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ORIGINAL ARTICLE

Evaluation of pleural fluid cytology for the diagnosis of malignant pleural effusion: a retrospective cohort study

Lorna Pairman,[1] Lutz E. L. Beckert,[1,2] Mark Dagger[3] and Michael J. Maze [1,2]

[1]Department of Medicine, University of Otago, and Departments of [2]Respiratory Medicine, and [3]Anatomical Pathology, Canterbury District Health Board, Christchurch, New Zealand

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Correspondence
Michael J. Maze, Department of Medicine, University of Otago, 2 Riccarton Road, Christchurch, New Zealand.
Email: michael.maze@otago.ac.nz

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Abstract

Background: Cytological examination of pleural fluid has good specificity, but imperfect sensitivity for the diagnosis of malignant pleural effusion (MPE). Published estimates of sensitivity vary and predictors of false negative cytology are not well established.

Aims: To estimate pleural fluid cytology sensitivity and identify risk factors for false negative cytology.

Methods: We conducted a retrospective cohort study of patients who had cytology testing of pleural fluid at Christchurch Hospital, New Zealand, from July 2017 to October 2019. Data on clinical and pleural fluid characteristics were collected. MPE was defined by positive pleural fluid cytology, tissue histology or multidisciplinary meeting consensus. We estimated sensitivity of the first pleural cytology assessment. We performed multivariate logistic regression to ascertain patient groups at greatest risk of false negative results.

Results: Initial pleural fluid cytology was diagnostic in 117 of 156 patients, providing a sensitivity (95% confidence interval (CI)) of 75.0% (67.4–81.6%). The sensitivity was 79.0% (66.8–88.3%) for lung cancer, 91.3% (72.0–98.9%) for breast cancer and 33.3% (95% CI 11.8–61.6%) for mesothelioma. Cloudy appearance of pleural fluid (odds ratio (OR) 0.12; 95% CI 0.03–0.54) and yellow/gold pleural fluid (OR 0.24; 95% CI 0.06–0.96) reduced the odds of false negative pleural cytology. Pleural thickening on computed tomography scan (OR 3.3; 95% CI 1.2–9.4) was a risk factor for false negative cytology.

Conclusion: Sensitivity of pleural fluid cytology was greatest in primary lung and breast cancer, and lowest in mesothelioma. Clinicians should be alert to false negative results when suspecting mesothelioma or if pleural thickening is present.

Introduction

A malignant pleural effusion (MPE) signifies advanced malignancy and a poor prognosis, with a median survival of 3–12 months.[1] Rapid diagnosis is important to inform prognosis and management. International guidelines recommend thoracentesis to obtain pleural fluid for cytology as the initial method to diagnose MPE.[2]

Abbreviations: AIC, Akaike information criterion; MPE, malignant pleural effusion

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The reported sensitivity of pleural fluid cytology varies between 40% and 90%[3] and is influenced by tumour histopathology, fluid volume sampled, geographical location and clinical setting.[1,2,4] Given the wide variation in estimates of sensitivity, local estimates are important to inform clinical practice.

When the sensitivity of pleural fluid cytology is low, a negative result can lead to additional invasive procedures and delay diagnosis. Currently, the primary malignancy type is the only recognised feature that influences the sensitivity of pleural fluid cytology.[5] While useful, this information is often not identified until after diagnosis is confirmed. Although routinely collected, clinical features

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and pleural fluid biochemistry are rarely considered as features that might alter fluid sensitivity. Understanding the clinical and fluid characteristics that lower sensitivity could allow early identification of patients who might need a thoracoscopy or percutaneous procedure and aid more rapid diagnosis. We aimed to estimate sensitivity of pleural fluid cytology for diagnosing MPE in our institution, and to identify characteristics of the clinical presentation or pleural fluid associated with low sensitivity.

Methods

We conducted a retrospective cohort study of all patients with MPE at Christchurch Hospital from 21 July 2017 to 31 October 2019. Christchurch Hospital is the major secondary care hospital in Canterbury, New Zealand, and serves a population of 600 000.[6]

All patients who had undergone a pleural procedure were identified from a prospectively recorded departmental database. Participants were included if they were diagnosed with an MPE at any point subsequently. We defined confirmed MPE as any patient with pleural fluid cytology identifying malignant cells, pleural histology confirming malignancy or consensus that the pleural fluid is malignant at a thoracic oncology multidisciplinary meeting. We collected data regarding clinical, radiographic and pleural fluid characteristics using a standardised report form. Age, sex, ethnicity, functional status (measured by Eastern Co-operative Oncology Group score), method of MPE confirmation, asbestos exposure, and cancer site and type were the clinical characteristics recorded, whereas pleural fluid volume, pH, lactate dehydrogenase concentration and polynucleated cell proportion were the pleural fluid characteristics recorded. Radiologically, pleural thickening was recorded from the computed tomography (CT) report in cases where CT was completed prior to pleural fluid sampling. Cancer site was determined through multidisciplinary assessment involving pathological features, including immunohistochemistry, radiology and clinical features. Pleural fluid appearance, including colour and cloudiness, was subjectively assessed by a laboratory scientist. Resolution of the pleural effusion was not recorded and ultrasound measurements were not obtained.

Statistical analysis was performed using Stata 16.0 (Statacorp LLC, College Station, TX, USA). Sensitivity was defined as the proportion of patients with MPE who had a positive cytology result on the first pleural fluid sample. Confidence intervals (CI) for sensitivity estimates are reported at 95% confidence using the exact Clopper-Pearson method. For variables with $P > 0.1$ in *t*-tests (binary variables) or analysis of variance tests (categorical and continuous variables), a bivariate logistic regression was performed. We performed bivariate and multivariate logistic regression to evaluate risk factors for false positive cytology. Initially, the fluid or cancer characteristics investigated, as listed previously, were those consistently available to clinicians and recommended by The British Thoracic Society Pleural Disease Guidelines (2010).[2] Variables were selected for the initial multivariate model if they had a statistically significant likelihood ratio (LR) ($P < 0.05$) and where multicollinearity was not present. The final model was attained through backwards selection to generate the lowest Akaike information criterion (AIC).

This study was approved by the University of Otago Ethics Committee (Health) (HD19/031) and conducted in accordance with the Declaration of Helsinki.

Results

Of 607 pleural procedures screened, we identified 156 (25.7%) patients with MPE for inclusion in the present study. The mean age was 69.8 years (95% CI 67.8–71.7 years) and 88 (56.4%) were female (Table 1). The most common primary malignancies were lung ($n = 62$; 39.7%) and breast cancer ($n = 23$; 14.7%). Adenocarcinoma was the most commonly identified histological type in 69 patients (44.2%). Of 16 primary pleural malignancies, 15 (93.8%) were mesothelioma and 1 (6.2%) was unable to be fully typed.

Of the 156 patients, 117 (75.0%; 95% CI 67.4–81.6%) had positive cytology from the first pleural fluid assessment. Sensitivity was highest for adenocarcinoma (89.9%; 95% CI 80.2–95.8%) and lowest for patients with mesothelioma (33.3%; 95% CI 11.8–61.6%; Table 2). Pleural fluid cytology was most sensitive to diagnose MPE related to breast cancer (91.3%; 95% CI 72.0–98.9%).

In a bivariate logistic regression, variables that were associated with an increased odds of false negative cytology were pleural thickening on CT (odds ratio (OR) 4.5; 95% CI 1.8–11.4), asbestos exposure (OR 3.6; 95% CI 1.1–12.1) and fluid volumes of 50–99 mL (OR 2.7; 95% CI 1.1–6.4). Variables that were associated with reduced odds of false negative results included cloudy appearing pleural fluid (OR 0.12; 95% CI 0.03–0.41) or yellow pleural fluid (OR 0.17; 95% CI 0.05–0.59; Table 3). Biochemical characteristics of the fluid did not influence the sensitivity of cytology.

The variables cloudy fluid, fluid colour, pleural thickening on CT and asbestos exposure were included in the final multiple logistic regression model. The LR $\chi^2(7) = 42.4$ and $P < 0.01$ with pseudo-R^2 (Mc Fadden 1974) $= 0.24$. The AIC $= 148.5$. The model used was

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Table 1 Characteristics of patients with malignant pleural effusions, Christchurch, New Zealand, 2017–2019

Variable	Frequency (%)
Age, mean (range) (years)	69.8 (31–93)
Sex, female	88 (56.4)
Ethnicity†	
NZ European/Pakeha	131 (84.0)
Other European	34 (21.8)
Other	28 (17.9)
Asian	11 (7.1)
Maori	8 (5.1)
Pacific	4 (2.6)
Eastern Co-operative Oncology Group score	
0	12 (7.7)
1	63 (40.4)
2	21 (13.5)
3	17 (10.9)
4	1 (0.64)
Not available	42 (26.9)
Method of confirming malignant effusion†	
Cytology	120 (76.9)
Pleural histology	11 (7.1)
MDM staging	34 (21.8)
Pleural fluid volume, median (range)	50 (5–2000)
Cancer site‡	
Lung	62 (39.7)
Breast	23 (14.7)
Pleural	16 (10.3)
Lymphoma	12 (7.7)
Bowel	10 (6.4)
Gynaecological	9 (5.8)
Other	15 (9.6)
Undetermined	9 (5.8)
Cancer type§	
Adenocarcinoma	69 (44.2)
Mesothelioma	15 (9.6)
Ductal/tubular	14 (9.0)
B-cell lymphoma	12 (7.7)
Undetermined	12 (7.7)
Small-cell carcinoma	6 (3.8)
Squamous cell carcinoma	5 (3.2)
Serous carcinoma	5 (3.2)
Non-small-cell carcinoma (not further defined)	5 (3.2)
Other	13 (8.3)
pH, mean (range)	7.37 (6.88–7.62)
Lactate dehydrogenase concentration, median (range) (U/L)	375 (87–5756)
Polynucleated cell proportion, mean (95% CI) (%)	23.3 (19.4–27.3)
Pleural thickening on chest computed tomography scan	
Yes	68 (43.6)
No	58 (37.2)
No CT	30 (19.2)
Asbestos exposure	
Asbestos exposure	12 (7.7)
No asbestos exposure	110 (70.5)
Asbestos exposure not recorded	34 (21.8)

†Percentages do not add to 100% as some patients fit multiple categories.

‡Other sites include kidney/urethral, prostate, skin, stomach, thyroid, soft tissue, pancreas, abdomen, oesophagus and chest.

§Other types include sarcomatoid carcinoma, neuroendocrine tumours, transitional cell carcinoma, lobular, adenosquamous carcinoma, melanoma, spindle cell carcinoma and papillary carcinoma.

CI, confidence interval; CT, computed tomography; MDM, multidisciplinary meeting; NZ, New Zealand.

determined to be a good fit (Pearson $\chi^2(37) = 42.9$ and $P < 0.01$). Cloudy pleural fluid was less likely to produce false negative cytology results (OR 0.12; 95% CI 0.03–0.54), as was yellow/gold fluid (OR 0.24; 95% CI 0.06–0.96). Pleural thickening on CT increased the likelihood of false negative cytology (OR 3.3; 95% CI 1.2–9.4).

Discussion

The present study estimates the sensitivity of pleural fluid cytology in patients with confirmed pleural malignancy and evaluates whether clinical and fluid characteristics might help clinicians identify patients at risk of false negative cytology results. For all patients with MPE, pleural fluid cytology had a sensitivity of 75.0%. Pleural fluid cytology sensitivity was most strongly influenced by cancer site and type, with highest sensitivity estimates in patients with adenocarcinoma of breast or lung origin and lowest sensitivity estimates in those with mesothelioma. The sensitivity estimate of 75.0% in our centre was higher than in recent studies, although the variation according to cancer type is consistent with existing literature indicating sensitivity is lowest in patients with mesothelioma.[3–5,7] A key result of the present study is that information available prior or at the time of thoracentesis can inform clinician estimates of test sensitivity: cloudy fluid, potentially indicative of heavily cellular fluid and yellow/gold fluid increased test sensitivity,[8–10] and pleural thickening on CT reduced test sensitivity.

Sensitivity of pleural fluid varied by cancer site and histologic type, in keeping with existing literature,[3–5,7] and was higher in patients with lung and breast cancer, and lower in those with mesothelioma. This might reflect that adenocarcinoma of the breast and other sites may desquamate easily in the pleural cavity.[4] The variability in sensitivity by cancer type might explain some of the variability in estimates of the sensitivity of pleural fluid cytology in the present study compared with existing literature: the sensitivity from our study broadly matches a recent study from a tertiary Australian hospital where the distribution of malignancy subtypes was similar.[3] In contrast, a large prospective study from the United Kingdom (UK) estimated the sensitivity of pleural fluid substantially lower at 46% (95% CI 42–58%).[5] Notably, in the UK study, 16% of their cohort were diagnosed with mesothelioma; the sensitivity of diagnosing mesothelioma was only 6.1% (2.8–11.2%). Their estimates for patients with adenocarcinoma of the lung or breast were similar to our own.

For clinicians investigating undifferentiated pleural effusion, features that influence cytology sensitivity would be helpful to know, particularly when faced with negative results. While reduced sensitivity for some

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Table 2 Pleural fluid cytology sensitivity estimates in patients with malignant pleural effusions, Christchurch, New Zealand, 2017–2019

Variable	*n*/*N*	Sensitivity (95% confidence interval) (%)	*P*-value
Cancer site			<0.01
Lung	49/62	79.0 (66.8–88.3)	
Breast	21/23	91.3 (72.0–98.9)	
Lymphoma	9/12	75.0 (42.8–94.5)	
Undetermined	6/9	66.7 (29.9–92.5)	
Pleural	5/16	31.3 (11.0–58.7)	
Cancer type			<0.01
Adenocarcinoma	62/69	89.9 (80.2–95.8)	
B-cell lymphoma	9/12	75.0 (42.8–94.5)	
Mesothelioma	5/15	33.3 (11.8–61.6)	
Small-cell carcinoma	5/6	83.3 (35.9–99.6)	
Undetermined	4/12	33.3 (9.9–65.1)	

malignancies is well established,[3,11,12] literature on risk factors for false negative cytology available at the time of thoracentesis is limited. Pleural thickening, which is an established marker of pleural malignancy,[1] was associated with reduced sensitivity of pleural fluid cytology. Hence, in patients with pleural thickening on CT, a negative cytology result should not be reassuring. In addition, we found that cloudy fluid, potentially indicative of heavily cellular fluid and yellow/gold fluid increased test sensitivity. Other fluid characteristics, such as the pH, lactate dehydrogenase and the predominant inflammatory cell type did not influence test sensitivity. Confirmation by other studies would be important, especially due to the broad CI around the estimated effects. Importantly, we were unable to confirm a previous report of increased sensitivity associated with high pleural fluid protein content.[11] If repeatedly found, it might support a strategy of leaving sufficient pleural fluid for additional procedures based on radiological and visual fluid characteristics, or use of techniques, such as pleural biopsy or thoracoscopy simultaneous to pleural fluid sampling.

In the present study just over half of the samples collected had a volume greater than 50 mL. A fluid volume of 50–99 mL was associated with increased sensitivity on bivariate analysis in our study, but was not included in multivariate analysis. This is broadly in keeping with existing literature and protocols that indicate sampling at least 50 mL of pleural fluid[13–15] optimises sensitivity, but collecting larger volumes beyond 50 mL does not necessarily increase yield.[16] It might be that improvement in overall sensitivity could be obtained with stricter adherence to pleural fluid volume recommendations. It also serves as a reminder of the importance of regular audit of pleural procedures to ensure an adequate sample volume. An additional implication is that in patients with large fluid volumes, leaving residual volume may prove beneficial to allow for subsequent thoracoscopy

Table 3 Risk factors for false negative pleural fluid cytology, Christchurch, New Zealand, 2017–2019

Variable	*n*/*N*	Bivariate logistic regression		Multivariate logistic regression	
		Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Cloudy fluid appearance	142/156	0.12 (0.03–0.41)	<0.01	0.12 (0.03–0.54)	0.01
Colour					
Red	78/155	1.0	NA	1.0	NA
Orange/peach/brown	40/155	0.55 (0.23–1.3)	0.18	0.91 (0.33–2.5)	0.86
Yellow/gold	37/155	0.17 (0.05–0.59)	0.01	0.24 (0.06–0.96)	0.04
Pleural thickening on CT					
No	58/156	1.0	NA	1.0	NA
Yes	68/156	4.5 (1.8–11.4)	<0.01	3.3 (1.2–9.4)	0.03
No CT	30/156	1.8 (0.55–6.0)	0.33	1.1 (0.29–4.5)	0.84
Asbestos exposure					
No asbestos exposure	110/156	1.0	NA	1.0	NA
Asbestos exposure	12/156	3.6 (1.1–12.1)	0.04	2.5 (0.65–9.7)	0.18
Asbestos exposure not recorded	34/156	0.08 (0.01–0.59)	0.01	0.10 (0.01–0.80)	0.03
Volume (mL)					
0–49	67/154	1.0	NA	NA	NA
50–99	52/154	2.7 (1.1–6.4)	0.02	NA	NA
≥100	35/154	1.8 (0.65–4.8)	0.27		NA
pH	NA	0.14	0.23	NA	NA
Lactate dehydrogenase concentration	NA	1.0	0.72	NA	NA
Polynucleated cell proportion	NA	0.99	0.34	NA	NA

CI, confidence interval; CT, computed tomography; NA, not applicable.

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following inconclusive fluid cytology.[17] Other papers recommend removing large fluid volumes where possible, so subsequent procedures will contain a higher concentration of recently exfoliated malignant cells, and fewer degenerated cells.[18]

Although not used at our centre during the study period, there is evidence that molecular methods of diagnosis could be useful in situations of false negative cytology where MPE is strongly suspected. This is because carcinoma cells are identified in cytology through their characteristic morphological appearance, and mutation positive, but degenerate/fragmented cells can lead to false-negative pleural fluid cytology, but positive molecular analysis.[19] The molecular diagnostic techniques have high sensitivity and provide a relatively non-invasive method of monitoring known metastatic cancer using pleural fluid, and of identification of new mutation development.[20]

Strengths of the present study are that we have included a comprehensive dataset from the only pleural service operating within the study area and that a nationally linked hospital identifying number allowed follow up to be completed on all patients. Our study has retrospective study limitations that influence interpretation. Missing data precluded some variables, notably performance status from inclusion in modelling. We also highlight that we did not assess whether non-pleural radiographic features of malignancy might influence sensitivity of pleural fluid cytology. Potential bias in the study could also have arisen from the inclusion of multidisciplinary consensus within the definition for MPE. However, we considered it necessary as many patients with widely disseminated malignancy might not have repeated procedures to confirm the presence of malignant cells in the pleural space due to frailty or lack of benefit. Our sensitivity estimates were negatively influenced by 18 patients for whom clinicians postulated MPE as the cause of the effusion without a formal multidisciplinary discussion and therefore did not meet our case criteria. Finally, our sample size was determined to adequately assess the overall sensitivity of cytology, and our study had limited power to assess sensitivity of pleural fluid cytology in uncommon cancer types, and to identify less common risk factors for false negative cytology.

Conclusion

The main implication of the present study for clinical practice is that in patients with suspected MPE due to breast or lung origin, pleural fluid cytology remains a good first diagnostic test. Patients with a suspected mesothelioma or those with radiologically identified pleural thickening are likely to gain little benefit from pleural fluid cytology and alternative methods of initial diagnosis, such as pleural biopsy should be considered.[21–23]

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Data availability statement

The data used in this study are included in supplementary materials.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Supplementary File. Dataset of patients with malignant pleural effusion at Christchurch Hospital, 21 July 2017 to 31 October 2019.

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