of overall survival. The black squares represent the HR value, whilst the diamond represents the combined result of the included studies. HR, hazard ratio; CI, confidence interval.

1,766 were excluded after screening the titles and abstracts, including reviews, meeting abstracts, laboratory studies and other articles irrelevant to the present meta-analysis. Among them, 739 articles did not report survival risks, 954 articles did not involve patients using ICI and 73 articles were case reports that did not have sufficient data.

After reviewing and screening the full text of the remaining 49 articles, 36 additional articles were excluded according to the aforementioned inclusion and exclusion criteria. Finally, 13 retrospective studies were included in the present meta-analysis (25,36-47). The search process is shown in Fig. 1. All included studies were published between 2016 and 2020. A total of 2,387 patients were included in

the present meta-analysis, while the sample sizes ranged from 36-313 participants. Patients were primarily diagnosed with NSCLC (6/13; 46.2%), melanoma (2/13; 15.4%), renal cell carcinoma (3/13; 23.1%) and urothelial carcinoma (2/13; 15.4%). The applications of ICI include anti-CTLA-4, anti-PD-1 and anti-CTLA-4 combined with anti-PD-1 inhibitors. The proportion of males was 53-87% in each study, and the mean age was 59-70 years. Regarding prognostic indicators of baseline CRP levels in patients receiving ICIs, three articles reported OS and PFS, five reported OS only and five reported PFS only. The CRP cut-off values were between 3 and 50 mg/l and the value of 10 mg/l was used frequently. The NOS scores of the included studies ranged from 5-7.

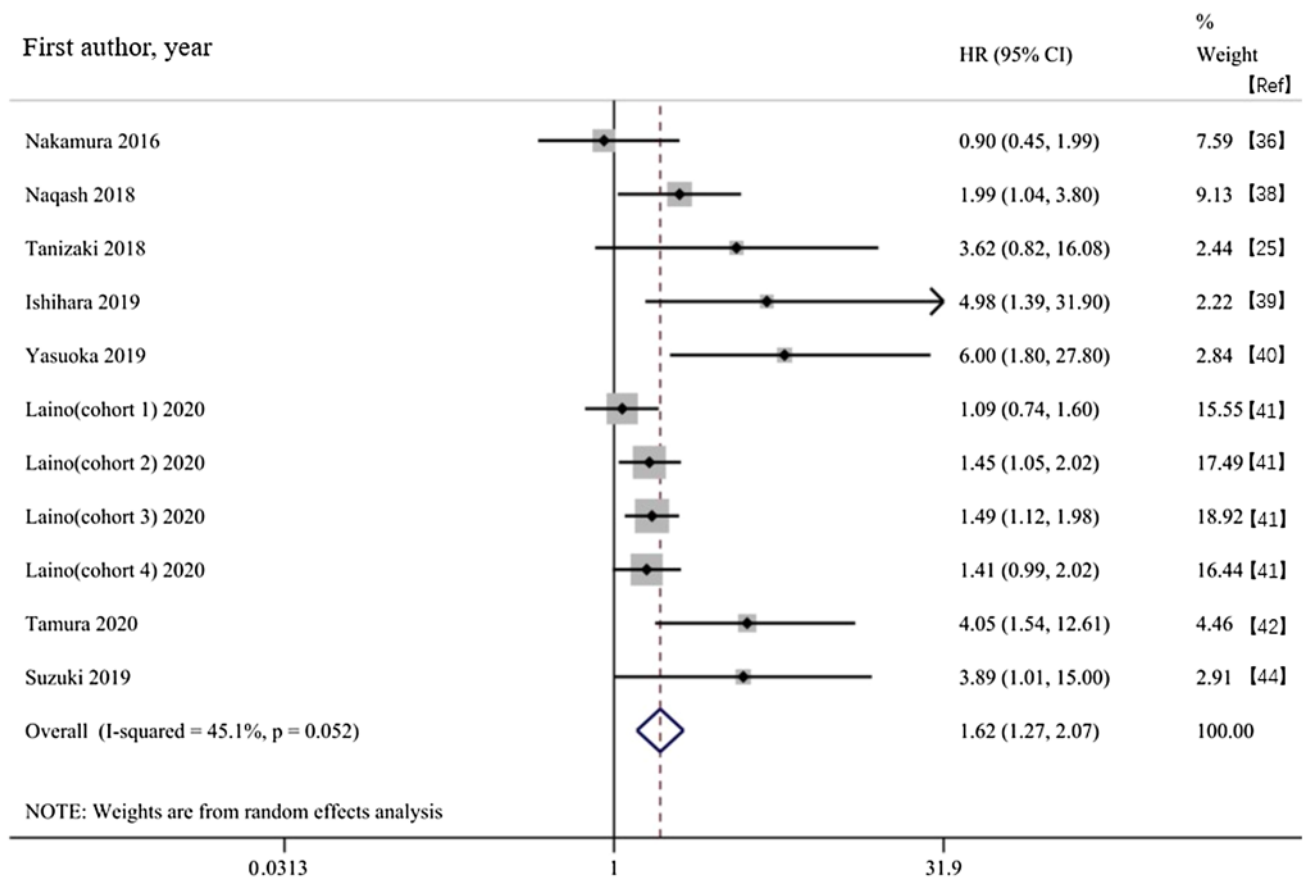


Figure 3. Forest plot of progression-free survival. The black squares represent the HR value, whilst the diamond represents the combined result of the included studies. HR, hazard ratio; CI, confidence interval.

The baseline characteristics of included studies are shown in Table I; other characteristics, including study design, country, study period and adjusted covariates, are listed in Table SI.

Survival outcome

Association between the baseline CRP and OS in patients receiving ICIs. Of the 13 included studies, eight provided the baseline CRP and OS. The random effects model showed a significant association between high baseline CRP levels and shortened OS time in patients receiving ICIs (HR, 1.62; 95% CI, 1.27-2.07; $P < 0.001$; Fig. 2). The subgroup analysis based on type of cancer found that a high baseline CRP in patients with multiple cancer types treated with ICIs was associated with a poor OS. Subgroup analysis based on the CRP cut-off value of 10 mg/l showed that an increased baseline CRP was associated with poor OS regardless of whether the CRP levels were >10 mg/l; prognosis of patients with CRP ≥ 10 mg/l was worse (Table II).

Association between the baseline CRP and PFS in patients receiving ICIs. A total of eight studies evaluated PFS outcomes. The fixed-effects model meta-analysis showed that an increased baseline CRP was associated with a shorter PFS time in patients treated with ICIs (HR, 1.54; 95% CI, 1.28-1.84; $P < 0.001$; Fig. 3). The subgroup analysis stratified by cancer type showed consistent results with OS, indicating that a high baseline CRP in patients with multiple cancer types treated with ICIs was associated with a poor PFS time. The subgroup analysis stratified by the CRP cut-off value showed

that CRP ≥ 10 mg/l was associated with poor PFS. Although HR values of PFS corresponding to CRP <10 mg/l were high, the difference was not statistically significant (Table III).

Sensitivity analysis. A sensitivity analysis was performed by excluding each study individually. The pooled HR values of the remaining studies ranged from 1.53-1.74 for OS and 1.48-1.60 for PFS, and the lower and upper thresholds of the 95% CI were >1 . The exclusion of any study from the meta-analysis did not significantly change the summary estimate, showing that the results were not driven by any single study. The pooled HRs for OS and PFS were robust and the present meta-analysis was reliable (Figs. 4 and 5)

Publication bias. Begg's test funnel plot was drawn for the increased baseline CRP and the outcome indicators of OS and PFS. The scatter points were symmetrical, indicating a small possibility of publication bias (OS, $P = 0.087$; PFS, $P = 0.174$). Egger's test confirmed no publication bias in studies reporting the association between baseline CRP levels and PFS ($P = 0.233$), but the analysis of the association between baseline CRP and OS suggested significant publication bias ($P = 0.012$).

The trim and fill methods were used to evaluate the effect of publication bias on the meta-analysis outcomes. After trimming and filling, the scatter points were symmetrical in the funnel plot, indicating no publication bias (Fig. 6). For the pooled HRs for OS before and after trimming and filling, the

Table III. Subgroup analysis of progression-free survival.

Subgroup	Number of studies	Heterogeneity test		Effect model	Meta-analysis		(Refs.)
		P-value	I ² , %		HR (95%CI)	P-value	
NSCLC	5	0.296	18.6	Fixed	1.52(1.25,1.86)	<0.001	(25,37,43,45,47)
RCC	3	0.903	0.00	Fixed	1.61(1.06,2.44)	0.024	(39,44,46)
CRP cut-off, mg/ml							
<10	2	0.485	0.00	Fixed	1.30(0.96,1.76)	0.089	(25,47)
≥10	6	0.723	0.00	Fixed	1.69(1.35,2.12)	<0.001	(37,39,43,44,45,46)

NSCLC, non-small cell lung cancer; RCC, renal cell cancer; UC, urothelial carcinoma; CRP, C-reactive protein.

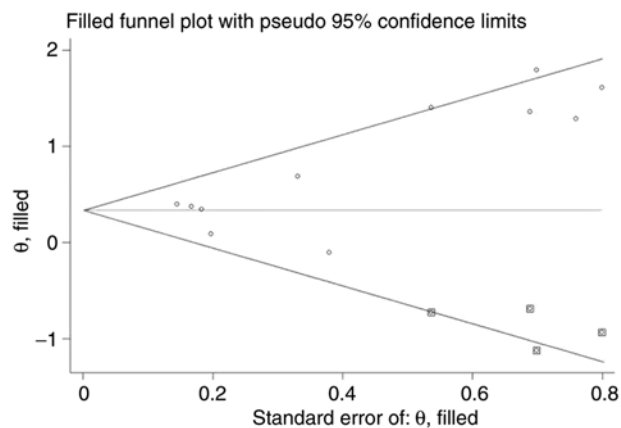


Figure 4. Sensitivity analysis of overall survival. The empty circles represent the hazard ratio value after excluding this study. CI, confidence interval.

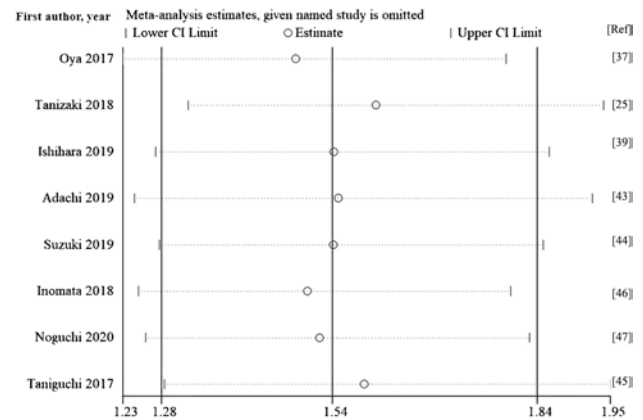


Figure 6. Funnel plot of overall survival after trimming and filling. The data-points in squares indicate supplementary studies.

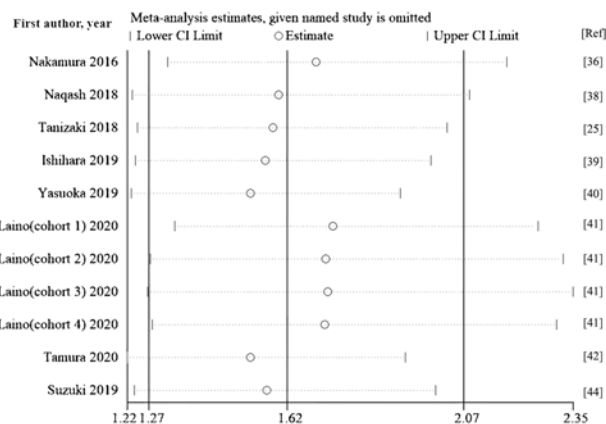


Figure 5. Sensitivity analysis of progression-free survival. The empty circles represent the hazard ratio value after excluding this study. CI, confidence interval.

fixed effect model were 1.493 (95% CI, 1.282-1.738; $P<0.001$) and 1.398 (95% CI, 1.206-1.621; $P<0.001$), and in the random effects model were 1.624 (95% CI, 1.272-2.074; $P<0.001$) and 1.410 (95% CI, 1.068-1.863; $P=0.016$), respectively. After eliminating the influence of publication bias, the result did not change significantly, suggesting that publication bias had little effect on the results of the meta-analysis.

Discussion

Inflammation is associated with all stages of cancer development and increased levels of systemic inflammation are associated with poor survival in patients with solid tumors (48). CRP is an acute-phase serum protein synthesized by hepatocytes and its expression is significantly increased in inflammatory disease (49). Moreover, CRP is associated with the prognosis of various cancer types (50). The association between cancer prognosis and serum CRP levels may be due to tumorigenesis that leads to increased CRP, which in turn promotes tumor progression. Tumor cells can produce CRP themselves and may produce and release cytokines and chemokines, such as IL-6 and IL-8, which increase the serum CRP concentration. Tumor growth and invasion cause tissue inflammation, leading to an increase in CRP levels. The innate and adaptive immune systems may respond to tumor antigens by increasing CRP levels (51). In addition, CRP induces DNA damage and weakens the immune system, thereby promoting carcinogenesis and tumor progression (22).

The present study analyzed current clinical evidence to assess the prognostic value of baseline CRP levels in patients with cancer in the context of immunotherapy. The meta-analysis showed that increased baseline CRP levels were associated with poor survival in patients with cancer treated with ICIs. Retrospective analyses by Tong *et al* (52) and

Minichsdorfer *et al* (53) showed that increased baseline CRP levels were associated with shorter median PFS and OS in patients receiving immunotherapy. The present meta-analysis combined PFS and OS to provide improved evidence for clarifying the association between baseline CRP levels and prognosis in patients with advanced cancer receiving immunotherapy. However, certain studies showed opposite results, suggesting that an increased CRP was not associated with decreased OS and PFS in patients with melanoma and NSCLC treated with immunotherapy (35,36). This disagreement may be due to the lower number of patients with retrospective data, and different CRP level cut-off values used in those studies. There is no uniform standard for the CRP cut-off value, but a previous study suggested that the optimal cut-off value for CRP as a prognostic marker is 10 mg/l, which was also the upper limit of normal for CRP in most studies (23).

The present subgroup analysis based on cancer type found that the elevated baseline CRP was associated with poor survival outcomes in multiple cancers. Using two independent multicenter real-world cohorts (discovery and validation cohorts), Iivanainen *et al* (23) found that the elevated baseline CRP was correlated with shortened OS and PFS among patients treated with PD-1/PD-L1 in both cohorts. In the present subgroup analysis based on cancer type, the association between increased baseline CRP levels with survival outcomes was significant in melanoma (two cohorts) and NSCLC (validation cohort). Although not statistically significant, a trend consistent with the general population was also observed in renal cell and urothelial carcinoma, as well as with other cancer types, which indicates the elevated baseline CRP was correlated with poor OS and PFS times. Survival differences were similar among all the studies (23). In the current meta-analysis, the subgroup analysis based on the CRP cut-off value of 10 mg/l found that both PFS and OS reported higher mortality risk in patients with CRP ≥ 10 mg/l. CRP < 10 mg/l was also associated with poor OS, although the corresponding HR value for PFS was increased and the difference was not statistically significant. This may be due to the small number of studies with CRP < 10 mg/l included in the PFS analysis. A larger number of high-quality studies should be included in the future to evaluate the impact of CRP cut-off values on the prognosis of patients treated with ICIs and CRP cut-off levels should be further validated in future clinical applications. CRP levels may reflect a specific biological tumor characteristic associated with insensitivity to immunotherapy, which would prompt physicians to use a therapeutic strategy targeting CRP in combination with ICIs. A recent study showed that blocking synthesis and/or activity of CRP in combination with ICIs improves response and survival in patients with melanoma (41). Larger studies are needed to find the best immunotherapy strategy. The present study had limitations. All the included studies were retrospective with several confounding factors; moreover, the number of studies and the sample size were limited, which may lead to potential bias. Furthermore, the included studies were heterogeneous in terms of CRP cut-off values and ICI drugs. The present meta-analysis only focused on the association between baseline CRP levels and prognosis; the impact of post-treatment CRP and dynamic changes in CRP on survival outcomes should be further considered. Finally, although the

trim and fill method confirmed the results, there was some publication bias.

In summary, the current evidence suggested that compared with patients with low baseline CRP levels, increased baseline CRP levels were associated with poor OS and PFS in patients receiving ICIs. Furthermore, a CRP ≥ 10 mg/l indicated a worse prognosis. Therefore, baseline CRP levels might serve as a marker for the prognosis of patients with certain solid tumors treated with ICIs. Due to the limited quality and quantity of the included studies, a larger number of prospective well-designed studies are required to verify the present findings.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YX, JYW and KM conceived and designed the study. YX, KM, FZ and MTM performed the experiments. LH, SJW, SPL, JYW and PPS analyzed data and drafted the manuscript. JYW and SJW prepared the figures. SJW, KM and PPS edited the manuscript. YX, JYW and SJW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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