

The prognostic value of METTL3 in cancer patients: a meta-analysis

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Abstract

Background: M6A methylation modification of RNA can regulate the development of tumor cells. METTL3 is one of the modified methyltransferases. A growing number of studies have shown that high expression of METTL3 may be associated with the unfavorable prognosis in cancer patients and may become a new biomarker. Therefore, this meta-analysis was used to evaluate the prognostic value of METTL3 in cancer patients through the available literature information.

Methods: Relevant studies were retrieved from electronic literature databases including six English databases and three Chinese databases. Correlation analysis was conducted by Stata SE 15.1 and RevMan 5.3 software. We analyzed 11 eligible studies with a total of 1638 cancer patients in this meta-analysis. We took advantage of HRs and ORs with 95% confidence intervals to evaluate the prognostic value of METTL3 in tumors. Besides, the article was qualified by MOOSE check lists and PRISMA Checklist.

Results: The results of the meta-analysis indicated that high expression of METTL3 was associated with low overall survival (OS) (HR=2.67, 95%CI:2.19-3.25, $P < 0.00001$) and disease-free survival (DFS) (HR=2.23, 95%CI:1.60-3.11, $P < 0.00001$) in various cancers. Stratified analysis of cancer types showed that over expressed METTL3 was related to poor prognosis in digestive system cancer patients, including CRC (HR=2.29, 95%CI:1.50-3.49, $P = 0.0001$), GC (HR=2.96, 95%CI:2.13-4.12, $P = 0.00001$) and liver cancer (HR=2.70, 95%CI:1.88-3.88, $P = 0.00001$). Meanwhile, the elevated METTL3 expression also affected the lymph node metastasis (OR=3.40, 95%CI=1.58-7.33, $p = 0.002$), vascular invasion (OR=2.04, 95%CI=1.06-3.95, $p = 0.03$) and the tumors progression (III/IV vs. I/II: OR = 3.72, 95% CI: 1.94 - 7.13, $P < 0.0001$).

Conclusion: The existing analysis indicates that METTL3 is associated with low OS and DFS in cancer patients and may serve as a biomarker to assess prognostic value.

Background

Cancer, a major public health problem, is a great threat to human health in the 21st century. In the past decade, the death rate of many cancers has increased, including liver cancer, male pancreatic cancer, uterine cancer, small intestine cancer, reproductive system cancer, as well as the cancers related to human papillomavirus (HPV). [1]. Numbers of cancer patients and deaths are increasing worldwide, especially in low and middle-income countries [2]. Early diagnosis of many tumors and long-term survival rate after treatment are not encouraging. Despite according to recent studies, advances has been made in the molecular aspects of tumorigenesis and development, the specific mechanism is not fully clear [3-5]. Therefore, what we need to explore is a new tumor marker that is conducive to early diagnosis, treatment and prognosis evaluation .

The key to controlling gene expression at different levels is chemical modification of the nucleobases, which can affect the translation of related mRNA, proteins and regulate signal pathways[6]. Among more than 100 RNA chemical modifications identified, N6- methyl- adenosine (m6A) was the most common

internal modification of mRNA and long non-coding RNA in eukaryotes. [7, 8]. Including RNA processing, splicing, migration, translation and decay, m6A modification affects many aspects of RNA metabolism [9-11]. The occurrence of m6A modification is encoded by methyltransferase complex. It can add, remove and read m6A sites respectively through the writer, eraser and reader[12-15].New evidences showed that by controlling the expression of oncogenes or tumor suppressor genes, m6A modification could regulate the occurrence, differentiation and metastasis of tumors[14, 16, 17].

METTL3 (methyltransferase like 3) is one of N6 methyladenosylmethy transferases, which plays an important role in mRNA pre-splicing, 3' - terminal processing and translation regulation[18-21].According to recent studies, METTL3 can also influence the tumorigenesis and growth of tumor by regulating the m6A modification [21-23].This mechanism has been found in a variety of tumor tissues[24-26]. Striking discoveries indicated that METTL3 played a carcinogenic role in tumors. METTL3 promoted the growth and invasion of human lung cancer cells by enhancing the translation of mRNA, and played a role of oncogene in the tumorigenesis of gastric cancer[27-29]. In addition, recent studies have indicated that METTL3 is up-regulated in many cancer tissues and associated with poor prognosis of patients [30, 31]. It suggests that METTL3 may be a potential biomarker for cancer patients. Therefore, it is important to research the prognostic value of METTL3 expression in cancer patients. We conducted a meta-analysis of relevant studies to obtain the relationship between the expression of METTL3 and long-term survival of cancer patients.

Methods

Methods and materials

This meta-analysis is based on the meta-analysis report standard of observational research(MOOSE check list)(Additional file 1.)

Literature search

We searched six English databases including Pubmed, Wed of Science, springer, Embase, Cochrane Library and ScienceDirect, and three Chinese databases including Weipu and Wanfang and CNKI database. No lower limit was set for the retrieval date, and the deadline was April 21,2020.We used retrieval formula: ("methyltransferase-like 3" OR "METTL3" OR "Writers") AND ("carcinoma" OR "cancer" OR "tumor" OR "neoplasm") AND ("prognosis" OR "prognostic") and their Chinese forms to search in the above online databases.After retrieving all eligible studies, we manually searched the references cited in the study to find more publications that were relevant.

Inclusion and exclusion criteria

Eligible studies should meet the following criteria: 1) The patients in the studies were definitely diagnosed with cancer; 2) To study the effect of METTL3 on survival outcomes of cancer patients; 3) Information containing survival curve or providing HR and 95% confidence intervals (CI). Exclusion is based on the

following criteria: 1) Studies lacking survival outcomes; 2) Reviews, non-human studies, case reports, correspondence articles, and other studies without original data; 3) Repeated studies.

Data extraction

The two authors carefully read the included texts, extracted the data, checked and discussed. If there was any difference, an investigator (LQY) would arbitrate it to reach a consensus. The necessary information for all eligible articles includes: the name of the first author; year of publication; type of cancer; type of studies; survival analysis type; cancer stage; form of specimen; cut-off; total number of cases; follow-up; METTL3 detection method; the source of the HR. The survival information directly get from the original dates or obtain from the Kaplan–Meier survival curves data with the Engauge Digitizer (Version 4.1) software by the previously described method [32-34].

Quality assessment

Two authors (PXZ and LHL) carefully reviewed the details of the each included study independently. The enrolled literature were then qualified based on the Newcastle-Ottawa Scale, which included three aspects: queue selection, comparability and results [35]. In the selection and result categories, a maximum of one score can be obtained for each item. In the category of comparability, a maximum of two scores can be given. According to the scores, the research level was rated as low quality, medium quality and high quality [36]. All the included studies were of medium and above quality.

Statistical analysis

All analyses were performed using Stata SE 15.1 and RevMan 5.3 software. Potential publication bias was evaluated by funnel plot and Egger's test [37]. The heterogeneity of the included studies was assessed by I^2 statistical test, with $I^2 > 50\%$ as evidence of heterogeneity. According to the test results, if $I^2 > 50\%$, the random effect model should be selected; if $I^2 < 50\%$, the fixed effect model should be selected [33, 34, 38]. A sensitivity analysis was performed to assess the impact of a single study on overall HR. P value less than 0.05 was statistically significant.

Results

Eligible researches

The studies were screened according to the following procedure [19,39-48](Fig. 1). At first, We retrieved a total of 349 articles from the online database. After preliminary screening and duplicate checking, 253 articles were retained. Through reading the title and abstract of the articles, the articles were further screened. Studies of 207 related to METTL3 expression and cancer prognosis were excluded according to exclusion criteria. After reading the rest 46 articles carefully, 35 articles were eliminated. The remained articles were then evaluated for quality, finally, 11 articles were included in this study.

Features of articles included

The meta-analysis included 11 studies from 9 publishers, with a total of 1638 patients (Table 1). The expression of METTL3 in frozen or formalin fixed paraffin embedded specimens was detected by qRT-PCR. The cancer tissue samples in the study were from ovarian carcinoma, hepatocellular carcinoma, hepatoblastoma, thyroid carcinoma, bladder cancer, gastric cancer and colorectal cancer. The cut-off values of METTL3 were different in these studies. Of the 11 studies, 10 studies evaluated the relationship between METTL3 expression and OS, three of which evaluated the relationship between METTL3 and OS and DFS at the same time, and one evaluated PFS. Table 1 summarizes the main details of these studies.

The relationship between METTL3 expression and survival outcome

Because there was no significant heterogeneity in the nine studies related to OS ($I^2 = 0\%$) the fixed effect model was used to calculate the combined effect. The results showed that the increased expression of METTL3 was significantly related to the low OS (HR=2.67, 95%CI:2.19-3.25, $P < 0.00001$, Fig. 2A) and DFS (HR=2.23, 95%CI:1.60-3.11, $P < 0.00001$, Fig 2.B) of various cancers.

Stratified analysis

Then we analyzed the subgroups according to the sample size, specimen types, degree of differentiation, patient ages, quality scores, cancer types, lymph node metastasis, vascular invasion and tumor stage. Because the vascular infiltration ($I^2 = 57\%$) and tumor stage ($I^2 = 51\%$) subgroups had heterogeneity, the random effect model were used, and the other subgroups used fixed models to combine the effect values. In stratified analysis of the different cancer types, we found that elevated expression of METTL3 was related to poor prognosis in digestive system cancer patients, including CRC (HR=2.29, 95%CI:1.50-3.49, $P = 0.0001$), GC (HR=2.96, 95%CI:2.13-4.12, $P = 0.00001$) and liver cancer (HR=2.70, 95%CI:1.88-3.88, $P = 0.00001$) (Fig. 3A). Subgroup analysis showed that patients with high expression of METTL3 had a higher risk of lymph node metastasis, indicating that METTL3 might be related to lymph node metastasis (OR=3.40, 95%CI=1.58-7.33, $p = 0.002$, Fig. 4A). We found the same result between vascular invasion and METTL3 (Fig. 4B). In addition, the improvement of METTL3 level was related to tumor progression (III/IV vs. I/II: OR = 3.72, 95% CI: 1.94 - 7.13, $P < 0.0001$, Fig. 4C).

Heterogeneity & sensitivity analysis

There was no heterogeneity in this meta-analysis. In order to determine the impact of each study on the combined HRs, we conducted a sensitivity analysis. The results showed that excluding any of the studies had no significant effect on the METTL3 combined HR (Fig. 5).

Publication bias

In order to evaluate the publication bias of this meta-analysis, we evaluated the funnel plot and Egger's test, and found that the funnel plot was basically symmetrical (Fig. 6A). The examination results of Egger's test showed that there was no significant publication bias ($P = 0.127$, Fig. 6B). Therefore, there was no obvious publication bias in our results.

Discussion

RNA methylation plays an important role in many biological processes and is widely involved in human development and disease occurrence[49]. N6-methyladenosine (m6A) is a conserved internal modification of most eukaryotic nuclear RNA, which is closely related to the splicing, stability and translation efficiency of mRNA and noncoding RNA [28,50]. With further studies, M6A can catalyse the M6A modification in the mRNA of oncogenes or tumor suppressor genes, and recognize the changes through molecular biological mechanism to regulate the expression of oncogene and tumor suppressor gene[51]. The evidence showed that the change of m6A level was involved in the occurrence and development of tumor by affecting the expression of tumor-related genes BRD4, SOCS2 and EGFR[52].

METTL3 was considered to be a methyltransferase, part of the methyltransferase complex, and was responsible for the m6A modification[27,53]. METTL3 was involved in many signal pathways such as PI3K / Akt [31,54-58], MAPK [22], Wnt /beta-Catenin [47,59,60] and p38 / ERK [61] pathways, which were all associated with tumor deterioration. In addition, METTL3 could influence the development of tumor by regulating some transcription factors or important oncogenes. Studies had found that METTL3 could positively regulate the expression of oncogene EZH2 [24,25,62]. It promoted the expression of MYC as well as increased stability of protein by regulating the m6A methylation of MYC mRNA to lead to carcinogenesis in PCA and gastric cancer, promote the occurrence of OSCC tumor and affect the growth and invasion of BCA cells[40,63-66]. When METTL3 was silenced, it inhibited the activity of the Wnt pathway by reducing the m6A methylation level of LEF1 mRNA and reducing protein expression [59,67].

Besides, some studies have shown that METTL3 can be used as a new marker to evaluate the prognosis of multiple tumors. Xiao Li et al. found that the survival time of RCC patients with positive METTL3 expression was significantly longer, and the expression of METTL3 in RCC is lower than that in paracancerous tissues[68]. Deng et al. noted that the positive expression of METTL3 was an obstacle to the proliferation, migration and invasion of colorectal cancer cells [61]. On the contrary, it had been reported that the high expression of METTL3 was a factor of poor prognosis, which might be a new prognosis or treatment target for lung cancer, gastric cancer and ovarian cancer[39,41,42,54,69]. It can be seen that the expression and role of METTL3 in different tumors are still controversial, which may be due to differences in tumor type, extracellular microenvironment, and samples' source and size. Up to now, the prognostic value of METTL3 in various tumors has not been systematically analyzed, so according to the existing reports, we studied the prognostic value of METTL3 in cancer.

A total of 11 studies, including 1638 patients, are included in this meta-analysis, which is reasonable to believe that the analysis results are reliable. This study included the relationship between the high expression of METTL3 and the prognosis of ovarian cancer, HCC, hepatoblastoma, thyroid carcinoma, bladder cancer, gastric cancer, colorectal cancer. The results showed that METTL3 expression could affect the prognosis of OS (HR = 2.67, 95% CI: 2.19-3.25, P < 0.00001) and DFS (HR = 2.23, 95% CI: 1.60-3.11, P < 0.00001), and METTL3 could predict the prognosis of digestive system cancers, including CRC (HR=2.29, 95%CI:1.50-3.49, P=0.0001), GC(HR=2.96, 95%CI:2.13-4.12, P=0.00001) and liver cancer

HR=2.70, 95% CI: 1.88-3.88, P=0.00001). In other subgroups of METTL3 expression and overall survival, we performed analysis based on sample size, specimen type, and quality evaluation (The detailed results are shown in table 2). According to the result in group of sample size, we discovered that METTL3 in small sample group (≤ 100) had a more significant prognosis than in large sample group (> 100) (Fig. 3B), which indicated that the sample size might lead to the instability of results. In addition, METTL3 was associated with tumor progression (III / IV vs. I / II: OR = 3.72, 95% CI: 1.94 - 7.13, P < 0.0001). Subgroup analysis showed that METTL3 had a potential role in the prediction of lymph node metastasis (OR=3.40, 95% CI=1.58-7.33, p=0.002) and vascular invasion (OR=2.04, 95% CI=1.06-3.95, p=0.03), but more articles need to be included for further study. However, the expression of METTL3 was not related to the age of the patients or the degree of tumor differentiation (Table 3.)

However, this meta-analysis had some limitations. First of all, the small number of studies included and the insufficient sample size might affect the reliability of the results and hinder the stability of the results of further stratified analysis. Secondly, although the statistical method did not detect publication bias, there might be potential bias. Besides, the accuracy of the method of extracting HR from the survival curve was not high, which would affect the combined HRs. Finally, the cancer patients in our study were Asian, and the results were a good indication of the association between METTL3 and prognosis in Asian patients, but the association with patients of other races was not clear. In a word, in order to make the conclusion more convincing, further research is needed.

Conclusions

In summary, our meta-analysis showed that high expression of METTL3 was associated with poor OS and DFS in cancer patients, vascular invasion, as well as with lymph node metastasis of the tumor. Cancer patients would be still at risk of recurrence or metastasis after treatment. Therefore, it is of great significance to find effective prognostic markers to solve the problems faced by patients in the process of treatment. In the future, we need to further explore the prognostic value of METTL3 in large-scale, standard and multi-ethnic clinical researches, in order to apply METTL3 as a novel marker of prognosis in the clinical guidance of cancer patients as soon as possible.

Abbreviations

METTL3	methyltransferase like 3
m6A	N6- methyladenosine
OS	overall survival
DFS	disease free survival
PFS	progression free survival
HR	hazard ratio
OR	odds ratio
95%CI	95% confidence interval
NOS	Newcastle-Ottawa Scale
NA	not available
qRT-PCR	quantitative reverse transcription PCR
IHC	Immunohistochemistry
TNM	Tumor Node Metastasis
FIGO	Federation International of Gynecology and Obstetrics
KM	Kaplan-Meier
Uni	Univariate
N	number
OC	ovarian carcinoma
GC	gastric cancer
CRC	colorectal cancer
BCA	bladder cancer
HCC	hepatocellular carcinoma
HB	hepatoblastoma
THCA	thyroid carcinoma
OSCC	oralsquamous cell cancer
RCC	renal cell carcinoma
PCA	prostatic cancer
BRD4	bromodomain-containing protein 4
SOCS2	suppressor of cytokine signaling 2

EGFR	epidermal growth factor receptor
MAPK	mitogen-activated protein kinase
Wnt / β -Catenin	Canonical Wnt/ β -catenin pathway
EZH2	Enhancer Of Zeste Homolog 2
LEF1	Lymphoid enhancer-binding factor 1

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data used in the study are included in this article.

Competing interests

The authors declare that they have no competing interests in this section.

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Authors' contributions

QYL and XZP conceived and designed the experiments. XZP, HLL, YYX and CCH collected materials and prepared the tools for analysis. QHL, XKW and QYL screened and analyzed the collected data. CCH, HLL, XZP performed the experiments. XZP, HLL and YYX wrote this article. All authors read the final manuscript and approved it.

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Tables

Due to technical limitations Table 1-3 are available as downloads in the Supplementary Files.

Table 1: Summary of the included studies.

Table 2: Meta-analysis of METTL3 expression and overall survival.

Table 3: The relationship between the expression of mettl3 and clinical characteristics.

Figures

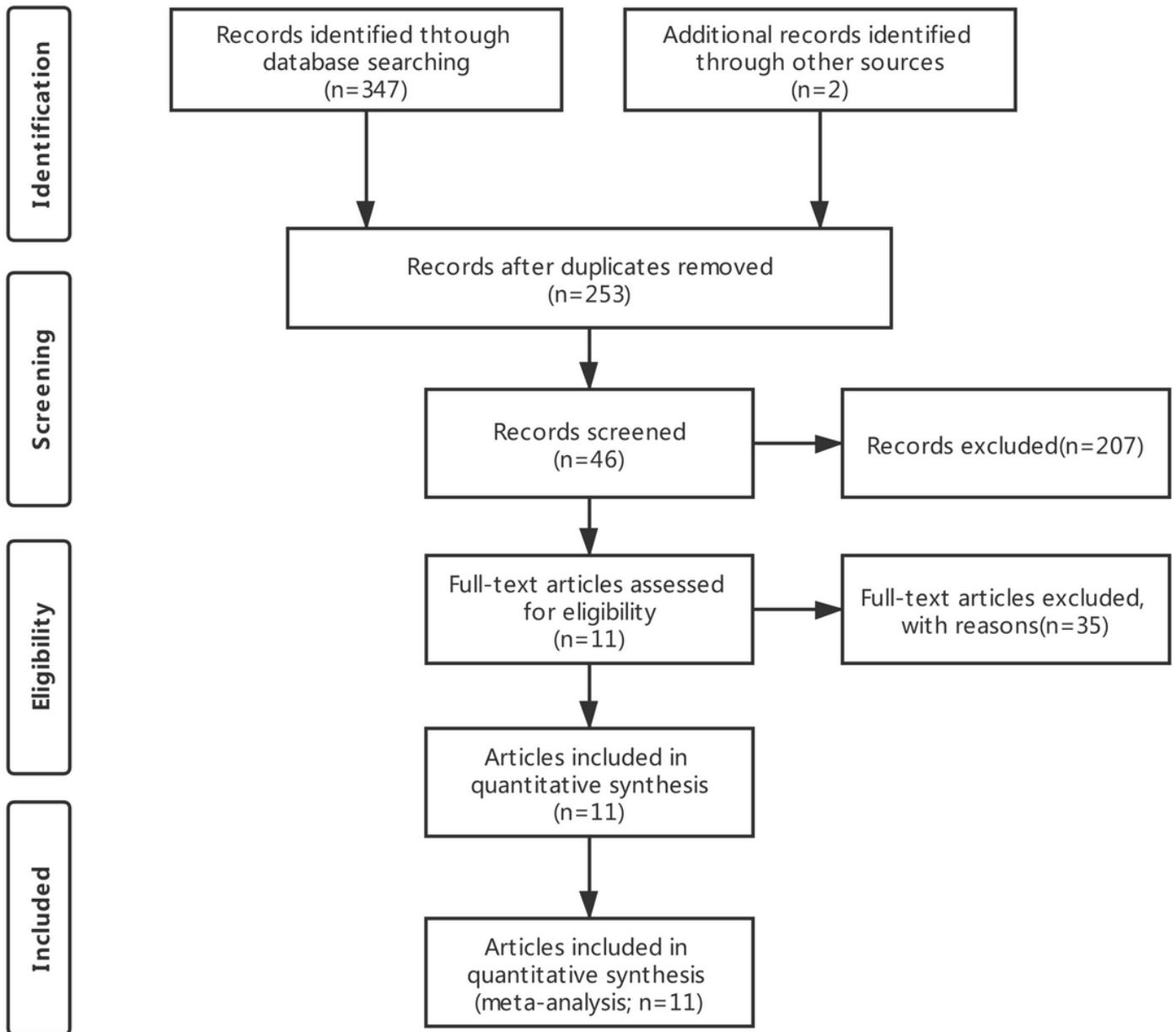


Figure 1

Flow chart of the process of searching and selecting articles.

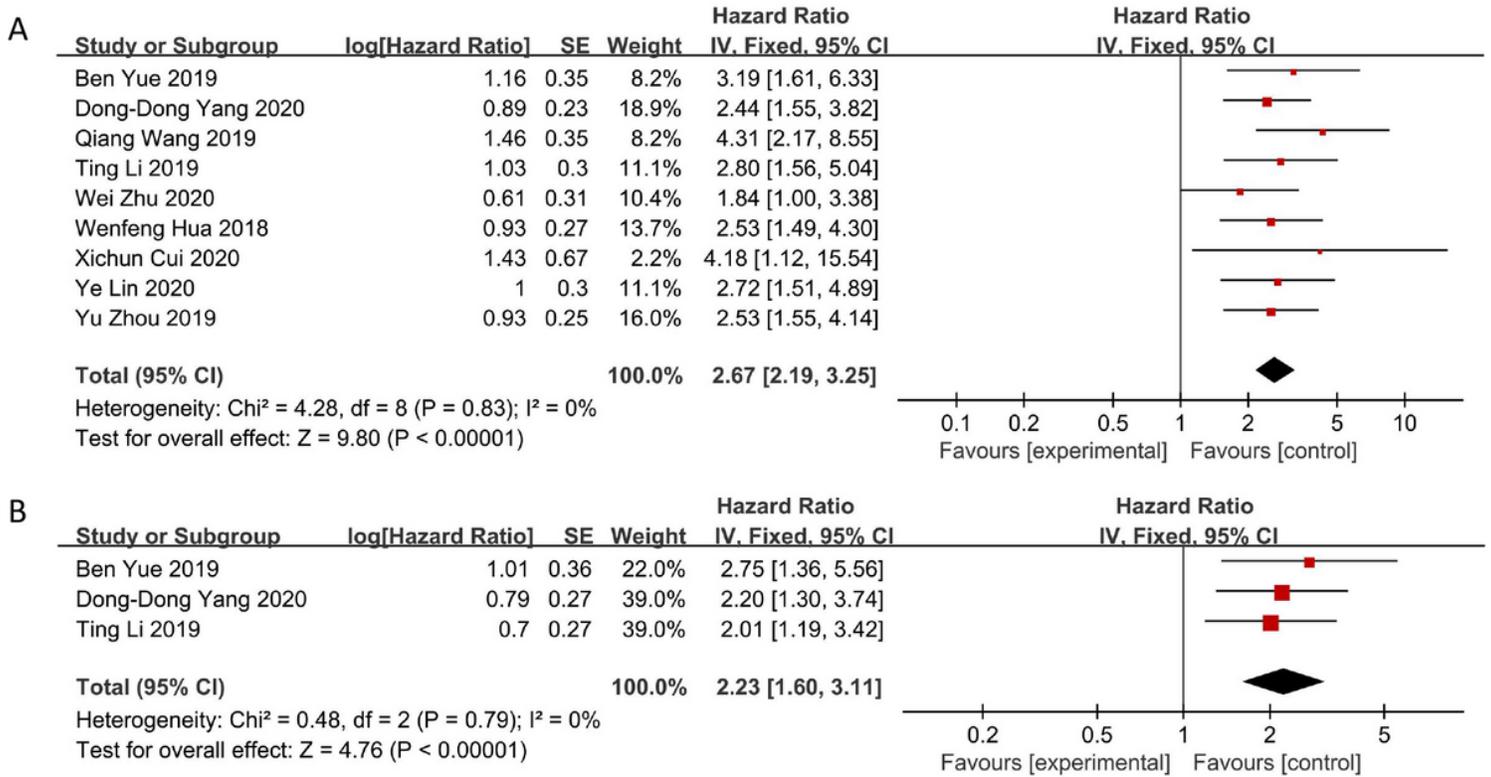


Figure 2

Forest plot of METTL3 and prognosis: A Forest plot for the relationship between the expression of METTL3 and overall survival rate (OS). B Forest plot for the relationship between the expression of METTL3 and disease-free survival(DFS).

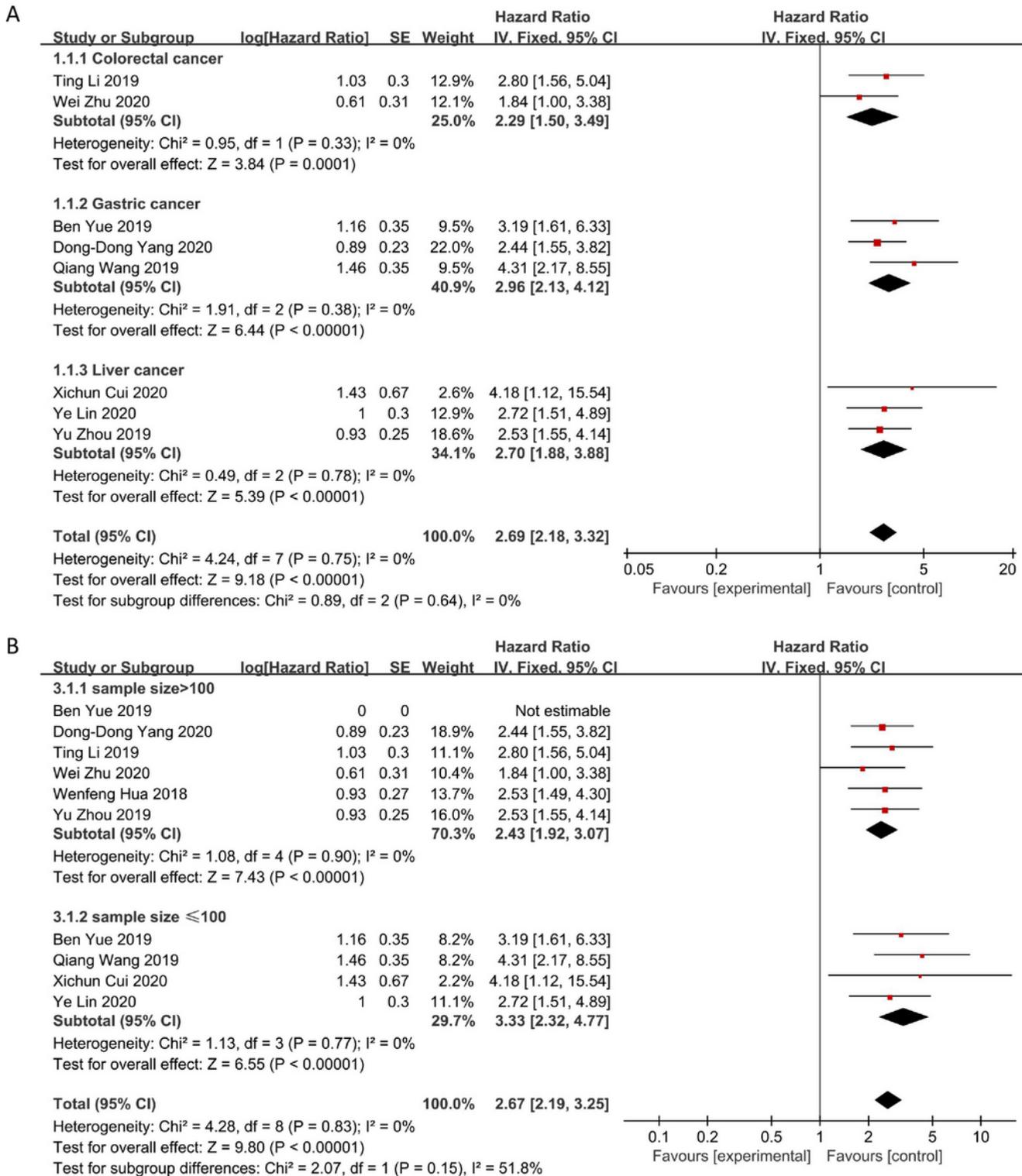


Figure 3

Stratified analyses for the relationship between METTL3 expression and overall survival (OS): A Subgroup analysis of HRs of OS by cancer type. B Subgroup analysis of OS by samples size.

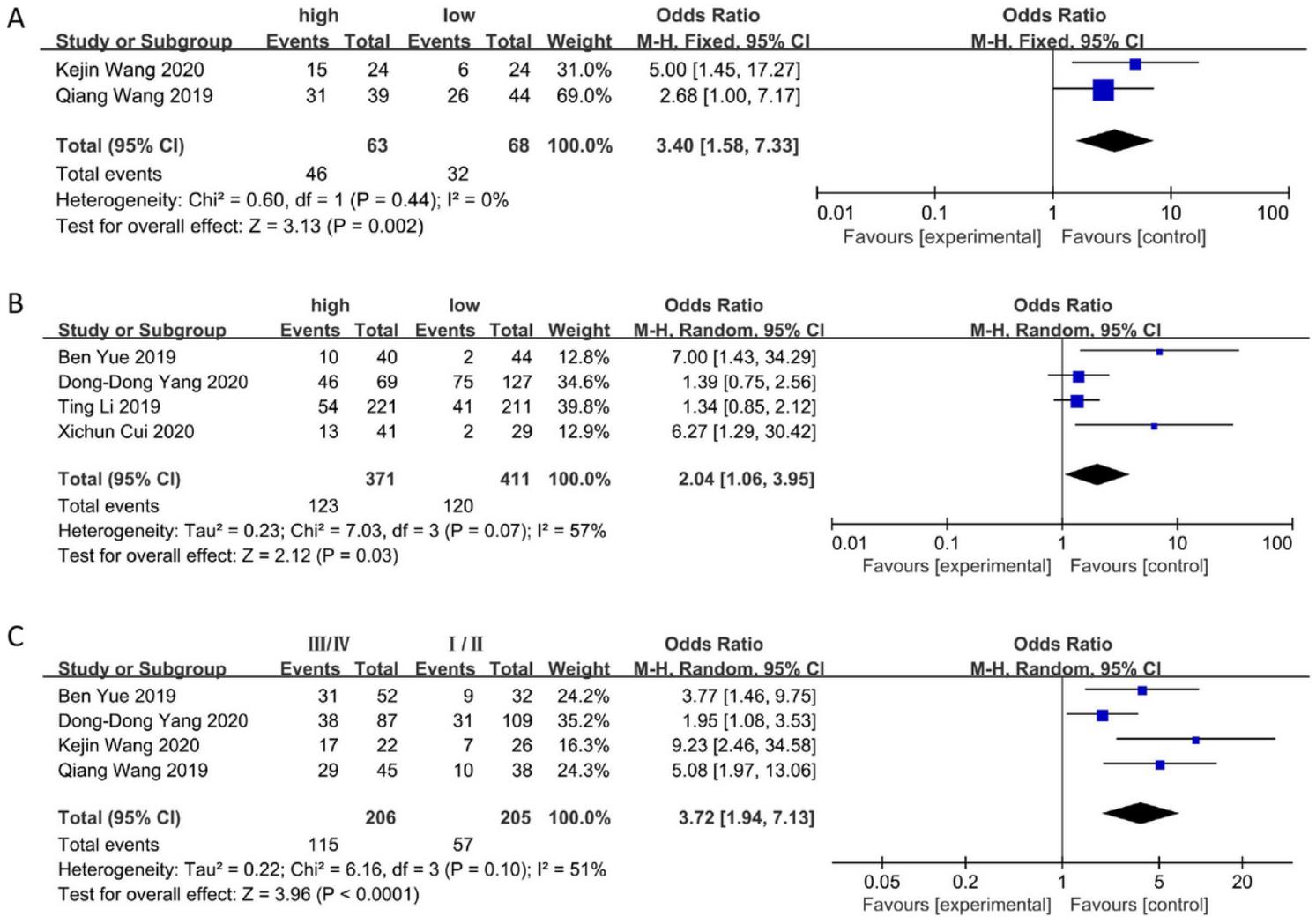


Figure 4

Subgroup analysis A Forest plot for the relationship between METTL3 expression and lymph node metastasis . B Forest plot for the relationship between METTL3 expression and vascular invasion . C Forest plot for the relationship between METTL3 expression and TNM stage (III/IV vs. I/II).

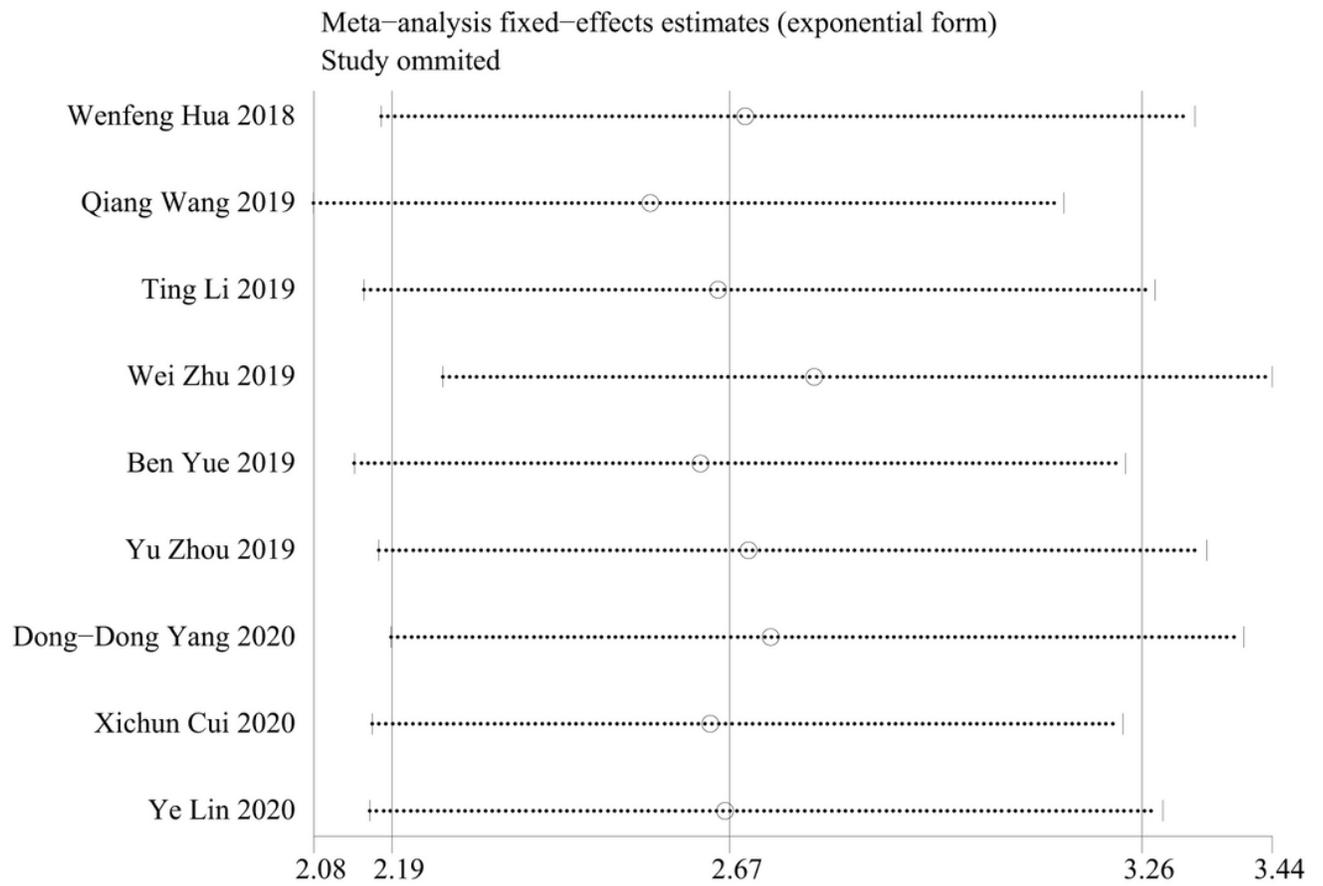


Figure 5

Sensitivity analysis of the impact of a single study on combined HRs.

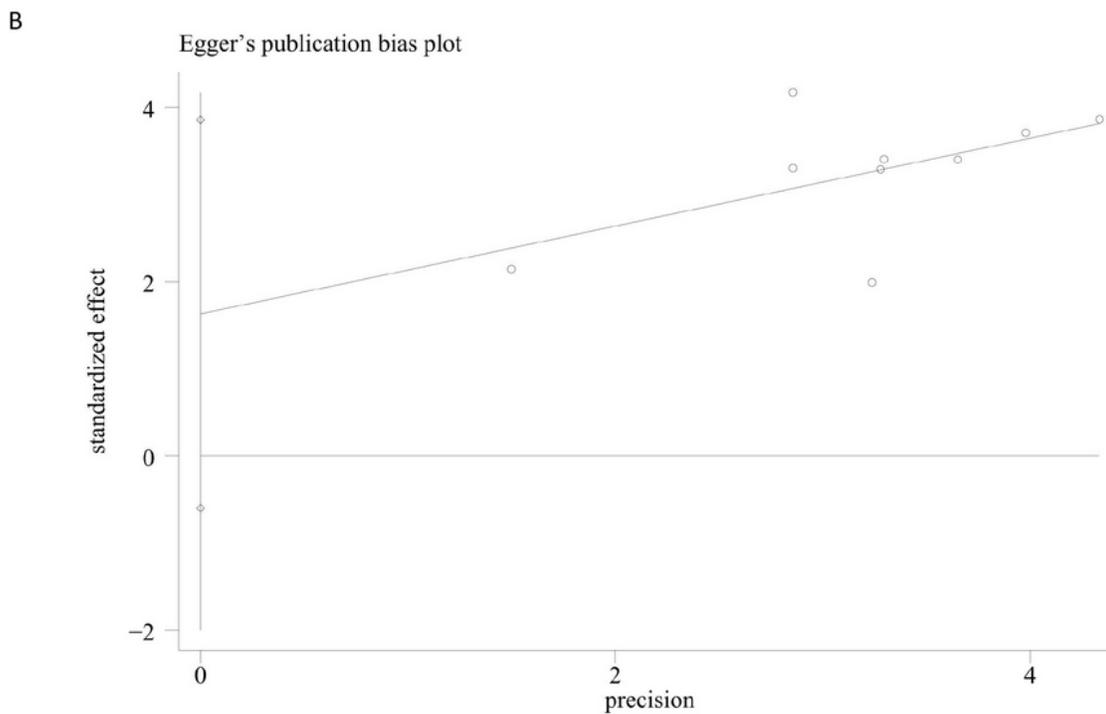
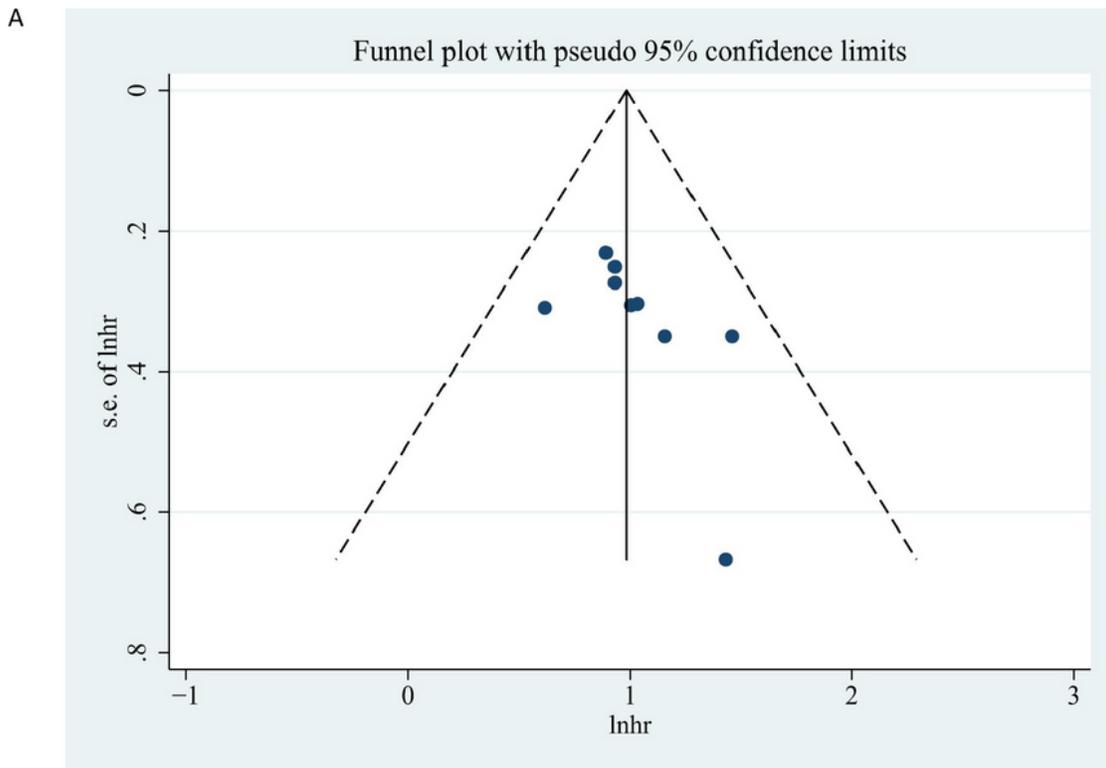


Figure 6

Publication bias: A Funnel plot of the publication bias for overall survival. B Egger's test of the publication bias for overall survival.

Supplementary Files

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