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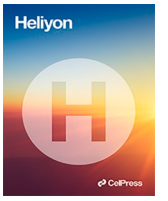

Association of serum tumor markers with serous effusion in systemic lupus erythematosus

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ABSTRACT

The objective of this study was to investigate the relationship between serum tumor markers and serous effusion in systemic lupus erythematosus (SLE) patients, thereby contributing preliminary data on the utility of these tumor markers in diagnosing serous effusion. In this retrospective analysis, clinical data of SLE patients were extracted from electronic medical records. This included the levels of serum tumor markers, including pro-gastrin-releasing peptide, neuron-specific enolase (NSE), cytokeratin-19 fragments (CYFRA 21-1), various carbohydrate antigens (CA 153, CA 125, CA 19-9), along with carcinoembryonic antigen, and alpha-fetoprotein. Positivity of tumor markers was established based on serum levels surpassing the upper threshold of the respective reference ranges. This study included 149 eligible patients with SLE, of whom 38 (25.50%) had serous effusion, and the prevalence of pleural, pericardial, and peritoneal effusions was 11.41%, 14.77%, and 6.71%, respectively. The analysis revealed that patients with serous effusion had higher scores on the SLE Disease Activity Index 2000 (SLEDAI 2000) than those without serous effusion. Notably, this disparity remained significant when the serositis score was excluded from the SLEDAI 2000 calculation. The positivity rate and serum levels of CA 125 were higher in patients with serous effusion and pleural effusion. Patients with pericardial effusion demonstrated an elevated CYFRA 21-1 positivity rate and serum CA 125 and CYFRA 21-1 levels compared to patients without pericardial effusion. CA 125 and NSE were higher both in terms of positivity rate and serum levels for patients with peritoneal effusion. Through receiver operating characteristic curve analysis, a moderate relationship was discerned between the conjoined levels of CYFRA 21-1 and CA 125 and the occurrence of pericardial effusion. Additionally, CA 125, NSE, and their combination revealed the moderate diagnostic ability of peritoneal effusion. In summary, this study observed elevated serum levels of various tumor markers in SLE patients exhibiting serous effusion, which is likely attributable to lupus-induced inflammation. These findings suggest that serum tumor markers can be valuable in diagnosing pericardial and peritoneal effusions.

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease frequently encountered and is associated with the formation of

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multiple autoantibodies. This leads to sustained and progressive inflammatory responses in several organs and tissues, including the nervous system, hematopoietic cells, lungs, kidneys, serous membranes, joints, and the skin [1]. A notable symptom contributing substantially to the morbidity observed in this disease is serous effusion, also termed lupus-associated serositis, which results from inflammation of the serous membranes induced by SLE [2]. Lupus-associated serositis, which encompasses conditions such as pleuritis and pericarditis but excludes peritonitis, is included as one of the criteria in the revised American College of Rheumatology (ACR-1997) classification for SLE [3] and is also included in the 2012 Systemic Lupus International Collaborating Clinics classification criteria (SLICC-2012) [4], as well as the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria (EULAR/ACR-2019) [5]. Additionally, the occurrence of hypoalbuminemia as a consequence of lupus nephritis represents another crucial risk factor in the onset of serous effusion.

Research has consistently indicated that many individuals with connective tissue disease (CTD) present with increased serum tumor marker levels, yet without the presence of accompanying neoplasms [6–9]. For instance, carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 15-3, CA 125, and CA 19-9 significantly elevated in the serum of patients with CTD-associated interstitial lung disease (ILD), and they also participate in the pathological process of ILD [10–12]. Likewise, Miret C et al. revealed significantly high serum CA 125 levels only in SLE patients with nephrotic syndrome, indicating an association between nephrotic syndrome and CA 125 [13]. Basaran et al. reported that elevated serum CA 125 levels in SLE patients with nephrotic syndrome were mainly due to the development of peritoneal effusion rather than the nephrotic syndrome itself [14]. However, no association has been demonstrated between serum tumor markers other than CA125 and serous effusion in patients with SLE by far.

Therefore, the objective of our study was to investigate the potential correlation between the occurrence of serous effusion in SLE patients and their serum tumor markers, aiming to contribute preliminary evidence on the diagnostic utility of these markers in the development of serous effusion.

2. Methods

2.1. Patient recruitment

This study, characterized as retrospective and cross-sectional in design, was undertaken in the Department of Rheumatology and Immunology at the Second Affiliated Hospital of Soochow University. Medical records were collected from patients hospitalized due to SLE who had been tested for at least one tumor marker in the timeframe spanning June 2013 to November 2022. All participants in the study met the criteria as outlined by either the EULAR/ACR-2019, SLICC-2012, or ACR-1997 guidelines. Exclusion criteria for patients with SLE in this study included: (1) a diagnosis of other autoimmune diseases, including but not limited to systemic sclerosis, inflammatory myopathy, and rheumatoid arthritis; (2) a pre-existing or concurrent tumor diagnosis within the study's reference period; (3) conditions potentially altering tumor marker levels, including amyloidosis, infectious diseases, and pregnancy.

This study adhered to the ethical standards set forth in the World Medical Association's Declaration of Helsinki. The research protocol received approval from the Human Ethics Review Committee of the Second Affiliated Hospital of Soochow University (Approval No. JD-HG-2023-27). Given the retrospective nature of the study, the requirement for informed consent from patients was waived by the aforementioned Ethics Committee.

2.2. Definition of serous effusion

Serous effusion in this study was defined as peritoneal, pericardial, and pleural effusion. However, serous effusion caused by other reasons (*e.g.*, heart failure, thromboembolism, or cirrhosis) was excluded. Ultrasound imaging and computed tomography served as the basis for confirming diagnoses of serous effusion.

2.3. Study variables

For all participants included in the study, the following variables were meticulously retrieved and systematically recorded: demographics; specific SLE clinical variables (fever, rash, alopecia, oral ulcers, arthritis, ILD, lupus nephritis, Raynaud phenomenon, pulmonary hypertension, and vasculitis); immunological variables (IgG, IgA, IgM, complement 4 [C4], C3, anti-nucleosome, anti-Ro52, anti-SSB, anti-Ro60, anti-histone, anti-ribosomal P protein, anti-U1RNP, anti-Smith, and anti–double-stranded DNA [anti-dsDNA]; laboratory variables (glutamic oxalate transaminase, glutamic pyruvate transaminase, serum albumin, blood urea nitrogen, serum creatinine, C-reactive protein, erythrocyte sedimentation rate [ESR], platelet count, hemoglobin, lymphocyte count, neutrophil count, and leukocyte count); and serum tumor markers (pro-gastrin-releasing peptide, neuron-specific enolase [NSE], cytokeratin-19 fragments [CYFRA 21-1], CA 15-3, CA 125, CA 19-9, CEA, and alpha-fetoprotein). The positivity of tumor markers was determined based on serum levels exceeding the upper boundaries of their respective reference values. In this study, leukopenia was identified when leukocyte counts were repeatedly under 3.5×10^9/L, thrombocytopenia with platelet counts less than 125×10^9/L on multiple occasions, and anemia as having hemoglobin levels consistently below 115 g/L. The study also involved the calculation of the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI 2000) score. Modified SLEDAI 2000 without serositis score (mSLEDAI 2000) was analyzed to exclude the effect of serositis itself on SLEDAI 2000.

2.4. Statistical analysis

In this analysis, categorical variables were expressed as both absolute frequencies and their relative percentages. The study also included an assessment of inter-group variations, which were evaluated using the Fisher's exact test or chi-square test as appropriate. Continuous variables with a skewed distribution were presented as median, 25th, and 75th percentiles (P_{25}, P_{75}) and were analyzed using the Mann–Whitney *U* test. To investigate the correlation between serous effusion and tumor markers, Spearman's rank correlation method was applied. In assessing the likelihood of tumor markers predicting serous effusion, logistic regression was employed. This model considered the incidence of serous effusion in SLE patients as the dependent variable, and used tumor markers—either individually or in significant combinations differentiating patients with and without serous effusion—as covariates. The discriminative potential of tumor marker levels in identifying serous effusion was investigated using receiver operating characteristic (ROC) curve analysis. The comparison of the area under the ROC curve (AUC) was performed by the z-test. Statistical analyses were performed using MedCalc version 20.217 (MedCalc Software Ltd, Ostend, Belgium), IBM Statistical Package for the Social Sciences for Windows version 25.0 (IBM Corp., Armonk, NY) and GraphPad Prism V.8.0.0 software (San Diego, California, USA). The significance level was set at $p < 0.05$.

3. Results

3.1. Characteristics of patients

In this study, 149 patients diagnosed with systemic lupus erythematosus (SLE) were deemed eligible, among whom 38 (25.50%) presented with serous effusion. This group included 10 cases of pleural effusion, 15 of pericardial effusion, 5 of peritoneal effusion, 3 with concurrent pleural and pericardial effusions, 1 with both pleural and peritoneal effusions, 1 with pericardial and peritoneal effusions, and 3 exhibiting pleural, pericardial, and peritoneal effusions. Therefore, the prevalence of pleural, pericardial, and peritoneal effusions in the patient with SLE cohort was 11.41% (17/149), 14.77% (22/149), and 6.71% (10/149), respectively.

There were no significant differences in patients with SLE with and without serous effusion in terms of age or sex distribution. Comparative analysis of laboratory findings and clinical characteristics between patients exhibiting serous effusion and those without is detailed in Supplementary Tables 1 and 2 The results indicated that albuminuria, hematuria, anemia, thrombocytopenia, and anti-ribosomal P protein positivity were significantly associated with serous effusion. Patients with SLE with serous effusion had higher blood urea nitrogen levels than patients with SLE without serous effusion, while patients with SLE with serous effusion had lower hemoglobin, C3, and serum albumin levels than those without serous effusion. Additionally, this research also explored the relationship between the activity of SLE and the incidence of serous effusion. Patients in the serous effusion group exhibited elevated levels of the SLEDAI 2000. This difference in SLEDAI 2000 scores between the two groups persisted as statistically significant even after the exclusion of the serositis score, as reflected in the modified SLEDAI 2000 (mSLEDAI 2000). In contrast, the assessment of laboratory findings and other clinical indicators yielded no significant distinctions between the groups.

3.2. Association between serum tumor markers and serous effusion

The CA 125 positivity rate was 18.42% and 5.41% in patients with SLE with and without serous effusion ($p = 0.034$), respectively.

Table 1
Differential assessment of the positivity rates and serum tumor marker levels in SLE patients, segmented into groups with and without serous effusion.

Variables	SLE with serous effusion		SLE without serous effusion		*p*
	Values	N	Values	N	
AFP, n (%)	0 (0.00)	38	0 (0.00)	111	NA
CEA, n (%)	0 (0.00)	38	1 (0.90)	111	1.000
CA 19-9, n (%)	3 (7.89)	38	9 (8.11)	111	1.000
CA 125, n (%)	7 (18.42)	38	6 (5.41)	111	0.034
CA 15-3, n (%)	1 (2.86)	35	3 (3.06)	98	1.000
CYFRA 21-1, n (%)	11 (28.95)	38	18 (16.36)	110	0.092
NSE, n (%)	5 (13.16)	38	6 (5.45)	110	0.229
ProGRP, n (%)	1 (2.63)	38	6 (5.50)	109	0.784
AFP (ng/mL)	1.85 (1.15, 2.81)	38	2.13 (1.53, 2.65)	111	0.273
CEA (ng/mL)	1.16 (0.69, 2.20)	38	1.13 (0.85, 1.88)	111	0.812
CA 19-9 (U/mL)	9.07 (4.21, 16.82)	38	8.30 (5.49, 15.61)	111	0.970
CA 125 (U/mL)	18.17 (12.02, 29.96)	38	12.40 (9.24, 18.55)	111	0.001
CA 15-3 (U/mL)	11.80 (7.22, 16.27)	35	9.54 (7.08, 14.58)	98	0.391
CYFRA 21-1 (ng/mL)	2.29 (1.69, 3.50)	38	2.00 (1.50, 2.77)	110	0.142
NSE (ng/mL)	10.37 (8.38, 14.59)	38	9.96 (8.81, 11.69)	110	0.272
ProGRP (pg/mL)	27.95 (19.13, 39.76)	38	25.70 (19.11, 36.75)	109	0.910

Median values are used throughout, except in cases where alternative measures are explicitly indicated (P_{25}, P_{75}).
SLE systemic lupus erythematosus; *ProGRP* pro-gastrin-releasing peptide. *NSE* neuron-specific enolase; *NA* not applicable; *CYFRA 21-1* cytokeratin 19-fragments; *CEA* carcinoembryonic antigen; *CA* carbohydrate antigen; *AFP* Alpha-fetoprotein.

Elevated CA 125 levels were observed in patients presenting with serous effusion compared to those without serous effusion, as detailed in Table 1. However, no significant differences were found in other tumor markers.

Only the positive rate and serum levels of CA 125 showed a statistical difference in terms of tumor markers between patients with and without pleural effusion (Table 2). Patients with pericardial effusion demonstrated an elevated positivity rate of CYFRA 21-1 and increased serum CA 125 and CYFRA 21-1 levels compared to patients without pericardial effusion (Table 3). CA 125 and NSE were higher both in terms of positivity rate and serum levels for patients with peritoneal effusion (Table 4).

Spearman's analysis further confirmed the above analysis, but the correlation coefficients were all in the range of 0.200–0.300, indicating a low correlation level (Supplementary Table 3).

3.3. Predictive probability of tumor markers for serous effusion

Utilizing logistic regression, the predictive probability of tumor markers for serous effusion was determined, drawing upon the univariate analysis detailed in Table 5. Only NSE ($p = 0.004$, odds ratio [OR] = 1.195, 95% confidence interval [CI] = 1.058–1.351) was significantly associated with peritoneal effusion in terms of the serum tumor marker levels. However, all tumor markers that differed between the two groups in the above analysis can predict the presence of the corresponding effusion for the positivity rate. CA 125 positivity was a risk factor for serous effusion ($p = 0.020$, OR = 3.952, 95% CI = 1.237–12.627) and pleural effusion ($p = 0.004$, OR = 6.458, 95% CI = 1.823–22.877). CYFRA 21-1 positivity ($p = 0.002$, OR = 4.693, 95% CI = 1.778–12.389) was significantly associated with pericardial effusion. For peritoneal effusion, CA 125 and NSE positivities were simultaneously included in the regression model, and the results revealed that both (for CA 125, $p = 0.018$, OR = 6.942, 95% CI = 1.399–34.451; for NSE, $p = 0.012$, OR = 7.847, 95% CI = 1.560–39.456) were risk factors for peritoneal effusion.

3.4. The diagnostic significance of serum tumor marker levels in serous effusion

To evaluate the diagnostic utility of serum tumor marker levels in serous effusion, including CA 125, CYFRA 21-1, and NSE, a ROC assessment was carried out (Fig. 1). The AUC of CA 125 for serous and pleural effusion diagnoses were 0.673 (95% CI = 0.576–0.770) and 0.695 (95% CI = 0.553–0.837), respectively. CA 125 (AUC = 0.670, 95% CI = 0.554–0.786) and CYFRA 21-1 (AUC = 0.692, 95% CI = 0.565–0.819) had similar diagnostic values for pericardial effusion ($p = 0.820$), and the combination of both (AUC = 0.723, 95% CI = 0.601–0.845) increased the AUC, however this did not achieve statistical significance when compared with the individual variables. CA 125 (AUC = 0.771, 95% CI = 0.645–0.897) and NSE (AUC = 0.760, 95% CI = 0.581–0.938) revealed better diagnostic values for peritoneal effusion, and the combination of both increased the AUC to 0.838 (95% CI = 0.742–0.934), although it did not reach statistical difference.

4. Discussion

Serositis, a well-documented clinical feature of SLE and an integral part of its classification criteria and disease activity assessment [3–5,15], has only recently become the focus of detailed studies. These studies primarily investigate its prevalence, associated risk factors, and prognostic implications [16–18]. The scope of our investigation includes an in-depth examination of the broader

Table 2
Differential assessment of the positivity rates and serum tumor marker levels in SLE patients, segmented into groups with and without pleural effusion.

Variables	SLE with pleural effusion		SLE without pleural effusion		*p*
	Values	N	Values	N	
AFP, n (%)	0 (0.00)	17	0 (0.00)	132	NA
CEA, n (%)	0 (0.00)	17	1 (0.76)	132	1.000
CA 19-9, n (%)	2 (11.76)	17	10 (7.58)	132	0.901
CA 125, n (%)	5 (29.41)	17	8 (6.06)	132	0.006
CA 15-3, n (%)	1 (6.67)	15	3 (2.54)	118	0.384
CYFRA 21-1, n (%)	2 (11.76)	17	27 (20.61)	131	0.589
NSE, n (%)	2 (11.76)	17	9 (6.87)	131	0.816
ProGRP, n (%)	1 (5.88)	17	6 (4.62)	130	0.585
AFP (ng/mL)	1.88 (1.12, 2.66)	17	2.06 (1.46, 2.66)	132	0.583
CEA (ng/mL)	1.14 (0.81, 2.00)	17	1.15 (0.83, 1.93)	132	0.969
CA 19-9 (U/mL)	9.01 (3.78, 21.19)	17	8.45 (5.05, 14.94)	132	0.770
CA 125 (U/mL)	23.71 (12.73, 41.20)	17	13.37 (9.33, 18.88)	132	0.009
CA 15-3 (U/mL)	11.80 (9.08, 16.27)	15	9.54 (6.92, 15.10)	118	0.192
CYFRA 21-1 (ng/mL)	2.00 (1.68, 2.47)	17	2.13 (1.54, 2.91)	131	0.969
NSE (ng/mL)	9.99 (8.86, 16.08)	17	10.10 (8.75, 11.81)	131	0.528
ProGRP (pg/mL)	24.93 (18.64, 40.70)	17	26.57 (19.27, 38.39)	130	0.721

Median values are used throughout, except in cases where alternative measures are explicitly indicated (P_{25}, P_{75}).
SLE systemic lupus erythematosus; *ProGRP* pro-gastrin-releasing peptide; *NSE* neuron-specific enolase; *NA* not applicable; *CYFRA 21-1* cytokeratin 19-fragments; *CEA* carcinoembryonic antigen; *CA* carbohydrate antigen;*AFP* Alpha-fetoprotein.

Table 3
Differential assessment of the positivity rates and serum tumor marker levels in SLE patients, segmented into groups with and without pericardial effusion.

Variables	SLE with pericardial effusion		SLE without pericardial effusion		*p*
	Values	N	Values	N	
AFP, n (%)	0 (0.00)	22	0 (0.00)	127	NA
CEA, n (%)	0 (0.00)	22	1 (0.79)	127	1.000
CA 19-9, n (%)	3 (13.64)	22	9 (7.09)	127	0.537
CA 125, n (%)	3 (13.64)	22	10 (7.87)	127	0.635
CA 15-3, n (%)	1 (5.00)	20	3 (2.65)	113	0.483
CYFRA 21-1, n (%)	10 (45.45)	22	19 (15.08)	126	0.003
NSE, n (%)	2 (9.09)	22	9 (7.14)	126	1.000
ProGRP, n (%)	1 (4.55)	22	6 (4.80)	125	1.000
AFP (ng/mL)	1.85 (1.26, 2.84)	22	2.07 (1.46, 2.60)	127	0.902
CEA (ng/mL)	1.28 (0.91, 2.59)	22	1.12 (0.81, 1.86)	127	0.101
CA 19-9 (U/mL)	9.17 (4.21, 20.50)	22	8.32 (5.24, 15.28)	127	0.581
CA 125 (U/mL)	18.42 (13.15, 29.96)	22	13.25 (9.32, 18.97)	127	0.011
CA 15-3 (U/mL)	12.83 (9.09, 17.31)	20	9.45 (7.06, 14.10)	113	0.098
CYFRA 21-1 (ng/mL)	2.82 (1.91, 4.14)	22	1.99 (1.50, 2.66)	126	0.004
NSE (ng/mL)	9.99 (7.98, 12.53)	22	10.14 (8.92, 11.91)	126	0.670
ProGRP (pg/mL)	36.04 (19.88, 40.33)	22	25.10 (19.10, 35.63)	125	0.173

Median values are used throughout, except in cases where alternative measures are explicitly indicated (P_{25}, P_{75}).
SLE systemic lupus erythematosus; *ProGRP* pro-gastrin-releasing peptide. *NSE* neuron-specific enolase; *NA* not applicable; *CYFRA 21-1* cytokeratin 19-fragments; *CEA* carcinoembryonic antigen; *CA* carbohydrate antigen; *AFP* Alpha-fetoprotein.

Table 4
Differential assessment of the positivity rates and serum tumor marker levels in SLE patients, segmented into groups with and without peritoneal effusion.

Variables	SLE with peritoneal effusion		SLE without peritoneal effusion		*p*
	Values	N	Values	N	
AFP, n (%)	0 (0.00)	10	0 (0.00)	139	NA
CEA, n (%)	0 (0.00)	10	1 (0.72)	139	1.000
CA 19-9, n (%)	1 (10.00)	10	11 (7.91)	139	0.580
CA 125, n (%)	3 (30.00)	10	10 (7.19)	139	0.044
CA 15-3, n (%)	1 (11.11)	9	3 (2.42)	124	0.247
CYFRA 21-1, n (%)	4 (40.00)	10	25 (18.12)	138	0.204
NSE, n (%)	3 (30.00)	10	8 (5.80)	138	0.028
ProGRP, n (%)	1 (10.00)	10	6 (4.38)	137	0.396
AFP (ng/mL)	2.01 (0.90, 2.91)	10	2.03 (1.46, 2.65)	139	0.663
CEA (ng/mL)	1.79 (0.38, 2.94)	10	1.13 (0.84, 1.88)	139	0.719
CA 19-9 (U/mL)	11.00 (5.57, 20.50)	10	8.30 (4.80, 15.69)	139	0.459
CA 125 (U/mL)	24.35 (14.67, 49.00)	10	13.44 (9.35, 18.97)	139	0.004
CA 15-3 (U/mL)	10.76 (6.40, 16.90)	9	9.92 (7.13, 15.10)	124	0.918
CYFRA 21-1 (ng/mL)	2.28 (1.55, 4.73)	10	2.03 (1.55, 2.80)	138	0.361
NSE (ng/mL)	13.42 (10.70, 19.19)	10	9.98 (8.63, 11.59)	138	0.006
ProGRP (pg/mL)	20.67 (17.05, 42.38)	10	27.11 (19.65, 37.98)	137	0.698

Except where indicated otherwise, values are median (P_{25}, P_{75}).
SLE systemic lupus erythematosus*; ProGRP* pro-gastrin-releasing peptide; *NSE* neuron-specific enolase; *NA* not applicable; *CYFRA 21-1* cytokeratin 19-fragments; *CEA* carcinoembryonic antigen; *CA* carbohydrate antigen; *AFP* Alpha-fetoprotein.

Table 5
Logistic regression analysis of predictive probability of tumor markers for serous effusion in SLE.

Serum tumor markers	Dependent variable	Odds ratio	95% confidence interval	*p*
CA 125 positivity	Serous effusion	3.952	1.237, 12.627	0.020
CA 125 positivity	Pleural effusion	6.458	1.823, 22.877	0.004
CYFRA 21-1 positivity	Pericardial effusion	4.693	1.778, 12.389	0.002
CA 125 positivity	Peritoneal effusion	6.942	1.399, 34.451	0.018
NSE positivity		7.847	1.560, 39.456	0.012
NSE levels	Peritoneal effusion	1.195	1.058, 1.351	0.004

CA carbohydrate antigen; *CYFRA 21-1* cytokeratin 19-fragments; *NSE* neuron-specific enolase; *SLE* systemic lupus erythematosus.

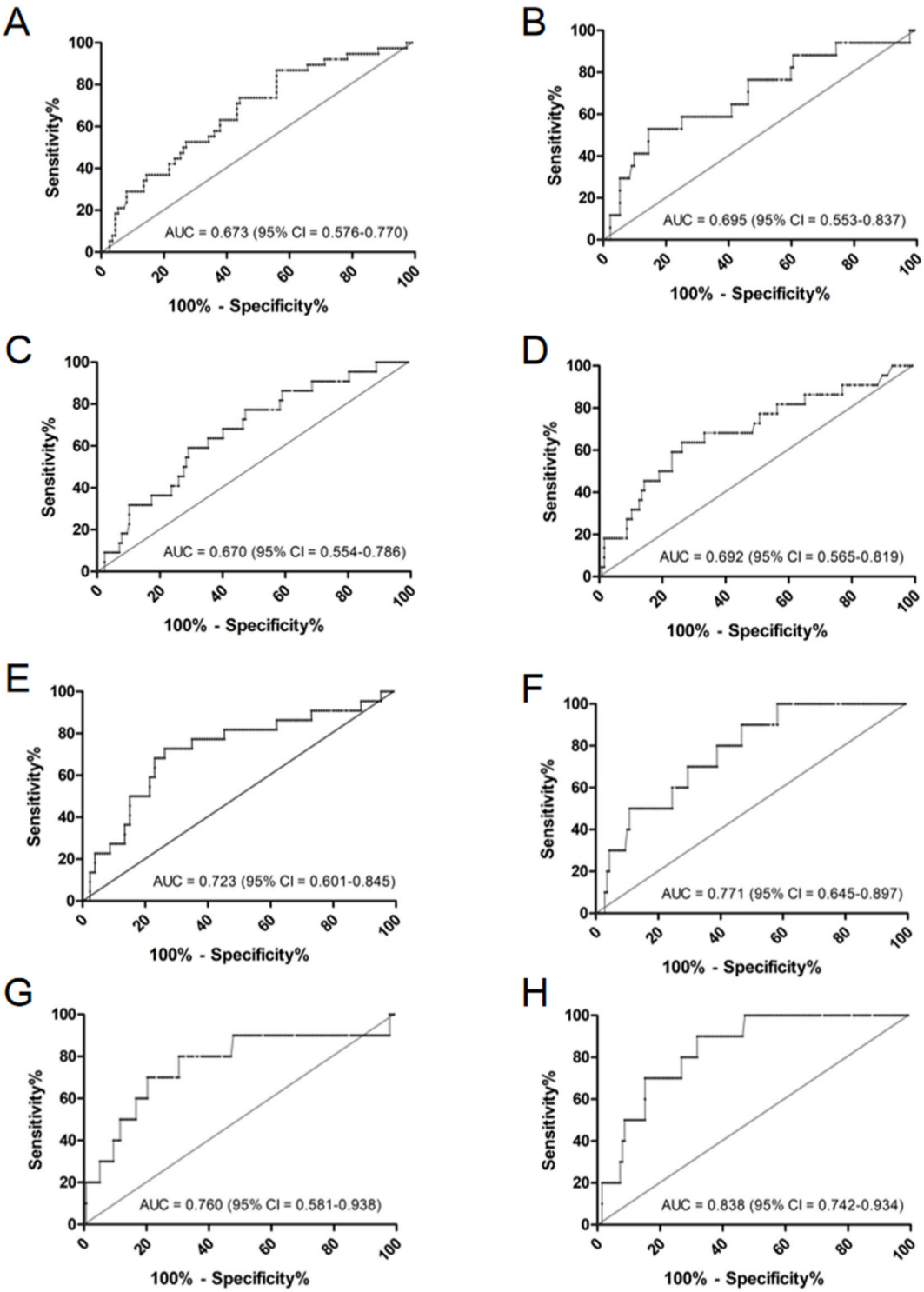

Fig. 1. Receiver operating characteristics (ROC) curves for CA 125 for discriminating between patients with and without serous effusion (A), and between patients with and without pleural effusion (B). ROC curves for CA 125 (C), CYFRA 21-1 (D), and the combination of both (E) for discriminating between patients with and without pericardial effusion. ROC curves for CA 125 (F), NSE (G), and the combination of both (H) for discriminating between patients with and without peritoneal effusion.

connection of serositis in SLE patients to serum tumor markers.

This study enrolled SLE patients with at least one serum tumor marker tested, and the serous effusion was defined to include pleural, pericardial, and peritoneal effusions, excluding other causes of effusion, such as infection, cirrhosis, and heart failure, but not patients with hypoalbuminemia secondary to lupus nephritis. Lupus nephritis-induced hypoalbuminemia can result in transudatory serous effusion, while several studies revealed that lupus-induced serositis is significantly associated with lupus nephritis [16,17]. Thus, both types of effusions can be mixed in patients with hypoalbuminemia secondary to lupus nephritis, and with some difficulty in clinical differentiation. The median serum albumin level of patients in the serous effusion group in this study was 32.50 g/L, which was mildly reduced, and with a transudative factor in the development of serous effusion in some patients, but the effect of this factor should not be significant. Therefore, the presence of serous effusion in this study should be mainly due to SLE itself.

The incidence of serositis in SLE manifests significant worldwide variability, attributable to racial differences, study methodologies, and the criteria for inclusion. A recent Spanish study disclosed that serositis was diagnosed in 9.43% of the examined patient cohort [18]. The incidence of serositis caused by lupus in Hong Kong has been documented to be 12% [2]. Data from the Chinese SLE Treatment and Research group revealed that 16.40% of 2104 patients with SLE had serositis (excluding peritonitis), which was significantly associated with lupus nephritis, ILD, pulmonary hypertension, leukocytopenia, thrombocytopenia, hypocomplementemia, anti-dsDNA, and active disease [16]. Additionally, 3.99% of patients presented with lupus-induced peritonitis, with similar clinical manifestations and laboratory parameters as serositis [16]. Another study reported that 17.87% of patients with SLE with pleuritis and/or pericarditis showed a close connection to fever, lupus nephritis, thrombocytopenia, anti-Smith, active disease, fibrinogen, D-dimer, high ESR, low C4, low C3, and anti-dsDNA [17]. The prevalence of serous, pleural, pericardial, and peritoneal effusions in the present study was 25.50%, 11.41%, 14.77%, and 6.71%, respectively, which were slightly higher than in the above-mentioned studies, probably due to the patient enrollment criteria. Additionally, the present study revealed a significant association between the presence of albuminuria, hematuria, anemia, thrombocytopenia, and anti-ribosomal P protein positivity and serous effusion, and patients with SLE with serous effusion had higher blood urea nitrogen levels and lower hemoglobin, C3, and serum albumin levels. Moreover, patients with serous effusion presented higher SLEDAI 2000 scores, and the difference remained significant after excluding the serositis score from the SLEDAI 2000. Therefore, the presence of serositis is often indicative of disease activity in patients with SLE, suggesting a more pronounced state of inflammation and immune disorder.

Tumor markers, traditionally understood to be biological entities originating from tumor cells or related cells, have also been found to be products of inflammatory cells, with their expression influenced by inflammatory conditions. This suggests a possible involvement of tumor markers in the sustained presence of inflammation [9,10]. CA 125, a glycoprotein with high molecular weight, is expressed not solely in epithelial ovarian and endometrial adenocarcinomas but also in normal tissues including fallopian tubes, endometrium, endocervical lining, as well as in lung, breast, conjunctiva, and prostate tissues [19,20]. Mesothelial cells that line the pleura, pericardium, and peritoneum also express CA 125, and its expression is particularly high in inflammation and adhesion areas [19,20]. As a segment of cytokeratin-19, CYFRA 21-1 is associated with structural proteins within the intermediate filament proteins, playing a vital role in the stabilization of epithelial cells [21]. In patients with idiopathic pulmonary fibrosis, CYFRA 21-1 concentrations in bronchoalveolar lavage fluid were significantly elevated, exhibiting a notable correlation with the count of neutrophils and eosinophils [22]. NSE, which is an isozyme of glycolytic enzymes, is considered as a multifunctional protein [23]. Beyond its linkage to cancer, alterations in the cellular localization and varied expression of Neuron-Specific Enolase (NSE) have been linked to a range of pathologies, including infections, inflammatory conditions, and autoimmune diseases [23,24]. Patients with Crohn's disease have higher serum NSE levels than healthy individuals, and serum NSE levels are higher in Crohn's disease patients experiencing severe inflammation than in those with moderate or mild inflammatory symptoms [25]. In patients with chronic rhinosinusitis, serum and nasal secretion levels of NSE were significantly higher compared to healthy controls, and NSE levels were significantly higher in patients with chronic rhinosinusitis with nasal polyps than those without nasal polyps [26].

The present study revealed higher serum CA 125 levels in all types of serous effusion, higher serum CYFRA 21-1 levels in pericardial effusion, and higher serum NSE levels in peritoneal effusion, which was consistent with higher inflammation levels in patients with SLE with serositis. Therefore, the speculation of Basaran et al. that the development of ascites secondary to protein loss is the primary cause of elevated serum CA 125 in patients with SLE with nephrotic syndrome rather than the nephrotic syndrome itself is partially correct based on our study results [14]. The elevation of tumor markers, including CA 125, should be primarily related to inflammation induced by lupus and may be partly due to hypoalbuminemia.

The logistic regression analysis revealed that serum CA 19-9 levels were associated with ILD in rheumatoid arthritis [27]. For individuals diagnosed with primary Sjogren's Syndrome (pSS), those exhibiting higher serum CA 153 and CEA levels are observed to have roughly quadruple and triple the risk of developing ILD, respectively [10]. In this study, only NSE was significantly associated with peritoneal effusion in terms of the serum levels; however, CA 125 positivity had approximately four-fold and six-fold risks of serous and pleural effusions, respectively; CYFRA 21-1 positivity had approximately five-fold risk of pericardial effusion; and CA 125 and NSE positivities have approximately seven-fold and eight-fold risks of peritoneal effusion, respectively. In clinical practice, serologic positives are easier to identify relative to higher serologic levels. Therefore, patients with positivities for these tumor markers should be evaluated for corresponding plasma membrane cavities to clarify the occurrence of effusion.

To evaluate the discriminatory capability of tumor marker levels in distinguishing serous effusion, the present study employed ROC curve analysis. Findings from the study indicated that serum levels of a single tumor marker were of limited value in diagnosing serous, pleural, and pericardial effusions. However, the combined use of CA 125 and CYFRA 21-1 enhanced the diagnostic accuracy for pericardial effusion, as evidenced by an AUC of 0.723 and a 95% CI ranging from 0.601 to 0.845. CA 125, NSE, and the combination of both revealed moderate diagnostic ability for peritoneal effusion, especially the combination of both with an AUC of >0.8. In rheumatoid arthritis, ROC curve analysis revealed a moderate relationship between serum CA 125 levels and ILD (AUC = 0.78, 95% CI =

0.68–0.88) [28]. For the diagnosis of ILD in patients with pSS, CA15-3 emerged as the sole tumor marker demonstrating an AUC exceeding 0.7, specifically recording an AUC of 0.743 with a 95% CI ranging from 0.70 to 0.79 [10]. Therefore, serum tumour markers are of value in the diagnosis of pericardial effusion, peritoneal effusion and ILD associated with CTD, but their potential role should be further evaluated.

Unlike previous studies on serous effusion associated with SLE, the present study focused on serum tumour markers in patients with SLE with serous effusion, and excluded other factors that can affect tumour marker levels, such as infection, pregnancy and other CTD. Moreover, all diagnoses of serous effusion were confirmed by computed tomography or ultrasound in the present study. However, several limitations of the study must be acknowledged. Initially, the retrospective design of our study precluded the analysis of a causal relationship between tumor markers and the development of serous effusion in Systemic Lupus Erythematosus (SLE) patients. Second, the relatively small size of this cohort may introduce a bias factor. Third, the effect of therapeutic factors on tumor markers was not considered, which may affect the results' accuracy.

Conclusively, there is an elevation in serum tumor marker levels among Systemic Lupus Erythematosus patients with serous effusion, which is probably predominantly associated with lupus-induced inflammation. These tumor markers are also valuable in diagnosing pericardial and peritoneal effusions. In the future, a few large-scale experiments are needed to confirm these findings.

Ethics approval and informed consent

In alignment with the guidelines of the World Medical Association's Declaration of Helsinki, this study was sanctioned by the Human Ethics Review Committee of the Second Affiliated Hospital of Soochow University, bearing the approval number JD-HG-2023-27. The requirement for informed consent from patients was waived, as sanctioned by the Human Ethics Review Committee, given that the study utilized pre-existing medical records of the participants.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Ying Zhong: Formal analysis, Investigation, Software, Visualization, Writing – original draft. **Jinlu Ma:** Formal analysis, Investigation, Software, Visualization, Writing – original draft. **Lin Zhang:** Formal analysis, Software. **Zhichun Liu:** Conceptualization, Supervision. **Leixi Xue:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23213.

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