LncRNA AWPPH as a prognostic predictor in human cancers in Chinese population: evidence from meta-analysis

Yongfeng Li¹, Xinmiao Rui³, Daobao Chen², Haojun Xuan², Hongjian Yang², Xuli Meng¹,³*

¹ Department of Breast Surgery, Zhejiang Provincial People’s Hospital, Affiliated People’s Hospital, Hangzhou Medical college, Hangzhou, Zhejiang 310022, P.R. China
² Department of Breast Surgery, Institute of Cancer Research and Basic Medical Sciences of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Zhejiang, China
³ 2nd Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, P.R. China

Correspondence: Xuli Meng

E-mail: xulim9106@126.com
Abstract

Background: Long non-coding RNA associated with poor prognosis of hepatocellular carcinoma (AWPPH) is dysregulated in a variety of human cancers. However, the prognostic value of AWPPH in various cancers remains unclear.

Methods: Comprehensive literature search was performed in PubMed, Web of Science, CNKI and Wangfang databases, and eligible studies were obtained according to the inclusion and exclusion criteria. The pooled hazard ratios (HRs) and odds ratios (ORs) were applied to assess the clinical value of AWPPH expression for overall survival (OS) and clinicopathological features.

Results: A total of 19 articles including 1699 cancer patients were included in the study. The pooled results demonstrated that evaluated AWPPH expression was positively related to a poorer overall survival of patients with cancers (HR=1.79, 95%CI: 1.44-2.14, P<0.001). Subgroup analysis revealed that tumor type and sample size affect the predictive value of AWPPH on OS, whereas cut-off value and HR estimation method have no impact on it. In addition, the pooled data also showed that AWPPH was positively linked to advanced TNM stage (OR=2.50, 95%CI: 1.94-3.22, P<0.001), bigger tumor size (OR=2.64, 95%CI:1.47-4.73, P=0.001), macro-vascular invasion (OR=2.08, 95%CI: 1.04-4.16, P=0.04) and lymph node metastasis (OR=2.68, 95%CI: 1.82-3.96, P<0.001). Moreover, the results of the trim and fill analysis confirmed the reliability of our finding.
Conclusions: Up-regulation of AWPPH was associated with advanced TNM stage, bigger tumor size, worse lymph node metastasis, macro-vascular invasion, and shorter overall survival, suggesting that AWPPH may serve as a biomarker for prognosis and clinicopathological characteristics in human cancers among the Chinese population.

Keywords: long non-coding RNA; AWPPH; prognosis; meta-analysis
Background

Cancer is a major public health problem worldwide, and it has been the leading cause of death in China since 2010 [1]. Cancer is a highly complex disease involving numerous molecular changes, including chromosomal translocations, deletions and amplification, epigenetic alterations and genetic mutations [2-4], which make it more difficult to be cured than ordinary diseases. Although great advances have been achieved in diagnoses and treatments, the clinical prognosis remains undesirable in most cancer patients. Therefore, the exploration of effective molecular biomarkers which can be used to guide clinical prevention, treatment, and prognosis prediction of cancer is becoming imminent.

LncRNA is a typical kind of non-coding RNA without meaningful open reading frame, which also possesses many significant functions and plays important roles in tumorigenesis and tumor progression. Most lncRNA transcripts involved in the epigenetic, transcriptional, and posttranscriptional regulation of cancer cells [5]. Furthermore, a variety of lncRNA could function as enhancers [6], splicing regulators [7], as well as chromatin remodelers [8]. Notably, accumulating evidence demonstrated that dysregulated lncRNA occurred in a broad spectrum of human cancers [9, 10]. These cancer-related lncRNAs have been proved to participate in cancer initiation and progression, which may have potential value as clinical biomarkers and therapeutic targets. Recently, the long non-coding RNA associated with poor prognosis of hepatocellular carcinoma (AWPPH) attracted increasing
AWPPH, also well-known as AK001796, MIR4435-2HG, LINC00978 and other names, was localized at 2q13 and found to be dysregulated in many human cancers. Growing evidence showed that AWPPH was associated with tumorigenesis and prognostic outcome [11-13]. However, abundant studies reported the prognostic value of AWPPH for human cancers were constrained by sample size and discrete outcome so far. Consequently, we performed this systematic review and meta-analysis on the basis of eligible retrospective studies to investigate the potential prognostic value of AWPPH for cancer patients.

Methods

Literature collection

This meta-analysis was performed in accordance with the PRISMA 2009 guidelines (Supplement S1)[14]. We performed literature search using PubMed, Web of Science, CNKI and Wangfang database for eligible studies which reported the relationship between lncRNA AWPPH and prognosis of human cancers before October 5, 2020. Search terms used as follows: (“carcinoma” OR “cancer” OR “tumor” OR “neoplasm”) AND (“prognosis” OR “outcome” OR “diagnosis” OR “survival”) AND (“AWPPH” OR “LINC00978” OR “MIR4435-1HG” OR “MORRBID” OR “AGD2” OR “MIR4435-12HG” OR “AK001796” OR “MIR4435-2HG”). The reference lists of primary publications were also manually
searched to obtain potential eligible studies. There is no requirement for patient
consent or ethical approval due to all the analyses were conducted on the basis of the
prior published researches.

Inclusion and exclusion criteria

Eligible studies should meet the following inclusion criteria: 1) Studies evaluated
the association between AWPPH and cancer patient samples; 2) Available prognosis
outcomes or clinicopathologic features data; 3) sufficient information to obtain hazard
ratio (HR) or odds ratio (OR) with 95% confidence interval (95% CI); The following
articles were excluded from the study: 1) reviews, letters, or case reports; 2)
non-human studies; 3) duplicated publication; 4) studies with insufficient data for
HR/OR/95%CI extraction.

Data extraction and quality assessment

Eligible articles were reviewed by 2 reviewers (Li and Rui) independently
according to the inclusion and exclusion criteria. Disagreement was resolved during a
consensus with a third reviewer (Chen). The essential information was screened and
extracted from each eligible study, including the name of first author, year of
publication, origin country, cancer type, sample size, detection method of AWPPH,
HR and corresponding 95%CI for OS, as well as clinicopathological features. The
HRs with 95%CIs were obtained directly from studies which performed the
multivariate analysis, and the Kaplan–Meier curves were used for the extraction of the
survival information if the 95% CIs and HRs have not been directly reported from the
researches according to the method described in the previous publication [15]. The
Newcastle-Ottawa Scale (NOS) was applied to evaluate the quality of the included
study. The NOS scores ranged from 0 to 9 and studies with a NOS score >6 were
considered to be high quality.

**Statistical analysis**

The present meta-analysis was performed with STATA SE 15.0 (Stata Corporation). HR and corresponding 95%CI for OS were applied to determine the pooled effect for clinical outcomes, and the odds ratio (OR) with 95%CI were used to evaluate the correlation between LncRNA AWPPH and clinicopathological parameters. Statistical heterogeneity was assessed using the $I^2$ test as well as the chi-based Q-test, to determine heterogeneity between several studies. Heterogeneity was considered as statistically significant with $I^2 < 50\%$. The fixed-effect model was used if heterogeneity exists ($I^2 > 50\%$ and $p < 0.05$), otherwise, the random-effect model was applied. Publication bias was assessed using Begg’s funnel plot and Egger’s regression test. The sensitivity analysis was used to check the stability of the combined results and to determine the source of any heterogeneity. The $P$-value less than 0.05 was considered to be statistically significant.

**Results**

**Summary of eligible studies**
As shown in Figure 1, a total of 143 potentially relevant articles were obtained from the first attempt to search by using the keywords. There are 57 duplicate articles and 60 irrelevant articles excluded after screening the titles and abstracts. Finally, 7 studies with insufficient data were excluded and the remain 19 studies were included in the subsequent meta-analysis. The main characteristics of the included 19 studies have been summarized in Table 1. A total of 1699 patients from 19 studies between 2016 and 2020 were included [11-13, 16-31]. The respective sample sizes ranged from 36 to 195 patients. 19 studies had addressed 12 different types of cancer: including hepatocellular carcinoma (HCC, n=3), colorectal adenocarcinoma (CRC, n=3), ovarian carcinoma (OC, n=2), triple-negative breast cancer (TNBC, n=1), non-small cell lung cancer (NSCLC, n=2), osteosarcoma (n=1), cervical cancer (CC, n=1), oral squamous cell carcinoma (OSCC, n=1), clear cell renal cell carcinoma (CCRCC, n=1), GC (n=1), prostate carcinoma (PC, n=1), breast cancer (BC, n=1), esophageal squamous cell carcinoma (ESCC, n=1). Clinical outcomes were recorded including 19 studies for overall survival (OS), 3 for recurrence-free survival (RFS), 1 for progression-free survival (PFS), and 1 for disease free survival (DFS). HRs with corresponding 95% CIs were obtained from the original data in 4 studies, and calculated from Kaplan–Meier curves for the rest 15 studies. In addition, for the quality assessment, the Newcastle-Ottawa Scale (NOS) score of individual cohort studies was ranged from 6 to 8, which indicated that the methodological quality of included studies was medium or high. The clinicopathological features of the included studies were summarized in Table 2.
Prognostic value of AWPPH

A total of 19 studies with 1699 patients reported the relationship between OS and AWPPH in human cancers. As shown in Figure 2A, a significant correlation was observed between elevated AWPPH expression and poor OS (HR=1.79, 95%CI: 1.44-2.14, P<0.001) with non-significant heterogeneity ($I^2=0\%$, P=0.737).

Furthermore, subgroup analysis across several different variables, including cancer type, sample size, HR estimation method, and cut-off value, were further performed to explore the association between HRs and OS. The results showed that cancer type and sample size influence the prognostic value of AWPPH on OS (Figure 3 and 4), whereas the HE estimation methods and cut-off value have no impact on it (Figure 5 and 6). There was a negatively relationship between AWPPH expression and OS in the patients HCC (HR=2.22, 95%CI: 1.05-3.38), NSCLC (HR=2.01, 95%CI: 1.03-2.99), BC (HR=2.01, 95%CI: 1.02-3.00), and other cancers (HR=1.62, 95%CI: 1.10-2.15) (Figure 3). Moreover, the effect of AWPPH over-expression on predicting short OS occurred in the studies with sample size >70 (HR=1.99, 95%CI: 1.55-2.44) (Figure 4).

Association between AWPPH and clinicopathological features

The correlation between AWPPH expression and clinicopathological characteristics were examined with OR analysis in 15 studies with 1332 cancer patients (Figure 7 and Table 3). 12 studies with 1143 patients were included to analysis the link between AWPPH and TNM stage, and the pooled data found an
obvious association between AWPPH over-expression and advanced TNM stage (OR=2.50, 95%CI: 1.94-3.22, P<0.001) (Figure 7B). The results also showed that over-expression of AWPPH predicts larger tumor size (OR=2.64, 95%CI:1.47-4.73, P=0.001, Figure 7D). In addition, 2 studies with 137 patients were included to analyze the link between AWPPH and macro-vascular invasion, the results revealed an obvious association between AWPPH expression and MVI (OR=2.08, 95%CI: 1.04-4.16, P=0.039, Figure 7E). As shown in Figure 7F, 491 cancer patients from 5 studies were included to evaluate the correlation between AWPPH and LNM, and the results indicated that the patients with elevated AWPPH expression were more susceptibility to develop LNM (OR=2.68, 95%CI: 1.82-3.96, P<0.001).

**Publication bias and sensitivity analysis**

Begg’s funnel plot and Egger’s linear regression tests were introduced to evaluate potential publication bias in our present meta-analysis. In the analysis of evaluating the association between AWPPH expression and OS, visual inspection of the Begg’s funnel plot did not reveal asymmetry (Figure 2C), and Egger’s test also suggested the absence of publication bias (t=0.06, p=0.953). Sensitivity analyses were performed to evaluate whether individual study influenced pooled HRs by excluding one study by turns. The results showed that the pooled HR was not significantly changed after removing each study, suggested that the results were stable (Figure 2D).

**Discussion**
Evidence from multiple publications demonstrated that IncRNA AWPPH is closely associated with cancers. AWPPH was first discovered in breast cancer as the name of LINC00978 [26]. In breast cancer patients, the expression of AWPPH was negatively associated with hormone receptor status, and high AWPPH expression predicted poor DFS. In recent years, it has been shown from prior studies that AWPPH serves as a dysregulated oncogene in several cancers, such as GC [24], CRC [24], NSCLC [30]. AWPPH can promote cell proliferation, migration, and invasion in a variety of human cancers, and played an crucial role in tumor progression, metastasis and prognosis. However, a persuasive support of the AWPPH in clinical practice is still controversial. In order to combine previous research results about AWPPH and cancers to arrive at a summary conclusion, a comprehensive study was carried out.

In this meta-analysis, we pooled data from a total of 19 retrospective eligible studies with 1699 cancer patients to systematically explore the relationship between AWPPH and prognosis. We found that elevated AWPPH expression was an unfavorable prognostic factor in multiple cancer patients. Furthermore, the results also demonstrated that high AWPPH expression level was positively related to advanced TNM stage, higher risk of LNM and MVI, and bigger tumor size.

The exact mechanisms underlying the association between aberrant AWPPH expression and poor clinical prognosis remains elusive. The molecular mechanism of AWPPH in various cancers from prior studies were illustrated in Figure 8. Previous
study reported that AWPPH regulates cell proliferation and cell cycle via modulating MDM2/p53 signaling in ESCC [33]. AWPPH acted as an oncogene to interact with YBX1 to activate the expression of SNAIL1 and PI3K/AKT pathway in the HCC [11]. Wnt/β-catenin signal pathway involved in the regulation of cell proliferation, migration, and invasion in certain cancers [34, 35], and AWPPH could promote the proliferation, migration, and invasion of BC, OC, and NSCLC by activating this pathway [12, 30, 36]. Several important pathways were also conformed to be modulated by AWPPH in cancers, including MDM2-p53 pathway esophageal squamous cell carcinoma [33], and MEK/ERK pathway in HCC [22]. Furthermore, AWPPH could inhibit colon cancer cell proliferation by down-regulating GLUT-1 [37] and mediate the metastasis and postoperative distant recurrence by up-regulating TGF-β1 [29, 38, 39]. Liu et al. demonstrated that AWPPH contributes to cisplatin resistance by inducing the expression of CDK1 and GTSE5, and suppressing the expression of CCNC and BIRC5. This provided a brand new insight for the cisplatin resistance of gastric cancer NSCLC [40].

Additionally, a number of studies revealed that AWPPH could act as a key competing endogenous RNA (ceRNA) or sponge for miRNAs to regulate the initiation, development, and chemoresistance of cancer. For example, in gastric cancer, Bu et al. demonstrated that AWPPH promotes cell proliferation and tumorigenesis by regulating miR-497/NTRK3 axis [24]. Recently, miR-128-3p was confirmed as a target of AWPPH in ovarian cancer by Zhu et al. [23]. In NSCLC, Wu et al. found
that AWPPH could directly interacted with miR-204 and functioned as a ceRNA, thus regulating the expression of CDK6 [13]. Furthermore, AWPPH functioned as a ceRNA to promote malignant progression of human cancers through competitive sponging of miR-93-3p in osteosarcoma [28], miR-802 in melanoma [41], miR-206 in CRC [18], miR-1224-5p in glioblastoma [42], and miR-513a-5p in CCRCC [43].

Nevertheless, several limitations to this meta-analysis should be taken into account. First, all included studies were performed in the population from China, which may limit the applicability of our results for other ethnic population. Second, the cut-off values were lack of uniform standard in different types of cancer, which may result in some heterogeneity and affect the results of the study. Third, some of the HRs were calculated based on data extracted from the survival curves, which may not be very accurate and result in a calculation bias.

**Conclusion**

To conclude, this meta-analysis revealed that AWPPH expression level served as a prognostic indicator in multiple cancers in the Chinese population. Higher expression of AWPPH was significantly associated with poorer overall survival in patients with cancers, and correlated with advanced TNM stage, higher risk of LNM and MVI, and bigger tumor size. Ultimately, more high-quality studies were required to certify clinical utility of AWPPH in cancers.

**Abbreviations**
AWPPH: Long non-coding RNA associated with poor prognosis of hepatocellular carcinoma, ORs: odds ratios, OS: overall survival, RFS: recurrence-free survival, PFS: progression-free survival, DFS: disease free survival, NOS: Newcastle-Ottawa Scale, HCC: hepatocellular carcinoma, CRC: colorectal adenocarcinoma, OC: ovarian carcinoma, TNBC: triple-negative breast cancer, NSCLC: non-small cell lung cancer, CC: cervical cancer, OSCC: oral squamous cell carcinoma, CCRCC: clear cell renal cell carcinoma, GC: gastric cancer, PC: prostate carcinoma, BC: breast cancer, ESCC: esophageal squamous cell carcinoma, qRT-PCR: quantitative real-time polymerase chain reaction, LNM: lymph node metastasis, MVI: macro-vascular invasion, DM: distant metastasis, ceRNA: competitive endogenous RNA

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.
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**Authors’ contributions**

Conceived and designed the study: Yongfeng Li and Daobao Chen. Selected the studies and collected the data: Yongfeng Li, Xinmiao Rui, and Daobao Chen. Analyzed the data: Haojun Xuan, Hongjian Yang. Drafted the paper: Yongfeng Li. Revised the draft paper: Yongfeng Li and Xuli Meng.

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**Conflict of interest**

The authors have declared that no competing interest exists.

**Data Availability Statement**

The data used to support the findings of this study are available from the
corresponding author upon request.
References

1. Chen W., Zheng R., Baade P.D., Zhang S., Zeng H. and Bray F. et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016, 66, 115-132.

2. Arenz A., Patze J., Kornmann E., Wilhelm J., Ziemann F. and Wagner S. et al. HPV-negative and HPV-positive HNSCC cell lines show similar numerical but different structural chromosomal aberrations. Head Neck. 2019, 41, 3869-3879.

3. Helleux A., Debien V., Fadloun A., Rippinger M., Lebedinsky S. and Davidson I. et al. Epigenetic alterations in kidney cancers. Bull Cancer. 2019, 106, 839-841.

4. Johansson P.A., Nathan V., Bourke L.M., Palmer J.M., Zhang T. and Symmons J. et al. Evaluation of the contribution of germline variants in BRCA1 and BRCA2 to uveal and cutaneous melanoma. Melanoma Res. 2019, 29, 483-490.

5. Chen Y., Wang J., Fan Y., Qin C., Xia X. and Johnson J. et al. Absence of the long noncoding RNA H19 results in aberrant ovarian STAR and progesterone production. Mol. Cell. Endocrinol. 2019, 490, 15-20.

6. Fico A., Fiorenzano A., Pascale E., Patriarca E.J. and Minchiotti G. Long non-coding RNA in stem cell pluripotency and lineage commitment: functions and evolutionary conservation. Cell. Mol. Life Sci. 2019, 76, 1459-1471.

7. Porto F.W., Daulatabad S.V. and Janga S.C. Long Non-Coding RNA Expression Levels Modulate Cell-Type-Specific Splicing Patterns by Altering Their Interaction Landscape with RNA-Binding Proteins. Genes (Basel) 2019, 10, 593.

8. Tang Y., Wang J., Lian Y., Fan C., Zhang P. and Wu Y. et al. Linking long non-coding RNAs and SWI/SNF complexes to chromatin remodeling in cancer. Mol. Cancer 2017, 16, 42.

9. Cui R.J., Fan J.L., Lin Y.C., Pan Y.J., Liu C. and Wan J.H. et al. miR-124-3p availability is antagonized by LncRNA-MALAT1 for Slug-induced tumor metastasis in hepatocellular carcinoma. Cancer Med. 2019, 8, 6358-6369.

10. Xu Y., Deng J., Wang G. and Zhu Y. Long Non-coding RNAs in Prostate Cancer: Functional Roles and Clinical Implications. Cancer Lett. 2019, 464, 37-55.

11. Zhao X., Liu Y. and Yu S. Long noncoding RNA AWPPH promotes hepatocellular carcinoma progression through YBX1 and serves as a prognostic biomarker. Bba.-Mol. Basis Dis. 2017, 1863, 1805-1816.
Yu G., Wang W., Deng J. and Dong S. LncRNA AWPPH promotes the proliferation, migration and invasion of ovarian carcinoma cells via activation of the Wnt/-catenin signaling pathway. Mol. Med. Rep. 2019, 19, 3615-3621.

Wu D., Qin B.Y., Qi X.G., Hong L.L., Zhong H.B. and Huang J.Y. LncRNA AWPPH accelerates the progression of non-small cell lung cancer by sponging miRNA-204 to upregulate CDK6. Eur. Rev. Med. Pharmacol. 2020, 24, 4281-4287.

Liberati A., Altman D.G., Tetzlaff J., Mulrow C., Gøtzsche P.C. and Ioannidis J.P. et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann. Intern. Med. 2009, 151, W65-94.

Tierney J.F., Stewart L.A., Ghersi D., Burdett S. and Sydes M.R. Practical methods for incorporating summary time-to-event data into meta-analysis. 2007, 8, 16.

Han Q.L., Chen B.T., Zhang K.J., Xia S.T., Zhong W.W. and Zhao Z.M. The long non-coding RNA AK001796 contributes to poor prognosis and tumor progression in hepatocellular carcinoma. Eur Rev Med Pharmacol Sci 2019, 23, 2013-2019.

Zong M.Z., Shao Q. and An X.S. Expression and prognostic significance of long noncoding RNA AK001796 in esophageal squamous cell carcinoma. Eur Rev Med Pharmacol Sci 2019, 23, 181-186.

Zong M.Z., Shao Q. and An X.S. Expression and prognostic significance of long noncoding RNA AK001796 in esophageal squamous cell carcinoma. Eur Rev Med Pharmacol Sci 2019, 23, 2013-2019.

Han Q.L., Chen B.T., Zhang K.J., Xia S.T., Zhong W.W. and Zhao Z.M. The long non-coding RNA AK001796 contributes to poor prognosis and tumor progression in hepatocellular carcinoma. Eur Rev Med Pharmacol Sci 2019, 23, 2013-2019.

Dong X., Yang Z., Yang H., Li D. and Qiu X. Long Non-coding RNA MIR4435-2HG Promotes Colorectal Cancer Proliferation and Metastasis Through miR-206/YAP1 Axis. FRONTIERS IN ONCOLOGY 2020, 10, 160.

Ma X. and Sheng M. Prognostic value of serum MIR4435-2HG in oral squamous cell carcinoma. Chinese Journal of Stomatology 2020, 55, 15-19.

Shen M.Y., Zhou G.R. and Z.Z. LncRNA MIR4435-2HG contributes into colorectal cancer development and predicts poor prognosis. Eur Rev Med Pharmacol Sci 2020, 24, 1771-1777.

Wu K., Hu L., Lv X., Chen J., Yan Z. and Jiang J. et al. Long non-coding RNA MIR4435-1HG promotes cancer growth in clear cell renal cell carcinoma. Cancer biomarkers: section A of Disease markers 2020, 29, 39-50.

Zhang Q., Cheng S., Cao L., Yang J., Wang Y. and Chen Y. LINC00978 promotes hepatocellular carcinoma carcinogenesis partly via activating the MAPK/ERK pathway. Bioscience Rep. 2020, 40, BSR20192790.

Zhu L., Wang A., Gao M., Duan X. and Li Z. LncRNA MIR4435-2HG triggers ovarian cancer progression by regulating miR-128-3p/CKD14 axis. Cancer Cell Int. 2020, 20, 145.
24 Bu J., Lv W., Liao Y., Xiao X. and Lv B. Long non-coding RNA LINC00978 promotes cell proliferation and tumorigenesis via regulating microRNA-497/NTRK3 axis in gastric cancer. Int. J. Biol. Macromol. 2019, 123, 1106-1114.

25 Zhang H., Meng H., Huang X., Tong W., Liang X. and Li J. et al. IncRNA MIR4435-2HG promotes cancer cell migration and invasion in prostate carcinoma by upregulating TGF-beta 1. Oncol. Lett. 2019, 18, 4016-4021.

26 Deng L., Chi Y., Liu L., Huang N., Wang L. and Wu J. LINC00978 predicts poor prognosis in breast cancer patients. Sci. Rep.-UK 2016, 6, 37936.

27 Chen X., Qu J., Yao L. and Chen X. Expression and clinicopathological significance of IncRNA AWPPH and miR-203a in cervical cancer [In Chinese]. Journal of Clinical and Experimental Pathology 2020, 9, 1052-1057.

28 Li C., Wang F., Wei B., Wang L. and Kong D. LncRNA AWPPH promotes osteosarcoma progression via activation of Wnt/β-catenin pathway through modulating miR-93-3p/FZD7 axis. Biochem Biophys Res Commun 2019, 514, 1017-1022.

29 Liu C., Han B., Xin J. and Yang C. LncRNA-AWPPH activates TGF-β 1 in colorectal adenocarcinoma. Oncol. Lett. 2019, 18, 4719-4725.

30 Song Z., Du J., Zhou L. and Sun B. IncRNA AWPPH promotes proliferation and inhibits apoptosis of non-small cell lung cancer cells by activating the Wnt/β-catenin signaling pathway. Mol. Med. Rep. 2019, 19, 4425-4432.

31 Wang K., Li X., Song C. and Li M. LncRNA AWPPH promotes the growth of triple-negative breast cancer by up-regulating frizzled homolog 7 (FZD7). Bioscience Rep. 2018, 38, BSR20181223.

32 Liu C., Han B., Xin J. and Yang C. LncRNA-AWPPH activates TGF-β 1 in colorectal adenocarcinoma. Oncol. Lett. 2019, 18, 4719-4725.

33 Liu B., Pan C.F., Yao G.L., Wei K., Xia Y. and Chen Y.J. The long non-coding RNA AK001796 contributes to tumor growth via regulating expression of p53 in esophageal squamous cell carcinoma. Cancer Cell Int. 2018, 18, 38.

34 Hseu Y.C., Lin Y.C., Rajendran P., Thigarajan V., Mathew D.C. and Lin K.Y. et al. Antrodia salmonea suppresses invasion and metastasis in triple-negative breast cancer cells by reversing EMT through the NF-kappaB and Wnt/beta-catenin signaling pathway. Food Chem. Toxicol. 2019, 124, 219-230.

35 Liu M., Sun X. and Shi S. MORC2 Enhances Tumor Growth by Promoting Angiogenesis and Tumor-Associated Macrophage Recruitment via Wnt/beta-Catenin in Lung Cancer. Cell. Physiol.
382 Biochem. 2018, 51, 1679-1694.

383 36 Xiu D., Liu G., Yu S., Li L., Zhao G. and Liu L. et al. Long non-coding RNA LINC00968 attenuates drug resistance of breast cancer cells through inhibiting the Wnt2-/catenin signaling pathway by regulating WNT2. J. Exp. Clin. Canc. Res. 2019, 38, 94.

386 37 Bai J., Xu J., Zhao J. and Zhang R. Downregulation of lncRNA AWPPH inhibits colon cancer cell proliferation by downregulating GLUT-1. Oncol. Lett. 2019, 18, 2007-2012.

388 38 Yanxia H., Aimin L. and Zhihua W. LncRNA AWPPH participates in the metastasis of non-small cell lung cancer by upregulating TGF-β 1 expression. Oncol. Lett. 2019, 18, 4246-4252.

390 39 Tang L., Wang T., Zhang Y., Zhang J., Zhao H. and Wang H. et al. Long Non-Coding RNA AWPPH Promotes Postoperative Distant Recurrence in Resected Non-Small Cell Lung Cancer by Upregulating Transforming Growth Factor beta 1 (TGF-β 1). Med Sci Monit 2019, 25, 2535-2541.

393 40 Liu B., Pan C., Ma T., Wang J., Yao G. and Wei K. et al. Long non-coding RNA AK001796 contributes to cisplatin resistance of non-small cell lung cancer. Mol. Med. Rep. 2017, 16, 4107-4112.

395 41 Ma D., Sun D., Wang J., Jin D., Li Y. and Han Y. Long non-coding RNA MIR4435-2HG recruits miR-802 from FLOT2 to promote melanoma progression. Eur. Rev. Med. Pharmacol. 2020, 24, 2616-2624.

398 42 Xu H., Zhang B., Yang Y., Li Z., Zhao P. and Wu W. et al. LncRNA MIR4435-2HG potentiates the proliferation and invasion of glioblastoma cells via modulating miR-1224-5p/TGFBR2 axis. J. Cell. Mol. Med. 2020, 24, 6362-6372.

399 43 Zhu K., Miao C., Tian Y., Qin Z., Xue J. and Xia J. et al. lncRNA MIR4435-2HG promoted clear cell renal cell carcinoma malignant progression via miR-513a-5p/KLF6 axis. J. Cell. Mol. Med. 2020, 24, 10013-10026.
Figure captions

Figure 1. Flow chart of literature search

Figure 2. Meta-analysis of the association between AWPPH expression and prognosis index. (A,B) Forest plot and of studies evaluating the association between AWPPH expression and OS and RFS. (C) Begg’s publication bias plots of OS, and (D) sensitivity analysis for OS.

Figure 3. Forest plots of subgroup analysis for the HRs of OS by tumor type.

Figure 4. Forest plots of subgroup analysis for the HRs of OS by sample size.

Figure 5. Forest plots of subgroup analysis for the HRs of OS by cut-off value.

Figure 6. Forest plots of subgroup analysis for the HRs of OS by HR estimation method.

Figure 7. Meta-analysis for the association between AWPPH expression with clinicopathological parameters. The investigated clinicopathological parameters are: (A) differentiation status, (B) TNM stage, (C) distant metastasis, (D) tumor size, (E) macro-vascular invasion, and (F) lymph node metastasis.

Figure 8. Schematic diagrams of various molecules and signaling pathways associated with AWPPH in human cancers.

Supplementary S1. The PRISMA checklist of the meta-analysis.
Articles identified from database search
- PubMed (n=45)
- Web of Science (n=59)
- CNKI (n=19)
- Wangfang (n=20)

Articles excluded by duplicates (n=57)

Articles screened by titles and abstracts (n=86)

Articles excluded (n=60)
- reviews (n=10)
- Irrelevant topics (n=50)

Eligibility of the full-text articles evaluated (n=26)

Articles excluded by insufficient clinical data (n=7)

Studies included in this meta-analysis (n=19)
Figure 2

(A) Begg's funnel plot with pseudo 95% confidence limits

(B) Meta-analysis fixed-effects estimates (linear form)

Study omitted

| Study        | HR (95% CI)    | Weight |
|--------------|----------------|--------|
| Zhao XD (2017) | 2.58 (1.42, 4.67) | 4.44   |
| Li H (1999)  | 0.56 (0.14, 2.29) | 0.49   |
| Overall (I-squared = 55.2%, p = 0.107) | 1.55 (0.04, 3.07) | 0.00   |

NOTE: Weights are from random effects analysis

(C) Study omission

(D) Study omission

NOTE: Weights are from random effects analysis
| Study ID          | HR (95% CI)                  | Weight |
|------------------|------------------------------|--------|
| **HCC**          |                              |        |
| Han QL (2019)    | 2.02 (1.04, 3.92)            | 5.88   |
| Zhang Q (2020)   | 1.96 (0.66, 5.84)            | 1.82   |
| Zhao XD (2017)   | 3.51 (1.57, 7.82)            | 1.25   |
| Subtotal (I-squared = 0.0%, p = 0.681) | 2.22 (1.05, 3.38) | 8.94   |
| **CRC**          |                              |        |
| Dong XH (2020)   | 1.30 (0.44, 3.80)            | 4.32   |
| Liu CC (2018)    | 1.51 (0.74, 3.07)            | 8.98   |
| Shen MY (2020)   | 2.57 (0.98, 6.74)            | 1.47   |
| Subtotal (I-squared = 0.0%, p = 0.752) | 1.55 (0.65, 2.46) | 14.76  |
| **OC**           |                              |        |
| Yu GY (2019)     | 2.05 (1.01, 4.14)            | 4.97   |
| Zhu LJ (2020)    | 1.85 (0.65, 5.26)            | 2.29   |
| Subtotal (I-squared = 0.0%, p = 0.888) | 1.99 (0.69, 3.28) | 7.27   |
| **BC**           |                              |        |
| Deng LL (2016)   | 2.27 (1.24, 4.17)            | 5.68   |
| Wang KN (2018)   | 1.79 (0.90, 3.59)            | 6.73   |
| Subtotal (I-squared = 0.0%, p = 0.636) | 2.01 (1.02, 3.00) | 12.41  |
| **NSCLC**        |                              |        |
| Song Z (2018)    | 1.78 (0.99, 3.20)            | 9.98   |
| Wu D (2020)      | 2.86 (1.44, 5.69)            | 2.70   |
| Subtotal (I-squared = 0.0%, p = 0.377) | 2.01 (1.03, 2.99) | 12.68  |
| **OTHER**        |                              |        |
| Bu JY (2018)     | 1.97 (1.24, 3.14)            | 13.50  |
| Chen XH (2020)   | 2.10 (1.22, 3.63)            | 8.39   |
| Ho JQ (2020)     | 2.98 (0.52, 17.17)           | 0.18   |
| Li H (2019)      | 0.53 (0.14, 2.00)            | 14.09  |
| Ma XD (2020)     | 7.24 (1.58, 33.10)           | 0.05   |
| Zhang H (2019)   | 1.83 (0.83, 4.03)            | 4.76   |
| Zong MZ (2019)   | 3.35 (1.42, 4.56)            | 2.99   |
| Subtotal (I-squared = 39.3%, p = 0.130) | 1.62 (1.10, 2.15) | 43.95  |

Heterogeneity between groups: p = 0.897
Overall (I-squared = 0.0%, p = 0.737) 1.79 (1.44, 2.14) 100.00
| Study ID  | HR (95% CI)          | Weight |
|----------|----------------------|--------|
| >70      |                      |        |
| Bu JY (2018) | 1.97 (1.24, 3.14) | 13.50  |
| Chen XH (2020) | 2.10 (1.22, 3.63) | 8.39   |
| Deng LL (2016) | 2.27 (1.24, 4.17) | 5.68   |
| Dong XH (2020) | 1.30 (0.44, 3.80) | 4.32   |
| Han QL (2019)  | 2.02 (1.04, 3.92) | 5.88   |
| Ho JQ (2020)   | 2.98 (0.52, 17.17) | 0.18   |
| Liu CC (2018)  | 1.51 (0.74, 3.07) | 8.98   |
| Ma XD (2020)   | 7.24 (1.58, 33.10) | 0.05   |
| Shen MY (2020) | 2.57 (0.98, 6.74) | 1.47   |
| Song Z (2018)  | 1.78 (0.99, 3.20) | 9.98   |
| Zhao XD (2017) | 3.51 (1.57, 7.82) | 1.25   |
| Zong MZ (2019) | 3.35 (1.42, 5.46) | 2.99   |
| Subtotal (I−squared = 0.0%, p = 0.936) | 1.99 (1.55, 2.44) | 62.64  |
| ≤70      |                      |        |
| Li H (2019)  | 0.53 (0.14, 2.00) | 14.09  |
| Wang KN (2018) | 1.79 (0.90, 3.59) | 6.73   |
| Wu D (2020)  | 2.86 (1.44, 5.69) | 2.70   |
| Yu GY (2019) | 2.05 (1.01, 4.14) | 4.97   |
| Zhang H (2019) | 1.83 (0.83, 4.03) | 4.76   |
| Zhang Q (2020) | 1.96 (0.66, 5.84) | 1.82   |
| Zhu LJ (2020) | 1.85 (0.65, 5.26) | 2.29   |
| Subtotal (I−squared = 11.0%, p = 0.345) | 1.51 (0.89, 2.14) | 37.36  |
| Overall (I−squared = 0.0%, p = 0.737) | 1.79 (1.44, 2.14) | 100.00 |

NOTE: Weights are from random effects analysis
Figure 5

| Study ID | HR (95% CI) | Weight |
|----------|-------------|--------|
| Median   |             |        |
| Bu JY (2018) | 1.97 (1.24, 3.14) | 13.50 |
| Dong XH (2020) | 1.30 (0.44, 3.80) | 4.32 |
| Han QL (2019) | 2.02 (1.04, 3.92) | 5.88 |
| Ho JQ (2020) | 2.98 (0.52, 17.17) | 0.18 |
| Li H (2019) | 0.53 (0.14, 2.00) | 14.09 |
| Liu CC (2018) | 1.51 (0.74, 3.07) | 8.98 |
| Song Z (2018) | 1.78 (0.99, 3.20) | 9.98 |
| Wang KN (2018) | 1.79 (0.90, 3.59) | 6.73 |
| Wu D (2020) | 2.86 (1.44, 5.69) | 2.70 |
| Yu GY (2019) | 2.05 (1.01, 4.14) | 4.97 |
| Zhao XD (2017) | 3.51 (1.57, 7.82) | 1.25 |
| Zhu LJ (2020) | 1.85 (0.65, 5.26) | 2.29 |
| Zong MZ (2019) | 3.35 (1.42, 5.46) | 2.99 |
| Subtotal (I−squared = 1.9%, p = 0.427) | 1.70 (1.30, 2.10) | 77.84 |
| Mean     |             |        |
| Chen XH (2020) | 2.10 (1.22, 3.63) | 8.39 |
| Deng LL (2016) | 2.27 (1.24, 4.17) | 5.68 |
| Ma XD (2020) | 7.24 (1.58, 33.10) | 0.05 |
| Shen MY (2020) | 2.57 (0.98, 6.74) | 1.47 |
| Zhang H (2019) | 1.83 (0.83, 4.03) | 4.76 |
| Zhang Q (2020) | 1.96 (0.66, 5.84) | 1.82 |
| Subtotal (I−squared = 0.0%, p = 0.984) | 2.12 (1.38, 2.86) | 22.16 |
| Overall (I−squared = 0.0%, p = 0.737) | 1.79 (1.44, 2.14) | 100.00 |

NOTE:Weights are from random effects analysis.
| Study ID     | HR (95% CI)       | Weight |
|-------------|-------------------|--------|
| **U/M**     |                   |        |
| Chen XH (2020) | 2.10 (1.22, 3.63) | 8.39   |
| Deng LL (2016) | 2.27 (1.24, 4.17) | 5.68   |
| Zhao XD (2017) | 3.51 (1.57, 7.82) | 1.25   |
| Zong MZ (2019) | 3.35 (1.42, 5.46) | 2.99   |
| Subtotal (I-squared = 0.0%, p = 0.662) | 2.45 (1.64, 3.27) | 18.30  |
| **Indirectly** |                   |        |
| Bu JY (2018) | 1.97 (1.24, 3.14) | 13.50  |
| Dong XH (2020) | 1.30 (0.44, 3.80) | 4.32   |
| Han QL (2019) | 2.02 (1.04, 3.92) | 5.88   |
| Ho JQ (2020) | 2.98 (0.52, 17.17) | 0.18   |
| Li H (2019) | 0.53 (0.14, 2.00) | 14.09  |
| Liu CC (2018) | 1.51 (0.74, 3.07) | 8.98   |
| Ma XD (2020) |                   |        |
| Shen MY (2020) | 2.57 (0.98, 6.74) | 1.47   |
| Song Z (2018) | 1.78 (0.99, 3.20) | 9.98   |
| Wang KN (2018) | 1.79 (0.90, 3.59) | 6.73   |
| Wu D (2020) | 2.86 (1.44, 5.69) | 2.70   |
| Yu GY (2019) | 2.05 (1.01, 4.14) | 4.97   |
| Zhang H (2019) | 1.83 (0.83, 4.03) | 4.76   |
| Zhang Q (2020) | 1.96 (0.66, 5.84) | 1.82   |
| Zhu LJ (2020) | 1.85 (0.65, 5.26) | 2.29   |
| Subtotal (I-squared = 0.0%, p = 0.820) | 1.64 (1.25, 2.03) | 81.70  |
| **Overall** (I-squared = 0.0%, p = 0.737) | 1.79 (1.44, 2.14) | 100.00 |

**NOTE:** Weights are from random effects analysis.
### Table

| Study ID | OR (95% CI)   | Weight |
|----------|---------------|--------|
| Dong XH (2020) | 0.70 (0.30, 1.61) | 14.13 |
| Han QL (2019)  | 0.57 (0.19, 1.69)  | 12.11 |
| Ma XD (2020)  | 12.53 (3.63, 43.32) | 10.95 |
| Shen MY (2020) | 1.66 (0.73, 3.73)  | 14.28 |
| Zhang Q (2020) | 0.95 (0.31, 2.96)  | 11.74 |
| Zhao XD (2017) | 1.89 (0.51, 6.99)  | 10.47 |
| Zhu Lj (2020)  | 1.54 (0.42, 5.61)  | 10.57 |
| Zong MZ (2019) | 0.57 (0.30, 1.06)  | 15.76 |
| Overall (I−squared = 70.4%, p = 0.001) | 1.28 (0.67, 2.43) | 100.00 |

### Diagram

![Figure 7](http://portlandpress.com/bioscirep/article-pdf/doi/10.1042/BSR20210012/912607/bsr-2021-0012.pdf)

**NOTE:** Weights are from random effects analysis
| Section/topic | # | Checklist item                                                                                                                                                                                                 | Reported on page # |
|---------------|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| **TITLE**     | 1 | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                              | 1                 |
| **ABSTRACT**  | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2-3               |
| **INTRODUCTION** | 3 | Describe the rationale for the review in the context of what is already known.                                                                                                                                   | 4-5               |
| **Objectives** | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                          | 5                 |
| **METHODS**   | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.                                           | NA               |
| **Protocol and registration** | 5 |                                                                                                                                                                                                                |                   |
| **Eligibility criteria** | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 5                 |
| **Information sources** | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                         | 5                 |
| **Search**    | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                  | 5                 |
| **Study selection** | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                        | 5                 |
| **Data collection process** | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                         | 6                 |
| **Data items** | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                         | 6                 |
| **Risk of bias in individual studies** | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 6                 |
| **Summary measures** | 13 | State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                                                   | 6                 |
| **Synthesis of results** | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis.                                                      | 6                 |
## PRISMA 2009 Checklist

### RESULTS

| Section/topic                  | #   | Checklist item                                                                                                                                                                                                 | Reported on page # |
|-------------------------------|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Risk of bias across studies   | 15  | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).                                                                   | 6                 |
| Additional analyses           | 16  | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.                                                                  | 7                 |

| Section/topic                  | #   | Checklist item                                                                                                                                                                                                 | Reported on page # |
|-------------------------------|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Study selection               | 17  | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.                                              | 7-8               |
| Study characteristics         | 18  | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.                                                                   | 7-8               |
| Risk of bias within studies   | 19  | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).                                                                                                         | 7-8               |
| Results of individual studies | 20  | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.   | 8-9               |
| Synthesis of results          | 21  | Present results of each meta-analysis done, including confidence intervals and measures of consistency.                                                                                                           | 8-9               |
| Risk of bias across studies   | 22  | Present results of any assessment of risk of bias across studies (see Item 15).                                                                                                                               | 10                |
| Additional analysis           | 23  | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).                                                                                           | 10                |

### DISCUSSION

| Section/topic                  | #   | Checklist item                                                                                                                                                                                                 | Reported on page # |
|-------------------------------|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Summary of evidence           | 24  | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).                                  | 10-12             |
| Limitations                   | 25  | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).                                                  | 12                |
| Conclusions                   | 26  | Provide a general interpretation of the results in the context of other evidence, and implications for future research.                                                                                         | 13                |

### FUNDING

| Section/topic                  | #   | Checklist item                                                                                                                                                                                                 | Reported on page # |
|-------------------------------|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Funding                       | 27  | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.                                                                | 14                |

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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed.1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org)
| Author  | Year | Country | Tumor       | Sample size | Cut-off value | Detection method | Outcomes | HR estimation method | HR(95% CI)               | No S |
|---------|------|---------|-------------|-------------|---------------|------------------|----------|----------------------|--------------------------|------|
| Zhao XD | 2017 | China   | HCC         | 88          | Median        | qRT-PCR          | OS/RFS   | U/M                  | OS:3.509(1.574-7.820)   | 8    |
|         |      |         |             |             |               |                  |          |                      | RFS:2.579(1.425-4.668)  |      |
| Liu CC  | 2018 | China   | CRC         | 86          | Median        | qRT-PCR          | OS       | Indirectly           | 1.51(0.74,3.07)          | 8    |
| Yu GY   | 2019 | China   | OC          | 58          | Median        | qRT-PCR          | OS       | Indirectly           | 2.05(1.01,4.14)          | 7    |
| Wang KN | 2018 | China   | TNBC        | 68          | Median        | qRT-PCR          | OS       | Indirectly           | 1.79(0.90,3.59)          | 8    |
| Song Z  | 2018 | China   | NSCLC       | 88          | Median        | qRT-PCR          | OS       | Indirectly           | Tissue: 1.78(0.99,3.20)  | 8    |
|         |      |         |             |             |               |                  |          |                      | Serum: 1.66(0.91,3.05)   |      |
| Li H    | 2019 | China   | Osteosarcoma| 36          | Median        | qRT-PCR          | OS/RFS   | Indirectly           | OS:0.53(0.14,2.00)       | 7    |
|         |      |         |             |             |               |                  |          |                      | RFS:0.56(0.14,2.29)      |      |
| Wu D    | 2020 | China   | NSCLC       | 56          | Median        | qRT-PCR          | OS       | Indirectly           | 2.861(1.439-5.686)       | 8    |
| Chen XH | 2020 | China   | CC          | 75          | Mean          | qRT-PCR          | OS       | U/M                  | 2.104(1.221-3.626)       | 8    |
| Name    | Year | Country | Cancer | Sample Size | Methodology | Endpoint | Hazard Ratio (95% CI) |
|---------|------|---------|--------|-------------|-------------|----------|---------------------|
| Ma XD   | 2020 | China   | OSCC   | 82          | Mean        | qRT-PCR  | OS                  | Indirectly 7.24(1.58,33.10) |
| Dong XH | 2020 | China   | CRC    | 90          | Median      | qRT-PCR  | OS                  | Indirectly 1.30(0.44,3.80) |
| Ho JQ   | 2020 | China   | CCRCC  | 118         | Median      | qRT-PCR  | OS/RFS              | Indirectly OS: 2.98(0.52,17.17) |
| Bu JY   | 2018 | China   | GC     | 150         | Median      | qRT-PCR  | OS                  | Indirectly 1.97(1.24,3.14)  |
| Zhu LJ  | 2020 | China   | OC     | 42          | Median      | qRT-PCR  | OS                  | Indirectly 1.85(0.65,5.26)  |
| Zhang H | 2019 | China   | PC     | 68          | Mean        | qRT-PCR  | OS                  | Indirectly 1.83(0.83,4.03)  |
| Shen MY | 2020 | China   | CRC    | 102         | Mean        | qRT-PCR  | OS/PFS              | Indirectly OS: 2.57(0.98,6.74) |
| Zhang Q | 2020 | China   | HCC    | 49          | Mean        | qRT-PCR  | OS                  | Indirectly 1.96(0.66,5.84)  |
| Deng LL | 2016 | China   | BC     | 195         | Mean        | qRT-PCR  | OS                  | U/M 2.27(1.237,4.165) |
| Han QL  | 2019 | China   | HCC    | 73          | Median      | qRT-PCR  | OS                  | Indirectly 2.02(1.04,3.92)  |
| Zong MZ | 2019 | China   | ESCC   | 175         | Median      | qRT-PCR  | OS/DFS              | U/M OS:3.347(1.423,5.457) DFS:3.568(1.537,5.778) |
Note: HCC: hepatocellular carcinoma; CRC: colorectal adenocarcinoma; OC: ovarian carcinoma; TNBC: triple-negative breast cancer; NSCLC: non-small cell lung cancer; CC: Cervical cancer; CCRCC: clear cell renal cell carcinoma; OSCC: oral squamous cell carcinoma; PC: prostate carcinoma; BC: breast cancer; GC: gastric cancer; ESCC: esophageal squamous cell carcinoma; OS: overall survival; RFS: Recurrence-free survival; PFS: progression-free survival; DFS: disease free survival; U/M: univariate/multivariate analysis; NOS: Newcastle-Ottawa Scale
Table 2. The clinicopathological features of the included studies.

| Author    | Year | AWPPH expression | TNM | Tumor size | Macro-vascular invasion | Lymph node metastasis |
|-----------|------|------------------|-----|------------|-------------------------|----------------------|
|           |      | high             | low | >I stage in HG | >I stage in LG | >50 in HG | >50 in LG | Yes in HG | YES in LG | Yes in HG | YES in LG | |
| Zhang Q   | 2020 | 26               | 23  | 16         | 16             | 14        | 14        | 10        | 7         |           |           |
| Zhu LJ    | 2020 | 21               | 21  | 11         | 7              |           |           |           | 13        | 6         |           |
| Ma XD     | 2020 | 20               | 62  | 12         | 22             |           |           |           | 9         | 8         |           |
| Dong XH   | 2020 | 45               | 45  | 24         | 10             | 29        | 17        |           | 32        | 30        |           |
| Han QL    | 2019 | 37               | 36  | 19         | 8              | 25        | 9         |           |           |           |           |
| Shen MY   | 2020 | 55               | 47  | 30         | 15             | 40        | 15        |           | 38        | 14        |           |
| Zhao XD   | 2017 | 44               | 44  | 33         | 24             | 26        | 24        | 28        | 18        |           |           |
| Zong MZ   | 2019 | 87               | 88  | 39         | 24             |           |           |           | 35        | 22        |           |
| Wang KN   | 2018 | 34               | 34  | 26         | 14             | 14        | 5         |           |           |           |           |
| Ho JQ     | 2020 | 59               | 59  | 32         | 11             |           |           |           |           |           |           |
|   |   |   |   |   |
|---|---|---|---|---|
| Deng LL | 2016 | 49 | 146 | 18 | 37 |
| Zhang H | 2019 | 31 | 37 | 17 | 21 |
| Li H | 2019 | 19 | 17 | 15 | 6 |
| Yu GY | 2019 | 29 | 29 |   |   |
| Song Z | 2018 | 44 | 44 |   |   |

Note: HG represented the group with high AWPPH expression, LG represented the group with low AWPPH expression.
Table 3. The p-values obtained from either the fixed or random model for the risk association analyses

| Risk factors           | Models     | P value |
|------------------------|------------|---------|
| Differentiation        | random effect | 0.45    |
| Distant metastasis     | random effect | 0.854   |
| Lymph node metastasis  | fixed model | <0.001  |
| Macro-vascular invasion| fixed model | 0.039   |
| TNM stage              | fixed model | <0.001  |
| Tumor size             | random effect | 0.001   |