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TITLE PAGE

Is pleural infection associated with longer survival in mesothelioma? A population-based cohort study using data from Hospital Episode Statistics.

Anna C Bibby[1,2], Duneesha de Fonseka[1,2], David J Carslake[3,4] & Nick A Maskell[1,2]

Affiliations

1. Academic Respiratory Unit, Bristol Medical School, University of Bristol, UK
2. North Bristol Lung Centre, North Bristol NHS Trust, Bristol, UK
3. MRC Integrative Epidemiology Unit, University of Bristol, UK
4. Population Health Sciences, Bristol Medical School, University of Bristol, UK

Corresponding author
Dr Anna C Bibby
Academic Respiratory Unit, University of Bristol, 2nd Floor Learning & Research Building, Southmead Hospital, Bristol, BS10 5NB.
Email: Anna.bibby@Bristol.ac.uk
Tel: (+44) 0117 414 8049

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Ethics & governance
The research was granted ethical approval by the Proportionate Review Sub-Committee of the National Research Ethics Service (NRES) Committee London – Central on 10/7/14 (REC reference 14/LO/1258).

All investigators who had access to patient-level pseudonymised or sensitive data had been granted Approved Researcher status by ONS and thus had a legal basis for access to the data. The overall

data application was approved following review by the Health and Social Care Information Centre (HSCIC) Data Access Advisory Group (DAAG), with whom a Data Sharing Agreement was signed.

Contributors statement

ACB conceived the study, designed the methodology, cleaned & analysed the data, interpreted the results and wrote the manuscript. DDF helped refine the methodology, assisted with data analysis and contributed to manuscript writing. DJC developed the statistical analysis plan, assisted with data analysis, interpreted the results and helped write the manuscript. NAM developed the study concept, reviewed the analysis plan, assisted with interpretation of results and refined the manuscript. All authors reviewed and approved the final document. ACB is the guarantor for the published study, including all data and analyses.

Data sharing statement

The study data will not be made available. This is because the data is owned by NHS Digital (previously the Health & Social Care Information Centre), and contractual conditions forbid data sharing with third parties. The code for statistical analysis can be requested from the corresponding author.

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Abbreviations

BCG	Bacillus Calmette-Guérin
CI	Confidence interval
HES	Hospital Episode Statistics
HR	Hazard ratio
ICD-10	International Classification of Diseases Tenth Edition
IMD	Index of multiple deprivation
IoM	Isle of Man
IQR	Interquartile range
NI	Northern Ireland
ONS	Office of National Statistics
OPCS-4	OPCS Classification of Interventions and Procedures
SD	Standard deviation.

ABSTRACT

Background

Historically pleural infection was thought to be associated with longer survival in thoracic malignancies. The aim of this population-based cohort study was to investigate this hypothesis in mesothelioma, using national data from a high incidence country.

Methods

Case records for all patients with mesothelioma seen in English hospitals between 01/01/2005 and 31/12/2014 were extracted from Hospital Episode Statistics using International Classification of Diseases Tenth Edition (ICD-10) codes. Episodes of pleural infection were identified. Linked mortality data was obtained from the Office of National Statistics.

The primary outcome was all-cause mortality. The explanatory variable was pleural infection. Cox proportional hazards model was used to analyse survival, with pleural infection, chemotherapy and thoracic surgery handled as time-variable co-factors.

Results

Of 22,215 patients with mesothelioma, 512 (2.3%) developed pleural infection at some point in their illness. Overall median survival was 7.0 months (IQR 2.3-16.4). Pleural infection was associated with shorter survival in the immediate post-infection period (up to 30 days – HR 1.81, 95% CI 1.45 to 2.22) and longer term (>30 days – HR 1.81, 95% CI 1.63 to 1.99). Other factors associated with increased mortality were age, male gender and being diagnosed as an inpatient. Receiving chemotherapy and being less economically deprived were associated with longer survival.

Conclusion

Pleural infection occurred in 2.3% of people with mesothelioma and was associated with shorter survival. This refutes previous reports suggesting pleural infection may be associated with better outcomes in thoracic malignancy.

Key words

Mesothelioma

Empyema, pleural

Survival

Background

Mesothelioma is an aggressive tumour that usually affects the pleura, although the peritoneum, pericardium and tunica vaginalis may be affected.[1,2] Treatment options are limited, but several novel therapies are under investigation, with immunotherapy of particular interest.[3-6]

Prior to the modern era of immunotherapy, a more rudimentary approach existed, using bacterial products to stimulate immune responses. In the early 1900s, Coley's toxin, a mixture of killed *Streptococcus pyogenes* and *Serratia marcescens,* was used to treat sarcoma, whilst in the 1970s, trials were conducted exploring the anti-cancer effects of intra-pleural Bacillus Calmette-Guérin (BCG) and *Corynebacterium parvum*.[7-10] Unfortunately, heterogeneous methodologies and high risk of bias in all study designs made the results of these trials difficult to interpret.[11]

Bacteria can also occur in the pleural space due to infection, either arising spontaneously (often in association with pneumonia) or iatrogenically following pleural intervention. Treatment of pleural infection consists of draining the infected fluid, providing appropriate antimicrobial cover and supporting patients' nutritional status.[12] In approximately one third of patients, however, this initial management will fail, and a surgical procedure is required.[13] Fortunately the majority of people who experience pleural infection make a full recovery, although there is a not-insignificant mortality rate of between 10% and 20%, usually related to older patients or those with multiple medical co-morbidities.[13,14]

Despite the mortality risk associated with pleural infection, historic reports suggested that it was associated with longer survival in patients who had undergone lung cancer surgery.[15-17] Similarly, an observational study reported longer survival in mesothelioma patients with infected indwelling pleural catheters, compared with patients with mesothelioma without infection.[18] These studies hypothesised that bacteria in the pleural space were stimulating protective immune responses, with associated anti-cancer activity. However, patient numbers were small in all four studies, and confidence intervals wide, such that any true effect size may have been clinically meaningless.

This study aimed to investigate the hypothesis that pleural infection is associated with longer survival in mesothelioma, using national data to ensure accurate and precise results.

Methods

Study design & data sources

This was a population-based cohort study using historic data from Hospital Episode Statistics (HES) and the Office of National Statistics (ONS). The research was approved by the Proportionate Review Sub-Committee of the National Research Ethics Service (NRES) Committee London – Central (14/LO/1258).

Study participants included all patients with mesothelioma who attended an English hospital between 01/01/05 and 31/12/14. Participants were identified from HES, a database containing details of every NHS-related activity in England, using the International Classification of Diseases Tenth Edition (ICD-10) codes for mesothelioma (C45, C45.0, C45.1, C45.2, C45.7, C45.9). Episodes of pleural infection were identified using ICD-10 codes J86, J86.0 and J86.9.

Records were linked to ONS for 01/01/05 to 28/03/16, using individual, pseudonymised patient identifiers. ONS contains death certificates information for all deaths in England and Wales.

Study variables

The exposure variable was pleural infection. The primary outcome was survival, defined as date of mesothelioma diagnosis to date of death. Patients with zero survival time and death certificate diagnoses of mesothelioma were excluded.

Data on potential confounders were extracted from HES, using ICD-10 and OPCS Classification of Interventions and Procedures (OPCS-4) codes. These included sex, age at diagnosis, disease site (pleural; peritoneal; pericardial; other or unspecified), socio-economic status based on index of multiple deprivation (IMD) quintile (1=least deprived; 5=most deprived), rural/urban location (urban area of population >10000; town or fringe; village; hamlet or isolated dwelling), comorbidities at presentation (defined as number of additional diagnostic codes), mode of initial attendance (outpatient appointment; inpatient admission; procedure or operation), year of diagnosis (before or after 01/01/2008 as this was the year pemetrexed and cisplatin chemotherapy became standard care in the UK[19]), documented asbestos exposure, documented pleural plaques, undergoing a biopsy, thoracoscopy (medical or surgical) or pleurodesis (bedside talc slurry or thoracoscopic poudrage), number of pleural interventions, average number of hospital episodes per year and undergoing chemotherapy, radiotherapy or thoracic surgery. Thoracic surgical procedures included diagnostic surgery, curative or debulking mesothelioma procedures and interventions to control pleural fluid, including video-assisted thoracic surgery (VATS) biopsy, extra-pleural pneumonectomy, extended pleurectomy/decortication, pleurectomy, pleural stripping and pleural abrasion. Chemical pleurodesis undertaken at VATS was coded within the pleurodesis category.

Statistical analysis

Patient characteristics were summarised using descriptive statistics, stratified by pleural infection. Means with 95% confidence intervals (CI), and medians with inter-quartile ranges (IQR) were calculated for normal and non-normally distributed continuous data. Categorical and binary data were reported as proportions. Significance tests were performed using t-tests and Kruskal-Wallis tests for normal and non-normally distributed data respectively. χ^2 was used for binary, ordinal or categorical variables, with Fisher's exact test employed if the expected frequency in any group was less than 10. The only variable with missing data was socioeconomic status. A separate 'missing' category was created for this variable and used in all analyses.

Pleural infection incidence rate was calculated per 1000 person-years. Because the incidence of pleural infection was likely to vary over time, separate rates were calculated for the periods 0-30 days, 31-90 days and 90+ days post-mesothelioma diagnosis. Factors associated with pleural infection were investigated using Cox proportional hazards models, with time since mesothelioma diagnosis as the time axis. Potential interactions between pre-specified variables (comorbidities, age, IMD quintile, number of pleural procedures, average number of hospital attendances per year, diagnosed after 2008) were tested using the Mantel Haenszel method.

Median survival was reported for the whole group, and for patients who did and did not experience pleural infection. Kaplan Meier curves were plotted in people with and without pleural infection. Median survival was calculated for patients diagnosed before and after 2008, the year that pemetrexed and cisplatin chemotherapy became standard care in the UK.

Survival analyses were undertaken using Cox proportional hazards models, having checked the validity of the proportional hazards assumption using Schoenfield residuals and visually with "log-

log" plots. All variables were included in the adjusted model, regardless of significance on univariable testing. Collinearity of variables was tested using variance inflation factors (VIF), and any factors with VIF higher than 5 were removed and the model re-run to evaluate impact. Because any potential hazard associated with pleural infection could only occur after the infection began, and due to suspicion that the hazard may change following recovery from infection, pleural infection was handled as a time-varying covariable by splitting follow-up into pre-infection, ≤30 days post-infection and >30 days post-infection. Thoracic surgery and chemotherapy were handled similarly, with follow-up split at the time of first treatment. Survival was censored on 28/03/2016.

The primary analysis assessed all-cause mortality, with mesothelioma-specific mortality modelled as a secondary analysis, censoring participants who died of other causes on date of death. The main analysis included all patients. *A priori* sub-group analysis investigated patients with pleural mesothelioma, since pleural infection was likely to be most relevant to these patients.

Results

22,896 patient records were identified, of whom 22,215 met the inclusion criteria, contributing 24,809 patient-years in total (Figure 1).

Of 22,215 patients, 81.7% were male, mean age was 71.8 years (range 18-102), and the majority had pleural mesothelioma (51.5% pleural, 5.0% peritoneal, 0.4% pericardial, 42.9% not specified). For 16,144 patients (72.7%), the first recorded diagnosis of mesothelioma occurred during an inpatient admission, whilst 5,216 (23.5%) were diagnosed at operation or procedure, and 855 (3.9%) during an outpatient appointment. The median number of comorbid codes at presentation was 5 (IQR 3-7), with essential hypertension (n=6,428; 28.9%), drug, alcohol or tobacco use (n=4,269; 19.2%) and ischaemic heart disease (n=3,789; 17.1%) the most frequent.

Pleural infection

512 of 22,215 patients (2.3%) developed pleural infection. The incidence rate was 24.4 per 1000 patient-years (95% CI 19.2-22.8). Pleural infection incidence was higher in the first 30 days after diagnosis with mesothelioma (170.0 per 1000 patient-years, 95% CI 151.4-190.9), and fell for the period 31-90 days (33.9 per 1000 patient-years, 95% CI 27.7-41.4) and 90+ days post-diagnosis (6.5 cases per 1000 patient-year, 95% CI 5.5-7.7).

Patients with pleural infection were more likely to be male, comorbid and diagnosed as inpatients (Table 1). Pleural drainage, thoracoscopy, thoracic surgery and pleurodesis were more common in patients with pleural infection, who underwent more pleural interventions overall and had more hospital episodes per year than patients without infection. Pleural infection occurred more frequently in patients with pleural mesothelioma and was less likely in people who received chemotherapy.

In multivariable analysis, pleural infection was associated with male gender, number of co-morbidities, pleural drainage, thoracic surgery and total number of pleural interventions (Table 2). Pleural infection was less common in outpatients, non-pleural mesothelioma, patients who underwent thoracoscopy, percutaneous biopsy or pleurodesis, and patients who received chemotherapy.

Table 1 – Characteristics of 22,215 patients with mesothelioma, stratified by pleural infection. P values derived from t-tests, Kruskal-Wallis tests, χ^2 test and Fisher's exact test. IMD – index of multiple deprivation; IoM – Isle of Man; IQR – interquartile range; NI – Northern Ireland; SD – standard deviation.

	Pleural infection N=512	No pleural infection N=21,703	p
Male, n (%)	455 (88.9)	17,686 (81.5)	<0.001
Age, mean (SD)	70.9 (9.83)	71.8 (9.94)	0.044
IMD quintile, n (%)			
1 (least deprived)	93 (18.2)	4,218 (19.4)	
2	101 (19.7)	4,192 (19.3)	
3	117 (22.9)	4,193 (19.3)	
4	100 (19.5)	4,199 (19.4)	
5 (most deprived)	93 (18.2)	4,195 (19.3)	
Missing	8 (1.6)	706 (3.3)	0.132
Rural/urban location, n (%)			
Urban with ≥10,000 population	385 (75.2)	17,079 (78.7)	
Town and Fringe	65 (12.7)	2,202 (10.2)	
Village	42 (8.2)	1,688 (7.8)	
Hamlet or isolated dwelling	18 (3.5)	670 (3.1)	
Scotland, NI, IoM or Channel Islands	2 (0.4)	64 (0.3)	0.339
Mode of initial attendance, n (%)			
Outpatient appointment	1 (0.2)	854 (3.9)	
Inpatient admission	431 (84.2)	15,713 (72.4)	
Day case procedure/operation	80 (15.6)	5,136 (23.7)	<0.001
No. of comorbid codes, median (IQR)	5 (4-8)	4 (3-7)	<0.001
Documented asbestos exposure, n (%)	107 (20.9)	3,423 (15.8)	0.002
Documented pleural plaques, n (%)	33 (6.5)	1,166 (5.37)	0.288
Pleural interventions			
Pleural drainage/aspiration	354 (69.1)	7,678 (35.4)	<0.001
Thoracoscopy	276 (53.9)	7,621 (35.1)	<0.001
Percutaneous pleural biopsy	149 (29.1)	5,771 (26.6)	0.204
Pleurodesis	170 (33.2)	5,941 (27.4)	0.004
Total no of pleural procedures, median (IQR)	3 (1-4)	1 (0-2)	<0.001
Diagnosed after 2008, n (%)	313 (61.1)	13,216 (60.9)	0.913
Site of disease, n (%) Pleural	319 (62.3)	11,125 (51.3)	
Peritoneal	7 (1.4)	1,109 (5.1)	
Pericardial	0 (0)	81 (0.4)	
Not specified	186 (36.3)	9,388 (43.3)	<0.001
Average no. of hospital episodes per year, median (IQR)	3.5 (2-5.5)	3 (1.5-5)	<0.001
Treatment received, n (%)			
Chemotherapy	51 (10.0)	3,955 (18.2)	<0.001
Radiotherapy	2 (0.4)	227 (1.1)	0.183
Thoracic surgery	255 (45.9)	3,449 (15.9)	<0.001
Infection/sepsis cause of death	3 (0.6)	118 (0.6)	0.913

Table 2 – Factors associated with pleural infection in 22,215 patients with mesothelioma, from unadjusted and adjusted Cox proportional hazards models. All listed variables were included in the multivariable model. CI – confidence interval; HR – Hazard ratio for pleural infection; IMD – Index of multiple deprivation; IoM – Isle of Man; IQR – interquartile range; NI – Northern Ireland; SD – standard deviation.

	Unadjusted analysis			Adjusted analysis		
	HR	95% CI	p	HR	95% CI	p
Male gender	1.91	1.45 to 2.52	<0.001	1.66	1.25 to 2.20	<0.001
Age at diagnosis ≤65	1	-	-	1	-	-
66 to 70	0.87	0.67 to 1.14	0.313	0.81	0.62 to 1.06	0.123
71 to75	0.92	0.71 to 1.19	0.538	0.83	0.64 to 1.08	0.168
76 to 80	1.06	0.82 to 1.38	0.632	0.94	0.71 to 1.23	0.641
81+	0.96	0.73 to 1.25	0.743	0.81	0.60 to 1.07	0.140
IMD quintile						
1 (least deprived)	0.77	0.59 to 1.02	0.066	0.77	0.59 to 1.02	0.065
2	0.84	0.64 to 1.10	0.197	0.83	0.63 to 1.08	0.163
3	1	-	-	1	-	-
4	0.86	0.65 to 1.12	0.251	0.84	0.64 to 1.10	0.199
5 (most deprived)	0.81	0.62 to 1.06	0.130	0.77	0.58 to 1.01	0.061
Missing	0.30	0.14 to 0.61	<0.001	0.62	0.27 to 1.42	0.256
Rural/urban location						
Urban ≥10,000 population	1	-	-	1	-	-
Town and Fringe	1.31	1.01 to 1.70	0.044	1.25	0.95 to 1.63	0.105
Village	1.09	0.80 to 1.49	0.616	0.94	0.67 to 1.30	0.689
Hamlet/ isolated dwelling	1.14	0.71 to 1.83	0.579	1.04	0.65 to 1.68	0.868
Scotland, NI, IoM, Channel Islands	0.93	0.23 to 3.75	0.921	1.76	0.35 to 8.78	0.491
Mode of initial attendance						
Outpatient appointment	0.04	0.01 to 0.25	<0.001	0.12	0.02 to 0.86	0.035
Inpatient admission	1	-	-	1	-	-
Operation/procedure	0.57	0.45 to 0.72	<0.001	0.87	0.68 to 1.11	0.257
Diagnosed after 2008	0.98	0.82 to 1.17	0.809	0.83	0.69 to 1.01	0.057
No. of comorbid codes	1.14	1.11 to 1.17	<0.001	1.13	1.10 to 1.16	<0.001
Non-pleural mesothelioma	0.67	0.56 to 0.80	<0.001	0.80	0.67 to 0.97	0.021
Documented asbestos exposure	1.39	1.13 to 1.73	0.002	0.91	0.73 to 1.13	0.385
Documented pleural plaques	1.28	0.90 to 1.83	0.166	0.90	0.63 to 1.29	0.560
Pleural interventions						
Pleural drainage/aspiration	3.76	3.11 to 4.53	<0.001	1.58	1.26 to 1.98	<0.001
Thoracoscopy	1.79	1.51 to 2.14	<0.001	0.64	0.50 to 0.81	<0.001
Percutaneous pleural biopsy	1.09	0.89 to 1.31	0.279	0.76	0.62 to 0.93	0.007
Pleurodesis	1.10	0.92 to 1.33	0.293	0.44	0.36 to 0.55	<0.001
Total no. of pleural procedures	1.50	1.44 to 1.56	<0.001	1.51	1.42 to 1.61	<0.001
Average no. of hospital episodes per year	1.01	0.99 to 1.03	0.341	1.01	0.99 to 1.04	0.260
Treatment received						
Chemotherapy	0.45	0.33 to 0.60	<0.001	0.60	0.44 to 0.83	0.002
Radiotherapy	0.33	0.08 to 1.33	0.121	0.41	0.10 to 1.66	0.212

Thoracic surgery	5.14	3.99 to 6.63	<0.001	2.26	1.67 to 3.07	<0.001

With regard to pleural infection, there was evidence of interaction between several variables, including comorbidity, total number of pleural procedures and average number of hospital episodes per year. However, subsequent univariable analyses controlling for the interacting variable did not alter the observed associations to any great degree (see Appendix 1).

Survival

20,380 deaths occurred over 24,809 patient-years. Censored participants were followed up for 14.9 months minimum (range 14.9-134.5, median 40.4). Median survival was 7.0 months (IQR 2.3-16.4), increasing to 7.8 months (IQR 2.6-17.2) in patients diagnosed after 2008 (n=13,529). Median survival was 6.2 months in patients with pleural infection (IQR 2.6-14.9) compared with 7.0 months (IQR 2.3-16.4) in those without (unadjusted HR 1.12, 95% CI 1.02-1.22, p=0.013). Unadjusted Kaplan Meier survival curves are shown in Figure 2.

All-cause mortality was higher after pleural infection, both in the 30-day post-infection period and 30+ days post-infection. This remained the case in the adjusted survival model (Table 3). Factors associated with all-cause mortality were age, male gender, being diagnosed as an inpatient, undergoing percutaneous biopsy, undergoing a drainage procedure, documented asbestos exposure, pleural plaques and having undergone thoracic surgery. Non-pleural mesothelioma, being diagnosed after 2008, low socioeconomic deprivation, undergoing thoracoscopy or pleurodesis and receiving chemotherapy were positive prognostic variables.

The majority of patients died of mesothelioma (18,604/22,215; 84%), consequently the results for mesothelioma-specific mortality were similar to the primary analysis (see Appendix 2). Sub-group analysis of patients with pleural mesothelioma did not reveal any differences compared with the main results (see Appendix 3). There was no evidence of collinearity between variables in the multivariable survival analysis (see Appendix 4).

Table 3 – Factors associated with all-cause mortality in 22,215 patients with mesothelioma, from adjusted and unadjusted survival models. All listed variables were included in the multivariable model. CI – confidence interval; HR – Hazard ratio for all-cause mortality; IMD – index of multiple deprivation; IoM – Isle of Man; IQR – interquartile range; NI – Northern Ireland; SD – standard deviation.

	Unadjusted analysis			Adjusted analysis*		
	HR	95% CI	p	HR	95% CI	p
Pleural infection						
Pre-infection/no infection	1	-		1	-	-
First 30 days post-infection	1.72	1.39 to 2.11	<0.001	1.81	1.47 to 2.22	<0.001
30+ days post-infection	1.70	1.54 to 1.87	<0.001	1.81	1.63 to 1.99	<0.001
Male gender	1.24	1.20 to 1.29	<0.001	1.26	1.21 to 1.30	<0.001
Age at diagnosis ≤65	1	-	-	1	-	-
66-70	1.19	1.14 to 1.25	<0.001	1.17	1.12 to 1.22	<0.001
71-75	1.39	1.33 to 1.45	<0.001	1.34	1.28 to 1.40	<0.001
76-80	1.71	1.64 to 1.79	<0.001	1.59	1.52 to 1.67	<0.001
≥81	2.21	2.12 to 2.30	<0.001	1.98	1.90 to 2.08	<0.001
IMD quintile						
1 (least deprived)	0.94	0.90 to 0.98	0.004	0.95	0.91 to 0.99	0.013
2	0.93	0.89 to 0.97	<0.001	0.95	0.91 to 0.99	0.018
3	1	-	-	1	-	-
4	0.98	0.94 to 1.02	0.328	0.98	0.93 to 1.02	0.298
5 (most deprived)	1.03	0.99 to 1.08	0.145	1.02	0.98 to 1.07	0.282
Missing	0.19	0.17 to 0.22	<0.001	0.27	0.24 to 0.31	<0.001
Rural/urban location						
Urban ≥10,000 population	1	-	-	1	-	-
Town and Fringe	1.05	1.01 to 1.10	0.025	1.03	0.98 to 1.08	0.255
Village	0.99	0.94 to 1.04	0.721	1.01	0.96 to 1.07	0.687
Hamlet/ isolated dwelling	0.92	0.85 to 0.99	0.049	0.96	0.88 to 1.04	0.270
Scotland, NI, IoM, Channel Islands	0.12	0.07 to 0.19	<0.001	0.38	0.23 to 0.62	<0.001
Mode of initial attendance						
Outpatient appointment	1	-	-	1	-	-
Hospital inpatient	2.30	2.11 to 2.50	<0.001	1.17	1.07 to 1.28	<0.001
Operation/procedure	2.29	2.10 to 2.50	<0.001	1.06	0.97 to 1.17	0.196
Diagnosed after 2008	0.86	0.84 to 0.89	<0.001	0.87	0.85 to 0.90	<0.001
No. of comorbid codes	1.02	1.02 to 1.03	<0.001	0.99	0.98 to 0.99	<0.001
Non-pleural mesothelioma	1.06	1.03 to 1.09	<0.001	0.95	0.92 to 0.98	<0.001
Documented asbestos exposure	1.05	1.01 to 1.09	0.014	1.07	1.03 to 1.12	<0.001
Documented pleural plaques	1.20	1.13 to 1.28	<0.001	1.11	1.05 to 1.18	<0.001
Pleural interventions						
Pleural drainage/aspiration	0.89	0.87 to 0.92	<0.001	1.21	1.16 to 1.26	<0.001
Thoracoscopy	0.65	0.63 to 0.67	<0.001	0.88	0.84 to 0.91	<0.001
Percutaneous pleural biopsy	0.92	0.89 to 0.95	<0.001	1.07	1.03 to 1.11	<0.001
Pleurodesis	0.66	0.64 to 0.68	<0.001	0.88	0.84 to 0.91	<0.001
Total no. of pleural procedures	0.87	0.86 to 0.87	<0.001	0.87	0.85 to 0.88	<0.001
Average no. of hospital episodes per year	0.97	0.965 to 0.973	<0.001	0.98	0.97 to 0.98	<0.001
Treatment received						
Chemotherapy	0.56	0.54 to 0.58	<0.001	0.96	0.93 to 0.99	0.031
Radiotherapy	0.61	0.53 to 0.70	<0.001	0.95	0.82 to 1.10	0.512
Thoracic surgery	0.61	0.59 to 0.64	<0.001	1.05	1.01 to 1.10	0.020

Discussion

This large mesothelioma cohort, using population level data allowed the most rigorous examination of the relationship between pleural infection and survival to date. Pleural infection was more likely to occur in the first 30 days after diagnosis with mesothelioma and was associated with increased mortality.

The hazard associated with pleural infection was similar to that seen in a Canadian study of patients with lung cancer and pleural infection.[20] Although that study was conducted in the post-operative setting, rather than general follow-up, post-operative empyema (or pneumonia or mediastinitis) was a negative prognostic factor, with an adjusted hazard ratio of 1.67 (95% confidence interval 1.39–2.01).

Interpretation

Causality cannot be determined from this observational study and for several variables the observed association may be bi-directional. For example, although patients who undergo multiple pleural interventions are at higher risk of iatrogenic pleural infection, once infection occurs they will also require more interventions to manage it. This interpretation could also apply to the primary outcome, i.e. dying patients may be more likely to develop pleural infection, rather than infection being implicated in shortening their life.

When interpreting these results, it is important to differentiate between statistical significance and clinical meaningfulness. The large sample size generated high statistical power, with low p values for several analyses. However, p values provide no information on the size of an effect or clinical relevance. For example, although the variable 'comorbidities' was associated with a "statistically

significant" reduction in mortality, a HR of 0.99 is unlikely to represent a meaningful survival benefit. Additionally, the idea of a threshold p value below which a result is "statistically significant" is controversial, with many researchers preferring to interpret absolute p-values as a measure of the strength of an association and 95% confidence intervals to evaluate the size and precision of the observed association.[21] Importantly, the hazard associated with pleural infection in this study was both clinically meaningful and statistically strong.

Our results confirm previously reported prognostic factors in mesothelioma. Male gender and increasing age have been repeatedly shown to be associated with shorter survival,[2,22,23] whilst being diagnosed during an acute or emergency presentation is a poor prognostic indicator in several cancer types.[24] Socio-economic position is a predictor of outcome in many medical conditions, both malignant and non-malignant, although this association has never been demonstrated in MPM.[25-27] In fact, a recent French study showed that socio-economic status was not associated with survival in mesothelioma, however a different index was used to determine deprivation and it is plausible that the impact of socioeconomic status varies across different healthcare systems.[28]

Chemotherapy was associated with a small mortality benefit. This reflects the fact that for several years there was no effective chemotherapy for mesothelioma. Survival outcomes improved following the introduction of pemetrexed and cisplatin, however, the mortality benefit remained modest, due to the limited efficacy and low response rates associated with current chemotherapy.[5] Regarding other treatments, our results support the British Thoracic Society guidance that radiotherapy has no role in the radical treatment of mesothelioma, and that surgery may be harmful.[2,39,40]

Pleural procedures have no disease-modifying ability and the lower mortality associated with these interventions in this study is likely to reflect confounding by indication, e.g. patients must be sufficiently fit to undergo thoracoscopy, and this fitness determined their subsequent survival. The corollary is that patients in whom thoracoscopy was contra-indicated (e.g. due to frailty) were more likely to be investigated via less-invasive pathways, i.e. percutaneous biopsies, thus survival was worse in this group. Similarly, pleurodesis is generally undertaken in patients who are expected to live long enough for recurrent fluid to be a problem, whilst patients with shorter life expectancy are often treated with recurrent aspirations.

Patients with missing socioeconomic data and those from Scotland/NI/IoM/Channel Islands had dramatically better survival outcomes. Whilst this could represent a genuine result, it is more likely that some of these patients were missing data for other variables, e.g. date of death, resulting in apparent longer survival. Post-hoc investigations revealed that patients in these groups were more likely to have been right-censored, supporting this theory. However, patient numbers were small, and a sensitivity analysis omitting these patients resulted in near-identical results.

Strengths & limitations

This study has several strengths, including use of a resource with national coverage which minimised selection bias. The use of standardised coding ensured that participant identification was comprehensive. Compared with national cancer registry data, we identified between 94.3% and 100% of patients diagnosed with mesothelioma in England each year.[29] The number of deaths in 2006-2014 represented between 91.5% and 98.4% of deaths recorded by the Health and Safety Executive for England for those years.[30] Finally, 1-year survival rates and the proportion of patients who received chemotherapy were comparable to the national lung cancer audit (38.8% *vs* 43.1% and

36.0% *vs* 36.5% respectively).[31] We are confident, therefore, that our results are a reliable representation of the mesothelioma population in England during this period.

This is the first study to report the incidence of pleural infection in mesothelioma, and therefore we cannot be certain that case identification was comprehensive. We assume that pleural infection was identified as sensitively as mesothelioma, since the same method was used. Of note, pleural infection incidence in the general population is 6-22 per 100,000, significantly lower than the incidence observed here.[12,32] Pleural infection appears more common in patients with mesothelioma, most likely as an iatrogenic phenomenon due to pleural interventions.

The majority of mesothelioma cases in which disease site was not specified were likely to be pleural tumours, as globally over 90% of mesothelioma affects the pleura.[33] Therefore, although pleural infection appeared more prevalent in pleural mesothelioma, a different result may have been seen if disease site had been universally recorded. Additionally, cases where disease site was not specified may have been associated with lower data quality in other domains, although the sub-group analysis of pleural cases only did not reveal any great differences compared with the main analysis (see Appendix 3).

Another strength was the statistical methodology. Handling infection as a time-varying covariable reduced the risk of immortal-time bias, i.e. patients with pleural infection had to live long enough to develop pleural infection. The same is true for chemotherapy and thoracic surgery.

Certain data are not collected in HES and could not be adjusted for. Specifically, performance status and tumour histological type were not available, and this may have introduced confounding as these

are known prognostic factors. It may be that pleural infection was more likely in patients with worse performance status, with the higher mortality related to poor performance status rather than infection. We created the variable "comorbidities" as a surrogate for performance status, however we recognise that this approach was imperfect, as performance status is a global measure of function that encompasses more than co-existent medical conditions. Nonetheless, it was reassuring that the mortality hazard associated with pleural infection was not greatly affected by adjustments for potential confounders, suggesting the effect of confounding was relatively minor, at least for the variables for which data was available.

Confounding by indication is the most likely explanation for the observed discrepancy between the adjusted and unadjusted HR associated with chemotherapy. Specifically, age and comorbidities are often used to determine suitability for chemotherapy treatment and, therefore, once these variables were included in the fully adjusted model, the overall survival benefit of chemotherapy was attenuated.

Details relating to pleural infection were also unavailable and, importantly, HES contained no information on causative organisms. This is relevant, as different bacterial species elicit differing immunological responses. For example, gram-positive and gram-negative bacteria induce different patterns of cytokine release with varying, sometimes opposing, down-stream responses.[34,35] Additionally, some species secrete virulence factors known as superantigens, which bypass classic antigen-binding pathways and induce dramatic inflammatory responses.[36] It is possible that evaluating all aetiologies of pleural infection together may have masked a true effect related to a single organism or species.

Prospective data collection could overcome some of these limitations, although the study population would need to be large. A multi-centre observational mesothelioma study is underway in the UK (ASSESS-meso ISRCTN61861764) with data collection ongoing for the next decade. Another approach could link HES to a third dataset with information on the variables of interest, e.g. the National Lung Cancer Audit.

Conclusion

In this national cohort of mesothelioma patients, pleural infection was associated with higher 30-day and long-term mortality. However, unavailable data for certain prognostic variables may have introduced confounding, and the lack of information about bacteria meant that associations between individual organisms and survival could not be explored. Nonetheless, this large, well-conducted study refutes previous hypotheses that pleural infection is associated with longer survival in mesothelioma.

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