JBUON 2015; 20(2): 631-644
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Prognostic role of the let-7 family in various carcinomas: A meta-analysis update

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Summary

Purpose: *The role of let-7 family members in cancer prognosis has been the subject of increasing interest; however, the correlation between let-7 expression and cancer prognosis remains unknown. The goal of this study was to investigate the prognostic role of let-7 expression by performing a meta-analysis update of 31 studies.*

Methods: *All relevant studies were searched on PubMed and Web of Science. The pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated, and subgroup analysis was performed for overall survival (OS) and disease-free survival (DFS) to evaluate the relationship between high let-7 expression and cancer prognosis. Heterogeneity and publication bias were also investigated.*

Results: *We discovered that high let-7 expression can predict a better OS (pooled HR=0.69, 95% CI 0.60–0.80, transformed from lnHR and its 95% CI) and DFS (pooled HR=0.72, 95% CI 0.54–0.96, transformed from lnHR and its 95% CI) in various carcinomas, especially in digestive cancer. Subgroup analysis showed that high let-7 expression was significantly associated with a better DFS in Asians (pooled HR=0.50, 95% CI 0.39–0.64, transformed from lnHR and its 95% CI).*

Conclusions: *This meta-analysis showed that high let-7 expression is a prognostic factor for better OS and DFS in cancer patients, with particularly better DFS among the Asian populations. These results suggest that clinicians should treat patients with low let-7 expression more carefully. Future studies in large-scale populations among different ethnicities and regions are needed to definitively determine if let-7 expression can be used as a predicative biomarker for clinical assessment.*

Key words: *cancer, let-7 family, meta-analysis, prognosis*

Introduction

In 1993, microRNAs (miRNAs), which are endogenous, stable, single-stranded, non-coding RNAs, were discovered. MiRNAs act on gene expression at the posttranscriptional level, thereby regulating many key biological processes, including development, differentiation, proliferation, and apoptosis [1,2] . The dysregulation of miRNA expression has been discovered in various human cancers; therefore, miRNAs are increasingly considered diagnostic or prognostic biomarkers.

Let-7 miRNA was first identified in the nematode Caenorhabditis elegans, and was subsequently found as the first known human miRNA that controls the timing of stem-cell division and differentiation [3]. Currently, ten mature subtypes of the let-7 family have been identified in humans, including let-7a, let-7b, let-7c, let-7d, let-7e, let-7f, let-7g, let-7i, miR-98 and miR-202, in which mature let-7a and let-7f are produced by precursor sequences (let-7a-1, let-7a-2, let-7a-3; let-7f-1, let-7f-2) [4]. Let-7 is widely viewed as a tumor suppressor miRNA. Consistent with this charac-

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Received: 21/10/2014; Accepted: 10/11/2014

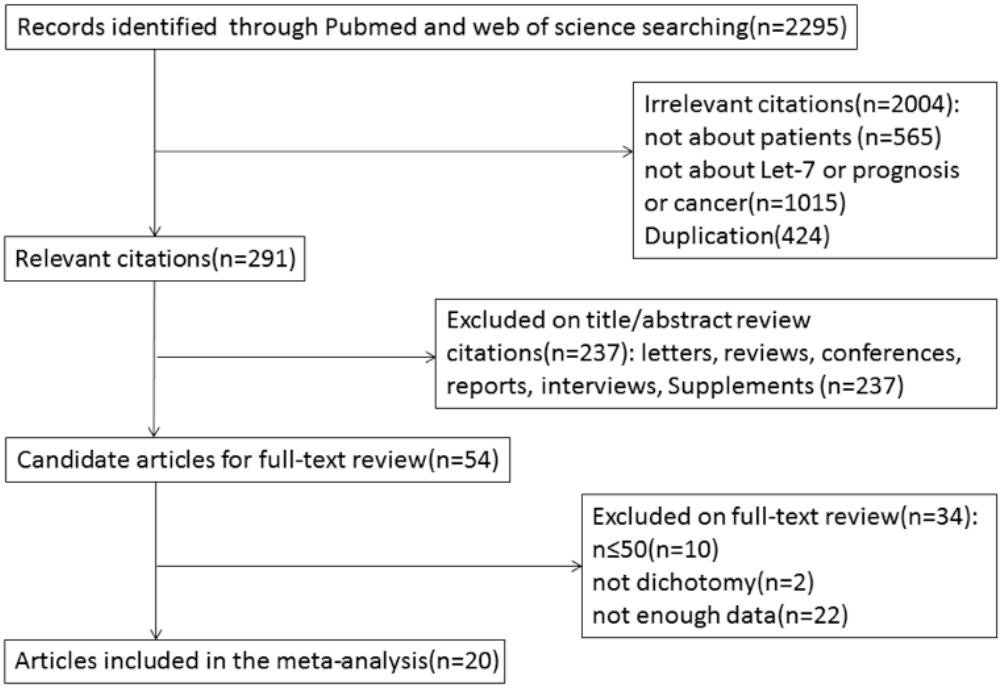


Figure 1. Flow diagram of study inclusion.

teristic, the expression of most or all let-7 family members is downregulated in many types of cancers compared to normal tissue. Loss of let-7 expression indicates poor survival. For example, the downregulation of let-7, namely let-7a-2, was found to correlate with poor survival in lung cancer [5]. In addition, decreased expression of let-7d in head and neck squamous cell carcinoma and ovarian cancer was also indicative of poor survival [6,7].

However, the high expression of some let-7 family members has also been detected in several cancers, indicating that let-7 does not act as a tumor suppressor under all situations or in all cancers. High grade transformation of lymphoma is related to increased expression of let-7b and let-7i [8], suggesting that the upregulation of let-7 may be a prognostic biomarker for evaluating high-risk grade transformation cancer patients. Therefore, it is clear that the search for the prognostic value of let-7 family expression has produced different results. Several studies [9-20] have found that high let-7 family expression confers a protective role against cancer; however, other studies have come to the opposite conclusion [14,15,20-28]. Despite these inconsistent results, the let-7 family is still viewed as an appealing biomarker for evaluating cancer survival and progression. Here in, we conducted a meta-analysis to determine the precise role of the let-7 family in OS and DFS in various human carcinomas.

Methods

Literature search strategy

We performed a network search using Pubmed and Web of Science for original articles analyzing the prognostic value of let-7 family in various cancers. We chose studies with different combinations of the following keywords: cancer ("Neoplasm", "cancer*", "carcinoma", "carcinoma*", "neoplasm*", "tumor", "tumor*"), let-7 ("mirnlet7*", "let-7*", "hsa-let-7*", "mirnlet7", "hsa-let-7", "mirnlet7"). The last search was conducted on October 21, 2014. We increased the integrity and accuracy of the search process by manually screening the reference lists of associated articles to further select potential studies.

Inclusion and exclusion criteria

We implemented the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement issued in 2009 [29] as guidelines. Articles were viewed as eligible if they met the following criteria: (i) the relationship between let-7 expression levels and patient survival outcomes in any type of cancer was studied; (ii) the study directly provided a HR and 95% CI, or gave relevant data that allowed estimation of the HR and 95% CI; (iii) the study was in accordance with the definition of OS and DFS; (iv) the number of patients in

each study was more than 50; (v) studies with dichotomous data (high or low let-7 expression) were investigated.

OS was defined as the time from the date of surgery to the date of death from any case. Patients were censored at the date of the last follow-up. DFS was defined as the time from the date of surgery to the date of recurrence or last follow-up [30]. We found 3 articles with progression-free survival (PFS), one article with recurrence-free survival (RFS) and one article with tumor-free survival (TFF) [19,22,27] in 5 articles that were supposed to have DFS according to our definition. Every cohort in one article was considered to be one study. Studies that fit the abovementioned criteria were further assessed and excluded depending on the selection process shown in Figure 1.

Data extraction

Details of the study, including first author, publication year, origin of population, sample source, disease, number of patients, storage method, let-7 family, cut-off value, HR, and follow-up, were collected for each eligible publication. If both univariate and multivariate analyses were used to obtain the HR, the univariate analysis result was preferably taken. If survival data were not directly reported, they were extracted from original papers as described by Parmar et al. [31]. Kaplan-Meier curves were read by Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/). The significance and orientation (protective or hazardous) of survival data were extracted simultaneously.

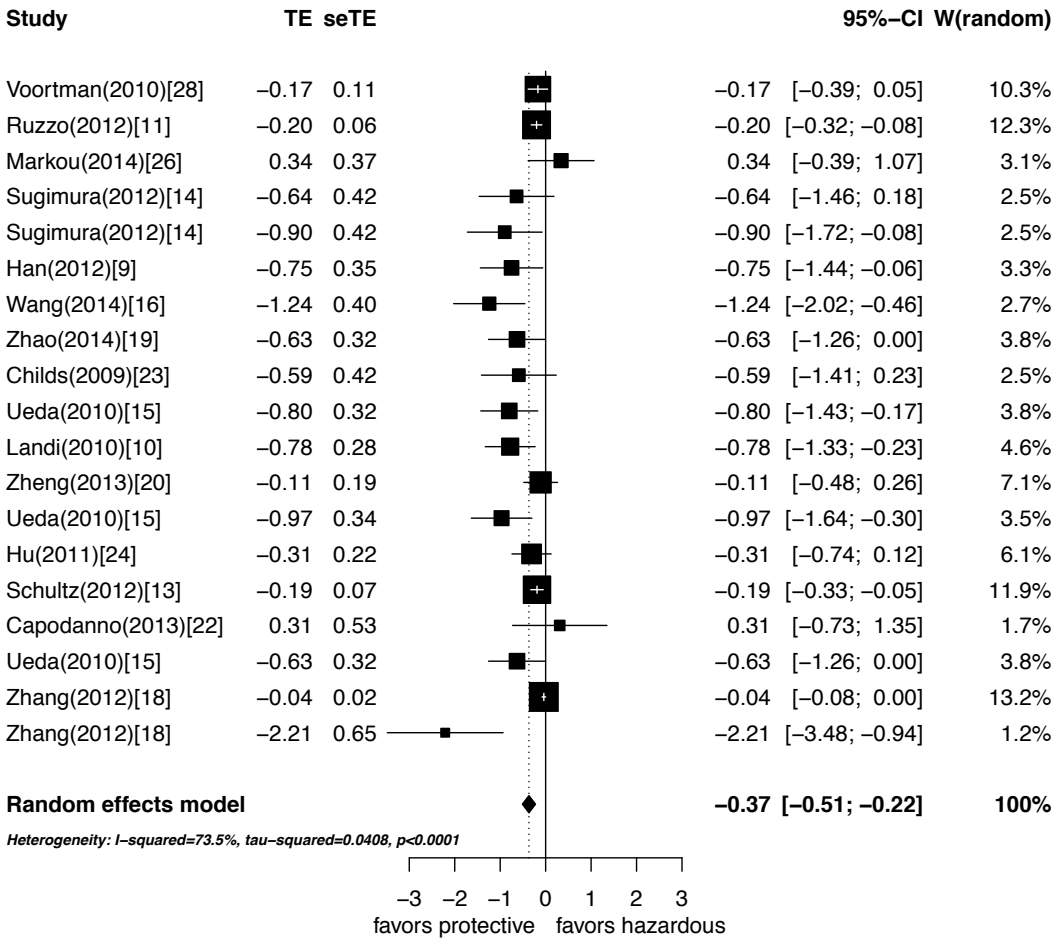
We requested original data or data such as HR

Table 1. Summary of included studies concerning overall survival

First author	*Year*	*Origin of population*	*Sample source*	*Disease*	*N*	*Storage method*	*Let-7 family*	*Cut-off*	*Hazard ratio*	*Follow-up (months)*
Yanaihara, N.	2006	USA	Tissue	Lung cancer	52	Fr	Let-7a	Mean	R	NM
Childs, G.	2009	USA	Tissue	HNSCC	104	Fr	Let-7d	Mean$^{\Delta}$CT	SC	NM
Landi, M. T.	2010	Italy	Tissue	Lung cancer	107	FFPE	Let-7e	Median	R	NM
Ueda, T.	2010	Japan	Tissue	Gastric cancer	101	Fr	Let-7e,g,i	Mean	R	26.2(5.3-102.3)
Voortman, J.	2010	IALT	Tissue	Lung cancer	638	FFPE	Let-7a	Median	R	NM
Hu, Y.	2011	USA	Tissue	Esophageal cancer	99	FFPE	Let-7g	NM	R	NM
Han, H. B.	2012	China	Tissue	Colorectal cancer	83	Fr	Let-7c	2.27	SC	NM
Ruzzo, A.	2012	Italy	Tissue	Colorectal cancer	59	FFPE	Let-7a	4.2$^{\Delta}$CT	R	NM
Schultz, N. A.	2012	Denmark	Tissue	Pancreatic cancer	225	FFPE	Let-7g	NM	R	NM
Sugimura, K.	2012	Japan	Tissue	Esophageal cancer	74	Fr	Let-7b,c	Median	DE	22.4
Zhang, Y. K.	2012	China	Tissue	Lung cancer	51,54	Fr	Let-7e	AD:0.19,SCC:0.56	R	NM
Capodanno, A.	2013	Italy	Tissue	Lung cancer	55	FFPE	Let-7g	NM	DE	32(7-98)
Zhao, B.	2013	China	Tissue	Lung cancer	94	Fr	Let-7c	Median	SC	NM
Zheng, H.	2013	China	Plasma	Ovarian cancer	360	Fr	Let-7f	Median	R	NM
Markou, A.	2014	Greece	Tissue	Breast cancer	112	FFPE	Let-7a	Median	R	NM
Wang, H. Y.	2014	China	Plasma	NPC	100	Fr	Let-7c	NM	R	77 (4–114)

AD: adenocarcinomas, DE: data extrapolation, FFPE: formalin-fixed, paraffin-embedded, Fr: frozen, HNSCC: head and neck squamous cell carcinoma, IALT: international adjuvant lung cancer trial, NM: no mention, NPC: nasopharyngeal cancer, R: reported, SC: survival curve, SCC: squamous-cell carcinomas, CT: cycle threshold value, $^{\Delta}$CT: CT (miRNA)-CT (reference gene)

A



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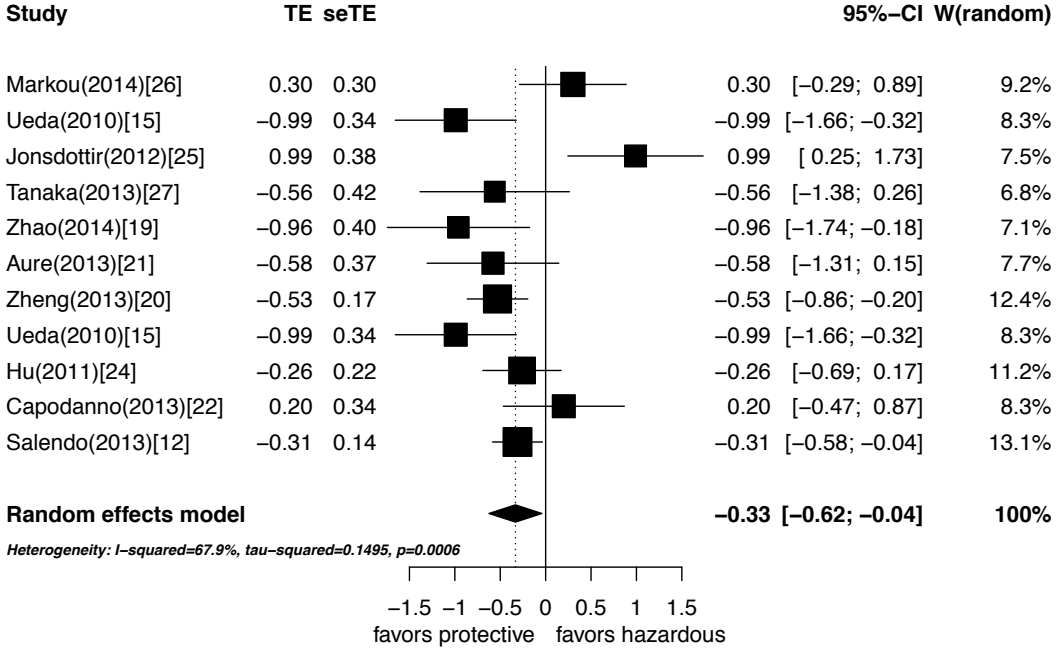

Figure 2. A: Forest plot for effect of high let-7 expression on overall survival (OS) and disease-free survival (DFS) in patients with cancer. Results are presented as individual and pooled lnHR and 95% CI (random effects model). lnHR: natural logarithm of hazard risk; selnHR: standard error of lnHR; CI: confidence interval. **B:** Forest plot of high let-7 expression on DFS in patients with cancer.

Table 2. Summary of included studies concerning disease-free survival

First author	*Year*	*Origin of population*	*Sample source*	*Disease*	*N*	*Storage method*	*Let-7 family*	*Cut-off*	*Survival analysis*	*Hazard ratio*	*Follow-up, months (range)*
Ueda, T.	2010	Japan	Tissue	Gastric cancer	101	Fr	Let-7b,g	Mean	DFS,DFS	R	26.2(5.3-102.3)
Hu, Y.	2011	USA	Tissue	Esophageal cancer	99	FFPE	Let-7g	NM	DFS	R	NM
Jonsdottir, K.	2012	Norway	Tissue	Breast cancer	204	FFPE	Let-7b	3.2792	DMFS	R	122(10-178)
Aure, M. R.	2013	Norway	Tissue	Breast cancer	86	Fr	Let-7e	Median	DFS	SC	NM
Capodanno, A.	2013	Italy	Tissue	Lung cancer	55	FFPE	Let-7g	NM	DFS	DE	32(7-98)
Salendo, J.	2013	Germany	Tissue	Colorectal cancer	128	Fr	Let-7g	Median	DFS	AP	NM
Tanaka, K.	2013	Japan	Plasma	Esophageal cancer	64	Fr	Let-7c	Median	DFS	SC	NM
Zhao, B.	2013	China	Tissue	Lung cancer	94	Fr	Let-7c	Median	DFS	SC	NM
Zheng, H.	2013	China	Plasma	Ovarian Cancer	360	Fr	Let-7f	Median	DFS	R	NM
Markou, A.	2014	Greece	Tissue	Breast cancer	112	FFPE	Let-7a	Median	DFI	R	NM

AP: author provided, DE: data extrapolation, DFS: disease-free survival, DFI: disease-free interval, DMFS: distant metastasis free survival, FFPE: formalin-fixed, paraffin-embedded, Fr: frozen, NM: no mention, R: reported, SC: survival curve

and 95% CI from authors of the primary studies if not enough data were found in articles. However, we did not weight studies by a quality score, because no scoring system is widely accepted as suitable for use in a meta-analysis deriving data from observational studies.

Two researchers (Zhang CL and Wu Y) independently performed the above mentioned steps, and resolved any disagreements by a consensus reviewer (Li Z).

Statistics

Forest plots were used to estimate the effect of let-7 expression on survival outcome. The heterogeneity of individual HRs was calculated using a Chi-square-based Q statistic and inconsistency index (I^2) statistic [32]. A p value less than 0.10 and an I^2 statistic index greater than 50% indicated the presence of substantial heterogeneity (I^2=0–25%, no heterogeneity; I^2=25–50%, moderate heterogeneity; I^2=50–75%, large heterogeneity; I^2=75–100%, extreme heterogeneity) [33]. If HRs had fine homogeneity, a fixed effect model was used for secondary analysis [34]; if not, a random-effect model was used [35]. The pooled HR with a 95% CI were obtained by calculating a weighted average of the individual log (HR) estimates. A pooled HR >1 implied a worse survival for the group with high let-7 expression. To analyze the inter-study heterogeneity, we also conducted meta-regression and subgroup analyses based on similar characteristics, such as cancer type, origin of population, let-7 family, number of patients, and survival type. Funnel plots and Egger's tests were used to evaluate publication bias, and sensitivity analysis was performed to evaluate the influence of a single study on the overall effect [36].

Statistical analyses were estimated using R/meta and R/metafor software (RStudio 3.0.3), (R Development Core Team, 2013). All statistical tests performed in this study were two-tailed and p values less than 0.05 were considered statistically significant, unless otherwise stated.

Results

Summary of included studies

Depending on the process of study selection, 2295 articles on the let-7 family and cancer were identified from primary articles found via searching Pubmed and Web of Science. After manually screening the title and abstract, we excluded 2004 articles; an additional 237 papers, such as reviews, letters, and reports were excluded, and 34 papers were excluded after evaluation of the full text (Figure 1). Eventually, we identified 20 eligible articles (31 studies) for this meta-analysis, which explored the potential association between let-7 expression and patient survival or progression in cancer.

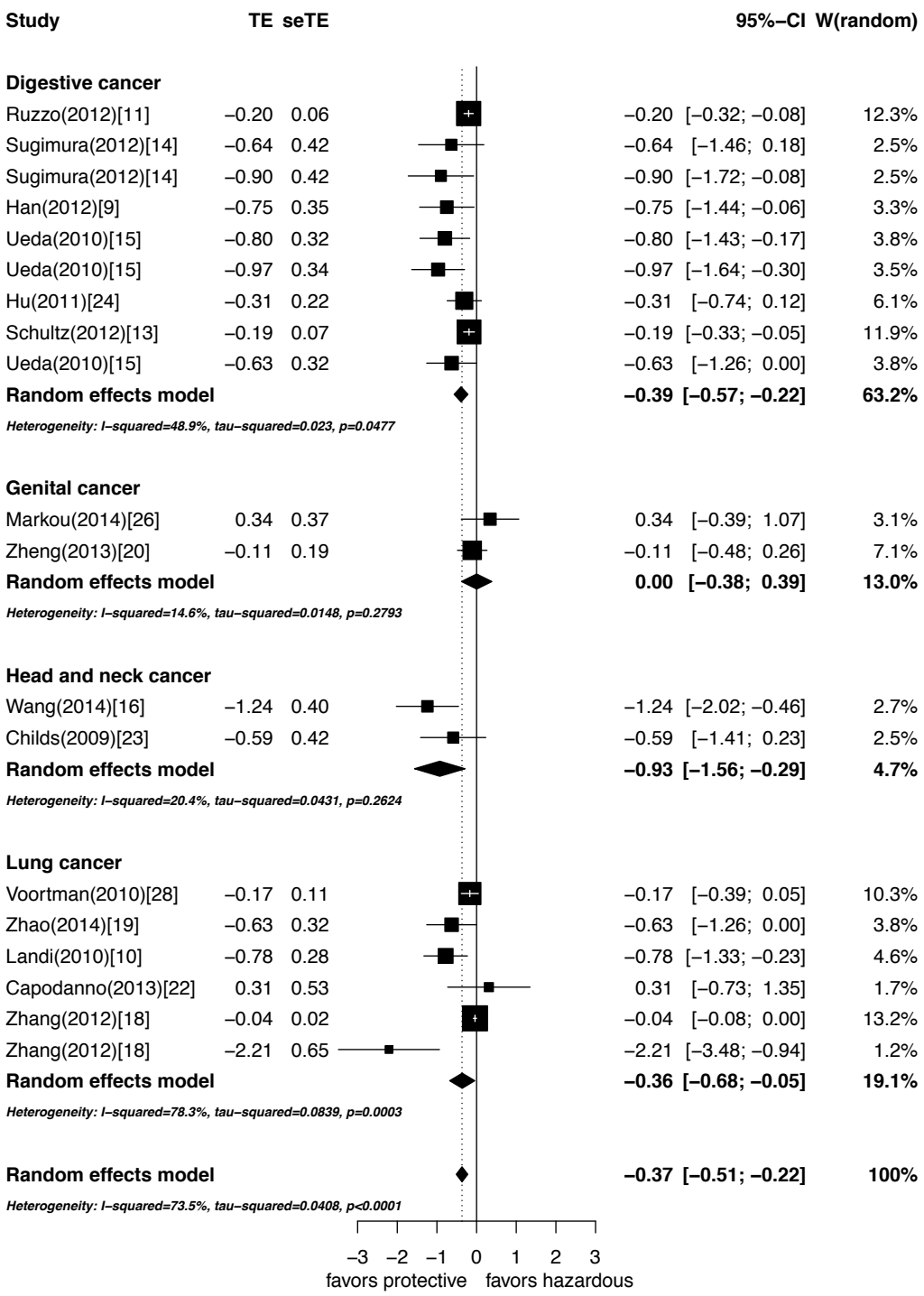

Figure 3. Forest plot of subgroup analysis (cancer type) for effect of high let-7 expression on OS in patients with cancer. Results are presented as individual and pooled lnHR and 95% CI. lnHR: natural logarithm of hazard risk; selnHR: standard error of lnHR; CI: confidence interval.

Our analysis included 4048 patients, ranging from 51–638 patients per study. Sixteen articles (20 studies and 2644 patients) investigated the relationship between let-7 expression and OS, and ten articles (11 studies and 1404 patients) investigated the relationship between let-7 expression and DFS.

All studies were retrospective. Let-7 expression was detected by quantitative real-time polymerase chain reaction (qRT-PCR) in tissue samples; three studies used qRT-PCR in plasma or serum samples. Among these studies, 12 articles (13 studies) directly reported the HR and 95% CI. These essential statistical variables were calculat-

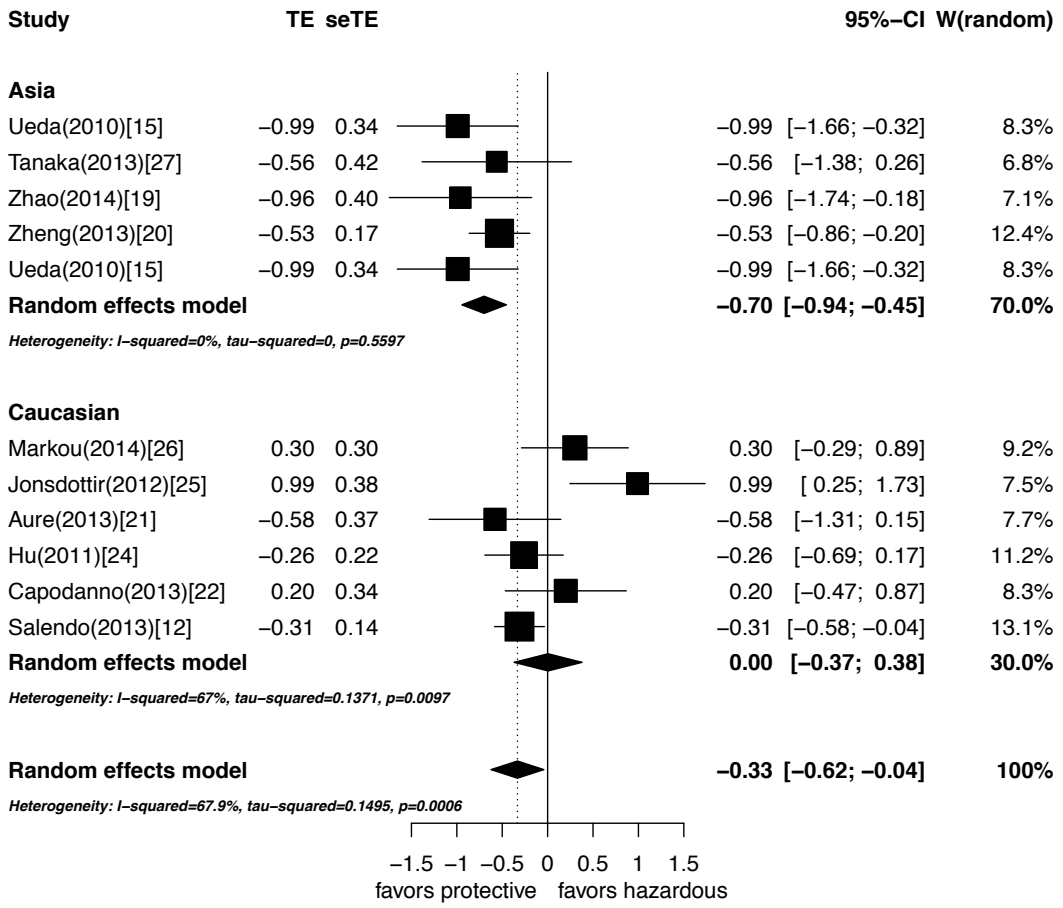

Figure 4. Forest plot of subgroup analysis (origin of population) for effect of high let-7 expression on DFS in patients with cancer. Results are presented as individual and pooled lnHR and 95% CI. lnHR: natural logarithm of hazard risk; selnHR: standard error of lnHR; CI: confidence interval.

ed by survival curves in 5 studies, and were extrapolated with available numerical data in another 2 articles (3 studies). For one primary research paper, we received original data from the author. The data were summarized according to the publication date to investigate dynamic trends over time (Tables 1 and 2).

High let-7 expression and prognosis

A total of 16 articles (20 studies and 2644 patients) were included in the OS analysis (Table 1, Figure 2A) with significant heterogeneity ($p<0.0001$, $I^2=73.5\%$). Hence, a random model was applied for merging OS data. We discovered that patients with high let-7 expression had a significantly better OS (pooled HR=0.69, 95% CI 0.60–0.80, transformed from lnHR and its 95% CI; Figure 2A). Subgroup analysis in various cancer types showed that high let-7 expression led to a better OS (HR=0.68, 95% CI 0.57–0.80, transformed from lnHR and its 95% CI) in digestive cancer (Figure 3).

A total of 10 articles (11 studies and 1404 patients) focused on DFS (Table 2, Figure 2B), and among these studies, significant heterogeneity was observed ($p=0.0006$, $I^2=67.9\%$). A random-effects model was performed to calculate the pooled HR and 95% CI, and we discovered that patients with high let-7 expression had significantly better DFS than those with low let-7 expression (pooled HR=0.72, 95% CI 0.54–0.96, transformed from lnHR and its 95% CI; Figure 2B). We also conducted meta-regression and subgroup analysis by cancer type, origin of population, let-7 family, number of patients and survival type. The results showed that the origin of population ($p=0.005$) and survival type ($p=0.001$) significantly correlated with heterogeneity, whereas other factors did not (Table 3). Moreover, subgroup analysis revealed a significant relationship between high let-7 expression and DFS in studies with origin of population (pooled HR=0.50, 95% CI 0.39–0.64, transformed

Table 3. Meta-regression and subgroup analysis of the studies reporting the association of let-7 expression and disease-free survival

Stratified analysis	*No. of studies*	*No. of patients*	*Pooled lnHR(95% CI), Random*	*Meta-regression (p value)*	*Heterogeneity*	
					I^2 (%)	*p value*
Cancer type				0.312		
Digestive cancer	5	493	-0.52(-0.82,-0.22)		41.6	0.144
Genital cancer	4	762	0.01(-0.67, 0.70)		82.8	0.001
Lung cancer	2	149	-0.36(-1.50, 0.78)		79.5	0.027
Let-7 family				0.844		
Let-7a	1	112	0.30(-0.29, 0.89)		——	1
Let-7b	2	305	-0.01(-1.95, 1.93)		93.4	0.0001
Let-7c	2	158	-0.77(-1.34,-0.20)		0	0.490
Let-7e	1	86	-0.58(-1.31, 0.15)		——	1
Let-7f	1	360	-0.53(-0.86,-0.20)		——	1
Let-7g	4	383	-0.33(-0.67, 0.02)		52.4	0.098
No. of patients				0.721		
>100	6	1006	-0.28(-0.73, 0.17)		80.3	0.0001
<100	5	398	-0.38(-0.73,-0.02)		30.4	0.219
Origin of population				0.003		
Asian	5	720	-0.70(-0.94,-0.45)		0	0.560
Caucasian	6	684	0.00(-0.37, 0.38)		67	0.010
Survival type				0.0003		
DFS	9	1088	-0.49(-0.71,-0.27)		35.9	0.131
DFI/DMFS	2	316	0.61(-0.07, 1.28)		50.8	0.154

DFS: disease-free survival, DFI: disease-free interval, DMFS: distant metastasis free survival, HR: hazard ratio

from lnHR and its 95% CI; Figure 4), and in studies with survival type (pooled HR=0.61, 95% CI 0.49–0.76, transformed from lnHR and its 95% CI; Figure 5). Subgroup analysis on other factors such as let-7 type, number of patients, and cancer type (Figures 6-8) did not change the significant prognostic impact of upregulated let-7 expression.

Publication bias and sensitivity analysis

We evaluated publication bias for both OS and DFS by funnel plots and Egger's tests, respectively. The p values from the Egger's test were 0.000 for OS and 0.9147 for DFS. Therefore, publication bias was supposed to exist for OS, whereas there was no proof of significant publication bias in the meta-analysis of DFS. Sensitivity analysis revealed that deleting any single study did not significantly affect the pooled HRs.

Discussion

This meta-analysis aimed to assess the relationship between high let-7 expression and the prognosis of cancer patients. Our analysis included the outcomes of 4048 cancer patients from 31 individual studies, and suggested that varied let-7 expression was associated with the OS (HR=0.68, 95% CI 0.59–0.79) and DFS (HR=0.72, 95% CI 0.54–0.96) of cancer patients. We observed significant heterogeneity of the included studies on both OS (p<0.0001, I^2=73.5%) and DFS (p=0.0006, I^2=67.9%). In sensitivity analysis, the heterogeneity was not reduced through eliminating any individual study, which did not help to elucidate the source of heterogeneity. Meta-regression and subgroup analysis indicated that the origin of population and survival type might separately account for part of the inter-study heterogeneity. Concerning the origin of population, subgroup analysis indicated that high let-7 expression was significantly correlated with better prognosis in the Asian population (HR=0.50, 95% CI 0.39–0.64). Since the characteristics of cancer in different regions may vary because of diverse environmental factors and genetic and epigenetic backgrounds, the prognostic value of biomarkers such as high let-7 expression in cancer might differ in different study locations. In addition, a previous study [37] confirmed that gefitinib has better therapeutic effect and leads to better survival outcomes among the Asian population; however the mechanism by which this occurs is still unknown. Our results

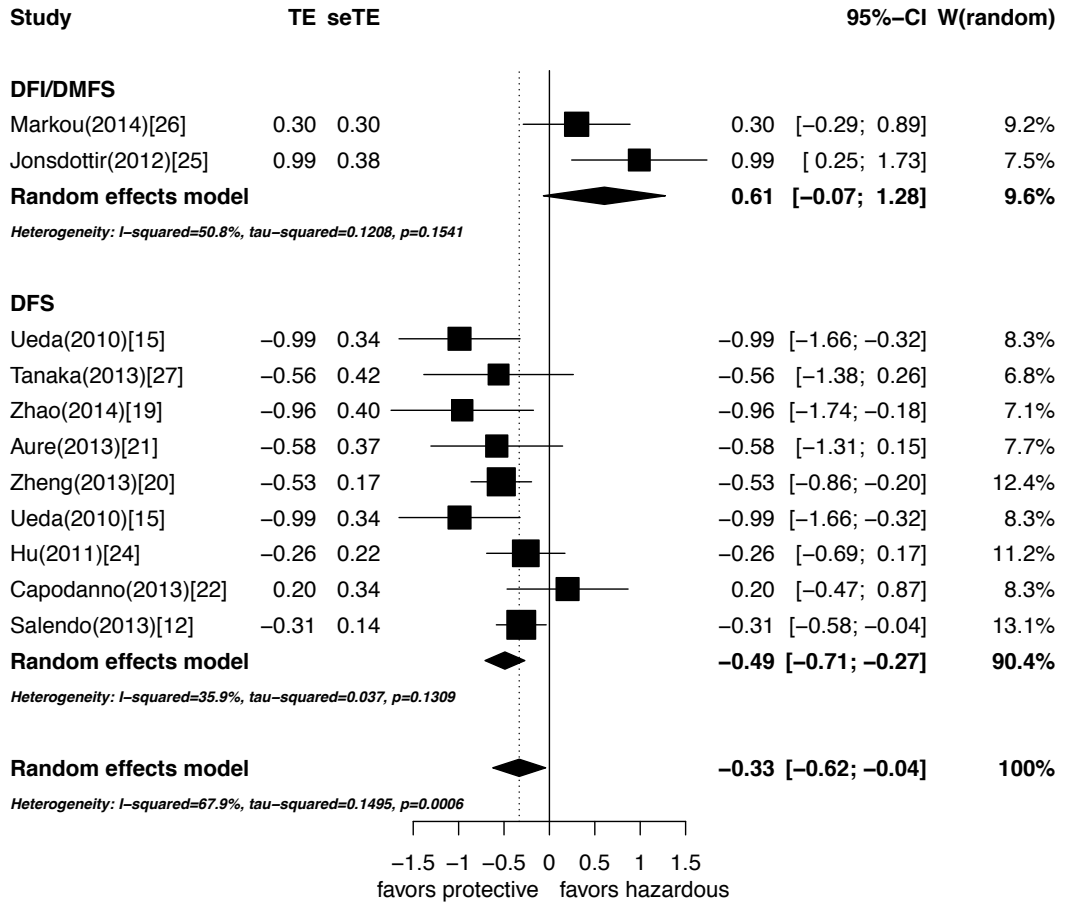

Figure 5. Forest plot of subgroup analysis (survival type) for effect of high let-7 expression on DFS in patients with cancer. Results are presented as individual and pooled lnHR and 95% CI. lnHR: natural logarithm of hazard risk; selnHR: standard error of lnHR; CI: confidence interval.

suggest that gefitinib may have some relationship with let-7, but further studies are needed to confirm this theory. Our findings suggest that let-7 not only functions as a biomarker for cancer prognosis, but may also give insight into the type of cancer therapy that will be most beneficial. For survival type, subgroups of disease-free interval (DFI) and distant metastasis free survival (DMFS) showed strong heterogeneity (p=0.154, I^2=50.8%), because the two articles [25,26] did not give clear definitions of DFI and DMFS, which may have led to potential differences in DFS. More clinical studies should be done to further demonstrate the prognostic value of let-7 expression in cancer patients worldwide.

The let-7 family primarily participates in physiological development, muscle formation, cell adhesion, and gene regulation. Let-7 family members also strongly and directly regulate multiple oncogenes, including RAS, HMGA2, and MYC in cultured human cells. LIN-28 functions as an RNA-binding protein that may inhibit processing of the let-7 precursor, leading to a reduction in let-7 expression. In addition, let-7 family members can control the cell cycle by targeting genes such as CDC25A, CDK6, and cyclin D1 [38].

Our study had several strengths. First, compared to previous studies with inadequate statistical power, our analysis included a sufficient number of cases and participants, which strengthened the statistical power and generated an accurate and reliable assessment. Second, more than 50 studies were included in this meta-analysis, which allowed the avoidance of bias due to a small sample size. Third, our findings that high let-7 expression significantly correlates with a better prognosis in the Asian population also supports the theory that high let-7 expression may play a key role in gefitinib treatment in cancer, which might have clinical significance. Finally, we explain the source of heterogeneity using meta-regression and subgroup analysis.

There were also several limitations to this meta-analysis. The let-7 samples were not uni-

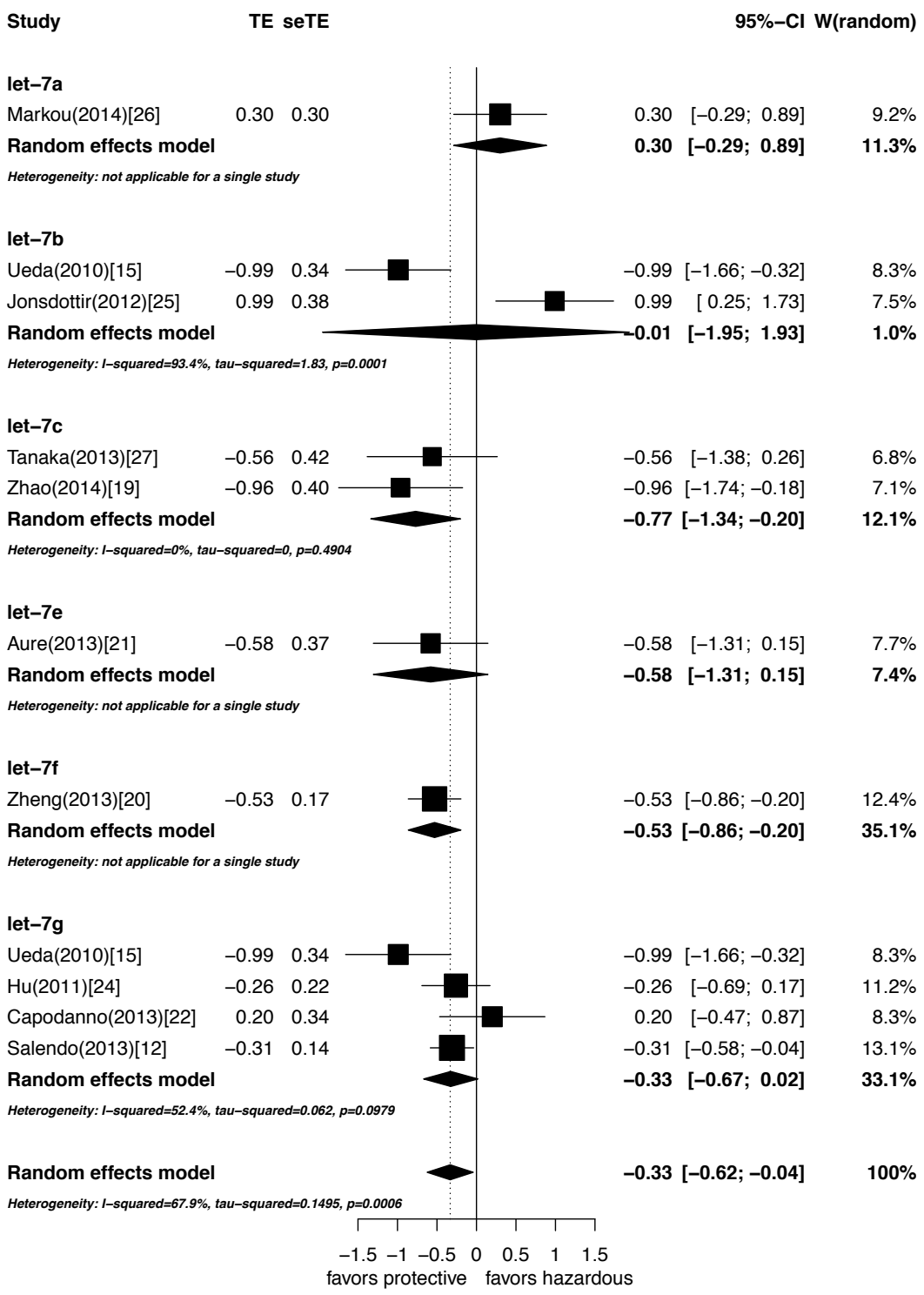

Figure 6. Forest plot of subgroup analysis (let-7 type) for effect of high let-7 expression on DFS in patients with cancer. Results are presented as individual and pooled lnHR and 95% CI. lnHR: natural logarithm of hazard risk; selnHR: standard error of lnHR; CI: confidence interval.

form, as some samples were from tissues and others were from plasma, and the storage methods also differed (i.e., frozen and FFPE). Moreover, the qRT-PCR primers applied and let-7 promoter regions detected by the studies were not identical, which could affect the sensitivity and specificity of qRT-PCR. Subgroup analysis did not explain this technical issue, since the small groups of studies used identical primers and other qRT-PCR circumstances. Furthermore, because there is not an optimal threshold for qRT-PCR , the cutoff of let-7 expression differs by cancer type, which may lead to a certain degree of heterogeneity. Another potential factor leading to bias was the approach

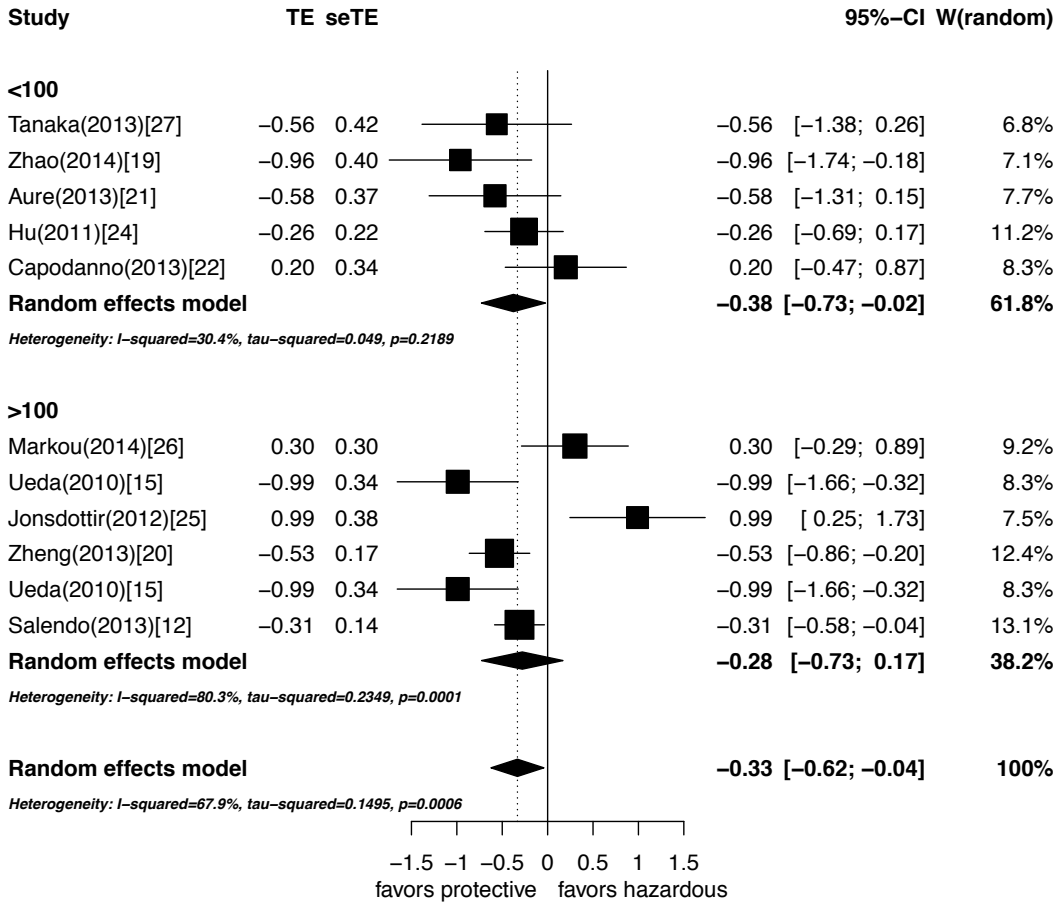

Figure 7. Forest plot of subgroup analysis (number of patients) for effect of high let-7 expression on DFS in patients with cancer. Results are presented as individual and pooled lnHR and 95% CI. lnHR: natural logarithm of hazard risk; selnHR: standard error of lnHR; CI: confidence interval..

of extrapolating the HRs from studies. We calculated HRs depending on the data provided in the studies, or extrapolated the information from the survival curves, when they were not directly reported in the studies; thus, we cannot completely eliminate possible imprecision. However, we did not discover any primary deviation in the publications when comparing our extracted HRs and 95% CIs with the outcomes in the published studies. In addition, studies with different follow-up times could also lead to bias.

Publication bias between the relationship between let-7 family expression and OS has been shown on Egger tests and funnel plots. To the best of our knowledge, studies that do not generate statistically significant outcomes are difficult to be published, and even if these outcomes are published, they are difficult to find and are rarely available for analysis. Moreover, we also know that the studies with positive results tend to be published in the English language [35]. In this analysis, only fully published studies and studies in English were included; we excluded unpublished studies and articles like reviews and conference abstracts, because data from those kinds of articles could not be used for methodological assessment and meta-analysis. We performed a complete literature search for eligible studies to minimize possible bias, and the large sample of cancer patients included in this analysis also guaranteed the reliable outcome.

Conclusions

Despite the limitations of our study, this meta-analysis indicated that high let-7 expression is a prognostic factor for better OS and DFS in cancer patients, with particularly better DFS among the Asian population. These data suggest that clinicians should treat patients with low let-7 expression more carefully and follow up in such patients should be more close. Future studies in a large-scale population are needed to determine if let-7 expression can be used as a predicative bi-

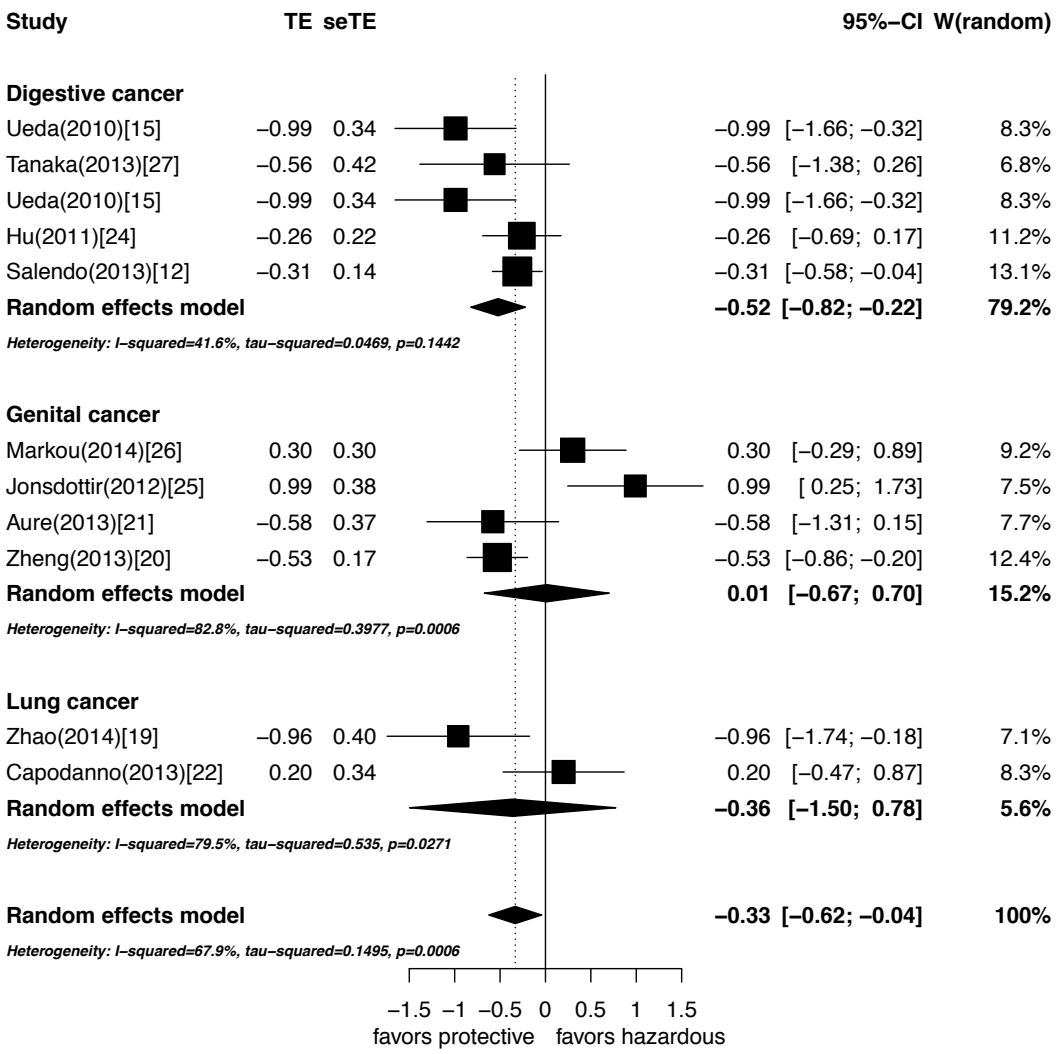

Figure 8. Forest plot of subgroup analysis (cancer type) for effect of high let-7 expression on DFS in patients with cancer. Results are presented as individual and pooled lnHR and 95% CI. lnHR: natural logarithm of hazard risk; selnHR: standard error of lnHR; CI: confidence interval.

omarker for clinical assessment among different ethnicities and regions.

Acknowledgements

We appreciate the help of Dr. Christoph Kahlert of the Surgery Department, University of Heidelberg, Heidelberg, Germany and Dr. Jochen of University Medical Center, Gottingen, Germany for providing original data.

This work was supported in part by the Chinese National Foundation of National Sciences grants (No.81172198, No.81372485 and No. 81302023), Fund of the Education Department of Liaoning Province (No. L2012278).

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