Aberrant kinesin family member 2A signifies tumor size and invasion, and may help predict prognosis of patients with papillary thyroid carcinoma

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Abstract. Kinesin family member 2A (KIF2A) has been reported as an oncogene and potential biomarker for the progression of numerous cancer types; however, its role in papillary thyroid carcinoma (PTC) has remained elusive. The present study aimed to assess KIF2A expression in patients with PTC and explore the potential association between KIF2A, clinicopathological features and the prognosis of PTC. A total of 200 patients with PTC who received surgical resection were retrospectively reviewed. KIF2A expression was detected using immunohistochemistry (IHC) in 200 pairs of carcinoma/para-carcinoma tissues and using reverse transcription-quantitative PCR in 91 pairs of carcinoma/para-carcinoma tissues. Clinical and pathological data, disease-free survival (DFS) and overall survival (OS) rates of all patients were obtained. The results of the present study demonstrated that KIF2A protein and mRNA expression were both elevated in carcinoma tissues compared with those in para-carcinoma tissues. KIF2A protein expression in carcinoma tissues was positively associated with increased tumor size and a higher pathologic tumor-nodes-metastasis (pTNM) stage. However, KIF2A mRNA expression in carcinoma tissues was only associated with an increased pTNM stage and not with any other clinicopathological features. In addition, high levels of KIF2A protein expression in carcinoma tissues led to a poor predicted DFS, but were not associated with OS. Following adjustments using a multivariate Cox regression model, high KIF2A protein expression levels were indicated to be independently associated with a decreased DFS. In conclusion, aberrant KIF2A signifies tumor size and invasion, and may help to predict prognosis in patients with PTC.

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Abbreviations: PTC, papillary thyroid carcinoma; KIF2A, kinesin family member 2A; FFPE, formalin-fixed paraffin-embedded; pTNM, pathologic tumor-nodes-metastasis; DFS, disease-free survival; OS, overall survival; IHC, immunohistochemistry; RT-qPCR, reverse transcription-quantitative PCR; ROC, receiver operating characteristic; IQR, interquartile range; HR, hazard ratio

Key words: kinesin family member 2A, papillary thyroid carcinoma, IHC, RT-qPCR, clinicopathological features, prognosis

Introduction

Papillary thyroid carcinoma (PTC), a common type of differentiated thyroid cancer, exhibits an increasing global incidence rate (1). PTC management involves surgery followed by hormonal therapy, with or without adjuvant radioiodine therapy (2). Although the majority of patients with PTC present with a favorable prognosis with a 5-year disease-free survival (DFS) rate ranging from 80-97.4%, a small number of patients may develop extrathyroidal invasion and recurrence, resulting in poor prognosis (3-5). Of note, several biomarkers have been identified to help monitor disease progression and predict the recurrence risk for patients with PTC (6-8). However, the discovery of additional biomarkers is required to further improve the prognosis of PTC.

Kinesin family member 2A (KIF2A), a member of the kinesin-13 family, is a microtubule depolymerase that regulates microtubule assembly, spindle organization and chromosome congression, to further mediate the cell cycle during cell division (9-12). Results of previous studies have demonstrated that KIF2A is an oncoprotein in different types of cancer (13-15). For instance, KIF2A promotes malignant behaviors of oral squamous carcinoma cells via activating the PI3K/AKT signaling pathway (13). Furthermore, KIF2A induces cell proliferation and invasion, while suppressing cell apoptosis in nasopharyngeal carcinoma (14). Within clinical practice, KIF2A exhibits key prognostic value for the management of

gastric cancer, colorectal cancer and nasopharyngeal carcinoma (15-17). However, to the best of our knowledge, there are currently no studies focusing on the clinical role of KIF2A in patients with PTC.

Thus, the present study aimed to detect the expression levels of KIF2A in carcinoma and para-carcinoma tissues obtained from patients with PTC, and explore the potential association between KIF2A, clinical features and prognosis. The present study aimed to provide a novel theoretical basis for the management of PTC.

Materials and methods

Patients. A total of 200 patients with PTC who received surgical resection at the Central Hospital of Wuhan (Wuhan, China) between January 2014 and December 2020 were retrospectively reviewed. Patients were eligible for inclusion in this study if they met the following criteria: i) Pathological diagnosis of PTC; ii) 18-80 years of age; iii) underwent surgical resection; iv) available formalin-fixed paraffin-embedded (FFPE) samples of carcinoma tissues and para-carcinoma tissues; and v) clinical characteristics and follow-up data were available. The patients who had a prior history of other malignancies/solid tumors were excluded from the study. The present study was approved by the Ethics Committee of The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China) with approval number WHZXKYL2022-101.

Data collection. The clinical characteristics of all patients were obtained from their medical records, including age, sex, tumor size, extrathyroidal invasion, pathologic tumor-nodes-metastasis (pTNM) stage and radioiodine treatment. The Eighth Edition of the TNM staging criteria was used, based on which the patients treated prior to 2016 were reclassified. In addition, follow-up data of all patients were collected and the final date of recording was March 31, 2021. Subsequently, disease-free survival (DFS) and overall survival (OS) were obtained for prognostic evaluation. DFS was defined as the duration from surgical resection to disease relapse; OS was defined as the duration from surgical resection to disease relapse or patient death.

Sample collection and detection. FFPE samples of carcinoma and para-carcinoma tissues were obtained from all patients to assess KIF2A protein expression using immunohistochemistry (IHC) as previously described (18). Rabbit polyclonal anti-KIF2A antibody (1:200 dilution; cat. no. ab197988; Abcam) was used as the primary antibody and incubation was performed at room temperature for 2 h. Goat anti-rabbit IgG (H&L; 1:1,000 dilution; cat. no. ab150077; Abcam) was used as the secondary antibody and incubated with the sample at room temperature for 1.5 h. Following staining, IHC scores were determined using a light microscope based on the intensity and density of stained cells (19). In detail, the intensity was scored as four grades: 0 (negative), 1 (weak), 2 (moderate) and 3 (strong); the density was scored as five grades: 0 (0%), 1 (1-25%), 2 (26-50%), 3 (51-75%) and 4 (76-100%), representative examples are provided in Fig. S1. The IHC score was a product of the intensity score and the density score with a maximum score of 12. The assessment of the IHC score was performed by two independent pathologists who were blinded to the clinical information of the patients. The final IHC score was the average of two scores proposed by the two independent pathologists.

Furthermore, carcinoma and para-carcinoma tissue samples that were stored in liquid nitrogen were collected from 91 patients to detect KIF2A mRNA expression using reverse transcription-quantitative (RT-q)PCR. After extraction of total RNA using TRIzol® reagent (Invitrogen; Thermo Fisher Scientific, Inc.) from the specimens, RT-PCR was subsequently performed using an iScript™ cDNA Synthesis kit (Bio-Rad Laboratories, Inc.). qPCR was carried out using a KOD SYBR® qPCR Mix with SYBR® Green I fluorophore (Toyobo). The thermocycling conditions were 1 cycle of 98˚C for 30 sec and 40 cycles of 98˚C for 10 sec and 68˚C for 30 sec. The relative expression of KIF2A was calculated based on the $2^{-\Delta\Delta Cq}$ method and β-actin was used as the internal reference (20). The primers for KIF2A and β-actin were designed as follows: KIF2A forward, 5'-GCCTTTGATGACTCAGCT CC-3' and reverse, 5'-TTCCTGAAAAGTCACCACCC-3'; β-actin forward, 5'-TGACGTGGACATCCGCAAAG-3' and reverse, 5'-CTGGAAGGTGGACAGCGAGG-3' (21).

Statistical analysis. SPSS version 24.0 (IBM Corp.) and R version 4.0.5 (TSHRC package, available at www.r-project.org) were used to analyze the clinical data of patients and GraphPad Prism version 7.01 (GraphPad Software Inc.) was used to construct the graphs. Comparisons of KIF2A expression between samples of carcinoma and para-carcinoma tissues were performed using the Wilcoxon signed-rank test or χ^2 test. The ability of KIF2A expression to distinguish between carcinoma and para-carcinoma tissue samples was evaluated using a receiver operating characteristic (ROC) curve. Comparison of KIF2A expression among patients with different clinical features was performed using a Mann-Whitney U-test. The correlation between KIF2A expression and clinical data was assessed by determining Spearman's rank correlation coefficient. DFS and OS were presented using Kaplan-Meier curves and were analyzed using the log-rank test or two-stage test followed by post-hoc comparisons with Bonferroni's test according to a previous study (22). Factors affecting DFS and OS were determined using multivariate regression analysis with Cox's proportional hazards model. In the survival analysis, KIF2A protein expression was classified as high expression (final IHC score, >3) or low expression (final IHC score, ≤3), and KIF2A mRNA expression was based on the median expression value of carcinoma tissues (2.630) and classified as high expression (≥2.630) and low expression (<2.630). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinical features of patients with PTC. Initially, 283 patients were enrolled. Subsequently, 83 patients who met the exclusion criteria or who disobeyed the inclusion criteria were excluded. In detail, the FFPE samples of 46 patients were not available, the clinical data of 28 patients were not available, 5 patients were aged below 18 years and 4 patients had a previous cancer history. Thus, 200 patients were finally enrolled. Among all

Table I. Characteristics of the patients (n=200).

Item	Value
Age, years	45.2±11.7
Sex	
Female	142 (71.0)
Male	58 (29.0)
Tumor size, cm	3.6±1.7
Extrathyroidal invasion	
No	122 (61.0)
Yes	78 (39.0)
pT stage	
pT1	37 (18.5)
pT2	45 (22.5)
pT3	59 (29.5)
pT4a	43 (21.5)
pT4b	16 (8.0)
pN stage	
pN0	67 (33.5)
pN1	133 (66.5)
pTNM stage	
I	139 (69.5)
II	36 (18.0)
III	19 (9.5)
IV	6 (3.0)
Radioiodine therapy	
No	102 (51.0)
Yes	98 (49.0)

Values are expressed as the mean ± standard deviation or n (%). PTC, papillary thyroid carcinoma; pT, pathologic tumor; pN, pathologic nodal; pTNM, pathologic tumor-nodes-metastasis.

recruited patients with PTC, the mean age was 45.2±11.7 years (Table I). The cohort comprised 142 (71.0%) females and 58 (29.0%) males. Furthermore, 78 (39.0%) patients presented with extrathyroidal invasion, while the remaining 122 (61.0%) patients did not exhibit any extrathyroidal invasion. In terms of pTNM stage, 139 (69.5%), 36 (18.0%), 19 (9.5%) and 6 (3.0%) patients had been diagnosed as pTNM stage I, II, III and IV, respectively. A total of 98 (49.0%) patients received adjuvant radioiodine therapy, while 102 (51.0%) patients did not. The detailed clinical features of the patients with PTC are presented in Table I.

KIF2A expression in patients with PTC. The IHC score for KIF2A was elevated in carcinoma tissues compared with that in para-carcinoma tissues [median, 4.0 vs. 2.0; interquartile range (IQR), 3.0-7.8 vs. 1.0-3.5; P<0.001; Fig. 1A and B]. In addition, KIF2A was intracellularly located within the PTC cells (both in the cytoplasm and nuclei). Furthermore, positive KIF2A protein expression (defined as IHC score >3) was increased in carcinoma tissues compared with para-carcinoma tissues (56.5 vs. 25.5%; P<0.001; Fig. 1C). KIF2A mRNA expression levels were also increased in carcinoma tissues compared with para-carcinoma tissues (median, 2.630 vs. 1.000; IQR, 2.220-3.930 vs. 0.770-1.490; P<0.001; Fig. 1D). The results of the ROC curve analyses demonstrated that the KIF2A IHC score [area under ROC curve (AUC), 0.747; 95% confidence interval (CI), 0.700-0.794] and KIF2A mRNA expression (AUC, 0.906; 95% CI, 0.862-0.951) may be used to differentiate carcinoma tissues from para-carcinoma tissues (Fig. 1E and F). In addition, high KIF2A expression in carcinoma tissues was related to high KIF2A levels in para-carcinoma tissues from patients with PTC (P=0.007; Table SI).

Association between KIF2A and clinical features of patients with PTC. An increased KIF2A IHC score in carcinoma tissues was associated with tumor size >4 cm (P=0.001) and advanced pathological tumor (pT) stage (P=0.001), while there was no significant association between the KIF2A IHC score in carcinoma tissues and extrathyroidal invasion (P=0.077), pathological node (pN) stage (P=0.053) or pTNM stage (P=0.173; Fig. 2A-E).

Furthermore, KIF2A mRNA expression was only associated with a higher pT stage (P=0.022), while no association was observed between KIF2A mRNA expression and tumor size (P=0.106), extrathyroidal invasion (P=0.089), pN stage (P=0.076) or pTNM stage (P=0.891; Fig. 2F-J).

Association of KIF2A with relapse and survival. At the last follow-up date, 20 (10.0%) patients had relapsed and 11 (5.5%) patients had died. There was no significant association between KIF2A IHC score and relapse (P=0.154; Fig. 3A) or between KIF2A IHC score and death (P=0.742; Fig. 3B). Further Kaplan-Meier curve and log-rank test analyses demonstrated that high levels of KIF2A protein expression were associated with shorter DFS (P=0.015; Fig. 3C), but not significantly associated with OS (P=0.071; Fig. 3D). Due to the small sample size, KIF2A mRNA levels were not significantly associated with DFS or OS (Fig. S2A and B).

Subgroup analyses indicated that DFS was longer in patients with PTC with low KIF2A in their carcinoma tissues and low KIF2A in their para-carcinoma tissues compared to that in patients with high KIF2A in their carcinoma tissues and low KIF2A in their para-carcinoma tissues (P=0.033), as well as that in patients with high KIF2A expression in both their and carcinoma and para-carcinoma tissues (P=0.025; Fig. S3A). Furthermore, OS was prolonged in patients with PTC with low KIF2A in their carcinoma tissues and low KIF2A in their para-carcinoma tissues compared to that in patients with low KIF2A expression in their carcinoma tissues and high KIF2A in their para-carcinoma tissues (P=0.011; Fig. S3B).

Adjustment using multivariate Cox regression analysis. After applying multivariate Cox regression for adjustment, KIF2A protein expression [high vs. low; hazard ratio (HR), 5.842; 95% CI, 1.178-28.983; P=0.031] was independently associated with shorter DFS, but no significant influence of KIF2A protein expression on OS was obtained (HR, 7.602; 95% CI, 0.732-78.939; P=0.089; Table II). Furthermore, a higher pTNM stage was identified as an independent factor for determining reduced DFS (HR, 4.403; 95% CI, 1.125-17.224; P=0.033).

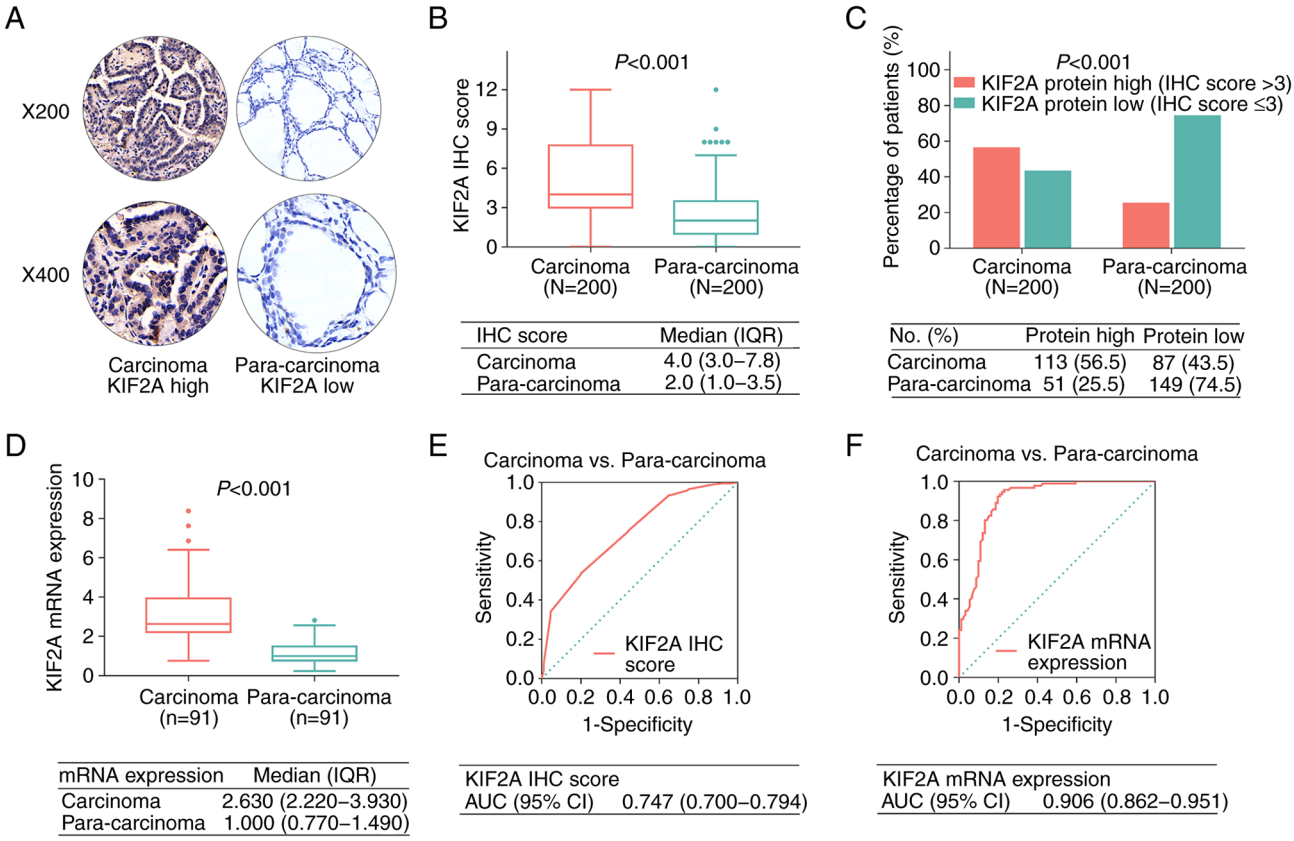

Figure 1. KIF2A expression is elevated in PTC tissues. (A) IHC images (magnification, x200 in upper and x400 in lower panel) and (B) comparison of KIF2A IHC score between carcinoma and para-carcinoma tissues in patients with PTC. (C) Comparison of KIF2A protein expression between carcinoma and para-carcinoma tissues. (D) Comparison of KIF2A mRNA expression between carcinoma and para-carcinoma tissues. ROC curve analyses of (E) KIF2A IHC score and (F) KIF2A mRNA expression in distinguishing between carcinoma and para-carcinoma tissues. KIF2A, kinesin family member 2A; IQR, interquartile range; PTC, papillary thyroid carcinoma; IHC, immunohistochemistry; ROC, receiver operating characteristic; AUC, area under the ROC curve.

Discussion

In the clinic, increased expression of KIF2A has been reported in various types of solid tumor, such as gastric cancer, colorectal cancer and laryngeal squamous cell carcinoma (15-17). However, the expression of KIF2A in patients with PTC had remained to be determined. The results of the present study demonstrated that KI2FA expression (both mRNA and protein) was increased in carcinoma tissues, compared with that in para-carcinoma tissues of patients with PTC, which may be used to distinguish between carcinoma and para-carcinoma tissues. This may be due to KIF2A being able to regulate multiple oncogene-related pathways, such as the PI3K/AKT pathway and the RhoA/rho-associated coiled-coil containing protein kinase pathway, to initiate the pathogenesis of PTC (13,15,23,24). Thus, the results of the present study demonstrated that KIF2A was increased in carcinoma tissues compared with that in para-carcinoma tissues in patients with PTC.

In addition to its aberrant expression, the association between KIF2A and the clinicopathological features of patients with cancer is also of great interest. For instance, upregulation of KIF2A has been associated with distal metastasis of patients with gastric or ovarian cancer (15,25). Furthermore, results of previous studies demonstrated that KIF2A expression was positively associated with pTNM stage in patients with either colorectal or gastric cancer (16,26). The results of the present study demonstrated that increased KIF2A protein expression was associated with tumor size >4 cm and advanced pT stage, whereas increased KIF2A mRNA expression was only associated with larger tumor size in patients with PTC. This may be because an increase in the expression of KIF2A promoted cell proliferation via mediating the cell cycle while inhibiting cell apoptosis, thus leading to tumor growth and increased tumor size in patients with PTC (10-12). Conversely, the sample size was relatively small, which may have impacted the power of the statistical analysis. Of note, there was a negative association between KIF2A and extrathyroidal invasion in patients with PTC, but this result was not statistically significant. However, increased KIF2A expression was associated with increased tumor size and extrathyroidal invasion to a certain extent, thus demonstrating an association with pT stage in patients with PTC.

The results of previous studies indicated that upregulated expression of KIF2A was associated with a poor survival prognosis in patients with cancer (16,17,25). For instance, upregulated KIF2A expression was associated with a reduced 5-year OS rate in patients with ovarian cancer or gastric cancer (16,25). A further study reported that high expression of KIF2A was independently associated with declined OS in patients with laryngeal squamous cell carcinoma (17). The results of the present study demonstrated that high KIF2A

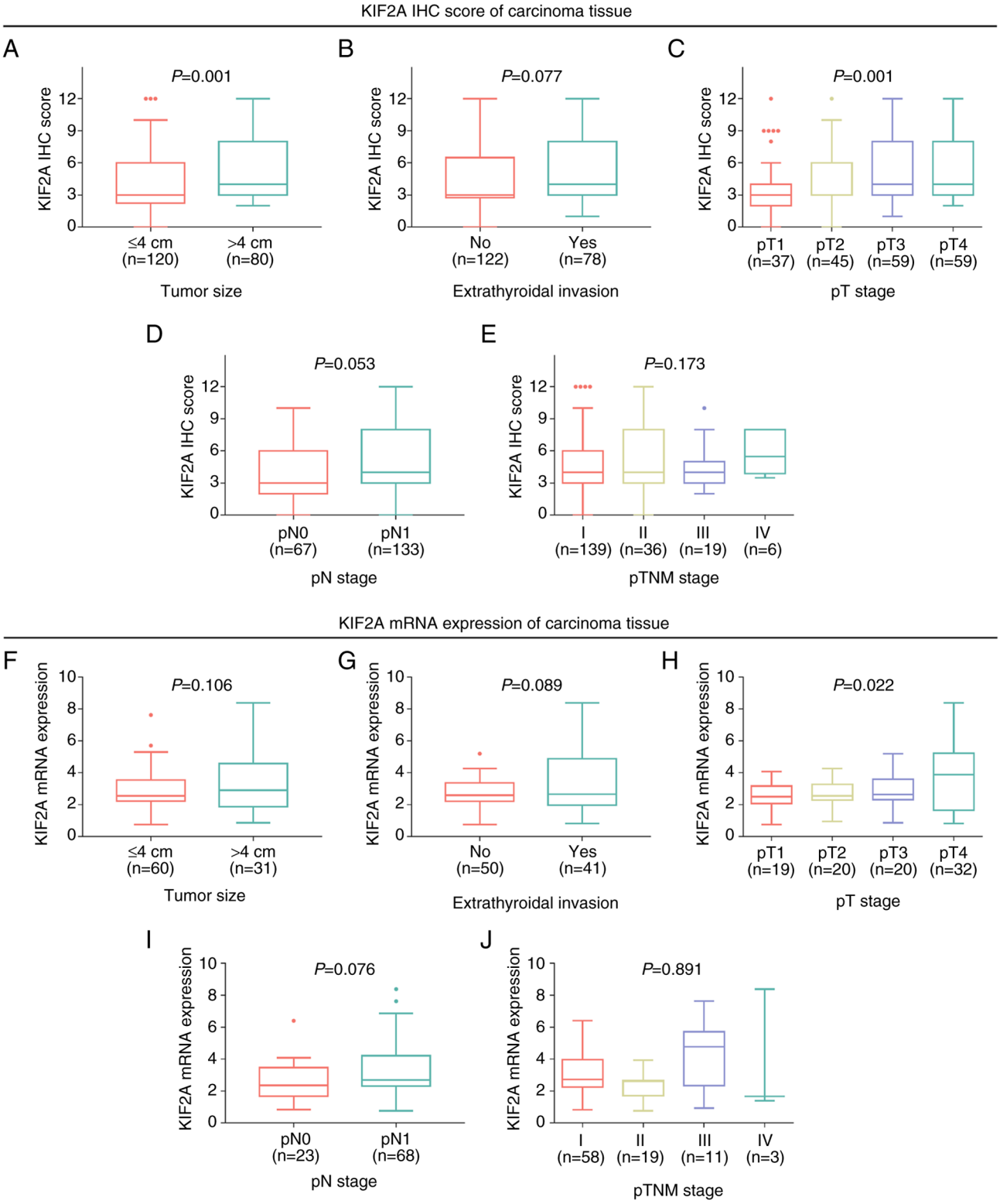

Figure 2. Elevated KIF2A expression is associated with larger tumor size and pT stage. Association of KIF2A IHC score with (A) tumor size, (B) extrathyroidal invasion, (C) pT stage, (D) pN stage and (E) pTNM stage in patients with PTC. Association of KIF2A mRNA expression with (F) tumor size, (G) extrathyroidal invasion, (H) pT stage, (I) pN stage and (J) pTNM stage in patients with PTC. pT, pathological tumor; KIF2A, kinesin family member 2A; IHC, immunohistochemistry; pN, pathological nodal; pTNM, pathologic tumor-nodes-metastasis; PTC, papillary thyroid carcinoma.

protein expression was independently associated with shorter DFS, but was not associated with OS. This may be because KIF2A promotes PTC cell invasion and migration, which further results in local invasion and distal metastasis, thereby leading to an elevated risk of recurrence and shorter DFS in patients with PTC (23). Of note, the follow-up period was relatively short in the present study and the survival profile of patients with PTC was frequently favorable, as only a small number of deaths were recorded in patients with PTC. This may have impacted the statistical analysis.

Table II. Multivariate Cox proportional hazards regression analysis for DFS and OS.

	DFS		OS	
Item	P-value	HR (95% CI)	P-value	HR (95% CI)
KIF2A protein expression (high vs. low)	0.031	5.842 (1.178-28.983)	0.089	7.602 (0.732-78.939)
Age (≥55 vs. <55 years)	0.528	0.397 (0.023-6.986)	0.894	1.290 (0.031-54.402)
Sex (male vs. female)	0.625	1.405 (0.359-5.501)	0.954	1.053 (0.185-6.004)
Higher pTNM stage	0.033	4.403 (1.125-17.224)	0.211	3.020 (0.534-17.089)
Radioiodine therapy (yes vs. no)	0.617	1.615 (0.246-10.582)	0.673	1.757 (0.128-24.122)

DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; KIF2A, kinesin superfamily protein 2A; pTNM, pathologic tumor-nodes-metastasis.

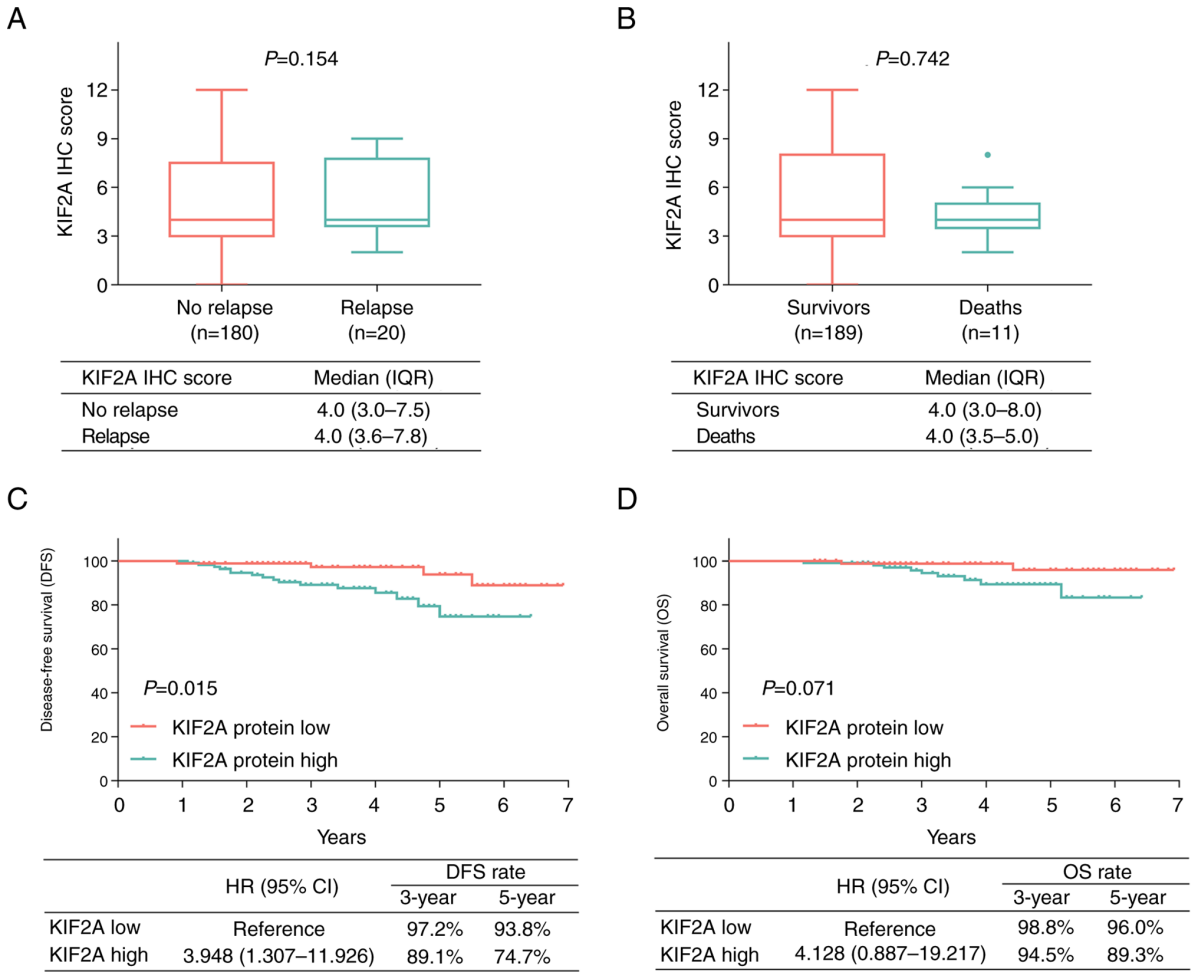

Figure 3. KIF2A protein expression is associated with shorter DFS. Association of KIF2A IHC score with (A) relapse and (B) death of patients with PTC. Association of KIF2A protein expression with (C) DFS and (D) OS in patients with PTC. KIF2A, kinesin family member 2A; IHC, immunohistochemistry; PTC, papillary thyroid carcinoma; DFS, disease-free survival; OS, overall survival; HR, hazard ratio; IQR, interquartile range.

Several further limitations exist in the present study. For instance, it was a single-center study, which may lead to regional selection bias, and further multi-center studies are required to validate the results of the present study. Furthermore, patient selection bias existed in the current study (i.e., only those patients with available clinical and follow-up data were enrolled), which may not be possible to avoid due to the retrospective nature of the study. In addition, further *in vitro* and *in vivo* studies are required to explore the effects of KIF2A on PTC cell behaviors and the underlying mechanisms. Furthermore, the present study only recruited patients with PTC, while the prognostic value of KIF2A in patients with other types of thyroid cancer, such as follicular thyroid cancer, was not determined.

In conclusion, aberrant KIF2A expression may signify tumor size and invasion and may help to predict an unfavorable prognosis in patients with PTC.

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Availability of data and materials

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

Authors' contributions

XYZ and MW contributed to the study design. XYZ, MW, GLP, WHL, ZG and HL reviewed the medical documents and collected the clinical characteristics of the patients. XYZ, MW and MJ contributed to the data acquisition and analysis. XYZ, MW, GLP and WHL wrote the manuscript. XYZ and MW confirmed the authenticity of all the raw data. XYZ and MJ revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript. MJ agrees to be accountable for all aspects of the work in ensuring that questions associated with the accuracy or integrity of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

The study was approved by The Ethics Committee of The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China). All patients or their families 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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