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Original Article

Factors influencing disease-free survival after radical endometrial cancer surgery: an analysis of the competitive risk prediction mode

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Abstract: Objective: To investigate the factors influencing disease-free survival (DFS) of patients with endometrial cancer after surgery and construct a competing risk prediction model. Methods: Clinical data of endometrial cancer patients admitted to the First People's Hospital of Qinzhou City from October 2015 to January 2021 were retrospectively analyzed. A total of 280 patients were included, randomly split into a training set (202 cases) and a validation set (78 cases) in a 7:3 ratio using RStudio software. A Fine-Gray competing risk model was applied to the training set to identify factors associated with reduced postoperative DFS. Based on these factors, a prognostic prediction model was established, and a nomogram was created. The model's performance was evaluated using the concordance index (C-index), receiver operating characteristic (ROC) curve and calibration curve. Results: Multifactorial analysis revealed that age, body mass index (BMI), diabetes mellitus, depth of basal infiltration, cancer antigen 125 (CA125), and human epididymis protein 4 (HE4) were the factors influencing postoperative DFS in endometrial cancer patients ($P < 0.05$). In the training set, the constructed model showed AUC values of 0.773, 0.802, and 0.858 in predicting 1-, 2-, and 4-year DFS, respectively. In the validation set, the AUC values were 0.923, 0.829, and 0.746, respectively. The C-index in the training set and the validation set was 0.786 and 0.515, respectively. The calibration curve indicated that the predicted cumulative survival probabilities closely matched the actual probabilities in both the training and validation sets. Conclusions: The Fine-Gray competing risk prediction model is effective in identifying factors influencing postoperative DFS in patients with endometrial cancer. The nomograms derived from this model have a strong predictive value and can help clinicians in identifying high-risk patients and tailoring individualized interventions.

Keywords: Endometrial cancer, disease-free survival, competing risk model, nomogram, influencing factors

Introduction

Endometrial cancer, also known as uterine body cancer, is a common malignancy of the female reproductive system. Its incidence and mortality rates are on the rise, posing a serious threat to the life and health of women [1, 2]. The latest statistics from the International Agency for Research on Cancer (IARC) revealed nearly 400,000 new cases and approximately 90,000 deaths from endometrial cancer in 2022 [3]. While surgical treatment provides relatively favorable survival outcomes for patients with early-stage endometrial cancer, about 10% of patients are still at risk of postoperative recurrence, affecting the quality of life of patients and increasing the burden of medical resources [4]. Therefore, developing effective prognostic assessment tools is crucial for early identification of high-risk patients, guiding individualized treatment, and optimizing medical resource allocation.

Commonly used methods for assessing postoperative survival factors in cancer include Logistic regression, Kaplan-Meier method (K-M) and Cox proportional hazards regression model. However, traditional statistical methods have limitations in dealing with competing events, such as recurrence and pre-recurrence death, as they can only analyze a single endpoint event. In data processing, death prior to recurrence is often treated as a censored event, potentially leading to an overestimation of the

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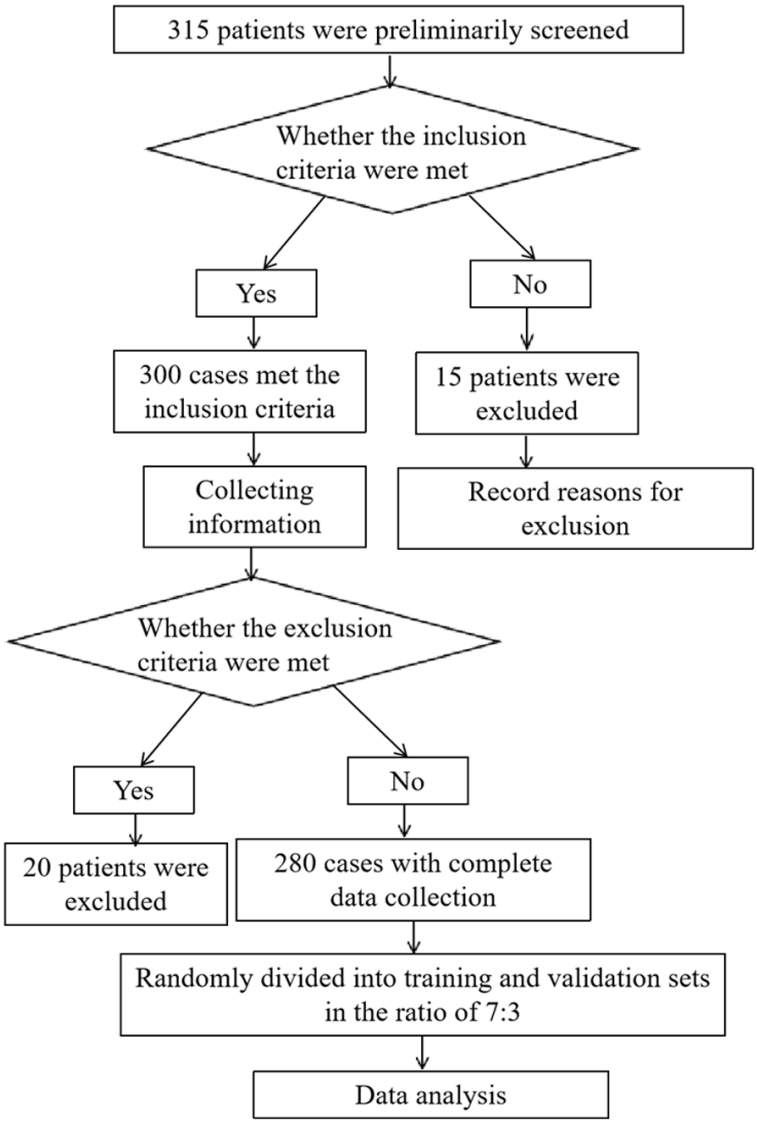

Figure 1. Flow chart of patient selection.

recurrence risk [5, 6]. As a survival analysis method that can deal with a variety of competing times, a competing risk model can effectively address the defects of traditional methods, thus more accurately predict the risk of outcome events [7].

Based on this, this study applied the competitive risk model to explore the factors influencing disease-free survival (DFS) after radical surgery for endometrial cancer. A nomogram was constructed to predict the risk of postoperative recurrence, representing an innovative approach in the prognosis assessment of endometrial cancer. Using a Fine-Gray competitive risk model, this study identified key factors affecting disease-free survival, providing clinicians with a new tool to assess high-risk patients and develop individualized interventions. In addition, this study also visually demonstrated the prediction results through a column graph, enhancing the clinical utility of the model and providing a basis for more informed decision-making in the diagnosis and treatment of endometrial cancer.

Materials and methods

Research subjects

This study retrospectively analyzed the clinical data of 315 patients with endometrial cancer treated at the gynecological oncology ward of the First People's Hospital in Qinzhou City from October 2015 to January 2021. Inclusion criteria: (1) Patients with histopathologically confirmed endometrial cancer; (2) Patients without communication disorders; (3) Complete clinical data. Exclusion criteria: (1) Pregnant women or women in labor; (2) Patients with immunodeficiency diseases; (3) Patients who had recently undergone other surgical treatments; (4) Patients who had no regular follow-up or short follow-up duration of less than one month.

According to the inclusion and exclusion criteria, a total of 280 cases were included in this study. These patients were randomly divided into a training set (202 cases) and a validation set (78 cases) at a ratio of 7:3. This study was approved by the Medical Ethics Committee of the First People's Hospital in Qinzhou City. The flow chart of patient selection is shown in **Figure 1**.

Data collection

Clinical and pathological data for the enrolled patients were obtained from the hospital information system. (1) General data: age, history of hypertension, body mass index (BMI), and history of diabetes. (2) Disease characteristics:

differentiation degree (low, medium, high), tumor diameter, pathological type (endometrioid adenocarcinoma, non-endometrioid adenocarcinoma), depth of myometrial invasion (< 1/2 myometrial, ≥ 1/2 myometrial), surgical treatment (laparotomy, laparoscopic surgery), adjuvant treatment (chemotherapy or not), postoperative complications, etc. (3) Laboratory examination indicators: Hemoglobin (HB), serum albumin (ALB), and neutrophil count. HB and ALB levels were measured using an automatic biochemical analyzer [Beckman Coulter (USA) Inc., Model: AU680]. Neutrophil count was measured using the Sysmex XE-2100D automatic blood cell analyzer. (4) Tumor markers: Cancer Antigen 125 (CA125) and Human epididymis protein 4 (HE4). Serum CA125 was determined using the AIA2000 electrochemiluminescence apparatus and reagent (Roche e601 type) from Tocho Company, Japan. Serum HE4 was determined with Roche's Cobas 601 electroluminescence apparatus.

Outcome measures

The primary measure of this study was DFS in patients with endometrial cancer after radical surgery. DFS was defined as the time from the date of surgery until the tumor recurrence or death before recurrence. All patients were followed up, with follow-up conducted in the form of an outpatient review: once every six months in the first year after discharge, and then annually thereafter.

Reexamination included laboratory examination and imaging examination. Endometrial cancer recurrence was diagnosed if both of the following two criteria were met: ① Ultrasound examination showing abnormal echoes or mass in the uterine cavity; ② Tissue biopsy of the lesion site confirming malignancy. The observation period began at the time of the first surgical treatment. At the final follow-up, patients who were still alive and had not relapsed were considered censored. Death before recurrence was treated as a competing risk event. Follow-up continued until February 15, 2022, with a maximum cumulative duration of 62 months, a survival time of 3 to 62 months, and a median survival time of 41.5 months.

Statistical treatment

Data were analyzed using SPSS 27.0 software and R Studio software. Count data were presented as rates and comparisons between groups were performed using the chi-square test. Measurements conforming to a normal distribution were presented as mean ± standard deviation ($\bar{x} \pm s$), and t-tests were used for comparisons between groups. The Gray test was used for univariate analysis, and the competitive risk model (Fine-Gray) was employed for multi-factor analysis. The patients were randomly split into training and validation sets in a ratio of 7:3. In the training set, all variables were included, and the cumulative incidence function (CIF) of recurrence was estimated. Gray's test for survival differences was used to identify potential prognostic variables with a *P* value < 0.05. Multifactorial competitive risk analysis was conducted based on the Fine-Gray method, followed by the construction of prognostic prediction models and nomograms. The predictive performance of the nomogram was assessed using receiver operating characteristic (ROC) curve analysis, concordance index (C index) and the calibration curve. The significance level was set at $\alpha = 0.05$.

Results

Balance test between training set and validation set

A total of 280 patients with endometrial cancer were included and randomly assigned in a 7:3 ratio into the training set (202 patients) and the validation set (78 patients). After comparison of all clinical data between the training and validation sets, no statistically significant differences were found (P > 0.05) (**Table 1**). This indicates that the statistical models developed in the training set are valid for use in the validation set.

Univariate analysis of postoperative DFS

In the training set, the CIF for recurrence was estimated, and Gray's test was performed. The results showed that age, BMI, diabetes, degree of differentiation, pathological type, muscle infiltration depth, neutrophil count, CA125 and HE4 were significant factors affecting the patients' postoperative DFS (all P < 0.05). In contrast, hypertension, tumor diameter, chemotherapy, surgical method, postoperative complications, HB and ALB were not significantly associated with patients' postoperative DFS (all P > 0.05). The detailed results are shown in **Table 2** and **Figures 2**, **3**.

Table 1. Comparison of patient clinical data between the training and validation sets [$\bar{x} \pm s$, n (%)]

Variables	Training set (n = 202)	Validation set (n = 78)	χ^2	*P*
Age (yrs)			1.018	0.313
< 60	67 (33.17)	21 (26.92)		
≥ 60	135 (66.83)	57 (73.08)		
BMI (kg/m^2)			5.092	0.052
< 18.5	20 (9.90)	6 (7.69)		
18.5-23.9	85 (42.08)	22 (28.21)		
> 23.9	97 (48.02)	50 (64.10)		
Hypertension			0.034	0.853
No	83 (41.09)	33 (42.31)		
Yes	119 (58.91)	45 (57.69)		
Diabetes			1.883	0.170
No	69 (34.16)	20 (25.64)		
Yes	133 (65.84)	58 (74.36)		
Differentiation degree			3.236	0.198
Low	78 (38.61)	38 (48.72)		
Medium	73 (36.14)	27 (34.62)		
High	51 (25.25)	13 (16.66)		
Tumor diameter			0.506	0.477
> 2 cm	95 (47.03)	33 (42.31)		
≤ 2 cm	107 (52.97)	45 (57.69)		
Chemotherapy			0.386	0.534
With	99 (49.01)	35 (44.87)		
Without	103 (50.99)	43 (55.13)		
Pathological type			0.096	0.757
Endometrioid adenocarcinoma	66 (32.67)	27 (34.62)		
Non-endometrial adenocarcinoma	136 (67.33)	51 (65.38)		
Muscular infiltration depth			0.079	0.779
< ½	84 (41.58)	31 (39.74)		
≥ ½	118 (58.42)	47 (60.26)		
Operation method			0.193	0.660
Laparotomy	72 (35.64)	30 (38.46)		
Laparoscopic	130 (64.36)	48 (61.54)		
Postoperative complication			0.275	0.600
With	76 (37.62)	32 (41.03)		
Without	126 (62.38)	46 (58.97)		
HB (g/L)			3.054	0.217
< 120	75 (37.13)	35 (44.87)		
120-160	65 (32.18)	27 (34.62)		
> 160	62 (30.69)	16 (20.51)		
ALB (g/L)			2.575	0.276
< 35	76 (37.62)	35 (44.87)		
35-50	60 (29.70)	25 (32.05)		
> 50	66 (32.67)	18 (23.08)		
Neutrophil count (×10^9/L)			3.686	0.158
< 1.8	47 (23.27)	25 (32.05)		
1.8-6.3	64 (31.68)	27 (34.62)		
> 6.3	91 (45.05)	26 (33.33)		

CA125 (U/mL)			0.581	0.446
≤ 40	78 (38.61)	34 (43.59)		
> 40	124 (61.39)	44 (56.41)		
HE4 (pmol/L)			0.634	0.426
≤ 90	83 (40.09)	28 (35.90)		
> 90	119 (58.91)	50 (64.10)		

Notes: BMI, Body mass index; HB, Hemoglobin; ALB, albumin; CA125, Cancer Antigen 125; HE4, Human epididymis protein 4.

Table 2. Univariate analysis for postoperative disease-free survival in the training set

Variable	Gray's test	*P* value	12-month	36-month	48-month
Age	44.000	< 0.001			
< 60			0.00%	6.7%	21%
≥ 60			6.0%	41%	60%
BMI (kg/m^2)	26.400	< 0.001			
< 18.5			0.00%	5.0%	12%
18.5-23.9			5.9%	24%	35%
> 23.9			3.1%	40%	70%
Hypertension	1.020	0.310			
With			2.4%	30%	57%
Without			5.1%	30%	42%
Diabetes	25.700	< 0.001			
With			0.00%	14%	27%
Without			6.0%	38%	58%
Differentiation degree	24.500	< 0.001			
Low			5.1%	39%	67%
Medium			1.4%	14%	24%
High			5.9%	42%	63%
Tumor diameter	1.030	0.310			
> 2 cm			2.1%	28%	54%
≤ 2 cm			5.6%	32%	43%
Chemotherapy	2.140	0.140			
With			3.0%	29%	56%
Without			4.9%	31%	41%
Pathological type	5.450	0.020			
Endometrioid adenocarcinoma			0.00%	17%	40%
Non-endometrial adenocarcinoma			5.9%	36%	51%
Muscular infiltration depth	24.100	< 0.001			
< ½			1.2%	15%	34%
≥ ½			5.9%	40%	57%
Operation method	0.612	0.430			
Laparotomy			1.4%	28%	56%
Laparoscopic			5.4%	31%	44%
Postoperative complication	0.381	0.540			
With			2.6%	28%	57%
Without			4.8%	31%	43%
HB (g/L)	1.980	0.370			
< 120			2.7%	23%	46%
120-160			3.1%	34%	43%
> 160			6.5%	35%	55%

ALB (g/L)	3.760	0.150			
< 35			3.9%	32%	56%
35-50			6.8%	34%	49%
> 50			1.5%	24%	38%
Neutrophil count ($\times 10^9$/L)	11.700	0.003			
< 1.8			4.3%	21%	36%
1.8-6.3			3.1%	23%	40%
> 6.3			4.4%	40%	62%
CA125 (U/mL)	28.600	< 0.001			
≤ 40			1.3%	13%	25%
> 40			5.7%	39% (30%, 48%)	59%
HE4 (pmol/L)	32.300	< 0.001			
≤ 90			0.00%	8.5%	21%
> 90			6.7%	6.7%	6.7%

Notes: BMI, Body mass index; HB, Hemoglobin; ALB, albumin; CA125, Cancer Antigen 125; HE4, Human epididymis protein 4.

Multivariate analysis of postoperative DFS

The significant factors identified in the univariate analysis were further analyzed using the Fine-Gray method, with the variable assignment table shown in **Table 3**. The results showed that age, BMI, diabetes, myometrial invasion depth (≥ 1/2 myometrium), CA125 > 40 U/mL, HE4 > 90 pmol/L were independent factors influencing DFS in patients with endometrial cancer after surgery (all $P < 0.05$) (**Table 4**).

Construction of a prognostic nomogram for patients with endometrial cancer

Based on the results of competitive risk analysis, a nomogram was constructed incorporating age, BMI, diabetes, myometrial invasion depth, CA125, and HE4 as predictors. This nomogram is designed to predict the 1-year, 2-year, and 4-year survival probabilities for endometrial cancer patients (**Figure 4**). By mapping each patient's clinical characteristics to the upper scale, corresponding scores were then summed to calculate a total score. Finally, this total score is mapped to the lower scale to determine the probability of shortened postoperative survival following radical resection.

Validation of nomogram prediction models

Consistency index (C-index), ROC curve and calibration curve were used to verify the prognostic accuracy of the nomogram. Model discrimination was evaluated by plotting ROC curves and calculating AUC values. The results showed that in the training set, the AUC values for the model in predicting 1-, 2-, and 4-year DFS were 0.773, 0.802, and 0.858, respectively. While in the validation set, the AUCs were 0.923, 0.829, and 0.746, respectively. This indicates that the nomogram model demonstrates good discrimination (**Figure 5**). For the training set and validation set, the C-index were 0.786 and 0.515, respectively. The calibration curve further indicated that the predicted probabilities closely matched the actual probabilities, supporting the good calibration of the nomogram model (**Figure 6**).

Discussion

Endometrial cancer is increasingly being diagnosed in younger patients, with its incidence showing a gradual upward trend, posing a significant threat to patient safety [8]. Most patients with early-stage endometrial cancer undergo surgical intervention followed by appropriate adjuvant therapy, which can extend survival and improve quality of life. However, a subset of patients still experience postoperative complications and unsatisfactory treatment outcomes [9]. Therefore, developing an effective prediction method is important for the early detection and intervention of endometrial cancer recurrence. The competing risk model is a statistical method to analyze survival data with multiple outcomes. It takes into account patients who die before the event of interest, offering a more accurate evaluation of cancer

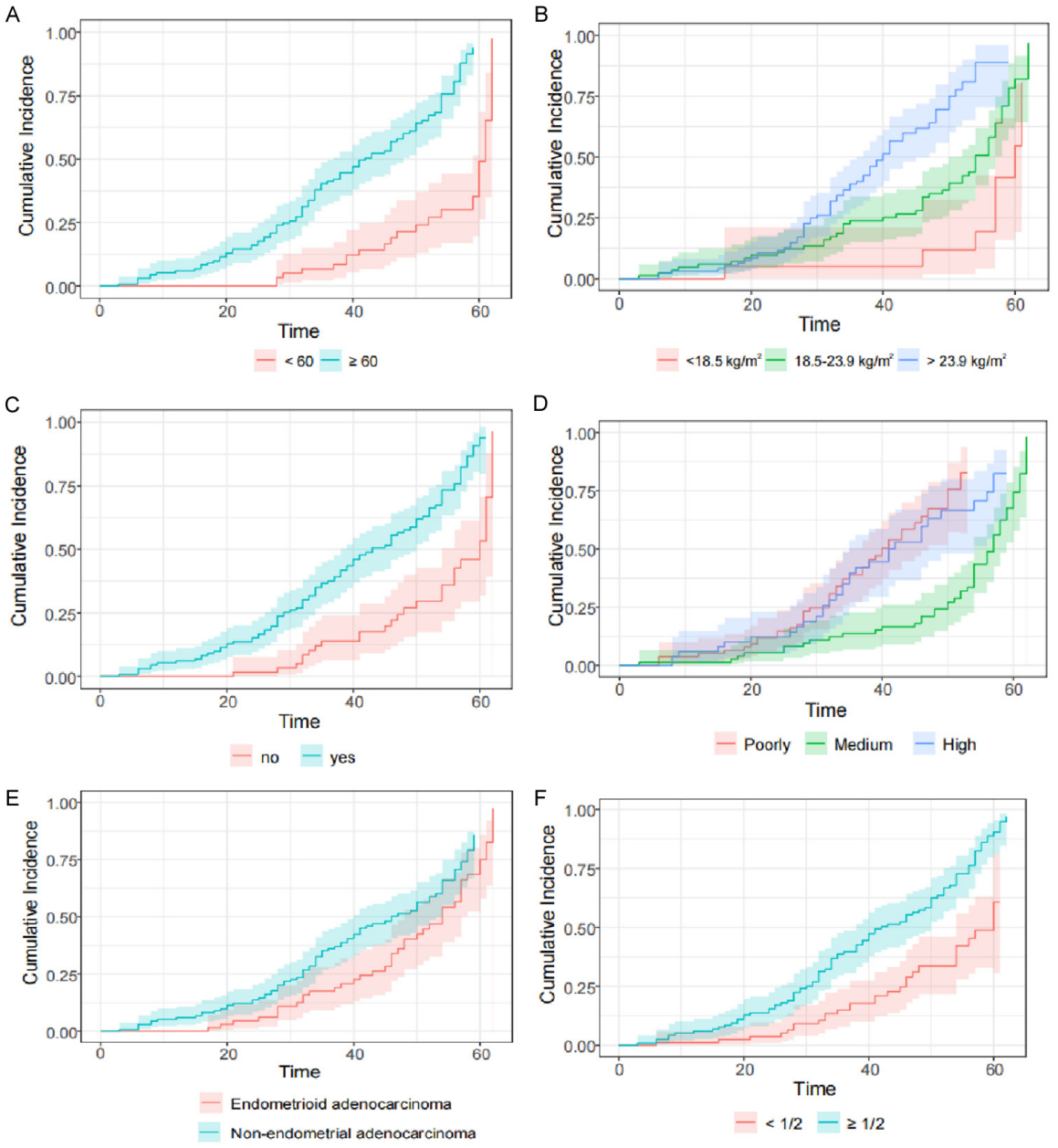

Figure 2. Cumulative incidence of each indicator. Note: (A) Age; (B) Body mass index; (C) Diabetes; (D) Differentiation degree; (E) Pathological type; (F) Muscular infiltration depth.

prognosis. It has been increasingly applied to various oncology fields, including bladder cancer and breast cancer [10, 11]. In this study, we employed the competing risk prediction model to assess the risk of disease-free survival in endometrial cancer patients following surgery, aiming to provide valuable insights for improving postoperative management and clinical prognosis.

Currently, well-established prognostic factors for endometrial cancer include age, pathological type, stage, tissue grade, lymph node metastasis [12]. The results of the competing risk model in this study showed that age, BMI, diabetes, myometrial invasion depth, CA125 and HE4 were independent factors influencing DFS of patients with endometrial cancer after surgery. Age is a key determinant of DFS, with

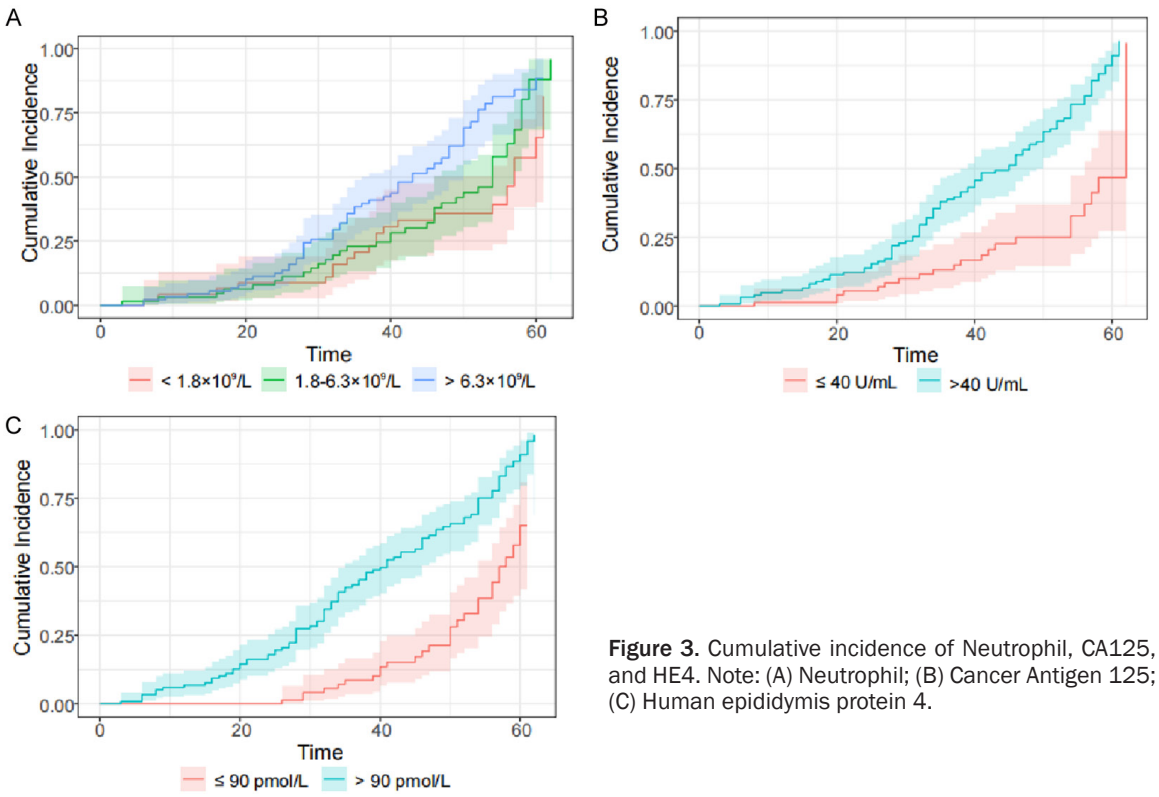

Figure 3. Cumulative incidence of Neutrophil, CA125, and HE4. Note: (A) Neutrophil; (B) Cancer Antigen 125; (C) Human epididymis protein 4.

Table 3. Assignment table

Factor	Assignment
Follow-up outcome	0 = deletion, 1 = death, 2 = race event
Age	< 60 = 0, ≥ 60 = 1
BMI	< 18.5 = 0, 18.5-23.9 = 1, > 23.9 = 2
Diabetes	No = 0, yes = 1
Differentiation degree	Poorly = 0, Medium = 1, High = 2
Pathological type	Endometrioid adenocarcinoma = 0, Non-endometrial adenocarcinoma = 1
Muscular infiltration	< 1/2 = 0, ≥ 1/2 = 1
Neutrophil count	< 1.8 = 0, 1.8-6.3 = 1, > 6.3 = 2
CA125	≤ 40 = 0, > 40 = 1
HE4	≤ 90 = 0, > 90 = 1

Notes: BMI, Body mass index; CA125, Cancer Antigen 125; HE4, Human epididymis protein 4.

Table 4. Multivariate analysis for postoperative disease-free survival in the training set

Variables	*B*	*SE*	*P*	HR	95% CI
Age	0.742	0.220	< 0.001	2.100	1.370-2.230
BMI	0.700	0.176	< 0.001	2.010	1.420-2.840
Diabetes	0.679	0.238	0.004	1.970	1.240-3.150
Muscular infiltration	0.678	0.204	< 0.001	1.970	1.320-2.940
CA125	0.478	0.236	0.043	1.610	1.010-2.560
HE4	1.090	0.247	< 0.001	2.970	1.830-4.820

Notes: BMI, Body mass index; CA125, Cancer Antigen 125; HE4, Human epididymis protein 4.

older patients generally experiencing worse postoperative outcomes due to factors such as reduced physiological tolerance and the presence of comorbidities. The study showed that the risk of death for patients aged ≥ 60 years was 2.100 times higher than for those < 60 years, which aligns with findings by Sahin et al. [13]. However, age group classifications vary across studies. For example,

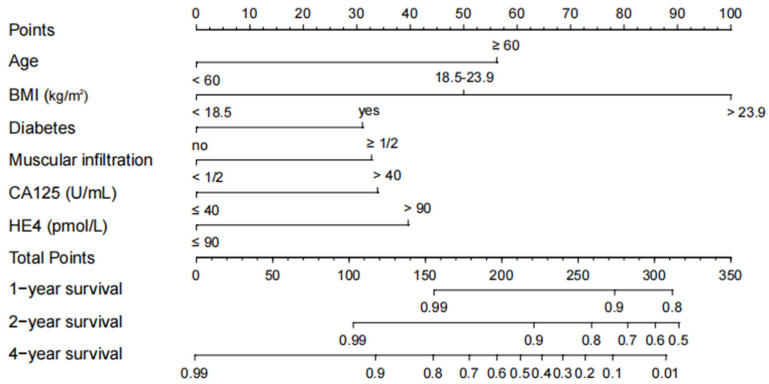

Figure 4. Nomogram for predicting disease-free survival after radical resection of endometrial cancer.

Yu et al. [14] reported patients aged ≥ 70 years had a 5.399 times higher death risk compared to those < 70 years. This discrepancy could be attributed to older women often neglecting early signs of vaginal bleeding and failing to undergo regular screenings. Additionally, tumors in older patients tend to be more aggressive, with a higher likelihood of poor histological grading and deep myometrial invasion [15, 16]. This study also highlighted BMI as a significant factor affecting disease-free survival, consistent with findings by Hafizz et al. [17]. A higher BMI is positively correlated with increased endometrial cancer incidence. Obesity, a primary manifestation of metabolic disorder syndrome, can promote the development of endometrial cancer through several mechanisms. Relevant studies suggest that obesity leads to abnormal glucose and lipid metabolism, insulin resistance, and hyperglycemia, all of which disrupt estrogen metabolism and foster tumor vascular proliferation [18, 19]. Additionally, obesity can modulate pathways that influence lipocalin production and the endocrine system, increasing the risk of recurrence and shortening progression-free survival [20]. Furthermore, diabetes mellitus was found to significantly affect disease-free survival, a result supported by Kolehmainen et al. [21]. Diabetes, characterized by elevated blood sugar, contributes to multiple complications that impact overall health. Diabetic patients not only face a higher risk of developing endometrial cancer, but their prognosis is also poorer. The mechanisms linking diabetes and endometrial cancer may involve disruptions in glucose metabolism, which increases insulin resistance, elevates blood glucose levels, and stimulates excessive insulin production. This fosters rapid cancer cell proliferation. Moreover, insulin resistance can induce hypertension, further complicating the clinical management of endometrial cancer and threatening patient survival [22, 23].

The results of this research demonstrated that the depth of myometrial infiltration is a crucial factor affecting DFS after endometrial cancer surgery, which aligns with the findings of Sun et al. [24]. Myometrial infiltration depth is one of the most important indicators for assessing the severity and prognosis of endometrial cancer. When the cancer progresses to invade the myometrium, it signifies a more advanced stage of the disease. At this point, the tumor has penetrated deeper into the uterine tissues, complicating treatment and significantly increasing mortality risk. In addition, CA125 and HE4 expression levels were also identified as important prognostic factors for DFS after endometrial cancer surgery, consistent with findings from Quan et al. [25]. CA125 is a well-known tumor marker for the diagnosis and prognosis assessment of endometrial cancer. Elevated CA125 level often indicates that the tumor has invaded the uterine seromuscular layer or has metastasized [26]. Studies suggest that CA125 can degrade the basement membrane of cervical blood vessels, leading to endometrial rupture and interstitial edema, thereby increasing the risk of tumor invasion and metastasis [27]. HE4 is a newly discovered tumor marker, clinically recognized for its abnormal expression in the serum of patients with endometrial and ovarian cancers and for its involvement in the process of tumorigenesis [28, 29]. The potential mechanism by which HE4 affects endometrial cancer may be linked to its elevated serum levels when the endometrial tissue proliferates abnormally. Higher HE4 expression levels correlate with an increased risk of developing endometrial cancer.

This study still has several limitations. First, as a retrospective cohort study, and it could not account for all potential confounders, which may introduce bias into the results. Second,

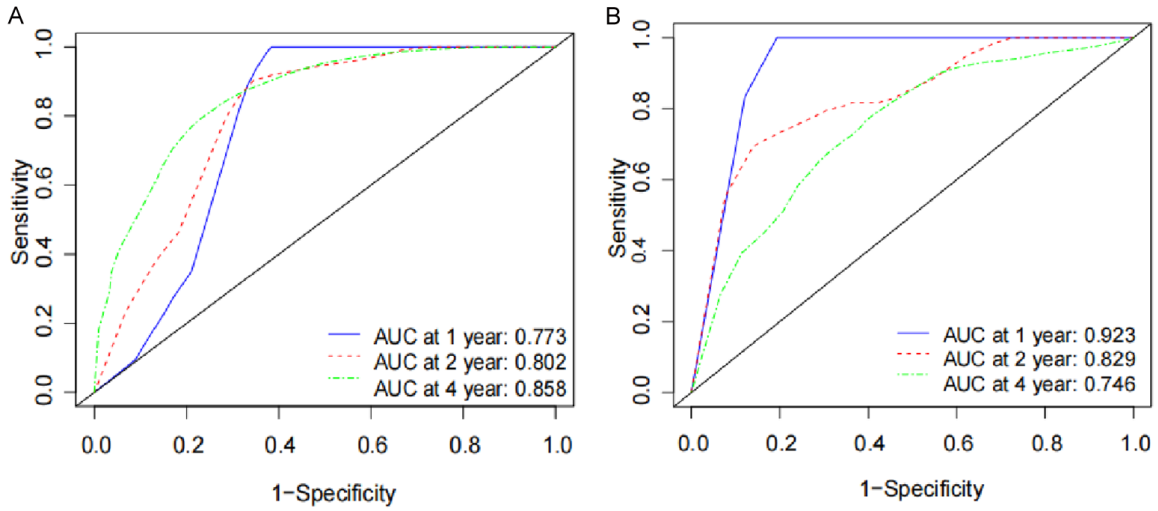

Figure 5. ROC curve analysis for the predictive model in the training set (A) and validation set (B).

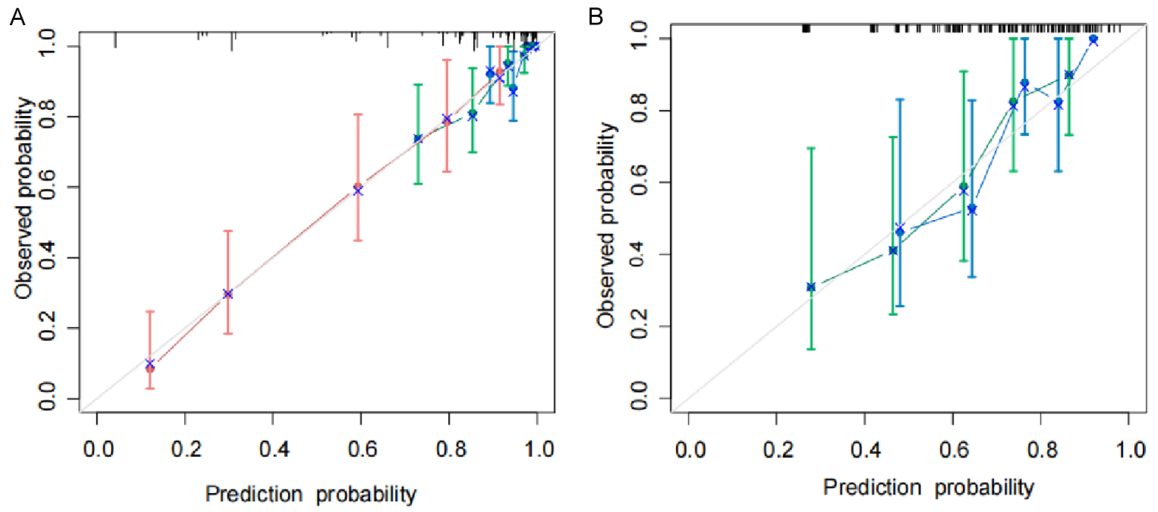

Figure 6. Calibration curve for the predictive model in the training set (A) and validation set (B).

the relatively small sample size may limit the stability and reliability of the results. Future research should involve multi-center studies with larger sample sizes to validate this model and identify predictors applicable to a broader population.

In summary, the Fine-Gray competing risk prediction model can effectively identify the factors influencing DFS in endometrial cancer patients after surgery. The nomograms developed from this model demonstrate strong predictive value, offering clinicians a tool to identify high-risk patients and tailor individualized treatment plans. Future studies should focus on external validation of the model, long-term follow-up data collection, and economic evaluations to further confirm its clinical utility.

Disclosure of conflict of interest

None.

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