Inter-observer variation and the prognostic importance of non-expansile lung in malignant pleural effusion

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SUMMARY AT A GLANCE

Non-expansile Lung (NEL) often complicates malignant pleural effusion management. This multicentre study identifies significant limitations in radiographic NEL detection and an association between NEL and adverse survival. These findings are relevant to clinical practice and should be considered in future trial design.

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Role	***Degree***	***Author initials*** *(reflecting the full author name on the manuscript)*
1 **-Conceptualization**	Lead	KGB
	Equal	
	Supporting	GAM, ACK, ST, AB
2 **- Data curation**	Lead	GAM
	Equal	ACK
	Supporting	ST, PH, AB, NM
3 **-Formal analysis**	Lead	
	Equal	GAM, KGB
	Supporting	
4 **- Funding acquisition**	Lead	
	Equal	
	Supporting	
5 **- Investigation**	Lead	
	Equal	GAM
	Supporting	
6 **- Methodology**	Lead	KGB
	Equal	
	Supporting	GAM
7 **- Project administration**	Lead	GAM
	Equal	
	Supporting	
8 **- Resources**	Lead	
	Equal	
	Supporting	
9 **- Software**	Lead	
	Equal	
	Supporting	
10 **- Supervision**	Lead	KGB
	Equal	
	Supporting	NM
11 **- Validation**	Lead	
	Equal	
	Supporting	
12 **- Visualization**	Lead	
	Equal	

	Supporting	
13 - **Writing – original draft**	Lead	
	Equal	GAM, KGB
	Supporting	
14 - **Writing – review & editing**	Lead	
	Equal	GAM, KGB
	Supporting	ACK, ST, PH, AB, NM

ABSTRACT

Background and objective: Non-expansile lung (NEL) frequently complicates management of malignant pleural effusion (MPE) and is an important factor in clinical practice and trials. NEL is frequently diagnosed on a single radiographic observation, but neither the inter-observer agreement of this approach nor the prognostic importance of NEL in MPE have been reported.

Methods: A multicentre retrospective cohort study was performed in 2 UK pleural centres. NEL was defined as <50% pleural re-apposition on post-drainage radiographs by primary and secondary assessors at each site. Inter-observer agreement was assessed by Cohen's Kappa (κ). Kaplan-Meier methodology and multivariate Cox models were used to assess the prognostic impact of NEL vs no NEL and 'Complete NEL' vs 'Complete expansion', based on a single assessor's results from each site.

Results: NEL was identified by the primary assessor in 33/97 (34%) in Cohort 1 and 15/86 (17%) in Cohort 2. Inter-observer agreement between assessors was only fair-to-moderate (Cohort 1 κ0.38 (95% CI:0.21–0.55), Cohort 2 κ0.51 (95% CI:0.30–0.72)). In both cohorts, NEL was associated with shorter median overall survival (Cohort 1: 188 vs 371 days, Cohort 2: 192 vs 412 days). This prognostic association was independent in Cohort 1 (HR 2.19, 95% CI:1.31–3.66) but not Cohort 2 (HR 1.42, 95% CI:0.71–2.87). Survival was inferior in both cohorts in cases of 'Complete NEL' vs 'Complete Expansion'.

Conclusion: Radiographic NEL is common but inter-observer agreement is only fair-to-

moderate. NEL is associated with adverse survival. These data do not support use of single radiographic assessments to classify NEL.

Keywords:

Malignant Pleural Effusion

Trapped Lung

Non-expansile Lung

Unexpandable Lung

Prognosis

Short title: Radiographic non-expansile lung

INTRODUCTION

Malignant Pleural Effusion (MPE) frequently leads to disabling breathlessness, requiring definitive palliation by one of several methods. In this regard, talc slurry pleurodesis (TSP) and indwelling pleural catheters (IPCs) deliver equivalent symptom control, based on two previously reported Phase III trials[1,2]. However, patients with known non-expansile lung (NEL), where TSP is contraindicated, were excluded from both studies and only small numbers with radiographically-occult NEL were included (6%[1] and 3%[2], in TIME2 and AMPLE, respectively). In the recently published IPC-PLUS trial[3], the addition of talc slurry to standard IPC care significantly improved pleurodesis success rates 10-weeks after catheter placement. However, in this study, a significant number of patients failed screening due to radiographically-defined NEL (41/339 (12%)), while an additional 32/250 (13%) of those recruited could not receive talc due to NEL that subsequently became apparent[3].

Radiographic detection of NEL is therefore an important factor in the planning of MPE treatment, and is routinely used as an eligibility criterion[4], stratification factor[5] and/or treatment determinant[6] in MPE trials. However, there are limited data supporting use of NEL in this manner, particularly with regard to inter-observer agreement, which should be high if single observers are used[7].

METHODS

Study Design and Patients

A multi-centre retrospective cohort study was performed. The *a priori* primary objective was to quantify the level of inter-observer agreement associated with NEL, as classified by 4 experienced clinicians using the definition below, as defined by Cohen's Kappa statistic. The secondary objective was to examine the relationship between NEL and subsequent survival, based on the output of a multivariable Cox regression model. Prospectively populated databases were used to identify consecutive patients treated at two UK pleural tertiary referral centres who underwent complete MPE drainage during diagnostic local anaesthetic thoracoscopy (LAT) between July 2010 and March 2018 (Cohort 1), and July 2013 and July 2017 (Cohort 2). Cases with any missing data specified below were excluded. Study activities were approved by the local ethics committees (References: 17/SC/0351, 08/H0102/11). This allowed use of unconsented linked anonymised data in Cohort 1. Patients in Cohort 2 provided written consent for use of their data as part of the Pleural Investigation Study, full details of which have been published elsewere.

Data Collection

Electronic records and digital chest radiographs (CXRs) were reviewed retrospectively. The presence or absence of NEL was evaluated on the post-LAT, pre-discharge CXR that showed the maximum expansion as judged by primary assessors at each site (GAM; PH). NEL was defined as <50% pleural apposition based on subjective visual estimation, extrapolating the British Thoracic Society (BTS) statement that pleurodesis is unlikely

to succeed below this value[8]. Blinded secondary assessors (ACK; AB) independently classified the same CXRs using the same definition. *Post hoc*, CXRs were further sub-classified by a single assessor at each site into extreme expansion phenotypes; 'Complete NEL' (where no lateral pleural apposition was achieved) and 'Complete Expansion' (where total pleural apposition was achieved). All assessors were experienced respiratory physicians who routinely assess CXRs for NEL in clinical practice. Demographics, LENT MPE prognostic score components (pleural fluid lactate dehydrogenase (LDH), performance status (PS), blood neutrophil-to-lymphocyte ratio (NLR), tumour type) acquired at/within 28 days of LAT were recorded. Overall survival (OS) was recorded from LAT to death (or censor).

Statistical Analysis

Patient characteristics and baseline variables were tabulated by study site; differences were assessed by unpaired t-test, Mann-Whitney or Fisher's exact test as appropriate. Inter-observer agreement regarding NEL, between primary and secondary assessors at each site, was quantified by Cohen's Kappa statistic. Kaplan-Meier curves and multivariable Cox regression (*a priori* model inputs: LDH, PS, NLR, LENT tumour risk score, NEL) were used to identify any association between the presence of NEL, as defined by the primary assessor, and OS in each cohort. For this purpose, Cohort 1 was used as a test set and Cohort 2 as an independent validation set. In a subsequent *post hoc* analysis, differences in OS between extreme re-expansion phenotypes ('Complete NEL' vs 'Complete Expansion') were compared using Kaplan-Meier methodology. Analyses were performed in SPSS v24.0 (Chicago, USA) and GraphPad Prism v8.0.2 (San Diego, USA).

RESULTS

214 eligible patients were identified. Complete data were available for 183/214 (86%: Cohort 1 n=97, Cohort 2 n=86); cases with any missing data were excluded (Cohort 1: 23 LDH, 4 PS; Cohort 2: 3 LDH, 2 PS). Demographics and clinical data were broadly similar between cohorts (Table 1). However, more patients in Cohort 2 were male and had a diagnosis of MPM, and more patients were in PS group 2. Maximal lung re-expansion was observed within 24 hours of LAT in 53/97 (55%) in Cohort 1 and 53/86 (62%) in Cohort 2. The prevalence of NEL, based on the radiographic classification made by the primary assessor at each site, was 34% (33/97) in Cohort 1 and 17% (15/86) in Cohort 2. However, inter-observer agreement between assessors at each site regarding NEL was only fair-to-moderate[9] (Cohort 1 κ 0.38 (95% CI:0.21–0.55); Cohort 2 κ 0.51 (95% CI:0.30–0.72)).

Patients with NEL, as defined by the primary assessor, had shorter median OS than patients without NEL in both cohorts (Figure 1). In Cohort 1, NEL defined in this manner, was independently associated with adverse survival (HR 2.19, 95% CI:1.31–3.66), but this was not replicated in Cohort 2 (HR 1.42, 95% CI:0.71–2.87 – Table 2). However, in a subsequent *post hoc* analysis, median OS was significantly shorter in both cohorts in cases with Complete NEL (Cohort 1, 6/97 (6%); Cohort 2, 5/86 (6%)) compared to those with Complete Expansion (Cohort 1, 19/97 (20%); Cohort 2, 44/86 (51%)), see Figure 2. Figure 3 shows examples of CXRs classified by the primary assessor in Cohort 1 as a) NEL on the basis of <50% pleural apposition for the primary outcome, and examples of extreme re-expansion phenotypes used in the *post hoc*

analysis: b) Complete NEL and c) Complete Expansion.

DISCUSSION

In this retrospective, multi-centre cohort study, NEL was relatively common in patients following LAT, based on visual assessment of pre-discharge CXRs by experienced clinicians (Cohort 1 34%, Cohort 2 17%). However, the level of agreement between clinicians was only fair-to-moderate (κ <0.5 for both cohorts). To our knowledge, this is the first study to report agreement between observers classifying lung re-expansion on CXR. The definition of NEL adopted here was based on guidance made in the 2010 BTS Pleural Guideline, which advises that pleurodesis is unlikely to be successful in cases with clear evidence of NEL, as defined by <50% pleural apposition[8]. However, this statement was not designed to be a precise diagnostic criterion for NEL and other studies have used alternatives (e.g. <75% pleural apposition)[3,10,11]. A different definition of NEL might improve inter-observer variability, but may be less clinically relevant since subtle NEL might still be amenable to a pleurodesis attempt.

The definition and incidence rate of NEL varies widely in previous prospective clinical trials of MPE, making it difficult to interpret the potential significance of our findings on these data and future studies. In the AMPLE trial[2], which compared TSP with IPC management, NEL, defined pragmatically as 'incomplete lung expansion', was reported in only 3% (5/146) participants. In contrast, 32% (28/87) patients had NEL in AMPLE-2[10], which compared different IPC drainage strategies, based on a definition of <75%

lateral apposition. Other studies report rates that lie between these extremes, possibly reflecting different definitions and/or exclusion criteria, e.g. 6% in TIME2 (based on <50% pleural apposition)[1], 13% in IPC-PLUS (based on <75% pleural apposition)[3], and 29% in the Phase III Intergroup Study (based on (<90% expansion)[12]. The explicit exclusion from most of these trials of patients with an expected survival of <3 months, may, in particular, inadvertently exclude most patients with NEL, given the survival disadvantage reported here. It does appear important whatever the true rate of NEL in clinical practice and future trials, that a more consistent definition is adopted and where possible, multiple observers are used to adjudicate on the presence of NEL, when this directs clinical care (e.g. the decision to instil talc or remove a chest drain) or affects trial recruitment eligibility.

In the current study, median OS was inferior in both cohorts in patients with NEL on univariate analysis – this was based on the primary assessor's adjudication and the definition of <50% lung re-expansion. NEL defined in this manner was also independently associated with adverse survival in Cohort 1 (HR for death 2.19, 95% CI:1.31–3.66, p=0.003), but this was not replicated in Cohort 2 (HR for death 1.42, 95% CI:0.71–2.87, p=0.322). This may reflect the smaller number of NEL cases in that series (17% (15/86) vs 34% (33/97)), reduced statistical power and a resultant type II statistical error. Additionally, the variability also reported in classifying NEL in this manner (<50% pleural apposition) leads to the obvious potential that borderline cases were differently classified by the primary assessors at each site. This possibility prompted the *post hoc* analysis conducted in extreme phenotypes since there is no real risk of misclassification in these cases. Since this analysis demonstrated significantly

inferior survival in cases with 'Complete NEL' vs those with 'Complete Expansion', see Figure 2, we conclude the prognostic effect identified is genuine.

In an earlier retrospective study, Leemans *et al* reported similar adverse survival (median OS 66 days vs 169 days) in patients with MPE (due to a range of tumour types) who failed thoracoscopic talc pleurodesis due to NEL[13]. In MPM, visceral pleural tumour, a frequent cause of NEL, has histrorically been associated with adverse survival via higher disease stage[14]. More recently, Bibby *et al* confirmed this association based on radiographic NEL. In that study the HR for death was 1.80 (95% CI:1.16–2.80))[11] in 192 patients with MPM, 64 of whom (33%) developed NEL at some point during their disease course. The use of serial chest radiographs over a long follow-up period in this study clearly differs from our own method but the observation of excess mortality is concordant with our own conclusions.

Radiographic interpretation is a cornerstone in the management of patients with MPE. In patients undergoing fluid drainage, CXR findings directly determine the timing of talc slurry instillation and chest drain removal[8]. As such, variation in CXR interpretation regarding lung re-expansion (and the presence of NEL) is of critical importance and could result in futile talc slurry instillation and inappropriate prolongation of hospitalisation if NEL is under-recognised. Conversely, such variation may also result in missed opportunities to deliver talc pleurodesis and lasting symptom control if expansile lung is mis-classified as NEL. Although data relating a particular CXR definition to subsequent TSP success do not exist, our finding of only fair-to-moderate interobserver agreement would support the use of consensus judgments regarding lung

re-expansion rather than relying on a single assessor. In particular, this approach should be considered in clinical trial design where patients may be excluded from enrolment or study procedures based on a single observer's judgement[4].

The level of disagreement reported here highlights the challenges involved in radiographic NEL assessment, even when experienced assessors are involved. Development of a reliable method of NEL detection should therefore be a clinical imperative. Evaluation of 3-dimensional lung expansion based on a 2-dimensional image is an inherently flawed concept and a technique which provides a global assessment of the pleural cavity is clearly required. To this end, a multicentre study addressing this challenge is currently recruiting the UK, using systematic multiplanar thoracic ultrasound scanning[15]. There is also interest in the potential use of pleural elastance (an intrinsic property of the pleural cavity derived from intra-pleural pressure change during thoracentesis) as a NEL biomarker to direct patient care[16]. Future research of novel NEL methods should also seek to establish the relationships between varying expansion thresholds and clinical outcomes.

The retrospective design of this study made missing data inevitable and reduced the size of the dataset available for analysis. The inherently constrained statistical power increases the risk of a type II error regarding an independent association between NEL and survival. In addition, patient numbers also precluded sub-group analyses and exploration of a potential interaction between MPM disease stage, NEL and mortality, which is entirely plausible based on earlier studies[14]. A larger study would be able assess this important question, since the adverse survival associated with NEL may

reflect greater pleural tumour burden, physiological compromise or the risks of repeat pleural procedures and hospitalisation.

Due to reliance on LAT databases, and its geographical basis in post-industrial coastal cities, this study included a higher proportion of patients with MPM than is encountered in routine practice in other areas. Since the natural course of MPM is to readily proliferate from parietal to visceral pleura surfaces, the generalisability of our prognostic findings to a more general MPE cohort should not be assumed and requires future validation. Additionally, in most centres, the majority of patients with symptomatic MPE will be managed by closed pleural drainage via some form of tube thoracostomy rather than open drainage at LAT. However, expansion outcomes are unlikely to vary meaningfully between thoracostomy and LAT since neither decortication nor any significant division of adhesions is undertaken during the latter.

In conclusion, radiographic evidence of NEL after MPE drainage was frequently observed, but associated with poor inter-observer agreement in this multi-centre retrospective cohort study. In both cohorts studied, NEL was associated with adverse survival, although the independence of this relationship has not been proven here. These data should be considered in clinical decision-making and MPE trial design, particularly when single observers are used. Future studies should seek biomarkers for NEL that are associated with less inter-observer variation.

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TABLES

Table 1. Patient demographics, clinical characteristics and median overall survival in two independent malignant pleural effusion cohorts who underwent diagnostic Local Anaesthetic Thoracoscopy (LAT).

	Cohort 1 (n=97)	**Cohort 2** (n=86)	**p**
Age, mean (95% CI)	71 (69 - 74)	72 (70 - 75)	0.581
Male, n (%)	65 (67)	69 (80)	**0.047**
Right sided, n (%)	56 (58)	44 (51)	0.457
Tumour type, n (%)			
Mesothelioma	56 (58)	64 (74)	**0.012**
Lung	21 (22)	10 (12)	**0.079**
Breast	6 (6)	5 (6)	0.999
Genitourinary	5 (5)	2 (2)	0.450
Gastrointestinal	3 (3)	3 (3)	0.999
Haematological	1 (1)	0 (0)	0.999
Other	5 (5)	2 (2)	0.450
Performance status, n (%)			
0	18 (19)	14 (16)	0.702
1	64 (66)	53 (62)	0.643
2	9 (9)	16 (19)	**0.085**
3	6 (6)	3 (3)	0.504
NLR, median (IQR)	4.2 (2.8 - 5.9)	4.16 (2.79 - 5.29)	0.878
LDH, median IU/mL (IQR)	0.36 (0.21 - 0.63)	0.52 (0.35 - 0.79)	**0.003**
Total LENT score, median (IQR)	1 (1 - 3)	1.5 (1 - 2)	0.534
Median overall survival, days (IQR)	267 (116 - 525)	360 (172 - 537)	0.122
NEL, n (%)	33 (34)	15 (17)	**0.012**

IQR, interquartile range; CI, confidence interval; CUP, carcinoma of unknown primary; SCC, squamous cell carcinoma; NLR, neutrophil-to-lymphocyte ratio; LDH, pleural fluid lactate dehydrogenase; NEL, non-expansile lung.

Table 2. Results of univariable and multivariable Cox regression analysis in two MPE cohorts. Multivariable model outputs report the association between predictors of overall survival (OS), including non-expansile lung (NEL) and individual components of the LENT prognostic score. Predictors independently associated with OS are highlighted in bold.

	Univariable analysis		**Multivariable analysis**	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**
COHORT 1 (n=97)				
NEL	**1.93 (1.21 – 3.06)**	**0.006**	**2.19 (1.31 – 3.66)**	**0.003**
LENT tumour score*	**1.69 (1.31 – 2.19)**	**0.000**	**1.65 (1.24 – 2.19)**	**0.001**
Pleural fluid LDH (IU/mL)	**1.29 (1.09 – 1.54)**	**0.004**	**1.25 (1.03 – 1.52)**	**0.025**
NLR	**1.12 (1.04 – 1.21)**	**0.004**	**1.09 (1.01 – 1.18)**	**0.026**
ECOG PS	**1.93 (1.40 – 2.67)**	**0.000**	1.27 (0.88 – 1.85)	0.206
COHORT 2 (n=86)				
NEL	**2.08 (1.07 – 4.04)**	**0.032**	1.42 (0.71 – 2.87)	0.322
LENT tumour score*	**1.78 (1.32 – 2.38)**	**0.000**	**2.24 (1.60 – 3.15)**	**0.000**
Pleural fluid LDH (IU/mL)	**2.04 (1.37 – 3.05)**	**0.000**	**2.34 (1.50 – 3.64)**	**0.000**
NLR	1.00 (0.93 – 1.07)	0.916	0.95 (0.88 – 1.02)	0.173
ECOG PS	1.26 (0.90 – 1.75)	0.184	1.27 (0.88 – 1.84)	0.197

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NLR, neutrophil-to-lymphocyte ratio; LDH, lactate dehydrogenase; IU/mL, International Units/millilitre; NEL, non-expansile lung. * Tumour-type risk score used in 'LENT' prognostic scoring system: mesothelioma or lymphoma = 0; breast, ovarian or renal cancer = 1; lung or other tumour-types

FIGURE LEGENDS

Figure 1

Overall Survival stratified by lung re-expansion status (Expansile lung vs Non-expansile Lung (NEL)) following Local Anaesthetic Thoracoscopy (LAT) in 2 cohorts of patients with MPE (Cohort 1 n=97, Cohort 2 n=86).

Figure 2

Overall Survival stratified by extreme expansion phenotypes (Complete Non-expansile Lung (NEL)) vs Complete Expansion) following Local Anaesthetic Thoracoscopy (LAT) in a *post hoc* analysis of subgroups of Cohort 1 (n=25) and Cohort 2 (n=49).

Figure 3

Examples of lung re-expansion classification based on subjective visual estimation before and after complete malignant pleural effusion drainage at Local Anaesthetic Thoracoscopy (LAT): (a) NEL on basis of <50% pleural apposition, (b) Complete expansion (c) Complete NEL, in this case associated with modest surgical emphysema following LAT.