Diagnostic value of aldo-keto reductase family 1 member B10 in human nasopharyngeal carcinoma

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Abstract. Aldo-keto reductase family 1 member B10 (AKR1B10) is a potential marker of several types of cancer; however, the role of AKR1B10 in nasopharyngeal carcinoma (NPC) remains unclear. In the present study, AKR1B10 RNA-seq data and clinical information were obtained from The Cancer Genome Atlas head and neck squamous cell carcinoma (HNSCC) database to evaluate the role of AKR1B10 in HNSCC. There was no statistically significant difference in the expression of AKR1B10 between HNSCC tissues and adjacent normal tissues, and high AKR1B10 expression was not associated with poor overall survival according to the public database. The present study further examined the role of AKR1B10 in patients with NPC using data obtained from the Gene Expression Omnibus database. Analysis of the GSE53819 and GSE61218 datasets showed that the there were no significant differences in the expression levels of AKR1B10 between NPC tissues and normal tissues. However, analysis of the GSE103611 dataset indicated that AKR1B10 may be associated with distance metastasis following radical treatment in NPC. Finally, serum samples from patients with NPC and healthy controls were collected and analyzed. The results revealed that AKR1B10 levels were significantly increased in samples from patients with NPC compared with those from healthy controls, and the area under the receiver operating characteristic curve was 0.909. In conclusion, unlike tissue AKR1B10 expression, serum AKR1B10 levels may be a promising biomarker for the diagnosis of NPC.

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Introduction

Nasopharyngeal carcinoma (NPC) is a type of cancer that arises from the nasopharyngeal epithelium. In 2020, ~133,354 new cases of NPC were diagnosed in 185 countries worldwide accounting for 0.7% of all cancer cases (1). The incidence of NPC has an age-standardized rate of 3.0/100,000 individuals in China and 0.4/100,000 individuals in predominantly Caucasian populations. Notably, its incidence has gradually but progressively declined, and NPC-associated mortality has been substantially reduced (2). However, some individuals, including the Bidayuh ethnic group in Borneo, the Naga ethnic group in northern India and the Inuit ethnic group in the Arctic regions have higher incidences of NPC, with an age-standardized incidence of >16/100 000 person-years in men (3). The hypothesis that NPC may originate from the Baiyue ethnic groups may account for the high incidence of NPC in a number of diverse populations worldwide, whose ancestry can be traced back to this population (4). However, how these genetic factors, which are probably carried by Baiyue women, actually contributes to the carcinogenesis of NPC remains unknown (4). Keratinizing squamous, non-keratinizing and basaloid squamous NPC are the subtypes of this type of cancer, according to the World Health Organization (2). The improved survival of patients with NPC has been suggested to be due to the widespread application of intensity modulated radiotherapy and optimization of chemotherapy strategies; however, further research should focus on biomarkers related to the diagnosis and prognostic risk of NPC (2).

Aldo-keto reductase family 1 member B10 (AKR1B10) was identified and characterized in 1998. Two previous studies independently identified a nicotinamide adenine dinucleotide phosphate ($NADP^+$)-dependent gene whose sequence exhibited high homology with the corresponding region of human aldose reductase (5,6). The AKR superfamily reduces $NADP^+$-dependent oxidoreductases that function in elimination reactions by modifying carbonyl groups on aldehyde or ketones to form primary or secondary alcohols, which are then conjugated with sulfates or glucuronide for excretion (7). AKR1B10 is a key member of the AKR superfamily and an essential enzyme in the metabolism of carbonyls, retinal and

farnesal/geranylgeraniol for detoxifying active carbonyls, maintaining cellular homeostasis of retinal-retinoid acid, and recycling farnesal/geranylgeraniol, the key intermediate products of cholesterol synthesis (8). AKR1B10 is primarily expressed in the human colon, small intestine and adrenal gland, with a low level also present in the liver (9).

AKR1B10 is a protein enzyme originally identified in human hepatocellular carcinoma (HCC) (5,6). A large-scale multicenter study validated that AKR1B10 could be a novel prevalent serum marker for HCC (10). AKR1B10 has also been reported to be associated with other tumors. AKR1B10 has been shown to be highly expressed, and to exert oncogenic or metastasis-promoting roles in the carcinogenesis in of a number of tumors, such as breast cancer (11-13), gastric cancer (14), lung cancer (15-17), pancreatic carcinoma (8,18), oral squamous cell carcinoma (OSCC) (19-21) and laryngeal squamous cell carcinoma (22). However, AKR1B10 exerts opposing roles in colorectal cancer (23,24) and endometrial cancer (25,26). Notably, different results have been reported in NPC. Guo *et al* (27) suggested that low expression of AKR1B10 may be an independent prognostic indicator in NPC, and that AKR1B10 could be involved in regulating the proliferation and migration of NPC cells. By contrast, another study revealed that AKR1B10 is overexpressed in nasopharyngeal hyperplasia, benign tumors and NPC (28).

To explore the role and diagnostic value of AKR1B10 in NPC, bioinformatics analysis was performed and clinical serum samples were analyzed in the present study.

Materials and methods

Ethics approval. The present study protocol was approved by the Ethics Committee of Zhuhai People's Hospital (Zhuhai, China). The present study followed the ethical standards on human experimentation of the institution. Written informed consent was obtained from the patients.

Mining analysis using The Cancer Genome Atlas (TCGA) database. AKR1B10 Mrna expression data from patients with head and neck squamous cell carcinoma (HNSCC) were downloaded from TCGA-HNSC dataset (http://gdc.cancer.gov). AKR1B10 RNA-seq data were obtained from 504 HNSCC tissues and 44 adjacent normal tissues from the patients with HNSCC; 43 pairs of tumor tissues and their corresponding normal tissues were selected according to TCGA labels. The extracted data were normalized by log2 transformation using R software version 4.2.1 (R Core Team). Clinical information from 502 HNSCC patients, including sex, age at initial pathological diagnosis, smoking history, alcohol history, pathological stage, TNM stage (2), overall survival (OS) status and OS times were also download from TCGA-HNSC dataset.

Mining analysis using the Gene Expression Omnibus (GEO) database. The GSE53819 (29) dataset consisting of data from 18 NPC primary tumors and 18 non-cancerous nasopharyngeal tissues; the GSE61218 (30) dataset consisting of data from 10 NPC and six normal healthy nasopharyngeal tissue specimens; and the GSE103611 (31) dataset consisting of data from 24 locoregionally advanced NPC (LA-NPC) tumor tissues with distant metastasis after radical treatment and 24 LA-NPC tumor tissues without distant metastasis after radical treatment were all downloaded from the GEO database (https://www.ncbi.nlm.nih.gov/geo/). The extracted data were normalized by log2 transformation using R software version 4.2.1.

Clinical serum samples. A total of 71 patients pathologically diagnosed with NPC and 30 healthy individuals without known diseases were selected from Sun Yat-sen University Cancer Center (Guangzhou, China) between December 2019 and May 2020 Serum samples were obtained by venipuncture from subjects after an overnight fast between 09:00 and 10:00 a.m. under standard conditions. Samples were clotted at 4-8˚C, and then centrifuged at 1,006 x g for 10 min at room temperature. The collected serum was distributed in 500-μl aliquots and stored at -80˚C until needed.

Measurement of AKR1B10. AKR1B10 ELISA kits (cat. no. E-EL-H5453) were purchased from Elabscience Biotechnology, Inc. and AKR1B10 was detected according to the manufacturer's instructions. All samples were analyzed simultaneously. Serum concentrations of AKR1B10 were determined using standard curves and expressed as unit per liter (ng/l). The linear ranges for AKR1B10 were 0-5,000 ng/l.

Statistical analysis. All statistical analyses were performed using SPSS software 18.0 (IBM Corp.). Comparisons between groups regarding AKR1B10 levels and clinical features were performed using unpaired or paired Student's t-tests. OS was analyzed using Kaplan-Meier analysis with log-rank test. Univariate and multivariate Cox proportional hazards models were used to evaluate the relative risk factors associated with OS, and hazard ratio with 95% confidence interval was obtained for each variable. Receiver operating characteristic (ROC) curves were generated and area under the curve (AUC) was calculated to determine the diagnostic power of AKR1B10 in NPC. The cut-off point was defined as the maximum Youden index. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Expression of AKR1B10 in patients with HNSCC. HNSCC includes cancer of the oral cavity, tongue, hypopharynx, nasopharynx, larynx and thyroid; therefore, the present study first analyzed the Mrna expression levels of AKR1B10 in a HNSCC cohort obtained from TCGA database. The results showed that there was no significant difference in the expression of AKR1B10 between HNSCC tissues (n=504) and normal epithelial tissues (n=44) (P=0.979; Fig. 1A). To further investigate the expression of AKR1B10, 43 pairs of HNSCC and adjacent normal tissues were analyzed. Similarly, there was no significant difference in the expression levels of AKR1B10 in HNSCC tissues compared with those in the adjacent normal tissues (P=0.346; Fig. 1B).

Relationship between AKR1B10 expression levels and clinicopathological factors in HNSCC. The present study next examined the association between AKR1B10 expression and the clinicopathological features of patients with HNSCC. In

Table I. Association between AKR1B10 expression and clinicopathological features of patients with head and neck squamous cell carcinoma in The Cancer Genome Atlas database.

Characteristics	n	AKR1B10 expression, mean ± SD	P-value
Sex			
Male	369	11.743±2.643	0.001[a]
Female	133	12.620±2.293	
Age			
<60 years	222	11.731±2.538	0.060
≥60 years	279	12.169±2.610	
Not available	1		
Smoking history			
Yes	287	11.984±2.629	0.931
No	215	11.964±2.525	
Alcohol history			
Yes	333	11.827±2.639	0.063
No	158	12.290±2.415	
Not available	11		
Pathological stage			
I + II	95	12.378±2.543	0.200
III + IV	339	11.997±2.564	
Not available	68		
Tumor stage			
T0 + T1 + T2	180	11.863±2.664	0.195
T3 + T4	267	12.186±2.514	
Not available	55		
Nodal stage			
N0	171	12.328±2.527	0.073
N1 + N2 + N3	238	11.873±2.522	
Not available	93		

[a]P<0.05. AKR1B10, aldo-keto reductase family 1 member B10.

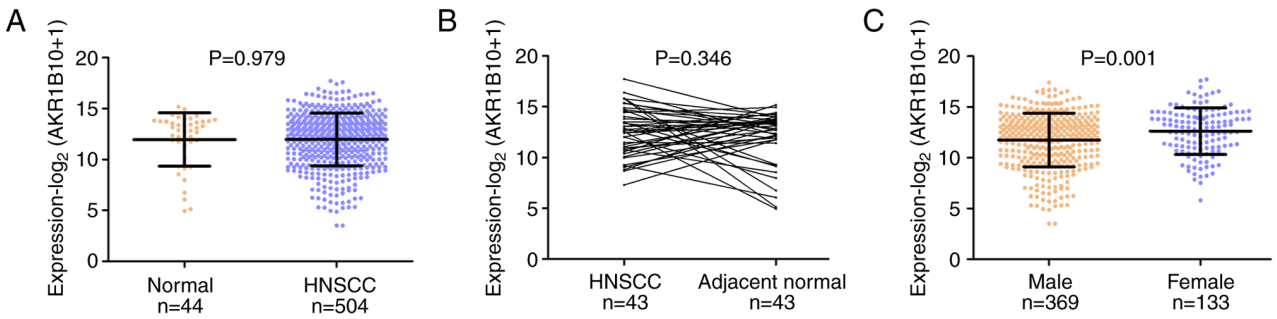

Figure 1. AKR1B10 expression in The Cancer Genome Atlas HNSCC database. No significant differences in AKR1B10 expression were detected (A) between HNSCC tissues and normal epithelial tissues, and (B) between paired HNSCC tissues and normal epithelial tissues. (C) AKR1B10 was significantly upregulated in tissues from female patients compared with from male patients with HNSCC. Data are presented as the (A and C) mean ± SD. AKR1B10, aldo-keto reductase family 1 member B10; HNSCC, head and neck squamous cell carcinoma.

TCGA database, AKR1B10 expression was not associated with age, smoking history, alcohol history, pathological stage, tumor stage or nodal stage (Table I). However, AKR1B10 expression was significantly higher in female patients with HNSCC than that in male patients (P=0.001; Fig. 1C).

High AKR1B10 expression is not associated with poor OS in patients with HNSCC. To investigate the prognostic value of AKR1B10 in HNSCC, Kaplan-Meier analysis was performed. Patients were divided into high expression and low expression groups according to the median

Table II. Univariate and multivariate Cox proportional hazard regression analyses of clinicopathological features and AKR1B10 expression for overall survival.

	Univariate analysis			Multivariate analysis		
Variables	HR	95% CI	P-value	HR	95% CI	P-value
Age (<60 vs. ≥60 years)	0.800	0.610-1.062	0.120	0.826	0.587-1.163	0.272
Sex (male vs. female)	0.740	0.560-0.996	0.047[a]	0.689	0.472-1.004	0.052
Smoking history (Yes vs. No)	1.100	0.840-1.546	0.300	0.410	0.613-1.319	0.587
Alcohol history (Yes vs. No)	1.000	0.770-1.389	0.810	1.202	0.832-1.738	0.328
Pathological stage (I + II vs. III + IV)	0.560	0.380-0.838	0.005[a]	0.958	0.418-2.194	0.920
Tumor stage (T0 + T1 + T2 vs. T3 + T4)	0.510	0.370-0.709	<0.001[a]	0.467	0.280-0.799	0.004[a]
Nodal stage (Negative vs. Positive)	0.520	0.370-0.730	<0.001[a]	0.567	0.376-0.856	0.007[a]
AKR1B10 (High vs. Low)	1.149	0.873-1.515	0.320	1.130	0.816-1.566	0.462

[a]P<0.05. AKR1B10, aldo-keto reductase family 1 member B10; CI, confidence interval; HZ, hazard ratio.

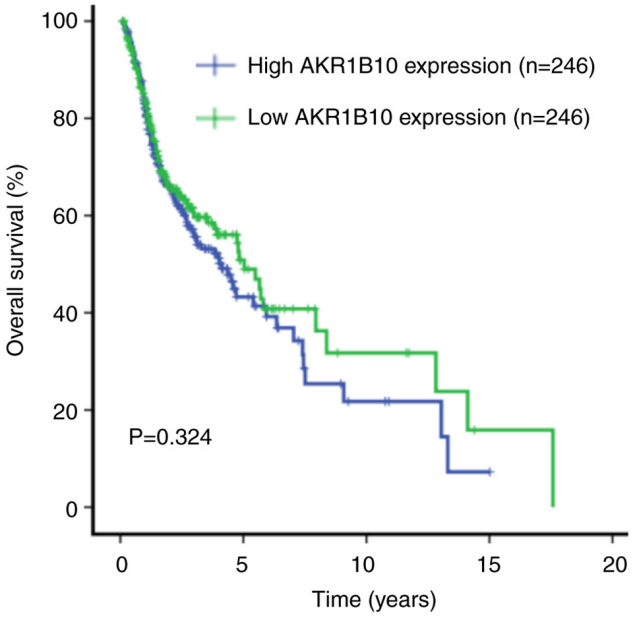

Figure 2. AKR1B10 expression is not associated with overall survival in patients with head and neck squamous cell carcinoma. AKR1B10, aldo-keto reductase family 1 member B10.

mRNA expression level. The Kaplan-Meier curve showed that the mRNA expression levels of AKR1B10 were not associated with the OS rate (P=0.324; Fig. 2). This finding was further confirmed by univariate and multivariate Cox proportional hazard regression analyses of clinicopathological features and AKR1B10 expression for OS (Table II). Univariate analysis showed that sex (P=0.047), pathological stage (P=0.005), tumor stage (P<0.001) and nodal stage (P<0.001) were associated with OS in patients with HNSCC. Subsequently, multivariate analysis showed that tumor stage (P=0.004) and nodal stage (P=0.007) were independent risk factor for OS in patients with HNSCC. However, AKR1B10 expression, similar to other clinical features (age, smoking history and alcohol history), was not associated with OS in patients with HNSCC.

Expression of AKR1B10 in patients with NPC. Since differences exist between NPC and other epithelial tumors in the head and neck region, the present study subsequently assessed the expression of AKR1B10 in NPC (3). The GEO database was used to analyze AKR1B10 expression in NPC. Two gene expression profile datasets (GSE53819 and GSE61218) demonstrated that the expression levels of AKR1B10 were not significantly different in NPC tissues compared with those in normal tissues (P=0.373; Fig. 3A; P=0.763; Fig. 3B). Notably, analysis of the GSE103611 dataset showed that the tumors from patients with LA-NPC and distant metastasis exhibited higher AKR1B10 expression than those without distant metastasis after radical treatment (P=0.019; Fig. 3C).

Diagnostic value of serum AKR1B10 in NPC. Serum samples were collected from healthy controls (n=30) and patients with NPC (n=71). The levels of AKR1B10 in the serum were measured using ELISA kits. The results revealed that AKR1B10 levels were significantly increased in the serum samples from patients with NPC compared with those from health controls (P<0.001; Fig. 4A). Since AKR1B10 expression was higher in HNSCC tissues from female patients compared with those from male patients, the present study analyzed the serum levels of AKR1B10; the results revealed that sex did not affect AKR1B10 levels in healthy controls (P=0.982 Fig. 4B) or in patients with NPC (P=0.562; Fig. 4C). A ROC curve was generated and the AUC was calculated to evaluate the diagnostic value of AKR1B10. The AUC was 0.909 (Fig. 4D). When the cutoff value (318.01 ng/l) was used, the sensitivity and specificity were 0.789 and 0.900. These results indicated the potential of serum AKR1B10 in NPC diagnosis.

Discussion

Recently, the role of AKR1B10 has been described in several types of cancer, including breast cancer, gastric cancer, lung cancer, pancreatic carcinoma, oral squamous cell carcinoma and laryngeal squamous cell carcinoma (8,11-21,32). HNSCC comprises a heterogeneous group of tumors that arise from the mucosal epithelium in the oral cavity, pharynx and larynx (33).

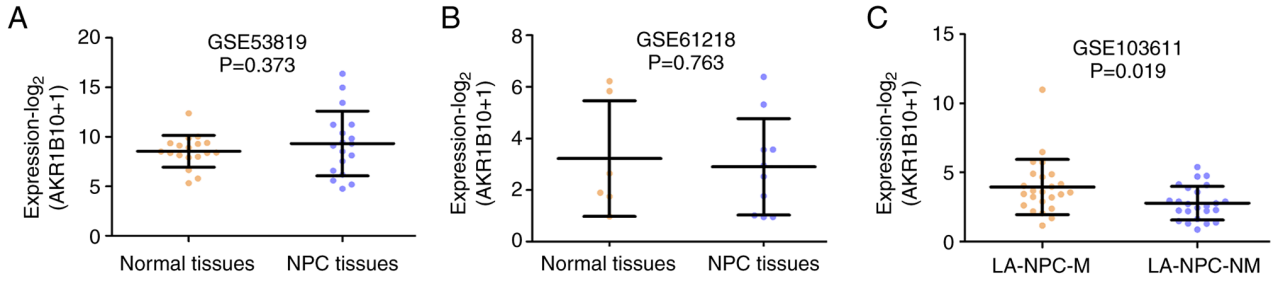

Figure 3. AKR1B10 expression in the Gene Expression Omnibus-NPC database. The expression levels of AKR1B10 were not significantly different in NPC tissues compared with those in normal tissues in the (A) GSE53819 and (B) GSE61218 datasets. (C) LA-NPC-M tissues exhibited higher expression levels of AKR1B10 than LA-NPC-NM tissues. Data are presented as the mean ± SD. AKR1B10, aldo-keto reductase family 1 member B10; LA-NPC, locoregionally advanced NPC; NPC, nasopharyngeal carcinoma; LA-NPC-M, LA-NPC tumor tissues with distant metastasis; LA-NPC-NM, LA-NPC tumor tissues without distant metastasis.

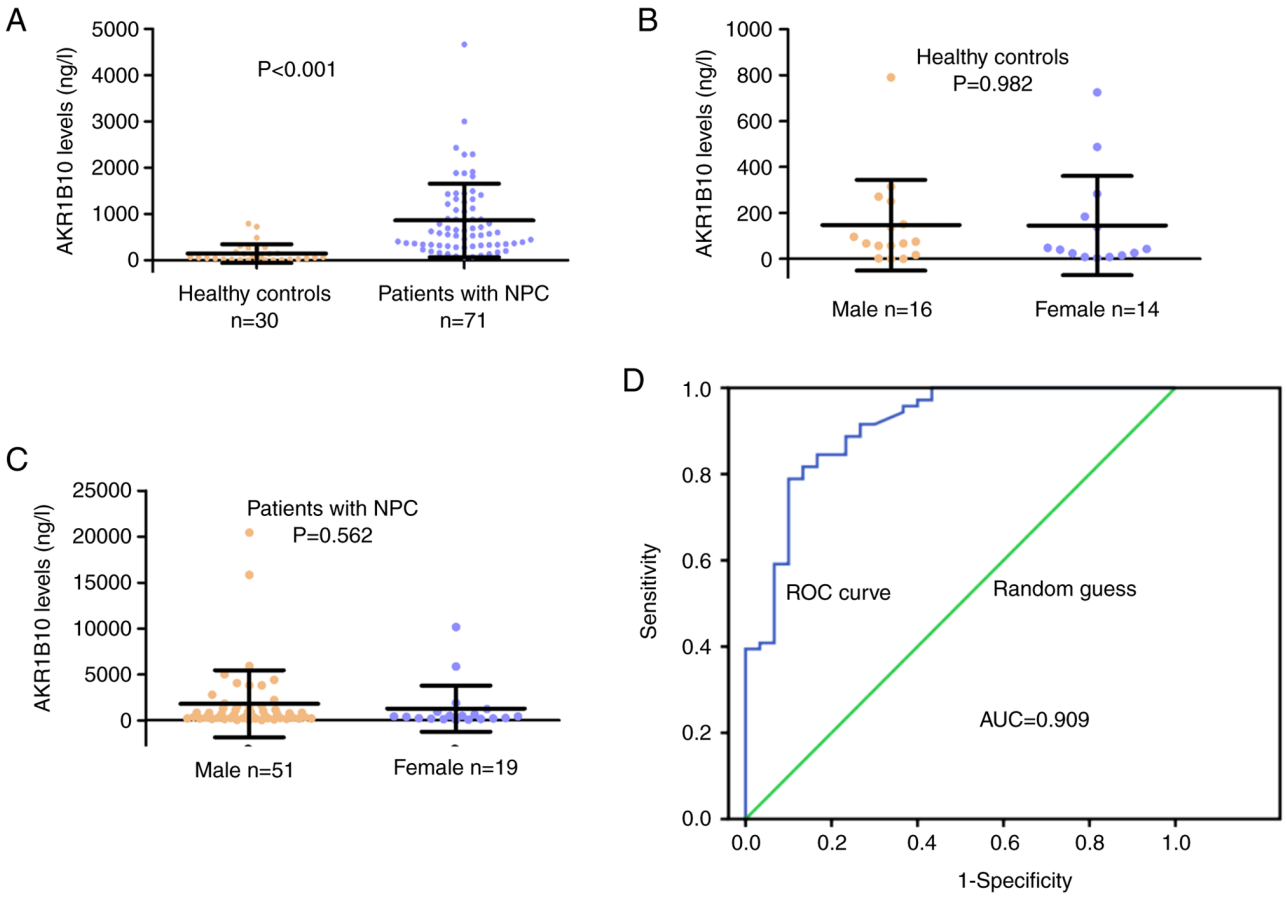

Figure 4. Serum levels of AKR1B10 in healthy controls and patients with NPC. (A) Serum levels of AKR1B10 were significantly upregulated in patients with NPC compared with in healthy controls. Sex did not affect AKR1B10 levels in (B) healthy controls or (C) patients with NPC. (D) Receiver operating characteristic curve of serum AKR1B10 in NPC. (A-C) Data are presented as the mean ± SD. AKR1B10, aldo-keto reductase family 1 member B10; AUC, area under the curve; NPC, nasopharyngeal carcinoma; ROC, receiver operating characteristic.

The roles of AKR1B10 in HNSCC have been assessed in previous years. It has been reported that high AKR1B10 expression is associated with reduced survival in patients with OSCC (19,21). Notably, salivary AKR1B10 levels may be a promising biomarker for screening high-risk patients with OSCC and monitoring the progression of OSCC (20). Similarly, AKR1B10 may be related to the development of laryngeal carcinoma and could be used as a prognostic indicator for laryngeal carcinoma (22). However, using TCGA database, the present study revealed that there were no significant differences in the expression of AKR1B10 between HNSCC tissues and adjacent normal tissues, and high expression of AKR1B10 was not associated with poor OS in HNSCC. These conflicting results may be due to the different samples assessed. Numerous agents and factors, such as ethoxyquin, MG-132, doxorubicin and smoking history, have previously been reported to induce upregulation of AKR1B10 (7,32); however, the present study did not verify the regulation of AKR1B10 by smoking history. Notably, although most of the clinicopathological features of patients with HNSCC were not associated with the AKR1B10 expression, the levels of AKR1B10 were higher in tissues, but

not serum samples, from female patients with HNSCC patients compared with in male patients. To the best of our knowledge, no previous studies have assessed the sex differences of AKR1B10 expression and the mechanism is unclear; therefore, our future research will focus on this.

NPC is a type of HNSCC, which is distinctly different from other types of HNSCC. Epstein-Barr virus infection is perhaps the most studied etiological factor for NPC (3). Lifestyle and environmental changes, enhanced understanding of the pathogenesis and risk factors of NPC, population screening, advancements in imaging techniques, and individualized comprehensive chemoradiotherapy strategies may be the reason for the declined incidence and mortality of NPC (2,3). Identifying biomarkers related to the diagnosis and prognostic risk of NPC should be the focus in the next few decades. Notably, contrasting roles of AKR1B10 in NPC have been reported in previous studies: a previous study suggested that low expression of AKR1B10 may be an independent prognostic indicator in NPC (27), whereas another study revealed that AKR1B10 is overexpressed in nasopharyngeal hyperplasia, benign tumors and NPC (28). Another study reported that AKR1B10 could induce radiotherapy resistance and promote cell survival in NPC (34). In the present study, analysis of GEO datasets suggested that the expression levels of AKR1B10 were not significantly different in NPC tissues compared with those in normal tissues. However, the serum levels of AKR1B10 were revealed to be higher in patients with NPC than in healthy controls and the ROC curve analysis indicated that AKR1B10 may be a potential marker for NPC diagnosis.

Besides the diagnostic and prognostic value of AKR1B10, other roles of AKR1B10 have been reported. In gastric cancer, AKR1B10 has been shown to participate in the chemotherapy resistance of gastric cancer (14,35,36) and human lung cancer (37). Similarly, AKR1B10 confers resistance to radiotherapy in NPC (34). Using the GSE103611 dataset, the present study indicated that AKR1B10 may be associated with distant metastasis after radical treatment of NPC. The mechanism underlying the effects of AKR1B10 on NPC require further investigation. A number of pathways are involved in AKR1B10 regulation in other types of cancer; notably, AKR1B10 can active the diacylglycerol second messenger (13) and PI3K/AKT/NF-Kb pathway (12) in breast cancer; and can regulate the fibroblast growth factor 1-dependent pathway in colorectal cancer (38). Furthermore, AKR1B10 can mediate liver cancer cell proliferation through sphingosine-1-phosphate (39).

The present study has some limitations. First, tissues were not collected from patients with NPC and healthy controls. Second, a larger cohort should be used to assess the value of serum AKR1B10. Finally, the mechanism underlying the effects of AKR1B10 on NPC require further investigation. Taken together, the present study revealed that serum levels of AKR1B10 in patients with NPC were relatively higher than those in healthy controls; therefore, AKR1B10 may be a potential marker for NPC diagnosis.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JL analyzed the public data and wrote the manuscript. TK collected the serum used in the experiments. ZZ designed the project and performed the ELISA experiments. JL and ZZ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Zhuhai People's Hospital (approval no. ZY2019-26). Patients and healthy controls provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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