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Can serum ferritin serve as a biomarker for the prognosis of gynecological malignant tumors? A retrospective cohort study

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Abstract.

PURPOSE: It is widely accepted that there is a strong relationship between iron levels and cancer. This study aimed to investigate the relationship between serum ferritin levels and the severity and prognosis of gynecological malignant tumors.

METHODS: This retrospective study included patients with gynecological malignant tumors at Sir Run Run Shaw Hospital in the Department of Obstetrics and Gynecology from January 2013 to June 2019. Patients were grouped according to their serum ferritin level: low (< 13 μg/L), normal (13–150 μg/L), and high (> 150 μg/L). Correlation analyses were performed between serum ferritin level and other factors. Cox univariable and multivariable analysis and Kaplan-Meier survival curves were used to assess the impact of ferritin on survival in patients with gynecologic tumors.

RESULTS: The 402 total patients were divided into a low ($n = 37$), normal ($n = 182$), and high ($n = 183$) ferritin level group. Correlation analyses were performed that WBC, MCV, CRP, CA125, and CA153 were significantly positively correlated with serum ferritin level. The Kaplan-Meier survival curves revealed that of the three groups analyzed, the high serum ferritin level group had a significantly shorter survival time versus the normal and low serum ferritin level groups (log-rank $P = 0.003$). Univariable Cox regression analysis identified that patients with high serum ferritin levels had a significant correlation with risk of death compared to the patients with lower and normal serum ferritin levels. Serum ferritin was not found to be significant (HR $=$ 0.792, 95% CI: 0.351–1.787, $P = 0.574$) in the multivariable Cox analysis.

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CONCLUSION: Although this study did not find serum ferritin to be a significant independent prognosis indicator in gynecological malignant tumors, this study did identify that gynecological malignant tumor patients with high serum ferritin levels have significantly less survival time than patients with low or normal serum ferritin levels.

Keywords: Ferritin, gynecological cancer, clinical parameters, prognosis, biomarkers

1. Introduction

Gynecological cancer is one of the main causes of cancer-related mortality in females worldwide [1,2,3, 4,5]. According to the global incidence statistics on new cancer cases in women for the year 2020, there were 314,000 cases of ovarian cancer, 604,000 cases of cervical cancer, and 417,000 cases of endometrial cancer. These malignancies represented 3.4%, 6.5%, and 4.5% of the total female cancer cases, respectively. Correspondingly, the number of deaths attributed to these cancers was 207,000 for ovarian cancer, 342,000 for cervical cancer, and 97,000 for endometrial cancer. These mortality figures accounted for 4.7%, 7.7%, and 2.2% of the overall female cancer-related deaths, respectively [6]. With the rate of gynecological cancer increasing every year [4,5], there is an urgent need for new biomarkers for the screening, therapy selection, or improving the diagnostic, prognostic performance for gynecological cancer.

The high mortality rate of gynecological cancer can be attributed to two factors [7,8,9,10,11,12,13]: vague and non-specific symptoms, and current biomarkers have low sensitivity and specificity. Both of these factors lead to patients being diagnosed in advanced metastatic stages when the prognosis is poor [7,10,11, 12]. Ovarian tumors especially are difficult to diagnose due to these non-specific symptoms and are at most times diagnosed when the tumor mass has reached large proportions, when complications occur, or when disseminated into neighboring organs [7]. Gynecological malignancies, particularly ovarian cancer, exhibit a pronounced mortality burden attributed to challenges associated with early detection [14]. Cancer antigen 125 (CA125) is the most widely used blood biomarker for the progression and monitoring of cancer in general, but it cannot be used to screen ovarian cancer because of too high false-positive rates due to its low specificity and sensitivity. CA125 is also expressed in patients with benign gynecological disorders and epithelial cells; thus, CA125's low specificity and sensitivity for the early-stage disease are extremely limited [7]. Due to these two factors, it is critical to identify a marker that can be used to improve the current biomarkers' diagnostic and prognostic values.

Ferritin is a cytosolic protein used for iron storage and is involved in proliferation, angiogenesis, immunosuppression, and carcinogenesis. Serum ferritin is commonly elevated in many cancers, and its increased levels are associated with poor prognosis in cancer patients. Studies have suggested that ferritin might be used as a diagnostic and prognostic biomarker for various malignancies. Studies have also shown that ferritin can discriminate cancer patients, even during early-stage disease, and therefore might be a valuable biomarker and diagnostic marker [13,15,16,17]. With this in mind, this study aimed to investigate the relationship between serum ferritin levels and the severity and prognosis of patients with gynecological malignant tumors.

Hence, the prognostic value of serum ferritin expression was evaluated against other well-known prognostic factors in cancer [18,19,20,21,22,23], including CA125, albumin (ALB), C-reactive protein (CRP), carcinoembryonic antigen (CEA), hemoglobin (Hb), white blood cell (WBC), alpha-fetoprotein (AFP), cancer antigen 153 (CA153), and alanine aminotransferase (ALT). ALB is a common indicator of nutritional status, while CRP is a marker that correlates with inflammation [18]. Studies have shown that CEA has the highest sensitivity among other common diagnostic markers in cancer [20]. AFP was one of the first protein tumor markers discovered and is not only used for screening and diagnosis of cancers but also as means to drive therapeutic choice and to monitor treatment [21]. CA153 is a glycoprotein commonly upregulated in epithelial carcinomas, including breast cancer and ovarian cancer [23]. It is an independent predictor of cancer recurrence, a strong prognostic indicator for patients at advanced-stage breast cancer, and the best biomarker in diagnosing pleural effusions in lung cancer [22,23].

2. Methods

2.1. Study design and participants

This retrospective, observational, single-center cohort study included patients with gynecological malignant tumors at Sir Run Run Shaw Hospital (Hangzhou, Zhejiang, China) in the Department of Obstetrics and Gynecology from January 2013 to June 2019. Gyneco-

logical cancer patients (endometrial, cervical, or ovarian) who were diagnosed by obstetricians and gynecologists according to international guidelines and in relatively good physical condition with an expected survival time of more than one year were included. Patients already treated with radiotherapy and chemotherapy, that had undergone surgery, with acute or were critically ill (including infection or organ failure), with no available serological data, or with pathological results that suggested a primary tumor that was a non-gynecological malignancy were excluded from the study.

The data included in this study contains patients with gynecological malignant tumors and their age, cancer type, menopause status, BMI, FIGO stage (FIGO 2009) [24], lymphatic metastasis, tumor size, and other baseline characteristics.

This study was approved by the Ethics Committee of Sir Run Run Shaw Hospital (approval No. 2022-610-01). Informed consent was waived by the ethics committee.

2.2. Biochemistry

Peripheral blood samples were collected prior to any anti-cancer treatment with the following considered to be the normal range: ALB, 40–55 g/L; Hb, 115–150 g/L; mean corpuscular volume (MCV), 82–100 fL; WBC, 3.5–9.5 $\times$ 10^9/L; CRP, 0–5 mg/L; serum ferritin, 13–150 μg/L; CA125, 0–35 U/mL; CEA, 0–5 ng/mL; ALT, 7–40 U/L; AFP, 0–8.78 ng/mL; and CA153, $<$ 25 U/mL. The patients were divided into three groups according to their serum ferritin level: low ($<$ 13 μg/L), normal (13–150 μg/L), and high ($>$ 150 μg/L).

2.3. Follow-up and outcomes

Follow-up was conducted in the outpatient clinic or by telephone and was ended in June 2019. The primary outcome of this study was death due to gynecological cancer. Overall survival (OS) was defined as the time from the first visit to the date of all-cause death or the last follow-up. When the patient was lost to follow-up, the patient was censored. The survival time of censored patients was defined by the period from the first visit to the last day of follow-up or to the date on which survival was investigated. The exact date of death was recorded from a relative or by a medical report.

2.4. Statistical analysis

The chi-square test was used to compare the correlation between groups of classified data. Spearman rank correlation test was performed to assess the relationship between serum ferritin and other markers. Kaplan-Meier curves and the log-rank test were used to compare the expression level of serum ferritin and the prognosis of gynecological cancer patients. Right censoring was used in survival analysis if the survival time was incomplete. Univariable and multivariable Cox regression models were performed to evaluate the correlation between serum ferritin levels, clinical parameters, pathological parameters, biochemical parameters, and prognosis in patients with gynecological malignant tumors. Multivariate proportional hazards regression was performed with statistically significant factors from the univariate analysis (p-values less than 0.05) and controlling confounding factors, such as age and menopause. Hazard ratios were also calculated. P values < 0.05 were deemed statistically significant. All analyses were performed with SPSS 20.0 (IBM, Armonk, NY, USA) and GraphPad Prism 8.0.1 (GraphPad Software Inc., La Jolla, CA, USA).

3. Results

3.1. Participant enrollment

A total of 402 patients with gynecological malignant tumors were treated at our hospital during the study and included 126 patients with endometrial cancer, 126 patients with cervical cancer, and 150 patients with ovarian cancer. By the end of follow-up in June 2019, 29 patients died of gynecological malignant tumors, and 351 patients survived, 22 patients were lost to follow-up.

3.2. Participant characteristics

The patients were grouped according to their serum ferritin level: low ($<$ 13 μg/L, $n = 37$), normal (13–150 μg/L, $n = 182$), and high ($>$ 150 μg/L, $n = 183$). Between the three groups, there was a significant age difference: 37, 150, and 85 patients were $<$ 60 years old, while 0, 32, and 98 patients were $>$ 60 years old in the low, normal, and high ferritin groups, respectively ($P <$ 0.0001). The cancer type was significantly different. The number of patients with endometrial cancer in the low, normal, and high ferritin groups were 14, 54, and 58, respectively; the number of cervical cancer patients in the low, normal, and high ferritin groups were 17, 71, and 38, respectively; the number of patients with ovarian cancer in the low, normal, and high ferritin

Table 1
Clinical characteristics of patients with gynecological malignant tumor and serum ferritin expression

Characteristic	Serum ferritin*			χ^2	P value
	Low ($n = 37$)	Normal ($n = 182$)	High ($n = 183$)		
Age				73.432	< 0.0001
< 60	37	150	85		
$\geqslant 60$	0	32	98		
Cancer type				24.429	< 0.0001
Endometrial	14	54	58		
Cervical	17	71	38		
Ovarian	6	57	87		
Menopause				120.122	< 0.0001
No	35	94	21		
Yes	2	88	162		
BMI (kg/m^2)				5.401	0.249
< 18.5	2	6	13		
18.5–24	23	96	86		
> 24	12	80	84		
ALB (g/L)				9.824	0.007
< 40	8	40	66		
$\geqslant 40$	29	142	117		
WBC ($\times 10^9$/L)				2.889	0.577
< 3.5	1	4	3		
3.5–9.5	34	172	167		
> 9.5	2	6	13		
Hb (g/L)				33.851	< 0.0001
< 115	22	28	45		
115–150	15	153	136		
> 150	0	1	2		
MCV (fL)				68.84	< 0.0001
< 82	20	19	10		
$\geqslant 82$	17	163	173		
CRP (mg/L)				32.625	< 0.0001
$\leqslant 5$	33	150	108		
> 5	4	30	75		
ALT (U/L)				0.757	0.685
$\leqslant 40$	36	171	174		
> 40	1	11	9		
CA125 (U/mL)				18.623	< 0.0001
< 35	27	122	86		
$\geqslant 35$	10	60	97		
CEA (ng/mL)				1.273	0.529
$\leqslant 5$	35	164	162		
> 5	2	18	21		
AFP (ng/mL)				2.803	0.246
$\leqslant 8.78$	36	177	182		
> 8.78	1	5	1		
CA153 (U/mL)				25.987	< 0.0001
< 25	33	156	121		
$\geqslant 25$	3	23	60		
FIGO stage				49.694	< 0.0001
I	33	115	75		
II	2	29	25		
III	1	29	25		
IV	1	9	37		
Lymphatic metastasis				14.838	0.001
No	32	141	114		
Yes	5	41	69		
Ascites				21.628	< 0.0001
No	35	155	125		
Yes	2	27	58		
Tumor size (cm)**				3.223	0.2
< 4	25	103	95		
$\geqslant 4$	12	79	88		

χ^2, chi-square test; BMI, body mass index; ALB, albumin; WBC, white blood cell; Hb, hemoglobin; MCV, mean corpuscular volume; CRP, C-reactive protein; ALT, alanine aminotransferase; CA125, cancer antigen 125; CEA, carcinoembryonic antigen; AFP, alpha fetoprotein; CA153, cancer antigen 153; FIGO, Inter-national Federation of Gynecology and Obstetrics. *Patients were divided into three groups according to their serum ferritin level: low (< 13 μ/L), normal (13–150 μg/L), and high (> 150 μg/L). **Cervical cancer has a cut-off point of 4 cm.

groups were 6, 57, and 87, respectively ($P < 0.0001$). Menopause was significantly different: 2, 88, and 162 patients were post-menopausal, while 35, 94, and 21 patients were premenopausal in the low, normal, and high ferritin groups, respectively ($P < 0.0001$). There was a significant difference in serum levels of ALB, Hb, MCV, CRP, ALT, CA125, and CA153. There was a significant difference in FIGO stage: 33, 115, and 75 patients in stage I; 2, 29, and 25 patients in stage II; 1, 29, and 25 in stage III; and 1, 9, and 37 in stage IV in the low, normal, and high ferritin groups, respectively ($P < 0.0001$). There was a significant difference in lymphatic metastasis: 5, 41, and 69 patients had tumors that had metastasized to the lymph nodes, while 32, 141, and 114 patient tumors did not metastasize in the low, normal, and high ferritin groups, respectively ($P = 0.001$). Finally, there was a significant difference in patients with ascites: 2, 27, and 58 patients had ascites, while 35, 155, and 125 patients did not have ascites in the low, normal, and high ferritin groups, respectively ($P < 0.0001$) (Table 1).

3.3. *Serum ferritin expression and its association with other clinical factors*

We examined the subset of gynecological malignant tumor patients with different serum ferritin expressions (Table 1). All three low, normal, and high ferritin groups had more patients that expressed low cancer biomarkers (CEA, AFP, and CA153), high ALB levels, low serum levels (CRP and ALT), positive for ascites, and positive for lymphatic metastasis versus patients that did not. Differences existed within the groups. We identified the high ferritin level group had predominately more elderly patients, more ovarian cancer patients, and more patients that were premenopausal. We identified the low ferritin level group had no elderly patients ($\geqslant 60$ years old), fewer ovarian cancer patients, more patients that were menopausal, low CA125, and high FIGO stage I patients. Differences also existed between the groups. The high ferritin group had more ovarian cancer patients, post-menopausal patients, older patients, high CA125 level, and FIGO stage IV patients versus the low and normal ferritin groups, respectively.

3.4. *Correlations between serum ferritin and other factors*

According to correlation analysis, ALB ($r = -0.142$, $P = 0.004$), WBC ($r = 0.166$, $P = 0.01$), MCV ($r = 0.191$, $P < 0.0001$), CRP ($r = 0.439$, $P < 0.0001$), CA125 ($r = 0.253$, $P < 0.0001$), and CA153 ($r = 0.281$, $P < 0.001$) were significantly correlated with serum ferritin (Table 2).

Table 2
Correlations between serum ferritin and other factors

Characteristic	Correlation coefficients	P value
ALB	−0.142	0.004
WBC	0.166	0.010
Hb	0.052	0.296
MCV	0.191	< 0.0001
CRP	0.439	< 0.0001
ALT	0.089	0.074
CA125	0.253	< 0.0001
CEA	0.062	0.213
AFP	0.078	0.120
CA153	0.281	< 0.0001

ALB, albumin; WBC, white blood cell; Hb, hemoglobin; MCV, mean corpuscular volume; CRP, C-reactive protein; ALT, alanine aminotransferase; CA125, cancer antigen 125; CEA, carcinoembryonic antigen; AFP, alpha fetoprotein; CA153, cancer antigen 153.

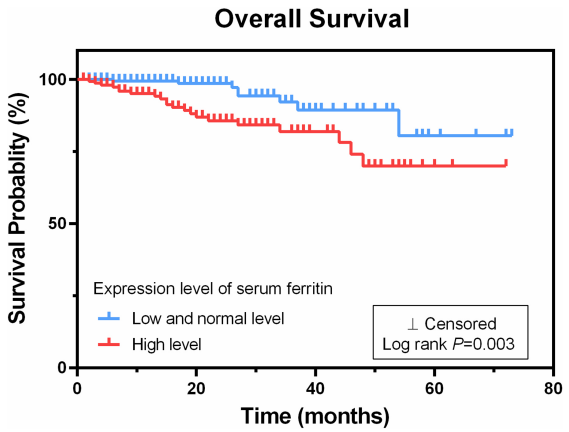

Fig. 1. High serum ferritin expression level in gynecological malignancies correlates with poor overall survival. The Kaplan-Meier survival curve for 402 patients revealed that the high ferritin level group (> 150 μg/L) had significantly less overall survival time when compared to the low and normal ferritin level groups ($\leqslant 150$ μg/L) (log-rank $P = 0.003$).

3.5. *Survival analysis of expression levels of serum ferritin in gynecological cancer patients*

By the end of the follow-up in June 2019, 29 patients had died, 351 patients survived, and 22 patients were censored. The Kaplan-Meier survival curves revealed that of the three groups analyzed, the high ferritin level group (> 150 μg/L) had significantly less survival time vs. the normal and low ferritin level groups ($\leqslant 150$ μg/L) (log-rank $P = 0.003$) (Fig. 1). Compared to other groups, low Hb (< 115 g/L) and Low serum ferritin (< 13 μg/L) level group had no impact on overall survival (log-rank $P > 0.05$) (Fig. 2).

3.6. *Association of clinical factors and mortality*

Univariable Cox regression analysis identified pa-

Table 3
Univariable and multivariable analysis in patients with gynecological malignant tumor for OS

Clinicopathologic factors	Univariable analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	3.964	1.885–8.336	< 0.001	2.847	1.108–7.32	< 0.05
Menopause	4.362	1.518–12.536	< 0.01	2.729	0.737–10.109	0.133
BMI index	0.563	0.445–1.555	0.563			
Albumin	0.113	0.048–0.267	< 0.001	0.824	0.291–2.33	0.715
WBC	1.528	0.411–5.681	0.527			
Hb	0.331	0.159–0.687	< 0.01	0.648	0.278–1.51	0.315
MCV	1.701	0.470–6.156	0.418			
CRP	11.918	4.842–29.334	< 0.001	7.644	2.215–26.374	0.001
ALT	1.166	0.157–8.654	0.881			
CA125	9.055	3.144–26.075	< 0.001	5.445	1.365–21.727	< 0.05
CEA	3.917	1.780–8.620	0.001	4.492	1.759–11.471	< 0.05
AFP	2.814	0.655–12.086	0.164			
CA153	4.601	2.212–9.572	< 0.001	1.564	0.637–3.84	0.329
Ferritin	2.72	1.324–5.590	< 0.01	0.792	0.351–1.787	0.574
Lymphatic metastasis	4.795	2.261–10.166	< 0.001	1.022	0.359–2.909	0.968
Ascites	6.915	3.192–14.979	< 0.001	1.048	0.359–3.056	0.932
Tumor size	2.201	1.016–4.766	< 0.05	0.395	0.154–1.012	0.053
FIGO stage	2.989	2.058–4.342	< 0.001	1.235	0.301–5.074	0.77

OS: overall survival; HR, hazard ratio; CI: confidence interval; BMI, body mass index; ALB, albumin; WBC, white blood cell; Hb, hemoglobin; MCV, mean corpuscular volume; CRP, C-reactive protein; ALT, alanine aminotransferase; CA125, cancer antigen 125; CEA, carcinoembryonic antigen; AFP, alpha fetoprotein; CA153, cancer antigen 153; FIGO, Inter-national Federation of Gynecology and Obstetrics.

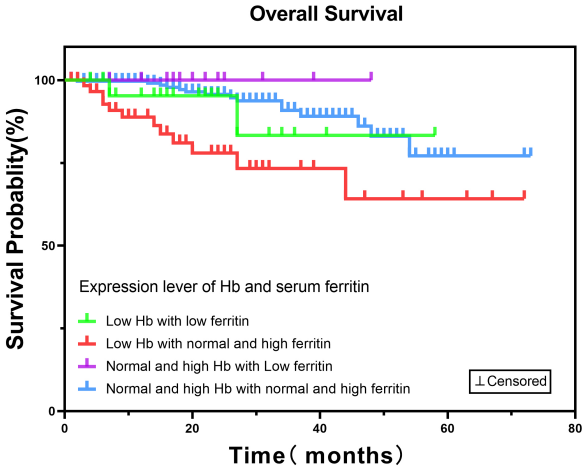

Fig. 2. Low hemoglobin (Hb) and Low serum ferritin expression level in gynecological malignancies has no impact on overall survival. The Kaplan-Meier survival curve for 402 patients revealed that the low Hb ($<$ 115 g/L) and Low serum ferritin ($<$ 13 μg/L) level group had no impact on survival when compared to other groups. Low Hb with low ferritin vs. Low Hb with normal and high ferritin ($\geqslant$ 13 μg/L): $P = 0.211$, Low Hb with low ferritin vs. Normal and high Hb ($\geqslant$ 115 g/L) with Low ferritin: $P = 0.31$, Low Hb with low ferritin vs. Normal and high Hb with normal and high ferritin: $P = 0.45$.

tients with a high expression level of ferritin ($>$ 150 μg/L) had a significant correlation with risk of death when compared to the patients with lower and normal ferritin levels ($\leqslant$ 150 μg/L) (HR = 2.72, 95% CI: 1.324–5.590, $P < 0.01$) (Table 3).

3.7. *Independent prognosis indicators in gynecological malignancies*

Multivariable Cox analyses after adjusting for age, menopause and other factors revealed four significant parameters as independent prognosis indicators in gynecological malignant tumors: age (HR = 2.847, 95% CI: 1.108–7.32, $P < 0.05$), CRP (HR = 7.644, 95% CI: 2.215–26.374, $P = 0.001$), CA125 (HR = 5.445, 95% CI: 1.365–21.727, $P < 0.05$), and CEA (HR = 4.492, 95% CI: 1.759–11.471, $P < 0.05$). Serum ferritin was not found to be an independent prognosis indicators on survival (HR = 0.792, 95% CI: 0.351–1.787, $P =$ 0.574) (Table 3 and Fig. 3).

4. Discussion

This study aimed to investigate the relationship between serum ferritin levels and the severity and prognosis of patients with gynecological malignant tumors. We found that the high ferritin level group had more elderly, menopausal, ovarian cancer patients, high CA125 levels, and more patients in FIGO stage IV, especially patients exhibiting high ferritin levels demonstrated a significantly poorer prognosis compared to their counterparts with lower or normal ferritin levels.

The relationship between ferritin levels and cancer may be due to the relationship between ferritin and ox-

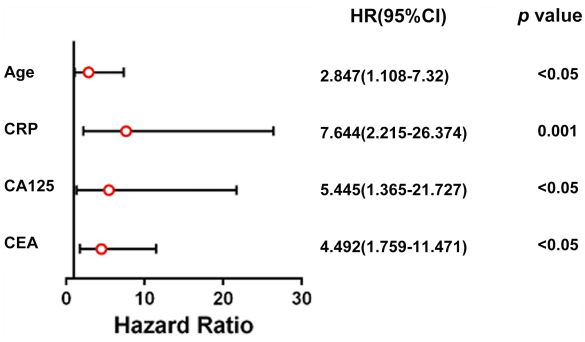

Fig. 3. A forest plot of significant independent prognosis indicators in gynecological malignancies. Multivariable Cox analyses revealed four significant parameters as independent prognosis indicators in gynecological malignant tumors: age (hazard ratio [HR] = 2.847, 95% CI: 1.108–7.32, $P < 0.05$), C-reactive protein (CRP) (HR = 7.644, 95% CI: 2.215–26.374, $P = 0.001$), cancer antigen 125 (CA125) (HR = 5.445, 95% CI: 1.365–21.727, $P < 0.05$), and carcinoembryonic antigen (CEA) (HR = 4.492, 95% CI: 1.759–11.471, $P < 0.05$).

idative stress [25,26,27,28]. Yildirim et al. [19] found serum ferritin was significantly elevated in lymphatic metastatic lung cancer patients, which is similar to our study's findings. Furthermore, Lee et al. [18] concluded patients with recurrent or refractory metastatic colorectal cancer had a high expression level of ferritin. Scutiero et al. [29] showed that iron accumulation leads to oxidative stress, causing DNA hypermethylation and histone modifications. These changes due to oxidative stress contribute to the malignant transformation process of cells.

In this study, correlation analyses were performed between serum ferritin level and other factors. WBC, MCV, CRP, CA125, and CA153 were significantly positively correlated with serum ferritin level, whereas ALB was negatively correlated. Based on these results, ferritin was closely related to nutrition, inflammation and tumor markers. This finding implies that the increased serum ferritin was significantly associated with poor survival quality. It was also suggested that ferritin can assist in the diagnosis of gynecological malignant tumors.

It is worth noting that there was no significant correlation between hemoglobin and ferritin in this study, which is consistent with the results of another study [18]. This may be related to the increase of ferritin as an acute phase protein in infection, malignant tumor or chronic inflammation [30]. In addition, when the loss of iron exceeds the absorption or the absorption is lower than the demand, the initial iron storage will be exhausted, resulting in the reduction of ferritin level, and hemoglobin is still normal at this time, which is called non-anaemic iron deficiency (NAID). However, when ferritin decreases further, the hemoglobin concentration will eventually fall below the lower limit of the normal range [31]. And in later Kaplan-Meier survival analyses of hemoglobin and serum ferritin expression revealed that anemia combined with low ferritin had no significant correlation with survival results. It may be related to previous findings that patients with low ferritin were relatively younger, had lower FIGO grade tumors, had fewer ovarian cancers, and thus recoverd more quickly.

The Kaplan-Meier survival analyses of serum erritin expression revealed that the high ferritin level group had significantly less survival time than normal and low ferritin level groups. It indicates that serum ferritin could predict a poor prognosis for patients with gynecological malignant tumors. The univariable Cox regression analysis identified patients with a high level of ferritin (> 150 μg/L) had a significant correlation with the risk of death compared to the patients with low and normal ferritin levels. Studies have also shown iron elevation in cancer is significant. Based on the results of univariate analyses, the multivariate COX analysis controlling confounding factors identified four significant parameters as independent prognosis indicators in gynecological malignant tumors: age, CRP, CA125, and CEA. Ferritin was not found to be significant. Therefore, serum ferritin levels cannot be used as an independent prognosis indicator in gynecological malignant tumor patients.

Though our study did not show significant data for ferritin as an independent prognosis indicator, other studies have. Orlandi et al. [32] showed serum concentrations of hepcidin and ferritin were satisfactory predictors of malignant breast cancer; High ferritin levels were associated with poor prognosis in breast cancer, lung cancer, pancreatic cancer, multiple myeloma, hepatocellular carcinoma and colorectal cancer patients [33].

Our study showed that there is a significant relationship between ferritin levels and gynecological cancer. Still, other studies indicate that there is a relationship between ferritin and anti-cancer efficacy. Ihlow et al. [34] showed that ferritin levels are related to the response to the course and duration of chemotherapy. Shi et al. [35] ferritin levels were related to platinum-based chemotherapy efficacy in patients with lung cancer. Despite an initial response to ovarian cancer therapy, most patients develop chemoresistance and ultimately terminal disease. Basuli et al. [36] reported that this drug resistance might be due to alterations in iron metabolism

and retention in excess iron that contributes to tumor growth, thereby recommending a new strategy for the use of iron chelators with anticancer therapy. These studies suggest a significant relationship between ferritin and cancer therapy and may also suggest a need for iron therapeutic management in combination with anticancer therapy. It could drastically improve morbidity and mortality of gynecological cancer in the future.

This study has several limitations. The included patients were from one hospital only, resulting in a small sample size and limiting the statistical power or generalizability of the results. It may be particularly true since the population was homogeneous regarding ethnicity and the limited geographical area. We did not include the expression of other proteins related to iron metabolism that may be relevant to the study, such as transferrin or iron regulatory proteins. Finally, this was a retrospective study; therefore, the results should be considered preliminary. Though there were strengths to our study, including studying a combination of different gynecological cancers, a prospective, multicenter study with a larger study population is needed.

5. Conclusion

In this study focusing on gynecological malignancies, we identified a notable prevalence of elevated ferritin levels among elderly patients with menopausal gynecologic tumors. Specifically, individuals within the high-ferritin in the gynecologic tumor population faced an increased risk of mortality. These findings have substantial implications for prognostic assessment and therapeutic approaches in elderly patients with menopausal gynecologic tumors, particularly those afflicted with ovarian cancer, as ferritin levels hold potential as a valuable prognostic indicator. Moreover, patients exhibiting high ferritin levels demonstrated a significantly poorer prognosis compared to their counterparts with lower or normal ferritin levels. However, it is imperative to acknowledge that this study's scope remains limited to data obtained from a single center, necessitating further validation through extensive, prospective, and multicenter clinical trials.

Ethics approval

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved by Taizhou Hospital of ZheJiang Province. This article is a retrospective study. Therefore the Institutional waived the requirement to obtain distinct written informed consent from the patients.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conception: WZ.
Interpretation or analysis of data: WZ and QC.
Preparation of the manuscript: WZ and QC.
Revision for important intellectual content: YC, JT, RT and MW.
Supervision: JY and YP.

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