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Review

Prognostic value of Ki-67 in stage I non-small-cell lung cancer: A meta-analysis involving 1931 patients

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ABSTRACT

There is growing interest in exploring the prognostic value of Ki-67 in non-small-cell lung cancer (NSCLC). However, whether Ki-67 can be regarded as a routine biomarker in clinical practice is still under debate. The present meta-analysis investigated the relationship between Ki-67 and the overall survival (OS) or disease-free survival (DFS) of patients suffering from stage I NSCLC. We searched the Web of Science, Cochrane, and PubMed databases to extract eligible articles. In total, 15 studies involving 1931 patients were included. Pooled hazard ratio (HR) analysis revealed that patients with high Ki-67 labeling index (LI) had poorer OS (HR = 1.95, 95% confidence interval (CI) = 1.43–2.66, $P < 0.0001$) and DFS (HR = 3.12, 95% CI = 2.17–4.48, $P < 0.00001$) than those with low Ki-67 LI. In subgroup analysis, high Ki-67 LI was significantly associated with poor prognoses in stage I adenocarcinoma. In future studies, a consensus for the optimal cutoff value for high Ki-67 LI needs to be explored and demonstrated in stage I NSCLC patients.

1. Introduction

Non-small-cell lung cancer (NSCLC) is one of the leading causes of cancer-related death worldwide [1]. There is consensus about postoperative therapy for stages II–IV NSCLC. For stage I NSCLC patients, the first-line treatment is radical surgery. However, approximately 30%–60% of patients experience recurrence soon after surgery and die due to cancer [2]. Postoperative management is controversial for this patient population. The latest European Society for Medical Oncology (ESMO) guidelines implied that adjuvant chemotherapy leads to a worse outcome in stage IA patients. For stage IB, only patients with tumors larger than 4 cm have been found to receive a small overall benefit from postoperative chemotherapy [3]. In the National Comprehensive Cancer Network (NCCN) guidelines, adjuvant chemotherapy is recommended for stage IB patients with high-risk factors, such as poorly differentiated tumors, vascular invasion, wedge resection, tumors > 4 cm, visceral pleural involvement, and unknown lymph node status. These factors may not independently indicate stage I NSCLC outcomes. Therefore, a standard biomarker for stage I NSCLC patients is highly desirable to assist in the development of personalized postoperative treatment [4].

The heterogeneity of cancer biology can cause different clinical outcomes regarding recurrences and prognoses. In NSCLC, several markers have been reported to predict the risk of recurrence [5]. Ki-67, a protein expressed in proliferating cells, is a marker of proliferative activity that has been used to identify groups of high-risk patients in various cancers [6,7]. Although previous studies have shown the potential prognostic value of Ki-67 in NSCLC, Ki-67 is not yet a routine tumor marker [8,9]. Here, we performed a literature-based meta-analysis to quantify the strong connection between Ki-67 and stage I NSCLC patient survival.

2. Methods

This meta-analysis was performed in accordance with the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10]. The PubMed, Cochrane and Web of Science databases were searched for relevant articles published until April 18th, 2018. The search terms included non-small-cell lung cancer, stage I, Ki-67, and prognosis and survival. We reviewed all the eligible papers using the above terms, and the reference lists were also examined for additional studies. This systematic literature search was carried out independently by two authors. A third author participated in making a final decision if consensus could not be reached through discussion.

3. Inclusion and exclusion criteria

To be considered eligible for this meta-analysis, the relevant papers

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had to fulfill the following criteria: 1) the patients were diagnosed with stage I NSCLC with confirmed pathology, 2) immunohistochemistry (IHC) was used to measure Ki-67 in primary cancer tissue, 3) the relationships between Ki-67 and overall survival (OS) and disease-free survival (DFS) were explored, with OS and DFS data provided directly as a hazard ratio (HR) so that survival data could be calculated, and 4) the study was published in the English language. Studies were excluded from the analysis if they were earlier reports of data updated in subsequent publications.

The exclusion criteria for the primary studies were as follows: 1) the cancer was not stage I NSCLC, 2) the measurement of Ki-67 was not based on tissue, 3) there was overlap among articles or duplicated data, 4) the studies were animal experiments, or 3) insufficient data was provided to estimate HRs and 95% confidence interval (CIs), as was the case for conference data, letters, expert opinions, case reports or reviews.

4. Data extraction and statistical analyses

Two authors conducted the data extraction independently. The basic information extracted from each paper included the author names, publication year, baseline characteristics, Ki-67 cutoff values, median follow-up duration, adjuvant settings, and survival data.

The investigated parameters were high Ki-67 labeling index (LI) in relation to survival outcomes, including OS and DFS. HRs with 95% CIs were used where possible. If HRs and 95% CIs were not directly reported, we extracted data from K-M curves with Engauge Digitizer 4.1 and then calculated these indexes. We used the Newcastle-Ottawa Scale (NOS) score [11] to evaluate the quality of each included study. Cochran's Q analysis and the Higgins I^2 statistic were used to assess the heterogeneity among the studies. A fixed-effects model was applied when the I^2 was below 50%. Otherwise, a random-effects model was employed [12]. Funnel plots with Egger's tests were employed to evaluate publication bias [13]. We pooled estimates for similar subsets of patients, if available, to conduct subgroup analyses. All generated P-values < 0.05 were considered statistically significant. All meta-analyses were carried out using RevMan5.3 software. Egger's tests were conducted using Stata SE12.0 software.

5. Results

5.1. Study selection

On the basis of the inclusion criteria, a total of 103 studies were retrieved from the electronic databases PubMed, Cochrane Library, and Web of Science. After careful review, fifteen studies [14–28] including 1931 stage I NSCLC patients were eventually selected (Fig. 1). The characteristics of these studies are listed in Table 1.

5.2. Overall analyses

Ten studies with 1510 patients were included in the meta-analysis of OS. A random-effects model was employed to estimate the pooled HR. The heterogeneity test revealed a $P = 0.01$ and an I^2 value of 58%. This result showed that high Ki-67 LI was associated with poor OS in stage I NSCLC (HR = 1.95, 95% CI = 1.43–2.66, $P < 0.0001$; Fig. 2).

Seven studies with 747 patients were selected to investigate the role of Ki-67 in DFS for stage I NSCLC. The overall HR was 3.12 (95% CI = 2.17–4.48, $P < 0.00001$), with no heterogeneity ($I^2 = 0\%$; Fig. 3).

5.3. Subgroup analyses

Subgroup analyses were performed for stage I adenocarcinoma patients. High Ki-67 LI was significantly associated with worse OS in stage I adenocarcinoma (HR = 2.64, 95% CI = 1.29–5.40, $P = 0.008$; Fig. 4), based on data from five studies with 589 patients. In addition, according to data from three studies with 516 patients, there was an inverse correlation between Ki-67 and DFS in stage I adenocarcinoma (HR = 3.04, 95% CI = 1.85–5.00, $P < 0.0001$; Fig. 5).

5.4. Relationships between Ki-67 and OS in stage I NSCLC cancer using different cutoff values

The cutoffs for high Ki-67 LI differed within the selected studies. When we chose 20% as the cutoff value, patients with high Ki-67 LI still suffered from worse OS than those with low Ki-67 LI. The pooled HR was 2.28 (95% CI = 1.07–4.86, $P = 0.03$; Fig. 6).

Furthermore, data for all cutoffs (including 5, 10, 14, 20, 25, 33, and 40%) was introduced to elucidate the optimal cutoff of high Ki-67 LI. Subgroup analyses indicated that the relationship between Ki-67 and OS was not significant using various high Ki-67 cutoff values (14%, 20%). The pooled HRs and 95% CIs were as follows: 2.17 (95% CI 1.25–3.76) vs. 2.12 (95% CI 1.48–3.05) for a cutoff value of 14%, 2.16 (95% CI 1.45–3.20) vs. 2.21 (95% CI 1.29–3.77) for a cut-off value of 20% (Figs. 7 and 8).

5.5. Bias assessment

We performed Egger's tests to evaluate the potential bias. The results derived from the Egger's test showed that there was a marked bias in the overall analyses, but there was no indication of bias for the subgroup analyses (Table 2, Fig. 9).

6. Discussion

Prognostic markers are suggested to be associated with several clinical outcomes, particularly time-to-event outcomes such as OS or DFS, independent of any therapy, and they may be useful in therapy management [29]. Ki-67 was first identified as a monoclonal antibody in the 1980s. As Ki-67 is expressed in all stages of the cell cycle except the G0 stage, it was suggested to be a marker of proliferation. The prognostic value of Ki-67 is clear in various cancers, such as breast cancer and prostate cancer [30,31], and high Ki-67 LI is significantly associated with poor prognoses in early breast cancer and prostate cancer patients. The potential role of high Ki-67 LI in NSCLC has also been analyzed in many studies. Most previous studies combined stage I NSCLC patients with stage II-IIIA patients, defining them as early NSCLC patients. The connection between Ki-67 and the prognosis of stage I patients is unclear from these studies. Moreover, the management of stage I NSCLC has been inconsistent in past decades; therefore, a definitive prognostic marker is needed to aid in decision-making processes regarding treatment.

Our analyses suggested that in patients with stage I NSCLC, high Ki-67 LI was a predictor of worse OS (HR = 1.95, 95% CI = 1.43–2.66, $P < 0.0001$) and DFS (combined HR = 3.12, 95% CI = 2.17–4.48, $P < 0.00001$). This result was consistent with those of previous meta-analyses [32,33]We note that a greater number of studies and patients were included in our meta-analysis than in previous meta-analyses, thus enhancing the reliability of our conclusion.

NSCLC is a cancer with various subtypes, and patients of different types may have different clinical outcomes [34]. In the current meta-analysis, the prognostic impact of Ki-67 on both OS and DFS was also examined in stage I adenocarcinoma patients. This was the first meta-analysis to focus on stage I lung adenocarcinoma. Further studies investigating the association between Ki-67 and nonadenocarcinoma lung cancer are needed to better understand the heterogeneity of NSCLC.

No significant heterogeneity was detected for any analysis, as the I^2 did not exceed 70%. The different cutoff values for high Ki-67 LI on in the included studies may be the cause of the observed heterogeneity. The subgroup analyses indicated that the relationship between Ki-67 and OS was not significant using various high Ki-67 cutoff values.

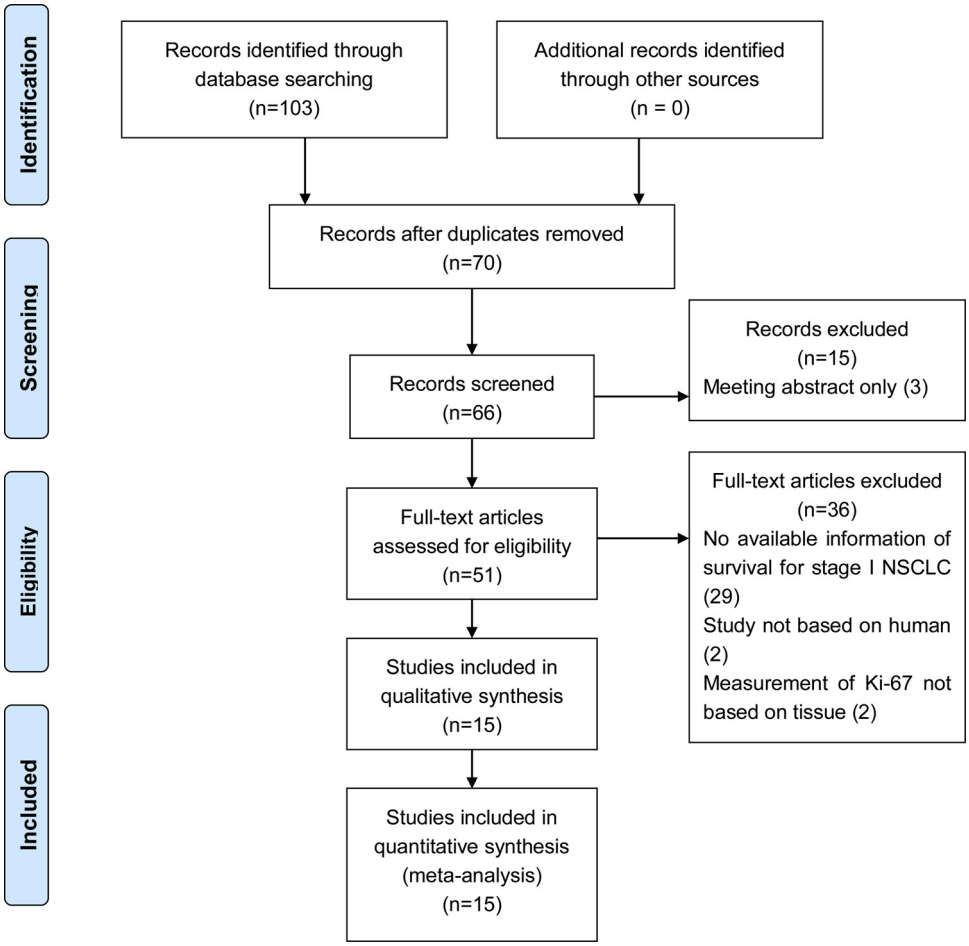

Fig. 1. Prisma flow diagram.

Table 1
Main characteristics of included studies.

Study	Age (year)	No. of patients	Cut-off	Follow-up (month)	Adjuvant therapy	NOS
Harpole 1995	63 ± 8#	271	10%	56 (0.2–161)*	NA	7
D'Amico 1999	62.9 ± 8.9#	408	NA	60	No	7
Demarchi 2000	59.8 ± 11.1#	29	20%	51.9 ± 41.27#	No	8
Shiba 2000	62.4 (34–80)*	53	20%	68.4*	No	8
Minami 2002	64 (41–81) #	47	20%	89*	NA	7
Haga 2003	NA	187	10%	60	NA	7
Poleri 2003	60.8 ± 8.7#	53	33%	59 (9–168)*	NA	7
Huang 2005	67 (35–76)*	97	25%	77.0 ± 28.9*	54.6%: UFT	8
Maddau 2006	NA	92	25%	47	NA	7
Ludovini 2008	66 (31–84)*	76	25%	37*	NA	7
Woo 2009	7.8 ± 8.4#	190	10%	35.9 (1.1–82.5)*	IA: no IB: 32% yes	8
Yamashita 2011	NA	44	5%	24.8*	No	8
Maki 2012	65 (29–83)*	105	+ vs. −	59.7*	NA	7
Ahn 2014	65 (24–81)*	42	40%	72	No	8
Yazawa 2016	NA	221	14%	47.9*	NA	7

NA: not available; UFT: a combination of tegafur and uracil; *: median; #: mean; +: positive; −: negative.

Future prospective studies need to be conducted to confirm the cutoff threshold for high Ki-67 LI in stage I NSCLC patients.

The current meta-analysis has some limitations. First, our results were derived from pooled data from various studies rather than from individual data, which might have resulted in insufficient information. For example, the influence of adjuvant chemotherapy on I NSCLC patients with high Ki-67 LI was out of range in our analyses. Second, the overall analyses suffered from significant publication bias, which might be due to the literature search strategy. Our search was limited to studies published in English journals; therefore, potential language bias might exist. Third, in the subgroup analyses for stage I adenocarcinomas, the P value from Egger's test is large enough. However, the number of included studies in the subgroup analyses is relatively low (5 and 3). More clinical studies focused on adenocarcinoma patients should be carried out in the future to demonstrate the prognostic value of Ki-67 and survival.

However, there are several advantages of our meta-analysis. First, a total of 15 studies with 1931 stage I patients were analyzed, and the

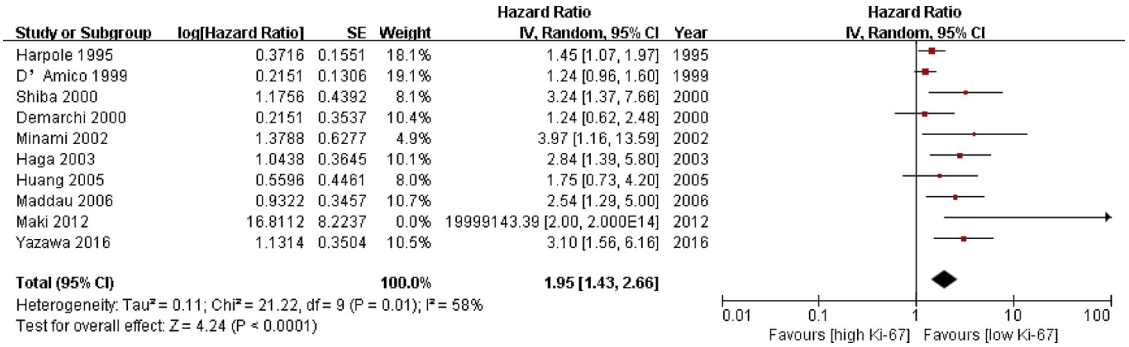

Fig. 2. Meta-analysis of the relationship between Ki-67 and overall survival of stage I NSCLC patients.

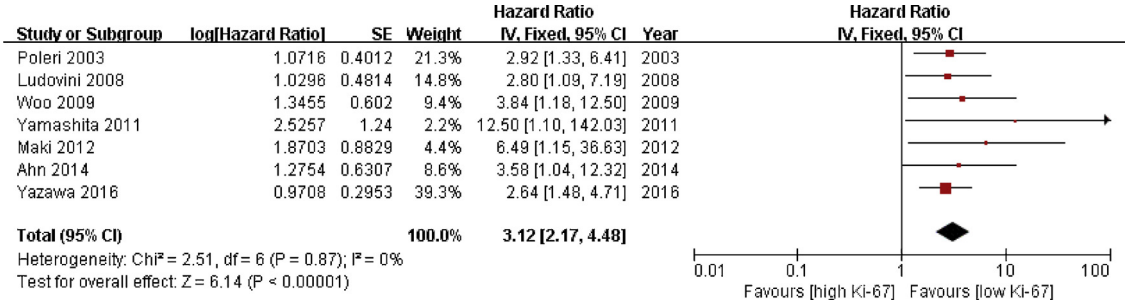

Fig. 3. Meta-analysis of the relationship between Ki-67 and disease free survival of stage I NSCLC patients.

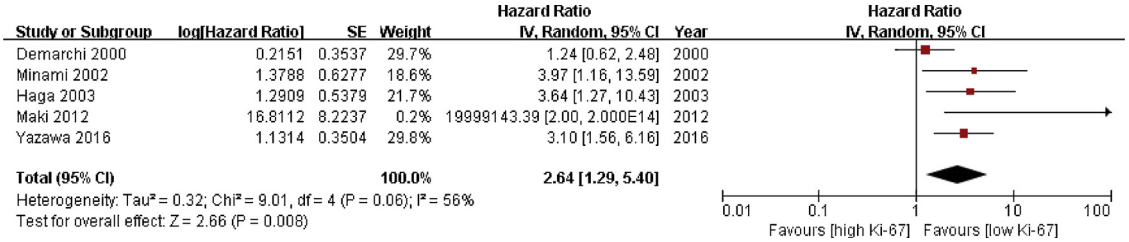

Fig. 4. Meta-analysis of the relationship between Ki-67 and overall survival of stage I adenocarcinoma patients.

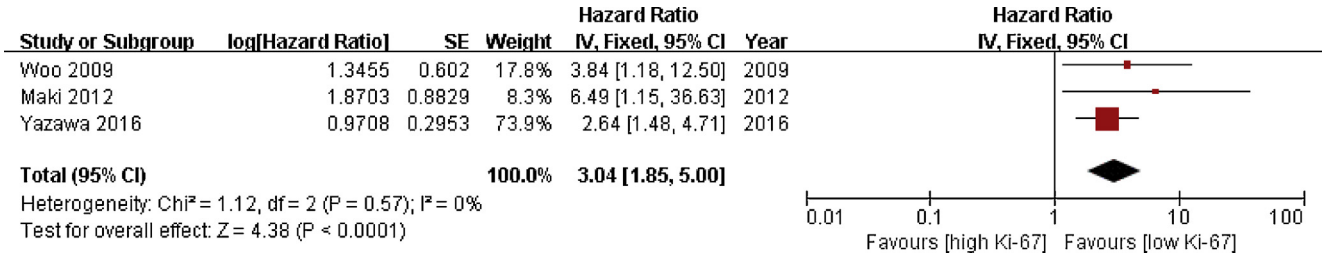

Fig. 5. Meta-analysis of the relationship between Ki-67 and disease free survival of stage I adenocarcinoma patients.

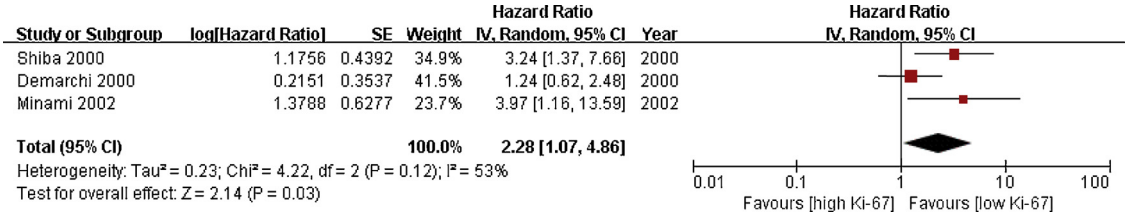

Fig. 6. Meta-analysis of the relationship between high Ki-67 LI (using 20% as cut-off value) and overall survival of stage I NSCLC patients.

quality of each study was relatively high. Second, the relationship between Ki-67 and stage I adenocarcinoma was investigated. This was the first meta-analysis to focus on this subtype of NSCLC. Third, because our meta-analysis was carried out using published data rather than individual data, the cost of our analysis was low.

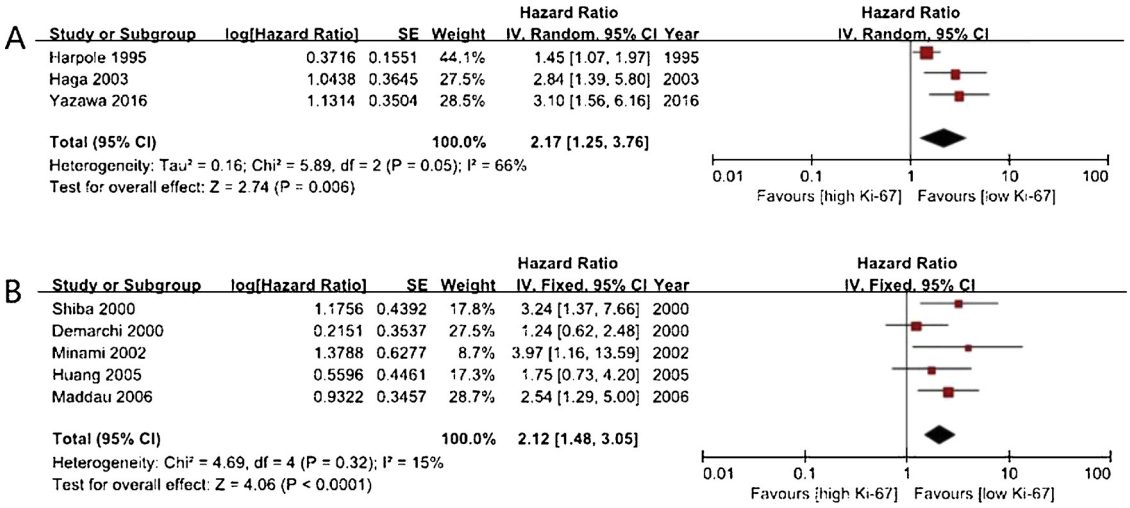

Fig. 7. Cutoff value ≤14% (A) and cutoff value > 14% (B). HR of Ki-67 associated with overall survival in all stage I NSCLC patients subgroup.

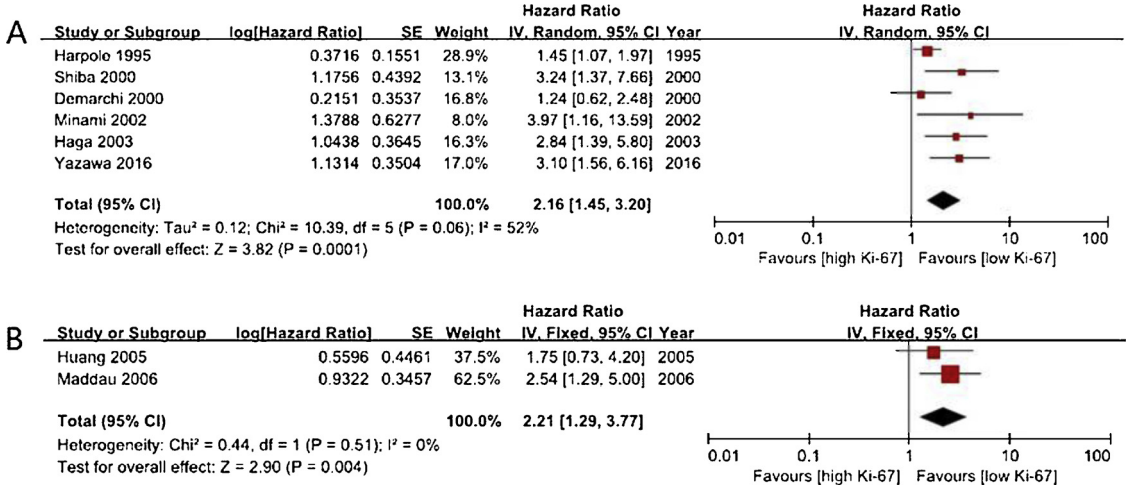

Fig. 8. Cutoff value ≤20% (A) and cutoff value > 20% (B). HR of Ki-67 associated with overall survival in all stage I NSCLC patients subgroup.

Table 2
Analyses of outcomes by categories.

Outcome	No. of studies	No. of patients	HR(95%CI)	*P* for Egger's test
OS for stage I NSCLC	10	1510	1.95 [1.43, 2.66]	0.002
DFS for stage I NSCLC	7	747	3.12 [2.17, 4.48]	0.001
OS for stage I adenocarcinoma	5	589	2.64 [1.29, 5.40]	0.123
DFS for stage I adenocarcinoma	3	516	3.04 [1.85, 5.00]	0.074
OS for cut-off = 20%	3	129	2.28 [1.07, 4.86]	0.363
OS for cut-off≤14%	3	679	2.17 [1.25–3.76]	0.072
OS for cut-off > 14%	5	318	2.12 [1.48, 3.05]	0.337
OS for cut-of≤20%	6	808	2.16 [1.45, 3.20]	0.072
OS for cut-off > 20%	2	189	2.21 [1.29, 3.77]	NA

7. Conclusion

In conclusion, this meta-analysis confirmed the prognostic value of Ki-67 in stage I NSCLC patients. In addition, the prognostic value of Ki-67 was also shown for stage I adenocarcinoma. Based on these results, we recommend Ki-67 as a biomarker for routine clinical use in stage I NSCLC. Adjuvant therapy might benefit stage I NSCLC patients with high Ki-67 LI.

Author contributions

J.X. and G.S. designed the project and led manuscript preparation. J.X. and P.L. led data extraction. J.X. performed statistical analyses. J.X. wrote the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors have stated that they have no conflict of interest.

Acknowledgement

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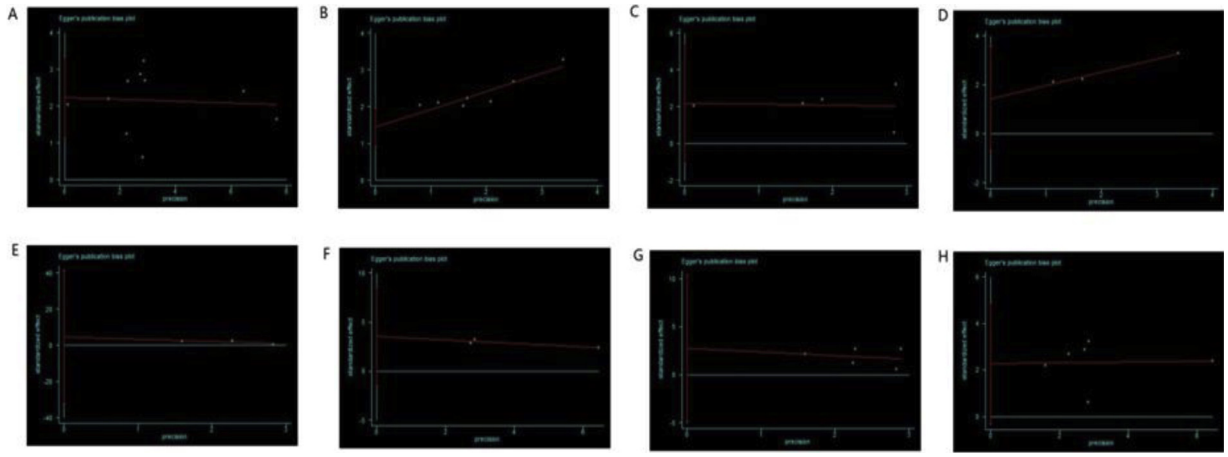

Fig. 9. Funnel Plots of Egger's tests were used to detect publication bias on overall survival (OS) and disease free survival (DFS). OS for all stage I NSCLC patients (A), DFS for all stage I NSCLC patients (B), OS for stage I adenocarcinoma patients (C), DFS for stage I adenocarcinoma patients (D), OS for stage I NSCLC patients when using 20% as cutoff value of high Ki-67 LI (E), OS for stage I NSCLC patients when using ≤14% as cutoff value of high Ki-67 LI (F), OS for stage I NSCLC patients when using > 14% as cutoff value of high Ki-67 LI(G), OS for stage I NSCLC patients when using ≤20% as cutoff value of high Ki-67 LI (F).

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