CHEST

Breathlessness Predicts Survival in Patients With Malignant Pleural Effusions

Meta-analysis of Individual Patient Data From Five Randomized Controlled Trials

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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 analog scale for dyspnea (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 analyzed. VASD was recorded at baseline and daily after 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 10-mm 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: hazard ratio [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 tumor type. Previous treatment with chemotherapy, performance status, pleural fluid lactate dehydrogenase, serum albumin, hemoglobin, 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 postprocedure, is a predictor of survival in patients with MPE. CHEST 2021; 160(1):351-357

KEY WORDS: breathlessness; malignant pleural effusion; survival

FOR EDITORIAL COMMENT, SEE PAGE 29

ABBREVIATIONS: CRP = C-reactive protein; HR = hazard ratio; IPC = intermittent pneumatic compression; LDH = lactate dehydrogenase; MPE = malignant pleural effusion; RCT = randomized controlled trial; VASD = visual analog scale for dyspnea

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Take-home Points

Study Question: Is breathlessness associated with survival in patients with malignant pleural effusion?
Results: Meta-analysis of patient level data from five randomized controlled trials demonstrated a significant association between increasing breathlessness and worse survival.
Interpretation: Breathlessness is a predictor of survival in patients with malignant pleural effusion.

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 randomized 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 dyspnea with therapeutic aspiration alone may be most appropriate.[2] However, in patients with a better prognosis, intermittent pneumatic compression (IPC) or chest drain and pleurodesis to give prolonged dyspnea relief and prevent the 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 dyspnea score is associated with poor survival.[12,13] In patients presenting with acute congestive cardiac failure, subacute dyspnea is predictive of poor 1-year mortality.[14] Cancer patients presenting to the ED with breathlessness have a mean survival of only 12 weeks.[15] The BODE index, a validated prognostic score for patients with COPD, includes dyspnea as well as BMI, airflow obstruction, and exercise.[16] A previous systematic review has demonstrated that breathlessness is a predictor of mortality in the general population.[17] These data demonstrate that in a wide range of conditions and in the healthy population, breathlessness is associated with poor survival.

The visual analog scale for dyspnea (VASD) is a validated measure of breathlessness for patients with MPE.[18] This is a 100-mm 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 19 mm.[19] The VASD has been used as a primary or secondary outcome measure in several randomized 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.

Methods

We conducted a meta-analysis using individual-level data from five RCTs that recruited patients with MPE to study the impact of different interventions.[1,20-23] Details of the trials are summarized 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 enrollment 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 (Table 1). Analysis was done on baseline VASD, mean VASD over the first 7 days postintervention (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 randomization until death. Tumor type was categorized as mesothelioma, lung, breast/gynecological, 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 the end of the trial (Table 1). Patients lost to follow-up or alive at the end of the trial were censored.

Stata 16.1/SE/ (StataCorp, 2019) was used for all statistical analysis. Univariate Cox regression was used to identify factors

TABLE 1] Summary of RCTs Included in This Analysis

Trial	No. of Patients	Main Inclusion Criteria	Main Exclusion Criteria	Trial Design	Duration of Follow-up	Duration of VAS Diary
Davies et al,[1] 2012 (TIME2)	106	Recurrent MPE	Expected survival <3 mo, previous pleurodesis	Chest drain and talc pleurodesis vs IPC	1 y	Daily for 42 d
Thomas et al,[23] 2017 (AMPLE-1)	145	Recurrent MPE	Expected survival <3 mo, previous pleurodesis	Chest drain and talc pleurodesis vs IPC	1 y	Daily for 14 d, then 1, 3, 6, 9, and 12 mo
Mishra et al,[20] 2018 (TIME3)	71	Significant nondraining MPE with chest drain in situ	Expected survival < 28 d, trapped lung	Urokinase vs placebo	1 y	Daily for 28 d
Muruganandan et al,[22] 2018 (AMPLE-2)	87	MPE with IPC	Expected survival < 2 mo	Daily drainage vs symptom-guided drainage	6 mo	Daily for 60 d, then weekly for 6 mo
Bhatnagar et al,[21] 2018 (IPC-plus)	154	MPE with IPC	Expected survival < 2 mo, trapped lung	Talc vs placebo given via IPC	70 d	Daily for 84 d

IPC = indwelling pleural catheter.

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 nonlinear 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, tumor type, baseline VASD, mean 7-day VASD, and total mean VASD. No variable selection techniques were used, because 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, that is, the maximum length of time during which the VASD was collected.

Results

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

No difference was seen 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 10-mm 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 10-mm increase [95% CI, 1.19-1.34] and for total VASD, HR 1.25 for 10-mm increase [95% CI, 1.15-1.37]), but the changes from baseline were not. When divided into equal quartiles based on mean 7-day VASD, there was a significant difference between groups (Fig 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 with no previous treatment; worsening Eastern Cooperative Oncology Group performance status; higher pleural fluid lactate dehydrogenase (LDH); higher serum CRP; higher serum neutrophil: lymphocyte ratio; smaller pleural effusion; lower serum albumin; and lower hemoglobin. Patients with mesothelioma, breast, and gynecological cancers had better survival than those with lung and other cancers.

TABLE 2] Baseline Demographic Data

Characteristic	Data
Sex, female	278/553 (50.3%)
Age, y; median (IQR)	68 (61-76)
Previous chemotherapy	149/337 (44.2%)
Previous radiation therapy	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)
Hemoglobin (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 chest radiograph (% hemithorax), median (IQR)	60.0 (60.0-80.0)
Tumor type	
Mesothelioma	110 (19.9%)
Lung	173 (31.3%)
Breast/gynecological	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%)

CRP = C-reactive protein; ECOG = Eastern Cooperative Oncology Group; IPC = indwelling pleural catheter; IQR = interquartile range; LDH = lactate dehydrogenase; PF = pleural fluid; PS = performance status.

Adjusted Predictors of Survival

Multivariable Cox regressions showed a linear association between mean 7-day VASD/mean total VASD and survival. Predictors of survival from baseline were baseline VASD, serum CRP, and tumor type. Patients with a baseline VASD of 67 to 100 mm had worst survival (HR, 1.73 [95% CI, 1.17-2.54]) compared with patients with a baseline VASD of 0 to 33. A 10-unit increase in CRP was associated with a worse survival (HR, 1.06 [95% CI, 1.03-1.08], $P < .001$) and both "other" (HR, 2.28 [95% CI, 1.43-3.63]) and lung (HR, 2.13 [95% CI, 1.36-3.31]) tumors had worse survival compared with mesothelioma.

Predictors of Survival at 1 Week

At 1 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 tumor 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. These data demonstrate that breathless patients with MPE have a worse survival compared with those who are not breathless. This meta-analysis used patients from five different RCTs.

The breathlessness experienced by patients with MPE is multifactorial, not caused by the MPE alone. This will

TABLE 3] Results of Unadjusted and Adjusted Analysis of Baseline Factors Associated With Survival in Patients With MPE

Baseline Factor	Unadjusted (No. of Participants, N = 533; No. of Events, E = 311		Adjusted (Baseline Only) (n = 360; E = 204)	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex male:female	0.81 (0.65-1.02)	.070	0.87 (0.61-1.25)	.459
Previous chemotherapy	1.89 (1.46-2.46)	<.001	…	…
Previous radiation therapy	1.24 (0.85-1.80)	.267	…	…
Age, 5-year increase	1.04 (0.99-1.10)	.084	1.05 (0.98-1.13)	.190
PF LDH, 500 unit change	1.05 (1.03-1.08)	<.001	…	…
PF pH	1.27 (0.69-2.34)	.446	…	…
PF glucose	0.99 (0.95-1.03)	.650	…	…
Serum CRP, 10-unit increase	1.06 (1.05-1.08)	<.001	1.06 (1.03-1.08)	<.001
Serum albumin	0.96 (0.94-0.98)	<.001	…	…
Hemoglobin, per 10 unit increase	0.85 (0.8,0.92)	<.001	…	…
Neutrophil: lymphocyte ratio	1.10 (1.07-1.13)	<.001	…	…
Size of effusion on chest radiograph at baseline (% hemithorax)	0.32 (0.18-0.57)	<.001	…	…
Trial (vs AMPLE-1)				
AMPLE-2	0.91 (0.65-1.27)	.581	…	…
IPC+	0.37 (0.21-0.63)	<.001	…	…
TIME2	1.27 (0.95-1.72)	.11	…	…
TIME3	2.61 (1.90-3.59)	<.001	…	…
ECOG PS (vs 0)				
1	2.29 (1.21-4.32)	.011	…	…
2	4.45 (2.35-8.42)	<.001	…	…
3	8.77 (4.59-16.73)	<.001	…	…
4	25.61 (11.12-58.99)	<.001	…	…
Tumor type (vs mesothelioma)				
Lung	2.29 (1.64-3.21)	<.001	2.13 (1.36-3.31)	.001
Breast/gynecological	1.33 (0.91-1.93)	.135	1.25 (0.69-2.25)	.460
Other	2.54 (1.79-3.60)	<.001	2.28 (1.43-3.63)	.001
Baseline VASD, 10-unit increase	1.10 (1.06-1.15)	<.001	…	…
Split: 0-33 mm	1	…	…	…
34-66 mm	1.28 (0.95-1.74)	.110	0.94 (0.64-1.39)	.773
67-100 mm	1.85 (1.39-2.48)	<.001	1.73 (1.17,2.54)	.006

CRP = C-reactive protein; ECOG = Eastern Cooperative Oncology Group; IPC = indwelling pleural catheter; LDH = lactate dehydrogenase; MPE = malignant pleural effusion; PF = pleural fluid; PS = performance status; VASD = visual analog scale for dyspnea.

include pleural factors (such as trapped lung caused by extensive tumor involvement), involvement in the lung by cancer (eg, metastases, lymphangitis carcinomatosis, pulmonary embolism) and other common comorbidities (eg, COPD, congestive cardiac failure). Breathlessness also leads to a downward cycle of decreased activity, deconditioning, and worsening breathlessness.[25] We hypothesize 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 that predict prognosis in patients with MPE and used these to develop prognostic scores (LENT and PROMISE).[7,8] Most of the variables identified are related to systemic and inflammatory factors (serum lymphocyte: neutrophil ratio, performance status, tumor type, previous chemotherapy or radiation therapy, hemoglobin, serum white cell count, serum CRP) rather than those specific to the effusion (pleural fluid LDH alone). This suggests that it is the

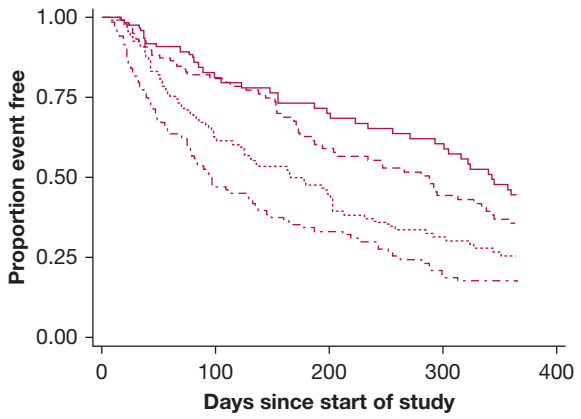

Figure 1 – *Kaplan-Meier survival curve from day 7 of patients divided into four equal quartiles by mean 7-day VASD. Continuous line = mean 7-day VASD 0-10 mm; dashed line = mean 7-day VASD 10-22 mm; dotted line = mean 7-day VASD 22-37 mm; dashed/dotted line = mean 7-day VASD 38-90 mm. VASD = visual analog scale for dyspnea.*

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 were available in three studies (TIME3 and AMPLE-1 and -2). This is in contrast to other studies that have found that larger effusions were associated with worse survival.[26,27] This may be because these data come from different cohorts of patients: the studies by Jimenez et al[27] and Martinez-Moragon et al[26] were at presentation, whereas the patients in TIME3 were hospitalized patients with a nondraining 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 that 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, such as the BODE score for COPD.[16] Breathlessness should be assessed in future tools that attempt to predict mortality in patients with MPE.

Inclusion criteria for TIME2, AMPLE-1, and AMPLE-2 were similar, explaining the similar mortality. Mortality was better in IPC-plus, which excluded patients with nonexpansile 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 were collected as part of five separate RCTs, rather than specifically to answer this question. First, not all baseline variables were recorded in the different trials, so they could not be included in the statistical analysis. Second, 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 fulfill 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 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 attributable to the way the VASD was used to measure breathlessness. The VASD was not standardized between the studies. In TIME2 and TIME3, it was as described in the introduction, whereas in AMPLE-1 and 2, the 100-mm point was marked "worst imaginable breathlessness." Furthermore, the VASD was the opposite way around in AMPLE-1 compared with 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 100-mm point was marked "worst possible breathlessness." A standardized script was not used to explain the VASD to patients. Language also may have been a limitation for some patients, with all studies

providing the VASD diary in English only. Future work should use a standardized VASD, and further research may be required to determine the best way to measure breathlessness to predict mortality.

Interpretation

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

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