

Original Article

The *BRAF* V600E mutation predicts poor survival outcome in patients with papillary thyroid carcinoma: a meta analysis

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Abstract: Introduction: There have been contradictory data on whether or not *BRAF* V600E mutation should be regarded as a poor prognosis predictor of papillary thyroid carcinoma (PTC). To settle down the conflict, this meta-analysis is prepared to clarify the present prognostic role of *BRAF* V600E mutation in patients with PTC. Methods and materials: The relevant published researches were incorporated according to the defined inclusion/exclusion criteria from PubMed. The effect sizes of outcome parameters were estimated by hazard ratios (HRs). Results: The current meta-analysis included 19 researches with a total of 6087 patients. We have found that patients with *BRAF* V600E mutation have a poor overall survival (the pooled HR=2.91, 95% confidence interval (CI): 1.35-6.29). Furthermore, subgroup analysis of the recurrence-free survival (RFS) of PTC patients by races indicated that *BRAF* V600E mutation predicts poor RFS of patients (the pooled HR=1.63, 95% CI: 1.37-1.93), both Caucasian (the pooled HR=1.57, 95% CI: 1.30-1.90) and Asian (the pooled HR=1.91, 95% CI: 1.28-2.87). Conclusions: The poor prognosis predicted role of *BRAF* V600E mutation in PTC was certified from the current meta-analysis. The *BRAF* V600E mutation may be used as a prognostic predictor of patients with PTC.

Keywords: Thyroid, thyroid papillary carcinoma (PTC), *BRAF* V600E mutation, meta-analysis

Introduction

As a common malignant tumor type of endocrine system, thyroid papillary carcinoma (PTC) including several subtypes such as common conventional PTC, follicular-variant PTC [1]. Compared to other types of malignancy, PTC is relatively a highly curable disease. PTC patients usually have high rate of overall 10-year survival (>90%), however, the main troubles of patients with PTC are regional recurrences and distant metastases [2]. To evaluate the prognosis of patients, several clinicopathologic factors were implemented, including age (>45 years old), gender (male), lymph nodes metastasis, extra-thyroidal extension, distant metastasis, aggressive histological subtype and advanced disease stages [3].

In addition, some biochemical markers (especially the *BRAF* V600E mutation) also used to predict the cancer associated prognos-

is of PTC patients. As we known that, the *BRAF* V600E mutation is the most common mutation of PTC and associated with activation of the mitogen activated protein Kinase signaling pathway [4]. Numerous researches have revealed the *BRAF* V600E mutation statue in different subtypes of PTC, furthermore, estimated the correlation between the *BRAF* V600E mutation statue and various clinicopathologic factors of patients with PTC. And a recent study have pooled the reported data and conducted a meta-analysis to comprehensively evaluate the relationship between *BRAF* mutation and clinicopathological features of PTC [5]. Researchers [5] displayed that *BRAF* mutation is associated with male gender, LNM, stage, extra-thyroidal extension, tumor size, multifocality, classic PTC, and tall-cell variant PTC in PTC.

However, there is still conflicting about whether or not the *BRAF* V600E mutation could be a poor prognosis predictor of PTC patients. Some

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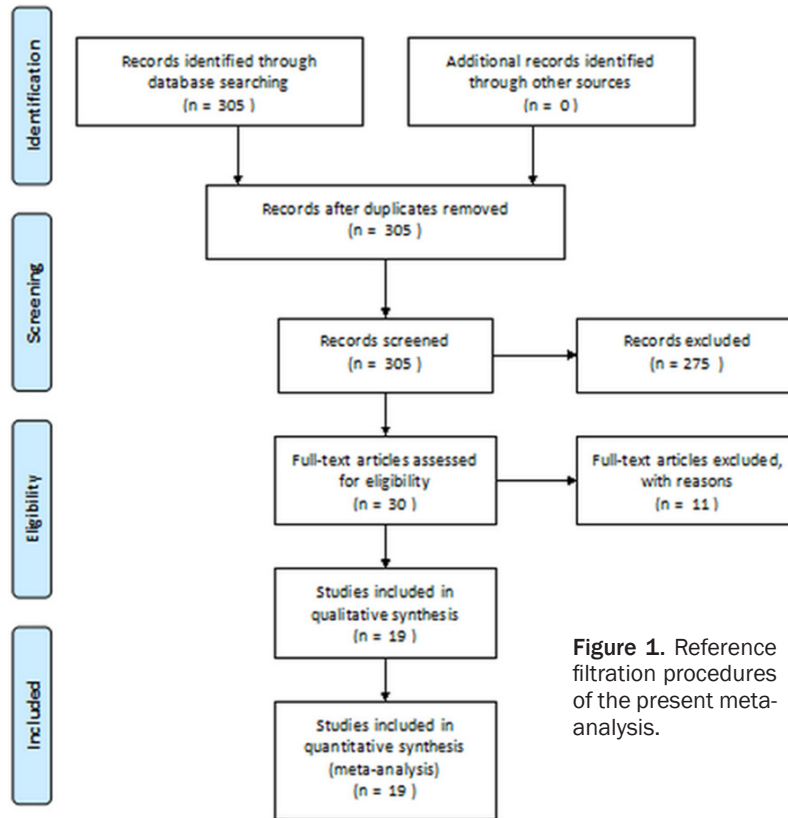


Figure 1. Reference filtration procedures of the present meta-analysis.

Eligibility criteria

Inclusion criteria: (I) the target disease is thyroid papillary carcinoma; (II) the prognostic role of the *BRAF* V600E mutation was studied including overall survival (OS), progression free survival or disease free survival (PFS/DFS); (III) the latest or most informative single article was included when articles were derived from the same authors/groups. Exclusion criteria: (I) these article types are excluded: review, letter, laboratory research, or mechanism study; (II) the article is duplicated; (III) it lacked critical original data for meta-analysis.

Data extraction and Statistical analysis

The above references were screened according to the inclusion/exclusion criteria, by two authors. The reported data about the relationship between the *BRAF* V600E mutation and survival outcomes (OS, RFS and DFS) of PTC patients were extracted, the data types including reported survival data, the Kaplan-Meier (K-M) curves or HR and 95% CI. Also, the baseline characteristics of eligible articles were extracted by the other two researchers independently. The K-M curves' data was extracted by Engauge Digitizer 4.1 (<http://sourceforge.net>). The multivariate cox hazard regression analysis data is first choice, if cannot obtained, univariate Cox hazard regression analysis or K-M survival curves of survival outcomes were instead, then reported survival data was the last choice for HR (95% CI) calculation.

STATA 11.0 (STATA Corporation, College Station, TX) was used to conduct the current meta-analysis. Heterogeneity was defined as $P < 0.05$ or $I^2 \geq 50\%$, a fixed effect model was used for pooled HRs calculation. On the contrary, if heterogeneity was fine ($P \geq 0.05$, $I^2 < 50\%$), a random effect model was used for pooled HRs calculation. If the pooled $HR > 1$ and the 95% CI exclude 1, it indicated a significant worse outcome for

studies found that there have no significant relationship between the *BRAF* V600E mutation and PTC prognosis [6]. But other researches implied that the *BRAF* V600E mutation predicts poor overall survival (OS) and/or recurrence-free survival (RFS) of PTC patients [7]. For comprehensively understanding the role of the *BRAF* V600E mutation in PTC prognosis, it's necessary for us to conduct a meta-analysis to quantitatively pool the reported data and completely explore the relationship between the *BRAF* V600E mutation and survival of PTC patients.

Methods and materials

Database and retrieval strategy

Because of its comprehensive coverage fraction of published researches, we used PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) as our target database for reference retrieval. The retrieval strategy involving the following keywords variably combined by "*BRAF* V600E mutation", "thyroid", "thyroid papillary carcinoma", "carcinoma", "survival outcomes" and "prognosis".

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Table 1. The baseline characteristics of included references

Ref.	Ethnic	Accounts	Follow up	Survival outcomes	Attitudes of BRAF mutation	Study type	Measurement of BRAF mutation
Niederer-Wüst SM et al. 2015	Caucasian	116	2-252 mon.	OS/RFS	Insignificance	Retrospective	PCR
Daliri M et al. 2014	Asian	69	12-192 mon.	OS/RFS	Insignificance	Prospective	SSCP
McKelvie PA et al. 2013	Caucasian	77	20-192 mon.	OS/RFS	Insignificance	Prospective	C-PCR
Ito Y et al. 2014	Asian	766	13-191 mon.	OS/RFS	Insignificance	Retrospective	PCR
Elisei R et al. 2012	Caucasian	319	5.3±0.8 yr.	DFS	Poor prognosis	Prospective	SSCP
Pelttari H et al. 2012	Caucasian	51	16 yr.	RFS	Insignificance	Retrospective	Allelic specific PCR with Scorpions rt-PCR
Guerra A et al. 2012	Caucasian	168	3-195 mon.	RFS	Insignificance	Retrospective	BigDye terminator sequencing and pyrosequencing
Elisei R et al. 2008	Caucasian	102	15 yr.	OS/DFS	Poor prognosis	Retrospective	SSCP
Kim TY et al. 2006	Asian	203	10 yr.	DFS	Poor prognosis	Retrospective	PCR amplification and direct sequencing
Huang FJ et al. 2014	Asian	214	12-50 mon.	RFS	Poor prognosis	Prospective	Sanger sequencing
Henke LE et al. 2015	Caucasian	508	8.0 yr.	OS/RFS	Insignificance	Retrospective	SSCP
Prescott JD et al. 2012	Caucasian	205	5.0 yr.	RFS	Poor prognosis	Retrospective	SSCP
Danilovic DL et al. 2014	Caucasian	178	33.5±7.2 mon.	RFS	Poor prognosis	Retrospective	Re-PCR genotyping technique
He G et al. 2014	Asian	187	24 mon.	RFS	Poor prognosis	Retrospective	Allelic specific PCR
Xing M et al. 2015	Caucasian	2099	13-67 mon.	RFS	Poor prognosis	Retrospective	BigDye terminator sequencing and pyrosequencing
Xing M et al. 2005	Caucasian	219	14 yr.	RFS	Poor prognosis	Retrospective	BigDye terminator sequencing and pyrosequencing
Kebebew E et al. 2007	Caucasian	314	72±33 mon.	RFS	Poor prognosis	Retrospective	BigDye terminator sequencing and pyrosequencing
Russo M et al. 2014	Caucasian	103	56.9±14.1 mon.	RFS	Insignificance	Retrospective	PCR
Pelizzo MR et al. 2014	Caucasian	189	1-156 mon.	RFS	Insignificance	Retrospective	SSCP

Months, mon.; Overall survival, OS; Recurrence-free survival, RFS; Year, yr.; Disease-free survival, DFS; polymerase chain reaction, PCR; PCR-single-strand conformation polymorphism analysis.

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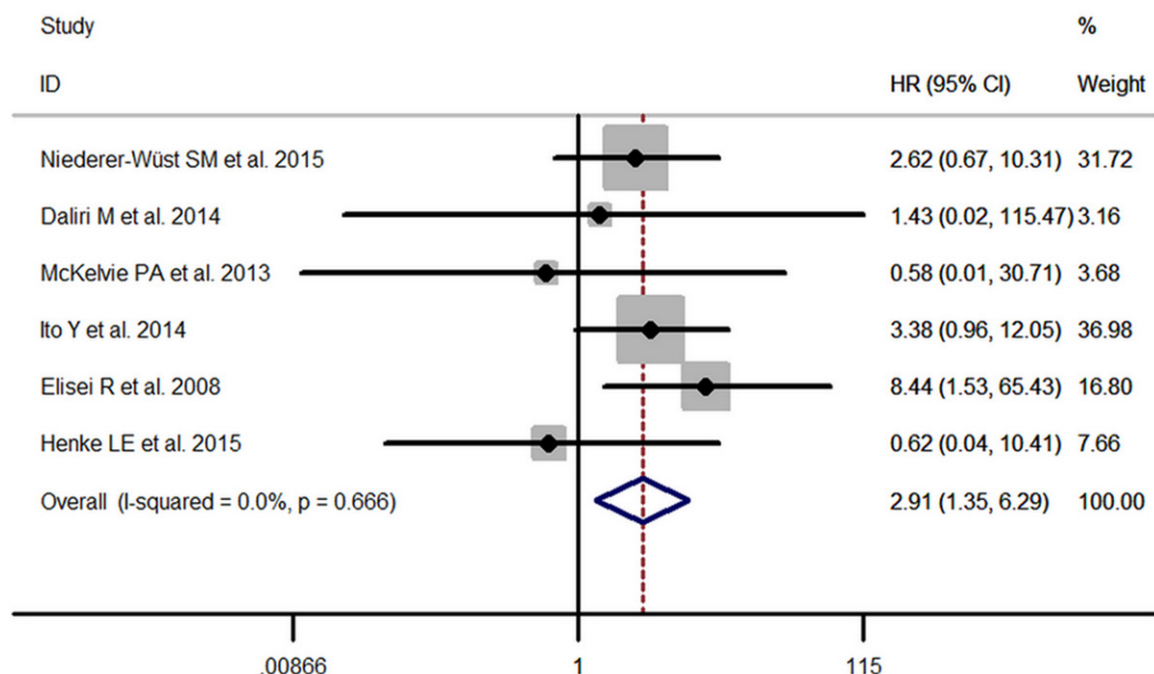


Figure 2. The pooled hazard ratio (HR, 95% CI) between the *BRAF* V600E mutation and overall survival (OS) of PTC patients.

the case group compared to the control group. The publication bias was tested by Begg's test and Egger's test, $P < 0.05$ indicating that potential publication bias existed.

Results

Eligible articles filtration process

After total two steps of filtration, 19 articles [6-24] were recognized as final eligible articles (**Figure 1**). At the first step, we initially included 305 references after retrieving the database of PubMed. Then 275 articles were excluded after reading the titles and abstracts. Among them, 68 articles were not associated with the prognostic role of the *BRAF* V600E mutation in PTC. 51 articles were review articles. 50 articles were excluded because they were focused on mechanism researches. 42 articles were excluded because they were not referred to the *BRAF* V600E mutation and/or PTC. 39 articles were just referred to diagnosis studies. 15 articles were case report articles, 5 articles were meta-analysis articles and the other 5 articles were not published in English. At the second step, 30 articles were included for comprehensive filtration, and 11 articles were further excluded because 5 articles were not associ-

ated with the prognostic role of the *BRAF* V600E mutation in PTC, 3 articles have not enough original data for meta-analysis and 3 articles were published by the same authors/groups. The baseline characteristics of eligible articles were listed in **Table 1**.

OS

Six articles listed the relationship between the *BRAF* V600E mutation and OS of PTC patients. The heterogeneity has not been found ($P = 0.666$, $I^2 = 0.0\%$), and a fixed effect model was used. We found that the pooled HR (95% CI) is 2.91 (1.35, 6.29) (**Figure 2**).

RFS

Only two articles have reported the DFS data, however the remaining articles are all reported the RFS data. For convenience of meta-analysis, we have combined DFS data and RFS data to calculate the pooled HR (95% CI). The heterogeneity test revealed that $P = 0.130$ and $I^2 = 27.4\%$, therefore a fixed effect model was used. We found that the pooled HR (95% CI) is 1.63 (1.37, 1.93) (**Figure 3**). Furthermore, subgroup analysis indicated that *BRAF* V600E mutation predicts poor RFS of patients, both

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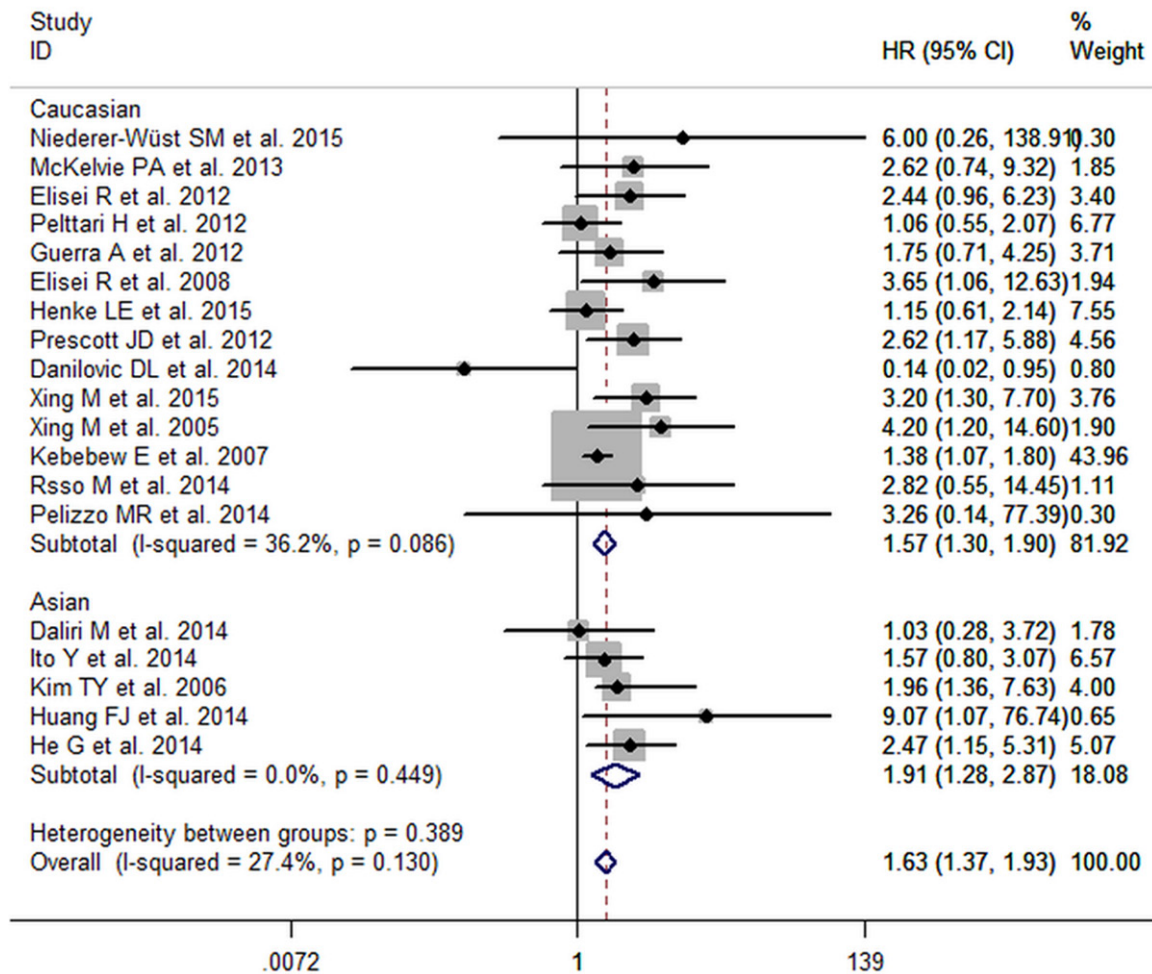


Figure 3. The pooled hazard ratio (HR, 95% CI) between the *BRAF* V600E mutation and relapse-free survival (RFS) of PTC patients, based on subgroup analysis of races (Asian and Caucasian).

Caucasian (the pooled HR=1.57, 95% CI: 1.30-1.90) and Asian (the pooled HR=1.91, 95% CI: 1.28-2.87) (**Figure 3**).

Publication bias

We have not found any publication bias through Begg's funnel plot (**Figure 4**) and Egger's test. The *P* value of Egger's test is 0.069. In addition, we have conducted sensitivity analysis both for RFS and OS, to exam their stability. And the results were displayed in [Supplementary Figure 1](#). A is the result for OS, and B is for RFS. We cannot found instability of results from the sensitivity analysis.

Discussion

Even though various types of meta-analysis have been conducted to evaluate the relation-

ships between the *BRAF* V600E mutation and clinicopathologic characteristics of PTC patients. There have no associated meta-analysis which was implemented to analysis the correlation between the *BRAF* V600E mutation and long term survival of PTC patients, including OS and RFS. As we known that, the present meta-analysis is initially implemented to evaluate the correlation between the *BRAF* V600E mutation and long term survival of PTC patients. Although there have no consistent opinions about whether or not the *BRAF* V600E mutation statue of PTC patients correlated with poor long term survival (OS and/or RFS). After pooled survival data of included articles, we found that the *BRAF* V600E mutation statue of PTC patients (either Asian or Caucasian) significantly predicts poor survival outcomes (both OS and RFS).

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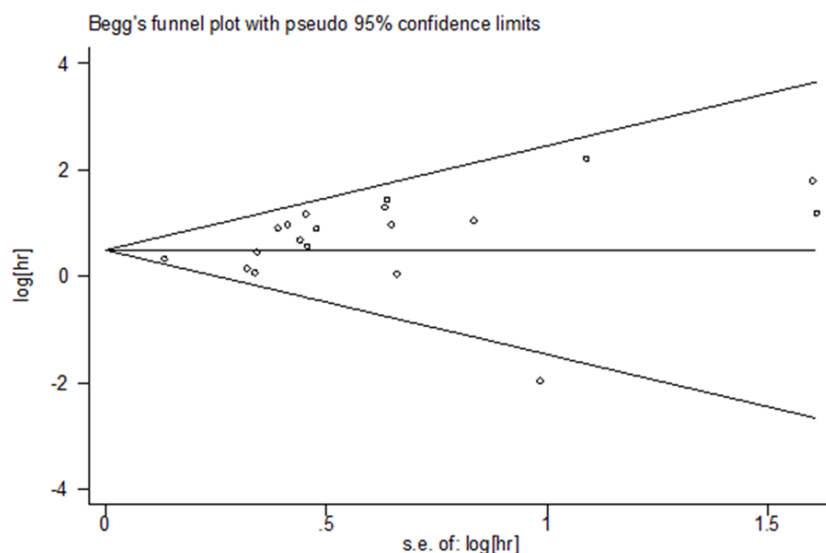


Figure 4. The Begg's funnel plot revealed little publication bias between the included references.

Several mechanisms have been demonstrated to try to explain the poor prognostic role of the positive *BRAF* V600E mutation status in PTC patients. First of all, *BRAF* V600E mutation may result in the excessive activation of RAS/BRAF/MAPK signal pathway, which was believed to act as a critical role in the tumorigenesis and progression of PTC. Animal experiments [25] discovered that normal rat thyroid cells with *BRAF* V600E mutation were likely to promote tumor invasion by expressing certain gene products and degrading the extracellular matrix of PTC. In addition, researchers also found that the *BRAF* V600E mutation in PTC was correlated with transportation and metabolism of iodide, and resulted in radioiodine treatment failure [26]. Furthermore, the *BRAF* V600E mutation induced silence of several tumor-suppressor genes and further promoted the invasiveness of PTC. Xing et al. [27] discovered that the *BRAF* V600E mutation in PTC was correlated with methylation of following tumor suppressor genes including tissue inhibitor of metalloproteinase-3 (TIMP3), SLC5A8, death-associated protein kinase (DAPK), and retinoic acid receptor b2 (RARb2).

In addition to the PTC prognosis prediction, the *BRAF* V600E mutation also has critical value in diagnosis and treatment of PTC patients. A number of studies [28] have demonstrated that the sensitivity, specificity, negative predictive value and positive predictive value of fine-needle aspiration biopsy (FNAB) for PTC were all

been significantly improved after combined analysis of *BRAF* V600E mutation status. And, some inhibitors have been developed to inhibit the excessive activation of RAS/BRAF/MAPK signal pathway. These inhibitors including sorafenib, PLX4032, RAF265, PLX4720.

In summary, our meta-analysis indicates that the *BRAF* V600E mutation in PTC is significantly associated with poor survival outcomes including OS and RFS. The *BRAF* V600E mutation may be used as a prog-

nostic predictor of patients with PTC. However, further large sample size and multicentric clinical researches should be carried out to confirm our findings.

Disclosure of conflict of interest

None.

Authors' contribution

Study design: Xinguang Qiu, Jianhua Li; Document retrieval: Shuijun Zhang, Shouhua Zheng; Data selection: Jianhua Li, Shuijun Zhang, Danhua Zhang; Wrote the paper: Jianhua Li, Xinguang Qiu.

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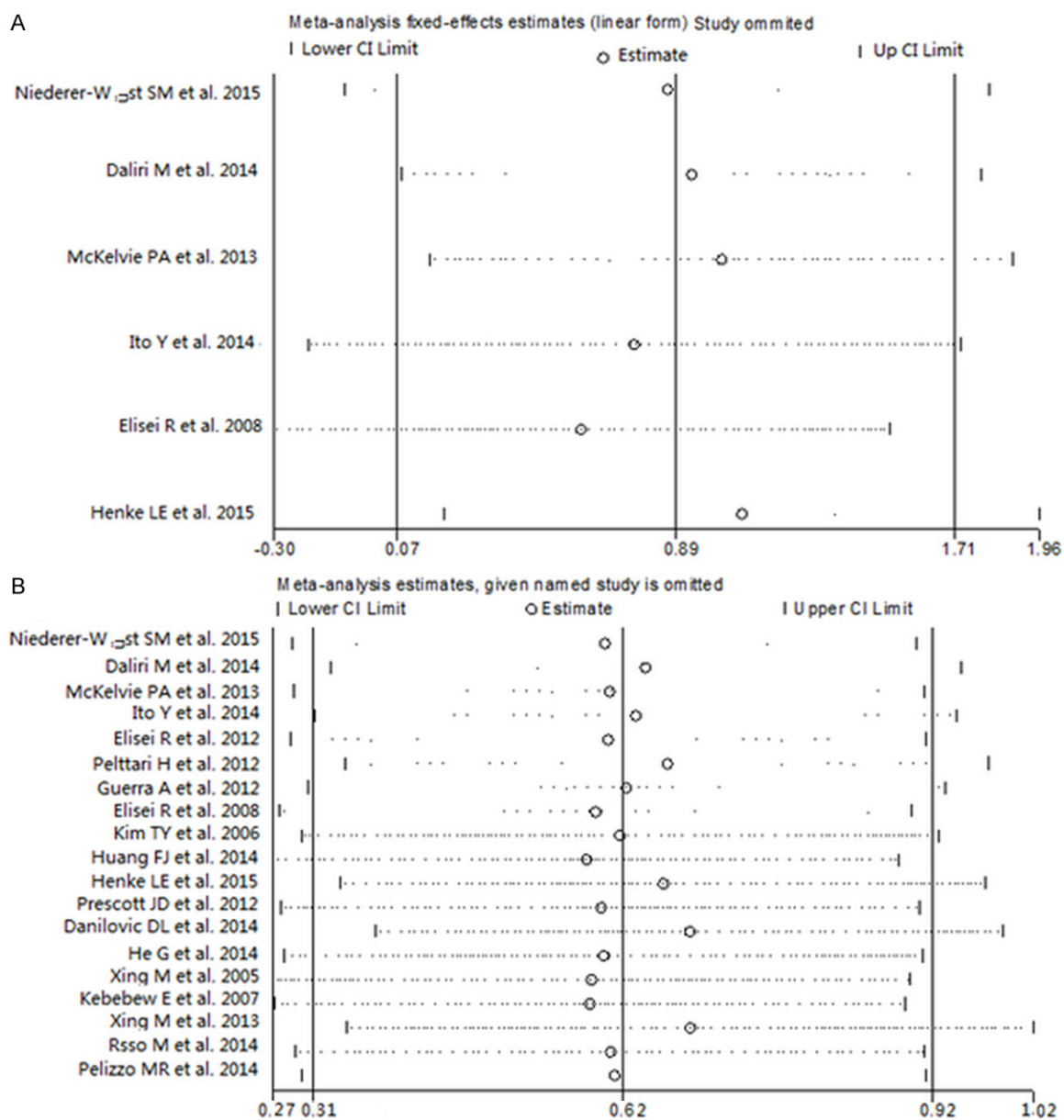
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Supplementary Figure 1. Sensitivity analysis of OS (A) and RFS (B).