Diagnostic and prognostic value of HABP2 as a novel biomarker for endometrial cancer

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Background: Endometrial cancer is the fifth most common malignant disorder in women, with its incidence increasing. A biomarker with diagnostic and prognostic value remains to be found. The HABP2 protein, or Factor VII-activating protease, encodes a hyaluronic acid-binding protein.

Methods: Patient data including clinical characteristics and RNAseq information of HABP2 was obtained from The Cancer Genome Atlas (TCGA), and analyzed by R statistic packages. A total of 370 women with endometrial cancer were enrolled in the study. To study the diagnostic value of HABP2 in patients with endometrial cancer, receiver operating characteristic (ROC) curves were plotted by the pROC package. To study the prognostic value of HABP2 in patients with endometrial cancer, the survival package in R was used and the Cox model was established.

Results: HABP2 expression was lower in endometrial cancer compared with normal endometrial tissues. HABP2 showed moderate diagnostic value for endometrial cancer, with HBP2 expression associated with vital status, histologic grade, and residual tumor. HABP2 was an independent prognostic factor, with low HABP2 expression indicating a better overall survival.

Conclusions: HABP2 has diagnostic and prognostic value and maybe a novel biomarker for endometrial cancer.

Keywords: Endometrial cancer; HABP2; diagnosis; prognosis; biomarker

Introduction

Endometrial cancer is the fifth most prevalent malignant disorder in women, with its morbidity rate increasing (1-3). The cumulative risk of women developing endometrial cancer by age 75 is 1%, and 0.2% for death (4). In developed countries, endometrial cancer is the most prevalent gynaecological tumor, however it is less prevalent in developed countries (1,2). Endometrial cancer generally occurs in postmenopausal women, while 14% are premenopausal, and 5% are less than 40 years old (5). Several factors may be associated with endometrial cancer, including obesity, diabetes, and age (2). Endometrial carcinoma have increased markedly over the last decades. Although the majority of women with endometrial carcinoma have good outcomes, women with advanced disease or more aggressive subtypes may not be curable with adjuvant therapy. we are in desperate need of new approaches, including diagnostic tools, to manage this cancer. There are many unanswered questions in endometrial carcinoma pertaining to diagnosis and optimal management.

The plasma protein HABP2, also known as Factor VII-activating protease, encodes a hyaluronic acid-binding protein (6). HABP2 degrades the extracellular matrix and

functions in coagulation via activating Factor VII and pro-urokinase (6,7). More importantly, HABP2 exhibits a tumor-suppressive effect in epithelial cells (8). Most studies of HABP2 have focused on thyroid cancer, especially familial non-medullary thyroid cancers (8-12). There are few reports on the role of HABP2 in endometrial cancer. This is the first study of HABP2 as a potential novel biomarker in endometrial cancer. Molecular classification of endometrial cancer (copy number low/p53 wild-type, copy number high/p53 abnormal, polymerase E mutant, and mismatch repair deficient) has shown great promise, proving to be reproducible, and demonstrating associations with clinical outcomes. Unfortunately, to identify these four genomic subgroups, including genome sequencing, were costly, complex and unsuitable for wider clinical application. Our study aimed was to determine whether the some molecular subgroups could be identified and the survival curves reproduced with assays that could be used in routine clinical practice.

Herein, the expression of HABP2 in patients with endometrial cancer was assessed and related clinical features examined. The diagnostic and prognostic values of HABP2 were evaluated using receiver operating characteristic (ROC) curves and Cox model analysis, respectively. We present the following article in accordance with the REMARK reporting checklist (available at http://dx.doi.org/10.21037/atm-20-5744).

Methods

Data mining

Data from patients suffering from endometrial cancer, including clinical characteristics and RNSseq of HABP2, were downloaded from The Cancer Genome Atlas (TCGA) database by UCSC Xena. TCGA is open to the public and no ethics approval was required. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethic Committee of Beijing Chao-Yang Hospital (No. 2019-331).

A total number of 370 women with endometrial cancer, comprising 72 women below the age of 55 and 298 women over the age of 55 and over, were enrolled in the study.

Software

R version 3.5.2 packages were used for bioinformatics analysis.

Evaluation of RNA expression

The RNA expression of HABP2 is shown in boxplots. Vertical lines represent 95% confidence intervals (CI).

Evaluation of diagnostic value

ROC curves were plotted by pROC package (13). The calculated area under the curves (AUC) indicated the diagnostic value. The high and low expression were grouped according to the identified threshold level of HABP2.

Evaluation of prognostic value

The R survival package and Cox model were established (14) and evaluation of sub-groups were performed.

Statistical analysis

The Wilcoxon rank-sum examination was used to compare the two groups. The Kruskal-Wallis examination was involved in comparing differences between three or more groups. The chi-squared test was performed, and corrected by Fisher's exact test. A P value of less than 0.05 was considered statistically significant.

Results

Characteristics of patients

Clinical information including age, histology, stage, diabetes, hypertension, histologic grade, menopause status, residual tumor, vital status, HABP2 expression, overall survival, and recurrence-free survival are shown in *Table 1*. The histological type of most patients was endometrioid (81.89%), and 65.95% of the patients had stage 1 disease. Nearly one quarter of patients suffered from diabetes, and one half suffered from hypertension. The histologic grade with the highest incidence rate was G3. Most women were post-menopause (81.08%).

High HABP2 expression in tumor

Compared with normal tissue, HABP2 was found to highly expressed in endometrial tumors (P=0.017; *Figure 1A*). Furthermore, the association of HABP2 expression with histological type, stage, histologic grade, age, diabetes, hypertension, menopause status, residual

Table 1 Clinical characteristics of the patients with endometrial cancer

Characteristics	Number (%)
Age	
<55	72 (19.46)
≥55	298 (80.54)
Histological type	
Endometrioid	303 (81.89)
Mixed	10 (2.70)
Serous	57 (15.41)
Stage	
I	244 (65.95)
II	28 (7.57)
III	79 (21.35)
IV	19 (5.14)
Diabetes	
No	209 (56.49)
Yes	84 (22.7)
NA	77 (20.81)
Hypertension	
No	127 (34.32)
Yes	188 (50.81)
NA	55 (14.86)
Histologic grade	
G1	85 (22.97)
G2	100 (27.03)
G3	178 (48.11)
High grade	7 (1.89)
Menopause status	
Indeterminate	14 (3.78)
Peri-menopause	14 (3.78)
Post-menopause	300 (81.08)
Pre-menopause	26 (7.03)
NA	16 (4.32)
Residual tumor	
R_0	265 (71.62)
R_1	18 (4.86)

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Number (%)
R_2	11 (2.97)
R_x	23 (6.22)
NA	53 (14.32)
Vital status	
Deceased	58 (15.68)
Living	312 (84.32)
HABP2	
High	188 (50.81)
Low	182 (49.19)
Overall survival	
No	58 (15.68)
Yes	312 (84.32)
Recurrence-free survival	
No	73 (19.73)
Yes	297 (80.27)

tumor and vital status was evaluated in endothelial tumors (*Figure 1B,C,D,E,F,G,H,I,J*). As shown in *Figure 1D*, the histologic grade of G3 showed the lowest HABP2 expression, and G1 showed the highest HABP2 expression (P=1.2e-15). The HABP2 expression in high grade was close to that in G2, between G3 and G1. As for residual tumor, the HABP2 expression of the most common R_0 (71.62%; *Table 1*) was higher than R_2 and R_1 (P=0.03). No significant were found in other subgroup analyses.

Diagnostic value of HABP2 for endometrial cancer

The ROC analysis was first performed in all patients, indicating a modest diagnostic value with AUC of 0.711 (*Figure 2A*). Then, different stages of endometrial cancer were further analyzed (*Figure 2B,C,D,E*). Results showed that the diagnostic value was decreasing with stage, with the AUC increasing from stage I (AUC =0.726) to stage II (AUC =0.711) to stage III (AUC =0.685) finally to stage IV (AUC =0.629).

Correlation of HABP2 expression with clinical features

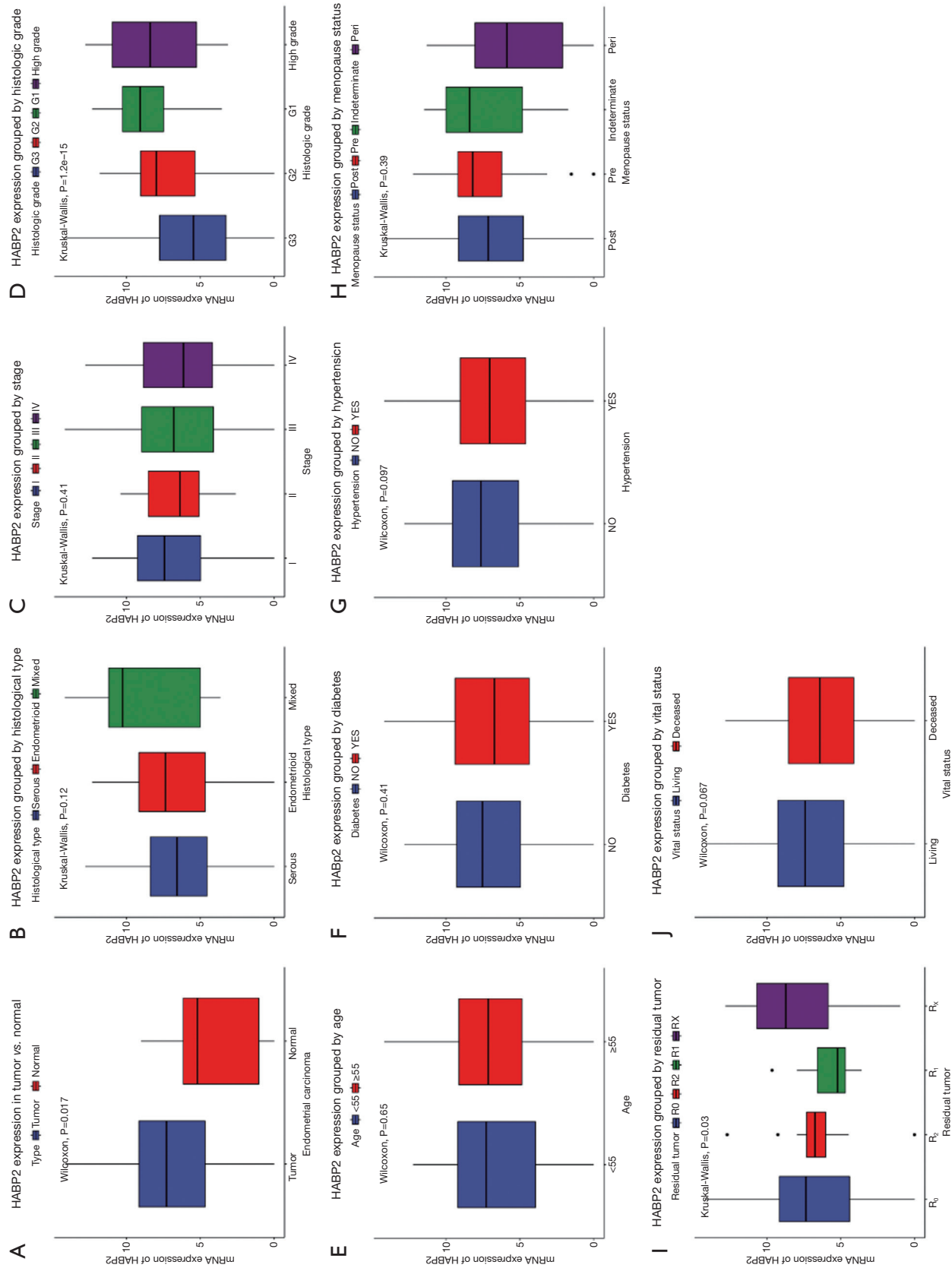Patients were divided into high HABP2 (n=188) and low

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Figure 1 Expression of HABP2 in endometrial cancer, with a comparison of tumor and adjacent normal tissue (A); grouped by histological type (B); stage (C); histologic grade (D); age (E); diabetes (F); hypertension (G); menopause status (H); residual tumor (I); and vital status (J).
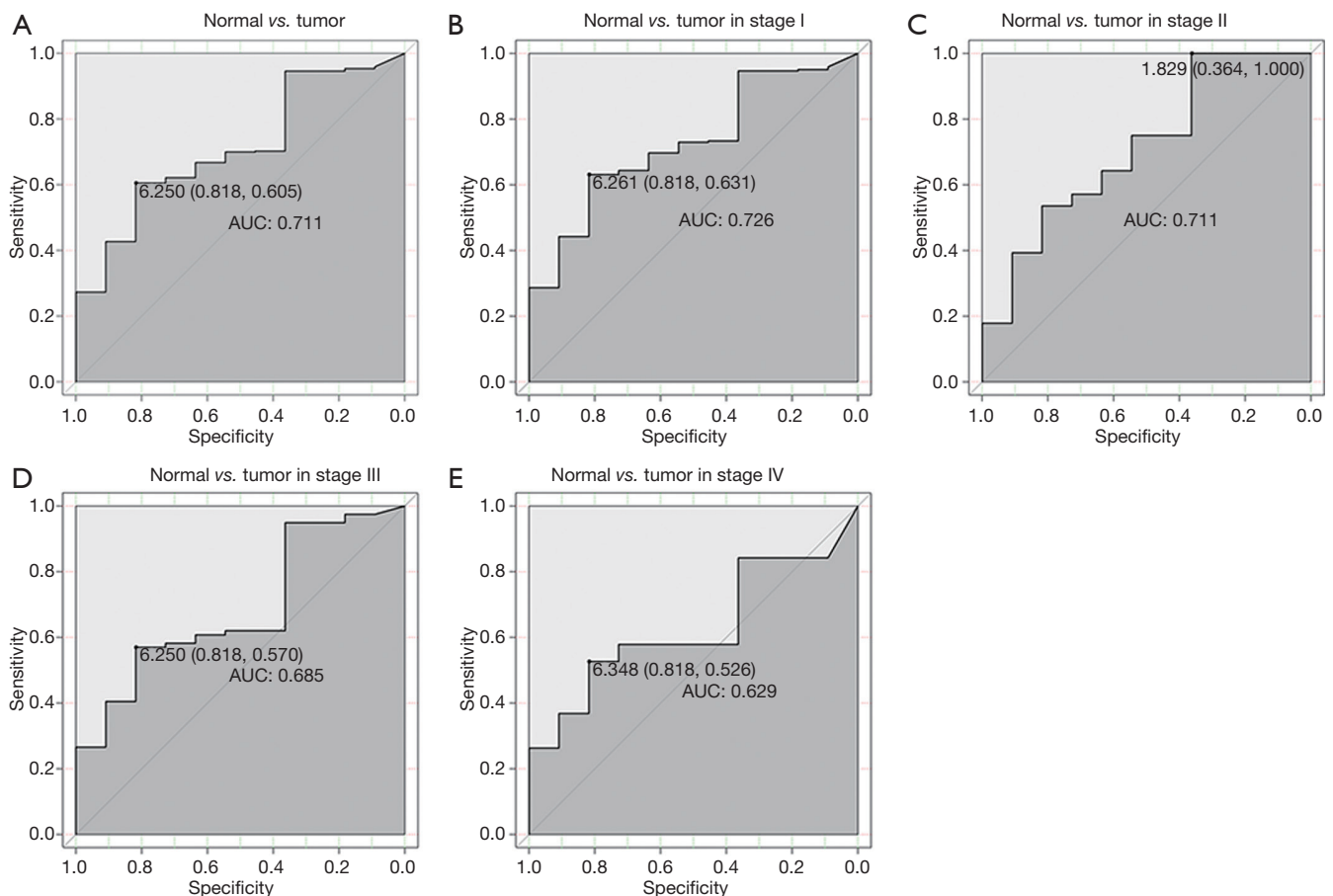
Figure 2 ROC (Receiver operating characteristic) curves of HABP2 expression in patients with endometrial cancer, including normal *vs.* overall tumor (A); normal *vs.* stage I tumor (B); normal *vs.* stage II tumor (C); normal *vs.* stage III tumor (D); and normal *vs.* stage IV tumor (E).

HABP2 (n=182) expression groups. As shown in *Table 2*, HABP2 expression was associated with vital status (P=0.023), histologic grade (P<0.001), and residual tumor (P=0.007). No association was found between HABP2 expression and age (P=0.982), histological type (P=0.312), stage (P=0.481), diabetes (P=0.616), hypertension (P=0.314), and menopause status (P=0.626).

Prognostic value of HABP2 for endometrial cancer

Given that HABP2 was correlated with survival, the prognostic value of HABP2 was further studied. As shown in *Figure 3A*, patients with low HABP2 expression presented an improved overall survival rate (P=0.0027). Analysis of subgroups (patients in different age, stage and grade) showed that HABP2 had significant prognostic value

in G3 and G4 (P=0.037) and elderly patients (patients older than 55 years) (P=0.00061) (*Figure 3B,C,D,E,F,G*).

A univariate Cox model was established (*Table 3*). No obvious differences were observed in relation to diabetes (P=0.619), histologic grade (P=0.329), histological type (P=0.248), hypertension (P=0.887), residual tumor (P=0.183) and stage (P=0.561). Age (P=0.021) and menopause status (P=0.017) showed significant differences. HABP2 may be a risk factor (HR =1.41; P=0.003). As shown in *Table 4*, the multivariate analysis further confirmed HABP2 was a risk factor and an independent prognostic indicator for overall survival (HR =1.37; 95% CI: 1.09–1.73; P=0.008).

Discussion

In this bioinformatics study, HABP2 was shown to be highly

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Table 2 Relationship between the clinical features and HABP2 expression in patients with endometrial cancer

Clinical characteristics	Variable	Number of patients	HABP2 expression		χ^2	P value
			High, n (%)	Low, n (%)		
Age	<55	72	36 (19.15)	36 (19.78)	0.001	0.982
	≥55	298	152 (80.85)	146 (80.22)		
Histological type	Endometrioid	303	158 (84.04)	145 (79.67)	2.282	0.312
	Mixed	10	6 (3.19)	4 (2.2)		
	Serous	57	24 (12.77)	33 (18.13)		
Stage	I	244	130 (69.15)	114 (62.64)	2.525	0.481
	II	28	13 (6.91)	15 (8.24)		
	III	79	38 (20.21)	41 (22.53)		
	IV	19	7 (3.72)	12 (6.59)		
Diabetes	No	209	113 (72.9)	96 (69.57)	0.251	0.616
	Yes	84	42 (27.1)	42 (30.43)		
Hypertension	No	127	71 (43.29)	56 (37.09)	1.014	0.314
	Yes	188	93 (56.71)	95 (62.91)		
Histologic grade	G1	85	69 (36.7)	16 (8.79)	63.087	<0.001
	G2	100	60 (31.91)	40 (21.98)		
	G3	178	55 (29.26)	123 (67.58)		
	High grade	7	4 (2.13)	3 (1.65)		
Menopause status	Indeterminate	14	9 (4.92)	5 (2.92)	1.759	0.626
	Peri-menopause	14	6 (3.28)	8 (4.68)		
	Post-menopause	300	153 (83.61)	147 (85.96)		
	Pre-menopause	26	15 (8.2)	11 (6.43)		
Residual tumor	R_0	265	139 (85.8)	126 (81.29)	11.839	0.007
	R_1	18	4 (2.47)	14 (9.03)		
	R_2	11	3 (1.85)	8 (5.16)		
	R_x	23	16 (9.88)	7 (4.52)		
Vital status	Deceased	58	21 (11.17)	37 (20.33)	5.197	0.023
	Living	312	167 (88.83)	145 (79.67)		

expressed in endometrial cancer. HABP2 expression was associated with vital status, histologic grade, and residual tumor type. Although diabetes and menopause status are highly related with endometrial tissue, no association was found between these and HABP2 expression. Further, HABP2 presented a moderate diagnostic value for endometrial cancer.

The HABP2 gene mutation has been commonly studied in thyroid cancer (10), and the HABP2 variant is a susceptibility gene for familial non-medullary thyroid cancer (7). HABP2 has also been studied in lung cancer (15), atherosclerosis (16), deep venous thrombosis (17), and female infertility (18). A study conducted by Mirzapoiazova *et al.* suggested that HABP2 may directly activate uPA and promote lung cancer progression (15). Increased HABP2 expression has been observed in tissue of different
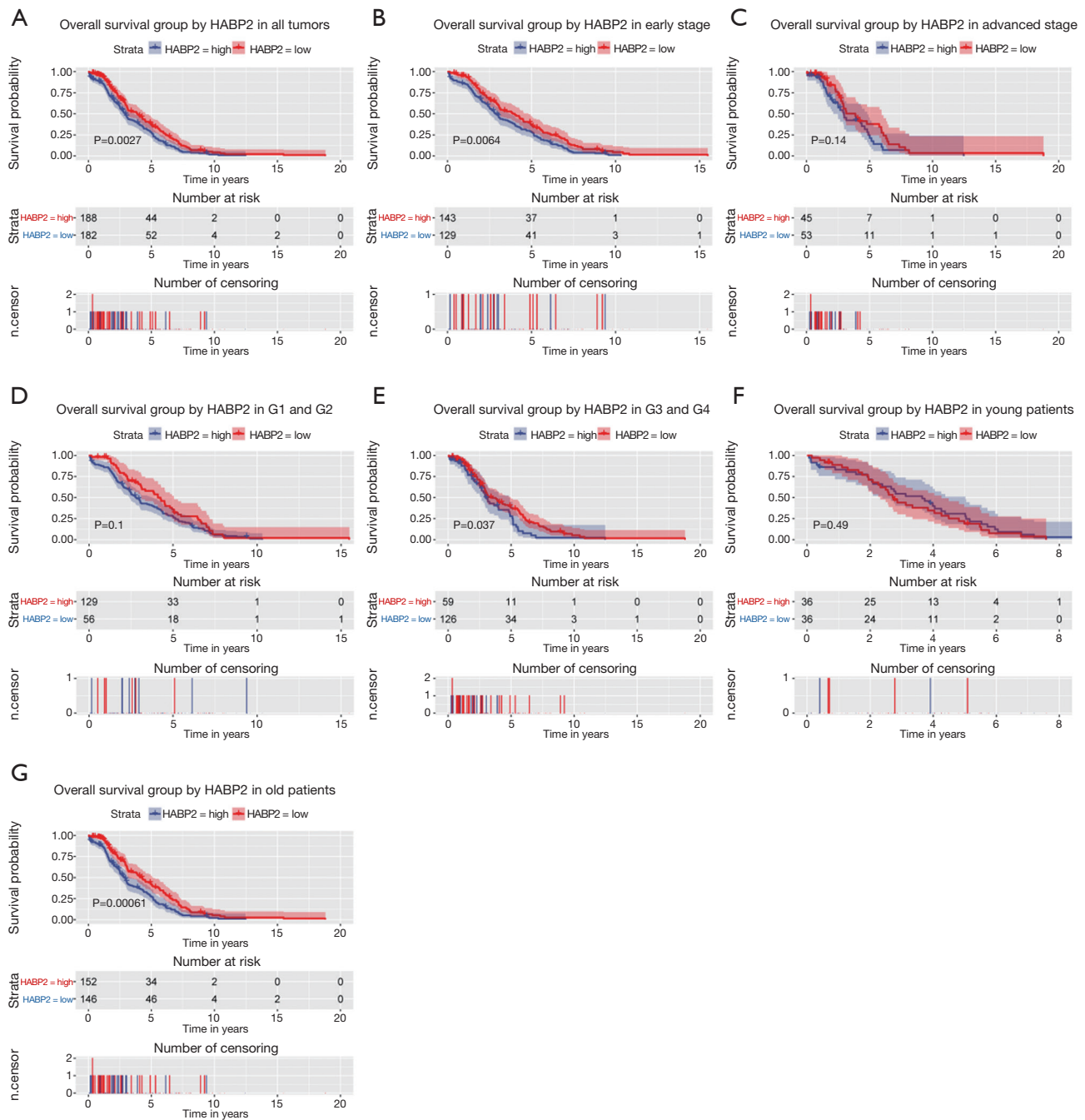
Figure 3 Relationship of HABP2 expression with overall survival in all patients with endometrial cancer (A); patients in early stage (B); patients in advanced stage (C); patients in G1 and G2 (D); patients in G3 and G4 (E); young patients (F); and elderly patients (G).

non-small cell lung cancer (15). HABP2 regulates cell proliferation mediated by growth factor and migration (19,20). Additionally, HABP2 regulates the function of endothelial cells, including vascular integrity and neointima formation (21,22).

In recent years, biomarker research by data mining has become popular (23-34). The exploration of biomarkers for endometrial cancer is ongoing. Abnormal expression of PICT-1 is a risk factor for human endometrial cancer (35). PTEN expression, reported by Yang *et al.*, may also be a risk

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Table 3 Univariate analysis of overall survival in patients with endometrial cancer

Parameters	Hazard ratio	95% CI	P value
Age	0.72	0.55–0.95	0.021
Diabetes	0.96	0.81–1.13	0.619
HABP2	1.41	1.13–1.76	0.003
Histologic grade	0.94	0.82–1.07	0.329
Histological type	0.91	0.77–1.07	0.248
Hypertension	0.99	0.85–1.15	0.887
Menopause status	0.85	0.75–0.97	0.017
Residual tumor	1.09	0.96–1.23	0.183
Stage	0.96	0.85–1.09	0.561

Table 4 Multivariate analysis of overall survival in patients with endometrial cancer

Parameters	Hazard ratio	95% CI	P value
Age	0.82	0.57–1.18	0.281
HABP2	1.37	1.09–1.73	0.008
Menopause status	0.93	0.78–1.1	0.382

factor (36). Merritt *et al.* studied the association of Insulin/IGF (insulin-like growth factor) and sex hormones with risk factors (37). We reported HABP2 to be a risk factor for endometrial cancer.

From our results, HABP2 is a risk factor for endometrial cancer, and low HABP2 expression is associated with better overall survival. HABP2 is suggested to effect endometrial receptivity for embryo implantation(38). HABP2 has been shown to be down-regulated in sub-fertile women, women with refractory conditions, and unexplained infertility (18). As observed by Altmae *et al.*, HABP2 is involved in the angiogenesis and extracellular matrix degradation of endometrium cells (18). These findings indicate that HABP2 may significantly affect the function of the endometrium and further be involved in the development, progress and metastasis of endometrial cancer.

Our research first suggests a diagnostic and prognostic value of HABP2 for endometrial cancer. The major limitation is that this study analyzed the data from a single database. Further verifications in different areas and populations are required. Additional *in vivo* and *in vitro* function experiments and exploration of its molecular mechanism would further illuminate the role of HABP2 in endometrial cancer.

Conclusions

In conclusion, HABP2 was lower expressed in endometrial cancer in comparison with normal endometrial tissues. HABP2 expression was associated with vital status, histologic grade and residual tumor. HABP2 had a moderate diagnostic value for endometrial cancer. HABP2 was an independent prognostic factor and low HABP2 expression indicated a better overall survival. HABP2 may be a novel biomarker for endometrial cancer.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-5744

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-5744). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the working ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethic Committee of Beijing Chao-Yang Hospital (No. 2019-331). Individual informed consent was waived.

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