The prognostic relevance of 14-3-3ξ expression in cancers: A meta-analysis

Caihong Li, Honglan Zhu, Changlu Liu, Ya Liu, Ting Huang, Daishun Liu

Abstract

Objective: To gain an enhanced understanding of the prognostic importance of 14-3-3ξ levels in cancer patients.

Methods: The meta-analysis and systematic review was conducted in October 2019. Two reviewers independently reviewed Web of Science, Embase and PubMed databases to identify published studies using relevant key words. The correlation between the level of 14-3-3ξ and cancer patient survival was assessed based upon pooled hazard ratios and 95% confidence intervals derived from the selected studies. Data was analysed using STATA 12.

Results: Of the 244 studies initially identified, 22(9%) were included, and they comprised 2,676 patients. Elevated 14-3-3ξ level correlated significantly with poorer overall survival (hazard ratio: 1.93; 95% confidence interval: 1.42-2.61) in cancer patients. With respect to disease-free survival, the pooled hazard ratio for cancer patients expressing high levels of 14-3-3ξ was 1.89 (95% confidence interval: 1.56-2.30). Patients with elevated 14-3-3ξ expression also exhibited reduced cancer-specific survival (hazard ratio: 3.47; 95% confidence interval: 2.12-5.69).

Conclusions: Higher level of 14-3-3ξ correlated with poorer patient prognosis in a range of cancer types.

Keywords: Meta-analysis, Prognosis, 14-3-3 proteins. (JPMA 71: 1206; 2021)

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Introduction

Cancer is one of the primary causes of global deaths, with over 18.1 million diagnoses and 9.6 million deaths worldwide in 2018 alone.[1] Appropriate treatment and management of cancer are dependent upon detecting the disease in its early stages and determining the optimal treatment strategy, with such determinations being dependent upon identifying the markers specifically associated with patient prognosis.[2] The identification of novel tumour-associated biomarkers that allow for the sensitive and specific analysis of patient prognosis is therefore essential.

Tryptophan 5-Monooxygenase/Tyrosine 3-Monooxygenase Activation (14-3-3) protein family members are known to interact with a broad range of target proteins, thus allowing them to regulate key cellular processes, including survival, proliferation and migration. During the cell cycle, a variety of protein kinases and phosphatases that transition from G2 (Gap2) to M (Mitosis) phase are regulated by 14-3-3, and, in addition, in apoptosis, 14-3-3 can interact with the BH3 (Bcl-2 homology 3) domains on the apoptosis-associated proteins Bad and Bax to exhibit anti-apoptotic properties.[3,4] Seven different 14-3-3 strains were detected in mammals; beta (β), sigma (σ), gamma (σ), zeta (ξ), epsilon (ε), eta (η) and tau (τ).[5] They are encoded by different genes and these genes are located on different chromosomes. For example, the gene encoding 14-3-3ξ is located at chromosome 8q22.3 and the gene encoding 14-3-3γ is located at chromosome 7q11.23.[6,7] Of these genes, 14-3-3ξ, also called YWHAZ, has been shown to suppress the onset of apoptotic cell death and to promote cellular proliferation, adhesion and survival in several cancer types.[8] Over-expression of 14-3-3ξ has been shown to lead to oncogene activation, which has the potential to result in poorer survival in a range of cancers.[8]

Elevated 14-3-3ξ expression has been linked to a poorer patient prognosis in lung, tongue, ovarian, breast and gastric cancers.[9-13] However, a high-level overview of the prognostic relevance of 14-3-3ξ expression across a range of cancer types is not currently available.[14,15] The current meta-analysis and systematic review was planned to assess the relevance of prognosis of 14-3-3ξ in cancer patients.

Materials and Processes

The meta-analysis and systematic review was conducted in October 2019, and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16] Two reviewers independently searched Embase, PubMed and the Web of Science databases for all the published articles in order to identify studies for inclusion. Search terms included "14-3-3ξ or 14-3-3 zeta or YWHAZ or Tryptophan 5-Monooxygenase Activation Protein zeta / Tyrosine 3-Monooxygenase" and "tumour or carcinoma or cancer or neoplasm or malignancy or tumour" and "survival or prognosis or prognostic." The references of all previous reviews and

Department of Respiratory, The Third Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, China.

Correspondence: Daishun Liu. Email: ldslwtg@126.com

pertinent articles were also manually reviewed to identify any additional studies eligible for inclusion.

Criteria for study selection: Study inclusion criterion had three elements: (1) level of 14-3-3ξ was estimated in tumour specimens; (2) studies evaluated 14-3-3ξ and its relation with overall survival (OS), disease-free survival (DFS), or progression-free survival (PFS), or cancer-specific survival (CSS); and (3) the studies included sufficient information to allow for 95% confidence interval (CI) and hazard ratio (HR) estimation based on 14-3-3ξ expression. the exclusion criterion had four elements: (1) case reports, commentaries, expert opinions, letters, meeting records, reviews and non-human trials; (2) studies that were duplicates; (3) studies lacking the information necessary to calculate HRs and 95% CIs; and (4) sample size <40. The reviewers independently conducted title and abstract review to identify irrelevant studies which were then subjected to full-text review in order to further assess their relevance to the present meta-analysis. All disagreements were resolved via consensus.

Data extraction: The reviewers used a predesigned data-abstraction form to independently derive the following pieces of data from the included studies: last name of the first author, publication date, study location, cancer type, sample size, mean or median age, gender distribution, tumour stage, method of 14-3-3ξ quantification, 14-3-3ξ cut-off value, and HRs with 95 CIs for OS, CSS, DFS and/or PFS. If both univariate and multivariate analyses were used to evaluate data in a given study, the latter was used for the present meta-analysis. When HRs were not directly provided in a given study, they were calculated via Tierney's method[17] following the extraction of relevant survival data from Kaplan-Meier curves or other sources using Engauge Digitizer v.5.1.

Quality assessment: The reviewers independently and systematically assessed study quality as per the recommendations of Strengthening the Reporting of Observational studies in Epidemiology (STROBE).[18] Articles were score-based study design, tumour stage, cut-off values, outcome assessment definitions, clearly defined 14-3-3ξ measurements, the consideration of potential confounding factors in multivariate analyses, follow-up duration, bias, and limitations. Possible quality scores ranged 0-8, with all eligible studies in the present meta-analysis scoring 5-8. Each of these studies was therefore included in subsequent analyses.

Statistical analysis: Elevated 14-3-3ξ expression was determined in the light of the cut-off values used in individual articles. How 14-3-3ξ expression was related to cancer patient survival was assessed using pooled HRs and 95% CIs. HR values >1 was consistent with patients in the high level of 14-3-3ξ group having a prognosis worse than before compared to patients expressing lower levels of this gene, whereas the opposite was true for HR values <1. Among the studies, heterogeneity was evaluated by Cochran's Q test as well as the I-squared statistic.[19] When heterogeneity was significant ($p \leq 0.05$ or $I^2 \geq 50\%$), the model of random effects was employed. In any other case, fixed effects models were used. STATA v12.0 was used for all statistical analysis. $P<0.05$ was considered significant.

Results

Of the 244 studies initially identified, 22(9%) were included, and they comprised 2,676 patients (Figure-1). A summary of the basic characteristics of these 22 studies, published between 2007 and 2019, was prepared (Table-1). The

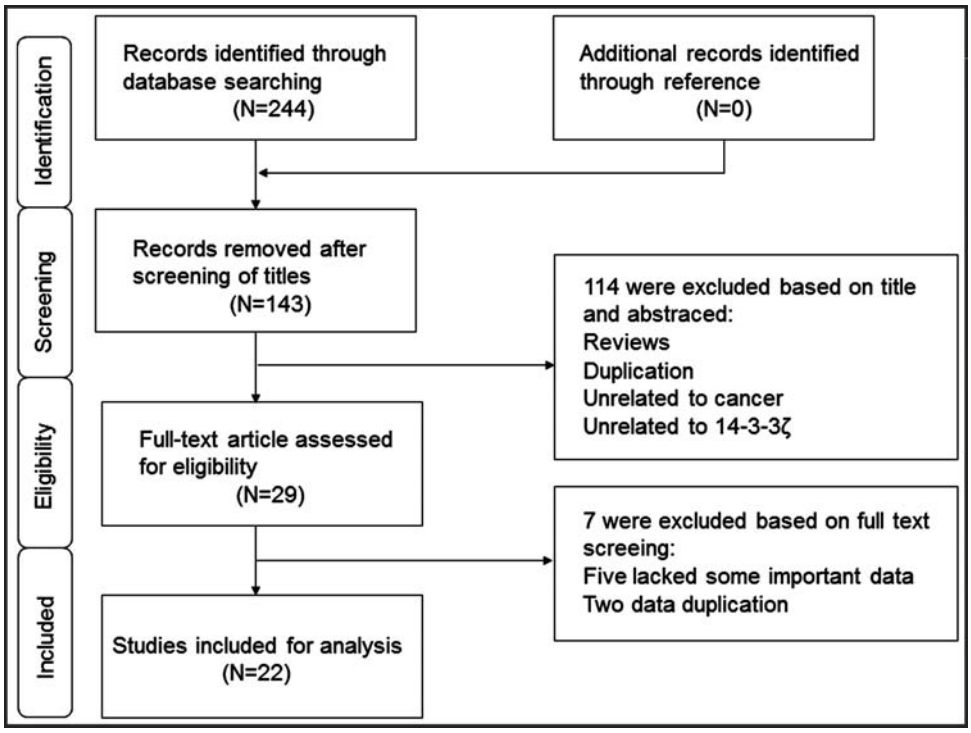

Figure-1: The study flowchart.

Table-1: Characteristics of eligible studies.

Study	Year	Country	Cancer	Study design	Cases	Age	Sex (M/F)	Stage	Sample	Test method	Cut-off value	High expression n(%)	Outcome measure	HR and 95%CI	Multivariate analysis
Fan[10]	2007	China	Lung	P	148	NA	89/59	TNM I	Tissue	IHC	IHC>10%	94(63.5%)	OS,CSS	SC	No
Jin[11]	2016	China	Tongue	P	42	Median 58.7	25/17	Grade I-III	Tissue	IHC	score ≥2	26(61.9%)	OS	SC	No
Kim[12]	2018	Korea	Ovarian	P	88	53(24-78)	NA	Grade I-III	Tissue	IHC	score ≥3	47(53.4%)	OS,DFS	SC	No
Neal[13]	2009	China	Breast	R	121	50.6(25-81)	NA	Grade I-III	Tissue	IHC	score ≥3	51(42.1%)	OS,DFS	report	Yes
Nishimura[9]	2013	Japan	Gastric	R	141	Mean 63	94/47	TNM I-III	Tissue	IHC	score ≥4	72(51.1%)	OS	report	Yes
Ruenauver[35]	2014	Germany	Prostate	P	213	Median 64	NA	T T1-PT4	Tissue	IHC	Quartiles	54(25.4%)	OS	SC	No
Tang[23]	2018	China	Liver	P	200	NA	182/18	BCLC A-C	Tissue	IHC	Median	100(50%)	OS	report	Yes
Tong[20]	2018	China	Esophagus	R	77	NA	44/33	TNM I-III	Tissue	IHC	NA	39(50.6%)	DFS	report	Yes
Watanabe[21]	2016	Japan	Gastric	R	92	67(37-83)	71/21	TNM I-III	Tissue	IHC	score ≥2	42(45.7%)	OS,DFS	report	Yes
Zhao[27]	2016	China	Lung	P	81	NA	69/12.0	TNM I-IV	Tissue	IHC	score ≥2	45(55.6%)	OS,DFS	report	Yes
Zhao[28]	2014	China	Lung	P	209	NA	149/60	TNM I-IV	Tissue	IHC	IHC >40%	114(54.5%)	OS	SC	Yes
Zhang[24]	2015	China	Liver	R	120	NA	49/71	TNM I-IV	Tissue	IHC	score ≥2	46(38.3%)	OS	SC	No
Zhang[22]	2017	China	Gastric	P	178	NA	130/48	TNM I-IV	Tissue	IHC	score ≥3	118(66.3%)	OS	SC	No
Zang[29]	2010	China	Lung	P	110	60(30-76)	79/31	TNM I	Tissue	IHC	IHC>10%	68(61.8%)	OS	SC	No
Yu[36]	2019	China	Bladder	R	295	NA	216/79	TNM I-IV	Tissue	IHC	score ≥3	70(23.7%)	CSS	report	Yes
Yang[25]	2016	China	Liver	P	64	56.5(38-79)	NA	TNM I-IV	Tissue	IHC	score >4	36(56.3%)	OS	SC	No
Yang[34]	2011	China	Brain	R	47	43.6(24-71)	22/25	NA	Tissue	IHC	IHC >10%	35(74.5%)	OS	SC	No
Tong[26]	2016	China	Lung	P	61	NA	33/28	TNM I-IV	Tissue	IHC	Median	30(49.2%)	DFS	report	Yes
Shi[32]	2019	China	Ovarian	R	83	NA	NA	FIGO I-IV	Tissue	IHC	score ≥2	51(61.4%)	OS	SC	No
Li[30]	2018	China	Lung	R	105	NA	56/49	TNM I-III	Tissue	IHC	score ≥2	58(55.24%)	OS	report	Yes
Li[33]	2019	China	Brain	P	49	NA	27/22	Grade I-IV	Tissue	IHC	NA	18(36.7%)	DFS	report	Yes
Deng[31]	2019	China	Lung	P	152	NA	95/57	TNM I-IV	Tissue	IHC	scores>4	83(54.6%)	OS	report	Yes

M: Male. F: Female, P: Prospective, R: Retrospective, NA: Not available, TNM: Tumour-node-metastasis staging system, FIGO: International Federation of Gynaecology and Obstetrics staging system, BCLC: Barcelona Clinic Liver Cancer staging system, IHC: Immunohistochemistry, DFS: Disease-free survival, CSS: Cancer-specific survival, SC: Survival curve, OS: Overall survival, CI: Confidence interval, HR: Hazard ratio.

Table-2: Quality assessment of the 22 studies.

Study	Cohort design	Description eligibility criteria	Tumor stage described	Definition of cut-off value	Outcome assessment definition	Summarize follow-up time	Confounders factors considered in multivariate analysis	Limitations and bias considered	Quality Score (0-8)
Fan[10]	Yes	No	Yes	Yes	Yes	No	No	Yes	5
Jin[11]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	6
Kim[12]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	6
Neal[13]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Nishimura[9]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Ruenauver[35]	Yes	No	Yes	Yes	Yes	Yes	No	Yes	6
Tang[23]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
Tong[20]	Yes	No	Yes	No	Yes	No	Yes	Yes	5
Watanabe[21]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Zhao[27]	Yes	No	Yes	Yes	Yes	No	Yes	Yes	6
Zhao[28]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
Zhang[24]	Yes	No	Yes	Yes	Yes	No	No	Yes	5
Zhang[22]	Yes	No	Yes	Yes	Yes	No	No	Yes	5
Zang[29]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	6
Yu[36]	Yes	No	Yes	Yes	Yes	No	Yes	Yes	6
Yang[25]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	6
Yang[34]	Yes	Yes	No	Yes	Yes	Yes	No	Yes	6
Tong[26]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
Shi[32]	Yes	No	Yes	Yes	Yes	No	No	Yes	5
Li[30]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
Li[33]	Yes	No	Yes	No	Yes	No	Yes	Yes	5
Deng[31]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7

Table-3: Overall survival (OS) and disease-free survival (DFS) pooled hazard ratio (HR) in individual subgroups.

Subgroups	Outcome	Studies	Patients	HR(95%CI)	P-value	Model	Heterogeneity I^2(%)	P-value
All	OS	18	2194	1.93(1.42-2.61)	<0.001	Random	75.4%	<0.001
	DFS	2	569	1.89(1.56-2.30)	<0.001	Fixed	0.0%	0.897
	CSS	7	443	3.47(2.12-5.69)	<0.001	Fixed	24.7%	0.249
Tumour type								
Lung	OS	6	805	1.97(1.12-3.47)	0.019	Random	87.2%	<0.001
	DFS	2	142	2.01(1.35-3.00)	0.001	Fixed	0.0%	0.632
Digestive system	OS	6	985	1.79(1.04-3.08)	0.035	Random	79.6%	<0.001
	DFS	2	169	1.96(1.35-2.86)	<0.001	Fixed	0.0%	0.422
Others	OS	6	594	2.26(1.50-3.41)	<0.001	Fixed	0.0%	0.945
	DFS	3	285	1.81(1.37-2.38)	<0.001	Fixed	0.0%	0.567
Sample size								
>100	OS	11	1697	1.68(1.19-2.39)	0.003	Random	81.1%	<0.001
	DFS	1	121	2.45(1.06-5.67)	-	-	-	-
≤100	OS	7	496	2.61(1.86-3.66)	<0.001	Fixed	0.0%	0.478
	DFS	6	448	1.89(1.54-2.32)	<0.001	Fixed	0.0%	0.570
Analysis type								
Univariate	OS	11	1214	1.78(1.26-2.52)	0.001	Random	55.1%	0.014
	DFS	3	261	2.29(1.34-3.92)	0.002	Fixed	17.3 %	0.298
Multivariate	OS	7	980	1.78(1.11-2.85)	0.016	Random	82.9%	<0.001
	DFS	4	308	1.86(1.50-2.31)	<0.001	Fixed	0.0%	0.732
HR obtained method								
Reported	OS	6	771	1.80(1.02-3.20)	0.043	Random	85.5%	<0.001
	DFS	4	308	1.88(1.52-2.32)	<0.001	Fixed	0.0 %	0.692
Extrapolated	OS	12	1423	1.66(1.37-2.01)	<0.001	Fixed	46.9%	0.037
	DFS	3	261	2.29(1.34-3.92)	0.002	Fixed	17.3%	0.298

CSS: Cancer-specific survival, CI: Confidence interval.

studies assessed 22 cancer types; 7(31.8%) digestive cancer,[9,20-25] 7(31.8%) lung cancer 10,[26-31] 2(9%) ovarian cancer,[12,32] 2(9%) glioblastoma,[33,34] 1(4.5%) breast cancer,[13] 1(4.5%) squamous cell carcinoma (SCC) of the tongue,[11] 1(4.5%) prostate cancer,[35] and 1(4.5%) bladder carcinoma.[36] Overall, 21(95.5%) studies focussed on Asian patient cohorts, and 1(4.5%) focussed on a Caucasian cohort. Expression of 14-3-3ξ in these studies was assessed via immunohistochemistry (IHC) in all (100%) cases. OS was assessed as an endpoint in 18(82%) studies, while CSS was assessed in 2(9%) and DFS was assessed in 7(31.8%) studies. When the quality of the 22 studies was assessed, the mean quality score was found to be 6.23±1.02 (range: 5-8) (Table-2).

Prognostic relevance: A total of 18(82%) studies comprising 2,194(82%) of all the patients provided HRs for OS (Table-3). Owing to the heterogeneity among these studies at significant levels (I^2=75.4%, p<0.001), they were analysed using a random effects model, revealing elevated 14-3-3ξ expression to be significantly linked to worse OS (HR: 1.93, 95% CI: 1.42-2.61, p<0.001) (Figure-2A). Besides, 7(%)studies reported DFS results, with non-significant heterogeneity in their results (I^2: 0.0%, p=0.897), and they were assessed using a fixed effects model. The analysis revealed higher 14-3-3ξ expression to correspond to a poorer patient prognosis (HR: 1.89, 95% CI: 1.56-2.30, p<0.001) (Figure-2B). It was further observed that higher 14-3-3ξ levels were linked with poorer CSS (HR: 3.47, 95% CI: 2.12-5.69, p<0.001) (Figure-2C), which was determined using a fixed effects model based on the low heterogeneity between these 2 relevant datasets (I^2: 24.7%, p=0.249).

In subgroup analyses, when the studies were stratified according to tumour type, elevated 14-3-3ξ expression was in lung cancer was linked with both worse OS (HR: 1.97, 95% CI: 1.12-3.47, p=0.019) and DFS (HR: 2.01, 95% CI: 1.35-3.00, p=0.001), with significant heterogeneity in OS analyses (I[2=87.2%, p<0.001) (Figure-3). In addition, digestive system tumours showed elevated 14-3-3ξ expression to be linked with poorer OS (HR: 1.79, 95% CI: 1.04-3.08, p=0.035) in the light of significant statistical heterogeneity (I^2=79.6%, p<0.001). Further, digestive system tumours revealed higher 14-3-3ξ expression to correspond to poorer DFS (HR: 1.96, 95% CI: 1.35-2.86, p<0.001), and the relevant studies showed no heterogeneity (I^2=0.0%, p=0.422). All other tumour types were pooled into a single subgroup, showing elevated 14-3-3 expression to be significantly associated with

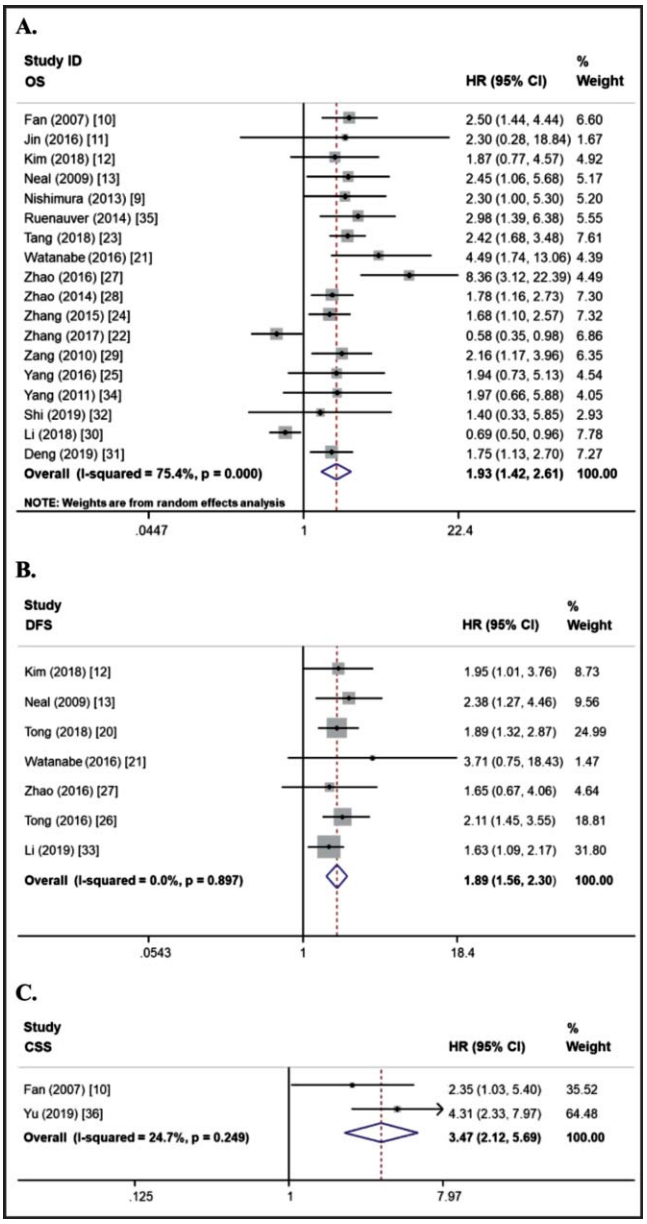

Figure-2: The relationship between elevated 14-3-3ξ expression and cancer patient survival, as assessed using forest plots. (A) Overall survival (OS), (B) Disease-free survival (DFS), and (C) Cancer-specific survival (CSS).

worsened OS (HR: 2.26, 95% CI: 1.50-3.41, p<0.001) and DFS (HR: 1.81, 95% CI: 1.37-2.38, p<0.001), with no significant between-studies heterogeneity (p>0.05).

In other subgroups, the relationship between elevated 14-3-3ξ expression and OS remained significant (p<0.05). This was true in studies with >100 participants (HR: 1.68, 95% CI: 1.19-2.39, p=0.003), <100 participants (HR: 2.61, 95% CI: 1.86-3.66, p<0.001), studies involving univariate analyses (HR: 1.78, 95% CI: 1.26-2.52, p=0.001), studies having conducted multivariate analyses (HR: 1.78, 95% CI:

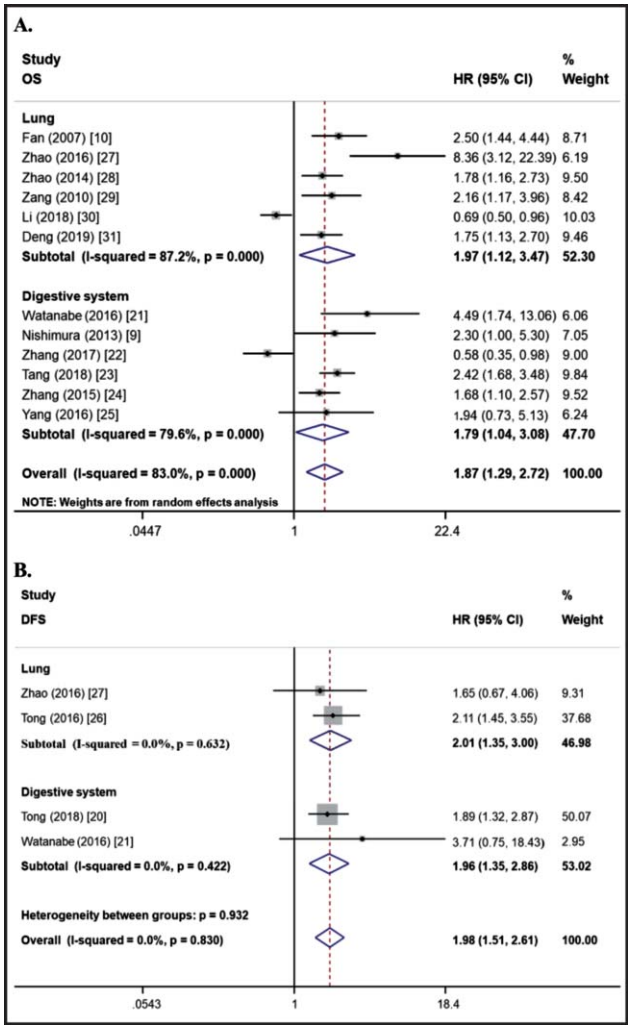

Figure-3: The relationship between elevated 14-3-3ξ expression and cancer patient survival in patients with lung and digestive system tumours, as assessed using forest plots. (A) Overall survival (OS), and (B) Disease-free survival (DFS).

1.11-2.85, p=0.016), studies with results reported in the text (HR: 1.80, 95% CI: 1.02-3.20, p<0.001), and studies for which data was extrapolated (HR: 1.66, 95% CI: 1.37-2.01, p<0.001). Likewise, the elevated 14-3-3ξ level also correlated with reduced DFS in studies with sample sizes <100 participants (HR: 1.89, 95% CI: 1.54-2.32, p<0.001), studies that conducted univariate analyses (HR: 2.29, 95% CI: 1.34-3.92, p=0.002), studies that conducted multivariate analyses (HR: 1.86, 95% CI: 1.50-2.31, p<0.001), studies with results reported in the text (HR: 1.88, 95% CI: 1.52-2.32, p<0.001), and studies where data was extrapolated (HR: 2.29, 95% CI: 1.34-3.92, p=0.002).

Sensitivity Analysis: The pooled HR for OS and DFS did not change significantly during the sensitivity analysis (Figure-4).

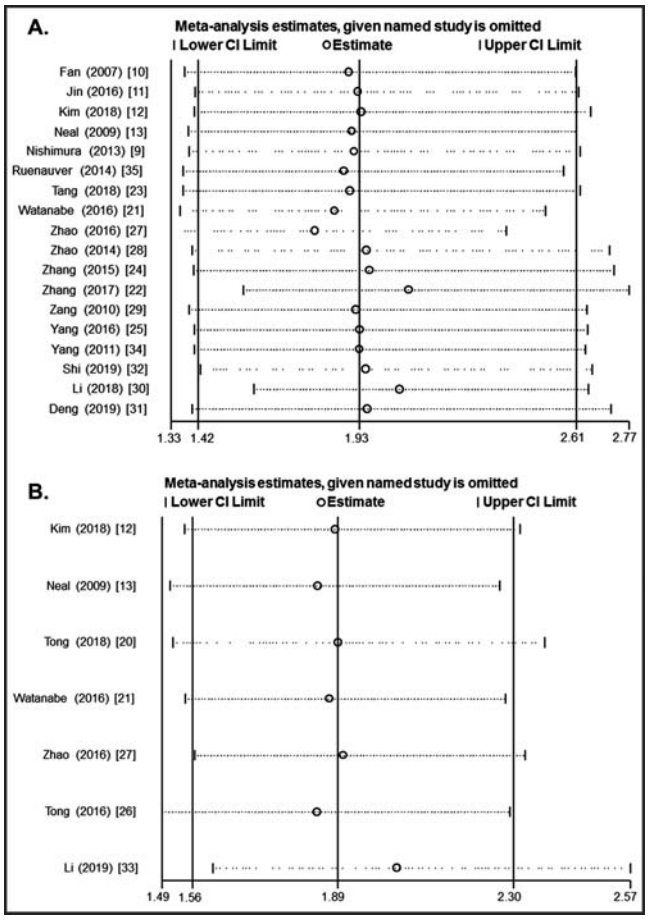

Figure-4: Sensitivity analysis assessing the relationship between the level of 14-3-3ξ and survival of cancer patients. (A) Overall survival (OS), and (B) Disease-free survival (DFS).

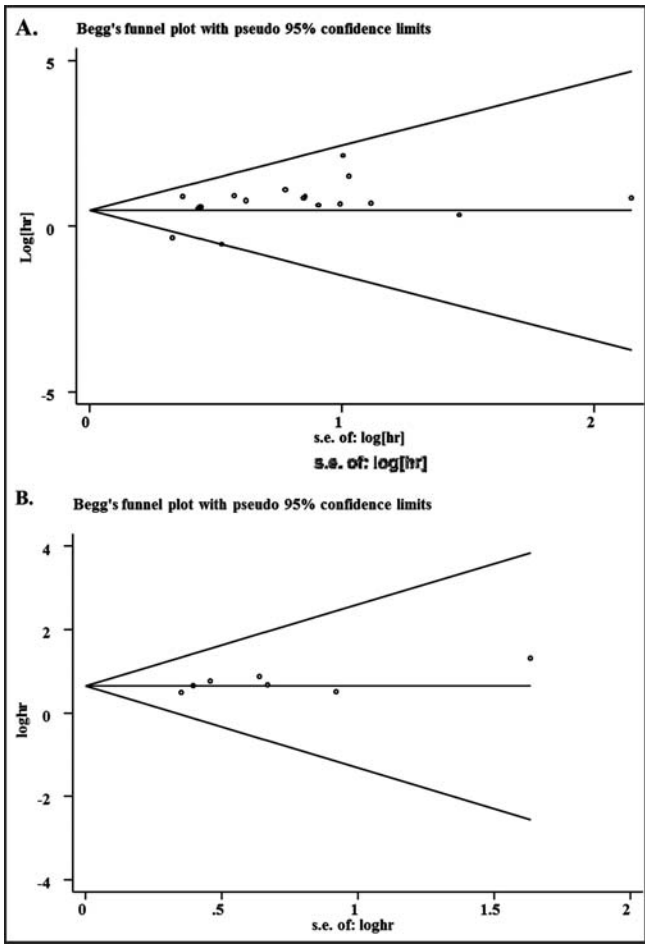

Figure-5: Assessment of publication bias using funnel plots. (A) Overall survival (OS), and (B) Disease-free survival (DFS).

Evaluation of publication bias: The studies reporting OS (Figure-5A) and DFS (Figure-5B) exhibited largely symmetrical funnel plots which were significant ($p<0.05$ each), indicating the absence of any significant bias in publication for the studies included in the current meta-analysis.

Discussion

The meta-analysis systematically assessed the relationship between elevated 14-3-3ξ expression and cancer patient prognosis. For OS, the overall pooled HR suggested that increased 14-3-3ξ level corresponded to a worse patient prognosis across a range of cancer types. In addition, elevated 14-3-3ξ expression was found to be linked to reduced DFS and CSS in cancer patients. Subgroup analyses further showed that higher levels of 14-3-3ξ were associated with poorer DFS regardless of tumour type, sample size, analysis type, or means of HR calculation. Similarly, levels of 14-3-3ξ were found to correspond to both worse OS and DFS in lung cancer, and the same was true for tumours of the digestive system.

Roles for 14-3-3ξ have been identified in a range of cellular processes, wherein it can drive proliferation, survival, migration and metastasis in many types of cancers.[13,15,20] Li et al. found that 14-3-3ξ was able to activate PI3K (phosphatidylinositol 3-kinase)/Akt (protein kinase B) signalling and to thereby regulate Snail activity, thus enhancing glioma cell migration.[33] Silencing of 14-3-3ξ led to enhanced caspase 3 activation and impaired cancer cell survival and migration, and enhanced level of 14-3-3ξ associated with tumour-node-metastasis (TNM)staging system stage, lymphatic metastasis of the patient, and poorer prognosis.[11] Similarly, 14-3-3ξ knockdown has also been shown to be linked to the migration, invasion and epithelial-to-mesenchymal transition of the cells of gastric cancer, with such knockdown being associated with impaired Wnt (wingless/integrated)/β-catenin signalling.[37] Kim et al. reported that patients with gastric carcinoma over-

expressing 14-3-3ξ were found to have poorer OS rates compared to patients who were not over-expressing 14-3-3ξ.[12] In addition, 14-3-3ξ expression was associated with lung SCC and lung adenocarcinoma cancer progression,[20,27] which is in line with the findings of the present meta-analysis. As such, these findings strongly suggest that elevated 14-3-3ξ expression correlates with a significantly poorer patient prognosis with many different cancer types.

Several recent studies have shown that 14-3-3ξ can inhibit tumour cell metastasis, and is thus associated with a better patient prognosis. For example, one study found that 35.7% of gastric cancer tissue samples expressed 14-3-3ξ levels which were lower than in paracancerous paired normal tissues.[22] Li et al. also found that stronger 14-3-3ξ staining was linked to both longer OS and greater differentiation, leading them to determine that enhanced level of this protein was correlated independently with OS in a multivariate analysis.[30] Liu et al. also found that over-expression of 14-3-3ξ was associated with a trend towards prolonged survival in bladder cancer in a study of the Cancer Genome Atlas database.[38] The results of these studies are in contrast with the findings of many previous reports[9-13] and with the outcomes of the present meta-analysis. These contrasting results may be because of the different tumour stages assessed when analysed individually. The simultaneous combined assessment of the expression of both 14-3-3ξ and other prognostic biomarkers may allow for the more accurate determination of patient prognosis. For example, one study found that microRNA-206 low/14-3-3ξ high expression had the poorest prognosis in NSCLC patients.[39] As such, future studies of such combined analytical approaches are warranted in order to improve the accuracy of 14-3-3ξ in terms of predicting cancer patient prognosis.

The current meta-analysis has several limitations. Many of the included studies had a relatively small sample size, thus potentially reducing the study effect. The cut-off values applied to determine whether or not the expression of 14-3-3ξ was elevated varied across studies, thus potentially influencing the validity of using 14-3-3ξ as a prognostic biomarker in cancer patients. Additionally, for some studies, HRs had to be calculated by digitally extracting data from survival curves, which may have introduced slight statistical variations into the results. Lastly, the number of studies evaluating 14-3-3ξ in many cancer types was limited, preventing us from, for example, assessing the specific importance of the level of 14-3-3ξ in bladder cancer, and, as such, the analysis may have led to an inaccurate over-estimation of the association between the level of 14-3-3ξ and cancer prognosis.

Conclusions

Enhanced 14-3-3ξ expression is possibly linked to poorer patient survival in a range of cancer types. However, as this meta-analysis is subject to many limitations, these results should be interpreted with caution. Further analyses are needed to confirm the current findings.

Disclaimer: None.

Conflicts of Interest: None.

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