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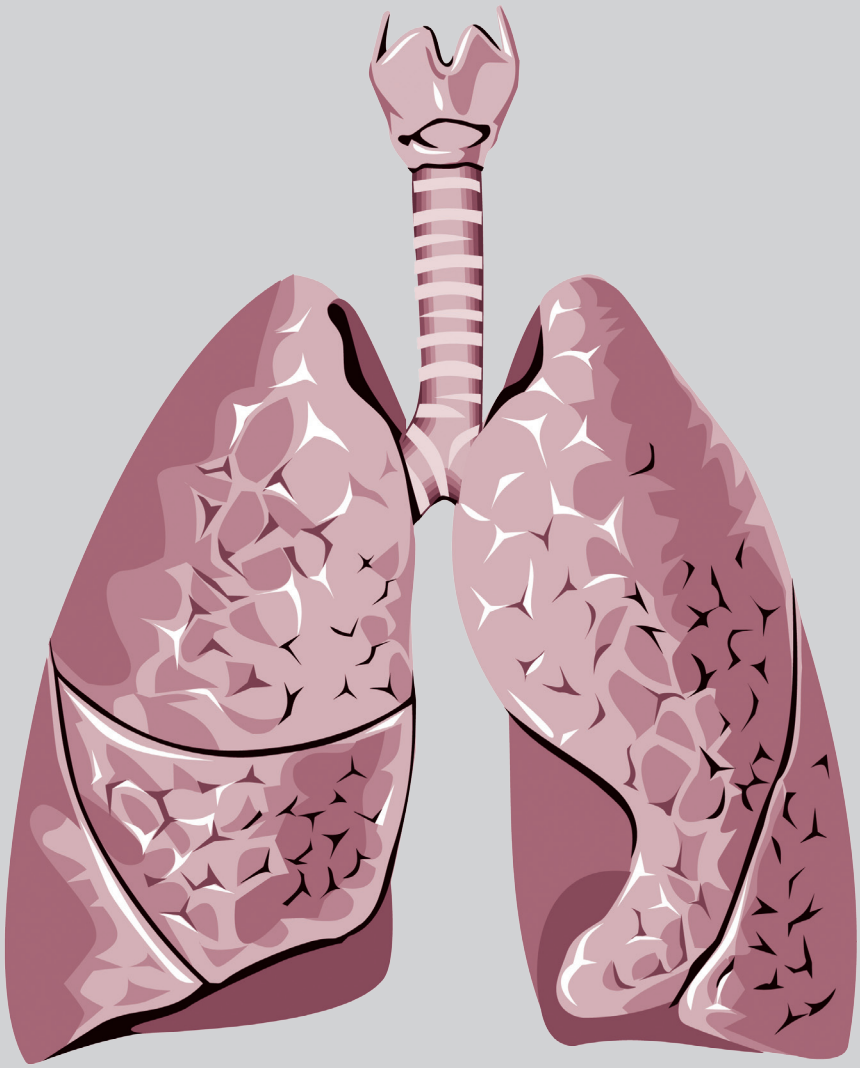

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Orginial Articles

Case Reports

Atrial Fibrillation and Central Sleep Apnea in Patients with Ischemic Stroke

Ping-Chi Liu*, Chung-Yao Chen**,***, Chung-Chieh Yu*,**,****

Introduction: Atrial fibrillation (AF) and central sleep apnea (CSA) are both common in patients with ischemic stroke and have been associated with adverse outcomes. However, whether AF is associated with CSA in patients with stroke has not been well studied. The primary objective of this study was to investigate the association between AF and CSA in patients with ischemic stroke.

Methods: This retrospective study consecutively included patients with ischemic stroke that were admitted for neurorehabilitation, had clinically suspected sleep-disordered breathing, and that had undergone in-hospital overnight polysomnography. The basic clinical data, underlying diseases and test results of the CSA and non-CSA patients were compared and analyzed.

Results: Of the 116 patients with sleep-disordered breathing, 26 (22.4%) were found to have CSA. Patients in the CSA group had a higher prevalence of AF than those in the non-CSA group (42.3% versus 11.1%). AF was positively associated with the presence of CSA (OR, 7.381; 95% CI, 1.39-27.25; $P = 0.003$), after adjusting for common confounders.

Conclusion: The co-aggregation of AF and CSA suggests important clinical implications for simultaneous screening and management of both conditions in patients with ischemic stroke. ***(Thorac Med 2020; 35: 1-9)***

Key words: atrial fibrillation, central sleep apnea, ischemic stroke

Introduction

Sleep-disordered breathing (SDB), including obstructive sleep apnea (OSA) and central sleep apnea (CSA), are commonly observed in patients with stroke and have been associated with adverse outcomes. CSA is characterized by recurrent cessation or attenuation of respiration during sleep, resulting from an absence or decline of ventilatory effort [1]. CSA can enhance arrhythmogenicity because of the repetitive breathing cessation during sleep [2-3]. In a systematic review that included 2,342 patients that had experienced a stroke or transient ischemic attack, SDB was identified in 72% of the patients. Of those, about 7% had CSA or Cheyne-

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Stokes respiration (CSR) as their predominant respiratory abnormality [4]. The important predictors of CSA were male gender, heart failure, atrial fibrillation (AF), pulmonary hypertension, stroke, and chronic prescribed opioid use [5].

Atrial fibrillation is the most common cardiac arrhythmia and is associated with significant morbidity and mortality. The large population burden of AF is highlighted by a progressively increasing prevalence -- estimated to reach 10 million in the United States by 2050 -- and contributes to substantial health care costs and morbidity [6-9]. The most serious and most common complication of AF is ischemic stroke. Several large studies of patients with AF who did not take anticoagulants have reported rates of thromboembolism of 4-5% per year [10-11]. AF may also lead to CSA through a mechanism like that associated with congestive heart failure [12-13]. In a study involving 2,500 consecutive patients who underwent diagnostic polysomnography (PSG), the prevalence of AF in patients with idiopathic CSA was 16-fold higher than that of the OSA group [14]. An existing prospective observational study of older men also demonstrated that patients with CSA were 2.58 times more likely to develop AF [15].

The interactions between AF, CSA and ischemic stroke are complex. Whether AF is associated with CSA in patients with stroke is not well studied. Elucidating the SDB characteristics that correlate with AF in patients with ischemic stroke may help clinicians identify specific pathophysiologic determinants of CSA in the secondary prevention of ischemic stroke. Therefore, the primary objective of this study was to investigate the association between AF and CSA in patients with ischemic stroke.

Methods

Participants and study design

This retrospective study consecutively included patients with stroke that were admitted for neurorehabilitation, had clinically suspected SDB, and that had undergone an in-hospital overnight PSG exam in the period from January 1, 2014 to December 31, 2017. The inclusion criteria were recent ischemic stroke (within 12 months) diagnosed by full clinical assessment with detailed neurological examinations and neuroimaging studies, including computed tomography (CT) or magnetic resonance imaging (MRI). The exclusion criteria were hemorrhagic stroke, traumatic brain injury, degenerative brain disorders, unstable vital signs, incomplete PSG data, and age less than 18 years. The basic clinical data, underlying diseases, and test results (PSG, echocardiography, CT or MRI) were collected. The presence of AF was documented by 12-lead electrocardiogram (ECG), or 24-hour Holter ECG, which included paroxysmal and persistent AF. The diagnosis of heart failure was established by Framingham criteria (at least 2 major or 1 major and 2 minor criteria for congestive heart failure) [16-17]. This study was approved by the institutional review board of Chang Gung Memorial Hospital (201900349B0).

Polysomnography and scoring method

Polysomnography for individual patients (Embla, USA; Compumedics, Australia) was performed at the sleep laboratory from 10:00 pm to 7:00 am. Measurements were recorded using 6-channel electroencephalography (F3-A1, F4-A2, C3-A1, C4-A2, O1-A1, and O2-A2), ECG, electro-oculography, chin and bilateral anterior tibial surface electromyography,

airflow sensors (nasal pressure cannula and oronasal thermistor), thoracic and abdominal movement detectors (inductance plethysmography), and finger pulse oximetry.

Obstructive apnea was defined as the absence of airflow for at least 10 seconds in the presence of respiratory effort, while central apnea was defined as the absence of airflow for at least 10 seconds without concurrent respiratory effort. Hypopnea was determined when the airflow dropped by ≥ 30% of pre-event baseline for ≥ 10 seconds in association with either ≥ 3% arterial oxygen desaturation or an arousal. Indices per hour of sleep included the apnea–hypopnea index (AHI; measuring the number of obstructive and central apneas and hypopneas per hour), obstructive apnea index (OAI; measuring the number of obstructive apnea events per hour), and central apnea index (CAI; measuring the number of central apnea events per hour). Scoring of respiratory events and sleep stages was performed based on the criteria of the American Academy of Sleep Medicine, version 2017 [18-19]. The oxyhemoglobin desaturation index (DI) was defined as the number of desaturation events (>3%) per hour. DI, mean SpO2 (oxyhemoglobin saturation measured by pulse oximetry), desaturation depth (difference between the highest and lowest SpO2 in 1 desaturation event) and mean desaturation (average desaturation depth) were calculated by the manufacturer and scored using Remlogic 2.0 software (Embla, USA).

Definition of CSA and CSR

Regarding the definition of CSA, analyses of previous studies, such as the Sleep Heart Health Study (SHHS) and the Outcomes of Sleep Disorders in Older Men (MrOS Sleep) cohorts, all mentioned the limitation of distinguishing central from obstructive hypopneas in clinical PSG scoring. Considering this scoring limitation, SHHS criteria (CAI ≥ 5 per hour) [15,20-21], instead of International Classification of Sleep Disorders (ICSD-3) criteria, were used to define CSA in our study. For the same reason, CSR was defined by the presence of at least 3 consecutive central apneas separated by a crescendo and decrescendo change in breathing amplitude with a cycle length of at least 40 seconds, and that there were at least 5 central apneas per hour associated with the crescendo/decrescendo breathing pattern recorded over ≥ 2 hours of monitoring [15,18-21].

Statistical Analysis

Patients were divided into 2 groups based on the presence of CSA. Statistical analyses were performed using SPSS 24.0 software (SPSS Inc., Chicago, Illinois, USA). The normality of each data distribution was assessed. The Chi-square test was used for categorical variables, the t-test for normally distributed continuous variables, and the Mann-Whitney U test for continuous variables with skewed distributions. The association between AF and subsequent CSA risk was assessed using logistic regression. The results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Values of $P<0.05$ were regarded as statistically significant.

Results

A total of 156 patients were initially recruited for our study. Thirty-six patients in this group were excluded due to the presence of hemorrhagic stroke, traumatic brain injury, or degenerative brain disorders; 2 patients that could not complete the PSG study and 2 that

did not have SDB were also excluded (Figure 1). Of the 116 patients that met the inclusion criteria, 71.6% were male. Average age and body-mass index (BMI) were 65.7 years and 24.9 kg/m^2, respectively. Twenty-six patients (22.4%) were found to have CSA; of those, 9 had CSR. Patients in the CSA group had a significantly greater prevalence of AF than those in the non-CSA group (42.3% versus 11.1%, P=.001). The differences in age, gender, BMI, neck circumference and Epworth Sleepiness Scale between the 2 groups were insignificant. Both groups had similar rates of co-morbid diseases (Table 1). PSG variables were analyzed in relation to the presence of CSA (Table 2). Overall, total sleep time, sleep structure, and sleep efficiency did not significantly differ between the 2 groups, but the CSA group had significantly higher AHI, CAI, DI, mean desaturation, total arousal, and respiratory arousal indices. Although the stroke territory analysis revealed that patients with infratentorial stroke had a significantly lower rate of CSA compared to that of patients with supratentorial stroke (0% versus 69.2%, P=0.048), multivariate logistic regression analysis revealed that only AF was significantly associated with the presence of CSA (OR, 7.381; 95% CI, 1.39-27.25; P=0.003). There were no statistically significant differences in stroke territory after adjustment for age, gender, BMI, neck circumference, chronic kidney disease and heart failure (Table 3).

Discussion

To the best of our knowledge, this is the first study to evaluate the association between AF and CSA in patients with ischemic stroke.

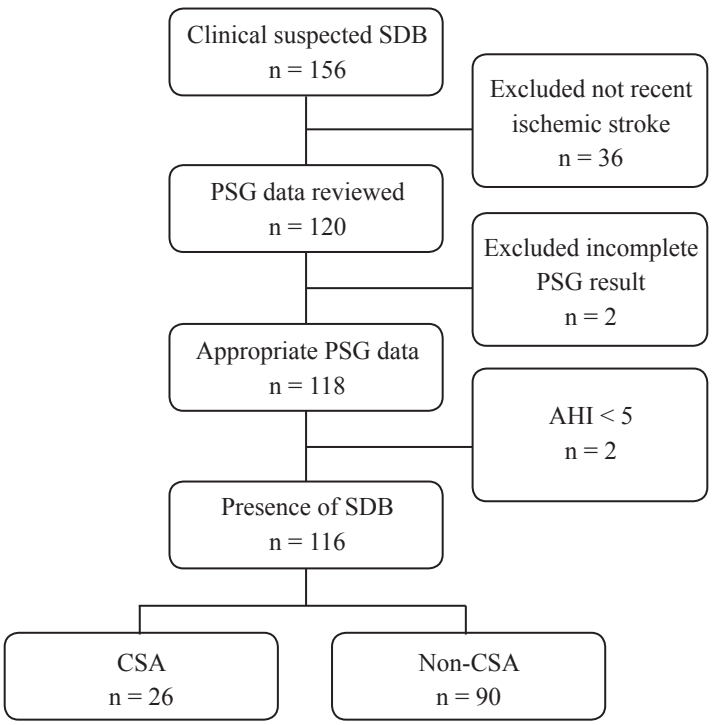

Fig. 1. Schematic Representation of the Studied Population
Acronyms: SDB: sleep-disordered breathing; PSG: polysomnography; AHI: apnea-hypopnea index; CSA: central sleep apnea

Table 1. Epidemiological Factors and Clinical Variables Stratified by the Presence of Central Sleep Apnea

	CSA (n=26)	Non-CSA (n=90)	*P* value
Age, years	68.7 ± 11.4	64.9 ± 11.5	0.118
Male, n (%)	22 (84.6%)	61 (67.8%)	0.094
BMI, kg/m^2	25.6 ± 3.9	24.6 ± 3.4	0.198
Neck circumference, cm	39.1 ± 3.2	37.7 ± 3.2	0.068
Epworth Sleepiness Scale	10.1 ± 4.9	9.1 ± 5.2	0.282
Stroke territory			0.048*
Supratentorial stroke, n (%)	18 (69.2%)	51 (56.7%)	
Infratentorial stroke, n (%)	0 (0.0%)	16 (17.8%)	
Multiple locations, n (%)	8 (30.8%)	23 (25.6%)	
Hypertension, n (%)	24 (92.3%)	80 (88.9%)	1.000
Diabetes mellitus, n (%)	12 (46.2%)	41 (45.6%)	0.957
Chronic kidney disease, n (%)	3 (11.5%)	7 (7.8%)	0.691
Parkinsonism, n (%)	0 (0.0%)	2 (2.2%)	1.000
Hyperthyroidism, n (%)	2 (7.7%)	2 (2.2%)	0.217
Heart failure, n (%)	5 (19.2%)	8 (8.9%)	0.163
Atrial fibrillation, n (%)	11 (42.3%)	10 (11.1%)	0.001*

* $p<0.05$

For continuous variables, means and SDs are presented; for categorical variables, number and percentage are given.

Acronyms: CSA = central sleep apnea; BMI = body mass index.

Meta-analyses of previous studies of patients with stroke and transient ischemic attack have determined that the prevalence of CSA was 7-12%, and the mean AHI was 26.0/h [4,22]. In our study, the prevalence of CSA was 22.4% of total SDB patients, and a much higher AHI was observed. These discrepancies may be due to the differences in our studied population compared with prior epidemiologic studies. The majority of our patients were admitted for neurorehabilitation; therefore, patients with a mild form of stroke or transient ischemic attack, without neurological sequelae, were not included. The prevalence of AF in our study was 18%, which falls within the 15% to 38% range that was reported in previous studies of patients with ischemic stroke [23-24]. Multivariate logistic regression analysis revealed that AF was strongly associated with CSA, even after adjusting for common confounders. This finding is consistent with previous evidence associating AF with CSA in different subgroups of individuals. In a retrospective analysis of 450 individuals with heart failure, Sin *et al* found that AF led to a 4-fold increase in the risk of CSA [25]. Leung *et al*. also reported that the prevalence of AF among patients with idiopathic CSA was significantly higher than that found in patients with OSA (27% versus 1.7%) [14]. In a large, retrospective national sample-based study from the US Veterans Administration national administrative databases, Ratz *et al*. found that an important predictor of CSA was AF, with a 1.83 odds ratio [5]. May *et al*. reported a prospective observational study that showed CSA could predict the incidence of AF

Table 2. Sleep and Sleep-Related Breathing Parameters in CSA and Non-CSA Patients

	CSA (n=26)	Non-CSA (n=90)	*P* value
TST, min	283.9 ± 56.6	284.1 ± 52.8	0.913
SE, %	71.5 ± 12.9	71.8 ± 12.5	0.871
N1 (%TST)	7.6 ± 5.3	6.8 ± 6.6	0.273
N2 (%TST)	35.0 ± 12.1	32.0 ± 10.6	0.181
N3 (%TST)	21.6 ± 16.5	25.9 ±14.9	0.081
REM (%TST)	9.6 ± 7.6	11.4 ± 6.5	0.227
Arousal index	28.8 ± 15.6	17.9 ± 11.8	0.004*
Respiratory	26.4 ± 15.2	15.2 ± 11.7	0.002*
Leg movement	0.0 ± 0.0	0.2 ± 1.1	0.372
Spontaneous	1.2 ± 1.8	2.7 ± 3.2	0.004*
PLM index	1.6 ± 4.7	4.4 ± 7.5	0.068
AHI	53.6 ± 15.3	36.3 ± 19.2	0.000*
OAI	11.2 ± 14.9	12.9 ± 16.6	0.713
CAI	18.0 ±14.2	0.6 ± 1.1	0.000*
DI	51.5 ± 14.7	32.6 ± 20.9	0.000*
Mean SpO2	93.0 ± 2.4	93.5 ± 2.1	0.214
Mean desaturation	10.9 ± 5.5	6.4 ± 3.1	0.000*

* $p<0.05$

Means and SDs are presented for each parameter.

Acronyms: CSA = central sleep apnea; TST = total sleep time; SE = sleep efficiency; PLM = periodic limb movements; AHI = apnea–hypopnea index; OAI = obstructive apnea index; CAI = central apnea index; DI = oxygen desaturation index; SpO2 = oxyhemoglobin saturation by pulse oximetry.

Table 3. Logistic Regression Models of Factors Associated with Central Sleep Apnea

Variable	OR	95% CI of OR	*P* value
Age	1.050	0.998-1.105	0.061
Male	6.032	0.880-41.361	0.067
BMI	1.139	0.928-1.390	0.217
Neck circumference	0.996	0.756-1.313	0.980
Chronic kidney disease	0.887	0.145-5.411	0.897
Heart failure	1.611	0.353-7.363	0.538
Atrial fibrillation	7.381	1.995-27.313	0.003*
Stroke territory	0.708	0.381-1.316	0.275

* $p<0.05$

[15]. The findings in our study were consistent with those of these different cohorts. AF conferred a 7-fold increase in the risk of CSA in patients with ischemic stroke. The stronger connection implied the complexity of the crosstalk between the heart, brain, and lungs and its role

in the development of CSA.

The reasons for the strong association between AF and CSA are not fully understood. Prior studies have found that AF leads to decreased ventricular function, including loss of atrial contractions, irregular ventricular filling, and an irregular high ventricular rate. The net result is lowered cardiac output and increased pulmonary vascular pressure. These hemodynamic changes can trigger hyperventilation and lead to hypocapnia through the stimulation of pulmonary-vagal irritant receptors [26-27]. Hypocapnia, combined with a lowered cardiac output, causes respiratory instability and induces CSA [12-13]. CSA results in further intermittent hypoxia and hypercapnia, and causes autonomic nervous system fluctuations and intrathoracic pressure swings that contribute to atrial arrhythmogenicity [2-3]. This vicious cycle seems to be how AF and CSA interact with each other. Furthermore, the central chemoreceptors play a primary role in respiratory control via a loop-gain feedback system that is dependent on the partial pressure of CO_2 ($PaCO_2$) detected. Lesions in this pathway can disturb chemosensitivity to $PaCO_2$ and contribute to CSA [28]. This is a possible reason why AF and CSA are even more severe in patients with stroke.

To define CSA, the current International Classification of Sleep Disorders (ICSD-3) requires a central AHI $\geq$ 5 with central apneas and hypopneas accounting for more than 50% of all apneas and hypopneas [1]. Controversies still remain regarding the recognition of central respiratory events, especially central hypopnea [18,29]. Esophageal pressure measurement through manometry or electromyogram is the gold standard method to assess respiratory effort and to differentiate between the different types of hypopneas [30]. However, this method is poorly accepted by patients due to the invasiveness and the costliness of the procedure, resulting in its limited use in routine clinical practice. Correctly defined central hypopneas using a PSG-based algorithm were reported in only 60.5% of cases, compared to those defined using esophageal pressure measurement [31]. Considering the limitations related to the definition of central hypopnea, an alternative CSA definition was used. In the SHHS, a CAI $\geq$ 5 was defined as CSA [20-21]. Since the same considerations relate to central hypopnea, the SHHS definition was used in our study.

The debate on the potential role of lesion location in the development of CSA in patients with stroke remains inconclusive. Several case-control studies showed higher AHI, and particularly CSA, in patients with infratentorial stroke than in patients with a supratentorial lesion [32-33]. However, other studies showed no association between lesion location and SDB type [34-36]. Our study demonstrated that there is a lack of association between lesion location and the presence of CSA after co-variant adjustment. This is still a controversial issue and further research is warranted.

However, our study has some limitations. The first limitation is the lack of a confirmed diagnosis of heart failure among our studied patients. This was a retrospective study and not all patients in our study population underwent detailed cardiac evaluation by cardiologists. We found no significant association between heart failure and CSA in our study, even though there is a CSA prevalence of 38.5% in patients with heart failure. This lack of a significant association may be due to underdiagnosed cases of heart failure. The lack of patients with severe heart failure in our study is another contributing factor. Patients with severe heart failure

could not be admitted to the neurorehabilitation ward due to the severity of their disease, and ultimately, they were not included in our study. Another limitation of this study is that only those patients admitted for in-patient stroke rehabilitation were included. We were not able to include patients with less severe stroke because they often underwent rehabilitation on an outpatient basis. Moreover, patients with severe stroke complicated by impaired mental status were also not analyzed since they could not undergo rehabilitation. Therefore, our conclusion may not be extended all patients with stroke.

Conclusion

AF is an independent predictor of CSA in patients with ischemic stroke admitted for neurorehabilitation. Increased awareness of SDB and AF as possible complicating factors in patients with stroke may alter the approach to their therapy. The co-aggregation of AF and CSA indicates the importance and clinical implications of simultaneous screening and management of both conditions in such individuals.

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Effect of Surgery Waiting Times on Disease-Free Survival of Patients with Screen-Detected cT1N0 Lung Adenocarcinoma

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Introduction: The relationship between waiting time for surgery and clinical outcomes of patients with early-stage screen-detected lung cancer remains unclear. This study aimed to evaluate if delayed surgery affects disease-free survival (DFS) of patients with screen-detected cT1N0 lung adenocarcinoma.

Methods: This retrospective study reviewed the data of 700 patients with a preoperatively undiagnosed single cT1N0 lung adenocarcinoma who underwent surgical resection in our institute from March 2011 to January 2016. The patients were classified as the early group if the waiting time for surgery was 30 days or less, and the delayed group if the wait was 31 days or longer. Propensity-matched analysis was used to compare the clinical outcomes of these groups.

Results: The median waiting time for surgery was 16 days. In total, 513 (73.3%) and 187 (26.7%) patients were in the early and delayed group, respectively. The early group was correlated with a larger consolidation-to-tumor ratio, solid component diameter, and total tumor diameter. Patients in the delayed group received more staging workup before surgery than those in the early group. Multivariable analysis showed that smaller consolidation-to-tumor ratio, solid component diameter and serum carcinoembryonic antigen level were significantly correlated with better DFS. Delay in surgery did not affect DFS. After propensity-matching of clinical and demographic characteristics, there was no difference in DFS among the early and delayed groups.

Conclusion: Among patients with a preoperatively undiagnosed single cT1N0 lung adenocarcinoma, the results showed that a delay of up to 30 days from the time of diagnosis to the time of surgery may not affect DFS, and may be considered safe for such patients. ***(Thorac Med 2020; 35: 10-20)***

Key words: disease-free survival, lung adenocarcinoma, surgery waiting time

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Introduction

With the increasing use of low-dose computed tomography (LDCT) for lung cancer screening, more people have been found to have early-stage lung cancer through image studies [1-3]. Surgical resection is the mainstay treatment for early-stage lung cancer. However, not all patients can receive surgery immediately, and some may experience a delay from the time of diagnosis to the time of surgery. Factors shown to be associated with a delay include age, race, comorbidity, and image studies for staging workup [4-5]. A delay in surgical resection may lead to disease progression [6-8], and some studies have found survival to be affected by a delay in surgery [4-5,9]. while others argue that survival is not affected by this delay [10-11].

Most screen-detected lung nodules are small, ground-glass nodules (GGN) in CT images [12-13]. Determining follow-up treatment for these screen-detected lung nodules is challenging for chest physicians and thoracic surgeons. There are currently several guidelines for follow-up treatment and management of screen-detected lung nodules [13-14]. These guidelines suggest when biopsy or surgery is necessary and when the nodules should be observed. However, research analyzing the effects of an extended waiting time for surgery on the prognosis of screen-detected early-stage lung cancer is lacking.

The purpose of this retrospective study is to investigate how a delay in surgical treatment of screen-detected early-stage lung cancer affects clinical outcomes, and to provide information for future treatment guidelines. Since the majority of screen-detected lung nodules is classified as adenocarcinoma, especially in Asian countries, this study will specifically focus on the population of patients diagnosed with screen-detected cT1N0 lung adenocarcinoma in Asian countries.

Materials and Methods

The medical records of 1836 consecutive patients who underwent lung tumor resection by a single thoracic surgical team using the same clinical protocols, care patterns, and perioperative orders at National Taiwan University Hospital (NTUH), from March 2011 to January 2016, were reviewed retrospectively. The medical records of 965 patients with preoperatively undiagnosed single cT1N0 lung tumors were analyzed. Staging was based on the eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging system. The patient enrollment algorithm can be seen in Figure 1. Finally, 700 patients with cT1N0 lung adenocarcinoma were enrolled in this study. The study was approved by the NTUH Research Ethics Committee (project approval number 201804035RINB).

All 700 enrolled patients were asymptomatic and the lung tumor was confirmed either by LDCT lung cancer screening or incidental finding on imaging studies performed for other purposes. In our group, the surgical indications for patients with indeterminate lung nodules included enlargement of the nodule size, persistence of a part-solid GGN with a solid component of 5.0 mm or more, and persistence of a pure GGN with a diameter of 8.0 mm or more on follow-up CT images. In patients with stationary part-solid GGN with a solid component of less than 5.0 mm or pure GGN with a diameter of less than 8.0 mm, tumor excision was performed at the patient's request, due to anxiety about the condition. The staging workup included brain

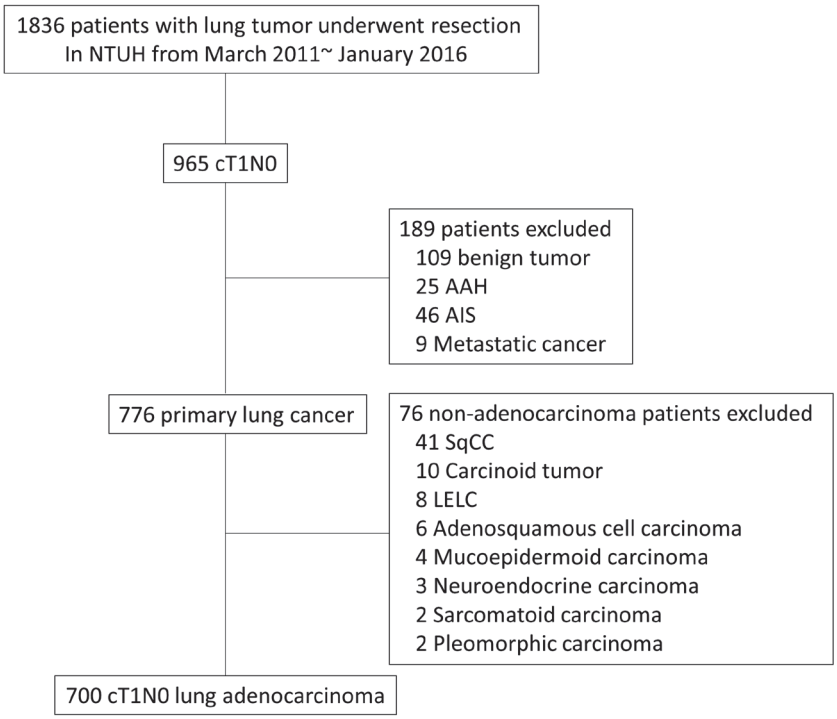

Fig. 1. Algorithm for patient selection.
AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; SqCC, squamous cell carcinoma; LELC, lymphoepithelioma-like carcinoma

magnetic resonance imaging (MRI), brain CT, whole body positron emission tomography (PET) and bone scanning. For those patients who did not undergo these procedures before surgery, a staging workup (brain MRI/CT and PET/bone scan) was completed postoperatively, after confirmed diagnosis.

Diagnosis timing was defined as the time that chest surgeons considered surgery for this indeterminate nodule and made arrangements for staging workup or surgery. The timing of diagnosis was retrospectively confirmed by reviewing the medical records. Surgery waiting time was further defined as the duration from the time of diagnosis to the day of surgery. The patients were further classified into 2 groups according to their surgery waiting time. The early group was comprised of patients whose waiting time was within 30 days, while patients in the delayed group had a waiting time longer than 30 days. The 30-day cutoff value was chosen based on previous literature and the distribution of surgery waiting time for the study cohort [5].

After the patients underwent operation, they were regularly monitored in the outpatient clinic using various examinations, including chest CT, every 3 months for the first 2 years. Thereafter, patients were regularly monitored with similar examinations every 3 to 6 months. If recurrence was suspected clinically, additional workup would be done for confirmation.

Clinical information was collected from the medical records. Parameters collected from CT images included the CT total diameter, CT solid diameter, consolidation-to-tumor ratio (C/T ratio), and depth of the tumor. These image characteristics were determined through a standard picture archive and communication system

using a commercially available viewer (IMPAX 5.2; Agfa HealthCare, Mortsel, Belgium). Two (of 6) thoracic surgeons (T.-M. Tsai, H.-C. Liao, X.-H. Chiang, K.-C. Tsou, C.-Y. Liu, and M.-W. Lin) independently used this viewer and the characteristics were recorded after the surgeons reached a consensus.

Descriptive statistics are expressed as mean ± standard deviation. Differences in baseline characteristics between the 2 surgical groups were compared using a Chi-square test for categorical variables and a t-test for continuous variables before propensity score (PS) matching. These values were also estimated, after PS matching, using McNemar's test or Bowker's test for categorical variables and a paired t-test for continuous data. Based on a full cohort, the differences in disease-free survival (DFS) between the 2 surgery groups were plotted using the Kaplan-Meier method, and the log rank test was performed to compare the difference. To minimize any bias in the full cohort due to confounding by indications, the multivariable Cox proportional hazards regression model was used to adjust for significant confounding factors in the univariable model, and similar comparison groups were created using PS matching based on the Greedy matching algorithm. The PS was calculated by logistic regression, and included CT solid diameter, age, sex, smoking status, prevalence of diabetes mellitus (DM), cardiovascular disease, hypertension (HTN), or end-stage renal disease (ESRD), depth, CEA level, surgical method, staging workup, forced vital capacity (FVC, %) and forced expiratory volume in 1 second (FEV1, %). The C/T ratio and total tumor diameter were not matched due to their significant relation to the CT solid diameter. Statistical significance was set at $P<0.05$. Data were analyzed by statisticians using the Statistical Package for the Social Sciences, version 24 (SPSS Inc., Chicago, IL, USA) and SAS 9.4 (SAS Institute Inc.).

Results

Our study included 700 patients with a single cT1aN0 lung adenocarcinoma and a median follow-up time of 37.0 months. Over half of the patients were female (66.1%; 463/700) and nonsmoker (88.4%; 619/700). The solid component diameter in the CT images was 0.0-1.0 cm, 1.0-2.0 cm and 2.0-3.0 cm in 487 (69.6%), 142 (20.3%) and 71 (10.1%) patients, respectively. The median waiting time from the time of diagnosis to the time of surgery for the entire cohort was 16 days, while that for the early and delayed group, respectively, was 13 days and 51 days. There were 513 (73.3%) and 187 (26.7%) patients in the early and delayed group, respectively. The patients in the delayed group had a significantly smaller C/T ratio ($P<0.001$), smaller solid diameter ($P<0.001$) and total tumor diameter ($P<0.001$), according to CT images. Also, patients in the delayed group were more likely to receive staging workup before operation ($P<0.001$) and sublobar resection ($P<0.001$). There were no other statistically significant differences between the 2 groups. Demographic and clinical data are detailed in Table 1.

Univariable analysis identified several significant risk factors for recurrence: surgery waiting time of less than 30 days, older age, male, underlying cardiovascular disease, larger C/T ratio, larger CT image solid component diameter, larger CT total diameter, elevated serum CEA level, surgical method used for lobectomy, and poor preoperative pulmonary function (Table 2). In multivariable analysis, C/T ratio

Table 1. Demographic and Clinical Features of cT1N0 Lung Adenocarcinoma Patients who Received Early and Delayed Surgery.

Variable	Full Cohort			Propensity-matched Cohort		
	Early (≤ 30 days)	Delayed (> 30 days)	*P* value	Early (≤ 30 days)	Delayed (>30 days)	*P* value
Patient No.	513	187		177	177	
Age (years)			0.489			>0.99
≤65	373 (72.71)	131 (70.05)		124 (70.06)	124 (70.06)	
>65	140 (27.29)	56 (29.95)		53 (29.94)	53 (29.94)	
Sex			0.338			0.646
Female	334 (65.11)	129 (68.98)		127 (71.75)	123 (69.49)	
Male	179 (34.89)	58 (31.02)		50 (28.25)	54 (30.51)	
Smoking	59 (11.5)	22 (11.76)	0.923	17 (9.6)	19 (10.73)	0.715
DM	39 (7.6)	11 (5.88)	0.434	10 (5.65)	10 (5.65)	>0.99
Cardiovascular disease	161 (31.38)	60 (32.09)	0.860	53 (29.94)	54 (30.51)	0.900
ESRD	5 (0.97)	2 (1.07)	1.000	3 (1.69)	1 (0.56)	0.317
C/T ratio			<0.001			0.211
0-25%	242 (47.17)	118 (63.1)		121 (68.36)	110 (62.14)	
25-50%	74 (14.42)	35 (18.72)		22 (12.43)	34 (19.20)	
≥50%	197 (38.40)	34 (18.18)		34 (19.20)	33 (18.64)	
CT solid diameter			<0.001			0.753
0-1 cm	328 (63.94)	159 (85.03)		148 (83.62)	150 (84.75)	
1-2 cm	116 (22.61)	26 (13.9)		26 (14.69)	25 (14.12)	
2-3 cm	69 (13.45)	2 (1.07)		3 (1.69)	2 (1.13)	
CT total diameter			<0.001			0.581
0-1 cm	125 (24.37)	61 (32.62)		60 (33.90)	56 (31.63)	
1-2 cm	210 (40.94)	97 (51.87)		83 (46.89)	92 (51.98)	
2-3 cm	135 (26.32)	27 (14.44)		29 (16.38)	27 (15.25)	
≥3 cm	43 (8.38)	2 (1.07)		5 (2.82)	2 (1.13)	
Tumor depth on CT			0.186			0.873
≥1.5 cm	126 (24.56)	37 (19.79)		36 (20.34)	35 (19.77)	
<1.5 cm	387 (75.44)	150 (80.21)		141 (79.66)	142 (80.23)	
CEA level			0.070			0.763
≤5	478 (93.18)	181 (96.79)		172 (97.18)	171 (96.61)	
>5	22 (4.29)	6 (3.21)		5 (2.82)	6 (3.39)	
N/A	13 (2.53)	0 (0)				0.637
Surgical method			<0.001			
Sublobar	272 (53.02)	149 (79.68)		142 (80.23)	140 (79.1)	
Lobar	241 (46.98)	38 (20.32)		35 (19.77)	37 (20.9)	
Staging workup	373 (72.71)	160 (85.56)	<0.001	151 (85.31)	151 (85.31)	>0.99
PFT						
FEV_1%	108.6 ±18.5	109.9 ±19.3	0.392	109.7 (19.2)	109.5 (18.9)	0.870
FVC%	110.9 ±56.7	113.7 ±68.7	0.627	115.9 (92.0)	113.5 (69.7)	0.789

Data are presented as mean ± SD (range) or number (percentage).

C/T ratio, consolidation-to-tumor ratio; CT, computed topography; CEA, carcinoembryonic antigen; DM, diabetes mellitus; ESRD, end-stage renal disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PFT, pulmonary function test; N/A, not available; SD, standard deviation.

Table 2. Univariable Analyses of Correlations between Clinicopathological Features and Disease-Free Survival of cT1N0 Lung Adenocarcinoma Patients.

Variables	HR (95%CI)	*P* value
Delay in surgery	0.29 (0.11 - 0.72)	0.008
Age (years)		
>65 vs ≤65	2.16 (1.29 - 3.63)	0.004
Sex		
Male vs Female	1.89 (1.13 - 3.16)	0.016
Smoking	1.24 (0.59 - 2.62)	0.570
DM	1.85 (0.84 - 4.09)	0.127
Cardiovascular disease	2.51 (1.5 - 4.21)	0.001
C/T ratio		
25-50% vs 0-25%	8.30 (1.61 - 42.8)	0.012
≥50% vs 0-25%	49.18 (11.97 - 202.12)	<0.001
CT solid diameter		
1-2 cm vs 0-1 cm	14.25 (5.80 - 35.02)	<0.001
2-3 cm vs 0-1 cm	43.61 (18.09 - 105.12)	<0.001
CT total diameter		
1-2 cm vs 0-1 cm	9.65 (1.28 - 73.02)	0.028
2-3 cm vs 0-1 cm	34.21 (4.65 - 251.61)	0.001
≥3 cm vs 0-1 cm	60.26 (7.95 - 456.82)	<0.001
Tumor depth on CT		
≥1.5 cm vs <1.5 cm	1.12 (0.62 - 2.02)	0.704
CEA level		
>5 vs ≤5	7.17 (3.69 - 13.93)	<0.001
Surgical method		
Lobar vs Sublobar	2.62 (1.50 - 4.58)	0.001
Staging workup	0.84 (0.46 - 1.54)	0.572
Pulmonary function test		
FVC%	0.98 (0.97 - 1)	0.028
FEV_1%	0.99 (0.97 - 1)	0.074

DM, diabetes mellitus; C/T ratio, consolidation-to-tumor ratio; CT, computed topography; CEA, carcinoembryonic antigen, FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity

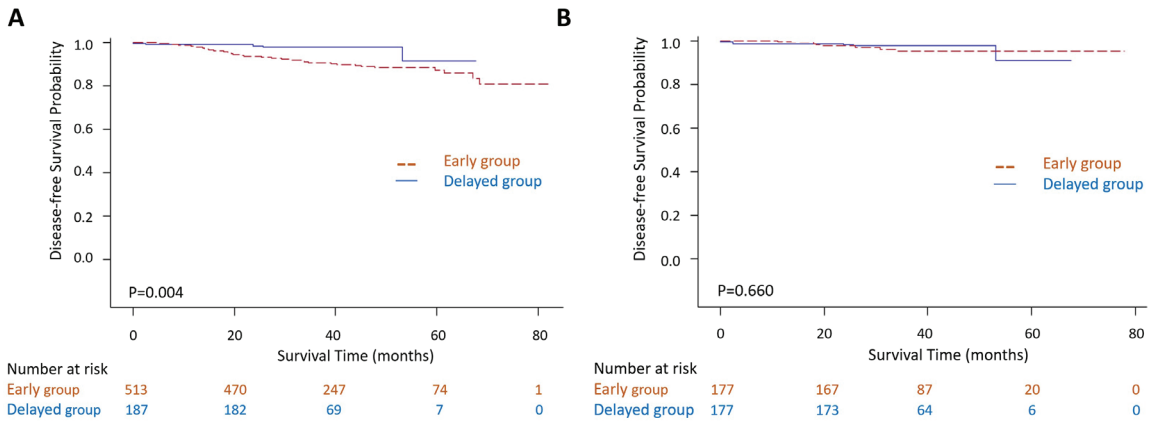

Fig. 2. Kaplan-Meier survival curves for disease-free survival. (A) Before propensity-matching (B) After propensity-matching

Table 3. Multivariable Analyses of Correlations between Clinicopathological Features and Disease-Free Susvival of cT1N0 Lung Adenocarcinoma Patients.

Variables	HR (95%CI)	*P* value
Delay in surgery	1.00 (0.37 - 2.73)	>0.99
Age (years)		
>65 vs ≤65	1.03 (0.54 - 1.98)	0.921
Sex		
Male vs Female	1.20 (0.66 - 2.16)	0.550
Cardiovascular disease	1.46 (0.81 - 2.61)	0.208
C/T ratio		
25-50% vs 0-25%	3.93 (0.63 - 24.42)	0.142
≥50% vs 0-25%	7.06 (1.09 - 45.63)	0.040
CT solid diameter		
1-2 cm vs 0-1 cm	3.68 (0.98 - 13.82)	0.054
2-3 cm vs 0-1 cm	11.02 (2.13 - 56.94)	0.004
CT total diameter		
1-2 cm vs 0-1 cm	1.65 (0.18 - 15.32)	0.660
2-3 cm vs 0-1 cm	1.28 (0.12 - 13.75)	0.841
≥3 cm vs 0-1 cm	1.44 (0.12 - 16.83)	0.773
CEA level		
>5 vs ≤5	4.11 (1.93 - 8.77)	<0.001
Surgical method		
Lobar vs Sublobar	1.07 (0.55 - 2.08)	0.849
FVC%	1 (0.98 - 1.01)	0.564

DM, diabetes mellitus; C/T ratio, consolidation-to-tumor ratio; CT, computed tomography; CEA, carcinoembryonic antigen; FVC, forced vital capacity

≥50% (*P*=0.040), CT solid component diameter larger than 2.0 cm (*P*=0.004), and abnormal serum CEA level (*P*<0.001) remained significant independent risk factors for recurrence (Table 3). Notably, early or delayed surgery waiting time was not associated with a difference in outcome (*P*>0.99), using multivariable analysis.

Multivariable analysis was repeated with different cutoff values of 40, 50, and 60 days for delay, with the other factors remaining the same. The results, again, showed that delayed surgery had no effect on clinical outcome. Moreover, when a 60-day cutoff was used, there were only 71 patients in the delayed group, and the analysis became underpowered to detect a survival difference.

PS matching yielded 177 paired patients in each group (Table 1). There were no significant differences in demographics and clinical characteristics between the early and delayed groups after matching. The survival curve of the 2 groups, before and after PS matching, is displayed in Figure 2. The curve demonstrates that delay was not associated with differences in DFS (*P*=0.660).

Discussion

This study examined whether the outcome of clinical T1N0 adenocarcinoma is affected by

timing of surgery. The median waiting time was 16 days, and the "delayed group" was defined as having a surgery waiting time longer than 30 days. In this study, the delayed group had significantly better DFS according to univariable analysis, but multivariable analysis showed no effect on DFS. The median waiting time in this study was shorter than in other studies, in which the median surgery waiting time ranged from 20 to 38 days [4-5,10-11]. The shorter waiting time in this study is largely due to the unique design and wide coverage of Taiwan's National Health Insurance [15-16]; that is, the costs of surgery and hospitalization are mostly covered by the National Health Insurance program in Taiwan. Furthermore, the patient can visit the outpatient department of a medical center without referral. Therefore, about one-fourth of patients with LDCT screen-detected or an incidental finding of indeterminate lung nodules in Taiwan came to our institute for a second opinion and further surgical intervention. This may be the reason for the shorter median surgery waiting time in this study, compared to the longer median waiting time in other studies.

Prior studies have shown that a delay in treatment might lead to disease progression [6], but the results of univariable analysis in this study showed worse DFS in the early group. In the present study, the delayed group had a significantly smaller C/T ratio, and smaller solid component and total tumor diameter on CT images. This result is related to the selection bias of thoracic surgeons. Surgeons may prefer to perform surgery earlier in patients with larger tumors or tumors with a more aggressive presentation, to prevent further tumor progression during the longer surgery waiting time. Similar results have been shown in previous studies [17-18]. Other causes of delay include receiving staging workup imaging before surgery. Gomez *et al*. suggested delays between diagnosing and treating non-small cell lung cancer (NSCLC) were associated with the arrangement of PET for staging [4]. Our results showed similar findings, in that patients in the delayed group received more staging workup than those in the early group. Treatment would be provided earlier if the clinical practice protocol could be changed to reduce the time to staging workup.

All of the previous studies were performed using lung cancer databases. The correlation of surgery waiting times with prognosis in early-stage lung cancer is controversial [4-5,9-11]. Yang *et al* used different cutoff values for the evaluation of stage I squamous cell carcinoma patients [5], with a 38-day waiting time affecting overall survival, but a 30-day waiting time not having an effect. Samson *et al* reported that delay in surgery is significantly associated with decreased median survival in clinical stage I NSCLC [9]. Similarly, Gomez *et al* reported that diagnosis-to-treatment intervals of less than 35 days were associated with improved survival for patients with localized NSCLC, and suggested that reducing the time to treatment may improve survival for patients with manageable disease at diagnosis [4]. However, 2 other studies showed results similar to ours; they indicated that delayed surgery time may not affect clinical outcomes in early-stage NSCLC [10-11]. The different conclusions of each study may result from different study populations, despite all studies focusing on early-stage lung cancer (Table 4).

Ninety percent of patients in this study had a tumor solid component diameter ≤ 2.0 cm. The 5-year DFS was 83% in this study. This study included screen-detected indeterminate lung nodules; therefore, the staging may be

Table 4. Summary of Studies Discussing the Survival Correlation of Delayed Surgery in Early-Stage Lung Cancer Patients.

	Study period	Data source	Patients	Histologic type	Clinical stage	Median surgery waiting time (days)	Cut-off value for delayed surgery (days)	Survival Correlation
This study	2011-2016	Taiwan	700	Adenocarcinoma	IA	17	30	No correlation to DFS
Yang *et al* [5]	2006-2011	United States *	4984	SqCC	IA	38	30 or 38	30-day: No correlation to OS 38-day: Poor OS
Samson *et al* [9]	1998-2010	United States *	27022	NSCLC	I	N/A	56	Poor OS
Gomez *et al* [4]	2004-2007	United States +	7960	NSCLC	Localized	27	35	Poor OS
Aragoneses *et al* [10]	1993-1997	Spain π	1082	NSCLC	I, II	35	1-20, 21-40, 41-60, >60	No correlation to OS
Shin *et al* [11]	2006	Korea **	398	NSCLC	Localized, regional	20	<7, 7-28, 28-56, 56-84, >84	No correlation to OS

DFS, disease-free survival; NSCLC, Non-small-cell-lung cancer; OS, overall survival; SqCC, squamous cell carcinoma

* National Cancer Data Base (NCDB)

+ Surveillance, Epidemiology, and End Results (SEER)-Medicare and Texas Cancer Registry, (TCR)-Medicare database

π Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumonology and Thoracic Surgery (GCCB-S) database

** Korean Central Cancer Registry (KCCR) database

earlier than in other studies, with stage IA1-IA2 being in the majority in this study. Further, the definition of diagnosis may differ among studies. The diagnosis in this study was standardized and decided on by the surgeon based on radiological imaging, and the timing that indicated surgical intervention was evident in the medical records. Aragoneses *et al* included patients diagnosed with pathological biopsy only [10]. In contrast to the present study, many other studies did not have uniform criteria for diagnosis due to the lack of clear information in the database. Diagnosis by pathological biopsy would result in a shorter defined waiting time compared to using radiological imaging for diagnosis.

The findings in this study give insight into the disease progression of early-stage lung cancer. As LDCT becomes increasingly used to screen for lung cancer in many countries, early-stage lung cancer will comprise a larger proportion of newly diagnosed lung cancer cases [1-3]. Currently, there are several guidelines for follow-up and management of screen-detected lung nodules [13-14]. However, there is still a lack of research that focuses on the correlation between delayed surgery and clinical outcomes among patients with cT1N0 lung adenocarcinoma. The results of the present study suggest that screen-detected cT1N0 lung adenocarcinoma had little to no progression within 1 month after the decision to perform surgery. Due to easy access to medical treatment in our country, most patients with newly diagnosed lung cancer are treated within 1 month. The 1-month waiting time may be considered safe for screen-detected early-stage lung adenocarcinoma.

This study has several limitations. First, it was a retrospective study from a single center, which could potentially have confounding and selection bias. We tried to limit the bias by using multivariable analysis and propensity matching. Second, this study discusses only clinical T1N0 adenocarcinoma, in which the diagnosis

was confirmed after surgery. Therefore, the results of this study may not apply to other stages or histological types of lung cancer. Third, the time interval between CT examination for lung nodule detection and diagnosis timing might be different in our study cohort. Diagnosis timing was defined as the time that the chest surgeons considered surgery for these nodules. The differences in the time interval between initial detection and diagnosis timing may result in lead time bias. Besides, the median waiting time for surgery was relatively short in this study. This may be related to both our surgical team and the National Health Insurance system in Taiwan having the same treatment policy [15-16]. Although receiving surgery within 30 to 60 days did not result in worse clinical outcomes in the present study, the maximum safe waiting period is still unknown. Compared with other related studies using national databases [4-5,9-11], the disadvantages of the present study are the relatively small patient population and the lack of diversity within the study cohort. However, the advantage of this study compared to other studies using national databases is that information on surgery waiting time was very clear. The medical report of each patient in this study was carefully rechecked. The patient genetic backgrounds and clinical behaviors of lung cancer may differ from western to eastern countries [19]. Only 1 previous study has focused on an Asian population [11], and that study reported the same conclusion as this study, which may provide useful information for clinicians from Asian countries. Further multicenter studies with diverse study populations are necessary to validate these results and to evaluate the upper limit of delays that would not affect survival.

Conclusion

This is the first report discussing the effect of surgery waiting times on prognosis for screen-detected early-stage lung cancer. Our results showed that a delay in surgery from diagnosis of up to 30 days may not affect DFS in screen-detected cT1N0 lung adenocarcinoma, and 30 days of waiting time may be considered safe for such patients. Factors associated with a delay in surgery include staging workup before operation and smaller tumor on CT images.

Acknowledgments

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Safety Issues Associated with Midazolam Use in Elderly Patients Undergoing Procedural Sedation for Flexible Bronchoscopy

Meng-Cheng Ko, Ting-Yu Lin, Allen Chung-Cheng Huang, Yo-Lun Lo

Introduction: The incidence of lung disorders and cancers is higher in elderly individuals, who constitute a large proportion of patients who require bronchoscopy. This study aimed to assess safety issues in elderly patients undergoing a rigorous sedation protocol for flexible bronchoscopy (FB).

Methods: A retrospective analysis of 249 patients (inpatients and outpatients) who underwent midazolam sedation for FB during an 18-month period was performed. Patients were divided into 2 groups according to age (elderly [≥ 65 years] and young [< 65 years]). Patients were pretreated with alfentanil (5 mcg/kg), and then, based on clinical judgment, they received incremental midazolam boluses to achieve moderate sedation.

Results: Elderly patients accounted for 50% (n=124) of all patients analyzed. Of all 249 patients who received midazolam sedation, 37% experienced hypoxemia. Compared with the young patients, the elderly patients exhibited a significantly greater desaturation ratio (45% vs 30%; *P*=0.01) and lower hypotension rate (1% vs 7%; *P*=0.01).

Conclusion: Hypoxemia is a common safety issue in sedation for FB. Elderly patients undergoing midazolam sedation for FB were more likely to develop desaturation than young patients. Hypotension episodes were more likely to occur in young patients undergoing midazolam sedation for FB than in elderly patients. ***(Thorac Med 2020; 35: 21-27)***

Key words: safety issues, midazolam, elder, procedural sedation

Introduction

Procedural sedation using sedatives for flexible bronchoscopy (FB) is widely performed. As populations age, the prevalence of lung cancer increases, and the incidence of lung cancer in older patients is higher; as such, the elderly constitute a large proportion of patients who require bronchoscopy [1]. Although bronchoscopy has been reported to have a 0.3% risk of complications [2], hypotension and hypoxemia during sedation may occur. When mean arterial pressure (MAP) is <65 mmHg, the constant autoregulation of cerebral blood flow becomes

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pressure-passive [3]. Hypoxemia may indicate that the patient is already in a hypoventilation state or that there is an airway obstruction that must be addressed. Moreover, aging increases sensitivity to sedative drugs and reduces lung function [4-5], which should prompt caution given the possibility of sedative-related hypotension and hypoxemia in elderly individuals.

The safety of midazolam sedation for FB in elderly patients (age ≥65 years) remains unclear. This study retrospectively evaluated data from a previous prospective randomized study addressing safety issues in moderately sedated elderly patients who underwent a rigorous sedation protocol. We analyzed the safety profiles of a commonly used sedative drug (midazolam) in elderly patients.

Methods

Using data from a previous prospective randomized study [6], a retrospective analysis of 249 hospitalized patients and outpatients who underwent sedation with midazolam (No. 97-0257B) for FB was performed. Given the retrospective nature of the study, the requirement for formal ethics committee approval was waived. Patients were divided according to age (elderly [≥65 years] and young [<5 years]) for analysis. The American Society of Anesthesiologists (ASA) classification was used to define preprocedural risk. Exclusion criteria are detailed in the authors' previous work [6].

Induction was performed using alfentanil following a 2 mg midazolam bolus. If the patient was not adequately sedated after 2 min, additional midazolam boluses were given in increments of 1 mg/min until moderate sedation (purposeful response to verbal or tactile stimulation) was achieved. For maintenance, 1 mg/min midazolam boluses were administered based on clinical judgment to achieve moderate sedation, or if persistent patient movement or severe cough interfered with the procedure.

Blood pressure was monitored using an automated pressure cuff, and heart rate and rhythm were monitored using 3-lead electrocardiography. A peripheral pulse oximeter was used to monitor oxyhemoglobin saturation (SpO_2), while a nasal cannula delivered 2 L/min of oxygen to the patient. An intravenous catheter was placed in the forearm for drug administration. All parameters were monitored continuously, except for blood pressure, which was recorded every 3 min. Pre-sedative vital signs, including heart rate, systolic blood pressure (SBP), MAP, and SpO_2, were recorded. One investigator responsible for sedation techniques monitored cardiopulmonary functions to determine the need for intervention(s), such as increasing oxygen delivery to 6 L/min to maintain oxygen saturation >90%, jaw support, manual-assisted ventilation with an Ambu bag for persistent desaturation to maintain adequate airways or fluid resuscitation, and leg elevation for hypotension. After the procedure, the patients were transferred to the recovery room and monitored continuously until full recovery. Recovery time to orientation was defined as the duration between completion of FB and the point when the patient could spontaneously open their eyes, recall their date of birth, and correctly perform the finger-to-nose test. After recovery, the patients responded to a global tolerance index for the entire procedure on a 10-point verbal analog scale (VAS; 0: no bother, 10: worst imaginable).

Adverse events were evaluated as the proportion of patients who experienced at least 1 hypotension event (SBP 90 mmHg or MAP 65

mmHg, of any duration) or hypoxemia (SpO_2 90%, of any duration) during FB. The lowest SpO_2 and blood pressure values were also recorded. The sedative doses and the duration of induction, as well as of the procedures, were recorded. Induction time was defined as the duration between alfentanil administration and the point when the desired sedation level was attained. FB duration was defined as the time between insertion and removal of the bronchoscope.

Statistical analysis of normally distributed data between the elderly and young patients was performed using Student's t test, and proportions were analyzed using the chi-squared test. The relationship between sequential variable data was analyzed using Spearman's correlation; statistical significance was set at $p < 0.05$. Statistical analyses were performed using SPSS version 22 (IBM Corporation, Armonk, NY, USA).

Results

Midazolam-sedated elderly patients had a significantly higher ASA score (53% of all midazolam-sedated patients), pre-procedural SBP (148 ± 24.4 mmHg), pre-procedural MAP (100.4 ± 18.2 mmHg), and male patient ratio (63.7%) than the young patients (Table 1). Except for ASA and pre-procedure blood pressure, both age groups had comparable basic characteristics, indications, vital signs before the procedure, and FB procedures. Elderly patients had

Table 1. Patient Characteristics

	Midazolam	
Characteristic	Age < 65 (n=125)	Age ≥ 65 (n=124)
ASA ≥ 3 (%)	34.4*	53.2*
Male sex (%)	48.0*	63.7*
Indication (%)		
Mediastinum mass	22.4	26.6
Lung mass or nodule	38.4	50.0
Lung infiltration	13.6	15.3
Endobronchial obstruction	11.3*	2.42*
Vital signs before FB		
Saturation (%)	97.8 ± 2.6	97.7 ± 2.4
SBP (mmHg)	134.0 ± 20.5*	148.0 ± 24.4*
MAP (mmHg)	93.0 ± 22.7*	100.4 ± 18.2*
Heart rate (beats/min)	83.2 ± 18.6	80.0 ± 16.8
Drug dose and sedation time		
Total dose of drug (mg)	7.6 ± 3.8	6.1 ± 3.9
Procedure time (min)	24.9 ± 17.9	26.0 ± 14.4
Induction dose (mg)	4.4 ± 2.8*	3.2 ± 2.0*
Induction time (min)	5.9 ± 3.2*	4.7 ±2.8*
Recovery time (min)	28.4 ± 25.9	30.9 ± 27.7
Cooperation (VAS)	1.8 ± 2.0	1.6 ± 1.9

Data presented as mean ± standard deviation unless otherwise indicated.

Acronyms: ASA: American Association of Anesthesiologists classification; VAS: verbal analog scale; FB: flexible bronchoscopy; MAP: mean arterial pressure; SBP: systolic blood pressure. *Statistically significant difference between elderly and young patients ($p < 0.05$).

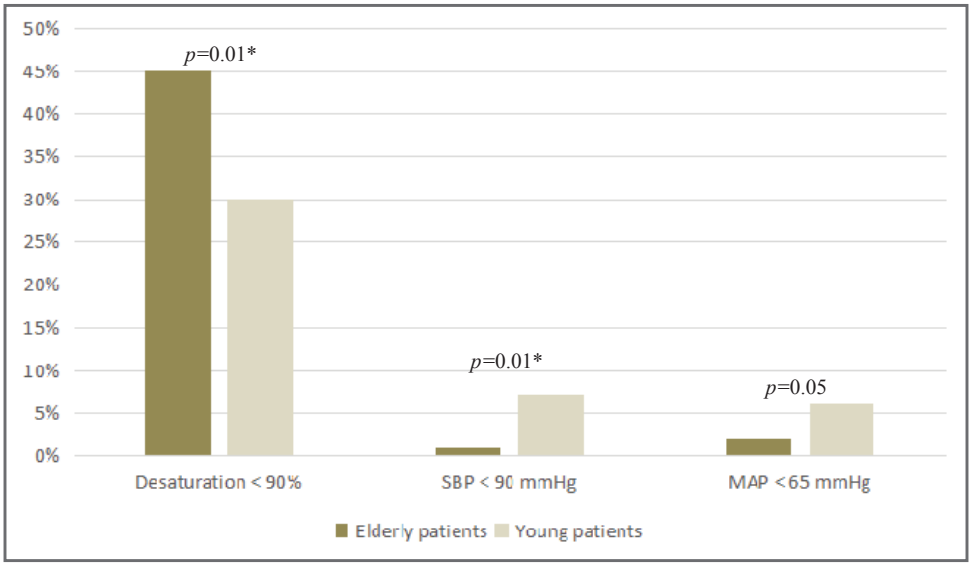

Fig. 1. Comparison of elderly (≥65 years of age [n=124]) and young (<65 years of age [n=125]) patients among those who underwent midazolam sedation for flexible bronchoscopy. *Statistically significant difference. SBP: systolic blood pressure; MAP: mean arterial pressure.

a significantly shorter induction time (4.7 ± 2.8 min), required lower induction doses (3.2 ± 2.0 mg), and exhibited better cooperation (1.6 ± 1.9) than the young patients (Table 1).

Of the 249 patients who underwent midazolam sedation, 37% experienced hypoxemia. Compared with the young patients, elderly patients exhibited a significantly greater desaturation ratio (45% vs 30%; p=0.01) (Figure 1). The rate of hypotension in the elderly patients during midazolam sedation or recovery was significantly lower than that in the young patients (1% vs 7%; p=0.01) (Figure 1). Reduction in MAP was 14.7 ± 13.3 mmHg in the midazolam group. Differences in midazolam-related MAP reduction between the elderly and young patients (15.17 ± 14.34 vs 14.12 ± 11.99 mmHg, respectively) were not statistically significant. Spearman's correlation analysis of midazolam was not significant (r=0.10, p=0.12) (Figure 2). All patients with hypotension events recovered spontaneously or following proper management, and vasopressor administration was not required.

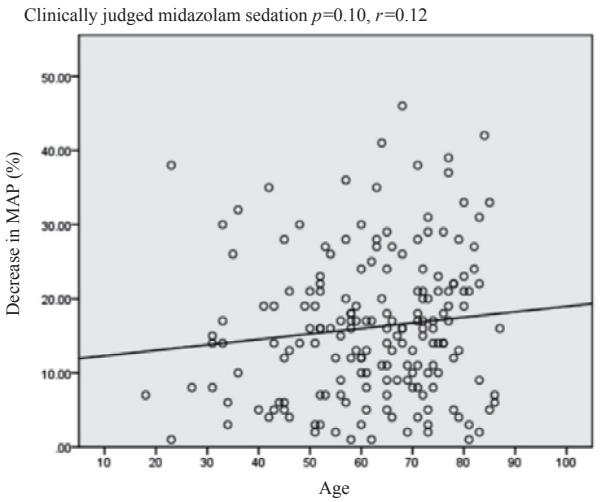

Fig. 2. Spearman's correlation between midazolam groups. x axis = age, y-axis (MAP before sedation – lowest MAP during sedation) / MAP before sedation. MAP: mean arterial pressure.

Severe complications, such as respiratory failure, were not common in these patients; mortality was also not recorded. Important complications are documented in the previously

published report [6], and the patients recovered without sequelae.

Discussion

Our results revealed that elderly patients were more likely to develop desaturation than young patients during midazolam sedation for FB. This study revealed that desaturation was a common safety issue among the elderly patients undergoing FB sedation, and must be addressed. Elderly patients undergoing midazolam sedation exhibited a significantly shorter induction time, lower induction doses, and better cooperation. In our study, elderly patients had a higher ASA score than the young patients, which may indicate more severe underlying disease. However, we did not find a correlation between ASA scores and safety issues (hypoxemia and hypotension events) in the statistical analysis. In addition, we found that the proportion of males was higher among the elderly patients than among the young patients. This finding may be related to lung cancer epidemiology in the Taiwanese population [7].

In our study, hypoxemia, as a safety concern, occurred very frequently in patients undergoing sedation for FB. Hypoxemia occurred in 45% of all elderly patients and 30% of all young patients, which was a statistically significant difference. Midazolam is a long-established anesthetic; it acts on the gamma-aminobutyric acid (GABA)-alpha receptor and has hypnotic, sedative, anxiolytic, amnestic, anticonvulsant, and centrally produced muscle-relaxing properties [8]. Midazolam can flatten the response of the respiratory curve to carbon dioxide [9]. However, its effect on muscular tone leads to an increased risk of upper airway obstruction [10]. It also has an inhibitory effect on the respiratory center and depresses the hypoxic ventilatory response [11]. The deleterious effects of midazolam, such as respiratory depression, hypoxemia and apnea, are related to dose and age [12]. In addition, aging increases sensitivity to the hypnotic effects of midazolam [13]. In a randomized, double-blind, placebo-controlled study, Christe *et al* reported that 65 elderly hospitalized patients (mean age, 84 ± 7 years) that underwent gastroscopy experienced a higher frequency of hypoxemia with midazolam sedation than with placebo (44% vs 18%; p=0.03) [14]. In our study, the greater saturation proportion (45%) observed in elderly patients after midazolam sedation was consistent with that reported in previous studies [15-16].

The effects of midazolam on blood pressure are remarkable. This effect is exerted mainly on the hypothalamic paraventricular nucleus, rostral ventrolateral medulla, and GABA-ergic signaling, and on nitric oxide, affecting the regulation of blood volume and arterial blood pressure [17]. In a randomized double-blind study, Sun *et al*. reported that a given dose of midazolam (0.02 or 0.06 mg/kg) for elderly patients (age >60 years) resulted in significant reductions in MAP. However, differences in the decline of MAP between elderly and young patients did not reach statistical significance [12]. In another study by Christe *et al*, 65 geriatric inpatients who underwent gastroscopy with midazolam sedation experienced a MAP decrease of approximately 10 mmHg, with no clinically significant hypotension [14]. Similar to the study by Christe *et al*, our midazolam-sedated elderly patients also experienced a greater drop in MAP (15.2 ± 14.3 mmHg), and virtually no hypotension (1%). Only 1 elderly patient in our study developed hypotension during midazolam sedation, and this incidence was significantly lower

than that of the young patients. This phenomenon may be due to the significantly higher preprocedural MAP in the elderly and the blood pressure-lowering effect of midazolam that does not change with age (Figure 2).

Our study had several limitations, the first of which was its retrospective cross-sectional design, which may have affected the results. Second, whether temporary hypoxemia or hypotension during procedural sedation will cause irreversible complications is not clear. Even though the sedative drug, old age, and MAP < 65 mmHg have the potential to reduce cerebral blood flow, the sedative drug itself also has a cerebral protective effect [18]. Although we are unsure of the relevance, we still need to be highly cautious when encountering sedative-related desaturation and hypotension, especially if the patients have serious comorbidities or brain diseases [19].

Conclusion

This study found that hypoxemia was a common safety issue in patients undergoing sedation for FB. Elderly patients were more likely to develop desaturation than young patients undergoing midazolam sedation, and elderly patients exhibited a shorter induction time, required lower induction doses, and demonstrated better cooperation.

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Comparison of Quality of Medical Care for Prolonged Mechanical Ventilation Patients with and without Ventilator-Associated Pneumonia

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Background: The number of patients on prolonged mechanical ventilation in Taiwan is increasing every year because of the aging population, the increase in chronic diseases, and recent advances in medical equipment. Ventilator use often leads to complications, such as ventilator-associated pneumonia, and increased health care resource utilization.

Methods: This study used secondary data from Taiwan's National Health Insurance Research Database, Longitudinal Health Insurance Dataset, 2010 (LHID2010) provided by the Ministry of Health and Welfare. The study period was 2008-2012. The total number of patients was 2,992; there were 1,048 long-term ventilator-dependent patients without ventilator-associated pneumonia and 1,944 patients with ventilator-associated pneumonia. Logistic regression analysis was used to explore the odds ratio for the quality of medical care results between ventilator-dependent patients with and without ventilator-associated pneumonia.

Results: The quality of medical care results showed that there was a statistically significant correlation between multiple readmissions to the intensive care unit and hospital deaths and long-term respiratory disease without lung cancer; there was also a statistically significant correlation with demographic characteristics at the hospital level.

Conclusion: Follow-up research using the questionnaire or long-term medical record tracking to further explore the results of medical care, such as weaning success, in-hospital death, and nosocomial infection among ventilator-dependent patients with different respiratory diseases is needed. ***(Thorac Med 2020; 35: 28-34)***

Key words: prolonged mechanical ventilation patients, pneumonia in prolonged mechanical ventilation patients, quality of medical care

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Introduction

According to the National Nosocomial Infections Surveillance System, the incidence of ventilator-associated pneumonia is approximately 5-16% [1]. In a review of articles related to ventilator-associated pneumonia in the Medline literature database from 1966 to 2007, Arabi *et al*. [2] found that the prevalence rates of ventilator-associated pneumonia ranged from 10% to 41.7% (number of person/ventilator days) in developing countries. Mortality rates ranged from 16% to 94% (the mortality rate of the control group was between 0.2% and 51%) [2]. Ventilator-associated pneumonia increased the average intensive care unit (ICU) stay by 6–10 days and medical expenses by US$10,000–15,000 [3-4].

Nosocomial infection is an important indicator of hospital quality management. Poor control of nosocomial infections increases the morbidity and mortality of hospitalized patients and increases related medical expenses [5]. Hospital-acquired pneumonia is the second most frequently occurring nosocomial infection, next to urinary tract infection, but has the highest mortality rate, accounting for approximately 60% of all hospital infections [6].

Most of the relevant studies [7-9], however, are based on the experience of a respiratory care unit or single regional ventilator weaning center, which may not be an objective estimation. Therefore, we analyzed real-world data from Taiwan's National Health Insurance Research Database (NHIRD) to evaluate the impact of prolonged mechanical ventilation on patients with and without ventilator-associated pneumonia.

Methods

Data source

This nested case control study was conducted using data (2008–2012) retrieved from Taiwan's NHIRD. From 1996 to the present day, Taiwan's National Health Insurance (NHI) has been providing compulsory universal health insurance that covers all forms of health-care services for 99% of the population. The National Health Research Institutes has cooperated with the Bureau of NHI and created the NHIRD, which is a representative database of all NHI enrollees.

Study participants

Diseases were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Initially, 21,242 prolonged mechanical ventilation patients (identified by NHI claim codes 57001B, 57002B, and 57023B) were recruited for this study. We excluded 49 patients aged <18 years to limit the study sample to an adult population and excluded 18,200 patients without 21 consecutive days of prolonged mechanical ventilation. Patients with newly diagnosed pneumonia (identified by ICD-9-CM codes 480, 481, 482, 483, 485, and 486) from January 1, 2008 to December 31, 2012 were selected. For the non-pneumonia control group, patients without a history of pneumonia from insured cases were selected. We further defined the index date as the date of the patients' first ambulatory care visits for the purpose of receiving prolonged mechanical ventilation.

Outcome measures

All study outcomes were based on the guideline: ICU readmission (NHI claim codes: 03010E, 03011F, and 03012G), return to home care (NHI claim codes: 54007C1 and P5406C),

readmission to the respiratory care ward (without NHI claim codes: 57001B, 57002B, and 57023B ≥5 days).

Variates included sex, age group (18–39, 40–69, and >70 years), and hospital level (medical center, regional hospital, and district hospital).

Statistical analyses

Categorical variables were compared using the chi-squared test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each variable using logistic regression. Statistical analyses were performed using SAS V.9.4 software (SAS Institute, Cary, North Carolina, USA). The level of significance was set at 0.05.

Results

A total of 21,242 prolonged mechanical ventilation patients were identified using the NHIRD, which contains data on 1,000,000 individuals. All patients were aged between 18 and 100 years. After exclusion based on the aforementioned exclusion criteria, there were 1,211 patients in the prolonged mechanical ventilation complicated with pneumonia group, and 1,110 patients without pneumonia in the control group.

The distribution of demographic characteristics between the study and comparison groups is shown. The χ^2 test revealed significant differences in regional (p<0.001) and district (p< 0.001) hospitals (Table 1).

Multivariate logistic regression, after controlling factors such as sex, age, and hospital level, revealed the following. The prolonged mechanical ventilation complicated with pneumonia group was associated with a higher risk of admission to the ICU, with an OR of 1.75 (p< 0.0001), than the non-pneumonia group (Table 2), and was also associated with a higher risk of possible death, with an OR of 1.57 (p=0.017), than the non-pneumonia group (Table 3).

Table 1. Demographic and Clinical Characteristics of Prolonged Mechanical Ventilation with Differences between Groups

Variables	PMV+P (N=1,211)	PMV (N=1,110)	*p* value
Sex			0.568
Male	61.57%	56.97%	
Female	38.43%	43.03%	
Age group (years)			
17–39	2.57%	5.53%	0.074
40–69	29.12%	37.6%	0.476
≥70	68.31%	56.87%	0.163
Hospital level			
Medical center	28.7%	34.54%	0.711
Regional hospital	42.95%	46.76%	<0.0001***
District hospital	28.34%	18.7%	<0.0001***

PMV = Prolonged mechanical ventilation; PMV+P = Prolonged mechanical ventilation complicated with pneumonia

***p<0.001; **p<0.01; *p<0.05

Table 2. Multivariate Logistic Regression Analysis of Potential Predictors of Admission to the Intensive Care Unit

Variables	OR	95% CI	*p*
Sex			
Male	0.90	0.78–1.05	0.186
Female (ref)	1.00	-	-
Age group (years)			
17–39	0.91	0.61–1.36	0.670
40–69	0.98	0.82–1.15	0.836
≥70 (ref)	1.00	-	-
Hospital level			
Medical center	2.90	2.35–3.57	<0.0001***
Regional hospital	2.74	2.26–3.34	<0.0001***
District hospital	1.00	-	
Group			
Prolonged mechanical ventilation (ref)	1.00	-	-
Prolonged mechanical ventilation complicated with pneumonia	1.75	1.49–2.05	<0.0001***
Hosmer Lemeshow*	-	-	0.836

* Hosmer Lemeshow test;

***p<0.001, **p<0.01., *p<0.05.

OR = odds ratio.

CI = confidence interval.

Adjusted for the variables listed in the logistic regression table

Table 3. Multivariate Logistic Regression Analysis of Potential Predictors of in-Hospital Death

Variables	OR	95% CI	*p*
Sex			
Male	1.36	0.93–1.99	0.113
Female (ref)	1.00	-	-
Age group (years)			
17–39	0.58	0.18–1.87	0.427
40–69	0.86	0.58–1.28	0.718
≥70 (ref)	1.00	-	-
Hospital level			
Medical center	0.72	0.45–1.15	0.421
Regional hospital	0.72	0.47–1.11	0.374
District hospital	1.00	0.93–1.99	0.113
Group			
Prolonged mechanical ventilation (ref)	1.00	-	-
Prolonged mechanical ventilation complicated with pneumonia	1.57	1.08–2.27	0.017*
Hosmer Lemeshow*	-	-	0.759

* Hosmer Lemeshow test;

***p<0.001, **p<0.01., *p<0.05.

OR = odds ratio. CI = confidence interval.

Adjusted for the variables listed in the logistic regression table

Table 4. Multivariate Logistic Regression Analysis of Potential Predictors of Return to Home Care

Variables	OR	95% CI	*p*
Sex			
Male	0.67	0.49–0.91	0.010*
Female (ref)	1.00	-	-
Age group (years)			
17–39	2.53	1.36–4.72	0.011*
40–69	1.31	0.94–1.82	0.343
≥70 (ref)	1.00	-	-
Hospital level			
Medical center	2.46	1.56–3.91	<0.0001***
Regional hospital	1.75	1.11–2.76	0.509
District hospital	1.00	-	-
Group			
Prolonged mechanical ventilation (ref)	1.00	-	-
Prolonged mechanical ventilation complicated with pneumonia	0.77	0.55–1.07	0.116
Hosmer Lemeshow*	-	-	0.326

* Hosmer Lemeshow test; ****p*<0.001, ***p*<0.01., **p*<0.05.

OR = odds ratio. CI = confidence interval.

Adjusted for the variables listed in the logistic regression table

Table 5. Multivariate Logistic Regression Analysis of Potential Predictors of Readmission to the Respiratory Care Ward

Variables	OR	95% CI	*p*
Sex			
Male	1.04	0.88–1.22	0.655
Female (ref)	1.00	-	-
Age group (years)			
17–39	0.75	0.48–1.19	0.330
40–69	0.89	0.75–1.07	0.833
≥70 (ref)	1.00	-	-
Hospital level			
Medical center	0.73	0.59–0.91	0.003**
Regional hospital	0.92	0.76–1.12	0.368
District hospital	1.00	-	-
Group			
Prolonged mechanical ventilation (ref)	1.00	-	-
Prolonged mechanical ventilation complicated with pneumonia	1.12	0.94–1.33	0.201
Hosmer Lemeshow*	-	-	0.993

* Hosmer Lemeshow test; ****p*<0.001, ***p*<0.01., **p*<0.05.

OR = odds ratio. CI = confidence interval.

Adjusted for the variables listed in the logistic regression table

No significant differences were observed between patients in the prolonged mechanical ventilation complicated with and without pneumonia groups for return to home care and readmission to the respiratory care ward (Tables 4 and 5). In the multivariate logistic regression analysis model, hospital level was significant for all outcomes (Tables 2–5).

Discussion

In this study, we found that prolonged mechanical ventilation patients had a higher chance of developing ventilator-associated pneumonia and returning to the ICU. This is consistent with the results of Rello *et al*. [10], Bird *et al*. [11], and Ramirez *et al*. [12]. They all found that prolonged mechanical ventilation use by patients with ventilator-associated pneumonia increased the possibility of patients' returning to the ICU and influenced the quality of medical care during hospitalization.

The study also indicated that prolonged mechanical ventilation patients with ventilator-associated pneumonia had a lower chance of being transferred to home care than those without ventilator-associated pneumonia. Higher infection rates of patients with prolonged mechanical ventilation complicated with ventilator-associated pneumonia resulted in a poorer prognosis [10-12], which reduced the chance of being transferred to home care.

Furthermore, we found no significant differences in sex, age, and ventilator weaning success rates; however, medical centers had a greater likelihood of experiencing successful ventilator weaning than regional hospitals. This result is consistent with the findings of Ramirez *et al*. [12]. The longer the time taken for ventilator weaning, the higher the risk of mortality and greater cost. Only early formulation of the patient's weaning plan can reduce the burden on patients and their families and economize on both medical costs and the use of medical resources. Effective use of medical resources will improve the quality of life of patients.

Multivariate regression analysis revealed that prolonged mechanical ventilation patients with ventilator-associated pneumonia had a higher in-hospital death rate than those without ventilator-associated pneumonia. In-hospital death rates of patients with ventilator-associated pneumonia are 2–8 times higher than that of patients without ventilator-associated pneumonia [13].

However, there are some limitations to this study. First, since the NHIRD does not provide complete individual information, such as educational level, personal history of smoking and alcohol consumption, BMI, socioeconomic status, etc., all of which are known to contribute to pneumonia, we could not control all confounders. Second, we could not evaluate the severity of prolonged mechanical ventilation patients. Last, the NHIRD does not contain data on laboratory tests. Therefore, evaluating the effects of various parameters known to be associated with pneumonia was impossible.

Conclusion

Pneumonia might be a risk factor for the survival of prolonged mechanical ventilation patients. Further prospective studies should be conducted to validate the results of this study.

Acknowledgements

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Legionella Pneumonia Complicated by Acute Respiratory Distress Syndrome Requiring Venovenous Extracorporeal Membrane Oxygenation and Continuous Renal Replacement Therapy Support: A Case Report

Bo-Ruei Huang, Jiin-Torng Wu, Chih-Yu Hsu, Ming-Huang Chiu

Legionella species is a common atypical bacterial pathogen in both community- and hospital-acquired pneumonia. *Legionella* pneumonia may lead to severe medical sequelae, such as acute respiratory distress syndrome (ARDS) and multiple organ failure. Herein, we report the case of a 54-year-old man with type 2 diabetes mellitus, hypertension, and coronary artery disease. He was diagnosed with *Legionella* pneumonia complicated by severe ARDS and acute kidney injury. He was successfully treated with antibiotics and venovenous extracorporeal membrane oxygenation (ECMO) in combination with continuous renal replacement therapy (CRRT) support. This case report highlights the usually underdiagnosed *Legionella* infection and its substantial presentation. *Legionella* pneumonia should be detected earlier, and appropriate ECMO referral should be considered for *Legionella* pneumonia-associated refractory respiratory failure. In Taiwan, there is a paucity of reported cases of *Legionella* pneumonia that progressed to ARDS and were successfully treated with venovenous ECMO and CRRT support. ***(Thorac Med 2020; 35: 35-39)***

Key words: *legionella* pneumonia, acute respiratory distress syndrome, extracorporeal membrane oxygenation

Introduction

Legionella species are aerobic, nutritionally fastidious, Gram-negative bacilli and facultative intracellular pathogens. They are usually transmitted by exposure to contaminated water or soil. *Legionella* species are a recognized causative agent of severe community-acquired pneumonia (CAP) [1].

Acute respiratory distress syndrome (ARDS) is an acute, diffuse, inflammatory lung injury that leads to increased alveolar capillary permeability, increased lung weight, and loss of aerated lung tissue. ARDS manifests clini-

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cally as hypoxemia, with bilateral opacities on chest radiography, and is associated with decreased lung compliance and increased venous admixture and physiological dead space [2]. Extracorporeal membrane oxygenation (ECMO) is an extracorporeal technique used to provide cardiac and respiratory support to patients with severe acute cardiac or pulmonary failure [1]. ECMO was reported to improve the outcomes of adult patients with ARDS who had failed conventional management [3]. Herein, we describe a case of *Legionella pneumonia* complicated by severe ARDS and multiple organ failure requiring venovenous ECMO (V-V ECMO) in combination with continuous renal replacement therapy (CRRT) support.

Case presentation

A 54-year-old man with type 2 diabetes mellitus, hypertension, and coronary artery disease presented to our emergency department with a 1-week history of fever, productive cough, and shortness of breath. On evaluation, his vital signs were blood pressure: 165/98 mmHg, PR: 133 bpm, RR: 28/min, BT: 38.7°C, and SpO_2: 90%. On physical examination, he appeared to be acutely ill with severe shortness of breath and accessory muscle usage. Bilateral crackles were noted on auscultation. A hemogram revealed neutrophil leukocytosis (WBC: 23,260/μL), slight thrombocytopenia (platelet count, 142,000/μL), a high C-reactive protein (CRP) level (29.898 mg/dL), and kidney function impairment (Cr level: 3.83 mg/dL). An initial chest X-ray (Figure 1A) showed left upper lobe consolidation. The patient developed severe respiratory distress a few hours later, with observable blood gas (pH: 7.469, $PaCO_2$: 23.4 mmHg, and PaO_2: 68.7 mmHg when using a non-rebreathing mask of 15 L/min). The patient was immediately intubated. The initial heart sonography revealed borderline left ventricle function with a left ventricular ejection fraction of 53%, with no regional wall abnormality, and normal right ventricle function with an estimated right ventricular systolic pressure of 22 mmHg. The patient was immediately intubated at the emergency department. He was intravenously administered levofloxacin and subsequently admitted to the medical intensive care unit (ICU). The *Legionella* urine antigen test was positive for *L. pneumophila* on the second day of ICU admission (*Legionella* infection was also confirmed later, through paired serology, as *L. pneumophilia* serogroup 1).

The patient's severe respiratory distress with hypoxemia had not resolved on day 6 (Figure 1B), even under maximum ventilator support, and he was fully paralyzed. Blood gas readings under 100% FiO_2 use were pH: 7.249, $PaCO_2$: 60.4 mmHg, and PaO_2: 53.8 mmHg. Chest X-ray (Figure 1B) revealed degenerating bilateral lung consolidation, which resulted in ARDS (PaO_2/FiO_2: 53.8). V-V ECMO was then administered. On the next day, CRRT was also introduced due to acute kidney injury with anuria. We maintained the lung-protective ventilation strategy during the V-V ECMO support period.

On day 26 (Figure 2), we noted a significant improvement both in the blood gas PaO2 level and chest X-ray findings. We then discontinued ECMO support. On day 31, the patient was successfully weaned off the ventilator. On day 33, he was transferred to the general ward.

Discussion

L. pneumophilia is a fairly recently dis-

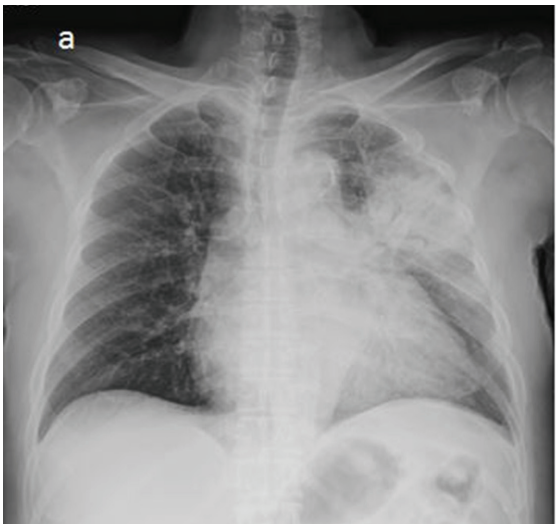

Fig. 1A. Initial chest X-ray upon arrival.

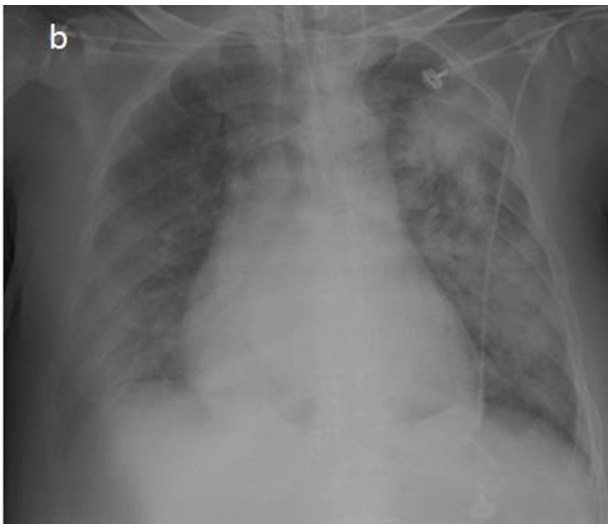

Fig. 1B. Chest X-ray before ECMO on day 6.

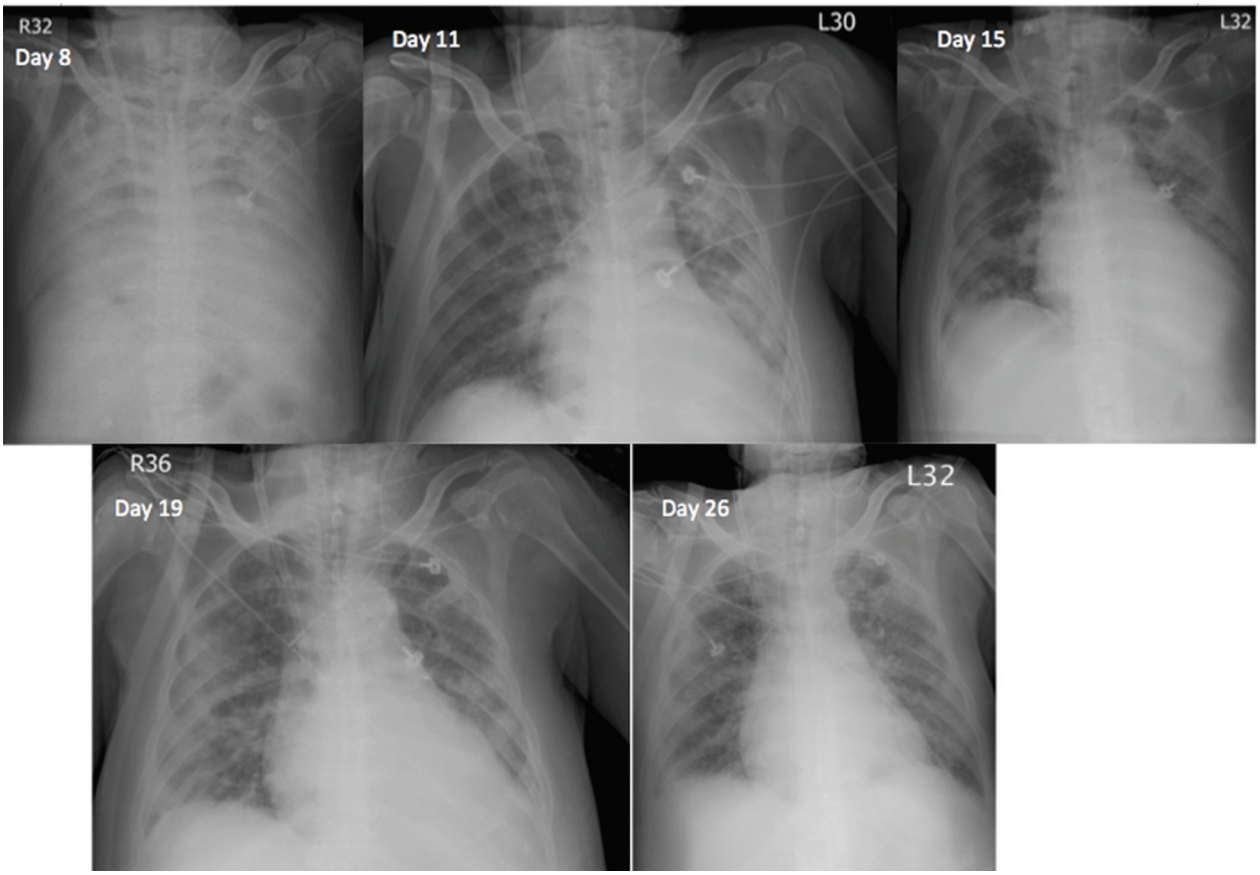

Fig. 2. Chest X-ray images during treatment. Note the gradual improvement in bilateral infiltrates.

covered bacteria that was named after its first outbreak in 1976 among veterans attending an American Legion convention in Philadelphia. *Legionella* species are a kind of atypical bacteria that accounts for approximately 1%–10% of CAP cases [4-5]. The spectrum of clinical presentations of *Legionella* infection ranges from mild flu-like symptoms to severe bronchopneumonia, which is also known as Legionnaires' disease (LD). LD is a kind of severe CAP associated with a higher case-fatality rate (up to approximately 30%) than CAP caused by other atypical pathogens [6]. Up to 44% of CAP patients diagnosed with *Legionella* pneumonia have been reported to require admission to the ICU [4-5].

Even with its severe clinical sequelae with a high fatality rate, an adequate scoring system to facilitate early prediction of *Legionella* pneumonia has not been developed yet. Fiumefreddo *et al*. proposed a potentially highly sensitive scoring system to predict *Legionella* pneumonia, as follows: high fever (>39.4°C), high CRP level (>187 mg/L), high lactate dehydrogenase level (>225 mmol/L), thrombocytopenia (platelet count <171×109/L), underproductive cough, and hyponatremia (serum Na level <133 mmol/L) [7]. Our patient had a high fever, high CRP level and slight thrombocytopenia, and therefore met 3 of the 6 criteria proposed by Fiumefreddo. Regarding imaging characteristics, no typical radiographic features reliably distinguish LD from other types of CAP. The most common radiographic findings are patchy unilobar infiltrates and rapid progression to consolidation. Our patient also showed unilobar consolidation on the initial chest X-ray, which is compatible with the current knowledge of the most common imaging presentation of LD.

Although *Legionella* species are a well-known CAP pathogen that can be countered with effective antimicrobial regimens, some cases still progress to a critical condition despite early initiation of adequate antibiotics. Kojicic M, *et al* reported that ARDS developed in one-third of patients with microbiologically proven *Legionella* pneumonia and was associated with a prolonged ICU stay [8].

ECMO was reported to improve the outcomes of patients with *Legionella*-associated severe hypoxemic respiratory failure who had failed conventional ventilator management [3]. Bryner *et al*. suggested that ECMO can be an effective management strategy for severe ARDS associated with *Legionella* pneumonia when mechanical ventilation fails, and should be utilized early in the course [9].

In our case, LD was recognized during the early clinical stage, and appropriate antibiotics were administered; the subsequent ARDS with multiple organ failure was managed successfully with V-V ECMO and CRRT. Clinicians should be vigilant for the potential development of ARDS when treating *Legionella* pneumonia patients, and promptly initiate ECMO in cases of high clinical severity such as refractory hypoxemic ARDS. Furthermore, the benefits of ECMO relative to conventional mechanical ventilation in the prone position should be further explored. More specific clinical features should be identified, and a more validated scoring system for earlier recognition of *Legionella* pneumonia should be developed.

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Amiodarone-Induced Unilateral Interstitial Pneumonitis: A Case Report

Erh-Lun Chen

Amiodarone is an anti-arrhythmic drug that is commonly used for patients with supraventricular and ventricular arrhythmias. One of the most severe side effects of amiodarone use is pulmonary toxicity. Here, we reported a patient with unilateral interstitial pneumonitis induced by amiodarone use. In light of this case, we should always keep in mind that interstitial pneumonitis may occur in patients with a history of taking amiodarone. However, other etiologies should be also excluded before making the diagnosis. Cessation of administration of amiodarone and initiation of corticosteroid use may be helpful in patients with this condition. ***(Thorac Med 2020; 35: 40-43)***

Key words: amiodarone, unilateral interstitial pneumonitis, drug induced pulmonary toxicity

Introduction

Amiodarone is widely used in the management of both supraventricular and ventricular arrhythmias, especially in patients with heart failure, because it has very little negative inotropic activity [1] . However, pulmonary toxicity is among its most severe forms of toxicity. Pulmonary diseases that occur in patients treated with amiodarone, include interstitial pneumonitis, eosinophilic pneumonia, organizing pneumonia, diffuse alveolar hemorrhage, acute respiratory distress syndrome, pulmonary nodular or mass lesions, and pleural effusion (Table 1) [2]. Interstitial pneumonitis is the most common presentation of amiodarone induced pulmonary disease, especially in patients treated for up to 2 months. Risk also increases in patients taking amiodarone exceeding 400 mg per day [3].

Patients with this disease often present with nonproductive cough and dyspnea, and fever is reported in 30~50% of cases. High-resolution chest computed tomography (HRCT) shows features specific to amiodarone-induced interstitial pneumonitis. Bronchoalveolar lavage is helpful for exclusion of alternative diagnoses. Lung biopsy is usually not necessary for the diagnosis in patients with typical radiographic findings. Prognosis of this disease is favorable and resuming the drug is not recommended.

Case Report

An 85-year-old female patient had underlying chronic kidney disease, congestive heart failure, and chronic atrial fibrillation. She re-

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Table 1. Common Side Effects and Amiodarone-Induced Pulmonary Toxicities

Common side effects	Amiodarone-induced pulmonary toxicity
Skin photosensitivity	Interstitial pneumonitis
Corneal deposits	Eosinophilic pneumonia
Thyroid dysfunction	Organizing pneumonia
Liver dysfunction	Diffuse alveolar hemorrhage
Coagulopathy	Acute respiratory distress syndrome
Neuropathy	Pulmonary nodular or mass lesions
Lung diseases	Pleural effusion

ceived regular follow-up at our cardiovascular outpatient department and had been taking amiodarone 200mg twice a day for more than 16 months prior to presentation at our emergency room (ER). She was brought to our ER due to an insidious onset of nonproductive cough and shortness of breath. On arrival, her body temperature was 36.6°C, blood pressure was 105/65 mmHg, and respiratory rate was 19/min. Initial laboratory data were as follows: leukocyte count: 9.6K/μL with 85% segmented forms, hemoglobin: 11.5g/dl, and C-reactive protein: 16.3mg/dl. Chest radiography showed increased right lung field patchy opacity with an interstitial pattern (Figure 1), compared with her baseline chest film before taking amiodarone. She was then admitted under the tentative diagnosis of community-acquired pneumonia and was treated with levofloxacin 0.75gm/day after admission. During the first days of hospitalization, mild fever was recorded, but it subsided after antibiotic administration. However, her symptoms, such as dyspnea showed little improvement on the subsequent chest film 6 days later. HRCT was arranged, and showed diffuse right lung field interstitial pneumonitis (Figure 2). Non-contrast chest CT revealed the following: 1. high attenuation of the liver, compared with other solid organs such as the spleen (Figure 3).

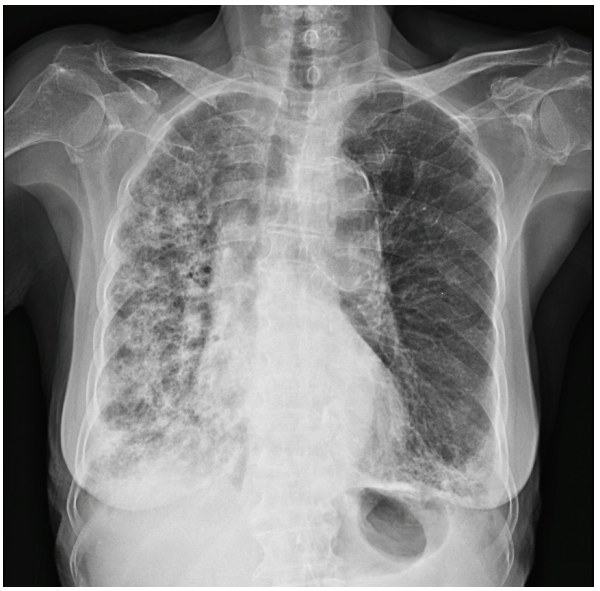

Fig. 1. Chest X-ray showed increased patchy opacity with an interstitial pattern, right lung field-predominant

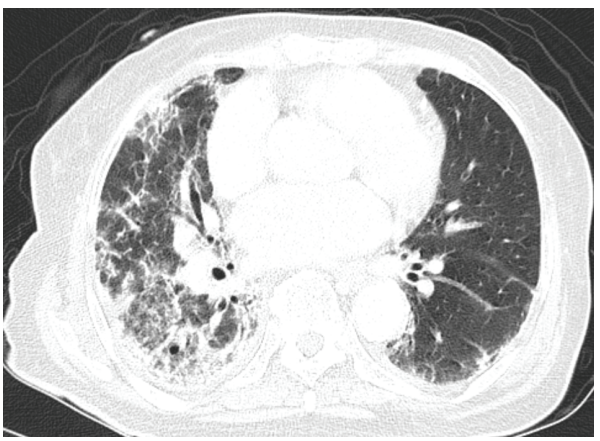

Fig. 2. High-resolution CT showing predominantly right lung field interstitial pneumonitis

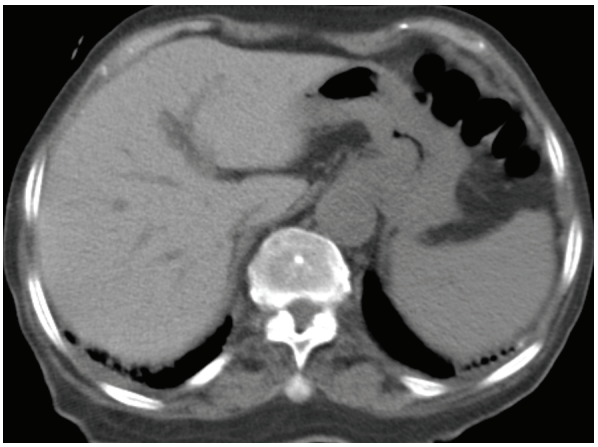

Fig. 3. Non-contrast CT showing high attenuation of the liver

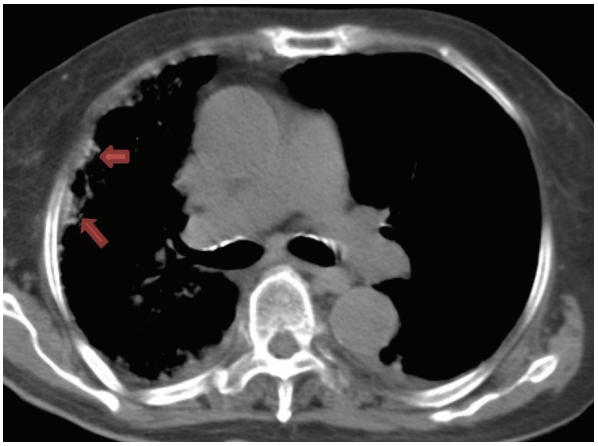

Fig. 4. Red arrows indicate some high-density deposition on the pleura

2. Organization of the right lung parenchyma, mainly in a pattern of basal and subpleural distribution and some high-density deposition on the pleura (Figure 4). CT features such as these are highly suggestive of interstitial pneumonitis induced by amiodarone, while chest film findings might be nonspecific. Amiodarone was then discontinued in this patient, and she was given oral prednisolone 10mg twice a day after discharge. After 4 months of treatment, chest film revealed almost full resolution (Figure 5).

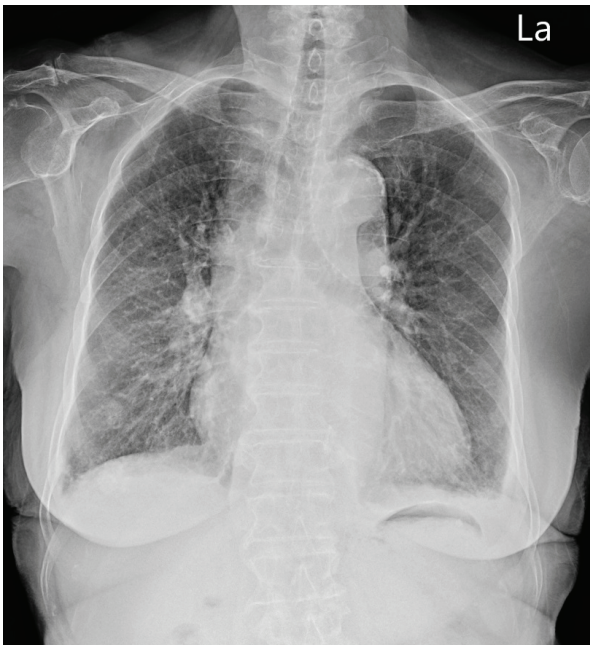

Fig. 5. Chest film after 4 months of oral prednisolone administration revealed almost full resolution

Discussion

The diagnosis of drug-induced interstitial pneumonitis remains challenging in many clinical settings. It is diagnosed on the basis of clinical, physiological and radiological findings that are consistent with interstitial lung disease, a relationship between onset of symptoms and drug exposure, exclusion of other possible causes, and improvement on withdrawal of the drug [4]. In this case, based on the patient's clinical presentation and chest X-ray screening, we learned that amiodarone-induced interstitial pneumonitis can often be neglected and misdiagnosed as pneumonia or other diseases in the beginning.

In our case, community-acquired pneumonia was suspected initially, but little improvement was found after antibiotic treatment. Therefore, a thorough review of the patient's

underlying diseases and drug history is important. The cumulative dose is an important risk factor for amiodarone-related interstitial pneumonitis, and the combination of high doses over longer periods is more strongly associated with the disease than dose or duration alone [5]. Furthermore, due to the accumulation of iodinated amiodarone in tissue macrophages, chest CT may show some features common and specific to amiodarone use, including: (1) pulmonary interstitial fibrosis with bronchiectasis, pleural thickening, and linear atelectasis, (2) pulmonary consolidation or ground-glass opacity, and (3) pulmonary lesions with a high CT-attenuation not related to the calcification of another pulmonary disease [6]. The first 2 features are common findings of amiodarone-induced interstitial lung disease and the third is a typical feature. It is postulated that amiodarone-induced pneumonitis is hematogenously spread. In theory, bilateral patchy opacity is more common than the unilateral variety. In our case, it is unclear that amiodarone-interstitial pneumonitis primarily affect the right lung field. Treatment of the disease mainly consists of discontinuation of the drug, and in some patients with more severe symptoms, corticosteroid use However, due to its long half-life (approximately 45 days), pulmonary toxicity may progress even after discontinuation of the drug. Resuming the drug after recovering from the disease is not suggested, as it will lead to further recurrence and pulmonary fibrosis.

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