Title: A systematic review of comorbidities and outcomes of patients with pleural infection

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Funding TC is funded as an Academic Clinical Fellow by the National Institute of Health Research and by a Wellcome Trust PhD Training Fellowship for Clinicians [grant number 211042/Z/18/Z]. MH is a recipient of the European Respiratory Society Long Term Research Fellowship - ERS 2016 7333.

Author contribution:

MH, JPC and NMR conceptualised and planned the study. EH conducted the literature review. TC and MH screened abstracts for inclusion. TC extracted and analysed the data and prepared the manuscript. DJM and NMR critically revised the first draft.
All authors reviewed the final manuscript prior to submission.

Abstract

Background

Pleural infection remains an important cause of mortality. This study aimed to investigate worldwide patterns of pre-existing comorbidities and clinical outcomes of patients with pleural infection.

Methods

Studies reporting on adults (over 18 years) with bacterial pleural infection between 2000-2017 were identified from a search of Embase and Medline. Papers reporting exclusively on tuberculous, fungal or post pneumonectomy infection were excluded. Two reviewers assessed 20980 records for eligibility.

Results

211 studies met the inclusion criteria. 135 papers (227,938 patients, mean age 52.7 years) reported comorbidity and/or outcome data. The majority of studies were retrospective observational cohorts (n=106, 79%) and the most common region of reporting was East Asia (n=33, 24%) followed by North America (n=27, 20%).

86 papers (50,796 patients) reported comorbidity. The median percentage prevalence of any comorbidity was 72% (IQR 58-83%), with respiratory illness (20%, 16-32%) and cardiac illness (19%, 15-27%) most commonly reported. 126 papers (192,338 patients) reported outcome data. The median length of stay was 19 days (IQR 13-27) and median in-hospital or 30-day mortality was 4% (IQR 1-11%).

In regions with high-income economies (n=100, 74%) patients were older (mean 57.3 vs. 43.9 years, p<0.0001) but there were no significant differences in reported prevalence of comorbidities, length of hospital stay or mortality.

Conclusion

Patients with pleural infection have high levels of pre-existing comorbidity, long hospital stays and an important mortality burden. Most reported data are derived from high-income economy settings. Epidemiological data on pleural infection in lower-income regions is needed to better understand regional trends in pleural infection and to enable optimal resource provision going forward.

Key words

Pleural infection, empyema, systematic review

Introduction

Infection of the pleural space causes serious morbidity and is often life threatening.[1] Despite advances in management, mortality remains high reported at between 9 - 10.5% in a recent Danish cohort.[2] This is especially true among older patients where the 30-day mortality has been reported at 20.2% in patients aged over 80 years.[2–4]

Pleural infection is common with over 30,000 diagnoses between the years 2000-2011 in the largest and most recent population based cohort in Taiwan.[5] In recent years, incidence rates have been trending upwards[2,3,6] and coupled with advancing therapeutic techniques, the management of pleural infection represents a growing resource strain with reported median hospital stays in a Canadian study averaging nearly 22 days.[6] The use of intrapleural fibrinolytics[7] as well as the improved safety profile for endoscopic thoracic surgery increased the average cost of hospitalisation in a Taiwanese based study to reach 4400 US dollars per admission in 2008, an increase in excess of 60% over the preceding 12 years of the study.[4]

The underlying drivers of the rise of pleural infection cases are not fully established. Possible mechanisms include the rise of multimorbidity in aging populations as well as immunosuppressive states such as HIV, predisposing individuals to the condition. This is supported by data from large population based cohorts demonstrating that incidence is skewed towards older persons and is rising more quickly in this group.[2,6] Further, rates of comorbidity in pleural infection have been reported as being as high as 74%,[2,5] and patients with increased pre-existing comorbidity have higher mortality rates (20.6% if Charlton comorbidity score (CCS) of over 2 points, 6% if CCS 0 points).[2]

This tripartite trend of increasing incidence of pleural infection, accelerated cases amongst older persons and higher mortality amongst older and comorbid persons are consistently reported in a handful of large population base cohorts from Canada, Taiwan, Denmark and the United States.[2–6] However, these data do not necessarily represent worldwide patterns and to date no study has comprehensively reviewed the published data available. To address this, we performed a systematic review of the literature reporting the clinical characteristics and outcomes of patients with pleural infection, with a comparison between high and lower-income economies of which reports from the latter are sparse. More research in low-economic settings will be essential going forward to understand regional trends and inform local resource provision.

Methods

This review was carried out according to PRISMA guidelines and the protocol registered on the PROSPERO International prospective register of systematic reviews (CRD42017076418).[8]

Search Strategy

Ovid MEDLINE and EMBASE were searched between 2000-2017 using the keywords 'empyema'. 'pleural infection' and 'pleuritis'. The full search strategy is reported in detail elsewhere (PROSPERO, CRD42017076418).[8]

Data extraction

All records were screened independently by two authors (TC and MH).

The following inclusion criteria were used:

- Population – adults (age over 18) with bacterial pleural infection/empyema in any setting (community, secondary or tertiary hospital care).
- Intervention – Any intervention including conservative management with antibiotics and chest tube, intrapleural medication or any form of surgical procedure.
- Comparator – no comparator assessed; and
- Outcomes – In-hospital mortality, length of stay, escalation to surgical intervention in mixed cohort studies, any recorded co-morbidity on admission.

Randomised and non-randomised controlled trails as well as observational or cross-sectional studies were included. Records with fewer than 20 participants were excluded due to the case selective nature of these reports.

Reports where over half of participants were aged under 18 or with tuberculous, fungal or post pneumonectomy pleural infection were excluded, as the aetiology and outcome in these groups are not comparable to bacterial pleural infection in adults. Non-English language studies were included when suitable translation was available.

Data was extracted where available into a Microsoft Excel proforma. Countries of studies included in this review were classified by income as per the world bank definition for the 2019 fiscal year [9] with gross national income (GNI) per capita in the year 2017 as follows: [10]

- Low-income economies **(**995 Dollars GNI per capita or less)
- Lower-middle income economies **(**996-3895 Dollars GNI per capita)
- Upper-middle income economies **(**3896-12055 Dollars GNI per capita)

- High-income economies **(**12055 Dollars GNI per capita)

Collectively in this article low, lower-middle and upper-middle economies are referred to as lower-income economies.

Subgroup analysis

Comorbidity data is reported as number and percentage of total participants in each study. Studies that specifically recruited patients with empyema and a specific disease exclusively (e.g. human immunodeficiency virus) were excluded from the analysis of that particular comorbidity. Data was presented as prevalence of comorbidity both by affected organ/system and by specific disease.

Outcome analysis

Data on 30-day/in-hospital mortality, length of hospital stay, need for surgical intervention and institution of intrapleural fibrinolytic therapy were collected. Studies where an entire cohort was comprised of a single intervention were excluded from analysis of that particular outcome.

Statistical analysis was performed in Prism (Graph Pad version 8.0). Median values were transformed where possible to means using the formula: mean = ((lower limit + (2*median) + upper limit))/4. Student's t-test for parametric data or Mann-Whitney U test for non-parametric data was performed for statistical comparison between two groups.

Results

Cohort characteristics

Of the 20,980 publications returned from the initial search, 211 studies met the inclusion criteria. 135 papers (totaling 227,938 patients)[2,4–7,11–140] reported comorbidity and/or outcome data (characteristics summarised in Supplementary Table 1 and Supplementary Figure 1). The remaining papers were excluded due to lack of relevant data (n=48), duplicate datasets (n = 12), special populations pre-defined for exclusion in the protocol (n = 5), included less than 20 patients (n = 10) or unable to obtain original article (n=1).

The majority of studies (n=106, 79%) were retrospective observational cohorts, while 17 studies (13%) were prospective observational studies and 11 (8%) were randomised controlled trials. The published data were skewed towards reports from high-income economies (n=100, 74%) with over a quarter from low, low-middle and upper-middle economies combined (n=35, 26%). The most common region of reporting was East Asia (n=33, 24%) followed by North America (n=27, 20%).

The mean age of individuals in all studies was 54.6 years (95% confidence interval (CI) 52.4 – 56.8 years). Patients in cohorts from high-income economies were significantly older than patients from lower-income economies (57.3 years vs. 43.9 years, $p<0.0001$).

Patients with pleural infection have a high prevalence of pre-existing comorbidity

Eighty-six papers reported comorbidity data, (totaling 50,796 patients). The majority of published data were from countries with high-income economies (n=68, 79%, totaling 48,703 patients). Most reports were single/multicentre retrospective or prospective observational cohorts (n=64, 74% and n=11, 13% respectively). Thirty-eight studies were cohorts including empyema treated exclusively by surgery or fibrinolysis (n=27, 31% and n=11, 13% respectively).

Twenty-eight studies reported the presence of overall co-morbidity levels within their dataset. The percentage prevalence of pre-existing comorbidity in patients with empyema was high (median 72%, interquartile range (IQR) 58-83%, Supplementary Figure 2a).

Supplementary Figure 2a shows the median percentage prevalence of reported co-morbidity grouped by organ system affected. The percentage prevalence of smokers in patients with empyema had a median of 42%, (IQR 30-52%, data reported in 22 studies). The median percentage prevalence of alcohol excess in patients with empyema was 15%, (IQR 8-25%, 30 studies). The median percentage prevalence of respiratory comorbidity in patients with empyema was 20% (IQR 16-32%, 17 studies). This was similar to the percentage prevalence of cardiac disease (median 19%, IQR 15-27%, 21 studies) and higher than the percentage prevalence of malignancy (median 12%, IQR 8-23%, 32 studies) and liver disease (median 5%, IQR 3-11%, 33 studies).

Supplementary Figure 2b shows the median percentage prevalence of different comorbidities by specific disease. The median percentage prevalence of hypertension in patients with empyema was 23% (IQR 17-38%, 21 studies). This was higher than the percentage prevalence of diabetes (reported in 67 studies, median 17%, IQR 10-27%), cerebrovascular attack (reported in 21 studies, median 13%, IQR 5-20%), ischaemic heart disease (reported in 12 studies, median 11%, IQR 5-16%), chronic obstructive pulmonary disease (reported in 41 studies, median 10%, IQR 6-19%) and chronic kidney disease (reported in 33 studies, median 7%, IQR 5-13%). The reported presence of immunosuppressive states was relatively low, with Human Immunodeficiency virus (HIV) median percentage prevalence of 4% (IQR 1-9%, reported in 16 studies), median percentage prevalence of steroid use in 4% (IQR 2-16%, reported in 6 studies) and median percentage prevalence of recent chemotherapy in 4% (IQR 1-15%, reported in 3 studies).

Where possible, we compared comorbidity prevalence between high-income and lower-income economies. There were no significant differences between studies reporting from high-income economies compared to low-income economies in prevalence of overall pre-existing comorbidity (median 73% vs. 58%, p=0.623) but studies from higher income economies reported a higher prevalence diabetes mellitus (median 20% vs. 14%, p=0.05). Comparisons for other specific comorbidities were not attempted due to the paucity of data reported from lower income economies.

Patients with pleural infection have long length of stay in hospital

Data on outcome of pleural infection was reported in 126 papers (totalling 192,338 patients). Studies reported long inpatient hospital stays (median 19 days, IQR 13-27, reported in 79 studies, totalling 180,931 patients) and median mortality in hospital or within 30 days was 4% (IQR 1-11%, from 106 studies totalling 179,071 patients). Prevalence of patients requiring either fibrinotlytic treatment (median 31%, IQR 17-52%, from 38 studies totalling 30,071 patients) or surgery (median 20%, IQR 1-32%, from 66 studies totalling 37,370 patients) were also reported.

Supplementary Figure 3 shows the differences in outcome parameters according to the income category of the country of study. There was no significant difference between studies reporting from high-income compared to lower-income economies in mean length of stay (18.7 days vs. 19.7 days, supplementary figure 3a), percentage prevalence of patients receiving surgery (median 19.5% vs. 20.0%, supplementary figure 3b) or fibrinolytic treatment (median 41% vs. 24%, p=0.1) or 30-day/in-hospital mortality (median 5% vs. 4%).

Discussion

This is the first systematic review describing the comorbidities and outcomes of studies reporting on patients with pleural infection since the turn of the 21st century. We found the percentage prevalence of pre-existing co-morbidity was high (median 72%) with a wide range of chronic conditions affecting the major organ systems. This is consistent with large population-based studies, which have reported comorbidity prevalence of up to 74%[5] and supports the hypothesis that the rise in the incidence of pleural infection in recent years might be associated with an increasingly aging, multi-morbid population.

Chronic respiratory and cardiovascular conditions had the highest percentage prevalence and where specific conditions were reported, hypertension, diabetes mellitus, cerebrovascular and ischaemic heart disease all had median prevalence rates between 11 and 23%. As the majority of studies were from high-income settings where these conditions are endemic, this finding may seem unsurprising and indeed known risk factors for these diseases including smoking and alcohol excess were also reported (median 42% and 15% respectively).

When comparing studies from high and lower-income economies, there was an increased reported prevalence of diabetes mellitus (median 20% vs. 14%, p=0.05). The mean age of patients in studies from high-income economies was also significantly higher than from lower-income economies (56.3 years vs. 42.1 years, p<0.001), which likely reflects the longer life expectancy in high-income economies and the increasing prevalence of diabetes mellitus with age[141].

Evidence from large prospective population-based cohort studies will be required to investigate whether there is a causative link between the rise in chronic non-communicable conditions such as diabetes mellitus and the increased incidence in pleural infection and whether there are true differences between high and lower-income economies.

Immunosuppressive states through diseases such as HIV or iatrogenically induced by steroids, immunomodulatory and chemotherapeutic agents can be associated with pleural infection.[47,68] We found a relatively low prevalence of these conditions amongst studies of patients with pleural infection, however this is likely an underestimation as only a small number of studies collected this data. Studies from lower-income economies reported higher levels of HIV compared to high-income economies (median 14% vs. 4%), in keeping with current HIV trends, but this was not statistically significant. [142] Future studies should focus on the routine collection of this data to better understand the risk, pathogenesis and outcomes of pleural infection in these specific groups where the microbiological milieu and immune response are likely to differ from those in immunocompetent persons.

When analysing outcomes of pleural infection, we confirmed patients have long hospital stays (median 19 days), comparable to previously reported length of stay data.[2,6] This supports that pleural infection is an important use of healthcare resources.

We found a median in hospital/30-day mortality of 4%, which is lower than has been previously reported. The British Thoracic Society guidelines quote mortality at

20%[143], based on data from a large prospective UK cohort of patients with pleural infection with an 18% mortality rate at 6 months[144] and the MIST-1 cohort in which 12% had died by 1 year[145]. We recorded 30-day or in hospital mortality rather than 6 or 12 months, as this was most commonly reported in the studies we analysed. Our finding of a median 4% in-hospital mortality is consistent with a prospective single centre study of pleural infection reported in 1999, where in hospital deaths were 4.7% rising to 14% mortality within 400 days of chest tube insertion.[146] However in the largest most recently published population based cohort study of pleural infection cases in Denmark, overall unadjusted 30-day mortality was reported at between 9-10.5% [2]

One explanation for this is that our dataset is comprised of observational studies with low numbers of participants and significant risk of bias. There was a weakly positive correlation between the percentage mortality reported and number of participants (r=0.2, p=0.03, Supplementary Figure 4A). Studies with under 300 participants had a lower median mortality that studies with over 300 participants (4% vs 9%, p=0.06, Supplementary Figure 4B) and reported a wider range of mortality estimates. There was no association between numbers of participants and age or year of publication but as expected there is an association between mortality and age in line with previous data (r=0.35, p=0.0003, data not shown). We were not able to investigate whether there was an association between co-morbidity and outcome as the data was not reported in such a way in the original studies.

Studies with more participants are less susceptible to inclusion bias, as data is obtained from databases using ICD-10 codes assigned at hospital discharge rather than locally curated cohorts. These larger studies therefore likely provide more reliable mortality estimates than our combined unadjusted estimate and this is weakness of our approach. Overall our analysis supports the seriousness of pleural infection in both loss of life but likely underestimates the true mortality prevalence.

Despite a significant difference in mean age of patients in studies from high and lower-income economies, the length of hospital stay, percentage of patients requiring surgery and 30-day/in-hospital mortality were similar between groups. Studies from higher-income economies reported a trend towards increased use of fibrinolytics (median 41% vs. 24%), which offers an option for symptomatic drainage of loculated pleural effusions in patients that are not suitable for surgery. This is consistent with a trend towards increasing use of fibrinolytics over time in one high-income based cohort.[4] However prospective randomised trials have failed to show a mortality benefit from fibrinolytic treatment and further studies are needed to explore this area of practice.[7,85]

This study describes the results of 135 papers reporting data from over 200,000 patients and thus is the most comprehensive work to date examining the comorbidities and outcomes of patients with pleural infection worldwide. However, the findings may not be generalisable to all settings or fully representative of real-world trends, as the majority of studies are relatively small retrospective observational cohorts from secondary care institutions in high-income settings. Mixed cohorts were included in the analysis to maximise inclusion and therefore some of the results will reflect patient populations with a proportion of tuberculosis, post-surgical and childhood empyema, which differ in aetiology and outcome to adult bacterial pleural infection.

In conclusion, this study confirms that pleural infection remains an important disease. Patients have a high prevalence of pre-existing comorbidity and are older in high-income economies. Importantly this study highlights the paucity of data on pleural infection from lower-income economies and calls for large prospective registries at the population level in these settings to better understand regional trends in pleural infection and to enable optimal resource provision.

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Supplementary Figure Legends

Supplementary Figure 1: PRISMA showing the identification, screening, eligibility and inclusion process.

Supplementary Figure 2: Pre-existing prevalence of comorbidity in studies of patients with pleural infection. Percentage prevalence of comorbidities in each study were extracted and data from high and lower-income economies were compared A: Percentage prevalence of comorbidity, smoking, alcohol excess and disease by organ system affected. B: Percentage prevalence of comorbidity by specific diseases. (HIV = human immunodeficiency virus.) Median and interquartile range shown. Mann-Whitney test to compare median prevalence of diabetes mellitus in high income economies and lower-income economies *= $p<0.05$.

Supplementary Figure 3: Prevalence of outcomes in studies of patients with pleural infection. Percentage prevalence of outcomes in each study were extracted and data from high and lower-income economies were compared. A: Mean length of stay (days) B: Percentage prevalence of mortality, patients requiring fibrinolysis and patients requiring surgical treatment. Median and interquartile range shown.

Supplementary Figure 4: Percentage prevalence of in-hospital/30-day mortality of patients with pleural infection. A: Correlation plot showing log transformed number of participants plotted against percentage mortality. Spearman rank r value shown, *= $p<0.05$. **B:** Scatter plot showing percentage mortality for all included studies (left bar), studies with under 300 participants (middle bar) and over 300 participants (right bar) are shown. Median and range shown. Mann-Whitney test to compare median mortality of all included data sets with dataset with over 300 participants, ns = not significant