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Worse lung cancer outcome in patients with lower respiratory tract infection confirmed at time of diagnosis

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Keywords
Lower respiratory tract infection; lung cancer; survival; treatment.

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Abstract

Background: Pulmonary malignancy is one of the most frequent and fatal cancers in older patients. As data on lower respiratory tract infection (LRTI) and the outcome of lung cancer are scarce, our objective was to determine the impact of LRTI on therapeutic possibilities and one-year mortality.

Methods: Patients undergoing bronchoscopy in 2017 who had bronchial microbial sampling at the time of the lung cancer diagnosis (n = 143) were included. Group 1 (LRTI+) included patients with confirmed infection (n = 74) while Group 2 (LRTI-) included patients without infection (n = 69). Clinical characteristics, pathogen profile and one-year survival were analyzed.

Results: Age, gender, TNM stage, histology type, comorbidities or underlying lung disease did not differ among groups. The most common LRTI pathogens included aerobic (n = 49), anaerobic (n = 14) and fungal (n = 26) infections. Chemo/-immune/target therapy alone, or in combination with radiotherapy were significantly less frequently used, whilst palliative care was more common in Group 1 (LRTI+). Multiple pathogen LRTI patients were significantly older, less frequently diagnosed with adenocarcinoma and had worse performance status compared to solitary pathogen LRTI patients. One-year median survival was 274 days (235 vs. 305 days Group 1 vs. Group 2). Risk factors for increased one-year mortality included performance status ≥2 (OR 30.00, CI 95% 5.23–313.00), performance status 1 (OR 11.87, CI 95% 4.12–33.78), male gender (OR 4.04, CI 2.03–8.04), LRTI with multiple pathogens (OR 2.72, CI 1.01–6.81) and nonadenocarcinoma histology (OR 2.26, CI 1.15–4.56).

Conclusion: LRTIs in lung cancer patients, especially multiple pathogen infections, are associated with less oncotherapeutic possibilities and significant risk for lower one-year median survival.

Key Points

Significant findings of the study

Patients with LRTI less frequently had adencocarcinoma, significantly worse ECOG performance status withholding several treatment possibilities and lower one-year survival. Patients with multiple pathogen LRTI were less eligible for oncotherapy and had significantly increased risk of one-year mortality.

What this study adds

More attention should be given to LRTI lung cancer patients and the pathogen profile described in our series could assist with empiric treatment selection. Treatable threats are important elements to improve survival of this special patient population.

Introduction

Lung cancer is one of the leading causes of malignancy-associated mortality worldwide.[1] The prevalence in older age has risen considerably in the past decade,[2] with more than 2 000 000 patients recognized yearly with pulmonary malignancy.[3]

Lung cancer is often asymptomatic in the early stages; on the other hand, most cases are diagnosed only when the disease is at an advanced stage.[4] No established screening strategies are available; however, the results of the NELSON trial, using a low dose CT, are promising for the future.[5]

Advanced disease, older age and comorbidities often make histological verification difficult and may also be associated with less favorable treatment options.[6] Lung cancer often develops in damaged lungs (e.g., chronic obstructive lung disease, emphysema, idiopathic pulmonary fibrosis [IPF]) and underlying lung diseases might make diagnosis and treatment even more difficult.[7,8] In addition to lung disease, numerous factors can additionally predispose lung cancer patients to develop lower respiratory tract infection (LRTI), including damage to anatomical barriers during invasive procedures.[9] With subtle or absent respiratory symptoms, the diagnosis of infection is often delayed, which can readily lead to increased morbidity and mortality especially for elderly individuals.[10–12]

Despite the high mortality rate of lung cancer, additional treatable threats should be considered when treating patients, particularly with extensive disease. In this study, we aimed to determine LRTI in Hungarian lung cancer patients and assess its impact on treatment possibilities and one-year survival.

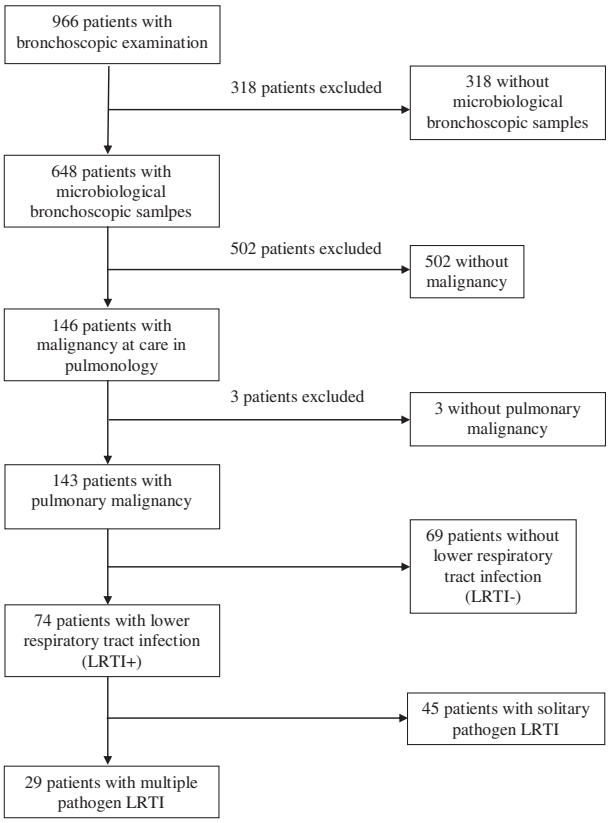

Figure 1 Selection of the study population.

Methods

Study population

The medical records of 966 patients undergoing bronchoscopy at Semmelweis University, Department of Pulmonology in the year 2017 were reviewed. All patients who underwent bronchoscopy for microbiological sampling (n = 648) were selected, out of whom all with confirmed pulmonary malignancy (n = 143) were included in this retrospective analysis. The selection of the study population is summarized in Fig 1.

Two groups were compared: Group 1, (n = 74) consisting of patients with concomitant lower respiratory tract infection (LRTI+) at the time of the diagnosis, and Group 2 (LRTI-; n = 69). Demographic information (age, gender), smoking habits, stage (TNM classification of malignant tumors), body mass index (BMI), underlying lung disease (presence of chronic obstructive pulmonary (COPD) and/or interstitial lung disease (ILD), anatomical localization of the cancer, ECOG (Eastern Cooperative Oncology Group) performance status, comorbidities, peripheral blood neutrophil/lymphocyte ratio (NLR), tumor histology were summarized. Forced vital capacity (FVC), forced expiratory volume in one second ($FEV_{1)}$, FEV_1/ FVC|) was measured by means of electronic spirometer and plethysmography (PDD-301/s, Piston, Budapest, Hungary) according to the American Thoracic Society guidelines.[13] Three technically acceptable maneuvers were performed and the highest used.

Additionally, cancer therapy, including curative intent surgery/radiotherapy, chemotherapy and/or radiotherapy as well as the best supportive care were analyzed. All treatment decisions were made at the multidisciplinary tumor board according to national regulations and ESMO (European Society for Medical Oncology) guidelines.[14–16] All patients were followed for at least one year. One-year survival was assessed in all patients and the results of the groups were analyzed.

Lower respiratory tract infection

Bronchoscopies with microbiological test results from bronchial lavage were selected. Microbial analysis was more frequently performed in bronchoscopic procedures in patients with purulent endobronchial mucus, which may have contributed to some extent to selection bias. The samples were analyzed for aerobic and anaerobic bacteria, fungal and Mycobacterium infections. Infections appearing in

further areas, such as global septicemia or urinary tract infection, were not considered for the current research. LRTI was confirmed when samples contained pathogens of colony forming units (CFU) $\geq 10^2$, while lower CFU was considered as potential upper-airway contamination. Infections with samples positive for only one pathogen were acknowledged as solitary pathogen infections. LRTI with at least two microorganisms were determined as multiple pathogen LRTI. All clinical data, oncotherapy and one-year survival were additionally assessed in solitary pathogen and multiple pathogen subgroups of Group 1 (LRTI+).

Statistical analysis

Data are reported as means ± SEM or median (range). Statistical analysis was performed with the GraphPad software (Graph Pad Prism 5.0 by Graph Pad Software Inc., San Diego, USA). Normally distributed data were analyzed by an unpaired *t*-test, for categorical data, the Chi-square test was used. Survival was analyzed with the Kaplan Meier test. Risk factors for one-year mortality were calculated with determining odds ratios (Graph Pad Prism 5.0 by Graph Pad Software Inc., San Diego, USA and IBM SPSS, Armonk, New York, USA). $P < 0.05$ was considered as statistically significant.

Results

Baseline characteristics

Our analysis included slightly more men than women, and these were mostly ever-smokers (Table 1.). Histology distribution, anatomical location, and underlying lung diseases were not different between the groups and TNM stages were similarly distributed. Most of the patients were discovered in more advanced stages, not eligible for curative intent therapies, which was similar in both groups. Most patients had an ECOG performance status of 0–1; however, we could see significantly more patients with the best performance state in Group 2 (LRTI-). No differences in the number of comorbidities were noted. Significantly higher NLR was observed in Group 1 (LRTI+).

In Group 1 (LRTI+) the pathogen profile is summarized according to the histology type in Table 2. Aerobic, anaerobic and fungal infections did not differ, but significantly more solitary pathogens were noted in adenocarcinoma patients. Most common solitary pathogens in Group 1 (LRTI+) included *Candida albicans* (n = 19), *H. influenzae* (n = 15), *S. aureus* (n = 13), *S. pneumoniae* (n = 10), *Enterobacter* spp. (n = 10), *P. aeruginosa* (n = 7) and other pathogens (n = 42). Isolates of multiple pathogen LRTI were similarly distributed, and included *Candida albicans (n = 14), S. pneumoniae (n = 7), S. aureus (n = 7), P. aeruginosa (n = 6), H. influenzae (n = 6)* and other pathogens *(n = 31);* although there were proportionally more *Candida albicans, S. pneumonia* and *P. aeruginosa infections* detected. The percentage of *H. influenzae* was notably lower than in the solitary pathogen LRTI individuals (8.45% vs. 20%).

Oncotherapy possibilities are summarized in Table 3. Curative intent interventions were not different between groups; less than 15% were eligible. Chemo/immune/target therapy alone or in combination with radiotherapy were significantly less frequent in Group 1 (LRTI+) as compared to Group 2 (LRTI-). Conversely, significantly more patients in Group 1 (LRTI+) could only receive the best supportive care (BSC) as compared to Group 2 (LRTI-). In general, nearly one-quarter of the patients were not eligible for palliative oncotherapeutic interventions.

The one-year median survival for all patients was 274 days, lower for Group 1 (LRTI+) with 235 days as compared to Group 2 (LRTI-) where it was 305 days. Kaplan Meier analysis did not show any statistically significant differences between the groups (P = 0.244, HR: 1292 [95% CI: 0.84–1.99], Fig 2).

Between the subgroups, made according to the presence of solitary or multiple pathogens, patients in the latter group were significantly older and had worse ECOG performance status (Table 1). Significantly less adenocarcinoma was noted in this subgroup and the curative intent interventions were less common in these cases. Significantly more patients could only receive BSC compared to solitary pathogen LRTI (Table 1). Lung cancer patients with solitary pathogen LRTI had longer median one-year survival as compared to patients with multiple pathogens (306 vs. 146 days, HR: 1.57 [95% CI: 0.87–2.99], P = 0,318; Fig 2). Patients with multiple pathogen infections had shorter median one-year survival than lung cancer patients in Group 2 (LRTI-) (146 vs. 305 days, HR: 1.67 [95% CI: 0.98–3.23], P = 0.057).

Odds ratio analysis data are presented in Table 4. Significantly higher risk could be observed for one-year mortality in case of performance status ≥2, male gender, LRTI with multiple pathogens and nonadenocarcinoma histology.

Discussion

In our study, lung cancer treatment possibilities and one-year survival were analyzed according to the presence of LRTI at the time of bronchoscopy intervention. Interaction of LRTI and lung cancer outcome data is scarce, and our data demonstrated worse outcome in patients with lung malignancies, having LRTI at diagnosis. In the case of LRTI patient's ECOG performance status was significantly worse; consequently, patients had less therapeutic possibilities. This is in line with the Italian survey, confirming the

Table 1 Baseline patient characteristics

Parameter	All (n = 143)	Group 1: LRTI+ (n = 74)	Group 2: LRTI- (n = 69)	P-value Group 1 *vs.* Group 2	Solitary pathogen (n = 45)	Multiple pathogen (n = 29)	P-value Solitary vs. Multiple pathogen
Age: years	66.26 ± 9.3	66.77 ± 8.38	65.72 ± 10.23	0.50	64.93 ± 8.69	69.62 ± 7.1	0.01
Gender: (n [%])							
Male: female	79:64 (55.24:44.76)	43:31 (58.11:41.89)	36:33 (52.17:47.83)	0.47	25:20 (55.55:44.44)	18:11 (62.07:37.93)	0.57
Smoking: (n [%])							
Ever-smoker	117 (81.82)	65 (87.84)	52 (75.36)		39 (86.66)	26 (89.65)	
Never-smoker	18 (12.59)	6 (8.11)	12 (17.39)	0.15	4 (8.88)	2 (6.90)	0.92
Smoking status not available	8 (5.59)	3 (4.05)	5 (7.25)		2 (4.44)	1 (3.45)	
BMI: kg/m^2	25.84 ± 10.93	25.02 ± 5.62	26.72 ± 14.63	0.37	25.84 ± 5.56	23.76 ± 5.58	0.12
Underlying lung disease:							
COPD/ILD							
Yes (n [%])	63 (44.06)	36 (48.65)	27 (39.13)		20 (44.44)	16 (55.17)	
				0.25			0.36
No (n [%])	80 (55.94)	38 (51.35)	42 (60.87)		25 (55.55)	13 (44.83)	
Anatomical type							
Peripheral carcinoma (n [%])	83 (58.04)	44 (59.46)	39 (56.52)		28 (62.22)	16 (55.17)	
				0.72			0.54
Central type carcinoma (n [%])	60 (41.96)	30 (40.54)	30 (43.48)		17 (37.77)	13 (44.83)	
Histology (n [%])				0.71			
Adenocarcinoma	56 (39.17)	31 (41.89)	26 (37.68)		25 (55.55)	6 (20.69)	0.01
Squamous cell carcinoma	42 (29.37)	24 (32.43)	18 (26.09)		12 (26.66)	12 (41.38)	0.18
SCLC	23 (16.08)	10 (13.51)	12 (17.39)		5 (11.11)	5 (17.25)	0.45
Mixed tumor	9 (6.29)	4 (5.41)	5 (7.25)		1 (2.22)	3 (10.34)	0.13
Other lung cancer	13 (9.09)	5 (6.76)	8 (11.59)		2 (4.44)	3 (10.34)	0.32
TNM (n [%])							
T1-2	45 (31.46)	23 (31.08)	22 (31.88)	0.91	15 (33.33)	8 (27.59)	0.60
T3-4	98 (68.54)	51 (68.92)	47 (68.12)		30 (66.66)	21 (72.41)	
N0	25 (17.48)	16 (21.62)	9 (13.04)		9 (20.00)	7 (24.14)	
N1-2	94 (65.73)	44 (59.46)	50 (72.47)	0.24	29 (64.44)	15 (51.72)	0.52
N3	24 (16.79)	14 (18.92)	10 (14.49)		7 (15.55)	7 (24.14)	
M0	57 (39.86)	31 (41.89)	26 (37.68)	0.60	20 (44.44)	11 (37.93)	0.57
M1	86 (60.14)	43 (58.11)	43 (62.32)		25 (55.55)	18 (62.07)	
I	7 (4.90)	3 (4.05)	4 (5.80)		2 (4.44)	1 (3.45)	
II	14 (9.79)	10 (13.51)	4 (5.80)		9 (20.00)	1 (3.45)	
IIIA	13 (9.09)	5 (6.76)	8 (11.60)	0.49	3 (6.66)	2 (6.90)	0.29
IIIB-C	24 (16.78)	13 (17.57)	11 (15.94)		6 (13.33)	7 (24.14)	
IV	85 (59.44)	43 (58.11)	42 (60.86)		25 (55.55)	18 (62.06)	

Table 1 Continued

Parameter	All (n = 143)	Group 1: LRTI+ (n = 74)	Group 2: LRTI- (n = 69)	P-value Group 1 *vs.* Group 2	Solitary pathogen (n = 45)	Multiple pathogen (n = 29)	P-value Solitary vs. Multiple pathogen
ECOG performance status (n [%])							
0	72 (50.35)	30 (40.54)	42 (60.87)	0.01	23 (51.11)	7 (24.14)	0.02
1	40 (27.97)	23 (31.08)	17 (24.64)	0.39	14 (31.11)	9 (31.04)	0.99
2	14 (9.79)	9 (12.16)	5 (7.24)	0.32	3 (6.66)	6 (20.69)	0.07
3	9 (6.29)	7 (9.46)	2 (2.90)	0.10	3 (6.66)	4 (13.79)	0.30
4	8 (5.60)	5 (6.76)	3 (4.35)	0.53	2 (4.44)	3 (10.34)	0.32
Number of comorbidities (n [%])							
0	26 (18.18)	11 (14.86)	15 (21.75)		8 (17.77)	3 (10.34)	
1	42 (29.37)	22 (29.73)	20 (28.98)	0.66	13 (28.88)	9 (31.04)	0.70
2	47 (32.87)	27 (36.49)	20 (28.98)		17 (37.77)	10 (34.48)	
≥3	28 (19.58)	14 (18.92)	14 (20.29)		7 (15.55)	7 (24.14)	
NLR value	5.13 ± 4.30	5.95 ± 5.55	4.24 ± 1.99	0.01	5.38 ± 5.62	6.83 ± 5.41	0.27

P-value was calculated for Group 1 vs. Group 2 and for solitary vs. multiple pathogen. BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; IPF, idiopathic pulmonary fibrosis; LRTI, lower respiratory tract infections, NLR, neutrophil:lymphocyte ratio; n, number; SCLC, small cell lung cancer; TNM, classification of malignant tumors.

most common cause of patient exclusion from first-line chemotherapy, which is the poor ECOG performance status (2–4).[17] The ECOG performance status is a crucial predictive factor when allowing for treatment with chemotherapy, and the higher the number is connected with shorter survival as also noted in previous studies[18,19] and confirmed in our analysis.

Similarly to other researches, the NLR was higher in patients with lung malignancy, associated with LRTI and lower in those with noninfectious cases.[20] High NLR at diagnosis is an accepted prognostic marker of worse prognosis and therapy response for patients with lung cancer.[21–23] As infections are often associated with high neutrophil count it could have contributed to the worse outcome in Group 1 (LRTI+) patients, most pronounced in patients with multiple pathogen infections.

The incidence of adenocarcinoma was the highest in our study population in agreement with international literature.[4] Adenocarcinoma histology was associated with a more favorable outcome in our study population. Lung adenocarcinoma is mainly observed as a peripheral lesion, but in advanced stages, it also appears centrally,[24] similarly to the other histological subtypes.[25] Central carcinoma is readily associated with bronchial stricture and underlying pneumonia, which can advance in lung atelectasis. Consequently, microorganism colonization may evolve to infection. These known differences in the location could have contributed to the higher number of solitary pathogens (80.65% vs. 46.51%) in adenocarcinoma patients; however, in our analysis, the locations of the tumors did not notably differ in the case of LRTI.

Patients with LRTI had worse one-year survival as compared to patients without an infection and significant increase of risk of one-year mortality. This is in line with previous observations, where patients with multiple pathogen LRTI got shorter median survival than patients with the solitary pathogen LRTI (8.0 vs. 15.0 months, $P = 0.003$).[26]

The lungs although previously considered sterile in health are regularly colonized with varied communities of microbes from the oropharynx and other locations. The most common Bacteroidetes and Firmicutes are the *Prevotella*, *Veillonella* and *Streptococcus* spp. Microbiota of the lung which mostly correspond to those of the mouth than of other body sites. In cases of respiratory tract inflammation, intra-alveolar catecholamines and inflammatory cytokines advance the growth of selected bacterial species (e.g., *P. aeruginosa, S. pneumoniae, Staphylococcus aureus, Burkholderia cepacia* complex).[27]

The most predominant pathogen in our lung cancer patients were *Candida albicans*, pursued by *H. influenzae*, *S. aureus*, *S. pneumoniae* and *Enterobacter spp*. These pathogens have been regularly recognized in lung infections,

Table 2 LRTI pathogens in bronchoscopic samples at the time of cancer diagnosis

Pathogen	Group 1 LRTI + (*n* = 74)	Adenocarcinoma (*n* = 31)	Squamous cell carcinoma (*n* = 24)	SCLC (*n* = 10)	Other lung cancer (*n* = 9)	*P*-value
Aerobic (*n* [%])	49 (55.06)	21 (60.00)	16 (59.26)	7 (58.33)	5 (33.33)	0.32
Anaerobic (*n* [%])	14 (15.73)	5 (14.29)	4 (14.81)	2 (16.66)	3 (20.00)	0.96
Fungal (*n* [%])	26 (29.21)	9 (25.71)	7 (25.93)	3 (25.00)	7 (46.66)	0.44
Solitary pathogen (*n* [%])	45 (60.81)	25 (80.65)	12 (50.00)	5 (50.00)	3 (33.33)	0.02
Multiple pathogen (*n* [%])	29 (39.19)	6 (19.35)	12 (50.00)	5 (50.00)	6 (66.66)	

P-value was calculated for different cancer types in Group 1. LRTI, Lower respiratory tract infections; *n*, number; SCLC, small cell lung cancer.

Table 3 Oncotherapy in patients with pulmonary malignancy

Oncotherapy	All (*n* = 143)	Group 1: LRTI+ (*n* = 74)	Group 2: LRTI- (*n* = 69)	*P*-value Group 1 vs. Group 2	Solitary pathogen (*n* = 45)	Multiple pathogen (*n* = 29)	*P*-value Solitary vs. multiple pathogen
Curative intent surgery+/– chemo/radiotherapy (*n* [%])	19 (13.29)	11 (14.86)	8 (11.60)	0.56	10 (22.22)	1 (3.45)	0.02
Chemo–/immune–/target therapy (*n* [%])	62 (43.36)	25 (33.78)	37 (53.62)	0.02	15 (33.33)	10 (34.48)	0.91
Chemo + radiotherapy (*n* [%])	16 (11.19)	4 (5.41)	12 (17.39)	0.02	2 (4.44)	2 (6.90)	0.64
Radiotherapy (*n* [%])	5 (3.49)	5 (6.76)	0	Not valid	2 (4.44)	3 (10.34)	0.32
BSC (*n* [%])	34 (23.78)	24 (32.43)	10 (14.49)	0.01	11 (24.44)	13 (44.83)	0.06
Lost from medical attendance (*n* [%])	7 (4.89)	5 (6.76)	2 (2.90)	0.28	5 (11.11)	0	Not valid

P-value was calculated for Group 1 vs. Group 2 and for Solitary vs. multiple pathogen. BSC, best supportive care; LRTI, lower respiratory tract infections; *n*, number.

but the incidence of the microorganisms is different in recent studies, where the isolates of *Enterobacter* spp. (40.86%), followed by *S. aureus* (21.51%), *H. influenzae* (16.13%) and *S. pneumoniae* (7.53%) were recorded.[28] The nonfermenting Gram-negative bacteria were *Pseudomonas* spp. (6.45%) and *Acinetobacter* spp. (3.23%). Among fungal species, the most common was *Candida albicans* (63.77%).[28,29]

Infections increase the incidence of several malignancies (e.g., Human papillomavirus types 6 and 11 DNA sequences in cervical cancers, Helicobacter pylori infection in colorectal carcinoma).[30,31] Lung cancer often evolves in damaged lungs (e.g., COPD, emphysema, IPF).[7,8] In these lung diseases, mucociliary abnormality can grant mutagens from the smoke or further air pollution longer contact period at these locations, promoting the progress of pulmonary malignancy formation.[32] Constant irritation, caused by airway obstruction and the imbalance among oxidants and antioxidants may lead to DNA changes.[33] The incidence of pulmonary malignancy in patients with IPF (4.8% to 48%) is significantly higher than in patients without IPF (2.0% to 6.4%).[34,35] The mechanism of increased cancer development in IPF might be associated with increased inflammatory reaction, cell damage, abnormal fibroblast production and the activation of specific signaling pathways (e.g., Wnt/β-catein).[36–39] In our data set, about half of the patients had a significant underlying lung disease (COPD/IPF); however, this was not associated with differences in patients' characteristics of histology in the presence of LRTI.

In conclusion, LRTI, detected in bronchial samples at the time of diagnosis of lung malignancies influences the treatment options and outcome of these patients. Our data confirmed that LRTI+ patients had a worse ECOG performance status, withholding several treatment possibilities and so resulting in lower one-year survival. Patients with multiple pathogen LRTI were particularly less eligible for oncotherapy; however, no differences in stage, cancer histology subtype, gender or age were noted.

Our data emphasize that more attention should be given to LRTI and its treatment in lung cancer patients. The pathogen profile described in our series may assist with the selection of empiric treatment and hopefully decrease the observed risk of one-year mortality. Treatable threats are

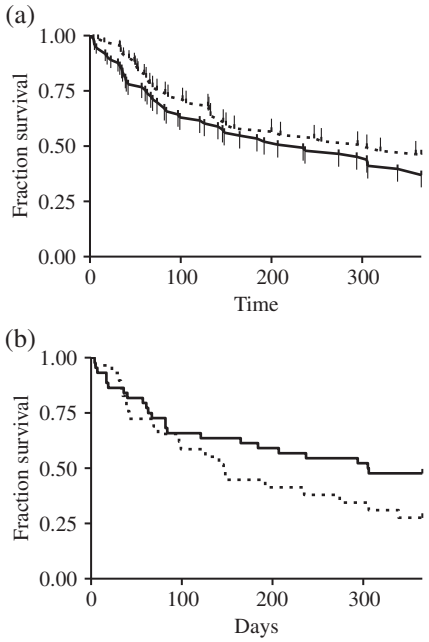

Figure 2 One-year survival of patients with pulmonary malignancy according to the presence of LRTI (**a**) (——) Group 1 (LRTI+), and (- - - -) Group 2 (LRTI–) and solitary and multiple pathogen LRTI (**b**) (- - - -) Multiple pathogen (LRTI+), and (——) Solitary pathogen (LRTI+).

Table 4 Risk factors for one-year mortality

One-year mortality	OR	CI 95%	*P*-value
LRTI	1.19	0.62–2.28	>0.05
LRTI with multiple pathogen	2.72	1.01–6.81	0.04
LRTI with solitary pathogen	1.19	0.45–1.640	>0.05
Male gender	4.04	2.03–8.04	<0.01
Nonadenocarcinoma	2.26	1.15–4,56	0.02
Ever-smoker	2.89	0.87–8.88	0.09
ECOG performance status 1	11.87	4.12–33.78	<0.01
ECOG performance status ≥ 2	30.00	5.23–313.00	<0.01

ECOG, Eastern Cooperative Oncology Group; LRTI, lower respiratory tract infection. [Correction added on 25 July 2019, after first online publication: in Table 4, 'One-year survival' in first column has been corrected to 'One-year mortality'].

important elements to improve therapy and survival of this special patient population.

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Disclosure

There are no conflicts of interest.

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