# Association between serum lactate dehydrogenase and lymph node metastasis in cervical cancer

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**Abstract.** The aim of the present study was to evaluate the association between serum lactate dehydrogenase (LDH) and the risk of lymph node metastasis (LNM) in the International Federation of Gynecology and Obstetrics (FIGO) 2009 cervical cancer (CC) stages IB1-IIA2. All patient medical records with FIGO 2009 stage IB1-IIA2 CC between January 2012 and January 2022 were analyzed retrospectively. The association between serum LDH and LNM was assessed using uni- and multivariate logistic regression analyses, subgroup analyses and P-splines. The present study included 586 patients, 91 (15.5%) of whom had LNM. Patients with an elevated LDH level were more likely to have a deep stromal invasion, lymph-vascular space invasion, LNM and to be of an older age. Multivariate logistic regression revealed a significant association between LNM and LDH levels. After adjusting for age, FIGO stage, tumor markers and risk factors according to the Sedlis criteria, patients in the highest LDH quartile had an increased risk of LNM compared with those in the lowest LDH quartile (odds ratio, 3.5; 95% CI, 1.57-7.81). Furthermore, P-spline regression revealed a dependence of LNM on LDH. The predictive value of LDH level remained significant in the subgroup analysis. The present study suggested that a higher LDH level was independently associated with CC and LNM, and that LDH level may serve as a potential tumor marker and treatment-related indicator.

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## Introduction

Cervical cancer (CC) is one of the prevalent malignant tumors affecting the reproductive system in female patients and ranks as the fourth most common malignant tumor globally (1). According to the International Federation of Gynecology and Obstetrics (FIGO) clinical staging system, radical hysterectomy with pelvic lymphadenectomy (RHPL) with or without para-aortic lymphadenectomy is the standard surgical treatment for patients with stage IB1-IIA2 CC. Patients with local advanced CC are usually given concurrent chemoradiotherapy (2). The Sedlis criteria classifies lymph node metastasis (LNM), surgical margin and parametrial involvement as high risk factors and stromal invasion, lymphatic space involvement and primary tumor size as intermediate risk factors related to the diagnosis, prognosis and treatment of CC (3). Moreover, hematological indices, including hemoglobin, lymphocyte, cancer antigen 125 (Ca125) and squamous cell carcinoma antigen (SCC-Ag), are particularly valuable for predicting LNM and prognosis (4-6).

Serum lactate dehydrogenase (LDH), a rate-limiting enzyme, contributes to the conversion of pyruvate to lactic acid under hypoxic conditions (7), serving an important role in tumor cell proliferation and metastasis (8). Hypoxia can promote cancer development, contributing to treatment resistance through new blood vessel formation (9). Serum LDH has been associated with the prognosis of several cancer types, including non-Hodgkin lymphoma, colon and lung cancer (8,10,11), and elevated LDH levels have been reported to be associated with poor prognosis in CC (12-14). Research by Ye *et al* (14) provided evidence for the association between elevated LDH and poor prognosis of CC using RNA-seq and microarray datasets. Wang *et al* (13) reported the prognostic role of the combination of C-reactive protein and LDH in patients with locally advanced CC. However, these studies failed to demonstrate the relationship between LDH and LNM in CC, as well as the lack of adjustment for relevant risk factors. Therefore, the aim of the present retrospective study was to investigate the relationship between LDH levels and LNM in patients who have undergone RHPL treatment, adjusting for other risk factors (Sedlis criteria) and hematological indices.

## Materials and methods

*Study design and population*. A total of 586 patients with CC who underwent a radical hysterectomy, pelvic lymphadenectomy with or without para-aortic lymphadenectomy, were admitted to Fujian Provincial Maternity and Children's Hospital (Fuzhou, China) between January 2012 and January 2022 and used in the present retrospective study. The following inclusion criteria were applied: i) First treatment was administered and completed in the hospital, ii) the case was assessed preoperatively by >2 gynecological oncologists with senior professional titles in the hospital and was determined to fall within stages IB1-IIA2 according to the staging standards of FIGO (2009), iii) pathological diagnosis of CC, iv) complete information, including lymph node dissection and hematological data. Exclusion criteria were as follows: i) Patients staged as Ia or IIB, ii) Missing LDH data, iii) patients with a history of other malignant tumors, myocardial infarction, or liver disease. The hematological data of patients were tested routinely within two weeks prior to surgery. The other detailed inclusion and exclusion criteria are listed in Fig. 1. Patient age range was 24-73 years. The tumor size was divided into three groups: <2, ≥2 and <4, ≥4 cm; and DSI was divided into three groups: <1/3, ≥1/3 and <2/3, ≥2/3 of cervical stroma thickness.

*Data collection*. Clinical information, pathological results and hematological data were collected from each patient. Clinical information included age, FIGO stage, tumor size and neoadjuvant chemotherapy (NACT). Pathological results included LNM, pathological type, deep stromal invasion (DSI), lymph-vascular space invasion (LVSI), surgical margin and parametrial involvement. DSI definition was primarily based on the ratio of the tumor invading the cervical stroma. Hematological data, including white blood cell (WBC) count, neutrophil (NE) count, lymphocyte (LY) count, platelet count (PLT), cancer antigen 199 (Ca199), Ca125, α-fetoprotein (AFP), LDH and SCC-Ag, were collected one week before treatment.

LDH was detected using the lactate to ketone acid method. The detection range of LDH is 30-4,500 U/l, the normal reference range is 125-250 U/l and the maximum detection values for the blank limit, detection limit and quantification limit were 9, 15 and 25 U/l, respectively (15,16).

*Statistical analysis*. All analyses were performed using the statistical software packages R 3.3.2 (R-project.org; The R Foundation) and Free Statistics software v1.3 (clinicalscientists.cn/freestatistics/). Patient characteristics were calculated according to stratified LDH quartiles. LDH was entered as a categorical variable (quartiles) and a continuous variable [with odds ratio (OR)/hazard ratio (HR) calculated per 10 U/l LDH increase]. Data were expressed as the mean ± SD if normally distributed or as median and interquartile range if skewed. The $\chi^2$ test or Fisher's exact probability method was used to compare the differences in the rate/composition ratio between groups for the count data. Uni-/multi-variate analysis was used to identify the influencing factors. Further analyses were adjusted cumulatively for logistic stepwise regression analysis and professional knowledge. Additional subgroup analyses were performed when effect modification was observed or differences in LDH were expected in patient subgroups. OR and 95% CI were calculated to assess the association between LDH and LNM using logistic regression models. Statistical significance was set at P<0.05. Missing data were imputed by multiple imputations (17). Splines were fitted using a logistic regression model based on restricted cubic splines and model adjustments used (18,19).

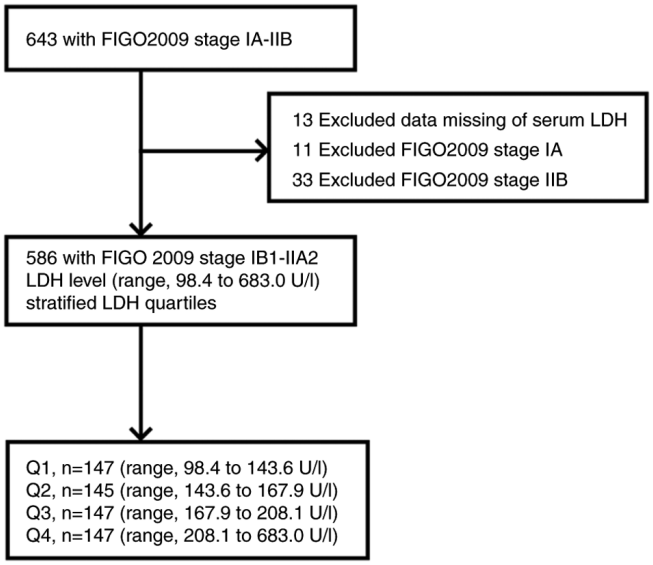


Figure 1. Study design. A total of 643 patients with cervical cancer were recruited, of which 586 patients met the inclusion criteria. These patients were divided into four groups, namely Q1, Q2, Q3, and Q4, based on their levels of LDH. FIGO, the International Federation of Gynecology and Obstetrics; LDH, lactate dehydrogenase.

## Results

*Patient characteristics*. The present study included 586 female patients with confirmed pathological diagnoses; among them, 91 patients were diagnosed with LNM. The first, second and third quartiles of LDH level (range, 98.4-683.0 U/l) were 143.6, 167.9 and 208.1 U/l, divided into Q1, Q2, Q3 and Q4 groups. According to this grouping of LDH levels, the LNM rates of patients were 8.8, 13.8, 15.6 and 23.8%, for Q1, Q2, Q3 and Q4, respectively (P=0.005). Table I displays the baseline patient characteristics for age, pathology, SCC-Ag, Ca199, Ca125, AFP, NE, LY, PLT, LNM, NACT, tumor size, DSI, LVSI, parametrial involvement, surgical margin, WBC count and FIGO stage. The groups with an higher LDH level were more likely to have LVSI, DSI, LNM and be of an older age.

*Univariate and multivariate analyses for LNM*. Univariate analysis indicated that LDH of groups age, FIGO stage, NACT, tumor size, DSI, LVSI, parametrial involvement, surgical margin, Ca125 and SCC-Ag were linked to LNM (all P<0.05; Fig. 1; Table II). Multivariate analysis confirmed LDH, NACT, DSI, age and LVSI as independent factors for LNM (all P<0.05; Table II). In multivariable logistic regression analyses, there was a 2.5-fold increased risk of LNM in Q4 group compared to Q1 group (OR 3.50; 95% CI, 1.57-7.81; P=0.002; Table II).

Table I. Comparison of clinicopathological characteristics between patients in the different LDH level groups.

| Clinicopathological characteristic | Serum lactate dehydrogenase level quartiles[a] | | | | | | |
|---|---|---|---|---|---|---|---|
| | Total (%), n=586 | Q1 (%), n=147 | Q2 (%), n=145 | Q3 (%), n=147 | Q4 (%), n=147 | P-value | $\chi^2$ |
| FIGO stage | | | | | | 0.489 | 8.454 |
| IB1 | 317 (54.1) | 88 (59.9) | 80 (55.2) | 77 (52.4) | 72 (49.0) | | |
| 1B2 | 110 (18.8) | 29 (19.7) | 29 (20.0) | 28 (19.0) | 24 (16.3) | | |
| IIA1 | 80 (13.7) | 15 (10.2) | 18 (12.4) | 22 (15.0) | 25 (17.0) | | |
| IIA2 | 79 (13.5) | 15 (10.2) | 18 (12.4) | 20 (13.6) | 26 (17.7) | | |
| Median age, years (IQR) | 47.0 (42.0, 53.0) | 43.0 (38.0, 51.0) | 47.0 (42.0, 55.0) | 49.0 (44.0, 54.0) | 48.0 (42.0, 54.5) | <0.001 | 24.582 |
| Tumor size, cm | | | | | | 0.791 | 3.143 |
| <2 | 226 (38.6) | 59 (40.1) | 55 (37.9) | 59 (40.1) | 53 (36.1) | | |
| ≥2-<4 | 218 (37.2) | 59 (40.1) | 55 (37.9) | 50 (34.0) | 54 (36.7) | | |
| ≥4 | 142 (24.2) | 29 (19.7) | 35 (24.1) | 38 (25.9) | 40 (27.2) | | |
| Pathology | | | | | | 0.428 | 5.960 |
| Squamous cell carcinoma | 466 (79.5) | 117 (79.6) | 110 (75.9) | 117 (79.6) | 122 (83.0) | | |
| Adenocarcinoma | 74 (12.6) | 16 (10.9) | 25 (17.2) | 20 (13.6) | 13 (8.8) | | |
| Other | 46 (7.8) | 14 (9.5) | 10 (6.9) | 10 (6.8) | 12 (8.2) | | |
| Deep stromal invasion | | | | | | 0.018 | 15.324 |
| <1/3 | 267 (45.6) | 68 (46.3) | 77 (53.1) | 66 (44.9) | 56 (38.1) | | |
| ≥1/3-<2/3 | 202 (34.5) | 48 (32.7) | 47 (32.4) | 42 (28.6) | 65 (44.2) | | |
| ≥2/3 | 117 (20.0) | 31 (21.1) | 21 (14.5) | 39 (26.5) | 26 (17.7) | | |
| Lymph-vascular space invasion | | | | | | 0.002 | 15.339 |
| Negative | 388 (66.2) | 99 (67.3) | 110 (75.9) | 99 (67.3) | 80 (54.4) | | |
| Positive | 198 (33.8) | 48 (32.7) | 35 (24.1) | 48 (32.7) | 67 (45.6) | | |
| Lymph node metastasis | | | | | | 0.005 | 13.027 |
| Negative | 495 (84.5) | 134 (91.2) | 125 (86.2) | 124 (84.4) | 112 (76.2) | | |
| Positive | 91 (15.5) | 13 (8.8) | 20 (13.8) | 23 (15.6) | 35 (23.8) | | |
| Parametrial involvement | | | | | | 0.905 | Fisher |
| Negative | 575 (98.1) | 144 (98.0) | 143 (98.6) | 145 (98.6) | 143 (97.3) | | |
| Positive | 11 (1.9) | 3 (2.0) | 2 (1.4) | 2 (1.4) | 4 (2.7) | | |
| Surgical margin | | | | | | 0.417 | 2.841 |
| Negative | 565 (96.4) | 141 (95.9) | 143 (98.6) | 141 (95.9) | 140 (95.2) | | |
| Positive | 21 (3.6) | 6 (4.1) | 2 (1.4) | 6 (4.1) | 7 (4.8) | | |
| Neoadjuvant chemotherapy | | | | | | 0.362 | 3.197 |
| No | 392 (66.9) | 97 (66.0) | 99 (68.3) | 105 (71.4) | 91 (61.9) | | |
| Yes | 194 (33.1) | 50 (34.0) | 46 (31.7) | 42 (28.6) | 56 (38.1) | | |
| White blood cell count, $x10^9$/l | | | | | | 0.847 | 2.691 |
| <3.5 | 26 (4.4) | 7 (4.8) | 9 (6.2) | 5 (3.4) | 5 (3.4) | | |
| 3.5-9.5 | 529 (90.3) | 133 (90.5) | 129 (89) | 132 (89.8) | 135 (91.8) | | |
| >9.5 | 31 (5.3) | 7 (4.8) | 7 (4.8) | 10 (6.8) | 7 (4.8) | | |
| Neutrophil count, $x10^9$/l | | | | | | 0.723 | 3.656 |
| <1.8 | 22 (3.8) | 7 (4.8) | 3 (2.1) | 7 (4.8) | 5 (3.4) | | |
| 1.8-6.3 | 542 (92.5) | 137 (93.2) | 136 (93.8) | 134 (91.2) | 135 (91.8) | | |
| >6.3 | 22 (3.8) | 3 (2.0) | 6 (4.1) | 6 (4.1) | 7 (4.8) | | |
| Lymphocyte count, $10^9$/l | | | | | | 0.971 | Fisher |
| <1.1 | 47 (8.0) | 11 (7.5) | 12 (8.3) | 12 (8.2) | 12 (8.2) | | |
| 1.1-3.2 | 525 (89.6) | 132 (89.8) | 130 (89.7) | 130 (88.4) | 133 (90.5) | | |
| >3.2 | 14 (2.4) | 4 (2.7) | 3 (2.1) | 5 (3.4) | 2 (1.4) | | |

Table I. Continued

| Clinicopathological characteristic | Serum lactate dehydrogenase level quartiles[a] Total (%), n=586 | Q1 (%), n=147 | Q2 (%), n=145 | Q3 (%), n=147 | Q4 (%), n=147 | P-value | $\chi^2$ |
|---|---|---|---|---|---|---|---|
| Platelet count, x$10^9$/l | | | | | | 0.659 | Fisher |
| <125 | 8 (1.4) | 0 (0) | 3 (2.1) | 2 (1.4) | 3 (2) | | |
| 125-350 | 534 (91.1) | 138 (93.9) | 131 (90.3) | 134 (91.2) | 131 (89.1) | | |
| >350 | 44 (7.5) | 9 (6.1) | 11 (7.6) | 11 (7.5) | 13 (8.8) | | |
| Ca125, ng/ml | | | | | | 0.848 | 0.806 |
| <35 | 540 (92.2) | 136 (92.5) | 135 (93.1) | 133 (90.5) | 136 (92.5) | | |
| ≥35 | 46 (7.8) | 11 (7.5) | 10 (6.9) | 14 (9.5) | 11 (7.5) | | |
| Ca199, ng/ml | | | | | | 0.299 | 3.672 |
| <37 | 563 (96.1) | 140 (95.2) | 143 (98.6) | 141 (95.9) | 139 (94.6) | | |
| ≥37 | 23 (3.9) | 7 (4.8) | 2 (1.4) | 6 (4.1) | 8 (5.4) | | |
| -fetoprotein, ng/ml | | | | | | 0.633 | Fisher |
| <8.78 | 584 (99.7) | 147 (100) | 144 (99.3) | 147 (100) | 146 (99.3) | | |
| ≥8.78 | 2 (0.3) | 0 (0) | 1 (0.7) | 0 (0) | 1 (0.7) | | |
| Squamous cell carcinoma antigen, ng/ml | | | | | | 0.064 | 7.267 |
| <1.5 | 290 (49.5) | 76 (51.7) | 68 (46.9) | 84 (57.1) | 62 (42.2) | | |
| ≥1.5 | 296 (50.5) | 71 (48.3) | 77 (53.1) | 63 (42.9) | 85 (57.8) | | |

[a]First, second and third quartiles of LDH level (range, 98.4-683.0 U/l) were 143.6, 167.9 and 208.1 U/l, divided into Q1, Q2, Q3 and Q4 groups. Ca, cancer antigen; FIGO, the International Federation of Gynecology and Obstetrics; IQR, interquartile range.

*Association between LDH and LNM*. The following adjustments were made to assess the robustness of the findings of the present study: i) Model 1 was not adjusted, ii) Model 2 was adjusted for age, iii) Model 3 was adjusted for age and FIGO stage, iv) Model 4 was adjusted for age, FIGO stage and NACT, v) Model 5 was adjusted for age, FIGO stage, NACT and hematological indicator variables (SCC-Ag and Ca125), vi) Model 6 was adjusted for age, FIGO stage, NACT, hematological indicator variables and high risk factors (surgical margin and parametrial involvement) and vii) Model 7 was adjusted for age, FIGO stage, NACT, hematological indicator variables, high risk factors and intermediate risk factors (tumor size, LVSI and DSI).

In multivariable logistic regression analysis with LDH quartiles, Q4 group were associated with a 2.37-fold increased risk of LNM compared to Q1 group, independent of potential confounders (Model 7; OR 3.37; 95% CI, 1.54-7.36; P=0.055; Table III). The risk of LNM in the Q2 group is 1.65-2.79 times higher than in the Q1 group after adjusting for confounding factors (Models 1-7; Table III). The risk of LNM in the Q3 group is 1.91-2.66 times higher than in the Q1 group after adjusting for confounding factors (Models 1-7; Table III). LDH was entered as a continuous variable per 5 U/l increase, and LDH and LNM remained significantly associated (OR 1.03; 95% CI, 1.00-1.04).

*Subgroup analyses*. Subgroup analysis was used to address the association between LDH and LNM. Additional subgroup and sensitivity analyses concerning the role of confounding factors are presented in Table III, Fig. 2 and the supplementary material (Tables SI-SVIII and Fig. S1). When LDH was >167.9 ng/ml, factors that were related to LNM include FIGO stage, DSI, LVSI, surgical margin, SCC-Ag, tumor size (all P<0.05). Similar associations were discovered between LDH and LNM in some subgroup analyses. Special attention should be paid among patients with FIGO IIA stage (OR 1.83; 95% CI, 1.18-2.84; P=0.007; Table SI), age ≥45 (OR 1.94; 95% CI, 1.35-2.78; P<0.001; Table SII), SCC-Ag ≥1.5 ng/ml (OR 1.41; 95% CI, 1.06-1.88; P=0.019; Table SV), Ca125 <35 ng/ml (OR 1.48; 95% CI, 1.16-1.88; P<0.001; Table SIII), LVSI positive (OR 1.39; 95% CI, 1.00-1.93; P=0.047; Table SVI), DSI ≥2/3 (OR 1.58; 95% CI, 0.95-2.64; P=0.077; Table SVII), tumor size <2 cm (OR 1.64; 95% CI, 1.05-2.56; P=0.029; Table SVIII) and squamous cell carcinoma (OR 1.40; 95% CI, 1.09-1.79; P=0.009; Table SIV).

*Value-dependent effects of LDH on LNM*. Fig. 3 depicts a multivariable-adjusted restricted cubic spline for the association between LDH and LNM to quantify the effect of LDH on LNM. The analysis indicated that the risk of LNM increased sharply when LDH <167.9 ng/ml. The risk of LNM began to decline in the Q3 range. The risk of LNM entered a plateau in the Q4 range (Fig. 3A). After adjustment for potential confounders (Model 7; Fig. 3B), this trend became more notable regarding the association between LDH and LNM.

## Discussion

The present study aimed to evaluate the association between serum LDH level and the risk of LNM in patients with CC.

Table II. Univariate and multivariate logistic regression for predicting LNM.

| Clinicopathological characteristic | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR (95% CI) | P-value | OR (95% CI) | P-value |
| Trend[a] | 1.44 (1.17-1.78) | 0.001 | 1.4 (1.11-1.78) | 0.005 |
| Q2 | 1.65 (0.79-3.45) | 0.185 | 2.79 (1.19-6.55) | 0.018 |
| Q3 | 1.91 (0.93-3.94) | 0.079 | 2.52 (1.07-5.9) | 0.034 |
| Q4 | 3.22 (1.63-6.38) | 0.001 | 3.5 (1.57-7.81) | 0.002 |
| Age, years | 0.97 (0.95-1) | 0.045 | 0.95 (0.92-0.98) | 0.001 |
| FIGO stage | | | | |
| IB2 | 1.86 (1.01-3.44) | 0.048 | 0.99 (0.47-2.11) | 0.985 |
| IIA1 | 2.59 (1.36-4.9) | 0.004 | 1.78 (0.83-3.83) | 0.140 |
| IIA2 | 3.44 (1.86-6.34) | <0.001 | 1.71 (0.76-3.85) | 0.195 |
| Neoadjuvant chemotherapy | 2.15 (1.37-3.39) | 0.001 | 2.04 (1.1-3.8) | 0.024 |
| Tumor size, cm | | | | |
| ≥2-<4 | 1.49 (0.85-2.58) | 0.161 | 0.6 (0.3-1.23) | 0.164 |
| >4 | 2.34 (1.32-4.15) | 0.004 | 0.72 (0.31-1.68) | 0.446 |
| DSI | | | | |
| ≥1/3-<2/3 | 3.99 (2.17-7.36) | <0.001 | 3.04 (1.52-6.1) | 0.002 |
| ≥2/3 | 6.43 (3.38-12.24) | <0.001 | 4.89 (2.21-10.79) | <0.001 |
| Lymph-vascular space invasion positive | 3.76 (2.37-5.97) | <0.001 | 2.09 (1.17-3.72) | 0.012 |
| Parametrial involvement positive | 27.05 (5.74-127.46) | <0.001 | 6.57 (0.97-44.67) | 0.054 |
| Surgical margin positive | 5.43 (2.23-13.2) | <0.001 | 3.16 (0.92-10.88) | 0.068 |
| Pathology | | | | |
| Adenocarcinoma | 0.6 (0.28-1.31) | 0.2 | 0.85 (0.33-2.16) | 0.726 |
| Other | 0.61 (0.23-1.58) | 0.307 | 0.63 (0.21-1.93) | 0.419 |
| WBC count, 3.5-9.5x$10^9$/l | 0.97 (0.32-2.88) | 0.95 | 0.59 (0.15-2.3) | 0.45 |
| WBC count, >9.5x$10^9$/l | 1.91 (0.5-7.27) | 0.341 | 0.99 (0.15-6.34) | 0.988 |
| NE count, 1.8-6.3x$10^9$/l | 1.78 (0.41-7.77) | 0.442 | 2.38 (0.32-17.5) | 0.395 |
| NE count, >6.3x$10^9$/l | 4.67 (0.85-25.75) | 0.077 | 4.51 (0.3-67.94) | 0.277 |
| LY count, 1.1-3.2x$10^9$/l | 0.67 (0.32-1.39) | 0.279 | 1.46 (0.35-6.1) | 0.603 |
| LY count, >3.2x$10^9$/l | 0.28 (0.03-2.44) | 0.252 | 0.5 (0.03-9.44) | 0.643 |
| Platelet count, x$10^9$/l | | | | |
| 125-350 | 0.53 (0.1-2.67) | 0.44 | 0.51 (0.06-4.3) | 0.538 |
| >350x$10^9$/l | 0.77 (0.13-4.48) | 0.773 | 0.45 (0.04-4.68) | 0.506 |
| Ca125, ≥35 ng/ml | 2.63 (1.34-5.16) | 0.005 | 2.3 (0.98-5.39) | 0.055 |
| Ca199, ≥37 ng/ml | 2.49 (1-6.25) | 0.051 | 1.37 (0.42-4.47) | 0.606 |
| α-fetoprotein, ≥8.78 ng/ml | 0 (0-Inf) | 0.984 | 0 (0-Inf) | 0.983 |
| Squamous cell carcinoma antigen, ≥3.75 ng/ml | 2.12 (1.33-3.39) | 0.002 | 1.55 (0.82-2.91) | 0.175 |

[a]First, second and third quartiles of LDH level (range, 98.4-683.0 U/l) were 143.6, 167.9 and 208.1 U/l, divided into Q1, Q2, Q3 and Q4 group. Ca, cancer antigen 199; DSI, deep stromal invasion; FIGO, International Federation of Gynecology and Obstetrics; LNM, lymph node metastasis; LY, lymphocyte; NE, neutrophil; OR, odds ratios; WBC, white blood cell; Inf, infinity.

LDH level may serve as a potential tumor maker and treatment-related indicator. The present study has demonstrated that patients with elevated LDH levels were more likely to have LVSI, DSI, LNM and be of an older age. After adjusting for other factors, patients in the highest LDH quartile had an increased risk of LNM compared with those in the lowest LDH quartile. A multivariable-adjusted restricted cubic spline also confirmed the association between LDH and LNM. If LDH levels are elevated, further MRI or lymph node biopsy is needed to clarify the lymph node status to determine whether to perform radical surgery or concurrent radiotherapy treatment (2).

Unlike previous reports (13,14), the present study was a comprehensive association analysis that focused on the detailed relationship between serum LDH and LNM. Particularly noteworthy was that even after adjusting for other

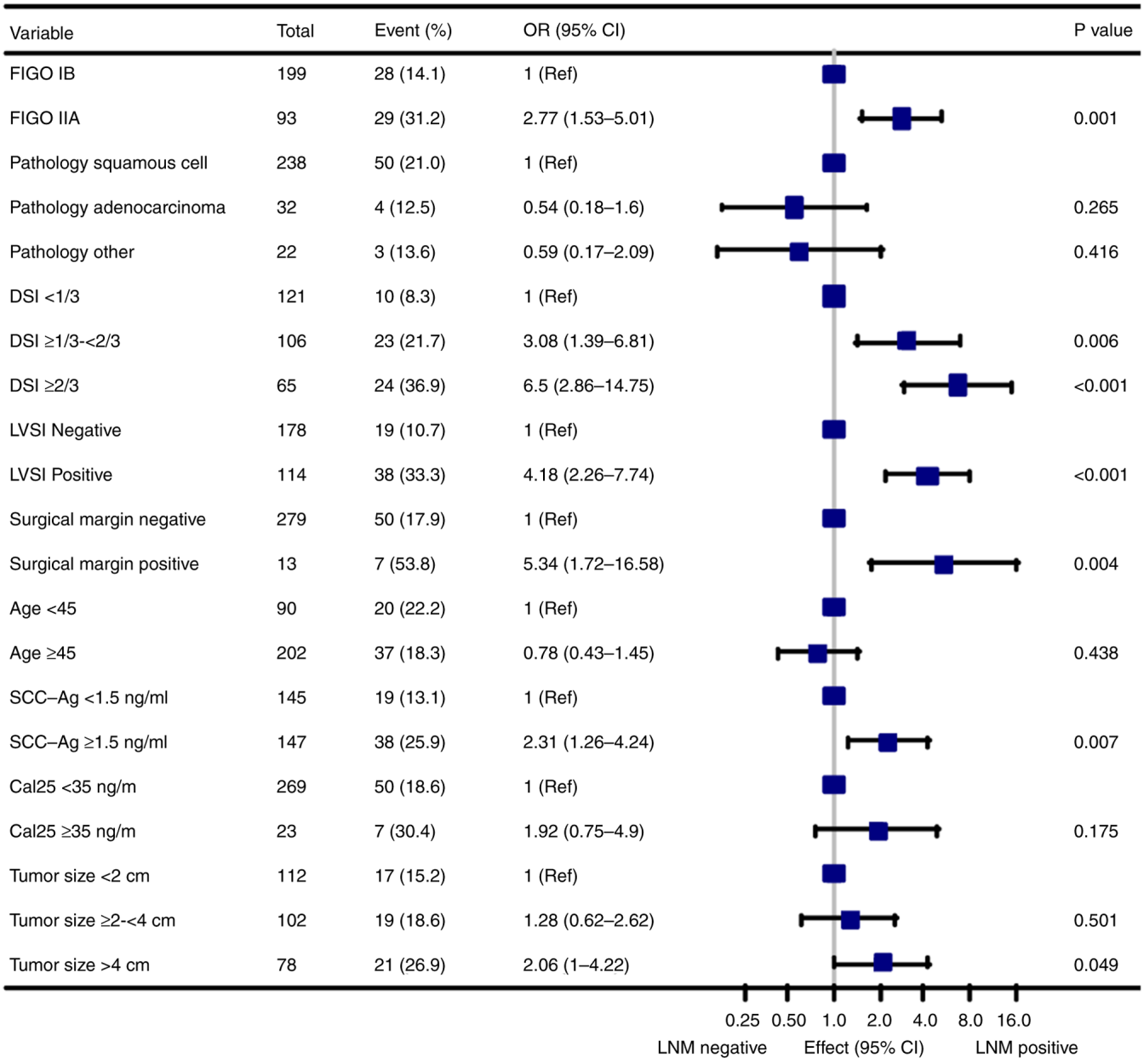


Figure 2. Forest graph of LNM and the subgroups in LDH level ≥167.9 U/l. Ca125, cancer antigen 125; DSI, deep stromal invasion; FIGO, International Federation of Gynecology and Obstetrics; LDH, serum lactate dehydrogenase; LNM, lymph node metastasis; LVSI, lymph-vascular space invasion; OR, odds ratio; SCC-Ag, squamous cell carcinoma antigen.

important prognostic factors, LDH still demonstrated its value. The present study comprehensively analyzed the association between LDH and LNM in CC. A previous study reported that LDH was related to a poor prognosis in CC; however, the small number of cases was insufficient to analyze relevant influencing factors (13). Unlike previous reports on non-surgical patients, to the best of our knowledge, this is the first study on patients undergoing radical surgery in the early stage and is the largest population-based analysis of LDH in CC.

Serum LDH is associated with the prognosis of numerous cancer types, including non-Hodgkin lymphoma, colon, lung, breast cancer and melanoma (8,10,11,20). Ovarian and uterine cancer have been associated with elevated LDH expression and aggressive phenotypes among gynecologic malignancies (13,20). This accords with a previous study, which discovered that high LDH levels were more likely to have LVSI, DSI and LNM in CC (13). Contrary to earlier findings, patients with elevated LDH levels were linked to older age and were not likely to have a high level of SCC-Ag (12). Therefore, the present study included these factors in subsequent model adjustments and subgroup analyses.

Univariate and multivariate analyses confirmed that LDH was an independent factor for LNM. Other factors related to LNM include age, NACT, SCC-Ag, Ca125, FIGO stage, tumor size, DSI, LVSI, parametrial involvement and surgical margin. According to the Sedlis criteria, LNM, surgical margin and parametrial involvement are high risk factors, whereas stromal invasion, lymphatic space involvement and primary tumor size are intermediate risk factors, and a previous study has reported on other factors related to LNM, such as age, NACT, SCC-Ag,

Table III. Multivariable logistic regression to assess the association of serum LDH with LNM.

| | LDH level[b], U/l | | Q1, n=147 | Q2, n=145 | Q3, n=147 | Q4, n=147 | Trend |
|---|---|---|---|---|---|---|---|
| Model[a] | OR (95% CI) | P-value | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| 1 | 1.03 (1.01-1.05) | 0.002 | 1 (Ref) | 1.65 (0.79-3.45) | 1.91 (0.93-3.94) | 3.22 (1.63-6.38) | 1.44 (1.17-1.78) |
| 2 | 1.03 (1.01-1.05) | 0.002 | 1 (Ref) | 1.88 (0.89-3.98) | 2.29 (1.09-4.8) | 3.74 (1.86-7.53) | 1.51 (1.22-1.86) |
| 3 | 1.03 (1.01-1.05) | 0.006 | 1 (Ref) | 1.91 (0.89-4.1) | 2.26 (1.06-4.79) | 3.45 (1.69-7.03) | 1.46 (1.18-1.81) |
| 4 | 1.03 (1.01-1.05) | 0.006 | 1 (Ref) | 1.98 (0.92-4.27) | 2.42 (1.13-5.18) | 3.54 (1.72-7.26) | 1.47 (1.18-1.82) |
| 5 | 1.03 (1.01-1.05) | 0.007 | 1 (Ref) | 1.94 (0.9-4.21) | 2.36 (1.09-5.08) | 3.38 (1.64-6.97) | 1.45 (1.16-1.8) |
| 6 | 1.02 (1-1.04) | 0.054 | 1 (Ref) | 2.21 (0.99-4.96) | 2.66 (1.19-5.95) | 3.71 (1.74-7.94) | 1.47 (1.18-1.84) |
| 7 | 1.02 (1-1.04) | 0.055 | 1 (Ref) | 2.79 (1.21-6.4) | 2.55 (1.11-5.86) | 3.37 (1.54-7.36) | 1.39 (1.1-1.75) |

[a]LDH was entered as a continuous variable per 5 U/l increase. Model 1, no adjustment; Model 2, adjusted for age in analyses; Model 3, adjusted as for model 2, additionally adjusted for International Federation of Gynecology and Obstetrics stage; Model 4, adjusted as for model 3, additionally adjusted for neoadjuvant chemotherapy; Model 5, adjusted as for model 4, additionally adjusted for squamous cell carcinoma antigen, cancer antigen 125; Model 6, adjusted as for model 5, additionally adjusted for surgical margin and parametrial involvement; Model 7, Adjusted as for model 6, additionally adjusted for tumor size, lymph-vascular space invasion and deep stromal invasion. [b]First, second and third quartiles of LDH level (range, 98.4-683.0 U/l) were 143.6, 167.9 and 208.1 U/l, divided into Q1, Q2, Q3 and Q4 group. LDH, serum lactate dehydrogenase; LNM, lymph node metastasis; OR, odds ratio; Ref, reference.

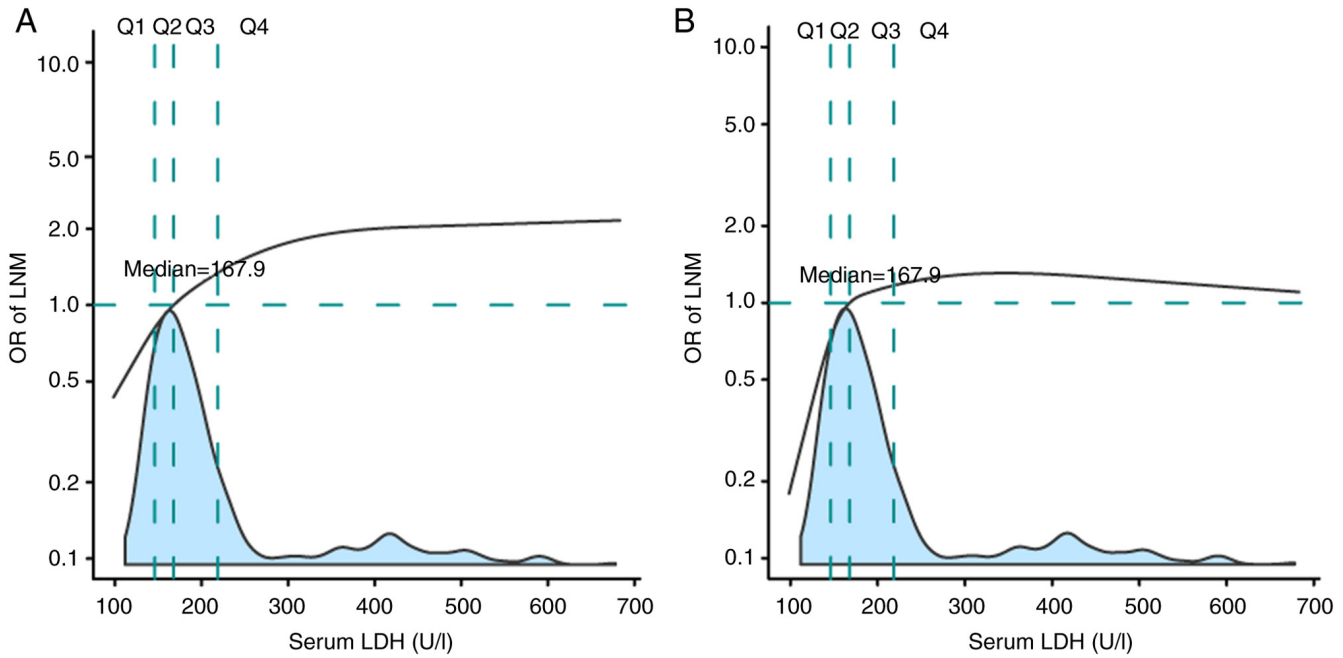


Figure 3. Effects of LDH level on LNM are modeled with a P-spline expansion. (A) no adjustment; (B) adjusted for age, International Federation of Gynecology and Obstetrics stage, neoadjuvant chemotherapy, squamous cell carcinoma antigen, cancer antigen 125, surgical margin and parametrial involvement, tumor size, lymph-vascular space invasion and deep stromal invasion. The first, second and third quartiles of LDH level (98.4-683.0 U/l) were 143.6, 167.9 and 208.1 U/l, divided into Q1, Q2, Q3 and Q4 group. LDH, serum lactate dehydrogenase; LNM, lymph node metastasis; OR, odds ratio.

Ca125 (3). Therefore, these confounders were adjusted in the present study.

In the present study, a positive association between LDH and LNM was consistently observed, independent of important covariates and confounders. One possible explanation could be because LDH is a ubiquitous cellular enzyme and comprises the rate-limiting step in converting pyruvate to lactic acid under anaerobic conditions (21). Hypoxia is a characteristic property of solid tumors owing to rapid cancer cell proliferation, high metabolic demands and functional angiogenesis (22). Therefore, elevated LDH levels indicate an aggressive phenotype, which is more prone to LNM. Secondly, higher LDH levels cause lactic acid accumulation due to anaerobic glycolysis, resulting in an acidic tumor microenvironment and promoting invasion and metastasis (23). Thirdly, vascular density is significantly higher in patients with elevated LDH levels, suggesting aggressive angiogenesis (24). Patients with increased LDH levels are more likely to have LNM, DSI and LVSI, as angiogenesis is essential for tumor proliferation and metastasis (12,13). Additionally, vascular density

is significantly associated with tumor VEGFA and VEGFR expression, and treatment with bevacizumab, an angiogenesis inhibitor, can significantly improve the prognosis, particularly in metastatic colorectal cancer with high LDH levels (25). Vascular density is significantly higher in patients with elevated LDH levels, suggesting aggressive angiogenesis (24). In cervical cancer with elevated LDH levels (25), it is worth noting that bevacizumab is recommended as a first-line treatment in the treatment guidelines for advanced cases (26). Hence, future attention can be directed towards assessing whether there could be more advantages in patients with high LDH levels.

A subgroup analysis was also conducted in the present study to investigate the association between LDH and LNM, which revealed a significant relationship between LDH and LNM in the FIGO IIA stage, age ≥45 years, SCC-Ag <1.5 ng/ml, Ca125 <35 ng/ml, LVSI positive, DSI ≥2/3, tumor size <2 cm, and squamous cell carcinoma. The possible explanation could firstly be due to the more advanced tumor stage, larger tumor size, more vascular invasion, high tumor burden, increased vascular density and tumor cell invasion into endothelial lymphatic vessels and/or blood vessels to form emboli that release tumor cells through lymphatic system and blood vessels (27). In high tumor burdens, elevated LDH levels indicate increased tumor glycolysis and hypoxia-induced tumor necrosis (28). Secondly, advanced age is a risk factor for different degrees of angiosclerosis and cardiovascular disease associated with hypoxia (29). Therefore, this might strengthen the link between LNM and LDH elevation.

A significant positive association was found between the two factors when a multivariable-adjusted restricted cubic spline was used to determine the association between LDH and the risk of LNM. The present study discovered a rapid rise in the risk of LNM with low LDH levels (LDH <167.9 U/l). Thereafter, the risk of LNM growth slowed and plateaued. If the cut-off point was set to 167.9 U/l, this was lower than previous studies (12,13), because one patient was operable earlier in the present study. Previous studies have reported heterogeneous cut-offs for LDH (12,13,30). A meta-analysis incorporating data from 68 studies included 31,857 patients with CC reported that high levels of LDH were associated with a poor prognosis in solid tumors, whereas variations in LDH cut-off do not affect its prognosis (30).

The present study had several limitations. First, it was a retrospective study, which might have led to selection bias. Second, five-year overall survival rate was high due to the short follow-up and early-stage tumor patients. Therefore, the link between LDH and LNM did not reflect the benefit of survival analysis. Finally, data regarding serial dynamic serum LDH levels are lacking.

In conclusion, results from the present study suggested that higher LDH levels were independently associated with CC and LNM. LDH values may serve as a potential tumor marker, and these convenient clinical indicators may be combined to guide the future personalized treatment of patients with CC.

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## Availability of data and materials

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

## Authors' contributions

XZ and SL conceptualized and designed the work. QH, SL and XC participated in the study design and wrote the manuscript. CH, YC, YH and YL performed data analyses.QH prepared the manuscript. YW contributed to the analysis of the data and critically revised the manuscript for important intellectual content. XZ and YW confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

## Ethics approval and consent to participate

The study was conducted in accordance with The Declaration of Helsinki and was approved by The Ethics Committee of the Fujian Maternity and Child Health Hospital, an Affiliated Hospital of Fujian Medical University (Fuzhou, China; approval no. SFY2022KYLLR1206). Informed consent was waived, considering the retrospective nature of the study.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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