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Breathlessness predicts survival in patients with malignant pleural effusions: Meta-analysis of individual patient data from five randomized controlled trials

Short title: Dyspnoea and survival in malignant pleural effusion

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Abbreviations

CRP	C reactive protein
ECOG	Eastern Cooperative Oncology Group
HR	hazard ratio
LDH	lactate dehydrogenase
MPE	malignant pleural effusion
PS	performance status
RCT	randomised controlled trial
VASD	visual analogue scale for dyspnoea

Abstract

Background

Patients with malignant pleural effusions (MPEs) experience breathlessness and poor survival. Breathlessness is associated with poor survival in other conditions.

Research question

Is breathlessness, measured using a visual analogue scale for dyspnoea (VASD), associated with survival in patients with MPE?

Study design and methods

Individual patient data from five randomized controlled trials of 553 patients undergoing interventions for MPE were analysed. VASD was recorded at baseline and daily post-intervention. Patients were followed up until death or end of trial. Univariate and multivariable Cox-regression were used to identify factors associated with survival.

Results

Baseline VASD was significantly associated with worse survival, with a hazard ratio of 1.10 (95% CI 1.06-1.15) for a 10mm increase in VASD. On multivariable regression, it remained a significant predictor of survival. Mean 7 day VASD and mean total VASD were also predictors of survival (mean 7 day VASD, HR 1.26 (95% CI 1.19-1.34), total VASD, HR 1.25 (95% CI 1.15-1.37)). Other predictors of survival were serum C reactive protein level and tumour type. Previous treatment with chemotherapy, performance status, pleural fluid lactate dehydrogenase, serum albumin, haemoglobin, serum neutrophil:lymphocyte ratio and size of effusion were associated with survival on univariate but not multivariable analysis.

Interpretation

Breathlessness, measured using VASD at baseline and post-procedure, is a predictor of survival in patients with MPE.

Introduction

Malignant pleural effusions (MPEs) are common and cause disabling breathlessness. MPEs are associated with poor survival, with a mean prognosis of approximately 6 months. However, significant variation in survival exists. For example, a randomised trial comparing drainage methods demonstrated an interquartile range for survival of 2 to 11 months[1]. Choice of treatment depends on prognosis – in patients with a prognosis of less than 28 days, palliation of dyspnoea with therapeutic aspiration alone may be most appropriate[2]. However, in patients with a better prognosis, IPC or chest drain and pleurodesis to give prolonged dyspnoea relief and prevent need for further pleural procedures is more appropriate. In some patients with malignant pleural mesothelioma with a very good prognosis, pleurectomy may be indicated[3]. Therefore, accurate determination of prognosis is important to guide treatment, as well as to inform patients.

Previous studies have identified baseline variables associated with prognosis, such as serum albumin, C reactive protein (CRP) and performance status[4-6]. Two prognostic scores, the LENT score and the PROMISE score, can be used to predict prognosis at baseline[7,8]. The disadvantages of these scores is that they require invasive pleural fluid and blood sampling and may be misleading in some subgroups of patients and at an individual level[9-11].

In other chronic respiratory and cardiac diseases associated with poor survival and breathlessness, increased breathlessness has been shown to be predictive of poor survival. In patients with idiopathic pulmonary fibrosis, breathless assessed using the Medical Research Council chronic dyspnoea score is associated with poor survival[12,13]. In patients with presenting with acute congestive cardiac failure, subacute dyspnoea is predictive of poor 1 year mortality[14]. Cancer patients presenting to the emergency department with breathlessness have a mean survival of only 12 weeks[15]. The BODE index, a validated prognostic score for patients with chronic obstructive pulmonary disease includes dyspnoea as well as body mass index, airflow obstruction and exercise[16]. A previous systematic review has demonstrated that breathlessness is an predictor of mortality in the general population[17]. This data demonstrates that in a wide range of conditions and in the healthy population, breathlessness is associated with poor survival.

The visual analogue scale for dyspnoea (VASD) is a validated measure of breathlessness for patients with MPE[18]. This is a 100mm line anchored at one end with ‘no breathlessness’ and at the other with ‘maximum possible breathlessness’. Patients are asked to mark across the line to represent their level of breathlessness. This is scored by measuring from ‘no breathlessness’ to the patient’s mark. A higher score represents more severe breathlessness. The minimal important difference is 19mm[19]. The VASD has been used as a primary or secondary outcome measure in several randomised controlled trials (RCTs) studying the effects of different interventions in patients with MPE[1,20-23].

The aim of this study was to investigate whether breathlessness measured using VASD predicts mortality in patients with MPE, using individual patient data collected as part of five RCTs.

Materials and Methods

We conducted a meta-analysis using individual-level data from five RCTs which recruited patients with MPE to study the impact of different interventions[1,20-23]. Details of the trials are summarised in table 1. All studies recruited adults (18 years or older) with MPE, based on either

histological or cytological confirmation or recurrent exudative pleural effusion with confirmed cancer elsewhere. All patients gave written informed consent at the time of enrolment into these studies for the use of data collected in the trial for further analysis. All studies measured breathlessness using VASD diaries, in which patients recorded baseline VASD (before trial intervention) and subsequently for a varying time period (table 1). Analysis was done on baseline VASD, mean VASD over first 7 days post intervention (7 day VASD) and mean of all post intervention VASD (total VASD). For IPC-plus, the intervention used was IPC insertion, not pleurodesis. Survival was measured in days from randomisation until death. Tumour type was categorised as mesothelioma, lung, breast/gynaecological or other. Size of effusion was measured as a percentage of the hemithorax, either measured using a validated electronic method or as a visual estimate[24]. Follow up was until death or end of trial (table 1). Patients lost to follow up or alive at end of trial were censored.

Stata 16.1/SE/ (StataCorp. 2019.) was used for all statistical analysis. Univariate Cox-regression was used to identify factors associated with survival. Factors that were recorded in all trials were included a multivariable Cox-regression model with stratification by trial. For VASD, a linear association with log-survival was assessed using cubic splines. This assessment found a non-linear association between baseline VASD and survival, and therefore baseline VASD was split into thirds. The assumptions of the Cox-model were assessed using Schoenfeld residuals. Univariate predictors were estimated using data from all available studies. Potential multivariable predictors were only those measured in all studies, specifically sex, age, serum CRP, tumour type, baseline VASD, mean 7 day VASD and total mean VASD. No variable selection techniques were used as these are known to introduce bias.

Analysis using baseline VASD was survival from baseline; for mean 7 day VASD, survival was from day 7; and for total mean VASD, survival was from 84 days i.e. the maximum length of time that the VASD was collected for.

Results

Demographic data is summarised in table 2. Only patients with at least one recorded VASD were included in analysis. A total of 311/553 (56.2%) of patients died during the follow-up period. The median time from enrolment to death was 194 (95% CI 160-213) days. Mean baseline VASD was 45.9mm (SD 28.8mm), but 113/507 (22%) patients had a VASD of less than 19mm. Less than half (194/411, 47.2%) recorded a decrease in mean 7 day VASD of at least 19mm but this proportion was 133/215 (61.9%) for mean total VASD.

There was no difference in survival between patients recruited to TIME2, AMPLE1 and AMPLE2 (table 3). Patients recruited to TIME3 had a worse survival and patients recruited to IPC-plus had a better survival.

Univariate predictors of survival

Unadjusted analysis demonstrated that baseline VASD was significantly associated with worse survival, with a hazard ratio (HR) of 1.10 (95% CI 1.06-1.15) for a 10mm increase in VASD. For both mean 7 day and total VASD, the actual values were associated with survival (for mean 7 day VASD, HR 1.26 for 10mm increase (95% CI 1.19,1.34) and for total VASD, HR 1.25 for 10mm increase (95% CI 1.15,1.37), but the change from baseline were not. When divided into equal quartiles based

on mean 7 day VASD, there was a significant difference between groups (figure 1). Other factors significantly associated with survival are reported in table 3. The following variables were associated with worse survival: previous treatment with chemotherapy compared to no previous treatment; worsening Eastern Cooperative Oncology Group performance status (ECOG PS); higher pleural fluid lactate dehydrogenase (LDH); higher serum CRP; higher serum neutrophil:lymphocyte ratio; smaller pleural effusion; lower serum albumin; and lower haemoglobin. Patients with mesothelioma, breast and gynaecological cancers had better survival than those with lung and other cancers.

Adjusted predictors of survival

Multivariable Cox-regressions showed a linear associated between mean 7 day VASD/mean total VASD and survival. Predictors of survival from baseline were baseline VASD, serum CRP and tumour type. Patients with a baseline VASD of 67-100mm had worst survival (HR 1.73 (95% CI 1.17-2.54)) compared to patients with a baseline VASD of 0-33. A 10 unit increase in CRP was associated with a worse survival (HR 1.06 (95% CI 1.03, 1.08), p<0.001) and both 'other (HR 2.28 (95% CI 1.43, 3.63)) and lung (HR 2.13 (95% CI 1.36, 3.31)) tumours had worse survival compared to mesothelioma.

Predictors of survival at one week

At one week, factors independently associated with future survival were mean 7 days VASD (HR 1.14 (95% CI 1.06-1.23)), baseline serum CRP (HR 1.05 (95% CI 1.02-1.07)) and tumour type. At 84 days, only mean total VASD was significantly associated with future survival (HR 1.19 (95% CI 1.04-1.37)).

Discussion

Our results demonstrate a significant negative correlation between breathlessness assessed by VASD and survival in patients with MPEs. This is true at baseline, mean VASD over 7 days and mean total VASD. This relationship is independent of other factors known to predict survival. This data demonstrates that breathless patients with MPE have a worse survival compared to those who are not breathless. This meta-analysis used patients from five different RCTs.

The breathlessness experienced by patients with MPE is multifactorial, not due to the MPE alone. This will include pleural factors (such as trapped lung caused by extensive tumour involvement), involvement in the lung by cancer, (e.g. metastases, lymphangitis carcinomatosis, pulmonary embolism) and other common comorbidities (e.g. chronic obstructive pulmonary disease, congestive cardiac failure). Breathlessness also leads to a downward cycle of decreased activity, deconditioning and worsening breathlessness[25]. We hypothesise that breathlessness is a strong predictor of mortality because these underlying factors cause both breathlessness and poor survival.

Previous studies have identified independent baseline variables which predict prognosis in patients with MPE and used these to develop prognostic scores (LENT and PROMISE)[7,8]. Interestingly, most of the variables identified are related to systemic and inflammatory factors (serum lymphocyte:neutrophil ratio, performance status, tumour type, previous chemotherapy or radiotherapy, haemoglobin, serum white cell count, serum CRP) rather than those specific to the effusion (pleural fluid LDH alone). This suggests that it is the patient's overall condition that predicts mortality rather than the characteristics of the pleural effusion. The strength of using breathlessness as a predictor of survival is that it is a representation of the patient's overall condition.

A surprising finding of our study was that larger effusions were associated with improved survival. Data on effusion size was available in three studies (TIME3 and AMPLE-1 and -2). This is in contrast to other studies which have found larger effusions were associated with worse survival[26,27]. This may be because this data comes from different cohorts of patients: the studies by Jimenez et al. and Martinez-Moragon were at presentation whereas the patients in TIME3 were hospitalised patients with a non-draining effusion and AMPLE-1 and -2 were patients with recurrent MPE undergoing a definitive procedure. Further research is required to explore this relationship.

These results are in keeping with other studies which have demonstrated a correlation between breathlessness and survival across a wide range of other diseases, as well as the healthy population[12-15]. A variety of different ways of measuring breathlessness have been used in these studies, but despite this, results are consistent across studies. This demonstrates that it is the symptom of breathlessness that is significant, not the specific tool used to assess it. This commonality demonstrates that breathlessness may be a universal predictor of mortality and should be considered when attempting to predict mortality in specific populations.

Breathlessness is associated with survival at a population level in patients with MPE, as well as a wide range of other conditions. However, this association does not appear to be strong enough to predict prognosis in individual patients. It may be more appropriate to use it as part of a clinical score, like the BODE score for chronic obstructive pulmonary disease[16]. Breathlessness should be assessed in future tools which attempt to predict mortality in patients with MPE.

Inclusion criteria for TIME2, AMPLE1 and AMPLE-2 were similar, explaining the similar mortality. Mortality was better in IPC-plus, which excluded patients with non-expansile lung, a group with worse mortality[28]. The significantly worse mortality in patients recruited to TIME3 demonstrates that inpatients with MPE, a chest drain and a septated pleural effusion have poor survival.

There are limitations of this study, mainly because the data was collected as part of five separate RCTs, rather than specifically to answer this question. Firstly, not all baseline variables were recorded in the different trials, so they could not be included in the statistical analysis. Secondly, these trials had specific inclusion/exclusion criteria, and these results may not necessarily apply to the wider population of patients with MPE. Specifically, most patients had not had a previous definitive pleural procedure and most trials specified a minimum predicted survival (table 1). Further research is needed into the relationship between breathlessness and survival in patients with MPE who do not fulfil these trial criteria. In addition, the length of time patients completed a VASD diary for varied between the studies, but this did not seem to impact on results. Finally, the trial interventions could potentially confound this result by influencing both breathlessness and survival. The results of these studies showed no difference in mortality between groups, but were not powered to assess a survival difference.

Other limitations are due to the way the VASD was used to measure breathlessness. The VASD was not standardised between the studies. In TIME2 and TIME3, it was as described in the introduction, whereas in AMPLE-1 and 2, the 100mm point was marked ‘worst imaginable breathlessness’. Furthermore, the VASD was the opposite way round in AMPLE-1 compared to the other studies, with ‘no breathlessness’ at the right hand end. For IPC-plus, patients were asked ‘how much breathlessness are you feeling at the moment?’ and the 100mm point was marked ‘worse

possible breathlessness'. A standardised script was not used to explain the VASD to patients. Language may have also been a limitation for some patients, with all studies providing the VASD diary in English only. It is important that future work uses a standardised VASD and further research may be required to determine the best way to measure breathlessness to predict mortality.

In summary, meta-analysis of individual patient data from five RCTs has demonstrated a association between breathlessness and survival in patients with MPE.

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Table 1: Summary of RCTs included in this analysis. IPC – indwelling pleural catheter

Trial	No. of patients	Main inclusion criteria	Main exclusion criteria	Trial design	Duration of follow up	Duration of VAS diary
Davies 2012 (TIME2)[1]	106	Recurrent MPE	Expected survival <3 months, previous pleurodesis	Chest drain and talc pleurodesis versus IPC	1 year	Daily for 42 days
Thomas 2017 (AMPLE-1)[23]	145	Recurrent MPE	Expected survival <3 months, previous pleurodesis	Chest drain and talc pleurodesis versus IPC	1 year	Daily for 14 days, then 1, 3, 6, 9 and 12 months
Mishra 2018 (TIME3)[20]	71	Significant non-draining MPE with chest drain in situ	Expected survival< 28 days, trapped lung	Urokinase versus placebo	1 year	Daily for 28 days
Muruganandan 2018 (AMPLE-2)[22]	87	MPE with IPC	Expected survival <2 months	Daily drainage versus symptom-guided drainage	6 months	Daily for 60 days, then weekly for 6 months
Bhatnagar 2018 (IPC-plus)[21]	154	MPE with IPC	Expected survival <2 month, trapped lung	Talc versus placebo given via IPC	70 days	Daily for 84 days

Table 2: baseline demographic data

Characteristic		
Sex female		278/553 (50.3%)
Age (years), median (IQR)		68 (61-76)
Previous chemotherapy		149/337 (44.2%)
Previous radiotherapy		52/191 (27.2%)
PF LDH (U/L), median (IQR)		415 (250-833)
PF pH, median (IQR)		7.37 (7.26-7.43)
PF glucose (mmol/L), median (IQR)		5.40 (3.20-6.40)
Serum CRP (mg/L), median (IQR)		43.0 (15.0-98.5)
Serum albumin (g/dL), median (IQR)		37.0 (30.0-41.0)
Haemoglobin (g/dL), median (IQR)		129 (113-158)
Serum neutrophil:lymphocyte, median (IQR)		5.20 (3.50-7.40)
ECOG PS	0	48 (11.0%)
	1	179 (40.9%)
	2	119 (27.2%)
	3	79 (18.0%)
	4	13 (3.0%)
Size of effusion on CXR (% hemithorax), median (IQR)		60.0 (60.0-80.0)
Tumour type	Mesothelioma	110 (19.9%)
	Lung	173 (31.3%)
	Breast/Gynae	128 (23.2%)
	Other	141 (25.5%)
Intervention IPC:chest drain		355 (64.4%):196 (35.6%)
Died during follow up		311/553 (56.2%)

Table 3: Results of unadjusted and adjusted analysis of baseline factors associated with survival in patients with MPE

	Unadjusted (number of participants n =533; number of events E =311		Adjusted (baseline only) (n=360; E=204)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Sex male:female	0.81 (0.65,1.02)	0.070	0.87 (0.61,1.25)	0.459
Previous chemotherapy	1.89 (1.46,2.46)	<0.001		
Previous radiotherapy	1.24 (0.85,1.80)	0.267		
Age, 5 year increase	1.04 (0.99,1.10)	0.084	1.05 (0.98,1.13)	0.190
PF LDH, 500 unit change	1.05 (1.03,1.08)	<0.001		
PF pH	1.27 (0.69,2.34)	0.446		
PF glucose	0.99 (0.95,1.03)	0.650		
Serum CRP, 10 unit increase	1.06 (1.05,1.08)	<0.001	1.06 (1.03,1.08)	<0.001
Serum albumin	0.96 (0.94,0.98)	<0.001		
Haemoglobin, per 10 unit increase	0.85 (0.8,0.92)	<0.001		
Neutrophil: lymphocyte ratio	1.10 (1.07,1.13)	<0.001		
Size of effusion on CXR at baseline (% hemithorax)	0.32 (0.18,0.57)	<0.001		
Trial (vs AMPLE-1)				
AMPLE-2	0.91 (0.65,1.27)	0.581		
IPC+	0.37 (0.21,0.63)	<0.001		
TIME2	1.27 (0.95,1.72)	0.11		
TIME3	2.61 (1.90,3.59)	<0.001		
ECOG PS (vs 0)				
1	2.29 (1.21,4.32)	0.011		
2	4.45 (2.35,8.42)	<0.001		
3	8.77 (4.59,16.73)	<0.001		
4	25.61 (11.12,58.99)	<0.001		
Tumour type (vs mesothelioma)				
Lung	2.29 (1.64,3.21)	<0.001	2.13 (1.36,3.31)	0.001
Breast/Gynae	1.33 (0.91,1.93)	0.135	1.25 (0.69,2.25)	0.460
Other	2.54 (1.79,3.60)	<0.001	2.28 (1.43,3.63)	0.001
Baseline VASD, 10 unit increase	1.10 (1.06,1.15)	<0.001		

Split : 0 -33mm	1			
34 – 66mm	1.28 (0.95,1.74)	0.110	0.94 (0.64,1.39)	0.773
67-100mm	1.85 (1.39,2.48)	<0.001	1.73 (1.17,2.54)	0.006

Figure legends:

Figure 1: Kaplan-Meier survival curve from day 7 of patients divided into four equal quartiles by mean 7 day VASD. Continuous line mean 7 day VASD 0-10mm; dashed line mean 7 day VASD 10-22mm; dotted line mean 7 day VASD 22-37mm; dashed/dotted line mean 7 day VASD 38-90mm.

References

1. Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. *JAMA.* 2012;307(22):2383-2389.
2. Roberts ME, Neville E, Berrisford RG, Antunes G, Ali NJ. Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010. *Thorax.* 2010;65(Suppl 2):ii32-40.
3. Matthews C, Freeman C, Sharples LD, et al. MesoTRAP: a feasibility study that includes a pilot clinical trial comparing video-assisted thoracoscopic partial pleurectomy decortication with indwelling pleural catheter in patients with trapped lung due to malignant pleural mesothelioma designed to address recruitment and randomisation uncertainties and sample size requirements for a phase III trial. *BMJ Open Respir Res.* 2019;6(1):e000368.
4. Kasapoglu US, Arinc S, Gungor S, et al. Prognostic factors affecting survival in non-small cell lung carcinoma patients with malignant pleural effusions. *Clin Respir J.* 2016;10(6):791-799.
5. Zamboni MM, da Silva CT, Jr., Baretta R, Cunha ET, Cardoso GP. Important prognostic factors for survival in patients with malignant pleural effusion. *BMC Pulm Med.* 2015;15:29.
6. Verma A, Phua CK, Sim WY, et al. Pleural LDH as a prognostic marker in adenocarcinoma lung with malignant pleural effusion. *Medicine (Baltimore).* 2016;95(26):e3996.
7. Clive AO, Kahan BC, Hooper CE, et al. Predicting survival in malignant pleural effusion: development and validation of the LENT prognostic score. *Thorax.* 2014;69(12):1098-1104.
8. Psallidas I, Kanellakis NI, Gerry S, et al. Development and validation of response markers to predict survival and pleurodesis success in patients with malignant pleural effusion (PROMISE): a multicohort analysis. *Lancet Oncol.* 2018;19(7):930-939.
9. Abisheganaden J, Verma A, Dagaonkar RS, Light RW. An Observational Study Evaluating the Performance of LENT Score in the Selected Population of Malignant Pleural Effusion from Lung Adenocarcinoma in Singapore. *Respiration.* 2018;96(4):308-313.
10. Banka R. FR, Hung A., Gkogkou P., Mishra EK. Evaluation of the LENT and PROMISE score for malignant pleural mesothelioma by histological subtype. *Thorax.* 2019;74:A133-134.
11. Quek JC, Tan QL, Allen JC, Anantham D. Malignant pleural effusion survival prognostication in an Asian population. *Respirology.* 2020.
12. Manali ED, Stathopoulos GT, Kollintza A, et al. The Medical Research Council chronic dyspnea score predicts the survival of patients with idiopathic pulmonary fibrosis. *Respir Med.* 2008;102(4):586-592.
13. Guazzi M, Myers J, Peberdy MA, Bensimhon D, Chase P, Arena R. Maximal dyspnea on exertion during cardiopulmonary exercise testing is related to poor prognosis and echocardiography with tissue Doppler imaging in heart failure. *Congest Heart Fail.* 2009;15(6):277-283.
14. Sokolska JM, Sokolski M, Zymlinski R, et al. Patterns of dyspnoea onset in patients with acute heart failure: clinical and prognostic implications. *ESC Heart Fail.* 2019;6(1):16-26.
15. Escalante CP, Martin CG, Elting LS, et al. Dyspnea in cancer patients. Etiology, resource utilization, and survival-implications in a managed care world. *Cancer.* 1996;78(6):1314-1319.
16. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med.* 2004;350(10):1005-1012.
17. Pesola GR, Ahsan H. Dyspnea as an independent predictor of mortality. *Clin Respir J.* 2016;10(2):142-152.
18. Mishra EK. Measurement of breathlessness in patients with malignant pleural effusions. *Curr Pulmonol Rep.* 2016;5(1):1-6.

19. Mishra EK, Corcoran JP, Hallifax RJ, Stradling J, Maskell NA, Rahman NM. Defining the minimal important difference for the visual analogue scale assessing dyspnea in patients with malignant pleural effusions. *PLoS One.* 2015;10(4):e0123798.
20. Mishra EK, Clive AO, Wills GH, et al. Randomized Controlled Trial of Urokinase versus Placebo for Nondraining Malignant Pleural Effusion. *Am J Respir Crit Care Med.* 2018;197(4):502-508.
21. Bhatnagar R, Keenan EK, Morley AJ, et al. Outpatient Talc Administration by Indwelling Pleural Catheter for Malignant Effusion. *N Engl J Med.* 2018;378(14):1313-1322.
22. Muruganandan S, Azzopardi M, Fitzgerald DB, et al. Aggressive versus symptom-guided drainage of malignant pleural effusion via indwelling pleural catheters (AMPLE-2): an open-label randomised trial. *Lancet Respir Med.* 2018;6(9):671-680.
23. Thomas R, Fysh ETH, Smith NA, et al. Effect of an Indwelling Pleural Catheter vs Talc Pleurodesis on Hospitalization Days in Patients With Malignant Pleural Effusion: The AMPLE Randomized Clinical Trial. *JAMA.* 2017;318(19):1903-1912.
24. Rahman NM, Maskell NA, West A, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. *N Engl J Med.* 2011;365(6):518-526.
25. O'Donnell DE, Milne KM, James MD, de Torres JP, Neder JA. Dyspnea in COPD: New Mechanistic Insights and Management Implications. *Adv Ther.* 2020;37(1):41-60.
26. Martinez-Moragon E, Aparicio J, Sanchis J, Menendez R, Cruz Rogado M, Sanchis F. Malignant pleural effusion: prognostic factors for survival and response to chemical pleurodesis in a series of 120 cases. *Respiration.* 1998;65(2):108-113.
27. Jimenez D, Diaz G, Gil D, et al. Etiology and prognostic significance of massive pleural effusions. *Respir Med.* 2005;99(9):1183-1187.
28. Martin GA, Kidd AC, Tsim S, et al. Inter-observer variation in image interpretation and the prognostic importance of non-expansile lung in malignant pleural effusion. *Respirology.* 2020;25(3):298-304.