Comorbidities and causes of death of patients with asbestosis

Eerika Keskitalo, BM[1,2], Johanna Salonen, MD, PhD[1,2], Hanna Nurmi, MD, PhD[3,4], Hannu Vähänikkilä PhD[5], Riitta Kaarteenaho, MD, PhD[1,2]

[1] Research Unit of Internal Medicine, University of Oulu, Oulu, Finland

[2] Center of Internal and Respiratory Medicine, Medical Research Center (MRC) Oulu, Oulu, Finland

[3] Division of Respiratory Medicine, Institute of Clinical Medicine, School of Medicine, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland

[4] Center of Medicine and Clinical Research, Department of Respiratory Medicine, Kuopio University Hospital, Kuopio, Finland

[5] Northern Finland Birth Cohorts, Arctic Biobank, Infrastructure for Population studies, Faculty of Medicine, University of Oulu, Oulu, Finland

Corresponding author: Eerika Keskitalo

Research Unit of Internal Medicine, University of Oulu, Oulu, Finland

eerika.keskitalo@student.oulu.fi

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Conflict of Interest

The authors have the following competing interests that have not affected the contents of this study:

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Ethical considerations

The study protocol was approved by the Regional Ethics Committee of the Northern Ostrobothnia Hospital District. The permission to use data from death certificates was given by Statistics Finland. This study was conducted in compliance with the Declaration of Helsinki. No consents for inclusion into this study were collected since in accordance with Finnish legislation, consent was not required because of the register-based nature of the project.

Running Head Title

Asbestosis – Comorbidities and causes of death

ABSTRACT

Objective: Comorbidities are common and affect the prognosis of patients with interstitial lung diseases, but few previous studies have investigated patients with asbestosis.

Methods: We collected comorbidities and death causes of 116 patients with asbestosis treated in Oulu University Hospital. Causes of death were confirmed by autopsy in 68% of the cases.

Results: The most common comorbidities of asbestosis patients were pleural plaques (96%) and coronary artery disease (CAD) (67%). The prevalence of rheumatoid arthritis was 8.6%. The most common underlying causes of death were asbestosis (36%), CAD (24%) and lung cancer (LC) (10%). CAD and LC were associated with shorter survival in adjusted analyses.

Conclusions: Patients with asbestosis have multiple comorbidities. Prevention and treatment of CAD and LC may influence the prognosis of asbestosis patients.

KEYWORDS

Asbestosis, Cause of death, Comorbidity, Lung fibrosis, Prognosis

SMART LEARNING OUTCOMES

- Upon completion of this article, the reader should be able to
    - describe common comorbidities of patients with asbestosis
    - identify comorbidities that associate with mortality in patients with asbestosis
    - describe common causes of death in patients with asbestosis

INTRODUCTION

Interstitial lung disease (ILD) patients usually suffer from several comorbidities which also affect prognosis.[1,2] Most of the previous studies on comorbidities of ILD have evaluated patients with idiopathic pulmonary fibrosis (IPF). The common comorbidities of IPF patients are chronic obstructive pulmonary disease (COPD)/emphysema, pulmonary hypertension, obstructive sleep apnea, coronary artery disease (CAD) and gastroesophageal reflux disease (GERD).[3] Previous studies on the association of comorbidities with prognosis have shown that cardiovascular diseases and lung cancer (LC) associated with shortened survival in IPF patients.[1,4,5] In contrast, GERD has been shown to associate with a more favorable prognosis in IPF.[1] Previous studies on rheumatoid arthritis-associated ILD (RA-ILD) and chronic hypersensitivity pneumonitis revealed that hypertension, CAD and diabetes were common comorbidities.[2,6] However, to our knowledge, there are no previous published studies on comorbidities in asbestosis patients despite the presence of malignant diseases.

Asbestos exposure causes both benign diseases such as asbestosis and pleural plaques as well as malignant diseases such as LC, mesothelioma, ovarian and laryngeal cancers.[7,8] The majority of pleural mesothelioma cases are due to asbestos.[9] The association of asbestos exposure and other malignancies has been studied with variable results, as authors of recent reviews and meta-analyses have claimed that asbestos is a risk factor for esophageal and colorectal cancers while no association was found with kidney and prostate cancers.[10–13]

Given that little is known about the non-malignant comorbidities of asbestosis patients, our aim was to investigate the comorbidities as well as both the underlying and immediate causes of death of patients with asbestosis. Furthermore, the association of the most common comorbidities with the prognosis of asbestosis patients was evaluated.

METHODS

Data collection

The study cohort consisted of asbestosis patients treated in Oulu University Hospital between 1996 and 2015 as described previously.[14,15] We gathered the study population by applying the International Classification of Diseases 10th edition code J61 for asbestosis. We evaluated the correctness of the asbestosis diagnoses by applying the Helsinki criteria for asbestosis, based on the patients' medical records and radiological reports, and excluded patients who did not meet the diagnostic criteria for asbestosis.[16,17] In Oulu University Hospital, after primary evaluation by a clinical pulmonologist and thoracic radiologist, most ILD patients are re-evaluated in a multidisciplinary meeting, especially when there are difficulties in differential diagnosis. In addition, the cases with suspected occupational exposure are also discussed in another multidisciplinary meeting, namely the occupational multidisciplinary meeting. Clinical data was collected from medical records of the hospital and death certificates. Dates of birth, asbestosis diagnosis, death or latest visit at the hospital, pulmonary function test results, presence of comorbid diseases and underlying and immediate causes of death were gathered. Survival time was calculated as the interval from the date of diagnosis to the date of death or the latest visit at the hospital. Survival status was updated on 19 January 2022. Information of comorbid diseases was collected by

utilizing both medical record texts and diagnostic codes from the hospital's medical record system and death certificates. In addition to medical record texts, information about emphysema and pleural plaques was collected from radiological reports. Basal cell carcinomas of the skin were not taken into account when analyzing malignant diseases, but they were reported separately. Smoking data was collected both at the time of diagnosis and from the most recent medical records. Patients were classified as non-smokers if the smoking history was at most three pack-years; otherwise, they were classified as ever-smokers. Lung function data was determined closest to the first visit to the hospital at the time of asbestosis diagnosis as previously reported.[14]

Statistics

IBM SPSS statistics version 28 was used. Data is reported as number of patients, means or median values when appropriate. Categorical variables were compared with the Chi square test. Cox regression analysis was used for multivariate model of the comorbidities that were associated with survival in age-adjusted analyses. P-value under 0.05 was considered as statistically significant.

Ethics

The study protocol was approved by the Regional Ethics Committee of the Northern Ostrobothnia Hospital District. The permission to use data from death certificates was given by Statistics Finland. This study was conducted in compliance with the Declaration of Helsinki. No consents for inclusion into this study were collected since in accordance with

Finnish legislation, consent was not required because of the register-based nature of the project.

RESULTS

Patient characteristics

The study included 116 patients, most of whom were male (96%) and ever-smokers (74%). The characteristics of the patients are presented in detail in Table 1. Most of the patients were deceased at the end of the follow-up time (87%). Most of the causes of death were determined with autopsy (68%).

Comorbidities

The most common comorbidities were pleural plaques (111/96%), CAD (78/67%) and obstructive pulmonary disease (72/62%) (Table 2). The prevalence of asthma was 23% while that of RA was 8.6%. Forty-two (36%) patients had malignant diseases; 10 of these patients had two different cancers. The most common cancer types were LC (n=18) and prostate cancer (n=9). There were no statistically significant differences in the prevalence of any cancer, LC or CAD between non- and ever-smokers.

Comorbidities and survival

The median estimated survival in the whole cohort was 125 months. In the univariate analysis, there was no statistically significant association between the common comorbidities and survival. CAD and LC associated with shorter survival in both age-adjusted

and multivariate analysis (Table 3). Hypertension was associated with a favorable prognosis of survival after adjustment for age. There was no association with survival when obstructive pulmonary diseases were analyzed as a single group or separately as COPD/emphysema and asthma.

Causes of death

Asbestosis/lung fibrosis was the most common (36%) underlying cause of death (Table 4). CAD (24%) and malignancies (18%) were also common death causes. Ten patients died of LC and one of mesothelioma. Pneumonia (38%) was the most common immediate cause of death. CAD/myocardial infarction and asbestosis were also commonly reported as immediate causes of death. Two patients died of acute exacerbation of asbestosis.

DISCUSSION

We have reported comorbid diseases as well as both immediate and underlying causes of death in a cohort of about 100 patients with asbestosis. To our knowledge, there are no previously published studies on comorbidities other than malignant diseases in asbestosis patients. We observed that CAD and COPD/emphysema were common comorbidities in asbestosis patients, and furthermore, that asbestosis and CAD were the most common underlying causes of death. We also examined the association of common comorbidities with survival and found that CAD and LC associated with mortality in adjusted analyses. As far as we are aware, analyses of this kind have not been previously performed in asbestosis patients.

We observed that asbestosis patients commonly have multiple comorbid diseases. The most usual comorbidities were similar to those of IPF: CAD, COPD/emphysema and hypertension were common in asbestosis patients, similarly to the results of previous studies on IPF patients.[4,18,19] LC and other malignancies, asthma and RA were also frequent in asbestosis patients. The authors of a previous review article reported that the prevalence of RA was about 0.8% in Finnish population, while in our cohort the prevalence of RA was much higher, i.e., 8.6%, even though RA is more common in female patients and only 4% of our study cohort were female.[20,21] The high prevalence of RA may potentially be explained by asbestos exposure since an association of asbestos exposure with RA was observed in a Swedish study.[22] In addition to asbestos, the study also found an association between silica and RA.[22]

It is noteworthy that the prevalence of obstructive pulmonary diseases such as COPD, emphysema and asthma was high, as 62% of the patients had some obstructive pulmonary disease. The prevalence of asthma was as high as 23.3% in our study cohort whereas it was 10.9% in a recent Finnish study.[23] In a study of IPF patients the prevalence of asthma and other airway diseases was lower, being 1.7% for asthma and 5% for COPD, while the overlap of asthma and COPD was 3.3%.[24] To the best of our knowledge, the association of asbestos exposure and asthma has previously been little studied. One previous study reported that those exposed to asbestos had higher cumulative incidence of asthma and asthma symptoms.[25] In patients with IPF the prevalence of COPD/emphysema has varied from 6% to 67%; in our study, the prevalence was between those proportions (54%).[3]

In our study, CAD was the most common comorbid disease after pleural plaques, being also the second most common underlying cause of death. CAD was also the most commonly reported cardiovascular disease of IPF patients.[3] In line with our results, the prognostic role of CAD has previously been recognized in patients with IPF.[26] Surprisingly, we observed that hypertension was associated with a favorable prognosis after adjustment for age. To our knowledge, the association of hypertension with the prognosis of asbestosis patients has not previously been studied, while in the studies on IPF, hypertension did not affect survival.[1,18] On the contrary, cardiovascular diseases have associated with worse prognosis in IPF. In a Danish study, cardiovascular diseases (CAD, cerebral infarction or peripheral arterial disease) diagnosed after diagnosis of IPF were associated with mortality and in a Finnish study, cardiovascular diseases (CAD, hypertension or cerebral infarction) were associated with shortened survival.[4,18]

We observed that malignant diseases were prevalent in asbestosis patients since 36% of the patients suffered from some malignant disease. In a study of Finnish IPF patients the prevalence of malignant diseases was lower (LC 6.8% and other cancers 12.1%) than in our asbestosis cohort (LC 15.5% and other cancers 23.3%).[18] The risk of getting prostate cancer is 14.5% in Finnish male population, which explains the high prevalence of prostate cancer in our study.[27] Asbestos causes LC and predictably, LC was the most common malignancy in our study.[28] In addition, asbestos exposure combined with smoking history has been shown to associate with a higher risk of developing LC compared to the risk caused by only one of these risk factors.[29] Furthermore, LC risk has been shown to be higher in patients with

asbestosis than in patients with merely asbestos exposure without lung fibrosis.[28,30] However, in our study we observed no significant difference in LC in relation to smoking status. We evaluated self-reported smoking status at several points in medical reports. A previous Finnish dental research evaluating the accuracy of self-reported smoking revealed a misclassification rate of 6%.[31] Previous studies have revealed that LC was associated with shortened survival in IPF patients; these results are in line with the findings of the present study of asbestosis patients.[1,5]

Asbestosis was the most common cause of death in our study cohort. Lung fibrosis has also been the most common cause of death in previous studies of other ILDs, such as IPF, systemic sclerosis-associated ILD and RA-ILD.[6,32–35] CAD was reported as a common cause of death in the previous studies on IPF and RA-ILD, similarly as in our asbestosis cohort.[6,32,33,35] In our study, malignant diseases were relatively common causes of death (18%). Other investigators have revealed that malignant diseases, most importantly LC, were quite common causes of death in IPF patients as well.[32,33,35] However, the previous studies on IPF have reported lower proportions of deaths due to malignant diseases, while, in turn, reporting a higher proportion of deaths caused by pulmonary fibrosis compared to our asbestosis cohort.[32,33,35] Only few previous studies have reported both underlying and immediate causes of death in ILD patients. In our study, the most common immediate causes of death were pneumonia, CAD/myocardial infarction and lung fibrosis, which is in line with the findings from RA-ILD and IPF patients.[6,32]

The limitations of the study were caused by the retrospective nature of the study protocol. In consequence, we were not able to collect information reliably about certain comorbidities such as psychiatric diseases, hypercholesterolemia or obesity. However, we were able to collect relatively comprehensive data on common comorbidities of asbestosis patients and estimate their association with prognosis, which are novel results. Autopsies are shown to improve the accuracy of death certificates since the cause of death may be misclassified if autopsy is not performed.[36,37] A previous Finnish study revealed that 29.5% of the underlying causes of death would have been misdefined without forensic autopsy.[38] In our study, the autopsy rate was relatively high, 68%, supporting the reliability of our results.

CONCLUSION

Patients with asbestosis have multiple comorbidities of which pleural plaques, cardiovascular diseases, COPD/emphysema and malignancies were the most frequent. Although the disease course of asbestosis is usually relatively slow, asbestosis was the most common underlying cause of death. CAD and LC were associated with worse prognosis, being also common causes of death in asbestosis patients. Prevention and appropriate treatment of CAD and LC may influence the prognosis of asbestosis patients.

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Table 1. Characteristics of the patients with asbestosis

		Total (n=116)
Gender	Male	111 (95.7)
	Female	5 (4.3)
Age at diagnosis (years)		67.9±8.7
Smoking	Non-smoker	30 (25.9)
	Ever-smoker	86 (74.1)
FVC % predicted[A]		80.7±16.6
DLCO % predicted[A]		64.9±18.9
Vital status	Alive	15 (12.9)
	Dead	101 (87.1)

Data presented as number of patients (%) or mean±SD

Missing 19 patients[A]

Abbreviations: diffusing capacity for carbon monoxide (DLCO), forced vital capacity (FVC)

Table 2. Comorbidities of asbestosis patients

Comorbidity		Total (n=116)
Pleural plaques		111 (95.7)
Coronary artery disease		78 (67.2)
Obstructive pulmonary disease[A]		72 (62.1)
	COPD/emphysema	63 (54.3)
	Asthma	27 (23.3)
Hypertension		58 (50.0)
Atrial fibrillation		55 (47.4)
Heart failure[B]		45 (38.8)
Cancer[C]		42 (36.2)
	Lung	18 (15.5)
	Prostate	9 (7.8)
	Hematological	6 (5.2)
	Bladder	4 (3.4)
	Skin	4 (3.4)
	Gastrointestinal	3 (2.6)
	Pancreatic	3 (2.6)
	Liver	2 (1.7)
	Mesothelioma	1 (0.9)
	Renal	1 (0.9)
Diabetes		33 (28.4)
ASO		27 (23.3)
Stroke/TIA[D]		26 (22.4)
	CI/TIA	23 (19.8)
	ICH/SAH/SDH	7 (6.0)
Dementia		20 (17.2)
Other pulmonary disease[E]		15 (12.9)
GERD		14 (12.1)
Hypothyroidism		12 (10.3)
Rheumatoid arthritis		10 (8.6)
Gout		10 (8.6)
Basalioma		9 (7.8)

18 patients had both COPD/emphysema and asthma[A]
Includes cardiomyopathy[B]
10 patients had two different cancers[C]
4 patients had both CI/TIA and ICH/SAH/SDH[D]
Obstructive sleep apnea (n=5), bronchiectasis (n=3), pulmonary tuberculosis (n=3), other mycobacterial infection (n=1), pulmonary hypertension (n=1), sarcoidosis (n=1) and silicosis (n=1)[E]
Abbreviations: arteriosclerosis obliterans (ASO), cerebral infarction (CI), chronic obstructive pulmonary disease (COPD), gastroesophageal reflux disease (GERD), intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), subdural hemorrhage (SDH), transient ischemic attack (TIA)

Table 3. Association of comorbidities and mortality in patients with asbestosis

	Age adjusted analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age at diagnosis[A]	1.08 (1.06-1.11)	<0.001	1.11 (1.08-1.15)	<0.001
Ever-smoker	1.17 (0.74-1.85)	0.514	1.23 (0.77-1.97)	0.380
Coronary artery disease	1.94 (1.22-3.07)	0.005	1.91 (1.20-3.02)	0.006
Obstructive pulmonary disease	0.80 (0.53-1.20)	0.277		
COPD/emphysema	0.96 (0.64-1.44)	0.835		
Asthma	0.67 (0.41-1.10)	0.109		
Hypertension	0.56 (0.36-0.86)	0.008	0.59 (0.38-0.91)	0.016
Atrial fibrillation	0.83 (0.56-1.24)	0.372		
Heart failure	1.01 (0.68-1.53)	0.945		
Any malignancy	1.09 (0.73-1.65)	0.668		
Lung cancer	1.65 (0.97-2.80)	0.064	1.73 (1.02-2.93)	0.042
Diabetes	1.01 (0.66-1.57)	0.949		
GERD	0.69 (0.37-1.27)	0.229		

Multivariate analysis: Age, smoking, coronary artery disease, hypertension and lung cancer in the same analysis

Univariate analysis[A]

Abbreviations: confidence interval (CI), chronic obstructive pulmonary disease (COPD), gastroesophageal reflux disease (GERD), hazard ratio (HR)

Table 4. Underlying and immediate causes of death

Underlying cause of death		Total (n=100)	Autopsy (n=68)	No autopsy (n=32)
Asbestosis/Lung fibrosis		36	33	3
CAD		24	18	6
Cancer		18	9	9
	Lung	10	7	3
	Leukemia	2	0	2
	Pancreatic	2	0	2
	Bladder	1	0	1
	Colorectal	1	1	0
	Liver	1	1	0
	Mesothelioma	1	0	1
Alzheimer		5	0	5
COPD		4	2	2
Stroke		4	2	2
Other cardiovascular disease		3	1	2
Other		6	3	3
Immediate causes of death		**Total (n=100)**	**Autopsy (n=68)**	**No autopsy (n=32)**
Pneumonia		38	26	12
CAD/Myocardial infarction		18	13	5
Asbestosis/Lung fibrosis		11	11	0
Cancer		9	2	7
	Lung	4	2	2
	Pancreatic	2	0	2
	Bladder	1	0	1
	Leukemia	1	0	1
	Mesothelioma	1	0	1
Other cardiovascular disease		4	2	2
Respiratory insufficiency		4	4	0
Pulmonary embolism		3	2	1
Stroke		3	1	2
Acute exacerbation of asbestosis		2	2	0
COPD		2	1	1
Other		6	4	2

Data is presented as number of patients

Abbreviations: coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD)

Other cardiovascular disease: hypertension (n=2), cardiomyopathy (n=1) and heart failure (immediate cause of death n=1)