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Investigation and outcomes in patients with non-specific pleuritis: Results from the International Collaborative Effusion (ICE) database

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Keywords: non-specific pleuritis, thoracoscopy, pleural biopsy

Abbreviations

CT = Computed tomography

ERS = European Respiratory Society

ICE = International Collaborative Effusion

LAT = Local anaesthetic thoracoscopy

MDT = Multidisciplinary team

MPE = Malignant pleural effusion

MPM = Malignant pleural mesothelioma

NNF = Number needed to follow up

NSP = Non-specific pleuritis

PET = Positron emission tomography

TB = Tuberculosis

US = Ultrasound

Abstract (238/250 words)

Introduction

We present findings from the International Collaborative Effusion database, an ERS clinical research collaboration. Non-specific pleuritis (NSP) is a broad term that describes chronic pleural inflammation. Various aetiologies lead to NSP, which poses a diagnostic challenge for clinicians. A significant proportion of patients with this finding eventually develop a malignant diagnosis.

Methods

12 sites across 9 countries contributed anonymised data on 187 patients. 175 records were suitable for analysis.

Results

The commonest aetiology for NSP was recorded as Idiopathic (80/175, 44%). This was followed by pleural infection (15%), benign asbestos disease (12%), malignancy (6%) and cardiac failure (6%). The malignant diagnoses were predominantly mesothelioma (6/175, 3.4%) and lung adenocarcinoma (4/175, 2.3%). The median time to malignant diagnosis was 12.2 months (range 0.8-32).

There was a signal towards greater asbestos exposure in the malignant NSP group compared to the benign group (0.63 vs 0.27, p=0.07). Recurrence of effusion requiring further therapeutic intervention, nor initial biopsy approach were associated with a false negative biopsy. A computed tomography finding of a mass lesion was the only imaging feature to demonstrate a significant association (0.18 vs 0.01, p=0.02), though sonographic pleural thickening also suggested an association (0.27 vs 0.09, p= 0.09).

Discussion

This is the first multi-centre study of NSP and its associated outcomes. Whilst some of our findings are reflected by the established body of literature, other findings have highlighted important areas for future research, not previously studied in NSP.

Introduction (2958/3000 words)

The first investigative step in a pleural effusion is usually pleural fluid analysis, followed by pleural biopsies if the fluid is non-diagnostic. Thoracoscopic biopsies of the parietal pleura are considered the gold standard in the diagnosis of exudative pleural effusions, with a reported diagnostic yield over 95%.[1] Unlike granulomatous, malignant pleuritis or pleural vasculitis which show distinctive histological findings that are pathognomonic for their respective diagnoses, Non-specific pleuritis (NSP), also known as fibrinous pleuritis is a general term that describes chronic pleural inflammation and can represent a multitude of different aetiologies. Various datasets have described a finding of NSP following pleural biopsy, with a mean incidence of 40%, 95% CI (38 - 41%).[2–15]

The pathophysiological mechanisms underpinning NSP are poorly understood, and it may simply represent a final common inflammation or fibrotic pathway. There are no prospective databases on NSP, and all the evidence so far is based on single centre, retrospective studies. There is no consensus from experts or societies on the optimal approach to diagnostics, monitoring or management of NSP.[16] Based on retrospective case series data, 48%, 95% CI (45-50%) of cases with histological NSP are thought to represent idiopathic NSP,[2–8, 10, 11, 13, 14, 17–19] and the rest can be attributed to heart failure, asbestos, autoimmune causes, pulmonary embolism and drugs.

A particular conundrum following an NSP finding is whether it represents 'true negative' result, particularly when an underlying malignant process is suspected. NSP may represent inadequacies in the biopsy technique or may histologically reflect an early-stage process in the development towards malignancy (i.e. cancer that is not yet 'diagnosable'): when frank cancerous changes are neither visible (due to excessive fibrin deposition), or accessible via thoracoscopy (due to adhesions and a limited procedural view), inevitable sampling of the para-malignant areas may yield NSP, instead of a malignant finding.

Across existing datasets, 8%, 95% CI (7-10%) of cases, with a median time to evolution of 6 months (IQR 2-8), across a follow up period ranging from 18 - 143 months, are ultimately diagnosed with malignancy.[3–5, 7, 8, 10, 11, 13–15, 17–21]

To further add to the understanding of outcomes in NSP, we performed a multicentre retrospective cohort study, to collect data on NSP across a number of centres, encompassing both geographic diversity and differences in practice.

Methods

Approvals and entry criteria

Where required by local laws, participating centres obtained ethical approval to access and share anonymised data which had been collected as part of routine clinical care at their centre. Sites were asked to retrospectively screen local hospital records to identify patients, who were eligible for inclusion if they had been given a diagnosis of NSP between 2009 and 2020.

Definitions of NSP

Histology reported as, or a variation of one of the following: reactive fibrous pleural thickening, fibrinous pleurisy, fibrosis, florid reactive change, fibrous connective tissue, chronic inflammation, benign change or dense fibrous tissue in the absence of malignant pleural infiltration, granulomata, pleural vasculitis, or evidence of bacterial infection.[11, 16]

Data collection

Data were collected retrospectively as part of the International Collaborative Effusion (ICE) database project, a ERS Clinical Research Collaboration which was launched in 2017. The methodology behind the creation of the database has been previously described in detail.[22] In brief, research questions and data points to be collected were agreed as part of a multi-stage collaborative process involving all members of the ICE project, led by a smaller ICE database group (UB, CFK, NAM, JJ, RB).

The study database used REDCap (Vanderbilt university, USA), an electronic data capture tool, hosted at University of Bristol, UK.[23, 24]

Research questions

The following research questions were proposed by the ICE database group relating to NSP:

1. What are the relative contributions of the various aetiologies ultimately identified during the long-term follow up of patients initially diagnosed with NSP?
2. How many patients with an initial diagnosis of NSP developed malignancy during subsequent follow up (commencing from date of biopsy)?
3. What is the time to development of malignancy in NSP (commencing from date of biopsy)?
4. What is the minimal safe follow-up time of NSP to exclude MPE as eventual diagnosis?

A number of further exploratory outcomes were proposed, centred around features associated with false negative biopsies.

Sites reviewed individual patient clinical records to obtain data on demographics, clinical and radiological features, procedural information and final diagnosis, as determined by the treating physician with or without local multidisciplinary team consensus.

Statistical analysis

The database was analysed using SPSS Statistics, version 28.0 (SPSS Inc., Chicago, Ill., USA)

Parametric data is expressed as mean (+/- SD), whilst non-parametric data is expressed as median (+/- IQR). Fisher's exact test was used to compare categorical variables including relationships between the patient's demography, radiological features, procedural factors, and eventual diagnosis, specifically focusing on predictors for false-negative NSP results. All reported p values were two-sided, and effects were considered significant if $p < 0.05$.

Missing data

Complete case analysis was performed.

Results

In total, 187 cases were submitted for inclusion in the NSP dataset by 12 centres, across 9 countries, between October 2019- July 2021. Following data interrogation and correspondence with those centres, 12 cases were removed due to mislabelling as NSP. The remaining 175 cases were analysed in line with the research questions above.

Demographics and aetiology of NSP

The median age was 72 years (IQR 62-75) and 142 (81%) were male. 93 (53%) reported a smoking history, of whom 27 (15%) were current smokers and 52 (30%) reported asbestos exposure. The median length of follow up was 18 months (range 1-80). Table 1 highlights the baseline characteristics of the study population and the eventual aetiologies diagnosed.

The commonest aetiology of NSP was Idiopathic (44%). This was followed by pleural infection (15%), benign asbestos related disease (12%), malignancy (6%) and cardiac failure (6%). A small number of patients had dual aetiology contributing to their presentation with NSP (3.4%).

Pleural infection as a cause of NSP

In the patients with pleural infection as the cause for their NSP (n=27), 5 (19%) had developed a parapneumonic effusion in the 6-weeks prior to their NSP biopsy, whilst 3 (11%) and 1 (4%) had developed a frank empyema and TB pleuritis respectively. In the remainder (18, 67%), pleural infection as the cause for the patient's presentation with NSP was a de novo finding.

Malignancy following a finding of NSP and associated baseline characteristics

In 11 (6%) patients, a pleural malignancy developed during their follow up period. All missed diagnoses were found in the LAT group. 4/11 (36%) were lung adenocarcinoma, 6/11 (55%) were malignant pleural mesothelioma (MPM) and the in the remaining case, the cancer type was not known. 5 cases of MPM were diagnosed following repeat biopsy (two via LAT, two via surgical biopsy and one case via EBUS) with the remainder diagnosed based on radiological progression and multidisciplinary team (MDT) consensus. The lung adenocarcinoma cases were diagnosed via LAT in two cases and surgical biopsy in one. The remaining case was diagnosed on the basis of radiological progression and avidity on PET-CT, following MDT consensus.

Clinical characteristics between the 'benign' group and 'malignant' group are summarised in Table 2. Whilst there was a trend towards greater asbestos exposure in the malignant group compared to the 'benign' disease course group (63% vs 27%), this did not meet statistical significance (Fisher's exact test, two-tailed, $p = 0.07$). There was no significant association seen with the need for repeat therapeutic interventions and the development of a pleural malignancy, with 51/159 (32%) of

patients following a benign trajectory requiring >1 thoracocentesis following a biopsy result of NSP compared to 5/11 (46%), in those who evolved a malignancy (Table 2).

Imaging features and their association with a false negative NSP result are summarised in Table 3. A mass lesion on CT was the only significant association with a false negative biopsy ($p = 0.02$), though there was a signal towards association for pleural thickening visualised on ultrasound (US).

Time to development of malignancy following a finding of NSP

In patients with an eventual malignant diagnosis, the median time to diagnosing pleural malignancy was 12.2 months. The maximum time to developing malignancy within our dataset was 32 months, whilst the shortest was just 0.8 months. Separating those who were eventually diagnosed with pleural malignancy into early and late evolvers with thresholds set by the ERS ICE working group as <3 months and ≥3 months, 3/9 were early evolvers whilst 6/9 were late. Time to evolution of pleural malignancy was not known in 2 cases.

A similar analysis comparing the 'early' vs 'late' evolvers of pleural malignancy revealed no statistically significant results but did suggest that MPM was the more likely diagnosis amongst the late progressors (Table 4).

Discussion

We describe the first multi-centre, international dataset for NSP, through which we attempt to answer several research questions proposed by the ICE database group:

We demonstrated that NSP was idiopathic in 44%, a rate comparable to existing evidence (mean incidence 48%).[2–8, 10, 11, 13, 14, 17–19] However, 'idiopathic' NSP is difficult to define as there are over 60 known causes for pleural effusions and, therefore, only after exclusion of most or all of these aetiologies should the label be attributed. To date, a minimum standard panel of investigations to further investigate the aetiology of NSP has yet to be agreed upon, so this label is prone to inter-operator and inter-site variability.

The subsequent diagnosis of a pleural malignancy has been the focus for most NSP studies.[3–5, 7, 8, 10, 11, 13–15, 17–21] Our dataset demonstrated an incidence of eventual pleural malignancy following an NSP result of 6% (95% CI 3-11%). This is slightly lower than the rate described in the existing literature: 8% (95% CI 7-10%).[3–5, 7, 8, 10, 11, 13–15, 17–21] All eventual malignant diagnoses were lung cancer or MPM, with the latter more frequently observed. All cases save two were diagnosed histologically. The remaining two cases were diagnosed clinically based on suggestive radiological features and MDT consensus. This highlights an issue around the definitions for what constitutes a malignant effusion as opposed to the less well defined 'paramalignant' effusion. [13] The precise definition of malignant pleural disease requires histological or cytological confirmation, but in clinical practice this is not always possible nor appropriate. Often a clinical diagnosis is made based on many factors, including radiological evidence. Whilst a 'paramalignant' effusion has been described as an inflammatory pleuritis in the presence of an active malignancy, not explained by other aetiologies, but not due to malignant infiltration of the pleura, [13] there clearly exists a degree of overlap between these entities and there are difficulties in differentiating the conditions in clinical practice, which bears consideration and again highlights a need for standardised definitions.

With regards to risk stratification for those that will progress to an eventual malignant diagnosis, at any stage, asbestos exposure was the only baseline characteristic indicating a signal towards association, but not meeting statistical significance. CT appearances of a mass lesion, either within the lung or pleura, were the only imaging features associated with a false negative biopsy result, which is entirely intuitive. There was a trend towards identifying pleural thickening on US and an eventual malignant diagnosis, though this was not statistically significant. This finding is entirely consistent with previous work that has shown this feature is highly specific for malignant pleural disease.[28] As a readily performed point of care test, this can be of value in the risk stratification of

patients with NSP and further reinforces the need for standardisation in both performing thoracic ultrasound, and training therewithin, both a key ERS directive.[29] In contrast to other studies that demonstrated recurrence of effusion as a predictor for an underlying malignant process,[11] we detected no such associations, with repeat thoracocentesis being required equally often in both groups. We suggest that the need for repeat thoracocentesis and by extension, effusion recurrence in NSP depends entirely upon the prevalence of the different aetiologies driving the condition, rather than a specific feature of malignancy alone. All the 'false-negative' biopsies arose in the LAT group, but interpretation is difficult given how few patients with a surgical biopsy were included in this dataset. Though it is intuitive to think a difficult or incomplete thoracoscopic examination may provide an explanation for false negative biopsies, [10] most thoracoscopists would advocate an alternative biopsy modality, if faced with a technically challenging procedure and were not reassured they had satisfactorily inspected the pleural cavity, when there is a high pre-test probability for pleural malignancy. The TARGET study (awaiting publication) aimed to test this hypothesis, by directing patients with an initial non-diagnostic biopsy, with ongoing clinical suspicion to a PET-CT vs usual care.[30]

The median time to evolving malignancy was 12.2 months, with a wide range (0.8 – 32 months) Expert opinion suggests that the follow up period should be at least 24 months and perhaps the minimum period at least 12. This remains a difficult area to offer fixed recommendations for duration of follow up. In our dataset, 5/11 patients developed malignancy within 12 months, with 3 having done so within 3 months. The most delayed presentation was 32 months. Within the literature the longest follow-up period, after which time pleural malignancy was diagnosed, was 64 months.[21] It would be reasonable to surmise that the early progressors are more likely to represent a diagnostic accuracy problem, whilst the late progressors may truly represent an early or pre-malignant phase that is not diagnosable as a malignant process at time of biopsy, or indeed that they do not have malignancy of any kind, and the finding of NSP is unrelated (particularly relevant in the presence of various comorbidities). Therefore, the early progressors may well represent a genuine 'false-negative' following a thoracoscopic or other form of biopsy, whilst it would not be correct to label the late progressors as such. There are no agreed definitions on what constitutes a 'false-negative' biopsy, and whether this should take the form of an arbitrary time interval, or a more nuanced set of criteria (e.g. progressive radiological features, onset of 'red-flag' symptoms etc within a defined time period). Whilst it would be clinically useful to be able to differentiate between those who have truly benign disease from those who are likely to progress, it would be equally useful to risk stratify the early-developers from the late, to offer a more personalised follow-up plan.

There was little to differentiate between the two groups in our dataset, though we did observe that the late evolvers were often MPM and this would be entirely consistent with the natural history of MPM, with both a long latency from initial asbestos exposure and the recognition now of 'mesothelioma in-situ,' indicating a pre-invasive stage of disease. [25] As the research landscape evolves, we will understand the relationship between this precursor lesion and 'reactive atypical mesothelial hyperplasia,' a histological finding often encountered in NSP.[26, 27] With a general consensus of 3-6 monthly follow-up with regular cross-sectional imaging for a 12-24 month period, 9/11 of our cases of evolving pleural malignancy would have been captured, whilst missing two. In planning follow up for patients, clinicians should be open about the diagnostic uncertainties they are faced with and should settle on an appropriate follow-up schedule through a process of shared decision making, that is tailored to the patient. It would not be unreasonable to offer a more prolonged follow up in those in whom a diagnosis of MPM is suspected as opposed to an alternative malignancy, which is likely to manifest earlier. As with other screening interventions, it may be helpful for clinicians and patients to understand the concept of 'number needed to follow-up' (NNF) to diagnose one malignancy. In the largest series on NSP, by Reuter et al, they demonstrated the NNF was 18, to identify one malignancy during the first year, and gets less effective with increasing time: (NNF of 260 between year 1-3).[15]

There are a number of weaknesses to this study. As with all retrospective cohort studies, incomplete data and variation in the definitions used by participating sites for data entry does affect data integrity and results in significant inter and intra-site heterogeneity. This is clearly evident in the assigned aetiologies ascribed to NSP and there may well have been significant differences in the pathological tests and criteria used for diagnosis of NSP between centres, which this study is not able to account for. A prospective study with standardised definitions, an agreed minimal panel of both clinical and pathological tests, alongside an independent pathology review, following an NSP finding may overcome this. This may be particularly relevant in the diagnosis of MPM, where BAP-1 and p16 testing, in conjunction with other investigations have proven to be instrumental in securing a diagnosis of MPM, [25] which our study did not specifically look at. The study was underpowered for a number of the questions it was intended to explore. This was largely in part due to the Covid pandemic, which severely disrupted participating centres' ability to contribute to the study but may also have been impeded by recruiting participants primarily from clinical databases accessed by pulmonologists rather than pathology databases, contributing to selection bias. Additionally, the event rate of eventual pleural malignancy was lower than expected and therefore, much of the intended hypothesis testing based on our research questions, failed to meet statistical significance, though did show associations worthy of further research.

This is the first multi-centre study on NSP and its outcomes, enabled through the ERS ICE research collaborative. As well as providing additional knowledge regarding NSP, we have demonstrated that international centres with an interest in pleural disease can contribute data to better study under-researched areas and generate ideas for future areas of research.

Tables

Table 1 Baseline Characteristics of study population

	N = 175
Characteristics	
Age, years (median + IQR)	72 (62-75)
Male sex (n, %)	142 (81%)
Smoking status (n, %)	
Current	27 (15%)
Previous	66 (38%)
Never	82 (47%)
Asbestos exposure (n, %)	52 (30%)
Comorbidities (n, %)	
Cardiovascular	105 (60%)
Respiratory	42 (20%)
Gastroenterological/ Hepatic	18 (10.3%)
Renal	11 (6.3%)
Malignancy	26 (14.9%)
Other	54 (30.9%)
Cardiovascular	
Ischaemic heart diseaase	31 (17.7%)
Heart failure	20 (11.4%)
Hypertension	74 (42.3%)
Atrial fibrillation	42 (24%)
Cerebrovascular disease	17 (9.7%)
Respiratory	
Asthma	9 (5.1%)
Chronic obstructive pulmonary disease	20 (11.4%)
Interstitial lung disease	2 (1.1%)
Bronchiectasis	1 (0.6%)
Tuberculosis	3 (1.7%)
Other	
Type 1 Diabetes mellitus	1 (0.6%)
Type 2 Diabetes mellitus	31 (17.7%

Rheumatoid arthritis	8 (4.6%)
Connective tissue disease	1 (0.6%)
Hypothyroidism	5 (2.9%)
Procedure (n, %)	N = 175
Open surgical biopsy	1 (0.6%)
VATS biopsy	11 (6.3%)
LAT biopsy	136 (77%)
US guided	18 (10.3%)
CT guided biopsy	5 (2.9%)
Abrams (blind)	4 (2.3%)
Outcomes	
Eventual pleural based malignancy	11 (6.3%)
Length of follow up, months (median + range)	N = 95 18 (1-80)
Time to developing malignancy, months (median + range)	n = 9 12.2 (0.8-32)
Eventual Aetiology for NSP	N = 181
No clear cause identified 'Idiopathic'	80 (44.2%)
Pleural infection	27 (14.9%)
Benign asbestos related	22 (12.2%)
Cardiac failure	11 (6.1%)
Malignancy	11 (6.1%)
Autoimmune	7 (3.9%)
Rheumatoid arthritis	4 (2.2%)
Drug reaction	4 (2.2%)
Post-traumatic	3 (1.7%)
Renal failure	2 (1.1%)
Occupational exposure (non-asbestos)	2 (1.1%)
Haemothorax	2 (1.1%)
Post-operative	2 (1.1%)
Chronic Pancreatitis	1 (0.6%)
Thymoma	1 (0.6%)

Cirrhotic liver disease	1 (0.6%)

Table 2 Characteristics and associations between 'benign' and eventual malignant aetiologies for NSP

	'Benign' disease course following a histological result of NSP (n = 164)	**Eventual malignant aetiology following a histological result of NSP (n = 11)**	***p* value**
Age, years (median +/- IQR)	72 (62-78)	76 (68-77)	0.41
Male sex (n, %)	133 (81%)	9 (81%)	1.0
Smoking status (n, %)			
Current	25 (15%)	2 (18%)	0.68
Previous	60 (37%)	6 (55%)	0.34
Asbestos exposure (n, %)	45 (27%)	7 (63%)	0.07
History of malignancy (n, %)	24 (15%)	2 (18%)	0.67
Requiring >1 thoracocentesis (following NSP biopsy finding) (n, %)	51/159 (32%)	5/11 (46%)	0.51
Follow up performed?	139/164 (85%)	11/11 (100%)	
	N = 87	**N = 8**	
Duration of follow up (months, median +/- IQR)	18 (11-33)	22 (5-36)	0.09
Survival (months, median +/- IQR)	67 (32-10)	57 (24-70)	

	'Benign' disease course following a histological result of NSP (n = 164)	Eventual malignant aetiology following a histological result of NSP (n = 11)	*p* value
Procedural aspects			
1) Surgery	12/12 (100%)	0	0.6
a. Open (%)	1/125 (1%)	0	0.75
b. VATS (%)	11/125 (9%)	0	0.75
2) LAT	112/125 (90%)	11/11 (100%)	0.6
a. Rigid-thoracoscopy (%)	63/125 (50%)	7/11 (64%)	0.75
b. Semi-rigid thoracoscopy (%)	49/125 (39%)	4/11 (36%)	0.75
CT Features (%)			
Pleural thickening > 1 cm	37/164 (23%)	5/11 (46%)	0.14
Pleural nodules	9/164 (6%)	1/11 (9%)	0.49
Mass lesion	2/164 (1%)	2/11 (18%)	0.02
Pleural plaques	16/164 (10%)	2/11 (18%)	0.31
Pleural effusion	128/164 (78%)	6/11 (55%)	0.13
US Features (%)			
Pleural thickening	15/164 (9%)	3/11 (27%)	0.09
Pleural nodularity	3/164 (2%)	0	1
Diaphragmatic thickening	2/164 (1%)	0	1
Echogenic effusion	53/164 (32%)	4/11 (36%)	0.75
PET-CT (%)	**N = 18**	**N = 2**	
Pleural thickening	6/18 (33%)	0	1
Pleural avidity	9/18 (50%)	2/2 (100%)	0.48
Extra-pleural avidity	2/18 (11%)	0	0.88

Table 3 Factors associated with an eventual malignant aetiology

LAT: Local anaesthetic thoracoscopy, VATS: Video assisted thoracoscopic surgery, CT: Computed tomography, US: Ultrasound, PET: Positron emission tomography

Table 4 Early vs late evolution of pleural malignancy and associated features

	Evolution to pleural malignancy N = 9		
	Early (<3 months)	Late (≥3 months)	***p*-value**
Malignancy type			
Lung adenocarcinoma (%)	2/3 (67%)	1/3 (33%)	0.2
Mesothelioma (%)	1/6 (16%)	5/6 (83%)	
Procedural aspects			
LAT (%)	3/3 (100%)	6/6 (100%)	-
Imaging features			
Any features of malignancy (%)	2/3 (67%)	5/6 (83%)	1

Table 5 Outcomes for Idiopathic NSP cases

	Idiopathic NSP (n = 80)
Age (median + IQR)	72 (63 – 78)
Male gender (n, %)	64 (80%)
Requiring >1 thoracocentesis following NSP biopsy finding (n, %)	26/80 (33%)
Pleurodesis performed?	11/80 (14%)
Follow up performed?	76/80 (96%)
Duration of follow up, months (median + IQR)	24 (12 – 36)
Deceased? (n, %)	23/80 (29%)
Survival (months, median + IQR)	93.4 (65-109)

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