KIF2A correlates with lymphovascular invasion and higher tumor stage, and can be used to predict worse prognosis in patients with endometrial carcinoma

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Abstract. Kinesin family protein 2A (KIF2A) is a microtubule depolymerase that participates in the progression of various cancers; however, its clinical utility in endometrial carcinoma (EC) remains unclear. The aim of the present study was to assess KIF2A expression and its relationship with prognosis in patients with EC. Data from 230 patients with EC who underwent tumor resection were reviewed in the current, retrospective study. KIF2A expression was measured in 230 formalin-fixed paraffin-embedded (FFPE) specimens of tumor tissue and 50 FFPE specimens of non-tumor tissue using immunohistochemistry (IHC). KIF2A expression was elevated in EC tumor tissue vs. non-tumor tissue (P<0.001). Furthermore, tumor KIF2A expression was linked with lymphovascular invasion (P=0.004) and higher International Federation of Gynecology and Obstetrics (FIGO) stage (P=0.001). High tumor KIF2A expression (IHC score>3) was correlated with shorter disease-free survival (DFS; P=0.014) and overall survival (OS; P=0.012). Moreover, the time-dependent receiver operating characteristic curves revealed that tumor KIF2A expression had an acceptable use for estimating the relapse and death risks at each timepoint within 6 years, with each area under the curve remaining stable at ≥0.7. Notably, tumor KIF2A expression (high vs. low) independently forecast shorter DFS (hazard ratio, 2.506; P=0.013), but not OS (P>0.05). Furthermore, information from The Human Protein Atlas database indicated that high tumor KIF2A expression was associated with worse OS in patients with EC (P=0.027). Tumor KIF2A is not only associated with lymphovascular invasion and higher FIGO stage, but also reflects unfavorable survival in patients with EC.

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Introduction

Endometrial carcinoma (EC) is one of the most prevalent female genital tract malignancies worldwide (1-3). In 2019, the incidence rate of EC was 6.39 per 100,000 people in China and this is increasing (4). The standard treatment strategy for patients with EC is surgery, after which the decision to receive adjuvant radiotherapy or chemotherapy is made based on the patient's disease condition (5-8). Currently, some advances have been made in establishing a consensus on risk classification for EC, which is beneficial for best-tailored management to improve the prognosis of patients with EC (9,10). However, as a clinically heterogeneous disease, there are still certain patients with EC whose survival is unsatisfactory (11-13). Thus, identifying potential biomarkers for the stratified management of EC is vital.

Kinesin family protein 2A (KIF2A) is a member of the kinesin-13 family that functions by restraining the process of microtubule polymerization and is considered to participate in the progression of a variety of tumors, including gynecological cancers (14-17). For example, one study showed that KIF2A promotes the migration and invasion of cervical cancer cells (14). Additionally, another study suggested that the overactivation of KIF2A induces the depolymerization of microtubules, thereby promoting the progression of epithelial ovarian cancer (15). Clinically, a previous study indicated that KIF2A expression was elevated in tumor tissues compared with non-cancerous tissues, and high KIF2A expression was associated with unsatisfactory overall survival (OS) in patients with epithelial ovarian cancer (18). Additionally, another study indicated that KIF2A serves as a potential biomarker for disease monitoring and prognostication in patients with cervical cancer (19). However, to the best of our knowledge, the clinical role of KIF2A as a potential biomarker in patients with EC has not been previously investigated.

Therefore, the present study aimed to evaluate KIF2A expression as well as its correlation with prognosis in patients with EC.

Materials and methods

Patients. A total of 230 patients with EC who underwent surgical resection in Handan Central Hospital (Handan, China)

between January 2015 and December 2019 were retrospectively screened. The inclusion criteria were as follows: i) EC diagnosis by histopathological examination; ii) ≥18 years of age; iii) underwent surgical resection; iv) accessible and available tumor formalin-fixed paraffin-embedded (FFPE) specimens; and v) adequate clinical characteristics data and information for at least one follow-up. Patients who had other malignancies, were pregnant or were lactating were excluded. The present study was approved by the Ethics Committee of Handan Central Hospital (approval no. 2023020615; Handan, China), and informed consent (written or oral) was obtained from every patient or their family member.

Sample collection. Data on demographics, disease, treatment and follow-up were obtained from the patients with EC. Disease-free survival (DFS) and OS were calculated. The last follow-up was in January 2023. Additionally, 230 FFPE specimens of tumor tissue and 50 FFPE specimens of non-tumor tissue were obtained from the hospital for examination of KIF2A expression.

Immunohistochemical (IHC) staining. KIF2A expression was assessed using IHC staining. Stored specimens were cut into 4-μm thick sections, deparaffinized with xylene, and rehydrated using a descending ethanol series. Microwave heating (100˚C for 7 min) was used for antigen retrieval. Endogenous peroxidase activity was quenched using 3% H_2O_2. Sections were then blocked using 5% goat serum (cat. no. ab7481; Abcam) at room temperature for 10 min. In preliminary experiments, the sections were incubated with rabbit polyclonal anti-KIF2A antibodies (cat. no. ab197988; Abcam) at three different concentrations (1:100, 1:200 and 1:300) overnight at 4˚C. In the subsequent experiments, the slides were incubated overnight with rabbit polyclonal anti-KIF2A antibodies (1:200) at 4˚C. After incubation, the slides were washed three times with TBST (containing 0.1% Tween-20). The slides were then incubated with goat anti-rabbit IgG H&L (HRP) secondary antibodies (1:1,000; cat. no. ab6721; Abcam) at room temperature for one hour. After incubation, the slides were washed three times with TBST. The slides were then stained using a DAB Peroxidase Substrate Kit [Absin (Shanghai) Biotechnology, Co., Ltd.) and hematoxylin at room temperature for 30 min. Sections were then sealed with Glycerol Jelly Mounting Medium and imaged. A section in which the primary antibody was omitted served as a negative control. IHC scoring was performed by two investigators separately using a light microscopy and Image-Pro Plus 6.0 (Media Cybernetics Inc.), which was used to assess KIF2A density and intensity scores. Briefly, staining intensity was scored as 0 (negative), 1 (weak), 2 (moderate) or 3 (strong), and staining density was scored as 0 (0%), 1 (1-25%), 2 (26-50%), 3 (51-75%) or 4 (76-100%). The mean of the KIF2A density and intensity scores obtained by the two investigators was taken. The final IHC score (ranging from 0-12) was calculated by multiplying staining intensity and staining density. For subsequent analysis, tumor KIF2A expression was divided into high (IHC score >3) and low (IHC score ≤3) (20-22). The present study ensured consistency in personnel, experimental conditions, instrumentation and reagents to control for possible batch effects.

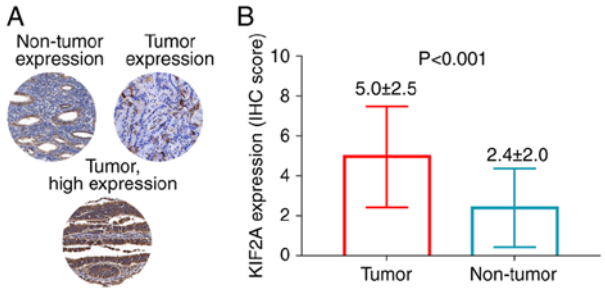

Figure 1. KIF2A expression in tumor and non-tumor tissues from patients with EC. (A) Representative micrograph images of KIF2A expression in non-tumor tissues, as well as low KIF2A and high KIF2A expressions in tumor tissues detected using immunohistochemistry. Overall magnification, x400. (B) T-test was used to compare KIF2A expression between tumor and non-tumor tissues in patients with EC. Data are presented as the mean ± standard deviation. KIF2A, kinesin family protein 2A; EC, endometrial carcinoma.

Database verification. To further verify the correlation between KIF2A expression and OS, information from 541 patients with EC was gathered from The Human Protein Atlas database (https://www.proteinatlas.org), in which the KIF2A expression was classified as low or high with a cut-off value of 5.2.

Statistical analysis. SPSS v24.0 (IBM Corp.) was used for statistical analysis, and GraphPad Prism v7.01 (Dotmatics) was utilized for graphing and statistical analysis. Comparisons were performed using an unpaired t-test or ANOVA with the Tukey's post hoc test. Correlations were analyzed using Spearman's rank correlation test. Kaplan-Meier curves with the log-rank test were used for DFS and OS assessment. Time-dependent receiver-operating characteristic analyses for relapse and death risk were performed and the area under the curve (AUC) was calculated (AUC >0.7 was considered to indicate good predictive utility). Independent factors related to DFS or OS were screened using forward-step multivariate Cox's proportional hazard regression analyses. P<0.05 was considered to indicate a statistically significant difference.

Results

Clinical features of patients with EC. There were 230 patients with EC with a mean age of 58.1±8.0 years. There were 46 (20.0%) and 184 (80.0%) premenopausal and postmenopausal patients with EC, respectively. Regarding the histological subtype, there were 163 (70.9%) patients with endometrioid carcinoma G1/G2, 17 (7.4%) patients with endometrioid carcinoma G3, 34 (14.8%) patients with serous endometrial carcinoma and 16 (7.0%) patients with clear cell endometrial carcinoma. Additionally, 66 (28.7%) patients demonstrated lymphovascular invasion. There were 137 (59.6%) patients with the International Federation of Gynecology and Obstetrics (FIGO) stage I, 27 (11.7%) patients with FIGO stage II, 45 (19.6%) patients with FIGO stage III and 21 (9.1%) patients with FIGO stage IV (FIGO 2009 revision) (23). Additional information on patients with EC was presented in Table I.

Comparison of KIF2A expression in tumor and non-tumor tissues in patients with EC. In non-tumor tissue, KIF2A was

Table I. Clinical characteristics of patients with endometrial carcinoma (n=230).

Clinical characteristic	Value
Mean age ± SD, years	58.1±8.0
Menopausal status, n (%)	
Pre-menopause	46 (20.0)
Post-menopause	184 (80.0)
Diabetes, n (%)	
No	176 (76.5)
Yes	54 (23.5)
Hypertension, n (%)	
No	140 (60.9)
Yes	90 (39.1)
Histological subtype, n (%)	
Endometrioid carcinoma G1/G2	163 (70.9)
Endometrioid carcinoma G3	17 (7.4)
Serous endometrial carcinoma	34 (14.8)
Clear cell endometrial carcinoma	16 (7.0)
Myometrial invasion ≥50%, n (%)	
No	139 (60.4)
Yes	91 (39.6)
Cervical invasion, n (%)	
None or epithelial	175 (76.1)
Stromal	55 (23.9)
Lymphovascular invasion, n (%)	
No	164 (71.3)
Yes	66 (28.7)
FIGO stage, n (%)	
I	137 (59.6)
II	27 (11.7)
III	45 (19.6)
IV	21 (9.1)
Adjuvant radiotherapy, n (%)	
No	61 (26.5)
Yes	169 (73.5)
Adjuvant chemotherapy, n (%)	
No	151 (65.7)
Yes	79 (34.3)

SD, standard deviation; FIGO, International Federation of Gynecology and Obstetrics.

Table II. Correlation of tumor KIF2A expression with clinical characteristics.

Clinical characteristic	KIF2A expression	P-value
Age, years		0.834
<60	4.9±2.3	
≥60	5.0±2.8	
Menopausal status		0.573
Pre-menopause	4.8±2.5	
Post-menopause	5.0±2.6	
Diabetes		0.917
No	4.9±2.5	
Yes	5.0±2.8	
Hypertension		0.490
No	4.9±2.5	
Yes	5.1±2.6	
Histological subtype		0.229
Endometrioid carcinoma G1/G2	4.8±2.3	
Endometrioid carcinoma G3	5.4±2.7	
Serous endometrial carcinoma	5.2±3.1	
Clear cell endometrial carcinoma	5.9±3.0	
Myometrial invasion ≥50%		0.159
No	4.8±2.5	
Yes	5.2±2.6	
Cervical invasion		0.091
None or epithelial	4.8±2.4	
Stromal	5.5±3.0	
Lymphovascular invasion		0.004
No	4.6±2.5	
Yes	5.7±2.6	
FIGO stage		0.001
I	4.6±2.4	
II	4.9±2.7	
III	5.2±2.3	
IV	6.7±3.0	
Adjuvant radiotherapy		0.253
No	4.6±2.6	
Yes	5.1±2.5	
Adjuvant chemotherapy		0.063
No	4.7±2.5	
Yes	5.4±2.7	

Data are presented as mean ± SD. KIF2A, kinesin family protein 2A; SD, standard deviation; FIGO, International Federation of Gynecology and Obstetrics.

expressed in glandular cells but not in endometrial stroma cells. Meanwhile, in tumor tissue, KIF2A was expressed in the cytoplasm, membranes and nucleus (Fig. 1A). An unpaired t-test analysis showed that KIF2A expression was significantly higher in tumor tissue compared with non-tumor tissue in patients with EC (P<0.001; Fig. 1B).

Correlation of tumor KIF2A expression with clinicopathologic features in patients with EC. KIF2A expression in tumor tissue was significantly related to lymphovascular invasion (P=0.004) and higher FIGO stage (P=0.001) in patients with EC. However, there was no linkage of KIF2A expression in tumor tissue with other clinicopathologic features in patients with EC, including menopausal status, diabetes, hypertension, histological subtype and cervical invasion (all P>0.05; Table II). Furthermore, the results for the comparison by

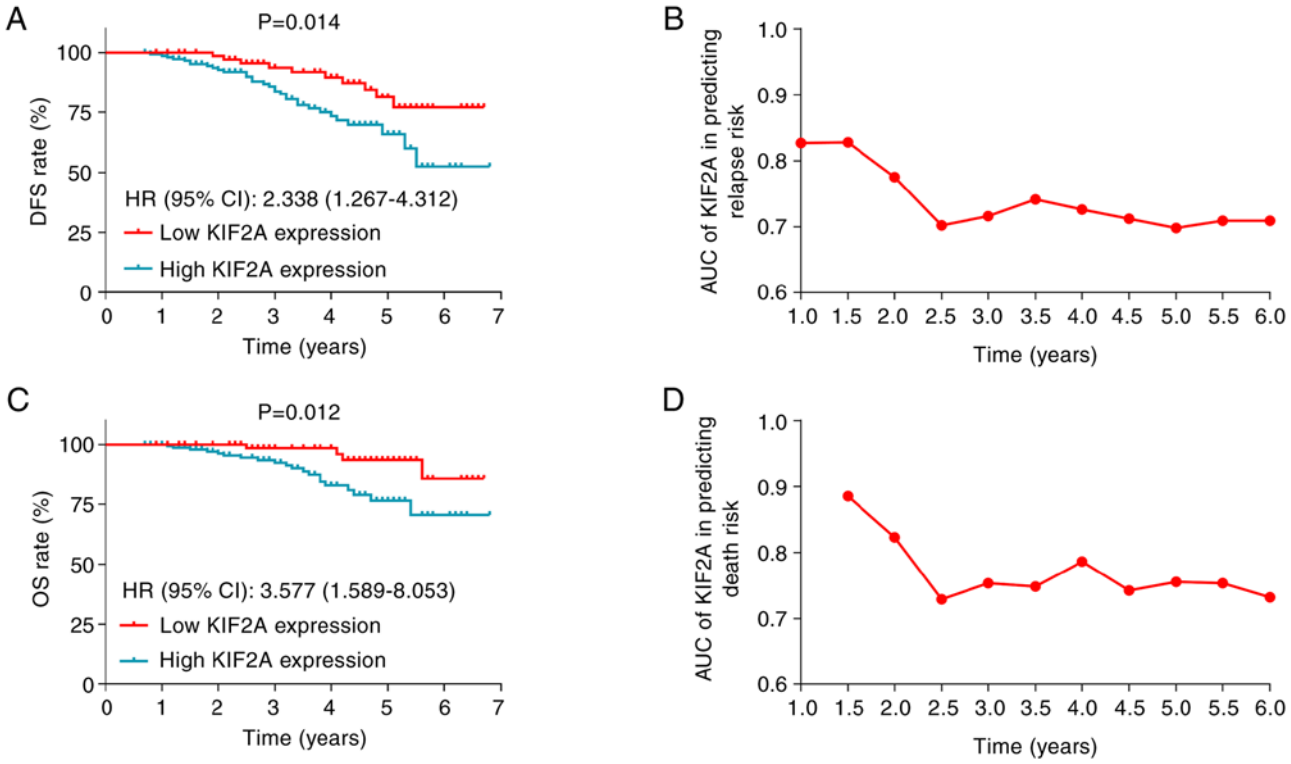

Figure 2. Association of KIF2A expression in tumor tissue with DFS and OS rates in patients with EC. (A) Kaplan-Meier curves with the log-rank test were used to assess the correlation of tumor KIF2A expression with DFS rate and (B) receiver-operating characteristic analyses were applied to assess the AUC of tumor KIF2A expression in forecasting relapse risk. (C) Kaplan-Meier curves with the log-rank test were used to assess the correlation of tumor KIF2A expression with accumulating OS rate and (D) receiver-operating characteristic analyses were applied to assess the AUC of tumor KIF2A expression in forecasting death risk in patients with EC. DFS, disease free survival; OS, overall survival; KIF2A, kinesin family protein 2A; EC, endometrial carcinoma; HR, hazard ratio; AUC, area under the curve.

Factors related to DFS by multivariate Cox's proportional hazards regression analysis

Variables	P-value	HR (95%CI)
Tumor KIF2A expression (high vs. low)	0.013	2.506 (1.214–5.170)
Age (≥60 years vs. <60 years)	0.015	2.485 (1.197–5.161)
Histological subtype		
Endometrioid carcinoma G1/G2	Reference	
Endometrioid carcinoma G3	0.427	1.567 (0.517–4.755)
Serous endometrial carcinoma	0.117	1.891 (0.853–4.194)
Clear cell endometrial carcinoma	0.005	4.211 (1.561–11.362)
Cervical invasion (stromal vs. none or epithelial)	<0.001	4.361 (2.282–8.334)

HR

Factors related to OS by multivariate Cox's proportional hazards regression analysis

Variables	P-value	HR (95%CI)
Age (≥60 years vs. <60 years)	0.001	5.670 (2.096–15.337)
Diabetes (yes vs. no)	0.011	2.912 (1.279–6.631)
Higher FIGO stage	<0.001	1.969 (1.425–2.720)

HR

Figure 3. Independent factors associated with DFS and OS in patients with EC. Multivariate Cox's proportional hazard regression analyses were used to identify independent predictors of (A) DFS and (B) OS in patients with EC. DFS, disease free survival; OS, overall survival; KIF2A, kinesin family protein 2A; HR, hazard ratio; FIGO, International Federation of Gynecology and Obstetrics.

Tukey's post hoc test regarding histological subtype and FIGO stage data are shown in Table SI.

Correlation of tumor KIF2A expression with accumulating DFS and OS rates in patients with EC. High tumor KIF2A expression was associated with significantly lower DFS in patients with EC [P=0.014; hazard ratio (HR)=2.338; Fig. 2A]. Moreover, the AUC of KIF2A expression in tumor tissues, for predicting relapse risk over 6 years remained stable at ≥0.7 (Fig. 2B). High KIF2A expression in tumor tissues was also correlated with significantly reduced OS in patients with EC (P=0.012; HR=3.577; Fig. 2C). Furthermore, the AUC of KIF2A expression in tumor tissues, for predicting death risk over 6 years also maintained stable at ≥0.7 (Fig. 2D).

Independent factors linked with DFS and OS in patients with EC. KIF2A expression in tumor tissues (high vs. low; HR=2.506; P=0.013), age (≥60 years vs. <60 years; HR=2.485; P=0.015), histological subtype (clear cell endometrial carcinoma vs. endometrioid carcinoma G1/G2; HR=4.211; P=0.005) and cervical invasion (stromal vs. none or epithelial; HR=4.361; P<0.001) independently estimated shorter DFS in patients with EC (Fig. 3A). KIF2A expression in tumor tissues was not independently associated with OS. However, age (≥60 years vs. <60 years; HR=5.670; P=0.001), diabetes (yes vs. no; HR=2.912; P=0.011) and higher FIGO stage (HR=1.969; P<0.001) were independently linked with shorter OS in patients with EC (Fig. 3B).

Data from the Human Protein Atlas database indicated that high tumor KIF2A expression was significantly associated with decreased OS in patients with EC (P=0.027; HR=1.585; Fig. 4).

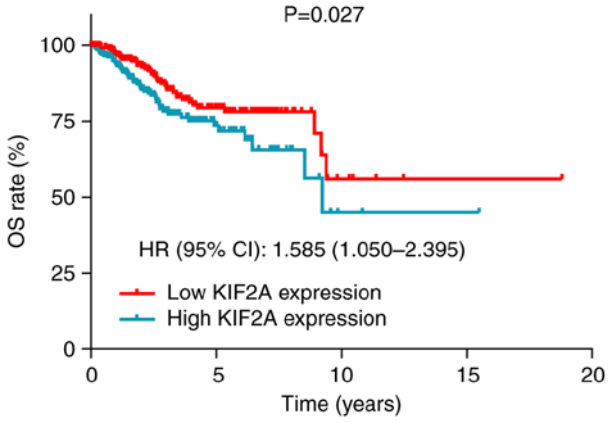

Figure 4. Prognostic value of tumor KIF2A expression in patients with EC from the Human Protein Atlas database. Kaplan-Meier curves with the log-rank test were used to assess the prognostic role of KIF2A expression in patients with EC. KIF2A, kinesin family protein 2A; EC, endometrial carcinoma.

Discussion

KIF2A is an oncogene that has been reported to be abnormally expressed in certain cancers, such as ovarian cancer, cervical carcinoma and breast cancer (24-27). These results demonstrated similarity to the present study, which revealed that KIF2A expression was significantly higher in tumor tissue compared with non-tumor tissue in patients with EC. This may be since the increase in KIF2A could reflect the increase in cell proliferation ability. Furthermore, the proliferative ability of EC cells in tumor tissues has been previously reported to be faster than that of cells in non-tumor tissues (28).

Clinically, high KIF2A expression is associated with worse tumor features in certain cancers (19,27). For example, one study reported that there was a positive correlation of KIF2A expression with lymph node metastasis and FIGO stage in patients with cervical cancer (19). Furthermore, another study reported that higher KIF2A expression was related to higher tumor stages in patients with breast cancer (27). The present study indicated that KIF2A was associated with lymphovascular invasion and higher FIGO stage in patients with EC. This could be because KIF2A might increase the migration and invasion of EC cells through the membrane type 1-matrix metalloproteinase and phosphatidylinositol-3-kinase/protein kinase B pathway signaling pathways (16,17), indicating a possible link with lymphovascular invasion. KIF2A could also increase the malignant behavior of EC cells by regulating microtubule dynamics, thus stimulating the progression of EC (29-31), indicating a possible link with FIGO stage (32,33).

Notably, previous studies have reported that KIF2A expression was correlated with unfavorable survival in many cancer patients (24,34). One study reported that KIF2A expression in tumor tissues was linked with unsatisfactory DFS in basal-like breast cancer patients (24). Furthermore, another study reported that KIF2A expression in tumor tissues was related to shortened OS in hepatocellular carcinoma patients (34). Similarly, the present study indicated that tumor KIF2A expression was related to shorter DFS and OS, and independently forecast unsatisfactory DFS in patients with EC. Moreover, data from the Human Protein Atlas database showed that patients with high KIF2A expression had shortened OS in patients with EC. The probable causes could be that, based on the content described above, KIF2A expression was related to unfavorable disease features and thus lead to poor survival in patients with EC. A possible cause could also be that KIF2A promoted EC progression through a series of pathways, including promoting membrane type 1-matrix metalloproteinase, facilitating phosphatidylinositol-3-kinase/protein kinase B pathway signaling pathways and regulating microtubule dynamics, thus negatively affecting the prognosis of patients with EC (16,17,29,30). Moreover, KIF2A might affect the chemosensitivity of EC cells to platinum-based regimens, thus reducing the survival rate of patients with EC (28).

The present study had several limitations. Firstly, this was a retrospective study, which could cause a certain degree of selection bias. Secondly, the present study only detected the KIF2A expression in tissues and further studies should consider exploring its expression in circulating samples. Thirdly, the detailed mechanism through which KIF2A participates in the progression of EC was not elucidated and requires further investigation in future studies.

In conclusion, KIF2A is highly expressed in tumor tissue and is associated with lymphovascular invasion and advanced FIGO stage, as well as undesirable DFS and OS in patients with EC.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YS and WZ contributed to study conception and design. Material preparation, data collection and analysis were performed by YS, LY, YH and JW. The first draft of the manuscript was written by YS, JW and WZ. LY, YH and WZ revised the manuscript. YS and WZ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study obtained the approval from the Ethics Committee of Handan Central Hospital (approval no. 2023020615; Handan, China), and informed consent (written or oral) was obtained from each patient or their family member.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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