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Elevated high mobility group A2 expression in liver cancer predicts poor patient survival

Yue-Chen Zhao[1], Yan Jiao[2], Yan-Qing Li[3], Zhuo Fu[4], Zhao-Ying Yang[5] and Miao He[6]

Departments of [1]Radiation Oncology and [6]Anesthesia. The Second Hospital of Jilin University. Changchun, Jilin. China. [2]Department of Hepatobiliary and Pancreatic Surgery. Jilin University. Changchun, Jilin. China. [3]Department of Pathophysiology. College of Basic Medical Sciences. Jilin University. Changchun, Jilin. China. [4]Department of Hand and Foot Surgery. The First Hospital of Jilin University. Changchun, Jilin. China. [5]Department of Breast Surgery. China-Japan Union Hospital of Jilin University. Changchun, Jilin. China

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Correspondence: Miao He. Department of Anesthesia. The Second Hospital of Jilin University. 218 Zi-qiang Street. Nan-guan District. 130022 Changchun, China
e-mail: hemiao201904@163.com

Zhao-Ying Yang[5] and Miao He[6] contributed equally to this article.

ABSTRACT

Background: liver cancer is a malignant tumor with a high morbidity and mortality that endangers human health. High mobility group A2 (HMGA2) is a chromosome associated protein that participates in embryogenesis, tissue development, tumorigenesis and development.

Objective: to explore the relationship between HMGA2 expression and the clinicopathological parameters and survival of liver cancer patients using The Cancer Genome Atlas Liver Hepatocellular Carcinoma (HCC) data.

Methods: RNA-sequencing data and the corresponding clinical characteristics of the patients were downloaded from the Atlas database. The Chi-squared test was used to assess the relationship between HMGA2 expression and clinical variables. Cox regression analysis

was used to compare survival rates between the high- and low-expressing groups; the p-values and Kaplan-Meier survival curves were compared using the log-rank test.

Results: RNA-seq data from 373 cases of liver cancer cases were analyzed. HMGA2 was overexpressed in liver cancer and significantly associated with gender (p = 0.0357), T classification (p = 0.0063), clinical classification (p = 0.0026) and overall survival (p = 0.0386). According to the multivariate analysis, HMGA2 could independently predict overall survival in liver cancer.

Conclusions: HMGA2 independently predicts poor prognosis in liver cancer and serves as a molecular marker to determine disease prognosis.

Keywords: High mobility group A2 (HMGA2). Liver neoplasms. Prognosis. The Cancer Genome Atlas (TCGA).

INTRODUCTION

Liver cancer (LC) is a common global cancer and a leading cause of cancer related death (1). Current treatments have improved patient quality of life, although the poor prognosis due to recurrence and metastasis persists (2). According to current statistics, the five-year overall survival (OS) rate of LC is less than 5% (3,4). Previous studies suggest the use of histological parameters to predict LC prognosis. However, the identification of predictive prognostic biomarkers is of significant interest to clinicians, but requires further exploration.

High mobility group proteins (HMG) are widely distributed in the nuclei of higher eukaryotes. The HMG family is sub-divided into HMGA, HMGB and HMGN. HMG regulates DNA transcription, replication, recombination and repair and regulates cell proliferation, differentiation, aging and death (5,6). High mobility group A2 (HMGA2) lacks transcriptional activity, but interacts with chromatin and regulates gene transcription, thereby influencing embryogenesis, tissue development and tumorigenesis (7). The HMGA2 protein is expressed at high levels during embryogenesis, but is largely absent in adult tissue (8,9). Most malignant tumors overexpress HMGA2, which correlates with survival, tumor grade and metastasis (10).

Recent studies have confirmed the role of HMGA2 in cancer and document its association with poor prognosis (11-14). However, the predictive utility of HMGA2 expression for LC is

undefined. This study retrospectively analyzed The Cancer Genome Atlas Liver Hepatocellular Carcinoma (TCGA-LIHC) database and investigated whether HMGA2 expression was associated with clinicopathological parameters, OS and RFS of LC patients.

MATERIALS AND METHODS

Data collection from the TCGA

Clinical and RNA-seq data (grade 3) were obtained from the TCGA database (https://cancergenome.nih.gov).

Statistical analysis

Boxplots were generated using the ggplot2 package in R (version 3.5.3) to determine the differences between variables (15,16). The Chi-squared test was performed using the SPSS software (version 19.0) to explore the relationship between HMGA2 expression and clinicopathological features. Receiver operator characteristic curves (ROC) were plotted using the proc software package to assess the diagnostic capabilities of the parameters (17). Patients were divided into high and low HMGA2 expression groups according to the threshold values identified from the ROC curves. Kaplan-Meier curves were generated to compare differences in total survival time between the groups and p-values were calculated using the logarithmic rank test, using the R-Survival package (18). A univariate Cox regression analysis, dependent on both HMGA2 expression and the clinicopathological characteristics, was used to assess OS and relapse-free survival (RFS). A multivariate Cox analysis was used to explore how HMGA2 expression affects OS, RFS and other clinical parameters.

RESULTS

Patient characteristics

TCGA data was obtained from 373 LC tissues and 50 normal tissue and the clinical parameters of all 373 patients was obtained. The specific demographics of the patients and their clinical features, such as age, gender, clinical classification, TNM classification and survival status are shown in table 1.

HMGA2 expression and disease parameters

High HMGA2 expression was observed in 373 liver cancer tissues compared to 50 normal tissues (p = 0.063). Age, gender, histological grade, radiotherapy use, residual tumors, clinical classification, TNM classification and survival status were grouped and boxplots were generated (Fig. 1). Differences were observed in HMGA2 expression according to age (p = 0.0015), gender (p = 0.046), T classification (p = 0.007) and stage (p = 0.00086). Patients were divided into high- and low- HMGA2 groups to examine the association between HMGA2 expression and the clinicopathological parameters of LC (Table 1). The Chi-squared tests indicated that elevated HMGA2 expression correlated with gender (p = 0.0357), clinical stage (p = 0.0026), T stage (p = 0.0063) and OS (p = 0.0386).

High HMGA2 levels independently predict poor survival

Survival curves were generated using OS rates and the logarithmic rank test. A correlation was observed between high HMGA2 expression and shorter survival times (p = 0.0041) (Fig. 2). Subgroup analysis demonstrated that elevated HMGA2 levels correlated with unsatisfactory survival rates in males, younger patients (p = 0.018 and p = 0.017), stage II/stage III cancer (p = 0.042 and p = 0.02, respectively) and G2 stage (p = 0.00056).

Cox regression analysis was used to assess OS and RFS. According to the univariate analysis, clinical stage, T stage, HMGA2 expression and the presence of residual tumors significantly correlated with OS (Table 2). Multivariate analysis showed that high HMGA2 expression independently predicted poor OS (hazard ratio: 0.66, 95% CI: 0.46-0.93, p = 0.02) (Table 2). According to the univariate analysis, clinical stage, T stage and residual tumors remarkably correlated with RFS (Table 3). Multivariate analysis showed that T stage and residual tumors were independent predictors of poor RFS (risk ratio: 1.63, 95% CI: 1.26-2.13, p = 0.000 and risk ratio: 1.33, 95% CI: 1.05-1.69, p = 0.017, respectively) (Table 3).

ROC curves of HMGA2 expression (including stage I-IV patients) from LC and normal samples were generated (Fig. 3) and the area under the curve (AUC) was 0.579, suggesting that HMGA2 has diagnostic value. Further subgroup analysis showed that the AUCs of stage II, III and IV were 0.623, 0.669 and 0.732, respectively, also suggestive of a moderate diagnostic value. These results suggest that HMGA2 has a diagnostic value for poor prognosis in LC patients, with an acceptable sensitivity and specificity.

DISCUSSION

Prognostic biomarkers are key to cancer identification and treatment (19-23). We found that HMGA2 overexpression correlated with gender, clinical stage, T stage and OS in LC patients. The prognosis of HMGA2-high LC patients was poor, particularly for stage II/III. These results were confirmed using Cox univariate analysis, showing that HMGA2 expression impacted on OS rates, indicating its value as a biomarker for LC prognosis.

Wu et al. (24) reported comparable results by examining HMGA2 expression in 107 LC patients. They determined that elevated HMGA2 levels correlated with poor prognosis and independently predicted OS. In contrast to our findings, there was no correlation between HMGA2 protein expression and age and gender. Since we analyzed HMGA2 mRNA levels and clinicopathological parameters, post-transcriptional and translational modifications may have led to these discrepancies (25).

Previous studies showed that HMGA2 expression is closely related to tumor invasion and metastasis (26,27). Epithelial mesenchymal transformation (EMT) is a common physiological and pathological phenomenon that primarily manifests as a loss of epithelial cell polarity and tight junctions, promoting the migration and infiltration of cancer cells (28). Previous studies have suggested that HMGA2 induces EMT (29), during which tumor cells acquire mesenchymal-like properties and lose their differentiated epithelial characteristics, enhancing their ability to invade and metastasize. Tumor angiogenesis is important for the growth and transformation of tumor cells. HMGA2 regulates cell proliferation, migration and the survival of endothelial cells and plays a crucial role in tumor angiogenesis (30). HMGA2 could inhibit cell cycle progression and apoptosis in cancer cells by regulating cyclin, ATM phosphorylation and other pathways, ultimately inducing cancer cell proliferation and progression (31,32).

HMGA2 expression has been identified in cancers of the esophagus, stomach, pancreas, colon, rectum, nasopharynx, thyroid and lung (11-14,33-35). Consistent with other cancers, we found that HMGA2 is highly expressed in LC and correlates with T stage and clinical stage. HMGA2 may promote the proliferation and progression of LC cells and enhance invasion, metastasis and anti-apoptotic ability by promoting EMT, angiogenesis and cell cycle regulation.

This is the first report to correlate HMGA2 levels and clinical variables in LC using TCGA-LIHC data and to suggest that HMGA2 independently predicts poor survival in LC. We believe that HMGA2 has value as a prognostic biomarker of LC. Due to the inadequate number of samples, we were unable to construct prediction models. In future studies, we intend to assess the prognostic significance of HMGA2 expression in larger patient cohorts, to establish an optimal prediction model for the expression of HGMA2 as a predictor of poor prognosis.

FUNDING

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Table 1. Correlation of HMGA2 mRNA expression in LC tissue with clinicopathologic variables

Clinical characteristics	Variable	No. of patients	HMGA2 expression				χ^2	p value
			High	%	Low	%		
Age	< 55	117	46	(36.22)	71	(28.98)	1.7121	0.1595
	≥ 55	255	81	(63.78)	174	(71.02)		
Gender	Female	121	51	(39.84)	70	(28.57)	4.3737	*0.0357*
	Male	252	77	(60.16)	175	(71.43)		
Histological type	Fibrolamellar carcinoma	3	1	(0.78)	2	(0.82)	1.6495	0.4281
	Hepatocellular carcinoma	363	123	(96.09)	240	(97.96)		
	Hepatocholangiocarcinoma (mixed)	7	4	(3.12)	3	(1.22)		
Histologic grade	G1	55	15	(11.90)	40	(16.53)	5.2126	0.1528
	G2	178	55	(43.65)	123	(50.83)		
	G3	123	51	(40.48)	72	(29.75)		
	G4	12	5	(3.97)	7	(2.98)		
Stage	I	172	44	(36.36)	128	(56.14)	13.2826	*0.0026*
	II	87	35	(28.93)	52	(22.81)		
	III	85	40	(33.06)	45	(19.74)		
	IV	5	2	(1.65)	3	(1.32)		
T classification	T1	182	48	(37.50)	134	(55.14)	13.1799	*0.0063*
	T2	95	38	(29.69)	57	(23.46)		
	T3	80	38	(29.69)	42	(17.28)		
	T4	13	4	(3.12)	9	(3.70)		

	TX	1	0	(0.00)	1	(0.41)		
N classification	N0	253	91	(71.09)	162	(66.39)	4.3883	0.0968
	N1	4	3	(2.34)	1	(0.41)		
	NX	115	34	(26.56)	81	(33.20)		
M classification	M0	267	99	(77.34)	168	(68.57)	4.1259	0.0870
	M1	4	2	(1.56)	2	(0.82)		
	MX	102	27	(21.09)	75	(30.61)		
Radiation therapy	No	340	119	(98.35)	221	(97.36)	0.0447	0.7187
	Yes	8	2	(1.65)	6	(2.64)		
Residual tumor	R0	326	108	(85.71)	218	(90.83)	4.7186	0.1753
	R1	17	6	(4.76)	11	(4.58)		
	R2	1	0	(0.00)	1	(0.42)		
	RX	22	12	(9.52)	10	(4.17)		
Vital status	Deceased	130	53	(41.41)	77	(31.43)	3.26	0.0669
	Living	243	75	(58.59)	168	(68.57)		
Sample type	Primary tumor	371	128	(100.00)	243	(99.18)	0.0774	0.5480
	Recurrent tumor	2	0	(0.00)	2	(0.82)		
OS	No	237	71	(57.26)	166	(68.31)	3.9163	*0.0386*
	Yes	130	53	(42.74)	77	(31.69)		
RFS	No	179	63	(57.27)	116	(55.24)	0.0527	0.8127
	Yes	141	47	(42.73)	94	(44.76)		

HMGA2: high mobility group A2; LC: liver cancer; OS: overall survival; RFS: relapse-free survival.

Table 2. Univariate and multivariate analyses of OS in LC patients

Parameters	*Univariate analysis*			*Multivariate analysis*		
	Hazard ratio	95% CI (lower-upper)	p value	Hazard ratio	95% CI (lower-upper)	p value
Age	1.00	0.69-1.45	0.997			
Gender	0.80	0.56-1.14	0.220			
Histological type	0.99	0.27-3.66	0.986			
Histologic grade	1.04	0.84-1.30	0.698			
Stage	1.38	1.15-1.66	0.001	0.86	0.70-1.07	0.180
T classification	1.66	1.39-1.99	0.000	1.82	1.44-2.29	0.000
N classification	0.73	0.51-1.05	0.086			
M classification	0.72	0.49-1.04	0.077			
Radiation therapy	0.51	0.26-1.03	0.060			
Residual tumor	1.42	1.13-1.80	0.003	1.39	1.09-1.78	0.009
HMGA2	0.60	0.42-0.85	0.005	0.66	0.46-0.93	0.020

OS: overall survival; LC: liver cancer; 95% CI: confidence interval 95%; HMGA2: high mobility group A2.

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Table 3. Univariate and multivariate analyses of RFS in LC patients

Parameters	*Univariate analysis*			*Multivariate analysis*		
	Hazard ratio	95% CI (lower-upper)	p value	Hazard ratio	95% CI (lower-upper)	p value
Age	0.90	0.63-1.28	0.550			
Gender	0.99	0.70-1.41	0.966			
Histological type	2.02	0.66-6.24	0.220			
Histologic grade	0.98	0.80-1.21	0.883			
Stage	1.66	1.38-1.99	0.000	1.13	0.88-1.46	0.333
T classification	1.78	1.49-2.12	0.000	1.63	1.26-2.13	0.000
N classification	0.97	0.67-1.40	0.874			
M classification	1.17	0.79-1.74	0.432			
Radiation therapy	0.74	0.26-2.16	0.584			
Residual tumor	1.28	1.01-1.61	0.042	1.33	1.05-1.69	0.017
HMGA2	0.88	0.62-1.25	0.482			

RFS: relapse-free survival; LC: liver cancer; 95% CI: confidence interval 95%; HMGA2: high mobility group A2.

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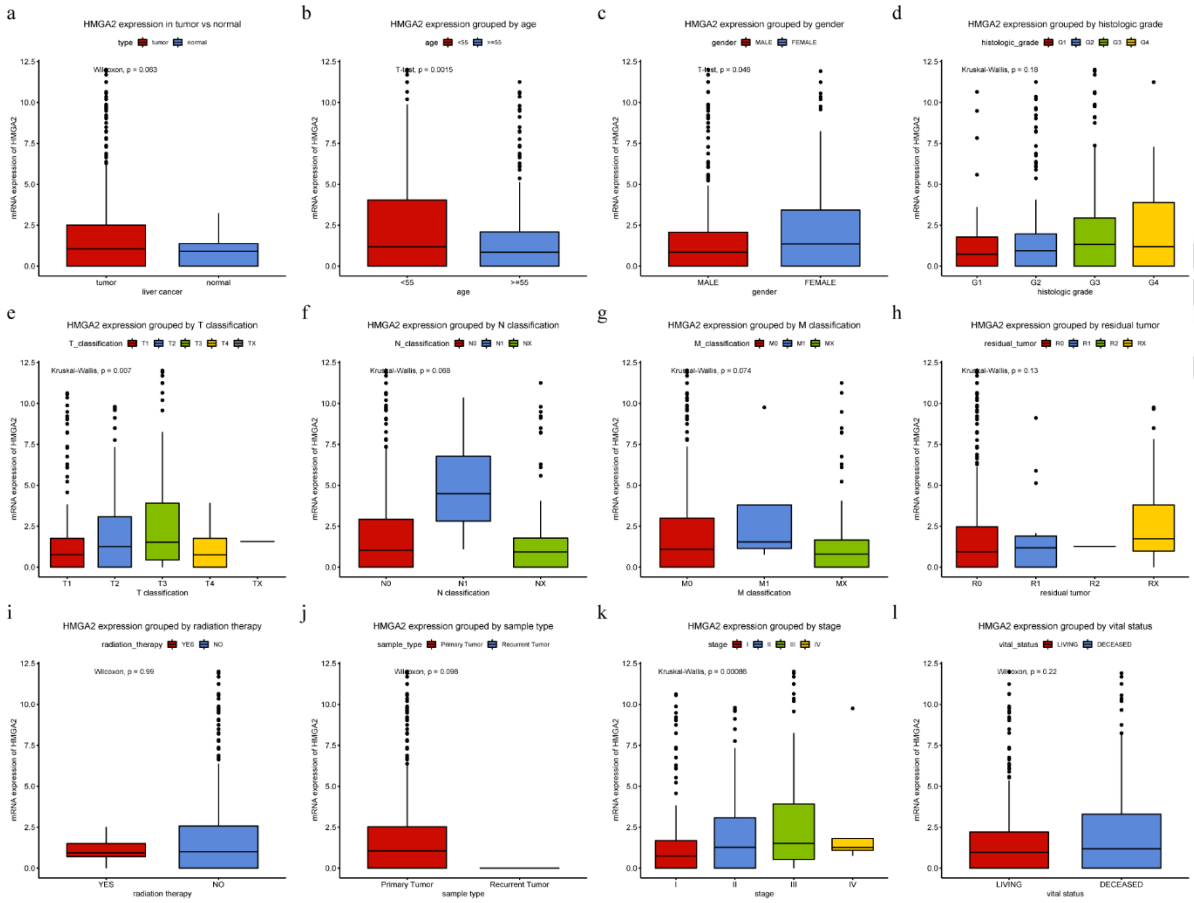

Fig. 1. Boxplots based on patient groups. The differences in HMGA2 expression according to patient age, gender, LC histological type, TNM stage, residual tumor, radiation therapy, sample type, clinical stage and survival status. HMGA2: high mobility group A2.

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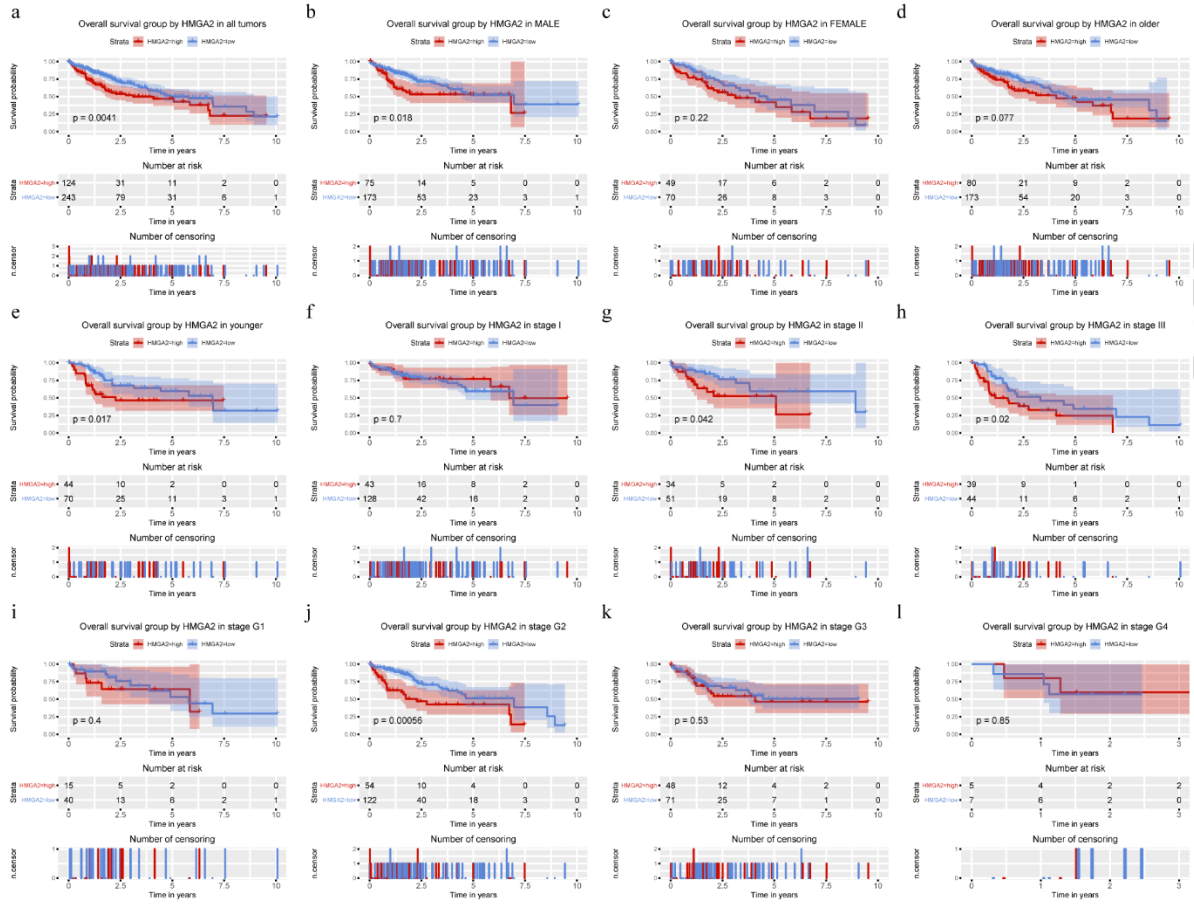

Fig. 2. Survival curves for LC patients according to HMGA2 expression in LC tissue. Median HMGA2 expression was used to classify patients into the high- and low-expression groups. Survival and subgroup analyses according to patient gender, age, clinical stage and G stage were performed based on survival curves. HMGA2: high mobility group A2; LC: liver cancer.

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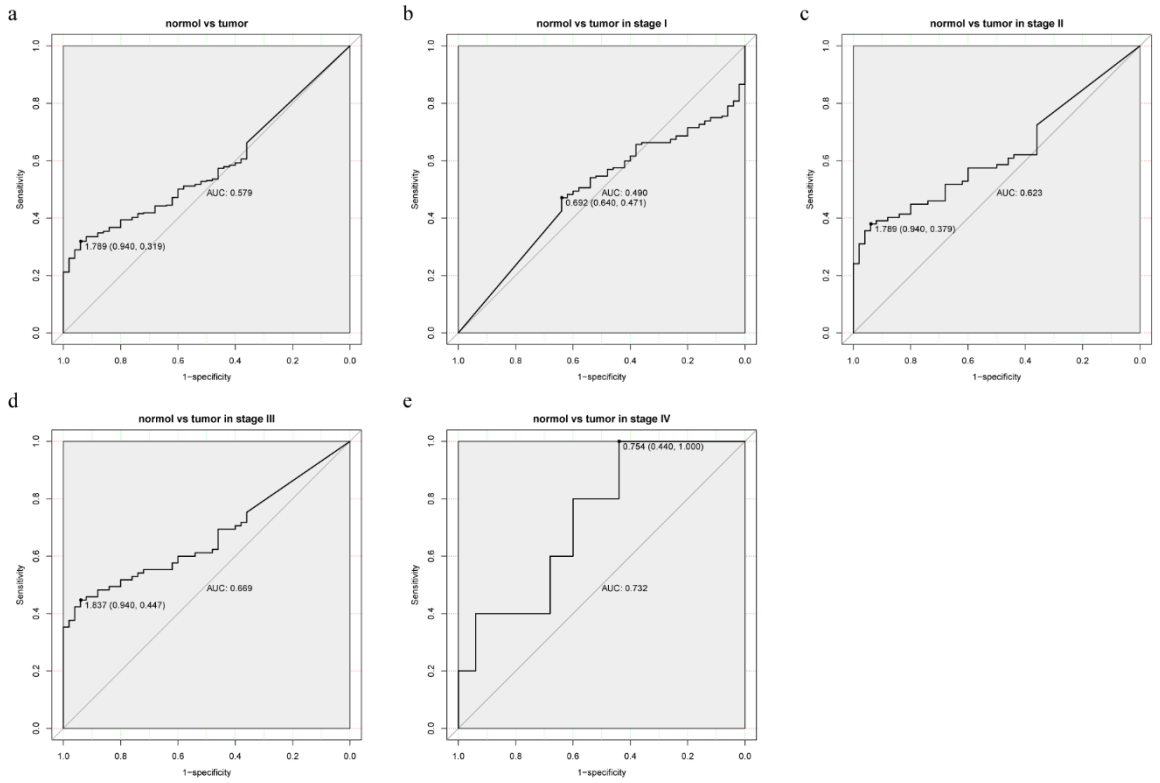

Fig. 3. ROC curves of HMGA2 in LIHC cohorts. A. Normal and tumor samples. B. Normal and stage I tumor samples. C. Normal and stage II tumor samples. d. Normal and stage III tumor samples. e. Normal and stage IV tumor samples. AUC: area under the curve; ROC: receiver operator characteristic curves; LIHC: liver hepatocellular carcinoma.