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ORIGINAL RESEARCH

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Prognostic value of Ki-67 in patients with ovarian cancer

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Abstract

This study aimed to investigate the prognostic value of Ki-67 antigen (Ki-67) in patients with epithelial ovarian cancer. A retrospective review identified a cohort of 78 patients with epithelial ovarian cancer. The association between Ki-67 expression and clinicopathological characteristics and survival was analyzed. High Ki-67 expression was significantly associated with high stage, high histological grade, ascites, and high level of cancer antigen 125 (CA125) (p = 0.011, p = 0.031, p = 0.033, p = 0.004, respectively). In addition, high Ki-67 expression was significantly associated with poor prognosis (p = 0.002), which was further confirmed using a multivariate Cox regression hazards model (Hazard Ratio (HR) = 1.797, 95% confidence interval (CI) = 1.038–3.111, p = 0.026). In conclusion, Ki-67 expression may be a significant prognostic factor in epithelial ovarian cancer.

Keywords

Ki-67; Ovarian cancer; Survival; Prognosis

1. Introduction

Ovarian cancer is the third most prevalent gynecological malignant tumor and is the most considerable cause of gynecological cancer-associated mortality [1]. Early diagnosis of ovarian cancer is made in only a few patients; these patients are often eligible for curative resection, followed by chemotherapy. Notably, approximately 75% of patients with ovarian cancer present with advanced disease at diagnosis [2]. Although the diagnosis and treatment of ovarian cancer have improved, the prognosis remains poor. For early ovarian cancer cases, the 5-year survival can be as high as 90%; however, for advanced cancer cases, the 5-year survival is <30% [3].

Due to the poor prognosis of ovarian cancer, several studies have been conducted to explore the different survival-related factors such as disease stage, age, performance status, histological tumor grade, genomic analysis, and biomarkers [4–6]. Effective prognosis-related factors can assist in stratifying specific patients into subgroups based on various survival rates; this is of great importance for tailored treatment decision-making [7].

Cancer proliferation significantly affects clinical and biological behavior. The Ki-67 antigen is a protein antigen related to cell proliferation and division in the cell nucleus. Its coding gene is located on chromosome 10 [8].

Ki-67, the factor indicating cancer proliferation, is significantly related to the prognosis of cancers such as non-small cell lung cancer (NSCLC) and breast cancer (BC) [8, 9]. Several studies have evaluated the use of Ki-67 levels in predicting the prognosis of ovarian cancer, but their findings remain conflicting [10, 11]. Moreover, limited data are available to investigate the clinicopathological features of Ki-67 in ovarian cancer. Consequently, the present work retrospectively analyzed the association between Ki-67 expression and clinicopathological characteristics and survival to identify potential molecular markers for predicting the prognosis of patients with ovarian cancer.

2. Materials and methods

2.1 Study subjects

This study was approved by the Ethics Committee of Wannan Medical College, and all patients provided written informed consent prior to tissue sample collection. We conducted a retrospective analysis of data from patients with epithelial ovarian cancer (EOC) who underwent surgery at the First Affiliated Hospital of Wannan Medical College between January 2014 and April 2017. The pathology was confirmed as EOC through both surgical cytology and histology, and the EOC histological diagnosis was primarily based on optical microscopy and evaluated by two independent pathologists.

There were 78 eligible patients aged 29–77 (average, 55) years. Clinicopathological features such as age, International Federation of Gynecologist and Obstetrics (FIGO) stage (low stage: I + II; high stage: III + IV), histological grade, tumor size, ascites status, CA125 serum level, lymph node metastasis (LNM), histological type, and Ki-67 expression were analyzed. The preoperative CA125 serum level ranged between 56.60 and 1000 u/mL, with a median value of 400 u/mL. The tumor diameter ranged from 1.9 to 20 cm, with a median value of 8 cm. Postoperative treatment and monitoring were conducted following specific guidelines. Patients were followed up for

3–113 (median, 44) months. Patient survival was determined between the diagnosis date and the final follow-up or death date. A total of 54 cases died and 24 patients were censored in follow-up.

2.2 Immunohistochemical (IHC) analysis

We carried out IHC analysis using the formalin-fixed, paraffin-embedded (FFPE) sections according to the manufacturer's instructions [7]. Molecular Immunology Borstel number 1 antibody (MIB-1) monoclonal antibody (MXB, Fuzhou) was used to detect Ki-67 levels. Nuclei were stained for Ki-67 expression, and the number of Ki-67-positive cancer cells number was determined from selected fields. We determined Ki-67 expression using the Ki-67-positive cancer cell proportion in 2000 cancer cells in the high-power fields (magnification, 400×). The expression of Ki-67 was independently evaluated by two experienced pathologists without knowledge of any clinical information on the samples, and discrepancies in expression level were resolved by a mutual discussion.

2.3 Statistical analysis

Categorical data were presented as numbers (n) or percentages, and any differences between groups were analyzed using the chi-square test. Alternatively, Fisher's exact test was used when the chi-square assumption was violated. Log-rank test and Kaplan-Meier analysis were used to assess survival. Univariate and multivariate analyses were performed using a Cox proportional hazards model to obtain hazard ratios (HRs). Variables with $p < 0.05$ upon univariate regression were included in a multivariate Cox analysis. $p < 0.05$ (two-tailed) was considered significant. SPSS 16.0 (SPSS Inc, Chicago, IL, USA) was employed for all statistical analyses.

3. Results

Out of the 78 included cases, 75 (96.2%) ovarian cancer cases expressed Ki-67; the expression was 0–90% (median, 50%). Ki-67 expression was classified into low (≤50%) and high (>50%) expression groups.

3.1 Association between Ki-67 level and clinical features

According to Table 1, high Ki-67 level was markedly related to high stage, high histological grade, ascites, and high CA125 level (p = 0.011, 0.031, 0.033 and 0.004, respectively). Age, LNM, tumor size, and histological type were not significantly associated with Ki-67 expression (p = 0.613, p = 0.927, p = 0.914 and p = 0.214, respectively).

3.2 Association between Ki-67 level and survival

A Kaplan-Meier analysis was conducted to examine patient survival (Fig. 1). The cumulative survival rate of patients with high expression of Ki-67 was 17.34%, whereas the cumulative survival rate of patients with low expression of Ki-67 was 38.57%. Cases with high Ki-67 levels had lower survival rates relative to those with low Ki-67 levels (p = 0.002). Stage, histological grade, ascites, and serous carcinoma (the non-serous pathological types of adenocarcinoma include clear cell carcinoma and mucinous cystadenocarcinoma) were also markedly related to survival (p = 0.000, 0.031, 0.001 and 0.031 respectively). However, age, tumor size, CA125 levels, and LNM did not significantly affect survival ($p > 0.05$).

Table 2 displays the Cox proportional hazards model. Upon univariate regression, high Ki-67 expression, high stage, high histological grade, ascites, and non-serous carcinoma were significantly associated with poor survival (high Ki-67 expression: HR = 2.263, 95% CI = 1.314–3.897, p = 0.003; high stage: HR = 6.678, 95% CI = 2.362–18.880, p = 0.000; high histological grade: HR = 2.882, 95% CI = 1.038–8.001, p = 0.042; ascites: HR = 3.267, 95% CI = 1.581–6.749, p = 0.001, non-serous carcinoma: HR = 1.985, 95% CI = 1.040–3.787, p = 0.038). Upon multivariate regression, both high Ki-67 expression, high stage, and non-serous independently predicted prognosis (high Ki-67 level: HR = 1.797, 95% CI = 1.038–3.111, p = 0.026; high stage: HR = 5.909, 95% CI = 2.067–16.896, p = 0.008; non-serous carcinoma: HR = 1.912, 95% CI = 1.080–3.284, p = 0.0000).

4. Discussion

The current work enrolled EOC cases in one center and investigated the effect of Ki-67 levels on clinicopathological characteristics and survival in EOC. Ki-67 level was markedly related to the FIGO stage, histological grade, ascites, and CA125 level at diagnosis. Cases with high Ki-67 expression had higher FIGO stages, higher histological grade, ascites, and higher levels of CA125. Accordingly, high Ki-67 expression markedly predicted poor prognosis, as evidenced by the Cox regression hazards model.

The survival of patients with ovarian cancer has moderately improved over the past 30 years. The majority of patients with ovarian cancer present with extensive peritoneal spread beyond the pelvic cavity and only 30% of these patients survive beyond 5 years [3]. Moreover, ovarian cancer is highly heterogenous, thus even cases showing advanced cancers with similar morphology may have different survival rates [2]. Therefore, identifying efficient prognosis-related factors is crucial to assist in tailoring treatment strategies and stratifying cases. Several articles on ovarian cancer prognosis-related factors have been published to explain survival heterogeneity [5]. Typically, prognosis-related factors with the highest reproducibility include stage extent, breast cancer susceptibility gene1/2 (*BRCA1/2*) status, and residual disease. Some additional prognosis-related factors such as age, CA125 levels, and histological grade have been investigated but no consistent results were obtained [12].

Cell proliferation plays an important role in ovarian cancer. Several reports have suggested that estimating the number of proliferative cells and measuring the degree of cell proliferation have prognostic value in ovarian cancer [13]. Many studies have reported that the Ki-67 protein proliferation index is an excellent prognostic factor in patients with EOC, and the median survival of patients with ovarian cancer who express high levels of Ki-67 is lower than that of those with low expression levels [14]. Similarly, the results of this study

TABLE 1. Association of Ki-67 expression with clinicopathological characteristics.

Characteristics	No.	Ki-67 expression		*p*
		Low	High	
Age				
≤55	44	26 (54.2)	18 (60.0)	0.613
>55	34	22 (45.8)	12 (40.0)	
Stage				
I–II	17	15 (31.2)	2 (6.7)	0.011
III–IV	61	33 (68.8)	28 (93.3)	
Histological grade				
low	11	10 (20.8)	1 (3.3)	0.031
high	67	38 (79.2)	29 (96.7)	
Tumor size				
≤8	37	23 (47.9)	14 (46.7)	0.914
>8	41	25 (52.1)	16 (53.3)	
Ascites				
no	24	19 (39.6)	5 (16.7)	0.033
yes	54	29 (60.4)	25 (83.3)	
CA125				
≤400	37	29 (60.4)	8 (26.7)	0.004
>400	41	19 (39.6)	22 (73.3)	
Lymph node metastasis※				
Negative	38	23 (48.9)	15 (50.0)	0.927
Positive	39	24 (51.1)	15 (50.0)	
Serous carcinoma				
yes	62	36 (75.0)	26 (86.7)	0.214
no	16	12 (25.0)	4 (13.3)	

※ *Unresected lymph in 1 case. CA125: cancer antigen 125.*

indicate that high expression of Ki-67 is a predictive factor for poor prognosis in ovarian cancer. Rödel *et al*. [15] found that patients with early-stage EOC (stage I/II, low-grade, serous) who have high expression levels of Ki-67 had significantly shorter progression-free survival and overall survival compared to patients with low expression levels. However, this significant difference was not observed in patients with late-stage EOC (stage III/IV) [15]. Therefore, the prognostic value of the Ki-67 index in ovarian cancer remains controversial.

The inconsistency among these studies may be attributable to several factors. First, the different cutoff values for high Ki-67 expression could be a contributing factor. Our present study used a cutoff value of >50% as a high expression, which is consistent with a previous study [11] but larger than that of other studies [14, 16]. Second, the variations in the study population could also be a limitation. Some studies included patients with stage I to IV ovarian cancer [12, 14], whereas only patients with advanced ovarian cancer were included in some other studies [17, 18]. Meanwhile, the included pathological types also differed. For example, the inclusion criterion was only restricted to low-grade serous ovarian cancer [19]. Nevertheless, other studies have included all pathological types of EOC [12, 14]. Third, spatial and temporal heterogeneity in Ki-67 levels also facilitated discrepancies between these studies [20].

With regards to the association between Ki-67 expression and clinicopathological characteristics, this present work showed that patients with high Ki-67 expression are more likely to have higher FIGO stage, higher histological grade, ascites, and higher levels of CA125. Such association indirectly indicates that Ki-67 upregulation predicates poor prognoses.

5. Conclusions

To sum up, this work proved that Ki-67 expression could significantly predict prognosis in EOC. Ki-67 upregulation is predictive of poor prognosis and could be a candidate marker to stratify cases for tailoring treatment strategies. However, it is important to exercise caution in interpreting the conclusions of this study. First, the retrospective nature of the study and the sample size may limit the generalizability of our survival analysis results. Additionally, the Ki-67 cutoff value used in this study was 50%, which was used as a binary threshold, and

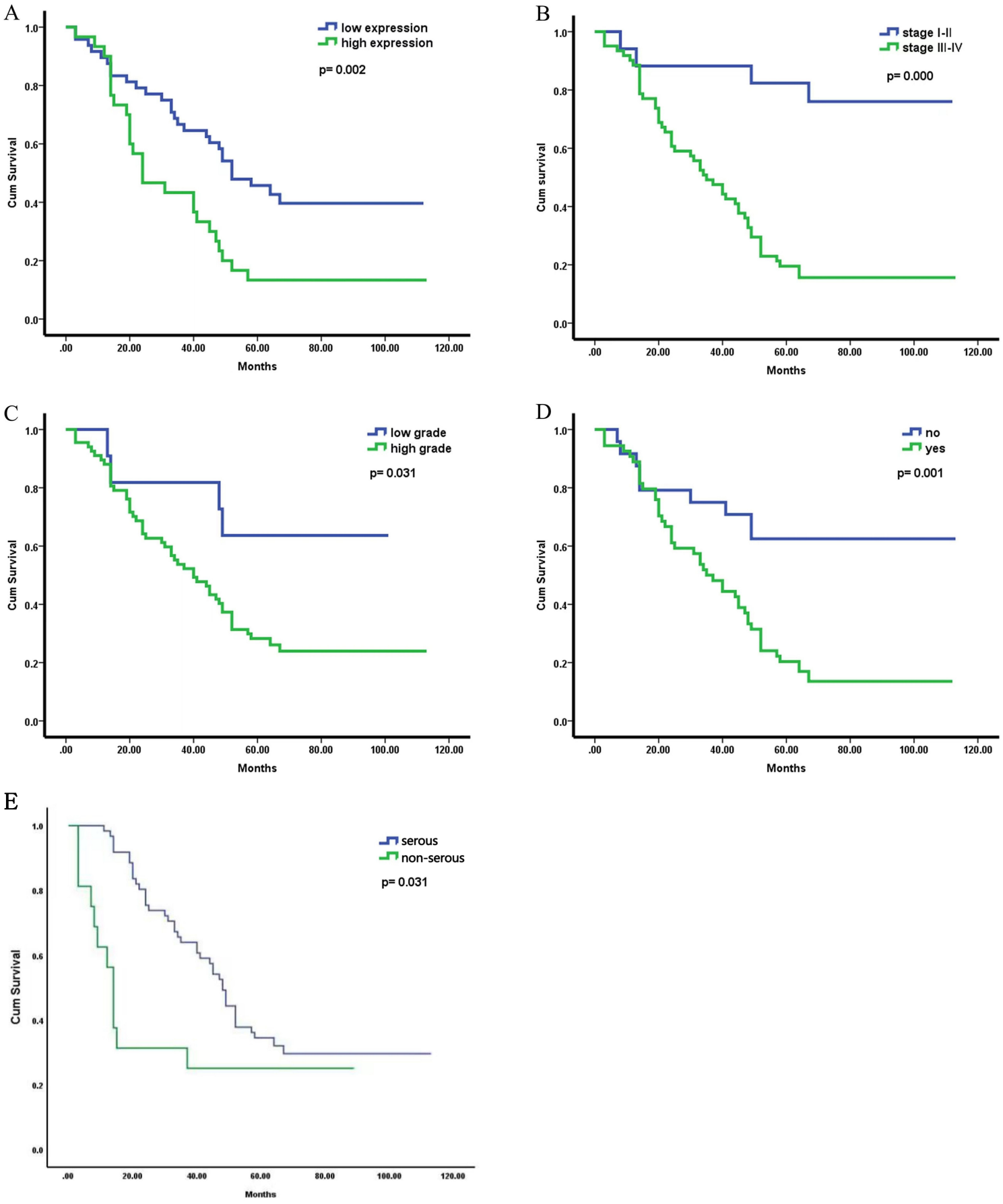

FIGURE 1. Overrall suivival (OS) analyzed by Kaplan-Meier method. OS examined by Kaplan-Meier analysis for Ki-67 expression (A), stage (B), histological grade (C), ascites (D) and Serous carcinoma (E).

TABLE 2. Univariate and multivariate analysis of prognostic factors.

Characteristics	Univariate			Multivariate		
	Hazard Ratio	95% CI	*p*	Hazard Ratio	95% CI	*p*
Stage						
I–II	1.000	2.362–18.880	0.000	1.000	2.067–16.896	0.008
III–IV	6.678			5.909		
Histological grade						
low	1.000	1.038–8.001	0.042	-	-	-
high	2.882			-		
Ascites						
no	1.000	1.581–6.749	0.001	-	-	-
yes	3.267			-		
Serous carcinoma						
yes	1.000	1.040–3.787	0.038	-	1.080–3.284	0.000
no	1.985			1.912		
Ki-67						
≤50	1.000	1.314–3.897	0.003	1.000	1.038–3.111	0.026
>50	2.263			1.797		

Abbreviation: CI, confidence interval.

further research is needed to determine the critical values of the third or fourth quartile of Ki-67. Third, more research is required to explore other prognostic factors for EOC patients, such as new biomarkers and clinical characteristics.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

SW and GTN—designed the research study. YW and QYJ—performed the research. CS and JD—analyzed the data. SW and HFD—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by Medical Ethic Committee of Wannan Medical College, No. 2023(44). All patients agreed to participate this study.

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CONFLICT OF INTEREST

The authors declares no conflict of interest.

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