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ORIGINAL ARTICLE AND META-ANALYSIS

Differences in respiratory-related physiological signal features among diverse histological subtypes and clinicopathology stages of lung cancers

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Abstract

Objectives: Lung cancer (LC) is a highly heterogeneous disease characterized by complex clinical repercussions, diverse histological subtypes, and clinicopathological stages. However, the relationship between physiological features and subtypes/stages of LCs remains unclear. This study aims to compare the differences in respiratory-related physiological features among LCs with diverse subtypes/stages.
Materials and Methods: Respiratory-related physiological signals, including airflow, transthoracic impedance, surface diaphragm electromyography, and lead II electrocardiogram, were recorded from 164 LCs and 80 healthy controls (HCs) in a resting state. Fifteen features obtained from these signals were compared between LCs and HCs, compared among subtypes of adenocarcinomas (ADC), squamous carcinomas (SCC), and small cell lung carcinomas (SCLC), and compared among stages of I, II, III, and IV.
Results: There were no statistical differences in baseline characteristics between LCs and HCs except that LCs had a higher smoking rate. Of all features in SCLC and ADC, eight features in SCC were significantly lower than HCs. One feature across the three subtypes and 12 features between the two subtypes differed significantly. Three features in stages I and II, 13 in stage III, and all in stage IV were significantly lower than HCs. Two features in stage II, 9 in stage III, and 13 in stage IV were significantly lower than in their respectively earlier stages.
Conclusion: Compared with HCs, respiratory-related physiological signal features for LCs are significantly decreased, especially in the SCLC and ADC subtypes. These features also differ markedly among subtypes. Besides, the number of features that vary among stages increases as the LC progresses.
Keywords: clinicopathology stage; histological subtype; lung cancer; respiratory-related physiological features.

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1. Introduction

Accounting for approximately 2.5 million newly diagnosed cases and 1.8 million deaths annually worldwide, lung cancer (LC) is a highly heterogeneous disease with complex clinical repercussions and poor prognosis [1]. Clinical research indicated that the prognosis of LC depends heavily on its histological subtypes and clinicopathological stages [2]. LC is classified into three histologic subtypes, including adenocarcinomas (ADC), squamous carcinomas (SCC), and small cell lung carcinomas (SCLC). The incidence rates were 55%, 25%, and 15%, respectively, and the five-year survival rates in all stages were 15%, 20%, and 10% [3-6]. Moreover, early diagnosis is crucial for the treatment of LC, as the survival rate drops sharply from 73% to 13% from stage I to stage IV [7]. Unfortunately, over 30% of ADC and SCC were diagnosed in stage III, over 40% of ADC and SCC were diagnosed in stage IV, and over 70% of SCLC were diagnosed in stage IV [8].

Although there are increasing therapeutic options for LC, including surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy, multimodal therapy, et al., the 4% improvement in the 5-year survival rate remains dismal [9,10]. In recent years, advancements in life support technologies and tumor diagnosis technologies have substantially altered the treatment strategies for LC [11]. Patient-centered precision and holistic treatment through the mutual support of multidisciplinary teams composed of oncology, surgery, respiratory critical care medicine, and medical imageology has shown a promising strategy to improve the quality of life and survival [12]. Continuous response evaluation and prognosis prediction are essential components of treatment and are crucial in optimizing therapy decisions [13]. Current methods for prognosis prediction mainly rely on imaging, sequencing, and pathological datasets, and the predictive performance remains suboptimal [14]. Therefore, more robust biomarkers are required to accurately predict prognosis and stratify patients for therapy and follow-up.

LC often has impaired lung function, which may limit treatment options and affect prognosis prediction [15]. However, the relationship between respiratory-rated physiological features and subtypes/ stages of LC remains unclear. This study aims to compare the differences in respiratory-related physiological features among LC with diverse histological subtypes and tumor node metastasis stages.

2. Methods

2.1. Study design and participants

This retrospective study was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Army Medical University, PLA (reference number: 2022-Research No. 027-01) and the Chinese Clinical Trial Registry (registration number: ChiCTR2300069713).

The observational study was carried out at the oncology department of the Second Affiliated Hospital of Army Medical University between May 2022 and October 2023. The inclusion criteria of LCs were:

1. A primary diagnosis of LC.
2. No distance metastasis or recurrences.
3. An age between 18 and 75 years.

The exclusion criteria of LCs were:

1. The presence of distant metastasis or active cancer.
2. Acute infectious diseases.
3. Unwillingness to cooperate with the study for any reason.

According to the 2021 edition of the WHO Tissue Classification Standard, three major histological subtypes of LC were considered: SCLC, ADC, and SCC. On the other hand, according to the latest 9th edition of TNM classification, four TNM stage subgroups of LC were also studied: stages I, II, III, and IV.

To accurately study the differences in respiratory-related physiological signal features among different subtypes/ stages of LCs, we included age- and sex-matched health controls (HCs). The inclusion criteria of HCs were:

1. Free of tumors.
2. Age between 18 and 75 years.
3. Consent to cooperate and sign the informed consent form.

The exclusion criteria of HCs were:

1. Acute infectious diseases.
2. Unwillingness to cooperate with the study for any reason.

2.2. Data acquisition.

The eligible participants were informed about the purposes of the study, the procedure, and the instructions to breathe. After the written informed consent, a thermal gas mass

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flow meter, connected to a ventilator tube with an anesthesia mask, was used to acquire the airflow (FLW) signal. Five disposable Ag-AgCl electrodes, which were attached to the body skin of participants in the bipolar configuration, were connected to a custom-designed amplification module to acquire three other respiratory-related physiological signals, transthoracic impedance (IMP) signal, surface diaphragm electromyography (sEMG), and lead II electrocardiogram (ECG).

These physiological signals were selected because they are representative of different measurement modalities and meet the requirements for lung function described in LCs. The FLW signal directly reflects the velocity and volume of respiratory airflow. IMP signals arise from lung volume changes and cardiac vector alterations resulting from respiratory movement, which are linear with lung volume. The sEMG is generated by the activity of the vital respiratory muscles, whose contraction causes changes in lung volume/movement in the longitudinal axis. HRV of ECG can indicate information about the cardiorespiratory and autonomic nervous systems.

Participants were forbidden from drinking coffee, tea, alcohol, vigorous exercise, and mood swings on the eve and day of monitoring. After resting for 5 min, each participant was seated comfortably in a chair, and the pulmonary function test was performed with a portable spirometer (SP-70B, Contec Medical Systems Co., Ltd. Qinhuangdao, Hebei, China) before and after the test to acquire the forced vital capacity to assist in assessing signal features. Then, the participants lay on the examination bed in the supine position, and their respiratory rate increased gradually from 10 to 16 breaths per minute under the guidance of yoga background music and breathing instruction. These four signals were synchronized and recorded for 5 minutes, and operations were carried out by trained personnel in a standardized way.

2.3. Signal feature extraction

The recorded FLW and IMP signals were digitally filtered using a zero-phase fourth-order Butterworth low-pass filter. The sEMG recordings were digitally filtered using a moving average filter to remove random noise. The ECG recordings were filtered with a high-pass filter to remove baseline drift and a low-pass filter to eliminate high-frequency interferences. Fifteen features were extracted from the processed signals, as shown in **Table 1**. The features of the FLW signal were related to lung capacity, reactivity, and reversibility; the IMP signal reflected lung compliance and elasticity, sEMG was associated with intrathoracic pressure, lung contraction, and diastole, and HRV reflects sympathetic nervous system changes that control bronchial constriction and relaxation.

TABLE 1 - Features and calculation of respiratory-related physiological signals. 1/2

Signal category	Features	Calculation	Related lung function
Airflow	Tidal volume (TV, L)	$TV = \sum_{i=1}^{N} (\int_{I_{on}}^{I_{off}} f(t)dt + \int_{E_{on}}^{E_{off}} f(t)dt) / N$ f(t), the signal I_{on}, I_{off}, E_{on}, E_{off}, the onset and offset of inhale and exhale	Lung capacity
	Exhale frequency to peak (EFF, Hz) [16]	$EFF = N / \sum_{i=1}^{N} (T_{Epeak(i)} - T_{Eon(i)})$ E_{peak}, E_{on}, the peak and onset of exhale	Lung reactivity
	Peak expiratory flow (FEF, L/min) [16]	$FEF = \sum_{i=1}^{N} (E_{peak(i)}) / N \cdot 60$ E_{peak}, the peak of exhale	Lung reversibility

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TABLE 1 - Features and calculation of respiratory-related physiological signals. **2/2**

Signal category	Features	Calculation	Related lung function
Impedance	Respiratory impedance (RI, Ω) [17]	$RI = \frac{1}{N}\sum_{i=1}^{N}\lvert x_i \rvert$ x_i, the impedance signal	Lung compliance
	Impedance peak to peak (IPP, Ω)	$IPP = \frac{1}{N}\sum_{i=1}^{N}(x_{\max(i)} - x_{\min(i)})$ x_{max}, x_{min}, the maximum and minimum values in the signal period	Elastic resistance
	Root mean square amplitude (RMSA, Ω)	$RMSA = (\frac{1}{N}\sum_{i=1}^{N}\sqrt{\lvert x_i \rvert})^2$ x_i, the impedance signal	Elastic retraction
	Rectified gravity frequency (RGF, s) [17]	$RGF = \sum_{k=1}^{K} s(k) / \sum_{k=1}^{K}[f_k \cdot s(k)]$ s(k), the frequency spectrum f_k, the frequency value of the k-th spectral line	Elastic retraction
sEMG	Integral electromyography (IEMG, μV)	$iEMG = \int_{i=1}^{N}\lvert x_i \rvert$ x_i, the sEMG signal	Intrathoracic pressure
	Root mean square (RMS, μV)	$RMS = \sqrt{\frac{1}{N}\sum_{i=1}^{N} x_i^2}$ x_i, the sEMG signal	Lung contraction and diastole
	Rectified willison amplitude (RWA, μV) [18]	$RWA = \sum_{i=1}^{N-1} f(\lvert x_i - x_{i+1} \rvert) \cdot FVC / 10$ Where $f(x) = \begin{cases} 1, x > \varepsilon \\ 0 \end{cases}$ x_i, the sEMG signal FVC, forced vital capacity	Lung contraction and diastole
	Rectified slope sign changes (RSSC, a.u.) [18]	$RSSC = \sum_{i=2}^{N-1} f[(x_i - x_{i-1}) \cdot (x_i - x_{i+1})] \cdot FVC / 10$ Where $f(x) = \begin{cases} 1, x > \varepsilon \\ 0 \end{cases}$ x_i, the sEMG signal FVC, forced vital capacity	Lung contraction and diastole
	Mean power frequency (MPF, Hz)	$MPF = \int_0^{\infty} f \cdot P(f) df / \int_0^{\infty} P(f) df$ P(f), signal power spectrum	Lung contraction and diastole
HRV	Root mean square of successive differences (RMSSD, ms) [19]	$SDNN = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(RR_i - \overline{RR})^2}$ $\overline{RR}$, the average value of RR interval	Bronchial contraction and diastole
	Relative power of the low frequency band (pLF, %) [19]	$pLF = LF / (TP - VLF) \cdot 100$ TP, total power; LF, low-frequency band; VLF, Very low frequency;	Bronchial contraction
	SD1/SD2 of poincare plot (SD1/SD2, a.u.) [19]	$SD1 / SD2 = \frac{\sqrt{\sum_{i=1}^{N}(RR_i - RR_{i+1})^2 / (2 \cdot N - 2)}}{\sqrt{\sum_{i=1}^{N}(RR_i - \sum_{i=1}^{N} RR_{i+1} / N)^2 / (2 \cdot N - 2)}}$ RR, adjacent heartbeat intervals	Bronchial contraction and diastole

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2.4. Statistical analysis

Continuous, normally distributed variables were presented as mean ± SD, and continuous, non-normal data were presented as median (interquartile range, IQR). Categorical variables were presented as quantities with percentages. A chi-square test was used for categorical data to analyze the difference between LCs and HCs and examine overall differences between the cross-sectional sub-cohorts. We performed the Shapiro-Wilk test for continuous features data to test the normality and Levene's test to test the homogeneity of variance. T-test was used to calculate normal data with homogeneity of variance, and Fisher's least significant difference was used for multiple comparisons between subgroups. The Mann-Whitney U test was used to analyze non-normal data, and the Kruskal-Wallis H test was used for multiple comparisons between subgroups. IBM-SPSS 27.0 was used for the data analyses, and $p<0.05$ was considered statistically significant.

3. Result

3.1. Participants characteristics

Three hundred participants were involved in this study, and 56 participants (48 LCs and 8 HCs) were excluded due to withdrawal from research and technical issues; for example, the participants' poor compliance led to deviation from the measurement results. Therefore, we included the data of 244 participants (164 LCs and 80 HCs) in the analysis, and **Table 2** summarizes the participants' background information. LCs were also divided into 60 (36.59%) SCLC, 55 (33.54%) SCC, 40 (24.39%) ADC, and 9 (5.49%) others. While 11 (6.71%) stage I (all men, 58.91 ± 6.11 years), and 8 (4.88%) stage II (all men, 53.13 ± 2.30 years), 89 (54.27%) stages III (84 men and five women, 58.74 ± 8.15 years), and 56 (34.15%) stage IV (49 men and seven women, 57.79 ± 7.40 years).

TABLE 2 - Participants background information.

Parameters	LCs (n=164)	HCs (n=80)	P value
Age, years	58.15 ± 7.64	58.30 ± 11.80	0.91
Men, n/%	147, 89.63%	67, 83.75%	0.11
Hight, cm	164.64 ± 5.98	163.31 ± 6.68	0.12
Wight, kg	65.36 ± 9.91	63.89 ± 7.99	0.25
BMI, kg/m^2	24.07 ± 3.08	23.99 ± 2.67	0.85
Chest, cm	95.37 ± 6.12	94.21 ± 6.06	0.16
Smoking , n (%)	81 (49.39%)	25 (31.25%)	0.01
Drinking, n (%)	28 (17.07%)	19 (23.75%)	0.24
Cardiac disease, n (%)	6 (3.66%)	4 (5.00%)	0.65
Hypertension, n (%)	29 (17.68%)	14 (17.50%)	0.97
Diabetes, n (%)	13 (7.93%)	10 (12.50%)	0.29
Subtype			
SCLC, n (%)	60 (36.59%)		
ADC, n (%)	40 (24.39%)		
SCC, n (%)	55 (33.54%)		
Other	9 (5.49%)		
Stage			
I, n (%)	11 (6.71%)		
II, n (%)	8 (4.88%)		
III, n (%)	89 (54.27%)		
IV, n (%)	56 (34.15%)		

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3.2. Features between LCs and HCs

There was no statistical difference in general demographic characteristics between LCs and HCs, except that LCs had a higher smoking rate (LCs 81, 49.39% vs. HCs 25, 31.25%, p=0.01) (Table 2). **Table 3** indicates the comparative results of the respiratory-related physiological signal features between the LCs and HCs. Among them, thirteen features, TV, EFF, RI, IPP, RMSA, RGF, IEMG, RMS, RWA, RSSC, RMSSD, pLF, and SD1/SD2, were significantly lower for LCs than HCs. However, only two features, FEF and MPF, were not significantly different between the LCs and HCs, while the MPF was also reduced in the LCs.

TABLE 3 - Comparison of respiratory-related physiological signals features between LCs and HCs.

Parameters	LCs (n=164)	HCs (n=80)	P value
TV, L	2.98 (1.22)	3.03 (1.29)	0.00
EFF, Hz	1.56 (0.91)	1.75 (1.09)	0.02
FEF, L/min	41.62 (15.27)	41.50 (15.16)	0.07
RI, Ω	1.43 (1.13)	1.98 (1.22)	0.00
IPP, Ω	4.46 (3.25)	5.85 (3.53)	0.00
RMSA, Ω	1.01 (0.85)	1.98 (1.24)	0.00
RGF, s	2.94 (1.05)	3.13 (1.00)	0.00
IEMG, μV	10.24 (7.05)	14.15 (6.28)	0.00
RMS, μV	16.38 (10.42)	23.8 (12.33)	0.00
RWA, μV	0.38 (0.16)	0.42 (0.17)	0.00
RSSC, a.u.	0.05 (0.03)	0.13 (0.05)	0.00
MPF, Hz	61.65 (4.64)	61.91 (6.23)	0.13
RMSSD, ms	13.28 (11.67)	21.32 (18.51)	0.00
pLF, %	51.95 (28.31)	57.96 (31.11)	0.00
SD1/SD2, a.u.	0.88 (0.13)	0.89 (0.11)	0.04

3.3. Features among diverse LC subtypes

SCC was older than SCLC and ADC (years 60.25 ± 6.96, 56.13 ± 6.57, 57.33 ± 9.37, respectively, p<0.01), and SCC had a lower proportion of alcohol consumption than SCLC (9% vs. 25.00%, p<0.05). In addition, ADC patients had a higher percentage of females, lower height, and lower weight than SCC and SCLC patients.

Figure 1 indicates the differences in the respiratory-related physiological signal features value among HCs and histological subtypes SCLC, ADC, and SCC. All features in SCLC and ADC, whereas only eight features in SCC were significantly lower than HCs, such as the lung compliance feature RI: SCC 1.58Ω (1.14Ω), ADC 1.40Ω (0.99Ω), SCLC 1.29Ω (1.27Ω) vs. HCs 1.98Ω (1.22Ω). Nine features, TV, FEF, RI, IPP, RMSA, RGF, MPF, RMSSD, and SD1/SD2, of SCLC and ADC were significantly lower than SCC, such as the lung capacity feature TV: SCLC 2.92L (1.20L), ADC 2.83L (1.24L) vs. SCC 3.15L (1.40L). Two features (IEMG and RMS) in SCLC and SCC were significantly lower than ADC. Of these, the feature IEMG representing intrathoracic pressure was SCLC 9.93μV (6.90μV), SCC 9.77μV (6.41μV), and ADC 12.77μV (7.71μV), respectively. Still, the feature EFF of SCLC and SCC was higher than ADC, and the feature pLF of ADC was markedly lower than SCC, with values 47.24Hz (23.78Hz) vs. 56.62Hz (28.76Hz). In contrast, the remaining two features (RWA and RSSC) were not statistically different among the three subtypes.

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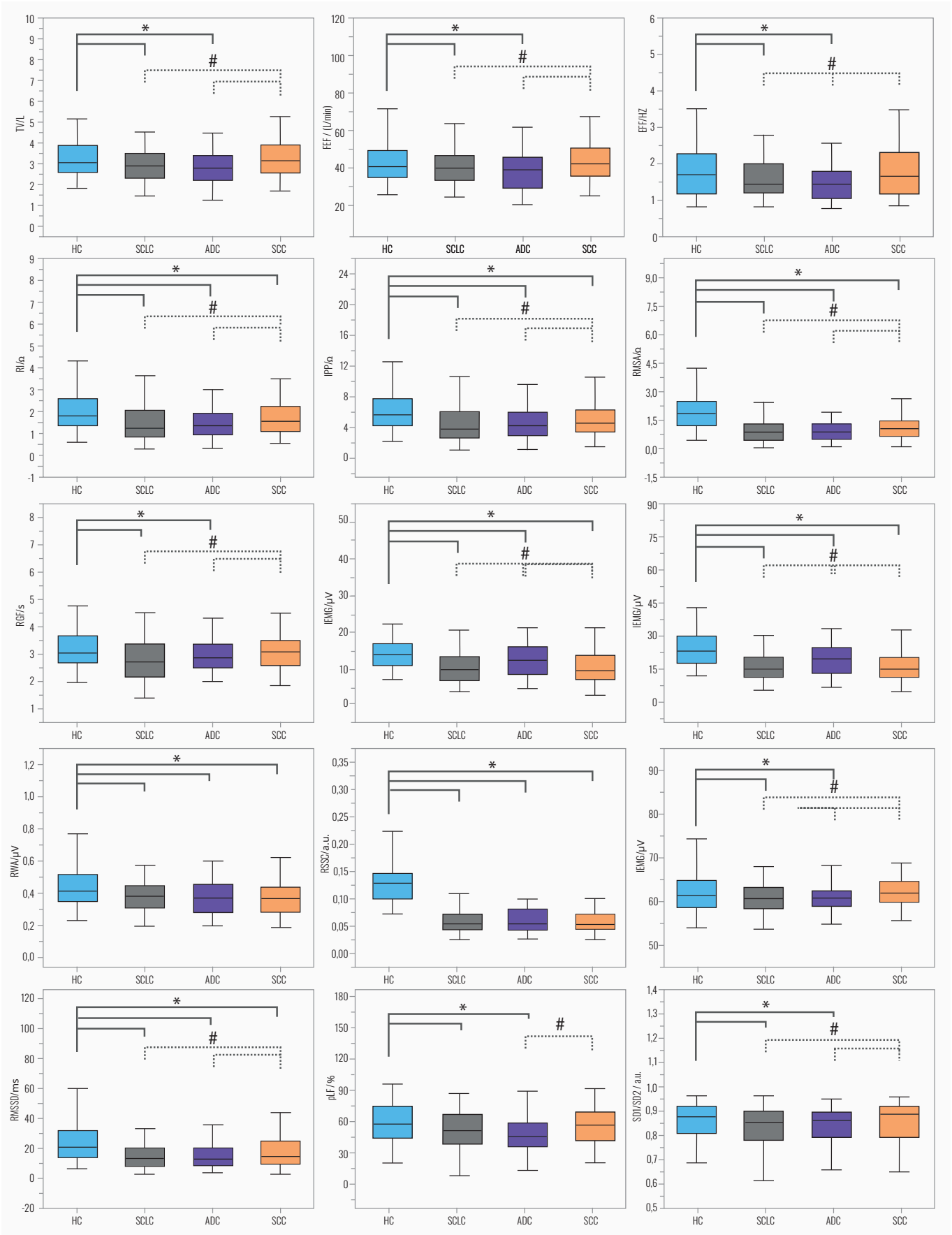
FIGURE 1 - Feature differences in respiratory-related physiological signals among diverse histological subtypes of LCs.



"#" represents differences between histological subtypes of LCs, and "*" represents differences between HCs and patients.

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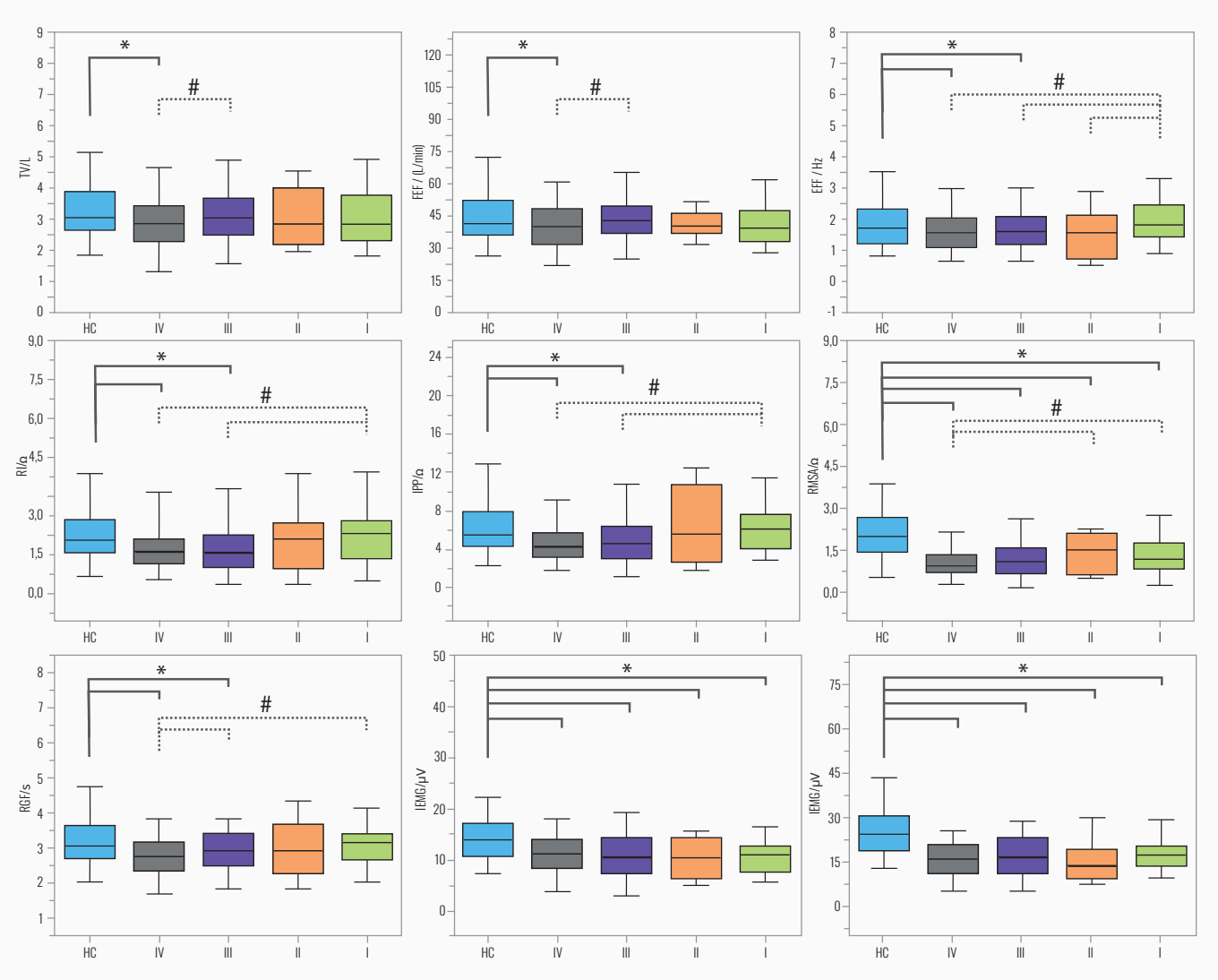
3.4. Features among diverse LC stages

Stage II patients were younger than the other three stages; that is, stage II 53.13 ± 2.30 years old, compared to stage I 58.91 ± 6.11 years old, stage III 58.74 ± 8.15 years old; stage IV 57.79 ± 7.40 years old, p<0.05. Besides, the proportion of alcohol consumption in stage II patients (50%) was significantly higher than that in stage III (18%) and stage IV (11%). Six of the stage III patients had cardiac disease, while none of the other three stage patients had it and were statistically significant.

Figure 2 indicates significantly different features of respiratory-related physiological signals for HCs and staging patients. All features in stage IV, thirteen (EFF, RI, IPP, RMSA, RGF, IEMG, RMS, RWA, RSSC, MPF, RMSSD, pLF, and SD1/SD2) in stage III and three (RMSA, IEMG, RMS) in stage I and II were significantly lower than HCs. The figure also displays that the feature value substantially decreased as the disease progresses, such as the feature RI for stage I 2.15Ω (1.44Ω), stage II 1.97Ω (1.83Ω), stage III 1.38Ω (1.12Ω), and stage IV 1.42Ω (0.88Ω), the feature TV for stage III 3.06L (1.19L), and stage IV 2.85L (1.11L), p<0.01. Thirteen features (TV, FEF, EFF, RI, IPP, RMSA, RGF, RWA, RSSC, MPF, RMSSD, pLF, and SD1/SD2) in stage IV, nine (EFF, RI, IPP, RWA, RSSC, MPF, RMSSD, pLF, and SD1/SD2) in stage III, and two (EFF and SD1/SD2) in stage II were significantly lower than their respectively earlier stages.

FIGURE 2 - Feature differences in respiratory-related physiological signals among diverse clinicopathology stages of LCs. **1/2**



"#" represents differences between the clinicopathology stages of LCs, and "*" represents differences between HCs and patients.

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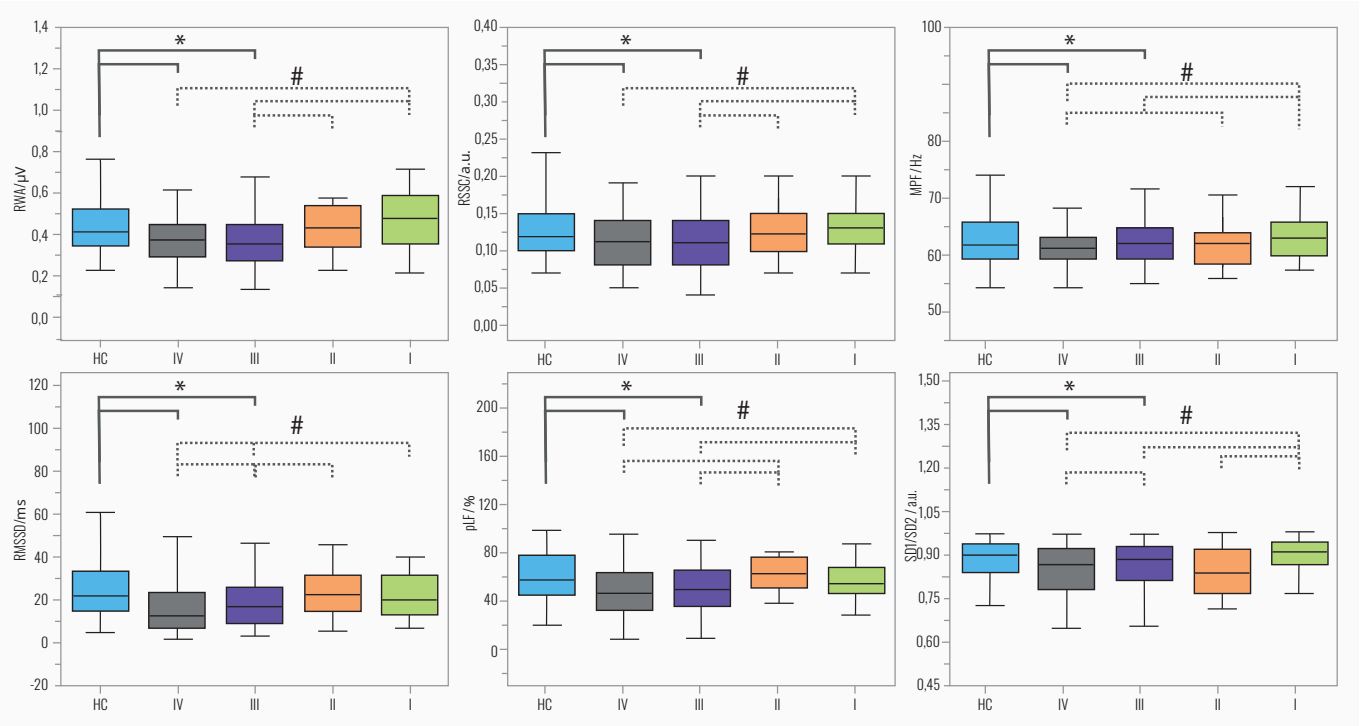
FIGURE 2 - Feature differences in respiratory-related physiological signals among diverse clinicopathology stages of LCs. **2/2**



"#" represents differences between the clinicopathology stages of LCs, and "*" represents differences between HCs and patients.

Discussion

This study compared the differences in 15 respiratory-related physiological features measured from FLW, IMP, sEMG, and ECG signals among 164 LCs with diverse subtypes/stages and 80 HCs. In particular, respiratory-related physiological signal features for LCs were significantly decreased compared to HCs, especially in the SCLC and ADC subtypes. These features also differed markedly among subtypes. Besides, the number of features that vary among stages increases as the LC progresses.

LC impairs lung function due to tumors destroying and compressing lung tissue. The pulmonary capillary permeability and cell space increase; afterward, the secretion of pro-inflammatory factors such as adhesion molecules increases. It promotes the aggregation and migration of white blood cells, accumulating protein-rich blood fluid and activating inflammatory cells in the alveoli. When the alveolar permeability reduces, the outside gas cannot enter the alveoli, and the body is hypoxia. The alveolar liquid clearance capacity depends on regulating the Na+-K+-ATP enzyme [20]. In a state of hypoxia, the function of Na+-K+-ATP enzyme to transport intracellular sodium ions to extracellular is inhibited, and ions accumulate in the cell. Thus, the dynamic balance is broken, and the alveolar fluid is complex to clear, so its function is impaired.

Lung obstructive changes mostly block the distal whole segment or lobe, and the gas in the distal alveolar absorbs into the blood, causing alveolar contraction or collapse. Airflow velocity and lung capacity (features TV, EFF, and FEF) can identify obstructive and limiting abnormalities and assess reversibility and response to treatment. This study confirms this possibility; the features were significantly lower in LCs than in HCs, especially SCLC and ADC. Although there was no statistical difference in FEF between LCs and HCs ($p=0.07$), the FEF of SCLC and ADC was significantly lower than that of HCs. The EFF of stage I was considerably higher than that of stages II, III, and IV, and the TV and FEF of stage III were significantly higher than those of stage IV. In addition, chronic obstructive pulmonary disease is a common complication, and the incidence in LCs can be as high as 71.6% [21]. It also can lead to the action of multiple inflammatory cells involved in simultaneously releasing various inflammatory

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mediators, including macrophages, neutrophils, and Tc 1, Th 1, Th 17, and ILC 3 lymphocytes, leading to irreversible lung damage [22].

LC is a highly heterogeneous disease with various oncogenic anomalies driving the pathogenesis in individual patients and relating to therapeutic response and resistance [23]. The heterogeneity is associated with two repair/carcinogenic pools of adult stem cells: one is the TRU, terminal respiratory unit that is the respiratory bronchiole and adjacent alveolar duct/ septae, the other being the adult central respiratory epithelium till the TRU [24]. In the preliminary study, CK7, CK5.7, TTF1, VIM, CD56, and Ki-67 proved sufficient to classify tumors based on cell population/ heterogeneity [24-27]. The histological examination is the gold standard for diagnosing the LC subtypes; however, consensus histological confirmation can sometimes be challenging and impacts optimal treatment choices [28,29]. The differences in respiratory-related physiological signals among subtypes are unknown in previous studies, and we expect to attract more respiratory critical care medicine applications for cancer in future studies.

In addition to the histological subtypes, the clinical symptoms of LC are also closely related to the growth site and tumor progression. Most of the SCC and SCLC are central types and present with localized thickening of the bronchial wall, irregular inner wall, and lumen stenosis in the early stage. SCLC increases and spreads to other sites, with tumor tissue doubling for about 73 days, while SCC grows a little slower and tumor tissue doubling for about 140 days. ADC is mostly peripheral LC, occurring in the fine bronchus and growing along the alveolar wall, leading to the wall thickening or adjacent alveolar secretions. The doubling time of tumor tissue in ADC is approximately 223 days [30]. These three subtypes in the middle and late stages have damaged normal respiratory function but also have adverse effects on lung blood vessels, and lung blood circulation is not smooth, aggravating lung ventilation dysfunction [31]. This is in accordance with our results; the lung function-related signal features worsen as the LC progresses.

Multidisciplinary team diagnosis and treatment for LC [32,33] can bring many benefits to patients through multi-dimensional discussion and analysis of diseases, such as providing more reasonable diagnosis and treatment paths and strategies, optimizing the use of medical resources, increasing patient enrollment opportunities in high-quality clinical trials, and improving patient prognosis and quality of life. Respiratory critical care medicine has a complete respiratory medicine system that is in line with the modern respiratory medicine pattern, and it has systematic organ monitoring and a standard respiratory support technology system. It serves as one of the mutual support of multiple disciplines of patient-centered precision and holistic treatment, reflecting the characteristics of the physiology and its dynamic changes, assisting LC diagnosis, patient stratification to therapy, and longitudinal monitoring [34].

We investigated four respiratory-related physiological signals with distinct origins and lung function-describing modalities. Airflow signal, as a most direct measurement method, reflects the breathing state and the degree of airway patency. Air filling the lung space causes thoracic expansion and contraction, forming changes in IMP signal, which can be serviced to understand the status of the lung. LC direct invasion or mechanical compression of the diaphragm or phrenic nerve will cause phrenic nerve paralysis, affecting the change in lung volume/movement on the vertical axis. For HRV of ECG, previously published studies suggested that under cancer-mediated stress, the neuronal vagal nerve controls the activity of the parasympathetic nervous system by releasing norepinephrine, dopamine, and bradykinin to trigger or inhibit the vascular endothelial growth factor [35].

Some limitations in this preliminary study must be investigated to improve our work further. First, we did not include the prognosis and efficacy evaluation in this trial. Although previous studies have indicated that HRV is a survival prognosticator [36], the relationship between airflow signal, IMP signal, and sEMG and the prognosis and efficacy of LC radiation therapy remains unknown, so the subsequent main study is to assess the radiotherapy prognosis and efficacy based on the physiological signals. Second, the generalizability of the results is limited to the sample size of patients in stages I and II in this staging study. Some signal features have shown trends in the progression of LC; however, the trend in patients of stages I and II could have been more apparent, which may be limited by the sample size. Therefore, additional large-scale sample studies are warranted to validate our findings regarding LC staging further. Third, the used algorithms were operated offline, and their real-time capabilities still need further development and evaluation.

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Conclusion

Compared with HCs, respiratory-related physiological signal features for LCs are significantly decreased, especially in the SCLC and ADC subtypes. These features also differ markedly among subtypes. Moreover, the number of features that differ between stages increases as the LC progresses. These findings may provide a basis for individualized radiotherapy and future efficacy evaluation of LC.

Acknowledgments

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Data availability statement

The data cannot be made publicly available upon publication due to legal restrictions preventing unrestricted public distribution. The data that support the findings of this study are available upon reasonable request from the authors.

Conflict of Interest

The authors declare no competing interests.

Author contributions

Xiaojuan Duan:
Writing-review & editing, Writing-original draft, Project administration, Investigation, Data collection, analysis and curation.
Xin Song and Liang Wei:
Writing-review & editing, Writing-original draft, Data acquisition system preparation.
Yushun Gong:
Writing-review & editing, Writing-original draft, Algorithm design.
Cailin Zhao: *Writing-review & editing, Writing-original draft, Signal discrimination.*
Lu Chen and Jianguo Sun:
Writing-review & editing, Writing-original draft, LC classification.
Yongqin Li: *Writing-review & editing, Writing-original draft, Investigation, Methodology, Funding acquisition.*

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