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ORIGINAL ARTICLE

Prognostic value of the long noncoding RNA *AFAP1-AS1* in cancers*

Lixiu Zhu[1], Jiawen Yan[1] (Co-first author), Guoqiang Xu[1] (Co-first author), Qiaoli Wang[2] (Co-first author), Tianrui Xu[1], Ruixue Cao[1], Chuanzheng Sun[3] (✉), Yan Xi[3] (✉), Wei Xiong[1] (✉)

[1] Department of Radiotherapy, Yunnan Cancer Hospital, The Third Affiliated Hospital of Kunming Medical University, Kunming 650000, China
[2] Department of Radiotherapy, People's Hospital of Yuxi City, The Sixth Affiliated Hospital of Kunming Medical University, Yuxi 653100, China
[3] Department of Head and Neck Surgery, Yunnan Cancer Hospital, The Third Affiliated Hospital of Kunming Medical University, Kunming 650000, China

Abstract

Objective This meta-analysis explored whether the expression of actin filament-associated protein 1 antisense RNA 1 (*AFAP1-AS1*) is related to the prognosis and clinicopathological features of patients with cancer.

Methods PubMed, EMBASE, and Cochrane Library were systematically searched. Hazard ratios (HRs) with 95% confidence intervals (CIs) were used to assess the prognostic value based on overall survival (OS), disease-free survival (DFS), and progression-free survival (PFS). Odds ratios (ORs) with 95% CIs were used to determine the relationships between *AFAP1-AS1* and clinicopathological features, such as large tumor size (LTS), high tumor stage (HTS), poor histological grade (PHG), lymph node metastasis (LNM), and distant metastasis (DM).

Results Thirty-five eligible articles and 3433 cases were analyzed. High *AFAP1-AS1* expression, compared to low *AFAP1-AS1* expression, correlated with significantly shorter OS (HR = 2.15, 95% CI = 1.97–2.34, $P < 0.001$), DFS (HR = 1.37, 95% CI = 1.19–1.57, $P < 0.001$), and PFS (HR = 1.97, 95% CI = 1.56–2.50, $P < 0.001$) in patients with cancer. In various cancers, elevated *AFAP1-AS1* expression was significantly associated with LTS (OR = 2.76, 95% CI = 2.16–3.53, $P < 0.001$), HTS (OR = 2.23, 95% CI = 1.83–2.71, $P < 0.001$), and PHG (OR = 1.39, 95% CI = 1.08–1.79, $P = 0.01$) but not LNM (OR = 1.59, 95% CI = 0.88–2.85, $P = 0.12$) or DM (OR = 1.81, 95% CI = 0.90–3.66, $P = 0.10$).

Conclusion High *AFAP1-AS1* expression was associated with prognostic and clinicopathological features, suggesting that *AFAP1-AS1* is a prognostic biomarker for human cancers.

Key words: long noncoding RNA (lncRNA); actin filament-associated protein 1 antisense RNA 1 (*AFAP1-AS1*); prognostic; meta-analysis

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Cancer is an important factor that affects human health and is a leading cause of death worldwide. According to recent epidemiological statistics, there are an estimated 19.3 million new cancer cases and nearly 10.0 million cancer deaths worldwide each year [1]. Global cancer cases are expected to reach 28.4 million cases in 2040, an increase of 47% compared to that in 2020, which may further increase the economic burden [1]. With advancements in medicine and science, cancer deaths have decreased; however, the five-year survival rate is still inadequate. Although many studies have focused on biomarkers for cancer diagnosis and prognosis, the results have not been optimistic. Therefore, new prognostic biomarkers are needed to drive cancer development.

Long noncoding RNAs (lncRNAs), which are transcriptional regulatory factors that operate in cis or trans, are defined as transcripts that do not encode proteins of more than 200 nucleotides [2]. lncRNAs are associated

✉ Correspondence to: Chuanzheng Sun. Email: scz007@126.com; Yan Xi. Email: xiyan616@126.com; Wei Xiong. Email: panda_wei_wei@163.com
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with a variety of functions, such as the regulation of epigenetic, transcriptional, and post-transcriptional mechanisms [3–4]. Mounting evidence has shown that lncRNAs are dysregulated in various cancers and play important roles in invasion and metastasis, suggesting that lncRNAs may act as regulators of gene expression and affect tumor progression [5]. Several studies have shown that lncRNAs have multiple functions in many cellular processes that may play important roles in carcinogenesis and cancer progression. Evidence supporting the use of abnormally expressed lncRNAs as biomarkers of various human cancers has facilitated the development of lncRNA-based diagnostic tools and treatments.

Actin filament-associated protein 1 antisense RNA 1 (*AFAP1-AS1*), the antisense transcript of the *AFAP1* gene, has a length of 6810 bp and is located in the 4p16.1 region of the human genome [6]. *AFAP1-AS1*, originally identified in 2013, has been shown to be present in esophageal adenocarcinoma [7]. Previous studies have indicated that lncRNAs can be used as molecular markers of location, time, developmental stage, and gene expression regulation [8]. Among lncRNAs with upregulated expression in cancer, *AFAP1-AS1* plays a carcinogenic role in different human cancer cells as well as an important regulatory role. Studies have shown that in hepatocellular carcinoma (HCC), the knockout of *AFAP1-AS1* with an *si-AFAP1-AS1* construct can reduce proliferation and invasion *in vitro* and *in vivo*, induce apoptosis, and block the cell cycle in the S phase [9]. In addition, lncRNAs can be used as guides to recruit chromatin-modifying enzymes to target genes [8]. Furthermore, *AFAP1-AS1* recruited LSD1 to the promoter region of HBP1 and inhibited its transcription by mediating H3K4me2 demethylation [10]. A previous study showed that AFAP1 expression could be regulated by DNA methylation [11]. lncRNAs also function by interacting with various RNA-binding proteins, leading to the inactivation or activation of gene expression through chromosomal reprogramming, DNA methylation, RNA decay, and histone modification [12]. In particular, *AFAP1-AS1*, an oncogene, binds to *EZH2* to inhibit p21 transcription and promote tumor cell formation [12].

Notably, these lncRNAs have more functions than those of the aforementioned lncRNAs. Studies have shown that lncRNAs can interfere with transcriptional mechanisms and maintain the structure of nuclear spots [13]. In addition, lncRNAs may hybridize with DNA and affect chromatin. Furthermore, lncRNAs interact with chromatin proteins to promote or inhibit their binding and activity in target regions [14]. Unfortunately, to date, investigations of *AFAP1-AS1* have been insufficient, and the above functions have not yet been identified for this lncRNA. In addition, the basic mechanisms and related functions of *AFAP1-AS1* remain unclear.

AFAP1-AS1 is a well-known lncRNA that is overexpressed in several malignancies. *AFAP1-AS1* is involved in cell proliferation, angiogenesis, invasion, and metastasis of various cancers [15]. In addition, *AFAP1-AS1* can be used as a diagnostic marker for various cancers. Moreover, high expression of *AFAP1-AS1* is closely related to clinical prognostic indicators, including overall survival (OS) [16], disease-free survival (DFS) [17], and progression-free survival (PFS) [10]. A meta-analysis reported that the *AFAP1-AS1* expression level was associated with clinical outcomes, including survival, tumor size and stage, and histological differentiation [18]. As the literature included in this article has been updated, we performed a meta-analysis to evaluate the prognostic utility of *AFAP1-AS1* in patients with cancer in a clinical setting.

Methods

Literature search

We searched for relevant articles in the PubMed, EMBASE, and Cochrane Library electronic databases. The search terms were as follows: ((“Neoplasia” OR “Neoplasias” OR “Neoplasm” OR “Tumors” OR “Tumor” OR “Cancer” OR “Cancers” OR “Malignancy” OR “Malignancies” OR “Malignant Neoplasms” OR “Malignant Neoplasm” OR “Neoplasm, Malignant” OR “Neoplasms, Malignant” OR “Benign Neoplasms” OR “Neoplasms, Benign” OR “Benign Neoplasm” OR “Neoplasm, Benign” OR “acral tumor” OR “acral tumour” OR “embryonal and mixed neoplasms” OR “germ cell and embryonal neoplasms” OR “glandular and epithelial neoplasms” OR “hormone-dependent neoplasms” OR “neoplasia” OR “neoplasms” OR “neoplasms by histologic type” OR “neoplasms, cystic, mucinous, and serous” OR “neoplasms, embryonal and mixed” OR “neoplasms, germ cell and embryonal” OR “neoplasms, glandular and epithelial” OR “neoplasms, hormone-dependent” OR “neoplasms, post-traumatic” OR “neoplastic disease” OR “neoplastic entity” OR “neoplastic mass” OR “post-traumatic neoplasms” OR “tumor” OR “tumoral entity” OR “tumoral mass” OR “tumorous entity” OR “tumorous mass” OR “tumour” OR “tumoural entity” OR “tumoural mass” OR “tumourous entity” OR “tumourous mass”) OR (“Neoplasms”[Mesh])) AND ((“lncRNA-AFAP1-AS1, human” OR “AFAP1 antisense RNA, human” OR “long non-coding RNA AFAP1-AS1” OR “lncRNA AFAP1-AS1” OR “AFAP1-AS1” OR “AFAP1 antisense RNA 1” OR “actin filament-associated protein 1 antisense RNA1”) OR (“AFAP1-AS1 long noncoding RNA, human” [Supplementary Concept])). The search was conducted on November 21, 2020. To obtain potential eligible papers, we manually reviewed the reference lists to identify additional relevant articles.

Inclusion and exclusion criteria

The following inclusion criteria were used: (1) articles with histopathologically confirmed carcinoma; (2) articles in which the expression levels of *AFAP1-AS1* in tissues of cancer patients were determined; (3) articles in which patients were divided into two distinct groups, including high- and low-expression groups; (4) articles that statistically analyzed patient prognosis or clinicopathological features; and (5) articles written in English.

The following exclusion criteria were applied: (1) articles not related to carcinoma; (2) letters, expert opinions, case reports, editorials, and reviews; (3) studies with duplicate data; and (4) studies without usable data or data from animal experiments.

Data extraction and quality assessment

Two reviewers (Lixiu Zhu and Guoqiang Xu) independently searched the databases for eligible articles based on the inclusion and exclusion criteria. Tianrui Xu and Ruixue Cao evaluated the quality of the included studies. Information was independently extracted from the included studies by two operators (Jiawen Yan and Qiaoli Wang). Upon disagreement, three authors (Lixiu Zhu, Guoqiang Xu, and Jiawen Yan) discussed and resolved the issue. The following information was collected for each qualified article: first author's last name, year of publication, country, tumor type, sample size, detection method, reference gene, cutoff values, number of patients with large tumor size (LTS), high tumor stage (HTS), poor histological grade (PHG), lymph node metastasis (LNM), and distant metastasis (DM) between the high and low expression groups. For studies that did not provide hazard ratios (HRs) and 95% confidence intervals (CIs), widely proven and accepted scientific methods were used, and Engauge Digitizer 10.8 was used to extract data from the survival curve [19–20]. The data were entered into an HR calculation spreadsheet developed by Tierney *et al* [21]. The HRs, standard errors (SE), and corresponding 95% CIs were then estimated according to the curve.

The Newcastle-Ottawa Scale (NOS) was used to appraise the quality of the literature; this method adopts a "star" rating system, with the full credit of 9 stars. It is generally used to judge the quality of a methodology, including the selection (0–4 stars), comparability (0–2 stars), and results (0–3 stars) [22]. Articles with scores > 5 were considered high quality; other articles were considered low quality.

External validation

Transcriptome and clinical data of 33 tumors were downloaded from the UCSC Xena database (http://xena.ucsc.edu/). The data were collated and the expression levels of *AFAP1-AS1* in each neoplastic tissue were extracted. According to the median expression level of *AFAP1-AS1* in each tumor, each cohort was divided into high and low expression groups using R. Cox regression analysis was used to evaluate the relationship between *AFAP1-AS1* expression and OS, DFS, and PFS in patients with tumors. The results were presented as forest maps. Statistical significance was set at $P < 0.05$.

Statistical analysis

Review Manager version 5.4 and R version 4.1.1 were used for all statistical analyses. The combined HRs and 95% CIs were used to estimate the prognostic significance of *AFAP1-AS1* in terms of OS, DFS, and PFS in various cancers. Comprehensive odds ratios (ORs) and 95% CIs were used to estimate the association between *AFAP1-AS1* and clinicopathological features, such as tumor size and stage, histological grade, LNM, and DM. Heterogeneity between articles was detected by the I^2 test, and both $P < 0.1$ and I^2 values > 50% were considered to indicate obvious heterogeneity. Therefore, random- and fixed-effects models were selected to analyze the data according to heterogeneity. The OS, DFS, and PFS of patients with different types of tumors were analyzed using R, and HR values were calculated based on the Cox proportional hazards model. Additionally, publication bias was measured using Begg's funnel plots.

Results

Study selection

After searching the PubMed, Embase, and Cochrane Library databases, a total of 228 studies were found; 94 studies were deleted due to duplication, of which 88 were reclassified as unqualified by automatic tools and six were reclassified as unqualified by manual assessment. Further exclusions were made by reviewing the full texts of the remaining 134 articles. After examining the titles and abstracts, 58 irrelevant studies were excluded. Further, four articles could not be retrieved and were excluded. Next, 37 articles were excluded: six meta-analyses or reviews, 30 articles with incomplete data, and one article written in Chinese. Finally, we included 35 studies that met the criteria [9–10, 12, 16–17, 23-52], with a total of 3433 patients. The flow diagram is shown in Fig. 1.

Characteristics of the included studies

All the included studies were conducted in China between 2015 and 2020. Patient sample sizes in the 35 studies ranged from 30 to 256, with an average sample size of 143. In all but one [25], the expression of the lncRNA *AFAP1-AS1* was measured by real-time quantitative polymerase chain reaction (qRT-PCR) [9–10, 12, 16–17, 23–24, 26-52]. The genes used for the normalization of *AFAP1-AS1* expression were not consistent, and *U6* [27, 36, 45], *GAPDH*

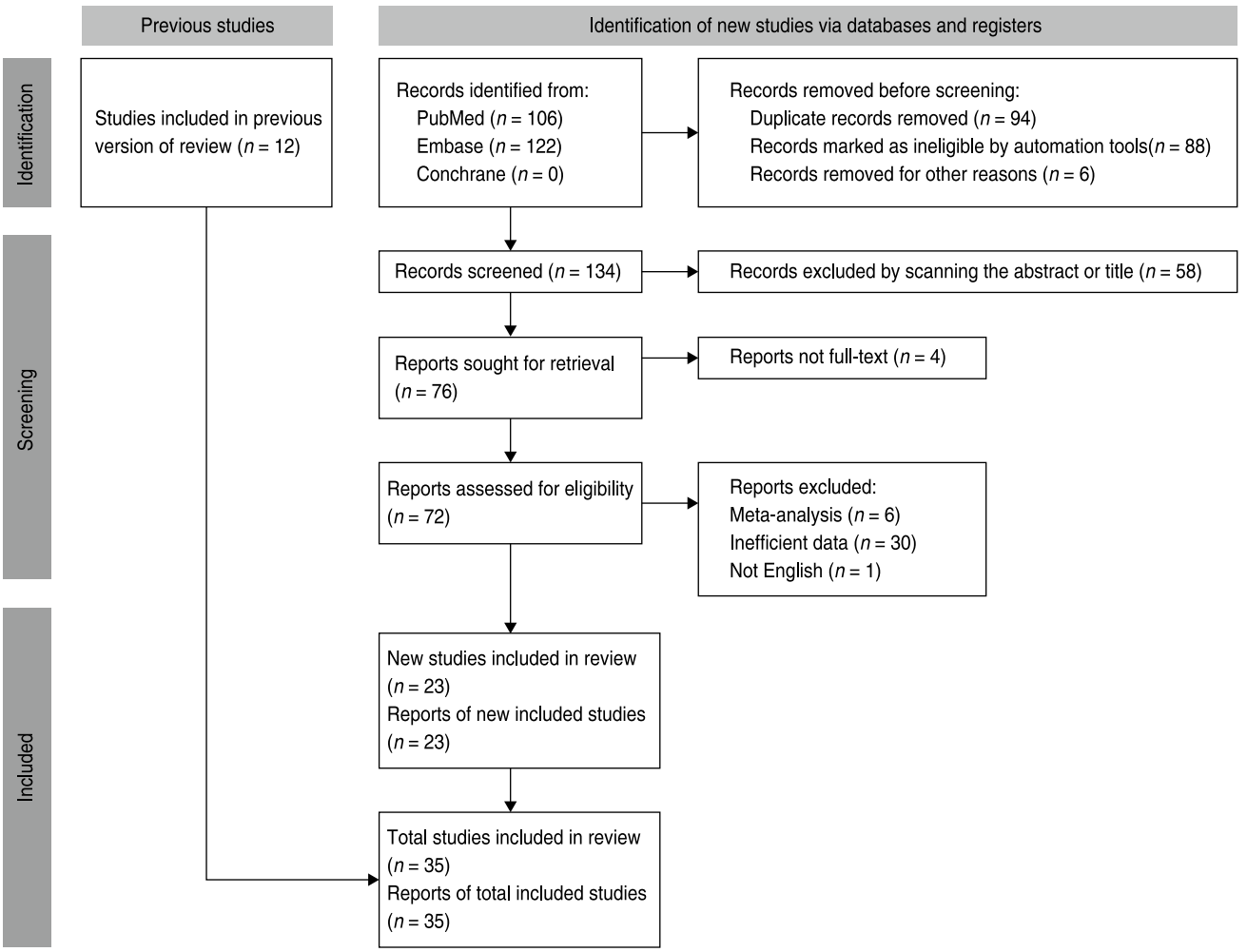

Fig. 1 Flowchart of the study search and screening in this meta-analysis

[9–10, 12, 16, 23–24, 26, 28–29, 33–35, 37–38, 40–41, 43–44, 46–51], *β-actin* [30–32, 39, 42, 52], and *HPRT1* [17] were used. The cutoff value was expressed in various forms; however, 13 studies did not provide a clear cutoff value. With regard to prognostic outcomes, OS was reported in 33 studies [9–10, 12, 16, 23–26, 28–32, 34–38, 40-46, 48, 50–52], DFS in six studies [17, 26, 32–33, 38, 42]; and PFS in four studies [10, 24, 30, 36]. In this meta-analysis, a total of 25 cancers were assessed: non-small cell lung cancer (NSCLC), endometrial carcinoma (EC), triple-negative breast cancer (TNBC), tongue squamous cell carcinoma (TSCC), prostate cancer (PCA), clear cell renal cell carcinoma (ccRCC), retinoblastoma (RB), bladder cancer (BCA), colon cancer (CC), lung adenocarcinoma (LUAD), esophageal squamous cell carcinoma (ESCC), lung cancer (LC), pancreatic ductal adenocarcinoma (PDAC), ovarian cancer (OC), gastric cancer (GC), colorectal cancer (CRC), gallbladder cancer (GBC), cholangiocarcinoma (CCA), nasopharyngeal carcinoma (NPC), breast cancer (BC), glioma, osteosarcoma (OS), HCC, thyroid cancer (TC), and pancreatic cancer (PC). The NOS score for the quality assessment of all studies ranged from 5 to 8, and the quality assessment achieved a good consensus between the two reviewers.

Association between *AFAP1-AS1* and prognosis

Association between AFAP1-AS1 and shorter OS

Of the 35 included studies, 33 reported prognosis in terms of OS according to *AFAP1-AS1* expression levels, with a total of 3141 patients. A fixed-effects model was used because of non-significant heterogeneity (I^2 = 12%, P_Q = 0.27). The pooled results showed that high expression of *AFAP1-AS1*, compared to low *AFAP1-AS1* expression, was associated with shorter OS (HR = 2.15, 95% CI: 1.97–2.34, Fig. 2).

Association between AFAP1-AS1 and shorter DFS and PFS

According to *AFAP1-AS1* expression levels DFS was reported for 978 patients in six articles and PFS was

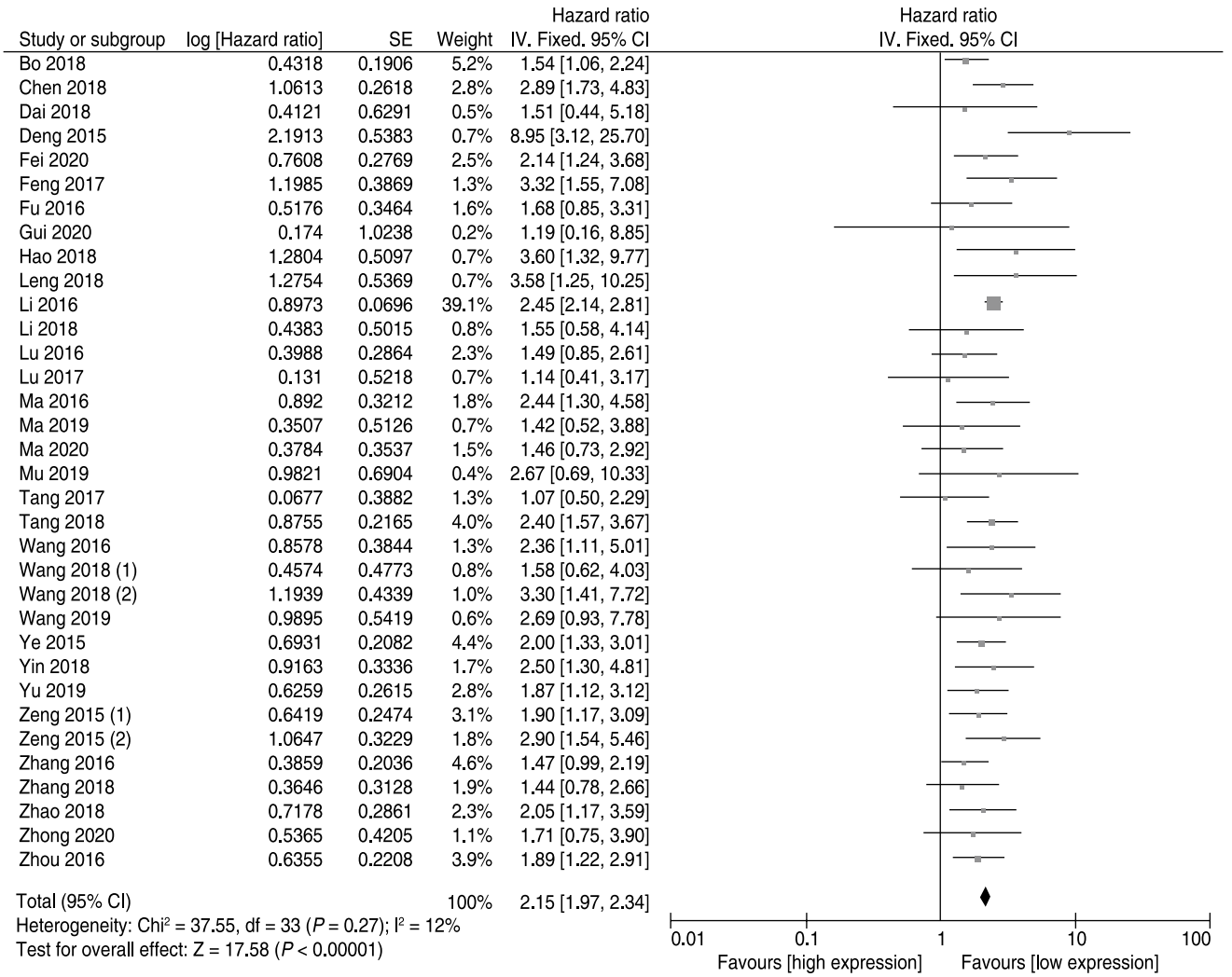

Fig. 2 Forest plot of HRs for the association between high *AFAP1-AS1* expression and OS

reported for 397 patients in four articles. There was no apparent heterogeneity among the studies (DFS: I^2 = 0%, P_Q = 0.51; PFS: I^2 = 0%, P_Q = 0.65); thus, a fixed-effects model was used to estimate the pooled HRs and the corresponding 95% CI values. These data indicated that the *AFAP1-AS1* expression level was associated with DFS (pooled HR = 1.37, 95% CI: 1.19–1.57, Fig. 3) and PFS (pooled HR = 1.97, 95% CI: 1.56–2.50, Fig. 4) in patients with various tumors.

Association between *AFAP1-AS1* and clinicopathological features

In this meta-analysis, 16 eligible studies with 1219 patients reported *AFAP1-AS1* expression levels according to LTS data. A fixed-effects model was adopted to account for the data because there was no apparent heterogeneity (I^2 = 17%, P_Q = 0.26). This analysis showed that there may be a significant positive association between the high expression level of *AFAP1-AS1* and LTS (OR = 2.76, 95% CI: 2.16–3.53, Fig. 5). Secondly, twenty-one eligible studies involving 1987 patients reported *AFAP1-AS1* expression levels according to HTS data. No obvious heterogeneity was detected (I^2 = 42%, P_Q = 0.02); therefore, a fixed-effects model was selected, and a pooled OR of 2.23 was obtained (95% CI: 1.83–2.71, Fig. 6). Fifteen eligible studies with 1339 patients reported *AFAP1-AS1* expression levels according to the histological grade. We selected a fixed-effects model because no significant heterogeneity was observed (I^2 = 45%, P_Q = 0.03). The integrated data suggested that elevated *AFAP1-AS1* expression predicted PHG in various cancers (OR = 1.39, 95% CI: 1.08–1.79, Fig. 7). Thirteen eligible studies with 1202 patients reported *AFAP1-AS1* expression levels in LNM. Because there was significant statistical

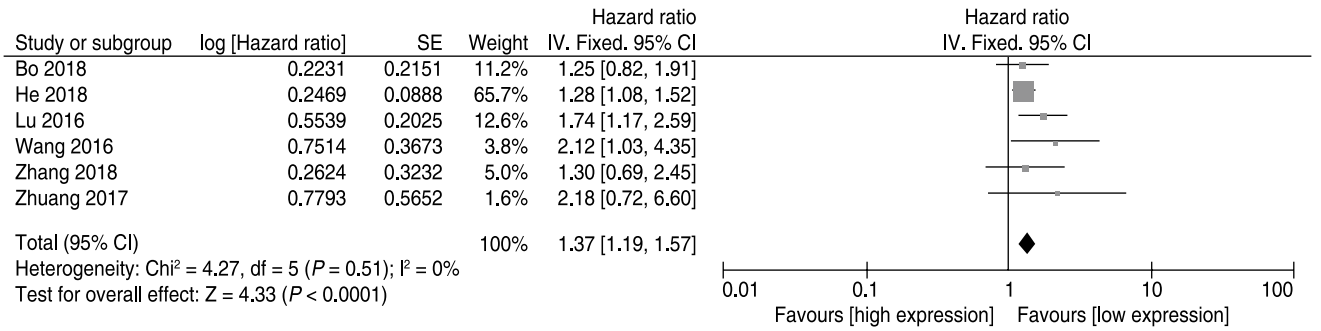

Fig. 3 Forest plot of HRs for the association between high *AFAP1-AS1* expression and DFS

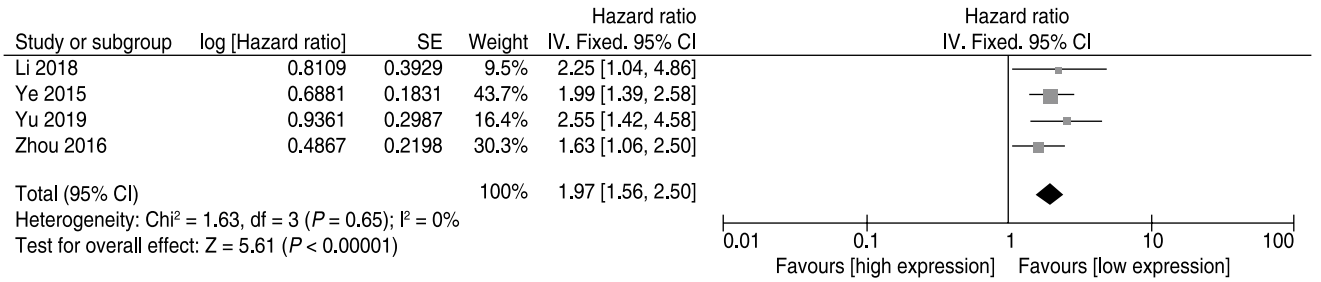

Fig. 4 Forest plot of HRs for the association between high *AFAP1-AS1* expression and PFS

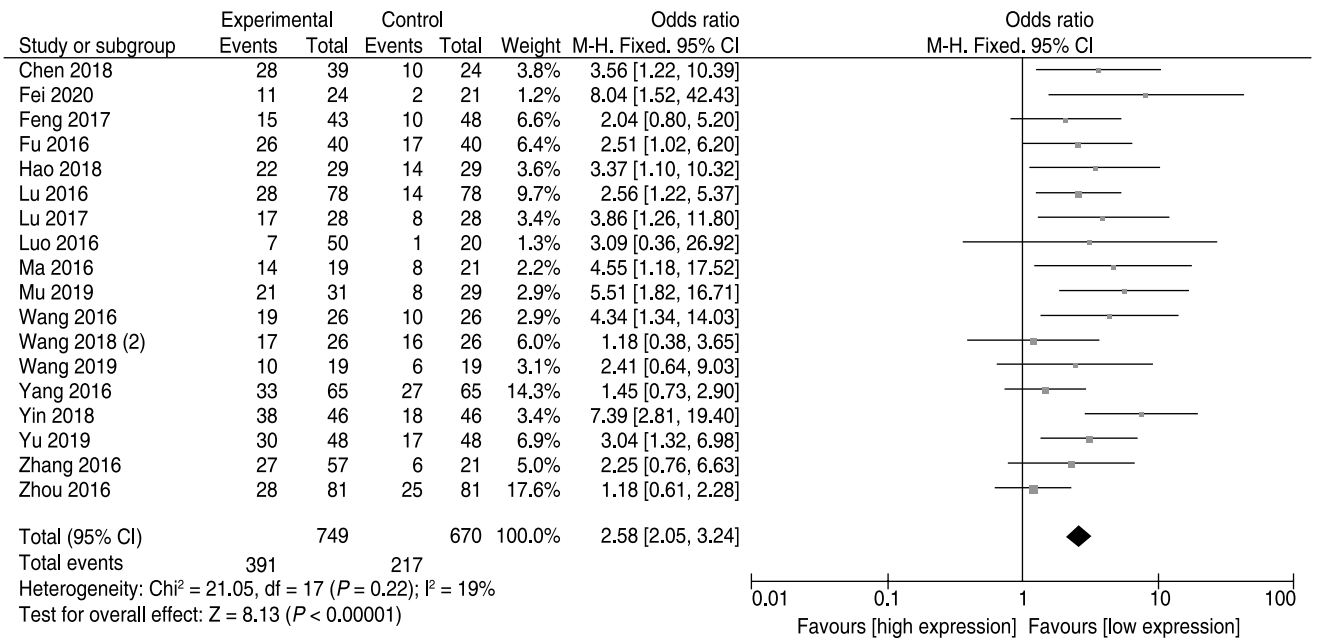

Fig. 5 Forest plot of HRs for the association between high *AFAP1-AS1* expression and LTS

heterogeneity (I^2 = 82%, P_Q < 0.00001), a random-effects model was used. The data showed a synthesized OR of 1.59 (95% CI: 0.88–2.85; high vs. low; Fig. 8). Sensitivity analysis was performed owing to the high heterogeneity. In the sensitivity analysis, the removal of one or two articles did not reduce heterogeneity. Eight eligible studies with 850 patients reported *AFAP1-AS1* expression levels according to DM. Due to severe heterogeneity (I^2 = 65%, P_Q = 0.005), a random-effects model was used. These data showed a pooled OR of 1.81 (95% CI: 0.90–3.66; high *AFAP1-AS1 vs.* low *AFAP1-AS1*; Fig. 9). In the sensitivity analysis, after the study by Wang *et al* [27] was excluded, the heterogeneity decreased (I^2 = 30%, P_Q = 0.20).

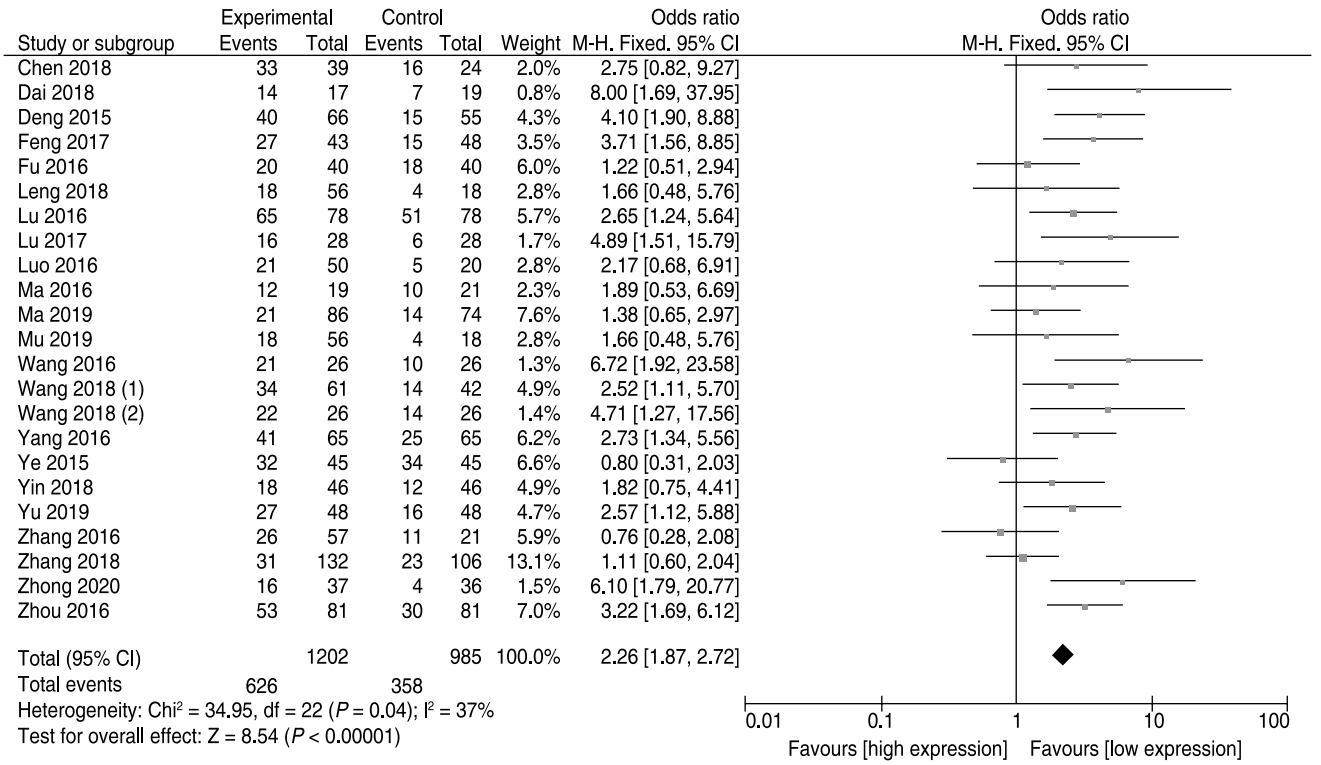

Fig. 6 Forest plot of HRs for the association between high *AFAP1-AS1* expression and HTS

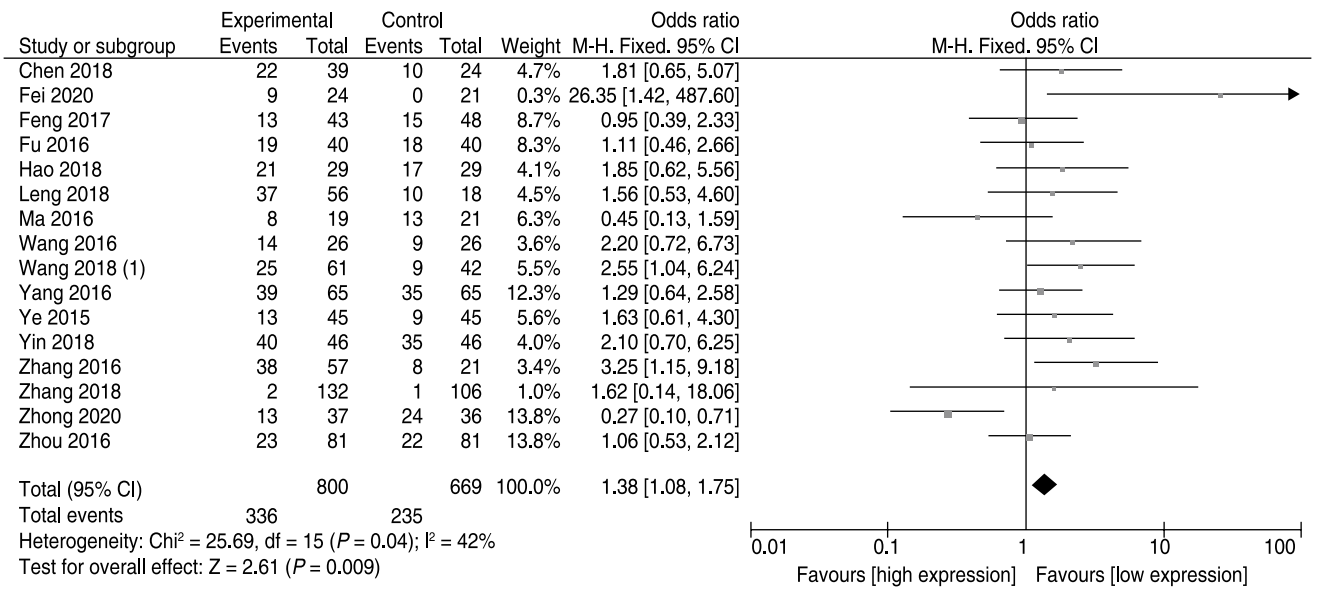

Fig. 7 Forest plot of HRs for the association between high *AFAP1-AS1* expression and PHG

External validation

We used R to analyze the OS, DFS, and PFS of patients with 33 cancer types associated with *AFAP1-AS1* expression. First, for OS, a fixed-effects model was used because of non-significant heterogeneity (I^2 = 41%, P_Q = 0.009). The comprehensive result suggests that high expression of *AFAP1-AS1* was associated with shorter OS (HR = 1.05, 95% CI: 1.02–1.08, Fig. 10). The relationship between *AFAP1-AS1* expression and DFS was studied in 28 of 33 tumors, and the relationship between *AFAP1-AS1* expression and PFS was studied in 32 tumors. There was no significant heterogeneity (DFS: I^2 = 0%, P_Q = 0.58;

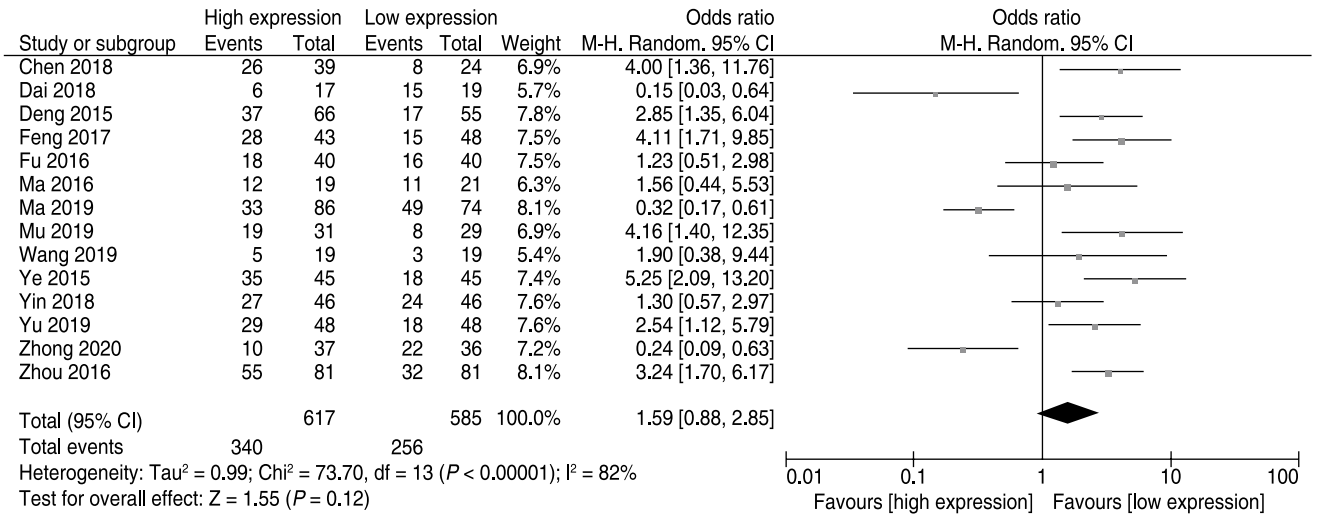

Fig. 8 Forest plot of HRs for the association between high *AFAP1-AS1* expression and LNM

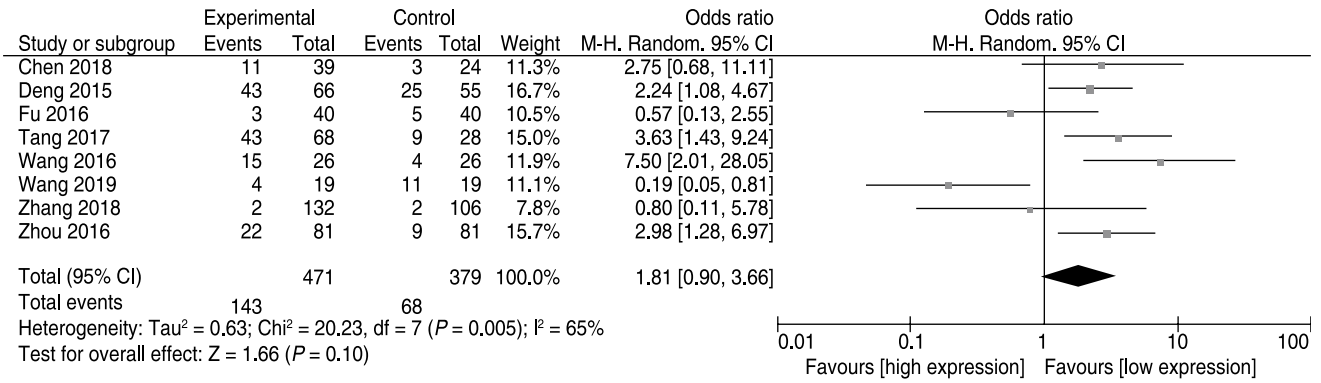

Fig. 9 Forest plot of HRs for the association between high *AFAP1-AS1* expression and DM

PFS: I^2 = 47%, P_Q = 0.002); therefore, we chose the fixed-effects model. The *AFAP1-AS1* expression level was related to DFS (pooled HR = 1.06, 95% CI: 1.00–1.11, Fig. 11) and PFS (pooled HR = 1.04, 95% CI: 1.01–1.07, Fig. 12) in patients with various tumors.

Publication bias

Funnel plots were used to detect publication biases in the included studies. The final results showed no significant asymmetry, suggesting no obvious bias in OS (Fig. 13a), DFS (Fig. 13b), or PFS (Fig. 13c).

Discussion

An increasing number of studies have shown that lncRNAs are abnormally expressed in tumor tissues and are involved in the occurrence and development of tumors. As a molecular blocker, lncRNA can act as a "sponge" to adsorb miRNA and block its inhibitory effect on its downstream target mRNA [53]. *AFAP1-AS1* also acts as a competitive endogenous RNA (ceRNA) that recruits miRNAs to promote tumor progression and metastasis. In endometrial cancer, *AFAP1-AS1* promotes the expression of *VEGFA* by adsorbing *miR-545-3p*, thereby promoting tumor growth and metastasis [16]. Ma *et al* proposed that *AFAP1-AS1* could also regulate the expression of *FGF7* through the sponge absorption of *miR-155-5p*, thereby promoting the GC process [40]. Fei *et al* demonstrated that *AFAP1-AS1* promotes the occurrence and progression of OS through competitive binding of *miR-497* and the regulation of IGF1R expression [46]. In prostate cancer, *AFAP1-AS1* enhances the proliferation, invasion, and metastasis of prostate cancer by regulating *miR-512-3p27*. Zhang *et al* showed that *AFAP1-AS1* promotes TNBC cell proliferation and invasion by targeting *miR-145* to regulate *MTH1* expression [54].

In addition, lncRNAs can be specifically transcribed and participate in specific signaling pathways as signal

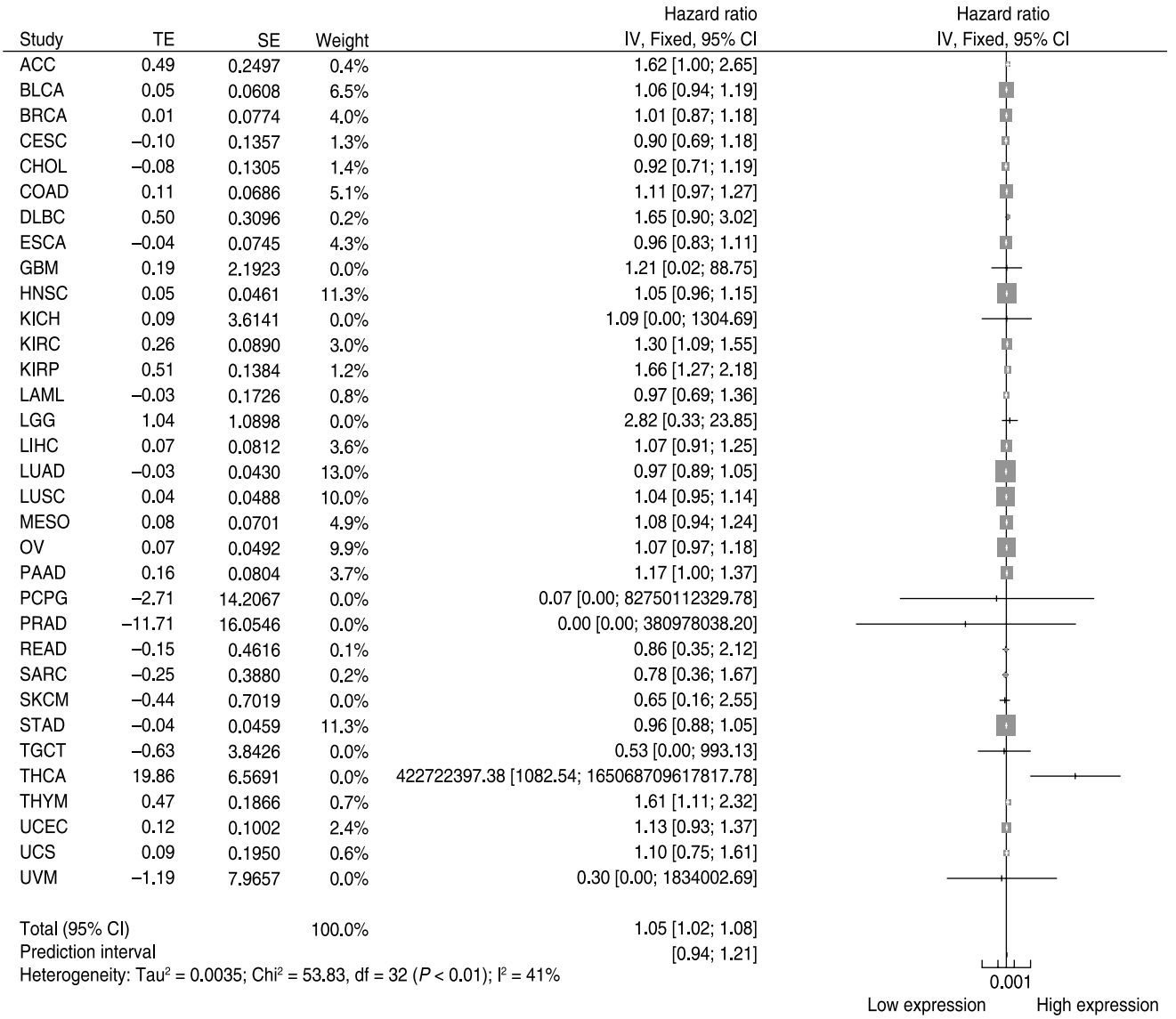

Fig. 10 Forest plot of HRs for the association between high *AFAP1-AS1* expression and OS by external validation

transduction molecules. For example, Shi *et al* confirmed that the lncRNA *AFAP1-AS1* is overexpressed in osteosarcoma and plays a tumorigenic role in osteosarcoma through the RhoC/ROCK1/p38MAPK/Twist1 signaling pathway [55]. *AFAP1-AS1* becomes an oncogene in TSCC by activating the Wnt/β-catenin signaling pathway and inhibiting the expression of EMT-related genes [29]. In pituitary adenomas, *AFAP1-AS1* promotes tumor growth by regulating the PTEN/PI3K/AKT signaling pathway [56].

Resistance to chemoradiotherapy is the main cause of tumor treatment failure; lncRNAs play an important role in this process. lncRNA *AFAP1-AS1* through activation of Wnt/β-catenin signaling pathway, which is induced by promoting cell proliferation, migration and TNBC radiation resistance [57]. Huang *et al* also confirmed that *AFAP1-AS1* promoted chemotherapeutic resistance of NSCLC cells by inhibiting *miR-139-5p* expression and promoting the RRM2/EGFR/AKT signaling pathway [58]. *AFAP1-AS1*, through the PI3K/AKT pathway, induces cisplatin resistance in NSCLC [59].

To investigate the prognostic effect of *AFAP1-AS1* and the relationship between *AFAP1-AS1* expression and the clinicopathological features of different tumors, we performed a meta-analysis of 35 qualified articles and 3433 cases. We found that patients with high *AFAP1-AS1* expression had shorter OS, suggesting that patients with high *AFAP1-AS1* expression may have a worse prognosis. This result was reported in a previous article [13]. In addition, there was no obvious heterogeneity in the included articles, which may have been due

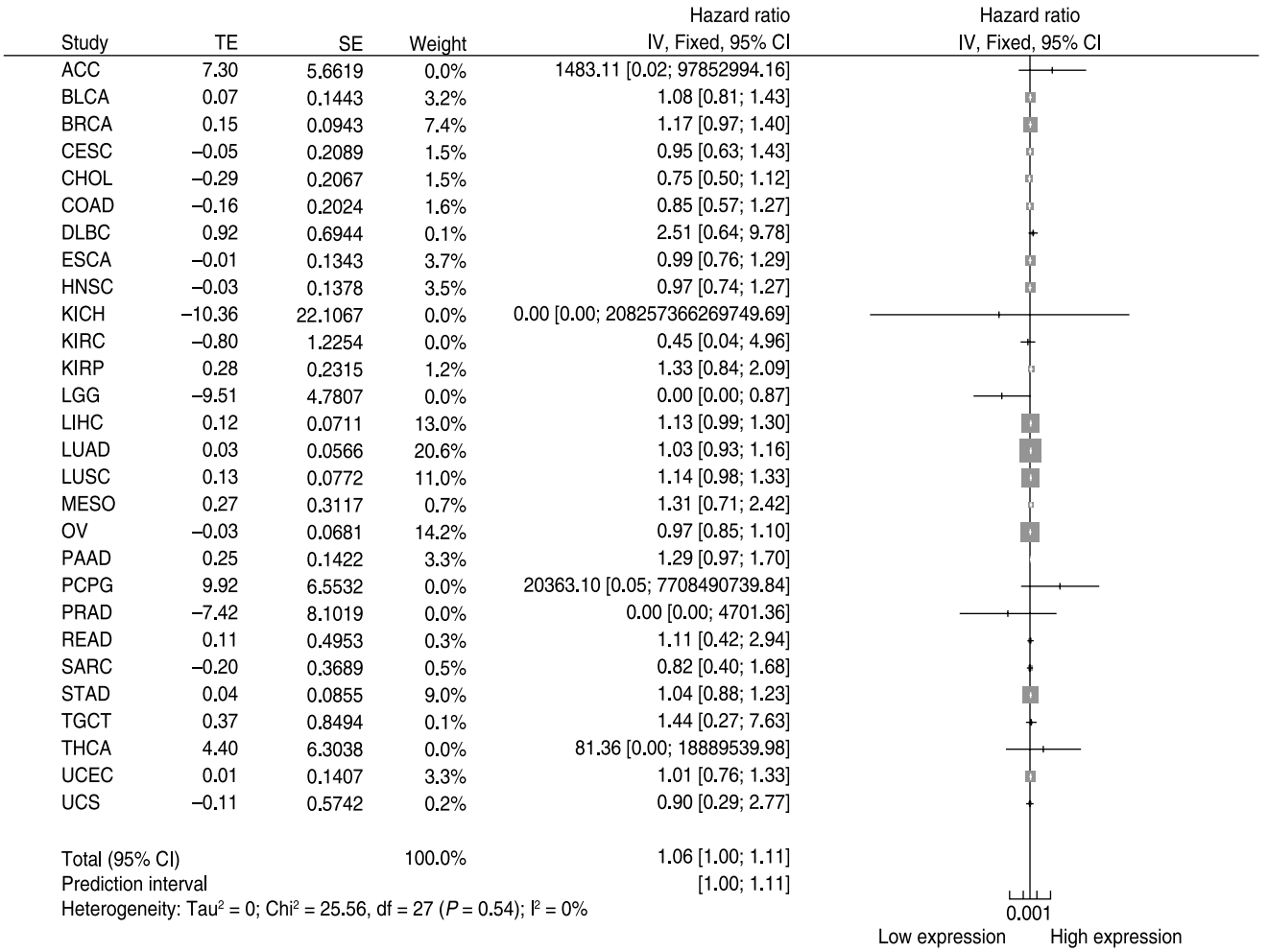

Fig. 11 Forest plot of HRs for the association between high *AFAP1-AS1* expression and DFS by external validation

to experimental errors, small sample sizes, too many cancer types, or different cutoff values. To eliminate heterogeneity, more experiments and sophisticated methods are required. We also observed a relationship between *AFAP1-AS1* expression and DFS and PFS; high *AFAP1-AS1* expression was associated with shorter DFS and PFS. To validate our results, we conducted external verification using R, and the results were found to be consistent with the conclusions of our meta-analysis. Therefore, we speculated that *AFAP1-AS1* could be used as a prognostic molecular marker for different types of cancer.

To examine the relationship between *AFAP1-AS1* and survival, we assessed the association between *AFAP1-AS1* and five clinicopathological features: LTS, HTS, PHG, LNM, and DM. The pooled data showed that high *AFAP1-AS1* expression was associated with LTS, HTS, and PHG, but not with LNM or DM. These results differ from those of previous studies [14, 18]. After accounting for data extraction errors, we analyzed the possible reasons for the differences in this meta-analysis. The included studies and carcinoma types were recently updated, and the inclusion of new cancer types or an increased number of cancer patients may have affected the final results of this study. In this study, considering the relationship between *AFAP1-AS1* and LNM, five new cancer types were identified: TC, GC, CCRCC, PCA, and EC. Additionally, the number of NSCLC cases has increased. Two new articles have been published to study the relationship between *AFAP1-AS1* and DM, and two new cancers, PCA and TNBC, have been added. Unfortunately, the exact reason for these discrepancies remains unknown. Therefore, a larger study with an improved design is required to verify our results.

It is worth noting that the gold standard for tumor diagnosis is pathological results, but tissue-based slices cause harm to patients; therefore, most scholars focus on serological markers. At present, whether lncRNAs can be used in the early stages of tumors or whether the expression of lncRNAs differs at different tumor stages is

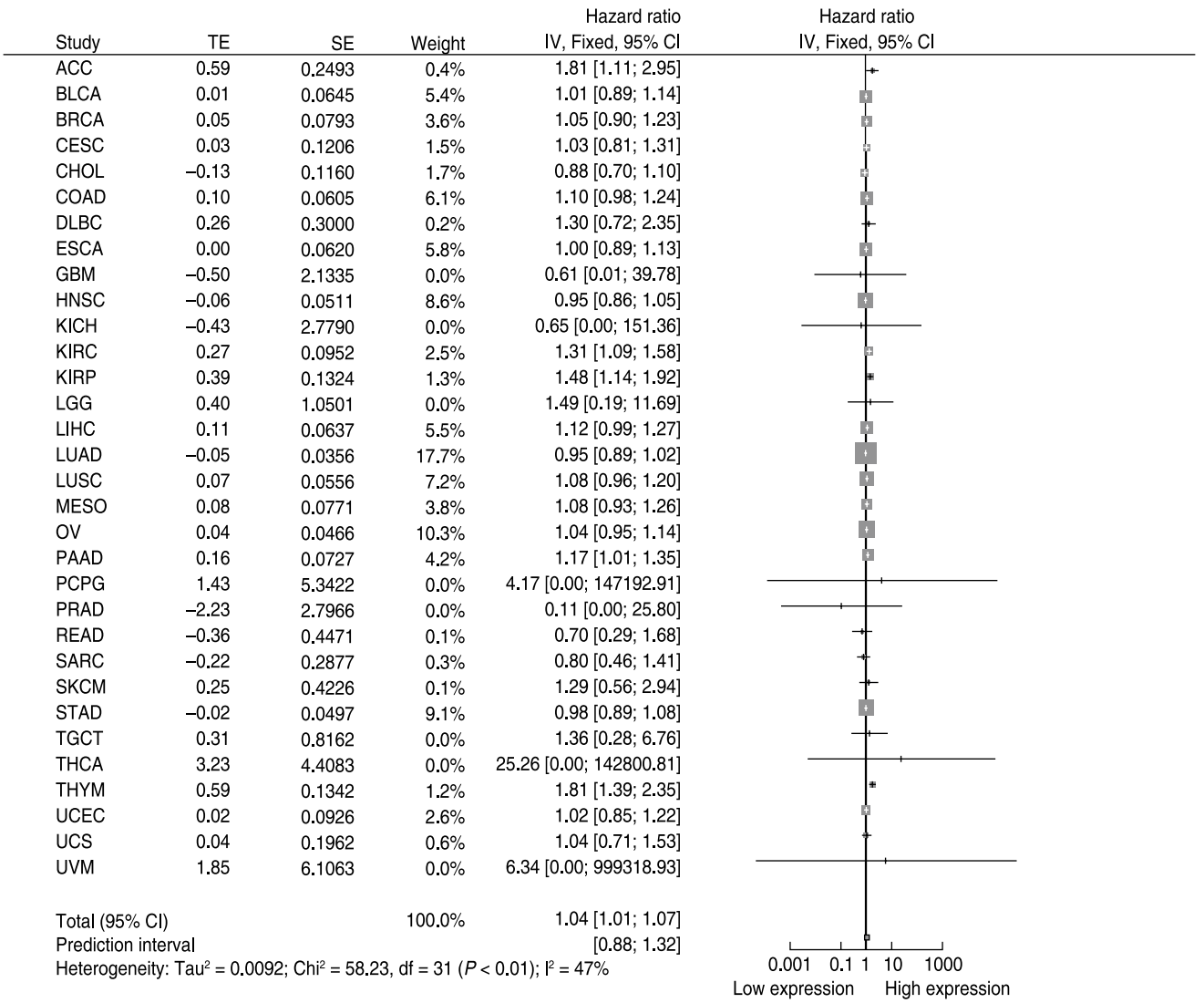

Fig. 12 Forest plot of HRs for the association between high *AFAP1-AS1* expression and PFS by external validation

a challenge that needs to be solved urgently. In addition, attention should be paid to specificity. For example, *AFAP1-AS1* is abnormally expressed in various tumors and is involved in tumorigenesis and development. Finally, the technology's immaturity and high price prevent its clinical use. Therefore, an increasing number of clinical trials must be conducted.

Some limitations of this meta-analysis should be considered. First, all included studies were conducted in China; therefore, our data and research results cannot be applied globally. Second, the data collection may have been inadequate, as non-English articles were excluded, and the number of patients and types of cancer were not sufficient. Third, 13 articles did not mention a cutoff value for high expression, and not all articles had the same cutoff value. Fourth, different types of cancers have different degrees of heterogeneity. Fifth, although the article quality evaluation was completed by two researchers, bias may still exist. Sixth, some HRs were calculated by reconstructing survival curves instead of being extracted directly from the original study; therefore, calculation errors may exist.

Conclusion

We comprehensively searched three databases for relevant studies and according to the inclusion and exclusion criteria, 35 studies with 3433 patients were included in this meta-analysis. It was concluded that an elevated level of lncRNA *AFAP1-AS1* in cancer patients was associated with shorter OS, DFS, and PFS, and that *AFAP1-AS1* was associated with LTS, HTS, and PHG in cancer patients but not with LNM or DM. Further studies

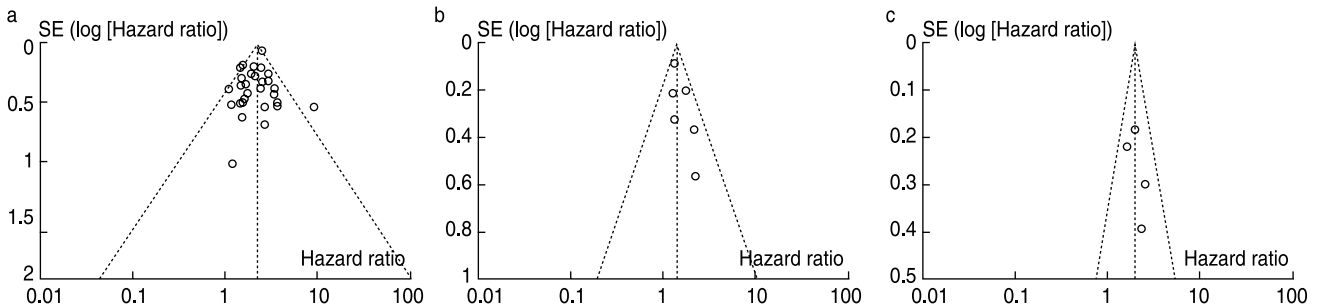

Fig. 13 Funnel plot analysis of potential publication bias in the survival and clinicopathological parameters group. (a) OS, (b) DFS, (c) PFS

are needed to validate the association between *AFAP1-AS1* expression, prognosis, and pathological features in patients with cancer.

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Conflicts of interest

The authors indicated no potential conflicts of interest.

Authors' contributions

All authors contributed to data acquisition and interpretation and reviewed and approved the final version of this manuscript.

Data availability statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval

Not applicable.

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