Evaluation of Pleural Fluid Cytology for the Diagnosis of Malignant Pleural Effusion: A Retrospective Cohort Study

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Research

Keywords: Cytology, effusion, malignancy, pleural

Posted Date: November 24th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-112086/v1>

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Version of Record: A version of this preprint was published at Internal Medicine Journal on February 21st, 2022. See the published version at <https://doi.org/10.1111/imj.15725>.

Abstract

Background

As median survival time for patients with malignant pleural effusions (MPE) is nine months, rapid and accurate diagnosis is important. Cytological examination of pleural fluid has a good specificity but imperfect sensitivity. Published estimates of sensitivity vary substantially and predictors of false negative cytology are not well established. We aim to establish a local estimate of 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 21 July 2017 to 31 October 2019. Data on patient demographic, clinical and pleural fluid characteristics were collected. MPE was defined by positive pleural fluid cytology, tissue histology, or multi-disciplinary 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

Of 156 patients with confirmed malignant pleural effusion included in our study, the initial pleural fluid cytology was diagnostic in 117, providing a sensitivity (95% confidence interval) 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 (OR 0.17, 95% CI 0.04-0.84), but not pH, lactate dehydrogenase or polynuclear cell ratio, reduced the odds of false negative pleural cytology.

Conclusion

Pleural fluid cytology was sensitive in diagnosing MPE due to primary lung and breast cancer, however it had low sensitivity in mesothelioma. Clinicians should be particularly alert to the high likelihood of false negative results when suspecting mesothelioma and consider early use of biopsy.

Background

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).

The reported sensitivity of pleural fluid cytology varies between 40–90% (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 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 may need a thoracoscopy or percutaneous procedure and aid more rapid diagnosis. We aimed to estimate sensitivity of pleural fluid cytology of MPE in our institution, and to identify characteristics of the clinical presentation or pleural fluid associated with lower pleural fluid cytology.

Methods

We conducted a retrospective cohort study of all patients with malignant pleural effusion 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, and participants were included if they were diagnosed with a 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.

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 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 ANOVA 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. 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

We identified 156 patients with MPE for inclusion in the study. The mean age was 69.8 years (95% confidence interval [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.

Table 1

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

Variable	Frequency (percentage)
Age	69.8 years, 31–93 years
Mean and range	
Sex	88 (56.4%)
Female	
Ethnicity*	131 (84.0%)
NZ European/Pakeha	34 (21.8%)
Other European	28 (17.9%)
Other	11 (7.1%)
Asian	8 (5.1%)
Maori	4 (2.6%)
Pacific	
Eastern co-operative oncology group score	12 (7.7%)
0	63 (40.4%)
1	21 (13.5%)
2	17 (10.9%)
3	1 (0.64%)
4	42 (26.9%)
Not available	
Method of confirming malignant effusion	120 (76.9%)
Cytology	11 (7.1%)
Pleural histology	34 (21.8%)
MDM staging	
Pleural fluid volume	50 ml, 5-2000 ml
Median, range	

* 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.

Variable	Frequency (percentage)
Cancer site**	62 (39.7%)
Lung	23 (14.7%)
Breast	16 (10.3%)
Pleural	12 (7.7%)
Lymphoma	10 (6.4%)
Bowel	9 (5.8%)
Gynaecological	15 (9.6%)
Other	9 (5.8%)
Undetermined	
Cancer type***	69 (44.2%)
Adenocarcinoma	15 (9.6%)
Mesothelioma	14 (9.0%)
Ductal/tubular	12 (7.7%)
B cell lymphoma	12 (7.7%)
Undetermined	6 (3.8%)
Small cell carcinoma	5 (3.2%)
Squamous cell carcinoma	5 (3.2%)
Serous carcinoma	5 (3.2%)
Non small cell carcinoma (not further defined)	13 (8.3%)
Other	
pH	7.37, 6.88–7.62
Mean, range	
Lactate dehydrogenase concentration	375 U/L, 87–5756 U/L
Median, range	
Polynucleated cell proportion	23.3%, 19.4–27.3%
Mean, 95% confidence interval	
<p>* 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.</p>	

Variable	Frequency (percentage)
Pleural thickening on chest computed tomography scan	86 (55.1%)
Yes	11 (7.1%)
No	59 (37.8%)
Not recorded	
* 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.	

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%).

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	49/62	79.0% (66.8% – 88.3%)	< 0.01
Lung	21/23	91.3% (72.0% – 98.9%)	
Breast	9/12	75.0% (42.8% – 94.5%)	
Lymphoma	6/9	66.7% (29.9% – 92.5%)	
Undetermined	5/16	31.3% (11.0% – 58.7%)	
Pleural			
Cancer type	62/69	89.9% (80.2% – 95.8%)	< 0.01
Adenocarcinoma	9/12	75.0% (42.8% – 94.5%)	
B Cell Lymphoma	5/15	33.3% (11.8% – 61.6%)	
Mesothelioma	5/6	83.3% (35.9% – 99.6%)	
Small Cell Carcinoma	4/12	33.3% (9.9% – 65.1%)	
Undetermined			

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	Odd Odds ratio (95% CI)	p value
Cloudy fluid appearance	142/156	0.15 (0.05–0.48)	< 0.01	0.17 (0.04–0.84)	0.03
Colour	78/155	1.0	n/a	1.0	n/a
Red	40/155	0.55 (0.23–1.3)	0.18	1.4 (0.47–4.4)	0.52
Orange/peach/brown	37/155	0.17 (0.05–0.59)	0.01	0.26 (0.05–1.3)	0.10
Yellow/gold					
Cancer site	62/156	1.0	n/a	1.0	n/a
Lung	23/156	0.36 (0.07–1.7)	0.20	0.39 (0.07–2.1)	0.27
Breast	16/156	8.3 (2.4–28.1)	< 0.01	5.5 (1.4–22.3)	0.02
Pleural	12/156	1.3 (0.30–5.3)	0.76	0.84 (0.16–4.4)	0.84
Lymphoma	9/156	1.9 (0.41–8.6)	0.412	1.8 (0.34–9.8)	0.49
Undetermined	3/156	1.9 (0.16–22.4)	0.62	0.80 (0.04–16.6)	0.89
Kidney/urethral					
Volume	67/154	1.0	n/a	1.0	n/a
0–49 ml	52/154	2.7 (1.1–6.4)	0.02	2.6 (0.87–7.9)	0.09
50–99 ml	35/154	1.8 (0.65–4.8)	0.27	0.83 (0.21–3.2)	0.79
100 + ml					
pH	n/a	0.14	0.23	n/a	n/a
Lactate dehydrogenase concentration	n/a	1.0	0.72	n/a	n/a
Polynucleated cell proportion	n/a	0.99	0.34	n/a	n/a

In a bivariate logistic regression, variables that were associated with an increased odds of false negative cytology were subsequently confirmed mesothelioma or other primary pleural malignancy (OR 8.3, 95% CI 2.4–28.1), 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 0.15, 95% CI 0.05–0.48), or yellow pleural fluid (OR 0.17, 95% CI 0.05–0.59). Biochemical characteristics of the fluid did not influence the sensitivity of cytology.

The variables cloudy fluid, fluid colour, cancer site and fluid volume were included in the final multiple logistic regression model. The LR $X^2(10) = 33.4$ and $p < 0.01$ with pseudo- R^2 (Mc Fadden 1974) = 0.24. The AIC = 129.6. The model used was determined to be a good fit (Pearson $\chi^2(37) = 43.1$ and $p = 0.23$). Cloudy pleural fluid was less likely to produce false negative cytology results (OR 0.17, 95% CI 0.04–0.84). Primary pleural malignancy increased the likelihood of false negative cytology (OR 5.5, 95% CI 1.4–22.3).

Discussion

Our study estimates the sensitivity of pleural fluid cytology in patients with confirmed pleural malignancy, and evaluates whether clinical and fluid characteristics may help clinicians identify patients at risk for false negative cytology results. We found a sensitivity of 75.0% of pleural fluid cytology in all patients with MPE. 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 least sensitive in those with mesothelioma. This sensitivity in our centre was higher than in recent studies although the variation according to cancer type is consistent with the existing literature with the lowest sensitivity in patients with mesothelioma (3–5, 7). In addition, cloudy fluid, potentially indicative of heavily cellular fluid, increased 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 than in those with mesothelioma. This may reflect that adenocarcinoma of the breast and other sites, may desquamate easily in the pleural cavity (4). The variability in sensitivity by cancer type may explain some of the variability in estimates of the sensitivity of pleural fluid cytology in our study compared to 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 UK estimated the sensitivity of pleural fluid at substantially lower at 46% (95% CI 42–58%) (5). Notable, in the UK study 16% of their cohort were diagnosed with mesothelioma; the sensitivity of diagnosing a 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 which increase the likelihood of a positive results will be helpful to know, particularly, when faced with negative results. Our study agrees with existing literature that understanding the likely primary malignancy can greatly aid interpretation, for example, in patients suspected to suffer a mesothelioma, a negative cytology result should not be reassuring. In addition, we found that cloudy fluid, potentially indicative of heavily cellular fluid, increased test sensitivity. Other fluid characteristics such as the pH, lactate dehydrogenase and the predominant inflammatory cell type did not influence test sensitivity and were not indicative for clinicians.

In our study just over half of the samples collected had a volume greater than 50 ml. Although our findings were not in concordance, current protocols recommend sampling more than 50 ml of fluid for

cytology as previous research shown that samples of > 50 ml have optimal sensitivity (8–10). It may 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.

Strengths of our study are that we have included a comprehensive data-set from the only pleural service operating within the study area and that a nationally linked hospital identifying number allowed follow-up was completed on all patients. Our study has retrospective study limitations that influence interpretation. Missing data precluded some variables, notably performance status and pleural thickening on computed tomography scan from inclusion in modelling. Potential bias in the study could also have arisen from the inclusion of multi-disciplinary consensus within the definition for MPE. However, we considered it necessary as many patients with widely disseminated malignancy may 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.

The main implication of our 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 are likely gain little benefit from pleural fluid cytology and alternative methods of initial diagnosis such as pleural biopsy should be considered (11–13). Further research is needed into an optimal diagnostic pathway for mesothelioma.

Abbreviations

MPE

Malignant pleural effusion

AIC

Akaike information criterion

Declarations

This study was approved by the University of Otago Ethics Committee (Health) (HD19/031)

Consent for publication: Not applicable.

Availability of data and material: The data used in this study are included in supplementary materials

Competing interests: The authors have no financial or non-financial competing interests.

Funding: LP was funded through a University of Otago Summer Studentship supported by the Cancer Society of New Zealand.

Authors' contributions: MM and LP had the initial idea. MM, LB, LP and MD designed the study. MM and LP performed the data collection and analysis. LP wrote the first draft of the manuscript. All authors revised the manuscript and approved the final draft.

Acknowledgements: Not applicable

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