Additional diagnostic value of the monocyte to red blood cell count ratio and the product of lymphocyte count and albumin concentration in lung cancer management

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Abstract. The present study aimed to evaluate the potential of the monocyte to red blood cell count ratio (MRR), the neutrophil to red blood cell count ratio (NRR), the lymphocyte to red blood cell count ratio (LRR) and the product of lymphocyte count and albumin concentration (LA) for the diagnosis of lung cancer. The cases of 216 patients with newly diagnosed lung cancer and 184 healthy volunteers were retrospectively analysed. The MRR and NRR were found to be higher in patients with lung cancer compared with those in healthy controls, while the LRR and LA were lower. The receiver operating characteristic curve analysis revealed that of the four markers, the MRR and LA yielded a higher area under the curve (AUC) (MRR: AUC, 0.810; 95% CI, 0.768-0.847; and LA: AUC, 0.721; 95% CI, 0.674-0.764). The combination of MRR, LA, carcinoembryonic antigen (CEA) and cytokeratin 19 fragment antigen 21-1 (CYFRA21-1) achieved the highest diagnostic value when compared with other single or combined markers (AUC, 0.882; 95% CI, 0.846-0.912; sensitivity, 81.9%; specificity, 81.0%). As the disease progressed, the MRR tended to increase, while LA exhibited a decreasing trend. Binary logistic regression analysis revealed an increase in the MRR, as well as in CEA and CYFRA21-1 concentrations, and a decrease in the LA, which could all be possible risk factors for lung cancer. Differences in the MRR and LA between patients with early stage (IA-IIIA) lung cancer and healthy controls were observed. Further analysis revealed that the MRR also exhibited the potential to detect early stage (IA-IIIA) lung cancer in the model. The present findings demonstrated that the MRR and LA may be used as auxiliary biomarkers for the diagnosis of lung cancer and could partly indicate disease progression.

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Introduction

Lung cancer is the leading cause of cancer-associated mortality worldwide (1). In 2022, lung cancer is expected to be the most common cause of death in both men and women in China (2). Despite precision medicine having brought novel therapy options and hope to patients with lung cancer, an early diagnosis is still most important for the prognosis of these patients. In recent years, low-dose computed tomography (LDCT) has been used in the early screening for lung cancer, and it has been demonstrated that this could reduce the mortality rate from lung cancer. However, accompanying radiation, misjudgment of lung lesions and further excluded examinations pose challenges to the success and cost-effectiveness of lung cancer screening with LDCT (3). Pathological examinations are also limited by their invasiveness and false-negative results. Therefore, easy to sample, lower cost and more effective biomarkers are urgently required for clinical practice.

Inflammation and immunity impact important steps of tumourigenesis (4). Various types of immune and inflammatory cells are frequently present within tumours; however, they are more easily captured in the peripheral blood (4). Numerous studies have demonstrated that haematological biomarkers, including the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) and platelet-to-lymphocyte ratio (PLR), exhibit prognostic value in malignancies such as lung and colorectal cancer (5-7). High NLR, PLR and MLR values prior to oncotherapy are associated with an unfavourable prognosis of the disease (8,9). The nutritional status of patients with cancer can reflect energy metabolism and indicate disease severity, disease progression and prognosis (10); this can be assessed by several blood biochemical, including serum albumin (11). As one of the negative acute phase proteins, serum albumin could also reflect the inflammatory state (12). Some markers that combine albumin with other hematological indexes, including the prognostic nutritional index, the albumin-to-alkaline phosphatase ratio and the C-reactive protein-to-albumin ratio, exhibit predictive values in the survival prognosis of patients with lung cancer (6,13,14).

Although these markers are considered to be useful in tracking and assessing the severity and prognosis of lung cancer, their utility for early diagnosis and timely treatment is barely satisfactory.

Novel markers have been explored, identified and applied to the disease diagnosis and prognostic evaluation. Monocytes, neutrophils and lymphocytes are part of the body's immune system. The peripheral absolute cell count of these immune cells might vary for each individual. Recently, the red blood cell count was introduced into the individualized evaluation of the peripheral immune response intensity (15). It has been demonstrated that markers such as the monocyte to red blood cell count ratio (MRR), the neutrophil to red blood cell count ratio (NRR) and the lymphocyte to red blood cell count ratio (LRR) could well reflect the intensity of circulating immune cells, including monocytes, neutrophils and lymphocytes (15). The product of lymphocyte count and albumin concentration (LA) has been reported as a potential novel prognostic biomarker for stage II/III rectal cancer (16). The present study aimed to explore the additional diagnostic value of these markers in the diagnosis of lung cancer, including in the early stages.

Materials and methods

Participants. In accordance with the following inclusion and exclusion criteria, a total of 216 patients newly diagnosed with lung cancer at the Affiliated Hospital of Jiangsu University (Zhenjiang, China) between June 2014 and June 2021 were selected, including 178 patients with non-small cell lung cancer (NSCLC) and 38 patients with SCLC. Additionally, 184 healthy volunteers who underwent a physical examination were selected as negative controls. The median age was 61 years (range, 48-78 years) for patients with lung cancer and 58 years (range, 47-80 years) for the healthy controls. All patients with lung cancer were newly diagnosed and previously untreated. These cases were confirmed using lung tissue biopsy, lymph node biopsy or pleural effusion cytology. On this basis, chest and abdominal enhanced or non-enhanced CT or total-body positron emission tomography/CT, brain magnetic resonance imaging and bone scans were further performed for the assessment of disease severity. Staging was performed according to the 8th Edition of the International Union Against Cancer Lung Cancer Tumor-Node-Metastasis staging criteria (17). The exclusion criteria for the patients with lung cancer were as follows: i) Acute and chronic infectious diseases; ii) hepatic diseases; iii) autoimmune diseases; iv) haematological diseases; v) diabetes; vi) history of malignant tumours; and vii) incomplete, inaccessible or obviously abnormal clinical and laboratory data. All cases were further classified into early (stage IA-IIIA) and advanced (stage IIIB-IV) according to the benefit from resectable and potentially resectable surgery (18-20). Healthy individuals were excluded if they had acute and chronic infectious diseases, vital organ diseases, a genetic family history of tumours, inaccessible or obviously abnormal blood tests, or any suspicious lesions found on chest CT scan. The present study was approved by the Ethics Committee of the Affiliated Hospital of Jiangsu University. Oral informed consent was obtained from all participants included in this retrospective study.

Laboratory assays. Baseline and clinical characteristics, as well as laboratory measurements of each eligible individual, were obtained from the electronic medical record system of the Affiliated Hospital of Jiangsu University. The latest peripheral blood samples were collected from patients with an empty stomach in the early morning before diagnosis and any treatment, with a time span of no more than 1 week between the two. Routine blood tests were performed using a SYSMEX XN3000 automated haematology analyzer (Sysmex Corporation). Serum albumin was detected using a BEKMAN AU5800 automatic biochemical analyzer (Beckman Coulter, Inc.). The serum carcinoembryonic antigen (CEA) and cytokeratin 19 fragment antigen 21-1 (CYFRA21-1) levels were determined using the ABBOTT ARCHITECT i2000sr (Abbott Pharmaceutical Co., Ltd.) and MAGLUMI X8 Analyzer (Shenzhen New Industry Biological Engineering Co., Ltd.), respectively, using a chemiluminescence immunoassay with kits from the corresponding manufacturer (cat. no. 7K68-78; cat. no. 130201013M). The normal range of all indicators was recorded according to the manufacturer's instructions. The MRR, NRR, LRR and LA of each group were calculated as follows: MRR was defined as the monocyte count ($x10^9$/l) to red blood cell count ($x10^{12}$/l) ratio, NRR was defined as the neutrophil count ($x10^9$/l) to red blood cell count ($x10^{12}$/l) ratio, LRR was defined as the lymphocyte count ($x10^9$/l) to red blood cell count ($x10^{12}$/l) ratio, and LA was defined as the product of the lymphocyte count ($x10^9$/l) and albumin concentration (g/l).

Statistical analysis. All data were analysed using IBM SPSS Statistics 22.0 (IBM Corp.), MedCalc 20.1.0. (MedCalc Software bvba) and GraphPad Prism 8.0 (GraphPad Software, Inc.). The Kolmogorov-Smirnov test was used to evaluate the distribution characteristics of the data. The continuous variables are presented as the mean ± (SD) or median (interquartile range). Age is presented as the median and range. Differences between two groups were analysed using the unpaired Student's t-test or Mann-Whitney U test. Comparisons of multiple groups were performed using Kruskal-Wallis H test with Bonferroni's correction for multiple post hoc comparisons. Categorical variables are presented as the number and percentage, and were compared using the χ^2 test. Receiver operating characteristic (ROC) curves were used to evaluate the diagnostic value of markers alone or in combination for lung cancer. The area under the curve (AUC) values of the markers were compared using the Z test. Binary logistic regression analysis was applied for the analysis of the risk factors of lung cancer. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression. Spearman's correlation analysis was used to assess correlations between peripheral lymphocyte count and serum albumin concentration. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Demographic, clinical and laboratory characteristics of all participants. A total of 216 patients with newly diagnosed lung cancer and 184 healthy volunteers were included in the present study. The former group included 148 patients with adenocarcinoma, 30 patients with squamous cell carcinoma and 38 patients with SCLC. Among these patients, 60.2% were

Table I. Clinical baseline characteristics of patients with lung cancer and healthy participants.

Variables	Normal range	Patients with lung cancer (n=216)	Healthy participants (n=184)	P-value
Median age (range), years	-	61 (48-78)	58 (47-80)	0.060
Sex, n (%)				0.543
Male	-	125 (57.9)	112 (60.9)	
Female	-	91 (42.1)	72 (39.1)	
Histopathological subtype, n (%)				
AC	-	148 (68.5)	-	-
SCC	-	30 (13.9)	-	-
SCLC	-	38 (17.6)	-	-
Invasion depth, n (%)				
T1+T2	-	149 (69.0)	-	-
T3+T4	-	67 (31.0)	-	-
Lymph node metastasis, n (%)				
N0	-	111 (51.4)	-	-
N1+N2+N3	-	105 (48.6)	-	-
Distant metastasis, n (%)				
M0	-	154 (71.3)	-	-
M1	-	62 (28.7)	-	-
Clinical stage, n (%)				
IA-IIIA	-	130 (60.2)	-	-
IIIB-IV	-	86 (39.8)	-	-
Laboratory parameters [median (IQR)]				
WBC ($x10^9$/l)	3.5-9.5	6.3 (5.1-7.5)	5.6 (4.7-6.4)	<0.001
RBC ($x10^{12}$/l)	4.3-5.8	4.4±0.5	4.7±0.4	<0.001
Neutrophils ($x10^9$/l)	1.8-6.3	3.9 (3.0-4.9)	3.1 (2.6-4.0)	<0.001
Monocytes ($x10^9$/l)	0.1-0.6	0.5 (0.4-0.6)	0.3 (0.3-0.4)	<0.001
Lymphocytes ($x10^9$/l)	1.1-3.2	1.6 (1.3-2.0)	1.9 (1.5-2.2)	<0.001
Albumin (g/l)	40.00-50.00	39.37±3.98	44.18±2.28	<0.001
CEA (ng/ml)	<5.00	3.14 (1.89-5.69)	1.97 (1.43-2.73)	<0.001
CYFRA21-1 (ng/ml)	<7.00	3.20 (2.40-4.48)	2.19 (1.69-2.83)	<0.001
MRR	-	0.10 (0.08-0.14)	0.07 (0.06-0.08)	<0.001
NRR	-	0.89 (0.68-1.12)	0.66 (0.55-0.82)	<0.001
LRR	-	0.37 (0.30-0.46)	0.39 (0.32-0.46)	0.043
LA	-	65.12 (50.81-76.37)	81.53 (67.61-97.91)	<0.001

AC, adenocarcinoma; CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin 19 fragment antigen 21-1; LA, the product of lymphocyte count and albumin concentration; LRR, lymphocyte count to red blood cell count ratio; IQR, interquartile range; MRR, monocyte count to red blood cell count ratio; NRR, neutrophil count to red blood cell count ratio; RBC, red blood cell count; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; WBC, white blood cell count.

at the early stages of the disease (IA-IIIA) and the remaining 39.8% were at the advanced stages (IIIB-IV). The median age of the patients with lung cancer was 61 years (range, 48-78 years), and males accounted for 57.9%. The median age of the healthy group was 58 years (range, 47-80 years), and males accounted for 60.9%. There was no statistical difference in age or sex composition between the two groups. The comparative analysis results of the laboratory tests are shown in Table I. White blood cell count, neutrophil count, monocyte count, CEA and CYFRA21-1 levels were significantly higher in the patients with lung cancer compared with those in the controls (all P<0.001), while the red blood cell count, lymphocyte count and albumin level were significantly lower (all P<0.001). Compared with those in healthy individuals, the MRR and NRR were significantly higher (both P<0.001), while the LRR and LA were significantly lower in patients with lung cancer (both P<0.05; Table I).

Effectiveness of candidate markers in the diagnosis of lung cancer. The ROC curve was used to evaluate the ability of the MRR, NRR, LRR and LA to distinguish patients with lung cancer from healthy individuals. The results revealed

Table II. Diagnostic value of MRR, LA, CEA and CYFRA21-1 alone or in combination in lung cancer.

Variables	AUC	Cut-off	Sensitivity, %	Specificity, %	95% CI	
					Lower limit	Upper limit
MRR	0.810[a]	0.08	69.9	79.3	0.768	0.847
NRR	0.707[a,b]	0.84	54.6	78.8	0.660	0.751
LRR	0.563[a,b]	0.37	53.2	61.4	0.513	0.612
LA	0.721[a,b]	75.39	73.6	67.4	0.674	0.764
CEA	0.712[a,b]	3.80	42.6	94.0	0.665	0.756
CYFRA21-1	0.748[a,b]	2.75	64.4	74.5	0.703	0.790
MRR + CEA	0.843[a,b]	-	73.1	85.3	0.804	0.877
MRR + CYFRA21-1	0.833[a,b]	-	68.1	86.4	0.793	0.869
CEA + CYFRA21-1	0.796[a]	-	60.6	83.7	0.753	0.835
MRR + CEA + CYFRA21-1	0.856[a]	-	75.9	83.2	0.817	0.889
MRR + LA	0.866[a]	-	72.2	88.0	0.828	0.897
MRR + LA + CEA + CYFRA21-1	0.882	-	81.9	81.0	0.846	0.912

[a]P<0.05 compared with the AUC of MRR + LA + CEA + CYFRA21-1. [b]P<0.05 compared with the AUC of MRR. AUC, area under the receiver operating characteristic curve; CEA, carcinoembryonic antigen; CI, confidence interval; CYFRA21-1, cytokeratin 19 fragment antigen 21-1; LA, the product of lymphocyte count and albumin concentration; LRR, lymphocyte count to red blood cell count ratio; MRR, monocyte count to red blood cell count ratio; NRR, neutrophil count to red blood cell count ratio.

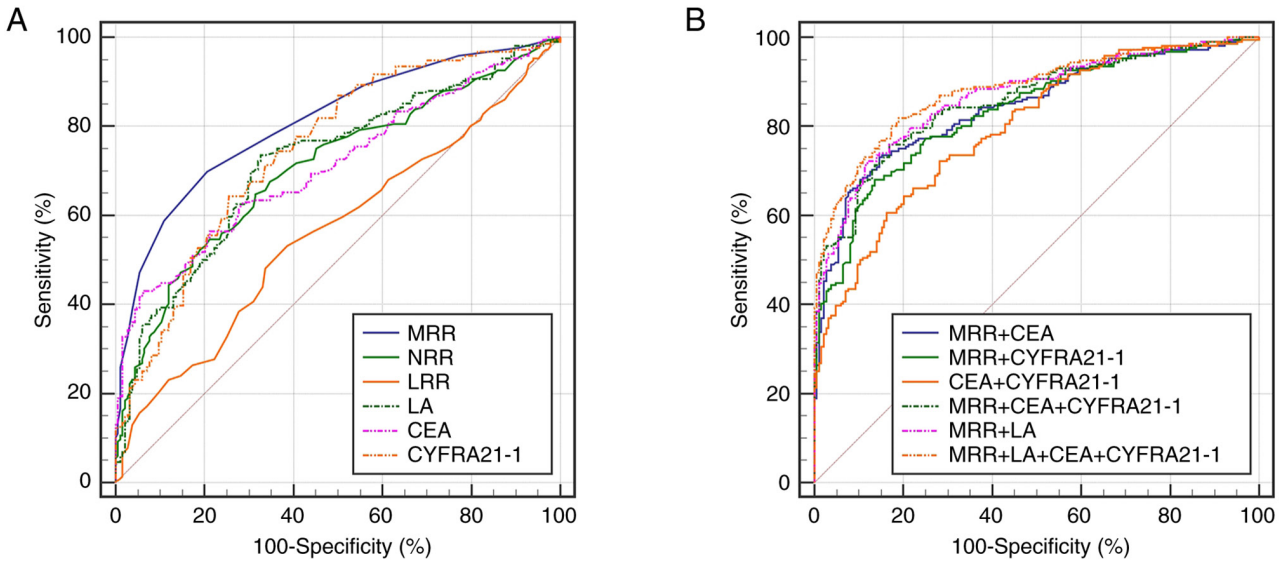

Figure 1. Receiver operating characteristic curve analysis of MRR, NRR, LRR, LA, CEA and CYFRA21-1 for the occurrence of lung cancer. (A) The ability of individual markers to identify the lung cancer. (B) The ability of combined markers to identify the lung cancer. MRR, monocyte count to red blood cell count ratio; NRR, neutrophil count to red blood cell count ratio; LRR, lymphocyte count to red blood cell count ratio; LA, the product of lymphocyte count and albumin concentration; CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin 19 fragment antigen 21-1.

that the MRR and LA had expected diagnostic value for lung cancer, and the MRR had the higher efficiency. The AUC of the MRR was 0.810 (95% CI, 0.768-0.847), and the sensitivity and specificity were 69.9 and 79.3%, respectively. The diagnostic efficiency of LA was inferior to MRR, but similar to that of CEA and CYFRA21-1, with an AUC of 0.721 (95% CI, 0.674-0.764), and a sensitivity and specificity of 73.6 and 67.4%, respectively (Fig. 1A; Table II). Due to their good performance in the ROC curve analysis, MRR and LA were selected for further analysis. It is widely known that serum CEA and CYFRA21-1 are common tumour markers for lung cancer (21,22). The MRR and LA were more sensitive for distinguishing patients with lung cancer from healthy controls (sensitivity of 69.9 and 73.6%, respectively), while CEA and CYFRA21-1 had higher specificity (specificity of 94.0 and 74.5%, respectively). Combined detection analysis revealed that the MRR could improve the diagnostic efficacy of CEA and CYFRA21-1. When CEA or CYFRA21-1 was combined with MRR, the AUC values reached 0.843 and 0.833, respectively, which was higher than those of

Table III. Binary logistic regression analysis of potential risk factors for lung cancer.

Variable	B	S.E.	Wald χ^2	P-value	OR (95% CI)
MRR[a]	-0.253	0.036	48.200	<0.001	0.776 (0.723-0.834)
LA	-0.031	0.006	25.741	<0.001	0.969 (0.958-0.981)
CEA	0.204	0.085	5.716	0.017	1.226 (1.037-1.449)
CYFRA21-1	0.265	0.113	5.558	0.018	1.304 (1.046-1.626)
Constant	4.375	0.937	21.789	<0.001	-

[a]MRR levels were reciprocal-transformed in the model. CEA, carcinoembryonic antigen; CI, confidence interval; CYFRA21-1, cytokeratin 19 fragment antigen 21-1; LA, the product of lymphocyte count and albumin concentration; MRR, monocyte count to red blood cell count ratio; OR, odds ratio; S.E., standard error.

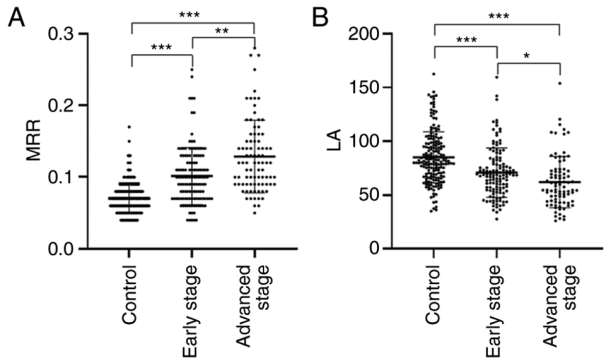

Figure 2. Comparison of MRR and LA levels among the control, early and advanced groups. (A) The MRR levels in the three groups. (B) The LA levels in the three groups. *P<0.05, **P<0.01 and ***P<0.001. MRR, monocyte count to red blood cell count ratio; LA, the product of lymphocyte count and albumin concentration.

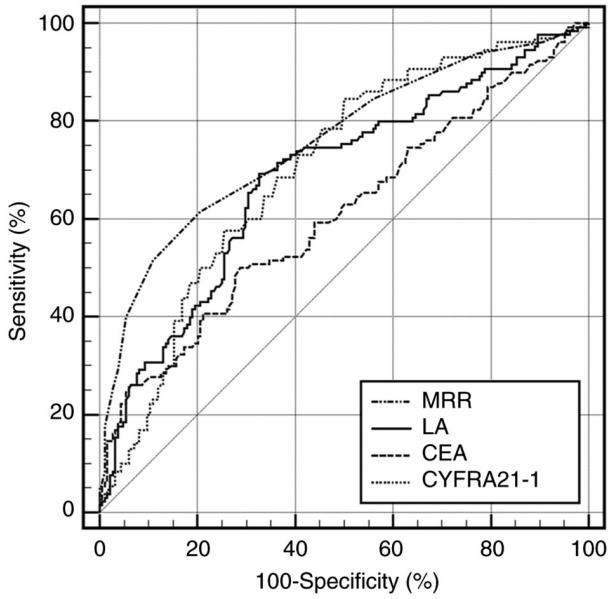

Figure 3. Receiver operating characteristic curve analysis of MRR, LA, CEA and CYFRA21-1 in identifying early stage lung cancer (IA-IIIA). MRR, monocyte count to red blood cell count ratio; LA, the product of lymphocyte count and albumin concentration; CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin 19 fragment antigen 21-1.

CEA (AUC, 0.712) or CYFRA21-1 (AUC, 0.748) alone, with improved sensitivity and specificity (sensitivity of 73.1 and 68.1%; specificity of 85.3 and 86.4%, respectively) (Table II). When the MRR, LA, CEA and CYFRA21-1 were combined for detection, the maximum diagnostic efficacy and a high sensitivity and specificity were obtained (AUC, 0.882; sensitivity, 81.9%; specificity, 81.0%; Fig. 1B; Table II). Subsequently, binary logistic regression analysis was used to evaluate the risk factors of lung cancer, and the results showed that reciprocal-transformed MRR (OR, 0.776; 95% CI, 0.723-0.834; P<0.001), LA (OR, 0.969; 95% CI, 0.958-0.981; P<0.001), CEA (OR, 1.226; 95% CI, 1.037-1.449; P=0.017) and CYFRA21-1 (OR, 1.304; 95% CI, 1.046-1.626; P=0.018) were all possible risk factors for lung cancer (Table III).

When the levels of MRR and LA were compared among the control, early stage and advanced stage groups, the advanced group showed the highest MRR and lowest LA, followed by the early group and then the control group (P<0.05; Fig. 2A and B). In order to further assess the ability of candidate diagnostic markers to detect patients with lung cancer at early stages, the age (P=0.346) and sex composition (P=0.056) of 184 healthy participants and 130 patients with lung cancer at stage IA-IIIA were analysed. The ROC curve analysis revealed that the ability of MRR in differentiating patients in the early stages from the healthy controls was stronger than that of CEA (AUC, 0.761; 95% CI, 0.710-0.807; sensitivity, 62.0%; specificity, 79.3%; Fig. 3; Table IV).

Associations among the MRR, LA and clinical characteristics in patients with lung cancer. The associations among MRR, LA, baseline characteristics (age and sex) and clinical characteristics (histopathological subtype, invasion depth, lymph node metastasis, distant metastasis and clinical stage) were analysed. Age and sex were identified as potential confounding factors and adjusted for using binary logistic regression. As shown in Table V, the MRR and LA were closely related to clinical characteristics in patients with lung cancer. High MRR levels were significantly related to invasion depth (P=0.012), regional lymph node metastasis (P=0.003), distant metastasis (P=0.025) and clinical staging (P=0.002), while LA was closely related to invasion degree (P<0.001), lymph node metastasis (P=0.009) and clinical staging (P=0.031). Patients with different pathological subtypes showed different levels of MRR and LA. In patients with SCLC,

Table IV. Ability of MRR, LA, CEA and CYFRA21-1 to identify patients with early stage (IA-IIIA) lung cancer.

					95% CI	
Variables	AUC	Cut-off	Sensitivity (%)	Specificity (%)	Lower limit	Upper limit
MRR	0.761	0.08	62.0	79.3	0.710	0.807
LA	0.683	75.39	69.0	67.4	0.628	0.734
CEA	0.610[a]	2.48	50.4	71.2	0.554	0.664
CYFRA21-1	0.702	2.18	84.5	50.0	0.648	0.752

[a]P<0.05 compared with the AUC of MRR. AUC, area under the receiver operating characteristic curve; CEA, carcinoembryonic antigen; CI, confidence interval; CYFRA21-1, cytokeratin 19 fragment antigen 21-1; LA, the product of lymphocyte count and albumin concentration; MRR, monocyte count to red blood cell count ratio.

Table V. Associations between MRR, LA levels and clinical characteristics in lung cancer.

Characteristics	n	MRR	P-value	LA	P-value
Sex			<0.001		0.018
Male	125	0.12 (0.09-0.15)		62.22 (44.73-74.13)	
Female	91	0.09 (0.07-0.11)		68.48 (56.70-82.28)	
Age, years			0.002		0.006
≤60	106	0.10 (0.07-0.12)		68.22 (55.01-83.25)	
>60	110	0.11 (0.09-0.14)		62.02 (45.92-72.73)	
Histopathological subtype			0.006		0.142
NSCLC	178	0.10 (0.07-0.13)		67.43 (53.01-78.78)	
SCLC	38	0.13 (0.10-0.16)		54.53 (44.10-67.39)	
Invasion depth			0.012		<0.001
T1+T2	149	0.10 (0.07-0.13)		68.76 (54.66-83.79)	
T3+T4	67	0.11 (0.09-0.16)		54.56 (43.08-68.48)	
Lymph node metastasis			0.003		0.009
N0	111	0.09 (0.07-0.12)		68.96 (57.90-83.38)	
N1-N3	105	0.12 (0.09-0.15)		54.74 (44.26-72.50)	
Distant metastasis			0.025		0.608
M0	154	0.10 (0.07-0.13)		66.94 (52.34-77.74)	
M1	62	0.12 (0.09-0.16)		61.97 (45.66-75.97)	
Clinical staging			0.002		0.031
IA-IIIA	130	0.10 (0.07-0.13)		68.70 (55.12-81.47)	
IIIB-IV	86	0.12 (0.09-0.15)		56.38 (44.17-72.42)	

Data are expressed as the median (interquartile range). Binary logistic regression analysis was used to control confounding factors. LA, the product of lymphocyte count and albumin concentration; MRR, monocyte count to red blood cell count ratio; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer.

relatively high levels of MRR could be seen compared with those of patients with NSCLC (P=0.006), while the levels of LA seem to be lower, but statistically non-significant (P=0.142). According to the present analysis, MRR tended to increase as the disease progressed, while LA exhibited the opposite trend.

Discussion

Numerous studies have demonstrated that hematological markers serve an important role in the pathogenesis and progression of malignancies (23-25). Lung cancer has the second highest incidence among all cancer types (1). A delayed diagnosis would result in disease progression and a poor prognosis. Histological diagnosis is still considered the gold standard for establishing a definite diagnosis. However, ideal non-invasive markers are being sought as an auxiliary method for diagnosis. Sensitivity and specificity are equally important for such diagnostic markers to reduce the rates of missed diagnosis and misdiagnosis. Several novel markers, such as MRR, LRR, NRR and LA, have initially been studied

in neoplastic diseases. Peng *et al* (26) demonstrated a close association between MRR and early stage colorectal cancer, and MRR had a better prognostic value for patients with highly or moderately differentiated tumours. Wang *et al* (15) proposed red blood cell count as a reference index to balance individual differences, and demonstrated that the MRR, NRR and LRR were independent prognostic factors for disease-free survival in patients with advanced breast cancer by reflecting the intensity of the inflammatory immunological reaction. Furthermore, Yamamoto *et al* (16) performed a comprehensive assessment of various circulating inflammatory markers in the prognosis prediction of patients with stage II/III rectal cancer undergoing radical resection, and found that LA was associated with overall survival and recurrence-free survival. Low levels of LA suggested a poor prognosis of the disease.

To the best of our knowledge, the roles of these markers in lung cancer remain unclear. The present study aimed to investigate the diagnostic value of the aforementioned markers among patients with lung cancer. High MRR and NRR, and low LRR and LA values were found in patients with newly diagnosed lung cancer. After adjusting for age and sex in binary logistic regression analysis, there were significant associations between MRR and histopathological subtype, lymph node metastasis, distant metastasis and clinical stage, and between LA and invasion depth, lymph node metastasis and clinical stage. MRR and LA had the potential to distinguish patients with lung cancer from the healthy controls, especially when combined with CEA and CYFRA21-1, which had a higher sensitivity. However, only the MRR showed an advantage in the detection of patients with lung cancer at early stages (IA-IIIA). Additionally, by analysing the present results, it could be hypothesized that increased MRR, as well as CEA and CYFRA21-1 concentrations, and decreased LA could be risk factors for lung cancer.

It is widely known that monocytes/macrophages are involved in tumour progression. Circulating monocytes are highly adaptive cells, migrating and differentiating with the change of certain circumstances. Derived from circulating monocytes, tumour-associated macrophages stimulate tumour cell proliferation, promote angiogenesis and lymphangiogenesis, and help with tumour invasion and metastasis, by secreting growth factors, cytokines and proteases (27). Although the exact mechanism behind the increase in total circulating monocytes remains unclear, the activation of the tumour-associated monocyte-macrophage system can be clearly observed. Regarded as the monocyte-adjusted red blood cell level, the MRR might be a better marker than the absolute monocyte count for lung cancer.

As another important type of tumour-related immune cells, lymphocytes mainly serve a role in immune surveillance and tumour cytotoxicity, and can interact with tumour-associated macrophages. Both circulating lymphocytes and tumour-infiltrating lymphocytes reflect the immune response to the tumour. Decreases in the circulating lymphocyte count and changes in lymphocyte subsets, including natural killer (NK) cells, $CD4^+$ T cells and $CD8^+$ T cells, are observed in most malignant tumours (28). Compared with those in healthy controls, the NK cell count and naive $CD4^+/CD4^+$ T lymphocyte numbers are decreased, and the percentage of activated $CD8^+$ T lymphocytes ($CD38^+/HLA\text{-}DR^+$) is increased in multiple solid tumours, including lung cancer, and these exhibit a corresponding trend as the disease progresses (29). In the present study, a decrease in the total count of circulating lymphocytes was also observed, which might reflect the weakened immune response to the tumour and the poor prognosis of the patients.

Serum albumin, as another valuable serum marker reflecting the systemic nutriture and inflammation, has also been demonstrated to be negatively associated with the risk of lung, liver and colorectal cancer (30). It has been reported that low albumin levels are associated with the poor prognosis in patients with advanced NSCLC treated with erlotinib (31). Although serum albumin is not specific to nutritional evaluation, it can partly reflect protein-energy wasting and the inflammatory response (32). Previous studies demonstrated that the lymphocyte levels were influenced by the nutritional status (33,34). However, an association between lymphocyte levels and albumin was not observed in the present study (Fig. S1). Based on the aforementioned preconditions, we hypothesized that LA could partly reflect the body's immune and nutritional conditions, and might have a potential role in distinguishing patients with lung cancer from healthy individuals.

Based on the aforementioned results, we hypothesized that the MRR and LA may be potential markers for the clinical auxiliary diagnosis of lung cancer and assessment of disease progression. MRR may be a promising marker supplementary to imaging examinations in screening for lung cancer at early stages. Due to insufficient sensitivity and specificity, it is inappropriate for MRR and LA to be used alone as an early-diagnostic marker for lung cancer. The MRR and LA might be influenced by other factors. It is therefore essential to augment MRR and LA monitoring with other biomarkers, including serum tumour markers, in order to decrease misdiagnoses and missed diagnoses. The changes in these markers may serve as wake-up calls for clinicians when observed with suspected lung cancer symptoms. Due to the universality and repeatability of these indicators, they have the potential to be used as auxiliary indicators in clinical diagnosis and treatment, especially in areas without sufficient medical resources.

To the best of our knowledge, this was a novel attempt to explore the roles of red blood cell-derived markers and LA in the field of lung cancer. There remain some limitations in the present study. Firstly, it was a retrospective, single-centre and single cut-off point study. The small sample size may affect the reported results. Although there were cut-off values for these markers in the present study, it is still hard to say that there are definite thresholds to indicate lung cancer. Larger, multicentre and prospective studies are required to examine the efficacy and to learn more about those markers in cases of lung cancer. Secondly, the present study focused on the comparison and analysis between the two groups, namely, patients with lung cancer and healthy individuals. Future studies could be conducted between benign lung diseases and lung cancer.

In conclusion, MRR and LA could be used as novel effective auxiliary markers for the diagnosis of patients with lung cancer, especially when combined with CEA and CYFRA21-1. MMR and LA could also partly indicate disease progression. As cheap, easily accessible and effective blood markers, MRR and LA may have potential value in clinical practice.

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Availability of data and materials

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

Authors' contributions

XXC and FHQ made substantial contributions to the conception and design of the work. XXC, STZ, XMY and SCH performed the data collection and data analysis. XXC interpreted the data, and was involved in drafting and revision of the manuscript. FHQ revised the manuscript critically for important intellectual content and gave final approval of the version to be published. XXC, STZ, XYM and SCH confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by The Ethical Review Committee of Jiangsu University Affiliated Hospital (Zhenjiang, China). All patients provided oral informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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