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Unfavorable prognosis and clinical consequences of APOBEC3B expression in breast and other cancers: A systematic review and meta-analysis

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Abstract.
INTRODUCTION: Controversy exists regarding the association of apolipoprotein B mRNA editing enzyme catalytic subunit 3B *APOBEC3B*, (*A3B*) overexpression and poor prognosis, metastasis, and chemotherapy drug resistance in cancers. Here we conducted a systematic review and meta-analysis to determine its prognostic value and clinicopathological features in breast cancer and some other malignancies.
MATERIALS AND METHODS: PubMed, Scopus, Cochrane Library, Web of Science, and EMBASE were searched up to Feb 2022 for the association of *A3B* with breast, ovarian, gastrointestinal and lung cancers. The pooled hazard ratios with 95% confidence interval (CI) were evaluated to assess disease-free survival (DFS), overall survival (OS), and recurrence-free survival (RFS) in cancers under study.
RESULTS: Over 3700 patients were included in this meta-survey. Elevated levels of *A3B* were significantly related to low OS (pooled HR = 1.30; 95% CI:1.09–1.55, $P < 0.01$), poor DFS (pooled HR = 1.66; 95% CI:1.17–2.35, $P < 0.01$) and poor RFS (HR = 1.51, 95% CI:1.11–2.04, $P = 0.01$). Subgroup analysis revealed that high *A3B* expression was associated with poor OS in lung (HR = 1.85, 95% CI: 1.40– 2.45), and breast cancers (HR = 1.38, 95% CI: 1.00–1.89). High expression of *A3B* did not display any significant association with clinicopathologic features.
CONCLUSION: *APOBEC3B* overexpression is related to poor OS, DFS and RFS only in some cancer types and no generalized role could be predicted for all cancers.

Keywords: *APOBEC3B*, *A3B*, overall survival, prognosis, biomarker

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1. Introduction

Cancer is regarded as major cause of mortality and morbidity all over the world [1]. In the year 2020, 19.3 million new cancer patients and 10.0 million cancer-associated deaths were reported worldwide. According to GLOBOCAN, 28.4 million new cancer cases are predicted for the year 2040 worldwide [2]. Despite many advances in cancer diagnosis and treatment, the cancer mortality rate is still high and cancer remains a major health problem all over the world [3–5]. It is generally believed that the accumulation of diverse mutations are important driving force for the development of neoplasia [6]. Mutations may originate from exogenous sources which are categorized as environmentally induced or rooted intracellularly [7]. DNA repair systems and their enzyme components are speculated as endogenous mutation sources. Based on the analyses of data from The Cancer Genome Atlas (TCGA), it is reported that APOBEC cytidine deaminase mutagenesis patterns are evident in cancers and could be implicated in the induction of somatic mutations leading to genome instability and carcinogenesis [8, 9].

APOBEC3 or A3 proteins are DNA cytidine deaminases that have a remarkable role in mutations in many different types of cancers [10, 11]. This family is specific to mammals, and in humans comprises seven members (A, B, C, D, F, G, and H) which are highly homologous. Their genes are located in a tandem cluster on chromosome 22q13; the proteins are involved in innate immunity and anti-viral immune response [12–14]. Current evidence, mainly resulting from studies on yeasts, suggest that APOBEC3A and APOBEC3B are responsible for somatic mutations in human cancers [15, 16] but due to the conflicting outcomes from studies performed on tumors, the mutagenic nature and role of APOBEC subtypes in various human cancers are not fully elucidated yet [17, 18].

Out of the seven members of the APOBEC3 enzyme family, APOBEC mutagenesis in tumors is attributed to A3A and A3B enzymes. Positive connection between mRNA level of A3A and A3B enzymes and APOBEC-signature mutations in tumors as well as *in vitro* overexpression studies strongly confirmed that high activity of these enzymes is mutagenic and genotoxic [7, 19]. Conclusions regarding the role of *A3A* and *A3B* expression in mutagenetic processes were mainly drawn through RNA-seq studies despite the fact that these highly homologous APOBECs are poorly resolved and their mRNAs cannot be confidently quantified by short sequencing reads. The dominant mutagenic potentials of *A3A* or *A3B* expression in different cancers are highly debated. For example, Banday et al. [20] based on their observations reported that *A3B* and not *A3A* is expressed in bladder cancer cell lines, which show a high load of APOBEC-signature mutations, demonstrating that in some cancer cell lines APOBEC-mediated mutagenesis is dominantly caused by the *A3B* activity. Tsubo M et al. [21] quantified A3B mRNA expression by RT-qPCR in fresh frozen tumors and paired adjacent normal breast tissue samples and reported that *A3B* mRNA expression was significantly higher in tumors comparing to the adjacent normal tissues.

Recently the clinical significance of A3B is extensively investigated because of its relevance to survival endpoints including DFS, OS, RFS in cancer patients [22, 23]. A3B is a unique member of the family with permanent nuclear localization [24]. This gene has cytidine deaminase activity and contains one catalytically active C-terminal domain (CTD) that bound to ssDNA and N-terminal pseudo-catalytic domain (NTD) [16, 25].

A3B is considered to induce mutation in breast cancer and overexpression of *APOBEC3B* is reported in variety of cell lines [26]. Also, A3B is introduced as the main factor contributing to mutations in various human cancers [16]. The expression of *A3B* is linked to the accumulation of somatic mutations during tumorigenesis and progression [26–28]. Recent studies have reported that *A3B* is significantly up-regulated in many cancers like ovarian, cervix, breast, lung, head & neck, and bladder [29, 30]. Abnormal overexpression of A3B promotes mutations in the *PIK3CA* gene in several human cancers [31, 32]. Through the knockdown experiments, it is revealed that endogenous A3B correlates with higher levels of genomic uracil, elevated frequencies of pathogenic mutations, and C-to-T transitions.

Also, experimentally *A3B* overexpression results in cell cycle deviation and cell death, DNA fragmentation and aggregation of γH2AX. Phosphorylation of H2AX in the Ser-139 residue causes the formation of γH2AX which is biomarker of DNA damage and genotoxicity [26, 33, 34].

There are different perspectives on the link between A3B and the cell cycle. Lackey et al. reported that the expression pattern of *A3B* is similar during the mitosis phase and S phase [35]. But, Hirabayashi et al. found that *A3B* mRNA is the only member of the APOBEC3 family that is differentially expressed at the G2/M-phase in myeloma and bone marrow mononuclear cells [36]. Ma et al. hypothesized that *A3B* expression induces human hepatocellular carcinoma (HCC) tumorigenesis through deaminase-independent activity and increases cycle progression in HCC cells [37]. McCann et al. stated that *A3B* can bind to *CDK4* and inhibit CDK4-dependent nuclear translocation of cyclin D1, thus delaying cell cycle progression. Overexpression of A3B leads to G1/S phase stalling and increases A3B access to its substrate (ssDNA). Thus, it may enhance the likelihood of mutation and genomic DNA deamination [38]. In addition, pan-cancer analysis showed that the expression of *A3B* is related to cell cycle-regulated genes [39]. Although these evidences proposed that cell cycle-dependent activities are linked to the regulation of expression of *A3B*, little is known about the mechanism of cell cycle-dependent regulation of *A3B* expression and many questions remain unresolved.

Recently, Du et al. argued that high expression of *APOBEC3B* was linked to worse OS and DSF in patients affected with ovarian cancer [40]. Besides, *A3B* upregulation can induce the expression of some immunotherapy response genes like; T-cell infiltration and PD-L1 in non-small cell lung cancer (NSCLC) patients, so it can be used as a predictive biomarker [41].

Although deregulation of *APOBEC3B* has been reported in many cancer types, the conclusions about the prognostic value of *A3B* for patients remain controversial. A large number of studies reported that high *A3B* expression is linked with adverse outcomes or poor prognosis in cancer patients [40, 42–44]. However, several studies reported that *A3B* expression improved OS in patients with cancer or have no correlations with disease-free or overall survival [32, 45, 46]. To date, no meta-analysis has been performed to comprehensively assess the prognostic significance of *APOBEC3B* expression in cancer patients. Therefore, we performed a systematic review and meta-analysis based on previously published data to assess the link between *APOBEC3B* expression and the clinicopathological factors and survival in patients with diverse types of cancer.

2. Materials and methods

2.1. Study strategy

We conducted the present study based on the standard guidelines (PRISMA Checklist) [47]. Two researchers (SJ and RS) separately searched the databases of the Cochrane Library, PubMed, Scopus, Web of Science, and EMBASE to collect all related studies published up to Feb 2022. The following Medical Subject Heading terms were used in this study: ("Cancer" OR "Tumor" OR "Carcinoma" OR "Neoplasm" OR "malignancy") AND ("APOBEC3B" OR "A3B" OR "Apolipoprotein B mRNA Editing Enzyme"). First the abstract and the title of the publications were retrieved and the full text of relevant articles were reviewed to make sure that the data of interest were included. Any conflicts were solved through discussion with a third researcher.

2.2. Inclusion and exclusion criteria

Studies included in this analysis were selected using the following criteria: 1) Studies were published as full paper in English 2) Any type of human malignancy or cancer was pathologically proven in

patients 3) Expression of *APOBEC3B* was evaluated in human tissues using any technique 4) Patients were divided into two groups (high /low or positive /negative) according to the expression levels of *A3B* and the correlations between *A3B* expression and clinicopathological data and/or survival outcome was investigated 4) Studies calculated hazard ratio (HR) for the prognostic outcome and odds ratios (ORs) for clinicopathological characteristics or provided sufficient data to extract them. Studies with insufficient data, non-human samples, reviews, reports, letters, and meeting abstracts were excluded.

2.3. Data extraction

Two researchers (SJ and RS) independently collected the following data from the studies: the first author's name, year of publication, tumor type, sample size, follow-up time, country/geographic region of the population, detection method, cut-off values, source of HRs, outcome and other related data. Overall survival, progression-free survival (PFS), disease-free survival and relapse-free survival (RFS) were considered as outcome. Hazard ratio (HR) and 95% confidence interval (CI) were extracted from text or calculated from the survival curves by using Tierney's method. Any disagreements were solved through discussion.

2.4. Quality assessment

Two authors (SJ and RS) evaluated the quality of articles independently using the Newcastle-Ottawa scale (NOS) rating system (0–9 stars). Studies with at least six scores were identified as high-quality studies. Any disagreements were solved by discussion.

2.5. Statistical analysis

To evaluate the connection between *A3B* and the clinicopathological factors in patients with cancer, ORs with corresponding 95% confidence intervals [48] were calculated. Our analysis was performed by pooling the HRs and 95% CIs of survival outcomes (OS, DFS, RFS) directly from the included studies. Some studies depicted the prognosis outcomes as Kaplan-Meier curves and in these cases, by the Get Data Graph Digitizer (version 2.24) the curves were read to contract HR estimates based on the Tierney et al. method [49]. For checking statistical heterogeneity between studies, the Higgins I2 statistic and Chi-Square test were applied. The random-effect model and subgroup analysis were applied to find the heterogeneity. To find any possible publication, bias Funnel plots combined with Begg's and Egger's linear regression tests were used. To evaluate the influence of each study on the combined effect values, sensitivity analysis was employed. The statistical analyses were carried out using the Stata13.0 software (Stata Corporation, College Station, TX) and metapackage under R 3.6.3 [50].

3. Results

3.1. Characteristics of studies

A total of 846 articles were obtained using the primary search according to PRISMA guidelines. Based on our defined exclusion criteria, 827 papers were excluded. Detailed excluding criteria and the number of papers failed to attain eligibility criteria are as follow: irrelevant studies ($n = 321$), duplicates ($n = 243$), reviews ($n = 17$), congress and scientific meeting abstracts ($n = 21$), letters ($n = 4$),

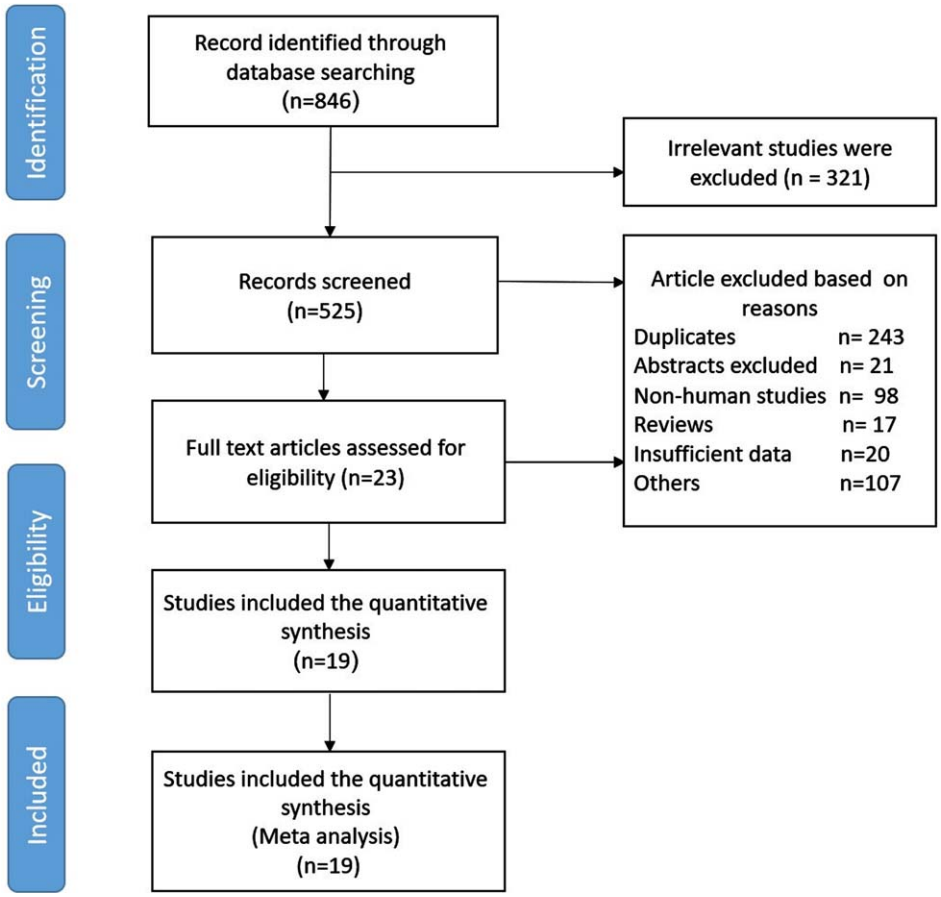

Fig. 1. Flow diagram of the study selection process in meta-analysis.

noncancerous studies ($n = 99$), animal studies ($n = 98$), cell line studies ($n = 4$), and studies lacking sufficient data ($n = 20$). Finally, 19 studies were included for this meta-analysis. The flow diagram of article selection is shown in Fig. 1. Among the 19 studies, 4 were from Japan, nine from China, three from the USA, the other three from Germany, the Netherlands and South Korea. The included studies contained seven types of cancers, namely breast cancer ($n = 5$), ovarian cancer ($n = 4$), non-small cell lung cancer ($n = 2$), nasopharyngeal carcinoma ($n = 1$), renal cell carcinoma ($n = 1$), gastric cancer ($n = 2$), squamous cell carcinomas ($n = 2$), neuroendocrine tumors ($n = 1$), bladder cancer ($n = 1$). In 11 studies the *A3B* expression level was detected by immunohistochemistry (IHC) and eight studies performed real time quantitative PCR (qRT-PCR) to detect *A3B* expression. The cut-off values for *A3B* expression were different among studies due to various definitions.

3.2. Study quality

NOS scores of all included studies ($n = 19$) ranges from 6 to 8. More information about the papers included in this study is given in Table 1.

Table 1
Characteristic of the included studies

Study	Year	Country	Cancer Type	Sample size	Follow-up (month)	Detection method	Cut-off value	Evaluation of expression (H or L /+or –)	Expression associated with poor prognosis	Source of HR	Outcome
Kim H, et al. [69]	2021	Korea	Metastatic Urothelial Carcinoma	94	NA	IHC	NA	High/low	Low	1	OS, PFS
Xia S, et al. [70]	2021	China	Gastric cancer	482	42	IHC	Mean	High/low	High	1	OS, DFS
Feng C, et al. [71]	2021	China	NPC	103	60	IHC	Median	High/low	High	NA	NA
Serebrenik A, et al. [45]	2020	USA	CCOC	48	24	IHC	Median	High/low	Low	1	OS PFS
Mao Y, et al. [44]	2020	China	Breast Cancer	116	97	IHC	Median	High/low	High	1,2	OS, RFS, DSF, DMFS
Gara SK, et al. [42]	2020	USA	ACC	38	NA	RT-qPCR	Median	High/low	High	1	OS
Feng C, et al. [72]	2019	China	GEP-NENs	158	NA	IHC	Median	High/low	High	NA	NA
Yan Du, et al. [29]	2018	China	Ovarian cancer	88	74.77	IHC	Positive $\geq 25\%$	Positive/ Negative	High	1	OS, DFS
Fujiki Y, et al. [46]	2018	Japan	Breast Cancer	173	63	RT-qPCR	NA	High/low	High	2	RFS

Rüder U, et al. [73]	2018	Germany	Ovarian cancer	469	NA	IHC, mRNA	Median	Positive/ Negative	High	1	OS PFS
Jiang Ch, et al. [74]	2018	China	NSCLC	203	60	IHC	Median	High/low	High	1	OS
Tokunaga E, et al. [75]	2016	Japan	Breast Cancer	305	59.16	RT-qPCR	Median	High/low	High	1	RFS
Leonard B, et al. [76]	2016	USA	HGSOC	354	NA	RT-qPCR	Median	High/low	Low	1	OS PFS
Yan Sh, et al. [43]	2016	China	NSCLC	221	60	IHC	Median	High/low	High	1	OS, DFS
Kosumi K, et al. [32]	2016	Japan	ESCC	147	45.6	IHC	Median	High/low	High	2	OS, DFS
Xu L, et al. [77]	2015	China	RCC	299	67	IHC	Median	High/low	High	1	RFS
Zang J, et al. [78]	2015	China	Gastric cancer	236	NA	IHC, RT-qPCR	Median	High/low	High	NA	NA
Tsuboi M, et al. [21]	2015	Japan	Breast Cancer	93	NA	RT-qPCR	Mean	High/low	High	2	OS, DFS
Sieuwerts AM, et al. [79]	2014	Netherlands	Breast Cancer	149	NA	RT-qPCR	Median	High/low	High	1	OS, DFS, MFS

NA: Not available, NPC: Nasopharyngeal carcinoma, NSCLC Non-small-cell lung carcinoma, CCOC: Clear cell ovarian carcinoma, RCC: Renal cell carcinoma, HGSOC: High-grade serous ovarian carcinoma, ACC: Adrenocortical carcinoma, GEP-NENs: Neuroendocrine neoplasms, HGSOC: Ovarian carcinoma, ESCC: Esophageal squamous cell carcinoma.

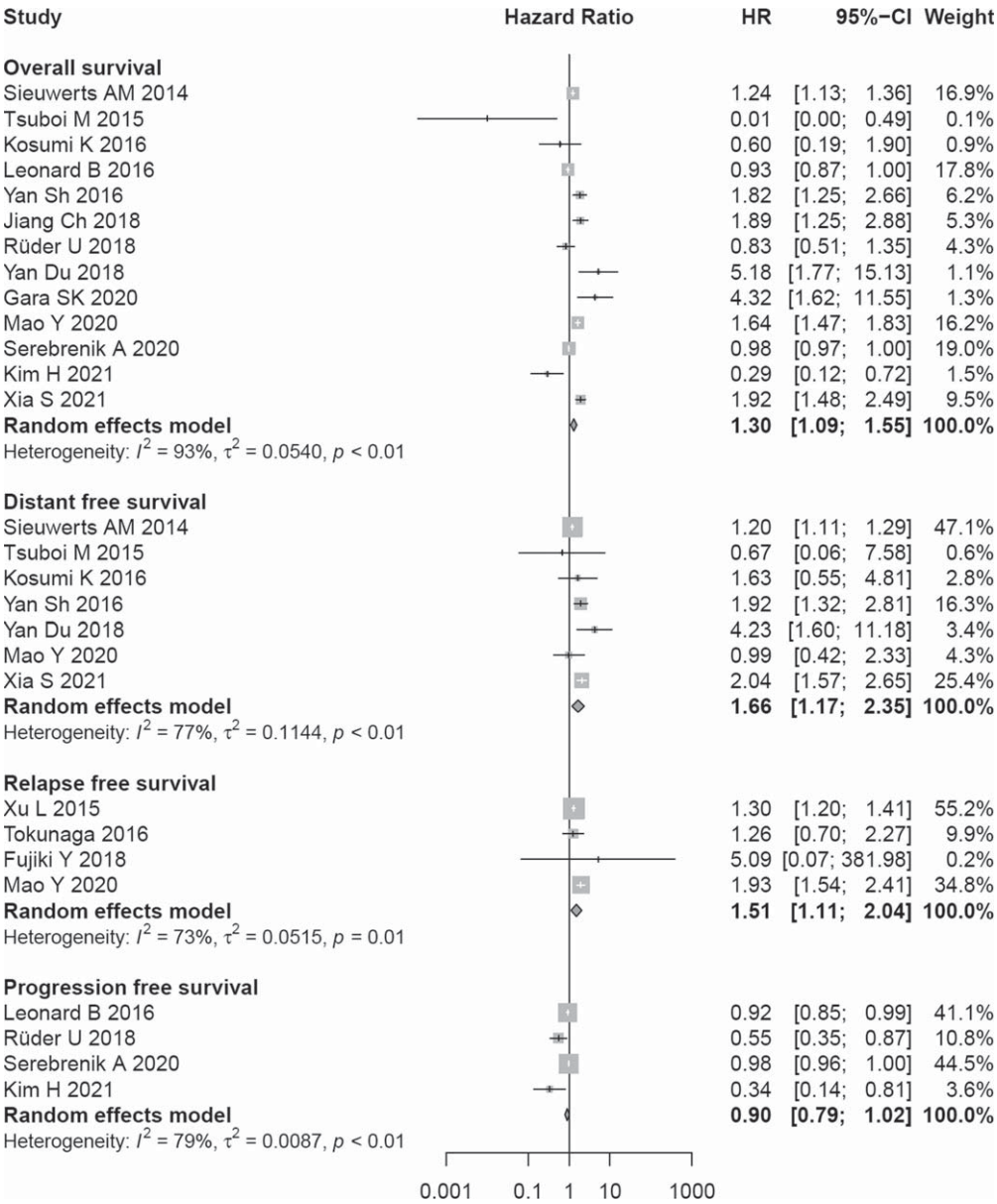

Fig. 2. Association between *A3B* expression and survival outcomes.

3.3. Relationship of A3B overexpression and prognosis outcome

A total of 13 studies with 2502 patients had reported the relationship between OS and *A3B* expression level. The random-effects model was used due to heterogeneity ($I^2 = 93\%$, $P < 0.01$).

Poor prognosis was significantly associated with higher *A3B* expression (pooled HR = 1.30; 95% CI:1.09–1.55) (Fig. 2). Subgroup analysis showed that *A3B* expression was associated with OS of patients with lung cancer (HR = 1.85, 95% CI:1.40– 2.45), and breast cancer (HR = 1.38, 95% CI:1.00–1.89). For the rest of cancers, no statistically significant results were obtained (Table 2).

To differentiate between RT-qPCR and IHC techniques used to determine A3B expression, subgroup analysis was performed. Only high expression of A3B detected by IHC method (8 studies)

Table 2
Results of subgroup analysis of pooled HRs with regard to overall survival

		n. study	HR	95% CI	I^2 %	p Heterogeneity
Overall		13	1.30	(1.10–1.55)	93.4	0.004
Region	East Asia	8	1.50	(1.08–2.08)	76.6	< 0.001
	USA	3	0.98	(0.87–1.09)	81.9	0.004
	Europe	2	1.09	(0.76–1.57)	60.9	0.110
Detection Method						
	IHC	8	1.41	(1.02–1.97)	95.1	< 0.001
	RT-qPCR	5	1.10	(0.83–1.47)	89.5	< 0.001
Cancer Type						
	Ovarian	4	0.97	(0.87–1.08)	75.0	0.007
	Breast	3	1.38	(1.00–1.89)	90.4	< 0.001
	Gastrointestinal	2	1.24	(0.41–3.74)	73.1	0.054
	Lung	2	1.85	(1.40–2.45)	0.0	0.896
	Others	2	1.12	(0.08–15.66)	93.6	< 0.001

CI = confidence interval, HR = hazard ratio, calculated by random effects meta-analysis.

was associated with overall survival (HR = 1.41, 95% CI:1.02–1.97). Subgroup analysis based on geographic regions showed correlation in patients from the East Asia region with 8 studies (HR = 1.50, 95% CI:11.08–2.08) (Table 2). Sensitivity analysis demonstrated that our result was stable based on estimates of the HRs (Fig. S1a). There was no evidence of publication bias by the Egger test ($P = 0.123$) and the Begg test ($P = 0.329$) (Fig. S1b).

A total of 7 studies with 1296 patients had reported the relationship between poor DFS and *A3B* expression level. The random-effects model was used due to heterogeneity ($I^2 = 77\%$, $P < 0.01$). Poorer outcome in terms of DFS was significantly associated with higher A3B expression (pooled HR = 1.66; 95% CI:1.17–2.35) (Fig. 2). Sensitivity analysis displayed that the result was stable based on estimates of the HRs (Fig. S2a). There was no evidence of publication bias by the Egger test ($P = 0.201$) and the Begg test ($P = 0.881$) (Fig. S2b).

A poor prognosis in terms of RFS also was associated with higher expression of *A3B* (HR = 1.51, 95% CI:1.11– 2.04, no. of studies = 4). A total of 4 studies reported the relationship between poor PFS and *A3B* expression level. The random-effects model was used due to heterogeneity ($I^2 = 79\%$, $P < 0.01$). Poorer outcome in terms of PFS was not associated with higher A3B expression (pooled HR = 0.90; 95% CI:0.79–1.02) (Fig. 2).

3.4. Association of A3B expression with age and gender groups

Subgroup analysis on the basis of age and gender was performed in relation to *A3B* expression but the results were not statistically significant (OR = 0.87, 95% CI:0.59–1.26, OR = 1.28, 95% CI:0.79–2.09) respectively (Fig. 3).

3.5. Association of A3B expression and clinical stage

OR values and corresponding CIs were pooled to evaluate the relationship between *A3B* expression and clinicopathological data. From the data of 10 studies, *A3B* expression was not associated with cancer stage (OR = 1.54, 95% CI: 0.95–2.50, $I^2 = 70\%$) (Fig. 4). In a subgroup analysis, higher expression of

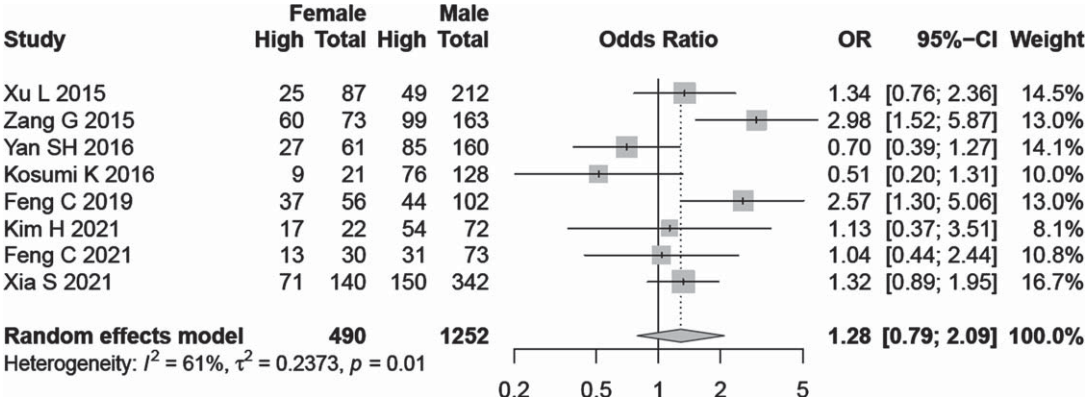

Fig. 3. Forest plot regarding the association of *A3B* expression with age and gender.

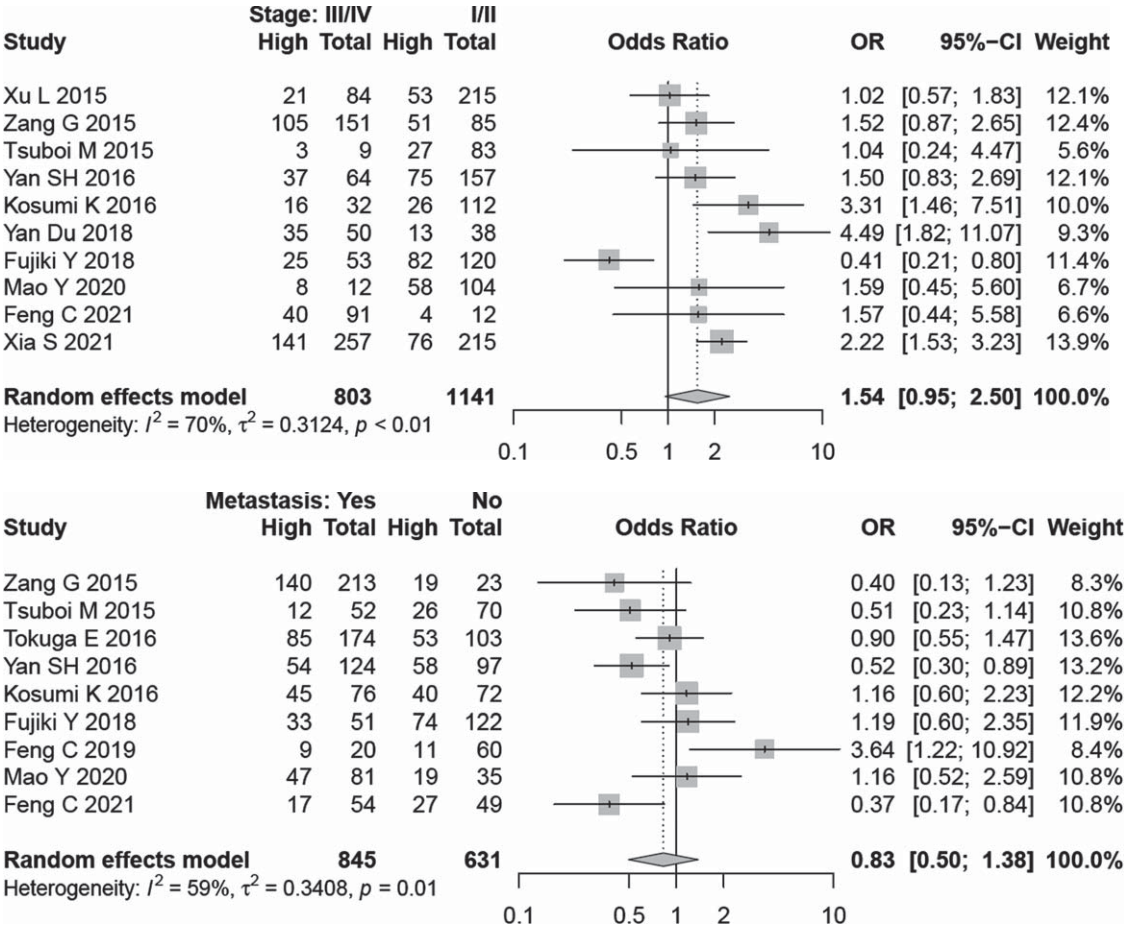

Fig. 4. Forest plot for the association between *A3B* expression and lymph node metastasis /cancer stage.

A3B detected by IHC method was associated with advanced tumor stage in all cancer types (OR = 1.89, 95% CI: 1.17– 3.07, I^2 = 50.6%, no. of studies = 6). There was no evidence of publication bias by Begg (P = 0.788) and Egger's test (P = 0.830) (Fig. S3)

3.6. Association of A3B expression and lymph node metastasis

Nine studies comprising 1476 patients were evaluated to assess *A3B* expression and lymph node dissemination. A random-effect model was applied because of inter-study heterogeneity ($I^2 = 59.0\%$, $P = 0.01$). The outcome is indicated that *A3B* expression has no relation with lymph node metastasis (OR = 0.83, 95% CI: 0.50–1.38) (Fig. 4).

The determined OR values remained the same by excluding any single article (Fig. S4). Begg funnel plot was symmetric ($P = 1.0$) and Egger test did not show a significant publication bias ($P = 0.756$) (Fig. S4).

3.7. Association of A3B expression with grade and tumor size

Eleven studies covering 2145 patients were analyzed for assessing the relationship of *A3B* expression and the clinical grade of tumors. A random-effect model was applied because of the inter-study heterogeneity ($I^2 = 79.1\%$, $P < 0.01$). Although half of the studies implied a direct association of clinical grade with higher *A3B* expression, overall effect size did not show a significant association (OR = 1.62, 95% CI: 0.94–2.77) (Fig. 5).

The determined OR values remained the same by excluding any single article (Fig. S5). Begg funnel plot was symmetric ($P = 0.484$) and Egger test did not show a significant publication bias ($P = 0.822$) (Fig. S5). *A3B* expression was not significantly correlated with tumor size (OR = 1.20, 95% CI = 0.45–2.24) (Fig. 5).

4. Discussion

Cancer is the most important challenge for life expectancy in both developing and developed countries of the world [1, 51]. Despite advances in clinical and molecular research to find effective biomarkers with prognostic significance in cancers, but steady rise in cancer incidence is indicative of the urgent need for reliable and effective cancer screening/prognosis biomarkers [52]. *APOBEC3B* is one of the main sources of mutagenesis in several human cancers including lung, bladder, head and neck, cervix, breast, etc [30, 53, 54]. Recently, many studies reported an abnormal expression of *A3B* in multiple cancer types which may contribute to the poor prognosis and therapeutic resistance [41, 55, 56]. Although the significance of A3B as a mutation source is becoming well-acknowledged, the prognostic value of *A3B* expression in cancers remains controversial. In this meta-analysis, we investigated the prognostic value and clinicopathological features of *A3B* expression in cancer patients. We evaluated survival data of 3776 patients in 19 studies. Our meta-analysis revealed that increased *A3B* expression was closely associated with poor OS, poor DFS and poor RFS in some of cancers.

To reduce the heterogeneity of studies, the sub-group and meta-regression analysis were conducted by factors including study region, cancer type, detection method and expression measurement method either by protein or mRNA quantification. Results from stratified analysis by study region showed that the associations between high *A3B* expression and poor OS were significant in the East Asia region but not in non-Asian populations, suggesting that the relation between *A3B* expression and poor OS could be ethnic-dependent. In the subgroup analysis based on cancer type, *APOBEC3B* expression was associated with poor OS in lung and breast cancer but this was not true in the case of ovarian cancer. This may be indicative of that *A3B* might have different biological behaviors and clinical characteristics in various cancer types.

Results from stratified analysis by method showed that the associations between high *A3B* expression and poor OS were significant in the studies that used the IHC method but not RT-qPCR. There is a

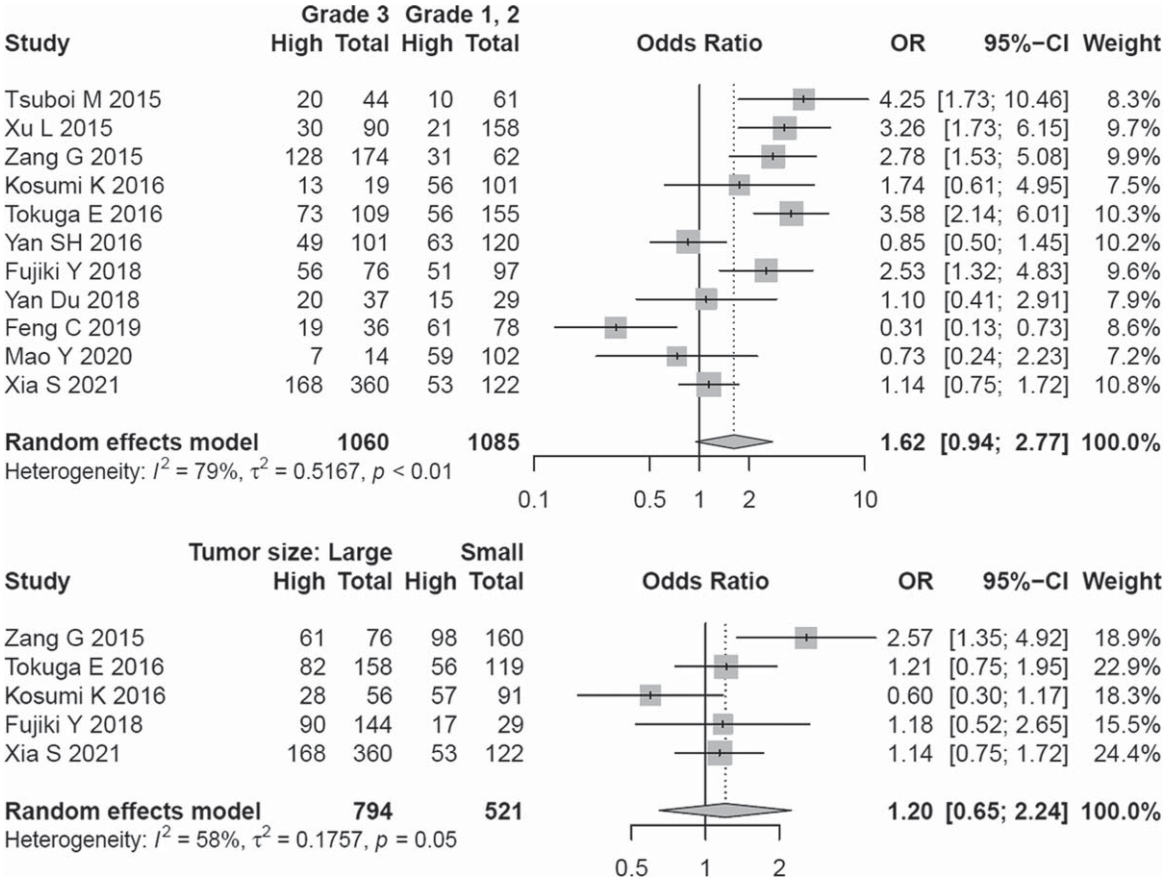

Fig. 5. Forest plot regarding the association of *A3B* expression and grade / tumor size.

possible explanation for these results. *APOBEC3* family have considerable nucleotide identity at the mRNA level so these high identities make some complication to the quantification of the mRNA expression [57–59]. Some of the included studies used RT-qPCR and their result may be affected by these high identities.

In addition, the role of *A3B* in cancer metastasis and progression should also be considered. For example, *A3B* overexpression can cause genomic instability in human cells by inducing C-to-T transitions which might lead to tumorigenesis [6]. Additionally, Yamazaki et al. found that highly expressed *A3B* in myeloma cells causes DNA substitutions and deletions. This shows that *A3B* could induce mutations in the tumor genome in a way that bypasses the DNA repair mechanism, potentially leading to genomic instability in myeloma [60]. Saito et al. also observed that irradiation can induce *APOBEC3B* expression and may lead to radiation-induced mutation in HepG2, HeLa and SAS cells [61].

The role of *A3B* expression in different malignancies suggested that common signaling pathways in various cancer types are likely to be involved in dysregulation of *A3B* expression. Maruyama et al. found that high expression of *A3B* has been induced by the PKC/IKK/NFkB signaling pathway in various cancer cells, which might lead to the accumulation of somatic mutations and genetic diversity in many common cancers [62]. Also, P53 is a serious inhibitor for *A3B* expression in cells and limits its mutagenicity. In cancer cells due to the loss of p53 through mutation, *A3B* overexpression can elevate the power of mutagenesis and tumor evolution [63].

Chemotherapy is the first-line approach to destroy cancer cells for many cancers. Recent, studies showed that *A3B* expression is correlated with resistance to chemotherapy. Periyasamy et al. found that chemotherapy can promote *A3B* expression via DNA-PKcs and ATM-mediated activation of the NF-κB pathways and therefore decrease the efficacy of chemotherapeutic treatments [64]. Serebrenik et al. suggested that in ovarian cancer, *APOBEC3B* is a predictive biomarker of response to platinum-based chemotherapy [45]. Furthermore, in ER-positive breast cancer, *A3B* expression can induce tamoxifen resistance. Such observations suggest that *A3B* has a role in the progression of tumors and inhibiting *APOBEC3B* expression might improve the efficacy of cancer treatments [65].

Mutation in *A3B* gene was reported to play role in malignancy development. For example, Radmanesh et al. demonstrated that truncating variant at the *A3B* locus (c.783delG) is related to the risk of breast cancer and early onset of the disease [66]. The results of one meta-analysis revealed that 30 kb *APOBEC3B* deletion can decrease *A3B* expression and does not link to the risk of breast and ovarian cancers in the European population [67]. However, Cescon et al. proved that in breast cancer, *A3B* overexpression reflects mitosis and cell cycle-related gene expression, whereas a deletion polymorphism is linked to immunological activation. The authors proposed that the A3Bdel polymorphism could be utilized to predict cancer immunotherapy [68].

In spite of the inspiring results, there are several limitations in the current meta-analysis that need to be taken into consideration. First, the cut-off value and detection method for *APOBEC3B* expression varied among the included studies, which may cause heterogeneity and bias. Second, all the studies included in our meta-analysis were in English, which might bring selection bias. Third, only a few included studies evaluated PFS and DFS, which might result in bias. Fourth, most of the eligible studies were conducted in Asia, this might also lead to bias and our results might be more relevant to Asian patients. Fifth, immune infiltration into the tumor microenvironment may contribute to an increase of APOBEC3B expression in qPCR measurements and may lead to bias. Finally, some HRs and 95% CIs were not mentioned directly in the included studies. Then, we extracted them from Kaplan–Meier curves which could not be precise enough.

In conclusion, to the best of our knowledge, the present study is the first comprehensive meta-analysis exploring the prognostic value of *APOBEC3B* overexpression in various cancers. The results indicated that high *APOBEC3B* expression is significantly related to poor clinical outcomes in cancer patients especially breast cancer. Therefore, *APOBEC3B* overexpression might be used as an adverse prognostic biomarker for cancer patients. However, further high quality studies are needed to strengthen these findings.

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Author contributions

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Conflict of interest

The authors have declared no conflict of interest.

Supplementary material

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